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Transition-Metal Catalyzed Cross-Coupling Reactions of Functionalized Organometallic Reagents, Nickel-Catalyzed Amination of Aryl Chlorides and Preparation and Reactions of Organozinc Reagents

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2. G. Manolikakes, A. Gavryushin, P. Knochel; An Efficient Silane-Promoted Nickel-Catalyzed Amination of Aryl and Heteroaryl Chlorides. *J. Org. Chem.* **2008**, *73*, 1429-1434.
3. G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel; Negishi Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents. *Org. Lett.* **2008**, *10*, 2765-2768.
4. A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel; A general preparation of polyfunctional benzylic zinc organometallic compounds. *Chem. Asian. J.* **2008**, *3*, 1678-1691.
5. G. Manolikakes, C. Munoz Hernandez, M. A. Schade, A. Metzger, P. Knochel; Palladium- and Nickel-Catalyzed Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Protons with Organozinc Reagents. *J. Org. Chem.* **2008**, *73*, 8422-8436.
6. G. Manolikakes, P. Knochel; Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents. *Angew. Chem. Int. Ed.* **2009**, *48*, 205.
7. Z. Dong, G. Manolikakes, L. Li, P. Knochel; Palladium-Catalyzed Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents. *Synthesis*, **2008**, *published online*, DOI: 10.1055/s-0028-1083286.
8. P. Knochel, P. Appukkuttan, G. Manolikakes, A. Metzger, M. Mosrin, F. M. Piller, C. J. Rohbogner, M. A. Schade, S. H. Wunderlich.; Functionalization of Heterocyclic Compounds using Polyfunctional Magnesium and Zinc Reagents. *Synthon* (Pfizer In-House Journal) **2008**.
9. G. Manolikakes, Z. Dong, H. Mayr, J. Li, P. Knochel; Negishi Cross-Couplings Compatible with Unprotected Amide Functions. *Chem. Eur. J.* **2009**, *15*, 1324.
10. Z. Dong, G. Manolikakes, L. Shi, J. Li, P. Knochel, H. Mayr; Relative Reactions Rates of Negishi Cross-Coupling Reactions in Substituted Bromobenzene and Arylzinc Derivatives. *manuscript in preparation*.
11. A. Metzger, G. Manolikakes, P. Knochel, P; Mg^{2+}-Promoted Addition of Organozinc Reagents to Carbonyl Compounds. *manuscript in preparation*.

12. M. A. Schade, G Manolikakes, P. Knochel; Direct Synthesis of Primary Amides From Functionalized Organozinc Reagents. *manuscript in preparation.*

Abbreviations:

Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
CH_2Cl_2	dichloromethane
cod	cycloocta-1,5-diene
d	day
dba	*trans,trans*-dibenzyledenacetone
DMSO	dimethyl sulfoxide
dppe	1,2-*Bis*-(diphenylphosphine)ethane
dppf	1,1'-*Bis*-(diphenylphosphino)ferrocene
Eq.	equation
equiv	equivalent
EI	electron-impact
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectrospcopy
*i*Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
M	molarity
m	meta
Me	methyl
min	minute
mp.	melting point
MS	mass spectroscopy
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance

o	ortho
Oct	octyl
p	para
Ph	phenyl
PEPPSI	[1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)-palladium(II) dichloride
R	organic substituent
s	second
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
tfp	tri-(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetrametyhlethylendiamine
TP	typical procedure
Ts	4-toluenesulfonyl
X	Halogen (Cl, Br, I)

1. Introduction

''Organic synthesis is considered, to a large extent, to be responsible for some of the most exciting and important discoveries of the twentieth century in chemistry, biology and medicine and continues to fuel the drug discovery and development processes with myriad processes and compounds for new medical breakthroughs and applications.'' Those words of K. C. Nicolaou[1] display the importance of synthetic organic chemistry over the last two centuries since *Wöhler's* synthesis of urea in 1828. They also point out the issues, organic chemists are facing in the twenty-first century: respond to an ever-growing demand for new, efficient and environmentally friendly methods to perform chemical transformations.[2] Among these transformations, the selective carbon-carbon and carbon-heteroatom bond formation are certainly of great importance, as unique tools for the construction of complex molecules.

Frankland's synthesis of diethylzinc in 1849[3] and the outstanding work of *Grignard* on organomagnesium reagents[4] have paved the way for the development of modern organometallic chemistry. Nowadays, it offers a highly diverse toolkit for organic chemists and there is an ongoing effort to increase its diversity. Nearly every metal in the periodic table has found some useful applications in synthetic organic chemistry up to now. Depending on the very nature of the metal, reactivity and selectivity of the organometallic reagent can be tuned.[5] Thus, very polar carbon-metal bonds, as for instance in organolithium compounds, are highly reactive towards many electrophiles, even at low temperatures. However, they are hardly compatible with sensitive functional groups and display poor chemoselectivity. On the other hand, carbon-metal bonds with more covalent character, such as in organozinc, -tin or -boron reagents, react with suitable electrophiles in a highly selective manner with a high tolerance towards a multitude of functional groups. Nevertheless, due to the comparably low reactivity of these reagents, the range of appropriate electrophiles is very limited. This lack of reactivity can be overcome by using transition metals like Cu, Ni or Pd.[6]

The development of these metal-catalyzed cross-coupling reactions over the past 30 years has revolutionized the way, carbon-carbon bonds as well as carbon-heteroatom bonds

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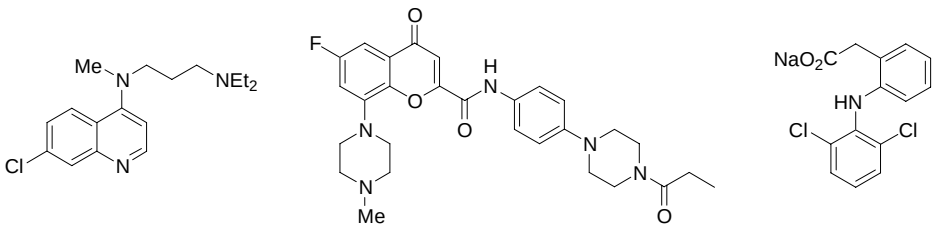
[1] K. C. Nicolaou, D. Vourloumis, N. Winsigger, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44.
[2] B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259.
[3] a) E. Frankland, *Liebigs Ann. Chem.* **1848-9**, *71*, 171; b) E. Frankland, *J. Chem. Soc.* **1848-9**, *2*, 263.
[4] a) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322; b) V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[5] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; b) P. Knochel, ed., *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**.
[6] a) A. de Meijere, F. Diederich, Eds., *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed., Wiley-VCH, Weinheim, **2004**; b) J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**.

are formed. These methods have profoundly changed the protocols for the synthesis of natural products, organic materials and polymers and pharmaceutical compounds. Cross-coupling reactions are quite effective for dissecting complex molecules into smaller entities. In combination with combinatorial chemistry, cross-coupling reactions provide an access to a high diversity of chemical structure, for instance in the lead identification and optimization of drug candidates. Also, for process development and the manufacture of fine chemicals, C-C and C-N coupling reactions have become an effective tool to develop enviromentally friendly and economically sound manufacturing processes in a shorter time period.[7]

1.1 Transition Metal-Catalyzed Aromatic Carbon-Nitrogen Bond Formation

The synthesis of aromatic amines has attracted much attention due to their important role in many fields of science and industry. These include natural products, pharmaceuticals, agrochemicals, dyes and polymers.[8] An aryl-nitrogen linkage is included in molecules like chloroquine, a widely used antimalarial drug,[9] ZM549865, a 5HT receptor antagonist developed by AstraZeneca,[10] or the Novartis blockbuster diclophenac (Voltaren^{TM}, Figure 1). Despite the simplicity of the arylamine moiety, the syntheses of these molecules are often



chloroquine ZM549864 diclophenac

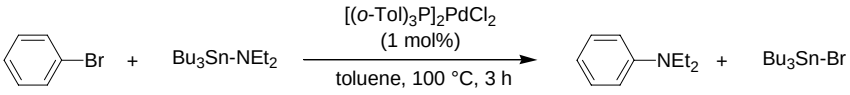
Figure 1. Biologically active arylamines.

[7] For the application of cross-coupling reactions in industrial processes, see: a) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; H.-U. Blaser, A. Indolese, F. Naud, U. Nettekoven, A. Schnyder, *Adv. Synth. Catal.* **2004**, *364*, 1583.
[8] a) A. Ricci, ed., *Modern Amination Methods*, Wiley-VCH, Weinheim, **2000**; b) B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599.
[9] G. D. Burchard, R. Bialek, C. Schönfeld, D. Nothdurft, *Deutsches Ärtzteblatt*, **1996**, *93*, 1995.
[10] G. E. Robinson, O. R. Cunningham, M. Dekhane, J. C. McManus, A. O'Kearney-McMullan, A. M. Miraikjar, V. Mishra, A. K. Norton, B. Venugopalan, E. G. Williams, *Org. Proc. Res. Devl.* **2004**, *8*, 925.

difficult. Traditional procedures involving nitration-reduction sequences or nucleophilic aromatic substitution (S_NAr) are incompatible with many functional groups and often involve protection and deprotection steps or the removal of activating groups.[11]

Therefore the development of efficient methods for the synthesis of aryl-nitrogen bonds is a matter of particular interest for organic chemists. In recent years, several new methodologies have been introduced for the preparation of this structural motif.[12] These include the synthesis secondary amines or diarylamines via electrophilic aromatic amination,[13] addition of nitrogen nucleophiles to benzyne intermediates[14] or the oxidative coupling of polyfunctional lithium amidocuprates.[15] Also great efforts have been made to improve the copper-mediated Ullmann-coupling[16] and turned it into a valuable method, especially with weakly nucleophilic nitrogen substrates, such as amides or imidazoles.[17]

Among all these synthetic methods, transition-metal catalyzed aminations of aryl halides and related substrates has become the most versatile tool for the preparation of arylamines.[18] The first palladium-catalyzed C(sp^2)-N bond-forming process was reported by *Migita* and *Kosugi* in 1983 (Scheme 1).[19] The treatment of bromobenzene (**1**) with the aminotin compound **2** in the presence of a palladium catalyst provided *N,N*-diethyl-aniline (**3**). However, this method requires the use of a stoichometric quantity of a toxic and moisture sensitive tin reagent.

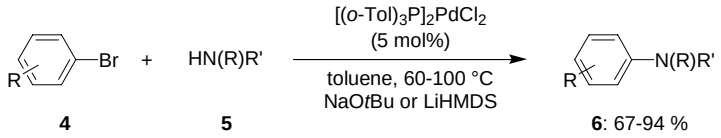


Scheme 1. First palladium-catalyzed arylaminantion using tributyltin amides.

These limitations were overcome by the pioneering work of *Buchwald* and *Hartwig* in 1995.[20] Both groups independently reported the palladium-catalyzed amination of aryl bromides (**4**)

[11] J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, Oxford, **2001**.
[12] For a general overview, see: M. Kienle, S. Dubbaka, K. Brade, P. Knochel, *Eur. J. Org. Chem.* **2007**, 4166.
[13] For selected recent publications, see: a) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680; b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 897; c) I. Sapountzis, P. Knochel, *J. Am. Chem. Soc.* **2002**, *124*, 9390.
[14] a) A. M. Dyke, A. J. Hester, G. C. Lloyd-Jones, *Synthesis* **2006**, *24*, 4093; b) W. Lin, I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 4258.
[15] V. del Amo, S. Dubbaka, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.
[16] F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.
[17] For an overview, see: S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
[18] L. Jiang, S. L. Buchwald in: *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed. (A. de Meijere, F. Diederich, eds.), Wiley-VCH, Weinheim, **2004**, 699.
[19] M. Kosugi, M. Kamayama, T. Migita, *Chem. Lett.* **1983**, *12*, 927.
[20] a) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34*, 1348; b) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995,** *36*, 3609.

with secondary amines (**5**) using a base, such as NaO*t*Bu or LiHMDS, affording the tertiary arylamines of type **6** in good to excellent yields (Scheme 2).



Scheme 2. Palladium-catalyzed aryl amination of aryl bromides.

The further development of this reaction led to a general and efficient tool for forming C(sp^2)-N-bonds. Nowadays, chemists both in industrial and academic laboratories routinely practice the palladium-catalyzed amination. It allows the cross-coupling of cheap and readily available aryl chlorides not only with amines, but also with hydrazines, amides, imines, nitrogen-containing heterocycles or ammonia.[8a, 18] Among all these efforts, fine tuning of the ligand has shown the biggest effect and led to two main and complementary classes of ligand: bulky biaryl monophosphine ligands and chelating bisphosphine ligands, such as X-Phos and John-Phos[21] or the Josiphos-type ligand CyPF-*t*Bu (Figure 2).[22] The synthesis of the κ-opiod receptor antagonist CJ-15,161 is one example for an application of the palladium-catalyzed amination using this novel phosphine ligands (Scheme 3).[23]

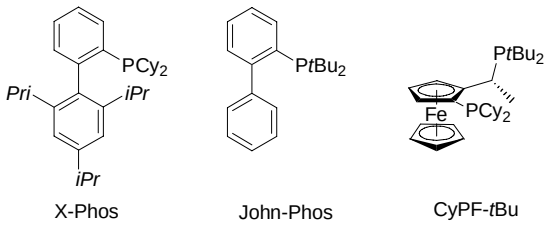
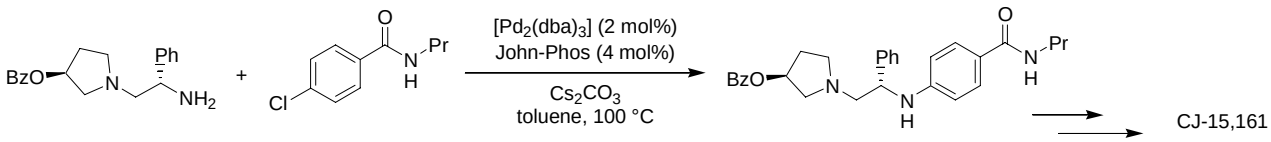


Figure 2. Phosphine ligands for palladium-catalyzed amination reactions.

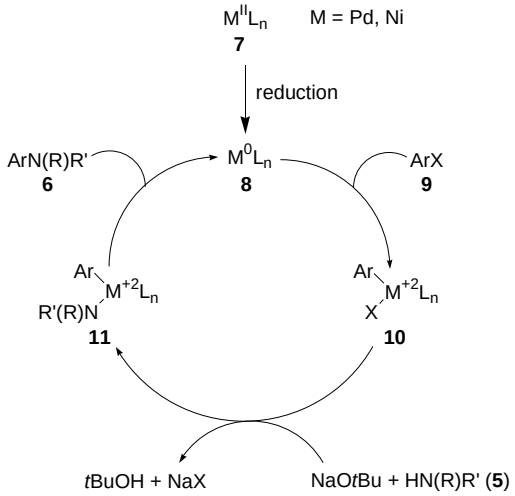


Scheme 3. Pfizer synthesis of a κ-opiod receptor antagonist.

[21] D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.
[22] T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 13848.
[23] A. Gosh, J. E. Sieser, S. Caron, T. J. N. Watson, *Chem. Comm.* **2002**, 1644.

On the other hand, nickel-catalyzed amination reactions have received less attention. *Buchwald* has reported the amination of aryl chlorides in the presence of $Ni(cod)_2$ and dppf or 1,10-phenanthroline.[24] This methodology was extended by using a heterogeneous Ni(0)/C catalyst[25] or employing 2,2'-bipyridine[26] or *N*-heterocyclic carbenes (NHC)[27] as ligands. However, these reactions require high amounts of nickel (5-10 mol%) and either unstable and expensive Ni(0) sources like $Ni(cod)_2$ or Ni(II)-precursors and reducing agents like NaH or MeMgBr, which are incompatible with several functional groups.

Blackwood, Buchwald and Hartwig have recently reported a detailed study of the amination of aryl halides in the presence of palladium complexes.[28] The first step is the oxidative insertion of the haloarene ArX (**9**) to the active M^0L_n-complex **8**, prior to the amine addition. The reaction of the $[ArML_2X]$-complex **10** with the amine **5** and the base (e.g. NaO*t*Bu) follows. Reductive elimination of the resulting amido complex **11** provides the desired arylamine **6** and regenerates the active complex **8**. If M^{+2}-salts are used, the active M^0-complex **8** has to be generated via reduction from the M^{2+}-precursor **7** (Scheme 4).



Scheme 4. Catalytic cycle for the transition metal-catalyzed amination.

For the corresponding nickel-catalyzed amination reaction no detailed mechanistic studies have been reported so far, although a similar mechanism is presumed.[27, 29]

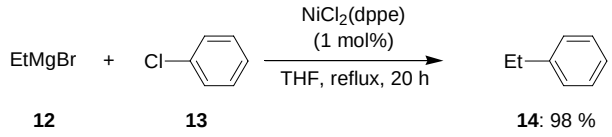
[24] J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6054.
[25] B. H. Lipshutz, H. Ueda, *Angew. Chem. Int. Ed.* **2000**, *39*, 6054.
[26] E. Brenner, R. Schneider, Y. Fort, *Tetrahedron* **1999**, *55*, 12829.
[27] C. Desmarets, R. Schneider, Y. Fort, *J. Org. Chem.* **2002**, *67*, 3029.
[28] S. Shekhar, P. Ryberg, J. F. Hartwig, J. S. Mathew, D. G. Blackmond, E. R. Strieter, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 3584.
[29] C.-Y. Gao, L.-M. Yang, *J. Org. Chem.* **2008**, *73*, 1624.

1.2 Transition Metal-Catalyzed Cross-Coupling Reactions

One of the most important methods for forming carbon-carbon-bonds is the coupling of an organometallic reagent with an organic halide or a related electrophile (Scheme 5). Despite their simplicity, these reactions were of limited use until the mid-1960's. Since mainly organomagnesium or organolithium compounds were used, this methodology was restricted to alkyl halides. Further disadvantages are the low chemoselectivity and possibly side reactions with alkyl halides (elimination, homo-coupling, etc.). The development of protocols based on organocopper reagents and copper-catalyzed alkylations solved some of these problems, although these methods were still limited to the use of alkyl halides.[30]

Scheme 5. Coupling reaction of an organometallic reagent with an alkyl halide.

The first transition metal-catalyzed cross-coupling of C(sp^2)-halides using organometallic compounds was independently reported by *Kumada*[31] and *Corriu*[32] in 1972. Thus, the reaction of EtMgBr (**12**) with chloro-benzene (**13**) in the presence of a nickel-phosphine catalyst provides the coupling product **14** in almost quantitative yield (Scheme 6).



Scheme 6. *Kumada's* nickel catalyzed cross-coupling reaction.

Since these reports, the development metal-catalyzed cross-coupling reactions for the efficient formation of new carbon-carbon-bonds has continued to progress dramatically.[6,33] Among them the very general and selective palladium-catalyzed Stille (involving organotin reagents) and Suzuki-Miyaura (involving boronic acids or esters) couplings have been particular popular. They have been successfully used in the synthesis of complex natural products like

[30] a) G. H. Posner, *Org. React.* **1975**, *22*, 253; b) B. H. Lipshutz in: *Organometallics in Synthesis. A Manual II*, M. Schlosser, ed., Wiley, Chichester, **1998**; c) R. J. K. Taylor, ed., *Organocopper Reagents*, Oxford University Press, Oxford, **1994**.
[31] T. Tamao, K. Sumitami, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374.
[32] R. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Comm.***1972**, 144.
[33] a) M. Beller, C. Bolm, eds., *Transition Metals for Organic Synthesis* 2nd ed., Wiley-VCH, Weinheim, **2004**; b) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Chemistry*, Wiley-Intersience, New York, **2002**.

cortistatin A (Stille-coupling)[34] or Merck's Cozaar™ (Suzuki-Miyaura-coupling),[35] a drug for treating hypertension (Figure 3).

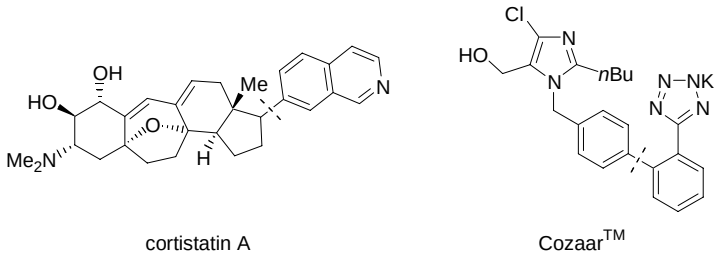
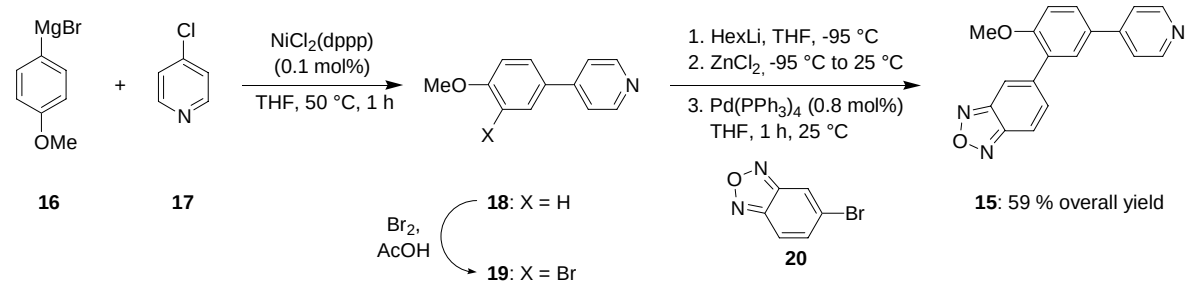


Figure 3. Cortistatin A and Cozaar™.

Other cross-couplings, using different organometallic species have been developed, offering chemists new methods to achieve C-C-bond formations. For instance, the palladium-catalyzed Hiyama- (organosilicon reagents), Negishi- (organozinc reagents), Sonogashira (alkynylcopper reagents) or the above mentioned Kumada-Corriu-reaction have proven to be highly valuable tools in organic synthesis. Chemists at Novartis used both a Kumada- and a Negishi-coupling to synthesize multi-kilogramm quantities of PDE 427 (**15**), a potential drug candidate for the treatment of asthma.[36] Nickel-catalyzed cross-coupling of the organomagnesium reagent **16** with 4-chloropyridine (**17**), followed by palladium-catalyzed cross-coupling of the benzoxadiazol **20** with the zinc reagent derived from **19** provided the pharmaceutical in 59 % overall yield (Scheme 7).

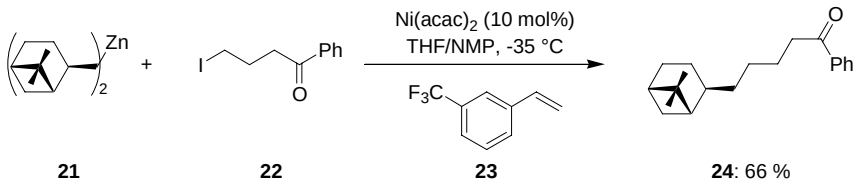


Scheme 7. Novartis synthesis of PDE 427 (**20**).

In addition, C(sp^3)-atoms, such as β-hydrogen containing alkyl halides, can now increasingly participate in these transformations.[37] For instance, *Knochel* reported a nickel-

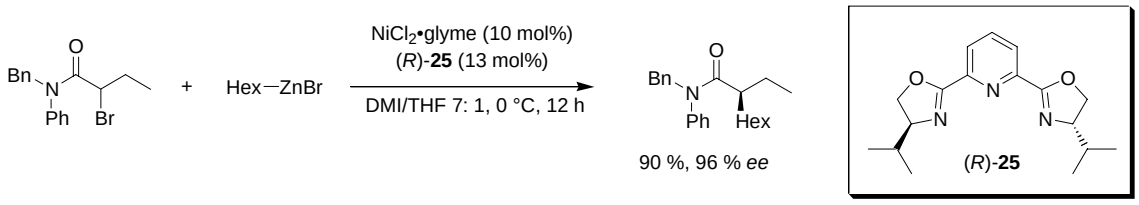
[34] R. A. Shenvi, C. A. Guerrero, J. Shi, C.-C. Li, P. S. Baran, *J. Am. Chem. Soc.* **2008**, 130, 7241.
[35] N. Yasuda, *J. Organomet. Chem.* **2002**, *253*, 279.
[36] P. W. Manley, M. Acemoglu, W. Marterer, W. Pachinger, *Org. Proc. Res. Devl.* **2003**, 436.
[37] For an overview, see: A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 674.

catalyzed $C(sp^3)$-$C(sp^3)$ cross-coupling, using *m*-trifluoromethylstyrene (**23**) as additive.[38] Thus, the reaction of the diorganozinc reagent **21** with the functionalized alkyl iodide **22** in the presence of catalytic amounts of $Ni(acac)_2$ and the additive **23** provided the substituted ketone **24** in 66 % yield (Scheme 8).



Scheme 8. *Knochel's* nickel-catalyzed alkyl-alkyl cross-coupling reaction.

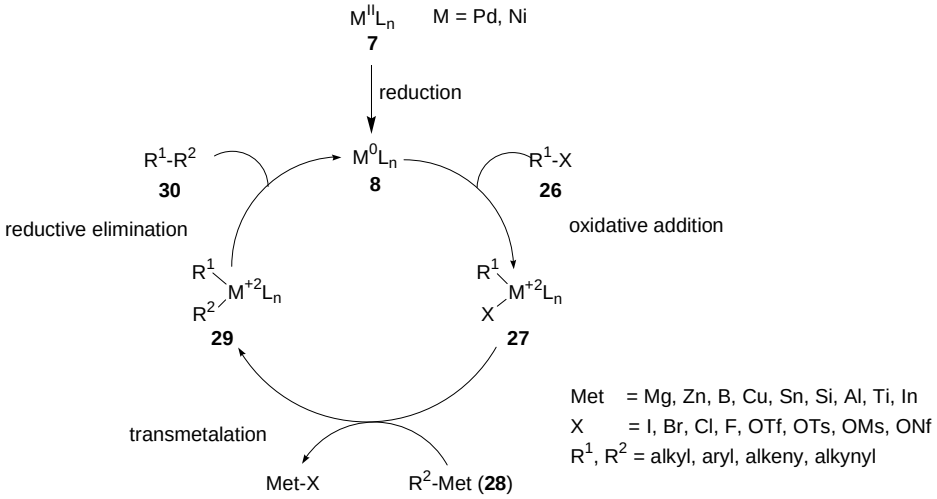
Recently, *Fu* developed a number of highly enantioselective nickel-catalyzed cross-coupling reactions of secondary alkyl halides with various organometallic reagents.[39] These reactions proceed with a high level of enantioselectivity, as shown in Scheme 9 for the asymmetric Negishi-coupling.



Scheme 9. *Fu's* asymmetric Negishi-coupling.

All the palladium- or nickel-catalyzed cross-coupling reactions have the particularity to share a common reaction mechanism (Scheme 10). The first step usually involves the *in situ* reduction of the catalyst precursor $M^{II}L_n$ (**7**) to the reactive species M^0L_n (**8**), either with the organometallic reagent or with an additional reducing agent. In the case of metal(0) precursors, such as $Pd(dba)_2$ or $Ni(cod)_2$ no preliminary reduction is required. This step is followed by an oxidative addition to the C-X bond of the electrophile R^1- X (**26**), affording the organometallic complex **27**. Subsequent ligand exchange reaction (respectively transmetalation) with the organometallic reagent R^2-Met (**28**) leads to the complex **29**. Reductive elimination provides the desired cross-coupling product R^1-R^2 (**30**) and regenerates the active catalyst M^0L_n (**8**). The exact structure of the active catalyst M^0L_n (**8**, n = 0-2) depends on the nature of the ligand L.

[38] R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 2387.
[39] For an overview, see: F. Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 8347.

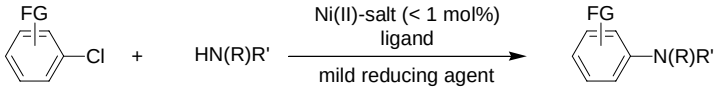


Scheme 10. Catalytic cycle of the transition metal-catalyzed cross-coupling reactions.

The structure of this ligand L plays an essential role among all the factors influencing the catalysts efficiency. For instance, electron-rich ligands facilitate the oxidative addition step, whereas sterically demanding ligands enhance the reductive elimination step.

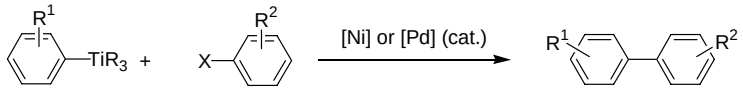
2. Objectives

As previously described, palladium-catalyzed arylamination has been one of the most widely used preparations of aryl amines. On the other hand, nickel-catalyzed amination reactions have received less attention. The aim of the first project was the development of an efficient catalyst system for the amination of aryl chlorides, preferentially based on a cheap Ni(II)-precursor and a mild reducing agent (Scheme 11).



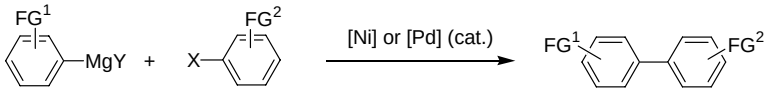
Scheme 11. Nickel-catalyzed amination of aryl chlorides.

So far organotitanium compounds have received less attention for the performance of cross-coupling reactions. Therefore, the transition metal-catalyzed cross-coupling reactions of organotitanium reagents with aryl halides were investigated (Scheme 12).



Scheme 12. Transition-metal catalyzed cross-coupling reactions with organotitanium compounds.

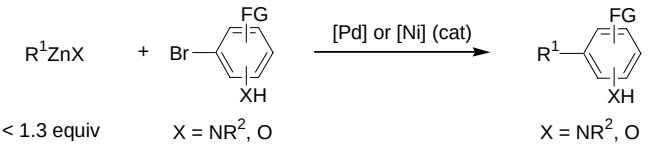
After the successful development of mild and selective methods for the preparation of organomagnesium compounds (I/Mg- or Br/Mg-exchange, LiCl-promoted Mg-insertion), it was interesting to apply these reagents directly without further transmetalation in transition metal-catalyzed cross-coupling reactions. The objectives of the third project were the direct application of these organomagnesium reagents in the Kumada-reaction and the extension to highly functionalized electrophiles, in particular those incompatible with Grignard reagents (Scheme 13).



Scheme 13. Preparation of highly functionalized biarlys via Kumada-coupling.

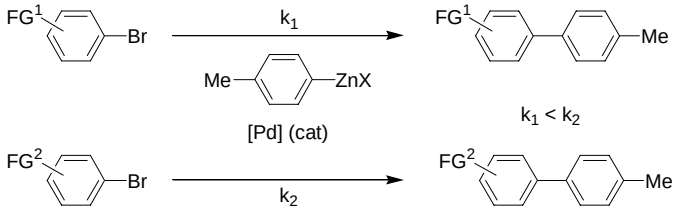
A further project involved the extension of the Negishi cross-coupling reaction to aryl halides bearing relatively acidic NH or OH groups. The objectives were the development of a

general method without the use of protection groups, large excess of the zinc reagent or the use of an extra base for deprotonation *prior* to the cross-coupling (Scheme 14).



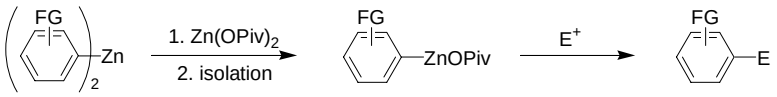
Scheme 14. Negishi cross-coupling in the presence of acidic protons.

In a fifth project, the relative reaction rates of the Negishi-coupling were investigated, to determine the influence of variuos substituents and their substitution pattern (Scheme 15).



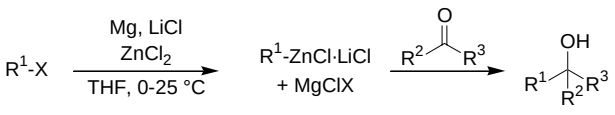
Scheme 15. Relative rates in the Negishi coupling.

Additionally, the preparation of air stable, solid zinc reagents was investigated. The objective was to synthesize sufficiently air and moisture sensitive dry zinc reagents, suitable for long time storage and easy handling (e.g. no glove-box techniques). Also their reactivity towards various was investigated.



Scheme 16. Preparation of dry zinc reagents and their application in synthesis.

Finally a MgX_2-promoted addition of organozinc reagents, prepared by the direct magnesium insertion in the presence $ZnCl_2$, to carbonyl compounds was developed (Scheme 17).



Scheme 17. MgX_2-promoted addition of organozinc reagents to carbonyl compounds**.**

3. Nickel-Catalyzed Amination of Aryl Chlorides

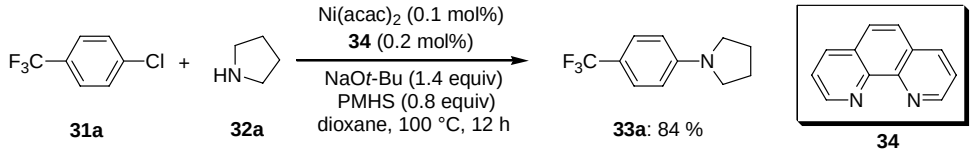
3.1 Introduction

As mentioned above, aromatic amines are important in a variety of fields, such as pharmaceuticals, agrochemicals and natural products[18] or as intermediates for the preparation of other important molecules, particularly heterocycles.[40] The palladium-catalyzed amination of aryl halides and related substrates has become one of the most efficient methods for the synthesis of arylamines. The corresponding nickel-catalyzed amination reactions have received less attention and the reported procedures require high catalyst loadings and either unstable and expensive Ni(0)-precursors or Ni(II)-salts and reducing agent incompatible with many functional groups.

Considering the nature of the ligands importance in palladium-catalyzed amination reactions, we presumed that the scope of a nickel-catalyzed amination reaction could be improved and extended by the development of a more active catalyst system.

3.2 Development and Optimization of the Nickel-Catalyzed Arylamination

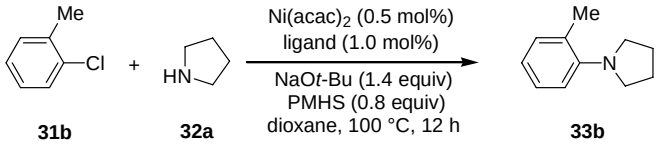
Preliminary studies in our group showed that polymethylhydrosiloxane (PMHS) can be successfully employed as a reducing agent in the nickel-catalyzed amination of aryl chlorides by using a stable and convenient Ni(II)-precursor, like $Ni(acac)_2$. The best results were obtained with phenanthroline based ligands.[41] Thus, the reaction of 1-chloro-4-trifluorometylbenzene (**31a**) with pyrrolidine (**32a**, 1.2 equiv) in the presence of catalytic amounts of $Ni(acac)_2$ and 1,10-phenanthroline (**34**) furnished the product **33a** in 84 % yield (Scheme 18).



Scheme 18. Nickel-catalyzed amination of 1-chloro-4-trifluoromethylbenzene (**31a**).

[40] R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, New York, **1999**.
[41] Georg Manolikakes, *Diploma thesis*, LMU München, **2005**.

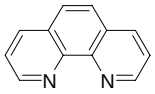
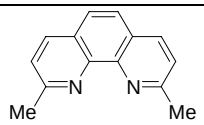
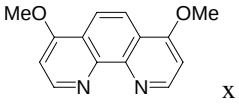
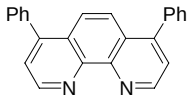
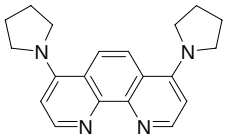
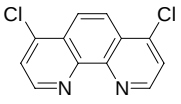
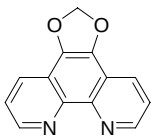
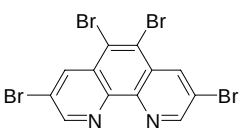
Too further optimize this catalytic system, we focused on this ligand class, using 2-chlorotoluene (**31b**) as a more demanding substrate (Scheme 19).



Scheme 19. Nickel-catalyzed amination of 2-chlorotoluene (**31b**) with pyrrolidine (**32a**).

Electron-rich phenanthrolines gave the amination product **33b** in 10-23 % yield (Table 1, entries 2-4), while the parent phenanthroline **34** afforded a 20 % yield of **33b** (entry 1). Thus, the higher electron density in the phenanthroline aromatic system was not a decisive factor for the catalytic activity. 2,9-Disubstituted phenanthrolines, like 2,9-dimethylphenanthroline (**38**), displayed almost no catalytic activity (entry 5). On the other hand, 4,7-aryl- or halogen-substituted phenanthrolines, such as 4,7-diphenyl-1,10-phenanthroline (**39**) and 4,7-dichloro-1,10-phenanthroline (**40**) lead to higher yields of **33b** (31-35 %, entries 6 and 7).

Table 1. Screening of phenanthroline-based ligands for the nickel-catalyzed arylamination.

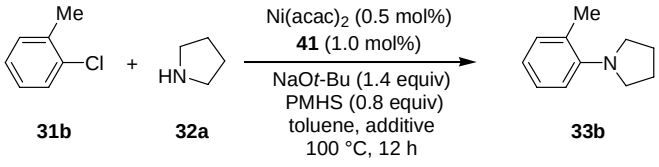
Entry	Ligand	Yield [%][a]	Entry	Ligand	Yield [%][a]
1	 **34**	20	5	 **38**	< 2
2	 **35**	16	6	 **39**	31
3	 **36**	10	7	 **40**	35
4	 **37**	23	8	 **41**	58

[a]Yields were determined by GC-analysis using tetradecane as internal standard.

These results prompted us to test 3,5,6,8-tetrabromo-1,10-phenanthroline (**41**), which can be easily prepared in one step from 1,10-phenanthroline.[42] This highly substituted phenanthroline was found to be the most efficient ligand, providing the *N*-(*o*-tolyl)-pyrrolidine (**33b**) in 58 % yield.

During previous experiments, we found dioxane to be a good solvent for this amination reaction. However, due to its toxicity, dioxane is not convenient for large scale applications. Besides, the further optimization of the solvent could be useful. Toluene would be an optimal one, although in pure toluene the amination of 2-chlorotoluene (**31b**) was too sluggish (yield < 2 %, Table 2, entry 1). For this reason, we examined various mixtures of toluene with cosolvents. Solvent mixtures of toluene with dioxane gave improved yields up to 41 % (entries 2 and 3). Better results were obtained with 1,2-dimethoxyethane (DME), which aaled to 73 % yield of **33b** (entry 6). The use of pyridine, *N,N,N',N'*-tetramethylethylendiamine (TMEDA) or triethyleneglycol dimethyl ether (triglyme) did not result in significantly higher yields (< 51 %, entries 7-10).

Table 2. Optimization of the solvent.



31b **32a** **33b**

Entry	Additive	Yield [%][a]	Entry	Additive	Yield [%][a]
1	-	< 2	6	DME (2 mol%)	73
2	dioxane 1:4 v/v	41	7	pyridine (10 mol%)	37
3	dioxane 1: 1v/v	8	8	pyridine (2 mol%)	51
4	DME (100 mol%)v	19	9	TMEDA (10 mol%)	21
5	DME (10 mol%)	56	10	triyglyme (10 mol%)	37

[a] Yields were determined by GC-analysis using tetradecane as internal standard.

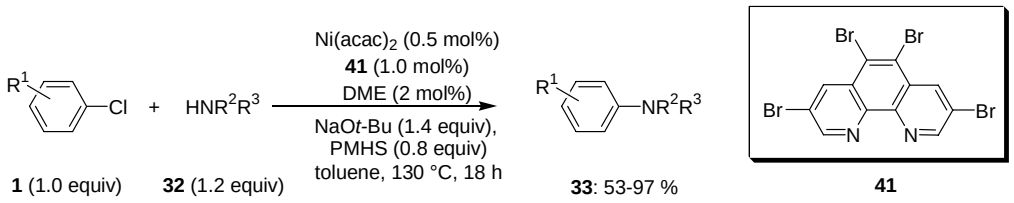
Several different siloxanes were screened as promoters in the coupling of 2-chlorotoluene (**31b**) and pyrrolidine (**32a**), using the optimized conditions. PMHS and *cyclo*-tetra-(methylhydrosiloxane) gave the best results (73 % and 74 % yield of **33b**) compared with yields below 40 % for other siloxanes. The amount of 0.8 equiv PMHS (in relation to the aryl halide) proved to be optimal. Siloxanes, not possessing a Si-H bond, did not promote the amination at all and only unreacted 2-chlorotoluene (**31b**) was recovered. This shows the

[42] S. Rau, R. Fischer, M. Jäger, B. Schäfer, S. Meyer, G. Kreisel, H. Görls, M. Rudolf, W. Henry, J. G. Vos, *Eur. J. Inorg. Chem.* **2004**, 2001.

necessity of the reduction of Ni(II) to Ni(0), using a silane R_3Si-H as reducing agent. We also assume, that siloxanes influence the catalytic activity of nickel by forming siloxane-bridged nickel clusters[43], and thus stabilizing the active catalytic species in solution. A variety of bases were also examined and the sterically hindered sodium alkoxides gave the best yields (73 % with NaO*t*Bu, and 72 % with NaO*t*Am). Other tested bases, such as NaOEt, NaOMe or NaOH, afforded yields lower than 15 %. The use of soluble Ni(II) salts, such as nickel(II) 2-ethylhexanoate, gave the same results as $Ni(acac)_2$, while the amination of 2-chlorotoluene (**31b**) with poorly soluble $NiCl_2$ or $NiBr_2$ proceeded in lower yield. Better yields and full conversion of the aryl chloride in this reaction could be achieved by increasing the reaction temperature to 130 °C (73 % at 100 °C, 83 % at 130 °C).

3.3 Amination of Aryl Chlorides

Using the optimized conditions $Ni(acac)_2$ (0.5 mol%), 3,5,6,8-tetrabromo-1,10-phenanthroline (**41**, 1 mol %), PMHS (0.8 equiv.), NaO*t*Bu (1.4 equiv.), DME (2 mol%) in PhMe, 130 ºC, 18 h), a broad range of substrates could be used in this amination reaction (Scheme 20 and Table 3).



Scheme 20. Nickel-catalyzed amination of aryl chlorides.

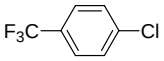
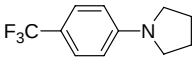
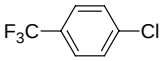
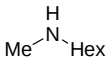
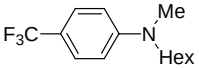
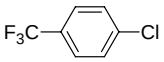
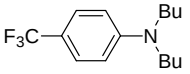
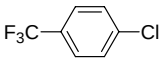
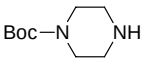
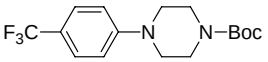
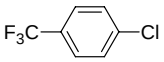
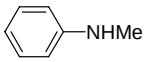
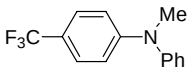
Both electron-poor (entries 1-3, 6, 12-15, and 20) and electron-rich (entry 11) aryl chlorides could be coupled with secondary cyclic or acyclic amines to provide the products in good to excellent yields. The only side product observed (typically < 5 %) was the corresponding arene, which results from the reduction of the starting aryl halide. The sterically hindered *ortho*-substituted aryl chlorides reacted with various amines without difficulty giving the desired products in 83-97 % yield (entries 6, 10 and 16). Moreover, substrates containing functional groups, such a non-enolizable ketone (entries 12 and 13), an ester (entries 14 and 15), a protected aldehyde (entries 16, 17-19) or a sulfonamide (entry 20) were converted to the aryl amines in 71-96 % yield. Acyclic amines, such as *N*-hexyl-*N*-methylamine (**32b**),

[43] S. Caddick, F. G. N. Cloke, P. B. Hitchcock, A. Lewis, *Angew. Chem. Int. Ed.* **2004**, *43*, 5824.

dibutylamine (**32c**) or *N*-methyl-benzylamine (**32i**) (entries 2, 3, 15 and 19) as well as cyclic amines, e.g. 1,2,3,4-tetrahydroquinoline (**32h**) (entry 18) were coupled efficiently. Using the standard conditions, secondary anilines coupled with aryl halides affording the desired products in 62-92 % yields (entries 4, 5 and 13).

Surprisingly, while pyrrolidine (**32a**) or piperidine (**32f**) efficiently reacted with 4-chlorotoluene (**31d**) in 83-87 % yields (entries 7 and 8), the reaction with morpholine gave toluene as a major product with only traces of the expected aryl amine. Other aryl chlorides reacted with morpholine similarly. Attempts to involve primary alkyl amines or anilines in this reaction failed, indicating a fast catalyst deactivation. This may be due to the formation of catalytically inactive nickel-species such as *bis*-(amino)- or *bis*-amido-bridged complexes, as was formerly observed for palladium-catalyzed amination reactions.[44]

Table 3. Nickel-catalyzed amination of aryl chlorides.

Entry	Aryl chloride	Amine	Product	Yield [%][a]
1				95
	31a	**32a**	**33a**	
2				96
	31a	**32b**	**33c**	
3				79
	31a	**32c**	**33d**	
4				92
	31a	**32d**	**33e**	
5				62
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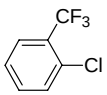
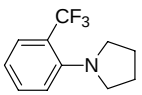
6				85
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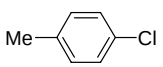
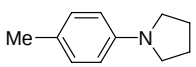
7				83
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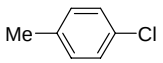
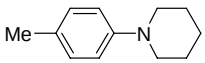
8				87
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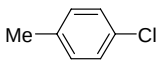
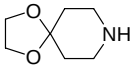
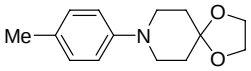
[44] R. A. Widenhoefer, S. L. Buchwald, *Organometallics* **1996**, *15*, 3534.

9				82
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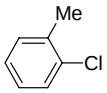
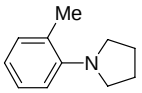
10				83
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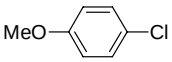
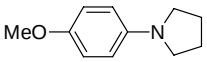
11				82
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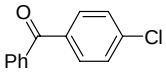
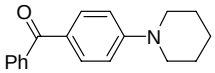
12				81
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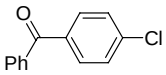
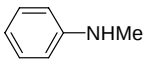
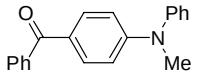
13				92 (94)[b]
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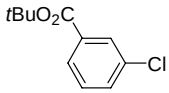
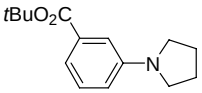
14				95
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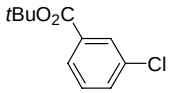
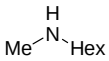
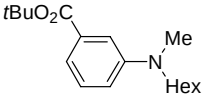
15				87
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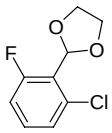
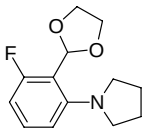
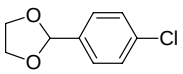
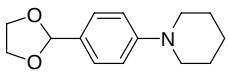
16				97
	31h	**32a**	**33p**	
17				91
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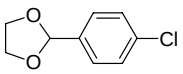
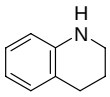
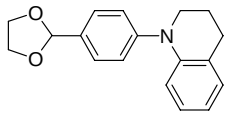
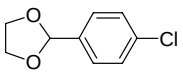
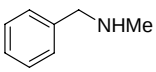
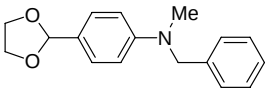
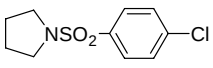
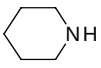
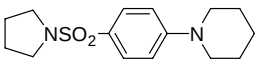
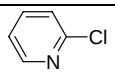
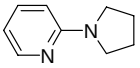
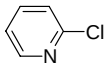
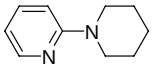
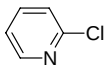
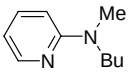
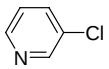
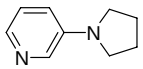
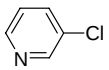
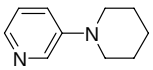
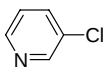
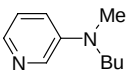
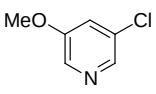
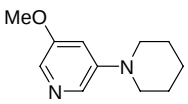
18				53[c]
	31i	**32h**	**33r**	
19				71
	31i	**32i**	**33s**	
20				96
	31j	**32f**	**33t**	

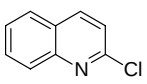
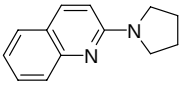
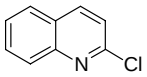
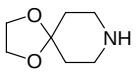
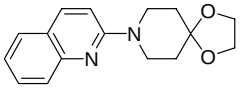
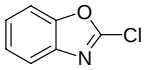
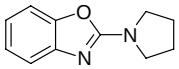
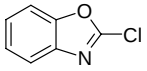
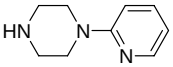
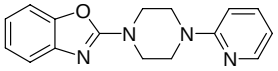
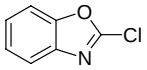
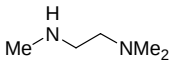
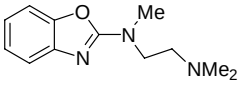
[a] Isolated yield of analytically pure product. [b] The reaction was run in a 25 mmol scale. [c] The reaction time was 42 h.

3.4 Amination of Heteroaryl Chlorides

As nitrogen-containing heterocycles possessing amino substituents often are of particular pharmaceutical interest, we have extended the scope of the nickel-phenanthroline-PMHS catalytic system to the amination of heteroaryl chlorides. As shown in Table 4, chloropyridines, quinolines and benzoxazoles afforded the amination products in 55-98 % yields, using the previously developed conditions. 2-Chloropyridine (**42a**) was reacted with cyclic or acyclic secondary amines in up to 92 % yield (entries 1, 2 and 3). Higher yields (80-98 %) were obtained in the amination of 3-chloropyridine (**42b**) (entries 4, 5 and 6). Using an electron-rich pyridine **42c**, the aryl amine **43g** was obtained in 55 % yield (entry 7). 2-Chloroquinoline (**42d**) reacted with secondary amines furnishing the products in 90-98 % yield (entries 8 and 9). The reaction of 2-chlorobenzoxazole (**42e**) proceeded comparably well with various amines such as the piperidine derivative **32k** (entry 11, 83 % yield) or the aminoalkylamine **32l** (entry 12, 84 % yield).

Table 4. Amination of heteroaryl chlorides.

Entry	Aryl chloride	Amine	Product	Yield [%][a]
1				80
	42a	**32a**	**43a**	
2				92
	42a	**32f**	**43b**	
3				64
	42a	**32j**	**43c**	
4				89
	42b	**32a**	**43d**	
5				98
	42b	**32f**	**43e**	
6				80
	42b	**32j**	**43f**	
7				55
	42c	**32f**	**43g**	

8				98
	42d	**32a**	**43h**	
9				90
	42d	**32g**	**43i**	
10				82
	42e	**32a**	**43j**	
11				83
	42e	**32k**	**43k**	
12				84
	42e	**32l**	**43l**	

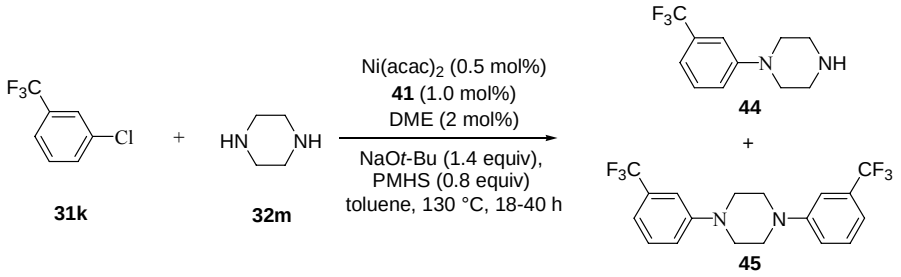
[a] Isolated yield of analytically pure product.

3.5 Arylation of Piperazine

We studied the mono- and *bis*-arylation of piperazine (**32m**), using the standard conditions with 1-chloro-3-trifluoromethylbenzene (**31k**) as a substrate (Scheme 3). A particularly interesting synthetic target is the monoarylated piperazine **44** due to its high affinity to 5-HT_1 and VMAT-receptors[45] as well as its promising antimalarial activity.[46] This reaction demonstrated a useful selectivity: by using 2 equiv of piperazine (**32m**) the mono-arylated amine **44** can be obtained almost exclusively in 86 % yield after 18 h at 130 ºC (Table 5). The *bis*-arylated product **45** could be prepared in moderate yield (53 %) and selectivity only if an excess (4 equiv) of the aryl chloride **31k** was used and the reaction time was prolonged to 40 h. Such selectivity can be useful for the selective preparation of monoarylated piperazines, avoiding protection-deprotection steps.

[45] a) M. V. Zlatovic, V. V. Sukalovic, C. Schneier, G. M. Roglic, *Biorg. Med. Chem.* **2006**, *14*, 2994; b) J. S. Partilla, A. G. Dempsey,A. S. Nagpal, B. E. Bluogh, M. H. Baumann, R. B. Rothmsnn, *J. Pharmacol. Exp. Ther.* **2006**, *319*, 237.
[46] C.-A- Molyneaux, M. Krugliak, H. Ginsburg, K. Chibale, *Biochem. Pharmacol.* **2005**, *71*, 61.

Table 5. Arylation of piperazine (**32m**).



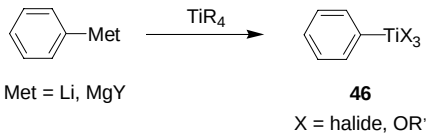
Entry	Reaction conditions	Yield of 44 [%][a]	Yield of 45 [%][a]
1	1 equiv of **31k** 2 equiv of **32m** 130 °C, 18 h	86	9
2	3 equiv of **31k** 1 equiv **32m** 130 °C, 18 h	45	26
3	4 equiv **31k** 1 equiv **32m** 130 °C, 40 h	31	53

[a] Isolated yield of analytically pure product.

4. Nickel-Catalyzed Cross-Coupling Reactions of Aryltitanium (IV) Alkoxides with Aryl Halides

4.1 Introduction

Palladium- or nickel catalyzed cross-coupling reactions between aryl organometallics and aryl or heteroaryl electrophiles are important methods for the preparation of biaryls in modern organic chemistry. Transition-metal catalyzed reactions of organomagnesium, -boron, -silicon, -zinc and -tin compounds have been extensively studied.[6,33] On the other hand, aryltitanium(IV) alkoxides of type **46** have been mainly used to perform addition reactions to carbonyl groups[47] and carbotitanation reactions.[48] Although the required organotitanium compounds can be easily prepared by transmetalation from the corresponding lithium or magnesium organometallics (Scheme 21),[49] they have received less attention for the performance of cross-coupling reactions.[50]



Scheme 21. Preparation of aryltitanium(IV) reagents.

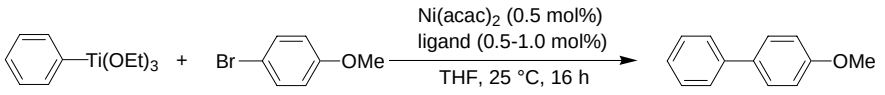
4.2 Optimization of the reaction conditions

Preliminary studies showed, that Ni(II)-salts as well as Pd-precursors can be successfully employed as catalyst in the cross-coupling of aryltitanium(IV) reagents with aryl bromides. In the light of this, we turned our attention to the use of nickel, intrinsically more active and

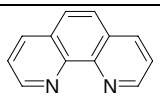
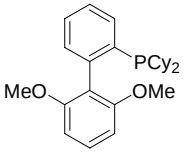
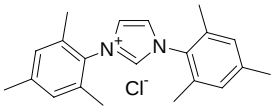
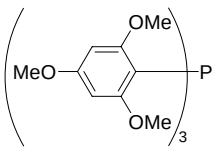
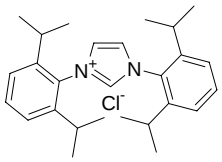
[47] a) R. Duthaler, A. Hafner, in: *Transiton Metals for Organic Synthesis* (M. Beller, C. Bolm, eds.), Wiley-VCH, Weinheim, **1998**; b) M. Reetz, *Organotitanium Reagents in Organic Synthesis*, Springer Verlag, Berlin, **1986**; c) B. Weidmann, D. Seebach, *Helv. Chim. Acta* **1980**, *63*, 2451.
[48] a) F. Sato, H. Urabe, in: *Titanium and Zirconium in Organic Synthesis* (I. Marek, ed.), Wiley-VCH, Weinheim, **2002**; b) O. Kulinkovich, A. de Meijere, *Chem. Rev.* **2000**, *100*, 2789; F. Sato, H. Urabe, S. Okamoto, *Chem. Rev.* **2000**, *100*, 2789.
[49] a) B. Weidmann, L. Widler, A. Olivero, C. Maycock, D. Seebach, *Helv. Chim. Acta* **1981**, *64*, 357; b) M. Reetz, *Top. Curr. Chem.* **1982**, *106*, 1.
[50] a) T. Tsuji, T. Ishii, *J. Organomet. Chem.* **1992**, *425*, 41; b) S. Fleming, K. Kabara, K. Nickisc, H. Neh, J. Westermann, *Tetrahedron Lett.* **1994**, *35*, 6075; c) M. Arai, B. Lipshutz, E. Nakamura, *Tetrahedron* **1992**, *48*, 5709; d) N. Bumagin, A. Ponomaryov, I. Beletskaya, *J. Organomet. Chem.* **1985**, *291*, 129; e) J. Han, N. Tokunaga, T. Hayashi, *Synlett* **2002**, 871; f) Y. Obora, H. Moriya, M. Tokunaga, Y. Tsuji, *Chem. Commun.* **2003**, 2820.

cheaper than palladium.[51] For the selection of the most effective catalysts system, the reaction between 4-bromoanisole (**47**) and phenyltitanium triethoxide (**46a**, 1.5 equiv) in the presence of $Ni(acac)_2$ (0.5 mol%) was chosen as model (Table 6). As expected, without a ligand a low yield of the biphenyl **48** (17 %) was obtained together with extensive homocoupling. A broad number of ligands were tested and *N*-heterocyclic carbene ligand precursor **51** (0.5 mol%)[52] and tris-(2,4,5-trimethoxy-phenyl)phosphine (**49**, 1.0 mol%) turned out to be the best (Table 6, entries 4 and 8). Other tested *N*-heterocyclic carbenes, phosphines, diphosphines or phenanthroline (**34**) were less effective (Table 6). Interestingly **49** afforded better results for the cross-coupling reaction with electron-rich aryl halides. However, for other aryl

Table 6. Optimization of the ligand.



46a **47** **48**

Entry	Ligand	Yield [%][a]	Entry	Ligand	Yield [%][a]
1		28	5	dppf	58
	34 (1.0 mol%)			(0.5 mol%)	
2	PPh_3	42	6		63
	(1.0 mol%)			S-Phos (1.0 mol%)	
3	$tBu_3P{\cdot}HBF_4$	66	7		54
	(1.0 mol%)			**50** (0.5 mol%)	
4		86	8		80
	49 (1.0 mol%)			**51** (0.5 mol%)	

[a] Yields were determined by GC-analysis using tetradecane as internal standard.

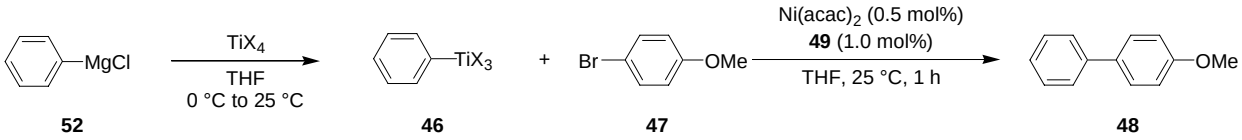
[51] Prices: $Ni(acac)_2$ 123 €/mol, $Pd(OAc)_2$ 6600 €/mol, Alfa Aesar catalogue 2008.

[52] a) A. Ardunego, R. Krafcyk, R. Schmutzler, H. Craig, J. Goerlich, W. Marshall, M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523 ; b) N. Marrion, O. Navarro, J. Mei, E. Stevens, N. Scott, S. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101.

halides, the phosphine **49** led to slow reactions and poor yields. Therefore, tris-(2,4,5-trimethoxy-phenyl)phosphine (**49**) was used for cross-coupling reactions with electron-rich halides and the carbene ligand **51** for all other substrates.

The required titanium(IV) reagents of type **46** were obtained by the transmetalation of an aryllithium or arylmagnesium halide with TiX_4. Several Ti(IV)-salts were investigated. Thus, PhMgCl (**52**) was transmetalated with TiX_4 and the resulting titanium(IV)-reagent (**46**) reacted with 4-bromanisole (**47**), in the presence of $Ni(acac)_2$ (0.5 mol%) and the phosphine (**49**, Table 7). The transmetalation with $Ti(OEt)_4$ (1.0 equiv) provided higher yields and shorter reaction times than a transmetalation with $TiCl_4$, TiF_4 or other titanium alkoxides, e.g. $Ti(OiPr)_4$ (Table 7).

Table 7. Optimization of the Ti(IV)-salt.

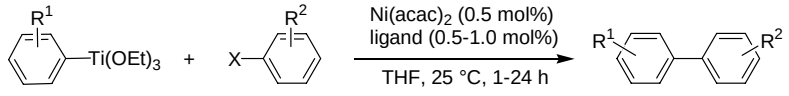


52 **46** **47** **48**

Entry	TiX_4[a]	Yield [%][b]	Entry	TiX_4	Yield [%][b]
1	$TiCl_4$	24	5	$Ti(OEt)_4$ (0.5 equiv)	74
2	TiF_4	6	6	$Ti(OEt)_4$ (1.5 equiv)	82
3	$Ti(OMe)_4$	40	7	$Ti(OiPr)_4$	38
4	$Ti(OEt)_4$	86	8	$Ti(OBu)_4$	29

[a] 1.0 Equiv of TiR_4 was used (based on PhMgCl) [b] Yields were determined by GC-analysis using tetradecane as internal standard.

The optimized reaction conditions allowed performing a broad range of cross-coupling reactions at room temperature within 1-24 h (Scheme 22 and Table 8).



46 (1.5 equiv) **31**: X = Cl **42**: HetAr-Cl **53**: X = Br **54** 54-98 %

Scheme 22. Nickel-catalyzed cross-coupling of aryltitanium(IV) reagents.

Thus, phenyltitanium triethoxide (**46a**, 1.5 equiv.) obtained from PhMgCl by transmetalation with $Ti(OEt)_4$, reacted with ethyl 4-bromobenzoate (**53a**) in the presence of $Ni(acac)_2$ (0.5 mol %) and ligand **51** (0.5 mol %) at 25 °C, and led to the cross-coupling

product **54a** (3 h, 95 % yield, Table 8, entry 1). By using ethyl 4-chlorobenzoate (**31m**) the same cross-coupling reaction required 24 h and gave **54a** in 73 % yield (entry 2). Cross-coupling of the indole derivative **53b** with $PhTi(OEt)_3$ (**46a**) provided the product **54b** in 78 % yield (entry 3). For most cases, aryl chlorides were suitable electrophiles. Cross-coupling of the protected aldehyde **31i** with *p*-tolyltitanium triethoxide (**46b**) afforded the biphenyl **54d** in 73 % yield (25 °C, 17 h, entry 5). Similarly, the reaction of **46b** with the sulfonamide **31j** furnished the desired cross-coupling product **54e** in 75 % yield (25 °C, 17 h, entry 6). By using the phosphine ligand **49**, *p*-tolyltitanium triethoxide (**46b**) reacted with the sterically hindered 2-chloro-1,4-dimethoxy-benzene (**31n**) only at 65 °C (3 h), giving the coupling product **54f** in 60 % yield (entry 7). Heterocyclic chlorides like 2-chloropyridine (**42a**) reacted with 1-naphthyltitanium triethoxide (**46c**) within 6 h at 25 °C, leading to the substituted pyridine **54h** in 98 % yield (entry 9). By using 3-chloropyridine (**42b**) the cross-coupling reaction with **46c** required 14 h and gave the expected product **54i** in 61 % yield (entry 10). Electron poor aryltitanium reagents reacted only well with aryl bromides. Thus, the cross-coupling of ethyl 4-bromo-benzoate (**53a**) with the titanium reagent **46d**, bearing a trifluoromethyl group, provided the biphenyl **54j** in 70 % yield (25 °C, 16 h, entry 11). The reaction of **46d** with the less reactive aryl chloride (**31m**) afforded product **54j** in only 49 % yield after 28 h reaction time (entry 12). Reaction of 2-chloroquinoline (**42d**) with the aryltitanium triethoxide **46e** afforded dubamine (**54l**), a haplophyllum alkaloid,[53] in 90 % yield (25 °C, 18 h, entry 14). The coupling of titanated heterocycles required elevated temperatures. Thus, 2-chloroquinoline (**42d**) reacted with 2-titanated *N*-methylpyrrole (**46f**), obtained from the corresponding lithium compound,[54] within 24 h at 65 °C, leading to the quinoline **54m** in 98 % yield (entry 15). In the case of titanated benzofurane **46g**, prepared by transmetalation from the lithium reagent,[55] the cross-coupling with 2-chloroquinoline (**42d**) afforded the heterocycle **54n** in 73 % yield after 24 h at 65 °C (entry 16). Aryl bromides may bear a keto function, but require lower temperatures. Thus, 4-bromo-valerophenone (**53c**) reacted with phenyltitanium triethoxide (**46a**) within 6 h at -10 °C leading selectively to the desired cross-coupling product **54c** (60 % yield, entry 4). Similarly, the reaction of **46e** with 4-bromo-valerophenone (**53c**) afforded the biphenyl **54k** within 6 h at –10 °C in 57% yield (entry 13). The cross-coupling reaction of 4-bromoacetophenone (**53d**) with **46b** required lower temperatures of –20 °C in order to avoid an addition on the keto function and furnished the expected product **54g** in 54 % yield (entry 8).

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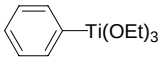
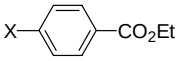
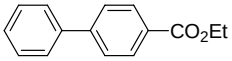
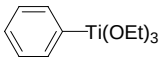
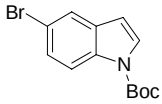
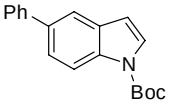
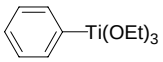
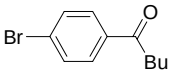
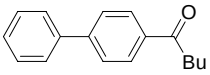
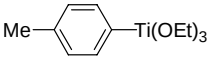
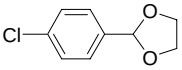
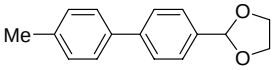
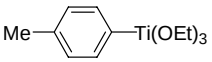
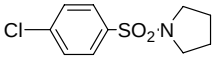
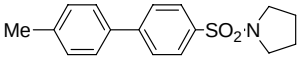
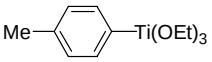
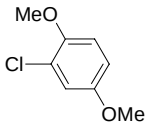
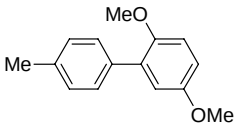
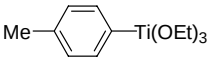
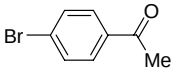
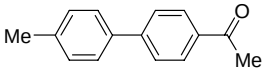
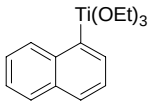
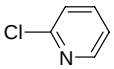
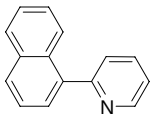
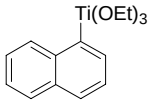
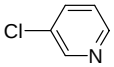
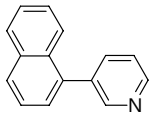
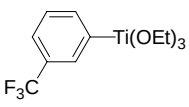
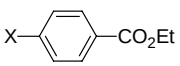
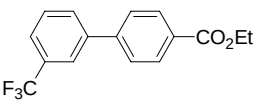
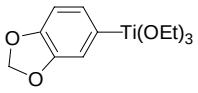
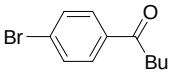
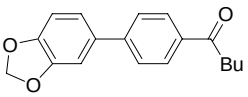
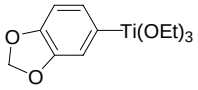
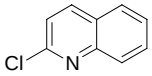
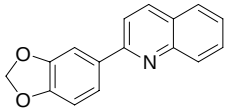
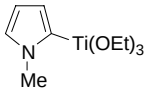
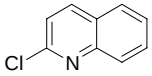
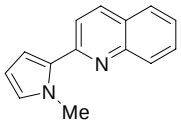
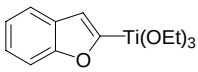
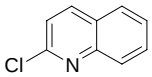
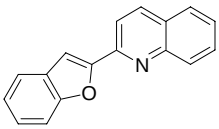
[53] S. Yunusov, G. Sidakin, *Zh. Obsch. Khim.* **1955**, 2009.
[54] J. Brittain, R. Jones, J. Arques, T. Saliente, *Synth. Commun.* **1982**, *12*, 231.
[55] T. Nguyen, E. Negishi, *Tetrahedron Lett.* **1991**, *32*, 5903.

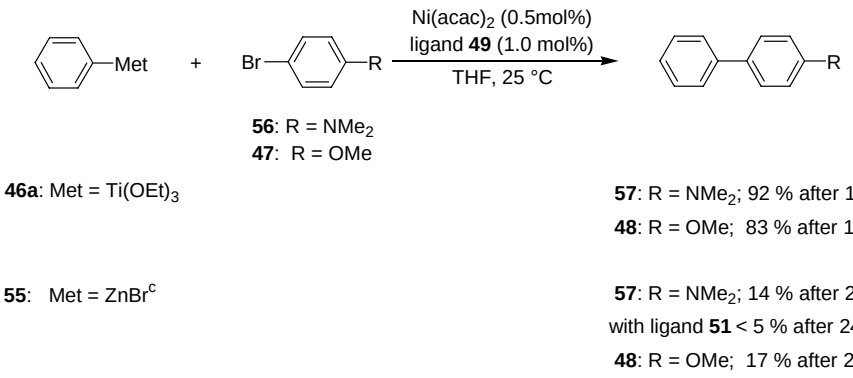
Table 8. Cross-coupling reactions of aryltitanium reagents with functionalized aryl halides.

Entry	Aryltitanium reagent	Aryl halide	Product	Ligand	time [h], temperature [°C]	Yield [%][a]
						
1	**46a**	**53a**: X = Br	**54a**	**51**	3, 25	95
2	**46a**	**31m**: X = Cl	**54a**	**51**	24, 25	73
3	 **46a**	 **53b**	 **54b**	**51**	18, 25	78
4	 **46a**	 **53c**	 **54c**	**51**	6, -10	60
5	 **46b**	 **31i**	 **54d**	**51**	17, 25	73
6	 **46b**	 **31j**	 **54e**	**51**	17, 25	75
7	 **46b**	 **31n**	 **54f**	**49**	3, 65	60
8	 **46b**	 **53d**	 **54g**	**51**	6, -20	54
9	 **46c**	 **42a**	 **54h**	**51**	6, 25	98
10	 **46c**	 **42b**	 **54i**	**51**	14, 25	61
						
11	**46d**	**53a**: X = Br	**54j**	**51**	16, 25	70
12	**46d**	**31m**: X = Cl	**54j**	**51**	28, 25	49

13				**51**	6, -10	57
	46e	**53c**	**54k**			
14				**51**	18, 25	90
	46e	**42d**	**54l**			
15				**51**	24, 65	98
	46f	**42d**	**54m**			
16				**51**	24, 65	73
	46g	**42d**	**54n**			

[a] Isolated yield of analytically pure product.

Finally we have compared the reactivity of organotitanium compounds with the corresponding arylzinc halides, which are widely used in Negishi cross-couplings. The reaction of $PhTi(OEt)_3$ (**46a**) with *N*,*N*-dimethyl-4-bromoaniline (**56**) affords biphenyl **57** in 92 % yield after 16 h at 25 °C (Scheme 23). The same reaction with the arylzinc halide **55** gives only 17 % of **57** at 25 °C after 24 h in the presence of a polar cosolvent like NMP.[56] The same behaviour is observed with 4-bromoanisole (**47**) as electrophile.



Scheme 23. Comparison of aryltitanium and –zinc reagents. [a] Isolated yield of analytically pure product. [b] Yield determined by GC-analysis using tetradecane as internal standard. [c] Solvent THF/NMP 8:1.

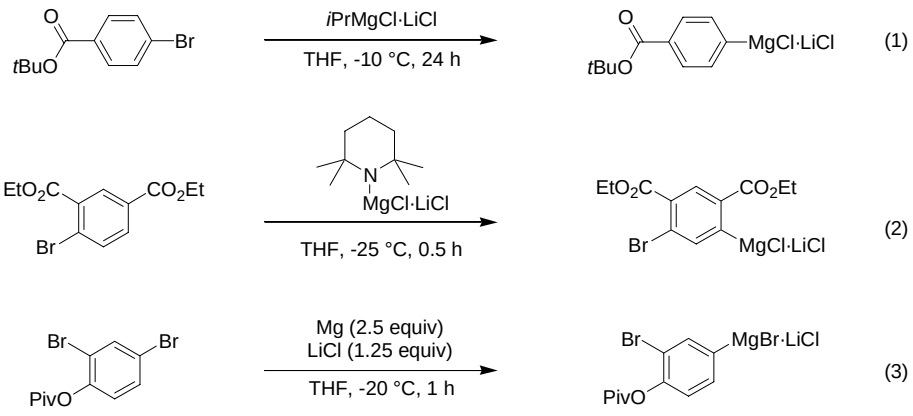
[56] No use of NMP led to heterogenous reaction mixtures and lower yields.

5. Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents

5.1 Introduction

The discovery of the nickel-catalyzed cross-coupling of organomagnesium reagents with C(sp^2)-halides by *Kumada*[31] and *Corriu*[32] (Scheme 6) and the corresponding palladium-catalyzed reaction by *Murahashi*,[57] established the use of transition-metal catalysts for the cross-coupling of Grignard reagents. However, issues with functional group tolerance, led to the development of alternate methods based on less reactive organometallic compounds (boron, tin, zinc, silicon). Still, the Kumada cross-coupling allows a direct transition-metal catalyzed carbon-carbon bond formation (without further transmetalation) and is therefore a highly atom-economical process.[58]

In recent years, *Knochel* and co-workers have pioneered the development of methods for the preparation of functionalized Grignard reagents. A wide range of polyfunctional organomagnesium compounds has become available through a halogen-magnesium-exchange (Scheme 24, equation 1),[59] a directed metalation using magnesium amides (equation 2)[60] or

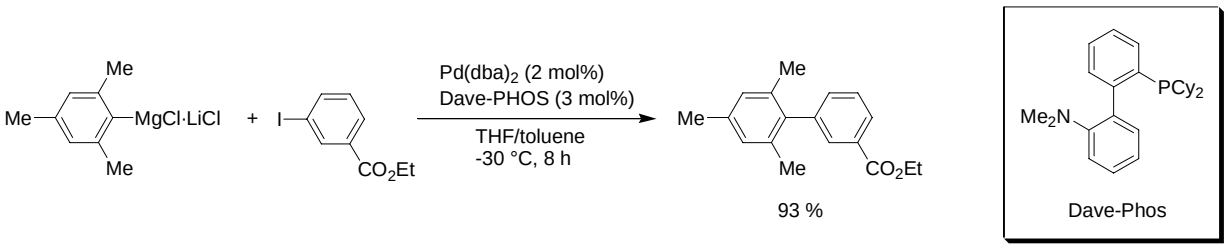


Scheme 24. Preparation of functionalized organomagnesium reagents.

[57] M. Yamamura, I. Moritani, S.-I. Murahashi, *J. Organomet. Chem.* **1975**, *91*, C39.
[58] B. M. Trost, *Science*, **1991**, *254*, 1471.
[59] For recent reviews, see: a) I. Hiriyakkanavar, O. Baron, A. J. Wagner, P. Knochel, *Chem. Commun.* **2006**, 583; b) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
[60] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed*. **2006**, *45*, 2958; b) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; c) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; d) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503.

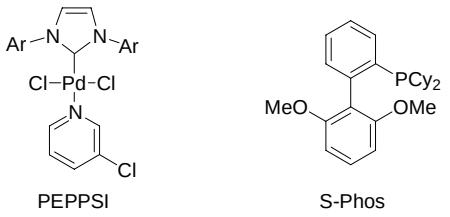
the direct magnesium insertion into aryl halides in the presence of LiCl (equation 3).[61] These studies showed, that arylmagnesium compounds are compatible with important functional groups, such as cyano or ester functions as well as sensitive heterocycles.

In most instances, however, these Grignard reagents cannot be used directly in cross-coupling reactions due to their instability at the temperatures required for these reactions. Recently, *Buchwald* has shown, that by using an appropriate phosphine ligand (Dave-Phos)[62] and low temperatures (-20 °C to –65 °C), functionalized *aryl and heteroaryl iodides* undergo a smooth cross-coupling with functionalized arylmagnesium halides (Scheme 25).[63, 64]



Scheme 25. *Buchwald's* Kumada cross-coupling reaction at low temperature.

Based on the development of new, very active catalyst systems and ligands, such as PEPPSI[65] or S-Phos (Scheme 26),[66] we envisioned that this methodology could be extended to readily available aryl bromides.



Scheme 26. PEPPSI and S-Phos. (Ar = 2,6-diisopropylphenyl).

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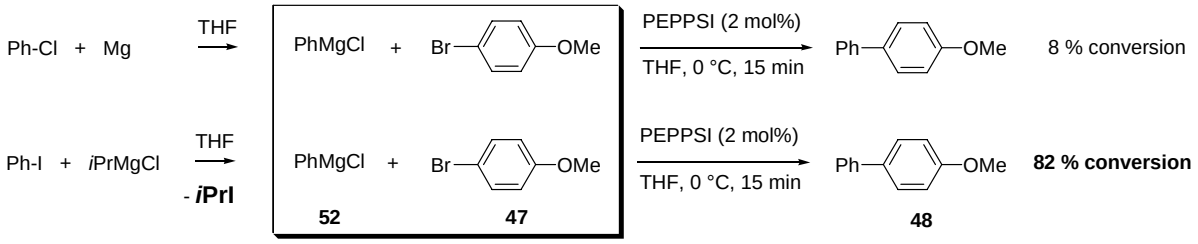
[61] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[62] D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722.
[63] R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3844.
[64] For some examples of Kumada couplings at low temperature see: a) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150; b) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429; c) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron Lett.* **2001**, *45*, 5717.
[65] a) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; c) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *J. Org. Chem.* **2005**, *70*, 8503.
[66] a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871; b) T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 5096; c) M. R. Biscoe, T. E. Barder, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 7232.

5.2 Preliminary Studies and Optimization of the Reaction Conditions

In preliminary experiments, we have observed that the reaction of PhMgCl (**52**) prepared by the direct insertion of magnesium turnings in the presence of lithium chloride[61] reacted slowly with 4-bromoanisole (**47**) in the presence of $Pd(OAc)_2$ and S-Phos or PEPPSI leading to 4-methoxybiphenyl (**48**). Only 8 % of conversion was observed at 0 °C after 15 min. In strong contrast, the reaction of PhMgCl (**52**) prepared by a I/Mg-exchange using *i*PrMgCl·LiCl[59] led to **48** with 82 % conversion after 15 min (Scheme 27).

