Anne Eeg Jensen

Transition Metal-Catalyzed Cross-Coupling Reactions of Functionalized Organometallic Reagents

München 2001

Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

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aus

Århus, Dänemark

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Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 von Professor Dr. Paul Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbsständig, ohne unerlaubte Hilfe erarbeitet.

München, am 11. Oktober 2001

Anne Eeg Jensen

Dissertation eingereicht am 11. Oktober 2001

1. Gutachter Prof. Dr. Paul Knochel
2. Gutachter Prof. Dr. Herbert Mayr

Mündliche Prüfung am 22. November 2001

This work was carried out from June 1998 to July 2001 under the supervision of Professor Paul Knochel at Fachbereich Chemie, Philipps-Universität, Marburg and Fakultät für Chemie und Pharmazie, Ludwig-Maximilians-Universität, Munich.

I would like to thank Prof. Paul Knochel for giving me the opportunity to do my Ph. D. in his group and for his invaluable support throughout this time.

I would also like to thank Prof. Mayr for agreeing to be my "Zweitgutachter", as well as Priv. Doz. Karaghiosoff, Priv. Doz. Müller, Prof. Pfaendler and Prof. Steglich for the interest shown in the present manuscript by accepting to be referee.

Nicole Harrington-Frost and Naka Seidel I thank for the correction of this manuscript.

I would like to thank L'Oréal, Paris (Parce que je le vaux bien) for financial support in form of a fellowship, and the Danish Research Academy for financial support to attend to conferences.

Furthermore, I would like to thank all the students and post-docs that came and went throughout my Ph. D. for their brief or lasting friendships, which have made my time here in Germany an enjoyable and worthwhile experience. I would especially like to thank Laurent Bérillon, Wolfgang Dohle, Kolja Knapp, Florence Volant and Ioannis Sapountzis for being a great lab team and for accepting that some days are made for "Modern Talking"…Hallelujah!!!

Special thanks also go to Vladimir Malakov, Krystina Becker and Gabi Fried for their help in organizing everyday life in the lab, as well as to the analytical team for their invaluable help.

Ein grosses Dankeschön geht auch an die Studentische Jägervereinigung Malepartus, München für die freundliche Aufnahme und für die einzigartige Chance einen bayrischen Bock zu schiessen – Weidmanns Heil.

Finally I would like to thank my family and friends in Denmark for their great support throughout my times abroad – your love is my greatest privilege.

Parts of this Ph.D. thesis have been published:

- M. Piber, A. E. Jensen and P. Knochel, New Efficient Nickel and Palladium Catalyzed Cross-Coupling Reactions Mediated by Tetrabutylammonium Iodide, *Organic Letters*, **1999**, 1326.

- A. E. Jensen, W. Dohle and P. Knochel, Improved Nickel-Catalyzed Cross-Coupling Reaction Conditions for *Ortho*-substituted Aryl Iodides and Nonaflates in Solution and in the Solid Phase, *Tetrahedron*, **2000**, *56*, 4197.

- G. Varchi, A. E. Jensen, W. Dohle, A. Ricci, G. Cahiez and P. Knochel, Preparation of Functionalized Magnesiated Aniline Derivatives, *Synlett*, **2001**, 477.

- A. E. Jensen and P. Knochel, Nickel Catalyzed Cross-Coupling between Functionalized Primary or Secondary Alkylzinc Halides and Primary Alkyl Halides, *J. Org. Chem*., **2001**, *in press*.

- A. E. Jensen and P. Knochel, Preparation of 2-Arylated 1,4-Phenylenediamines by Palladium-Catalyzed Cross-Coupling Reactions, *J. Organomet. Chem*., **2001**, *in press*.

- A. E. Jensen, F. Kneisel and P. Knochel, Ethyl 3-(*p*-cyanophenyl)propionate from ethyl 3-iodopropionate and *p*-cyanophenylzinc bromide, *Org. Synth.*, **2001**, *in press*.

- A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu and Paul Knochel, Practical Synthetic Procedures: Preparation and Reactions of Functionalized Arylmagnesium Reagents, submitted for publication in *Synthesis*.

- D. M. Lindsay, W. Dohle, A. E. Jensen, F. Kopp and Paul Knochel, Preparation of Polyfunctional Heterocycles using Highly Functionalized Aminated Arylmagnesium Reagents as Versatile Scaffolds, submitted for publication in *Angewandte Chemie*.

Evigt fremad
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H. Drachmann

Til min morfar Niels Jacob Jensen

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Introduction

1 An Overview

The continuous search for biologically active molecules for the pharmaceutical and cosmetic industries is probably one of the largest areas of research where synthetic organic chemistry plays a fundamental role. Since most molecules with biological activity, even natural products for commercial use, are not extracted from a natural source but synthesized in the chemical laboratory, there is a constant need for the development of new methods for selective carbon-carbon bond formation, which are mild and highly tolerant towards a wide range of functional groups.

With the synthesis of diethylzinc in 1849, E. Frankland lay the foundation stone for modern organometallic chemistry.[1] However, organomagnesium[2] and organolithium[3] reagents were the first to dominate this branch of organic chemistry, rather than zinc organometallics. This is presumably related to the low reactivity of organozinc reagents towards many electrophiles, which is a result of the covalent character of the carbon-zinc bond. As illustrated in Figure 1, the reactivity of an organometallic species increases with increased ionic character of the carbon-metal bond. Through the use of highly reactive species, selectivity is often compromised. Furthermore, reduced tolerance towards functional groups such as esters, cyano groups and ketones is observed.[4]

The discovery of the notable ability of organozinc reagents to undergo transmetallation with transition metal salts of palladium or nickel, led to the renaissance of organozinc chemistry. One of the early advances in this field was the development of the palladium-catalyzed Csp^2-Csp^2 cross-coupling reaction between aryl iodides and organozinc halides by Negishi in 1977.[5]

1 a) Frankland, E. *Liebigs Ann. Chem.* **1848-49**, *71*, 171; b) Frankland, E. *J. Chem. Soc.* **1848-49**, *2*, 263.

2 Grignard, V. *Compt. Rend.* **1900**, *130*, 1322.

3 a) Schlenk, W.; Holtz, J. *Chem. Ber.* **1917**, *50*, 262; b) Ziegler, K.; Colonius, H. *Liebigs Ann. Chem.* **1930**, *479*, 135.

4 Negishi, E. *Organometallics in Organic Synthesis*, Wiley, New York, **1980**.

5 Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

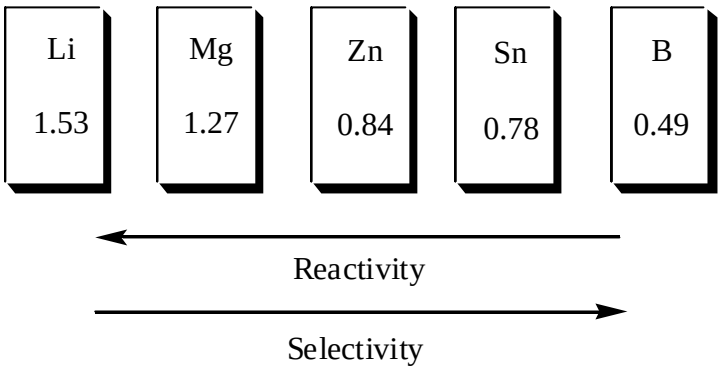
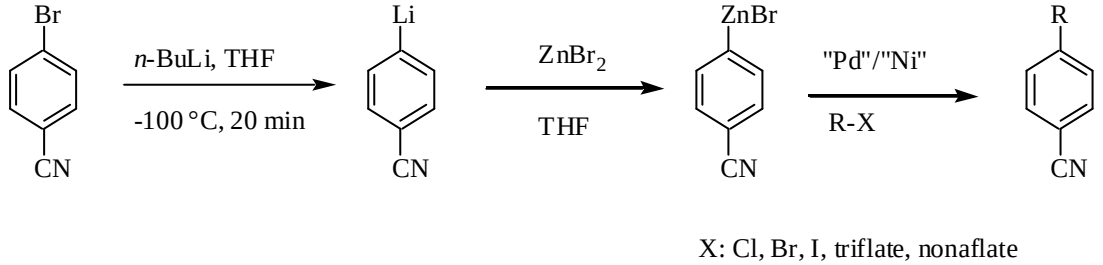


Figure 1. Electronegativity difference of some metals relative to carbon.[6]

1.1 Organometallic reagents in cross-coupling reactions

Organolithium reagents have a highly polar carbon-lithium bond, which makes them very reactive towards most functional groups. Through low-temperature preparation (-100 °C), a range of functionalities such as cyano groups, *tert*-butyl esters and free carboxylic acids[7] are tolerated. However, the high reactivity of organolithium compounds make them unsuitable for cross-coupling reactions, unless they are first transmetallated with, for example, magnesium or zinc, to give a less reactive species (Scheme 1).[8]



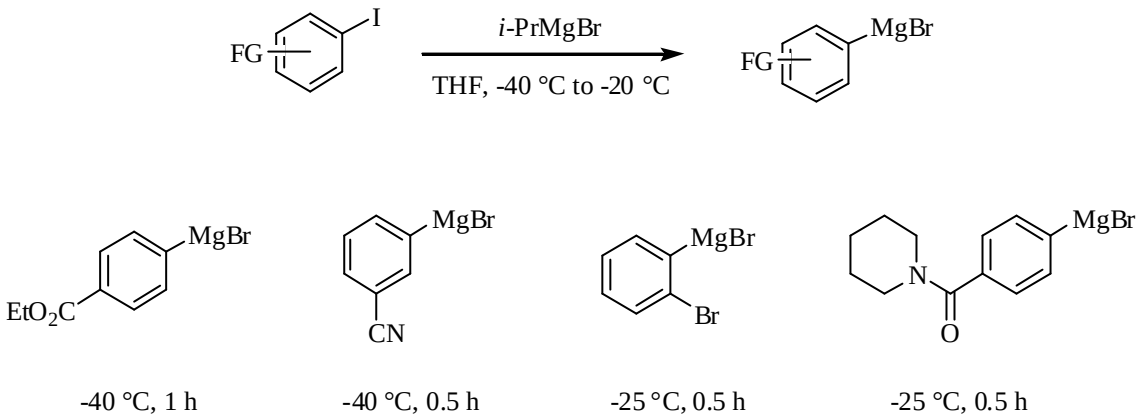
Scheme 1. Transmetallation of organolithium species for use in cross-coupling reactions.

6 Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem.* **2000**, *112*, 4585; *Int. Ed.* **2000**, *39*, 4415.

7 a) Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem.* **1975**, *40*, 2394; b) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187; c) Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257; d) Parham, W. E.; Boykin, D. W. *J. Org. Chem.* **1977**, *42*, 261; e) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983.

8 Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186.

Organomagnesium reagents, like organolithium reagents, have a highly polar carbon-metal bond which makes them rather reactive towards electrophiles. However, these species are more stable and tolerate most functional groups, provided reactions are carried out below -10 °C. The application of organomagnesium reagents in organic synthesis suffered a long set back due to a lack of mild preparative methods. The use of Rieke magnesium proved not to be general, since most polar functional groups coordinate to the surface of the activated magnesium and thereby inhibit the oxidative addition of the metal into the carbon-halogen bond.[9] Recently, a more general method has been developed, which makes use of a low-temperature iodine-magnesium exchange reaction (Scheme 2).[10]



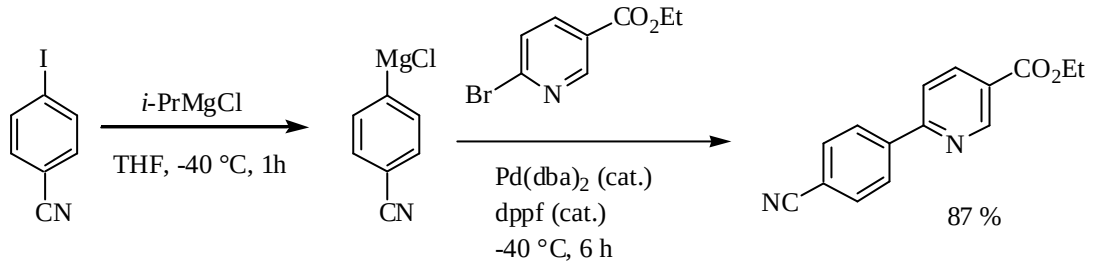
Scheme 2. Synthesis of Grignard reagents by low-temperature iodine-magnesium exchange reaction.

In the wake of this new methodology an array of applications of Grignard reagents in palladium-[11] and nickel-catalyzed[12] cross-coupling reactions has been developed (Scheme 3 and 4).

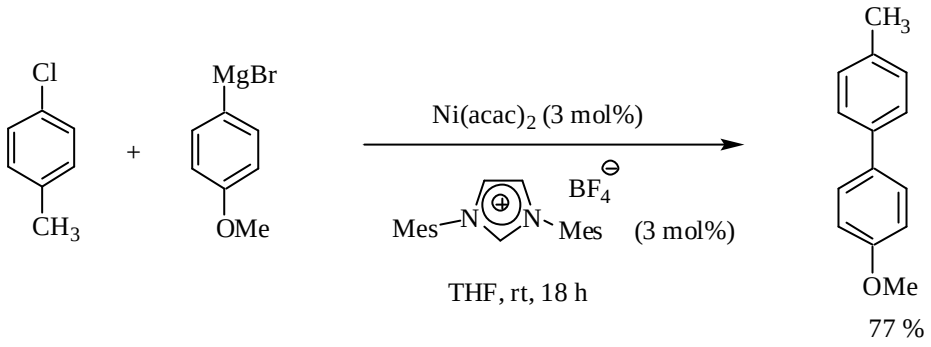
9 a) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674; b) Rieke, R. D. *Science* **1989**, *246*, 1260; c) Lee, J.; Vélarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.

10 a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801; *Int. Ed.* **1998**, *37*, 1701; b) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080. For a review article see: c) Rottländer, M; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.*, **2000**, *6*, 767.

11 a) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron* **2000**, *56* ,1349; b) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669; c) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.



Scheme 3. Synthesis of functionalized pyridines by palladium-catalyzed cross-coupling of functionalized arylmagnesium chlorides.



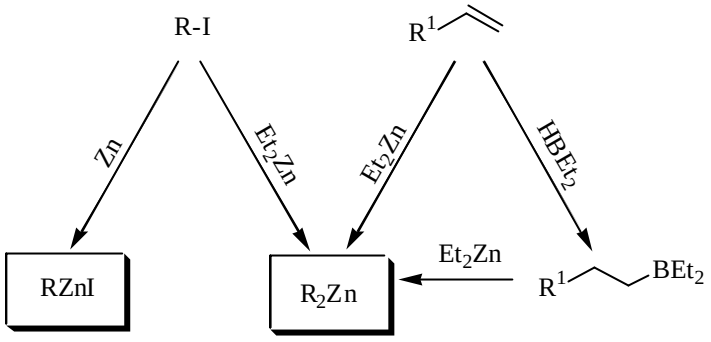
Scheme 4. Nickel-catalyzed Grignard cross-coupling at ambient temperature.

In spite of the low reactivity of organozinc reagents towards most electrophiles, the low-lying empty orbitals of the organozinc species favor transmetallation to more reactive transition metal organometallics of copper, nickel and palladium. Organozinc reagents are easily obtained via direct insertion[13] of activated zinc (foil or dust) into the carbon-halogen bond, by

12 a) Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem.* **2000**, *112*, 1672; *Int. Ed*. **2000**, *39*, 1602; b) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett*. **1998**, *39*, 7275.

13 a) Berk, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organometallics*, **1990**, *9*, 3053; b) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, A.; Reddy, C. K. *Angew. Chem.* **1997**, *109*, 1603; Int. Ed. **1997**, *36*, 1496; c) Rottländer, M.; Knochel, P. *Tetrahedron Lett*. **1997**, *38*, 1749; d) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.

transmetallation from the corresponding organolithium or organomagnesium compound,[14] or by boron-zinc exchange (Scheme 5).[15,16]



Scheme 5. Synthetic pathways to organozinc halides and diorganozinc reagents.

As organometallic species in transition metal-catalyzed reactions, organozinc reagents have proven to be versatile building blocks. The palladium-catalyzed Negishi cross-coupling reaction has found application as a key step in the synthesis of the triterpenoid mukopalide, where it shows high stereoselectivity (E:Z = >98: 2) (Figure 2, Scheme 6).[17]

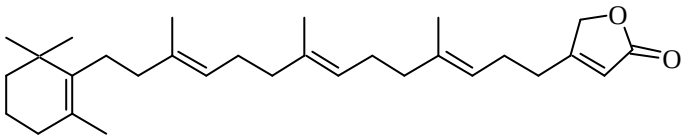


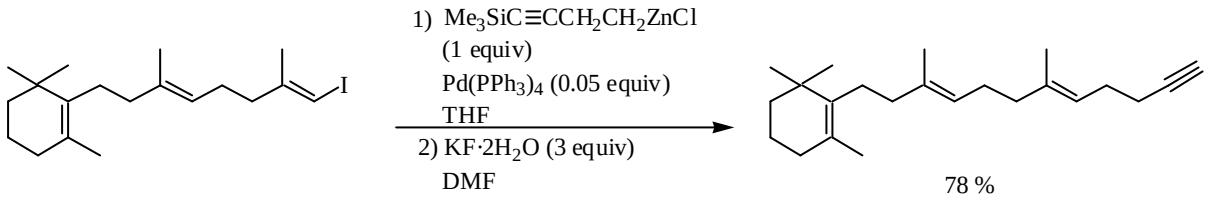
Figure 2. Natural triterpene: mukopalide.

14 Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P. *Tetrahedron*, **1996**, *52*, 7201.

15 a) Langer, F.; Waas, J.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 5261; b) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229; c) Langer, F.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *Synlett* **1994**, 410; d) Boudier, A.; Hupe, E.; Knochel, P. *Angew. Chem.* **2000**, *112*, 2396; *Int. Ed.* **2000**, *39*, 2294.