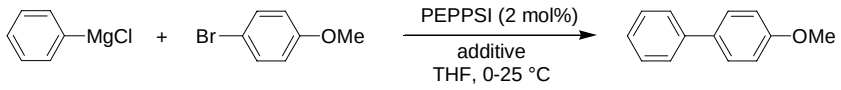


Scheme 27. Rate accelerating effect of *i*PrI in the Kumada-coupling reaction.

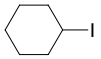
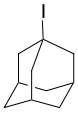
This difference was attributed to the presence of 1.1 equivalents of *i*PrI obtained as side product in the I/Mg-exchange. We have found that a range of alkyl iodides such as MeI, 1-iodoadamantane, neopentyl iodide or cyclohexyl iodide give similar rate enhancement (Table 9, entries 2-8, 11). The addition of the alkyl iodide after the preparation of the Grignard reagent had the same effect as the *i*PrI, produced as side-product during the I/Mg-exchange reaction (entries 2 and 3). Interestingly, with *i*PrBr no rate acceleration is observed (9 % conversion after 15 min at 0 °C, entry 5). Alkenes, such as cyclohexene, either completely inhibited the reaction, if present in stoichometric amounts (entry 9), or showed no effect (2.5 mol %, entry 10). Substoichometric amounts of *i*PrI resulted in the decomposition of the catalysts prior to full consumption of the starting aryl bromide. However, isopropyl iodide (1.1-1.2 equiv) was used for further experiments, since *i*PrI was produced in the I/Mg-exchange and since the above mentioned iodides displayed comparable catalytic activity.

For the selection of the catalyst no general rule could be observed. Depending on the substrates (Grignard reagent and aryl bromide), similar yields as well as quite different yields were obtained. Therefore, each reaction was investigated with both catalyst systems.

Table 9. Influence of the additive in the Kumada-coupling reaction.[a]



52 **47** **48**

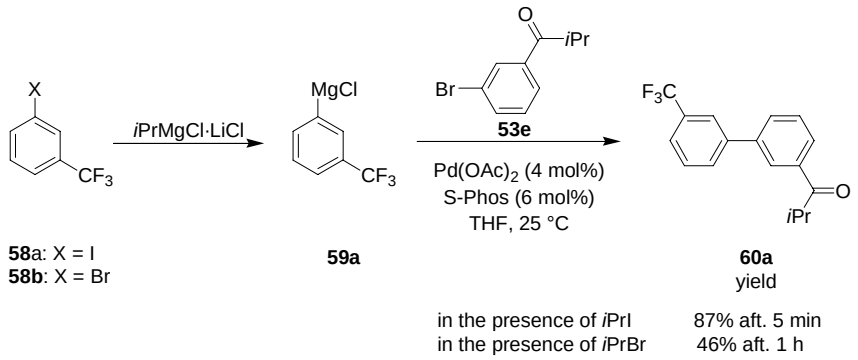
Entry	Additive (1.1 equiv)	Conv. after 15 min at 0 °C [%][b]	Yield after 18 h at 25 °C [%][b]
1	none	8	95
2	*i*PrI	80	97
3	*i*PrI[c]	82	96
4	*i*PrI (20 mol%)	71	78 (85% conv.)[d]
5	*i*PrBr	9	94
6		74	96
7	MeI	71	82
8		80	96
9		0	< 5[e]
10	 (2.5 mol%)	7	96
11		76	95

[a] PhMgCl (**52**) was prepared by direct magnesium insertion in the presence of LiCl. [b] determined by GC-analysis using tetradecane as internal standard. [c] PhMgCl (**52**) was prepared by an I/Mg- exchange. [d] The reaction conversion stopped after 30 min. [e] No product was observed by GC/MS.

5.2 Kumada-Cross-Coupling Reactions in the Presence of *i*PrI

This rate acceleration (*average reaction time: 5 min*) could be successfully applied to the cross-coupling of various functionalized aryl- or heteroaryl-magnesium reagents with *aryl bromides* at 25 °C. Thus, the cross-coupling of the arylmagnesium halide **59a** prepared from 3-iodobenzotrifluoride (**58a**) by a I/Mg-exchange with the bromoaryl ketone **53e** furnished *within 5 min at 25 °C* the functionalized biphenyl **60a** as a single product in 87 % isolated yield (Scheme 28). Interestingly, if the Grignard reagent **59a** was prepared from the

corresponding aryl bromide **58b** by a Br/Mg-exchange, no acceleration was observed and the biphenyl **60a** was isolated in only 46 % yield after 1 h.[67]



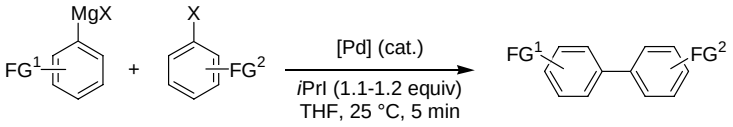
Scheme 28. Enhanced functional group tolerance of the Kumada-coupling reaction in the presence of *i*PrI.

As shown in Scheme 28, the presence of *i*PrI considerably enhances the functional group compatibility of this Kumada cross-coupling. Using this procedure, a range of functionalized arylmagnesium species were efficiently coupled with various functionalized aryl and heteroaryl bromides. Thus, the reaction of 3-trifluoromethylphenylmagnesium chloride (**59a**, 1.1 equiv) with 2-bromobenzonitrile (**53f**, 1.0 equiv) in the presence of PEPPSI (2 mol%) provided the coupling product **60b** within 5 min at 25 °C in 92 % isolated yield (Table 10, entry 1). Interestingly, this behaviour can be extended to functionalized arylmagnesium reagents having a low stability at room temperature. Thus, the ester substituted organomagnesium compound (**59b**, 1.1 equiv),[68] prepared by an I/Mg-exchange at -20 °C, reacted with the functionalized bromobenzenes **53g** and **53h** (1.0 equiv) in the presence of $Pd(OAc)_2$ (2 mol%) and S-Phos (3 mol%) or PEPPSI (2 mol%), affording after 5 min at 25 °C the biphenyls **60c** and **60d** in 82-84 % yield (entries 2 and 3). Similarly, electron-rich 4-bromoanisole (**47**) and the bromoaryl ketone **53e** could be coupled with the magnesium reagent **59b** within 5 min at 25 °C (1.1 and 1.2 equiv), furnishing the desired products **60e** and **60f** in 75-78 % yield (entries 4 and 5). The reaction of 1-bromo-3-chlorobenzene (**53i**) with the functionalized Grignard reagent **59c** proceeded chemoselectively, affording the chloro-biphenyl **60g** in 79 % yield (entry 6). Furthermore, heteroaryl bromides **53j** and **53b** reacted with the ester-substituted organomagnesium compound **59c** within 5 min at 25 °C, leading to the functionalized pyridine **60h** and indole **60i** in 74-83 % yield (entries 7 and 8). By performing the cross-coupling between the ester-substituted arylmagnesium reagent **59c** and

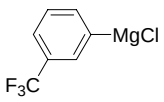
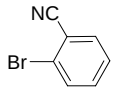
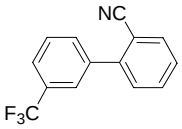
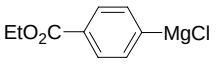
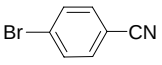
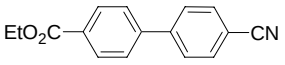
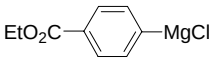
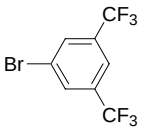
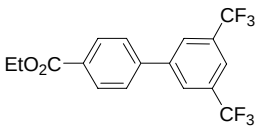
[67] After 1 h of reaction time the organomagnesium compound was completly consumed due to addition on the keto function and enolization.
[68] The arylmagnesium reagent **59b** is only stable below –20 °C and decomposes at 25 °C within 10 min.

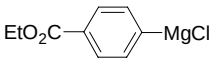
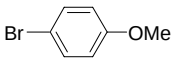
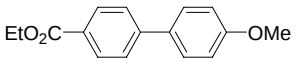
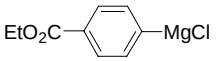
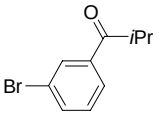
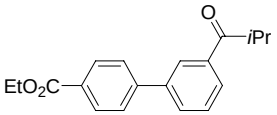
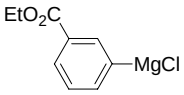
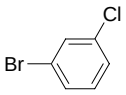
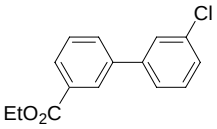
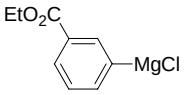
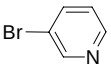
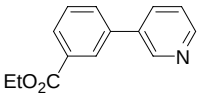
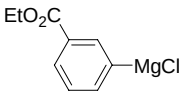
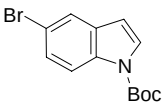
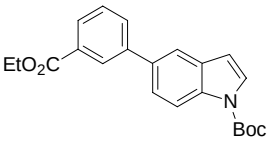
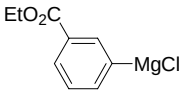
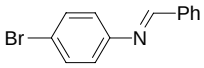
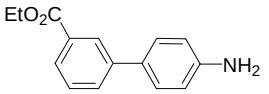
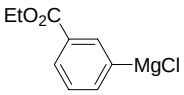
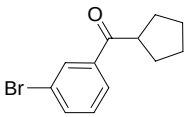
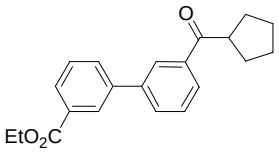
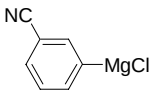
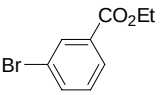
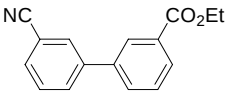
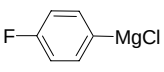
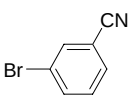
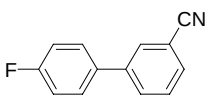
the imine **53k**, the aniline **60j** was obtained in 86 % yield after acidic hydrolysis (entry 9). Sensitive functions like an arylketone are perfectly tolerated in this reaction. The reaction of the Grignard reagent **59c** (1.2 equiv) with the bromoaryl ketone **53l** (1.0 equiv) yielded the polyfunctional biphenyl **60k** in 82 % (5 min, 25 °C, entry 10). Several other functionalized Grignard reagents were suitable for the cross-coupling procedure. Thus, 3-cyanophenylmagnesium chloride (**59d**) coupled with ethyl 3-bromobenzoate (**53m**) in 5 min at 25 °C, leading to the coupling product **60l** in 77 % yield (entry 11). Similarly, the reaction of 4-fluorophenylmagnesium chloride (**59e**) and the electron-rich 4-methoxyphenylmagnesium chloride (**59f**) with the bromobenzonitriles **53n** and **53o** afforded the biphenyls **60m** and **60n** in 84 % and 98 % yield (5 min, 25 °C, entries 12 and 13). Also, the sterically hindered mesitylmagnesium reagent **59g** reacted with the ester-substituted aryl bromide **53a**, leading to the biphenyl **60o** in 92 % yield after 5 min at 25 °C (entry 14).

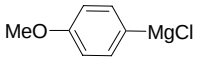
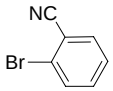
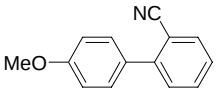
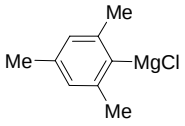
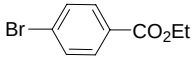
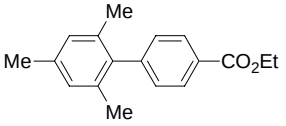
Table 10. Products of type **60** obtained by the cross-coupling between functionalized arylmagnesium reagents **59** and aryl bromides **53** in the presence of *i*PrI.



59 **53** **60:** 74-98 %

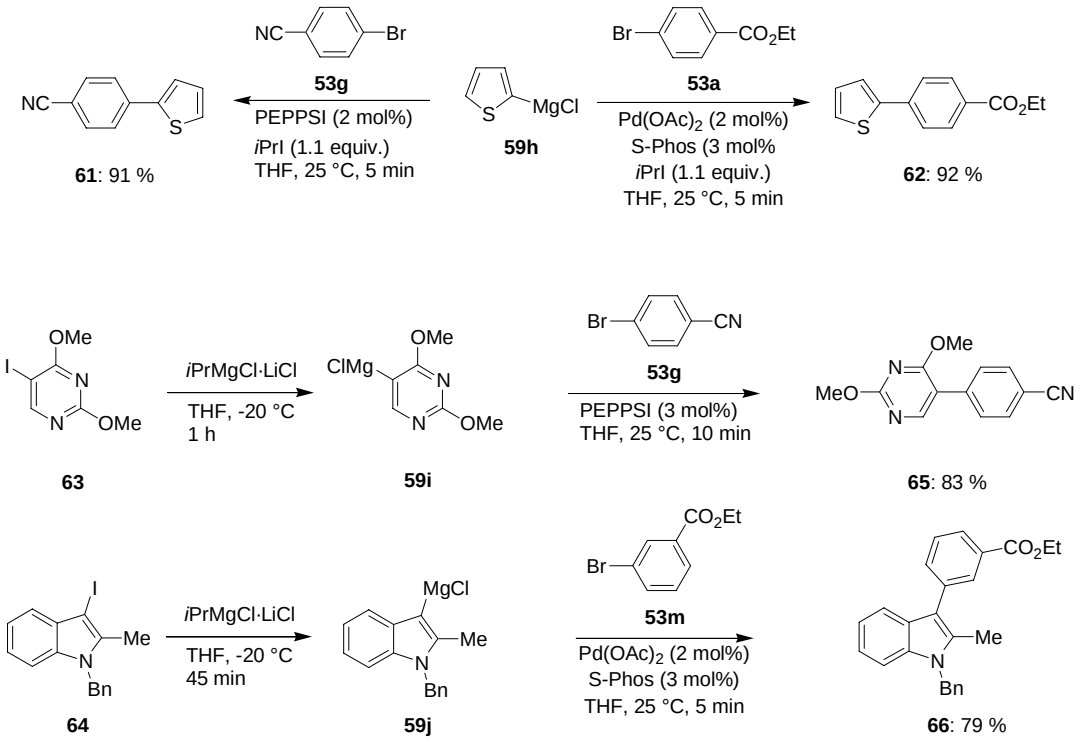
Entry	Magnesium Reagent	Aryl Bromide	Product	Yield [%][a]
1				92[b]
	59a	**53f**	**60b**	
2				84[c]
	59b	**53g**	**60c**	
3				82[b]
	59b	**53h**	**60d**	

4				78[c]
	59b	**47**	**60e**	
5				75[d]
	59b	**53e**	**60f**	
6				79[b]
	59c	**53i**	**60g**	
7				83[e]
	59c	**53j**	**60h**	
8				74[c]
	59c	**53b**	**60i**	
9				86[c,f]
	59c	**53k**	**60j**	
9				82[d]
	59c	**53l**	**60k**	
11				77[e]
	59d	**53m**	**60l**	
12				84[b]
	59e	**53n**	**60m**	

13				98[b]
	59f	**53f**	**60n**	
14				92[b]
	59g	**53a**	**60o**	

[a] Isolated yield of analytically pure product.[b] 2% PEPPSI was used as catalyst. [c] 2% $Pd(OAc)_2$ and 3% S-PHOS were used as catalyst.[d] 4% $Pd(OAc)_2$ and 6% S-Phos were used as catalyst.[e] 3% PEPPSI was used as catalyst.
[f] After hydrolysis with 2 M HCl.

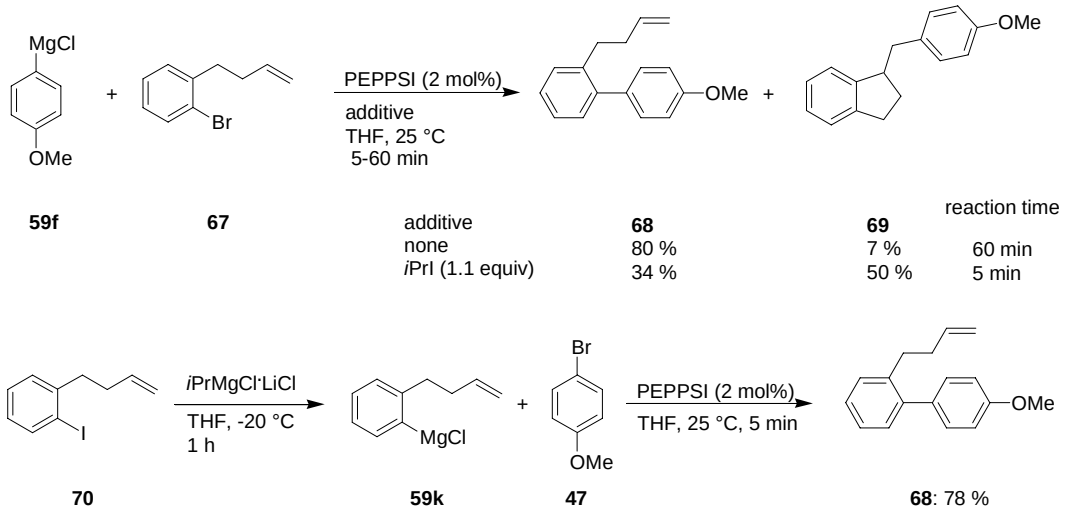
Encouraged by these results, we have successfully used several heteroarylmagnesium compounds in the *i*PrI accelerated Kumada coupling. Thus, 1-thienylmagnesium chloride (**59h**, 1.1 equiv.) reacted smoothly with the aryl bromides **53a** and **53g** (1.0 equiv.) and the functionalized thiophenes **61** and **62** were obtained in 91-92 % yield (5 min, 25 °C, Scheme 28). By using the heteroarylmagnesium reagents **59i** and **59j**, prepared from pyrimidine **63** and indole **64** by I/Mg-exchange reaction, the arylated heterocycles **65** and **66** were obtained in 83 % and 79 % yield after the reaction with aryl bromides **53g** and **53m** (Scheme 29).



Scheme 29. Kumada coupling reactions of heteroarylmagnesium reagents in the presence of *i*PrI.

5.3 Mechanistic Considerations

Since various alkyl halides such as MeI or neopentyl iodide lead to a similar rate accelerations and furthermore no rate acceleration was observed with aryl triflates, we suspected a radical mechanism for the cross-coupling catalysis based on the pioneering contributions of *Hegedus*, *Kochi* and *Osborn*.[69,70] We have therefore subjected the bromobenzene derivative **67** bearing a remote double bond to the cross-coupling conditions and obtained a mixture of the cyclized product **69** (50 % isolated yield) as well as the non-cyclized product **68** (34 %), supporting a radical intermediate. We verified that an organopalladium(II) intermediate of the type Ar^1PdAr^2 is not likely to be responsible for the cyclization process since the use of a Grignard reagent **59k** bearing a remote double bond did not lead to the cyclization product, but provided after cross-coupling with **47** only the biphenyl **68** in 78 % yield (Scheme 30). Also, the ratio of the obtained products did not change by adding a extra iodine source (TBAI or LiI) or performing the reaction with the organomagnesium reagent **59f**, prepared by magnesium insertion into the corresponding aryl iodide.



Scheme 30. Cross-coupling of substrates **59k** and **67** bearing a remote double bond.

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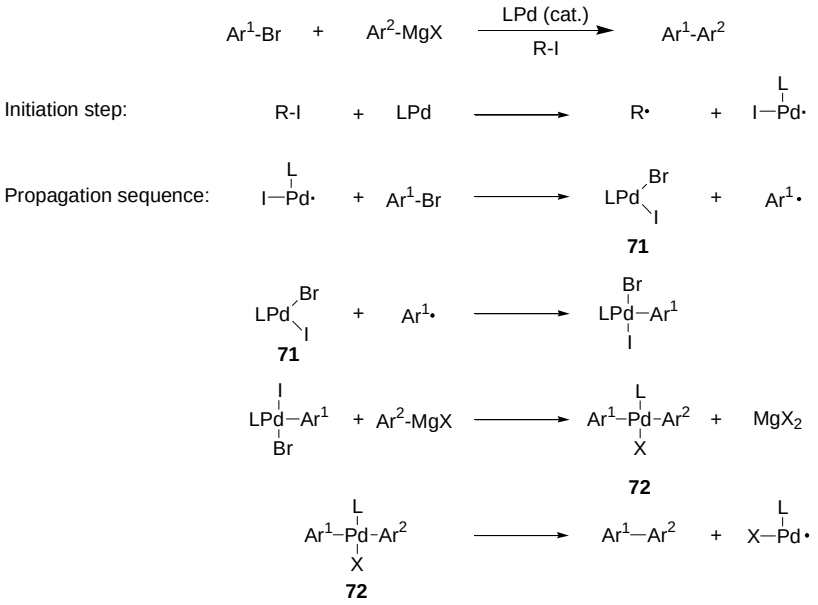
[69] a) E. J. Corey, M. F. Semmelhack, L. S. Hegedus, *J. Am. Chem. Soc.* **1968**, *90*, 2416; b) E. J. Corey, M. F. Semmelhack, L. S. Hegedus, *J. Am. Chem. Soc.* **1968**, *90*, 2417; c) L. S. Hegedus, E. L. Waterman, *J. Am. Chem. Soc.* **1974**, *96*, 6789; c) L. S. Hegedus, L. L. Miller, *J. Am. Chem. Soc.* **1975**, *97*, 459; d) L. S. Hegedus, D. H. P. Thompson, *J. Am. Chem. Soc.* **1985**, *107*, 5663; e) I. H. Elson, D. G. Morrell, J. K. Kochi, *J. Organomet. Chem.* **1975**, *84*, C7; f) T. T. Tsou, J. K. Kochi, *J. Am. Chem. Soc.* **1979**, *101*, 6319; g) T. T. Tsou, J. K. Kochi, *J. Am. Chem. Soc* **1979**, *101*, 7547; h) J. A. Labinger, A. V. Kramer, J. A. Osborn, *J. Am. Chem. Soc.* **1973**, *95*, 7908; i) A. V. Kramer, J. A. Labinger, J. S. Bradley, J. A. Osborn, *J. Am. Chem. Soc.* **1974**, *96*, 7145; j) A. V. Kramer, J. A. Osborn, *J. Am. Chem. Soc.* **1974**, *96*, 7832.

[70] For an overview of reactions of metal complexes with organic halides, see: a) J. K. Kochi, *Organometallic Mechanisms and Catalysis*, Academic Press, New York, **1978.** b) D. Astruc, *Electron Transfer and Radical Processes in Transition–Metal Chemistry*, Wiley-VCH, New York, **1995**.

These results led us to propose the tentative mechanism described in Scheme 31. The palladium(0)-catalyst (LPd(0)) reacts in an initiation step with the alkyl iodide (RI) affording a radical R• and a palladium(I) intermediate (LPdI, **71**). Previous reports from *Curran*, *Suzuki* and our laboratory have demonstrated, that alkyl iodides react via a radical path with Pd(0)-complexes (or Ni(0)-complexes).[71] Similarly, the reaction of the palladium(I) intermediate **71** with the aryl bromide (Ar^1-Br) furnishes an aryl radical (Ar^1•), which may undergo a ring closure in the presence of a remote double bond (see Scheme 30). The trapping of this aryl radical with $LPdX_2$ results in the formation of a Pd(III) intermediate ($Ar^1PdL(I)(Br)$), which after ligand exchange with Ar^2MgBr provides a diarylpalladium(III) halide **72**. Reductive elimination of **72** furnishes the cross-coupling product (Ar^1-Ar^2) and regenerates the Pd(I) radical chain carrier.



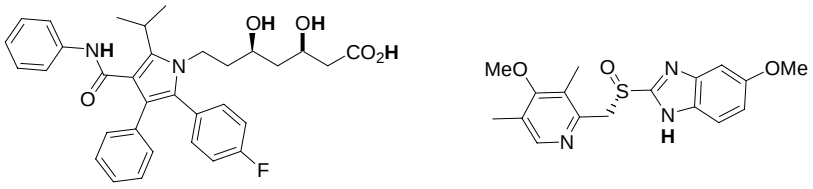
Scheme 31. Tentative mechanism of the palladium-catalyzed cross-coupling between an aryl bromide and an arylmagnesium reagent via a radical path.

[71] a) D. P. Curran, C.-T. Chang, *Tetrahedron Lett.* **1990**, *31*, 933; b) T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki, *Chem. Lett.* **1992**, 691; c) H. Stadtmüller, A. Vaupel, C. E. Tucker, T. Stüdemann, P. Knochel, *Chem. Eur. J.* **1996**, *2*, 1204; d) H. Stadtmüller, C. E. Tucker, A. Vaupel, P. Knochel, *Tetrahedron Lett.* **1993**, *49*, 7911; e) H. Stadtmüller, R. Lenz, C. E. Tucker, T. Stüdemann, W. Dörner, P. Knochel, *J. Am. Chem. Soc.* **1993**, *115*, 7027.

6. Negishi Cross-Coupling Reactions in the Presence of Acidic Protons

6.1 Introduction

Functional groups bearing acidic protons are contained in numerous bioactive compounds. They play a fundamental role in biochemistry, as they can interact with enzymes and receptor systems through H-bonding or lone pair donation. These functionalities are found in several important pharmaceuticals, for instance in atorvastatin (Lipitor™) or esomeprazole (Nexium™, Figure 4), two of the largest selling drugs in the world. Furthermore, the same abilities make them valuable parts of building blocks used in material science.



atorvastatin esomeprazole

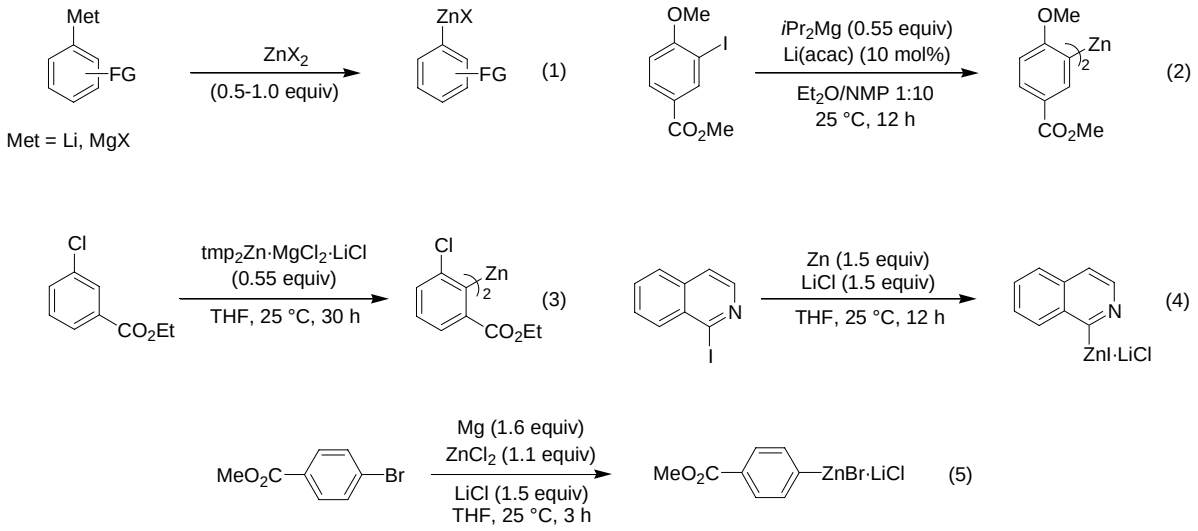
Figure 4. Drugs, bearing acidic protons.

As already mentioned, palladium- or nickel-catalyzed carbon-carbon bond forming reactions between organometallic reagents and unsaturated halides are important methods in modern synthetic organic chemistry. Among the possible nucleophilc substrates, only organoboronic acids and derivatives[72] as well as organotin compounds[73] have so far been reported to undergo general couplings with organic halides bearing acidic protons. Despite the advantages associated with these reagents, such as commercial availability, air stability and especially their high functional group tolerance, several difficulties remain. Organotin reagents are known for their toxicity and therefore not suitable for large scale processes (pilot and plant production).[7a] Problems with boronic acids and esters include their tendency to form

[72] a) N. Miyauara in: *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed. (A. de Meijere, F. Diederich, eds.), Wiley-VCH, Weinheim, **2004**, 41; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
[73] a) T. N. Mitchell in: *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed. (A. de Meijere, F. Diederich, eds.), Wiley-VCH, Weinheim, **2004**, 125; b) J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508.

boroxines and competitive protodeboronation during the cross-coupling reaction,[74] as well as the toxicity of the arising boron derived waste (for large scale applications).[75]

Also, due to the covalent nature of the C-B bond of boronic acids, these cross-couplings proceed as a rule under harsher conditions compared to the corresponding Negishi cross-couplings using organozinc compounds.[76] The required zinc reagents can be prepared by transmetalation from the corresponding lithium or magnesium organometallics (Scheme 32, equation 1),[77] by an I/Zn-exchange reaction (equation 2),[78] by a directed metalation using zinc amides (equation 3),[79] or by direct zinc insertion (equation 4).[80] Recently, *Knochel* and co-workers developed the magnesium insertion in presence of $ZnCl_2$ (equation 5).[61]



Scheme 32. Preparation of functionalized organozinc reagents.

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[74] For selected examples highlighting the problems with the use of oganoboron reagents, see: a) S. T. Handy, Y. Zhang, H. Bregman, *J. Org. Chem.* **2004**, *69*, 2362; b) H. Chaumeil, S. Signorella, C. LeDrian, *Tetrahedron* **2000**, *56*, 9655; c) T. Wanatabe, N. Miyaura, A. Suzuki, *Synlet*, **1992**, 207.

[75] Boric acid and boronate derivatives are considered as reprotoxic category 2 materials according to the classification proposal in 30 ATP (Adaption to Technical Progress) to Dangerous Substances Directive (67/548/EEC).

[76] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; c) E. Negishi, in: *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed. (A. de Meijere, F. Diederich, eds.), Wiley-VCH, Weinheim, **2004**, 815.

[77] For an general overview, see: a) P. Knochel, in: *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed. (A. de Meijere, F. Diederich, eds.), Wiley-VCH, Weinheim, **2004**, 619; b) Z. Rappoport, I. Marek, eds., *The Chemistry of Organozinc Compounds*, John Wiley & Sons, Chichester, **2006**; c) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**.

[78] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

[79] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

[80] a) A. Krasoskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45,* 6040; b) R. D. Riecke, *Science* **1989**, *246*, 1260.

Although organozinc reagents are reactive towards acidic hydrogens,[81] we envisoned that a highly active catalyst system may allow transition metal-catalyzed coupling reactions without the use of protecting groups or a large excess of the zinc reagent.

6.2 Preliminary Studies and Optimization of the Reaction Conditions

In order to investigate the reactivity of organozinc compounds with acidic protons, PhZnI·LiCl (**73a**), OctZnBr·LiCl (**74a**) or $PhCH_2ZnCl$·LiCl (**75a**) were treated with an equimolar amount of aniline (0.4 M solutions in THF, Figure 5). The addition of aniline to phenylzinc iodide (**73a**) resulted in a relatively fast protonation. After 15 min already more than 50 % of the corresponding zinc reagent was protonated. In comparison only 33 % of alkylzinc bromide **74a** and 6 % of benzylzinc chloride **75a** were protonated after 4 h. Also the long-term stability of the benzylic zinc reagent **75a** is noteworthy. After 1 day of stirring at 25 °C, 73 % of the active zinc reagent is still present, as confirmed by quenching with CuCN/allyl bromide (0 % for **73a**, 14 % for **74a**).

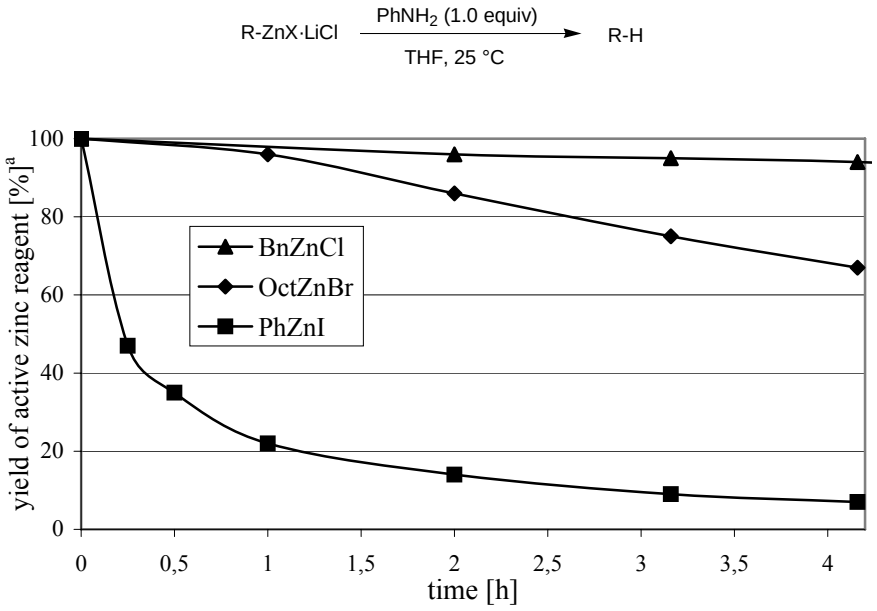


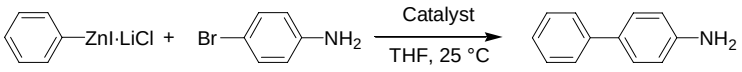
Figure 5. Stability of organozinc reagents towards aniline. [a] Yields are determined by quenching with CuCN/allyl bromide in THF and GC-analysis using tetradecane as internal standard.

[81] For the preparation and stability of organozinc reagents in the presence of acidic hydrogens, see: a) I. Rilatt, R. F. W. Jackson, *J. Org. Chem.* **2008**, *73*, 8694; b) H. P. Knoess, M. T. Furlong, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1991**, *56*, 5974.

These preliminary results indicate that the reactivity towards NH acids increases from *benzyl* < *alkyl* < *aryl* and that a very active cross-coupling catalysts will be required especially for arylzinc reagents to avoid competitive protonation.

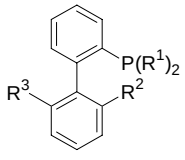
First, we have examined the palladium-catalyzed cross-coupling of organozinc reagents with aryl bromides in the presence of acidic hydrogens. The reaction of phenylzinc iodide (**73a**, 1.2 equiv), prepared by direct zinc insertion in the presence of LiCl,[80] with 4-bromoaniline (**76a**, 1.0 equiv) was chosen as model system. Various ligands were tested (Table 11). Several phosphines, like PPh_3, tri-(2-furyl)-phosphine (tfp) or PCy_3, gave low yields of the aniline **77a** (< 20 %, entries 1-3). Similar yields were obtained with *N*-heterocyclic carbene ligands, e.g. PEPPSI (entry 4). Electron-rich biaryl phosphines, introduced by *Buchwald*,[82] displayed the highest activity for this reaction and biphenyl **77a** was obtained in moderate to high yields (58-96 % yield, entries 5-8). In this class of ligands, S-Phos[66] in combination with $Pd(OAc)_2$, was identified as the most promising, leading to **77a** in 93 % isolated yield (entry 7).

Table 11. Screening of various palladium.ligand systems for the cross-coupling of unprotected aniline **76a**



73a **76a** **77a**

entry	catalyst system	yield [%][a]	entry	catalyst system	yield [%][a]
1	$Pd(PPh_3)_4$ (2 mol%)	-	5	$Pd(OAc)_2$ (1 mol%) John-Phos (2 mol%)	70
2	$Pd(dba)_2$ (2 mol%) tfp (4 mol%)	9	6	$Pd(OAc)_2$ (1 mol%) Dave-Phos (2 mol%)	57
3	$Pd(dba)_2$ (2 mol%) PCy_3 (4 mol%)	15	7	$Pd(OAc)_2$ (1 mol%) S-Phos (2 mol%)	96 (93)[b]
4	PEPPSI (2 mol%)	17	8	$Pd(dba)_2$ (1 mol%) S-Phos (2 mol%)	82



John-Phos: R^1=*t*Bu, R^2=R^3=H
Dave-Phos: R^1=*Cy*, R^2=NMe_2, R^3=H
S-Phos: R^1=*Cy*, R^2=R^3=OMe

[a] Yields were determined by GC-analysis using tetradecane as internal standard. [b] Isolated yield of analytically pure product.

[82] a) R. A. Altmann, S. L. Buchwald, *Nature Protoc.* **2007**, *2*, 3115; b) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028.

6.3 Palladium-Catalyzed Cross-Coupling Reaction

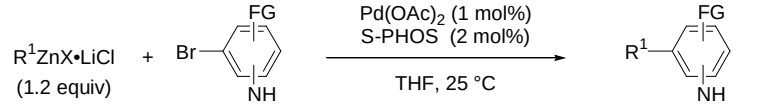
6.3.1 Negishi Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic NH Protons

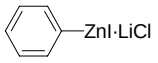
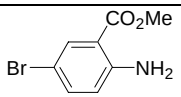
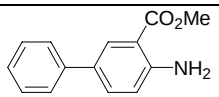
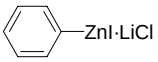
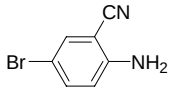
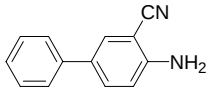
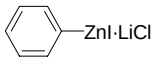
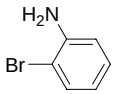
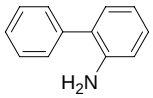
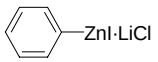
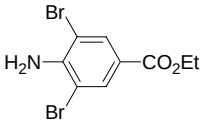
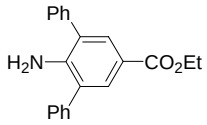
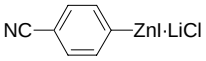
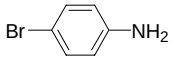
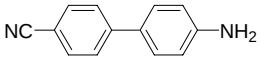
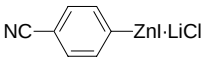
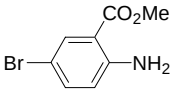
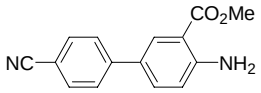
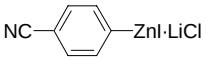
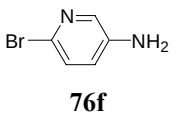
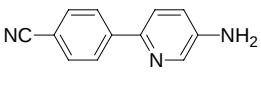
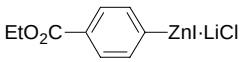
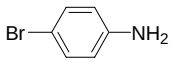
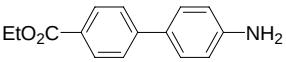
Using $Pd(OAc)_2$/S-Phos as catalytic system, a broad range of functionalized arylzinc reagents (1.2 equiv) reacted with various bromoanilines within 1-3 h at 25 °C in good to excellent yields (Table 12, entries 1-17). Zinc compounds bearing ester-, cyano- or trifluoromethyl-groups were suitable for the palladium-catalysis and afforded the corresponding polyfunctional anilines in 72-98 % yield (Table 12, entries 5-14). The relatively acidic NH_2 protons[83] did not disturb the cross-coupling reaction, which obviously occurred faster than the competitive deprotonation. Interestingly, the reaction can be extended to 2,5-dibromoanilines, although in moderate yields. Thus, the arylzinc reagents **73a** and **73c** reacted with the dibromoaniline **76e**, affording the 2,4,6-trisubstituted phenylamines **77e** and **77l**, which are useful building blocks for the synthesis of thioarylaminals, in 47-53 % yield (entries 4 and 11).[84] Also, 3-pyridylzinc iodide (**73e**) reacted with the bromoanilines **76c**, **76i** and **76j**, leading to the products **77p**-**77r** (70-98 % yield, entries 15-17). In the case of primary or secondary amines, such as the benzylamines **78a** and **78b**, the cross-coupling occurred satisfactorily. The deprotonation of these less acidic amines ($pk_a \sim 40$)[83] was not a concern, however we have observed a palladium catalyst deactivation, due to the high donor ability of these amines. The reaction temperature has therefore to be increased to 65 °C (3-16 h), providing the polyfunctional amines **79a**-**79f** in 61-97 % yield (entries 18-23). Interestingly, alkylzinc bromides of type **74**, prepared by direct zinc insertion in alkyl bromides,[80] were suitable for the palladium-catalyzed cross-coupling. Thus, octylzinc bromide (**74a**) and the functionalized alkylzinc compounds **74b** and **74c** reacted with various bromoanilines within 1-3 h at 25 °C, leading to the polyfunctional anilines **77s**-**77y** in 71-98 % yield (entries 24-30). Also, functionalized benzylic zinc reagents of type **75**, prepared by the direct zinc insertion into benzylic chlorides,[85] undergo a cross-coupling with various aryl bromides in 1-3 h at 25 °C, leading to the diarylmethanes **77z**-**77ab** in 81-98 % yield (entries 31-33). The

[83] Typical pk_a values (in DMSO) for anilines range between 20-30, for aliphatic amines ~ 40 ; for a comprehensive compilation of pk_a data see http://www.chem.wisc.edu/areas/reich/pkatable/index.htm and references cited therein.
[84] For the possible use of thioarylaminyls as spin source or building block for organic magnets, see: P. Lathi, ed., *Magnetic Properties of Organic Materials*, Marcel Dekker, New York, **1999**.
[85] A. Metzger, M. A. Schade, P. Knochel, P. *Org. Lett.* **2008**, *10*, 1107.

polyfunctional pyridine **77ab**, a useful intermediate for the synthesis of HIV integrase inhibitors,[86] was obtained in 92 % yield (entry 33) by the reaction of 4-fluorobenzylzinc chloride (**75d**) with bromo-pyridine **76k**.

Table 12. Palladium-catalyzed cross-coupling of anilines of type **76** and amines of type **78**.



Entry	Zinc reagent	Aryl bromide	Product	Time [h], T [°C]	Yield [%][a]
1				2, 25	94
	73a	**76b**	**77b**		
2				3, 25	81
	73a	**76c**	**77c**		
3				3, 25	67
	73a	**76d**	**77d**		
4				2, 25	53[b]
	73a	**76e**	**77e**		
5				2, 25	96
	73b	**76a**	**77f**		
6				2, 25	98
	73b	**76b**	**77g**		
7				2, 25	82
	73b	**76f**	**77h**		
8				1, 25	88(95)[c]
	73c	**76a**	**77i**		

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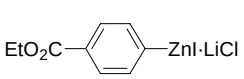
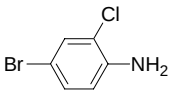
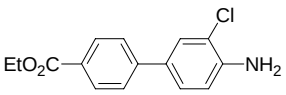
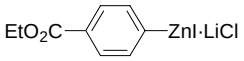
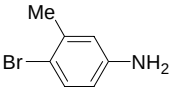
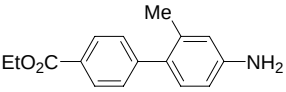
9				2, 25	87
	73c	**76g**	**77j**		
10				3, 25	72
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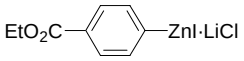
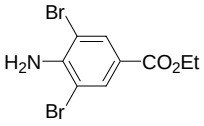
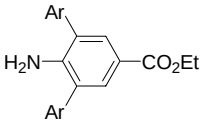
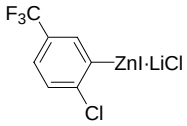
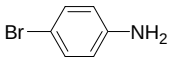
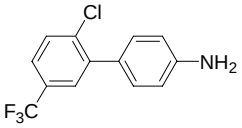
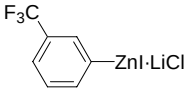
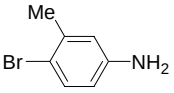
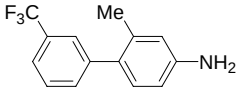
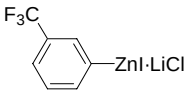
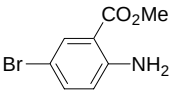
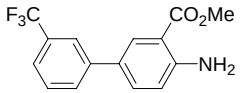
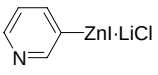
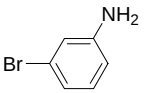
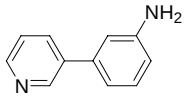
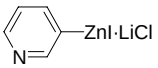
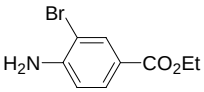
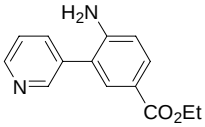
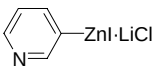
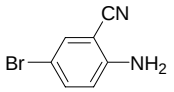
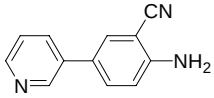
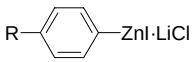
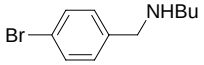
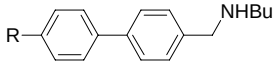
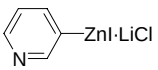
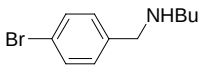
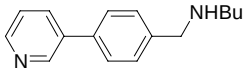
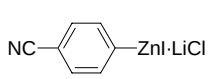
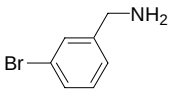
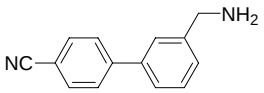
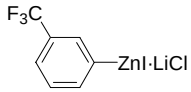
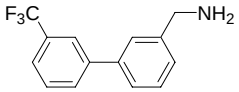
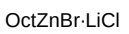
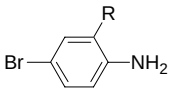
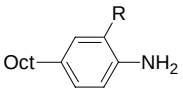
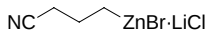
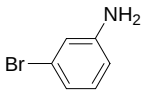
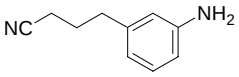
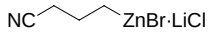
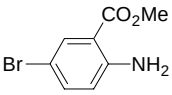
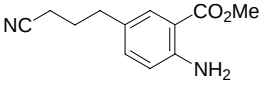
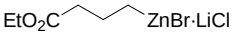
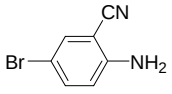
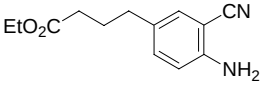
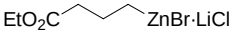
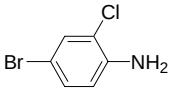
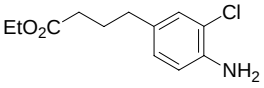
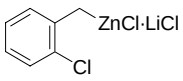
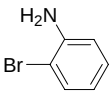
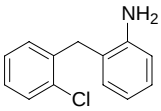
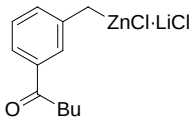
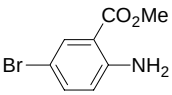
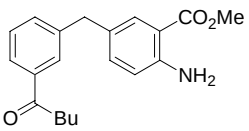
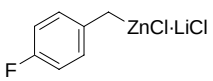
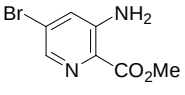
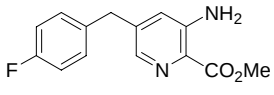
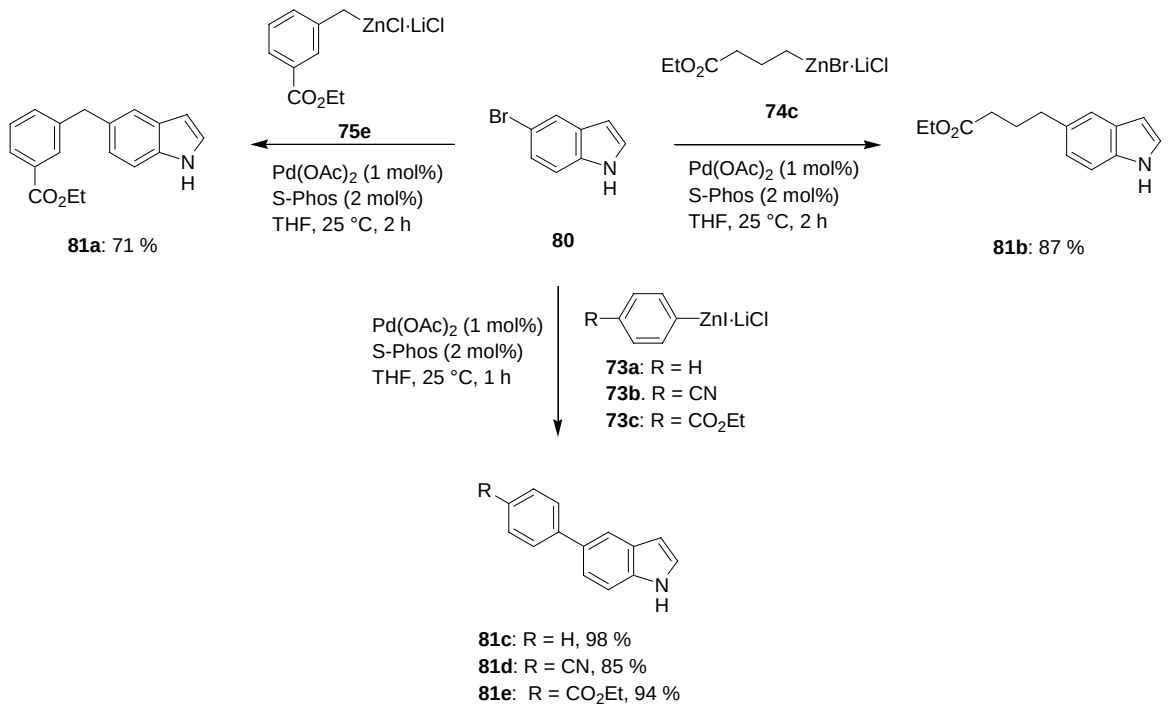
11				3, 25	47[b]
	73c	**76e**	**77l**: Ar = 4-$CO_2Et(C_6H_4)$		
12				2, 25	79[d]
	73d	**76a**	**77m**		
13				2, 25	93
	73e	**76h**	**77n**		
14				2, 25	98
	73e	**76b**	**77o**		
15				2, 25	98
	73f	**76i**	**77p**		
16				2, 25	70
	73f	**76j**	**77q**		
17				2, 25	87
	73f	**76c**	**77r**		
					
18	**73a**: R = H	**78a**	**79a**: R = H	4, 65	72
19	**73b**: R = CN	**78a**	**79b**: R = CN	17, 65	74
20	**73c**: R = CO_2Et	**78a**	**79c**: R = CO_2Et	16, 65	78
				3, 65	71
21	**73f**	**78a**	**79d**		

				3, 65	97
22	**73b**	**78b**	**79e**		
23				3, 65	61
	73e	**78b**	**79f**		
					
24	**74a**	**76a**: R = H	**77s**: R = H	2, 25	92
25	**74a**	**76b**: R = CO_2Me	**77t**: R = CO_2Me	2, 25	85
26	**74a**	**76c**: R = CN	**77u**: R = CN	2, 25	78
27				1.5, 25	95
	74b	**76i**	**77v**		
28				2, 25	98
	74b	**76b**	**77w**		
29				2, 25	73
	74c	**76c**	**77x**		
30				3, 25	71
	74c	**76g**	**77y**		
31				3, 25	81[e]
	75b	**76d**	**77z**		
32				2, 25	98
	75c	**76b**	**77aa**		
33				1.5, 25	92
	75d	**76k**	**77ab**		

[a] Isolated yield of analytically pure product. [b] 2.4 Equiv of the zinc reagent were used. [c] Reaction carried out on a 20 mmol scale. [d] The zinc reagent was added slowly over 90 min via syringe pump. [e] Reaction carried out on a 27 mmol scale.

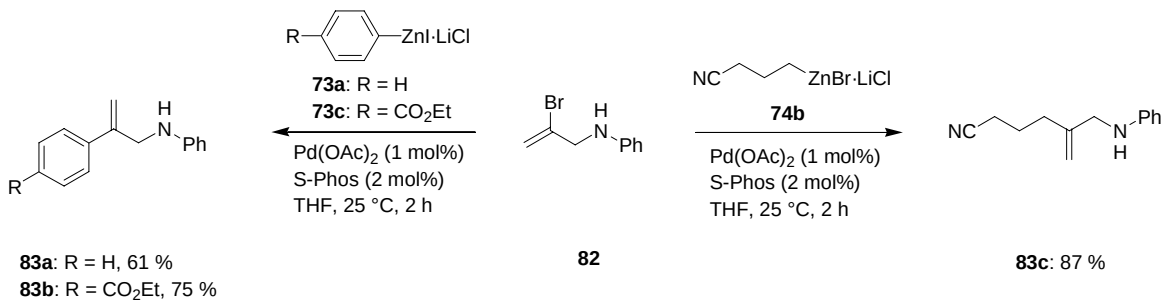
Unprotected indoles are also suitable electrophiles under the reaction conditions described above. Thus, the reaction of 5-bromoindole (**80**) with the benzylzinc reagent **75e** gave the expected product **81a** in 71 % yield (Scheme 33). Similarly, alkyl- or arylzinc[87] halides reacted with the unprotected indole **80**, furnishing the functionalized indoles **81b**-**81e** in 65-98 % yield (Scheme 33).



Scheme 33. Palladium-catalyzed cross-coupling of the unprotected indole **80**.

Alkenyl halides, bearing relatively acidic NH protons, could be coupled using the standard protocol. Thus, the reaction of phenylzinc iodide (**73a**) with the alkenyl bromide **82**, bearing an acidic NH proton, provided the aniline **83a** in 61 % yield. (Scheme 34). Also the functionalized arylzinc iodide **73c** and the alkylzinc bromide **74c** reacted smoothly with the 2-bromo-allylic amine **82**, leading to the allylic amines **83b** and **83c** in 75-87 % yield (Scheme 34).

[87] However for the coupling of 5-bromoindole (**80**), the arylzinc reagents **73a**-**73c** had to be prepared by trans-metalation from the corresponding magnesium reagents. Control experiments have revealed accelerated cross-coupling reactions in the presence of magnesium salts. For the preparation of organomagnesium reagents see references 59-61.



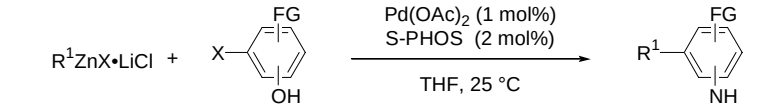
Scheme 34. Palladium-catalyzed cross-coupling of the alkenyl bromide **82**.

6.3.2 Negishi Cross-Couplings of Unsaturated Halides Bearing Unprotected OH Functions

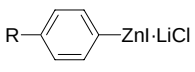
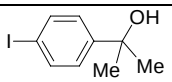
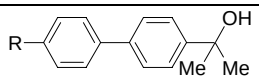
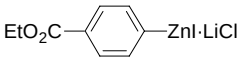
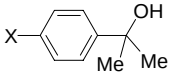
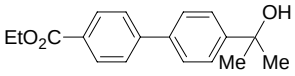
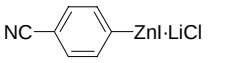
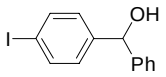
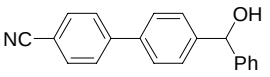
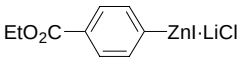
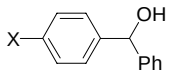
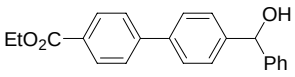
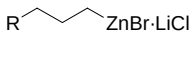
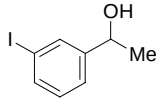
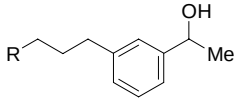
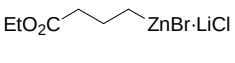
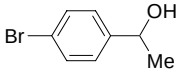
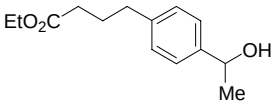
Interestingly, more acidic OH protons were tolerated as well by our protocol. Thus, slowly adding phenylzinc iodide (**73a**, 1.2 equiv) over 90 min (via syringe pump) to a solution of the sterically hindered tertiary iodobenzyl alcohol **84a** (1.0 equiv), $Pd(OAc)_2$ (1 mol%) and S-Phos (2 mol%) led to the cross-coupling product **86a** in 95 % yield (Table 13, entry 1). The slow addition of the zinc reagent was crucial for obtaining a high yield. The functionalized arylzinc reagents **73b** and **73c** also reacted with the iodide **84a** and gave the biaryls **86b** and **86c** in 78-87 % yield (entry 2 and 3). By using the corresponding bromobenzyl alcohol **84b** as electrophile, the cross-coupling product **86c** was obtained in 73 % yield (entry 4). Similarly, the sterically hindered diphenylmethanol **84c**, reacted with the arylzinc iodides **73b** and **73c**, leading to the products **86d** and **86e** in 81-91 % yield (entries 5 and 6). In the case of the corresponding, less reactive aryl bromide **84d**, the biphenyl **86e** was obtained in only 40 % yield (entry 7). The alkylzinc bromides **74b** and **74c** reacted with the less hindered secondary alcohols **84e** and **84f** and with the primary iodobenzyl alcohol **84g** furnishing the functionalized benzylic alcohols **86f-86i** in 59-88 % yield (entries 8-11). Interestingly, various functionalized benzylic zinc chlorides could be coupled with 4-bromobenzyl alcohol (**84h**) or the aryl bromides **84j** and **84k**, bearing relatively acidic NH and OH protons, leading to the products **86j-86o** in 64-98 % yield (entries 12, 14-17). However, with 2-bromobenzyl alcohol (**84i**) no coupling product was observed, probably due to an intramolecular coordination of the OH function. Benzylic zinc reagents tolerated even more acidic phenolic protons. Adding 2-chlorobenzylzinc chloride (**75g**, 1.3 equiv) slowly (over 90 min) to a solution of 4-bromophenol (**85a**, 1.0 equiv), $Pd(OAc)_2$ (1 mol%) and S-Phos (2 mol%) provided the phenol **87a** in 98 % yield (entry 18). Similarly, various functionalized benzylic zinc chlorides react smoothly with various bromophenols and bromonaphthol (**85b-85f**) resulting in the formation

of the corresponding diarylmethanes **87b-87j** in 73-96 % yield (entries 19-28). Remarkably, 5,5'-dibromobinaphthol **85g**, a common intermediate for various BINOL-based ligands,[88] is compatible with the cross-coupling conditions and the reaction with the benzylic zinc reagent **75e** (2.6 equiv) furnished binol **87k** in 76 % yield (entry 28).

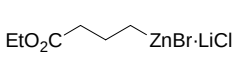
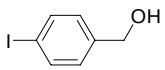
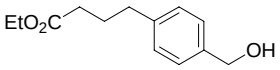
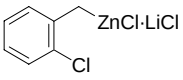
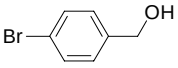
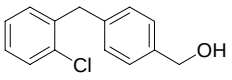
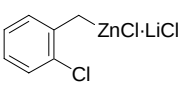
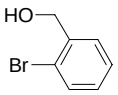
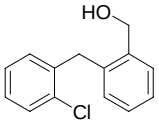
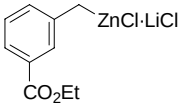
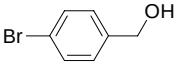
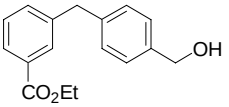
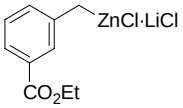
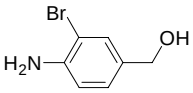
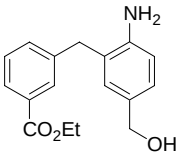
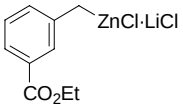
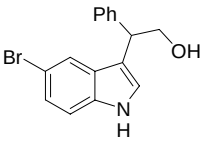
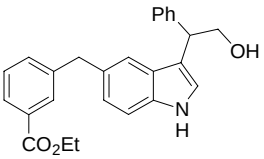
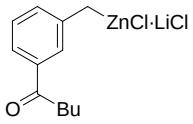
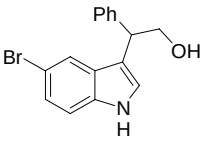
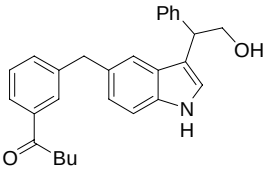
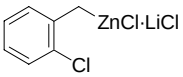
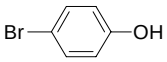
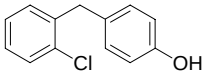
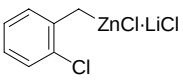
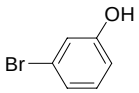
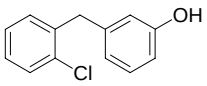
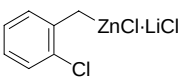
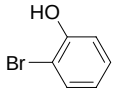
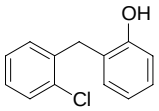
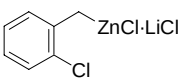
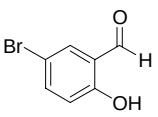
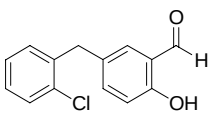
Table 13. Palladium-catalyzed cross-oupling of alcohols of type **84** and phenols of type **85**.

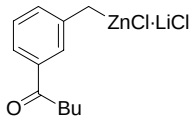
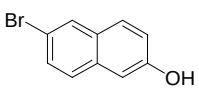
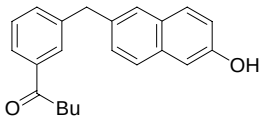
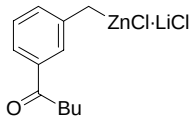
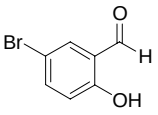
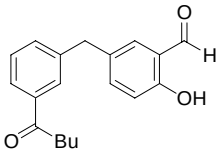
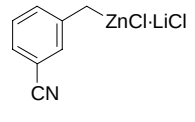
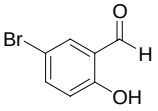
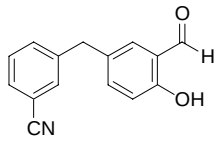
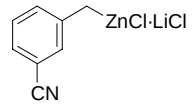
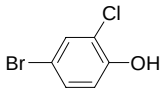
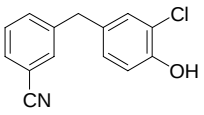
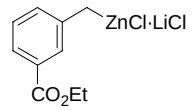
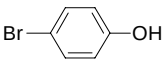
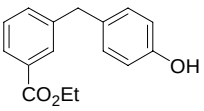
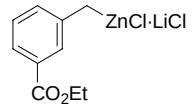
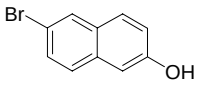
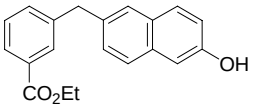
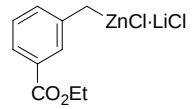
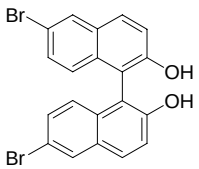
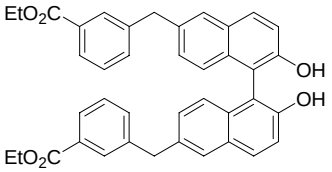


73-**75** (1.2-1.3 equiv) slow addition over 90 min — **84** and **85** — **86** and **87** 40-98 % yield

Entry	Zinc reagent	Aryl halide	Product	time [h], T [°C]	yield [%][a]
					
1	**73a**: R = H	**84a**	**86a**: R = H	2.5, 25	95
2	**73b**: R = CN	**84a**	**86b**: R = CN	2.5, 25	78
					
3	**73c**	**84a**: X = I	**86c**	2.5, 25	87
4	**73c**	**84b**: X = Br	**86c**	2.5, 25	73
5				2.5, 25	91
	73b	**84c**	**86d**		
					
6	**73c**	**84c**: X = I	**86e**	2.5, 25	81
7	**73c**	**84d**: X = Br	**86e**	2.5, 25	40
					
8	**74b**: R = CN	**84e**	**86f**: R = CN	2.5, 25	88
9	**74c**: R = CO_2Et	**84e**	**86g** : R = CO_2Et	2.5, 25	59
10				2.5, 25	70
	74c	**84f**	**86h**		

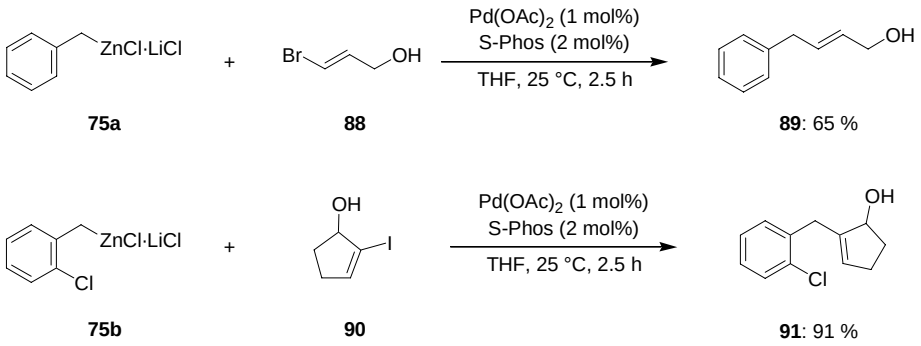
[88] E. N. Jacobsen, A. Pfaltz, H. Yamamoto, eds., *Comprehensive Asymmetric Catalysis*, Springer Verlag, Berlin, **1999**.

11	 **74c**	 **84g**	 **86i**	2.5, 25	65
12	 **75b**	 **84h**	 **86j**	2.5, 25	98
13	 **75b**	 **84i**	 **86k**	2.5, 25	0
14	 **75e**	 **84h**	 **86l**	2.5, 25	94
15	 **75e**	 **84j**	 **86m**	2.5, 25	64
16	 **75e**	 **84k**	 **86n**	2.5, 25	85
17	 **75c**	 **84k**	 **86o**	2.5, 25	72
18	 **75b**	 **85a**	 **87a**	2.5, 25	98
19	 **75b**	 **85b**	 **87b**	2.5, 25	91[b]
20	 **75b**	 **85c**	 **87c**	2.5, 25	82
21	 **75b**	 **85d**	 **87d**	2.5, 25	81

22	 **75c**	 **85e**	 **87e**	2.5, 25	82
23	 **75c**	 **85d**	 **87f**	2.5, 25	75
24	 **75f**	 **85d**	 **87g**	2.5, 25	73
25	 **75f**	 **85f**	 **87h**	2.5, 25	82
26	 **75e**	 **85a**	 **87i**	2.5, 25	89
27	 **75e**	 **85e**	 **87j**	2.5, 25	96
28	 **75e**	 **85g**	 **87k**	2.5, 25	76[c]

[a] Isolated yield of analytically pure product. [b] Reaction carried out on a 32 mmol scale. [c] 2.6 Equiv of the zinc reagent were used.

In addition, alkenyl halides, bearing relatively acidic OH protons, could be coupled with benzylic zinc reagents. Thus, adding benzylzinc chloride (**75a**, 1.2 equiv) slowly over 90 min (via syringe pump) to a solution containing $Pd(OAc)_2$ (1 mol%), S-Phos (2 mol%) and 3-bromoallyl alcohol (**88**, 1.0 equiv) afforded the allylic alcohol **89** in 65 % yield (Scheme 35). Similarly, the cross-coupling reaction of the cycloalkenyl iodide **90** with the benzylic zinc compound **75b** furnished the unsaturated alcohol **91** in 91 % yield (Scheme 35).



Scheme 35. Palladium-catalyzed cross-coupling of alkenyl halides, bearing unprotected OH functions.

6.3.3 Negishi Cross-Couplings Compatible with Unprotected Amide Functions

The amide function is ubiquitous in pharmaceutically active compounds[89] and is therefore especially important to be tolerated in cross-coupling reactions. We have found, that by using $Pd(OAc)_2$ (1 mol%) and S-Phos (2 mol%) and adding the zinc reagent within 90 min to the aryl bromide at 25 °C, it was also possible to perform efficient cross-coupling reactions between various aryl bromides bearing amide groups (1.0 equiv) and functionalized zinc reagents (1.2 equiv). As shown in Table 14, the cross-coupling proceeded well with arylzinc reagents, prepared by the direct zinc insertion in presence of LiCl (such as **73c** and **73e**; 92-96 % yield, entries 1 and 2). Zinc reagents derived from electron-poor heteroarenes, such as 3-pyridylzinc iodide (**73f**) and electron-rich heterocycles, such as 2-thienylzinc chloride (**73g**) or the uracil derived zinc reagent (**73h**)[90] reacted smoothly, providing the cross-coupling products **94c**-**94f** in 81-89 % yield (entries 3-6). Ester and nitrile substituted alkylzinc reagents **74b** and **74c** reacted at the same rate and after addition of the zinc reagent and 30 min of stirring at 25 °C, the cross-coupling of the primary or secondary amides were completed, furnishing the polyfunctional molecules **94g**-**94i** in 83-96 % yield (entries 7-9). Finally, the polyfunctional benzylic zinc reagents **75c**, **75e** and **75f** led to the cross-coupling products **94j**-**94l** in 78-96 % yield (entries 10-12). Interestingly, also iodo-sulfonamides such as **93a** and **93b** are excellent substrates, requiring no protection of the acidic N-H and cross-coupling with the alkylzinc reagents **74b** and **74c** and the benzylic zinc chlorides **75c** and **75f** afforded the desired polyfunctional sulfonamides (**95a**-**95e**) in 75-98 % yield (entries 13-17).

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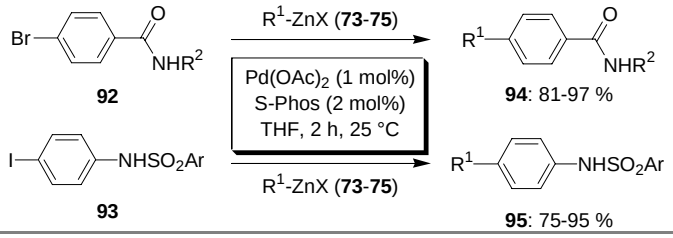
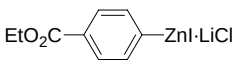
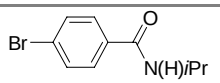
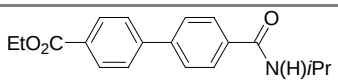
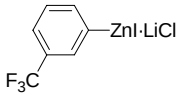
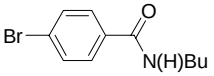
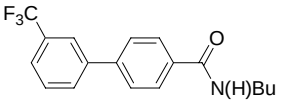
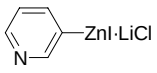
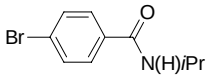
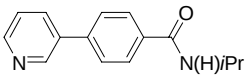
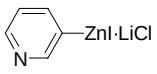
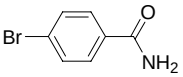
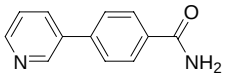
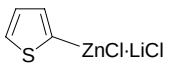
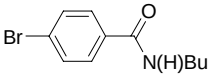
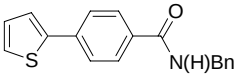
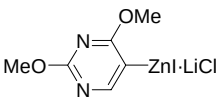
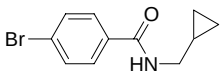
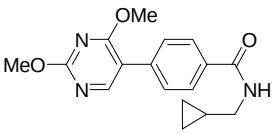
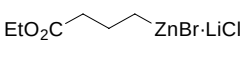
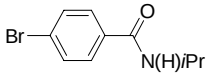
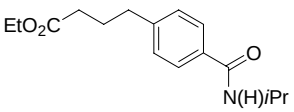
[89] a) B. Blaisdell ed., *Twenty-first Century Pharmaceutical Development*, Interpharm Press, Denver, Col., **2001**; b) D. S. Johnson ed., *The Art of Drug Synthesis*, Wiley, New York, **2007**; c) A. Kleemann, J. Engel, B. Kutscher, D. Reichert, *Pharmaceutical Substances* 3rd ed., Thieme, Stuttgart, **1999**.

[90] D. Soorukram, N. Boudet, V. Malakhov, P. Knochel, *Synthesis* **2007**, 3915.

Table 14. Palladium-catalyzed cross-coupling of amides of type **92** and sulfonamides of type **93**.



Entry	Zinc Reagent	Electrophile	Product	Yield [%][a]
1				96
	73c	**92 a**	**94a**	
2				92
	73e	**92b**	**94b**	
3				89
	73f	**92a**	**94c**	
4				81
	73f	**92c**	**94d**	
5				86
	73g	**92b**	**94e**	
6				87
	73h	**92d**	**94f**	
7				90
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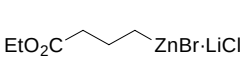
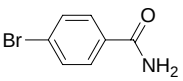
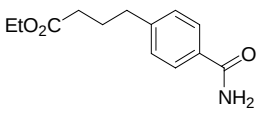
8				83
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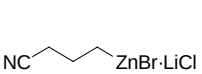
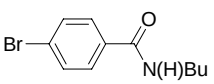
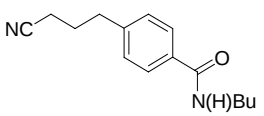
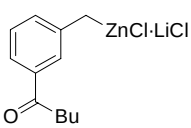
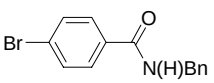
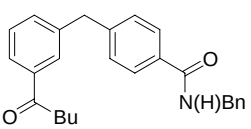
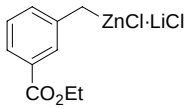
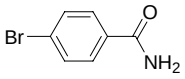
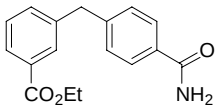
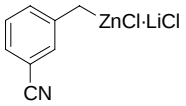
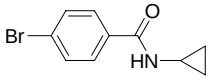
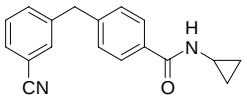
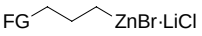
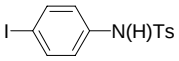
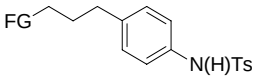
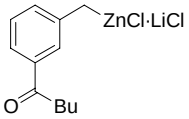
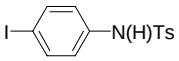
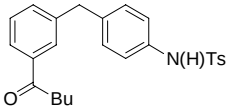
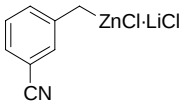
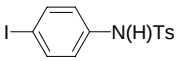
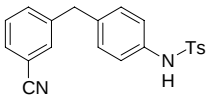
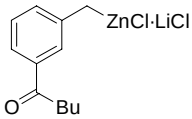
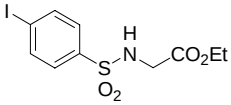
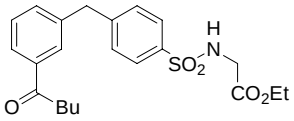
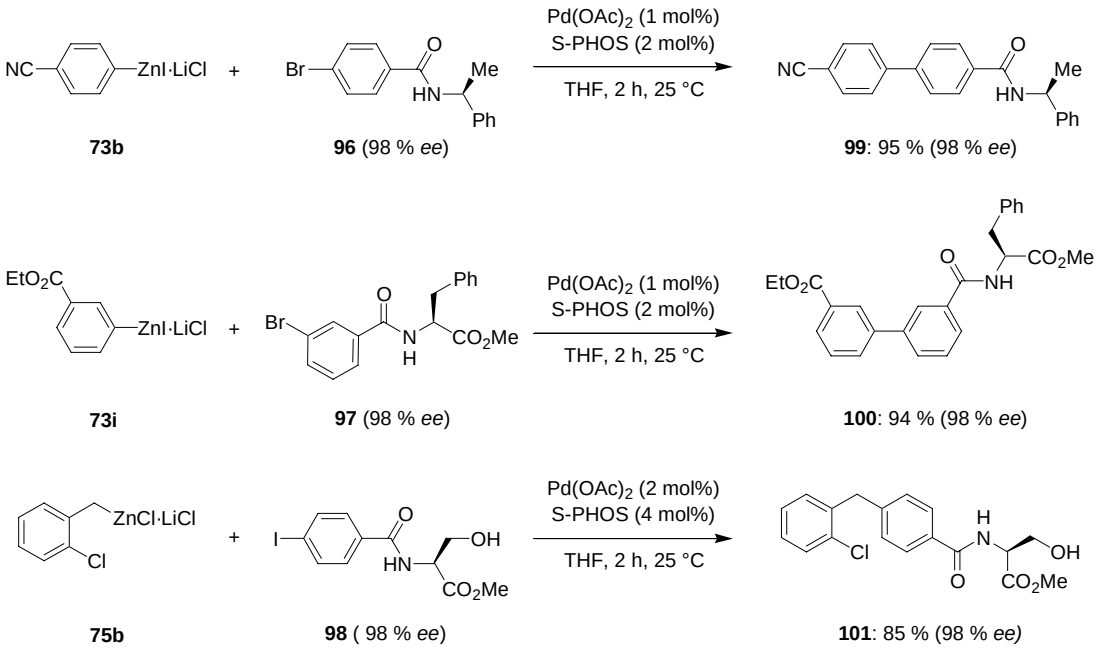
9				96
	74b	**92b**	**94i**	
10				96
	75c	**92e**	**94j**	

11	 **75e**	 **92c**	 **94k**	91
12	 **75f**	 **92f**	 **94l**	78
				
13	**74c**: FG = CO_2Et	**93a**	**95a**: FG = CO_2Et	75
14	**74b**: FG = CN	**93a**	**95b**: FG = CN	95
15	 **75c**	 **93a**	 **95c**	90
16	 **75f**	 **93a**	 **95d**	98
17	 **75c**	 **93b**	 **95e**	85

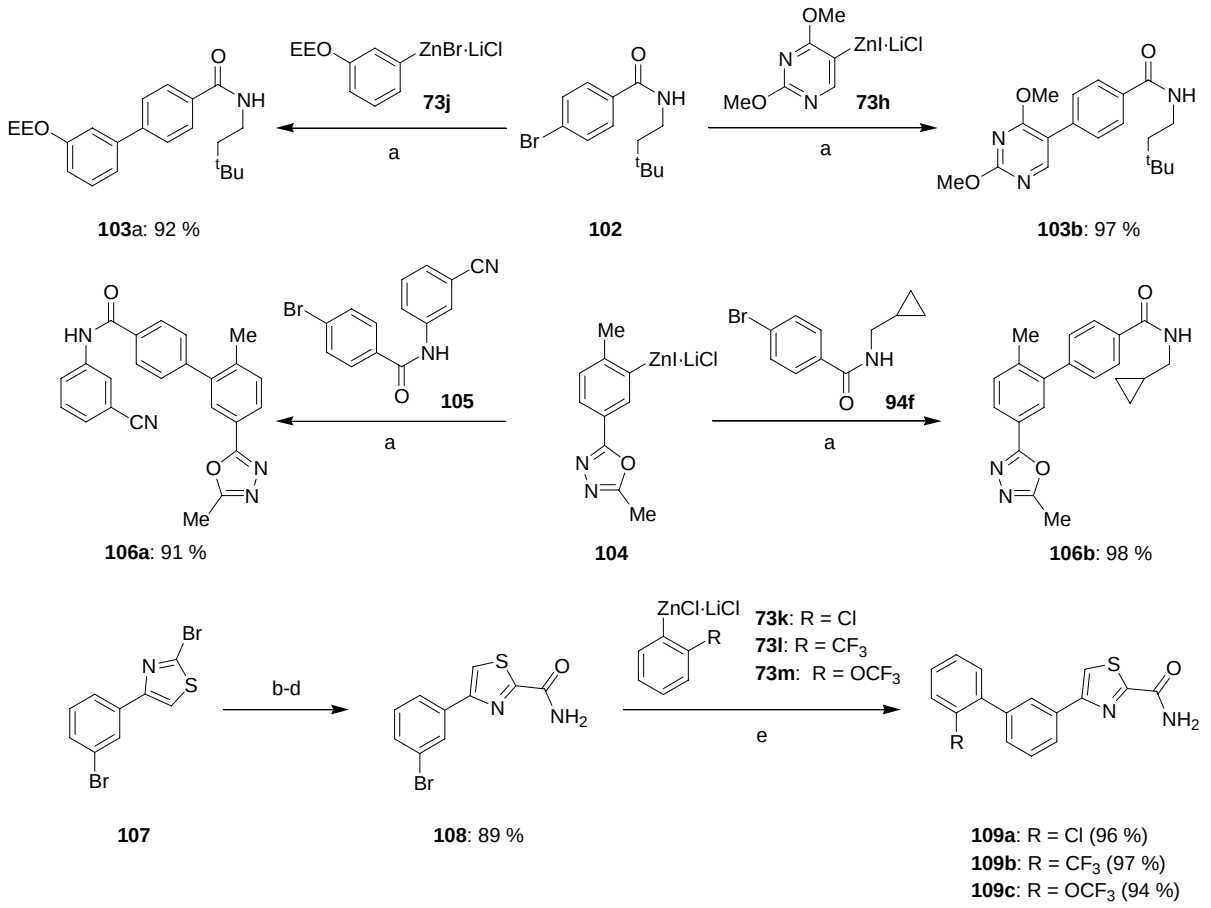
[a] Isolated yield of analytically pure product.



Scheme 36. Cross-coupling of optically active aryl halides with retention of configuration.

The cross-coupling conditions are mild enough, that chiral amides such as bromobenzamide **96** or amino-acid derivatives like **97** and **98** underwent Negishi cross-coupling with aryl and benzylic zinc reagents **73b**, **73i** and **75b** without racemization, leading to the products **99-101** in 85-94 % yield (> 98 % *ee*, Scheme 36).

As mentioned above, numerous pharmaceuticals bear an amide function with an acidic proton. To demonstrate the broad applicability of our method, we have prepared several biologically active compounds. Thus, the antiarrythmic agents **103a** and **103b** (Bristol-Myers Squibb)[91] were prepared in 92-97 % yield by the direct cross-coupling of the zinc reagents **73h** and **73i** under the standard conditions from the bromo-benzamide **102** (Scheme 37). The reaction of the heterocyclic zinc reagent **104**, prepared by direct zinc insertion into the heteroaryl iodide, with the secondary amides **94f** and **105** led to the kinase inhibitors **106a** and



Scheme 37. Preparation of biologically active biphenylamides: a) $Pd(OAc)_2$ (1 mol%), S-Phos (2 mol%), slow addition of the zinc reagent over 90 min, THF 25 °C; b) *i*PrMgCl·LiCl, THF, -30 °C, 45 min, then $ZnCl_2$, -30 °C to 25 °C; c) $Cl_3C(O)NCO$, -40 °C to 25 °C; d) K_2CO_3, MeOH, 25 °C, 16 h; e) $Pd(OAc)_2$ (2 mol%), S-Phos (4 mol%); EE = 1-ethoxyethyl.

[91] J. Lloyd, G. C. Rovyak, P. D. Stein, S. Ahmad, K. Atwal, T. J. Caulfield, M. A. Poss, WO9837068, **1998**.

106b (GlaxoSmithKline)[92] in 91-96 % yield (Scheme 37). Finally, the sodium channel blockers **109a**-**109c** (Merck) [93] were synthesized from the primary amide **108** and the zinc reagents **73k**-**73m**[94] in 94-97 % yield (Scheme 37).

6.3 Nickel-Catalyzed Cross-Coupling Reactions

We have also investigated the use of nickel, cheaper[95] and intrinsically more active than palladium in cross-couplings.[96] The reaction of phenylzinc iodide, prepared by the direct zinc insertion (**73a**, 1.2 equiv) with 4-bromoaniline (**76a**, 1.0 equiv) was chosen as test reaction (Table 15). Preliminary studies showed, that the slow addition of the zinc reagent **73b** (via syringe pump over 90 min) was crucial for obtaining high yields of the aniline **77a**. The best results together with complete consumption of the aryl bromide **76a** were obtained by using either PPh_3 or 2,2'-bipyridine, furnishing the biphenyl **77a** in 62 % and 77 % yield (Table 15, entries 1 and 2). Other phosphines, like 1,2-*bis*(diphenylphosphino)ethane (dppe) or *tris*-(2-furyl)-phosphine (tfp), gave only yields < 20 % (entries 3 and 4), presumably due to competitive deprotonation of the aniline **76a** prior to the cross-coupling reaction. Similar results were obtained with 1,10-phenanthroline (**34**), *N*-heterocyclic carbene ligand (**51**) or diethyl phosphite.[97]

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[92] a) R. M. Agnell, T. D. Angell, P. Bamborough, D. Brown, M. Brown, J. B. Buckton, S. G. Cockerill, C. D. Edwards, K. L. Jones, T. Longstaff, P. A. Smee, K. J. Smith, D. O. Somers, A. L. Walker, M. Wilson, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 324; b) R. M. Agnell, P. Bamborough, A. Cleasby, S. G. Cockerill, K. L. Jones, C. J. Mooney, D. O. Somers, A. L. Walker, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 318.

[93] B. Marron in *Annual Reports in Medicinal Chemistry,* Vol. 41 (A. Wood, Ed.), Elsevier, London, **2006**, pp. 59-73; b) P. K. Chakravaty, M. H. Fisher, W. H. Parsons, S. Tyagajan, B. Zhou, WO04094395, **2004**.

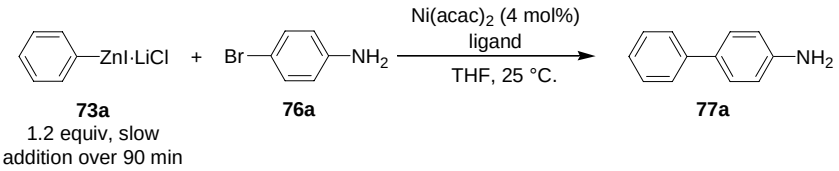
[94] The zinc reagents **73k**-**73m** were prepared by iodine-magnesium exchange and transmetalation with $ZnCl_2$. For the rate acceleration of Pd-catalyzed cross-couplings in the presence of *i*PrI, see above.

[95] $Ni(acac)_2$ (123 €/mol), $Pd(OAc)_2$ (6600 €/mol), 2,2'-bipyridine (130 €/g) and PPh_3 (18 €/mol) were purchased from Alfa Aesar, S-Phos (57200 €/mol) from Strem.

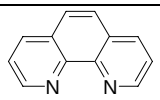
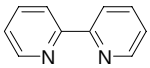
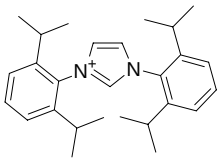
[96] a) L. Melzig, A. Gavryushin, P. Knochel, *Org. Lett.* **2007**, *9*, 5529; b) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *J. Org. Chem.* **1999**, *64*, 3544; c) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 2387.

[97] A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Org. Lett.* **2005**, *7*, 4871.

Table 15. Screening of various nickel-ligand systems for the Negishi cross-coupling of unprotected aniline **76a**.



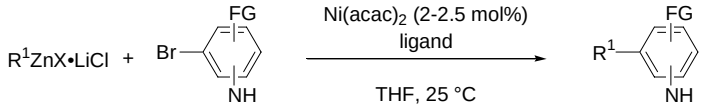
73a 1.2 equiv, slow addition over 90 min | **76a** | **77a**

entry	ligand	yield [%][a]	entry	ligand	yield [%][a]
1	PPh_3 (8 mol%)	62	5	 **34** (6 mol%)	18
2	 (3 mol%)[b]	77	6	 **51** (6 mol%)	16
3	tfp (8 mol%)	17	7	$(EtO)_2P(O)H$ (8 mol%)	15
4	dppe (6 mol%)	12			

[a] Yields were determined by GC-analysis using tetradecane as internal standard. [b] 2 mol% of $Ni(acac)_2$ was used instead.

Using the optimized conditions (2 mol% $Ni(acac)_2$, 3 mol% 2,2'bipyridine, slow addition of the zinc reagent), 4-bromo-aniline (**76a**) reacted with phenylzinc iodide (**73a**) leading to the biphenyl **77a** in 75 % isolated yield (2 h, 25 °C, Table 16, entry 1). Similarly the functionalized bromoanilines **76b-76l** reacted with **73a** within 2-3 h at 25 °C, leading to the biphenyl amines **77b-77ac** in 75-85 % yield (entries 2-4). In the case of the secondary amine **78a**, which is less acidic than anilines, the reaction temperature had to be increased to 60 °C, and the amine **79a** was obtained in 71% yield after 2 h (entry 5). Also, functionalized benzylic zinc reagents, prepared by direct zinc insertion in the presence of LiCl, could be used in this cross-coupling reaction, although the procedure had to be modified. A combination of $Ni(acac)_2$ (2.5 mol%) and PPh_3 (10 mol%) as catalyst system, together with an elevated reaction temperature (60 °C), NMP as cosolvent (10 % v/v) and a slow addition of the zinc reagent turned out to be superior compared to the conditions used for arylzinc halides. Thus, the benzylic zinc chlorides **75a** and **75f** reacted with the aryl bromides **76a-76l** within 2 h, affording the functionalized diarylmethanes **77ad-77ai** in 60-90 % yield (entries 6-13).

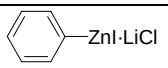
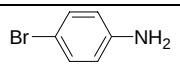
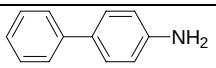
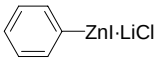
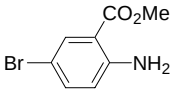
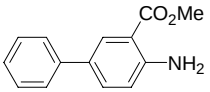
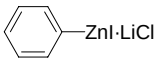
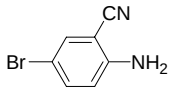
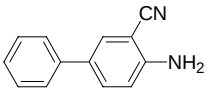
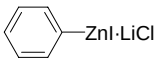
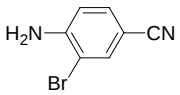
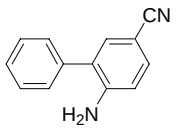
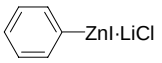
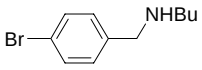
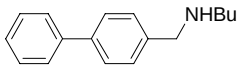
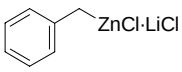
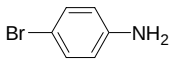
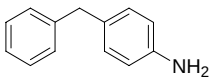
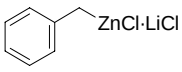
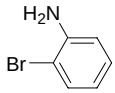
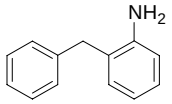
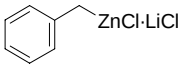
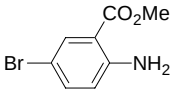
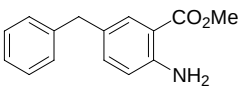
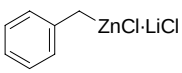
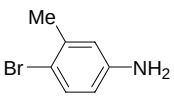
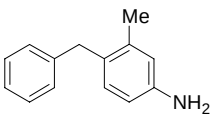
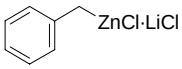
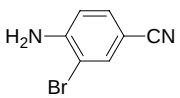
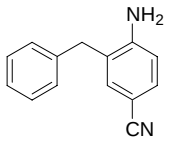
Table 16. Nickel-catalyzed cross-coupling of anilines of type **76** and amines of type **78**.

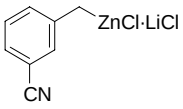
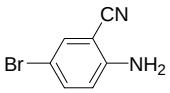
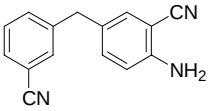


73 and **75**
1.2 equiv

76 and **78**

77 and **79**
60-90 % yield

entry	zinc reagent	Aryl bromide	Product	time [h], T [°C]	yield [%][a]
1				2, 25	75[b]
	73a	**76a**	**77a**		
2				2, 25	78[b]
	73a	**76b**	**77b**		
3				3, 25	85[b]
	73a	**76c**	**77c**		
4				3, 25	75[b]
	73a	**76l**	**77ac**		
5				2, 60	71[b]
	73a	**78a**	**79a**		
6				2, 60	90[c]
	75a	**76a**	**77ad**		
7				2, 60	75[c]
	75a	**76d**	**77ae**		
8				2, 60	77[c]
	75a	**76b**	**77af**		
9				2, 60	79[c]
	75a	**76h**	**77ag**		
10				2, 60	84[c]
	75a	**76l**	**77ah**		

11	 **75f**	 **76c**	 **77ai**	2, 60	81[c]

[a] Isolated yield of analytically pure product. [b] $Ni(acac)_2$ (2 mol%), 2,2'-bipyridine (3 mol%). [c] $Ni(acac)_2$ (2.5 mol%), PPh_3 (10 mol%), THF/NMP 10:1.

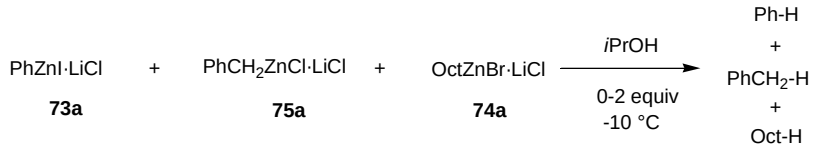
Although the nickel-catalyzed reaction afforded high yields combined with the use of cheap nickel and ligands, it displayed several disadvantages. Functionalized arylzinc compounds were not suitable and led to low yields (typically < 20 %). Also it was difficult to predict, if a chosen combination of zinc reagent and aryl bromide would afford the desired product in satisfactory yields.

6.4 Reactivity of Organozinc Reagents Towards Acidic Protons

In order to understand the chemoselectivity of the different zinc reagents towards aryl halides, bearing acidic OH protons, we next examined their relative reactivity towards and also their stability in the presence of relatively acidic hydrogens. To evaluate the relative reactity of various types of organozinc compounds, we have treated an equimolar mixture of PhZnI·LiCl (**73a**), OctZnBr·LiCl (**74a**) and $PhCH_2ZnCl$·LiCl (**75a**) with various amounts of *i*PrOH (Scheme 37). Interestingly, we have observed that a chemoselective protonation occurs. Thus, after the addition of one equivalent of *i*PrOH at –10 °C, 80 % of PhZnI·LiCl (**73a**) and 20 % of OctZnBr·LiCl (**74a**) were protonated, whereas almost no protonation of $PhCH_2ZnCl$·LiCl (**75a**) was observed. After the addition of the second equivalent of *i*PrOH, the protonation of more than 97 % of PhZnI·LiCl (**73a**) and 90 % of OctZnBr·LiCl (**74a**) was observed. These results indicate the relative reactivity of zinc reagents towards acidic hydrogens: *arylzinc halide* > *alkylzinc halide* > *benzylzinc halide*.[98]

[98] For the reactivity of 1,1-bimetallic species towards protonation see also: P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1986**, *27*, 1043

Table 17. Selective protonation of organozinc reagents.



Amount of *i*PrOH added	Yield of active zinc reagent [%][a]		
	PhZnI·LiCl (**73a**)	OctZnBr·LiCl (**74a**)	$PhCH_2ZnCl·LiCl$ (**75a**)
0	100	100	100
1	20	80	> 97
2	< 3	10	85

[a] Yields are determined by quenching with CuCN/allyl bromide in THF and GC-analysis using tetradecane as internal standard.

In order to investigate the stability of organozinc compounds in the presence of acidic protons, these organometallics were treated with an equimolar amount of an amine or an alcohol (for aniline see Figure 5). Thus, *N*-butylamine was added to a solution of PhZnI·LiCl (**73a**), OctZnBr·LiCl (**74a**) or $PhCH_2ZnCl·LiCl$ (**75a**) in THF (0.4 M, Figure 6). In the case of this comparatively weak acid, all three zinc reagents are quite unreactive. After 24 h only 25 % of PhZnI·LiCl (**73a**) are protonated. The less basic alkylzinc bromide **74a** led to only 8 % of protonation and almost no protonation of benzylzinc chloride (**75a**) occurred (98 % of active zinc reagent). These stabilities are in accordance with the results obtained in the cross-coupling reactions with primary and secondary amines (Table 1, entries 16-20), where long reaction times still led to full conversion of the aryl bromides prior to the protonation of the zinc reagents.

The same experiment with *i*PrOH as proton source led to a rapid protonation of all three organozinc compounds (Figure 7). PhZnI·LiCl (**73a**) was protonated immediately (0 % of active zinc reagent after 30 s) and 73 % of OctZnBr·LiCl (**74a**) was protonated after 5 min $PhCH_2ZnCl·LiCl$ (**75a**) was slightly more stable and after 15 min still 55 % of the active zinc reagent was detected. These results can explain the quite different reactivity of the three zinc reagents with various aryl halides, bearing acidic OH functions (Table 13). The strongly basic arylzinc reagents can only be coupled with sterically hindered alcohols and better yields can be obtained with more reactive aryl iodides, whereas alkylzinc bromides also tolerate less hindered alcohol functions. The least basic benzylic zinc reagents even tolerate more acidic phenolic protons. Using phenol as proton source led to an instant hydrolysis of phenylzinc iodide (**73a**) and octylzinc bromide (**74a,** 0 % of the active zinc reagent was observed after

30 s). Although ca. 70 % of $PhCH_2ZnCl \cdot LiCl$ (**75a**) were protonated with phenol after 30 s, the stability seems to be sufficient to undergo cross-coupling reaction prior to the capture of a proton, if the concentration of the reactive palladium species is high enough to react with the benzylic zinc compound.

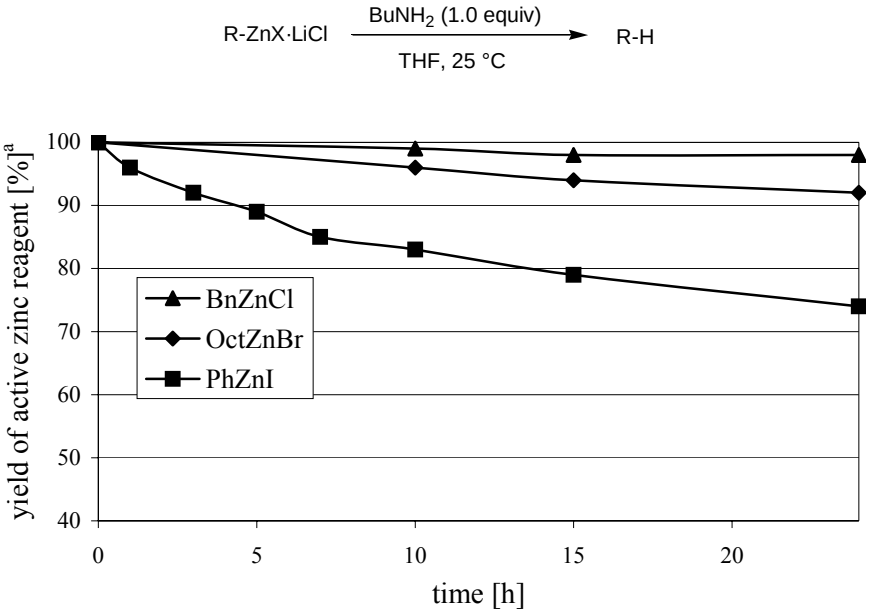


Figure 6. Stability of organozinc reagents towards butylamine.[a] Yields are determined by quenching with CuCN/allyl bromide in THF and GC-analysis using tetradecane as internal standard.

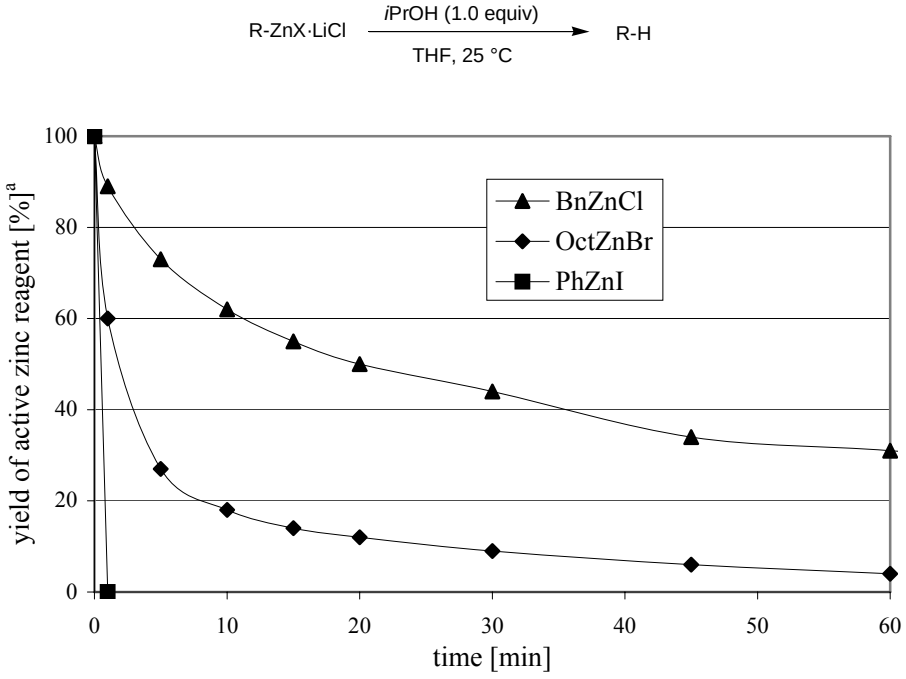


Figure 7. Stability of organozinc reagents towards *i*PrOH.[a] Yields are determined by quenching with CuCN/allyl bromide in THF and GC-analysis using tetradecane as internal standard.

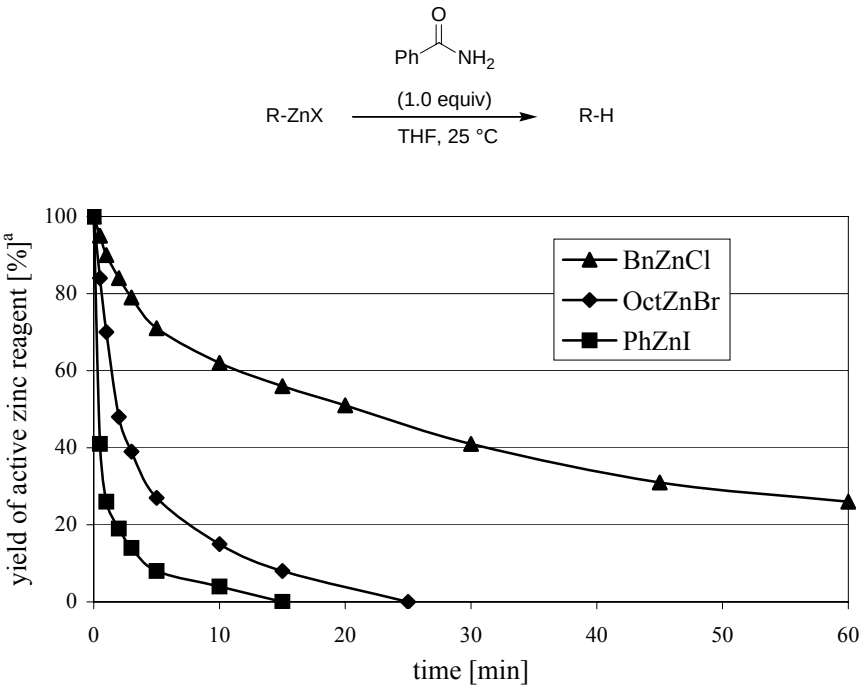


Figure 8. Stability of organozinc reagents towards benzamide. [a] Yields are determined by quenching with CuCN/allyl bromide in THF and GC-analysis using tetradecane as internal standard.

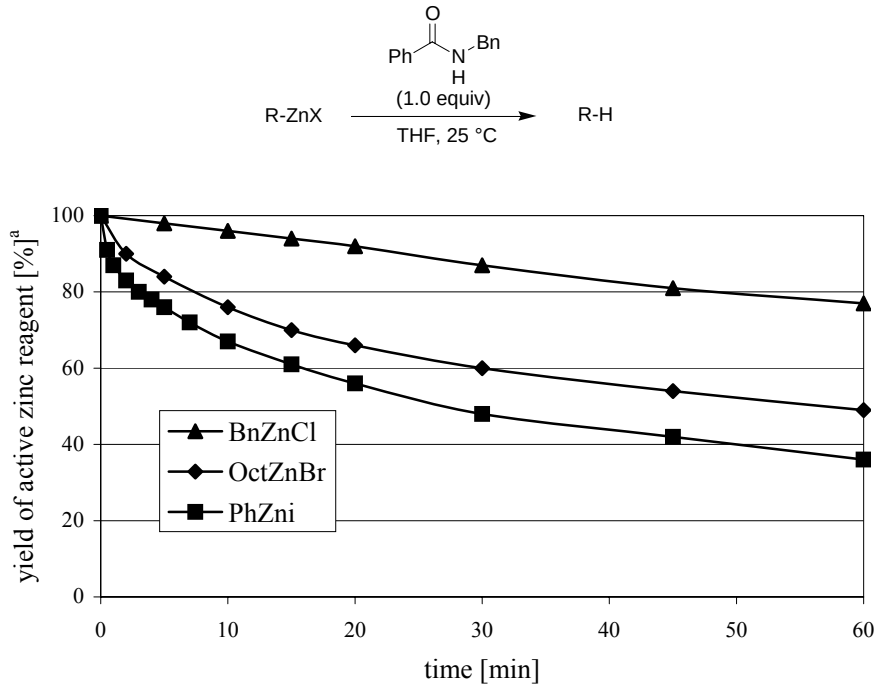


Figure 9. Stability of organozinc reagents towards N-benzyl-benzamide. [a] Yields are determined by quenching with CuCN/allyl bromide in THF and GC-analysis using tetradecane as internal standard.

Finally, similar experiments were conducted with a pimary and a secondary amide (Figure 8 and 9). Thus, a 0.4 M solution of OctZnBr (**74a**) is completlely protonated within 25 min at 25 °C when treated with 1 equivalent of benzamide (Figure 8). From the duration

for 50 % conversion of the zinc reagent (< 1 min for PhZnI, 2.5 min for OctZnBr and 20 min for BnZnCl) one can derive approximate structure reactivity relationships. For secondary amides, the protonation rate is somewhat lower, but 50 % of the zinc reagent are protonated within 30 min (for PhZnI), 60 min (for OctZnBr) and 2.5 h (for BnZnCl, Figure 9).

These results indicate the same relative reactivity: *arylzinc halide* > *alkylzinc halide* > *benzylzinc halide*. The reason for this different relative basicity of organozinc reagents compared to those of carbanions or organolithium compounds (alkyl > aryl > benzyl)[99] may result from different aggregation of zinc and lithium reagents.

[99] M. Schlosser, ed., *Organometallics in Synthesis: A Manual* 2nd ed, Wiley, Chichester, **2002**.

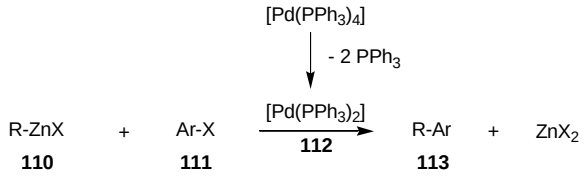
7. Relatives Rates of Negishi Cross-Coupling Reactions

7.1 Introduction

The Pd-catalyzed cross-coupling of unsaturated halides with organometallic reagents is one of the best methods for C(sp^2)-C(sp^2)-bond-formation.[6,33] Among many organometallics used in these cross-couplings, organozinc reagents have proven to react under very mild conditions.[76,77] Furthermore, organozinc compounds are compatible with many functionalities and allow therefore the elaboration of polyfunctional molecules without the need of protecting groups.[100]

However, so far most of the detailed mechanistic studies have focused on the coupling of other organometallic reagents, especially organostannanes, with organic electrophiles.[101] The conclusions that arise from studies conducted on the Stille-Reaction are considered to be general for cross-coupling reactions with other organometallic nucleophiles as well as for palladium-catalyzed carbon-heteroatom-bond formations and nickel-catalyzed cross-coupling reactions. The general mechanism is shown in Scheme 10 and the common catalytic cycle consists of a oxidative addition-transmetalation-reductive elimination-sequence, which furnishes the coupling product and regenerates the active catalyst. Depending on the transition-metal , the electrophile or nucleophile differences regarding some details in the catalytic cycle are observed.

In the following paragraphs, the single steps will be described briefly for a model reaction between the zinc reagent R-ZnX (**110**) and the aryl halide Ar-X (**111**) in presence of catalytic amounts of [$Pd(PPh_3)_4$], a widely used palladium catalyst (Scheme 38).



Scheme 38. Negishi cross-coupling reaction.

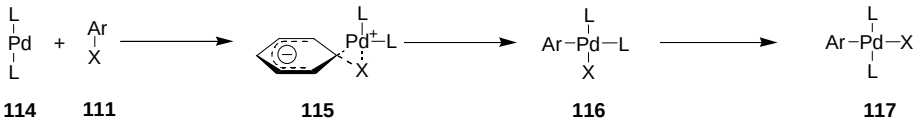
[100] For recent examples from our group, see: a) M. A. Schade, A. Metzger, S. Hug, P. Knochel, *Chem. Commun.* **2008**, *26*, 3046; b) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380; c) A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Tetrahedron.* **2006**, *62*, 7521.

[101] a) A. M. Eshavarren, D J. Cardenas, in: *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed. (A. de Meijere, F. Diederich, eds.) Wiley-VCH, Weinheim, **2004**, 1; b) A. M. Echavarren, P. Espinet, *Angew. Chem. Int. Ed,* **2004**, *43*, 4704; c) J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508.

The catalytic active palladium species $[Pd(PPh_3)_2]$ (**112**) is formed by dissociation of two phosphine ligands.

7.1.1 Oxidative Addition

The oxidative addition of organic halides (or related compounds) to PdL_2 (**114**, L = PPh_3) is the first step in cross-coupling reactions. The results of several studies on the mechanism of the oxidative addition of aryl halides to PdL_2 were consistent with an aromatic nucleophilic substitution, proceeding via the transition state **115** (Scheme 39).[102] In accordance with this three-centered transition state, electron-withdrawing substituents on the aryl halides led to rate acceleration.[103] The initially formed *cis*-$[PdArXL_2]$ (**116**) complexes are unstable, due to the destabilizing interaction between the mutually *trans* phosphine and aryl ligands (''transphobia'').[104] Therefore, these *cis*-complexes may undergo isomerization to the thermodynamically favoured *trans* isomer **117** (Scheme 39).[105]



Scheme 39. Oxidative Addition and *cis*/*trans* isomerization.

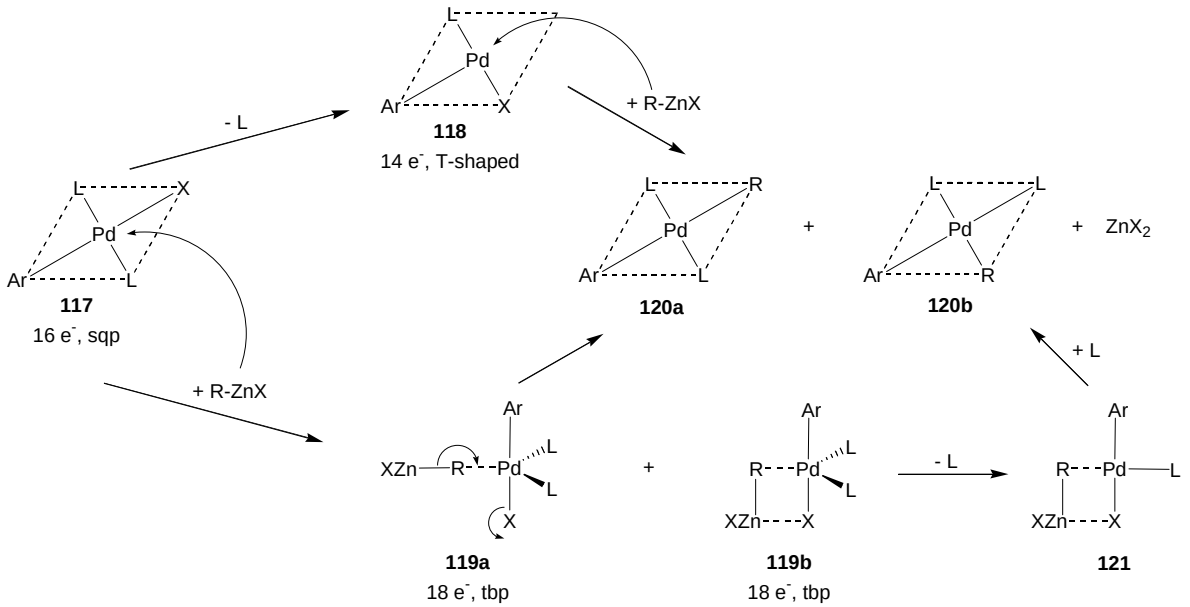
7.1.2 Transmetalation-Ligand Substitution

It can be assumed that the polarity of the organometallic nucleophile is important in determining the mechanism of the transmetalation and differences are expected for each different class of organometallic compounds, depending on the polarity of the carbon-metal-bond. The transmetalation is a ligand substitution on the $[PdArXL_2]$-complex (**117**). In principle, this tetra-coordinated square-planar 16-electron complexes can undergo ligand-substitution reactions by either by a dissociative or an associative pathway (Scheme 40). The dissociative pathway involves the 14-electron T-shaped species (**118**). Although dissociative

[102] J.-F. Fauvarque, F. Plüger, M. Troupel, *J. Organomet. Chem.* **1981**, *208*, 419
[103] a) A. Jutand, A. Mosleh, *Oranometallics* **1995**, *14*, 1810; b) M. Portnoy, D. Milstein, *Organometallics*, **1993**, *12*, 1655; c) M. Portnoy, D. Milstein, *Organometallics*, **1993**, *12*, 1665.
[104] J. Vincente, A. Arcas, D. Bautista, P. G. Jones, *Organometallics*, **1997**, *16*, 2127.
[105] A. L. Casado, P. Espinet, *Organometallics* **1998**, *17*, 954.

mechanisms are important in isomerization, β-*H*-elimination and reductive eliminations, they are rarely observed in ligand substitutions.[106,107]

The associative ligand substitution goes through an 18-electron trigonal bipyramidal complex **119** as transition state or intermediate (Scheme 40). For the associative transmetalation two reaction pathways were observed. The open associative transmetalation proceeds through transition state **119a**. It implies a R-for-X (or R-for-L) substitution, leading competively to the *cis* and *trans* complexes **120a** and **120b** and produces inversion of configuration at the transferred carbon. The cyclic associative transmetalation involves a L-for-R substitution through transition state **119b**, to furnish the bridged intermediate **121**. This intermediate affords directly the *cis* intermediate **120b**, with retention of configuration at the α-carbon.



Scheme 40. Possible reaction pathways for the transmetalation.

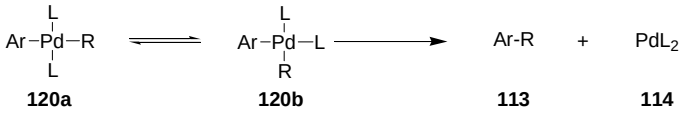
Compared to the Stille- or the Suzuki-reaction, relatively few details about the transmetalation step in the Negishi-reaction are known. However, the selective formation of *cis* complexes of type **120b** with MeZnCl,[108] as well as the complete retention of configuration in the cross-coupling of chiral zinc reagents[109] indicate a reaction pathway via the cyclic transition state **121**.

---

[106] a) J. Burgess, C. D. Hubbard, *Adv. Inorg. Chem.* **2003**, *54*, 71; b) J. A. Casares, P. Espinet, G. Sarkas, *Chem. Eur. J.* **2002**, *8*, 21; c) A. L. Casado, P. Espinet, *J. Am. Chem. Soc.* **1998**, *120*, 8978.
[107] For a possible exception with a very bulky ligand, see: J. Louie, J. F. Hartwig, *J. Am. Chem. Soc* **1995**, *117*, 11598.
[108] J. A. Casares, P. Espinet, B. Fuentes, G. Salas, *J. Am. Chem. Soc.* **2007**, *129*, 3508.
[109] K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, C. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 3538.

7.1.3 Reductive Elimination

The last step of the catalytic cycle, the reductive elimination, furnishes the cross-coupling product R-Ar **113** and regenerates the active catalyst PdL_2 **114** (Scheme 41).[110] Only the *cis* complex **120b** undergoes readily elimination with formation of the coupling product **113**. The corresponding *trans* complex **120a** undergoes isomerizaton to the *cis* species prior to reductive elimination.



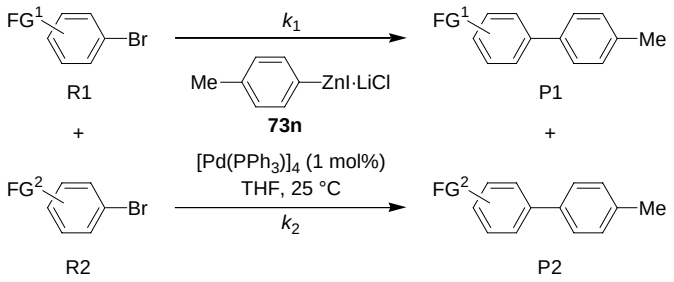
Scheme 41. *Cis-trans* isomerization and reductive elimination.

As shown in the previous chapter, the Negishi reaction is a powerful tool for the elaboration of polyfunctional molecules. However, compared to other cross-coupling reactions, the detailed mechanism of the Negishi reaction still remains unkown (rate-limiting step, transmetalation). Therefore, we were interested in gaining a more detailed insight into the mechanism. Also, from a synthetic chemist's point of view, it would be desirable to have detailed information about the influence of the substitution pattern of both the zinc reagent and the aryl halide.

[110] For a review, see: J. M. Brown, N. A. Cooley, *Chem. Rev.* **1988**, *88*, 1031.

7.2 Determination of Relative Reaction Rates by Competition Experiments

The influence of substituents on the rates of the Negishi cross-coupling reaction has been determined by competition experiments. For this purpose, mixtures of two differently substituted aryl halides have been combined with less than one equivalent of 4-toyllzinc iodide **73n** in the presence of catalytic amounts of a palladium precursor. Readily commercially available aryl bromides were chosen as electrophlies and [$Pd(PPh_3)_4$], a common and widely used catalyst, as palladium source. The ratio of the resulting biaryl was then derived by gas chromatographic determination of the product ratio obtained after quenching with NH_4Cl ([P1]/[P2], Scheme 42). All reactions were run in THF at 25 °C.



Scheme 42. Determination of relative cross-coupling rates.

The relative reactivities of the aryl bromides R1 and R2 with *p*-tolylzinc iodide (**73n**) can be calculated by Equation (1),[111] which also holds under conditions where the ratio [R1]/[R2] during the cross-coupling reaction varies. Substitution of $[R1]_0$ and $[R2]_0$ by Equations (2) and (3) (mass balance) yields Equation (4), which calculates the competition constant κ_1 from the ratios $[P1]_t/[[R1]_t$ and $[P2]_t/[[R2]_t$ determined by gas chromatography.

$$\kappa = \frac{k_1}{k_2} = \frac{\lg([R1]_0/[R1]_t)}{\lg([R2]_0/[R2]_t)} \quad (1)$$

$$[R1]_0 = [R1]_t + [P1]_t \quad (2)$$

$$[R2]_0 = [R2]_t + [P2]_t \quad (3)$$

[111] R. Huisgen, *Angew. Chem. Int. Ed.* **1970**, *9*, 751.

$$\kappa_1 = \frac{\lg(1 + [P1]_t / [R1]_t)}{\lg(1 + [P2]_t / [R2]_t)} \quad (4)$$

The direct calculation of κ values, represented as κ_2, by Equation (1) ($[R1]_t$ and $[R2]_t$ determined gas chromatographically with hexadecane as internal standard) was not very reliable, particularly in the cases of low conversion. An alternative way to calculate the competition constant κ, represented as κ_3 by substitution of $[R1]_0$ and $[R2]_0$ by Equations (5) and (6) (mass balance) yields Equation (7) ($[P1]_t$ and $[P2]_t$ determined by gas chromatography with hexadecane as internal standard). The obtained κ_3 values matched the κ_1 constants, however for all further calculations only the κ_1 values were used.[112]

$$[R1]_t = [R1]_0 - [P1]_t \quad (5)$$

$$[R2]_t = [R2]_0 - [P2]_t \quad (6)$$

$$\kappa_3 = \lg\left(\frac{[R1]_0}{[R1]_0 - [P1]_t}\right) / \lg\left(\frac{[R2]_0}{[R2]_0 - [P2]_t}\right) \quad (7)$$

From the fact that the competition constants κ are independent of the concentrations of the reactants it can be concluded, that the nature of the reactive organozinc species and the active catalyst do not change in the concentration range investigated. Furthermore, it is evidence that the first step, the oxidative insertion, is irreversible.

7.3 Relative Reaction Rates of Substituted Aryl Bromides and Zinc Reagents

Each of the 18 aryl bromides listed in Figure 10 was subjected to competition experiments with several other bromobenzene derivatives to give the 28 competition constants κ listed in Figure 10. Solving the resulting overdetermined set of linear equations (Equation 8) by least square minimization yielded the k_{rel} values listed in Figure 10.

$$\lg k_x - \lg k_y = \lg k \quad (8)$$

[112] All competition constants are presented in the experimental part.

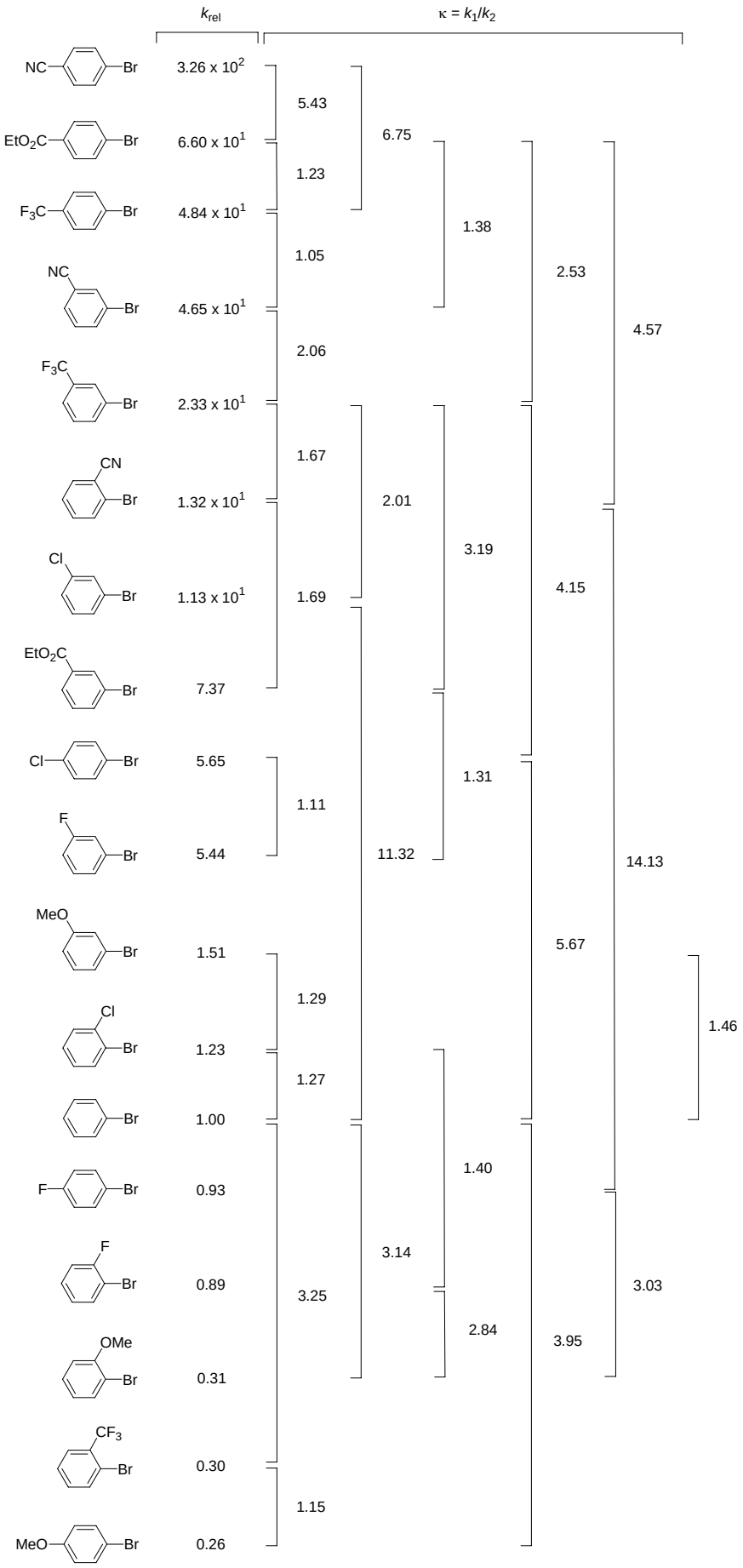


Figure 10. Relative reactivities of substituted bromobenzene derivatives.

Figure 10 shows a reactivity range of 10^3, from 4-methoxy-bromo-benzene, the least reactive compound, to 4-bromo-benzonitrile, the most reactive compound of this series. Like in typical electrophilic or nucleophilic aromatic substitutions, the activating and deactivating *para*-substituent effects are greater than the corresponding *meta* effects (Figure 11). The decrease in reactivity for *ortho*-substituted bromobenzene derivatives originates from the steric shielding of the Ar-Br-bond. Thus, the sterically demanding CF_3-group led to a sharp decline in the reactivity, whereas smaller substituents did not influence the reactivity in a similar manner (Figure 11).[113]

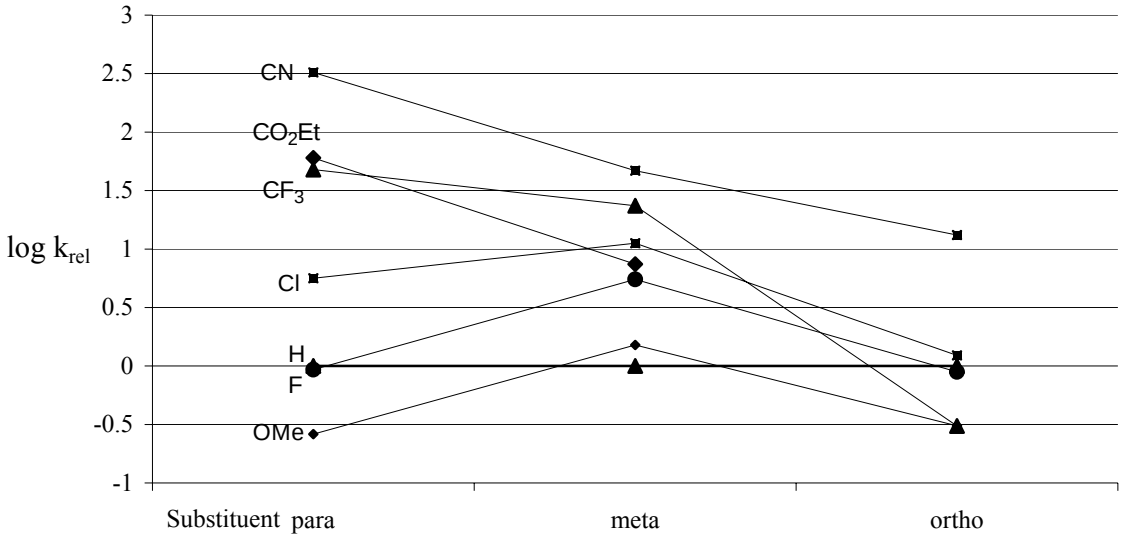


Figure 11. Substituent effects on the reactivities of arylbromides in the Negishi reaction.

Clearly mesomeric effects play an important role in the Negishi cross-coupling as one can derive from the order of the *para*-substituent effects (CN > CO_2Et > CF_3 > Cl > H ≈ F > OMe). A plot of the relative reactivities of *para*-substituted bromobenzene derivatives against the σ^- Hammett parameter[114] gave a ρ value of 2.42 and a correlation coefficient $R^2 = 0.99$ (Figure 12). The σ^- parameter yielded a better fit than the σ parameter (ρ = 3.38, $R^2 = 0.96$), indicating a strong resonance between the π-donor and π-acceptor substituents and the reaction center. Similarly, *meta* Hammett parameters produced a linear fit with a ρ = 3.01 and a correlation coefficient $R^2 = 0.95$ (Figure 13). The good correlation and the large ρ values are clear evidence that the oxidative addition proceeds via a nucleophilic aromatic substitution.

[113] 2-Bromo-benzoic acid ethyl ester was not suitable for the competition experiments. Several by-products were obtained, presumably due to intramolecular stablization of the $ArPdL_2X$ intermediate.
[114] Hammett parameters were obtained from: C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165.

Electron-withdrawing substituents on the aryl bromide increase the rate of he oxidative addition by stabilizing the transition state **115** (Scheme 39).

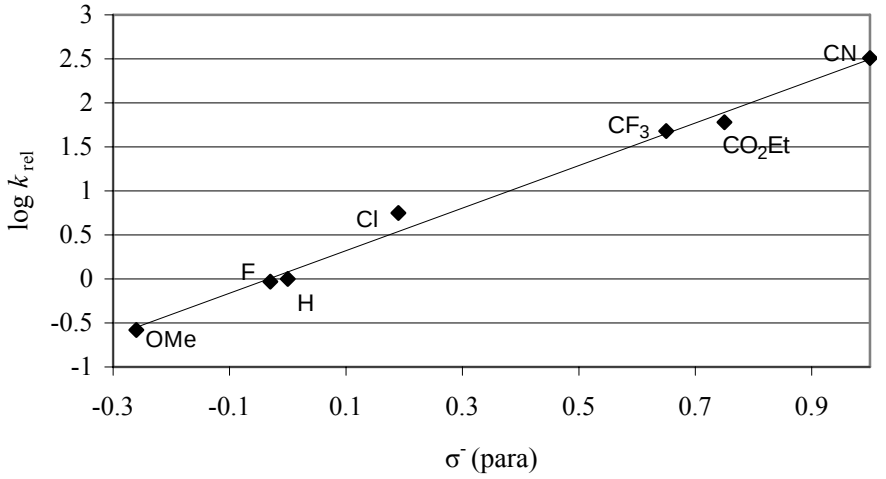


Figure 12. Hammett correlation for the Negishi-reaction of *para*-substituted aryl bromides ($\rho = 2.42$, $R^2 = 0.99$).

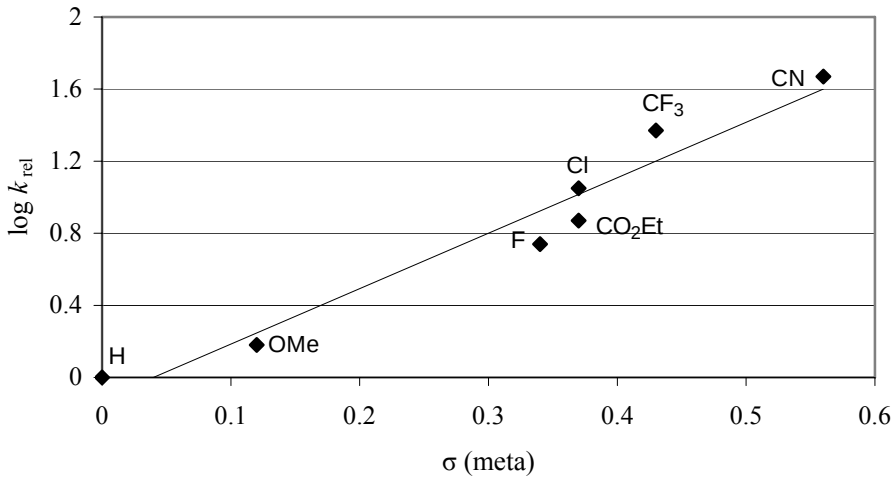
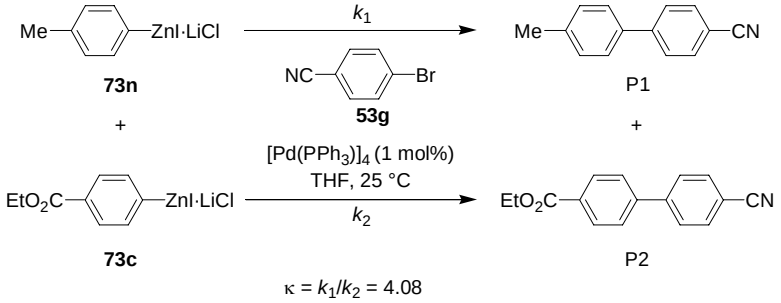


Figure 13. Hammett correlation for the Negishi-reaction of *meta*-substituted aryl bromides ($\rho = 3.01$, $R^2 = 0.95$).

In order to gain further insight into the detailed reaction mechanism, in a competition experiment two different substituted arylzinc reagents **73c** and **73n** were combined with 4-bromobenzonitrile in the presence of [$Pd(PPh_3)_4$] (1 mol%, Scheme 43). Calculation of the competition constant by Equation 4 ([R_1] = **73n**, [R_2] = **73c**) gave a κ value of 4.08. Changes in the reactivity involving different arylzinc reagents are related to changes in the rate constant for the step of the catalytic cycle involving the organozinc species, namely the transmetalation. The increased reactivity of 4-tolyllzinc iodide could be explained by the fact, that electron-donating groups enhance the nucleophilicity of the organozinc reagent for the

arylation of the ArPdX complex **117** (s. Scheme 40). The reactivity range of 4.08 from the *para*-methyl substituted (σ = –0.17) to the *para*-ester substituted zinc reagent (σ = 0.45) is evidence that the influence of the substitution of the arylzinc compound is relatively small compared to the substitution of the aryl bromide (reactivity range 66 from bromobenzene to 4-bromo-benzoic acid ethyl ester). This may not be the case for *ortho*-substituted zinc reagents, however more experiments regarding the substitution pattern of the zinc reagent are necessary.



Scheme 43. Relative reactivity of the arylzinc reagents **73n** and **73c**.

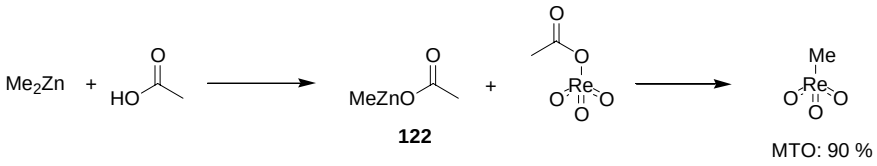
The data obtained from the competition experiments with different substituted aryl bromides as well the zinc reagents **73c** and **73n** , indicates that the oxidative insertion of the PdL_2 complex **114** into the aryl bromide is the rate-limiting step in this Negishi cross-coupling reaction. Furthermore, these allow to base the intuitive choice of arylzinc reagent and aryl halide for a Negishi coupling reaction on more empirical data.

8. Synthesis and Reactivity of Dry Organozinc Reagents

8.1 Introduction

Many organometallic reagents are nowadays used in synthetic organic chemistry. Among them especially organoboron[115] and -zinc[77] compounds are compatible with a broad range of functional groups at ambient temperature,[116] but much attention has been focused on the use of organoboron reagents. They are generally thermally stable and inert to water and air, thus allowing handling on air without special precautions. Also a broad range of functionalized aryl boronic acids and esters are commercially available on laboratory scale as solids. On the other hand, arylzinc reagents are commercially available only as solution in THF or ether and have to be handled and stored under a inert atmosphere, due to their reactivity towards moisture and oxygen.[117]

However, several solid alkylzinc carboxylates have been reported and studied for applications in the synthesis of metal-organic frameworks (MOF) and catalysts for polymerization.[118] Recently, methylzinc acetate (**122**) has been used in a synthesis of methyltrioxorhenium (MTO, Scheme 44).[119] A high thermic stability of $MeCO_2ZnMe$ (**122**) can be anticipated due to the strong Zn-O-bond and the compacte structure of the zinc reagent.



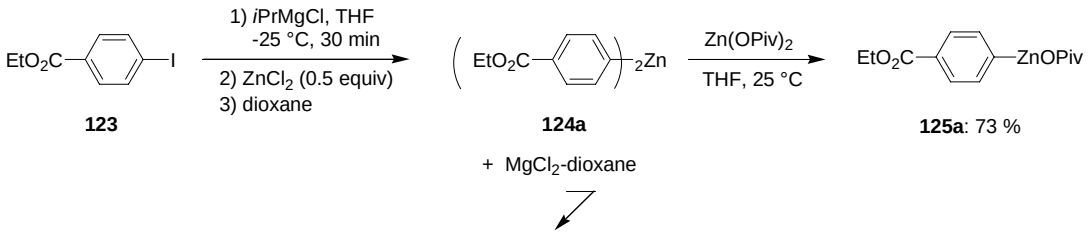
Scheme 44. *Herrmann's* MTO synthesis.

[115] P. Knochel, I. Hiriyakkanavar, T. J. Korn, O. Baron, in: *Handbook of Functionalized Organometallics* (P. Knochel, ed.), Wiley-VCH, Weinheim, **2005**, 45.
[116] Organotin reagents are also compatible with numerous functional groups. However, due to their high toxicity, these reagents are nowadays replaced by organoboron reagents.
[117] Only Ph_2Zn and $(C_6F_5)_2Zn$ are commercially available as solids.
[118] a) J. Lewinski, W. Bury, M. Dutkiewicz, M. Maurin, I. Justiniak, J. Lipkowski, *Angew. Chem. Int. Ed.* **2008**, *47*, 573; b) D. A. Dickie, M. C. Jennings, H. A. Jenkins, J. A. C. Clyburne, *Inorg. Chem* **2005**, *44*, 828; c) S. Inoue, M. Kobayashi, T. Tozuka, *J. Organomet. Chem.* **1974**, *81*, 17; c) G. E. Coates, D. Ridely, *J. Chem. Soc.* **1965**, 1870.
[119] W. A. Herrmann, A. M. J. Rost, J. K. M. Mitterpleininger, N. Szesni, S. Sturm, R. W. Fischer, F. Kühn, *Angew. Chem. Int. Ed.* **2007**, *46*, 7301.

We envisioned the synthesis of solid zinc reagents, using a suitable stabilizing oxygen ligand or an extra additive. The resulting dry organozinc compounds would be of great interest and extend the utility of zinc reagents.

8.2 Synthesis and Stability of Dry Organozinc Reagents

We focused our studies on the preparation of arylzinc reagents, since they are most widely used in organic synthesis and should presumably show the highest stability. The synthetic approach is shown in Scheme 45. First, the diorganozinc reagent **124a** is prepared from the aryl iodide **123** by an I/Mg-exchange reaction, followed by transmetalation with $ZnCl_2$ (0.5 equiv) and precipitation of $MgCl_2$ upon addition of dioxane. The diarylzinc compound **124a** is then added to a suspension of $Zn(OPiv)_2$ in THF and stirred until all solids are dissolved. Evaporation of the solvents afforded the zinc reagent **125a** as solid in 73 % yield.[120] However, during this work purification of the arylzinc pivalates of type **125** by recrystalization was unsuccessful. Therefore the unpurified crude product was used for all further transformations.



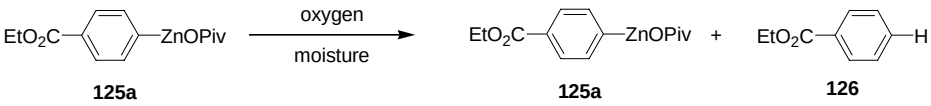
Scheme 45. Synthesis of arylzinc pivalate (**125a**).

In order to determine the stability towards oxygen and moisture, the solid zinc reagent (**125a**) was exposed to air (Table 18). Satisfactorily, the arylzinc pivalate **125a** was sufficiently stable to allow fast handling on air (weight out a certain amount for an experiment) without decomposition (Table 18, entry 1). Longer exposure to air led to a fast decomposition of the zinc reagent (50 % of active species after 15 min, entry 3). Interestingly, the only observed decomposition product was benzoic acid ethyl ester (**126**), derived from hydrolysis (ca. 50 % yield after 15 min). No side products derived from oxidation reactions, such as phenols, were observed. The zinc reagent **125a** was also suitable for long time storage. After 10 d in a closed vial almost no decomposition of the arylzinc pivalate was observed (entry 5). Storage of the zinc reagent in an exsiccator over beads of silica gel, a

[120] Determined by titration with I_2. See Experimental Part for further details.

convenient and commercial available drying agent, was sufficient enough to avoid those small losses in activity (entry 6).

Table 18. Stability of the arylzinc pivalate (**125a**).

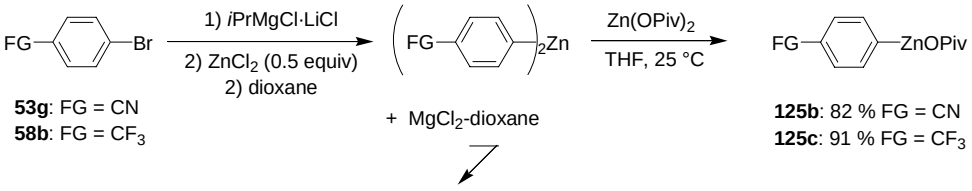


125a **125a** **126**

Entry	Treatment	Yield of active zinc reagent [%][a]
1	weight out in air (fast)	100
2	exposure to air (2 min)	90
3	exposure to air (15 min)	50
4	stored in closed vial (2 d)	100
5	stored in closed vial (10 d)	97
6	Stored in exsiccator (10d)	100

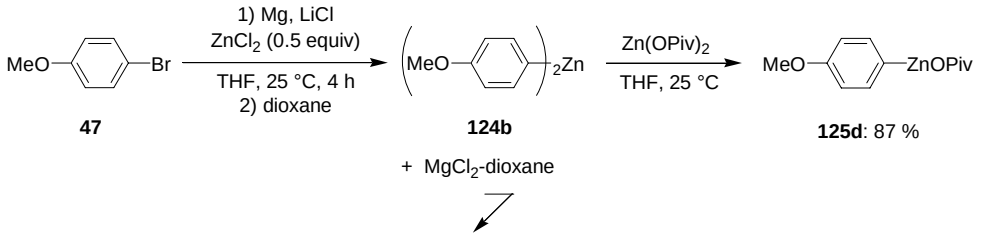
[a] Determined by quenching with I_2 and GC-analysis using tetradecane as internal standard.

In a similar manner, the two functionalized arylzinc pivalates **125b** and **125c** were prepared in 82-91 % yield from the corresponding aryl bromides **53g** and **58b** (Scheme 46). The LiCl from *i*PrMgCl·LiCl, was not separated from the crude product and the mixture used directly for all following transformations. All attempts to obtain crystals from the arylzinc pivalates were not successful.



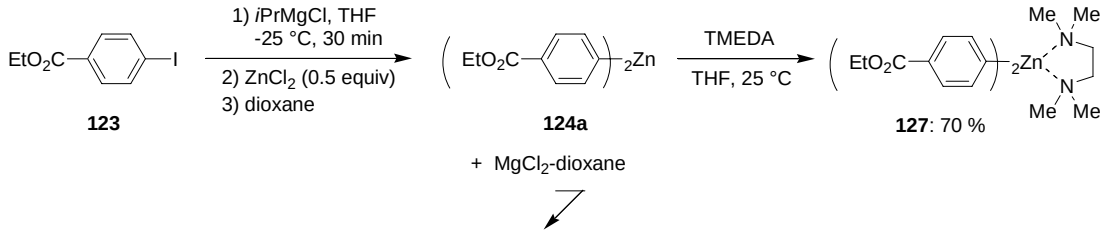
Scheme 46. Preparation of the arylzinc pivalates **125b** and **125c**.

The diorganonzinc reagent **124b** could be also prepared by a direct magnesium insertion in the presence of 0.5 equivalents of $ZnCl_2$,[61] an more convenient and cost-efficient method than the halogen/magnesium exchange reaction (Scheme 47). The arylzinc pivalate **125d** was obtained in 87 % yield and showed a similar stability as the ester-substituted zinc reagent **125a**.



Scheme 47. Synthesis of arylzinc pivalate **125d**.

In a second approach, the diarylzinc-TMEDA **125** complex was prepared (Scheme 48).[121] It showed a stability comparable to the arylzinc pivalates.



Scheme 48. Preparation of the diarylzinc-TMEDA-complex **127**.

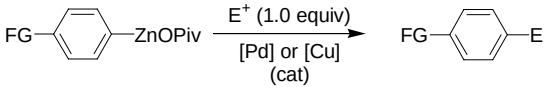
8.3 Reactivity of Dry Organozinc Reagents

With the solid zinc reagents in hand, we next examined their performance in palladium- and copper-catalyzed reactions with various electrophiles. Palladium-catalyzed Negishi-reactions with aryl halides proceeded smoothly and afforded the corresponding biaryls in high yields (Table 19). Thus, the reaction of the arylzinc pivalate **125a** (1.2 equiv) with 4-bromo-benzonitrile (**53g**, 1.0 equiv) in the presence of PEPPSI (1 mol%) furnished the desired coupling product **60c** in 91 % yield after 1 h at 25 °C (entry 1). In the case of the diarylzinc-TMEDA-complex **127**, the cross-coupling occurred satisfactorily. The presence of TMEDA is not a concern and the biaryl **60c** is obtained in 89 % yield after 1 h (0.6 equiv of **127** were used, entry 2). Using PEPPSI (1-2 mol%) as catalyst the solid zinc reagents **125a**-**125c** reacted with the aryl bromides **53a**, **53d** and **53g** within 1 h at 25 °C in 84-97 % yield (entries 4, 5, 7 and 9). Heterocyclic chlorides like the pyridine **42f** and 2-chloroquinoline (**42d**) reacted with the arylzinc pivalates **125b** and **125c**, leading to the coupling products **130a** and **130f** in 77-91 % yield (entries 3 and 8). The copper-catalyzed (0.5 mol% CuCN·2LiCl) reaction of the solid zinc reagent **125b** (1.2 equiv) with ethyl 2-bromomethyl-acrylate (**128**,

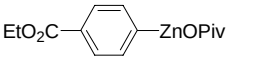
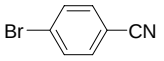
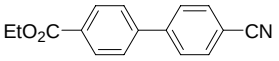
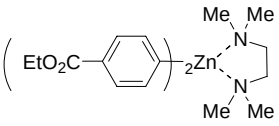
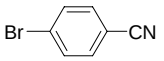
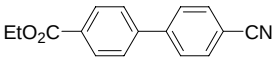
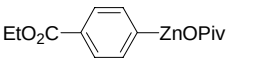
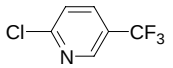
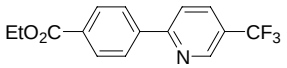
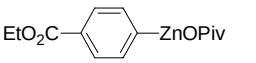
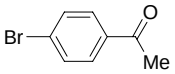
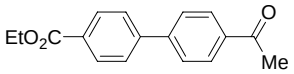
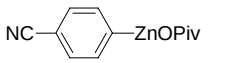
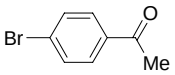
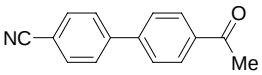
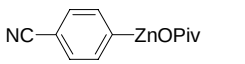
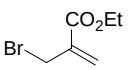
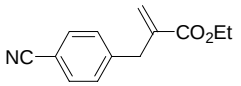
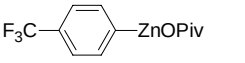
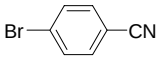
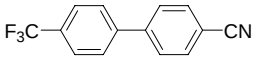
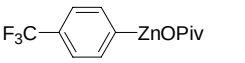
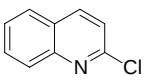
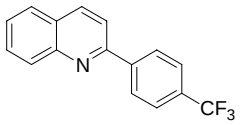
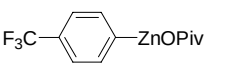
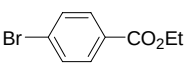
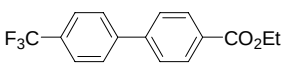
[121] $ZnCl_2$-TMEDA is a non-hygroscopic complex, see: M. Isobe, S. Kondo, N. Nagasawa, T. Goto, *Chem. Lett.* **1977**, 679.

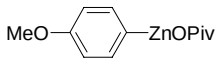
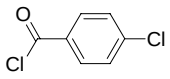
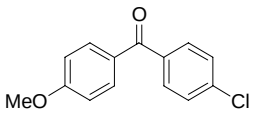
1.0 equiv) furnished the desired functionalized acrylate **130d** in 76 % yield (entry 6). The copper-catalyzed acylation of 4-methoxyphenylzinc pivalate (**125d**, 1.0 equiv) with 4-chlorobenzoyl chloride (**129**, 2.1 equiv) led to the diketone **130h** in 96 % yield (entry 10). In this case an excess of the electrophile had to be used, presumably due to competitive *O*-acylation of the pivalate.

Table 19. Reaction of dry zinc reagents with various electrophiles.



125 (1.2 equiv)

Entry	Zinc reagent	Aryl halide	Product	time [h], T [°C]	yield [%][a]
1				1, 25	91[b]
	125a	**53g**	**60c**		
2				1, 25	89[b]
	127	**53g**	**60c**		
3				3, 25	77[b]
	125a	**42f**	**130a**		
4				0.5, 25	91[c]
	125a	**53d**	**130b**		
5				0.5, 25	84[c]
	125b	**53d**	**130c**		
6				1, -25 to 0	76[d]
	125b	**128**	**130d**		
7				1, 25	93[b]
	125c	**53g**	**130e**		
8				3, 25	91[b]
	125c	**42d**	**130f**		
9				1, 25	97[b]
	125c	**53a**	**130g**		

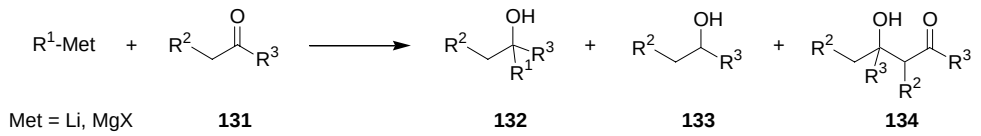
10				1, -25 to 0	96[e]
	125d	**129**	**130h**		

[a] Isolated yield of analytically pure product. [b] PEPPSI (1 mol%) was used as catalyst. [c] PEPPSI (2 mol%) was used as catalyst. [d] CuCN·2LiCl (0.5 mol%) was used as catalyst. [e] CuCN·2LiCl (20 mol%) was used as catalyst and 2.1 equiv of electrophile were used.

9. Mg^{2+}-Promoted Addition of Organozinc Reagents to Carbonyl Compounds

9.1 Introduction

The direct addition of organometallic reagents to aldehydes and ketones is a versatile method for the synthesis of secondary and tertiary alcohols.[5b,122] A number of synthetically useful addition reactions for the formation of carbon-carbon-bonds have been developed with organolithium,[123] -magnesium,[124] dialkylzinc[77b] and organotitanium[47] reagents as nucleophiles. Highly reactive organolithium and –magnesium compounds give the desired adducts (**132**) along with reduction products (**133**) due to *β*-hydride transfer of alkyl groups and aldol adducts (**134**) arising from the enolization of the carbonyl compound (Scheme 49). Additives, such as $CeCl_3$,[125] $LnCl_3{\cdot}LiCl$[126] or $ZnCl_2$,[127] have been used to activate the carbonyl compounds or enhance the nucleophilicity of the organometallic compound, providing the desired addition products in good yields and minimum side products. Despite this great progress, limitations in the scope of this reaction remain, especially with regard to functional group tolerance.



Scheme 49. Addition of organometall reagents to carbonyl compounds.

Organozinc reagents show an optimal compromise in terms of reactivity and wide functional group tolerance, but only a limited number of simple diorganozinc reagents (typically diethyl- or diphenylzinc) have been used for the addition to carbonyl compounds.[128] However, without any activation, addition of diorganozinc compounds to carbonyl compounds barely proceeds.

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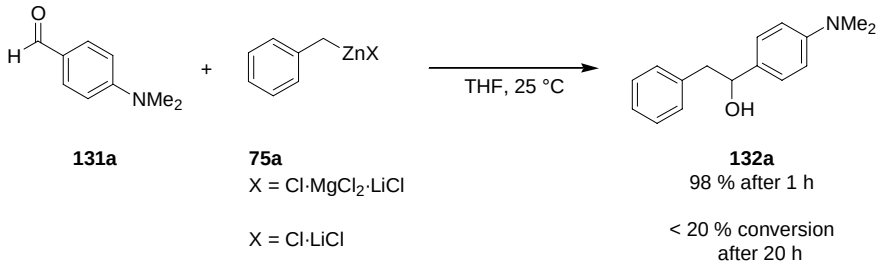
[122] M. Hatano, T. Miyamoto, K. Ishihara, *Curr. Org. Chem.* **2007**, *11*, 127.
[123] Z. Rappoport, I. Marek, eds., *The Chemistry of Organolithium Compounds*, Wiley, Chichester, **2004**.
[124] Z. Rappoport, I. Marek, eds., *The Chemistry of Organomagnesium Compounds*, Wiley, Chichester, **2007**.
[125] T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, Y. Kamiya, *J. Am. Chem. Soc.* **1989**, *111*, 4392.
[126] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
[127] M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998.
[128] K. Soai, T. Kawasaki, in: *The Chemistry of Organozinc Compounds* (Z. Rappoport, I. Marek, eds.), Wiley, Chichester, **2006**, 556.

Thus, either the carbonyl derivative is activated using a Lewis acid catalyst or the nucleophilicty of the zinc reagent is enhanced with a Lewis base catalyst.

Recently, a direct magnesium insertion into aryl and benzylic halides in the presence of $ZnCl_2$ has been developed in our group.[61,129] These organometallics were found to have a higher reactivity towards carbonyl compounds. Thus, the reaction of benzylzinc chloride (**135a**), prepared by a magnesium insertion in the presence of LiCl and $ZnCl_2$, with 4-(dimethylamino)-benzaldehyde (**131a**) furnished **132a** in 98 % yield after 1 h (Scheme 50). In contrast, reaction of benzylzinc chloride (**75a**), prepared by direct zinc insertion in the presence of LiCl, with the electron-rich benzaldehyde **131a** did not provide the expected product **132a** in appreciable amount (Scheme 50).



Scheme 50. Reactivity of benzylzinc chloride (**75a**) towards 4-(dimethylamino)-benzaldehyde (**132a**).

Considering the convenient preparation of these zinc reagents, we decided to further investigate their addition to carbonyl compounds. The development of ''specialized'' organozinc reagents for the addition to aldehydes, ketones or imines would certainly extend the scope of organozinc chemistry.

9.2 Mechanistic Considerations

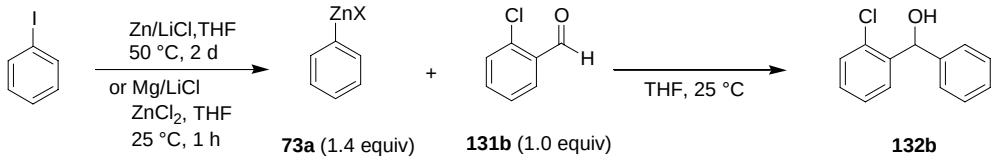
In order to investigate the enhanced reactivity in the presence of $MgCl_2$, phenylzinc iodide (**73a**, 1.4 equiv), prepared by different methods, was added to 2-chlorobenzaldehyde (**131b**, 1.0 equiv, Table 20).[130] The addition of the zinc reagent (**73a**), prepared by direct zinc insertion into the aryl iodide in the presence of LiCl, led to a slow reaction (> 95 % conversion after 18 h, entry 1). In contrast, the reaction of phenylzinc iodide, prepared by direct magnesium insertion in the presence of LiCl and $ZnCl_2$, was finished after only 15 min

[129] A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824.

[130] In the case PhCHO, < 20 % of conversion were observed with PhZnI·LiCl. Therefore more reactive 2-chloro-benzaldehyde (**132b**) was choosen as model substrate

at 25 °C. Interestingly, premixing $MgCl_2$ (1.4 equiv) and the benzaldehyde **131b** for 30 min prior to the addition of the zinc reagent **73a**, prepared by direct zinc insertion, resulted in a complete conversion of the starting aldehyde **131b** after 90 min (entry 3). This rate accelerating effect is based on a stoichiometric Lewis acid activation of the aldehyde.

Table 20. Influence of $MgCl_2$.

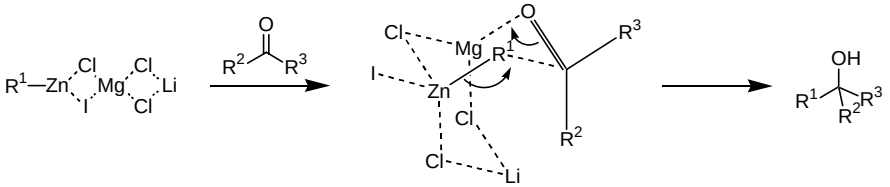


73a (1.4 equiv) **131b** (1.0 equiv) **132b**

Entry	Zinc reagent	Time for full conversion (> 95 %) [min][a]
1	PhZnI·LiCl	1080
2	$PhZnI·MgCl_2·LiCl$	15
3	PhZnI·LiCl + $MgCl_2$ (1.4 equiv)	90

[a] Determined by GC-analysis using tetradecane as internal standard.

These results indicate, that Lewis acid based activation of the carbonyl compound is one possible reason for the high reactivity of the zinc reagents, prepared by magnesium insertion in the presence of $ZnCl_2$. Also, the formation of a more reactive ate complex $R^1ZnI·MgCl_2·LiCl$ (**135**) during the *in situ* formation of the zinc reagent, might enhance the reactivity. The $R^1ZnI·MgCl_2·LiCl$ reagent coordinates to the carbonyl compound via the [MgCl] moiety to form a six-membered chair-like ring transition state **136**.[131] The attack of [Zn-R^1] on the activated [C=O]-group furnishes the alcohol **132** (Scheme 51).



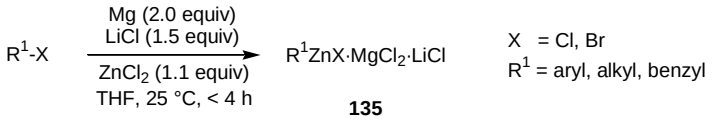
135 **136** **132**

Scheme 51. Proposed transition state for the addition of $R^1ZnI·MgCl_2·LiCl$.