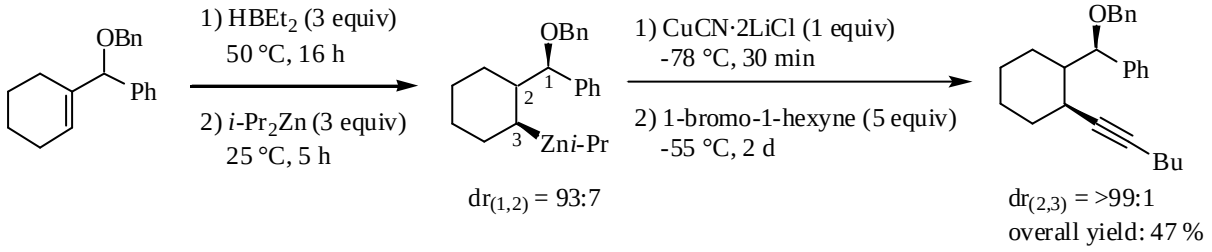
16 For reviews see: a) Erdik, E. *Tetrahedron* **1987**, *43*, 2203; b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117; c) Knochel, P.; Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.

17 a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223.

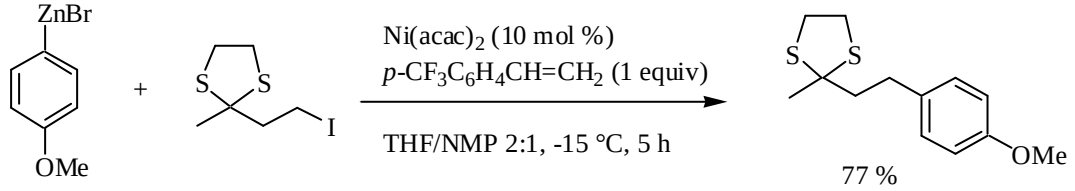


Scheme 6. A key step in the synthesis of the triterpenoid mukopalide is the Negishi cross-coupling reaction.

Furthermore, copper-mediated cross-coupling reactions of optically active secondary zinc reagents obtained through boron-zinc exchange, with a range of electrophiles, have been shown to occur under mild conditions with high stereochemical control and retention of configuration (Scheme 7).[15d]



Scheme 7. Copper-mediated cross-coupling reaction of an optically active alkylzinc reagent.



Scheme 8. Nickel-catalyzed cross-coupling reaction.

Nickel-catalyzed reactions of organozinc reagents have also found synthetic application (Scheme 8).[18] Nickel catalysts have the special ability to catalyze Csp^3-Csp^3 cross-coupling reactions.[19]

18 a) ref.8; b) Jensen, A. E.; Dohle, W.; Knochel, P. *Tetrahedron* **2000**, *56*, 4197.

Organotin reagents (Stille reaction)[20] as well as organoboron reagents (Suzuki reaction)[21] also have relatively non-polar covalent carbon-metal bonds. They react in an analogous fashion to organozinc reagents in cross-coupling reactions catalyzed by transition metals. The application of organoboranes in palladium-catalyzed cross-coupling reactions, developed by Suzuki, has proven to be a particularly mild, selective and versatile reaction.[22]

1.2 The Csp^3-Csp^3 cross-coupling reaction

Despite all the attention that organometallic chemistry has received in recent years, relatively few reactions have been reported where two Csp^3 centers have been successfully coupled.[23] The low reactivity of alkyl halides with alkyl nucleophiles gives rise to problems in all steps of the catalytic cycle. Firstly, the oxidative addition of Csp^3 centers to the metal catalyst is slower compared to the rate of addition of Csp^2 or Csp centers, particularly in the case of palladium.[24] Furthermore, the desired subsequent transmetallation must compete with a relatively fast ß-hydride elimination. Finally, the reductive elimination is slow due to the high electron density on the metal center.[25]

Although copper-mediated Csp^3-Csp^3 cross-coupling reactions have been known since the late sixties, a range of functional groups were precluded from this type of transformation, since the copper species were typically obtained from the corresponding lithium or Grignard reagent. Oxidative addition of activated copper into a carbon-halogen bond is another, milder method for cuprate synthesis, however this method is usually low yielding even in the presence of a large excess of the activated copper species.[26] Only after the development of mild methods for the synthesis of organozinc reagents, in combination with the use of higher

19 For a review on organozinc chemistry: a) Erdik, E. *Tetrahedron* **1992**, *48*, 9577; b) ref. 16c.

20 Stille, J. K. *Angew. Chem.* **1986**, *98*, 504.

21 For a review: a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

22 a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020; b) Littke, A. F.; Fu, G. C. *Angew. Chem.* **1998**, *110*, 3586; *Int. Ed.* **1999**, *38*, 2411. For a review see: c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; d) Miyaua, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

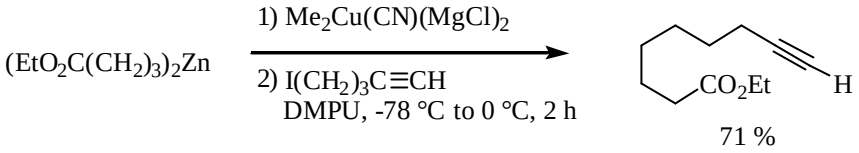
23 Cárdenas, D. J. *Angew. Chem.* **1999**, *111*, 3201.

24 Stille, J. K. *The Chemistry of the Metal-Carbon Bond, Vol 2*, Wiley, New York, **1985**, Chapter 9, 625.

25 Goliaszewsky, A.; Schwartz, J. *Tetrahedron* **1984**, *40*, 5779.

26 Ebert, G. W.; Rieke, R. U. *J. Org. Chem.* **1988**, *53*, 4482.

order cuprates, was improved tolerance towards functional groups obtained (Scheme 9).[27] The major drawback of this reaction is the requirement of stoichiometric amounts of transition metal salts.



Scheme 9. Csp^3-Csp^3 cross-coupling reaction with an organocuprate.

In spite of the problems associated with their application there have been a few reports of Csp^3-Csp^3 cross-coupling reactions using alkylboranes[28] or boronate esters.[29] Even though mild reaction conditions make these species tolerant towards a variety of functional groups, the products are unfortunately obtained in only poor to moderate yields. Developments in the area of organomagnesium reagents have suffered similar defeats as their cross-coupling reactions have so far been non-general, low-yielding reactions of unfunctionalized electrophiles and nucleophiles,[30] the major problems seeming to be reduction of the alkyl halide and ß-hydride elimination.[31]

A new protocol for the Csp^3-Csp^3 cross-coupling reaction employing organozinc reagents under nickel catalysis has recently been reported.[32] Reductive elimination is favored through the presence of a double bond in the electrophile. The lack of a double bond leads instead to a halogen-zinc exchange reaction (Scheme 10).[33]

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27 Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 4781.

28 Ishiyama, Y.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691.

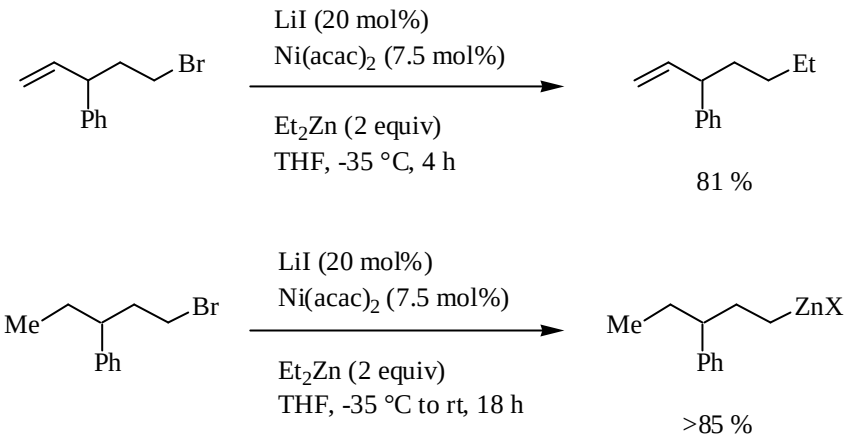
29 Charette, A. B.; Piereira De Freitas-Gil, R. *Tetrahedron Lett.* **1997**, *38*, 2809.

30 a) Castle, P. L.; Widdowson, D. A. *Tetrahedron Lett.* **1986**, *27*, 6013; b) Yuan, K.; Scott, W. J. *Tetrahedron Lett.* **1991**, *32*, 189; c) Park, K.; Yuan, K.; Scott, W. J. *J. Org. Chem.* **1993**, *58*, 4866; d) van Asselt, R.; Elsevier, C. J. *Tetrahedron* **1994**, *50*, 323.

31 a) Yuan, K.; Scott, W. J. *Tetrahedron Lett.* **1989**, *30*, 4779; b) Yuan, K.; Scott, W. J. *J. Org. Chem.* **1990**, *55*, 6188.

32 Devasagayaraj, A; Stüdemann, T.; Knochel, P. *Angew. Chem.* **1995**, *107*, 2952; *Int. Ed.* **1996**, *34*, 2723.

33 For palladium- or nickel-catalyzed halogen-zinc exchange reactions, see: a) Stadtmüller, H.; Lentz, R.; Dörner, W.; Stüdemann, T.; Tucker, C. E.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027; b) Vettel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7471.



Scheme 10. Nickel-catalyzed cross-coupling reaction or halogen-zinc exchange reaction, depending on the presence or absence of a double bond in the electrophile.

By adding an external double bond in the form of a styrene or ketone derivative, which can promote the desired reductive elimination by coordinating to the nickel center, a more general protocol was obtained (Figure 3, Scheme 11).[34]

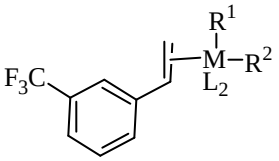
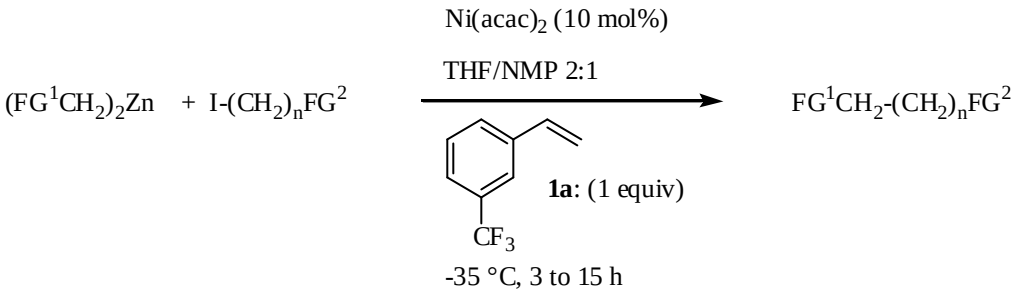


Figure 3. Lowering of the electron density at the metal center by coordination to an electron deficient styrene.

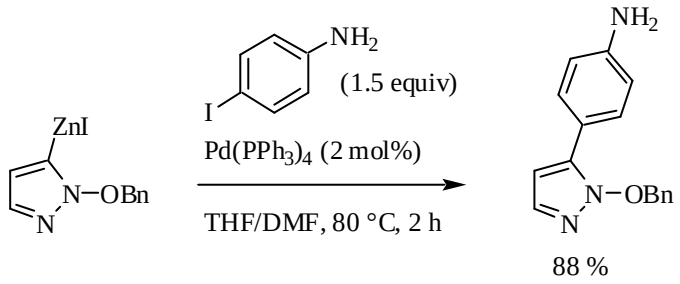
34 a) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 2512; *Int. Ed*. **1998**, *37*, 2387; b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544; For previous reports on the promoting effect of electron deficient double bonds on nickel-catalyzed Csp^3-Csp^3 cross-coupling reactions, see: c) Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc*. **1971**, *93*, 3350; d) Sustmann, R.; Lau, L. J.; Zipp, M. *Tetrahedron Lett*. **1986**, *27*, 5207; e) Sustmann, R.; Lau, L. J. *Chem. Ber*. **1986**, *119*, 2531.



Scheme 11. General scheme for the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of a functionalized alkyl iodide and a functionalized dialkylzinc reagent.

1.3 Amine substituents in the Negishi cross-coupling reaction

In most biologically active compounds, heteroatoms play a fundamental role for the binding and activity of the molecule, due to their ability to interact with enzymes and receptor systems. The Negishi cross-coupling reaction has proven to be tolerant towards most functional groups, such as ester, cyano, methoxy, nitro, imine, aldehyde and amide groups.[35] In several cases even free anilines have been coupled with this reaction (Scheme 12).[36]



Scheme 12. Negishi cross-coupling reaction between a benzopyrazol derivative and 4-iodoaniline.

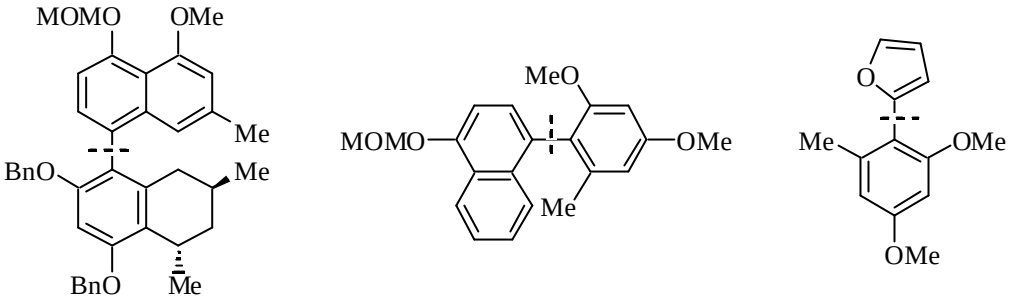
However, the use of the unprotected aniline functionality is limited to the electrophilic moiety, as the basic conditions under which the zinc reagent is prepared (i.e. during the

35 For a review, see: Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

36 a) Kristensen, J.; Begtrup, M.; Vedsø, P. *Synthesis* **1998**, 1604; b) Jensen, J.; Skjærbæk, N.; Vedsø, P. *Synthesis* **2001**, 128; c) Campbell, J. B.; Firor, J. W.; Davenport, T. W. *Synth. Commun.* **1989**, *19*, 2265.

halogen-magnesium exchange or halogen-lithium exchange) cause deprotonation and subsequent quenching of the organometallic species.

A further advantage of the Negishi cross-coupling reaction is its great tolerance towards steric hindrance, which makes it possible to synthesize not only highly functionalized products but also highly substituted ones (Figure 4).[37]



53 % 50 % 90 %

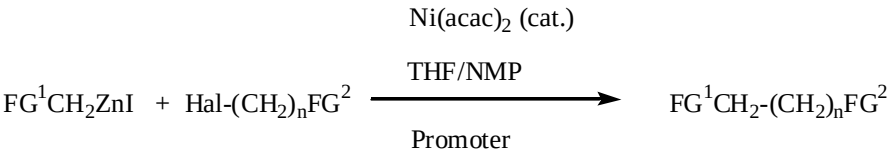
Figure 4. Sterically hindered products obtained by a Negishi cross-coupling reaction.

37 Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940.

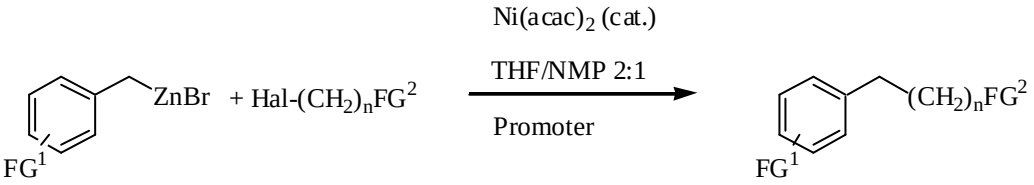
2 Objectives

After the successful development of a mild, nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of dialkylzincs with alkyl halides, it was of interest to further extend this chemistry. The objectives for an extension being:

- application of less reactive, but more easily accessible zinc organometallics, such as alkylzinc iodides and benzylic zinc bromides,
- use of less reactive, hence less costly, alkyl electrophiles, e.g. alkyl bromides,
- use of highly functionalized electrophiles.



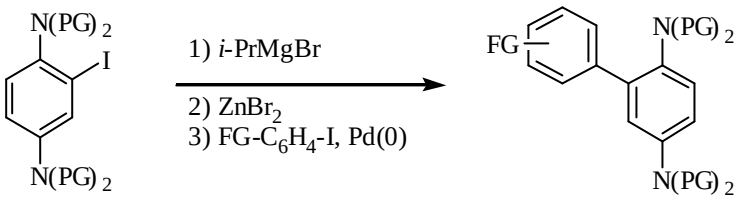
Scheme 13. Proposed nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of alkyl halides with alkylzinc iodides.



Scheme 14. Proposed nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of alkyl halides with benzylic zinc bromides.

A second project of special importance to L'Oréal, Paris was to develop a cross-coupling protocol for 1,4-phenylenediamine derivatives. The objectives for this work were to:

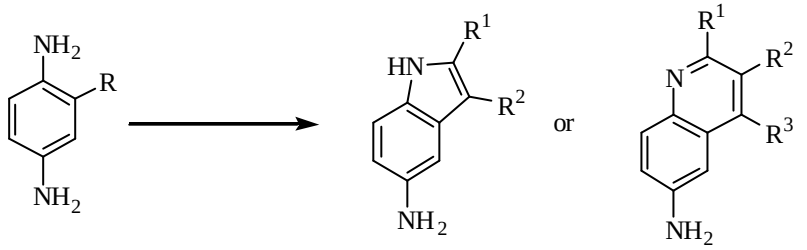
- identify a suitable protection-deprotection protocol,
- develop a general protocol for the halogen-magnesium exchange of such derivatives,
- subsequently develop a protocol for their application in the Negishi cross-coupling reaction.



Scheme 15. Proposed palladium-catalyzed cross-coupling reaction of 1,4-phenylene-diamine derivatives with aryl iodides.

After the successful cross-coupling reaction of the 1,4-phenylenediamine derivatives a further objective was:

- deprotection with subsequent cyclisation of suitable 1,4-phenylenediamine derivatives to obtain new functionalized, nitrogen-containing heterocycles such as indoles and quinolines.



Scheme 16. Proposed cyclization of 1,4-phenylenediamine derivatives to nitrogen-containing heterocycles.

Results and Discussion

1 Nickel-Catalyzed Csp^3-Csp^3 Cross-Coupling Reactions

Among the cross-coupling reactions, the coupling of two Csp^3 centers has turned out to be the most challenging. Many obstacles in the catalytic cycle have to be overcome for the successful coupling of such carbon centers. Nickel catalysis in combination with diorganozinc reagents has so far proven to be the best option for a general Csp^3-Csp^3 cross-coupling reaction under mild conditions.

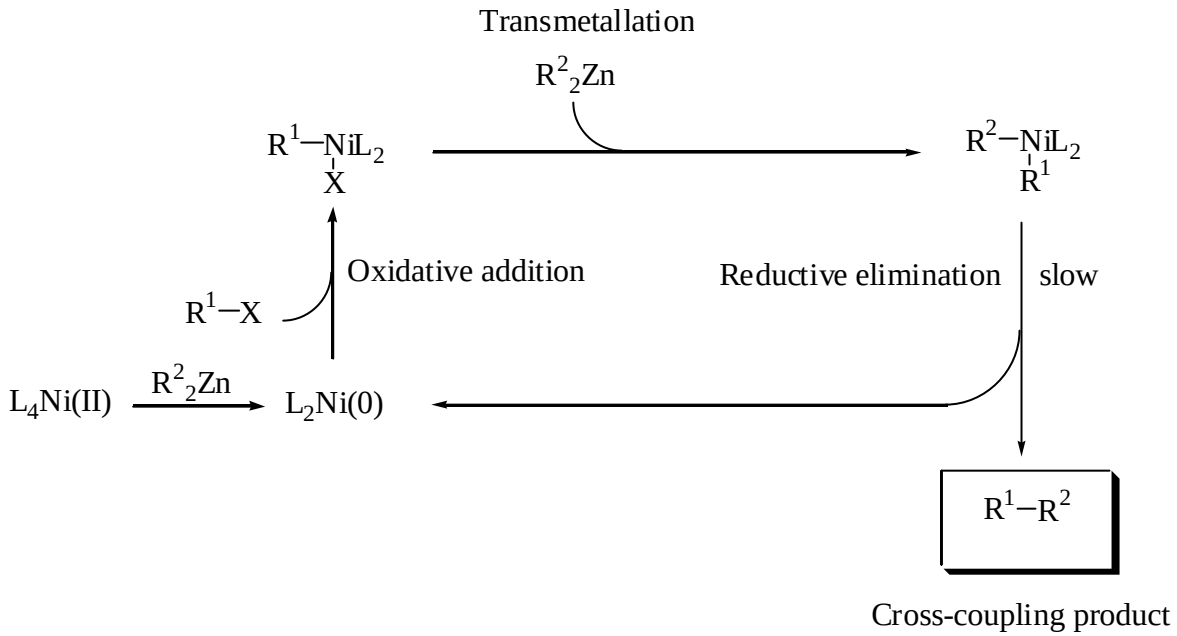


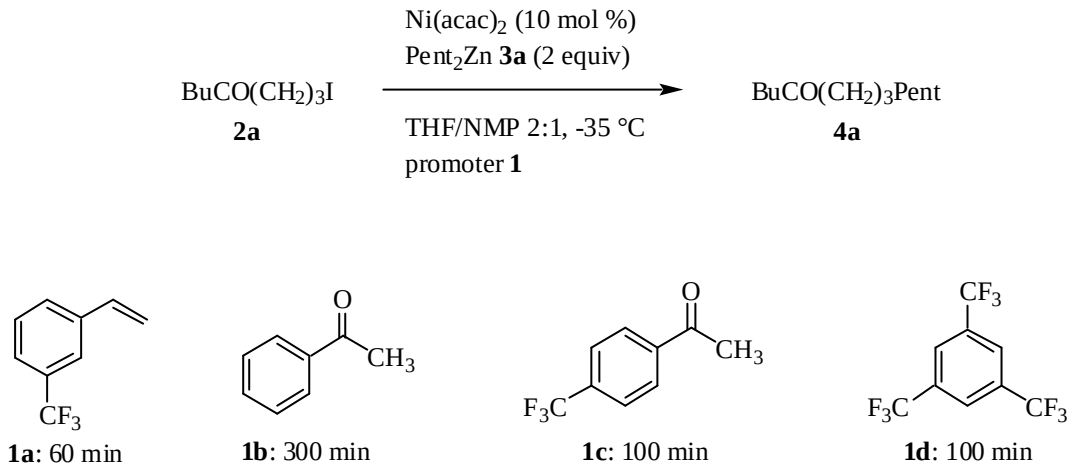
Figure 5. Proposed mechanism of the nickel catalyzed Csp^3-Csp^3 cross-coupling reaction.

According to the proposed mechanism (Figure 5), the cross-coupling reaction is initiated by the *in situ* reduction of the Ni(II) catalyst to Ni(0) by an excess of dialkylzinc reagent. The active Ni(0) catalyst thus generated, oxidatively inserts into the carbon-halogen bond of the electrophile leading to a new Ni(II) species. At low temperature, the Ni(II) complex now coordinates to an external double bond, e.g. an electron deficient styrene, whereupon the transmetallation from zinc to nickel can take place giving the heterosubstituted Ni(II) species $R^1R^2NiL_2$, and an alkylzinc halide. The reductive elimination, which normally proceeds very slowly in the Csp^3-Csp^3 cross-coupling reaction due to the high electron density on the nickel center, is promoted by the coordination of the nickel center to a double bond and proceeds

smoothly forming the cross-coupling product, as well as regenerating the Ni(0) catalyst and thereby continuing the catalytic cycle.[38]

1.1 The effect of styrene derivatives as promoters in the Csp^3-Csp^3 cross-coupling reactions

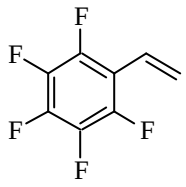
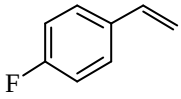
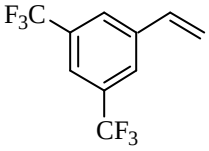
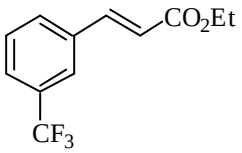
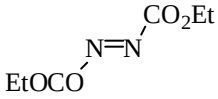
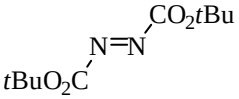
The promoting effect of a ligating double bond on the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction has been shown to be of key importance. A range of ketones, fluorinated toluene and mesitylene derivatives, and electron deficient styrenes, have already been tested for their ability to promote this type of cross-coupling reaction (Scheme 17).[34a,b]



Scheme 17. Reaction times for the Csp^3-Csp^3 cross-coupling reaction in the presence of some of the promoters tested.

In the coupling of the iodoketone **2a** with dipentylzinc (**3a**), use of either of the two promoters **1c** and **1d** led to fast reaction times, however in both cases the competing iodine-zinc exchange reaction was pronounced. Better results were obtained with **1a** and **1b**, in the presence of which the cross-coupling reaction was favored, yielding the cross-coupling product **4a** in 71 % and 74 % yield respectively.

38 a) ref. 34b; b) Stüdemann, T. *Dissertation*, Philipps-Universität Marburg, **1998**.

Promoter	% Conversion after 30 min at - 35 °C	Complete conversion (min)	Yield of **4a** (%)
 **1e**	0	180[a]	64
 **1f**	83	60	70
 **1g**	40	90	69
 **1h**	0	∞	–
 **1i**	87	90	64
 **1j**	nd[b]	20	47
CO **1k**	27	∞	–

[a]No cross-coupling product was observed until warmed to -20 °C

[b]The promoter was added slowly after dipentylzinc. The reaction was complete by the end of the addition

Table 1. Promoters in the Csp^3-Csp^3 cross-coupling reaction shown in Scheme 17.

The Csp^3-Csp^3 cross-coupling reaction of less reactive zinc reagents like alkylzinc iodide or benzylic zinc bromide did not, however, proceed under the above conditions. In order to determine whether an enhanced reactivity could be obtained through a more efficient

promoter, a range of other electron deficient styrenes, along with other potential promoters, were tested in the above cross-coupling reaction (Table 1).

Interestingly the Mitsunobu catalysts[39] diethyl azodicarboxylate (**1i**) and di-*tert*-butyl azodicarboxylate (**1j**) gave rise to very fast consumption of the alkyl iodide. However, the competing iodine-zinc exchange was pronounced, thus compromising the yields. The most promising results in this series of promoters were *p*-fluorostyrene (**1f**) and 3,5-*bis*-trifluoromethyl-styrene (**1g**)**,** which gave similar conversion times and resulted in comparable yields to the previously tested 3-trifluoromethyl-styrene (**1a**). Unfortunately, none of the promoter candidates tested in the cross-coupling reaction led to higher reactivity or to better yields. However, *p*-fluorostyrene (**1f**), as the less costly of the efficient promoters, replaced **1a** in the following investigations of the Csp^3-Csp^3 cross-coupling reaction.

1.2 The effect of salts on the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction

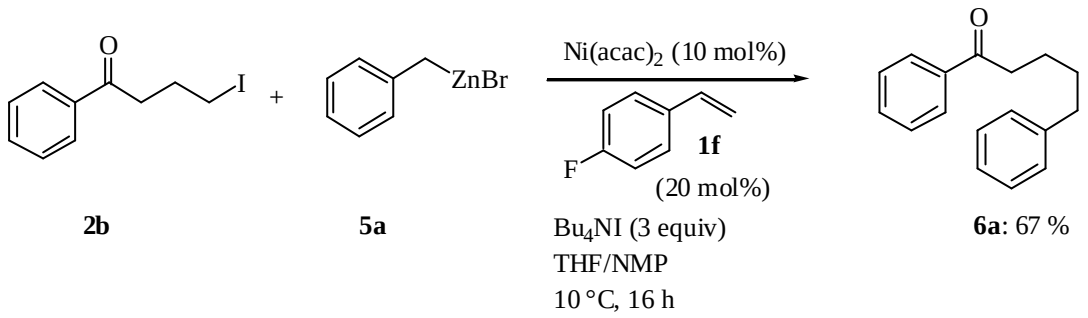
Since the early nineties there have been several reports on the beneficial effects of quaternary ammonium and metal salts in a range of cross-coupling reactions, e.g. the Suzuki,[40] the Sonogashira,[41] and the Heck[42] reactions. The reported effects are better chemoselectivities, higher reactivities and increased yields. The actual mode of action of these additives remains until now unexplained. However, as they were reported to have such a dramatic effect in other cross-coupling reactions, an application in the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction was attempted (Scheme 18).

39 a) Tsunoda, T.; Yamamiya, Y. *Tetrahedron Lett.* **1993**, *34*, 1639; for a review, see: Mitsunobu, O. *Synthesis* **1981**, 1.

40 a) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095; b) Reetz, M. T.; Breinbauer, R.; Wanninger, K. *Tetrahedron Lett.* **1996**, *37*, 4499.

41 a) Powell, N A.; Rychnovsky, S. D. *Tetrahedron Let.* **1996**, *37*, 7901; b) Nakamura, K.; Okubo, H.; Yamaguchi, M. *Synlett* **1999**, 549.

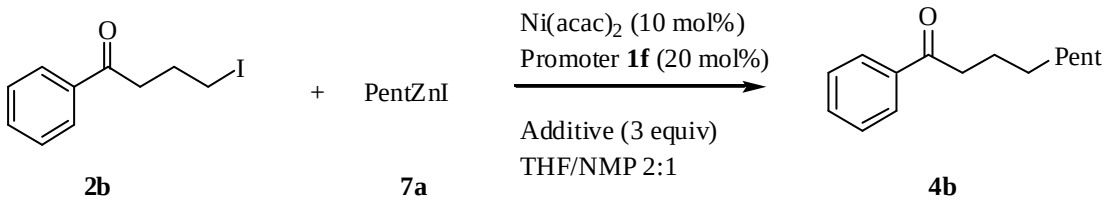
42 a) Merlic, C. A.; Semmelhack, M. F. *J. Organomet. Chem.* **1990**, *391*, C23; b) Jeffery, T.; Galland, J.-C. *Tetrahedron Lett.* **1994**, *35*, 4103; c) Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *App. Cat. A* **1999**, *182*, 399.



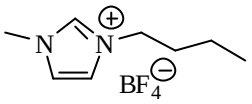
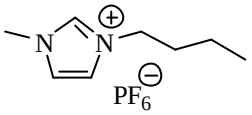
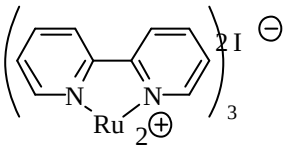
Scheme 18. First attempt at a nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction in the presence of TBAI.

By adding three equivalents of tetrabutylammonium iodide (TBAI) to the reaction mixture, it was for the first time possible to perform the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of an alkyl iodide with benzylic zinc bromide in the presence of the promoter **1f** (20 mol%). Alkyl iodide **2b** was thus coupled with benzylic zinc bromide **5a**, yielding the cross-coupling product **6a** in 67 % yield. Upon addition of just one equivalent TBAI the cross-coupling reaction already takes place, but an excess TBAI enhanced the reactivity and led to complete reaction within 16 h at 10 °C.

Further examinations of the Csp^3-Csp^3 cross-coupling reaction of pentylzinc iodide with the alkyl iodide **2b** were performed, with the initial aim of elucidating whether the cationic or the anionic part of TBAI was responsible for the remarkable effects on this cross-coupling reaction (Scheme 19 and Table 2).



Scheme 19. Nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction in the presence of an additive.

Entry	Additive	Reaction conditions (h, °C)	Yield of **4b** (%)[a]
1	Bu_4NI	16, -5	78
2	Me_4NI	—[b]	low conversion
3	$(C_{12}H_{25})_2Me_2NI$	—[b]	—[c]
4	Bu_4NBr	—[b]	low conversion
5	Bu_4PI	—[b]	low conversion
6		24, 10	43
7		18, 10	46
8		48, rt	58[d]
9	LiI	—[b]	—[c]
10	KI	16, -5[e]	68
11	KI, 18-Crown-6	24, -5	71

[a] Isolated yield of analytically pure product
[b] The reaction was followed over 24 h from -5 °C to rt
[c] Predominantly the competing iodine-zinc exchange reaction took place
[d] 20 mol% of additive was employed
[e] Only complete after additional 2 h at 0 °C

Table 2. Salt effects on the nickel-catalyzed cross-coupling reaction between **2b** and pentylzinc iodide.

By replacing TBAI with tetrabutylammonium bromide, a very slow cross-coupling reaction was observed. When tetrabutylammonium chloride was instead added, the alkyl iodide

immediately underwent halogen exchange, yielding the corresponding alkyl chloride, and with this substrate no further reaction was observed. This gave the impression that the iodide was responsible for the success of the cross-coupling reaction. However, when the quaternary ammonium cation was replaced, a similar lack of reactivity was observed, as illustrated in Table 2, entries 2 and 3.

As one equivalent of TBAI is insoluble in the reaction medium, and three equivalents have a greater effect on the course of the reaction, the ionic strength of the solution could be of importance. For this reason, traditional ionic liquids such as the imidazolium derivatives in entries 6 and 7 were evaluated, the results indicating that even though high ionic strength has a positive influence on the cross-coupling reaction, it does not explain the full effect of TBAI. The phase transfer catalyst (PTC) in entry 8[43] also has a positive influence on the cross-coupling reaction, though it seems to operate through a different mechanism, since its effect is already observed upon use of 20 mol% and does not increase with increased levels of PTC.

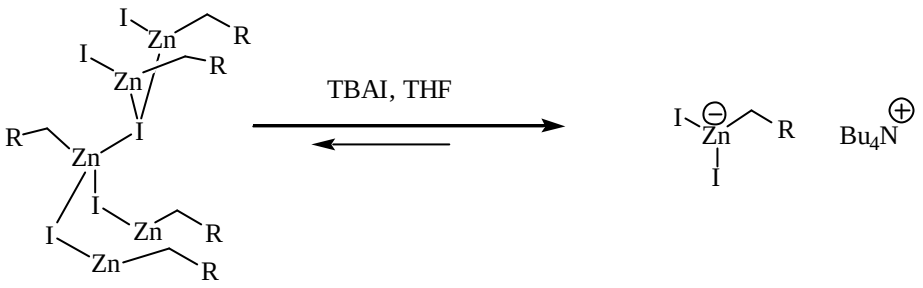
In addition alkali salts such as lithium and potassium iodide were tested (entries 9 and 10). Whereas lithium iodide showed no enhancement of the reaction, potassium iodide proved to be the best alternative to TBAI. A further experiment employing potassium iodide in the presence of the crown ether 18-crown-6, which complexes the potassium ion (entry 11), allowed the reaction to reach completion in 24 h at -5 °C.

The role of salts as mediators of the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction has not yet been elucidated, nor has it been possible to crystallize key intermediates and thereby gain solid proof of their role. However, as the best results were obtained with iodide in the presence of non-coordinating cations such as Bu_4N^+ or K^+, it seems evident that free iodide plays a key role.

In order to understand the dramatic effect observed upon addition of these salts, it is interesting to consider the possible role that free iodide plays in the mechanism. As iodide is employed in an equimolar amount relative to the zinc reagent, it might shift the equilibrium of the zinc reagent towards the monomeric form (Scheme 20).[44]

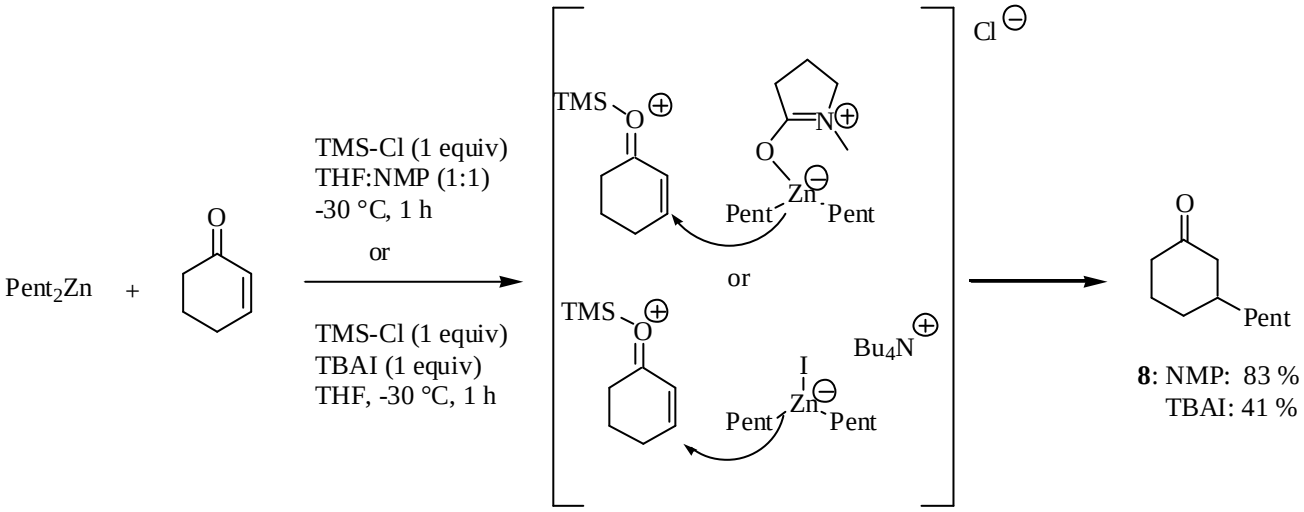
43 Rose, D.; Wilkinson, G. *J. Chem. Soc. A* **1970**, *10*, 1791.