[131] For ate-complexes and six-memebered ring assembly see; a) M. Uchiyama, S. Nakamura, T. Ohwada, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 10897; b) E. C. Ashby, L.-C. Chao, J. Laemmle, *J. Org. Chem.* **1974**, *39*, 3677; see also ref 112.

9.3 Addition of Organozinc Reagents to Aldehydes, Ketones and Imines

The organozinc compounds of type **135** were synthesized by the direct magnesium insertion into organohalides in the presence of LiCl and $ZnCl_2$ (Scheme 52). Using this convenient procedure aryl-,[61] alkyl-,[132] and benzylic zinc[114] reagents could be prepared rapidly (up to 4 h) at ambient temperature.



Scheme 52. Preparation of organozinc reagents by direct magnesium insertion in the presence of $ZnCl_2$.

These highly reactive zinc compounds were found to add smoothly to aldehydes and ketones. Thus, the reaction of 2-fluorophenylzinc bromide (**135a**, 1.2 equiv) with 2-nitro-piperonal (**131c**, 1.0 equiv) furnished the secondary alcohol **132c** in 87 % yield after 1 h at 0 °C (Table 21, entry 1). Noteworthy is the high chemoselectivity of the zinc reagent. Reaction of the corresponding organomagnesium reagent led to competitive attack on the nitro function and multiple by-products.[133] The aliphatic aldehyde **131d** reacted quantitatively with the benzylic zinc chloride **135b**, leading to the alcohol **132d** in 98 % yield (entry 2).[134] The benzylic zinc chloride **135b** added even to the benzophenone derivative **131e** and the tertiary alcohol was obtained in 93 % yield after 1 h at 25 °C (entry 3). The reaction of alkylzinc halides, bearing a remote ester function, yielded the corresponding lactones after intramolecular transesterification. Thus, the alkylzinc reagent **135c** reacted with 4-cyanobenzaldehyde (**131f**) within 1 h at 25 °C and the lactone **137a** was obtained in 70 % yield (entry 4). In the case of the less reactive α-tetralone (**131g**) the reaction temperature had to be increased to 55 °C, providing the spiro compound **137b** in 68 % yield (entry 5). Interestingly, addition of the alkylzinc reagent **135c** to the activated tosylimine **138** furnished the amine **139** in 65 % yield (entry 6).[135]

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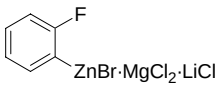
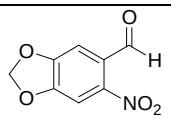
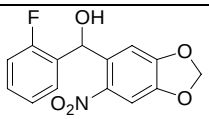
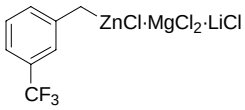
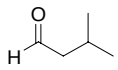
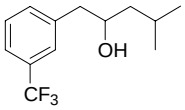
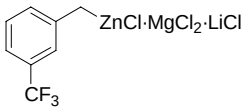
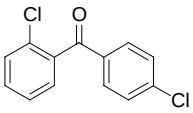
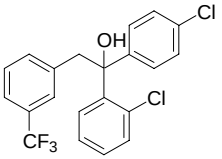
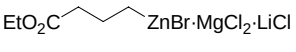
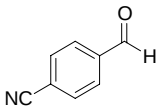
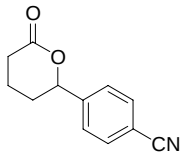
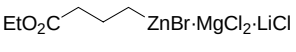
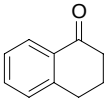
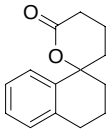
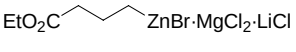
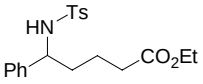
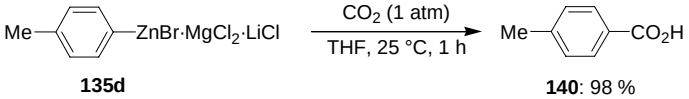
[132] T. Blümke, *Diploma thesis*, LMU München, **2008**.
[133] For reactions of Grignard reagents with NO_2-functions, see ref 13c and references cited therein.
[134] Benzylic zinc reagents, prepared by zinc insertion, only add to benzaldehyde derivatives. See ref 85 and 114.
[135] Organozinc halides have been scarely used as nucleophiles in the 1,2-addition to imines. For few exceptions, see: a) J. Esquivias, R. Gomez Arrayas, *Angew. Chem. Int. Ed.* **2007**, *46*, 9257; b) T. Iwai, T. Ito, T. Mizuno, Y. Ishino, *Tetrahedron Lett.* **2004**, *45*, 1083; c) K. P. Chiev, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry* **2002**, *13*, 2205.

Table 21. Addition of organozinc reagents to carbonyl compounds.

Entry	Zinc reagent	Electrophile	Product	time [h], T [°C]	yield [%][a]
1				1, 0	87[b]
	135a	**131c**	**132c**		
2				1, 25	98
	135b	**131d**	**132d**		
3				1, 25	93
	135b	**131e**	**132e**		
4				1, 25	70
	135c	**131f**	**137a**		
5				6, 55	68
	135c	**131g**	**137b**		
6				4, 25	65
	135c	**138**	**139**		

[a] Isolated yield of analytically pure product.

Finally, *p*-tolylzinc bromide (**135d**) reacted with CO_2 and the corresponding carboxylic acid **140** was obtained in 98 % yield after 1 h (Scheme 53). However, this behaviour was not general and only electron-rich zinc reagents were suitable for the reaction with CO_2.[136]



135d **140**: 98 %

Scheme 53. Reaction of *p*-tolylzinc bromide (**135d**) with CO_2.

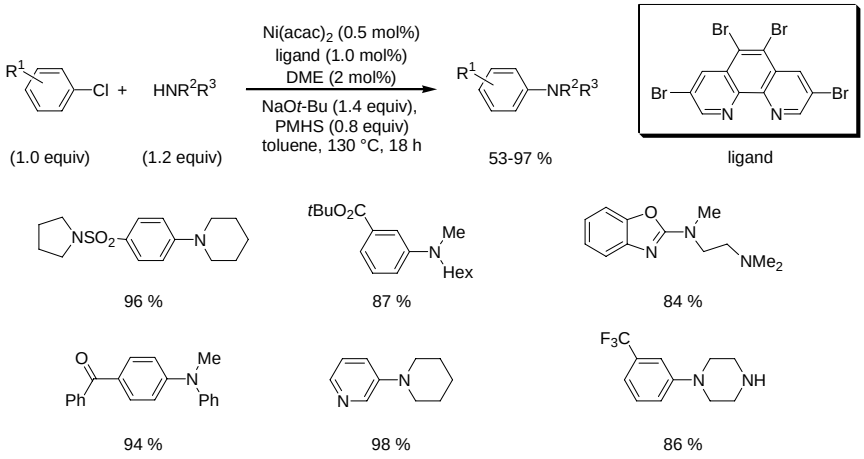
[136] A. Metzger, P. Knochel, *unpulished results*, LMU München, **2009**.

10. Summary and Outlook

This work was focused on the development of palladium- and nickel-catalyzed cross-coupling reactions with organomagnesium, titanium and zinc reagents, as well as nickel-catalyzed amination reactions. For one of these cross-coupling reaction, the Negishi-reaction, relative reaction rates of different substituted bromoarenes and zinc reagents were determined. Furthermore, the preparation and use of solid organozinc reagents was accomplished.

10.1 Nickel-Catalyzed Amination of Aryl Chlorides

A practical protocol for the silane-promoted nickel-catalyzed amination of aryl chlorides was developed. The $Ni(acac)_2$/3,5,6,8-tetrabromo-phenanthroline/PMHS catalyst system requires low loadings of 0.1-0.5 mol% and affords high yields in the arylation and heteroarylation of secondary amines and anilines. The use of the toluene/DME solvent system proved to be the most beneficial (Scheme 54).

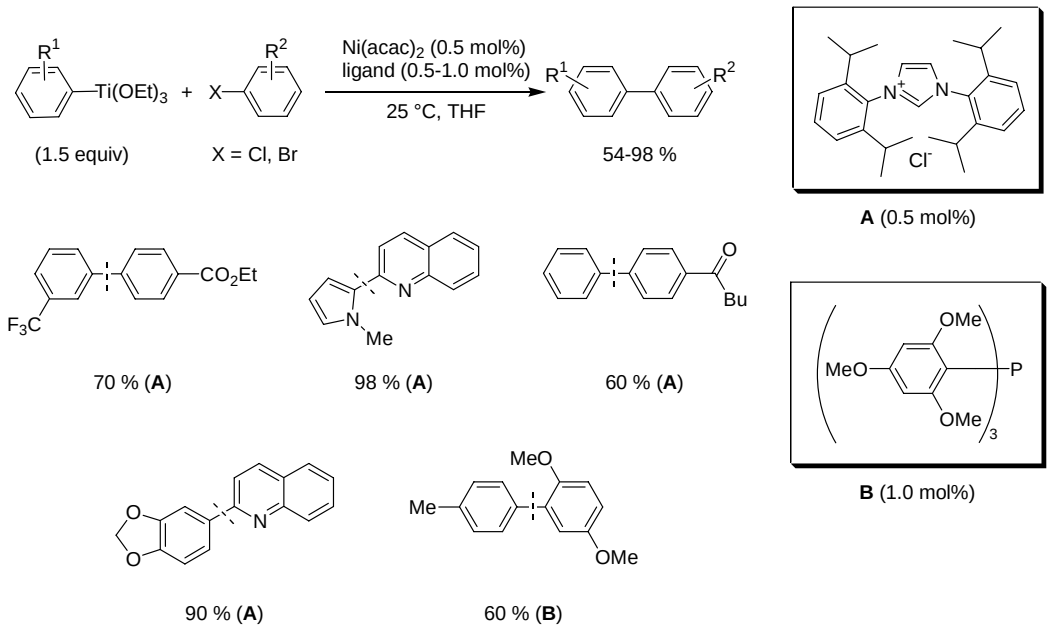


Scheme 54. Nickel-catalyzed aminations of aryl and heteroaryl chlorides.

Expanding the scope of this reaction to primary amines would be interesting. Furthermore, the role of PMHS in the formation of catalytically active system remains unknown and deserves further investigation.

10.2 Nickel-Catalyzed Cross-Coupling Reactions of Aryltitanium (IV) Alkoxides with Aryl Halides

An efficient Ni-catalyzed cross-coupling reaction of aryltitanium reagents with aryl chlorides and bromides was described. The reaction scope is broad and most of the cross-couplings proceeded at 25 °C or even below (Scheme 55).

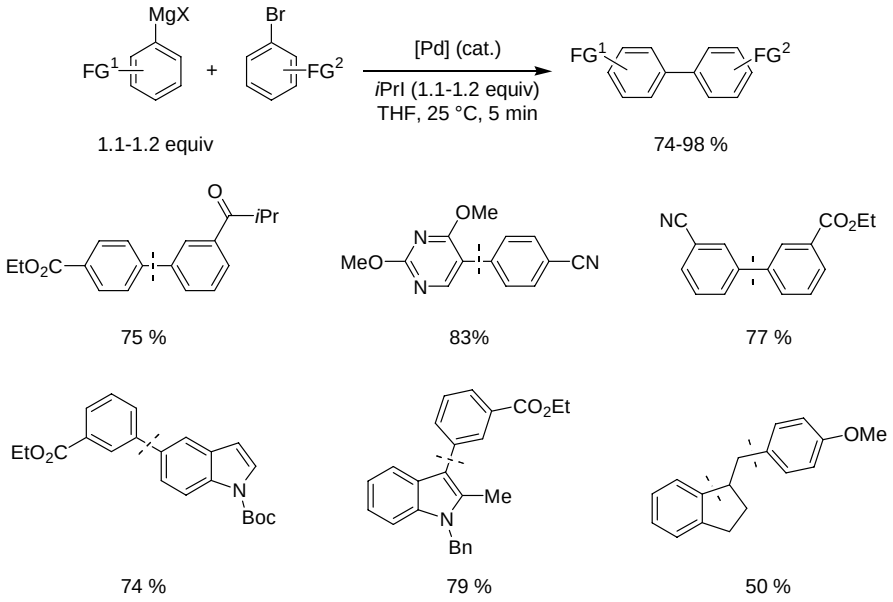


Scheme 55. Nickel-catalyzed cross-coupling reactions of aryltitanium reagents.

Further extensions of these methodology could be directed towards the application of organotitanium compounds obtained from carbotitanation reaction.

10.3 Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents

In a third project, a new *i*PrI catalyzed Kumada cross-coupling reaction was developed. It allows a rapid reaction (25 °C, 5 min) of a wide range of functionalized aryl- and heteroarylmagnesium reagents with aryl bromides and avoids the transmetalation of readily available Grignard reagents to zinc or boron intermediates, leading to a more atom economical Kumada reaction (Scheme 56). These reactions proceed via an radical pathway.



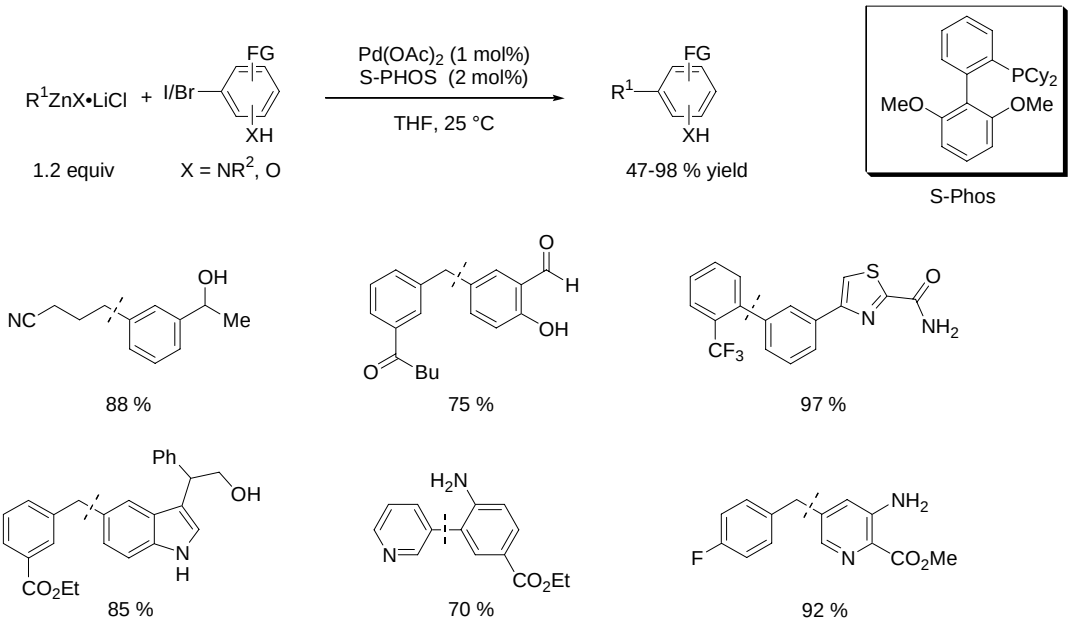
Scheme 56. Kumada cross-coupling reactions in the presence of *i*PrI.

The influence of alkyl iodides in other palladium-catalyzed cross-coupling reactions should be investigated. An extension of the ring-closure/cross-coupling domino-reaction might be challenging in terms of selective ring formation.

10.4 Negishi Cross-Coupling Reactions in the Presence of Acidic Protons

A general efficient protocol for the palladium-catalyzed cross-coupling of organozinc reagents with unsaturated halides bearing relatively acidic protons was developed. No protection or deprotonation by an additional base prior to the cross-coupling reaction of these acidic protons is required. The reaction has a broad scope and could be applied to various unsaturated halides bearing unprotected amide-, amine-, aniline-, alcohol- or even phenol-functions. Using this method, several biologically active compounds were synthesized in excellent yields (Scheme 57). Additionally, a nickel-catalyzed version of this reaction with smaller substrate scope, but more economical was reported. Also the relative reactivity and stability of the used zinc reagents towards NH and OH protons was investigated. Their relative reactivity towards acidic protons was found to be arylzinc halide > alkylzinc halide > benzylic zinc halide.

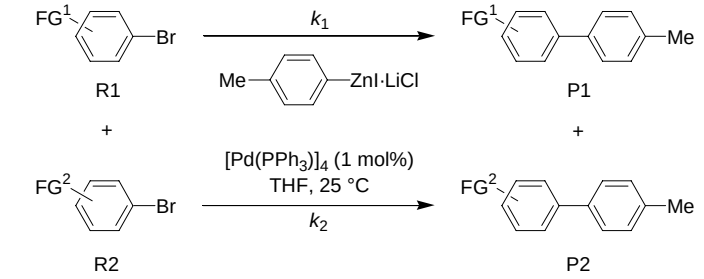
A useful extension would be the application of this method to unprotected heterocycles, especially uracil, purin or other biologically important substrates.



Scheme 57. Negishi cross-coupling reactions in the presence of acidic protons.

10.5 Relatives Rates of Negishi Cross-Coupling Reactions

The relative reaction rates of several substituted aryl bromides in the presence of [$Pd(PPh_3)_4$] (1 mol%) were determined (Scheme 58). Based on the collected data, a more detailed mechansim of the Negishi-reaction cold be obtained (oxidative insertion as rate-limiting step). The reactivity scale should be a useful tool for the synthesis of biaryls.

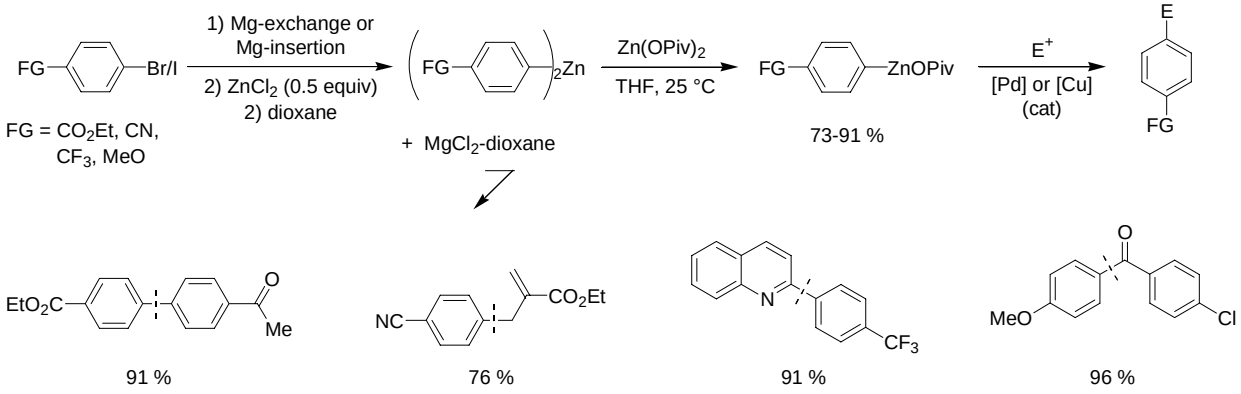


Scheme 58. Relative rates of Negishi cross-coupling reactions.

A similar detailed study on the substitution pattern of arylzinc reagents should allow to gain more insight in the transmetalation step. The extension to other electrophiles, such as aryl chlorides, iodides and triflates, as well as vinyl and heterorayl halides would be useful. Also the behaviour of alkyl or benzylic zinc compounds should be investigated.

10.6 Synthesis and Reactivity of Dry Organozinc Reagents

Moreover, the preparation of dry zinc reagents was developed. These reagents were sufficiently stable for handling on air and long-term storage. Their application in different transition-metal catalyzed reactions was investigated (Scheme 59).

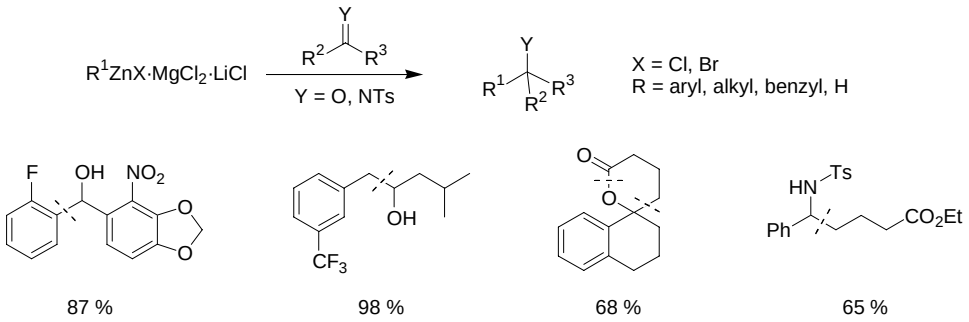


Scheme 59. Synthesis and reactivity of dry zinc reagents.

These reagents might become an alternative to solid boronic acids and derivatives. However, several parameters have to be investigated and optimized. One possibility is the change of the carboxylate counter ion with another suitable carboxylate or alkoxide. The addition of chelating ligands, such as TMEDA, might also be promising. Furthermore, a convenient protocol for isolation and especially the purification has to be developed.

10.7 Mg^{2+}-Promoted Addition of Organozinc Reagents to Carbonyl Compounds

Finally, the addition of organozinc reagents, prepared by direct magnesium insertion in the presence of $ZnCl_2$, to carbonyl compounds was investigated. These mixed zinc-magnesium reagents showed a high reactivity towards aldehydes, ketones and activated imines compared to organozinc halides, prepared by direct zinc insertion or transmetalation. The corresponding alcohols, lactones and amines were obtained in good to excellent yields (Scheme 60).



Scheme 60. Mg^2-Promoted addition of organozinc reagnets to carbonyl compounds

The use of these highly reactive zinc reagents is complementary to the use of organolithium or –magnesium compounds. Especially, the functionalized alkyl and benzylic lithium and magnesium compounds are difficult to prepare and unstable even at low temperatures, whereas the corresponding organozinc reagents can be synthesized and stored at ambient temperature. This allows access to new substances and further applications in this field can be envisioned. Additionally, the addition to chiral sufinylimines would open new applications in the synthesis of chiral amines and lactams.

11. Experimental Part

11.1 General Considerations

All reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame dried glassware under nitrogen. Syringes were used to transfer solvents and reagents, and were purged with nitrogen prior to use.

11.1.1 Solvents

Solvents were dried according to standard methods by distillation over drying agents as stated below and were stored under argon.

Dichloromethane was predried over CaH_2 and distilled from CaH_2.
Diethyl ether was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC (Al_2O_3, 1-3 mm, ICN, Eschwege, Germany).
DME was predried over $CaCl_2$ and distilled from sodium benzophenone ketyl.
DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.
Dioxane was predried over KOH and ditilled from sodium benzophenone ketyl.
Ethanol was treated with magnesium turnings (10 g/L), heated to reflux and distilled.
Methanol was treated with magnesium turnings (10 g/L), heated to reflux and distilled.
NMP was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.
Pyridine was dried over KOH and distilled .
Toluene was predried over $CaCl_2$ and distilled from CaH_2.
THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.
Triethylamine was dried over KOH and distilled.

11.1.2 Chromatoraphy

Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The spots were visiualized by UV light or by staining of the TLC plate with the solution below followed by heating if necessary:

- Phosphormolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12.0 mL) in water (230 mL)
- Iodine absorbed on silica gel
- $KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g), in water (300 mL).
- Ninhydrin (0.3 g) and AcOH (3.0 mL), in butanol (100 mL)

Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm, 230-400 mesh) from Merck.

11.1.3 Analytical Data

NMR-spectra were recorded on *Bruker* ARX 200, AC 300 WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak.
For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), q (quartet), qn (quintett), m (multiplet), as well as br (broad).

Melting points are uncorrected and were measured on a *Büchi* B.540 apparatus.

Infrared spectra were recorded from 4000-400 cm^{-1} on a Nicolet 510 FT-IR or a Perkin 281 IR spectrometer. Samples were measured either as film between sodium chloride plates (film), as potassium bromide tablets (KBr) or neat (ATR, Smiths Detection DuraSampl IR II Diamond ATR).
The absorption bands were reported in wavenumbers (cm^{-1}). For the characterization the following abbreviations were used: br (broad), vs (very strong), s (strong), m (medium), w (weak).

Gas chromatography was performed with machines of type *Hewlett-Packard* 6890 or 5890 series II, using a column of type HP 5 (*Hewlett-Packard*, 5% phenylmethylpolysiloxane;

length: 15 m, diameter: 0.25 mm; film thickness 0.25 µm) The detection was accomplished by using a flame ionization detector. The carrier gas was air Alkanes like decane or tetradecane were used as internal standards.

Mass Spectra were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument for electron impact ionization (EI). High resolution mass spectra (HRMS) were recorded on the same instrument.

11.1.4 Reagents

Commercial available starting materials were purchased and used without further purification. The following compounds were prepared according to literature procedures:
4-Amino-3-bromo-benzoic acid ethyl ester,[137] 3-amino-5-bromo-pyridine-2-carboxylic acid methyl ester,[138] 4-amino-3,5-dibromo-benzoic acid ethyl ester,[139] 1-benzyl-3-iodo-2-methyl-1*H*-indole,[140] (2-bromo-allyl)-phenyl-amine,[141] (4-bromo-benzyl)-butyl-amine,[142] 2-bromo-1-(3-bromo-phenyl)-ethanone,[143] 1-bromo-2-but-3-enyl-benzene,[144] 1-bromo-3-(2-ethoxy-ethoxy)-benzene[145], 2-(5-bromo-1*H*-indol-3-yl)-2-phenyl-ethanol,[146] 4-bromo-*N*-(1-phenyl-ethyl)-benz-amide,[147] (4-bromo-phenyl)-phenyl-methanol,[s.v] 2-(4-bromo-phenyl)-propan-2-ol,[148] 3-bromo-prop-2-en-1-ol,[149] 4,7-dichloro-1,10-phenanthroline,[150] 4,7-dimethoxy-1,10-phenanthroline,[151] 4,7-di-pyrrolidin-1-yl-[1,10]phenanthroline,[s.v] 1,3-dioxa-7,8-diaza-cyclopenta[l]-phenanthrene,[152] 1-iodo-2-but-3-enyl-benzene,[s.v] 2-iodo-cyclopent-2-enol,[153] 1-

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(3-iodo-phenyl)-ethanol,[154] 2-(3-iodo-4-methyl-phenyl)-5-methyl-[1,3,4]oxadiazole,[155] (4-iodo-phenyl)-phenyl-methanol,[156] NHC-ligands **50** and **51**[52] and PEPPSI.[65]
John-Phos, Dave-Phos and S-Phos were purchased from Strem or prepared according to literature procedures.[21,62,66]

CuCN·2LiCl solution was prepared by drying CuCN (8.96 g, 100 mmol) and LiCl (8.48 g, 200 mmol) in a *Schlenk*-flask under vacuum for 5 h at 140 °C. After cooling to 25 °C dry THF (100 mL) was added and the mixture was stirred for 24 h
$ZnCl_2$ (1.0 M) solution was prepared by drying $ZnCl_2$ (68.2 g, 500 mmol) under high vacuum (1 mbar) for 6 h at 150 °C. After cooling to 25 °C, dry THF (500 mL) was added and stirring was continued until the salts were all dissolved.
$ZnCl_2$/LiCl (1.1/1.5 M) solution was prepared by drying LiCl (15.9 g, 375 mmol) and $ZnCl_2$ (37.5 g, 275 mmol) under high vacuum (1 mbar) for 6 h at 150 °C. After cooling to 25 °C, dry THF (250 mL) was added and stirring was continued until the salts were dissolved.
PhMgCl was purchased as a solution in THF from Chemetall.
***i*PrMgCl·LiCl** was purchased as a solution in THF from Chemetall.
***i*PrMgCl** was purchased as a solution in THF from Chemetall.
***n*-BuLi** was purchased as a solution in hexane from Chemetall.
Noncommercial organomagnesium reagents were prepared either by direct magnesium insertion or magnesium insertion in the presence of LiCl into the corresponding aryl halide.[61]

The content of organometallic reagents was determined either by the method of *Paquette* (organolithium or –magnesium reagents)[157] or the method of *Knochel* (organomagnesium or –zinc reagents)[158] prior to use.

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11.2 Typical Procedures (TP)

11.2.1 Typical procedure for the amination of aryl and heteroaryl chlorides (TP1)

A 25 ml sealed tube, equipped with a Teflon screw cap, was loaded with NaOtBu (135 mg, 1.4 mmol), $Ni(acac)_2$ (1.3 mg, 0.005 mmol), 3,5,6,8-tetrabromophenanthroline (**41**, 5.0 mg, 0.01 mmol), 1,2-dimethoxyethane (2 µL, 0.02 mmol) and toluene (1.5 mL). Polymethylhydrosiloxane (0.05 mL, 0.8 mmol) was added and the mixture stirred for 15 min at ambient temperature. The amine (1.2 mmol) and the aryl chloride (1.0 mmol) were added. The tube was sealed with a Teflon screw cap and the mixture heated to 130 °C for the specified time. The reaction mixture was cooled to room temperature, diluted with ether (15 mL), filtered through a short plug of Celite and concentrated in vacuo. The crude product was purified by column chromatography.

11.2.2 Typical Procedure for the Cross-Coupling of Aryl(IV) Alkoxides (TP 2)

In a dry and N_2 flushed 10 mL flask, equipped with a magnetic stirrer and a septum, the corresponding arylmagnesium reagent in THF (1.50 mmol) was slowly added at 0 °C to a solution of $Ti(OEt)_4$ (342 mg, 1.50 mmol) in THF (1 mL). To this mixture, the electrophile (aryl halide, 1.00 mmol) was added, followed by $Ni(acac)_2$ (1.3 mg, 0.005 mmol) and the ligand (I*i*Pr·HCl (**51**) 2.1 mg, 0.005 mmol, or *tris*-(2,4,5-trimethoxyphenyl)phosphine (**49**) 5.3 mg, 0.01mmol). The mixture was stirred at the specified temperature until GC-analysis of a hydrolysed aliquot showed the reaction completion. Then, the reaction mixure was quenched with a sat. aq. NH_4Cl solution, extracted with ether and the crude residue obtained after evaporation of the solvents was purified by column chromatography.

11.2.3 Typical Procedure for the Kumada Cross-Coupling (preparation of the magnesium reagent by I/Mg-exchange, TP 3)

To a solution of *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF), cooled to the specified temperature, was added the corresponding aryl iodide (3.3 mmol). The reaction mixture was stirred for at this temperature until the reaction was complete (checked by GC-analysis of reaction aliquots). Then, the magnesium reagent was slowly added via a teflon canula to a solution of the electrophile (aryl bromide 3 mmol) and the palladium catalyst in THF (3 mL). The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.2.4 Typical Procedure for the Kumada Cross-Coupling (preparation of the magnesium reagent by Br/Mg-exchange, TP 4)

To a solution of *i*PrMgCl·LiCl (3.5 mL, 3.78 mmol, 1.08 M in THF), cooled to the specified temperature, was added the corresponding aryl bromide (3.3 mmol). The reaction mixture was stirred for at this temperature until the reaction was complete (checked by GC-analysis of reaction aliquots). Then, the magnesium reagent was slowly added via a teflon canula to a solution of the electrophile (aryl bromide, 3 mmol), the palladium catalyst in THF (3 mL). The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.2.5 Typical Procedure for the Kumada Cross-Coupling (preparation of the magnesium reagent by magnesium insertion, TP 5)

To the arylmagesium reagent, prepared by insertion (3.3 mmol)[61] was added *i*PrI (561 mg, 3.3 mmol). The solution was stirred for 5 min at 25 °C and then added slowly via a teflon canula to a solution of the electrophile (aryl bromide 3 mmol) and the palladium catalyst in

THF (3 mL). The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.2.6 Typical Procedure for the Palladium-Catalyzed Cross-Coupling of Organozinc Reagents with Amines, Anilines and Indoles (TP 6)

A dry and N_2-flushed 20 mL Schlenk-tube was charged with the electrophile (aryl halide or alkenyl halide, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) and THF (2 mL). After stirring the reaction mixture for 5 min, the organozinc reagent (3.6 mmol) was added. The reaction mixture was stirred for the specified time at the specified temperature. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether (3 x 25 mL). The combined organic phases were washed with an aq. thiourea solution and dried (Na_2SO_4). Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.2.7 Typical Procedure for the Palladium-Catalyzed Cross-Coupling of Organozinc Reagents with Amides, Alcohols and Phenols (TP 7)

A dry and N_2-flushed 20 mL Schlenk-tube was charged with the electrophile (aryl halide or alkenyl halide, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) and THF (2 mL). After stirring the reaction mixture for 5 min, the organozinc reagent (3.6 mmol) was added slowly over 90 min via syringe pump. The reaction mixture was stirred for additional 30-60 min. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed with an aq. thiourea solution and dried (Na_2SO_4). Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.2.8 Typical Procedure for the Nickel-Catalyzed Cross-Coupling of Arylzinc Reagents with Anilines and Amines (TP 8)

A dry and N_2-flushed 20 mL Schlenk-tube was charged with the aryl bromide (3 mmol), $Ni(acac)_2$ (15.4 mg, 0.06 mmol), 2,2'-bipyridine (4.7 mg, 0.09 mmol) and THF (2 mL). After stirring the reaction mixture for 5 min, the arylzinc reagent (3.6 mmol) was added slowly over 90 min via syringe pump. The reaction mixture was stirred for the specified time at the specified temperature. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.2.9 Typical Procedure for the Nickel-Catalyzed Cross-Coupling of Benzylic Zinc Reagents with Anilines (TP 9)

A dry and N_2-flushed 20 mL Schlenk-tube was charged with the aryl bromide (2 mmol), NMP (0.4 mL), PPh_3 (0.2 mmol), $Ni(acac)_2$ (0.05 mmol) and THF (2 mL). The reaction mixture was heated to 60 °C and the benzylic zinc chloride (2.4 mmol) was added slowly over 30 min via syringe pump. The reaction mixture was stirred for 0.5 h at 60 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.2.10 Typical Procedure for the Palladium-Catalyzed Cross-Coupling of Solid Zinc Reagents (TP 10)

A dry and N_2-flushed 20 mL Schlenk-tube is charged with the solid zinc reagent (2.4 mmol), the electrophile (aryl halide, 2.0 mmol) and THF (5 mL). The reaction mixture is stirred until all solids are dissolved. Then PEPPSI (13.6 mg, 0.02 mmol) is added and the reaction mixture stirred for the specified time at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed

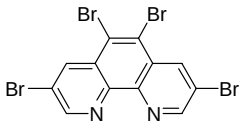
with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.2.11 Typical Procedure for the Addition of Organozinc Compunds to Carbonyl Derivatives

A dry and N_2-flushed 20 mL Schlenk-tube is charged with the electrophile (carbonyl compound, 1.5 mmol) and THF (2 mL). The zinc reagent (1.8 mmol) is added and the reaction mixture was stirred for the specified time at the specified temperature. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases are with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography yielded the product.

11.3 Nickel-Catalyzed Aminations of Aryl Chlorides

11.3.1 Preparation of 3,5,6,8-tetrabromophenanthroline (41)



1,10-phenanthroline monohydrate (4.0 g, 20 mmol) was dissolved in distilled $SOCl_2$ (200 mL). (Note: the presence of small ammounts of water seems to be important. In our hands the reaction with anhydrous 1,10-phenanthroline failed, while the addition of a few drops of water led to similar results as the use of 1,10-phenanthrolin monohydrate). Bromine (6.2 mL 120 mmol) was added slowly by a syringe. The mixture was refluxed for 40 h and cooled to room temperature. The yellow precipitate was filtered off and washed with aqueous NH_3 until the washing liquids became colorless. The white solid was redissolved in $CHCl_3$, washed with brine and dried over Na_2SO_4. Removal of the solvents gave 4.86 g of **41** (49 %) as colorless solid. The analytical data are in accordance with the literature.[42]

m.p.: 355-356 °C.

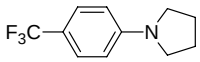
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 9.16 (d, J = 2.5 Hz, 2H), 8.89 (d, J = 2.5 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 152.4, 143.5, 138.9, 129.5, 125.1, 122.0.

MS (EI, 70 eV), *m/z* (%): 496 (100) [M^+], 415 (43), 336 (45), 257 (12), 177 (5).

11.3.2 Preparation of Aryl- and Heteroarylamines

1-(4-Trifluoromethylphenyl)-pyrrolidine (33a)



Prepared according to **TP 1** from 1-chloro-4-trifluoromethyl-benzene (**31a**, 181 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded **33a** as a colorless solid (204 mg, 95 %). The analytical data are in accordance with the literature.[159]

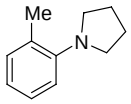
m.p.: 96-97°C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.44 (dd, *J* = 9.0, 0.5, 2 H), 6.56 (dd, *J* = 9.0, 0.5 Hz, 2 H), 3.32 (t, *J* = 6.6 Hz, 4 H), 2.04 (tt, *J* = 9.0, 3.2 Hz, 4 H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 149.7, 126.4, 125.3 (q, *J* = 270 Hz), 116.7 (q, *J* = 32 Hz), 110.9, 47.5, 25.4.

MS (EI, 70 eV), *m/z* (%): 215 (65) [M^+], 214 (100), 172 (16), 159 (43), 145 (25).

1-*o*-Tolylpyrrolidin (33b)



Prepared according to **TP 1** from 2-chloro-toluene (**31b**, 127 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded **32a** as a colorless oil (134 mg, 85 %). The analytical data are in accordance with the literature.[160]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.15-7.10 (m, 2 H), 6.92-6.82 (m, 2 H), 3.23-3.18 (m, 4 H), 2.34 (s, 3 H), 1.97-1.92 (m, 4 H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 149.4, 131.6, 128.7, 126.2, 120.2, 115.7, 51.0, 24.9, 20.5.

MS (EI, 70 eV), *m/z* (%): 161 (81) [M^+], 160 (100), 132 (65), 118 (43), 91 (26).

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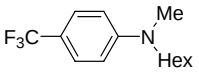
Hexyl-methyl-(4-trifluoromethyl-phenyl)-amine (33c)



Prepared according to **TP 1** from 1-chloro-4-trifluoromethyl-benzene (**31a**, 181 mg, 1.0 mmol) and *N*-methyl-hexylamine (**32b**, 138 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded **33c** as a colorless oil (250 mg, 96 %).

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.44 (d, *J* = 8.8 Hz, 2 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 3.35 (t, *J* = 7.6 Hz, 2 H), 2.98 (s, 3 H), 1.61–1.57 (m, 2 H), 1.36-1.31 (m, 6 H), 0.91 (t, *J* = 6.7 Hz, 3 H).

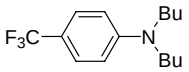
13C-NMR (CDCl3, 150 MHz, 25°C): δ = 151.0, 126.2 (q, J = 7.5 Hz), 125.1 (q, J = 270.0 Hz), 116.7 (q, J = 32.6 Hz), 110.6, 52.3, 38.1, 31.5, 26.6, 26.5, 22.5, 13.8.

MS (EI, 70 eV), m/z (%): 259 (11) [M^+], 240 (3), 189 (11), 188 (100), 172 (4).

HRMS m/z : calcd. for $C_{14}H_{20}NF_3$ 259.1548, found 259.1549.

IR (cm-1): 2930 (w), 2859 (w), 1616 (s), 1534 (m), 1485 (w), 1317 (vs), 1186 (m), 1158 (m), 1103 (vs), 1062 (vs), 1006 (w), 939 (w), 822 (s) 640 (w).

Dibutyl-(4-trifluoromethyl-phenyl)-amine (33d)



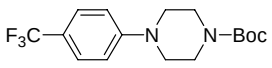
Prepared according to **TP 1** from 1-chloro-4-trifluoromethyl-benzene (**31a**, 181 mg, 1.0 mmol) and dibutylamine (**32c**, 155 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded **33d** as a colorless oil (216 mg, 79 %). The analytical data are in accordance with the literature.[161]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ 7.40 (d, *J* = 9.1 Hz, 2H), 6.62 (d, *J* = 9.1 Hz, 2H), 3.30 (t, *J* = 7.3 Hz, 4 H), 1.65-1.50 (m, 4 H), 1.45-1.27 (m, 4 H), 1.00-0.85 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 150.2, 126.5 (q, *J* = 3.9 Hz), 125.3 (q, *J* = 269.8 Hz), 116.3 (q, *J* = 32.6 Hz), 50.7, 29.2, 20.3, 13.9 .

MS (EI, 70 eV), *m/z* (%): 273 (27) [M^+], 230 (97), 188 (100), 174 (49), 145 (18).

4-(4-Trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (33e)



[161] M. Beller, T. H. Riermeier, C. P. Reisinger, W. A. Herrmann, *Tetrahedron Lett.* **1997**, *38*, 2073.

Prepared according to **TP 1** from 1-chloro-4-trifluoromethyl-benzene (**31a**, 181 mg, 1.0 mmol) and piperazine-1-carboxylic acid tert-butyl ester (**32d**, 224 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33e** as a colorless solid (304 mg, 92 %).

m.p.:128.3-129.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.49 (d, *J* = 8.7 Hz, 2 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 3.58 (t, *J* = 5.2 Hz, 4 H), 3.24 (t, *J* = 5.2 Hz, 4 H), 1.49 (s, 9 H).

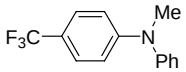
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 154.5, 153.2, 126.4, (q, *J* = 3.7 Hz), 124.6 (q, *J* = 270.3 Hz), 121.0, (q, *J* = 32.7 Hz), 114.9, 80.1, 48.1 28.4.

MS (EI, 70 eV), *m/z* (%): 330 (39) [M^+], 274 (100), 257(35), 200 (77), 188 (95).

HRMS *m/z* : calcd. for $C_{16}H_{21}F_3N_2O_2$ 330.1555, found 330.1568.

IR (cm^{-1}): 3002 (w), 2869 (w), 2821 (w), 1673 (s), 1615 (s), 1526 (m), 1482 (s), 1392 (m), 1327 (s), 1285 (m), 1232 (vs), 1157 8vs), 1105 (vs), 1070 (vs), 1000 (s), 924 (s), 830 (s), 772 (s), 632 (s).

Methyl-phenyl-(4-trifluoromethyl-phenyl)-amine (33f)



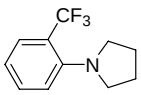
Prepared according to **TP 1** from 1-chloro-4-trifluoromethyl-benzene (**31a**, 181 mg, 1.0 mmol) and *N*-methyl-aniline (**32e**, 128 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33f** as a colorless oil (156 mg, 62 %). The analytical data are in accordance with the literature.[162]

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.44-7.38 (m, 4 H), 7.21-7.18 (m , 3 H), 6.85 (d, *J* = 8.8 Hz), 3.36 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 150 MHz, 25°C): δ = 151.5, 147.7, 129.8, 126.2 (q, *J* = 3.8 Hz), 125.3, 124.9, 124.8 (q, *J* = 270.5 Hz), 119.9 (q, *J* = 32.6 Hz), 40.2.

MS (EI, 70 eV), *m/z* (%): 252 (12) [M^+] , 215 (100), 250 (55), 167 (8), 145 (9).

1-(2-Trifluoromethyl-phenyl)-pyrrolidine (33g)



[162] L. Ackermann, R. Born, *Angew. Chem. Int. Ed.* **2005**, *44*, 2444.

Prepared according to **TP 1** from 1-chloro-2-trifluoromethyl-benzene (**31c**, 181 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded **33g** as a colorless solid (183 mg, 85 %).

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.58 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.38-7.35 (m, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.85 (t, *J* = 7.5 Hz, 1H), 3.33 (t, *J* = 6.4 Hz, 4 H), 1.96-1.94 (m, 4 H).

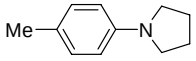
^{13}C-NMR ($CDCl_3$, 150 MHz, 25°C): δ = 148.2, 132.2, 128.2 (q, *J* = 6.3 Hz), 125.0 (q, *J* = 272.0 Hz), 117.9, 117.6, 51.6 (q, *J* = 2.7 Hz), 25.6.

MS (EI, 70 eV), *m/z* (%): 215 (48) [M^+], 214 (100), 172 (19), 159 (48), 145 (22).

HRMS *m/z* : calcd. for $C_{11}H_{12}F_3N$ 215.0922, found 215.0924.

IR (cm^{-1}): 2972 (w), 1606 (m), 1565 (w), 1488 (m), 1451 (s), 1346 (m), 1316 (s), 1263 (m), 1238 (m), 1173 (m), 1134 (s), 1094 (vs), 1063 (s), 1030 (vs), 953 (m) 840 (w), 747 (s), 661 (m).

1-*p*-Tolyl-pyrrolidine (33h)



Prepared according to **TP 1** from 4-chloro-toluene (**31d**, 127 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33h** as a colorless solid (133 mg, 83 %). The analytical data are in accordance with the literature.[163]

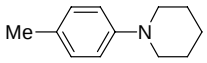
m.p.: 41-43 °C

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.05 (d, *J* = 8.3 Hz, 2 H), 6.53 (br s, 2 H), 3.29-3.24 (m, 4 H), 2.26 (s, 3H), 2.02-1.98 (m, 4 H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 146.2, 129.7, 124.6, 111.9, 47.9, 25.4, 20.3

MS (EI, 70 eV), *m/z* (%): 161 (69) [M^+], 160 (100), 133 (4), 118 (10), 105 (30).

1-*p*-Tolyl-piperidine (33i)



Prepared according to **TP 1** from 4-chloro-toluene (**31d**, 127 mg, 1.0 mmol) and piperidine (**32f**, 102 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after

[163] J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6054.

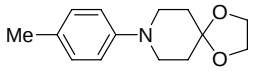
evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33i** as a colorless oil (152 mg, 87 %). The analytical data are in accordance with the literature.[164]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.06 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 3.10 (t, *J* = 5.4 Hz, 4 H), 2.27 (s, 3 H), 1.76-1.68 (m, 4 H), 1.60-1.52 (m, 2 H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 150.3, 129.5, 128.7, 116.9, 51.3, 25.9, 24.3, 20.4.

MS (EI, 70 eV), *m/z* (%): 175 (68) [M^+], 174 (100), 134 (12), 119 (28), 91 (24).

8-*p*-Tolyl-1,4-dioxa-8-aza-spiro[4.5]decane (33j)



Prepared according to **TP 1** from 4-chloro-toluene (**31d**, 127 mg, 1.0 mmol) and 1,4-dioxa-8-aza-spiro[4.5]decane (**32g**, 172 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33j** as a colorless solid (191 mg, 82 %). The analytical data are in accordance with the literature.[165]

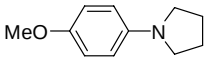
m.p.: 66.2-67.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.05 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.98 (s, 4H), 3.27-3.23 (m, 4H), 2.25 (s, 3H), 1.86-1.82 (m, 4H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 149.0, 129.6, 129.0, 117.1, 107.2, 64.3, 48.4, 34.6, 20.4.

MS (EI, 70 eV), *m/z* (%): 233 (100) [M^+], 188 (23), 172 (18), 146 (62), 119 (92).

1-(4-Methoxy-phenyl)-pyrrolidine (33k)



Prepared according to **TP 1** from 4-chloro-anisole (**31d**, 139 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33k** as a colorless solid (145 mg, 82 %). The analytical data are in accordance with the literature.[166]

m.p.: 44-46°C.

^{1}H-NMR ($CDCl_3$, 200 MHz, 25°C): δ = 6.86 (d, *J* = 9.0 Hz, 2 H), 6.54 (d, *J* = 9.0 Hz, 2 H), 3.76 (s, 3 H), 3.24 (t, *J* = 6.5 Hz, 4 H), 2.03-1.96 (m, 4 H).

^{13}C-NMR ($CDCl_3$, 150 MHz, 25°C): δ = 150.7, 143.2, 114.9, 112.6, 56.1, 48.1, 25.3.

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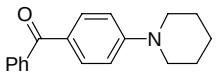
[164] T. Tsuji, K. T. Huh, Y. Ohsugi, Y. Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365.
[165] S. Urgaonkar, J.-H. Xu, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 8416
[166] S. C. Shim, K. T. Huh, W. H. Park, *Tetrahedron* **1986**, *42*, 259.

MS (EI, 70 eV), *m/z* (%): 177 (69) [M^+], 162 (100), 134 (9), 120 (13), 92 (5).

Phenyl-(4-piperidin-1-yl-phenyl)-methanone (33l)



Prepared according to **TP 1** from 4-chloro-benzophenone (**31f**, 217 mg, 1.0 mmol) and piperidine (**32f**, 102 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33l** as a light yellow solid (215 mg, 81 %). The analytical data are in accordance with the literature.[167]

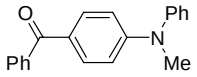
m.p.: 99.8-101.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.80-7.72 (m, 4 H), 7.56-7.42 (m, 3 H), 6.90-6.85 (m, 2 H), 3.38 (t, *J* = 5.6 Hz, 4 H), 1.73-1.65 (m, 6 H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 195.1, 154.3, 139.1, 132.6, 131.2, 129.5, 128.0, 126.2, 113.1, 48.6, 25.4, 24.4.

MS (EI, 70 eV), *m/z* (%): 265 (100) [M^+], 224 (10), 188(22), 132 (24), 105 (20).

[4-(Methyl-phenyl-amino)-phenyl]-phenyl-methanone (33m)



Prepared according to **TP 1** from 4-chloro-benzophenone (**31f**, 5.42 g, 25 mmol) and *N*-metyhl-aniline (**32e**, 3.21 g, 30 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33m** as a light yellow solid (6.75 g, 94 %). The analytical data are in accordance with the literature.[168]

m.p.: 81-82 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.69-7.64 (m, 4 H), 7.48-7.31 (m, 5 H), 7.18-7.13 (m, 3 H), 6.71 (dt, *J* = 9.0, 2.4 Hz, 2 H), 3.32 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 195.1, 152.5, 147.3, 139.0, 132.3, 131.3, 129.9, 129.5, 128.0, 126.7, 126.1, 125.6, 113.4, 40.2.

MS (EI, 70 eV), *m/z* (%): 287 (100) [M^+], 210 (74), 167 (29), 105 (8), 77 (20).

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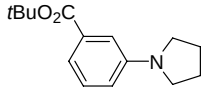
[167] A. H. Khuthier, K. Y. Al-Mallah, S. Y. Hanna, N. A. I. Abdulla, *J. Org. Chem.* **1987**, *52*, 1710.
[168] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217.

3-Pyrrolidin-1-yl-benzoic acid tert-butyl ester (33n)



Prepared according to **TP 1** from 3-chloro-benzoic acid tert-butyl ester (**31g**, 213 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **33n** as a colorless oil (234 mg, 95 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.32-7.28 (m, 2 H), 7.24-7.22 (m, 2 H), 6.75-6.71 (m, 1 H), 3.37-3.32 (m, 4 H), 2.04 (qn, *J* = 3.3 Hz, 4 H), 1.62 (s, 9 H).

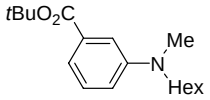
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.6, 147.8, 132.7, 128.8, 116.3, 115.5, 112.3, 80.5, 47.7, 28.2, 25.5.

MS (EI, 70 eV), *m/z* (%): 247 (19) [M^+], 191 (100), 191 (92), 174 (13), 135 (12).

HRMS *m/z* : calcd. for $C_{15}H_{21}NO_2$ 247.1572, found 247.1572.

IR (cm^{-1}):): 2932 (m), 1721 (s), 1597 (s), 1574 (w), 1498 (s), 1453(m), 1341 (s), 1245 (s), 1172(s), 1134 (s), 949 (m), 853 (m), 736 (vs).

3-(Hexyl-methyl-amino)-benzoic acid tert-butyl ester (33o)



Prepared according to **TP 1** from 3-chloro-benzoic acid tert-butyl ester (**31g**, 213 mg, 1.0 mmol) and *N*-methyl-hexylamine (**32b**, 138 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **33o** as a colorless oil (253 mg, 87 %).

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.27 (s, 1 H), 7.21-7.14 (m, 2 H), 6.75 (dd, *J* = 8.1, 2.3 Hz, 1 H), 3.25 (t, *J* = 7.6 Hz, 2 H), 2.88 (s, 3 H), 1.52-1.47 (m, 2 H), 1.51 (s, 9 H), 1.25-1.22 (m, 6 H), 0.82 (t, *J* = 6.8 Hz, 3 H).

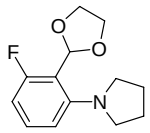
^{13}C-NMR ($CDCl_3$, 150 MHz, 25°C): δ = 166.5, 149.2, 132.7, 128.8, 116.7, 115.9, 112.7, 80.5, 52.7, 38.3, 31.7, 28.2, 26.8, 26.6, 22.6, 14.0.

MS (EI, 70 eV), *m/z* (%): 291 (16) [M^+], 235 (9), 220 (18), 218 (12), 164 (100).

HRMS *m/z* : calcd. for $C_{18}H_{29}NO_2$ 291.2198, found 291.2201.

IR (cm^{-1}): 2928 (m), 1710 (s), 1601 (s), 1577 (w), 1495 (s), 1450(m), 1366 (s), 1279 (s), 1253(s), 1165(s), 1112 (s), 995 (m), 850 (m), 750 (vs).

1-(2-[1,3]Dioxolan-2-yl-3-fluoro-phenyl)-pyrrolidine (33p)



Prepared according to **TP 1** from 2-(2-chloro-6-fluoro-phenyl)-[1,3]dioxolane (**31h**, 203 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33p** as a colorless oil (229 mg, 97 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.20-7.12 (m, 1H), 6.73-6.50 (m, 2H), 6.26 (d, *J* =1.3 Hz, 1H), 4.27-4.14 (m, 2H), 4.13-3.93 (m, 2H), 3.21-3.17 (m, 4H), 1.92-1.87 (m, 4H).

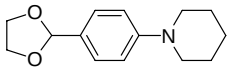
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 161.6 (d, *J* = 248.7 Hz), 152.1 (d, *J* = 7.3 Hz), 130.8 (d, *J* = 7.0 Hz), 130.3 (d, *J* = 10.8 Hz), 112.3 (d, *J* = 3.0 Hz), 108.9 (d, *J* = 22.5 Hz), 100.4 (d, *J* =2.1 Hz), 65.8, 53.2, 24.9.

MS (EI, 70 eV), *m/z* (%): 237 (6) [M^+], 163 (9), 147 (9), 137 (28), 124 (100).

HRMS *m/z* : calcd. for $C_{13}H_{16}FNO_2$ 237.1165, found 237.1163.

IR (cm^{-1}): 2967 8w), 2876 (w), 1610 (s), 1574 (m), 1398 (w), 1353 (w), 1238 (m), 1198 (s), 1137 (m), 1088 (vs), 1056 (vs), 1023 (s).

1-(4-[1,3]Dioxolan-2-yl-phenyl)-piperidine (33q)



Prepared according to **TP 1** from 2-(4-chloro-phenyl)-[1,3]dioxolane (**31i**, 185 mg, 1.0 mmol) and piperidine (**32f**, 102 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33q** as a colorless solid (212 mg, 91 %).

m.p.: 40.5-42.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.34 (ddd, *J* = 9.0, 2.7, 2.4 Hz, 2H), 6.91 (ddd, *J* = 9.0, 2.7, 2.4 Hz, 2H), 5.73 (s, 1H), 4.14-4.09 (m, 2H), 4.05-3.97 (m, 2H), 3.17 (t, *J* = 5.7 Hz, 4H), 1.72-1.65 (m, 4H), 1.61-1.54 (m, 2H).

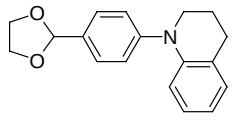
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 152.9, 127.7, 127.3, 115.9, 104.0, 65.1, 50.3, 25.6, 24.3.

MS (EI, 70 eV), *m/z* (%): 233 (83) [M^+], 232 (100),188 (17), 174 (43), 161 (16).

HRMS *m/z* : calcd. for $C_{14}H_{19}NO_2$ 233.1416, found 233.1397.

IR (cm^{-1}): 2961 (w), 2933 (m), 2895 (m), 2805 (m), (1612 (s), 1576 (w), 1517 (s), 1451 (m), 1384 (s), 1337 (s), 1312 (m), 1215 (vs), 1183 (s), 1125 (s), 1057 (vs), 1023 (s), 987 (s).

1-(4-[1,3]Dioxolan-2-yl-phenyl)-1,2,3,4-tetrahydro-quinoline (33r)



Prepared according to **TP 1** from 2-(4-chloro-phenyl)-[1,3]dioxolane (**31i**, 185 mg, 1.0 mmol) and 1,2,3,4-tetrahydro-quinoline (**32h**, 160 mg, 1.2 mmol). Reaction time: 42 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33r** as a colorless solid (149 mg, 53 %).

m.p.: 68.8-69.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.38-7.34 (m, 2H), 7.16 (dt, *J* = 8.8, 2.2 Hz, 2H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.88-6.82 (m, 1H), 6.74 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.67-6.62 (m, 1H), 5.70 (s, 1H), 4.10-4.02 (m, 2H), 4.01-3.91 (m, 2H), 3.57-3.52 (m, 2H), 2.77-2.73 (m, 2H), 1.98-1.90 (m, 2H).

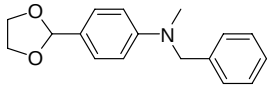
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 149.3, 143.9, 132.3, 129.3, 127.5, 126.3, 125.3, 123.7, 122.3, 121.4, 118.8, 116.5, 103.7, 65.3, 50.5, 27.6, 22.8.

MS (EI, 70 eV), *m/z* (%): 281 (100) [M^+], 259 (51), 233 (15), 221 (40), 209 (27).

HRMS *m/z* : calcd. for $C_{18}H_{19}NO_2$ 281.1416, found 281.1405.

IR (cm^{-1}): 3071 (w), 2940 (w), 2876 (m), 2841 (w), 1612 (w), 1594 (m), 1569 (m), 1514 (m), 1490 (s) 1454 (m), 1383 (m), 1348 (m), 1327 (s), 1262 (s), 1242 (s), 1225 (s), 1119 (m), 1075 (vs).

Benzyl-(4-[1,3]dioxolan-2-yl-phenyl)-methyl-amine (33s)



Prepared according to **TP 1** from 2-(4-chloro-phenyl)-[1,3]dioxolane (**31i**, 185 mg, 1.0 mmol) and *N*-methyl-benzylamine (**32i**, 144 mg, 1.2 mmol). Reaction time: 42 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **33s** as a colorless solid (191 mg, 71 %).

m.p.: 51.5-52.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.37-7.21 (m, 7H), 6.79-6.73 (m, 2H), 5.75 (s, 1H), 4.57 (s, 2H), 4.16-4.08 (m, 2H), 4.06-3.98 (m, 2H), 3.05 (s, 3H).

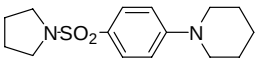
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 150.4, 138.6, 128.8, 128.5, 127.6, 126.8, 126.6, 125.2, 111.8, 104.2, 65.1, 38.5.

MS (EI, 70 eV), *m/z* (%): 269 (95) [M^+], 210 (38), 197 (21), 192 (19), 91 (100).

HRMS *m/z* : calcd. for $C_{17}H_{19}NO_2$ 269.1416, found 269.142.

IR (cm^{-1}): 3086 (w), 3022 (w), 2951 (w), 2887 8m), 1877 (w), 1613 (s), 1569 (w), 1529 (s), 1494 (m), 1452 (m), 1396 (s), 1357 (s), 1307 (m), 1257 (m), 1221 (s), 1182 (s), 1118 (m), 1067 (vs).

1-[4-(Pyrrolidine-1-sulfonyl)-phenyl]-piperidine (33t)



Prepared according to **TP 1** from 1-(4-chloro-benzenesulfonyl)-pyrrolidine (**31j**, 246 mg, 1.0 mmol) and piperidine (**32f**, 102 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **33t** as a colorless solid (291 mg, 96 %).

m.p.: 142.7-144.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.64 (ddd, *J* = 9.6, 2.9, 2.5 Hz, 2H), 6.88 (ddd, *J* = 9.6, 2.9, 2.5 Hz, 2H), 3.33-3.39 (m, 4H), 3.21-3.17 (m, 4H), 1.75-1.58 (m, 10H).

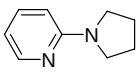
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 154.0, 129.3, 124.1, 113.8, 48.7, 47.8, 25.4, 25.1, 24.2.

MS (EI, 70 eV), *m/z* (%): 294 (90) [M^+], 224 (18), 207 (44), 176 (79), 160 (100).

HRMS *m/z* : calcd. for $C_{15}H_{22}N_2O_2S$ 294.1402, found 294.1409.

IR (cm^{-1}): 2937 (m), 2851 (m), 1587 (s), 1505 (m), 1449 (m), 1360 (m), 1327 (vs), 1247 (s), 1155 (vs), 1125 (vs), 1092 (vs), 1062 (s), 1004 (vs), 917 (s), 813 (s).

2-Pyrrolidin-1-yl-pyridine (43a)



Prepared according to **TP 1** from 2-chloro-pyridine (**42a**, 114 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **43a** as a colorless oil (119 mg, 80 %). The analytical data are in accordance with the literature.[169]

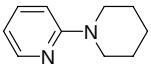
^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 8.09-8.08 (m, 1 H), 7.35-7.33 (m, 1 H), 6.44-6.41 (m, 1 H), 6.27 (d, *J* = 8.5 Hz), 3.37 (t, *J* = 6.6 Hz, 4 H), 1.95-1.91 (m, 4 H).

^{13}C-NMR ($CDCl_3$, 150 MHz, 25°C): δ = 157.3, 148.2, 136.8, 111.0, 106.4, 46.6, 25.5.

MS (EI, 70 eV), *m/z* (%): 148 (42) [M^+], 120 (34), 119 (100), 93 (13), 78 (22).

[169] M. C. Venuti, O. Ort, *Synthesis*, **1988** *12*, 985.

3,4,5,6-Tetrahydro-2*H*-[1,2']bipyridinyl (43b)



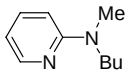
Prepared according to **TP 1** from 2-chloro-pyridine (**42a**, 114 mg, 1.0 mmol) and piperidine (**32f**, 102 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **43b** as a colorless oil (148 mg, 92 %). The analytical data are in accordance with the literature.[170]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.17-8.14 (m, 1H), 7.45-7.39 (m, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 6.53 (dd, *J* = 7.1, 5.3 Hz, 1H), 3.52-3.49 (m, 4H), 1.63 (br s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 159.7, 147.9, 137.3, 112.4, 107.1, 46.3, 25.5, 24.7 .

MS (EI, 70 eV), *m/z* (%): 162 (75) [M^+], 133 (100), 119 (51), 107 (49), 79(79).

Butyl-methyl-pyridin-2-yl-amine (43c)



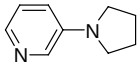
Prepared according to **TP 1** from 2-chloro-pyridine (**42a**, 114 mg, 1.0 mmol) and *N*-methyl-butylamine (**32j**, 105 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **43c** as a colorless oil (105 mg, 64 %). The analytical data are in accordance with the literature.[171]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.16-8.13 (m, 1 H), 7.41 (ddd, *J* = 10.6, 7.1, 2.0 Hz, 1 H), 6.51-6.45 (m, 2H), 3.49 (t, *J* = 7.4 Hz, 2H), 3.04 (s, 3H), 1.64-1.52 (m, 2H), 1.41-1.29 (m, 2 H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 158.6, 147.9, 137.0, 111.0, 105.6, 49.9, 36.2, 29.4, 20.3, 14.0.

MS (EI, 70 eV), *m/z* (%): 164 (21) [M^+], 135 (13), 121 (100), 107 (15), 78 (23).

3-Pyrrolidin-1-yl-pyridine (43d)



Prepared according to **TP 1** from 3-chloro-pyridine (**42b**, 114 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2/MeOH 25:25:1) yielded

[170] S. Urgaonkar, M. Nagarajan, J. G. Verkade, *Org. Lett.* **2003**, *5*, 815

[171] L. Strekowski, M. Dworniczak, A. Kowalewski, *Polish Journal of Chemistry* **1980**, *54*, 1557.

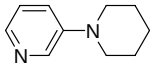
43d as a colorless oil (132 mg, 89 %). The analytical data are in accordance with the literature.[172]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.98-7.90 (m, 2 H), 7.09 (dd, *J* = 4.6, 3.7 Hz, 1 H), 6.82-6.77 (m, 1 H), 3.31-3.25 (m, 4 H), 2.05-1.98 (m, 4 H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 144.0, 137.2, 134.6, 123.7, 117.9, 47.5, 25.6.

MS (EI, 70 eV), *m/z* (%): 148 (81) [M^+], 147 (100), 119 (28), 105 (13), 92 (23).

3,4,5,6-Tetrahydro-2*H*-[1,3']bipyridinyl (43e)



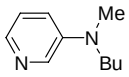
Prepared according to **TP 1** from 3-chloro-pyridine (**42a**, 114 mg, 1.0 mmol) and piperidine (**32f**, 102 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2/MeOH 25:25:1) yielded **43e** as a colorless oil (158 mg, 98 %). The analytical data are in accordance with the literature.[170]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.27 (d, *J* = 2.7 Hz, 1H), 8.01 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.16-7.06 (m, 2H), 3.15 (t, *J* = 5.5 Hz, 4H), 1.71-1.64 (m, 4H), 1.60-1.51 (m, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 147.6, 139.9, 138.9, 123.3, 122.5, 49.8, 25.5, 24.0.

MS (EI, 70 eV), *m/z* (%): 162 (70) [M^+], 161 (100), 133 (12), 121 (20), 106 (51).

Butyl-methyl-pyridin-3-yl-amine (43f)



Prepared according to **TP 1** from 3-chloro-pyridine (**42b**, 114 mg, 1.0 mmol) and *N*-methyl-butylamine (**32j**, 105 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2/MeOH 25:25:1) yielded **43f** as a colorless oil (131 mg, 80 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.09 (d, *J* = 3.1 Hz, 1H), 7.90 (dd, *J* = 4.6, 1.1 Hz, 1H), 7.07 (dd, *J* = 8.6, 4.6 Hz, 1H), 6.90 (ddd, *J* = 8.6, 3.1, 1.1 Hz, 1H), 3.29 (t, *J* = 7.5 Hz, 2H), 2.91 (s, 3H), 1.59-1.49 (m, 2H), 1.39-1.26 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H)..

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 145.0, 137.1, 134.7, 123.4, 118.0, 52.0, 37.9, 28.6, 20.2, 13.9, 14.1.

MS (EI, 70 eV), *m/z* (%): 164 (11) [M^+], 121 (100), 106 (3), 93 (4), 78 (7).

HRMS *m/z* : calcd. for $C_{10}H_{16}N_2$ 164.1313, found 164.1219.

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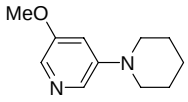
[172] S. Hashimoto, S. Otani, T. Okamoto, K. Matsumoto, *Heterocycles* **1988**, *27*, 319.

IR (cm^{-1}) 3040 (w), 2956 (m), 2930 (m), 2871 (m), 1582 (vs), 1493 (vs), 1425 (m), 1364 (s), 1243 (s), 1185 (m), 1112 (m), 1087 (m), 1050 (m), 1004 (m), 928 (m), 789 (vs), 706 (vs).

5'-Methoxy-3,4,5,6-tetrahydro-2*H*-[1,3']bipyridinyl (43g)



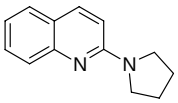
Prepared according to **TP 1** from 3-chloro-5-methoxy-pyridine (**42c**, 144 mg, 1.0 mmol) and piperidine (**32f**, 102 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2/MeOH 25:25:1) yielded **43g** as a colorless oil (105 mg, 55 %). The analytical data are in accordance with the literature.[173]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.95 (d, *J* = 2.5 Hz, 1H), 7.77 (d, *J* = 2.2 Hz, 1H), 6.68 (dd, *J* = 2.5, 2.2 Hz, 1H), 3.82 (s, 3H), 3.18 (t, *J* = 5.6 Hz, 4H), 1.73-1.66 (m, 4H), 1.63-1.56 (m, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 156.1, 148.6, 131.9, 126.7, 108.3, 55.5, 49.9, 25.5, 24.1.

MS (EI, 70 eV), *m/z* (%): 192 (79) [M^+], 191 (100), 151 (15), 136 (29), 108 (13).

2-Pyrrolidin-1-yl-quinoline (43h)



Prepared according to **TP 1** from 2-chloro-quinoline (**42d**, 164 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **43h** as a colorless solid (194 mg, 98 %). The analytical data are in accordance with the literature.[174]

m.p.:55.8-57.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.83 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.54-7.49 (m, 1H), 7.19-7.14 (m, 1H), 6.71 (d, *J* = 9.0 Hz, 1H), 3.64-3.60 (m, 4 H), 2.05-2.01 (m, 4 H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 155.7, 148.5, 136.9, 129.3, 127.3, 126.1, 122.5, 121.2, 110.2, 46.8, 25.5.

MS (EI, 70 eV), *m/z* (%): 198 (36) [M^+], 169 (100), 143 (14), 128 (22), 101 (9).

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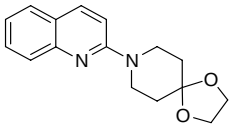
[173] S. Tandel, E. R. Biehl, *Heterocycles* **1999**, *50*, 843.
[174] M. E. Kuehne, *J. Am. Chem. Soc*. **1962**, *84*, 837.

2-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-quinoline (43i)



Prepared according to **TP 1** from 2-chloro-quinoline (**42d**, 164 mg, 1.0 mmol) and 1,4-dioxa-8-aza-spiro[4.5]decane (**32g**, 172 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **43i** as a colorless solid (243 mg, 90 %).

m.p.: 134.0-136.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.86 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.57 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.51 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.20 (ddd, *J* = 7.9, 7.0, 1.3 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 4.00 (s, 4H), 3.89-3.85 (m, 4H), 1.82-1.78 (m, 4H).

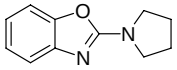
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 156.9, 148.0, 137.4, 129.4, 127.1, 126.6, 122.9, 122.2, 109.6, 107.6, 64.4, 43.4, 34.7.

MS (EI, 70 eV), *m/z* (%): 270 (61) [M^+], 201 (37),183 (29), 169 (100), 129 (56).

HRMS *m/z* : calcd. for $C_{16}H_{18}N_2O_2$ 270.1368, found 270.1383.

IR (cm^{-1}): 2985 (w), 2929 (m), 2870 (m), 1724 (w), 1616 (s), 1603 (s), 1556 (m), 1504 (s), 1482 (m), 1428 (s), 1402 (s), 1358 (s), 1318 8m), 1254 (m), 1224 (vs), 1144 (s), 1098 (vs), 1032 (s).

2-Pyrrolidin-1-yl-benzooxazole (43j)



Prepared according to **TP 1** from 2-chloro-benzooxazole (**42e**, 154 mg, 1.0 mmol) and pyrrolidine (**32a**, 85 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **43j** as a colorless solid (154 mg, 92 %). The analytical data are in accordance with the literature.[175]

m.p.: 136-137 °C.

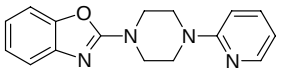
^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.33 (d, *J* = 7.8 Hz, 1 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.11 (t, *J* = 7.7 Hz, 1 H), 6.95 (t, *J* = 7.8 Hz, 1 H), 3.60 (t, *J* = 6.7 Hz, 4 H), 1.99-1.97 (m, 4 H).

^{13}C-NMR ($CDCl_3$, 150 MHz, 25°C): δ = 160.9, 148.9, 143.6, 123.6, 119.8, 115.8, 108.4, 47.3, 25.4.

[175] A. El-Faham, M. Chebbo, M. Abdul-Ghani, G. Younes, *J. Heterocyclic Chem.* **2006**, *43*, 599.

MS (EI, 70 eV), *m/z* (%): 188 (100) [M^+], 160 (57),146 (13), 133 (74), 92 (10).

2-(4-Pyridin-2-yl-piperazin-1-yl)-benzooxazole (43k)



Prepared according to **TP 1** from 2-chloro-benzooxazole (**42e**, 154 mg, 1.0 mmol) and 1-pyridin-2-yl-piperazine (**32k**, 196 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded **43k** as a colorless solid (196 mg, 83 %).

m.p.:143.6-144.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.23 (dd, *J* = 4.8, 1.3 Hz, 1 H), 7.56-7.50 (m, 1 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 7.19 (dt, *J* = 7.8, 0.8 Hz, 1 H), 7.05 (dt, *J* = 7.7, 0.8 Hz, 1 H), 6.73-6.67 (m, 2 H), 3.85-3.82 (m, 4 H), 3.73-3.69 (m, 4 H).

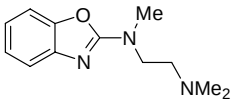
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 162.1, 159.1, 148.8, 148.0, 143.0, 137.7, 124.0, 120.8, 116.4, 114.0, 108.8, 107.3, 45.3, 44.7.

MS (EI, 70 eV), *m/z* (%): 280 (100) [M^+], 186 (64), 147 (71), 133 (92), 107 (100).

HRMS *m/z* : calcd. for $C_{16}H_{16}N_4O$ 280.1324, found 280.1325.

IR (cm^{-1}): 2992 (w), 2850 (w), 1630 (s), 1573 (vs), 1479 (s), 1463 (s), 1434 (vs), 1359 (m), 1239 (vs), 1163 (s), 1052 (m), 1042 (m), 979 (s), 931 (s), 777 (s), 744 (vs) 676 (m).

***N*-Benzooxazol-2-yl-*N,N',N'*-trimethyl-ethane-1,2-diamine (43l)**



Prepared according to **TP 1** from 2-chloro-benzooxazole (**42e**, 154 mg, 1.0 mmol) and *N,N,N'*-trimethyl-ethane-1,2-diamine (**32l**, 123 mg, 1.2 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (CH_2Cl_2/EtOH 10:1) yielded **43l** as a light yellow oil (184 mg, 84 %).

^{1}H-NMR (d_6-DMSO, 400 MHz, 25°C): δ = 7.35 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 3.59 (t, *J* = 6.4 Hz, 2 H), 3.13 (s, 3H), 2.54 (t, *J* = 6.4 Hz, 2H), 2.22 (s, 6 H).

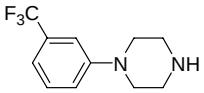
^{13}C-NMR (d_6-DMSO, 400 MHz, 25°C): δ = 162.2, 148.4, 143.4, 123.7, 119.8, 115.3, 108.5, 56.0, 47.3, 35.3.

MS (EI, 70 eV), *m/z* (%): 219 (1) [M^+], 161 (2), 149 (2), 71 (21), 58 (100).

HRMS *m/z* calcd. for $C_{12}H_{17}N_3O$ 219.1372, found 219.1375.

IR (cm^{-1}) 2994 (w), 2822 (w), 2771 (w), 1640 (vs), 1581 (vs), 1460 (s), 1246 (m), 1079 (s), 1050 (vs), 1024 (vs), 1001 (vs), 802 (m), 756 (s), 741 (s).

1-(3-Trifluoromethyl-phenyl)-piperazine (44)



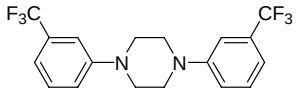
Prepared according to **TP 1** from 1-chloro-3-trifluoromethyl-benzene (**31k**, 181 mg, 1.0 mmol) and piperazine (**32m**, 172 mg, 2.0 mmol). Reaction time: 18 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (CH_2Cl_2/EtOH 10:1) yielded **44** as a yellow oil (198 mg, 86 %). The analytical data are in accordance with the literature.[176]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.34 (t, *J* = 7.94 Hz, 1H), 7.10-7.04 (m, 3H), 3.25-3.18 (m, 4H), 3.04 (dd, *J* = 9.5, 5.1 Hz, 4 H), 1.95 (s, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 151.8, 129.5, 119.2 (q, *J* = 32.2 Hz), 117.4 (q, *J* = 270.4 Hz) 118.9, 115.9 (q, *J* = 3.9 Hz), 112.3 (q, *J* = 3.9 Hz), 49.8, 45.9.

MS (EI, 70 eV), *m/z* (%): 230 (71) [M^+], 211(100), 161 (34), 173 (12), 145 (41).

1,4-Bis-(3-trifluoromethyl-phenyl)-piperazine (45)



Prepared according to **TP 1** from 1-chloro-3-trifluoromethyl-benzene (**31k**, 722 mg, 4.0 mmol) and piperazine (**32m**, 86 mg, 1.0 mmol). Reaction time: 42 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded **45** as a colorless oil (197 mg, 52 %). The analytical data are in accordance with the literature.[176.]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.39 (t, *J* = 7.9 Hz, 2 H), 7.18 (s, 2 H), 7.15-7.10 (m, 4 H), 3.39 (s, 8 H).

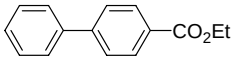
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 151.2, 131.6 (q, *J* = 31.5 Hz), 129.7, 124.3 (q, *J* = 272.6 Hz), 119.1, 116.4 (q, *J* = 3.9 Hz), 112.5 (q, *J* = 3.9 Hz), 48.8.

MS (EI, 70 eV), *m/z* (%): 374 (55) [M^+], 355 (12), 200 (47), 173 (100), 145 (37).

[176] E. Brenner, R. Schneider, Y. Fort, *Tetrahedron.* **2000**, *58*, 6913

11.4 Nickel-Catalyzed Cross-Coupling Reactions of Aryltitanium (IV) Alkoxides with Aryl Halides

Biphenyl-4-carboxylic acid ethyl ester (54a)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise phenylmagnesium chloride (0.84 mL, 1.79 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 4-bromo-benzoic acid ethyl ester (**53a**) (229 mg, 1.00 mmol). The reaction mixture was stirred for 2 h at 25 °C. The usual workup and purification by flash chromatography (pentane/ether 9:1) yielded **54a** as colorless solid (215 mg, 95 %). The same rection with 4-chloro-benzoic acid ethyl ester (**31m**,185 mg, 1.00 mmol) yielded 165 mg **54a** (0.73 mmol, 73 %). The analytical data are in accordance with the literature.[177]

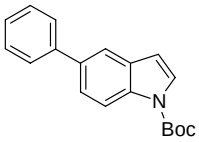
m.p.: 48-49 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz, 25°C): δ = 8.11 (dt, *J* = 8.7, 1.9 Hz, 2H), 7.68-7.57 (m, 3H), 7.51-7.35 (m, 4H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz, 25°C): δ = 166.5, 145.5, 140.0, 130.0, 129.2, 128.9, 128.1, 127.3, 127.0, 61.0, 14.4.

MS (EI, 70 eV), *m/z* (%): 226 (66), [M^+], 198 (35), 181 (100), 152 (60), 127 (9).

5-Phenyl-indole-1-carboxylic acid tert-butyl ester (54b)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise phenylmagnesium chloride (0.84 mL, 1.79 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 5-bromo-indole-1-carboxylic acid tert-butyl ester (**53b**) (296 mg, 1.00 mmol). The reaction mixture was stirred for for 18 h at 25 °C. The usual workup and purification by flash chromatography (pentane/ether 10:1) yielded **54b** as colorless oil (230 mg, 78 %).