44 Wilkinson, G.; Stone, F. G. A.; Abel, E. W. *Comprehensive Organometallic Chemistry*, Pergamon, **1982**, Chapter 16: *Zinc and Cadmium*, 823.



Scheme 20. Proposed monomerization of the organozinc iodide by coordination to iodide in the presence of TBAI.

Coordination of free iodide to the alkylzinc iodide would, possibly with a zincate as an intermediate, enhance the reactivity of the zinc reagent by increasing the nucleophilicity of the alkyl moiety.[45] In order to test this postulate, TBAI was used as an additive in the 1,4-addition reaction of dipentylzinc to cyclohexenone. Earlier experiments with this system had shown that NMP is needed as a co-solvent for the addition to take place.[46] In THF no reaction occurs. However, by adding TBAI (1 equiv) the addition reaction proceeded in the absence of a co-solvent, albeit in low yield (41 %) to give the desired product **8** (Scheme 21).



Scheme 21. Postulated intermediates in the 1,4-addition reaction of dipentylzinc to cyclohexenone.

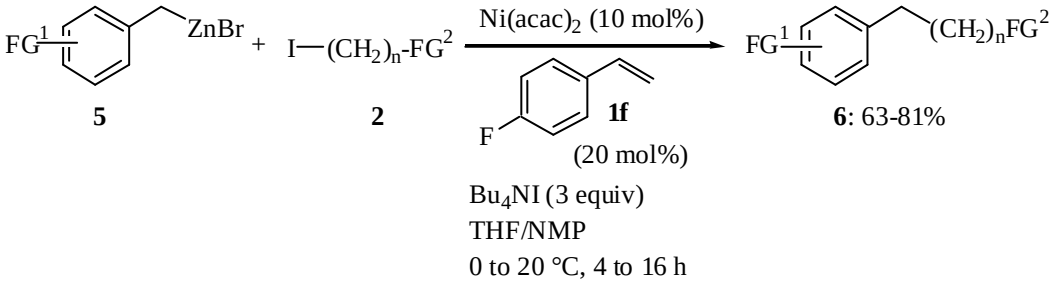
45 Investigations to elucidate the role of TBAI in the Csp^3-Csp^3 cross-coupling reaction are in progress.

46 Reddy, C. K.; Devasagayaraj, A.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 4495.

In this reaction NMP is postulated to coordinate to dipentylzinc, as illustrated in Scheme 20, thereby enhancing the nucleophilicity of the alkyl substituent, and favoring the attack of the alkyl group on the activated alkenone compound. The analogous intermediate in the TBAI-mediated addition reaction could be a zincate, thus supporting the hypothesis that these species exist as intermediates.[46]

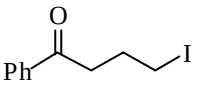
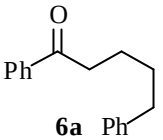
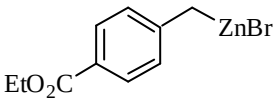
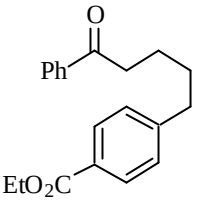
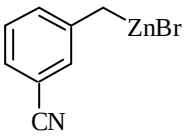
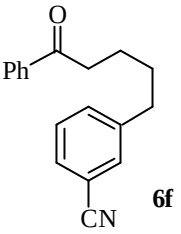
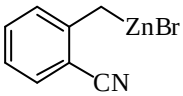
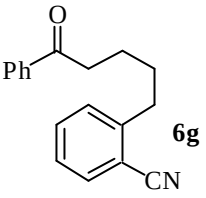
1.3 Benzylic zinc bromides in the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction

The mild introduction of a benzyl moiety into polyfunctionalized molecules is of great importance in the synthesis of biologically active substances, as well as in natural product synthesis.[47] Surprisingly, the introduction of such moieties through a transition metal-catalyzed cross-coupling reaction of functionalized benzylic zinc bromides and functionalized alkyl iodides has not previously been reported. Initial attempts to perform this type of cross-coupling reaction in the presence of a nickel catalyst and promoter system failed completely. However, in the presence of TBAI (3 equiv) and **1f** as promoter (0.2 equiv), efficient cross-coupling reactions occurred, leading to the desired Csp^3-Csp^3 cross-coupling products of type **6** in good yields (Scheme 22 and Table 3). The reaction is generally complete within a few hours between 0 and 20 °C and, importantly, tolerates a range of functional groups (ketone, ester, cyano, thioether) both in the benzylic zinc reagent and in the alkyl iodide.



Scheme 22. Nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of benzylic zinc bromides with alkyl iodides in the presence of TBAI and the promoter **1f**.

47 a) Riley, D. A; Simpkins, N. S. *Tetrahedron Lett.* **1999**, *40*, 3929; b) Trani, A.; Dallanonce, C.; Panzone, G.; Ripamonti,; F. Goldstein, B. P.; Ciabatti, R. *J. Med. Chem.* **1997**, *40*, 967.

Entry	Benzylic zinc reagent of type **5**	Alkyl iodide of type **2**	Reaction conditions (h, °C)	Product of type **6**	Yield (%)[a]
1	BnZnBr **5a**	 **2b**	16, 10	 **6a**	67
2	**5a**	Oct-I **2e**	4, 0	Oct-Bn **6b**	77
3	**5a**	$I(CH_2)_4OPiv$ **2c**	4, 0	$Bn(CH_2)_4OPiv$ **6c**	81
4	**5a**	$I(CH_2)_3SPh$ **2d**	16, rt	$Bn(CH_2)_3SPh$ **6d**	63
5	 **5b**	**2b**	16, rt	 **6e**	71
6	 **5c**	**2b**	16, 10	 **6f**	74
7	 **5d**	**2b**	24, rt	 **6g**	– [b]

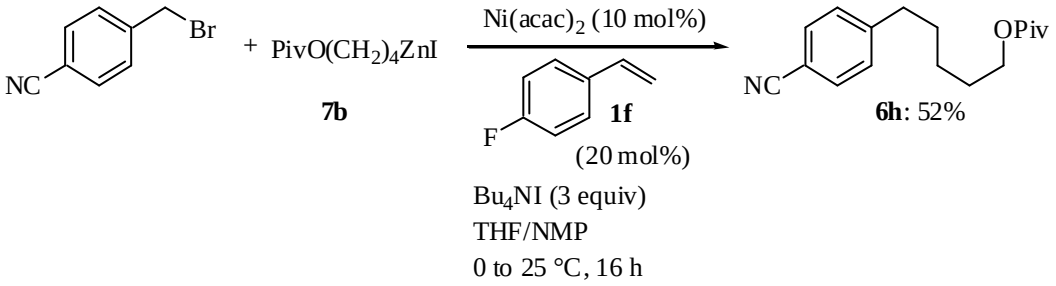
[a] Isolated yield of analytically pure product

[b] None of the desired cross-coupling product was observed, only homocoupling of the zinc reagent

Table 3. Nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of benzylic zinc bromides with primary alkyl iodides in the presence of **1f** and Bu_4NI.

The cross-coupling reaction of the *para*- and *meta*-substituted benzylic zinc bromides **5b** and **5c** with 4-iodo-1-phenyl-1-butanone **2b** led to the corresponding cross-coupling products **6e** and **6f** in good yields, whereas the more sterically hindered *ortho*-substituted benzylic zinc bromide **5d** failed to yield the desired product in the cross-coupling reaction with **2b** (entry 7).

On the other hand, the opposite reaction, namely the cross-coupling of a functionalized alkylzinc iodide with a functionalized benzylic bromide, is less general and often leads to extensive formation of the homocoupling product of the benzylic bromide moiety. When *p*-cyanobenzyl bromide undergoes nickel-catalyzed cross-coupling with the alkylzinc iodide **2b**, only 52 % of the desired product **6h** is formed (Scheme 23).



Scheme 23. Nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of a benzylic bromide with an alkylzinc iodide in the presence of TBAI and the promoter **1f**.

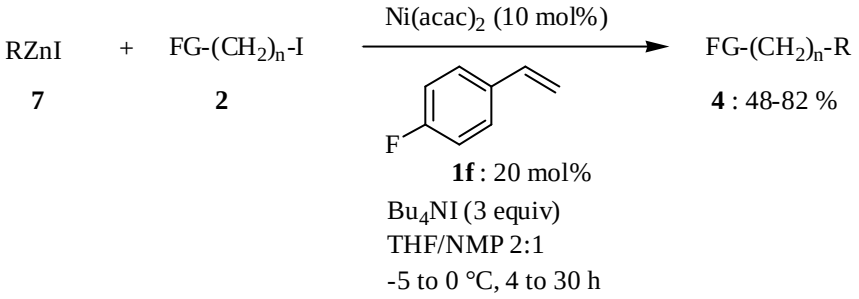
In conclusion, the Csp^3-Csp^3 cross-coupling reaction of benzylic zinc reagents with alkyl iodides is a mild method with high tolerance towards a variety of functional groups. However, it is sensitive to steric hindrance in the *ortho*-position of the zinc reagent.

1.4 Alkylzinc iodides in the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction

The cross-coupling reaction between an organometallic reagent and an organic halide is one of the most important methods for carbon-carbon bond formation.[48] With the recent development of a nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction, a very important milestone has been reached.[34a,b] By addition of a styrene promoter **1a**, which coordinates to the nickel center in order to lower the electron density on the transition metal, thus increasing the rate of the reductive elimination, a new methodology has been developed. However, although various diorganozinc reagents react well under these conditions with a range of alkyl

48 a) Diederich, F.; Stang, P. J., Eds. In *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, **1998**; b) Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis*; VCH: Weinheim, **1996**; pp 565-631.

iodides, the reaction does not proceed with alkylzinc halides. An extension of the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction to also include such organozinc reagents would significantly expand the scope of this reaction, as many highly functionalized alkylzinc halides are readily available from the corresponding alkyl iodides by insertion of zinc foil or dust.[49] After the discovery that TBAI mediates the nickel-catalyzed cross-coupling reaction of benzylic zinc bromides with alkyl iodides,[50] this reagent was also successfully employed as a mediator of the cross-coupling reaction of alkylzinc iodides with alkyl halides (Scheme 24, Table 4).

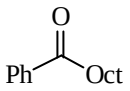
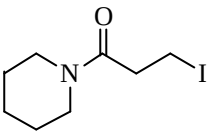
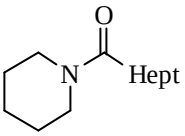
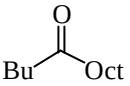
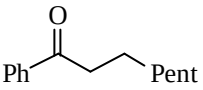
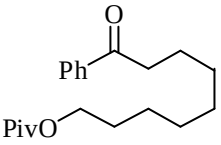


Scheme 24. Nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of alkylzinc iodides with alkyl iodides in the presence of TBAI and the promoter **1f**.

As demonstrated in Table 4, ketone and ester groups are well tolerated in the cross-coupling reaction, as is an amide function (entry 2). The presence of a functional group reduces the reactivity of the organozinc reagent through intramolecular complexation of zinc with the donor atom of the functional group. Thus, 5-pivaloyloxypentylzinc iodide (**7c**, entry 6) is less reactive than pentylzinc iodide (**7a**). However by increasing the amount of zinc reagent from three equivalents to five equivalents, the cross-coupling product **4f** can be obtained in good yield. In general, a larger excess of the alkylzinc halide allows an improvement in the chemical yields (entries 1, 2 and 6).

49 Knochel, P.; Jones, P. Eds. *Organozinc Reagents: A Practical Approach*, Oxford Press, **1999**.

50 Piber, M.; Jensen, A. E.; Rottländer, M.; Knochel. P. *Org. Lett*. **1999**, *1*, 1323.

Entry	Alkylzinc iodide	Alkyl iodide	Reaction conditions (h, °C)	Product of type **4**	Yield (%)[a]
1	n-PentZnI	$PhCO(CH_2)_3I$	16, -5		78 (82)[b]
	7a	**2b**		**4b**	
2	**7a**		30, 0		62 (71)[b]
		2c		**4c**	
3	**7a**	$BuCO(CH_2)_3I$	16, -5		52
		2a		**4a**	
4	**7a**	$EtO_2C(CH_2)_3I$	16, -5	$OctCO_2Et$	48
		2d		**4d**	
5	**7a**	$PhCOCH_2CH_2I$	4, -5		57
		2f		**4e**	
6	$PivO(CH_2)_5ZnI$	$PhCO(CH_2)_3I$	10, -5		57 (78)[b]
	7c	**2b**		**4f**	

[a] Isolated yield of analytically pure product

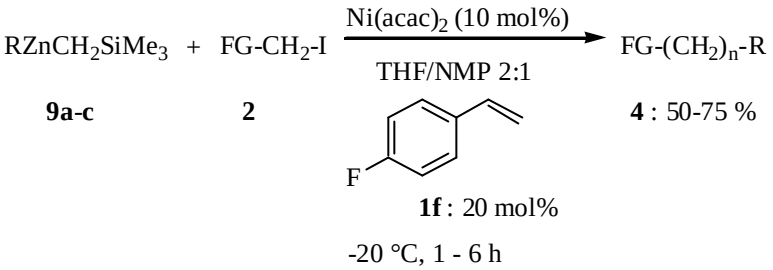
[b] Yield obtained by using 5 equiv of RZnI instead of 3 equiv

Table 4. Nickel-catalyzed cross-coupling reaction of primary alkyl iodides **2a-d**, **f** with alkylzinc iodides **7a**, **7c** in the presence of Bu_4NI (3 equiv) and **1f** (20 mol%) in THF/NMP.

1.5 Mixed dialkylzincs in the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction

The use of dialkylzincs, although they are more reactive than alkylzinc halides, has the disadvantage that only one alkyl group is transferred, leading to the waste of one alkyl

group.[51] However, the use of mixed diorganozincs bearing a non-transferable trimethylsilylmethyl group solves this problem. Thus, by using mixed diorganozinc reagents of the type $RZnCH_2SiMe_3$ (**9**),[52] the cross-coupling reaction with various alkyl iodides proceeds readily at -20 °C and does not require the use of TBAI as a reaction mediator. Only the addition of 4-fluorostyrene (**1f**) in combination with the nickel catalyst is necessary for the reaction to occur (Scheme 25 and Table 5).

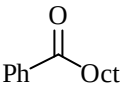
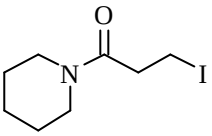
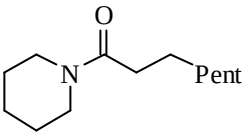
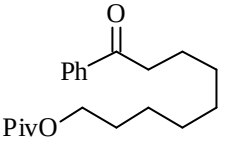
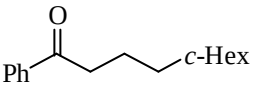


Scheme 25. Nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of mixed dialkylzincs with alkyl iodides in the presence of the promoter **1f**.

The mixed zinc reagents $RZnCH_2SiMe_3$ (RZnTMSM: **9**) were prepared by reacting the corresponding alkylzinc iodide (RZnI) with commercially available trimethylsilylmethyl lithium. The reaction of pentyl(trimethylsilylmethyl)zinc with various functionalized alkyl iodides furnished the expected cross-coupling products in 71-75 % yield (entries 1-3 of Table 5). The functionalized zinc reagent $PivO(CH_2)_5ZnTMSM$ (**9b**) reacted with 4-iodo-1-phenyl-1-butanone (**2b**) and provided the cross-coupling product **4e** in 50 % yield. In this case, the cross-coupling product with the TMSM group (phenyl trimethylsilyl ketone) was also isolated in 21 % yield (entry 4). The secondary alkyl reagent cyclohexyl(trimethylsilyl)methyl zinc (**9c**) reacted smoothly with **2b**, affording the coupling product **4h** in 65 % yield (entry 5).

51 a) Montgomery, J. *Acc. Chem. Res*. **2000**, *33*, 467; b) ref 8; c) Knochel, P.; Jones, P. Eds. *Organozinc Reagents: A Practical Approach*, Oxford Press, **1999**.

52 a) ref 13b b) Jones, P.; Reddy, K. C.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471; c) Jones, P.; Knochel, P. *J. Chem. Soc., Perkins Trans 1*, **1997**, 3117.

Entry	Zinc reagent	Alkyl iodide	Product of type **4**	Yield (%)[a]
1	*n*-PentZnTMSM	$PhCO(CH_2)_3I$		74
	9a	**2b**	**4b**	
2	**9a**			71
		2c	**4c**	
3	**9a**	$PhS(CH_2)_3I$	PhS-Oct	75
		2g	**4g**	
4	$PivO(CH_2)_5ZnTMSM$	**2b**		50[b]
	9b		**4e**	
5	*c*-HexZnTMSM	**2b**		65
	9c		**4h**	

[a] Isolated yield of analytically pure product

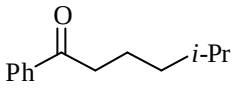
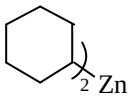
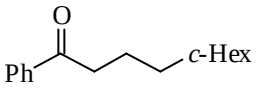
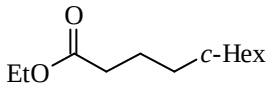
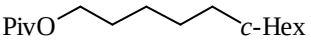
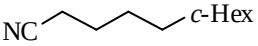
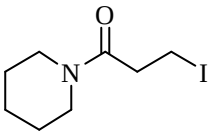
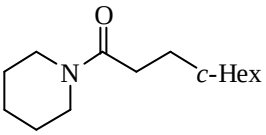
[b] 4-Trimethylsilylbutyl phenyl ketone was also isolated in 21 % yield

Table 5. Nickel-catalyzed cross-coupling reaction of mixed alkyl(TMSM)zincs **8a-c** with alkyl iodides in the presence of **1f** (20 mol%) in THF/NMP.

1.6 Secondary alkylzinc reagents in the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction

The nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of secondary alkylzinc reagents has only been examined sporadically.[34b] The above result in the cross-coupling reaction using a mixed dialkylzinc reagent (Table 5, entry 5), led us to examine in more detail the reaction of secondary dialkylzincs with alkyl iodides. With these reactive organozinc reagents, a fast cross-coupling reaction occurs at -30 °C (16 h), furnishing the products **4h-m** in 56–73 %

yield. Due to the higher reactivity of secondary dialkylzincs compared to primary or secondary alkylzinc iodides, the use of TBAI as an additive is unnecessary (Table 6).

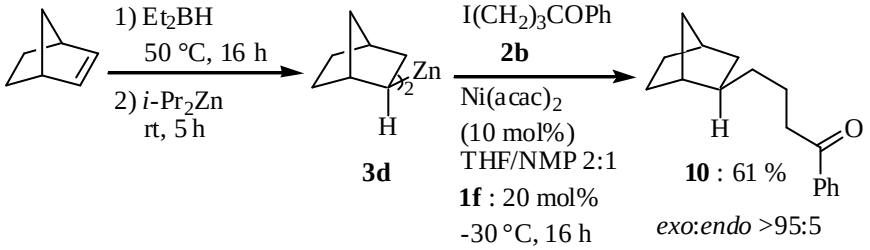
Entry	Zinc reagent	Alkyl iodide	Product of type **4**	Yield (%)[a]
1	*i*-Pr_2Zn	$PhCO(CH_2)_3I$		63
	3b	**2b**	**4i**	
2		**2b**		69
	3c		**4h**	
3	**3c**	$EtO_2C(CH_2)_3I$		61
		2d	**4j**	
4	**3c**	$PivO(CH_2)_5I$		56
		2h	**4k**	
5	**3c**	$NC(CH_2)_4I$		67
		2i	**4l**	
6	**3c**			73
		2c	**4m**	

[a] Isolated yield of analytically pure product

Table 6. Nickel-catalyzed cross-coupling reaction of secondary dialkylzincs **3b** and **3c** with alkyl iodides in the presence of **1f** (20 mol%) in THF/NMP.

Interestingly, di-*exo*-2-norbonylzinc **3d**, obtained by hydroboration of norbornene with Et_2BH and subsequent boron-zinc exchange[15b] using *i*-Pr_2Zn, reacted with the iodoketone **2b** to provide the diastereomerically enriched ketone **10** (>95:5) in 61 % yield (Scheme 26), thus

demonstrating that the nickel-catalyzed cross-coupling reaction proceeds with high retention of configuration at the zincated carbon of the secondary zinc reagent.[53]

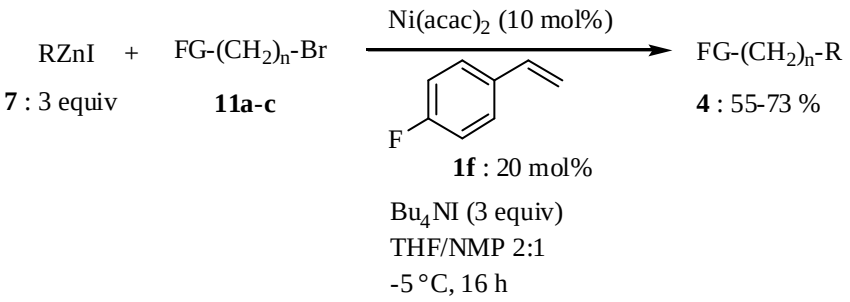


Scheme 26. Nickel-catalyzed cross-coupling reaction of a configurationally stable dialkylzinc reagent **3d** with alkyl iodide **2b** in the presence of TBAI and promoter **1f**.

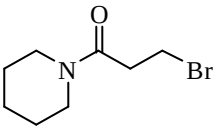
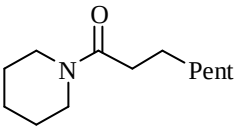
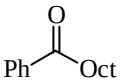
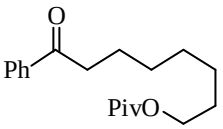
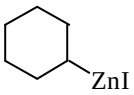
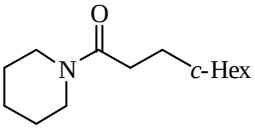
1.7 Alkyl bromides in the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction

To expand the utility of the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction, initial trials have been performed to determine the reactivity of alkyl bromides of type **11**. Although this type of electrophile has the advantage of being less costly compared to its iodide counterpart, its reactivity is also slightly lower, leading to less general applicability in cross-coupling reactions. In the presence of TBAI (3 equiv) the cross-coupling reaction takes place furnishing the desired product, either with dialkylzincs like $Pent_2Zn$ (entry 1 of Table 7), alkylzinc iodides like pentylzinc iodide (**7a**; entries 2 and 3) or the functionalized alkylzinc iodide reagent 4-pivaloyloxy(butyl)zinc iodide (**7b**; entry 4). Finally, the use of secondary alkylzinc iodide like *c*-HexZnI (**7d**) in the reaction with alkyl bromide **11b** led to the product **4m** in 63 % yield (Scheme 27 and Table 7).

53 a) Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 2748; b) Boudier, A.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 687; c) ref 15d.



Scheme 27. Nickel-catalyzed cross-coupling reaction of alkylzinc reagents with alkyl bromides in the presence of **1f** (20 mol%) and TBAI (3 equiv) in THF/NMP.

Entry	Zinc reagent	Alkyl bromide	Product of type **4**	Yield (%)[a]
1	*n*-$Pent_2Zn$[b]	$EtO_2C(CH_2)_3Br$	$OctCO_2Et$	55
	3a	**11a**	**4d**	
2	*n*-PentZnI			69
	7a	**11b**	**4c**	
3	**7a**	$PhCO(CH_2)_3Br$		70
		11c	**4b**	
4	$PivO(CH_2)_4ZnI$	**11c**		73
	7b		**4n**	
5		**11b**		63
	7d		**4m**	

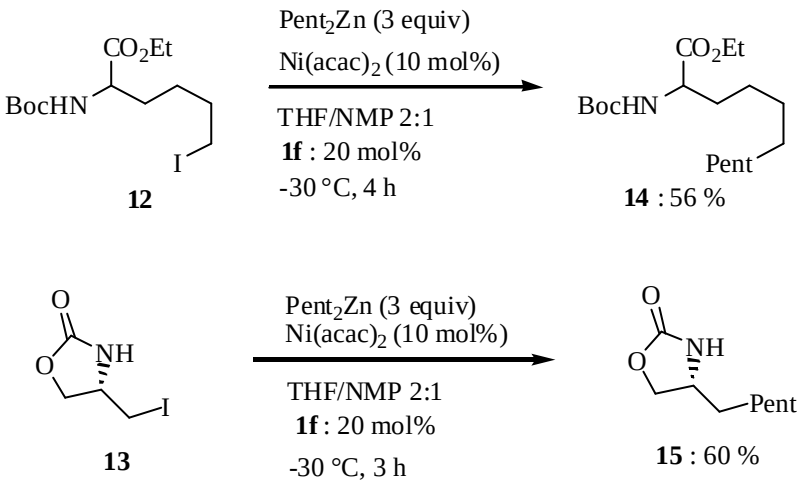
[a]Isolated yield of analytically pure product

[b]Reaction temperature: -25 °C, Bu_4NI was omitted

Table 7. Nickel-catalyzed cross-coupling of functionalized primary alkyl bromides with various zinc organometallics in the presence of TBAI (3 equiv) and **1f** (20 mol%) in THF/NMP.

1.8 Amino acid derivatives in the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction

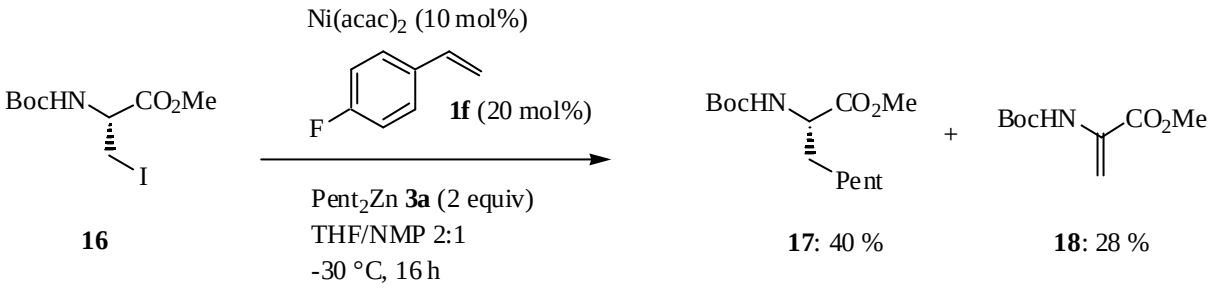
In order to demonstrate the high tolerance of this nickel-catalyzed cross-coupling reaction towards base- and nucleophile-sensitive functional groups, the above reaction conditions were applied to alkyl iodides bearing an amino functionality with an unprotected NH group. Thus, the reaction of $Pent_2Zn$ with the amino acid derivative **12** and the oxazolidinone **13**[54] provided, under the standard reaction conditions, the expected products **14** and **15** respectively in 56 % and 60 % yield (Scheme 28).



Scheme 28. Nickel-catalyzed cross-coupling reactions of amino acid derivatives with dialkylzincs in the presence of promoter **1f** (20 mol%).

However, in short chain amino acid derivatives like **16**, significant deprotonation took place, with subsequent elimination leading to the desired cross-coupling product **17** in just 40 % yield, along with 28 % of the elimination product **18** (Scheme 29).

54 Sibi, M. P.; Rutherford, D.; Sharma, R. *Perkins Trans. 1* **1994**, 1675.



16 **17**: 40 % **18**: 28 %

Scheme 29. Nickel-catalyzed cross-coupling reaction of a short chain amino acid derivative with $Pent_2Zn$ in the presence of the promoter **1f**.

1.9 The nickel-catalyzed Csp^3-Csp^2 cross-coupling reaction on a larger scale

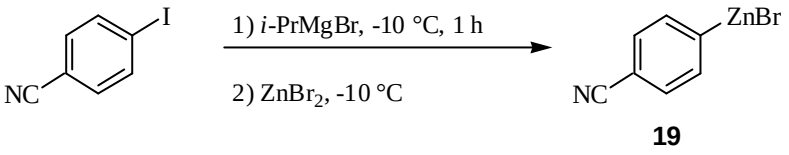
Cross-coupling reactions are receiving increased attention not only from university research laboratories, but from industrial laboratories as well.[55] It was therefore of interest to verify the suitability of such reactions for scaling up, as the normal scale used in the research laboratory is just 1-3 mmol. The test reaction for scaling up was sampled from a recently developed Csp^3-Csp^2 cross-coupling reaction protocol, coupling arylzinc bromides with alkyl iodides in the presence of a nickel catalyst and a commercially available styrene promoter (**1f**).[8] As in the case of the Csp^3-Csp^3 cross-coupling reaction, the role of 4-fluorostyrene is to reduce the electron density on the nickel intermediate [(Ar)Ni(Alkyl)] by coordination to the nickel center, thereby favoring the reductive elimination furnishing the aryl-alkyl product. The mild conditions under which the reaction is performed allows the presence of a broad range of functional groups such as ester, cyano, amide and halogen functionalities.[8]

Functionalized arylzinc reagents are best prepared either starting from an aryllithium obtained by halogen-lithium exchange, followed by a low-temperature (-80 °C) transmetallation[56] with $ZnBr_2$, or by performing an iodine-magnesium exchange reaction then transmetallating with $ZnBr_2$. The latter reaction tolerates the presence of functional groups at temperatures up to -10

55 Herrinton, P. M.; Owen, C. E.; Gage, J. R. *Org. Process Res. Dev*. **2001**, *5*, 80.

56 Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc*. **1992**, *114*, 3983.

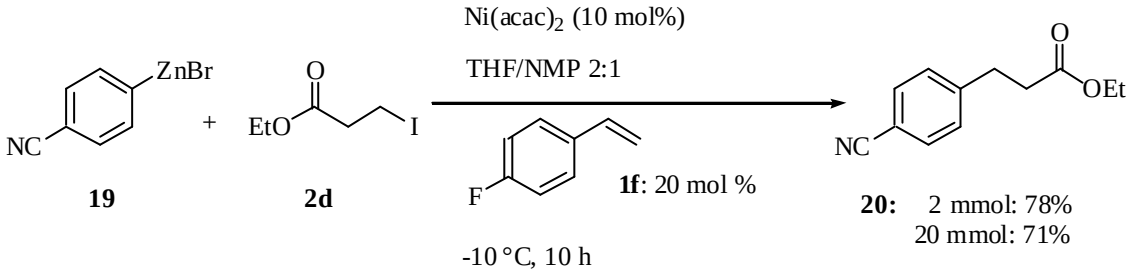
°C and is more convenient for industrial applications,[57] as one of the limitations of the industrial laboratory is to effectively reach temperatures below -15 °C (Scheme 30).



19

Scheme 30. Synthesis of an arylzinc bromide *via* an iodine-magnesium exchange at -10 °C and subsequent transmetallation with zinc bromide.

One of the features which is of key importance for a successful cross-coupling reaction, is the concentration of the reagents. Typically, a low concentration leads to prolonged reaction times and in turn extensive formation of unwanted side products. The optimum concentration of the zinc reagent was found to be 2.0-2.5 M. Arylzinc bromides in general are stable at rt, and can be concentrated to the desired concentration *in vacuo*. As illustrated in Scheme 31, the cross-coupling reaction can be scaled up from a 2 to a 20 mmol scale without significant loss of chemical yield.



19 **2d** **1f**: 20 mol %

20: 2 mmol: 78%
20 mmol: 71%

Scheme 31. Nickel-catalyzed Csp^3-Csp^2 cross-coupling reaction of an arylzinc bromide with an alkyl iodide.

Nickel salts are undesirable catalysts in the pharmaceutical and cosmetic industry due to their allergenic properties. An alternative palladium-based catalytic system was therefore sought for application in the Csp^3-Csp^3 cross-coupling reaction. However, all the palladium catalytic systems tested led to unfavorable ratios between the desired cross-coupling product and an

57 a) ref 10a; b) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett*. **1999**, *40*, 7449.

unwanted iodine-zinc exchange. The nickel catalytic system thus remains the only efficient method for transition metal-catalyzed cross-coupling of two Csp^3 centers. In order to determine a superior method for eliminating or minimizing the nickel content of the cross-coupling products, these were analyzed by a standard addition method on an atom absorption apparatus (Perkin-Elmer 1100B, HGA 700 graphite tube technique) after purification by flash chromatography or distillation.

- Nickel content after chromatography: 0.4 ppm
- Nickel content after distillation: 5.0 ppm

From the results, chromatography seems the better method for eliminating nickel from the cross-coupling product, with just 0.4 ppm remaining in the product. However, both means of purification give values which are below the limit value for the nickel content as dictated by European Pharmacopoeia.[58]

1.10 Summary

In summary, reaction conditions have been found for a versatile nickel-catalyzed cross-coupling reaction in the presence of an electron deficient styrene promoter, allowing for the first time:

- effective coupling of readily available functionalized alkylzinc halides and benzylic zinc bromides with functionalized alkyl iodides in the presence of TBAI
- the application of alkyl bromides in a Csp^3-Csp^3 cross-coupling reaction.

Furthermore,

- the presence of sensitive functional groups such as an amino function with an unprotected NH group is tolerated

58 a) *European Pharmacopoeia 2. ed.* **1991**, Maisonneuve S.A., France, Part V.3.2.15; b) http://www.emea.eu.int/pdfs/human/swp/444600en.pdf

- coupling of diastereomerically enriched zinc reagents proceed with high retention of configuration at the zincated carbon
- scaling up can be achieved without significant loss of chemical yield.

2 1,4-Phenylenediamine Derivatives in Cross-Coupling Reactions

The tolerance of heteroatoms together with a range of other functional groups is one of the many demands in the synthesis of natural compounds and pharmaceuticals. A recently developed method for the preparation of functionalized aryl- and heteroaryl magnesium reagents *via* an iodine-magnesium exchange has opened a path to a wide range of such products, as the mild exchange conditions comply with the high demands of functionality.[59] Recently, it has been reported that functionalized magnesiated aniline derivatives can be prepared and reacted with various electrophiles.[60] Since the 1,4-phenylenediamine moiety is an important building block in the cosmetic industry, the preparation and subsequent cross-coupling of 2-magnesiated-1,4-phenylenediamines is a highly desirable extension to magnesium chemistry.

2.1 1,4-Phenylenediamine protection strategies

The preparation of 2-iodo-1,4-phenylenediamine **21** proceeds in two steps from 4-nitroaniline by iodination[61] and subsequent reduction with $SnCl_2 \cdot 2H_2O$ in concentrated HCl (Scheme 32).[62]

For the protection of the two aniline functions formamidine was the protection group of choice, as it has been successfully applied to the synthesis of magnesiated aniline derivatives.[60] The protection of **21** went smoothly using dimethoxy-*N*,*N*-dimethylmethanamine in toluene to give the diformamidine derivative **24** (Scheme 33).[63]

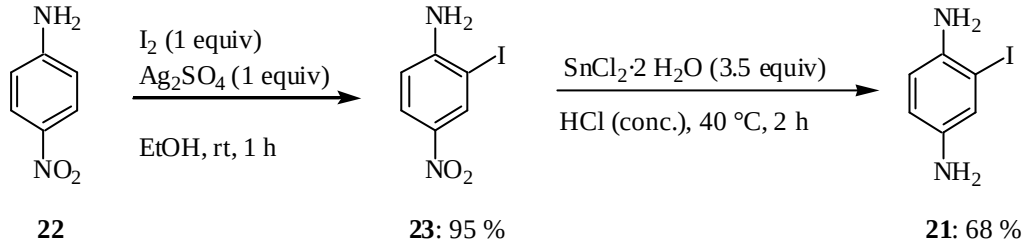
59 a) Rottländer, M; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.*, **2000**, *6*, 767**;** b) ref 10a; c) ref 57b; d) Abarbri, M.; Knochel, P. *Synlett*, **1999**, 1577; e) Avolio, S.; Malan, C.; Marek, I.; Knochel, P. *Synlett*, **1999**, 1820; f) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem. Int. Ed.*, **2000**, *39*, 2481.