[177] M. Julliard, C. Siv, G. Vernin, J. Metzger, *Hel. Chim. Acta* **1978**, *61*, 2941.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.21 (d, *J* = 8.8 Hz, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 3H), 7.57 (d, *J* = 7.1 Hz, 1H), 7.46 (t, *J* = 7.1 Hz, 2H), 7.34 (t, *J* = 7.1 Hz, 1H), 6.63 (d, *J* = 3.5 Hz, 1H), 1.70 (s, 9H).

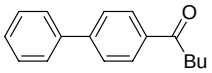
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 149.7, 141.9, 136.3, 134.6, 131.4, 129.0, 127.6, 127.1, 126.7, 124.0, 119.6, 115.6, 107.8, 84.0, 28.5.

MS (EI, 70 eV), *m/z* (%): 293 (21) [M^+], 237 (94), 193 (100), 165 (15), 57 (73), 41 (13).

HRMS *m/z* : calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1405.

IR (KBr) (cm^{-1}): 690 (vs), 722 (s), 742 (vs), 762 (s), 850 (s), 2604 (vw), 2718 (vw), 2868 (m), 2926 (m), 2954 (m), 3036 (w), 3062 (w), 3094 (vw).

1-Biphenyl-4-yl-pentan-1-one (54c)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise phenylmagnesium chloride (0.84 mL, 1.79 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 1-(4-bromo-phenyl)-pentan-1-one (**53c**) (241 mg, 1.00 mmol). The reaction mixture was stirred for 6 h at –10 °C. The usual workup and purification by flash chromatography (pentane/ether 70:1) yielded **54c** as colorless solid (145 mg, 60 %). The analytical data are in accordance with the literature.[178]

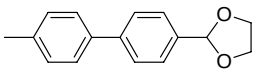
m.p.: 82–83 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.03 (d, *J* = 8.8 Hz, 2H), 7.69–7.61 (m, 4H), 7.49–7.36 (m, 3H), 2.99 (t, *J* = 7.5 Hz, 2H), 1.74 (quint, *J* = 7.5 Hz, 2H), 1.43 (sext, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 200.4, 145.8, 140.2, 136.1, 129.2, 128.9, 128.4, 127.5, 127.4, 38.6, 26.8, 22.8, 14.2.

MS (EI, 70 eV), *m/z* (%): 238 (9) [M^+], 196 (67), 181 (100), 152 (86), 127 (8), 76 (5).

2-(4'-Methyl-biphenyl-4-yl)-[1,3]dioxolane (54d)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise *p*-tolylmagnesium bromide (1.25 mL, 1.20 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 2-(4-chlor-phenyl)-[1,3]dioxolane (**31i**) (185 mg, 1.00 mmol). The reaction mixture was stirred for 17 h at 25 °C. The usual workup

[178] E. Riguet, M. Alami, G. Cahiez, *J. Organomet. Chem.* **2001**, *624*, 376–379.

and purification by flash chromatography (pentane/ether 9:1) yielded **54d** as colorless solid (172 mg, 73 %).

m.p.: 85–87 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.59 (m, 2H), 7.51–7.48 (m, 4H), 7.38 (m, 1H), 7.23 (m, 1H), 5.86 (s, 1H), 4.16–4.04 (m, 4H), 2.39 (s, 3H).

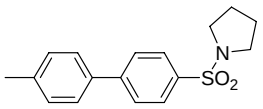
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 142.3, 137.5, 136.8, 129.7, 128.1, 127.3, 127.2, 127.1, 103.9, 65.6, 21.3.

MS (EI, 70 eV), *m/z* (%): 240 (48) [M^+], 195 (44), 168 (100), 165 (20), 152 (14).

HRMS *m/z* : calcd. for $C_{16}H_{16}O_2$ 240.1150, found 240.1154.

IR (KBr) (cm^{-1}): 630 (m), 646 (w), 686 (m), 706 (m), 722 (m), 740 (m), 804 (vs), 846 (m), 940 (s), 968 (s), 1070 (vs), 1402 (m), 2444 (vw), 2592 (vw), 2882 (w), 2918 (w), 2948 (vw), 3028 (w).

1-(4'-Methyl-biphenyl-4-sulfonyl)-pyrrolidine (54e)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise *p*-tolylmagnesium bromide (1.25 mL, 1.20 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 1-(4-chloro-benzenesulfonyl)-pyrrolidine (**31j**) (246 mg, 1.00 mmol). The reaction mixture was stirred for 17 h at 25 °C. The usual workup and purification by flash chromatography (pentane/ether 8:2) yielded **54e** as colorless solid (225 mg, 75 %).

m.p.: 172–173 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.87 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 3.28 (t, *J* = 6.6 Hz, 4H), 2.41 (s, 3H), 1.78 (t, *J* = 6.6 Hz, 4H).

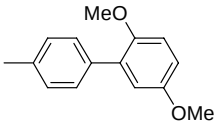
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 145.6, 138.7, 136.7, 135.5, 130.0, 128.3, 127.6, 127.4, 48.2, 25.5, 21.4.

MS (EI, 70 eV), *m/z* (%): 301 (100) [M^+], 232 (26), 168 (40), 167 (70), 152 (59), 70 (69).

HRMS *m/z* : calcd. For $C_{17}H_{19}O_2N_1{}^{32}S_1$ 301.1136, found 301.1137.

IR (KBr) (cm^{-1}): 630 (s), 722 (m), 764 (s), 808 (vs), 1000 (s), 1010 (s), 1046 (m), 1064 (s), 1096 (s), 1154 (vs), 1196 (m), 1330 (s), 1484 (m), 2594 (vw), 2862 (w), 2878 (w), 2922 (w), 2966 (w), 3288 (vw).

2,5-Dimethoxy-4'-methyl-biphenyl (54f)



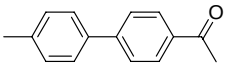
Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise *p*-tolylmagnesium bromide (1.25 mL, 1.20 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **49** (5.3 mg, 0.01 mmol) and 2-chloro-1,4-dimethoxy-benzene (**31n**) (246 mg, 1.00 mmol). The reaction mixture was stirred for 3 h at 65 °C. The usual workup and purification by flash chromatography (pentane/ether 9:1) yielded **54f** as colorless oil (151 mg, 60 %). The analytical data are in accordance with the literature.[179]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.79 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.28–7.19 (m, 3H), 4.15 (s, 3H), 4.10 (s, 3H), 2.75 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 154.0, 151.1, 137.0, 135.7, 132.0, 129.5, 129.0, 116.9, 113.1, 112.9, 56.6, 56.0, 21.4.

MS (EI, 70 eV), *m/z* (%): 228 (100) [M^+], 197 (10), 166 (7), 137 (9), 91 (14).

1-(4'-Methyl-biphenyl-4-yl)-ethanone (54g)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise *p*-tolylmagnesium bromide (1.25 mL, 1.20 M in THF), then $Ni(acac)_2$ (1.3 mg 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 4-bromoaceophenone (**53d**) (199 mg, 1.00 mmol). The reaction mixture was stirred for 6 h at -20 °C. The usual workup and purification by flash chromatography (pentane/ether 40:1) yielded **54g** as colorless solid (114 mg, 54 %). The analytical data are in accordance with the literature.[180]

m.p.: 120–122 °C.

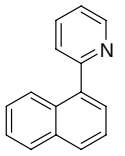
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.01 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.67 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.53 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 2H), 2.63 (s, 3H), 2.41 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 198.0, 146.0, 138.5, 137.2, 135.9, 129.9, 129.2, 127.4, 127.2, 26.9, 21.4.

MS (EI, 70 eV), *m/z* (%): 210 (57) [M^+], 195 (100), 165 (27), 152 (30), 139 (4), 97 (6).

[179] M. Stark, D. M. Arnold, *Chem. Comm.* **1982**, *8*, 434.
[180] M. Ueda, A. Saitoh, S. Oh-tani, N. Miyaura, *Tetrahedron* **1998**, *54*, 13079–13086.

2-Naphthalen-1-yl-pyridine (54h)



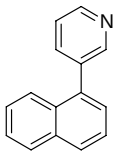
Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise 1-naphthyllmagnesium bromide (1.38 mL, 1.09 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 2-chloro-pyridine (**42a**) (114 mg, 1.00 mmol). The reaction mixture was stirred for 6 h at 25 °C. The usual workup and purification by flash chromatography (pentane/dichloromethane 7:3) yielded **54h** as colorless oil (201 mg, 98 %). The analytical data are in accordance with the literature.[181]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.79 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 8.11-8.06 (m, 1H), 7.93-7.89 (m, 2H), 7.83 (td, *J* = 7.9, 1.9 Hz, 1H), 7.62-7.53 (m, 3H), 7.51-7.45 (m, 2H), 7.33 (ddd, *J* = 7.6, 4.9, 1.1 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 159.3, 149.5, 138.5, 136.5, 133.9,131.2, 128.9, 128.3, 127.4, 126.4, 125.8, 125.6, 125.3, 125.0, 122.0.

MS (EI, 70 eV), *m/z* (%): 205 (37), [M^+], 204 (100), 176 (9), 151 (6), 102 (9).

3-Naphthalen-1-yl-pyridine (54i)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise 1-naphthyllmagnesium bromide (1.38 mL, 1.09 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 3-chloro-pyridine (**42b**) (114 mg, 1.00 mmol). The reaction mixture was stirred for 14 h at 25 °C. The usual workup and purification by flash chromatography (pentane/dichloromethane 1:1) yielded **54i** as colorless oil (126 mg, 61 %). The analytical data are in accordance with the literature.[182]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.77 (d, *J* = 1.8 Hz, 1H), 8.69 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.94-7.89 (m, 2H), 7.81 (dt, *J* = 7.9, 1.9 Hz, 2H), 7.57-7.40 (m, 5H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 150.5, 148.5, 137.3, 136.3, 136.2, 133.8, 131.4, 128.5, 128.4, 127.3, 126.5, 126.0, 125.3, 125.2, 123.1.

MS (EI, 70 eV), *m/z* (%): 205 (87), [M^+], 204 (100), 176 (21), 151 (12), 102 (10).

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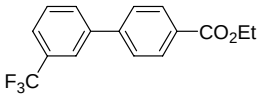
[181] C. Song, Y. Ma, Q. Chai, C. Ma, W. Jiang, M. Andrus, *Tetrahedron* **2005**, *61*, 7438.
[182] C. Cioffi, W. Spencer, J. Richards, R. J. Herr, *J. Org. Chem.* **2004** *69*, 2210.

3'-Trifluoromethyl-biphenyl-4-carboxylic acid ethyl ester (54j)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise 3-trifluoromethyl-phenylmagnesium bromide (1.88 mL, 0.80 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 4-bromo-benzoic acid ethyl ester (**53a**) (229 mg, 1.00 mmol). The reaction mixture was stirred for 16 h at 25 °C. The usual workup and purification by flash chromatography (pentane/ether 9:1) yielded **54j** as colorless solid (175 mg, 70 %). The same rection with 4-chloro-benzoic acid ethyl ester (**31m**, 185 mg, 1.00 mmol) yielded 122 mg **54j** (49 %). The analytical data are in accordance with the literature.[183]

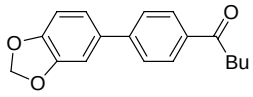
m.p.: 80-81 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ =8.14 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.85 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.66-7.63 (m, 3H), 7.57 (t, *J* = 7.8 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 125 MHz, 25°C): δ = 166.3, 143.9, 140.9, 131.4 (q, *J* = 32.5 Hz), 130.5 (q, *J* = 1.1 Hz), 130.2, 130.0, 129.4, 127.1, 124.7 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 272.0 Hz), 61.1, 14.3.

MS (EI, 70 eV), *m/z* (%): 249 (36), [M^+], 266 (34), 249 (100), 201 (38), 152 (23).

1-(4-Benzo[1,3]dioxol-5-yl-phenyl)-pentan-1-one (54k)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise benzo[1,3]dioxol-5-magnesium bromide (1.36 mL, 1.10 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 1-(4-bromo-phenyl)-pentan-1-one (**53c**) (241 mg, 1.00 mmol). The reaction mixture was stirred for 6 h at –10 °C. The usual workup and purification by flash chromatography (pentane/ether 20:1) yielded **54k** as colorless solid (161 mg, 57 %).

m.p.: 88–90 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.99 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.10 (dd, *J* = 7.0, 1.8 Hz, 2H), 6.89 (dd, *J* = 7.0, 1.8 Hz, 1H), 6.01 (s, 2H), 2.97 (t, *J* = 7.1 Hz, 2H), 1.73 (quint, *J* = 7.5 Hz, 2H), 1.42 (sext, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H).

[183] P. Gomes, H. Fillon, C. Gosmini, E. Labbé, J. Périchon, *Tetrahedron* **2002**, *58*, 8417.

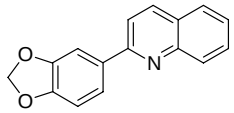
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 200.3, 148.6, 148.1, 145.5, 135.7, 134.5, 129.0, 128.9, 127.7, 127.1, 121.3, 109.0, 107.9, 101.6, 38.6, 26.9, 22.8, 14.2.

MS (EI, 70 eV), *m/z* (%): 282 (47) [M^+], 240 (57), 225 (100), 167 (9), 139 (32), 112 (5).

HRMS *m/z* : calcd. for $C_{18}H_{18}O_3$ 282.1256, found 282.1259.

IR (KBr) (cm^{-1}): 728 (m), 796 (vs), 814 (s), 848 (s), 934 (s), 1042 (s), 1228 (s), 1406 (s), 1482 (s), 1678 (s), 2498 (vw), 2512 (vw), 2534 (vw), 2588 (vw), 2788 (vw), 2868 (w), 2894 (w), 2928 (w), 2954 (m), 3042 (vw).

2-Benzo[1,3]dioxol-5-yl-quinoline (54l)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise benzo[1,3]dioxol-5-magnesium bromide (1.36 mL, 1.10 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 2-chloro-quinoline (**42d**) (164 mg, 1.00 mmol). The reaction mixture was stirred for 18 h at 25 °C. The usual workup and purification by flash chromatography (pentane/dichloromethane 7:3) yielded **54l** as colorless solid (225 mg, 90 %). The analytical data are in accordance with the literature.[184]

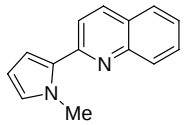
m.p.: 96–97 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.17 (d, *J* = 8.6 Hz, 1H), 8.12 (d , *J* = 8.6 Hz, 1H), 7.81–7.64 (m, 5H), 7.49 (t, *J* = 7.9 Hz, 1H), 6.94 (d , *J* = 8.4 Hz, 1H), 6.03 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 156.9, 149.1, 148.7, 148.5, 136.9, 134.4, 129.9, 129.8, 127.7, 127.3, 126.3, 122.0, 118.9, 108.7, 108.2, 101.6.

MS (EI, 70 eV), *m/z* (%): 249 (100) [M^+], 220 (4), 191 (33), 163 (9), 128 (9), 101 (7).

2-(1-Methyl-1H-pyrrol-2-yl)-quinoline (54m)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise *N*-methyl-2-pyrolllithium[54] (1.50 mL, 1.00 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 2-chloro-quinoline (**42d**) (164 mg, 1.00 mmol). The reaction mixture was stirred for 24 h at 65 °C. The usual workup and

[184] A. M. Echavarren, J. K. Stille, *J. Am. Chem. Soc.* **1987**, *109*, 5478.

purification by flash chromatography (pentane/dichloromethane 3:1) yielded **54m** as colorless oil (205 mg, 98 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.06–8.00 (m, 2H), 7.75–7.63 (m, 3H), 7.47–7.40 (m, 1H), 6.80–677 (m, 2H), 6.22 (t, *J* = 2.9 Hz, 1H), 4.20 (s, 3H).

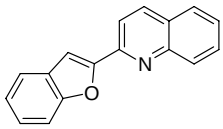
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 152.3, 147.7, 138.9, 135.8, 129.3, 129.0, 127.6, 127.4, 126.0, 125.4, 120.0, 112.3, 107.8, 37.7.

MS (EI, 70 eV), *m/z* (%): 208 (53) [M^+], 207 (100), 180 (4), 128 (6), 104 (6).

HRMS *m/z* : calcd. for $C_{14}H_{12}N_2$ 208.1000, found 208.0996.

IR (KBr) (cm^{-1}): 606 (s), 626 (s), 688 (s), 714 (vs), 754 (s), 780 (s), 794 (s), 822 v(s), 994 (m), 1340 (m), 2486 (w), 2558 (w), 2730 (w), 2950 (w), 3040 (w), 3054 (w).

2-Benzofuran-2-yl-quinoline (54n)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise 2-benzofuryl lithium[55] (1.50 mL, 1.00 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (2.1 mg, 0.005 mmol) and 2-chloro-quinoline (**42d**) (164 mg, 1.00 mmol). The reaction mixture was stirred for 24 h at 65 °C. The usual workup and purification by flash chromatography (pentane/dichloromethane 3:1) yielded **54n** as colorless solid (179 mg, 73 %).

m.p.: 124–126 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.22 (q, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.74 (t, *J* = 7.1 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.64 (s, 1H), 7.63 (d, *J* = 5.5 Hz, 1H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 7.0 Hz, 1H).

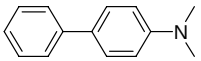
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 155.6, 149.0, 138.9, 136.8, 130.6, 130.0, 129.5, 128.8, 127.6, 127.0, 126.7, 125.5, 123.3, 122.3, 121.8, 118.1, 111.8.

MS (EI, 70 eV), *m/z* (%): 245 (100) [M^+], 216 (23), 189 (6), 128 (4), 122 (9), 96 (5).

HRMS *m/z* : calcd. for $C_{17}H_{11}NO$ 245.0841, found 245.0837.

IR (KBr) (cm^{-1}): 690 (s), 748 (vs), 816 (vs), 1006 (m), 1554 (m), 2494 (w), 2586 (vw), 2700 (w), 3016 (w), 3048 (w), 3058 (w).

Biphenyl-4-yl-dimethyl-amine (57)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise phenylmagnesium chloride (0.84 mL, 1.79 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **49** (5.3 mg, 0.01 mmol) and (4-bromo-phenyl)-dimethyl-amine (**56**) (200 mg, 1.00 mmol). The reaction mixture was stirred for 16 h at 25 °C. The usual workup and purification by flash chromatography (pentane/ether 40:1) yielded **57** as colorless solid (181 mg, 92 %). The analytical data are in accordance with the literature.[185]

m.p.: 122–123 °C.

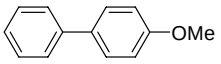
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.62 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.04 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 149.9, 141.2, 129.3, 128.6, 127.7, 126.3, 126.0, 112.8, 40.6.

MS (EI, 70 eV), *m/z* (%): 197 (100) [M^+], 181 (18), 152 (35), 115 (7), 98 (7), 50 (5).

m.p.: 122–123°C.

4-Methoxybiphenyl (48)



Prepared according to **TP 2**. To a $Ti(OEt)_4$ solution (1.0 mL, 1.5 M in THF) was added dropwise phenylmagnesium chloride (0.84 mL, 1.79 M in THF), then $Ni(acac)_2$ (1.3 mg, 0.005 mmol), the ligand **51** (5.3 mg, 0.01 mmol) and 4-bromo-anisole (**47**) (187 mg, 1.00 mmol). The reaction mixture was stirred for 1 h at 25 °C. The usual workup and purification by flash chromatography (pentane/ether 19:1) yielded **48** as colorless solid (215 mg, 86 %). The analytical data match those of the commercially available substrate.

m.p.: 86-87 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.58-7.51 (m, 4H), 7.45-7.40 (m, 2H), 7.34-7.27 (m, 1H), 7.01-6.96 (m, 2H), 3.85 (s, 1H).

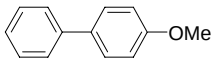
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 159.1, 140.8, 133.8, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3.

MS (EI, 70 eV), *m/z* (%): 184 (100) [M^+], 169 (43), 141 (38), 115 (36), 77 (9).

[185] L. Liang, P. Chien, M. Huang, *Organometallics* **2005**, *24*, 353–357.

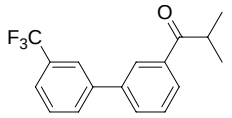
11.5 Kumada Cross-Coupling of Functionalized Grignard Reagents

4-Methoxy-biphenyl (48)



A solution of phenylmagnesium chloride (**52**, 1.94 mL, 3.3 mmol, 1.7 M in THF) and *i*PrI(561 mg, 3.3 mmol) is added to a solution of 4-bromo-anisol (**47**, 561 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06 mmol) in THF (3 mL) according to **TP 5**. The resulting solution was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded 4-methoxy-biphenyl (**48**) as a colorless solid (744 mg, 92 %). The analytical data match those of the commercially available substrate (see also p. 121).

2-Methyl-1-(3'-trifluoromethyl-biphenyl-3-yl)-propan-1-one (60a)



3-Trifluorophenylmagnesium chloride (**59a**) prepared from 3-trifluoromethyl-iodobenzene (**58a**, 979 mg, 3.6 mmol) and *i*PrMgCl·LiCl (3.5 mL, 3.78 mmol, 1.08 M in THF; I/Mg exchange: 1 h at –15 °C) is added to a solution of 1-(3-bromo-phenyl)-2-methyl-propan-1-one (**53e**, 681 mg, 3 mmol), $Pd(OAc)_2$ (27.6 mg, 0.12 mmol) and S-Phos (73.8 mg, 0.18 mmol) in THF (3 mL) according to **TP3.** The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded 2-methyl-1-(3'-trifluoromethyl-biphenyl-3-yl)-propan-1-one (**60a**) as a colorless solid (768 mg, 87 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.17 (t, *J* = 1.8 Hz, 1H), 7.96 (ddd, *J* = 7.9, 1.5, 1.3 Hz, 1H), 7.86-7.84 (m, 1H), 7.79-7.75 (m, 2H), 7.65-7.62 (m, 1H), 7.60-7.53 (m, 2H), 3.61 (qn, *J* = 6.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 6H).

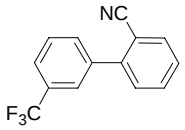
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 204.1, 141.1, 140.3, 137.0, 131.4, 131.3 (q, *J* = 32.2 Hz), 130.5 (q, *J* = 1.3 Hz), 129.4, 129.3, 127.8, 127.0, 124.4 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 272.5 Hz), 123.9 (q, *J* = 3.9 Hz), 35.5, 19.1.

HRMS *m/z* : calcd. for $C_{17}H_{15}F_3O$ 292.1075, found 292.1065.

MS (EI, 70 eV), *m/z* (%): 292 (7) [M^+], 273 (12), 249 (100), 201 (21), 152 (13).

IR (cm^{-1}): 3064 (w), 2973 (w), 2934 (w), 2874 (w), 1683 (s), 1599 (w), 1579 (w), 1467 (w), 1457 (w), 1438 (w), 1408 (w), 1383 (w), 1332 (s), 1307 (w), 1263 (s), 1206 (m), 1162 (s), 1120 (vs), 1096 (s), 1073 (s).

3'-Trifluoromethyl-biphenyl-2-carbonitrile (60b)



3-Trifluorophenylmagnesium chloride (**59a**) prepared from 3-trifluoromethyl-iodobenzene (898 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 1 h at –15 °C) is added to a solution of 2-bromobenzonitrile (53f, 546 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded 3'-trifluoromethyl-biphenyl-2-carbonitrile (**60b**) as a colorless solid (681 mg, 92 %). The analytical data are in accordance with the literature.[186]

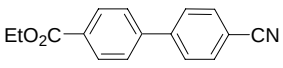
m.p.: 64.8-66.5 °C.

^{1}H-NMR (CDCl3, 300 MHz, 25°C): δ = 7.81-7.76 (m, 3H), 7.73-7.59 (m, 3H), 7.54-7.47 (m, 2H).

^{13}C-NMR (CDCl3, 75 MHz, 25°C): δ = 143.8, 138.8, 133.8, 133.0, 132.1 (q, J = 1.3 Hz), 131.2 (q, J = 32.5 Hz), 130.0, 129.2, 128.3, 125.6 (q, J = 3.9 Hz), 125.4 (q, J = 3.9 Hz), 123.9 (q, J = 272.2 Hz), 118.1, 111.4,

MS (EI, 70 eV), m/z (%): 247 (100) [M^+], 226 (23), 208 (19), 177 (17), 151 (12).

4'-Cyano-biphenyl-4-carboxylic acid ethyl ester (60c)



4-(Ethoxycarbonyl)phenylmagnesium chloride (**59b**) prepared from 4-iodo-benzoic acid ethyl ester (911 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of 4-bromobenzonitrile (**53g**, 546 mg, 3

[186] P. Gomes, H. Fillon, C. Gosmini, E. Labbe, J. Périchon, *Tetrahedron* **2002**, *58*, 8417.

mmol), Pd(OAc)2 (13.8 mg, 0.06) and S-Phos (36.9 mg, 0.09 mmol) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 85:15) yielded 4'-cyano-biphenyl-4-carboxylic acid ethyl ester (**60c**) as a colorless solid (636 mg, 84 %). The analytical data are in accordance with the literature.[186]

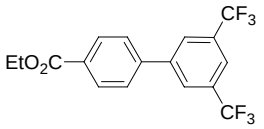
m.p.: 115.8-117.2 °C.

^{1}H-NMR (CDCl3, 300 MHz, 25°C): δ = 8.14 (dt, J = 8.6, 1.9 Hz, 2H), 7.77-7.69 (m, 4H), 7.64 (dt, J = 8.6, 1.9 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (CDCl3, 75 MHz, 25°C): δ = 166.1, 144.5, 143.3, 132.7, 130.6, 130.3, 127.9, 127.2, 118.6, 111.8, 61.2, 14.3.

MS (EI, 70 eV), m/z (%): 251 (51) [M^+], 223 (45), 206 (100), 177 (26), 151 (31).

3',5'-Bis-trifluoromethyl-biphenyl-4-carboxylic acid ethyl ester (60d)



4-(Ethoxycarbonyl)phenylmagnesium chloride (**59b**) prepared from 4-iodobenzoic acid ethyl ester (911 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of 3,5-bis-trifluoromethyl-bromobenzene (**53h**, 879 mg, 3 mmol) and PEPPSI (40.2 mg, 0.06 mmol) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95: 5) yields 3',5'-bis-trifluoromethyl-biphenyl-4-carboxylic acid ethyl ester (**60d**) as a colorless solid (891 mg, 82 %).

m.p.: 93.4-95.1 °C.

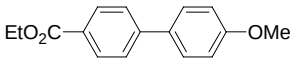
^{1}H-NMR (CDCl3, 300 MHz, 25°C): δ = 8.17 (ddd, J = 8.6, 1.9, 1.7 Hz, 2H), 8.0 (d, J = 0.8 Hz, 2H) 7.89 (d, J = 0.8 Hz, 1H), 7.67 (ddd, J = 8.6, 1.9, 1.7 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (CDCl3, 75 MHz, 25°C): δ = 166.0, 142.2, 132.2 (q, J = 33.3 Hz), 130.9, 130.5, 127.4-127.3 (m), 127.2, 123.2 (q, J = 272.7 Hz), 121.8-121.6 (m), 61.3, 14.3.

HRMS m/z : calcd. for $C_{17}H_{12}F_6O_2$ 362.0741, found 362.07727.

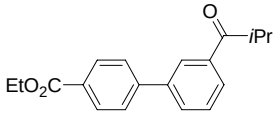
MS (EI, 70 eV), m/z (%): 362 (22) [M^+], 334 (34), 317 (100), 269 (26), 220 (14).
IR (cm-1): 3067 (w), 3051 (w), 2996 (w), 1714 (s), 1611 (m), 1516 (w), 1466 (w), 1401 (w), 1381 (s), 1371 (m), 1278 (s), 1258 (s), 1169 (s), 1113 (vs), 1053 (s).

4'-Methoxy-biphenyl-4-carboxylic acid ethyl ester (60e)



4-(Ethoxycarbonyl)phenylmagnesium chloride (**59b**) prepared from 4-iodo-benzoic acid ethyl ester (911 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of 4-bromoanisole (**47**, 561 mg, 3 mmol), $Pd(OAc)_2$ (13.8 mg, 0.06) and S-Phos (36.9 mg, 0.09 mmol) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9: 1) yielded 4'-methoxy-biphenyl-4-carboxylic acid ethyl ester (**60e**) as a colorless solid (598 mg, 78 %). The analytical data are in accordance with the literature.[100c]
m.p.: 107.1-108.8 °C.
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.08 (ddd, *J* = 8.4, 2.1, 1.9Hz, 2H), 7.63-7.54 (m, 4H), 6.99 (ddd, *J* =, 8.4, 2.1, 1.9 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.5, 159.8, 145.1, 132.4, 130.0, 128.6, 128.3, 126.4, 114.3, 60.9, 55.3, 14.3.
MS (EI, 70 eV), *m/z* (%): 256 (100) [M^+], 228 (28), 211 (87), 168 (17), 139 (38).

3'-Isobutyryl-biphenyl-4-carboxylic acid ethyl ester (60f)



4-(Ethoxycarbonyl)phenylmagnesium chloride (**59b**) prepared from 4-iodo-benzoic acid ethyl ester (911 mg, 3.6 mmol) and *i*PrMgCl·LiCl (3.5 mL, 3.78 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of 1-(3-bromo-phenyl)-2-methyl-propan-1-one (**53e**, 681 mg, 3 mmol), $Pd(OAc)_2$ (27.6 mg, 0.12) and S-Phos (73.8 mg, 0.18 mmol) in THF (3 mL) according to **TP 3.** The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether.

The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 12: 1) yielded 3'-isobutyryl-biphenyl-4-carboxylic acid ethyl ester (**60f**) as a colorless solid (664 mg, 75 %).

m.p.: 60.0-61.8 °C:

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.19 (t, *J* = 1.7 Hz, 1H), 8.15-8.11 (m, 2H), 7.96 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.80 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1H), 7.70-7.66 (m, 2H), 7.56 (t, *J* = 7.7 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.60 (qn, *J* = 6.8 Hz, 1H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 6H).

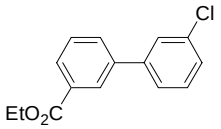
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 204.2, 166.3, 144.6, 144.3, 140.6, 136.9, 130.2, 130,1, 130.0, 129.8, 129.2, 127.9, 127.2, 127.1, 127.1, 61.1, 35.6, 19.2, 14.4.

HRMS *m/z* : calcd. for $C_{19}H_{20}O_3$ 296.1412, found 296.1399.

MS (EI, 70 eV), *m/z* (%): 296 (30) [M^+], 253 (100), 225 (12), 180 (16), 152 (41).

IR (cm^{-1}): 3071 (w), 3031 (w), 2974 (w), 2933 (w), 2873 (w), 1702 (s), 1679 (s), 1608 (m), 1584 (m), 1468 (w), 1429 (w), 1395 (w), 1383 (m), 1368 (m), 1303 (m), 1274 (s), 1211 (s), 1183 8m), 1166 (m), 1155 (m), 1103 (s).

3'-Chloro-biphenyl-3-carboxylic acid ethyl ester (60g)



3-(Ethoxycarbonyl)phenylmagnesium chloride (**59c**) prepared from 3-iodo-benzoic acid ethyl ester (911 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of 3-bromo-chloro-benzene (**53i**, 574 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06 mmol) in THF (3 mL) according to **TP 3.** The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 96:4) yielded 3'-chloro-biphenyl-3-carboxylic acid ethyl ester (**60g**) as a colorless oil (617 mg, 79 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.24, (t, *J* = 1.8 Hz, 1H), 8.04 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.74-7.71 (m, 1H), 7.60 (t, *J* = 1.7 Hz, 1H), 7.53-7.74 (m, 2H), 7.40-7.32 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H)

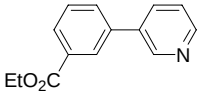
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.3, 142.0, 140.0, 134.8, 131.3, 131.2, 130.1, 128.9, 128.9, 128.1, 127.7, 127.3, 125.3, 61.2, 14.3.

HRMS *m/z* : calcd. for $C_{15}H_{13}ClO_2$ 260.0604, found 260.0588.

MS (EI, 70 eV), *m/z* (%): 260 (70) [M^+], 232 (29), 215 (100), 187 (11), 152 (62).

IR (cm^{-1}): 3066 (w), 2981 (w), 2939 (w), 2905 (w), 1715 (vs), 1595 (m), 1586 (m), 1566 (m), 1465 (m), 1446 (m), 1307 (s), 1294 8s), 1239 (vs), 1171 (m), 1108 (s).

3-Pyridin-3-yl-benzoic acid ethyl ester (60h)



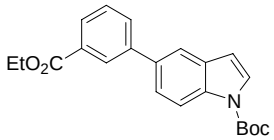
3-(Ethoxycarbonyl)phenylmagnesium chloride (**59c**) prepared from 3-iodo-benzoic acid ethyl ester (911 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of 3-bromo-pyridine (**53j**, 474 mg, 3 mmol) and PEPPSI (61.2 mg, 0.09 mmol) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 1:1) yielded 3-pyridin-3-yl-benzoic acid ethyl ester (**60h**) as a colorless oil (565 mg, 83 %). The analytical data are in accordance with the literature.[187]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.86 (dd, *J* = 2.2, 1.0 Hz, 1H), 8.61 (td, *J* = 3.2, 1.5 Hz, 1H), 8.25-8.24 (m, 1H), 8.07 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.90 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.77-7.73 (m, 1H), 7.58 (td, *J* = 7.9, 1.2 Hz, 1H), 7.40-7.35 (m, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.2, 148.9, 148.2, 138.1, 135.7, 134.4, 131.4, 131.3, 129.1, 129.1, 128.2, 123.6, 61.2, 14.3.

MS (EI, 70 eV), *m/z* (%): 227 (63) [M^+], 199 (28), 182 (100), 154 (52), 127 (30).

5-(3-Ethoxycarbonyl-phenyl)-indole-1-carboxylic acid tert-butyl ester (60i)



3-(Ethoxycarbonyl)phenylmagnesium chloride (**59c**) prepared from 3-iodo-benzoic acid ethyl ester (911 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of 5-bromo-indole-1-carboxylic acid tert-

[187] T. E. Barder, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 2649.

butyl ester (**60j**, 888 mg, 3 mmol), $Pd(OAc)_2$ (13.8 mg, 0.06 mmol) and S-Phos (36.9 mg, 0.09 mmol) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 12:1) yielded 5-(3-ethoxycarbonyl-phenyl)-indole-1-carboxylic acid tert-butyl ester (**60i**) as a colorless oil (812 mg, 74 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.33, (t, *J* = 1.8 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.01 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.84-7.80 (m, 2H), 7.63 (d, *J* = 3.6 Hz, 1H), 7.58 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.5 (t, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 3.6 Hz, 1H), 4.42 (q, *J* =7.2 Hz, 2H), 1.69 (s, 9H), 1.42 (t, *J* = 7.2 Hz, 3H).

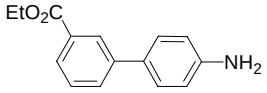
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.7, 149.7, 141.9, 134.9, 134.8, 131.6, 131.1, 131.0, 128.7, 128.3, 127.9, 126.6, 123.6, 119.5, 115.4, 107.5, 83.8, 61.0, 28.2, 14.4.

HRMS *m/z* : calcd. for $C_{22}H_{23}NO_4$ 365.1627, found 365.1618.

MS (EI, 70 eV), *m/z* (%): 265 (100) [M-Boc$^+$], 237 (42), 220 (31), 191 (36), 165 (19).

IR (cm^{-1}): 2980 (w), 2933 (w), 2905 (w), 2255 (w), 1715 (s), 1603 (w), 1585 (w), 1462 (m), 1437 (m), 1364 (s), 1338 (s), 1274 (m), 1251 (s), 1234 (s), 1195 (m), 1158 (s), 1135 (s), 1082 (s), 1022 (s).

4'-Amino-biphenyl-3-carboxylic acid ethyl ester (60k)



3-(Ethoxycarbonyl)phenylmagnesium chloride (**59k**) prepared from 3-iodo-benzoic acid ethyl ester (911 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of benzylidene-(4-bromo-phenyl)-amine (**53k**, 780 mg, 3 mmol), $Pd(OAc)_2$ (13.8 mg, 0.06 mmol) and S-Phos (36.9 mg, 0.09 mmol) in THF (3 mL) according to **TP 3**. The resulting solution was stirred for 5 min at 25 °C. Then aq. HCl (5 mL, 2 M) was added to the reaction and the mixture stirred for 2 h at 25 °C. The reaction was extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4'-amino-biphenyl-3-carboxylic acid ethyl ester (**60k**) as a yellow solid (623 mg, 86 %).

m.p.: 66.5-67.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.22 (t, *J* = 1.7 Hz, 1H), 7.94 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.71 (ddd, *J* = 7.8, 1.9, 1.3 Hz, 1H), 7.47-7.42 (m, 3H), .78 (ddd, *J* = 8.8, 2.6, 1.9 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

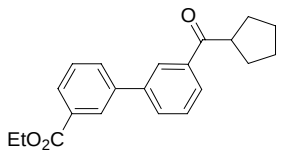
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.7, 145.9, 141.3, 130.9, 130.6, 130.6, 128.6, 128.0, 127.4, 127.3, 115.5, 61.0, 14.3.

HRMS *m/z* : calcd. for $C_{15}H_{15}NO_2$ 241.1103, found 241.1096.

MS (EI, 70 eV), *m/z* (%): 241 (100) [M^+], 213 (83), 196 (18), 168 (34), 84 (27).

IR (cm^{-1}): 3413 (w), 352 (w), 3218 (w), 3030 (w), 2974 (w), 2924 (w), 2990 (w), 1708 (s), 1698 (s), 1632 (m), 1602 (m), 1584 (m), 1519 (m), 1483 (w), 1446 (m), 1416 (m), 1390 (w), 1365 (m), 1295 (s), 1280 (s), 1244 (vs), 1182 (m), 1167 (s).

3'-Cyclopentanecarbonyl-biphenyl-3-carboxylic acid ethyl ester (60l)



3-(Ethoxycarbonyl)phenylmagnesium chloride (**59c**) prepared from 3-iodo-benzoic acid ethyl ester (994 mg, 3.6 mmol) and *i*PrMgCl·LiCl (3.5 mL, 3.78 mmol, 1.08 M in THF; I/Mg exchange: 30 min at –20 °C) is added to a solution of (3-bromo-phenyl)-cyclopentyl-methanone (**53l**, 759 mg, 3 mmol), $Pd(OAc)_2$ (27.6 mg, 0.12 mmol) and S-Phos (73.8 mg, 0.18 mmol) in THF (3 mL) according to **TP 3**. The resulting solution was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 12:1) yielded 3'-cyclopentanecarbonyl-biphenyl-3-carboxylic acid ethyl ester (**60k**) as a colorless oil (794 mg, 82 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.26 (t, *J* = 1.7 Hz, 1H), 8.18 (t, *J* = 1.8 Hz, 1H), 8.02 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.93 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.77-7.73 (m, 2H), 7.53-7.46 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.73 (qn, *J* = 7.8 Hz, 1H), 1.95-1.88 (m, 4H), 1.76-1.59 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H).

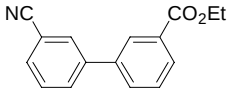
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 202.3, 166.2, 140.4, 140.4, 137.4, 131.3, 131.2, 131.1, 128.9, 128.8, 128.6, 128.0, 127.6, 126.9, 61.0, 46.3, 29.9, 26.2, 14.2.

HRMS *m/z* : calcd. for $C_{21}H_{22}O_3$ 322.1569, found 322.1562.

MS (EI, 70 eV), *m/z* (%): 322 (16) [M^+], 277 (111), 253 (100), 180 (7), 152 (19).

IR (cm^{-1}): 3061 (w), 2954 (w), 2868 (w), 1715 (s), 1679 (s), 1598 (w), 1585 (w), 1575 (w), 1471 (w), 1446 (w), 1436 (w), 1392 (w), 1366 (m), 1299 (m), 1244 (vs), 1199 (s), 1168 (m), 1108 (s).

3'-Cyano-biphenyl-3-carboxylic acid ethyl ester (60l)



A solution of 3-cyanophenylmagnesium chloride (**59d**), prepared from 3-bromobenzonitrile (3.3 mmol, 601 mg) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; Br/Mg exchange: 60 min at 0 °C), and *i*PrI (561n mg, 3.3 mmol) is added to a solution of 3-bromo-benzoic acid ethyl ester (**53m**, 687 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06 mmol) in THF (3 mL) according to **TP 4**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 3'-cyano-biphenyl-3-carboxylic acid ethyl ester (**60l**) as a colorless solid (581 mg, 77 %).

m.p.: 71.0-73.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.24-8.23 (m, 1H), 8.09 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.90-7.88 (m, 1H), 7.84 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.74 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H), 7.66 (dt, *J* = 7,8, 1.5 Hz, 1H), 7.59-7.54 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

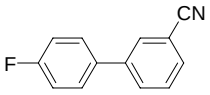
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.1, 141.5, 139.1, 131.5, 131.5, 131.3, 131.1, 130.7, 129.7, 129.4, 129.2, 128.1, 118.6, 113.2, 61.3, 14.4.

HRMS *m/z* : calcd. for $C_{16}H_{13}NO_2$ 251.0946, found 251.0938.

MS (EI, 70 eV), *m/z* (%): 251 (100) [M^+], 223 (54), 207 (29), 178 (40), 151 (26).

IR (cm^{-1}):3070 (w), 2996 (w), 2986 (w), 2958 (w), 2937 (s), 2235 (m), 1716 (vs), 1608 (w), 1576 (w), 1472 (w), 1453 (w), 1394 (w), 1316 (m), 1290 (s), 1271 (s), 1249 (vs), 1172 (m), 1120 (s).

4'-Fluoro-biphenyl-3-carbonitrile (60m)



4-Fluorophenylmagnesium chloride (**59e**) prepared from 4-fluoro-iodobenzene (733 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 60 min at 0

°C) is added to a solution of 3-bromo-benzonitrile (**53n**, 546 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06 mmol) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 4'-fluoro-biphenyl-3-carbonitrile (**60m**) as a colorless solid (495 mg, 84 %).

m.p.: 66.0-67.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.80-7.79 (m, 1H), 7.78-7.71 (m, 1H), 7.62 (ddd, *J* = 7.7, 1.5, 1.3 Hz, 1H), 7.56-7.48 (m, 3H), 7.19-7.12 (m, 2H).

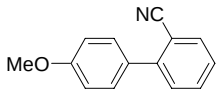
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 163.0 (d, *J* = 248.8 Hz), 141.4, 135.0 (d, *J* = 3.3 Hz), 131.3 (d, *J* = 0.5 Hz), 130.7, 130.5, 129.6, 128.8 (d, *J* = 8.0 Hz), 118.7, 116.1 (d, *J* = 21.8 Hz), 113.0.

HRMS *m/z* : calcd. for $C_{13}H_8FN$ 197.0641, found 197.0646.

MS (EI, 70 eV), *m/z* (%): 197 (100) [M^+], 176 (8), 169 (12), 98 (9), 85 (7).

IR (cm^{-1}): 3114 (w), 3068 (w), 3046 (w), 2230 (m), 1608 (w), 1597 (w), 1578 (w), 1513 (s), 1476 (s), 1433 (m), 1396 (w), 1359 (w), 1323 (w), 1306 (w), 1263 (w), 1223 (s), 1172 (m), 1159 (s), 1101 (m).

4'-Methoxy-biphenyl-2-carbonitrile (60n)



A solution of 4-methoxyphenylmagnesium chloride (**59f**, 2.75 mL, 3.3 mmol, 1.2 M in THF) and *i*PrI (561 mg, 3.3 mmol) is added to a solution of 2-bromobenzonitrile (**53f**, 546 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06 mmol)) in THF (3 mL) according to **TP 5**. The resulting solution was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 4'-methoxy-biphenyl-2-carbonitrile (**60n**) as a colorless solid (615 mg, 98 %). The analytical data are in accordance with the literature.[100c]

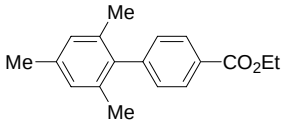
m.p.: 85.0-86.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.73 (ddd, *J* = 7.8, 0.7, 0.5, 1H), 7.61 (td, *J* = 7.7, 1.5 Hz, 1H), 7.53-7.47 (m, 3H), 7.39 (td, *J* = 7.7, 1.3 Hz, 1H), 7.04-6.99 (m, 2H), 3.86 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 160.1, 145.2, 133.7, 132.7, 130.5, 130.0, 129.9, 127.0, 118.9, 114.2, 110.0, 55.3.

MS (EI, 70 eV), *m/z* (%): 209 (100) [M^+], 194 (12), 166 (25), 140 (13), 113 (6).

2',4',6'-Trimethyl-biphenyl-4-carboxylic acid ethyl ester (60o)



A solution of 2,4,6-trimethylphenylmagnesium chloride (**59g**, 4.4 mL, 3.3 mmol, 0.75 M in THF) and *i*PrI (561 mg, 3.3 mmol) is added to a solution of 4-bromo-benzoic acid ethyl ester (**53a**, 687 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06 mmol)) in THF (3 mL) according to **TP 5**. The resulting solution was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded 2',4',6'-trimethyl-biphenyl-4-carboxylic acid ethyl ester (**60o**) as a colorless solid (744 mg, 92 %). The analytical data are in accordance with the literature.[188]

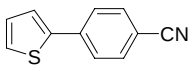
m.p.: 88.0-90.2 °C

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.15 (ddd, *J* = 8.4, 1.8, 1.7 Hz, 2H), 7.27 (ddd, *J* =8.4, 1.8, 1.7 Hz, 2H), 6.99 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 2.02 (s, 6H), 1.46 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.6, 146.2, 138.0, 137.0, 135.5, 129.7, 129.4, 128.9, 128.2, 60.9, 21.0, 20.6, 14.4.

MS (EI, 70 eV), *m/z* (%): 268 (100) [M^+], 223 (89), 195 (74), 180 (66), 1165 (81).

4-Thiophen-2-yl-benzonitrile (61)



A solution of *i*PrI (561 mg, 3.3 mmol) and 1-thienylmagnesium chloride (**59h**), prepared from 2-bromothiophene (538 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; Br/Mg exchange: 30 min at -20 °C), is added to a solution of 4-bromo-benzonitrile (**53g**, 546 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06 mmol) in THF (3 mL) according to **TP 4**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were

[188] G. Haefelinger, F. Hack, G. Westermayer, *Chem. Ber.* **1978**, *111*, 1323.

washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yields 4-thiophen-2-yl-benzonitrile (**61**) as a pale yellow solid (507 mg, 91 %). The analytical data are in accordance with the literature.[189]

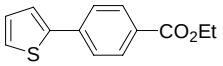
m.p.: 95.0-96.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ 7.70-7.61 (m, 4H), 7.42-7.38 (m, 2H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 142.0, 138.6, 132.7, 128.5, 127.0, 126.0, 125.1, 118.8, 110.5.

MS (EI, 70 eV), *m/z* (%): 185 (100) [M^+], 173 (7), 140 (15), 114 (8), 92 (5).

4-Thiophen-2-yl-benzoic acid ethyl ester (62)



A solution of *i*PrI (561 mg, 3.3 mmol) and 1-thienylmagnesium chloride (**59h**), prepared from 2-bromothiophene (538 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; Br/Mg exchange: 30 min at -20 °C), is added to a solution of 4-bromo-benzoic acid ethyl ester (**53a**, 687 mg, 3 mmol), $Pd(OAc)_2$ (13.8 mg, 0.06 mmol) and S-Phos (36.9 mg, 0.09 mmol) in THF (3 mL) according to **TP 4.** The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded 4-thiophen-2-yl-benzoic acid ethyl ester (**62**) as a pale yellow solid (643 mg, 92 %). The analytical data are in accordance with the literature.[189]

m.p.: 67.5-68.5 °C.

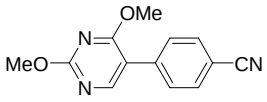
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.04 (ddd, *J* = 8.6, 1.9, 1.8 Hz, 2H), 7.65 (ddd, *J* = 8.6, 1.9, 1.8 Hz, 2H), 7.40 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.34 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.09 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.2, 143.1, 138.4, 130.2, 129.1, 128.2, 126.2, 125.4, 124.4, 60.9, 14.3.

MS (EI, 70 eV), *m/z* (%): 232 (64) [M^+], 204 (28), 187 (100), 159 (17), 115 (50).

[189] S. E. Denmark, J. D. Baird, C. S. Regens, *J. Org. Chem.*, **2008**, *73*, 1440.

4-(2,4-Dimethoxy-pyrimidin-5-yl)-benzonitrile (65)



2,4-Dimethoxypyrimindin-5-ylmagnesium chloride (**59i**) prepared from 5-iodo-2,4-dimethoxy-pyrimidine (**63**, 878 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 60 min at -20 °C) is added to a solution of 4-bromo-benzonitrile (**53g**, 546 mg, 3 mmol) and PEPPSI (61.2 mg, 0.09 mmol) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 10 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 7:3) yielded 4-(2,4-dimethoxy-pyrimidin-5-yl)-benzonitrile (**65**) as a colorless solid (601 mg, 83 %).

m.p.: 153.8-155.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.25 (s, 1H), 7.66 (ddd, *J* = 8.4, 1.8, 1.7 Hz, 2H), 7.59 (ddd, *J* = 8.4, 1.8, 1.7 Hz, 2H), 4.01 (s, 3H), 4.00 (s, 3H).

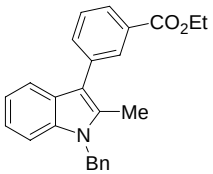
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 167.8, 165.4, 157.9, 138.1, 132.1, 129.2, 118.6, 114.3, 111.1, 55.0, 54.2.

HRMS *m/z* : calcd. for $C_{13}H_{11}N_3O_2$ 241.0851, found 241.0847.

MS (EI, 70 eV), *m/z* (%): 241 (100) [M^+], 226 (17), 211 (42), 169 (19), 141 (26).

IR (cm^{-1}): 3038 (w), 2964 (w), 2361 (w), 2227 (m), 1741 (m), 1602 (s), 1563 (s), 1550 (s), 1516 (w), 1466 (s), 1400 (s), 1380 (s), 1332 (m), 1276 (m), 1234 (s), 1206 (m), 1182 (m).

3-(1-Benzyl-2-methyl-1*H*-indol-3-yl)-benzoic acid ethyl ester (66)



1-Benzyl-2-methyl-1*H*-indol-3-ylmagnesium chloride (**59j**) prepared from 1-benzyl-3-iodo-2-methyl-1H-indole (**64**, 1146 mg, 3.3 mmol) and *i*PrMgCl·LiCl (3.2 mL, 3.45 mmol, 1.08 M in THF; I/Mg exchange: 45 min at -20 °C) is added to a solution of 3-bromo-benzoic acid ethyl ester (**53m**, 687 mg, 3 mmol), $Pd(OAc)_2$ (13.8 mg, 0.06 mmol) and S-Phos (36.9 mg, 0.09 mmol) in THF (3 mL) according to **TP 3**. The resulting mixture was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4.

Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 3-(1-benzyl-2-methyl-1H-indol-3-yl)-benzoic acid ethyl ester (**66**) as a yellow oil (601 mg, 83 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.28 (d, *J* = 1.4 Hz, 1H), 8.05 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.77-7.73 (m, 2H), 7.60-7.56 (m, 1H), 7.34-7.31 (m, 3H), 7.29.7.27 (m, 1H), 7.24-7.18 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 2H), 5.41 (s, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.8, 137.5, 136.5, 135.9, 134.0, 133.5, 130.8, 130.7, 128.8, 128.4, 127.3, 127.0, 126.9, 126.0, 121.6, 120.1, 118.5, 113.8, 109.2, 60.9, 46.6, 14.3, 11.0.

HRMS *m/z* : calcd. for $C_{25}H_{23}NO_2$ 369.1729, found 369.1733.

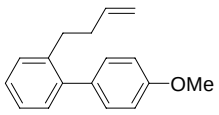
MS (EI, 70 eV), *m/z* (%): 369 (100) [M^+], 324 (11), 278 (20), 250 (7), 204 (7).

IR (cm^{-1}): 3032 (w), 2982 (w), 2938 (w), 2362 (w), 2252 (w), 1712 (s), 1605 (m), 1584 (w), 1558 (w), 1466 (m), 1454 (m), 1414 (w), 1367 (m), 1332 (m), 1282 (s), 1255 (s), 1209 (s).

2-But-3-enyl-4'-methoxy-biphenyl (68) and 1-(4-methoxy-benzyl)-indane (69)

A soluton of 4-methoxyphenylmagnesium chloride (**59f**, 2.75 mL, 3.3 mmol, 1.2 M in THF) and *i*PrI (561 mg, 3.3 mmol) is added to a solution of 1-bromo-2-but-3-enyl-benzene (**67**, 633 mg, 3 mmol) and PEPPSI (40.8 mg, 0.06 mmol)) in THF (3 mL) according to **TP 5**. The resulting solution was stirred for 5 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 250:1) yielded 2-but-3-enyl-4'-methoxy-biphenyl (**68**, 244 mg, 34%) and 1-(4-methoxy-benzyl)-indane (**69**, 359 mg, 50%) as colorless oils.

2-But-3-enyl-4'-methoxy-biphenyl (68)



^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.32-7.22 (m, 6H), 6.98 (ddd, *J* = 9.11, 2.7, 2.6 Hz, 2H), 5.83-5.69 (m, 1H), 4.99-4.97 (m, 1H), 4.95-4.90 (m, 1H), 3.89 (s, 3H), 2.75-2.70 (m, 2H), 2.29-2.21 (m, 2H),

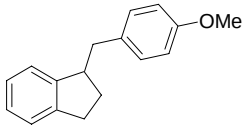
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 158.5, 141.5, 139.4, 138.1, 134.3, 130.3, 130.2, 129.1, 127.1, 125.7, 114.6, 113.5, 55.3, 35.2, 32.6.

HRMS *m/z* : calcd. for $C_{17}H_{18}O$ 238.1358, found 238.1358.

MS (EI, 70 eV), *m/z* (%): 238 (48) [M^+], 197 (100), 182 (20), 165 (34), 153 (14).

IR (cm^{-1}): 3062 (w), 2999 (w), 2952 (w), 2934 (w), 2834 (w), 1639 (w), 1610 (m), 1512 s), 1480 (m), 1463 (m), 1440 (m), 1412 (w), 1293 (m), 1264 (w), 1240 (vs), 1174 (s).

1-(4-Methoxy-benzyl)-indane (69)



^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.23-7.21 (m, 1H), 7.18-7.10 (m, 5H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.81 (s, 3H), 3.46-3.36 (m, 1H), 3.07 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.93-2.74 (m, 2H), 2.65 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.20-2.09 (m, 1H), 1.82-1.69 (m, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 157.9, 146.9, 144.2, 132.9, 129.9, 126.4, 125.9, 124.5, 123.8, 113.7, 55.2, 46.6, 40.5, 31.9, 31.1.

HRMS *m/z* : calcd. for $C_{17}H_{18}O$ 238.1358, found 238.1359.

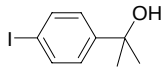
MS (EI, 70 eV), *m/z* (%): 238 (14) [M^+], 121 (100), 117 (49), 115 (16), 91 (8).

IR (cm^{-1}): 3065 (w), 3018 (w), 2950 (w), 2932 (w), 2911 (w), 2833 (w), 1610 (m), 1583 (w), 1510 (s), 1476 (m), 1457 (m), 1440 (m), 1419 (w), 1230 (m), 1242 (vs), 1175 (s), 1105 (s).

11.6 Negishi Cross-Coupling Reactions in the Presence of Acidic Protons

11.6.1 Starting Material Synthesis

2-(4-Iodo-phenyl)-propan-2-ol (84a):



The compound was prepared according to the $LnCl_3$-promoted addition of organomagnesium reagents to carbonyl compounds.[111] 1,4-Diiodobenzene (8.25 g, 25 mmol) was added at -20 °C to *i*PrMgCl·LiCl (21.7 mL, 1.2 M in THF, 26 mmol). The reaction was stirred at -20 °C for 2 h, until GC-analysis of an aliquot showed complete conversion to the monomagnesiated spezies.

In a second flask was placed aceton (1.84 mL, 25 mmol) and $LaCl_3{\cdot}2LiCl$ (83 mL, 0.30 M in THF, 25 mmol). The resulting solution was stirred for 30 min and then cooled to -10 °C. To this solution the organomagnesium compound was added slowly via canula. The reaction mixture was stirred for 2 h at –10 °C, quenched with aq. NH_4Cl solution (50 mL), extracted

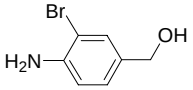
with ether (3 x 40 ml) and dried (Na_2SO_4). Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:1) yielded 2-(4-iodo-phenyl)-propan-2-ol (**84a**) as a yellow oil (3.70 g, 56%).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.62 (dd, *J* = 8.8, 2.4 Hz, 2H), 7.20 (dd, *J* = 8.8, 2.4 Hz, 2H), 1.52 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 148.8, 137.1, 126.6, 92.0, 72.2, 31.6.

MS (EI, 70 eV), *m/z* (%): 262 (21) [M^+], 246 (100), 203 (9), 127 (12), 77 (15).

(4-Amino-3-bromo-phenyl)-methanol (84j):



A solution of 4-amino-3-bromo-benzoic acid ethyl ester (6.1 g, 25 mmol) in THF (20 mL) was added slowly at -10 °C to a suspension of $LiAlH_4$ (530 mg, 14 mmol) in THF (25 mL). After warming to 0 °C and stirring for 3 h at this temperature the reaction mixture was quenched with $Na_2SO_4 \cdot 10\ H_2O$ (10.0 g), diluted with ether (100 mL) and filtered. The organic solution was dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded (4-amino-3-bromo-phenyl)-methanol (**84j**) as a white solid (3.87 g, 77%).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.40 (d, *J* = 1.8 Hz, 1H), 7.08 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 4.51 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 143.5, 132.2, 131.6, 127.6, 115.7, 109.1, 64.5.

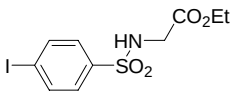
HRMS *m/z* : calc. for C_7H_8BrNO 200.9789, found 200.9785.

MS (EI, 70 eV), *m/z* (%): 203 (92), 201 (93) [M^+], 186 (68), 184 (67), 93 (100).

IR (cm^{-1}): 3392 (w), 3220 (m), 2911 (w), 2855 (w), 2629 (w), 1873 (w), 1612 (m), 1499 (s), 1572 (m), 1415 (m), 1363 (m), 1284 (m), 1203 (m), 1152 (m), 1085 (w)..

m.p.: 67.8-69.6 °C

(4-Iodo-benzenesulfonylamino)-acetic acid ethyl ester (93b)



A dry and nitrogen flushed 100 ml Schlenk-flak was charged with glycine ethyl ester hydrochloride (2.79 g, 20 mmol) and pyridine (40 mL). The mixture was cooled to 0 °C and 4-iodobenzenesulfonyl chloride (6.66 g, 22 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 18 h. Then 2 M HCl (40 mL) was added and the reaction

mixture extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with H_2O (30 mL), 2 M HCl (2x 30 mL), brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvents yielded (4-iodo-benzenesulfonylamino)-acetic acid ethyl ester (**93b**) as a colorless solid (7.23 g, 98 %).

m.p.: 116.9-118.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.86 (ddd, *J* = 8.8, 2.3, 2.1 Hz, 2H), 7.57 (ddd, *J* = 8.8, 2.3, 2.1 Hz, 2H), 5.21 (t, *J* = 5.4 Hz, 1H) 4.09 (t, *J* = 7.1 Hz, 2H), 3.77 (d, *J* = 5.4 Hz, 2H), 1.18 (q, *J* = 7.1 Hz, 3H).

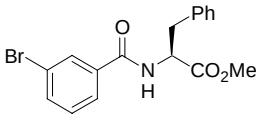
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 168.6, 139.0, 138.4, 128.6, 100.4, 62.0, 44.1, 14.0.

HRMS *m/z* : calcd. for $C_{10}H_{12}INO_4S$ 368.9532, found 368.9527

MS (EI, 70 eV), *m/z* (%): 369 (14) [M^+], 296 (100), 267 (67), 203 (37), 76 (21).

IR (cm^{-1}): (3272 (m), 3091 (w), 2985 (w), 2926 (w), 1736 (s), 1568 (m), 1473 (m), 1443 (w), 1422 (w), 1388 (m), 1366 (m), 1346 (s), 1323 (s), 1238 (s), 1217 (s), 1160 (vs), 1102 (s).

(3-Bromo-benzoylamino)-phenyl-acetic acid methyl ester (97)



A dry and nitrogen flushed 100 ml Schlenk-flak was charged with L-phenylalanine methylester hydrochloride (3.02 g, 14 mmol), NEt_3 (6.9 mL, 50 mmol) and CH_2Cl_2 (40 mL). The mixture was cooled to 0 °C and 3-bromo-benzoyl chloride (3.51 g, 16 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 18 h. Then H_2O (40 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with H_2O (30 mL), $NaHCO_3$ (2x 30 mL), brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvents yielded (3-bromo-benzoylamino)-phenyl-acetic acid methyl ester (**97**) as a light yellow solid (4.98 g, 98 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.86-7.85 (m, 1H), 7.63-7.58 (m, 2H), 7.32-7.24 (m, 4H), 7.13-7.10 (m, 2H), 6.54 (d, *J* = 6.9 Hz, 2H), 5.06 (ddd, *J* = 7.6, 5.7, 5.6 Hz, 1H), 3.76 (s, 3H), 3.32-3.17 (m, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 171.9, 165.4, 135.9, 135.6, 134.7, 130.3, 130.2, 129.3, 128.7, 127.3, 125.4, 122.8, 53.6, 52.5, 37.8.

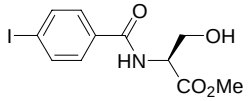
HRMS *m/z* : calcd. for $C_{17}H_{16}BrNO_3$ 361.0314, found 361.0306.

MS (EI, 70 eV), *m/z* (%): 361 (2) [M^+], 182 (54), 162 (100), 154 (13), 131 (12).

IR (cm^{-1}): 3455 (w), 3360 (m), 3061 (w), 3030 (w), 3006 (w), 2953 (w), 1734 (vs), 1638 (vs), 1604 (w), 1594 (w), 1566 (m), 1532 (vs), 1497 (m), 1474 (m), 1454 (m), 1438 (m), 1348 (w), 1310 (m), 1245 (vs), 1096 (m).

$[\alpha]_D^{20}$: +76.8 (c = 0.46, $CHCl_3$).

3-Hydroxy-2-(4-iodo-benzoylamino)-propionic acid methyl ester (98):



A dry and nitrogen flushed 100 ml Schlenk-flak was charged with L-serine methylester hydrochloride (1.56 g, 10 mmol), NEt_3 (6.9 mL, 50 mmol) and CH_2Cl_2 (40 mL). The mixture was cooled to 0 °C and 4-iodo-benzoyl chloride (2.93 g, 11 mmol) was added. The reaction mixture was warmed to 25 °C and was stirred for 18 h. Then H_2O (40 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with H_2O (30 mL), $NaHCO_3$ (2x 30 mL), brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvents yielded 3-hydroxy-2-(4-iodo-benzoylamino)-propionic acid methyl ester (**98**) as a colorless solid (3.32 g, 95 %).

m.p.: 79.8-81.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.74-7.69 (m, 2H), 7.54-7.50 (m, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 4.82-4.77 (m, 1H), 4.09-3.96 (m, 2H), 3.87 (s, 1H), 3.77 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 170.9, 166.8, 137.8, 132.9, 128.8, 99.0, 63.3, 55.3, 52.9.

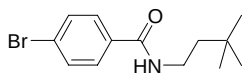
HRMS *m/z* : calcd. for $C_{11}H_{12}INO_4$ 348.9811, found 348.9803.

MS (EI, 70 eV), *m/z* (%): 348 (2) [M^+], 331 (24), 299 (31), 231 (100), 203 (22).

IR (cm^{-1}):3383 (m), 3271 (m), 3062 (w), 3025 (w), 2992 (w), 2949 (w), 1737 (s), 1675 (m), 1633 (s), 1617 (s), 1585 (s), 1531 (s), 1477 (s), 1434 (s), 1322 (s), 1265 (m), 1206 (vs), 1158 (s), 1113 (m).

$[\alpha]_D^{20}$: +44.1 (c = 0.37, $CHCl_3$).

4-Bromo-*N*-(3,3-dimethyl-butyl)-benzamide (102)



A dry and nitrogen flushed 250 ml Schlenk-flak was charged with 4-bromo-benzoyl chloride (5.49 g, 25 mmol), NEt_3 (6.9 mL, 50 mmol) and CH_2Cl_2 (100 mL). The mixture was cooled to 0 °C and 3,3-dimethyl-butylamine (2.83 g, 28 mmol) was added. The reaction mixture was

warmed to 25 °C and stirred for 18 h. Then H_2O (100 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with H_2O (50 mL), $NaHCO_3$ (2x 50 mL), brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvents yielded 4-bromo-*N*-(3,3-dimethyl-butyl)-benzamide (**102**) as a colorless solid (6.84 g, 96 %).

m.p.: 115.8-117.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.61 (ddd, *J* = 8.5, 1.9, 1.8 Hz, 2H), 7.54 (ddd, *J* = 8.5, 1.9, 1.8 Hz, 2H), 6.04 (bs, 1H), 3.48-3.41 (m, 2H), 1.54-1.48 (m, 2H), 0.96 (s, 9H).

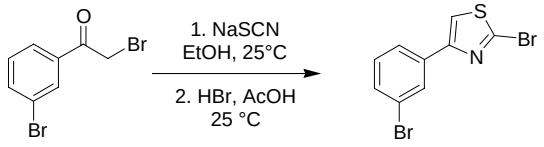
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.4, 133.7, 131.7, 128.4, 125.9, 43.3, 36.9, 30.0, 29.4.

HRMS *m/z* : calcd. for $C_{13}H_{18}BrNO$ 283.0572, found 283.0574

MS (EI, 70 eV), *m/z* (%): 283 (5) [M^+], 226 (20), 214 (11), 183 (100), 157 (13).

IR (cm^{-1}): 3280 (m), 3090 (w), 2959 (m), 2910 (w), 2867 (w), 1633 (vs), 1589 (s), 1549 (vs), 1483 (s), 1394 (w), 1362 (m), 1316 (s), 1262 (m), 1182 (m), 1154 (m).

2-Bromo-4-(3-bromo-phenyl)-thiazole (107)



A flask was charged with 2-bromo-1-(3-bromo-phenyl)-ethanone (13.8 g, 50 mmol) and EtOH (100 mL). NaSCN (4.9 g, 60 mmol) was added and the reaction mixture stirred at 25 °C for 16 h. Then the solvent was removed on a rotary evaporator and the residue taken up in H_2O (100 mL) and extracted with EtOAC (3 x 100 mL). The combined org. phases are washed with H_2O (100 mL), brine (100 mL) and dried over Na_2SO_4. Evaporation of the solvent yields 12.6 g of 1-(3-bromo-phenyl)-2-thiocyanato-ethanone as a yellow solid, which was used without further purification.

A dry and nitrogen flushed 250 ml Schlenk-flak was charged with HBr (100 mL, 33% in AcOH). 1-(3-Bromo-phenyl)-2-thiocyanato-ethanone (12.6 g) was added and the reaction was stirred at 25 °C for 18 h. Then, the reaction mixture was poured on ice and carefully neutralized with NaOH, keeping the temperature below 10 °C. The aq. solution was extracted with EtOAc (3 x 150 mL), the combined org. phases washed with H_2O (100 mL), brine (100 mL) and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/CH_2Cl_2 9:1) yielded 2-bromo-4-(3-bromo-phenyl)-thiazole (**107**) as a colorless solid (9.57 g, 60 % over two steps)

m.p.: 90.4-91.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.02 (t, *J* = 1.9 Hz, 1H), 7.77-7.75 (m, 1H), 7.47 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.43 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 1H).

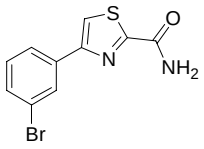
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ =.154.1, 136.2, 135.1, 131.6, 130.3, 129.2, 124.7, 123.0, 117.0,

HRMS *m/z* : calcd. for $C_9H_5Br_2NS$ 316.8509, found 316.8510

MS (EI, 70 eV), *m/z* (%): 319 (100), 316 (47) [M^+], 214 (22), 159 (47), 133 (21).

IR (cm^{-1}): 3091 (m), 3063 (w), 3009 (w), 1947 (w), 1872 (w), 1797 (w), 1768 (w), 1738 (w), 1592 (w), 1565 (m), 1525 (w), 1508 (m), 1469 (s), 1417 (m), 1307 (m), 1286 (m), 1253 (m).

4-(3-Bromo-phenyl)-thiazole-2-carboxylic acid amide (108)



To a solution of 2-bromo-4-(3-bromo-phenyl)-thiazole (**107**, 3.19 g, 10 mmol) in THF (10 mL), cooled to –30 °C, was added dropwise *i*PrMgCl·LiCl (8.2 mmol, 1.24 M in THF, 10.5 mmol). The reaction mixture was stirred for 45 min at this temperature. Then $ZnCl_2$ (10 mL, 1.0 M in THF, 10 mmol) was added and the resulting solution was warmed to 25 °C. After cooling the reaction mixture again to -40 °C, trichloro-acetyl isocyanate (1.3 mL, 11 mmol) was added dropwise with a syringe. The reaction was slowly warmed to 25 °C and stirred for 1 h. K_2CO_3 (2 g, 15 mmol) and MeOH (5 mL) were added and stirring at 25 °C was continued for 24 h. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (40 mL) and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 4:1) yielded 4-(3-bromo-phenyl)-thiazole-2-carboxylic acid amide (**108**) as a light yellow solid (2.51 g, 89 %)

m.p.: 156.5-157.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.07 (t, *J* = 1.72 Hz, 1H), 7.81-7.78 (m, 1H), 7.75 (s, 1H), 7.50 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.31 (t, *J* 7.9 Hz, 1H), 7.23 (bs, 1H), 6.03 (bs, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 162.8, 161.2, 154.9, 135.4, 131.6, 130.4, 129.5, 124.8, 123.1, 119.7

HRMS *m/z* : calcd. for $C_{10}H_7BrN_2OS$ 281.9462, found 281.9458

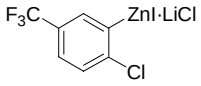
MS (EI, 70 eV), *m/z* (%): 281 (100) [M^+], 239 (37), 214 (55), 159 (27), 133 (51).

IR (cm^{-1}): 3498 (w), 3448 (w), 3382 (w), 3147 (w), 3110 (w), 1694 (vs), 1596 (m), 1574 (m), 1480 (m), 1441 (m), 1406 (w), 1384 (m), 1310 (w), 1292 (w), 1209 (w), 1129 (m), 1066 (m).

11.6.2 Preparation of the Zinc Reagents

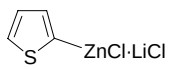
The aryl zinc reagents **73a**, **73b**, **73c**, **73e** and **73i** and 3-pyridylzinc iodide (**73f**) were prepared by the direct zinc insertion into the corresponding aryl iodides.[80a] The uracil derived zinc reagent **73h** was prepared by the direct zinc insertion into 5-iodo-2,4-dimethoxy-pyrimidine.[90] The alkylzinc reagents **74a-74c** were prepared by the direct zinc insertion into the corresponding alkyl bromides.[80a] The benzylic zinc reagents **75a-75f** were prepared by the direct insertion into the corresponding benzylic chlorides.[85] The concentration of all organozinc reagents was determined by titration with iodine in THF.[158.]

2-Chloro-5-trifluoromethylphenylzinc iodide (73d)



Anhydrous LiCl (28 mmol, 1.19g) was placed in an N_2-flushed flask and dried for 60 min at 150 °C under high vacuum (1 mbar). Zinc powder (38 mmol, 2.49 g,) was added under N_2 and the heterogenous mixture was dried again for 60 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with N_2 three times. THF (25 mL) was added and the zinc was activated with 1,2-dibromoethane (1.25 mmol, 0.11 mL) and TMSCl (1.25 mmol, 0.16 mL). 1-Chloro-2-iodo-4-trifluoromethyl-benzene (25 mol, 7.66 g) was added then neat and the reaction mixture was stirred for 18 h at 25 °C. The solution of **73d** was carefully separated from remaining zinc powder by using a syringe and transferred to another dry and N_2-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine, indicated a concentration of 0.98 M.

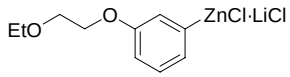
2-Thienylzinc chloride (73g)



Anhydrous LiCl (15 mmol, 636 mg) was placed in an N_2-flushed flask and dried for 60 min at 150 °C under high vacuum (1 mbar). Zinc chloride (11 mmol, 1.50 g,) was added under N_2 and the mixture was dried again for 60 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with N_2 three times. Magnesium powder (20 mmol, 486 mg) was added, followed by THF (15 mL). The reaction mixture was cooled with a waterbath to 25 °C. 2-Bromo-thiophene (10 mmol, 1.63 g) was added neat and the reaction mixture stirred for 4 h. The solution of **73g** was carefully separated from remaining magnesium powder by using a syringe and transferred to another dry and N_2-

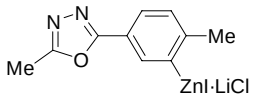
flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.55 M.

3-(2-Ethoxy-ethoxy)-phenylzinc chloride (73j)



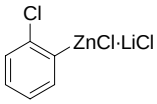
Anhydrous LiCl (15 mmol, 636 mg) was placed in an N_2-flushed flask and dried for 60 min at 150 °C under high vacuum (1 mbar). Zinc chloride (11 mmol, 1.50 g,) was added under N_2 and the mixture was dried again for 60 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with N_2 three times. Magnesium powder (20 mmol, 486 mg) was added, followed by THF (15 mL). The reaction mixture was cooled with a waterbath to 25 °C. 1-Bromo-3-(2-ethoxy-ethoxy)-benzene (10 mmol, 2.45 g) was added neat and the reaction mixture stirred for 4 h. The solution of **73j** was carefully separated from remaining magnesium powder by using a syringe and transferred to another dry and N_2-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.58 M.

[2-Methyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]zinc iodide (104)



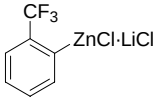
Anhydrous LiCl (20 mmol, 848 mg) was placed in an N_2-flushed flask and dried for 60 min at 150 °C under high vacuum (1 mbar). Zinc powder (30 mmol, 1.96 g,) was added under N_2 and the mixture was dried again for 60 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with N_2 three times. THF (20 mL) was added and the zinc powder was activated first by treatment with dibromo-ethane (94 mg, 0.5 mmol) and then with chlorotrimethylsilane (12 μL, 0.1 mmol). 2-(3-Iodo-4-methyl-phenyl)-5-methyl-[1,3,4]oxadiazole (3.0 g, 10 mmol) was added neat and the raection mixture stirred at 50 °C for 16 h. The mixture was diluted with THF (20 mL; note: the solubility of **104** in THF was low, therefore a high dilution is recommended) and the solution of **104** was carefully separated from remaining zinc powder by using a syringe and transferred to another dry and N_2-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.18 M.

2-Chloro-phenylzinc chloride (73k)



To a solution of *i*PrMgCl·LiCl (4.2 mL, 5.1 mmol, 1.24 M in THF), cooled to –25 °C, was added 1-chloro-2-iodo-benzene (5 mmol, 1.19 g). The reaction mixture was stirred for 60 min at this temperature. Then, zinc chloride (5 mL, 1.0 M in THF, 5 mmol) was added and the resulting solution warmed to 25 °C. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.48 M.

2-Trifluoromethyl-phenylzinc chloride (73l)

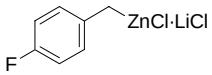


To a solution of *i*PrMgCl·LiCl (4.2 mL, 5.1 mmol, 1.24 M in THF), cooled to –25 °C, was added 2-iodo-1-trifluorometyl-benzene (5 mmol, 1.36 g). The reaction mixture was stirred for 60 min at this temperature. Then, zinc chloride (5 mL, 1.0 M in THF, 5 mmol) was added and the resulting solution warmed to 25 °C. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.51 M.

2-Trifluoromethoxy-phenylzinc chloride (73m)

To a solution of *i*PrMgCl·LiCl (4.2 mL, 5.1 mmol, 1.24 M in THF), cooled to –25 °C, was added 2-iodo-1-trifluoromethoxy-benzene (5 mmol, 1.44 g). The reaction mixture was stirred for 60 min at this temperature. Then, zinc chloride (5 mL, 1.0 M in THF, 5 mmol) was added and the resulting solution warmed to 25 °C. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.49 M.

4-Fluorobenzylzinc chloride (75d)

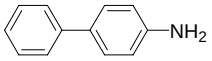


Anhydrous LiCl (28 mmol, 1.19g) was placed in an N_2-flushed flask and dried for 60 min at 150 °C under high vacuum (1 mbar). Zinc powder (38 mmol, 2.49 g,) was added under N_2 and the heterogenous mixture was dried again for 60 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with N_2 three times. THF

(20 mL) was added and the zinc was activated with 1,2-dibromoethane (1.25 mmol, 0.11 mL) and TMSCl (1.25 mmol, 0.16 mL). 4-Fluoro-benzylchloride (25 mol, 3.61 g) was added then neat and the reaction mixture was stirred for 18 h at 25 °C. The solution of **75d** was carefully separated from remaining zinc powder by using a syringe and transferred to another dry and N_2-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine, indicated a concentration of 1.0 M.

11.6.3 Palladium- and Nickel-Catalyzed Cross-Coupling Reactions

4-Amino-biphenyl (77a)



Phenylzinc iodide (**73a**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of 4-bromo-aniline (**76a**, 690 mg, 3 mmol), $Ni(acac)_2$ (15.4 mg, 0.06 mmol) and 2,2'-bipyridine (4.7 mg, 0.09 mmol) in THF (2 mL), according to **TP 8**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 4-amino-biphenyl (**77a**) as a colorless solid (381 mg, 75 %). The analytical data match those of the commercially available substrate.

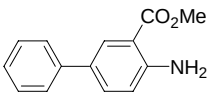
m.p.: 58.1-59.4 °C .

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.55-7.51 (m, 2H), 7.44-7.36 (m, 4H), 7.29-7.23 (m, 1H), 6.75 (ddd, *J* = 8.9, 2.7, 2.4 Hz, 2H), 3.71 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 145.8, 141.1, 131.6, 128.6, 128.0, 126.4, 126.2, 115.4.

MS (EI, 70 eV), *m/z* (%): 169 (100) [M^+], 141 (9), 115 (11), 83 (7), 63 (5).

4-Amino-biphenyl-3-carboxylic acid methyl ester (77b)



Phenylzinc iodide (**73a**, 3.6 mL, 1.0 M in THF) is added to a solution of 2-amino-5-bromo-benzoic acid methyl ester (**76b**, 690 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and

extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 4-amino-biphenyl-3-carboxylic acid methyl ester (**77b**) as a colorless solid (642 mg, 94 %). The analytical data are in accordance with the literature.[190]

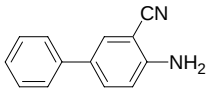
m.p.: 78.1-80.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.13 (d, *J* = 2.4 Hz, 1H), 7.56-7.53 (m, 3H), 7.43-7.37 (m, 2H), 7.31-7.25 (m, 1H), 6.74 (d, *J* = 8.4 Hz, 1 H), 5.78 (s, 2H), 3.90 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 168.5, 149.7, 140.4, 132.8, 129.5, 129.3, 128.7, 126.4, 126.2, 117.2, 110.9, 51.6.

MS (EI, 70 eV), *m/z* (%): 227 (100) [M^+], 195 (95), 167 (77), 139 (45), 83 (30).

4-Amino-biphenyl-3-carbonitrile (77c)



Phenylzinc iodide (**73a**, 3.6 mL, 1.0 M in THF) is added to a solution of 2-amino-5-bromo-benzonitrile (**76c**, 591 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4-amino-biphenyl-3-carbonitrile (**77c**) as a colorless solid (471 mg, 81 %). The analytical data are in accordance with the literature.[191]

m.p.: 147.8-150.0 °C.

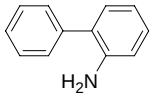
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.61 (d, *J* = 2.2 Hz, 1H), 7.57 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.49-7.45 (m, 2H), 7.44-7.38 (m, 2H), 7.34-7.28 (m, 1H), 6.81 (dd, *J* = 8.6, 0.4 Hz, 1H), 4.44 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 148.7, 139.1, 132.9, 131.5, 130.5, 128.9, 127.2, 126.3, 117.5, 115.7, 96.5.

MS (EI, 70 eV), *m/z* (%): 194 (100) [M^+], 166 (13), 139 (11), 97 (5), 63 (5).

[190] H. S. Andersen, et al., *J. Med. Chem.* **2002**, *45*, 4443.
[191] M. Siansburry, B. Webb, R. Schinazi, *J. Chem. Soc. Perkin Trans. 1* **1975**, 289.

2-Amino-biphenyl (77d)



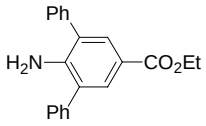
Phenylzinc iodide (**73a**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of 2-bromo-aniline (**76d**, 516 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 2-amino-biphenyl (**77d**) as a colorless oil (340 mg, 67%). The analytical data are in accordance with the literature.[192]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.57-7.51 (m, 4H), 7.46-7.41 (m, 1H), 7.27-7.23 (m, 2H), 6.95-6.90 (m, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 143.2, 139.5, 130.3, 129.0, 128.7, 128.4, 127.5, 127.0, 118.5.

MS (EI, 70 eV), *m/z* (%): 169 (100) [M^+], 139 (9), 115 (19), 83 (26), 77 (11).

2'-Amino-[1,1';3',1'']terphenyl-5'-carboxylic acid ethyl ester (77e)



Phenylzinc iodide (**73a**, 7.2 mL, 1.0 M in THF, 7.2 mmol) is added to a solution of 4-amino-3,5-dibromo-benzoic acid ethyl ester (**76e**, 969 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 10:1) yields 2'-amino-[1,1';3',1'']terphenyl-5'-carboxylic acid ethyl ester (**77e**) as a colorless solid (504 mg, 53%). The analytical data are in accordance with the literature.[193]

m.p.: 97.8-99.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.82 (d, *J* = 0.4 Hz, 2H), 7.51-7.44 (m, 8H), 7.41-7.35 (m, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.25 (s, 2H), 1.34 (t, *J* = 7.2 Hz, 3H).

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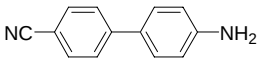
[192] J. R. Hwu, F. F. Wong, M. J. Shiao, *J. Org. Chem.* **1992**, *57*, 5254.
[193] Y. Miura, M. Momoki, M. Nakatsuji, Y. Teki, *J. Org. Chem.* **1998**, *63*, 1555.

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.8, 145.2, 138.8, 131.4, 129.3, 129.0, 127.7, 126.9, 119.7, 60.4, 14.5

MS (EI, 70 eV), *m/z* (%): 317 (100) [M^+], 293 (42), 272 (89), 243 (37), 215 (15).

4'-Amino-biphenyl-4-carbonitrile (77f)



4-Cyanophenylzinc iodide (**73b**, 3.8 mL, 0.95 M in THF, 3.6 mmol) is added to a solution of 4-bromo-aniline (**76a**, 516 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 4'-amino-biphenyl-4-carbonitrile (**77f**) as a light yellow solid (559 mg, 96 %. The analytical data are in accordance with the literature.[194]

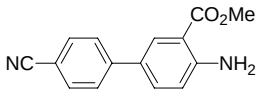
m.p.: 181.0-183.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.67-7.58 (m, 4H), 7.41 (ddd, *J* = 8.2, 1.5, 0.4 Hz, 2H), 6.76 (ddd, *J* = 8.2, 1.5, 0.4 Hz, 2H), 3.87 (s, 2H)..

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 147.2, 145.5, 132.5, 129.0, 128.2, 126.6, 119.3, 115.3, 109.5.

MS (EI, 70 eV), *m/z* (%): 194 (34) [M^+], 166 (44), 140 (29), 97 (14), 77 (11).

4-Amino-4'-cyano-biphenyl-3-carboxylic acid methyl ester (77g)



4-Cyanophenylzinc iodide (**73b**, 3.8 mL, 0.95 M in THF, 3.6 mmol) is added to a solution of 2-amino-5-bromo-benzoic acid methyl ester (**76b**, 690 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 4-amino-4'-cyano-biphenyl-3-carboxylic acid methyl ester (**77g**) as a light yellow solid (742 mg, 98 %).

m.p.: 147.0-148.7 °C

[194] M. Hird, A. J. Seed, K. J. Toyne, *Synlett* **1999**, *4*, 438.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.14 (d, *J* = 2.2 Hz, 1H), 7.69-7.60 (m, 4H), 7.53 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 5.92 (s, 2H), 3.90 (s, 3H).

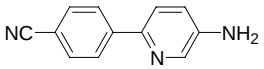
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 168.2, 150.7, 144.8, 132.6, 130.0, 127.9, 126.9, 126.5, 119.1, 117.4, 111.0, 109.8, 51.7.

HRMS *m/z* : calc. for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0894.

MS (EI, 70 eV), *m/z* (%): 252 (100) [M^+], 220 (86), 191 (49), 163 (24), 137 (8).

IR (cm^{-1}): 3478(m), 3363 (s), 3214 (w), 2952 (w), 2225 (m), 1677 (s), 1629 (s), 1602 (s), 1563 (m), 1491 (m), 1444 (s), 1328 (m), 1289 (m), 1231 (s) 1179 (s), 1110 (m), 1025 (m).

4-(5-Amino-pyridin-2-yl)-benzonitrile (77h)



4-Cyanophenylzinc iodide (**73b**, 3.8 mL, 0.95 M in THF, 3.6 mmol) is added to a solution of 6-bromo-pyridin-3-ylamine (**76f**, 519 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2 1:1) yielded 4-(5-amino-pyridin-2-yl)-benzonitrile (**77h**) as a light yellow solid (479 mg, 82 %).

m.p.: 189.8-191.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.18 (d, *J* = 2.9 Hz, 1H), 8.00 (ddd, *J* = 8.2, 1.9, 1.8 Hz, 2H), 7.68 (ddd, *J* = 8.2, 1.9, 1.8 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.05 (dd, *J* =8.6, 2.9 Hz, 1H), 3.88 (s, 2H).

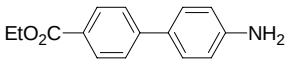
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 145.3, 143.6, 142.4, 137.4, 132.4, 126.2, 121.8, 121.3, 119.2, 110.8.

HRMS *m/z* : calc. for $C_{12}H_9N_3$ 195.0796, found 195.0791.

MS (EI, 70 eV), *m/z* (%): 195 (100) [M^+], 167 (6), 140 (8), 114 (2), 97 (4).

IR (cm^{-1}): 3405 (m), 3331 (m), 3198 (m), 2926 (w), 2227 (m), 1647 (m), 1584 (s), 1480 (m), 1424 (m), 1327 (m), 1296 (m), 1268 (m), 1252 (m), 1176 (m), 1148 (m), 1110 (m), 1012 (m).

4'-Amino-biphenyl-4-carboxylic acid ethyl ester (77i)



4-(Ethoxycarbonyl)phenylzinc iodide (**73c**, 25.5 mL, 0.94 M in THF, 24 mmol) is added to a solution of 4-bromo-aniline (**76a**, 3.44 g, 20 mmol), $Pd(OAc)_2$ (45 mg, 0.2 mmol), S-Phos (164 mg, 0.4 mmol) in THF (20 mL), according to **TP 6** (**Caution**: The reaction is exothermic. For conducting the reaction on a bigger scale, a reflux condenser was attached and the zinc reagent added over 10-15 min). The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4'-amino-biphenyl-4-carboxylic acid ethyl ester (**77i**) as a colorless solid (636 mg, 88 %).

m.p.: 86.8-88.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.05 (ddd, *J* = 8.5, 2.0, 1.9 Hz, 2H), 7.59 (ddd, *J* = 8.5, 2.0, 1.9 Hz, 2H), 7.48-7.43 (m, 2H), 6.78-6.73 (m, 2H), 4.38 (q, *J* =7.1 Hz, 2H), 3.79 (s, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

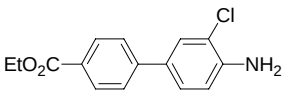
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.7, 146.7, 145.4, 130.1, 130.0, 128.2, 128.1, 125.9, 115.3, 60.8, 14.4.

HRMS *m/z* : calcd. for $C_{15}H_{15}NO_2$ 241.1103, found 241.1101.

MS (EI, 70 eV), *m/z* (%): 241 (100) [M^+], 213 (49), 196 (38), 167 (20), 139 (9).

IR (cm^{-1}): 3421 (w), 3334 (w), 2985 (w), 1693 (vs), 1629 (w), 1595 (m), 1532 (w), 1495 (m), 1473 (w), 1364 (m), 1276 (s), 1197 (m), 1132 (m), 1115 (m), 1023 (m).

4'-Amino-3'-chloro-biphenyl-4-carboxylic acid ethyl ester (77j)



4-(Ethoxycarbonyl)phenylzinc iodide (**73c**, 3.8 mL, 0.94 M in THF, 3.6 mmol) is added to a solution of 4-bromo-2-chloro-phenylamine (**76g**, 619 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 4'-amino-3'-chloro-biphenyl-4-carboxylic acid ethyl ester (**77j**) as a colorless solid (719 mg, 87 %).

m.p.: 65.3-67.0 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 8.06 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 1.5 Hz, 1H), 7.35 (dd, *J* = 8.3, 1.5 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.17 (s, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

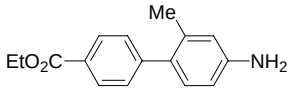
^{13}C-NMR ($CDCl_3$, 125 MHz, 25°C): δ = 166.5, 144.2, 142.9, 130.9, 130.1, 128.0, 126.5, 126.0, 119.6, 116.0, 60.9, 14.4.

HRMS *m/z* : calc. for $C_{15}H_{14}ClNO_2$ 275.0713, found 275.0709.

MS (EI, 70 eV), *m/z* (%): 275 (100) [M^+], 247 (27), 230 (36), 167 (26), 139 (8).

IR (cm^{-1}): 3476 (w), 3374 (m), 2982 (w), 1700 (s), 1638 (s), 1619 (s), 1599 (vs), 1526 (m), 1495 (s), 1393 (m), 1366 (m), 1270 (vs), 1255 (vs), 1184 (vs), 1107 (vs), 1014 (s).

4'-Amino-2'-methyl-biphenyl-4-carboxylic acid ethyl ester (77k)



4-(Ethoxycarbonyl)phenylzinc iodide (**73c**, 3.8 mL, 0.94 M in THF, 3.6 mmol) is added to a solution of 4-bromo-3-methyl-aniline (**76h**, 558 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 3 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yields 4'-amino-2'-methyl-biphenyl-4-carboxylic acid ethyl ester (**77k**) as a colorless solid (533 mg, 72%).

m.p.: 90.7-92.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.05 (ddd, *J* = 8.5, 2.0, 1.9 Hz, 2H), 7.36 (ddd, *J* = 8.5, 2.0, 1.9 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.61-6.56 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 2H), 2.20 (s, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

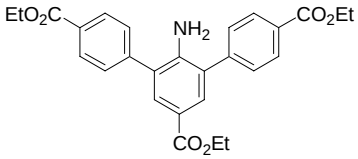
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.8, 146.8, 146.1, 136.3, 131.4, 130.7, 129.4, 129.3, 128.3, 116.9, 112.7, 60.8, 20.5, 14.4.

HRMS *m/z* : calcd. for $C_{16}H_{17}NO_2$ 255.1259, found 255.1266.

MS (EI, 70 eV), *m/z* (%): 255 (100) [M^+], 227 (31), 210 (23), 182 (17), 165 (4).

IR (cm^{-1}): 3467 (w), 3356 (w), 2957 (w), 1698 (s), 1648 (m), 1598 (s), 1272 (vs), 1249 (s), 1178 (s), 1102 (vs).

2'-Amino-[1,1';3',1'']terphenyl-4,5',4''-tricarboxylic acid triethyl ester (77l)



4-(Ethoxycarbonyl)phenylzinc iodide (**73c**, 7.7 mL, 0.94 M in THF, 7.2 mmol) was added to a solution of 2-amino-5-bromo-benzoic acid methyl ester (**73e**, 969 mg, 3 mmol), Pd(OAc)2 (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 3 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 2'-amino-[1,1';3',1'']terphenyl-4,5',4''-tricarboxylic acid triethyl ester (**77l**) as a yellow solid (651 mg, 47%).

m.p.: 129.5-131.6 °C

^{1}H-NMR (CDCl3, 600 MHz, 25°C): δ = 8.12 (d, J =8.2 Hz, 4H), 7.82 (s, 2H), 7.56 (d, J = 8.2 Hz, 4H), 4.39 (q, J = 7.1 Hz, 4 H), 4.31 (q, J = 7.1 Hz, 2H), 4.26 (s, 2H), 1.40 (t, J =7.1 Hz, 6H), 1.34 (t, J = 7.1 Hz, 3H).

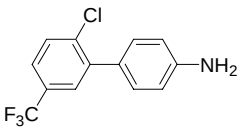
^{13}C-NMR (CDCl3, 75 MHz, 25°C): δ = 166.5, 166.2, 144.7, 143.2, 131.7, 130.3, 129.9, 129.2, 126.1, 120.1, 61.1, 60.6, 14.4, 14.4.

HRMS m/z: calcd. for $C_{27}H_{27}NO_6$ 461.1838, found 481.1846.

MS (EI, 70 eV), m/z (%):461 (100) [M^+], 416 (22), 388 (5), 287 (8), 241 (6).

IR (cm-1): 3453 (w), 3357 (w), 2979 (w), 1705 (vs), 1605 (s), 1464 (m), 1399 (m), 1366 (s), 1336 (m), 1283 (s), 1232 (vs), 1177 (s), 1098 (vs), 1048 (s), 1017 (s).

2'-Chloro-5'-trifluoromethyl-biphenyl-4-ylamine (77m)



2-Chloro-5-trifluoromethylphenylzinc iodide (**73d**, 3.7 mL, 0.98 M in THF, 3.6 mmol) is slowly added (90 min via syringe pump) to a solution of 4-bromo-aniline (**76a**, 516 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 0.5 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography

(pentane/ether 7:3) yields 2'-chloro-5'-trifluoromethyl-biphenyl-4-ylamine (**77m**) as a colorless oil (647 mg, 79 %).

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.56-7.53 (m, 2H), 7.44 (ddd, *J* = 8.4, 2,2, 0.7 Hz, 1H), 7.24 (ddd, *J* = 9.0, 2.6, 2.3Hz, 2H), 6.73 (ddd, *J* = 9.0, 2.6, 2.3 Hz, 2H), 3.78 (s, 2H).

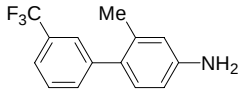
^{13}C-NMR ($CDCl_3$, 1255 MHz, 25°C): δ = 146.5, 142.3, 136.2, 130.4, 130.4, 129.2, (q, *J* = 33.4 Hz), 128.1 (q, *J* = 3.7 Hz), 128.0, 124.4 (q, *J* = 3.7 Hz), 123.8, (q, *J* = 272.6 Hz), 114.6.

HRMS *m/z* : calc. for $C_{13}H_9ClF_3N$ 271.0376, found 271.0379.

MS (EI, 70 eV), *m/z* (%): 271 (100) [M^+], 252 (4), 235 (4), 216 (7), 167 (12).

IR (cm^{-1}): 3469 (w), 3386 (w), 3034 (w), 1623 (s), 1609 (m), 1580 (w), 1520 (m), 1475 (m), 1433 (w), 1402 (m), 1332 (vs), 1284 (s), 1254 (s), 1168 (s), 1119 (vs), 1087 (vs), 1028 (vs).

2-Methyl-3'-trifluoromethyl-biphenyl-4-ylamine (77n)



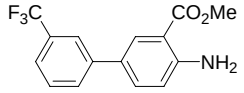
3-Trifluoromethylphenylzinc iodide (**73e**, 3.6mL, 1.0 M in THF) is added to a solution of 4-bromo-3-methyl-aniline (**76h**, 558 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yields 2-methyl-3'-trifluoromethyl-biphenyl-4-ylamine (**77n**) as a colorless oil (698 mg, 93 %). The analytical data are in accordance with the literature.[195]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.55-7.51 (m, 2H), 7.49-7.46 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.62-6.57 (m, 2H), 3.68 (bs, 2H), 2.19 (s, 3H)

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 146.1, 142.7, 136.3, 132.8, 130.8, 130.3 (q, *J* = 32.1 Hz), 128.4, 126.1, (q, 3.8 Hz), 124.3 (q, *J* =273.0 Hz), 122.9 (q, 3.8 Hz), 116.9, 104.8, 20.4

MS (EI, 70 eV), *m/z* (%): 251 (100) [M^+], 180 (28), 165 (22), 152 (11), 90 (20).

4-Amino-3'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (77o)



[195] A. Greenfield, et al., *Bio. Med Chem. Lett.* **2005**, *12*, 4985.

3-Trifluoromethylphenylzinc iodide (**73e**, 3.6mL, 1.0 M in THF) is added to a solution of 2-amino-5-bromo-benzoic acid methyl ester (**76b**, 690 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 4-amino-3'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester (**77o**) as a colorless oil (867 mg, 98 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.13 (d, *J* = 2.4 Hz, 1H), 7.79-7.77 (m, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.54-7.45 (m, 3H), 6.73 (d, *J* = 8.6 Hz, 1H), 5.88 (s, 2H), 3.91 (s, 3H).

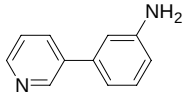
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 168.3, 150.2, 141.1, 132.5, 131.0 (q, *J* = 32.0 Hz), 129.6, 129.3, 129.1, 127.5, 124.2 (q, *J* = 272.4 Hz), 122.9 (q, *J* = 3.8 Hz), 122.7 (q, *J* = 3.8 Hz), 117.3, 110.9, 51.6.

HRMS *m/z* : calcd. for $C_{15}H_{12}F_3NO_2$ 295.0820, found 295.0824.

MS (EI, 70 eV), *m/z* (%): 295 (100) [M^+], 263 (59), 235 (23), 216 (7), 139 (4).

IR (cm^{-1}): 3458 (m), 3356 (m), 3180 (w), 052 (w), 3012 (w), 2987 (w), 2947 (w), 2912 (w), 1678 (s), 1631 (m), 1595 (m), 1562 (m), 1479 (m), 1433 (m), 1409 (w), 1327 (s), 1316 (s), 1240 (s), 1160(s), 1123 (vs), 1072 (vs), 1049 (s).

3-Pyridin-3-yl-phenylamine (77p)



3-Pyridylzinc iodide (**73f**, 3.9mL, 0.92 M in THF) is added to a solution of 3-bromoaniline (**76i**, 516 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2 1:1) yielded 3-pyridin-3-yl-phenylamine (**77p**) as a colorless solid (500 mg, 98 %). The analytical data are in accordance with the literature.[196]

m.p.: 74.4-75.8 °C.

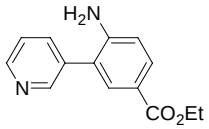
[196] S. P. Wright, *et al.*, *J. Med. Chem.* **2002**, *45*, 3856.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.81 (dd, *J* = 2.4, 0.7 Hz, 1H), 8.56 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.82 (ddd, *J* = 7.9, 2.4, 1.7 Hz, 1H), 7.32 (ddd, *J* = 8.1, 4.7, 0.9 Hz, 1H), 7.25 (td, *J* = 7.8, 0.4 Hz, 1H), 6.97-6.94 (m, 1H), 6.88-6.86 (m, 1H), 6.71 (ddd, *J* = 7.9, 2.3, 0.9 Hz, 1H), 3.78 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 148.4, 148.3, 147.0, 139.0, 136.8, 134.3, 130.0, 123.4, 117.5, 114.8, 113.6.

MS (EI, 70 eV), *m/z* (%): 170 (100) [M^+], 142 (7), 115 (12), 89 (8), 63 (8).

4-Amino-3-pyridin-3-yl-benzoic acid ethyl ester (77q)



3-Pyridylzinc iodide (**73f**, 3.9mL, 0.92 M in THF) is added to a solution of 4-amino-3-bromo-benzoic acid ethyl ester (**76j**, 732 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2 1:1) yielded 4-amino-3-pyridin-3-yl-benzoic acid ethyl ester (**77q**) as a colorless solid (511 mg, 70 %).

m.p.: 116.9-119.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.70 (dd, *J* = 2.3, 1.0 Hz, 1H), 8.62 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.88 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.80-7.75 (m, 2H), 7.39 (ddd, *J* = 7.7, 4.9, 1.0 Hz, 1H), 6.75 (d, *J* = 8.4 hz, 1H), 4.32 (q, *J* =7.2 Hz, 2H), 4.12 (s, 2H), 1.35 (t, *J* =7.2 Hz, 3H).

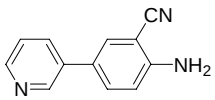
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.4, 150.0, 148.9, 148.0, 136.6, 134.3, 132.5, 131.2, 123.7, 122.7, 120.6, 114.8, 60.5, 14.4.

HRMS *m/z* : calcd. for $C_{14}H_{14}N_2O_2$ 242.1055, found 242.1048.

MS (EI, 70 eV), *m/z* (%): 242 (88) [M^+], 214 (24), 197 (100), 169 (25), 115 (10).

IR (cm^{-1}): 3430 (w), 3338 (w), 3218 (w), 2983 (w), 1670 (s), 1637 (m), 1602 (s), 1506 (m), 1480 (m), 1434 (m), 1365 (s), 1342 (m), 1293 (s), 1243 (vs), 1188 (s), 1157 (m).

2-Amino-5-pyridin-3-yl-benzonitrile (77r)



3-Pyridylzinc iodide (**73f**, 3.9 mL, 0.92 M in THF, 3.6 mmol) is added to a solution of 2-amino-5-bromo-benzonitrile (**76c**, 591 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2.5 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (CH_2Cl_2/ether 1:1) yielded 2-amino-5-pyridin-3-yl-benzonitrile (**77r**) as a colorless solid (509 mg, 87 %).

m.p.: 110.4-111.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.74 (d, *J* = 2.4 Hz, 1H), 8.55 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.78-7.74 (m, 1H), 7.60-7.54 (m, 2H), 7.33 (dd, *J* = 8.9, 4.5 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 1H), 4.58 (s, 2H).

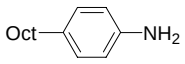
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 149.4, 148.4, 147.5, 134.7, 133.5, 132.7, 130.6, 127.8, 123.6, 117.2, 115.9, 96.7.

HRMS *m/z* : calc. for $C_{12}H_9N_3$ 195.0796, found 195.0791.

MS (EI, 70 eV), *m/z* (%): 195 (100) [M^+], 167 (6), 140 (9), 114 (4), 88 (3).

IR (cm^{-1}): 3428 (w), 3388 (w), 3318 (w), 3119 (m), 2210 (m), 1635 (m), 1610 (s), 1558 (w), 1512 (s), 1478 (s), 1431 (s), 1398 (w), 1320 (m), 1272 (s), 1158 (m), 1022 (m).

Preparation of 4-Octyl-phenylamine (77s)



1-Octylzinc bromide (**74a**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of 4-bromoaniline (**76a**, 516 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 4-octyl-phenylamine (**77s**) as a colorless oil (566 mg, 92 %). The analytical data are in accordance with the literature.[197]

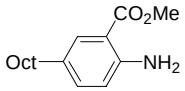
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 6.96 (dd, *J* = 8.0, 1.7 Hz, 2H), 6.61 (dd, *J* = 8.0, 1.7 Hz, 2H), 3.52 (s, 2H), 2.48 (t, *J* = 6.8 Hz, 2H), 1.56-1.52 (m, 2H), 1.3-1.26 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H).

[197] T. Ohe, N. Miyaura, A. Suzuki, *J. Org. Chem.* **1993**, *58*, 2201.

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 144.0, 133.1, 129.1, 115.2, 35.1, 31.9, 31.8, 29.5, 29.3, 29.3, 22.7, 14.1.

MS (EI, 70 eV), *m/z* (%): 205 (18) [M^+], 107 (7), 106 (100), 77 (3), 41 (2).

Preparation of 2-amino-5-octyl-benzoic acid methyl ester (77t)



1-Octylzinc bromide (**74a**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of 2-amino-5-bromo-benzoic acid methyl ester (**76b**, 690 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 2-amino-5-octyl-benzoic acid methyl ester (**77t**) as a colorless oil (674 mg, 85 %).

m.p.: 38.3-39.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.65 (d, *J* = 2.2 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.56 (s, 2H), 3.86 (s, 3H), 2.47 (t, *J* = 7.7 Hz, 2H), 1.59-1.57 (m, 2H), 1.32-1.24 (m, 10 H), 0.87 (t, *J* = 6.7 Hz, 3H).

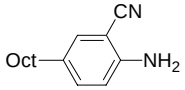
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 168.6, 148.4, 134.6, 130.7, 130.3, 116.8, 110.7, 51.4, 34.9, 31.9, 31.6, 29.5, 29.3, 29.2, 22.7, 14.1.

HRMS *m/z* : calcd. for $C_{16}H_{25}NO_2$ 263.1885, found 263.1865.

MS (EI, 70 eV), *m/z* (%): 263 (30) [M^+], 164 (100), 132 (27), 104 (6), 77 (3).

IR (cm^{-1}): 3462 (m), 3361 (m), 2918 (s), 2849 (m), 1681 (vs), 1634 (m), 1599 (m), 1564 (m), 1498 (w), 1464 (w), 1436 (s), 1297 (m), 1247 (s), 1207 (s), 1091 (s).

2-Amino-5-octyl-benzonitrile (77u)



1-Octylzinc bromide (**74a**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of 2-amino-5-bromo-benzonitrile (**76c**, 591 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution

and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 2-amino-5-octyl-benzonitrile (**77u**) as a colorless solid (541 mg, 78 %).

m.p.: 63.3-64.9 °C

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.17-7.12 (m, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 4.23 (s, 2H), 2.46 (t, *J* = 7.7 Hz, 2H), 1.57-1.48 (m, 2H), 1.31-1.21 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H).

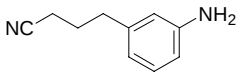
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 147.5, 134.5, 132.8, 131.4, 117.8, 115.3, 96.1, 34.5, 31.8, 31.3, 29.4, 29.2, 29.1, 22.6, 14.1.

HRMS *m/z* : calcd. for $C_{15}H_{22}N_2$ 230.1783, found 230.1784.

MS (EI, 70 eV), *m/z* (%): 230 (27) [M^+], 144 (3), 131 (100), 104 (3), 77 (3).

IR (cm^{-1}): 3455 (m), 3362 (s), 2953 (m), 2920 (vs), 2849 (m), 2212 (s), 1632 (vs), 1571 (m), 1504 (vs), 1416 (m), 1312 (m), 1267 (m), 1220 (w), 1160 (m).

4-(3-Amino-phenyl)-butyronitrile (77v)



4-Cyanobutylzinc bromide (**74b**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of 3-bromoaniline (**76i**, 51 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 1.5 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 1:1) yielded 4-(3-amino-phenyl)-butyronitrile (**77v**) as a colorless oil (455 mg, 95%).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.07 (t, *J* = 7.7 Hz, 1H), 6.57-6.48 (m, 3H), 3.67 (s, 2H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.27 (t, *J* = 7.1 Hz, 2H), 1.96-1.86 (m, 2H).

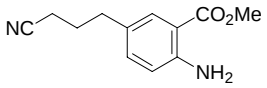
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 146.6, 140.7, 129.3, 119.5, 118.2, 114.8, 112.9, 34.0, 26.5, 16.0.

HRMS *m/z* : calcd. for $C_{10}H_{12}N_2$ 160.1000, found 160.9986.

MS (EI, 70 eV), *m/z* (%): 160 (67) [M^+], 120 (7), 107 (100), 77 (9), 64 (4).

IR (cm^{-1}): 3449 (w), 3367 (w), 3035 (w), 2934 (w), 2866 (w), 2245 (w), 1621 (s), 1604 (s), 1588 (s), 1492 (m), 1461 (s), 1421 (w), 1307 (m), 1289 (m), 1168 (m).

2-Amino-5-(3-cyano-propyl)-benzoic acid methyl ester (77x)



4-Cyanobutylzinc bromide (**74b**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of 2-amino-5-bromo-benzoic acid methyl ester (**76b**, 690 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 2-amino-5-(3-cyano-propyl)-benzoic acid methyl ester (**77x**) as a colorless solid (642 mg, 98 %).

m.p.: 187.6-188.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.63 (d, *J* = 2.2 Hz, 1H), 7.05 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 5.57 (s, 2H), 3.83 (s, 3H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.27 (t, *J* = 7.2 Hz, 2H), 1.93-1.83 (m, 2H).

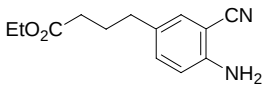
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 168.6, 149.4, 134.6, 130.8, 127.5, 119.9, 117., 110.9, 51.8, 33.6, 27.3, 16.5.

HRMS *m/z* : calc. for $C_{12}H_{14}N_2O_2$ 218.1055, found 218.1048.

MS (EI, 70 eV), *m/z* (%): 218 (53) [M^+], 186 (5), 164 (100), 132 (37), 104 (6).

IR (cm^{-1}): 3471 (m), 3364 (m), 3024 (w), 2955 (w), 2863 (w), 2247 (w), 1690 (s), 1625 (s), 1587 (s), 1564 (vs), 1497 (s), 1438 (s), 1343 (w), 1296 (vs), 1252 (vs), 1215 (vs), 1203 (vs), 1163 (vs), 1083 (vs).

4-(4-Amino-3-cyano-phenyl)-butyric acid ethyl ester (77x)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 4.6 mL, 0.78 M in THF, 3.6 mmol) is added to a solution of 2-amino-5-bromo-benzonitrile (**x**, 591 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4-(4-amino-3-cyano-phenyl)-butyric acid ethyl ester (**77x**) as a colorless solid (509 mg, 73 %).

m.p.: 56.3-58.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.17-7.12 (m, 2H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.28 (s, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.91-1.81 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

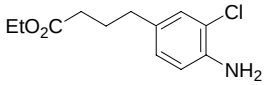
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 173.3, 147.9, 134.5, 131.6, 131.2, 117.6, 115.5, 96.1, 60.3, 33.7, 33.4, 26.4, 14.2.

HRMS *m/z* : calc. for $C_{13}H_{16}N_2O_2$ 232.1212, found 232.1208.

MS (EI, 70 eV), *m/z* (%): 232 (52) [M^+], 187 (22), 144 (100), 131 58), 104 (5).

IR (cm^{-1}): 3453 (m), 3363 (s), 3235 (w), 2984 (w), 2918 (w), 2209 (s), 1715 (vs), 1638 (s), 1567 (m), 1505 (s), 1345 (s), 1264 (s), 1253 (s), 1191 (vs), 1167 (s), 1152 (s), 1067 (m), 1020 (s).

4-(4-Amino-3-chloro-phenyl)-butyric acid ethyl ester (77y)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 4.6 mL, 0.78 M in THF, 3.6 mmol) is added to a solution of 4-bromo-2-chloro-aniline (**76g**, 591 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 4-(4-amino-3-chloro-phenyl)-butyric acid ethyl ester (**77y**) as a colorless oil (512 mg, 71 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.05 (d, *J* = 1.5 Hz, 1H), 6.86 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 2H), 2.51 (t, *J* = 7.6 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.93-1.83 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

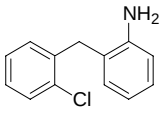
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 173.5, 140.9, 132.4, 129.2, 127.7, 119.2, 115.9, 60.3, 34.0, 33.5, 26.6, 14.2.

HRMS *m/z* : calcd. for $C_{12}H_{16}ClNO_2$ 241.0870, found 241.0866.

MS (EI, 70 eV), *m/z* (%): 241 (65) [M^+], 196 (29), 153 (96), 140 (100), 132 (6).

IR (cm^{-1}): 3469 (w), 3372 (w), 2980 (w), 2936 (w), 2866 (w), 1721 (vs), 1624 (s), 1507 (vs), 1445 (w), 1416 (w), 1373 (m), 1306 (m), 1260 (m), 1181 (s), 1144 (s), 1095 (m), 1044 (s).

2-(2-Chloro-benzyl)-phenylamine (77z)



2-Chlorobenzylzinc chloride (**75b**, 34.8 mL, 0.92 M in THF, 32 mmol) was added to a solution of 2-bromoaniline (**x**, 4.64, 27 mmol), $Pd(OAc)_2$ (60 mg, 0.27 mmol), S-Phos (221 mg, 0.54 mmol) in THF (20 mL), according to **TP 6** (**Caution**: The reaction is exothermic. For conducting the reaction on a bigger scale, a reflux condenser was attached and the zinc reagent added over 10-15 min). The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 5:1) yielded 2-(2-chloro-benzyl)-phenylamine (**76d**) as a pale yellow oil (4.76 g, 81 %).

^{1}H-NMR (600 MHz, CDCl3) δ: 7.43-7.41 (m, 1 H), 7.20-7.12 (m, 3 H), 7.04-6.99 (m, 2 H), 6.80-6.73 (m, 2 H), 3.99 (s, 2 H), 3.67 (s, 2 H).

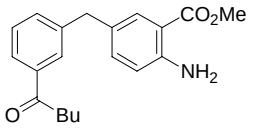
^{13}C-NMR (150 MHz, CDCl3) δ: 144.4, 136.8, 134.3, 130.8, 130.0, 129.4, 127.8, 127.8, 127.0, 123.6, 118.96, 115.89, 34.9.

HRMS m/z: calcd. for $C_{13}H_{12}N_1Cl_1$ 217.0658, found 217.0657.

MS (70 eV, EI) m/z (%): 217 (27) [M^+], 183 (16), 182 (100), 181 (19), 180 (69), 167 (12), 165 (16), 106 (11), 90 (13).

IR (cm-1): 3372, 3022, 1742, 1619, 1493, 1455, 1442, 1276, 1189, 1120, 1048, 1036.

2-Amino-5-(3-pentanoyl-benzyl)-benzoic acid methyl ester (77aa)



3-Pentanoylbenzylzinc chloride (**75c,** 2.8 ml, 0.87 M in THF, 2.4 mmol) is added to a solution of 2-amino-5-bromo-benzoic acid methyl ester (**76b**, 460 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.5 mg, 0.04 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 0.5 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:1) yields 2-amino-5-(3-pentanoyl-benzyl)-benzoic acid methyl ester (**77aa**) as a colorless solid (638 mg, 98 %).

m.p.: 76.8–79.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.78 – 7.74 (m, 2 H), 7.70 (dd, *J* = 2.2, 0.4 Hz, 1 H), 7.35 – 7.33 (m, 2 H), 7.07 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 5.63 (s, 2 H), 3.90 (s, 2 H), 3.84 (s, 3 H), 2.92 (t, *J* = 7.5 Hz, 2 H), 1.69 (ddd, *J* = 14.7, 7.6, 7.4 Hz, 2 H), 1.39 (td, *J* = 14.9, 7.3 Hz, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

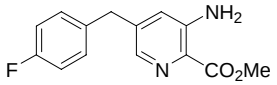
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 200.9, 168.7, 149.2, 142.3, 137.6, 135.1, 133.5, 131.3, 128.9, 128.5, 128.3, 126.2, 117.4, 110.9, 51.7, 41.0, 38.6, 26.8, 22.7, 14.2.

HRMS *m/z* : calc.for $C_{20}H_{22}NO_3$ 325.1678, found 325.1681.

MS (EI, 70 eV), *m/z* (%):326 (18), 325 (100) [M^+], 294 (6), 269 (9), 268 (67), 266 (4), 180 (8), 164 (25), 132 (14).

IR (cm^{-1}): 3444 (s), 3340 (s), 2956 (m), 2932 (m), 2872 (m), 1684 (s), 1668 (vs), 1624 (s), 1584 (s), 1564 (m), 1496 (m), 1432 (s), 1404 (m), 1364 (m), 1296 (s), 1248 (vs), 1228 (m), 1204 (s), 1180 (m), 1156 (s), 1100 (m), 1084 (m), 1024 (m), 980 (m), 832 (m), 792 (m), 760 (m), 688 (m), 580 (m).

3-Amino-5-(4-fluoro-benzyl)-pyridine-2-carboxylic acid methyl ester (77ab)



4-Fluorobenzylzinc chloride (**75d**, 2.1 mL, 1.0 M in THF, 2.1 mmol) is added to a solution of 3-amino-5-bromo-pyridine-2-carboxylic acid methyl ester (**76k**, 410 mg, 1.8 mmol), $Pd(OAc)_2$ (4.1 mg, 0.018 mmol), S-Phos (14.8 mg, 0.036 mmol) in THF (1.5 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 3:2) yielded 3-amino-5-(4-fluoro-benzyl)-pyridine-2-carboxylic acid methyl ester (**77ab**) as a pale yellow solid (423 mg, 92 %). The analytical data are in accordance with the literature.[86]

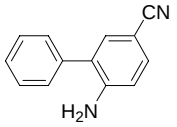
m.p.: 146.0-147.9 °C:

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.94 (d, *J* = 1.7 Hz, 1H), 7.13-7.08 (m, 2H), 7.02-6.95 (m, 2H), 6.74 (d, *J* = 1.7 Hz, 1H), 5.69 (bs, 2H), 3.94 (s, 3H), 3.89 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 167.6, 161.7, (d, *J* = 245.4 Hz), 147.0, 141.7, 139.3, 134.4 (d, *J* = 3.1 Hz), 130.4 (d, *J* = 7.7 Hz), 125.8, 124.5, 115.6 (d, *J* = 21.7 Hz), 52.3, 37.9.

MS (EI, 70 eV), *m/z* (%): 260 (30) [M^+], 202 (100), 174 (10), 109 (14), 80 (5).

2-Amino-biphenyl-5-carbonitrile (77ac)



Phenylzinc iodide (**73a**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added slowly over 90 min to a solution of 4-amino-3-bromo-benzonitrile (**76l**, 591 mg, 3 mmol), $Ni(acac)_2$ (15.4 mg, 0.06 mmol), 2,2'-bipyridine (4.7 mg, 0.09 mmol) in THF (2 mL), according to **TP 8**. The reaction mixture was stirred for 3 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 2-amino-biphenyl-5-carbonitrile (**77ac**) as a colorless solid (438 mg, 75 %). The analytical data are in accordance with the literature.[198]

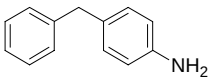
m.p.: 129.6-130.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.50-7.44 (m, 2H), 7.42-7.32 (m, 5H), 6.73 (d, *J* = 8.4 Hz, 1H), 4.23 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 147.7, 137.1, 134.4, 132.6, 129.2, 128.8, 128.1, 127.4, 120.0, 115.0, 100.5

MS (EI, 70 eV), *m/z* (%): 193 (100) [M^+], 166 (23), 139 (21), 115 (17), 83 (27).

4-Benzyl-phenylamine (77ad)



Benzylzinc chloride (**75a ,** 1.4 mL, 1.7 M in THF, 2.4 mmol) is added to a solution of 4-bromo-phenylamine (**76a**, 344 mg, 2 mmol), $Ni(acac)_2$ (0.5 mL, 0.1 M in THF, 0.05 mmol), , PPh_3 (0.5 mL, 0.4 M in THF, 0.20 mmol) in NMP (0.4 mL), according to **TP 9**. The reaction mixture was stirred for 1 h at 60 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution, extracted with ether and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 6:1) yielded 4-benzyl-phenylamine (**77ad**) as a brown oil (330 mg, 90 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.42-7.14 (m, 5H), 7.04 (d, *J* = 8.04 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 3.94 (s, 2H), 3.46 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 144.4, 141.9, 131.2, 129.7, 128.7, 128.3, 125.8, 115.3, 41.0.

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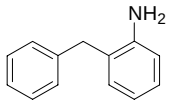
[198] B. Liu, K. K. Moffet, R. W. Joseph, B. D. Dorsey, *Tetrahedron Lett.* **2005**, *46*, 1779.

HRMS *m/z* : calc.for $C_{13}H_{13}N$ 183.1048, found 183,1045.

MS (EI, 70 eV), *m/z* (%): 183 (100) [M^+], 180 (8), 165 (13), 106 (33), 91 (14), 77 (9).

IR (cm^{-1}): 3448 (w), 3354 (m), 3214 (w), 3024 (m), 3002 (m), 2904 (w), 2838 (w), 1738 (m), 1620 (s), 1514 (vs), 1492 (m), 1452 (m), 1436 (m), 1366 (w), 1272 (m), 1178 (m), 1124 (w), 1074 (w).

2-Benzyl-phenylamine (77ae)



Benzylzinc chloride (**75a,** 1.4 mL, 1.7 M in THF, 2.4 mmol) is added to a solution of 2-bromo-phenylamine (**76d**, 344 mg, 2 mmol), $Ni(acac)_2$ (0.5 mL, 0.1 M in THF, 0.05 mmol), , PPh_3 (0.5 mL, 0.4 M in THF, 0.20 mmol) in NMP (0.4 mL), according to **TP 9**. The reaction mixture was stirred for 0.5 h at 60 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution, extracted with ether and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 6:1) yielded 2-benzyl-phenylamine (**77ae**) as a brown oil (274 mg, 75 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.35-7.28 (m, 2H), 7.26-7.18 (m, 3H), 7.17-7.05)m, 2H), 6.80 (dt, *J* = 7.3, 1.1 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 3.93 (s, 2H), 3.43 (s, 2H).

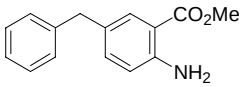
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 144.6, 139.3, 130.8, 128.6, 128.5, 127.6, 126.3, 125.1, 118.7, 115.9, 38.0.

HRMS *m/z* : calc.for $C_{13}H_{13}N$ 183.1048, found 183.1039.

MS (EI, 70 eV), *m/z* (%): 183 (100) [M^+], 180 (16), 167 (11), 165 (27), 106 (27), 77 (9).

IR (cm^{-1}): 3452 (m), 3370 (m), 3060 (m), 3024 (m), 2904 (w), 2838 (w), 1738 (m), 1620 (s), 1492 (vs), 1452 (s), 1366 (m), 1278 (m), 1074 (w).

2-Amino-5-benzyl-benzoic acid methyl ester (77af)



Benzylzinc chloride (**75a**, 0.75 mL, 1.6 M in THF, 1.2 mmol) is added to a solution of 2-amino-5-bromo-benzoic acid methyl ester (**76b**, 230 mg, 1 mmol), $Ni(acac)_2$ (0.25 mL, 0.1 M in THF, 0.025 mmol), PPh_3 (0.25 mL, 0.4 M in THF, 0.10 mmol) in NMP (0.4 mL), according to **TP 9**. The reaction mixture was stirred for 2 h at 60 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution, extracted with ether and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography

(pentane/ether 6:1) yielded 2-amino-5-benzyl-benzoic acid methyl ester (**77af**) as a colorless oil (367 mg, 77 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.71 (d, *J* = 2.21 Hz, 1H), 7.30-7.24 (m, 2H), 7.22-7.13 (m, 3H), 7.08 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.60 (d, *J* = 8.6 Hz, 1H), 5.59 (s, 2H), 3.86 (s, 2H), 3.85 (s, 3H).

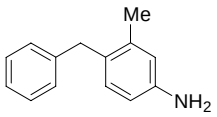
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 168.5, 148.8, 141.5, 135.0, 131.0, 128.8, 128.7, 128.4, 126.0, 117.1, 110.7, 51.5, 40.9.

HRMS *m/z* : calc.for $C_{15}H_{13}NO_2$ 241.1103, found 241.1080.

MS (EI, 70 eV), *m/z* (%): 241 (100) [M^+], 209 (36), 182 (22), 180 (21).

IR (cm^{-1}): 3476 (vs), 3376 (vs), 3024 (w), 2948 (w), 2920 (w), 1680 (s), 1624 (m), 1588 (m), 1560 (m), 1492 (m), 1436 (s), 1296 (s), 1244 (s), 1204 (s), 1160 (s), 1096 (m), 1072 (m).

4-Benzyl-3-methyl-phenylamine (77ag)



Benzylzinc chloride (**75a ,** 1.4 mL, 1.7 M in THF, 2.4 mmol) is added to a solution of 4-bromo-3-methyl-phenylamine (**76h**, 372 mg, 2 mmol), $Ni(acac)_2$ (0.5 mL, 0.1 M in THF, 0.05 mmol), PPh_3 (0.5 mL, 0.4 M in THF, 0.20 mmol) in NMP (0.4 mL), according to **TP 9**. The reaction mixture was stirred for 0.5 h at 60 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution, extracted with ether and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 4-benzyl-3-methyl-phenylamine (**77ag**) as a brown oil (312 mg, 79 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.31-7.25 (m, 2H), 7.22-7.18 (m, 2 H), 6.93 (d, *J* =7.9 Hz, 1H), 6.56-6.50 (m, 2H), 3.92 (s, 2H), 3.45 (s, 2H), 2.18 (s, 3H) .

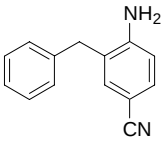
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 144.6, 141.2, 137.5, 130.8, 129.1, 128.5, 128.2, 125.6, 117.3, 112.7, 38.6, 19.7.

HRMS *m/z* : calc.for $C_{14}H_{15}N$ 197.1204, found 197.1185.

MS (EI, 70 eV), *m/z* (%): 197 (80) [M^+], 182 (55), 180 (11), 120 (100), 99 (10), 91 (21), 77 (13).

IR (cm^{-1}): 3448 (m), 3352 (m), 3214 (w), 3024 (m), 2914 (m), 1738 (m), 1622 (s), 1504 (vs), 1450 (s), 1378 (m), 1308 (m), 1278 (m), 1208 (m), 1072 (w), 1028 (m).

4-Amino-3-benzyl-benzonitrile (77ah)



Benzylzinc chloride (**75a,** 1.4 mL, 1.7 M in THF, 2.4 mmol) is added to a solution of 4-amino-3-bromo-benzonitrile (**76l**, 394 mg, 2 mmol), $Ni(acac)_2$ (0.5 mL, 0.1 M in THF, 0.05 mmol), PPh_3 (0.5 mL, 0.4 M in THF, 0.20 mmol) in NMP (0.4 mL), according to **TP 9**. The reaction mixture was stirred for 0.5 h at 60 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution, extracted with ether and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 6:1 to 3:1) yielded 4-amino-3-benzyl-benzonitrile (**77ah**) as a brown oil (350 mg, 84 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.40-7.13 (m, 7H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.34 (s, 2H), 3.88 (s, 2H).

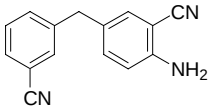
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.9, 140.4, 134.8, 131.9, 130.9, 128.7, 128.5, 126.3, 117.6, 115.5, 95.9, 40.4.

HRMS *m/z* : calc.for $C_{14}H_{12}N_2$ 208.1000, found 208.0986.

MS (EI, 70 eV), *m/z* (%): 208 (100) [M^+], 207 (60), 205 (8), 190 (8), 180 (6), 131 (25), 103 (5).

IR (cm^{-1}): 3460 (vs), 3366 (vs), 3238 (m), 3022 (m), 2218 (s), 1738 (w), 1634 (s), 1504 (s), 1492 (m), 1454 (m), 1422 (m), 1300 (m), 1262 (m), 1164 (m), 1072 (w), 1030 (w).

2-Amino-5-(3-cyanobenzyl)benzonitrile (77ai)



3-Cyanobenzylzinc chloride (**75f**, 3.0 mL, 0.88 M in THF, 2.4 mmol) is added to a solution of 2-amino-5-bromo-benzonitrile (**76c**, 394 mg, 2 mmol), $Ni(acac)_2$ (0.5 mL, 0.1 M in THF, 0.05 mmol), PPh_3 (0.5 mL, 0.4 M in THF, 0.20 mmol) in NMP (0.4 mL), according to **TP 9**. The reaction mixture was stirred for 1 h at 60 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution, extracted with ether and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:1) yielded 2-amino-5-(3-cyanobenzyl)benzonitrile (**77ai**) as a colorless oil (376 mg, 81 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.50-7.47 (m, 1H), 7.41-7.36 (m, 3H), 7.14-7.08 (m, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 4.35 (s, 2H), 3.86 (s, 2H).

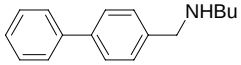
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 148.4, 142.0, 134.7, 133.2, 132.1, 132.0, 130.1, 129.3, 129.0, 118.7, 117.3, 115.7, 112.5, 96.0, 39.8.

HRMS *m/z* : calc.for $C_{15}H_{11}N_3$ 233.0953, found 233.0949.

MS (EI, 70 eV), *m/z* (%): 233 (100) [M^+], 232 (37), 215 (6), 205 (8), 131 (41), 103 (6).

IR (cm^{-1}): 3438 (s), 3320 (s), 3220 (m), 2224 (s), 2208 (s), 1738 (w), 1632 (s), 1504 (vs), 1478 (m), 1424 (m), 1320 (m), 1264 (m), 1170 (m).

Biphenyl-4-ylmethyl-butyl-amine (79a)



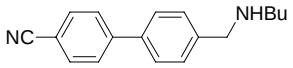
Phenylzinc iodide (**73a**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of (4-bromo-benzyl)-butyl-amine (**78a**, 727 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 4 h at 65 °C. Then, the reaction mixture was quenched with a sat. aq. K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 1:1) yielded biphenyl-4-ylmethyl-butyl-amine (**79a**) as a colorless oil (516 mg, 72 %). The analytical data are in accordance with the literature.[199]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.60-7.53 (m, 4H), 7.45-7.37 (m, 4H), 7.35-7.29 (m, 1H), 3.83 (s, 2H), 2.66 (t, *J* = 7.1 Hz, 2H), 1.56-1.47 (m, 2H), 1.42-1.30 (m, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 141.0, 139.8, 139.8, 128.7, 128.5, 128.3, 127.1, 127.0, 53.8, 49.3, 32.3, 20.5, 14.0.

MS (EI, 70 eV), *m/z* (%): 239 (56) [M^+], 196 (90), 167 (100), 152 (83), 98 (23).

4'-Butylaminomethyl-biphenyl-4-carbonitrile (79b)



4-Cyanophenylzinc iodide (**73b**, 3.8 mL, 0.95 M in THF, 3.6 mmol) is added to a solution of (4-bromo-benzyl)-butyl-amine (**78a**, 727 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 17 h at 65 °C. Then, the reaction mixture was quenched with a sat. aq. K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq.

[199] W. H. Pearson, W.-K. Fang, *J. Org. Chem.* **1995**, *60*, 4960.

thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yielded 4'-butylaminomethyl-biphenyl-4-carbonitrile (**79b**) as a yellow oil (587 mg, 74%). The analytical data are in accordance with the literature.[199]

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.69-7.64 (m, 4H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 3.83 (s, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 1.52-1.48 (m, 2H), 1.38 (s, 1H), 1.37-1.32 (m, 2H) 0.90 (t, *J* = 7.4 Hz, 3H).

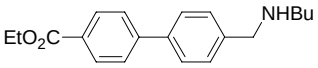
^{13}C-NMR ($CDCl_3$, 125 MHz, 25°C): δ = 145.3, 141.3, 137.5, 132.4, 128.7, 127.4, 127.1, 118.9, 110.6, 53.5, 49.2, 32.2, 20.4, 13.9.

HRMS *m/z* : calcd. for $C_{18}H_{20}N_2$ 264.1626, found 264.1631.

MS (EI, 70 eV), *m/z* (%): 262 (24), 233 (27), 219 (63), 190 (100), 177 (12).

IR (cm^{-1}): 3310 (w), 2958 (m), 2918 (m), 2822 (w), 2228 (m), 1606 (m), 1493 (m,), 1462 (m), 1391 (w), 1356 (w), 1334(w) 1304 (w), 1182 (m), 1120 (m).

4'-Butylaminomethyl-biphenyl-4-carboxylic acid ethyl ester (79c)



4-(Ethoxycarbonyl)phenylzinc iodide (**73c**, 3.8 mL, 0.94 M in THF, 3.6 mmol) is added to a solution of (4-bromo-benzyl)-butyl-amine (**78a**, 727 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 16 h at 65 °C. Then, the reaction mixture was quenched with a sat. aq. K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (CH_2Cl_2/EtOH 15:1) yielded 4'-butylaminomethyl-biphenyl-4-carboxylic acid ethyl ester (**79c**) as a colorless oil (731 mg, 78 %).

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 8.03 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* =8.1 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 1.60 (s, 1H), 1.48-1.43 (m, 2H), 1.34-1.27 (m, 5H), 0.86 (t, *J* =7.3 Hz, 3H).

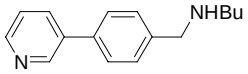
^{13}C-NMR ($CDCl_3$, 125 MHz, 25°C): δ = 166.14, 145.0, 140.4, 138.3, 129.8, 128.9, 128.4, 126.9, 126.5, 60.6, 53.4, 49.0, 32.0, 20.3, 14.1, 13.8.

HRMS *m/z* : calc. for $C_{20}H_{25}NO_2$ 311.1885, found 381.1886.

MS (EI, 70 eV), *m/z* (%): 309 (32), 280 (34), 266 (65), 239 (100), 165 (33).

IR (cm^{-1}): 3314 (w), 2957 (w), 2926 (w), 2862 (w), 2811 (w), 1702 (vs), 1605 (m), 1466 (m), 1274 (vs), 1399 (w), 1368 (m), 1274 (vs), 1173 (m), 1109 (vs), 1019 (m), 1005 (m).

Butyl-(4-pyridin-3-yl-benzyl)-amine (79d)



3-Pyridiylzinc iodide (**73f**, 2.6 mL, 0.92 M in THF, 2.4 mmol) is added to a solution of (4-bromo-benzyl)-butyl-amine (**78a**, 485 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 1**. The reaction mixture was stirred for 3 h at 65 °C. Then, the reaction mixture was quenched with a sat. aq. K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (CH_2Cl_2/EtOH 15:1) yielded butyl-(4-pyridin-3-yl-benzyl)-amine (**79d**) as a colorless oil (342 mg, 71 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.79-8.78 (m, 1H), 8.53-8.51 (m, 1H), 7.82-7.78 (m, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.31-7.26 (m, 1H), 3.82 (s, 2H), 2.74 (s, 1H), 2.63 (t, *J* = 7.3 Hz, 2H), 1.55-1.45 (m, 2H), 1.38-1.26 (m, 2H), 0.87 (t, *J* = 7.1 Hz, 3H).

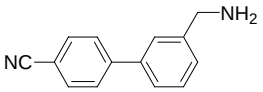
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 148.2, 148.1, 139.7, 136.4, 136.2, 134.1, 128.9, 127.0, 123.4, 53.2, 48.8, 31.8, 20.3, 13.9.

HRMS *m/z* : calcd. for $C_{16}H_{20}N_2$ 240.1626, found 240.1622.

MS (EI, 70 eV), *m/z* (%): 240 (6) [M^+], 209 (7), 197 (23), 167 (100), 156 (16).

IR (cm^{-1}): 3414 (w), 3028 (w), 2955 (m), 2926 (m), 2870 (m), 1611(w), 1472 (m), 1428 (m), 1396 (m), 1189 (w) 1104 (m) 1002 (m).

3'-Aminomethyl-biphenyl-4-carbonitrile (79e)



4-Cyanophenylzinc iodide (**73b**, 3.8 mL, 0.95 M in THF, 3.6 mmol) is added to a solution of 3-bromo-benzylamine (**78b**, 558 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 3 h at 65 °C. Then, the reaction mixture was quenched with a sat. aq. K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents

by flash chromatography (CH_2Cl_2/EtOH 10:1) yielded 4'-butylaminomethyl-biphenyl-4-carbonitrile (**79e**) as a yellow oil (604 mg, 97 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.73-7.66 (m, 4H), 7.56-7.55 (m, 1H), 7.49-7.35 (m, 3H), 3.96 (s, 2H), 1.69 (s, 2H).

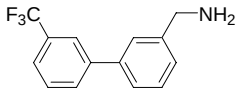
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 145.6, 143.9, 139.5, 132.6, 129.3, 127.8, 127.5, 126.1, 125.8, 118.9, 111.0, 46.3.

HRMS *m/z* : calcd. for $C_{14}H_{12}N_2$ 208.1000, found 208.0997.

MS (EI, 70 eV), *m/z* (%): 208 (60) [M^+], 207 (100), 191 (44), 180 (21), 152 (6).

IR (cm^{-1}): 3360 (w), 3294 (w), 3030 (w), 2921 (w), 2822 (w), 2224 (m), 1645 (w), 1604 (s), 1509 (w), 1481 (m), 1441 (w), 1400 (w), 1379 (w), 1292 (w), 1178 (w), 1115 (w), 1075 (w).

(3'-Trifluoromethyl-biphenyl-3-yl)-methylamine (79f)



3-Trifluorophenylzinc iodide (**73e**, 3.6 mL, 1.0 M in THF, 3.6 mmol) is added to a solution of 3-bromo-benzylamine (**78b**, 558 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 3 h at 65 °C. Then, the reaction mixture was quenched with a sat. aq. K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (CH_2Cl_2/EtOH 10:1) yielded (3'-trifluoromethyl-biphenyl-3-yl)-methylamine (**79f**) as a colorless oil (456 mg, 61 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.84-7.82 (m, 1H), 7.76 (ddd, *J* = 7.3, 1.5, 1.3 Hz, 1H), 7.61-7.40 (m, 5H), 7.37-7.33 (m, 1H), 3.96 (s, 2H), 1.96 (s, 2H).

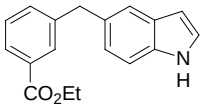
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 143.5, 141.9, 140.7, 131.1 (q, *J* = 32.2 Hz), 130.5, 129.2, 129.2, 126.9, 126.1, 125.8, 124.2 (q, *J* = 272.3 Hz), 123.9 (q, *J* = 3.9 Hz), 123.9 (q, *J* =3.9 Hz), 46.3.

HRMS *m/z* : calcd. for $C_{14}H_{12}F_3N$ 251.0922, found 251.0922.

MS (EI, 70 eV), *m/z* (%): 251 (58) [M^+], 250 (100), 234 (41), 183 (20), 165 (16).

IR (cm^{-1}): 3352 (w), 3279 (w), 3035 (w), 2924 (w), 2866 (w), 1606 (w), 1596 (w), 1476 (w), 1443 (w), 1412 (w), 1381 (w), 1332 (vs), 1266 (m), 1161 (s), 1117 (vs), 1096 (s), 1074 (s) 1002 (m).

3-(1*H*-Indol-5-ylmethyl)-benzoic acid ethyl ester (81a)



3-Ethoxycarbonylbenzylzinc chloride (**75e**, 1.8 mL, 1.34 M in THF, 2.4 mmol) is added to a solution of 5-bromo-indole (**80**, 392 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 3-(1*H*-indol-5-ylmethyl)-benzoic acid ethyl ester (**81a**) as a colorless oil (397 mg, 71 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (*br*. s, 1H), 7.98-7.94 (m, 1H), 7.86 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.44-7.43 (m, 1H), 7.39 (dt, *J* = 7.6, 1.5 Hz , 1H), 7.33 (dd, *J* = 7.7, 0.5 Hz, 1H), 7.28 (dt, *J* = 7.7, 0.7 Hz, 1H), 7.15 (t, *J* = 2.6 Hz, 1H), 7.01 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.49-6.45 (m, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.11 (s, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

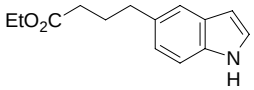
^{13}C NMR (75 MHz, $CDCl_3$): δ =166.8, 142.6, 134.5, 133.5, 131.9, 130.5, 129.9, 128.3, 128.1, 127.1, 124.5, 123.3, 120.5, 111.1, 102.4, 60.9, 41.8, 14.3.

HRMS *m/z* : calc. for $C_{18}H_{17}NO_2$ 279.1259, found 279.1264.

MS (EI, 70 eV), *m/z* (%): 279 (57) [M^+], 250 (100), 234 (27), 206 (36), 130 (48).

IR (cm^{-1}): 3403 (m), 2979 (w), 2904 (w), 2231 (w), 1697 (vs), 1603 (m), 1586 (m), 1474 (s), 1442 (s), 1366 (s), 1276 (vs), 1190 (vs), 1103 (vs).

4-(1*H*-Indol-5-yl)-butyric acid ethyl ester (81b)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 4.6 mL, 0.78 M in THF, 3.6 mmol) is added to a solution of 5-bromo-indole (**80**, 588 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.06 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 4-(1*H*-indol-5-yl)-butyric acid ethyl ester (**81b**) as a colorless oil (611 mg, 87 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.21 (m, 6H), 7.13 (d, *J* = 8.3 Hz, 2H), 5.80 (s, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.0 (*br*. s, 1H), 1.91 (quin., *J* = 7.4, Hz 2H), 1.22 (t, *J* = 7.2 Hz, 3H).

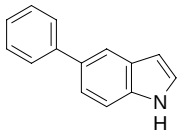
^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 143.9, 141.5, 140.8, 128.6, 128.4, 127.5, 126.6, 126.4, 76.1, 60.24, 34.7, 33.6, 26.4, 14.2.

HRMS *m/z* : calc. for $C_{14}H_{17}NO_2$ 231.1259, found 231.1247.

MS (EI, 70 eV), *m/z* (%): 231 (41) [M^+], 186 (20), 143 (85), 130 (100), 77 (9).

IR (cm^{-1}): 4478 (m), 3024 (w), 2850 (w), 2231 (m), 1713 (s), 1604 (s), 1493 (s), 1452 (m), 1420 (w), 1392 (m), 1290 (m), 1231 (m), 1189 (s), 1171 (s).

5-Phenyl-1*H*-indole (81c)



Phenylzinc chloride (**73a**, 5.7 mL, 0.63 M in THF, 3.6 mmol, prepared by transmetalation from the corresponding organomagnesium reagent[59-61]) is added to a solution of 5-bromo-indole (**80**, 588 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.06 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 5-phenyl-1*H*-indole (**81c**) as a colorless solid (568 mg, 98 %). The analytical data are in accordance with the literature.[200]

m.p.: 69.4-70.4 °C.

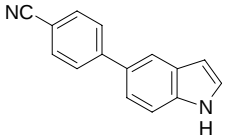
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.08 (s, 1H), 7.92-7.1 (m, 1H), 7.72-7.69 (m, 2H), 7.52-7.42 (m, 4H), 7.39-7.33 (m, 1H), 7.23-7.21 (m, 1H), 6.65-6.63 (m, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 142.5, 135.3, 133.4, 128.6, 128.4, 127.4, 126.3, 124.8, 121.9, 119.2, 111.2, 103.0,

MS (EI, 70 eV), *m/z* (%): 193 (100) [M^+], 165 (22), 193 (9), 95 (11), 63 (8).

[200] G. Miao, P. Ye, L. Yu, C. M. Baldino, *J. Org. Chem.* **2005**, *70*, 2332

4-(1*H*-Indol-5-yl)-benzonitrile (81d)



4-Cyanophenylzinc chloride (**73b**, 6.8 mL, 0.53 M in THF, 3.6 mmol, prepared by transmetalation from the corresponding organomagnesium reagent[59-61]) is added to a solution of 5-bromo-indole (**80**, 588 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.06 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4-(1*H*-indol-5-yl)-benzonitrile (**81d**) as a colorless solid (558 mg, 85 %).

m.p.: 122.6-123.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.90-7.83 (m, 2H), 7.39-7.27 (m, 2H), 7.14-7.02 (m, 2H), 6.65-6.55 (m, 1H), 4.53 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 2H), 3.06 (bs, 3H), 1.36 (t, *J* = 7.2 Hz, 3H).

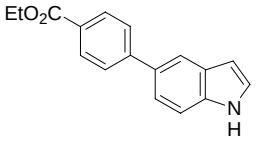
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.6, 144.1, 139.5, 132.9, 131.3, 130.8, 130.1, 129.6, 128.7, 127.6, 127.2, 124.4, 116.0, 65.2, 61.0, 37.6, 14.3.

HRMS *m/z* : calc. for $C_{17}H_{19}NO_3$ 285.1365, found 285.1359.

MS (EI, 70 eV), *m/z* (%): 285 (100) [M^+], 267 (32), 238 (55), 194 (86), 165 (32).

IR (cm^{-1}): 3371 (bw), 2981 (w), 2904 (w), 2871 (w), 1704 (s), 1615 (m), 1586 (m), 1507 (s), 1465 (m), 1442 (m), 1367 (m), 1276 (vs), 1187 (s), 1105 (s), 1081 (s), 1018 (s).

4-(1*H*-Indol-5-yl)-benzoic acid ethyl ester (81e)



4-(Ethoxycarbonyl)phenylzinc chloride (**73c**, 6.8 mL, 0.53 M in THF, 3.6 mmol, prepared by transmetalation from the corresponding organomagnesium reagent[59-61]) is added to a solution of 5-bromo-indole (**80**, 588 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.06 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by

flash chromatography (pentane/ether 7:3) yielded 4-(1*H*-indol-5-yl)-benzoic acid ethyl ester (**81e**) as a colorless solid (748 mg, 94 %).

m.p.: 122.6-123.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.25 (s, 1H), 8.11 (ddd, *J* = 8.6, 2.0, 1.8 Hz, 2H), 7.91-7.90 (m, 1H), 7.72 (ddd, *J* = 8.6, 2.0, 1.8 Hz, 2H), 7.48-7.46 (m, 2H), 7.26 (dd, *J* = 3.3, 2.4 Hz, 1H), 6.63-6.61 (m, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

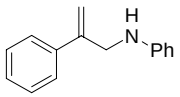
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.8, 147.0, 135.7, 132.1, 130.0, 128.4, 128.2, 127.1, 119.6, 111.4, 103.2, 60.8, 14.4.

HRMS *m/z* : calcd. for $C_{17}H_{15}NO_2$ 265.1103, found 265.1099.

MS (EI, 70 eV), *m/z* (%): 265 (100) [M^+], 220 (45), 191 (24), 111 (12), 97 (21).

IR (cm^{-1}): 3320 (m), 3033 (w), 2976 (w), 2924 (w), 1690 (s), 1604 (s), 1469 (m), 1430 (m), 1400 (w), 1368 (m), 1352 (m), 1320 (s), 1292 (vs), 1248 (s), 1176 (s), 1144 (m), 1131 (m), 1114 (s), 1100 (s), 1024 (m).

Phenyl-(2-phenyl-allyl)-amine (83a)



Phenylzinc iodide (**73a**, 2.4 mL, 1.0 M in THF, 2.4 mmol) is added to a solution of (2-bromo-allyl)-phenyl-amine (**82**, 424 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 5 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded phenyl-(2-phenyl-allyl)-amine (**83a**) as a colorless oil (254 mg, 61 %). The analytical data are in accordance with the literature.[201]

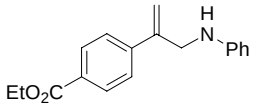
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56-7.53 (m, 2H), 7.47-7.36 (m, 3H), 7.30-7.24 (m, 2H), 6.84-6.78 (m, 1H), 6.72-6.69 (m, 2H), 5,57 (d, *J* = 0.8 Hz, 1H), 5.42 (d, *J* = 0.8 Hz, 1H),4.23 (s, 2H), 3.93 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 144.6, 139.2, 129.1, 128.4, 127.8, 126.0, 117.4, 113.5, 112.8, 47.9.

MS (EI, 70 eV), *m/z* (%): 209 (28) [M^+], 132 (58),106 (100), 92 (9), 77 (27).

[201] M. Johannsen, K. A. Joergensen, *J. Org. Chem.* **1994**, *59*, 214.

4-(1-Phenylaminomethyl-vinyl)-benzoic acid ethyl ester (83b)



4-(Ethoxycarbonyl)phenylzinc chloride (**73c**, 5.0 mL, 0.48 M in THF, 2.4 mmol, prepared by transmetalation from the organomagnesium reagent[59-61]) is added to a solution of (2-bromo-allyl)-phenyl-amine (**82**, 424 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 7 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded 4-(1-phenylaminomethyl-vinyl)-benzoic acid ethyl ester (**83b**) as a colorless solid (314 mg, 75 %).

m.p.: 42.6-43.8 °C**.**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 2H,), 7.52 (d, *J* = 8.4 Hz, 2H,), 7.21 (t, *J* = 8.4 Hz, 2H), 6.76 (t, *J* = 8.4 Hz, 1H,) 6.65 (d, *J* = 8.4 Hz, 2H), 5.59 (d, *J* = 0.9 Hz, 1H), 5.46 (d, *J* = 0.9 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.17 (s, 2H), 4.01 (*br*. s, 1H), 1.42 (t, *J* = 7.1 Hz, 3H).

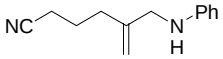
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 152.4, 141.1, 136.1, 133.4, 132.0, 130.8, 130.6, 130.0, 129.4, 128.8, 128.5, 127.5, 127.4, 124.6, 117.9, 111.0, 60.9, 41.5, 14.3.

HRMS *m/z* : calc. for $C_{18}H_{19}NO_2$ 281.1416, found 281.1398.

MS (EI, 70 eV), *m/z* (%): 218 (25) [M^+], 207 (13), 106 (100), 91 (5), 77 (17).

IR (cm^{-1}): 3437 (w), 3094 (w), 3050 (w), 2977 (w), 2927 (w), 1953 (w), 1832 (w), 1705 (vs), 1600 (vs), 1505 (s), 1443 (s), 1364 (m), 1318 (m), 1298 (m), 1270 (vs), 1190 (s), 1113 (vs).

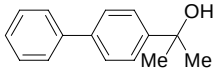
5-Phenylaminomethyl-hex-5-enenitrile (83c)



4-Cyanobutylzinc bromide (**74b**, 2.4 mL, 1.0 M in THF, 2.4 mmol) is added to a solution of (2-bromo-allyl)-phenyl-amine (**82**, 424 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 6**. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 1:1) yielded 5-phenylaminomethyl-hex-5-enenitrile (**83c**) as a colorless oil (350 mg, 87 %).

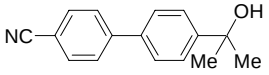
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 7.3, 8.7 Hz, 2H), 6.70 (tt, *J* = 1.1, 7.3 Hz, 1H), 6.58 (dd, *J* = 1.1, 8.7 Hz, 2H) 5.11 (d, *J* = 1.2 Hz, 1H), 4.93 (d, *J* = 1.2 Hz, 1H), 3.82 (br s, 1H), 3.69 (s, 2H), 2.35 (t, *J* = 7.3 Hz, 2H), 2.24 (t, *J* = 7.3 Hz, 2H), 1.84 (qn, *J* = 7.3 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 144.5, 129.2, 119.4, 117.6, 112.8, 111.9, 48.7, 32.6, 23.4, 16.6.
HRMS *m/z* : calc. for $C_{13}H_{16}N_2$ 200.1313, found 200.1308.
MS (EI, 70 eV), *m/z* (%): 200 (25) [M^+], 146 (6), 132 (10), 106 (100), 77 (17).
IR (cm^{-1}): 3396 (w), 2930 (w), 2245 (w), 1710 (m), 1691 (m), 1601 (vs), 1505 (s), 1443 (w), 1366 (w), 1274 (vs), 1178 (s), 1102 (s).

2-Biphenyl-4-yl-propan-2-ol (86a)



Phenylzinc chloride (**73a**, 5.7 mL, 0.63 M in THF, 3.6 mmol, prepared by transmetalation from the corresponding organomagnesium reagent[59-61]) is added to a solution of 2-(4-iodo-phenyl)-propan-2-ol (**84a**, 786 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 2-biphenyl-4-yl-propan-2-ol (**86a**) as a colorless solid (606 mg, 95 %). The analytical data are in accordance with the literature.[202]
m.p.: 90.9-92.7 °C.
^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.61-7.60 (m, 1H), 7.59-7.57 (m, 5H), 7.46-7.40 (m, 2H), 7.36-7.31 (m, 1H), 1.75 (br s, 1H), 1.63 (s, 6H).
^{13}C-NMR ($CDCl_3$, 125 MHz, 25°C): δ = 148.1, 140.8, 139.6, 137.2, 128.7, 127.2, 127.1, 127.0, 124.9, 72.4, 31.8.
MS (EI, 70 eV), *m/z* (%): 212 (83) [M^+], 197 (100), 177 (49), 152 (89), 98 (20).

4'-(1-Hydroxy-1-methyl-ethyl)-biphenyl-4-carbonitrile (86b)



4-Cyanophenylzinc chloride (**73b**, 4.7 mL, 0.51 M in THF, 3.6 mmol, prepared by transmetalation from the corresponding organomagnesium reagent[59-61]) is added to a solution

[202] D. L. Comins, J. M. Salvador, *J. Org. Chem.* **1993**, *58*, 4656.

of 2-(4-iodo-phenyl)-propan-2-ol (**84a**, 524 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4'-(1-hydroxy-1-methyl-ethyl)-biphenyl-4-carbonitrile (**86b**) as a colorless solid (371 mg, 78 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.71 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.67 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.61-7.58 (m, 2H), 7.57-7.55 (m, 2H), 1.80 (br s, 1H), 1.62 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 149.8, 145.3, 137.5, 132.8, 132.6, 127.9, 127.6, 127.0, 125.2, 118.9, 110.8, 72.4, 31.8.

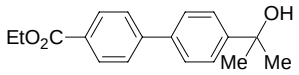
HRMS *m/z* : calc. for $C_{16}H_{15}NO$ 237.1154, found 237.1144.

MS (EI, 70 eV), *m/z* (%): 237 (12) [M^+], 222 (100), 180 (19), 151 (14), 111 (7).

IR (cm^{-1}): 3486 (m), 3068 (w), 2971 (w), 2230 (m), 1604 (m), 1492 (m), 1471 (w), 1395 (m), 1361 (m), 1316 (w), 1285 (w), 1214 (w), 1167 (m), 1092 (m), 1024 (m).

m.p.: 165.8-167.4 °C.

4'-(1-Hydroxy-1-methyl-ethyl)-biphenyl-4-carboxylic acid ethyl ester (86c)



4-(Ethoxycarbonyl)phenylzinc chloride (**73c**, 5.0 mL, 0.48 M in THF, 2.4 mmol, prepared by transmetalation from the corresponding organomagnesium compound[59-61]) is added to a solution of 2-(4-iodo-phenyl)-propan-2-ol (**84a**, 524 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4'-(1-hydroxy-1-methyl-ethyl)-biphenyl-4-carboxylic acid ethyl ester (**86c**) as a colorless solid (496 mg, 87 %).

m.p.: 106.5-107.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.09 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.60-7.57 (m, 4H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.91 (br s, 1H), 1.62 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 3H).

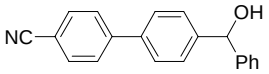
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.5, 149.1, 145.1, 138.3, 130.0, 129.1, 127.1, 126.8, 125.0, 72.4, 60.9, 31.7, 14.3.

HRMS *m/z* : calc. for $C_{18}H_{20}O_3$ 284.1412, found 284.1407.

MS (EI, 70 eV), *m/z* (%): 284 (16) [M^+], 269 (100), 239 (10), 199 (18), 152 (10).

IR (cm^{-1}): 3474 (w), 3371 (w), 2973 (w), 1710 (s), 1692 (vs), 1604 (m), 1465 (w), 1395 (m), 1368 (s), 1296 (s), 1276 (vs), 1211 (m), 1179 (s), 1160 (s), 1123 (s), 1103 (vs), 1017 (m), 1003 (s).

4'-(Hydroxy-phenyl-methyl)-biphenyl-4-carbonitrile (86d)



4-Cyanophenylzinc chloride (**73b**, 4.7 mL, 0.51 M in THF, 2.4 mmol, prepared by transmetalation from the corresponding organomagnesium compound[59-61]) is added to a solution of (4-iodo-phenyl)-phenyl-methanol (**84c**, 620 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 4'-(hydroxy-phenyl-methyl)-biphenyl-4-carbonitrile (**86d**) as a colorless solid (518 mg, 91 %).

m.p.: 112.9-115.5 °C:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.42-7.25 (m, 5H), 5.87 (s, 1H), 2.46 (br s, 1H).

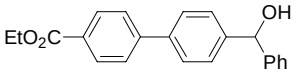
^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.2, 144.3, 143.5, 138.2, 132.5, 128.6, 127.8, 127.5, 127.2, 127.1, 126.5, 118.8, 110.8, 75.8.

HRMS *m/z* : calc. for $C_{20}H_{15}NO$ 285.1154, found 285.1139.

MS (EI, 70 eV), *m/z* (%): 285 (23) [M^+], 206 (57), 180 (22), 105 (100), 77 (25).

IR (cm^{-1}) = 3477 (m), 3057 (w), 3024 (w), 2848 (w), 2231 (m), 1930 (w), 1709 (w), 1603 (m), 1551 (w), 1492 (m), 1452 (w), 1419 (w), 1392 (m), 1290 (m), 1231 (m), 1189 (m).