60 Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett*, **2001**, 477.

61 Sy, W.-W. *Synth. Comm.*, **1992**, *22*, 3215.

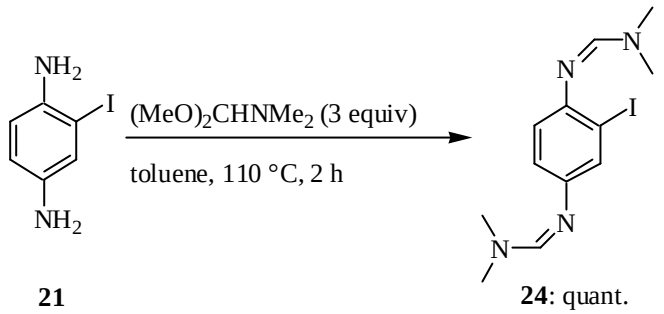
62 Nicolet, B. H.; Ray, W. L. *J. Am. Chem. Soc*., **1927**, *49*, 1801.

63 Meyers; A. I.; Elsworthy, T. R. *J.Org.Chem.* **1992**, *57*, 4732.



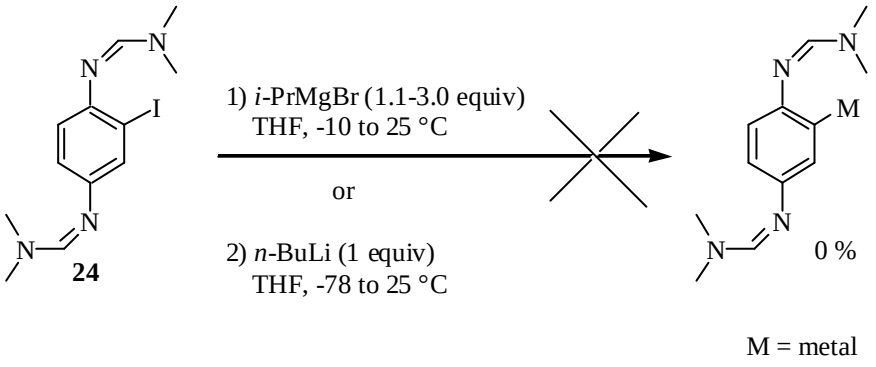
22 **23**: 95 % **21**: 68 %

Scheme 32. Two-step synthesis of 2-iodo-1,4-phenylenediamine.



21 **24**: quant.

Scheme 33. Formamidine protection of 2-iodo-1,4-phenylenediamine **21**.

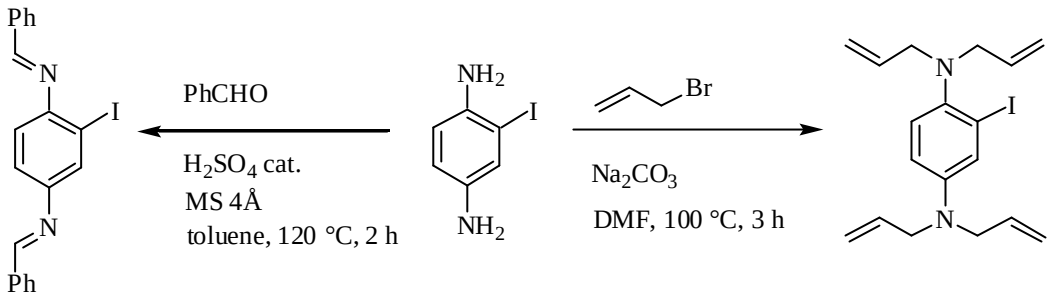


Scheme 34. Failed iodine-magnesium and iodine-lithium exchange of the 1,4-phenylenediamine derivative **24**.

Unfortunately, in the subsequent iodine-magnesium exchange reaction GC-analysis of hydrolyzed reaction aliquots indicated that the exchange had not taken place. Even an attempt at an iodine-lithium exchange failed to yield the lithiated product. The difficulty encountered with the magnesium- and lithium-iodine exchange reactions is probably due to the high electron density on the aromatic ring. In later trials using the corresponding 2-iodoaniline

derivative[64] the iodine-magnesium exchange reaction was slow and only occurred at room temperature (Scheme 34).

As an alternative strategy compound **21** was instead converted into the corresponding diimine **25** by treatment with benzaldehyde in toluene, and into the tetraallylated amine **26**, by treatment with allyl bromide (Scheme 35).[65]



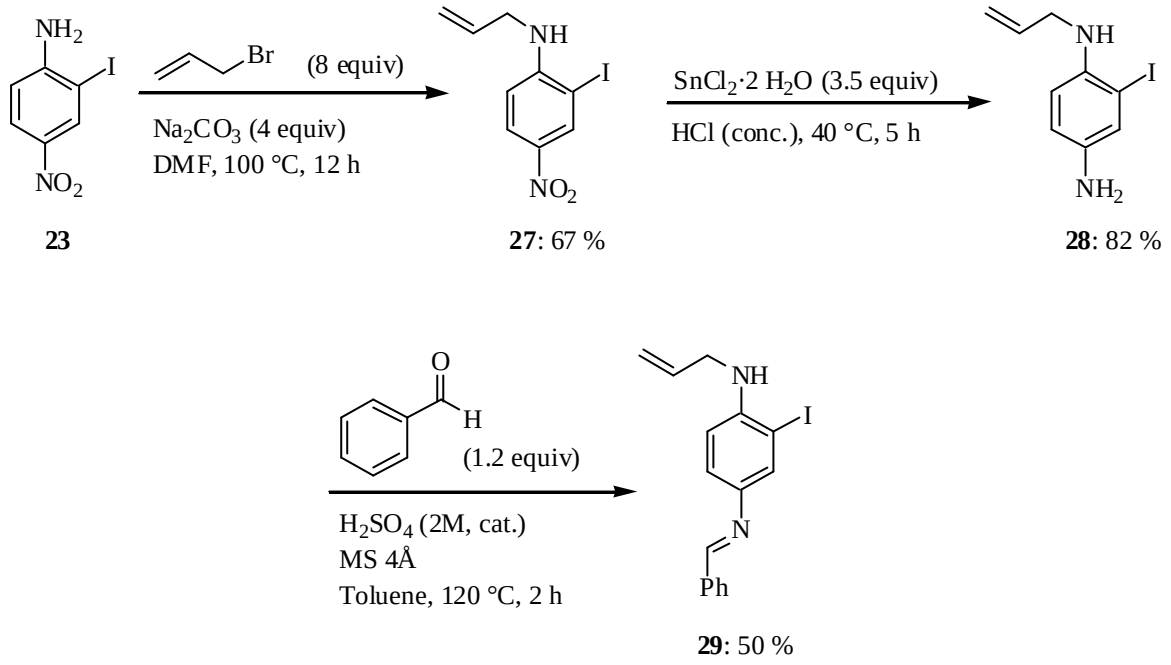
25: 79 % **21** **26**: 74 %

Scheme 35. Alternative protection strategies of 2-iodo-1,4-phenylenediamine.

In order to increase diversity in the synthesis of the phenylenediamine derivatives it would be desirable to introduce two different protecting groups, thereby enabling sequential deprotection. This would be possible by introducing the *N*,*N*-diallyl protecting group before reduction of the nitro group. However, as shown in Scheme 36 only the mono-allylated product **27** was formed. Thus, after reduction to compound **28** followed by protection with benzaldehyde, product **29** was obtained.

64 Dohle, W. *Unpublished results*.

65 Bailey, W. F.; Carson, M. W. *J. Org. Chem.*, **1998**, *63*, 9960.



23 **27**: 67 % **28**: 82 %

29: 50 %

Scheme 36. Protection strategy with two different protecting groups on 2-iodo-1,4-phenylenediamine.

2.2 Iodine-magnesium exchange on protected 1,4-phenylenediamine derivatives

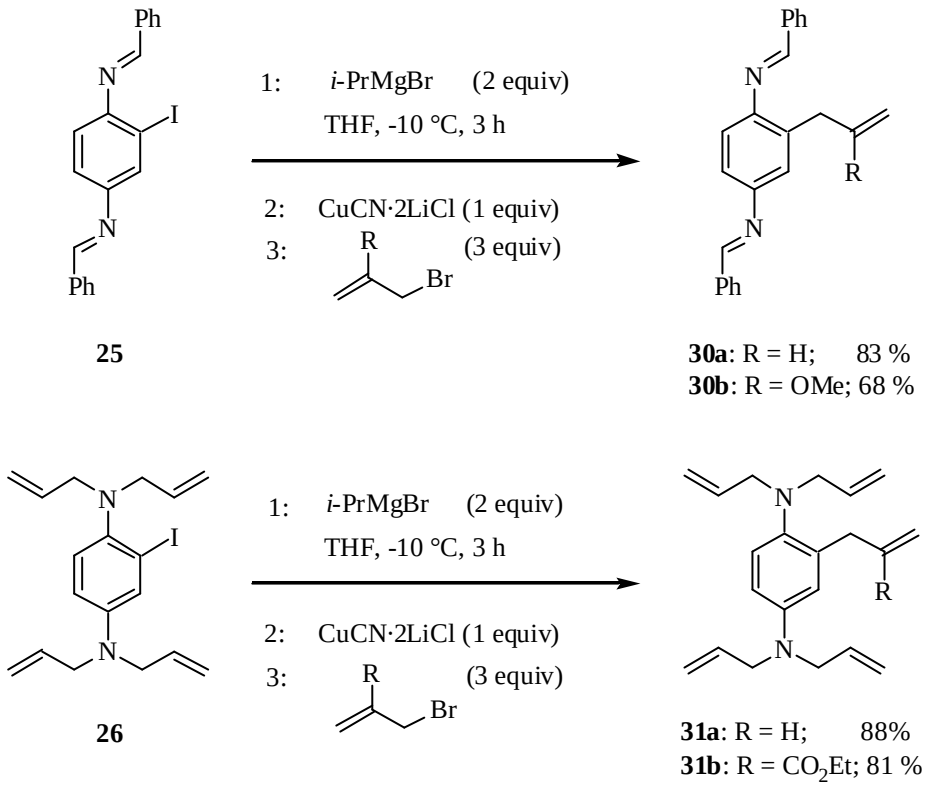
Since the magnesiated 1,4-phenylenediamine derivatives were intended as building blocks towards polyfunctionalized cross-coupling products, the exchange had to proceed preferably at -10 °C or above to be of practical use.

The iodine-magnesium exchange with the di-*N*-phenylmethyleneamine derivative **25** as well as with the di-bis-allylated compound **26** went smoothly in 3 h at -10 °C. Although two equivalents of *i*-PrMgBr were needed for the exchange to go to completion, it proceeded without attack on the protection group. After transmetallation to copper with CuCN·2LiCl,[66] a clean allylation reaction occurred with allyl bromide, 2-methoxyallyl bromide[67] or ethyl (bromomethyl)acrylate,[68] furnishing the expected products **30a-b** and **31a-b** in 68-88 % yield (Scheme 37).

66 Knochel, P.; Yeh, M. C. P.; Beck, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

67 Jacobson, R. M.; Raths, R. A.; McDonald, J. H. III *J. Org. Chem.* **1997**, *42*, 2545.

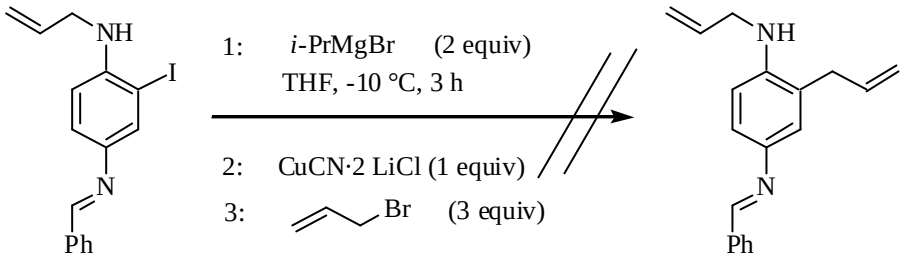
68 Villieras, J.; Rambaud, M. *Synthesis* **1982,** 924.



Scheme 37. Iodine-magnesium exchange of the 2-iodo-1,4-phenylenediamine derivatives **25** and **26** at -10 °C.

Derivative **29**, with one unprotected NH functionality, also underwent iodine-magnesium exchange in 3 h at -10 °C, followed by transmetallation to copper and subsequent allylation with allyl bromide. However, the acidic proton on nitrogen quenched the Grignard reagent and mainly the bis-allylated aniline was obtained (Scheme 38). Preliminary results on unprotected 2-iodoaniline derivatives show that the iodine-magnesium exchange and subsequent trapping with an electrophile proceed if the aniline is deprotonated with phenylmagnesium chloride prior to the exchange reaction.[69] It may, therefore, still be possible to successfully employ compound **29** for an iodine-magnesium exchange reaction.

69 Lindsay, D. M. *Unpublished results*.



29 **32**

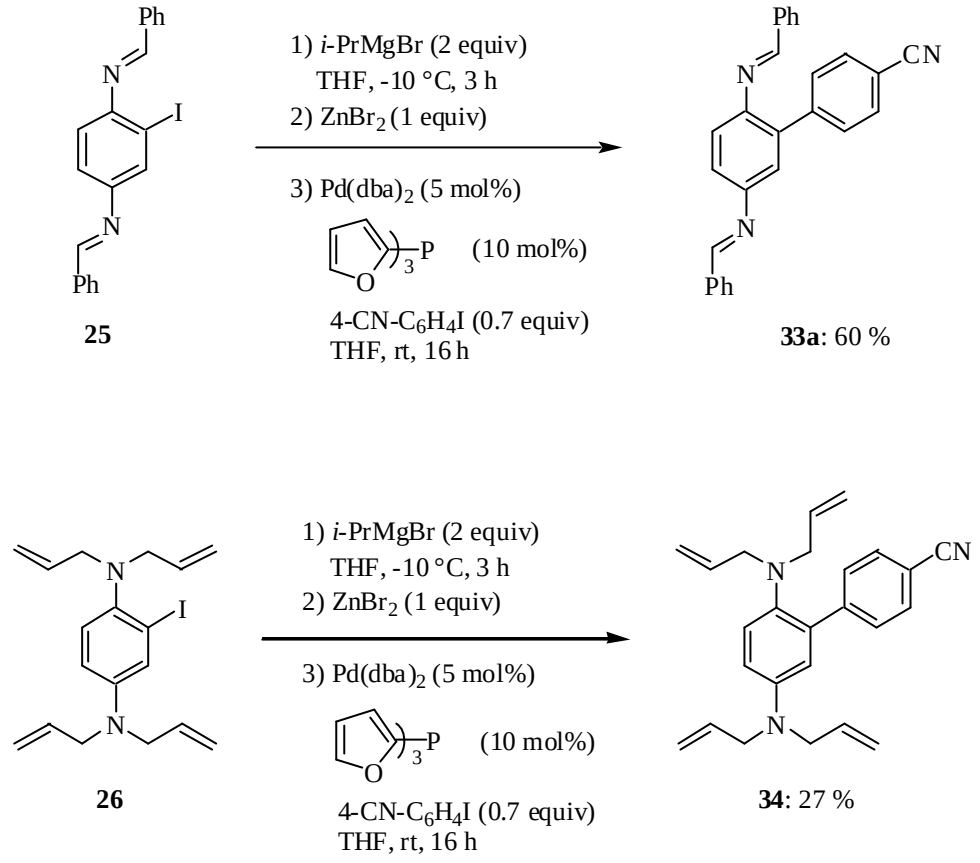
Scheme 38. Attempted iodine-magnesium exchange reaction of derivative **29**, containing a free NH-group.

2.3 Palladium-catalyzed cross-coupling reactions of aryl iodides with zincated 1,4-phenylenediamine derivatives

Having demonstrated that the 1,4-phenylenediamine Grignard reagent can be readily prepared and allylated, further investigations into the transmetallation of the intermediate arylmagnesium compounds to the corresponding organozinc reagents were carried out, with the purpose of application in palladium-catalyzed cross-coupling reactions with various aryl and heteroaryl iodides.[70]

In the case of the allylation reactions, the two symmetrically protected 2-iodo-1,4-phenylenediamine derivatives **25** and **26** led to similar yields. However, the di-*N*-benzylidene compound **25** proved to be better suited for the Negishi cross-coupling reactions, giving significantly higher yields than its di-bisallylated counterpart **26** (Scheme 39).

70 a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340; b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc*. **1980**, *102*, 3298; c) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223; d) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett*. **1986**, *27*, 955.



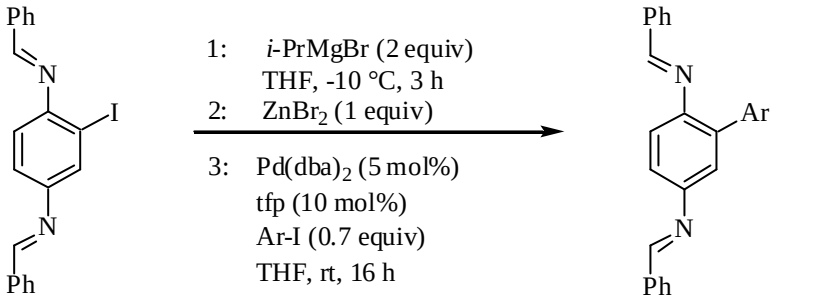
Scheme 39. Comparison of the Negishi cross-coupling reactions of zincated 1,4-phenylenediamine derivatives **25** and **26**.

Bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$)[71] was found to be the best source of palladium(0), whereas *tris*-*o*-furyl phosphine (tfp)[72] proved to be an excellent ligand for this type of cross-coupling reaction.[73] Most cross-coupling reactions were complete within 16 h at room temperature affording the expected products of type **33** in 52-79 % yield (Scheme 40 and Table 8).