4'-(Hydroxy-phenyl-methyl)-biphenyl-4-carboxylic acid ethyl ester (86e)



4-(Ethoxycarbonyl)phenylzinc chloride (**73c**, 5.0 mL, 0.48 M in THF, 2.4 mmol, prepared by transmetalation from the corresponding organomagnesium compound[59-61]) is added to a

solution of (4-iodo-phenyl)-phenyl-methanol (**x**, 620 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 4'-(hydroxy-phenyl-methyl)-biphenyl-4-carboxylic acid ethyl ester (**86e**) as a colorless solid (537 mg, 81%). The analytical data are in accordance with the literature.[203]

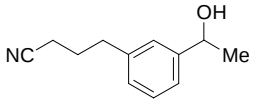
m.p.: 114.9-116.3 °C:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.43-7.25 (m, 5H), 5.88 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.29 (br s, 1H), 1.39 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 145.1, 143.7, 143.6, 139.3, 130.0, 129.3, 128.6, 127.7, 127.4, 127.0, 126.9, 126.5, 75.9, 60.9, 14.3.

MS (EI, 70 eV), *m/z* (%): 332 (27) [M^+], 303 (58), 287 (100), 255 (24), 225 (36).

4-[3-(1-Hydroxy-ethyl)-phenyl]-butyronitrile (86f)



4-Cyanobutylzinc bromide (**74b**, 2.4 mL, 1.0 M in THF, 2.4 mmol), is added to a solution of 1-(3-iodo-phenyl)-ethanol (**84e**, 496 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4-[3-(1-hydroxy-ethyl)-phenyl]-butyronitrile (**86f**) as a colorless oil (332 mg, 88 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.31-7.19 (m, 3H), 7.10-7.07 (m, 1H), 4.88 (q, J = 6.5 Hz, 1H), 2.78 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 2.03-1.94 (m, 2H), 1.81 (br s, 1H), 1.48 (d, J = 6.5 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 146.3, 140.0, 128.8, 127.5, 125.4, 123.6, 119.4, 70.3, 34.4, 26.9, 25.3, 16.5.

HRMS *m/z* : calc. for $C_{12}H_{15}NO$ 189.1154, found 189.1149.

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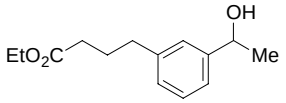
[203] O. Baron, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 3133.

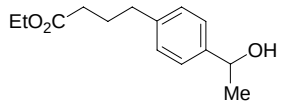
MS (EI, 70 eV), *m/z* (%): 189 (20) [M^+], 174 (73), 146 (100), 129 (52), 91 (41).
IR (cm^{-1}): 3416 (w), 2969 (w), 2928 (w), 2868 (w), 2248 (w), 1608 (w), 1590 (w), 1488 (w), 1448 (w), 1424 (w), 1368 (w), 1259 (w), 1160 (w). 1074 (s), 1012 (m).

4-[3-(1-Hydroxy-ethyl)-phenyl]-butyric acid ethyl ester (86g)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 3.1 mL, 0.78 M in THF, 2.4 mmol), is added to a solution of 1-(3-iodo-phenyl)-ethanol (**84e**, 496 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 4-[3-(1-hydroxy-ethyl)-phenyl]-butyric acid ethyl ester (**86g**) as a colorless oil (280 mg, 59 %).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30-7.14 (m, 3H), 7.06 (dt, *J* = 7.2, 1.5 Hz, 1H), 4.83 (q, *J* = 6.4 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 2.10 (br s, 1H), 1.92 (qn., *J* = 7.2 Hz, 2H), 1.45 (d, *J* = 6.4 Hz, 3H) 1.21 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 145.9, 141.6, 128.4, 127.5, 125.5, 122.9, 70.3, 60.2, 35.1, 33.6, 26.5, 25.1, 14.2.
HRMS *m/z* : calc. for $C_{14}H_{20}O_3$ 236.1412, found 236.1421.
MS (EI, 70 eV), *m/z* (%): 218 (100) [M^+-H_2O], 172 (73), 152 (66), 131 (63), 91 (87).
IR (cm^{-1}): 3418 (w), 2974 (w), 2930 (w), 1735 (vs), 1606 (w), 1446 (m), 1371 (s), 1183 (s), 1144 (s), 1018 (s).

4-[4-(1-Hydroxy-ethyl)-phenyl]-butyric acid ethyl ester (86h)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 3.1 mL, 0.78 M in THF, 2.4 mmol), is added to a solution of 1-(4-bromo-phenyl)-ethanol (**84f**, 402 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after

evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 4-[4-(1-hydroxy-ethyl)-phenyl]-butyric acid ethyl ester (**86h**) as a colorless oil (332 mg, 70 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 4.83 (q, *J* = 6.5 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.08 (br s, 1H). 1.91 (qn, *J* = 7.4 Hz, 2H), 1.45 (d, *J* = 6.5 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H).

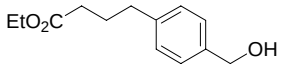
^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 143.5, 140.5, 128.5, 125.4, 70.1, 60.2, 34.7, 33.6, 26.5, 25.5, 14.2.

HRMS *m/z* : calc. for $C_{14}H_{20}O_3$ 236.1412, found 236.1399.

MS (EI, 70 eV), *m/z* (%): 218 (55) [M^+-H_2O], 189 (100), 147 (88), 130 (78), 117 (53).

IR (cm^{-1}): 3476 (m), 3024 (w), 2978 (w), 2849 (w), 1930 (w), 1712 (vs), 1603 (s), 1551 (w), 1492 (s), 1452 (m), 1419 (m), 1392 (m), 1290 (m), 1231 (m), 1189 (s), 1170 (s).

4-(4-Hydroxymethyl-phenyl)-butyric acid ethyl ester (86i)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 3.1 mL, 0.78 M in THF, 2.4 mmol), is added to a solution of 4-iodobenzyl alcohol (**84g**, 402 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yields 4-(4-hydroxymethyl-phenyl)-butyric acid ethyl ester (**86i**) as a colorless oil (290 mg, 65 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21-6.98 (m, 4H), 4.56 (s, 2H), 4.01 (q, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.21 (t, *J* = 7.3 Hz, 2H), 1.85 (qn, *J* = 7.3 Hz, 2H), 1.57 (br s, 1H), 1.14 (t, *J* = 7.0 Hz, 3H).

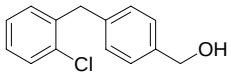
^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 141.8, 140.9, 128.6, 127.8, 127.1, 124.6, 65.4, 60.3, 35.1, 33.7, 26.5, 14.2.

HRMS *m/z* : calc. for $C_{13}H_{18}O_3$ 222.1256, found 222.1248.

MS (EI, 70 eV), *m/z* (%): 222 (5) [M^+], 204 (78), 158 (46), 131 (45), 117 (100).

IR (cm^{-1}): 3477 (m), 3024 (w), 2922 (w), 2849 (w), 2231 (w), 1712 (s), 1601 (s), 1488 (m), 1390 (m), 1185 (s), 1169 (m).

[4-(2-Chloro-benzyl)-phenyl]-methanol (86j)



2-Chlorobenzylzinc chloride (**75b**, 2.8 mL, 0.92 M in THF, 2.6 mmol) is added to a solution of 4-bromophenol (**84h**, 346 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded [4-(2-chloro-benzyl)-phenyl]-methanol (**86j**) as a colorless solid (456 mg, 98 % yield).

m.p.: 78.1-80.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.39-7.34 (m, 1H), 7.30-7.27 (m, 2H), 7.22-7.10 (m, 5H), 4.65 (s, 2H), 4.10 (s, 2H), 1.67 (s, 1H).

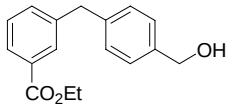
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 139.0, 138.8, 138.5, 134.2, 131.0, 129.5, 129.1, 127.7, 127.2, 126.8, 65.2, 38.9.

HRMS *m/z* : calc.for $C_{14}H_{13}ClO$ 232.0655, found 232.0647.

MS (EI, 70 eV), *m/z* (%): 232 (87) [M^+], 201 (44), 179(24), 165 (100), 107 (94).

IR (cm^{-1}): 3301 (m), 3049 (w), 3012 (w), 2914 (w), 2865 (w), 1514 (m), 1469 (m), 1443 (m), 1421 (m), 1344 (w), 1292 (w), 1210 (w), 1048 (m), 1033 (s), 1018 (s), 995 (m), 911 (m).

3-(4-Hydroxymethyl-benzyl)-benzoic acid ethyl ester (86l)



3-Ethoxycarbonylbenzylzinc chloride (**75e**, 1.8 mL, 1.34 M in THF, 2.4 mmol), is added to a solution of 4-bromobenzyl alcohol (**84h**, 374 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded [2-(2-chloro-benzyl)-phenyl]-methanol (**86l**) as a colorless oil (512 mg, 94 %).

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 7.89-7.84 (m, 2H), 7.36-7.33 (m, 2H), 7.30-7.26 (m, 2H), 7.18-7.15 (m, 2H), 4.64 8s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 1.82 (s, 1H), 1.37 (t, *J* = 7.1 Hz, 3H).

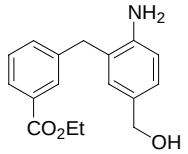
^{13}C-NMR ($CDCl_3$, 125 MHz, 25°C): δ = 166.7, 141.3, 140.0, 138.9, 133.4, 130.7, 129.9, 129.0, 128.5, 127.4, 127.3, 65.1, 60.9, 41.4, 14.3.

HRMS *m/z* : calcd. for $C_{17}H_{18}O_3$ 270.1256, found 270.1247.

MS (EI, 70 eV), *m/z* (%): 270 (92) [M^+], 241 (58), 225 (68), 207 (100), 165 (85).

IR (cm^{-1}): 3411 (w), 2981 (w), 2906 (w), 1713 (s), 1605 (w), 1587 (w), 1512 (w), 1464 (w), 1444 (m), 1420 (w), 1392 (w), 1368 (m), 1278 (vs), 1186 (s), 1104 (s), 1081 (s), 1016 (s).

3-(2-Amino-5-hydroxymethyl-benzyl)-benzoic acid ethyl ester (86m)



3-Ethoxycarbonylbenzylzinc chloride (**75e**, 1.8 mL, 1.34 M in THF, 2.4 mmol) is added to a solution of (4-amino-3-bromo-phenyl)-methanol (**84j**, 404 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/EtOAc 20:1) yielded 3-(2-amino-5-hydroxymethyl-benzyl)-benzoic acid ethyl ester (**86m**) as a colorless oil (365 mg, 64 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.90-7.83 (m, 2H), 7.39-7.27 (m, 2H), 7.14-7.02 (m, 2H), 6.65-6.55 (m, 1H), 4.53 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 2H), 3.06 (br s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H).

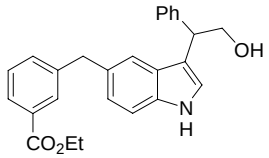
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.6, 144.1, 139.5, 132.9, 131.3, 130.8, 130.1, 129.6, 128.7, 127.6, 127.2, 124.4, 116.0, 65.2, 61.0, 37.6, 14.3.

HRMS *m/z* : calc. for $C_{17}H_{19}NO_3$ 285.1365, found 285.1359.

MS (EI, 70 eV), *m/z* (%): 285 (100) [M^+], 267 (32), 238 (55), 194 (86), 165 (32).

IR (cm^{-1}): 3371 (bw), 2981 (w), 2904 (w), 2871 (w), 1704 (s), 1615 (m), 1586 (m), 1507 (s), 1465 (m), 1442 (m), 1367 (m), 1276 (vs), 1187 (s), 1105 (s), 1081 (s), 1018 (s).

3-[3-(2-Hydroxy-1-phenyl-ethyl)-1*H*-indol-5-ylmethyl]-benzoic acid ethyl ester (86n)



3-Ethoxycarbonylbenzylzinc chloride (**75e**, 1.8 mL, 1.34 M in THF, 2.4 mmol) is added to a solution of 2-(5-bromo-1*H*-indol-3-yl)-2-phenyl-ethanol (**84k**, 632 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 1:1) yielded 3-[3-(2-hydroxy-1-phenyl-ethyl)-1*H*-indol-5-ylmethyl]-benzoic acid ethyl ester (**86n**) as a colorless oil (595 mg, 72 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.17 (s, 1H), 7.80-7.71 (m, 2H), 7.34-7.12 (m, 9H), 7.03 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.43 (t, J = 7.0 Hz, 1H), 4.20 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.12 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.04 (s, 2H), 2.90 (t, *J* = 7.4 Hz, 2H), 1.69 (m, 2H), 1.38 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

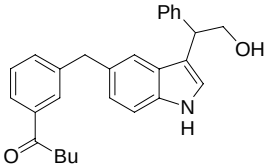
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 200.9, 142.6, 141.5, 137.1, 135.2, 133.4, 131.5, 128.5, 128.4, 128.3, 128.2, 127.2, 126.6, 125.7, 123.5, 122.3, 119.1, 115.7, 111.3, 66.3, 45.5, 41.9, 38.3, 26.5, 22.4, 13.9.

HRMS *m/z* : calc. for $C_{28}H_{29}NO_2$ 411.2198, found 411.2207.

MS (EI, 70 eV), *m/z* (%): 411 (5) [M^+], 396 (9), 380 (100), 294 (21), 204 (11).

IR (cm^{-1}): 3460 (m), 3331 (m), 3027 (w), 2869 (m), 2928 (m), 2953 (m), 1666 (vs), 1601 (m), 1582 (m), 1510 (w), 1483 (m), 1452 (m), 1435 (m), 1403 (m), 1367 (m), 1274 (s), 1232 (s), 1189(m).

1-{3-[3-(2-Hydroxy-1-phenyl-ethyl)-1*H*-indol-5-ylmethyl]-phenyl}-pentan-1-one (86o)



3-Pentanoylbenzylzinc chloride (**75c**, 2.2 mL, 1.08 M in THF, 2.4 mmol) is added to a solution of 2-(5-bromo-1*H*-indol-3-yl)-2-phenyl-ethanol (**84k**, 632 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a

sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 1:1) yielded 1-{3-[3-(2-hydroxy-1-phenyl-ethyl)-1*H*-indol-5-ylmethyl]-phenyl}-pentan-1-one (**86o**) as a colorless oil (595 mg, 72 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.17 (s, 1H), 7.80-7.71 (m, 2H), 7.34-7.12 (m, 9H), 7.03 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.43 (t, J = 7.0 Hz, 1H), 4.20 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.12 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.04 (s, 2H), 2.90 (t, *J* = 7.4 Hz, 2H), 1.69 (m, 2H), 1.38 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

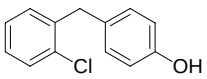
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 200.9, 142.6, 141.5, 137.1, 135.2, 133.4, 131.5, 128.5, 128.4, 128.3, 128.2, 127.2, 126.6, 125.7, 123.5, 122.3, 119.1, 115.7, 111.3, 66.3, 45.5, 41.9, 38.3, 26.5, 22.4, 13.9.

HRMS *m/z* : calc. for $C_{28}H_{29}NO_2$ 411.2198, found 411.2207.

MS (EI, 70 eV), *m/z* (%): 411 (5) [M^+], 396 (9), 380 (100), 294 (21), 204 (11).

IR (cm^{-1}): 3460 (m), 3331 (m), 3027 (w), 2869 (m), 2928 (m), 2953 (m), 1666 (vs), 1601 (m), 1582 (m), 1510 (w), 1483 (m), 1452 (m), 1435 (m), 1403 (m), 1367 (m), 1274 (s), 1232 (s), 1189(m).

4-(2-Chloro-benzyl)-phenol (87a)



2-Chlorobenzylzinc chloride (**75b**, 2.8 mL, 0.92 M in THF, 2.6 mmol) is added to a solution of 4-bromophenol (**85a**, 346 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 4-(2-chloro-benzyl)-phenol (**87a**) as a colorless oil (429 mg, 98 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.38-7.35 (m, 1H),7.21-7.12 (m, 3H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 8.2 Hz, 2H), 4.81 (br s, 1H), 4.03 (s, 2H).

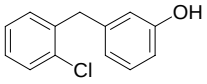
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 153.8, 139.0, 134.1, 132.4, 131.8, 130.8, 130.1, 129.5, 127.5, 126.8, 115.3, 38.3.

HRMS *m/z* : calc. for $C_{13}H_{11}ClO$ 218.0498, found 218.0495.

MS (EI, 70 eV), *m/z* (%): 218 (53) [M^+], 183 (100), 165 (24), 152 (19), 107 (30).

IR (cm^{-1}): 3204 (m), 3057 (w), 3020 (w), 2908 (w), 2841 (w), 1612 (w), 1596 (m), 1510 (s), 1472 (m), 1439 (s), 1364 (m), 1347 (m), 1214 (s), 1172 (s), 1156 (m), 1123 (m), 1051 (s), 1038 (s).

3-(2-Chloro-benzyl)-phenol (87b)



2-Chlorobenzylzinc chloride (**75b**, 45.6 mL, 0.92 M in THF, 42 mmol) is added to a solution of 3-bromophenol (**85b**, 5.53 g mg, 32 mmol), $Pd(OAc)_2$ (71 mg, 0.32 mmol), S-Phos (262 mg, 0.64 mmol) in THF (30 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 3-(2-chloro-benzyl)-phenol (**87b**) as a colorless oil (6.37 g, 91 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.36 (m, 1 H), 7.19-7.13 (m, 4 H), 6.80-6.78 (m, 1 H), 6.69-6.64 (m, 2 H), 4.96 (s, 1 H), 4.06 (s, 2 H).

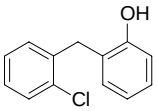
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.5, 141.5, 138.3, 134.2, 131.07, 129.6, 129.5, 127.8, 126.9, 121.5, 115.8, 113.3, 39.0.

HRMS: calcd. for $C_{13}H_{11}O_1Cl_1$ 218.0498, found 218.0496.

MS (70 eV, EI) *m/z* (%): 218 (55) [M^+], 183 (100), 165 (49), 153 (20), 152 (22).

IR (cm^{-1}): 3327, 1611, 1587, 1470, 1453, 1441, 1244, 1148, 1050, 1036, 953.

2-(2-Chloro-benzyl)-phenol (87c)



2-Chlorobenzylzinc chloride (**75b**, 2.8 mL, 0.92 M in THF, 2.6 mmol) is added to a solution of 2-bromophenol (**85c**, 346 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash

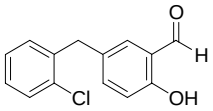
chromatography (pentane/ether 8:2) yielded 2-(2-chloro-benzyl)-phenol (**87c**) as a colorless oil (359 mg, 82 %). The analytical data are in accordance with the literature.[204]

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.39 (dd, *J* = 5.4, 3.9 Hz, 1H), 7.22-7.05 (m, 5H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 4.78 (s, 1H), 4.10 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 153.6, 137.5, 134.2, 130.9, 130.5, 129.4, 127.9, 127.7, 125.4, 121.0, 115.5, 33.3.

MS (EI, 70 eV), *m/z* (%): 218 (90) [M^+], 183 (100), 165 (23), 152 (17), 106 (14).

5-(2-Chloro-benzyl)-2-hydroxy-benzaldehyde (87d)



2-Chlorobenzylzinc chloride (**75b**, 2.8 mL, 0.92 M in THF, 2.6 mmol) is added to a solution of 5-bromo-salicylaldehyde (**85d**, 402 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 5-(2-chloro-benzyl)-2-hydroxy-benzaldehyde (**87d**) as a colorless oil (400 mg, 81 %).

^{1}H-NMR ($CDCl_3$, 600 MHz, 25°C): δ = 10.09 (s, 1H), 9.82 (s, 1H), 7.39-7.36 (m, 2H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.23-7.16 (m, 3H), 6.92 (d, *J* = 8.6 Hz, 1H), 4.07 (s, 2H).

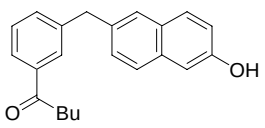
^{13}C-NMR ($CDCl_3$, 125 MHz, 25°C): δ = 196.5, 160.1, 138.0, 137.7, 134.2, 133.4, 131.0, 130.9, 129.8, 128.0, 127.0, 120.4, 117.7, 38.1.

HRMS *m/z* : calc. for $C_{14}H_{11}ClO_2$ 246.0448, found 246.0445.

MS (EI, 70 eV), *m/z* (%): 246 (100) [M^+], 217 (33), 211 (49), 181 (22), 165 (20).

IR (cm^{-1}): 3062 (w), 2917 8w), 2845 (w), 1652 (vs), 1624 (m), 1588 (m), 1481 (s), 1442 (s), 1375 (m), 1331 (w), 1278 (s), 1240 (m), 1207 (s), 1144 (s), 1051 (m), 1038 (s).

1-[3-(6-Hydroxy-naphthalen-2-ylmethyl)-phenyl]-pentan-1-one (87e)



[204] R. C. Huston, R. L. Guile, P. S. Chen, W. N. Headley, G. W. Warren, L. S. Baur, B. O. Mate, *J. Am. Chem. Soc.* **1933**, *55*, 4639.

3-Pentanoylbenzylzinc chloride (**75c**, 2.2 mL, 1.08 M in THF, 2.4 mmol) is added to a solution of 6-bromo-naphthalen-2-ol (**85e**, 446 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded 1-[3-(6-hydroxy-naphthalen-2-ylmethyl)-phenyl]-pentan-1-one (**87e**) as a colorless solid (516 mg, 82 %).

m.p.: 112.0-124.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.81 (s, 1H), 7.75 (dt, *J* = 7.0, 1.9 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.49 (s, 1H), 7.36 (dt, *J* = 7.0, 1.9 Hz, 1H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.19 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 7.03 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.15 (s, 1H), 4.10 (s, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 1.65 (m, 2H), 1.34 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

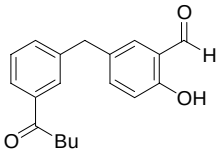
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 200.9, 153.2, 141.7, 137.3, 135.6, 133.6, 133.2, 129.4, 129.0, 128.7, 128.5, 128.0, 127.0, 126.7, 126.1, 117.9, 109.4, 41.8, 38.4, 26.5, 22.4, 13.9.

HRMS *m/z* : cal. for $C_{22}H_{22}O_2$ 318.1620, found 318.1626.

MS (EI, 70 eV), *m/z* (%): 318 (74) [M^+], 276 (43), 261 (100), 231 (22), 202 (25).

IR (cm^{-1}): 3330 (m), 3080 (m), 2954 (m), 2930 (w), 2870 (w), 1640 (vs), 1613 (s), 1582 (m), 1510 (s), 1481 (m), 1367 (m), 1287 (vs), 1266 (s), 1143 (s).

2-Hydroxy-5-(3-pentanoyl-benzyl)-benzaldehyde (87f)



3-Pentanoylbenzylzinc chloride (**75c**, 2.8 ml, 0.87 M in THF, 2.4 mmol) was added to a solution of 5-bromosalicylaldehyde (**85d**, 402 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 1:1) yielded 2-hydroxy-5-(3-pentanoyl-benzyl)-benzaldehyde (**87f**) as a colorless oil (450 mg, 75 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.9 (s, 1H), 9.80 (s, 1H), 7.84 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.81 (d, *J* = 1.4 Hz, 1H), 7.41-7.30 (m, 3H), 7.28 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 4.04 (s, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 1.72 (qn., *J* = 7.5 Hz, 2H), 1.41 (m,2H), 0.96 (t, *J* = 7.3 Hz, 3H).

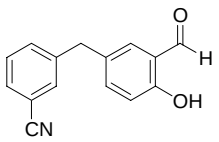
^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.4, 196.4, 160.2, 140.9, 137.6, 137.5, 133.3, 133.2, 131.9, 128.8, 128.2, 126.3, 120.4, 117.9, 40.5, 38.3, 26.4, 22.4, 13.9**.**

HRMS m/z : calc.for $C_{20}H_{19}O_3$ 296.1412, found 296.1416.

MS (EI, 70 eV), m/z (%): 296 (4) [M^+], 254 (11), 239 (18), 176 (100), 165 (17).

IR (cm^{-1}): 3459 (m), 3049 (w), 2951 (m), 2922 (m), 2868 (m), 1664 (vs), 1582 (m), 1450 (w), 1434 (m), 1367 (m), 1274 (m), 1232 (m), 1189 (s), 1136(m).

3-(3-Formyl-4-hydroxy-benzyl)-benzonitrile (87g)



3-Cyanobenzylzinc chloride (**75f**, 3.0 mL, 0.88 M in THF, 2.4 mmol) is added to a solution of 5-bromo-salicylaldehyde (**85d**, 402 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 3-(3-formyl-4-hydroxy-benzyl)-benzonitrile (**87g**) as a colorless solid (345 mg, 73 %).

m.p.: 97.9-98.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 10.91 (s, 1H), 9.84 (s, 1H), 7.53-7.50 (m, 1H), 7.45-7.44 (m, 1H), 7.43-7.37 (m, 2H), 7.34-7.30 (m, 2H), 6.96-6.93 (m, 1H), 3.99 (s, 2H).

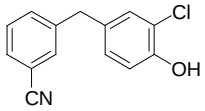
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 196.3, 160.44, 141.9, 137.6, 133.4, 133.2, 132.2, 130.9, 130.2, 129.5, 120.5, 118.7, 118.2, 112.8, 40.1.

HRMS *m/z* : calc. for $C_{15}H_{11}NO_2$ 237.0790, found 237.0790.

MS (EI, 70 eV), *m/z* (%): 237 (100) [M^+], 208 (48), 190 (19), 177 (8), 149 (19).

IR (cm^{-1}): 3204 (w), 3066 (w), 2924 (w), 2869 (w), 2228 (m), 1657 (s), 1600 (m), 1582 (m), 1484 (s), 1443 (m), 1428 (m), 1384 (m), 1313 (m), 1279 (s), 1236 (s), 1193 (s), 1172 (s), 1144 (s), 1095 (m).

3-(3-Chloro-4-hydroxy-benzyl)-benzonitrile (87h)



3-Cyanobenzylzinc chloride (**75f**, 3.0 mL, 0.88 M in THF, 2.4 mmol) is added to a solution of 4-bromo-2-chlorophenol (**85f**, 415 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 3-(3-chloro-4-hydroxy-benzyl)-benzonitrile (**x**) as a colorless solid (401 mg, 82 %).

m.p.: 74.3-76.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.52-7.48 (m, 1H), 7.44-7.42 (m, 1H), 7.40-7.36 (m, 2H), 7.10-7.09 (m, 1H), 6.96 (m, 2H), 5.84 (br s, 1H), 3.91 (s, 2H).

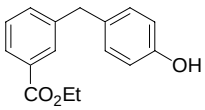
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 150.1, 142.2, 133.2, 132.7, 132.2, 130.1, 129.4, 129.2, 128.9, 120.3, 118.8, 116.5, 112.7, 40.2.

HRMS *m/z* : calcd. for $C_{14}H_{10}ClNO$ 243.0451, found 243.0450.

MS (EI, 70 eV), *m/z* (%): 243 (75) [M^+], 208 (100), 190 (21), 141 (22), 63 (15).

IR (cm^{-1}): 3387 (m), 3056 (w), 2926 (w), 2852 (w), 2233 8m), 1604 (w), 1581 (w), 1496 (vs), 1483 (s), 1439 (m), 1433 (m), 1416 (m), 1324 (m), 1298 (m), 1276 (s), 1256 (s), 1203 (m), 1173 (vs), 1160 (s), 1124 (m), 1051 (s).

3-(4-Hydroxy-benzyl)-benzoic acid ethyl ester (87i)



3-Ethoxycarbonylbenzylzinc chloride (**75e**, 1.8 mL, 1.34 M in THF, 2.4 mmol) is added to a solution of 4-bromo-phenol (**85a**, 346 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 3-(4-hydroxy-benzyl)-benzoic acid ethyl ester (**87i**) as a colorless oil (455 mg, 89 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.89-7.84 (m, 2H), 7.36-7.30 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* =8.5 Hz, 2H), 5.35 (br s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

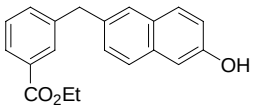
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 167.0, 154.2, 141.9, 133.4, 132.5, 130.5, 130.0, 129.9, 128.5, 127.3, 115.4, 61.1, 40.8, 14.3.

HRMS *m/z* : calcd. for $C_{16}H_{16}O_3$ 256.1099, found 256.1081.

MS (EI, 70 eV), *m/z* (%): 256 (100) [M^+], 227 (39), 210 (55), 183 (70), 165 (34).

IR (cm^{-1}): 3387 (m), 2982 (w), 2906 (w), 1715 (s), 1688 (s), 1613 (m), 1597 (m), 1512 (vs), 1442 (s), 1392 (w), 1368 (s), 1282 (vs), 1190 (vs), 1170 (s), 1100 (vs), 1080 (s), 1017 (s).

3-(6-Hydroxy-naphthalen-2-ylmethyl)-benzoic acid ethyl ester (87j)



3-Ethoxycarbonylbenzylzinc chloride (**75e**, 1.8 mL, 1.34 M in THF, 2.4 mmol) is added to a solution of 6-bromo-naphthalen-2-ol (**85e**, 446 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 3-(4-hydroxy-benzyl)-benzoic acid ethyl ester (**x**) as a colorless solid (586 mg, 96 %).

m.p.: 107.0-109.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.01 (s, 1H), 7.94 (d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.55-7.52 (m, 2H), 7.43-7.34 (m, 2H), 7.2 (d, *J* = 8.6 Hz, 1H), 7.15-7.11 (m, 2H), 6.59 (br s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 2H), 1.40 (t, *J* =7.1 Hz, 3H).

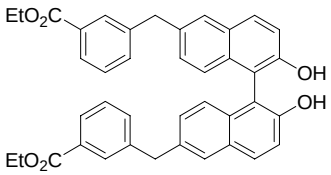
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 167.4, 153.5, 141.6, 135.3, 133.7, 133.2, 130.4, 130.0, 129.3, 128.8, 128.5, 127.8, 127.4, 126.9, 126.7, 118.1, 109.4, 61.3, 41.6, 14.2.

HRMS *m/z* : calcd. for $C_{20}H_{18}O_3$ 306.1256, found 306.1248.

MS (EI, 70 eV), *m/z* (%): 306 (100) [M^+], 277 (10), 261 (12), 233 (18), 157 (15).

IR (cm^{-1}): 3402 (m), 3023 (w), 2987 (w), 2957 (w), 1681 (s), 1632 (m), 1604 (s), 1519 (m), 1479 (m), 1441 (m), 1380 (m), 1362 (m), 1285 (s), 1195 (s), 1115 (s), 1001 (m).

3,3'-[(2,2'-Dihydroxy-1,1'-binaphthalene-6,6'-diyl)di(methylene)]-dibenzoate (87k)



3-Ethoxycarbonylbenzylzinc chloride (**75e**, 3.9 mL, 1.34 M in THF, 5.2 mmol) is added to a solution of 6,6'-dibromo-[1,1']binaphthalenyl-2,2'-diol (**85g**, 888 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 8:2) yielded 3,3'-[(2,2'-dihydroxy-1,1'-binaphthalene-6,6'-diyl)di(methylene)]-dibenzoate (**87k**) as a colorless solid (915 mg, 76 %).

m.p.: 90.0-94.6 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 (s, 2H), 7.86 (d, *J* = 7.7 Hz, 2H), 7.80 (dd, *J* = 3.7, 8.9 Hz, 2H), 7.61 (s, 2H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.27 (dd, *J* = 2.7, 8.9 Hz, 2H), 7.10 (dd, *J* = 1.5, 8.7 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 5.17- 5.14 (br s, 2H), 4.31 (q, *J* = 7.2 Hz, 4H), 4.10 (s,4H), 1.35 (t, *J* = 7.2 Hz, 6H).

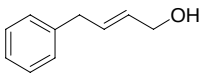
^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.6, 152.4, 141.1, 136.1, 133.4, 132.0, 130.8, 130.6, 130.0, 129.4, 128.8, 128.5, 127.5, 127.4, 124.6, 117.9, 111.0, 60.9, 41.5, 14.3.

HRMS *m/z* : calc. for $C_{40}H_{34}O_6$ 610.2355, found 610.2345.

MS (EI, 70 eV), *m/z* (%): 610 (100) [M^+], 564 (13), 536 (16), 464 (16), 282 (17).

IR (cm^{-1}): 3389 (m), 2977 (w), 1708 (vs), 1598 (s), 1473 (s), 1442 (m), 1365 (s), 1274 (vs), 1190 (vs), 1142 (vs).

(*E*)-4-Phenyl-but-2-en-1-ol (89)



Benzylzinc chloride (**75a**, 1.57 mL, 1.56 M in THF, 2.4 mmol,) is added to a solution of (*E*)-3-bromo-prop-2-en-1-ol (**88**, 247 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash

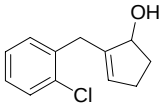
chromatography (pentane/ether 1:1) yielded (*E*)-4-phenyl-but-2-en-1-ol (**89**) as a yellow oil (190 mg, 65 %). The analytical data are in accordance with the literature.[205]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.25 (m, 2H), 7.22-7.15 (m, 3H), 5.85 (dtt, *J* = 15 Hz, 6.5, 1.3 Hz, 1H), 5.68 (dtt, *J* = 15, 6.8, 1.2 Hz, 1H), 4.10 (dd, *J* = 5.8, 1.2 Hz, 2H), 3.37 (d, *J* = 6.5 Hz, 2H), 1.45 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 131.5, 130.3, 128.5, 128.4, 126.1, 63.5, 38.6.

MS (EI, 70 eV), *m/z* (%): 148 (35) [M^+], 133 (17), 119 (9), 91 (100), 77 (12).

2-(2-Chloro-benzyl)-cyclopent-2-enol (91)



2-Chlorobenzylzinc chloride (**75b**, 2.6 mL, 0.92 M in THF, 2.4 mmol), is added to a solution of 2-iodo-cyclopent-2-enol (**90**, 420 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (16.4 mg, 0.04 mmol) in THF (2 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 2-(2-chloro-benzyl)-cyclopent-2-enol (**91**) as a colorless oil (380 mg, 91 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.33 (dd, *J* = 7.1, 2.0 Hz, 1H), 7.23 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.18 (dt, *J* = 7.3, 2.2 Hz, 1H), 7.13 (dd, *J* = 7.1, 2.0 Hz, 1H), 5.38 (s, 1H), 4.63 (s, 1H), 3.59 (dd, *J* = 15.5, 1.2 Hz, 2H) 2.45-2.12 (m, 3H), 1.77-1.67 (m, 1H), 1.49 (s, 1H).

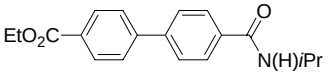
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 143.8, 137.5, 134.1, 131.0, 129.6, 129.5, 127.6, 126.7, 78.5, 33.9, 32.3, 29.7.

HRMS *m/z* : calc. for $C_{12}H_{13}ClO$ 208.0655, found 208.0651.

MS (EI, 70 eV), *m/z* (%): 208 (3) [M^+], 190 (11), 155 (21), 125 (43), 83 (100).

IR (cm^{-1}): 3346 (w), 3051 (w), 2930 (w), 2852 (w), 1694 (w), 1602 (m), 1506 (w), 1471 (m), 1442 (m), 1314 (w), 1274 (w), 1156 (w), 1049 (s), 1038 (s).

4'-Isopropylcarbamoyl-biphenyl-4-carboxylic acid ethyl ester (94a)



[205] A. M. Echavarren, D. R. Tueting, J. K. Stille, *J. Am. Chem. Soc.* **1988**, 110, 4039.

4-(Ethoxycarbonyl)phenylzinc iodide (**73c**, 3.6 mL, 0.94 M in THF, 2.4 mmol) was added to a solution of 4-bromo-*N*-isopropyl-benzamide (**92a**, 484 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yielded 4'-isopropylcarbamoyl-biphenyl-4-carboxylic acid ethyl ester (**94a**) as a colorless solid (597 mg, 96 %).

m.p.: 198.3-200.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.16-8.12 (m, 2 H), 7.89-7.84 (m, 2 H), 7.71-7.67 (m, 4 H), 5.97 (d, *J* = 7.8 Hz, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 4.37-4.28 (m, 1 H), 1.44 (t, *J* = 7.2 Hz, 3 H), 1.32 (s, 3 H), 1.30 (s, 3 H).

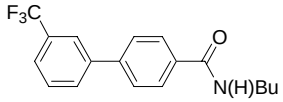
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 166.33, 144.30, 142.88, 134.43, 130.14, 129.89, 127.46, 127.36, 127.09, 61.07, 42.00, 22.89, 14.35, 1.01.

HRMS *m/z* : calcd. for $C_{19}H_{21}NO_3$ 311.1521, found 311.1519.

MS (70 eV, EI) *m/z* (%): 311 (55) [M^+], 266 (10), 253 (100), 225 (13), 152 (15).

IR (cm^{-1}): 3287, 2976, 2935, 1718, 1626, 1608, 1537, 1520, 1462, 1366, 1278, 1172, 1104, 1026, 1004.

3'-Trifluoromethyl-biphenyl-4-carboxylic acid butylamide (94b)



3-(Trifluoromethyl)phenylzinc iodide (**73e**, 4.3 mL, 0.84 M in THF, 3.6 mmol) was added to a solution of 4-bromo-*N*-butyl-benzamide (**92b**, 768 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and S-Phos (24.6 mg, 0.06 mmol) in THF (5 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 7:3) yields 3'-trifluoromethyl-biphenyl-4-carboxylic acid butyl-amide (**94b**) as a colorless solid (884 mg, 92 %).

m.p.: 103.6-105.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.86 (d, *J* = 8.1 Hz , 2H), 7.82 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.64-7.62 (m, 3H), 7.58-7.55 (m, 1H), 6.29 (s, 1H), 3.49-3.46 (m, 2H), 1.64-1.59 (m, 2H), 1.45-1.39 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

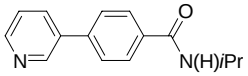
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 167.0, 142.5, 140.8, 134.2, 131.3 (q, *J* = 32.1 Hz), 130.4, 129.4, 127.6, 127.3, 124.6 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.4 Hz), 123.9 (q, *J* = 3.8 Hz), 39.9, 31.7, 20.2, 13.8.

HRMS *m/z* : calcd. for $C_{18}H_{18}F_3NO$ 321.1340, found 321.1336.

MS (EI, 70 eV), *m/z* (%): 321 (49) [M^+], 282 (100), 267 (27), 251 (65), 221 (23).

IR (cm^{-1}): 3342 (w), 3296 (m), 3063 (w), 2958 (w), 2934 (w), 1629 (s), 1610 (m), 1549 (s), 1513 (m), 1485 (w), 1438 (m), 1403 (w), 1330 (s), 1257 (s), 1163 (s), 1124 (vs), 1074 (s).

***N*-Isopropyl-4-pyridin-3-yl-benzamide (94c)**



3-Pyridylzinc iodide (**73f**, 5.4 mL, 0.66 M in THF, 3.6 mmol) was added to a solution of 4-bromo-*N*-isopropyl-benzamide (**92a**, 726 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and S-Phos (24.6 mg, 0.06 mmol) in THF (5 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2/MeOH 25:25:1) yielded *N*-isopropyl-4-pyridin-3-yl-benzamide (**94c**) as a colorless solid (640 mg, 89 %).

m.p.: 148.0-149.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.85 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.62 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.92-7.88 (m, 1H), 7.86 (ddd, *J* = 8.6, 2.0, 1.9 Hz, 2H), 7.62 (ddd, *J* = 8.6, 2.0, 1.9 Hz, 2H), 7.40 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 6.0 (d, *J* = 6.2 Hz, 1H), 4.36-4.25 (m, 1H), 1.28 (d, *J* = 6.9 Hz, 6H).

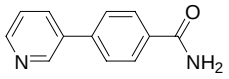
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.0, 148.7, 148.0, 140.5, 135.7, 134.7, 134.6, 127.7, 127.2, 123.7, 42.0, 22.9.

HRMS *m/z* : calcd. for $C_{15}H_{16}N_2O$ 240.1263, found 240.1269.

MS (EI, 70 eV), *m/z* (%): 240 (31) [M^+], 198 (7), 182 (100), 154 (19), 127 (18).

IR (cm^{-1}): 3287 (m), 3035 (w), 2970 (w), 2932 (w), 1626 (vs), 1610 (s), 1575 (m), 1535 (vs), 1459 (m), 1425 (m), 1388 (m), 1346 (m), 1294 (m), 1272 (m), 1194 (w), 1171 (m).

4-Pyridin-3-yl-benzamide (94d)



3-Pyridylzinc iodide (**73f**, 5.4 mL, 0.66 M in THF, 3.6 mmol) was added to a solution of 4-bromo-benzamide (**92c**, 600 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and S-Phos (24.6 mg, 0.06 mmol) in THF (5 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with CH_2Cl_2. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (CH_2Cl_2/MeOH 12:1) yielded 4-pyridin-3-yl-benzamide (**94d**) as a colorless solid (479 mg, 81 %).

m.p.: 193.2-195.7 °C.

^{1}H-NMR (DMSO- d_6, 400 MHz, 25°C): δ = 8.95 (d, *J* = 2.5 Hz, 1H), 8.59 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.14-8.11 (m, 1H), 8.05 (s, 1H), 8.00 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.82 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.50 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.42 (s, 1H).

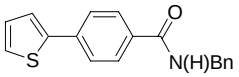
^{13}C-NMR (DMSO- d_6, 100 MHz, 25°C): δ = 167.3, 148.9, 147.8, 139.6, 134.6, 134.3, 133.7, 128.2, 126.7, 123.9.

HRMS *m/z* : calcd. for $C_{12}H_{10}N_2O$ 198.0793, found 198.0793.

MS (EI, 70 eV), *m/z* (%): 198 (78) [M^+], 182 (100), 154 (31), 127 (22), 77 (7).

IR (cm^{-1}): 3295 (w), 3045 (w), 1677 (s), 1619 (m), 1609 (m), 1511 (w), 1478 (w), 1423 (m), 1384 (s), 1344 (m), 1306 (m), 1233 (w), 1192 (m), 1142 (m).

***N*-Benzyl-4-thiophen-2-yl-benzamide (94e)**



2-Thienylzinc chloride (**73g**, 4.4 mL, 0.55 M in THF, 2.4 mmol) was added to a solution of *N*-benzyl-4-bromo-benzamide (**92b**, 580 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 8:2) yielded *N*-benzyl-4-thiophen-2-yl-benzamide (**94e**) as a colorless solid (503 mg, 86 %).

m.p.: 183.7-185.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.80 (ddd, *J* = 8.6, 2.0, 1.9 Hz, 2H), 7.65 (ddd, *J* = 8.6, 2.0, 1.9 Hz, 2H), 7.39-7.28 (m, 7H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.40 (s, 1H), 4.66 (d, *J* = 5.7 Hz, 2H).

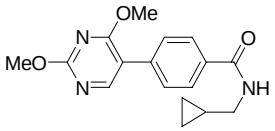
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.7, 143.0, 138.2, 137.5, 132.9, 128.8, 128.3, 128.0, 127.7, 127.6, 126.0, 125.8, 124.2, 44.2.

HRMS *m/z* : calcd. for $C_{18}H_{15}NOS$ 293.0874, found 293.0874.

MS (EI, 70 eV), *m/z* (%): 293 (92) [M^+], 187 (100), 159 (12), 115 (29), 91 (5).

IR (cm^{-1}): 3280 (w), 3093 (w), 3064 (w), 2927 (w), 1632 (s), 1604 (m), 1585 (w), 1547 (s), 1526 (s), 1492 (m), 1450 (m), 1423 (m), 1358 (w), 1314 (m), 1304 (s), 1259 (m), 1192 (m).

N-Cyclopropylmethyl-4-(2,4-dimethoxy-pyrimidin-5-yl)-benzamide (94f)



2,4-Dimethoxypyimidin-5-yl zinc iodide (**73h**, 3.0 mL, 0.80 M in THF, 2.4 mmol) was added to a solution of 4-bromo-*N*-cyclopropylmethyl-benzamide (**92d**, 508 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 3:2) yielded *N*-cyclopropylmethyl-4-(2,4-dimethoxy-pyrimidin-5-yl)-benzamide (**94f**) as a colorless solid (546 mg, 87 %).

m.p.: 138.4-139.8°C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 6.27 (s, 1 H), 4.05 (s, 3 H), 4.03 (s, 3 H), 3.33 (dd, *J* = 7.2, 5.4 Hz, 2 H), 1.10-1.04 (m, 1 H), 0.58-0.55 (m, 2 H), 0.28 (q, J = 4.8 Hz, 2 H).

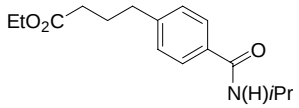
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 168.17, 166.89, 164.61, 157.37, 136.30, 133.87, 128.87, 127.04, 115.31, 55.04, 54.30, 44.96, 10.74, 3.48.

HRMS *m/z* : calcd. for $C_{17}H_{20}N_3O_3$ $[M+H]^+$ 314.1505, found 314.1501.

MS (70 eV, EI) *m/z* (%): 313 (19) [M^+], 284 (19), 243 (100), 242 (18), 200 (11).

IR (cm^{-1}): 3320, 2956, 2919, 1628, 1604, 1545, 1471, 1407, 1379, 1332, 1302, 1273, 1241, 1196, 1088, 1013.

4-(4-Isopropylcarbamoyl-phenyl)-butyric acid ethyl ester (94g)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 3.1 mL, 0.78 M in THF, 2.4 mmol) was added to a solution of 4-bromo-*N*-isopropyl-benzamide (**92a**, 484 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yielded 4-(4-isopropylcarbamoyl-phenyl)-butyric acid ethyl ester (**94g**) as a colorless solid (498 mg, 90 %).

m.p.: 73.8-75.2 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.70-7.66 (m, 2 H), 7.24-7.20 (m, 2 H), 6.02 (d, J = 7.2 Hz, 1 H), 4.36-4.22 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.69 (t, *J* = 7.2 Hz, 2 H), 2.30 (t, *J* = 7.5 Hz, 2 H), 2.00-1.90 (m, 2 H), 1.28-1.23 (m, 9 H).

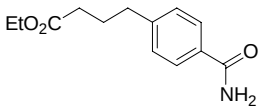
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 173.27, 166.56, 145.04, 132.75, 128.57, 126.98, 60.32, 41.81, 34.90, 33.50, 26.26, 22.85, 14.23.

HRMS *m/z* : calcd. for $C_{16}H_{23}NO_3$ 277.1678, found 277.1675.

MS (70 eV, EI) *m/z* (%): 277 (47) [M^+], 232 (16), 219 (100), 190 (52), 148 (11), 131 (23).

IR (cm^{-1}): 3260, 2968, 2937, 1730, 1620, 1546, 1505, 1453, 1348, 1326, 1290, 1251, 1171, 1121, 1069, 1026.

4-(4-Carbamoyl-phenyl)-butyric acid ethyl ester (94h)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 3.1 mL, 0.78 M in THF, 2.4 mmol) was added to a solution of 4-bromo-benzamide (**92c**, 400 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 3:7) yielded 4-(4-carbamoyl-phenyl)-butyric acid ethyl ester (**94h**) as a colorless solid (392 mg, 83 %).

m.p.: 114.8-116.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.73 (ddd, *J* = 8.2, 2.2, 2.0 Hz, 2H), 7.25 (ddd, *J* 0 8.2, 2.2, 2.0 Hz, 2H), 5.90 (bs, 2H), 4.11 (q, *J* = 7.0 Hz, 2H) 2.71-2.68 (m, 2H), 2.31 (t, *J* 0 7.4 Hz, 2H), 1.99-1.92 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H).

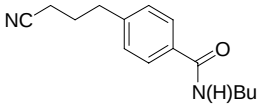
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 173.2, 169.1, 146.0, 131.1, 128.7, 127.5, 60.4, 35.0, 33.5, 26.2, 14.2.

HRMS *m/z* : calcd. for $C_{13}H_{17}NO_3$ 235.1208, found 235.1200.

MS (EI, 70 eV), *m/z* (%): 235 (25) [M^+], 190 (13), 148 (100), 131 (30), 105 (16).

IR (cm^{-1}): 3432 (m), 3365 (w), 3303 (w), 3150 (m), 3068 (w), 2995 (w), 2904 (w), 2830 (w), 1713 (vs), 1666 (vs), 1621 (vs), 1567 (s), 1474 (m), 1433 (m), 1415 (s), 1387 (vs), 1363 (s), 1298 (m), 1257 (s), 1177 (vs).

***N*-Butyl-4-(3-cyano-propyl)-benzamide (94i)**



4-Cyanobutylzinc bromide (**74b**, 2.4 mL, 1.0 M in THF, 2.4 mmol) was added to a solution of 4-bromo-*N*-butyl-benzamide (**92b**, 512 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yields *N*-butyl-4-(3-cyano-propyl)-benzamide (**94i**) as a colorless solid (469 mg, 96 %).

m.p.: 63.4-65.7 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.74-7.70 (m, 2 H), 7.26-7.22 (m, 2 H), 6.25 (s, 1 H), 3.48-3.42 (m, 2 H), 2.83 (t, *J* = 7.5 Hz, 2 H), 2.33 (t, *J* = 6.9 Hz, 2 H), 2.04-1.94 (m, 2 H), 1.65-1.55 (m, 2 H), 1.47-1.35 (m, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

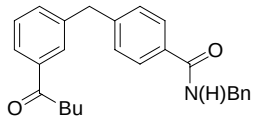
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.18, 143.24, 133.23, 128.58, 127.28, 119.24, 39.79, 34.15, 31.74, 26.63, 20.15, 16.39, 13.78.

HRMS *m/z* : calcd. for $C_{15}H_{20}N_2O$ 244.1576, found 244.1569.

MS (70 eV, EI) *m/z* (%): 244 (8) [M^+], 202 (15), 201 (19), 173 (13), 172 (100).

IR (cm^{-1}): 3314, 2959, 2931, 2868, 2244, 1632, 1537, 1505, 1458, 1308, 1258, 1190, 1150.

_N_-benzyl-4-(3-pentanoyl-benzyl)-benzamide (94j)



3-Pentanoyl-benzylzinc chloride (**75c**, 1.8 mL, 1.34 M in THF, 2.4 mmol) was added to a solution of *N*-benzyl-4-bromo-benzamide (**92e**, 580 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 4:1) yielded *N*-benzyl-4-(3-pentanoyl-benzyl)-benzamide (**94j**) as a colorless solid (755 mg, 96 %)

m.p.: 96.8-98.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.79-7.77 (m, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.33-7.32 (m, 5H), 7.29-7.25 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.48 (s, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 4.05 (s, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.70-1.65 (m, 2H), 1.41-1.35 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

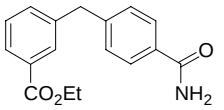
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 200.5, 167.1, 144.2, 140.8, 138.2, 137.4, 133.5, 132.5, 129.1, 128.8, 128.7, 128.3, 127.8, 127.5, 127.3, 126.2, 44.1, 41.5, 38.4, 26.4, 22.4, 13.9.

HRMS *m/z* : calcd. for $C_{26}H_{27}NO_2$ 385.2042, found 385.2049.

MS (EI, 70 eV), *m/z* (%): 385 (86) [M^+], 279 (25), 252 (35), 165 (28), 106 (100).

IR (cm^{-1}): 3285 (m), 3085 (w), 3003 (w), 2956 (w), 2933 (w), 1680 (s), 1637 (vs), 1610 (m), 1552 (vs), 1505 (m), 1497 (m), 1434 (m), 1329 (m), 1282 (m), 1191 (m), 1155 (s).

3-(4-Carbamoyl-benzyl)-benzoic acid ethyl ester (94k)



3-Ethoxycarbonyl-benzylzinc chloride (**75e**, 1.8 mL, 1.34 M in THF, 2.4 mmol) was added to a solution of 4-bromo-benzamide (**92c**, 400 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after

evaporation of the solvents by flash chromatography (pentane/EtOAc 3:7) yielded 3-(4-carbamoyl-benzyl)-benzoic acid ethyl ester (**94k**) as a colorless solid (516 mg, 91 %).

m.p.: 101.8-102.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.91-7.87 (m, 2H), 7.75-7.72 (m, 2H), 7.37-7.32 (m, 2H), 7.25-7.23 (m, 2H), 5.91 (bs, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

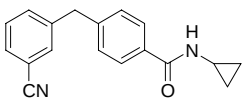
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 169.1, 166.5, 144.9, 140.4, 133.4, 131.4, 130.9, 130.0, 129.1, 128.6, 127.7, 127.7, 61.0, 41.5, 14.3.

HRMS *m/z* : calcd. for $C_{17}H_{17}NO_3$ 283.1208, found 283.1195.

MS (EI, 70 eV), *m/z* (%): 283 (100) [M^+], 267 (73), 238 (83), 220 (37), 165 (89).

IR (cm^{-1}): 3391 (w), 3161 (w), 2981 (w), 1708 (s), 1642 (s), 1615 (s), 1582 (w), 1568 (m), 1442 (w), 1416 (m), 1400 (s), 1328 (w), 1279 (vs), 1251 (vs), 1180 (vs), 1139 (m), 1103 (s).

4-(3-Cyano-benzyl)-*N*-cyclopropyl-benzamide (94lf)



3-Cyanobenzylzinc chloride (**75f**, 4.4 mL, 0.82 M in THF, 3.6 mmol) is added to a solution of 4-bromo-*N*-cyclopropyl-benzamide (**92f**, 720 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (5 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 3:2) yielded 4-(3-cyano-benzyl)-*N*-cyclopropyl-benzamide (**94l**) as a colorless solid (643 mg, 78 %).

m.p.: 136.5-138.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.68 (ddd, *J* = 8.3, 2.0, 1.9 Hz, 2H), 7.51-7.46 (m, 1H), 7.41 (m, 1H), 7.39-7.35 (m, 2H), 7.18 (ddd, *J* = 8.3, 2.0, 1.9 Hz, 2H), 6.30 (s, 1H), 4.02 (s, 2H), 2.92-2.83 (m, 1H), 0.87-0.81 (m, 2H), 0.59 (ddd, *J* = 7.0, 5.0, 4.1 Hz, 2H).

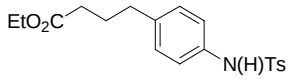
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 168.5, 143.0, 141.8, 133.3, 132.9, 132.3, 130.1, 129.4, 129.1, 127.4, 118.7, 112.6, 41.1, 23.1, 6.8.

HRMS *m/z* : calcd. for $C_{18}H_{16}N_2O$ 276.1263, found 276.1264.

MS (EI, 70 eV), *m/z* (%): 276 (10) [M^+], 220 (100), 160 (13), 165 (12), 116 (8).

IR (cm^{-1}): 3272 (m), 3064 (w), 3002 (w), 2928 (w), 2876 (w), 2228 (w), 1738 (w), 1629 (vs), 1612 (s), 1552 (vs), 1508 (s), 1482 (m), 1415 (m), 1362 (m), 1311 (s).

4-[4-(Toluene-4-sulfonylamino)-phenyl]-butyric acid ethyl ester (95a)



4-Ethoxy-4-oxobutylzinc bromide (**74c**, 3.1 mL, 0.78 M in THF, 2.4 mmol) was added to a solution of *N*-(4-iodo-phenyl)-4-methyl-benzenesulfonamide (**93a**, 746 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yielded 4-[4-(toluene-4-sulfonylamino)-phenyl]-butyric acid ethyl ester (**95a**) as a yellow oil (543 mg, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.67-7.63 (m, 2 H), 7.24-7.21 (m, 2 H), 7.06-6.97 (m, 4 H), 6.79 (s, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 2.58 (t, J = 7.2 Hz, 2 H), 2.39 (s, 3 H), 2.28 (t, J = 7.5 Hz, 2 H), 1.94-1.84 (m, 2 H), 1.26 (t, J = 7.2 Hz, 3 H).

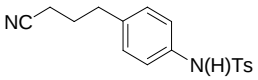
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.42, 143.73, 138.80, 136.20, 134.37, 129.58, 129.28, 127.26, 122.16, 60.32, 34.44, 33.54, 26.37, 21.52, 14.24.

HRMS *m/z* : calcd. for $C_{19}H_{23}NO_4S$ 361.1348, found 361.1341.

MS (70 eV, EI) *m/z* (%): 362 (22), 361 (100) [M^+], 316 (27), 273 (79), 260 (50), 205 (14),.

IR (cm^{-1}): 3252, 2931, 1729, 1708, 1512, 1456, 1397, 1375, 1334, 1305, 1290, 1222, 1185, 1156, 1091.

***N*-[4-(3-Cyano-propyl)-phenyl]-4-methyl-benzenesulfonamide (95b)**



4-Cyanobutylzinc bromide (**74b**, 2.4 mL, 1.0 M in THF, 2.4 mmol) was added to a solution of *N*-(4-iodo-phenyl)-4-methyl-benzenesulfonamide (**93a**, 746 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yielded *N*-[4-(3-cyano-propyl)-phenyl]-4-methyl-benzenesulfon-amide (**95b**) as a pale yellow oil (598 mg, 95 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, J = 8.1 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.07-7.01 (m, 5 H), 2.70 (t, *J* = 7.5 Hz, 2 H), 2.39 (s, 3 H), 2.28 (t, *J* = 7.2 Hz, 2 H), 1.97-1.90 (m, 2 H).

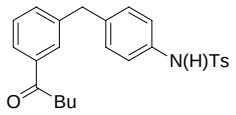
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 143.87, 136.82, 136.14, 135.01, 129.64, 129.28, 127.25, 122.04, 119.39, 33.68, 26.73, 21.54, 16.33.

HRMS *m/z* : calcd. $C_{17}H_{18}N_2O_2S$ 314.1089, found 314.1085.

MS (70 eV, EI) *m/z* (%): 315 (21), 314 (99) [M^+], 261 (12), 260 (75), 159 (43), 155 (23), 119 (100), 118 (23).

IR (cm^{-1}): 3249, 2927, 1511, 1457, 1398, 1334, 1290, 1155, 1090.

4-Methyl-*N*-[4-(3-pentanoyl-benzyl)-phenyl]-benzenesulfonamide (95c)



3-Pentanoyl-benzylzinc chloride (**75c**, 1.8 mL, 1.34 M in THF, 2.4 mmol, 2.4 mmol) was added to a solution of *N*-(4-iodo-phenyl)-4-methyl-benzenesulfonamide (**93a**, 746 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 7:3) yielded 4-methyl-*N*-[4-(3-pentanoyl-benzyl)-phenyl]-benzene-sulfonamide (**95c**) as a colorless oil (759 mg, 90 %).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.8 Hz, 1 H), 7.74 (s, 1 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 1 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.11 (s, 1 H), 7.03-7.00 (m, 4 H), 3.94 (s, 2 H), 2.92 (t, *J* = 7.8 Hz, 2 H), 2.36 (s, 3 H), 1.71-1.66 (m, 2 H), 1.42-1.36 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

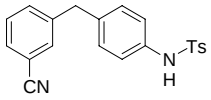
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.70, 143.75, 141.28, 137.53, 137.31, 136.15, 134.83, 133.36, 129.66, 129.59, 128.67, 128.31, 127.22, 126.10, 121.96, 41.02, 39.36, 26.47, 22.43, 21.49, 13.91.

HRMS *m/z* : calcd. for $C_{25}H_{27}NO_3S$ 421.1712, found 421.1711.

MS (70 eV, EI) *m/z* (%):421 (90) [M^+], 379 (54), 364 (100), 210 (37), 180 (29).

IR (cm^{-1}): 3249, 2957, 2930, 1673, 1510, 1441, 1399, 1336, 1155, 1091, 914, 812, 661, 588.

_N_-[4-(3-Cyano-benzyl)-phenyl]-4-methyl-benzenesulfonamide (95d)



3-Cyanobenzylzinc chloride (**75f**, 4.4 mL, 0.82 M in THF, 3.6 mmol) is added to a solution of *N*-(4-iodo-phenyl)-4-methyl-benzenesulfonamide (**93a**, 1.12 g, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (24.6 mg, 0.06 mmol) in THF (5 mL), according to **TP 7**. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. NH_4Cl solution and extracted with ether. The combined organic phases were washed with a aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded *N*-[4-(3-cyano-benzyl)-phenyl]-4-methyl-benzenesulfonamide (**95d**) as a colorless oil (1.07 g, 98 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.66 (d, *J* = 8.4 Hz, 2H), 7.50-7.44 (m, 1H), 7.39-7.34 (m, 3H), 7.22 (dd, *J* = 8.4, 0.5 Hz, 2H), 7.04-6.98 (m, 4H), 6.95 (s, 1H), 3.91 (s, 2H), 2.37 (s, 3H).

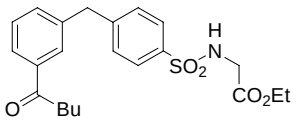
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 143.9, 142.2, 136.4, 136.1, 135.2, 133.3, 132.2, 130.0, 129.8, 129.6, 129.2, 127.2, 122.0, 118.8, 112.5, 40.6, 21.5 .

HRMS *m/z* : calcd. for $C_{21}H_{18}N_2O_2S$ 362.1089, found 362.1094.

MS (EI, 70 eV), *m/z* (%): 362 (65) [M^+], 207 (100), 180 (35), 155 (17), 91 (40).

IR (cm^{-1}): 3387 (w), 3280 (m), 3079 (w), 3075 (w), 2950 (w), 2926 (w), 2237 (m), 1600 (w), 1504 (m), 1423 (w), 1368 (m), 1324 (s), 1304 (m), 1212 (w), 1159 (vs), 1091 (s).

[4-(3-Pentanoyl-benzyl)-benzenesulfonylamino]-acetic acid ethyl ester (95e)

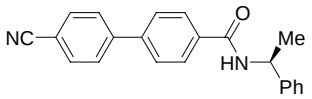


3-Pentanoyl-benzylzinc chloride (**75c**, 1.8 mL, 1.34 M in THF, 2.4 mmol, 2.4 mmol) was added to a solution of (4-iodo-benzenesulfonylamino)-acetic acid ethyl ester (**93b**, 738 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yielded *N*-[4-(3-cyano-propyl)-phenyl]-4-methyl-benzenesulfon-amide (**95e**) as a colorless solid (708 mg, 85 %).

m.p.: 70.9-72.3 °C.

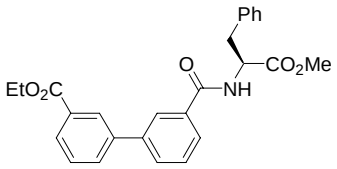
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81-7.75 (m, 4 H), 7.40-7.29 (m, 4 H), 5.15 (t, *J* = 5.2 Hz, 1 H), 4.07 (s, 2 H), 4.03 (q, *J* = 7.2 Hz, 2 H), 3.74 (d, *J* = 5.6 Hz, 2 H), 2.92 (t, *J* = 7.2 Hz, 2 H), 1.72-1.64 (m, 2 H), 1.42-1.33 (m, 2 H), 1.13 (t, *J* = 7.2 Hz, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.4, 168.7, 146.1, 140.1, 137.5, 137.2, 133.4, 129.5, 128.9, 128.4, 127.6, 126.5, 61.9, 44.1, 41.5, 38.4, 26.4, 22.4, 13.9, 13.9.
HRMS *m/z* : calcd. for $C_{22}H_{27}NO_5S$ 417.1610, found 417.1610.
MS (70 eV, EI) *m/z* (%): 417 (2) [M^+], 344 (36), 315 (53), 303 (33), 286 (100).
IR (cm^{-1}): 3267, 2956, 2932, 2870, 1732, 1688, 1598, 1369, 1350, 1326, 1316, 1239, 1210, 1159, 1104, 1090.

4'-Cyano-biphenyl-4-carboxylic acid (1-phenyl-ethyl)-amide (99)



4-(Cyano)phenylzinc iodide (**73b**, 5.1 mL, 0.71 M in THF, 3.6 mmol) was added to a solution of (4-bromo-*N*-(1-phenyl-ethyl)-benzamide (**96**, 913 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and S-Phos (24.6 mg, 0.06 mmol) in THF (5 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 7:3) yielded 4'-cyano-biphenyl-4-carboxylic acid (1-phenyl-ethyl)-amide (**99**) as a light yellow solid (953 mg, 95 %).
m.p.: 131.8-133.5 °C.
^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.88 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.41-7.35 (m, 4H), 7.30-7.27 (m, 1H), 6.42 (d, *J* = 6.9 Hz, 1H), 5.35 (qd, *J* = 7.1, 6.9 Hz, 1H), 1.62 (d, *J* = 7.1 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 165.8, 144.4, 142.9, 142.1, 134.5, 132.7, 128.8, 127.8, 127,7, 127.6, 127.4, 126.3, 118.7, 111.6, 49.4, 21.7.
HRMS *m/z* : calcd. for $C_{22}H_{18}N_2O$ 326.1419, found 326.1414.
MS (EI, 70 eV), *m/z* (%): 326 (31) [M^+], 307 (11), 206 (100), 178 (21), 120 (11).
IR (cm^{-1}): 3298 (w), 3060 (w), 2979 (w), 2934 (w), 2229 (m), 1732 (m), 1630 (vs), 1608 (s), 1573 (w), 1533 (s), 1516 (s), 1491 (s), 1444 (m), 1343 (m), 1296 (m), 1272 (m), 1240 (m), 1120 (m).
$[\alpha]_D^{20}$: +41.7 (c = 0.35, $CHCl_3$).

3'-(1-Methoxycarbonyl-2-phenyl-ethylcarbamoyl)-biphenyl-3-carboxylic acid ethyl ester (100)



4-(Ethoxycarbonyl)phenylzinc iodide (**73i**, 4.2 mL, 0.87 M in THF, 3.6 mmol) was added to a solution of 2-(3-bromo-benzoylamino)-3-phenyl-propionic acid methyl ester (**97**, 1.09 g, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and S-Phos (24.6 mg, 0.06 mmol) in THF (5 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 8:2) yielded 3'-(1-methoxycarbonyl-2-phenyl-ethylcarbamoyl)-biphenyl-3-carboxylic acid ethyl ester (**100**) as a colorless oil (1.22 g, 94 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.26 (t, *J* = 1.9 Hz, 1H), 8.05 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.99 (t, *J* = 1.9 Hz, 1H), 7.78-7.73 (m, 2H), 7.67 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.54-7.48 (m, 2H), 7.32-7.23 (m, 3H), 7.16-7.14 (m, 2H), 6.63 (d, *J* = 7.6 Hz, 1H), 5.11 (dt, *J* = 7.6, 5.7 Hz, 1H), 4.42 (q, *J* = 7.0 Hz, 2H), 3.77 (s, 3H), 3.34-3.21 (m, 2H), 1.41 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 172.0, 166.7, 166.4, 140.8, 140.4, 135.8, 134.7, 131.5, 131.2, 130.5, 129.3, 129.2, 128.9, 128.9, 128.7, 128.2, 127.3, 126.1, 125.9, 61.2, 53.6, 52.4, 37.9, 14.4.

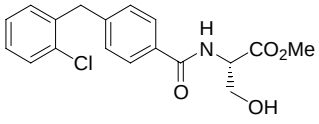
HRMS *m/z* : calcd. for $C_{26}H_{25}NO_5$ 431.1733, found 431.1721

MS (EI, 70 eV), *m/z* (%): 431 (5) [M^+], 386 (24), 269 (87), 253 (100), 224 (18).

IR (cm^{-1}): 3325 (w), 3063 (w), 3028 (w), 2983 (w), 2954 (w), 1742 (s), 1716 (s), 1643 (s), 1602 (m), 1580 (m), 1529 (s), 1497 (m), 1436 (s), 1392 (w), 1366 (m), 1285 (s), 1241 (vs), 1214 (s), 1172 (s).

$[\alpha]_D^{20}$: +82.1 (c = 0.98, $CHCl_3$).

2-[4-(2-Chloro-benzyl)-benzoylamino]-3-hydroxy-propionic acid methyl ester (101)



2-Chloro-benzylzinc chloride (**75b**, 3.6 mL, 0.81 M in THF, 2.6 mmol) was added to a solution of 3-hydroxy-2-(4-iodo-benzoylamino)-propionic acid methyl ester (**98**, 698 mg, 2

mmol), $Pd(OAc)_2$ (8.9 mg, 0.04 mmol) and S-Phos (32.8 mg, 0.08 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/CH_2Cl_2/MeOH 25:25:1) yielded 2-[4-(2-chloro-benzyl)-benzoylamino]-3-hydroxy-propionic acid methyl ester (**101**) as a pale yellow oil (594 mg, 85 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.74 (d, *J* = 8.2 Hz, 2H), 7.38-7.36 (m, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.19-7.17 (m, 2H), 7.14-7.10 (m, 1H), 4.84 (dt, *J* = 7.2, 3.6 Hz, 1H), 4.13 (s, 2H), 4.06-4.00 (m, 2H), 3.79 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 171.1, 167.5, 144.0, 137.7, 134.2, 131.4, 131.0, 129.7, 129.1, 128.0, 127.4, 127.0, 63.5, 55.2, 52.9, 39.1.

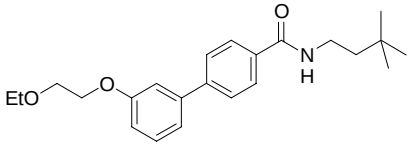
HRMS *m/z* : calcd. for $C_{18}H_{18}ClNO_4$ 347.0924, found 347.0918.

MS (EI, 70 eV), *m/z* (%): 328 (24), 317 (23), 270 (64), 230 (100), 166 (48).

IR (cm^{-1}): 3345 (bm), 3059 (w), 3015 (w), 2951 (w), 2931 (w), 1740 (s), 1638 (s), 1611 (m), 1589 (w), 1532 (s), 1500 (s), 1472 (s), 1436 (m), 1346 (m), 1301 (m), 1279 (m), 1209 (s), 1159 (m).

$[\alpha]_D^{20}$: -45.8 (c = 0.07, $CHCl_3$).

3'-(2-Ethoxy-ethoxy)-biphenyl-4-carboxylic acid (3,3-dimethyl-butyl)-amide (103a)



3-(2-Ethoxy-ethoxy)-phenylzinc chloride (**73j**, 4.1 mL, 0.58 M in THF, 2.4 mmol) was added to a solution of 4-bromo-*N*-(3,3-dimethyl-butyl)-benzamide (**102**, 568 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 7:3) yielded 3'-(2-ethoxy-ethoxy)-biphenyl-4-carboxylic acid (3,3-dimethyl-butyl)-amide (**103a**) as a colorless solid (679 mg, 92 %).

m.p.: 70.9-72.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.80 (ddd, *J* = 8.4, 2.0, 1.9 Hz, 2H), 7.61 (ddd, *J* = 8.4, 2.0, 1.9 Hz, 2H), 7.37-7.31 (m, 2H), 7.19-7.16 (m, 1H), 6.95-6.91 (m, 1H), 6.15 (s, 1H), 4.19-4.16 (m, 2H), 3.82-3.79 (m, 2H), 3.61 (q, *J* = 6.9 Hz, 2H), 3.51-3.44 (m, 2H), 1.56-1.51 (m, 2H), 1.24 (t, *J* = 6.9 Hz, 3H), 0.97 (s, 9H).

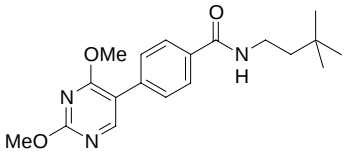
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 167.1, 159.2, 143.9, 141.4, 133.5, 129.8, 127.3, 127.2, 119.8, 113.9, 113.8, 68.9, 67.5, 66.9, 43.4, 36.8, 30.0, 29.4, 15.2.

HRMS *m/z* : calcd. for $C_{23}H_{31}NO_3$ 369.2304, found 369.2289.

MS (EI, 70 eV), *m/z* (%): 369 (36) [M^+], 354 (12), 269 (100), 213 (21), 197 (16).

IR (cm^{-1}): 3313 (m), 3072 (w), 2943 (m), 2874 (m), 1628 (s), 1610 (s), 1597 (s), 1556 (vs), 1516 (m), 1488 (s), 1394 (w), 1324 (s), 1312 (s), 1312 (s), 1280 (s), 1219 (vs), 1121 (vs).

4-(2,4-Dimethoxy-pyrimidin-5-yl)-N-(3,3-dimethyl-butyl)-benzamide (103b)



2,4-Dimethoxypyimidin-5-yl zinc iodide (**73h**, 3.0 mL, 0.80 M in THF, 2.4 mmol) was added to a solution of 4-bromo-*N*-(3,3-dimethyl-butyl)-benzamide (**102**, 568 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and S-Phos (16.4 mg, 0.04 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 3:2) yielded 4-(2,4-dimethoxy-pyrimidin-5-yl)-N-(3,3-dimethyl-butyl)-benzamide (**103b**) as a colorless solid (665 mg, 97 %).

m.p.: 141.7-142.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.26 (s, 1H), 7.79 (ddd, *J* = 8.5, 2.0, 1.9 Hz, 2H), 7.54 (ddd, *J* = 8.5, 2.0, 1.9 Hz, 2H), 6.14 (s, 1H),4.03 (s, 3H), 4.01 (s, 3H), 3.51-3.43 (m, 2H), 1.55-1.49 (m, 2H), 0.96 (s, 9H).

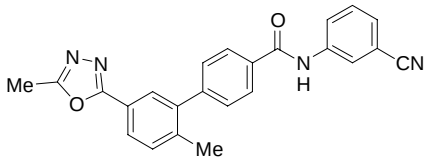
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 168.1, 166.9, 164.7, 157.6, 136.3, 133.9, 128.8, 126.9, 115.2, 55.0, 54.2, 43.3, 36.8, 30.0, 29.4.

HRMS *m/z* : calcd. for $C_{19}H_{25}N_3O_3$ 343.1896, found 343.1898.

MS (EI, 70 eV), *m/z* (%): 343 (20) [M^+], 259 (24), 243 (100), 229 (11), 200 (12).

IR (cm^{-1}): 3298 (m), 3039 (w), 2956 (m), 2912 (w), 2865 (w), 1651 (s), 1591 (s), 1567 (s), 1547 (s), 1478 (s), 1463 (vs), 1392 (vs), 1373 (vs), 1310 (s), 1298 (s), 1230 (s), 1189 (s).

2'-Methyl-5'-(5-methyl-[1,3,4]oxadiazol-2-yl)-biphenyl-4-carboxylic acid (3-cyano-phenyl)-amide (106a)



[2-Methyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]zinc iodide (**104**, 6.7 mL, 0.10 M in THF, 1.2 mmol) was added to a solution of 4-bromo-*N*-(3-cyano-phenyl)-benzamide (**105**, 301 mg, 1 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and S-Phos (8.2 mg, 0.02 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yielded 2'-methyl-5'-(5-methyl-[1,3,4]oxadiazol-2-yl)-biphenyl-4-carboxylic acid (3-cyano-phenyl)-amide (**106a**) as a light yellow solid (357 mg, 91 %).

m.p.: 201.6-203.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.67 (s, 1H), 8.13 (s, 1H), 7.95-7.94 (m, 3H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.82 (s, 1H), 7.46-7.44 (m, 1H), 7.41-7.38 (m, 4H), 2.57 (s, 3H), 2.28 (s, 3H).

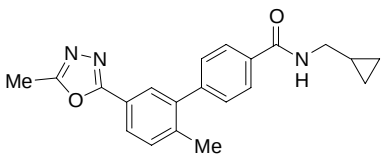
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 165.8, 164.7, 163.6, 144.5, 141.4, 139.4, 139.0, 133.1, 131.3, 129.9, 129.5, 127.8, 127.6, 127.3, 126.0, 124.5, 123.5, 121.6, 118.6, 112.9, 22.5, 11.1.

HRMS *m/z* : calcd. for $C_{24}H_{18}N_4O_2$ 394.1430, found 394.1420.

MS (EI, 70 eV), *m/z* (%): 394 (6) [M^+], 277 (100), 220 (9), 193 (7), 165 (14).

IR (cm^{-1}): 3285 (m), 3064 (w), 2924 (w), 2226 (m), 16720 (vs), 1607 (s), 1587 (m), 1574 (m), 1542 (vs), 1485 (vs), 1446 (m), 1410 (s), 1313 (vs), 1259 (s), 1235 (s), 1171 (m), 1112 (m).

2'-Methyl-5'-(5-methyl-[1,3,4]oxadiazol-2-yl)-biphenyl-4-carboxylic acid cyclopropyl-methyl-amide (106b)



[2-Methyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]zinc iodide (**104**, 6.7 mL, 0.10 M in THF, 1.2 mmol) was added to a solution of 4-bromo-*N*-cyclopropylmethyl-benzamide (**94f**, 254 mg, 1 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and S-Phos (8.2 mg, 0.02 mmol) in THF (3

mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/EtOAc 2:3) yielded 2'-methyl-5'-(5-methyl-[1,3,4]oxadiazol-2-yl)-biphenyl-4-carboxylic acid (3-cyano-phenyl)-amide (**106b**) as a colorless solid (345 mg, 98 %).

m.p.: 140.0-141-9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.90-7.88 (m, 1H), 7.86-7.85 (m, 3H), 7.38-7.37 (m, 3H), 6.49 (s, 1H), 3.33 (dd, *J* = 7.1, 5.5 Hz, 2H), 2.57 (s, 3H), 2.28 (s, 3H), 1.11-1.05 (m, 1H), 0.54 (dd, *J* = 8.1, 5.5, 4.5, Hz, 2H), 0.28-0.26 (m, 2H).

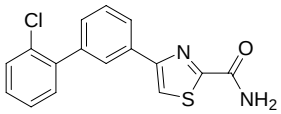
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 167.1, 164.7, 163.4, 143.6, 141.7, 139.4, 133.7, 131.2, 129.2, 127.7, 126.9, 125.8, 121.7, 44.9, 22.3, 20.5, 11.0, 3.5.

HRMS *m/z* : calcd. for $C_{21}H_{21}N_3O_2$ 347.1634, found 347.1628.

MS (EI, 70 eV), *m/z* (%): 347 (17) [M^+], 318 (14), 277 (100), 193 (8), 165 (16).

IR (cm^{-1}): 3302 (m), 2979 (w), 2926 (w), 1620 (vs), 1588 (m), 1554 (s), 1538 (vs), 1509 (s), 1482 (s), 1390 (m), 1352 (m), 1292 (s), 1279 (s), 1264 (m), 1230 (s), 1171 (m), 1136 (m).

4-(2'-Chloro-biphenyl-3-yl)-thiazole-2-carboxylic acid amide (109a)



2-Chloro-phenylzinc chloride (**73k**, 5.0 mL, 0.48 M in THF, 2.4 mmol) was added to a solution of 4-(3-bromo-phenyl)-thiazole-2-carboxylic acid amide (**108**, 566 mg, 2 mmol), $Pd(OAc)_2$ (8.9 mg, 0.04 mmol) and S-Phos (32.8 mg, 0.08 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/EtOAc 7:3) yielded 4-(2'-chloro-biphenyl-3-yl)-thiazole-2-carboxylic acid amide (**109a**) as a light yellow solid (603 mg, 96 %).

m.p.: 160.0-161.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.98 (s, 1H), 7.90 (d, *J* = 6.7 Hz), 7.76 (s, 1H), 7.52-7.48 (m, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.35-7.29 (m, 2H), 7.26 (s, 1H), 6.17 (s, 1H).