71 Takahashi, Y.; Ito, T.; Sakai, S.; Ishii, Y., *J. Chem. Soc., Chem. Commun.* **1970**, 1065.

72 a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, 113, 9585; b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

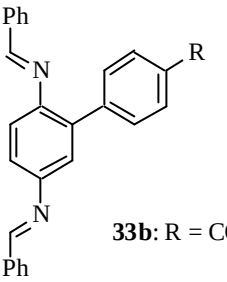
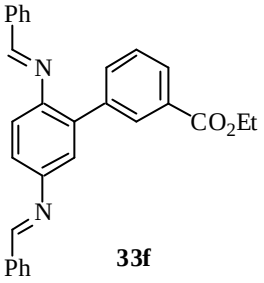
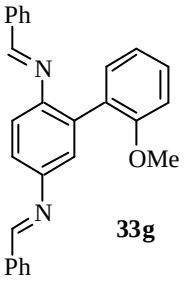
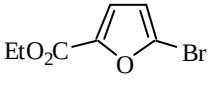
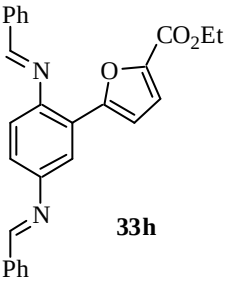
73 Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.



25 **33a** - **h**: 52 - 79 %

Scheme 40. Negishi cross-coupling reaction of 2-zincated di-*N*-benzylidene-protected 1,4-phenylenediamine.

As illustrated with the examples below, this cross-coupling reaction is tolerant towards steric effects as well as electronic ones. Both electron rich and electron poor aryl iodides give reasonable chemical yields, independent of the substitution pattern. Various *m*- or *p*-substituted aryl iodides rapidly undergo the expected cross-coupling reaction leading to the products **33a-f** in satisfactory yield (entries 1-6 of Table 8). Interestingly, the sterically more hindered *o*-methoxyiodobenzene reacted smoothly, leading to **33g** in 74 % yield (entry 7). Heterocyclic bromides undergo the coupling reaction, such as 5-bromo-2-carbethoxyfuran which furnished the heterocycle **33h** in 52 % yield (entry 8).

Entry	Aryl iodide	Product of type **33**	Yield (%)[a]
1	*p*-EtO_2C-C_6H_4I	 **33b**: R = CO_2Et	68
2	*p*-NC-C_6H_4I	**33a**: R = CN	60
3	*p*-Me-C_6H_4I	**33c**: R = Me	71
4	*p*-Cl-C_6H_4I	**33d**: R = Cl	62
5	*p*-MeO-C_6H_4I	**33e**: R = OMe	79
6	*m*-EtO_2C-C_6H_4I	 **33f**	62
7	*o*-MeO-C_6H_4I	 **33g**	74
8		 **33h**	52

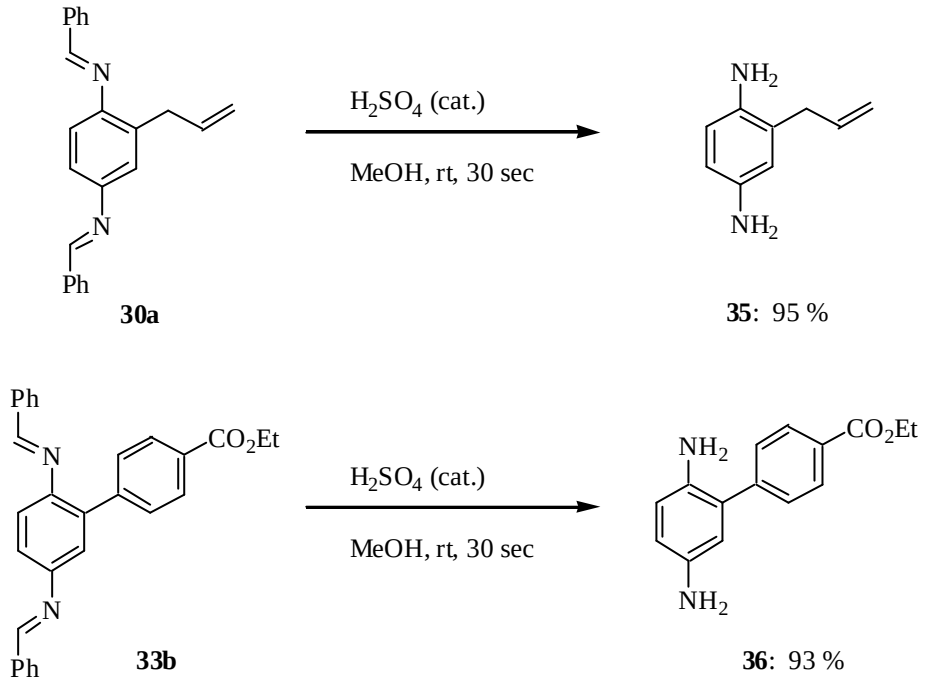
[a]Isolated yield of analytically pure product

Table 8. Negishi cross-coupling reaction of zincated 1,4-phenylenediamine derivatives with aryl iodides.

2.4 1,4-Phenylenediamine deprotection methods

After the successful cross-coupling or allylation reactions the resulting protected 1,4-phenylenediamine derivatives must be efficiently deprotected in order to obtain the desired polyfunctional products.

Protected 1,4-phenylenediamines of type **30** and **33** can be converted easily into the free 1,4-phenylenediamines by treatment with concentrated sulfuric acid in methanol (rt, 0.5 min)[74] leading to products of type **35** and **36** in 93-95 % yield (Scheme 41).

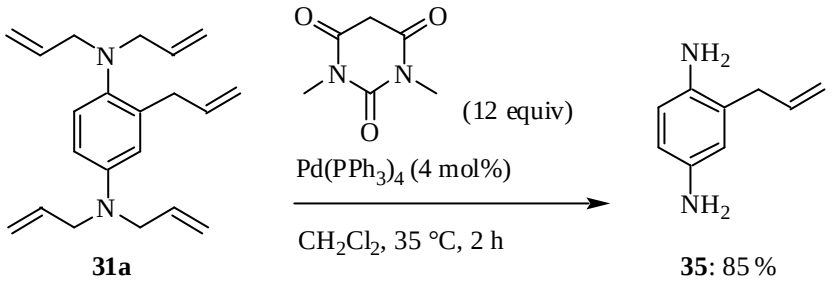


Scheme 41. Deprotection of di-*N*-benzylidene-protected 1,4-phenylenediamine derivatives.

The deprotection of the di-bisallylated 1,4-phenylenediamine derivatives of type **31** or **34** to the free 1,4-phenylenediamines was performed by *N*,*N*-dimethylbarbituric acid in the presence of a palladium catalyst (Scheme 42).[75]

74 Nozoe, T.; Okai, H.; Wakabayashi, H.; Ishikawa, S. *Bull. Chem. Soc. Jpn* **1989**, *62*, 2307.

75 Garro-Helion, F.; Merzouk, A.; Guibé, F. *J.Org.Chem.* **1993**, *58*, 6109-6113.



Scheme 42. Deprotection of di-bisallylated-protected 1,4-phenylenediamine derivatives.

2.5 Summary

In summary, an effective and high yielding protection-deprotection protocol has been developed for the iodine-magnesium exchange reaction of 2-iodo-1,4-phenylenediamine. The corresponding 2-magnesiated-1,4-phenylenediamine derivatives can be transmetallated either to copper:

- a subsequent allylation reaction furnishes the allylated products in good yield,

or to the corresponding zinc reagents:

- a subsequent smooth palladium-catalyzed cross-coupling reaction with a range aryl iodides furnishes the polyfunctionalized cross-coupling products in good yield,
- this cross-coupling reaction is highly tolerant towards electronic as well as steric effects.

3 Synthesis of Heterocyclic Compounds from 2-Iodoaniline Derivatives

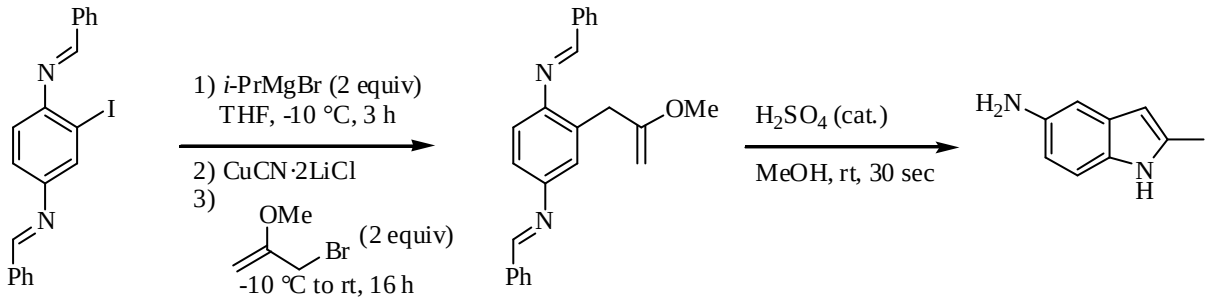
The preparation of polyfunctionalized heterocycles by using multi-coupling reagents[76] as versatile scaffolds has recently been extensively studied.[77] The application of such scaffolds in cross-coupling reactions allows the synthesis of a broad range of diversely functionalized heterocycles. Aminated arylmagnesium compounds, prepared by an iodine-magnesium exchange, can in this way function as key intermediates in the preparation of nitrogen-containing heterocycles.[60]

3.1 Synthesis of 2-methyl-1*H*-indole-5-amine

As an initial attempt at the synthesis of a nitrogen-containing heterocycle, the allylation product **30b**, mentioned in the previous chapter, was deprotected through treatment with dilute H_2SO_4 in MeOH (25 °C, 0.5 min). A subsequent spontaneous cyclization furnished the 5-amino-2-methyl-indole **37** in 71 % yield (Scheme 43).

76 a) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261; b) Achyutha Rao, S.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 4591; c) Rottländer, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, *61*, 5743.

77 a) Bienayme, H.; Bouzid, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2234; b) Gauzy, L.; Le Merrer, Y.; Depezay, J.-C.; Clerc, F.; Mignani, S. *Tetrahedron Lett.* **1999**, *40*, 6005; c) Lowik, D. W. P. M.; Lowe, C. R. *Tetrahedron Lett.* **2000**, *41*, 1837; d) Bienayme, H.; Ancel, J.-E.; Meilland, P.; Simonato, J.-P. *Tetrahedron Lett.* **2000**, *41*, 3339; e) Sun, X.; Janvier, P.; Zhao, G.; Bienayme, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877; f) Tietze, L. F.; Evers, H.; Topken, E. *Angew. Chem. Int. Ed.* **2001**, *40*, 903; g) Abrous, L.; Hynes, J.; Friedrich, S. R.; Smith III, A. B.; Hirschmann, R. *Org. Lett.* **2001**, *3*, 1089; h) Arrayas, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 6185; i) Neumann, H.; Wangelin, A. J. v.; Gördes, D.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2001**, *123*, 8398.



25 **30b**: 68 % **37**: 71 %

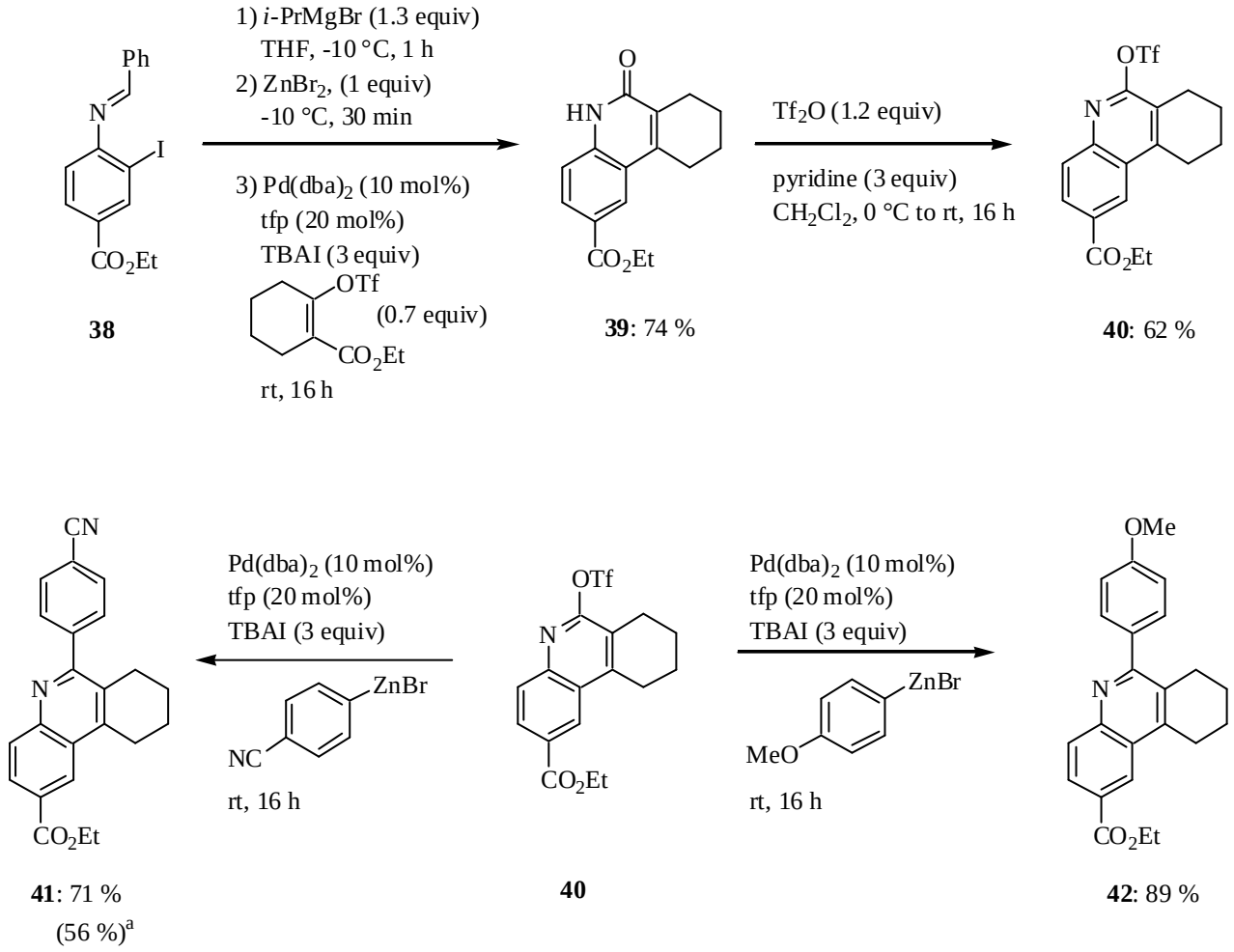
Scheme 43. Indole synthesis *via* spontaneous cyclization reaction of 1,4-phenylenediamine derivative after deprotection with H_2SO_4 in methanol.

3.2 Synthesis of quinoline derivatives

After this preliminary result, demonstrating that certain 1,4-phenylenediamine derivatives readily undergo cyclization to form an indole, a range of multi-coupling reagents were applied in the cross-coupling reactions of more stable and more easily obtainable *N*-protected aniline derivatives to extend this methodology to the synthesis of further nitrogen-containing heterocycles.

Ethyl 3-iodo-(phenylmethylidene-amino)benzoate **38** can be used for the preparation of quinolines. Thus, after the conversion of the iodoaniline derivative *via* sequential iodine-magnesium exchange and transmetallation with zinc bromide, into the corresponding zinc reagent, the zincated iodoaniline derivative participated successfully in a Negishi cross-coupling reaction with ethyl 2-trifluorosulfonyloxy-1-cyclohexene-1-carboxylate (0.7 equiv) in the presence of TBAI (3 equiv), furnishing the heterocycle **39** in 74 % yield. The amide functionality of **39** was converted into the corresponding triflate by reaction with Tf_2O and pyridine in CH_2Cl_2 to afford **40** in 62 % yield. Subsequent palladium-catalyzed cross-coupling with functionalized arylzinc bromides produced the polyfunctional quinolines **41** and **42** in 71 % and 89 % yield respectively. Interestingly, the yield of this cross-coupling reaction is greatly improved by adding TBAI. In the absence of this additive the yield of **41** is just 56 %.[41a,51] The enhanced reactivity is proposed to be due to a better stabilization of the

palladium catalyst as a palladate species, thereby facilitating oxidative addition into the carbon-triflate bond (Scheme 44).[78]



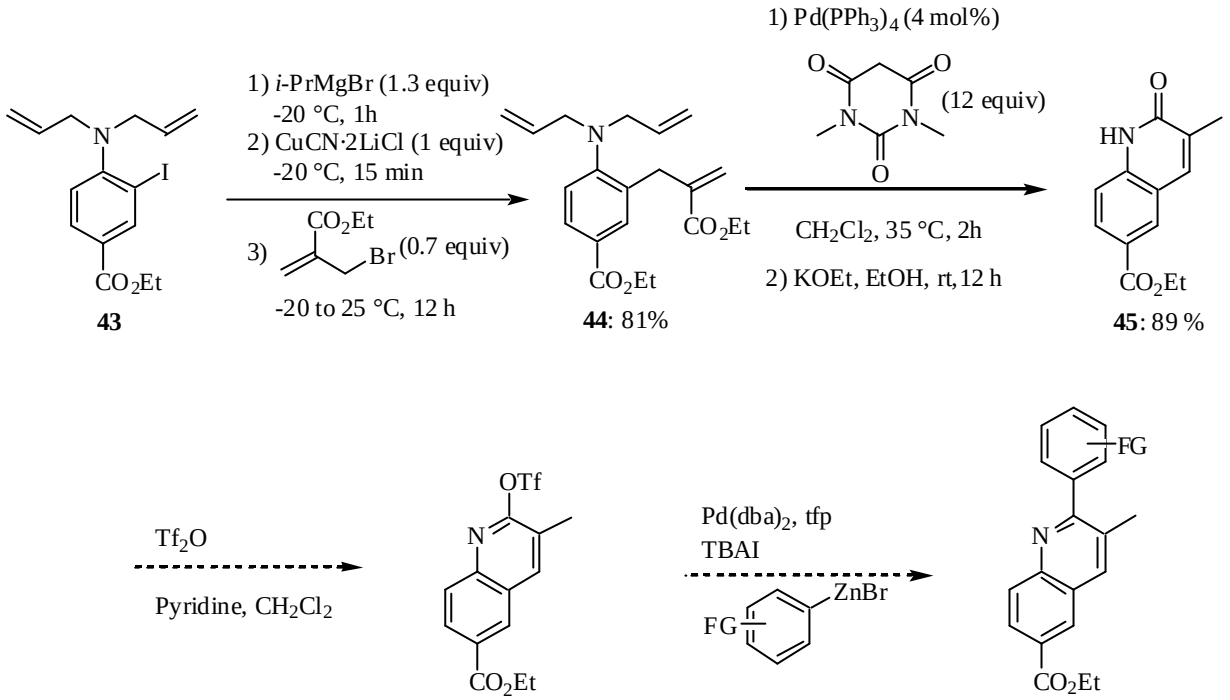
[a] Yield in the absence of TBAI

Scheme 44. Quinoline synthesis *via* a magnesiated aniline derivative.