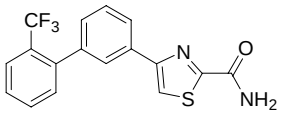
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 162.5, 161.5, 156.3, 140.1, 140.0, 133.4, 132.5, 131.3, 130.0, 129.8, 128.8, 128.6, 127.5, 126.9, 125.5, 119.1..

HRMS *m/z* : calcd. for $C_{16}H_{11}ClN_2OS$ 314.0281, found 314.0272.

MS (EI, 70 eV), *m/z* (%): 314 (100) [M^+], 271 (16), 244 (25), 208 (16), 165 (15).

IR (cm^{-1}): 3438 (w), 3212 (w), 3150 (w), 3104 (w), 1701 (vs), 1662 (m), 1598 (m), 1513 (w), 1482 (m), 1451 (m), 1412 (m), 1377 (m), 1248 (w), 1119 (m), 1092 (w).

4-(2'-Trifluoromethyl-biphenyl-3-yl)-thiazole-2-carboxylic acid amide (109b)



2-Trifluoromethyl-phenylzinc chloride (**73l**, 4.7 mL, 0.51 M in THF, 2.4 mmol) was added to a solution of 4-(3-bromo-phenyl)-thiazole-2-carboxylic acid amide (**108**, 566 mg, 2 mmol), $Pd(OAc)_2$ (8.9 mg, 0.04 mmol) and S-Phos (32.8 mg, 0.08 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/EtOAc 7:3) yielded 4-(2'-trifluoromethyl-biphenyl-3-yl)-thiazole-2-carboxylic acid amide (**109b**) as a colorless solid (679 mg, 97 %).

m.p.: 163.5-165.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.92 (d, *J* = 7.6 Hz, 1H), 7.89 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.75 (s, 1H), 7.59.7.57 (m, 1 H), 7.51-7.47 (m, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.35 (d, 7.6 Hz, 1H), 7.24 (s, 1H), 6.10 (s, 1H).

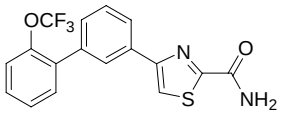
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 162.5, 161.5, 156.2, 140.8, 140.5, 133.1, 131.9, 131.4, 129.3, 128.5 (q, *J* = 29.7 Hz), 128.3, 127.6, 127.0, 126.1, (q, *J* = 5.3 Hz), 125.6, 124.1 (J = 273.9 Hz), 119.1.

HRMS *m/z* : calcd. for $C_{17}H_{11}F_3N_2OS$ 348.0544, found 348.0532.

MS (EI, 70 eV), *m/z* (%): 348 (100) [M^+], 330 (21), 305 (28), 278 (48), 246 (20).

IR (cm^{-1}): 3463 (w), 3278 (w), 3155 (w), 1687 (vs), 1599 (m), 1576 (w), 1494 (w), 1478 (w), 1458 (w), 1444 (m), 1385 (m), 1317 (vs), 1175 (s), 1165 (s), 1120 (vs), 1091 (vs), 1072 (s).

4-(2'-Trifluoromethoxy-biphenyl-3-yl)-thiazole-2-carboxylic acid amide (109c)



2-Trifluoromethoxy-phenylzinc chloride (**73m**, 4.9 mL, 0.49 M in THF, 2.4 mmol) was added to a solution of 4-(3-bromo-phenyl)-thiazole-2-carboxylic acid amide (**108**, 566 mg, 2 mmol), $Pd(OAc)_2$ (8.9 mg, 0.04 mmol) and S-Phos (32.8 mg, 0.08 mmol) in THF (3 mL), according to **TP 7**. The reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (ether/EtOAc 3:2) yielded 4-(2'-trifluoromethoxy-biphenyl-3-yl)-thiazole-2-carboxylic acid amide (**109c**) as a colorless solid (688 mg, 94 %).

m.p.: 127.8-129.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.01 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.76 (s, 1H), 7.53-7.47 (m, 3H), 7.42-7.37 (s, 3H), 7.25 (s, 1H), 6.10 (s, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 162.5, 161.5, 156.3, 146.2, 137.5, 134.8, 133.6, 131.5, 129.6, 129.0, 128.8, 127.3, 127.1, 125.6, 121.4, 120.4 (q, *J* = 275.8 Hz), 119.1.

HRMS *m/z* : calcd. for $C_{17}H_{11}F_3N_2O_2S$ 364.0493, found 364.0487.

MS (EI, 70 eV), *m/z* (%): 364 (100) [M^+], 346 (30), 321 (35), 294 (50), 262 (21).

IR (cm^{-1}): 3471 (m), 3349 (w), 3279 (w), 3151 (w), 3060 (w), 1686 (s), 1599 (m), 1500 (w), 1478 (m), 1456 (m), 1444 (m), 1403 (m), 1381 (m), 1308 (w), 1244 (vs), 1219 (vs), 1188 (s), 1155 (vs), 1125 (vs).

11.7 Relative Rates of Negishi Cross-Coupling Reactions

11.7.1 Starting Materials and Cross-Coupling Products

All aryl bromides were purchased from commercial sources (purity > 98 %) and used without further purification. All zinc reagents were prepared by direct zinc insertion into the corresponding aryl iodides in the presence of LiCl.[80a] The concentration of all zinc reagents was determined by titration with I_2 (average of 3 runs).[158] All cross-coupling products were synthesized according to literature procedures (purity > 95 %).[206]

[206] C. Dietl, *Bachelor thesis*, LMU München, **2008**.

11.7.2 Determination of Relative Response Factors

The relative response factors for the gas chromatographic analysis were calculated according to equation (1) and (2).[207]

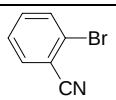
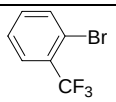
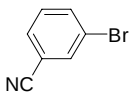
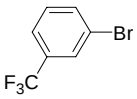
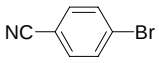
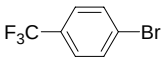
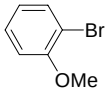
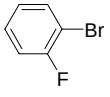
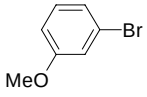
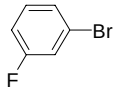
$$\frac{A_{R1}}{A_{IS}} = f_{R1}\frac{[R1]}{[IS]} \Rightarrow f_{R1} = \frac{A_{R1}[IS]}{A_{IS}[R1]} \qquad (1)$$

$$\frac{A_{P1}}{A_{IS}} = f_{R1}\frac{[P1]}{[IS]} \Rightarrow f_{R1} = \frac{A_{R1}[IS]}{A_{IS}[P1]} \qquad (2)$$

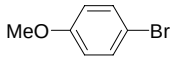
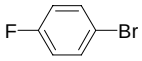
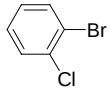
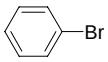
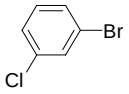
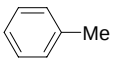
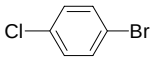
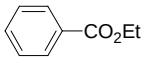
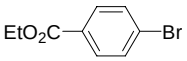
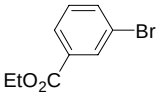
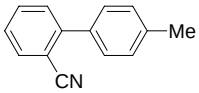
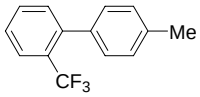
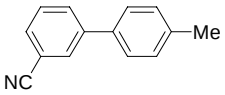
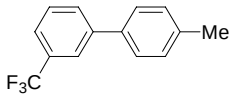
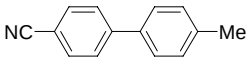
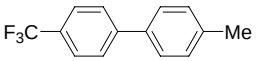
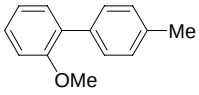
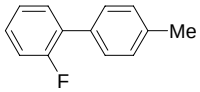
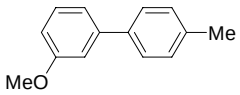
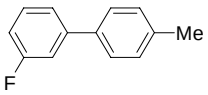
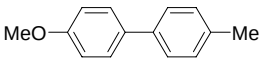
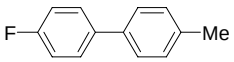
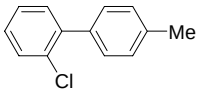
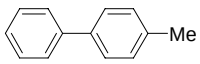
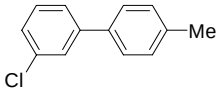
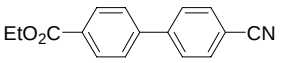
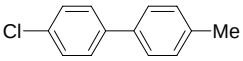
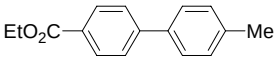
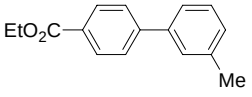
A_{R1}, A_{P1}, A_{IS} are the areas of R1 (reactant 1), P1 (product 1) and IS (internal standard, $n$$C_{16}H_{34}$). [R1], [R2] and [IS] are the corresponding concentartions.

For the determination of a response factor a mixture of [R1], [R2], [P1] or [P2] and a certain amount of internal standard ($n$$C_{16}H_{34}$) was analyzed by GC to give area ratios. For every compound [R_x] or [P_x] three different mixtures were analyzed and each mixture run at least three times. For each compound an appropriate relative response factor was obtained for each run. The reported values of the relative response factors are an average obtained from all runs (Table 22).

Table 22. Relative response factor *f* of aryl bromides and cross-coupling products *versus* hexadecane ($n$$C_{16}H_{34}$).

Entry	Compound	$f_{avg.}$	Entry	Compound	$f_{avg.}$
1		0.3739	20		0.4429
2		0.3498	21		0.4466
3		0.3802	22		0.4201
4		0.4019	23		0.3982
5		0.4010	24		0.3958

[207] D. J. David,*Gas Chromatographic Detectors*, Wiley, New York, **1974**.

6		0.3569	25		0.3971
7		0.3860	26		0.3944
8		0.3916	27		0.4486
9		0.3878	28		0.4876
10		0.4604	29		0.4894
11		0.8564	30		0.8432
12		0.8122	31		0.8728
13		0.8137	32		0.8583
14		0.7936	33		0.7927
15		0.8134	34		0.8032
16		0.7727	35		0.7998
17		0.7962	36		0.8084
18		0.7984	37		0.8165
19		0.7480	38		0.8949
			39		0.8909

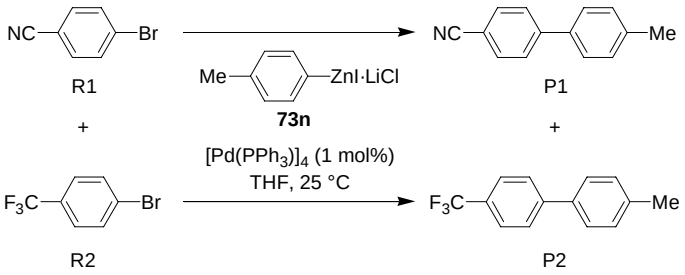
11.7.3 Determination of the Relative Reaction Rates

Typical Procedure for a Competition Experiment between two Aryl Bromides

A dry and N_2-flushed Schlenk-flask was charged with R1 (4-bromo-benzonitrile, 364.0 mg, 2 mmol), R2 (4-trifluoromethyl-bromo-benzene, 450.1 mg, 2 mmol), [$Pd(PPh_3)_4$] (23.1 mg, 0.02 mmol), $nC_{16}H_{34}$ (70 mg, 0.31 mmol) and THF (2 mL). The flask was cooled with a waterbath (25 °C). The zinc reagent **73n** (4.0 mL, 0.5 M in THF, 2.0 mmol) was added in one portion and the reaction mixture stirred at 25 °C. After certain times (for example 20 min), about 0.1 mL of the mixture was taken out with a syringe and poured into sat. aq. NH_4Cl solution (1 mL). The aqueous phase was extracted with diethyl ether (about 2 ~ 3 mL). The ethereal solutions were dried over Na_2SO_4 and analyzed by GC.

Combination of 0.33 M 4-bromo-benzonitrile (R1), 0.33 M 4-trifluoromethyl-bromo-benzene (R2) and 0.33 M *p*-tolylzinc iodide (**73n**) gave the following results (Table 23)

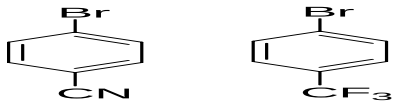
Table 23. Areas and κ values obtained from the competition experiment between 4-bromo-benzonitrile and 4-trifluoromethyl-bromo-benzene.



t(min)	A_{R1}	A_{R2}	A_{IS}	A_{P1}	A_{P2}	κ_1	κ_2	κ_3
10 min	32.7787	41.0194	14.5934	9.8848	1.7238	6.474444	-	6.403396
	32.6381	41.0072	14.4991	10.1366	1.7191	6.671472	-	6.599417
	32.5801	41.0586	14.5672	10.0726	1.7214	6.642554	-	6.543899
	Average value					6.596157	-	6.515571
20 min	27.6801	38.0969	13.7461	17.3195	3.1574	6.449769	-	6.471076
	27.6045	38.1254	13.7463	17.3674	3.1565	6.487673	-	6.493528
	26.3615	38.7281	13.9858	17.701	3.2236	6.833529	-	6.48168
	Average value					6.590324	-	6.482094
40 min	19.7747	34.331	12.842	27.4114	5.6409	6.455906	-	6.300286
	20.0081	33.9895	12.8137	27.541	5.6476	6.351608	-	6.335264
	19.7565	34.1569	12.7856	27.6776	5.6235	6.497388	-	6.408889
	Average value					6.434967	-	6.348146

60 min	13.1956	30.4355	12.0502	35.8536	8.4651	6.421515	-	6.140658
	13.2093	30.3507	12.0412	36.0276	8.3712	6.488968	-	6.2637
	13.0048	30.2757	12.0371	36.2511	8.3915	6.555619	-	6.309297
	Average value					6.488701	-	6.237885
80 min	8.2564	27.4855	11.5248	41.7415	10.9918	6.783261	9.089578	6.153452
	7.8507	27.542	11.597	41.9514	11.0589	6.976975	9.221445	6.140338
	8.2403	27.2128	11.5344	42.0032	11.0093	6.74379	8.441083	6.211464
	Average value					6.834675	8.917369	6.168418
100 min	6.717	25.9132	11.3012	43.8981	12.1705	6.764158	8.118361	6.176144
	6.8036	26.0026	11.2714	43.7745	12.1478	6.739629	8.318552	6.168517
	6.7602	25.8805	11.2389	44.0226	12.0978	6.78004	8.250744	6.288633
	Average value					6.761275	8.229219	6.211098
120 min	6.995	25.9589	11.2131	43.7682	12.0648	6.669483	8.29577	6.245503
	6.9663	25.922	11.2174	43.7479	12.1464	6.633623	8.2333	6.190354
	6.9498	25.9602	11.2331	43.7399	12.1171	6.664904	8.259396	6.196199
	Average value					6.656003	8.262822	6.210685
140 min	6.7239	26.1132	11.2539	43.7437	12.0654	6.848145	8.675544	6.215743
	6.9337	25.9998	11.2254	43.7598	12.0813	6.702076	8.379498	6.226774
	6.9919	26.0652	11.2163	43.6137	12.1129	6.658891	8.494608	6.170282
	Average value					6.736371	8.51655	6.204266
160 min	6.7803	25.9378	11.2835	43.7894	12.2089	6.707696	8.173124	6.132081
	6.7727	25.8685	11.2598	43.9497	12.1494	6.738445	8.140527	6.225578
	6.7617	25.8054	11.294	43.9477	12.1913	6.70844	7.917782	6.182748
	Average value					6.718194	8.077144	6.180136
180 min	7.21	25.9936	11.1207	43.6185	12.0571	6.559199	8.558972	6.256149
	7.3419	26.1063	11.1655	43.2941	12.0922	6.475414	8.485383	6.1149
	7.2783	25.8984	11.1346	43.6284	12.0603	6.502844	8.247414	6.249494
	Average value					6.512486	8.43059	6.206848
210 min	6.7251	25.8992	11.2594	43.9167	12.1995	6.743502	8.238868	6.187515
	6.598	26.1534	11.2842	43.8085	12.1559	6.886498	8.745939	6.167136
	6.7394	25.9885	11.2794	43.8065	12.1862	6.754277	8.317243	6.151977
	Average value					6.794759	8.434017	6.168876
Overall average value						6.65	8.41	6.27

In an analogous way, all other relative reactivities have been determined and the results are summarized in the following tables.

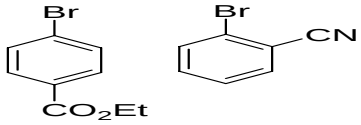


$\kappa = 6.75$

$\kappa_1 = 6.75 \quad \kappa_2 = 8.08 \quad \kappa_3 = 6.15$

t (min)	κ_1				κ_2			κ_3			
	0.33[a]:0.33[b]	0.33[a]:0.66[b]	0.17[a]:0.17[b]	0.17[a]:0.33[b]	0.33[a]:0.33[b]	0.17[a]:0.17[b]	0.17[a]:0.33[b]	0.33[a]:0.33[b]	0.33[a]:0.66[b]	0.17[a]:0.17[b]	0.17[a]:0.33[b]
10	6.60	6.67	6.54	6.19	-	-	-	6.52	6.58	6.18	5.90
20	6.60	6.59	6.63	6.58	-	-	-	6.48	6.40	6.17	5.99
40	6.43	6.46	6.73	6.58	-	-	-	6.35	6.41	6.03	5.96
60	6.49	6.78	6.87	6.74	-	-	-	6.24	6.29	6.00	5.91
80	6.83	7.01	6.38	7.07	-	7.24	-	6.17	6.30	6.08	5.88
120	6.66	6.80	6.77	7.25	8.26	7.16	-	6.21	6.30	6.09	5.93
160	6.72	6.90	7.19	7.04	8.08	7.36	8.62	6.18	6.27	5.88	5.86
180	6.51	6.71	6.97	7.21	8.43	7.34	8.99	6.21	6.30	5.99	5.84
210	6.79	6.92	6.84	6.72	8.43	7.12	8.49	6.17	6.26	6.04	5.94
Av	6.63	6.76	6.77	6.82	8.30	7.24	8.70	6.28	6.35	6.05	5.91

[a] Concentration of R1 and **73n**. [b] Concentration of R2.



$\kappa = 4.57$

$\kappa_1 = 4.57 \quad \kappa_2 = 5.87 \quad \kappa_3 = 4.33$

t (h)	κ_1				κ_2		κ_3			
	0.33[a]:0.33[b]	0.33[a]:0.66[b]	0.17[a]:0.17[b]	0.17[a]:0.33[b]	0.33[a]:0.33[b]	0.17[a]:0.33[b]	0.33[a]:0.33[b]	0.33[a]:0.66[b]	0.17[a]:0.17[b]	0.17[a]:0.33[b]
2	5.02	4.79	4.54	4.56	-	-	4.74	4.41	4.51	4.35
3.75	4.78	4.56	4.39	4.42	-	-	4.50	4.13	4.40	4.26
4.75	4.69	4.55	4.33	4.39	5.29	-	4.41	4.11	4.37	4.24
6	4.82	4.64	4.31	4.37	6.29	5.73	4.42	4.15	4.32	4.23
8	4.86	4.63	4.28	4.50	6.40	5.89	4.47	4.13	4.42	4.38
10	4.83	4.59	4.35	4.44	5.94	5.80	4.43	4.14	4.40	4.26
12	4.84	4.60	4.37	4.47	5.81	-	4.43	4.12	4.44	4.24
24	4.89	4.62	4.37	4.40	6.11	5.67	4.44	4.11	4.38	4.24
Av	4.84	4.62	4.37	4.44	5.97	5.77	4.48	4.16	4.41	4.27

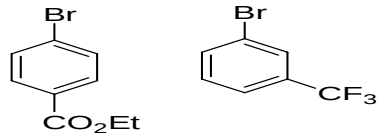
[a] Concentration of R1 and **73n**. [b] Concentration of R2.

$\kappa = 5.43$

$\kappa_1 = 5.43$ $\kappa_2 = -$ $\kappa_3 = 5.26$

t(min)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
70	4.98	5.24	6.01	7.28	11.07	9.46	4.81	5.14	5.79
180	5.01	5.36	5.98	7.13	10.57	9.59	4.84	5.13	5.81
Av	5.00	5.31	5.99	-	-	-	4.83	5.14	5.80

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

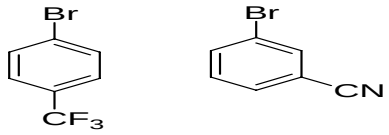


$\kappa = 2.53$

$\kappa_1 = 2.53$ $\kappa_2 = 2.26$ $\kappa_3 = 2.58$

t(h)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
3	2.72	2.53	2.31	2.37	2.42	1.99	2.82	2.24	2.47
6	2.75	2.53	2.34	2.57	2.2	2.02	2.71	2.66	2.54
Av	2.74	2.53	2.33	2.47	2.31	2.01	2.77	2.45	2.51

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

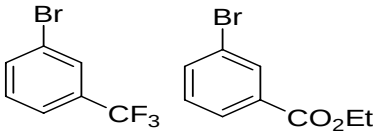


$\kappa = 1.05$

$\kappa 1 = 1.05$ $\kappa 2 = 1.05$ $\kappa 3 = 1.10$

t(h)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
2	1.07	0.96	1.21	0.98	1.22	1.03	1.11	0.91	1.28
4	1.03	0.96	1.09	0.93	1.24	0.87	1.11	0.90	1.28
Av	1.05	0.96	1.15	0.96	1.23	0.95	1.11	0.91	1.28

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

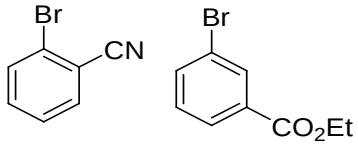


$\kappa = 3.19$

$\kappa_1 = 3.19$ $\kappa_2 = 2.55$ $\kappa_3 = 3.19$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]
6	3.26	3.10	3.27	2.07	2.88	2.58	3.53	2.94	3.33
10	2.99	3.17	3.32	2.22	2.93	2.58	3.07	2.99	3.29
Av	3.13	3.14	3.30	2.15	2.91	2.58	3.30	2.97	3.31

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

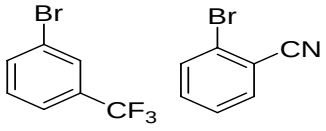


$\kappa = 1.69$

$\kappa_1 = 1.69$ $\kappa_2 = 1.38$ $\kappa_3 = 1.82$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]
8	1.48	1.72	1.84	1.23	1.34	1.43	1.60	1.90	1.97
10	1.56	1.69	1.84	1.35	1.33	1.58	1.65	1.87	1.93
Av	1.52	1.71	1.84	1.29	1.34	1.51	1.63	1.89	1.95

[a] Concentration of R1 and **73n**. [b] Concentration of R2.



$\kappa = 1.67$

$\kappa_1 = 1.67$ $\kappa_2 = -$ $\kappa_3 = 1.66$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]
8	1.70	1.75	1.55	1.50	2.73	1.31	1.75	1.57	1.62
10	1.72	1.75	1.55	1.50	2.54	1.33	1.79	1.59	1.63
Av	1.71	1.75	1.55	1.50	2.64	1.32	1.77	1.58	1.63

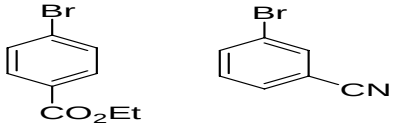
[a] Concentration of R1 and **73n**. [b] Concentration of R2.

$\kappa = 1.23$

$\kappa_1 = 1.23$ $\kappa_2 = 1.33$ $\kappa_3 = 1.19$

t(h)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
2	1.34	1.28	1.05	1.44	1.43	1.13	1.31	1.26	1.00
3	1.33	1.28	1.07	1.41	1.39	1.14	1.29	1.27	1.02
Av	1.34	1.28	1.06	1.43	1.41	1.14	1.30	1.27	1.01

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

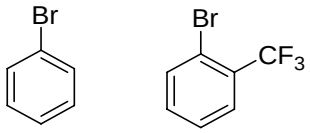


$\kappa = 1.38$

$\kappa_1 = 1.38$ $\kappa_2 = 1.54$ $\kappa_3 = 1.33$

t(h)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
1	1.68	1.26	1.32	-	1.70	1.17	1.56	1.20	1.37
12	1.48	1.27	1.25	1.73	1.68	1.21	1.36	1.19	1.27
Av	1.58	1.27	1.29	1.73	1.69	1.19	1.46	1.20	1.32

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

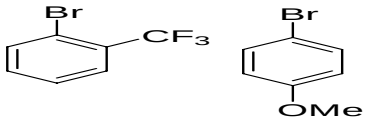


$\kappa = 3.25$

$\kappa_1 = 3.25$ $\kappa_2 = 1.43$ $\kappa_3 = 3.74$

t(day)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
5	3.53	3.40	2.89	1.51	1.74	0.98	4.00	3.63	3.71
7	3.42	3.40	2.83	1.55	1.80	0.97	3.87	3.56	3.67
Av	3.48	3.40	2.86	1.53	1.77	0.98	3.94	3.60	3.69

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

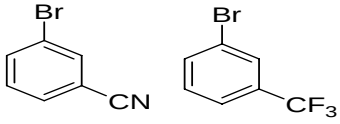


$\kappa = 1.15$

$\kappa_1 = 1.15$ $\kappa_2 = -$ $\kappa_3 = 0.80$

t(day)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
4	1.04	1.10	1.17	5.60	3.59	4.93	0.73	0.82	0.80
8	1.11	1.18	1.28	2.93	3.27	3.57	0.77	0.85	0.80
Av	1.08	1.14	1.23	4.27	3.43	4.25	0.75	0.84	0.80

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

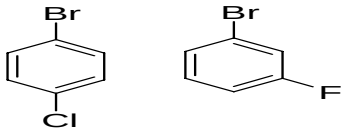


$\kappa = 2.06$

$\kappa_1 = 2.06$ $\kappa_2 = 2.04$ $\kappa_3 = 1.99$

t(h)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
3	1.94	2.06	2.03	1.97	2.03	1.97	1.93	2.06	2.01
6.5	2.09	2.05	2.15	2.13	1.97	2.18	1.87	2.07	1.96
Av	2.02	2.06	2.09	2.05	2.00	2.08	1.90	2.07	1.99

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

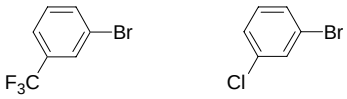


$\kappa = 1.11$

$\kappa_1 = 1.11$ $\kappa_2 = 1.37$ $\kappa_3 = 0.95$

t(h)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
22	1.07	1.07	1.23	1.09	1.66	-	1.04	0.87	0.93
48	1.06	1.02	1.19	1.05	1.41	1.53	1.05	0.86	0.92
Av	1.07	1.05	1.21	1.07	1.52	1.53	1.05	0.87	0.93

[a] Concentration of R1 and **73n**. [b] Concentration of R2.



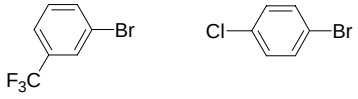
R1 R2

$\kappa = 2.01$

$\kappa_1 = 2.01$ $\kappa_2 = -$ $\kappa_3 = 2.20$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]
4	2.01	2.06	2.09	1.04	1.31	0.95	2.22	2.34	2.16
6	1.92	1.99	1.98	1.13	1.42	0.82	2.16	2.09	2.19
Av	1.97	2.03	2.04	-	-	-	2.19	2.22	2.18

[a] Concentration of R1. [b] Concentration of R2 and **73n**.



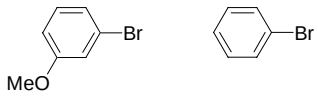
R1 R2

$\kappa = 4.15$

$\kappa_1 = 4.15$ $\kappa_2 = -$ $\kappa_3 = 4.31$

t(h)	κ_1				κ_3			
	0.33[a]/0.33[b]	0.66[c]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[c]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]
4	4.16	4.18	4.25	4.20	4.29	4.33	4.19	4.56
6	3.98	4.02	4.14	4.26	4.03	4.26	4.31	4.51
Av	4.07	4.10	4.20	4.23	4.16	4.30	4.25	4.54

[a] Concentration of R1 and **73n**. [b] Concentration of R2. [c] Concentration of R1; Concentration of **73**n = R2.



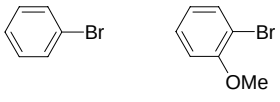
R1 R2

$\kappa = 1.46$

$\kappa_1 = 1.46$ $\kappa_2 = -$ $\kappa_3 = 1.46$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]
48	1.49	1.46	1.46	1.22	1.31	1.28	1.50	1.42	1.41
72	1.45	1.46	1.45	1.14	1.28	1.25	1.54	1.46	1.45
Av	1.47	1.46	1.46	1.18	1.30	1.27	1.52	1.44	1.43

[a] Concentration of R1. [b] Concentration of R2 and **73n**.



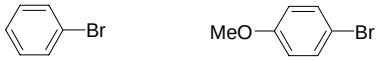
R1 R2

$\kappa = 3.14$

$\kappa_1 = 3.14$ $\kappa_2 = -$ $\kappa_3 = 2.74$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]
72	3.21	3.21	2.99	2.55	2.09	2.56	2.75	2.74	2.70
96	3.28	3.11	3.05	2.51	2.39	2.48	2.75	2.80	2.67
Av	3.25	3.16	3.02	2.53	2.24	2.52	2.75	2.77	2.69

[a] Concentration of R1. [b] Concentration of R2 and **73n**.



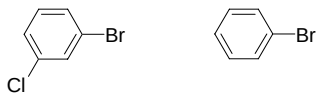
R1 R2

$\kappa = 3.95$

$\kappa 1 = 3.95$ $\kappa 2 = -$ $\kappa 3 = 3.56$

t(h)	κ_1				κ_3			
	0.33[a]/0.33[b]	0.66[c]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[c]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]
72	4.01	4.01	3.97	3.83	2.99	3.05	5.17	2.98
96	3.97	3.96	3.96	3.86	3.01	3.16	5.26	2.85
Av	3.99	3.99	3.97	3.85	3.00	3.11	5.22	2.92

[a] Concentration of R1 and **73n**. [b] Concentration of R2. [c] Concentration of R1; Concentration of **73**n = R2.



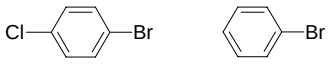
R1 R2

$\kappa = 11.32$

$\kappa_1 = 11.32$ $\kappa 2 = -$ $\kappa_3 = 9.10$

t(h)	κ_1				κ_3			
	0.33[a]/0.33[b]	0.66[c]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[c]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]
24	11.43	11.19	11.87	11.23	9.30	10.41	7.65	9.18
30	11.25	10.99	11.41	11. 17	9.15	10.37	7.67	9.06
Av	11.34	11.09	11.64	11.20	9.23	10.39	7.66	9.12

[a] Concentration of R1 and **73n**. [b] Concentration of R2. [c] Concentration of R1; Concentration of **73**n = R2.



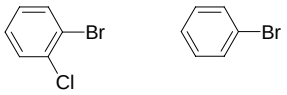
R1 R2

$\kappa = 5.67$

$\kappa_1 = 5.67$ $\kappa_2 = -$ $\kappa_3 = 5.46$

t(h)	κ_1				κ_3			
	$0.33^a/0.33^b$	$0.66^c/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.66^c/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
24	5.70	5.20	5.76	5.90	5.55	5.32	5.56	5.42
28	5.99	5.17	5.70	5.90	5.57	5.32	5.51	5.44
Av	5.85	5.19	5.73	5.90	5.56	5.32	5.54	5.43

[a] Concentration of R1 and **73n**. [b] Concentration of R2. [c] Concentration of R1; Concentration of **73**n = R2.



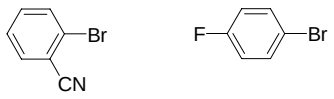
R1 R2

$\kappa = 1.27$

$\kappa_1 = 1.27$ $\kappa_2 = -$ $\kappa_3 = 1.37$

t(h)	κ_1			κ_2			κ_3		
	$0.33^a/0.33^b$	$0.66^a/0.33^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.66^a/0.33^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.66^a/0.33^b$	$0.17^a/0.17^b$
48	1.32	1.31	1.30	0.96	0.89	1.09	1.48	1.35	1.35
72	1.19	1.22	1.27	0.84	0.92	1.09	1.46	1.27	1.33
Av	1.26	1.27	1.29	-	-	-	1.47	1.31	1.34

[a] Concentration of R1. [b] Concentration of R2 and **73n**.



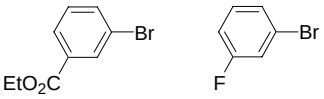
R1 R2

$\kappa = 14.13$

$\kappa_1 = 14.13$ $\kappa_2 = -$ $\kappa_3 = -$

t(h)	κ_1				κ_3			
	$0.33^a/0.33^b$	$0.66^c/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$	$0.33^a/0.33^b$	$0.66^c/0.33^b$	$0.33^a/0.66^b$	$0.17^a/0.17^b$
24	14.63	14.41	14.06	14.08	11.71	14.84	14.23	11.80
48	13.79	13.91	14.17	13.93	10.27	14.87	14.25	9.48
Av	14.21	14.16	14.12	14.01	10.99	14.86	14.24	10.64

[a] Concentration of R1 and **73n**. [b] Concentration of R2. [c] Concentration of R1; Concentration of **73**n = R2.



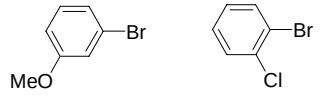
R1 R2

$\kappa = 1.31$

$\kappa_1 = 1.31$ $\kappa_2 = -$ $\kappa_3 = 1.23$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]
10	1.30	1.37	1.28	1.00	0.90	0.94	1.14	1.44	1.14
24	1.29	1.33	1.29	1.00	0.90	0.96	1.15	1.37	1.14
Av	1.30	1.35	1.29	1.00	0.90	0.95	1.15	1.41	1.14

[a] Concentration of R1. [b] Concentration of R2 and **73n**.



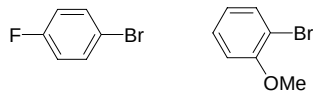
R1 R2

$\kappa = 1.29$

$\kappa_1 = 1.29$ $\kappa_2 = -$ $\kappa_3 = 1.12$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]
72	1.27	1.26	1.25	1.71	1.54	1.64	1.11	1.14	1.02
96	1.39	1.26	1.30	1.56	1.54	1.57	1.22	1.14	1.09
Av	1.33	1.26	1.28	1.64	1.54	1.61	1.17	1.14	1.06

[a] Concentration of R1. [b] Concentration of R2 and **73n**.



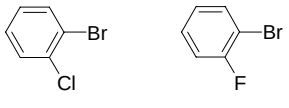
R1 R2

$\kappa = 3.03$

$\kappa_1 = 3.03$ $\kappa_2 = -$ $\kappa_3 = 2.79$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]
72	3.10	2.91	3.09	2.05	1.91	1.94	2.84	2.81	2.77
96	3.08	2.96	3.01	2.30	1.88	2.13	2.78	2.87	2.66
Av	3.09	2.94	3.05	2.18	1.90	2.04	2.81	2.84	2.72

[a] Concentration of R1. [b] Concentration of R2 and **73n**.



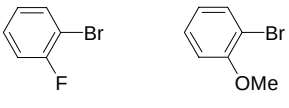
R1 R2

$\kappa = 1.40$

$\kappa_1 = 1.40$ $\kappa_2 = -$ $\kappa_3 = 1.50$

t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.66[a]/0.33[b]	0.17[a]/0.17[b]
72	1.49	1.20	1.51	1.21	1.02	1.32	1.60	1.28	1.69
96	1.55	1.18	1.49	1.33	0.99	1.27	1.57	1.27	1.60
Av	1.52	1.19	1.50	1.27	1.01	1.30	1.59	1.28	1.65

[a] Concentration of R1. [b] Concentration of R2 and **73n**.



R1 R2

$\kappa = 2.84$

$\kappa_1 = 2.84$ $\kappa 2 = -$ $\kappa 3 = 2.72$

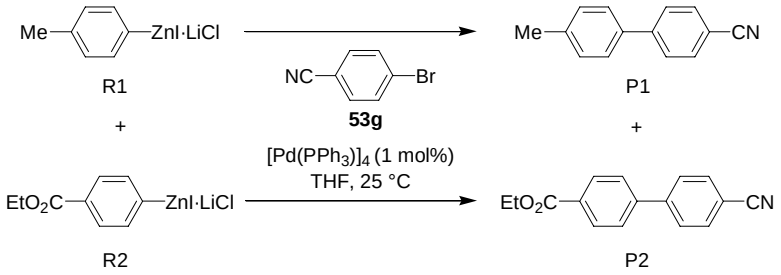
t(h)	κ_1			κ_2			κ_3		
	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]	0.33[a]/0.33[b]	0.33[a]/0.66[b]	0.17[a]/0.17[b]
72	2.80	2.80	2.92	2.21	2.09	2.32	2.75	2.59	2.80
96	2.85	2.81	2.85	2.28	2.17	2.16	2.77	2.74	2.66
Av	2.83	2.80	2.89	2.25	2.13	2.24	2.76	2.67	2.73

[a] Concentration of R1 and **73n**. [b] Concentration of R2.

Typical Procedure for a Competition Experiment between two Aryl zinc Reagents

A dry and N_2-flushed Schlenk-flask was charged with R1 (4-tolylzinc iodide **73n**, 4.0 mL, 0.5 M in THF, 2 mmol), R2 (4-(ethoxycarbonyl)-phenylzinc iodide **73c**, 3.5 mL, 0.57 M in THF, 2 mmol) and *n*$C_{16}H_{34}$ (70 mg, 0.31 mmol). The flask was cooled with a waterbath (25 °C). Then a solution of 4-bromo-benzonitrile ´(**53g**, 364.0 mg, 2 mmol) and [$Pd(PPh_3)_4$] (23.1 mg, 0.02 mmol) in THF (2 mL) was added in one portion and the reaction mixture was stirred at 25 °C. After certain times (for example 20 min), about 0.1 mL of the mixture was taken out with a syringe and poured into sat. aq. NH_4Cl solution (1 mL). The aqueous phase was extracted with diethyl ether (about 2 ~ 3 mL). The ethereal solutions were dried over Na_2SO_4 and analyzed by GC.

Table 24. Areas and κ values obtained from the competition experiment between 4-tolylzinc iodide and 4-(ethoxycarbonyl)-phenylzinc iodide



$\kappa_1 = 4.08$ $\kappa_3 = 4.06$

t(h)	κ_1			κ_3		
	0.21[a]/0.21[b]	0.11[a]/0.11[b]	0.16[a]/0.32[b]	0.21[a]/0.21[b]	0.11[a]/0.11[b]	0.16[a]/0.32[b]
0.5	4.15	4.21	4.32	3.94	4.18	4.06
2	3.78	4.06	3.91	4.02	3.94	4.2
Av	3.97	4.14	4.12	3.98	4.06	4.13

[a] Concentration of R1 and **53g**. [b] Concentration of R2.

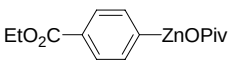
11.8 Synthesis and Reactivity of Solid Organozinc Reagents

11.8.1 Synthesis of Solid Organozinc Reagents

Preparation of Diorganozinc reagents

All diarylzinc reagents were prepared from the corresponding organomagnesium compounds by transmetalation with $ZnCl_2$ (0.5 equiv). The organomagnesium compounds were prepared according to literature procedures.[59-60] Di-[(4-methoxy)phenyl]zinc was prepared by direct magnesium insertion into 4-bromo-anisole (**x**) in the presence of $ZnCl_2$ (0.5 equiv) according to the literature procedure.[61] Mg-salts were precipitated upon addition of dioxane (10 % v/v). After stirring for 18 h at 25 °C , the Schlenk-flask was centrifuged for 75 min at 2000 rpm and the solution of the diorganozinc reagent transferred to another dry and N_2 flushed flask. The concentration of the zinc reagent was determined by titration with I_2 before further use.

4-(Ethoxycarbonyl)phenylzinc pivalate (125a)



Di-[4-(ethoxycarbonyl)phenyl]zinc (**124a**, 30 mL, 0.34 M in THF, 10.2 mmol) was added to $Zn(OPiv)_2$ (2.73 g, 10.2 mmol) in THF (10 mL). The reaction mixture was stirred for 4 h at 25 °C until all solids were dissolved and a clear solution was obtained. After evaporation of all solvents and drying for 12 h at 25 °C under high vacuum (1 mbar), 4-(ethoxycarbonyl)phenylzinc pivalate (**125a**) was obtained as a yellow solid (7.9 g), together with remaining impurities.

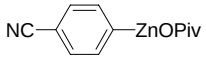
For the determination of the content of active zinc reagent, 148 mg of the solid were redissolved in THF (3 mL) and titrated with I_2 (1.0 M in THF, freshly prepared).[158]

From the amount of active zinc reagent titrated (0.28 mmol) [M_{Ti}] , the overall mass isolated (7.9 g) [m_{iso}] and the mass of the titrated solid (0.149 g) [m_{Ti}] the overall amount of active solid zinc reagent [M_{iso}] can be calculated. Therefore the isolated solid contained 18.4 mmol of active zinc reagent (73 % yield).

$[M_{iso}] = ([M_{Ti}] \times [m_{iso}])/[m_{Ti}] = (0.28 \text{ mmol} \times 7.9 \text{ g})/(0.149 \text{ g}) = 18.4 \text{ mmol}$

The unpurified product was used for all further transformations.

4-(Cyano)phenylzinc pivalate (125b)

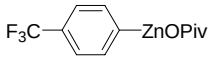


Di-[4-(cyano)phenyl]zinc (30 mL, 0.24 M in THF, 7.2 mmol) was added to $Zn(OPiv)_2$ (1.93 g, 7.2 mmol) in THF (10 mL). The reaction mixture was stirred for 3 h at 25 °C until all solids were dissolved and a clear solution was obtained. After evaporation of all solvents and drying for 12 h at 25 °C under high vacuum (1 mbar), 4-(cyano)phenylzinc pivalate (**125b**) was obtained as a red solid (8.62 g), together with remaining impurities.

The content was determined as described above ([m_{Ti}] = 146 mg, [M_{Ti}] = 0.20 mmol) and the isolated solid contained 11.8 mmol of active zinc reagent (82 % yield)

The unpurified product was used for all further transformations.

4-(Trifluoromethyl)phenylzinc pivalate (125c)



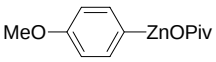
Di-[4-(trifluoromethyl)phenyl]zinc (**x**, 30 mL, 0.28 M in THF, 8.4 mmol) was added to $Zn(OPiv)_2$ (2.25 g, 8.4 mmol) in THF (10 mL). The reaction mixture was stirred for 4 h at 25 °C until all solids were dissolved and a clear solution was obtained. After evaporation of all solvents and drying for 12 h at 25 °C under high vacuum (1 mbar), 4-

(trifluoromethyl)phenylzinc pivalate (**125c**) was obtained as a yellow solid (10.55 g), together with remaining impurities.

The content was determined as described above ([m_{Ti}] = 490 mg, [M_{Ti}] = 0.71 mmol) and the isolated solid contained 15.3 mmol of active zinc reagent (91 % yield)

The unpurified product was used for all further transformations.

4-(Methoxy)phenylzinc pivalate (125d)

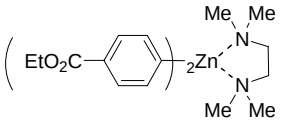


Di-[4-(methoxy)phenyl]zinc (**124b**, 12.8 mL, 0.2 M in THF, 2.56 mmol) was added to $Zn(OPiv)_2$ (685 mg, 2.56 mmol) in THF (5 mL). The reaction mixture was stirred for 3 h at 25 °C until all solids were dissolved and a clear solution was obtained. After evaporation of all solvents and drying for 12 h at 25 °C under high vacuum (1 mbar), 4-(methoxy)phenylzinc pivalate (**125d**) was obtained as a colourless solid (2.21 g), together with remaining impurities.

The content was determined as described above ([m_{Ti}] = 169 mg, [M_{Ti}] = 0.34 mmol) and the isolated solid contained 4.45 mmol of active zinc reagent (87 % yield)

The unpurified product was used for all further transformations.

Di-[4-(ethoxycarbonyl)phenyl]zinc-TMEDA complex (127)



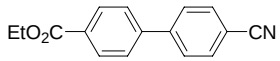
Di-[4-(ethoxycarbonyl)phenyl]zinc (**124a**, 10 mL, 0.34 M in THF, 3.4 mmol) was added to TMEDA (0.51 mL, 3.4 mmol) in THF (5 mL). The reaction mixture was stirred for 24 h at 25 °C. After evaporation of all solvents and drying for 12 h at 25 °C under high vacuum (1 mbar), di-[4-(ethoxycarbonyl)phenyl]zinc-TMEDA complex (**127**) was obtained as a yellow solid (1.92 g), together with remaining impurities.

The content was determined as described above ([m_{Ti}] = 121 mg, [M_{Ti}] = 0.15 mmol) and the isolated solid contained 2.38 mmol of active zinc reagent (70 % yield)

The unpurified product was used for all further transformations.

11.8.2 Palladium- and Copper-Catalyzed Reactions of Solid Zinc Reagents

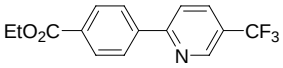
4'-Cyano-biphenyl-4-carboxylic acid ethyl ester (60c)



Prepared according to **TP 10** from 4-(ethoxycarbonyl)phenylzinc pivalate (**125a**, 1.28 g, 2.4 mmol), 4-bromobenzonitrile (**53g**, 364 mg, 2 mmol). Reaction time: 1 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 8:2) yielded **60c** as a colorless solid (458 mg, 91 %). The same reaction with di-[4-(ethoxycarbonyl)phenyl]zinc-TMEDA complex (**127**, 1.94 mg, 2 mmol) yielded 447 mg **60c** (89 %).

The analytical data match those of the above described (see p. 123, compound **60c**).

4-(5-Trifluoromethyl-pyridin-2-yl)-benzoic acid ethyl ester (130a)



Prepared according to **TP 10** from 4-(ethoxycarbonyl)phenylzinc pivalate (**125a**, 1.28 mg, 2.4 mmol), 2-chloro-5-trifluoromethyl-pyridine (**42f**, 363 mg, 2 mmol). Reaction time: 3 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded **130a** as a colorless solid (452 mg, 77 %).

m.p.: 133.8-135.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.97 (m, 1H), 8.17 (ddd, *J* = 8.4, 1.9, 1.7 Hz, 2H), 8.10 (ddd, *J* 0 8.1, 1.9, 1.7 Hz, 2H), 8.01 (ddd, *J* = 8.3, 2.4, 0.7 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

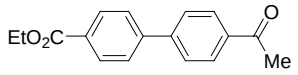
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.1, 159.5, 146.8 (q, *J* = 4.0 Hz), 141.8, 134.1 (q, *J* = 3.7 Hz), 131.7, 130.1, 127.2, 125.5 (q, *J* = 33.1 Hz), 123.6 (q, *J* = 272.3 Hz), 120.4, 61.2, 14.3

HRMS *m/z* : calcd. for $C_{15}H_{12}F_3NO_2$ 295.0820, found 295.0811

MS (EI, 70 eV), *m/z* (%): 295 (27) [M^+], 267 (35), 250 (100), 222 (43), 202 (10).

IR (cm^{-1}): 3061 (w), 2985 (w), 2944 (w), 1710 (s), 1603 (m), 1584 (m), 1513 (w), 1469 (w), 1414 8w), 1374 (w), 1324 (s), 1265 (s), 1130 (vs), 1097 (vs), 1011 (s).

4'-Acetyl-biphenyl-4-carboxylic acid ethyl ester (130b)



A solution of 4-(ethoxycarbonyl)phenylzinc pivalate (**125a**, 1.01 mg, 1.9 mmol) in THF (4 mL) was added dropwise via canula to a solution of 4-bromo-acetophenone (**53d**, 318 mg, 1.6 mmol) and PEPPSI (22 mg, 0.032 mmol) in THF (3 mL). The resulting reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 4'-acetyl-biphenyl-4-carboxylic acid ethyl ester (**130b**) as a colorless solid (392 mg, 91 %).

m.p.: 78.6-80.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.13 (ddd, *J* = 8.7, 1.9, 1.6 Hz, 2H), 8.04 (ddd, *J* = 8.6, 1.9, 1.6 Hz, 2H), 7.72-7.68 (m, 4H), 4.41 (q, *J* 0 7.1 Hz, 2H), 2.64 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

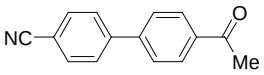
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 197.6, 166.3, 144.5, 144.1, 136.5, 130.2, 130.1,129.0, 127.4, 127.1, 61.1, 26.7, 14.4.

HRMS *m/z* : calcd. for $C_{17}H_{16}O_3$ 268.1099, found 268.1089.

MS (EI, 70 eV), *m/z* (%): 268 (42) [M^+], 253 (100), 223 (24), 207 (27), 152 (34).

IR (cm^{-1}): 2984 (w), 2936 (w), 1710 (vs), 1684 (vs), 1605 (m), 1578 (m), 1467 (w), 1418 (m), 1395 (m), 1360 (m), 1289 (s), 1267 (vs), 1178 (s), 1107 (s).

4'-Acetyl-biphenyl-4-carbonitrile (130c)



A solution of 4-(cyano)phenylzinc pivalate (**125b**, 876 mg, 1.2 mmol) in THF (4 mL) was added dropwise via canula to a solution of 4-bromo-acetophenone (**53d**, 199 mg, 1 mmol) and PEPPSI (13.6 mg, 0.02 mmol) in THF (3 mL). The resulting reaction mixture was stirred for 30 min at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with an aq. thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 4'-acetyl-biphenyl-4-carbonitrile (**130c**) as a pale yellow solid (186 mg, 84 %).

m.p.: 111.7-113.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.06 (ddd, *J* = 8.6, 1.9, 1.7 Hz, 2H), 7.77-7.66 (m, 6H), 2.64 (s, 3H).

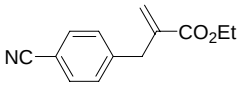
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 197.5, 144.3, 143.5, 136.8, 132.7, 129.1, 127.9, 127.4, 118.6, 111.8, 99.4, 26.7

HRMS *m/z* : calcd. for $C_{15}H_{11}NO$ 221.0841, found 220.0787 $[M-H]^-$.

MS (EI, 70 eV), *m/z* (%): 268 (42) $[M^+]$, 253 (100), 223 (24), 207 (27), 152 (34).

IR (cm^{-1}): 2962 (w), 2924 (w), 2226 (m), 1922 (w), 179 (s), 1601 (s), 1395 (m), 1358 (s), 1264 (s), 1179 (m).

2-(4-Cyano-benzyl)-acrylic acid ethyl ester (130d)



A solution of 4-(cyano)phenylzinc pivalate (**125b**, 876 mg, 1.2 mmol) in THF (3 mL) was cooled to -25 °C. CuCN·2LiCl (0.05 mL, 1.0 M in THF, 0.05 mmol) was added followed by 2-bromomethyl-acrylic acid ethyl ester (**128**, 193 mg, 1 mmol). The reaction mixture was warmed to 0 °C and stirred for 1 h. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 2-(4-cyano-benzyl)-acrylic acid ethyl ester (**130d**) as a colorless oil (164 mg, 76 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.56 (ddd, *J* = 8.4, 1.8, 1.7 Hz, 2H), 7.30 (ddd, *J* = 8.4, 1.8, 1.7 Hz, 2H), 6.28-6.27 (m, 1H), 5.53-5.52 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.66 (s, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).

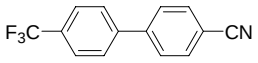
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.2, 144.5, 138.9, 132.1, 129.6, 127.0, 118.9, 110.2, 60.9, 38.3, 14.0.

HRMS *m/z* : calcd. for $C_{13}H_{13}NO_2$ 215.0946, found 215.951.

MS (EI, 70 eV), *m/z* (%): 215 (52) $[M^+]$, 186 (39), 170 (28), 141 (100), 115 (36).

IR (cm^{-1}): 3044 (w), 2989 (w), 2942 (w), 2223 (m), 1705 (vs), 1606 (m), 1555 (w), 1496 (w), 1469 (w), 1395 (m), 1364 (m), 265 (s), 1179 (s), 1098 (s).

4'-Trifluoromethyl-biphenyl-4-carbonitrile (130e)



Prepared according to **TP 10** from 4-(trifluoromethyl)phenylzinc pivalate (**125c**, 1.66 mg, 2.4 mmol), 4-bromobenzonitrile (**53g**, 364 mg, 2 mmol). Reaction time: 1 h. Purification of

the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **130e** as a colorless solid (460 mg, 93 %).

m.p.: 133.1-135.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.78-7.67 (m, 8H).

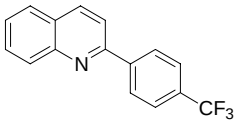
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 144.1, 142.6, 132.8, 130.3 (q, *J* = 32.7 Hz), 127.9, 127.6, 126.0 (q, *J* = 3.6 Hz), 124.0 (q, *J* = 272.2 Hz), 118.6, 111,9.

HRMS *m/z* : calcd. for $C_{14}H_8F_3N$ 247.0609, found 247.06023.

MS (EI, 70 eV), *m/z* (%): 247 (100) [M^+], 228 (11), 197 (8), 177 (9), 151 (8).

IR (cm^{-1}): 2961 (w), 2926 (w), 2230 (m), 1606 (m), 1394 (m), 1323 (vs), 1161 (s), 1121 (vs), 1112 (vs), 1069 (vs).

2-(4-Trifluoromethyl-phenyl)-quinoline (130f)



Prepared according to **TP 10** from 4-(trifluoromethyl)phenylzinc pivalate (**125c**, 1.66 mg, 2.4 mmol), 2-chloro-quinoline (**42d**, 327 mg, 2 mmol). Reaction time: 3 h. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **130f** as a colorless solid (497 mg, 91 %).

m.p.: 129.7-131.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.29-8.24 (m, 3H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.89-7.83 (m, 2H), 7.79-7.73 (m, 3H), 7.56 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 2H).

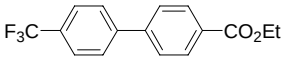
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 155.6, 148.1, 142.8, 137.2, 131.1 (q, *J* = 32.5 Hz), 130.0, 129.7, 127.9, 127.5, 127.4, 126.9, 125.7 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 272.2 Hz), 118.8.

HRMS *m/z* : calcd. for $C_{16}H_{10}F_3N$ 273.0765, found 274.0838 [$M+H^+$].

MS (EI, 70 eV), *m/z* (%): 273 (100) [M^+], 252 (12), 204 (38), 176 (9), 126 (5).

IR (cm^{-1}): 3068 (w), 1915 (w), 1738 (w), 1612 (w), 1593 (w), 1555 (w), 1519 (w), 1499 (w), 1432 (w), 1320 (s), 1306 (s), 1242 (w), 1122 (vs), 1104 (vs), 1070 (vs).

4'-Trifluoromethyl-biphenyl-4-carboxylic acid ethyl ester (130g)



Prepared according to **TP 10** from 4-(trifluoromethyl)phenylzinc pivalate (**125c**, 1.66 mg, 2.4 mmol), 4-bromo-benzoic acid ethyl ester (**53a**, 458 mg, 2 mmol). Reaction time: 1 h.

Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded **130g** as a colorless solid (573 mg, 97 %).

m.p.: 97.8-99.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 8.14 (ddd, *J* = 8.5, 1.9, 1.7 Hz, 2H), 7.71 (s, 4H), 7.65 (ddd, *J* = 8.5, 1.9, 1.7 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H).

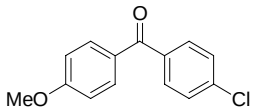
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 166.2, 143.9, 143.5, 130.2, 130.1, 130.1 (q, *J* = 32.5 Hz), 127.6, 127.2, 125.8 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 271.9 Hz), 61.1, 14.3.

HRMS *m/z* : calcd. for $C_{16}H_{13}F_3O_2$ 294.0868, found 294.0873.

MS (EI, 70 eV), *m/z* (%): 294 (31) [M^+], 266 (29), 249 (100), 201 (23), 152 (19).

IR (cm^{-1}): 3051 (w), 3001 (w), 2985 (w), 2936 (w), 1935 (w), 1738 (w), 1708 (s), 1609 (w), 1482 (w), 1396 (m), 1370 (w), 1318 (s), 1280 (s), 1161 (s), 1111 (vs), 1067 (s).

(4-Chloro-phenyl)-(4-methoxy-phenyl)-methanone (130h)



A solution of 4-(methoxy)phenylzinc pivalate (**125d**, 1.9 mg, 3.8 mmol) in THF (5 mL) was cooled to -25 °C. CuCN·2LiCl (3.8 mL, 1.0 M in THF, 3.8 mmol) was added followed by 4-chloro-benzoyl chloride (**129**, 1.4 g, 8 mmol). The reaction mixture was warmed to 0 °C and stirred for 1 h. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 95:5) yielded **(**4-chloro-phenyl)-(4-methoxy-phenyl)-methanone (**130h**) as a colorless solid (904 mg, 96 %).

m.p.: 123.8-125.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.81-7.76 (m, 2H), 7.70 (ddd, *J* = 8.4, 2.0, 1.9 Hz, 2H), 7.44 (ddd, *J* = 8.4, 2.0, 1.9 Hz, 2H), 6.98-6.93 (m, 2H), 3.88 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 194.3, 163.4, 138.3, 136.5, 132.4, 131.1, 129.8, 128.5, 113.7, 55.5.

HRMS *m/z* : calcd. for $C_{14}H_{11}ClO_2$ 246.0448, found 246.0450.

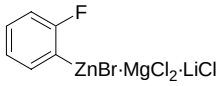
MS (EI, 70 eV), *m/z* (%): 246 (26) [M^+], 211 (5), 135 (100), 111 (7), 177 (8).

IR (cm^{-1}): 3016 (w), 2964 (w), 2936 (w), 1638 (vs), 1600 (vs), 1502 (m), 1482 (m), 141 (m), 1397 (m), 1285 (s), 1253 (vs), 1170 (s), 1147 (vs).

11.9 Mg^{2+}-Promoted Addition of Organozinc Reagents to Carbonyl Compounds

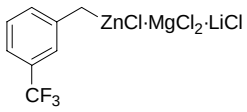
11.9.1 Preparation of the Zinc Reagents

2-Fluoro-phenylzinc bromide·Magnesium chloride (135a)



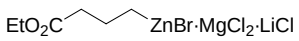
A dry and N_2-flushed Schlenk-flask was charged with Mg-powder (486 mg, 20 mmol) and THF (5 mL). $ZnCl_2$/LiCl (10 mL, 1.1 M/1.5 M in THF, 11/15 mmol) was added. The reaction mixture was cooled to 25 °C with an waterbath. 1-Bromo-2-fluoro-benzene (1.75 g, 10 mmol) was added neat and the reaction mixture stirred for 2 h. The solution of **135a** was carefully separated from remaining magnesium powder by using a syringe and transferred to another dry and N_2-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.52 M.

3-Trifluoromethyl-benzyllzinc bromide·Magnesium chloride (135b)



A dry and N_2-flushed Schlenk-flask was charged with Mg-powder (486 mg, 20 mmol) and THF (5 mL). $ZnCl_2$/LiCl (10 mL, 1.1 M/1.5 M in THF, 11/15 mmol) was added. The reaction mixture was cooled to 25 °C with an waterbath. 3-Trifluoromethyl-benzyl chloride (1.95 g, 10 mmol) was added neat and the reaction mixture stirred for 1.5 h. The solution of **135b** was carefully separated from remaining magnesium powder by using a syringe and transferred to another dry and N_2-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.42 M.

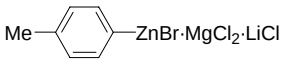
4-Ethoxy-4-oxobutylzinc bromide·Magnesium chloride (135c)



A dry and N_2-flushed Schlenk-flask was charged with Mg-powder (486 mg, 20 mmol) and THF (5 mL). $ZnCl_2$/LiCl (10 mL, 1.1 M/1.5 M in THF, 11/15 mmol) was added. The reaction mixture was cooled to 25 °C with an waterbath. 4-Bromo-butyric acid ethyl ester (1.95 g, 10 mmol) was added neat and the reaction mixture stirred for 1.5 h. The solution of **135c** was

carefully separated from remaining magnesium powder by using a syringe and transferred to another dry and N_2-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.40 M.

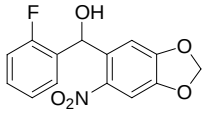
4-Methyl-phenylzinc bromide·Magnesium chloride (135d)



A dry and N_2-flushed Schlenk-flask was charged with Mg-powder (486 mg, 20 mmol) and THF (5 mL). $ZnCl_2$/LiCl (10 mL, 1.1 M/1.5 M in THF, 11/15 mmol) was added. The reaction mixture was cooled to 25 °C with an waterbath. 4-Bromo-toluene (1.71 g, 10 mmol) was added neat and the reaction mixture stirred for 4 h. The solution of **135d** was carefully separated from remaining magnesium powder by using a syringe and transferred to another dry and N_2-flushed flask. Titration of the zinc reagent (typically 1 mL) with iodine indicated a concentration of 0.42 M.

11.9.2 Addition to Carbonyl Compounds

(2-Fluoro-phenyl)-(4-nitro-benzo[1,3]dioxol-5-yl)-methanol (132c)



2-Fluoro-phenylzinc bromide·magnesium chloride (**135a**, 3.5 mL, 0.52 M in THF, 1.8 mmol) was added to a solution of 6-nitro-benzo[1,3]dioxole-5-carbaldehyde (**131c**, 293 mg, 1.5 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 1h at 0 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded (2-fluoro-phenyl)-(4-nitro-benzo[1,3]dioxol-5-yl)-methanol (**132c**) as a yellow oil (378 mg, 87 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.50 (s, 1H), 7.38-7.31 (m, 1H), 7.30-7.24 (m, 1H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 7.05-6.99 (m, 2H), 6.62 (s, 1H), 6.11-6.09 (m, 2H), 3.11 (br s, 1H).

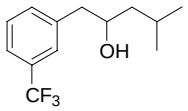
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 159.9 (d, *J* = 247.5 Hz), 152.2, 147.3, 142.1, 135.1, 129.7 (d, *J* = 8.3 Hz), 128.7 (d *J* = 20.7 Hz), 127.7 (d, *J* = 3.9 Hz), 124.2 (d, *J* = 7.6 Hz), 115.4 (d, *J* = 21.4 Hz), 108.2, 105.6, 103.7, 65.7 (d, *J* = 3.9 Hz).

HRMS *m/z* : calcd. for $C_{14}H_{10}FNO_5$ 291.0543, found 291.0567.

MS (EI, 70 eV), *m/z* (%): 291 (8) [M^+], 273 (25), 228 (31), 171 (100), 157 (28).

IR (cm^{-1}): 3387 (br), 3071 (w), 2990 (w), 2915 (w), 1737 (w), 1616 (w), 1586 (w), 1519 (s), 1504 (s), 1481 (vs), 1455 (s), 1422 (m), 1330 (s), 1256 (vs), 1173 (m), 1120 (m), 1095 (m), 1028 (vs).

4-Methyl-1-(3-trifluoromethyl-phenyl)-pentan-2-ol (132d)



3-Trifluoromethyl-benzylzinc bromide·magnesium chloride (**135b**, 4.3 mL, 0.42 M in THF, 1.8 mmol) was added to a solution of 3-methyl-butyraldehyde (**131d**, 129 mg, 1.5 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 4:1) yielded 4-methyl-1-(3-trifluoromethyl-phenyl)-pentan-2-ol (**132d**) as a colorless oil (361 mg, 98 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.50-7.44 (m, 2H), 7.42-7.39 (m, 2H), 3.90 (tt, *J* = 8.6, 4.2 Hz, 1H), 2.84 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.69 (dd, *J* = 13.6, 8.6 Hz, 1H), 1.86-1.74 (m, 1H), 1.56 (br s, 1H), 1.46 (ddd, *J* = 13.9, 8.6, 5.2 Hz, 1H), 1.34-1.25 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H).

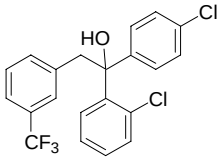
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 139.7, 132.9 (q, *J* = 1.6 Hz), 130.7 (q, *J* = 32.0 Hz), 128.8, 126.0 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 272.1 Hz), 70.5, 46.1, 44.2, 24.6, 23.4, 21.9.

HRMS *m/z* : calcd. for $C_{13}H_{17}F_3O$ 246.1231, found 246.1234.

MS (EI, 70 eV), *m/z* (%): 246 (4) [M^+], 227 (16), 189 (11), 160 (100), 149 (21).

IR (cm^{-1}): 3367 (br), 2958 (w), 2958 (w), 1739 (w), 1469 (w), 1450 (m), 1368 (w), 1327 (vs), 1202 (m), 1162 (s), 1120 (vs), 1073 (vs).

1-(4-Chloro-phenyl)-1-(2-chloro-phenyl)-2-(3-trifluoromethyl-phenyl)-ethanol (132e)



3-Trifluoromethyl-benzyllzinc bromide·magnesium chloride (**135b**, 4.3 mL, 0.42 M in THF, 1.8 mmol) was added to a solution of 2,4'-dichloro-benzophenone (**131e**, 377 mg, 1.5 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded 1-(4-chloro-phenyl)-1-(2-chloro-phenyl)-2-(3-trifluoromethyl-phenyl)-ethanol (**132e**) as a colorless oil (568 mg, 92 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.62-7.56 (m, 1H), 7.39-7.28 (m, 3H), 7.25-7.18 (m, 4H), 7.07-7.02 (m, 4H), 3.96 (d, *J* = 12.9 Hz, 1H), 3.49 (d, *J* = 12.9 Hz, 1H), 2.98 (br s, 1H).

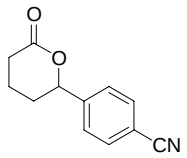
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 143.7, 141.8, 137.0, 134.2 (q, *J* = 1.3 Hz), 133.2, 132.2, 131.4, 129.7 (q, *J* = 32.0 Hz), 129.2, 128.2, 128.2, 127.8, 127.7 (q, *J* = 3.8 Hz), 127.6, 126.7, 124.1 (q, *J* = 272.4 Hz), 123.2 (q, *J* = 3.9 Hz), 77.8, 45.1

HRMS *m/z* : calcd. for $C_{21}H_{15}Cl_2F_3O$ 410.0452, found 410.0461.

MS (EI, 70 eV), *m/z* (%): 410 (2) [M^+], 391 (6), 322 (7), 251 (100), 139 (42).

IR (cm^{-1}): 3456 (br), 3068 (w), 2972 8w), 2936 (w), 1739 (w), 1593 (w), 1489 (m), 1450 (w), 1435 (w),1329 (vs), 1203 8m), 1160 (s), 1120 (vs), 1094 (s), 1074 (s).

4-(6-Oxo-tetrahydro-pyran-2-yl)-benzonitrile (137a)



4-Ethoxy-4-oxobutylzinc bromide·magnesium chloride (**135c**, 4.5 mL, 0.40 M in THF, 1.8 mmol) was added to a solution of 4-cyano-benzaldehyde (**131f**, 197 mg, 1.5 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 1:1) yielded 4-(6-oxo-tetrahydro-pyran-2-yl)-benzonitrile (**137a**) as a colorless oil (211 mg, 70 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.67 (ddd, *J* = 8.4, 2.0, 1.7 Hz, 2H), 7.46 (ddd, *J* = 8.4, 2.0, 1.7 Hz, 2H), 5.39 (dd, *J* = 10.7, 3.4 Hz, 1H), 2.73 (dtd, *J* = 17.8, 6.3, 1.0 Hz, 1H), 2.58 (dt, *J* = 17.8, 7.9 Hz, 1H), 2.24-2.15 (m, 1H), 2.06-1.96 (m, 2H), 1.86-1.72 (m, 1H).

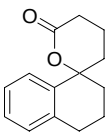
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 170.4, 144.8, 132.5, 126.2, 118.4, 112.1, 80.5, 30.5, 29.4, 18.6.

HRMS *m/z* : calcd. for $C_{12}H_{11}NO_2$ 201.0790, found 201.0783.

MS (EI, 70 eV), *m/z* (%): 201 (21) [M^+], 144 (13), 129 (70), 97 (23), 70 (100).

IR (cm^{-1}): 3045 (w), 2976 (w), 2360 (w), 2226 (m), 1727 (vs), 1607 (w), 1503 (w), 1407 (w), 1366 (m), 1353 (m), 1238 (s), 119 (m), 1070 (s).

3,4,4',5'-Tetrahydro-2*H*-spiro[naphthalene-1,2'-pyran]-6'(3'*H*)-one (137b)



4-Ethoxy-4-oxobutylzinc bromide·magnesium chloride (**135c**, 4.5 mL, 0.40 M in THF, 1.8 mmol) was added to a solution of α-tetralone (**131g**, 219 mg, 1.5 mmol) in THF (2 mL). The reaction mixture was stirred for 6 h at 55 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x 25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 20:1) yielded 3,4,4',5'-tetrahydro-2*H*-spiro[naphthalene-1,2'-pyran]-6'(3'*H*)-one (**137b**) as a pale yellow solid (211 mg, 70 %).

m.p.: 57.8-59.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.93 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.41-7.35 (m, 1H), 7.33-7.28 (m, 1H), 7.20-7.17 (m, 1H), 2.88 (dd, *J* = 7.9, 6.8 Hz, 2H), 2.64-2.59 (m, 2H), 2.51-2.46 (m, 2H), 1.76-1.62 (m, 2H), 1.02-0.85 (m, 4H).

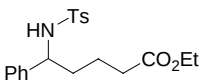
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 176.9, 140.7, 131.7, 127.5, 126.8, 125.8, 105.7, 99.4, 38.2, 31.4, 28.3, 22.4, 18.6, 13.9.

HRMS *m/z* : calcd. for $C_{14}H_{16}O_2$ 216.1150, found 216.1135.

MS (EI, 70 eV), *m/z* (%): 216 (48) [M^+], 173 (100), 145 (47), 115 (27), 105 (19).

IR (cm^{-1}): 3065 (w), 2960 (w), 2933 (w), 1614 (m), 1587 (s), 1557 (s), 1489 (m), 1411 (s), 1350 (s), 1296 (s), 1192 (s), 1051 (s).

5-Phenyl-5-(toluene-4-sulfonylamino)-pentanoic acid ethyl ester (139)



4-Ethoxy-4-oxobutylzinc bromide·magnesium chloride (**135c**, 4.5 mL, 0.40 M in THF, 1.8 mmol) was added to a solution of *N*-benzylidene-4-methyl-benzenesulfonamide (**138**, 389 mg, 1.5 mmol) in THF (2 mL). The reaction mixture was stirred for 4 h at 25 °C. Then, the reaction mixture was quenched with a sat. aq. NH_4Cl solution, extracted with ether (3 x

25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 5-phenyl-5-(toluene-4-sulfonylamino)-pentanoic acid ethyl ester (**139**) as a colorless oil (368 mg, 65 %).

^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C): δ = 7.52 (d, *J* = 8.6 Hz, 2H), 7.13-7.10 (m, 3H), 7.08 (d, *J* = 8.2 Hz, 2H), 7.00-6.98 (m, 2H), 5.30 (d, *J* = 7.2 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 2.21 (t, *J* = 7.2 Hz, 2H), 1.82-1.76 (m, 1H), 1.73-1.67 (m, 1H), 1.61-1.54 (m, 1H), 1.47-1.41 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

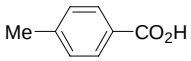
^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C): δ = 173.1, 142.9, 140.6, 137.6, 129.2, 128.4, 127.3, 127.0, 126.4, 60.3, 58.1, 36.8, 33.5, 21.4, 21.2, 14.2.

HRMS *m/z* : calcd. for $C_{20}H_{25}NO_4S$ 375.1504, found 330.1161 [M-OEt^+].

MS (EI, 70 eV), *m/z* (%): 330 (18) [M-OEt^+], 260 (100), 220 (32), 155 (25), 91 (21).

IR (cm^{-1}): 3274 (br), 3031 (w), 2981 (w), 2939 (w), 1729 (m), 1599 (w), 1496 (w), 1456 (m), 1322 (m), 1185 (m), 1154 (vs), 1091 (s).

4-Methyl-benzoic acid (140)



A dry and N_2-flushed Schlenk-flask was charged with 4-methyl-phenylzinc bromide·Magnesium chloride (**135d**, 7.5 mL, 0.42 M in THF, 3.2 mmol). A ballon was attached to the reaction flask using a short lenght rubber tubing (ca. 5 cm) and a needle adapter. $CO_{2(g)}$ was bubbled through the reaction mixture for ca. 5 min, until the ballon was inflated. The reaction mixture was stirred for 1 h, until the zinc reagent **135d** had been completely consumed (quenching of reaction aliquots with I_2 and GC-analysis). The reaction mixture was diluted with ether (30 mL) and sat. aq. $NaHCO_3$ (30 mL). The organic phase was separated and extracted with sat. aq. $NaHCO_3$ (2 x 30 mL). The combined aq. phases were carefully acidified with 5 M HCl (pH < 5) and extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over N_2SO_4. Evaporation off the solvents yielded 4-methyl-benzoic acid (**140**) as a colorless solid (427 mg, 98 %). The analytical data match those of the commercially available substrate.

m.p.: 182.6-184.3 °C.

^{1}H-NMR (DMSO-d_6, 300 MHz, 25°C): δ = 12.75 (br s, 1H), 7.82 (ddd, *J* = 8.2, 2.0, 1.7 Hz, 2H), 7.28 (ddd, *J* = 8.2, 2.0, 1.7 Hz, 2H), 2.35 (s, 3H).

^{13}C-NMR (DMSO-d_6, 75 MHz, 25°C): δ = 167.3, 143.0, 129.3, 129.1, 128.0, 21.1.

HRMS *m/z* : calcd. for $C_8H_8O_2$ 136.0524, found 136.0531.

12. Curriculum Vitae

Georg Manolikakes

Personal informations

Date of birth	July 16, 1979
Plave of birth	Ebersberg, Germany
Nationality	German

Education

1986 – 1990	Grundschule Ebersberg
1990 - 1999	Gymnasium Grafing completed with Allgemeine Hochschulreife (grade: 1.4)
1999-2000	Alternative civilian service, Offene Behindertenarbeit, BRK Ebersberg
2000-2005	Studies of chemistry at the Ludwig-Maximilians-University Munich
09/2005	Diploma thesis with Prof. Dr. P. Knochel (grade, 1.0)
2005-2008	PhD thesis with Prof. Dr. Knochel

Languages

German	mother tongue
English	fluent
Greek	basic

Work experience and internships

10/2002-04/2003	Teaching assistant for the ‘’Introduction to Organic Chemistry’’-lecture and tutorial (Prof. Dr. H. Mayr and Dr. B. Straub) at the LMU Munich
01/2003-06/2004	Research Assistant, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, LMU Munich
10/2003-11/2003	Physikalisch-Chemisches Fortgeschrittenen Praktikum with Prof. Dr. S. Mintova (Ludwig-Maximilians-University Munich) and Prof. Dr. M. Mostafavi (Université Paris-Sud XI, Orsay, France) funded by the BFHZ-CCUFB (Bavarian-French center for cooperation of universities)
02/2004-04/2004	Organisch-Chemisches Fortgeschrittenen Praktikum with Prof. Dr. D. M. Hodgson (University of Oxford, UK)

07/2004-12/2004	Research Assistant, 4SC AG, Medicinal Chemistry Department (Munich, Germany)

Awards and Distinctions

2003	Oskar-Karl-Forster Fellowship
2003-2004	Johann-Loesch Fellowship
2006	Römer Fellowship

Publications

1. Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P.; *Efficient Cross-Coupling of Functionalized Arylzinc Halides Catalyzed by a Nickel Chloride-Diethyl Phosphite System. Org. Lett.* **2005**, *7*, 4871-4874.

2. Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P.; *An efficient Negishi cross-coupling reaction catalyzed by nickel(II) and diethyl phosphite. Tetrahedron.* **2006**, *62*, 7521-7533.

3. Manolikakes, G.; Dastbaraverdeh, N.¸Knochel, P.; *Nickel-catalyzed cross-coupling reactions of aryltitanium(IV) alkoxides with aryl halides. Synlett* **2007**, *13*, 2077-2080.

4. Manolikakes, G.; Gavryushin, A.; Knochel, P.; *An Efficient Silane-Promoted Nickel-Catalyzed Amination of Aryl and Heteroaryl Chlorides. J. Org. Chem.* **2008**, *73*, 1429-1434.

5. Manolikakes, G.; Schade, M. A.; Munoz Hernandez, C.; Mayr, H.; Knochel, P.; Negishi Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents. *Org. Lett.* **2008**, *10*, 2765-2768.

6. Metzger, A.; Schade, M. A.; Manolikakes, G.; Knochel, P.; *A general preparation of polyfunctional benzylic zinc organometallic compounds. Chem. Asian. J.* **2008**, *3*, 1678-1691.

7. Manolikakes, G.; Munoz Hernandez, C.; Schade, M. A.; Metzger, A.; Knochel, P.; *Palladium- and Nickel-Catalyzed Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Protons with Organozinc Reagents. J. Org. Chem.* **2008**, *73*, 8422-8436.

8. Manolikakes, G.; Knochel, P.; *Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents. Angew. Chem. Int. Ed.* **2009**, *48*, 205-209.

9. Dong, Z.; Manolikakes, G.; Li, J.; Knochel, P.; *Palladium-Catalyzed Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents. Synthesis*, **2008**, *published online*, DOI: 10.1055/s-0028-1083286.

10. Knochel, P.; Appukkuttan, P.; Manolikakes, G.; Metzger, A.; Mosrin, M.; Piller, F. M.; Rohbogner, C. J.; Schade, M. A.; Wunderlich, S. H.; *Functionalization of Heterocyclic Compounds using Polyfunctional Magnesium and Zinc Reagents. Synthon* (Pfizer In-House Journal) **2008**.

11. Manolikakes, G.; Dong, Z.; Mayr, H.; Li, J.; Knochel, P.; *Negishi Cross-Couplings Compatible with Unprotected Amide Functions. Chem. Eur. J.* **2009**, *15*, 1324-1328.

12. Dong, Z.; Manolikakes, G.; Shi, l.; Li, J.; Knochel, P.; Mayr, H.; *Relative Reactions Rates of Negishi Cross-Coupling Reactions in Substituted Bromobenze and Arylzinc Derivatives. manuscript in preparation*.

13. Metzger, A.; Manolikakes, G.; Knochel, P.; *Mg^{2+}-Promoted Addition of Organozinc Reagents to Carbonyl Compounds. manuscript in preparation*.

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Patent Applications

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Poster and Presentations

G. Manolikakes, A. Gavryushin, P. Knochel, *Efficient Cross-Coupling of Functionalized Arylzinc Halides Catalyzed by a Nickel(II) and Diethyl Phosphite System* (Poster)

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