Ethyl 4-(diallylamino)-3-iodobenzoate **43** could also be applied in the preparation of quinolines. After transmetallation of the magnesiated species with CuCN·2LiCl to the corresponding copper reagent and subsequent allylation with ethyl 2-(bromomethyl)acrylate, the expected allylation product **44** was obtained in good yield (81 %). Palladium-catalyzed deprotection furnished the free aniline derivative, however no spontaneous cyclization was

78 a) Amatore, C.; Azzabi, M.; Juland, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375; b) Amatore, C.; Juland, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

observed, and the cyclization product **45** was only obtained after deprotonation of the aniline function with KOEt in ethanol at rt (Scheme 45). The final two steps in the synthesis of polyfunctional quinoline derivatives should proceed analogously to the two last steps in Scheme 44.



Scheme 45. Proposed quinoline synthesis from aniline derivative **43**.

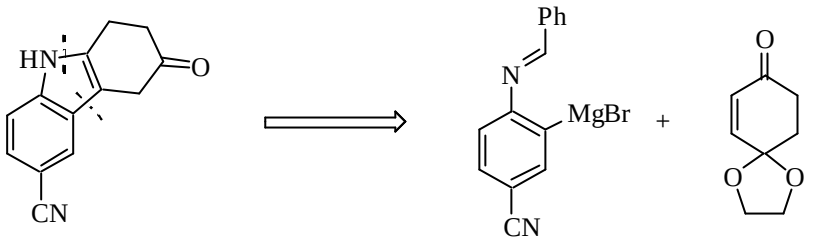
3.3 Attempted synthesis of 2,3,4,9-tetrahydro-3-oxo-1*H*-carbazole-6-carbonitrile

The anti-tumor drug **46** was adopted as a synthetic challenge for the magnesiated aniline chemistry. Retrosynthetically, the drug could be broken down into two segments as illustrated in Scheme 46. Thus, starting from a magnesiated aniline derivative and 1,4-dioxaspiro[4.5]dec-6-en-8-one,[79] transmetallation to copper with subsequent 1,4-addition to the electrophile under activation with TMS-Cl furnished the addition product **48** in 56 % yield.[80] However, traditional acidic conditions (e.g. dilute H_2SO_4 in methanol at rt, 2 M HCl/THF at rt to 60 °C) surprisingly failed to deprotect the aniline or the ketone functionality,

79 Kerr, W. J.; McLaughlin, M.; Morrison, A. J.; Pauson, P. L. *Org. Lett.* **2001**, *3*, 2945.

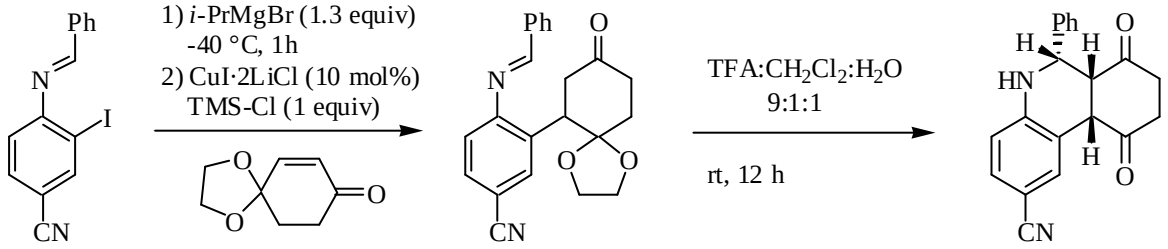
80 Varchi, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Tetrahedron* **2000**, 56, 2727.

each time leaving the starting material **48** untouched. After mild methods had failed, the more harsh conditions of trifluoroacetic acid in aqueous CH_2Cl_2 were tried. Although the aniline derivative **48** was partially deprotected using this procedure, an undesired heterocycle **49** was obtained through activation of the position a to the unprotected ketone, and this in reasonable yield (72 %) as a single stereoisomer (Scheme 47).



46

Scheme 46. By retrosynthetic analysis a magnesiated aniline species was proposed as a possible synthetic precursor to the anti-tumor drug **46**.



47 **48**: 56 % **49**: 72 %

Scheme 47. Attempted synthesis of **46**, thwarted by the use of an unsuitable protection group.

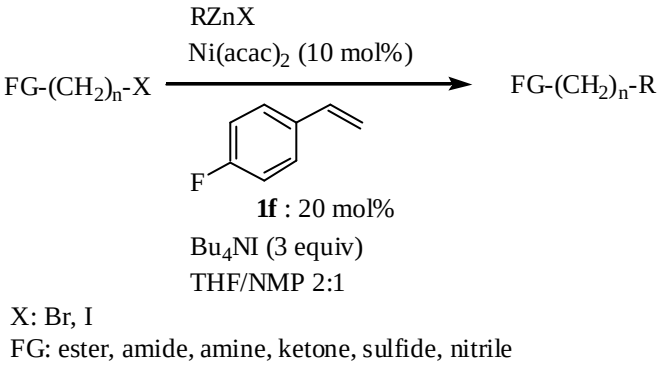
3.4 Summary

It has been demonstrated that magnesiated aniline derivatives, obtained from readily available *ortho*-iodoaniline derivatives, can act as versatile intermediates in the synthesis of a range of highly functionalized nitrogen-containing heterocycles such as indoles and quinolines, both of which are considered to be of great interest due to their potential pharmaceutical properties.

4 Summary and Outlook

This work has been focused on the application of organozinc reagents in transition metal-catalyzed cross-coupling reactions.

In the first part a protocol for a versatile nickel-catalyzed cross-coupling reaction of functionalized alkylzinc iodides or functionalized benzylic zinc bromides with alkyl iodides in the presence of a promoter **1f** and tetrabutylammonium iodide (TBAI) was developed. This is the first report of a transition metal-catalyzed Csp^3-Csp^3 cross-coupling reaction performed with these types of organometallic species (Scheme 47).



Scheme 47. General equation for the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction of alkylzinc iodides or benzylic zinc bromides with alkyl halides.

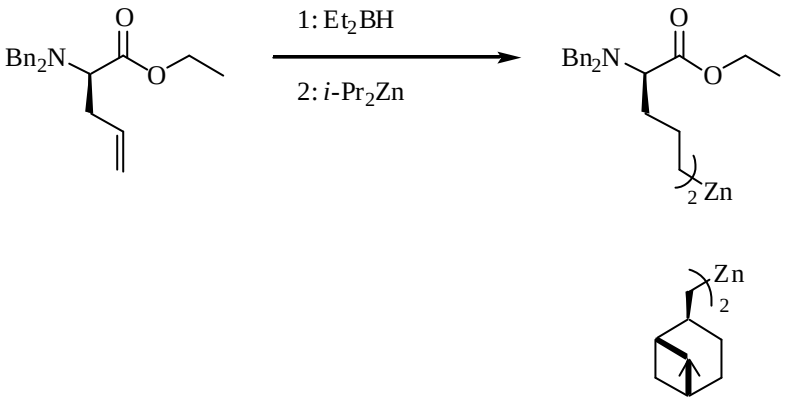
The styrene promoter plays an important role in the reductive elimination from the intermediate dialkylnickel species [R^1-Ni-R^2]. By coordination to the nickel center, the styrene lowers the electron density on the metal and thereby facilitates the formation of the cross-coupling product R^1-R^2.

The nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction has shown high tolerance towards a range of functional groups (ester, amide, ketone, sulfide, nitrile) and even tolerates a free NH-group. Furthermore, it has been demonstrated that the zincated carbon of a secondary zinc reagent is configurationally stable in the cross-coupling reaction.

Although the exact role of the TBAI has not yet been elucidated, it seems evident that free iodide plays a key role in the mediation of cross-coupling reactions involving benzylic zinc bromides or alkylzinc iodides.

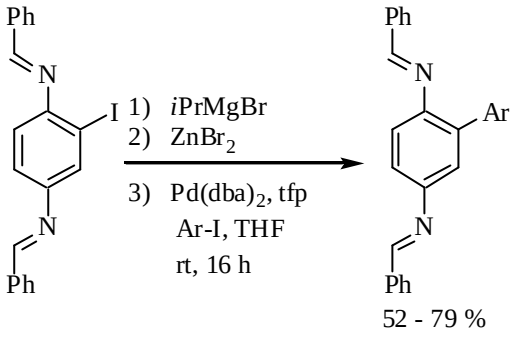
In order to further develop this unique reaction, elucidation of the role of the TBAI would be essential. This could be achieved either through crystal structures of the organozinc reagent in the presence of TBAI and/or in the presence of TBAI and the nickel catalyst or, for example, through electrochemical studies to determine the chemical potentials of the metals involved.

The mild reaction conditions would make this reaction ideal for further use with highly functionalized substrates such as amino acids, for example in connection with cyclic or open chain chiral zinc reagents (Scheme 48).



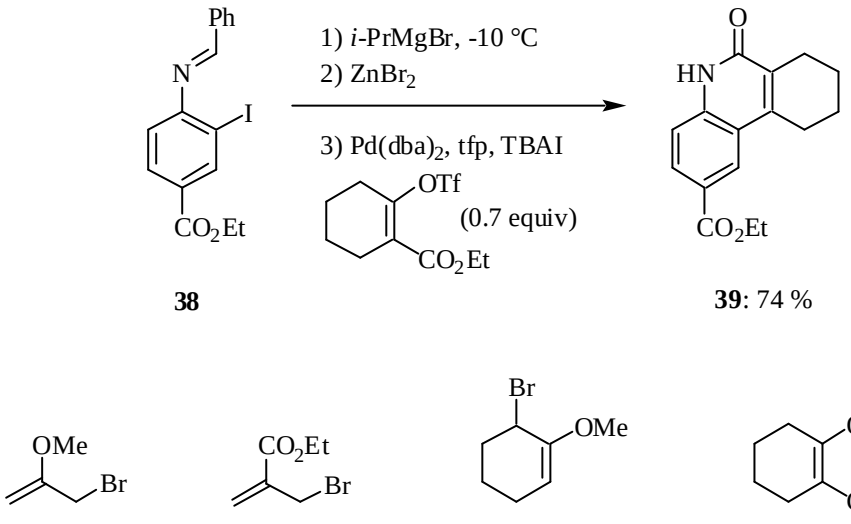
Scheme 48. Possible chiral organozinc reagents, obtained *via* a hydroboration, boron-zinc exchange sequence, for Csp^3-Csp^3 cross-coupling reactions.

In the second part a protecting group for 2-iodo-1,4-phenylenediamine was identified, which allowed a subsequent iodine-magnesium exchange to take place. The resulting magnesiated products were transmetallated to either copper or zinc, whereupon they successfully participated in allylation and cross-coupling reactions (Scheme 49).



Scheme 49. Negishi cross-coupling reaction of 1,4-phenylenediamine derivatives with aryl iodides.

In the deprotection step a range of multi-coupling reagents led to spontaneous formation of heterocycles such as indoles and 2-oxo-1,2-dihydro-6-quinolines.



Scheme 50. Examples of multi-coupling reagents for application in heterocyclic chemistry.

As an extension of the chemistry using 1,4-phenylenediamine and aniline derivatives, further multi-coupling reagents could be used (Scheme 50). Preliminary results have shown that it is possible to perform iodine-magnesium exchange in the presence of a free aniline function, provided that this has been deprotonated prior to the exchange.[69] The development of a general exchange and cross-coupling protocol for unprotected 2-iodoaniline derivatives would be of interest, as it would be possible to avoid the protection-deprotection steps.

Experimental Section

1 General Conditions

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

Solvents

Solvents were dried according to standard methods by distillation over drying agents as stated below and were stored under argon. CH_2Cl_2, DMF and pentane (CaH_2), diethyl ether and THF (Na/benzophenone), pyridine and triethylamine (KOH), toluene (Na).

Reagents

- Reagents of > 98 % purity were used as obtained.
- 1 M CuCN·2LiCl solution was prepared by drying CuCN (8.96 g, 0.1 mol) and LiCl (8.48 g, 0.2 mol) in a Schlenk flask under vacuum for 4 h at 120 °C. After cooling to rt, dry THF (100 mL) was added and stirring was continued until the salts were dissolved.
- 1 M $ZnBr_2$ solution was prepared by drying $ZnBr_2$ (33.78 g, 0.15 mol) under vacuum for 5 h at 150 °C. After cooling to rt, dry THF (100 mL) was added and stirring was continued until the salt was dissolved.
- *n*-Butyllithium was used as a 1.5 M solution in hexane.
- Diisopropylamine was distilled from CaH_2.
- The following reagents were prepared according to literature procedures: palladium(II)*bis*(dibenzylideneacetone),[81] tri-*o*-furylphosphine,[82] diethylborane,[83] diisopropylzinc,[84] dipentylzinc,[85] ethyl α-bromomethylacrylate,[70] 1-iodo-4-octanone,[32] 4-iodo-1-phenyl-1-butanone,[86] 5-iodopentanenitrile,[87] 3-iodo-1-piperidino-1-propanone,[34b]

81 Takahashi, Y.; Ito, T.; Sakai, S. *Chem. Comm.* **1970**, 1065.

82 Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc. Perkin Trans. II*, **1972**, 63.

83 Langer, F. *Dissertation*, Phillips-Universität Marburg **1996.**

84 Rathke, M. W.; Yu, H. *J. Org. Chem.*, **1972**, *37*, 1732.

85 Nützel, K. *Houben-Weyl, Methoden Org. Chem.*, Thieme, Stuttgart, **1973**, *13/2a*, 553.

86 Kimura, N.; Takamuku, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2433.

87 Booth, B. L.; Jibodu, K. O.; Procenca, M. F. *J. Chem. Soc. Perkin Trans. I* **1983**, 1067.

3-iodopropyl phenyl sulfide,[88] 5-iodopentanitrile,[89] 3-chloro-1-piperidino-1-propanone,[90] 5-iodopentyl pivalate,[91] ethyl 2-(trifluoromethylsulfonyl)oxy-1-cyclohexen-1-carboxylate,[92] 6-bromo-1-methoxy-1-cyclohexene,[93] 4-(iodomethyl)-1,3-oxazolidin-2-one,[94] 2-methoxyallyl bromide,[76] 1,4-dioxaspiro[4.5]dec-6-en-8-one.[79]

Content determination of organometallic reagents

Organolithium and organomagnesium solutions were titrated using the method of Paquette.[95] The concentrations of organozinc solutions were determined by back titration of iodine with an aqueous $Na_2S_2O_3$ solution.

Chromatography

- Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The chromatograms were viewed under UV light and/or by treatment of the TLC plate with one of the solutions below followed by heating with a heat gun:

  -$KMnO_4$ (3.0 g), K_2CO_3 (20 g), KOH (0.3 g) in water (300 mL).

  -Phosphormolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g), conc. H_2SO_4 (12 mL) in water (230 mL).

- Flash column chromatography was performed using SiO_2 60 (0.040-0.063 mm) from Merck.
- Gas chromatography (GC): Hewlett-Packard 5890 Series II.

  -Column A: 5 % phenylmethylpolysiloxane (HP Ultra 2) 12 m x 0.2 mm

  -Column B: 5 % phenylmethylpolysiloxane (HP 5) 5 m x 0.25 mm

  The compounds were detected with a flame ionisation detector.

88 Rao, S. A.; Chou, T.-S.; Schipor, I.; Knochel, P. *Tetrahedron*, **1992**, *48*, 2015.

89 Ostwald, R.; Chavant, P.-Y.; Stadtmüller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143.

90 Willy, W. E.; McKean, D. R.; Garcia, B. A. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1989.

91 Kuivila, H. G.; Maxfield, P. L. *J. Organomet. Chem.* **1967**, *10*, 41.

92 Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972.

93 Garbisch, E. W. *J. Org. Chem.* **1965**, *30*, 2109.

94 Sibi, M. P.; Rutherford, D.; Sharma, R. *J. Chem. Soc. Perkins Trans. 1* **1994**, 1675.

95 Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.

Analytical data

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

- **NMR** spectra were recorded on Brucker ARX 200, AC 300 or WH 400 instruments. Chemical shifts are reported as δ-values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δ_H: 7.27, δ_C: 77.0), CD_3OD (δ_H: 3.31, δ_C: 49.0). For the characterization of the observed signal multiplicities the following abbreviations were applied: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), as well as br (broad).

- **Infra red** spectra were recorded from 4000 - 400 cm^{-1} on a Nicolet 510 or a Perkin-Elmer 281 spectrophotometer. Samples were measured either as a film between sodium chloride plates or (for solids) as potassium bromide tablets. The absorption bands are reported in wave numbers (cm^{-1}). For the band characterization the following abbreviations were applied: s (strong), m (medium), w (weak).

- **Electron impact mass** (EI, 70 eV) spectra were recorded on a Varian MAT CH 7A instrument. High resolution mass spectra (HRMS) were recorded on a Varian MAT 711 instrument. Additionally, for the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890 / MSD 5973 was used.

  -Column C: 5 % phenylmethylpolysiloxane (HP 5) 30 m x 0.25 mm

- **Elemental analysis** was carried out on a Heraeus CHN-Rapid-Elementanalyzer in the microanalytical laboratories of Fachbereich Chemie, Philipps-Universität Marburg and Department für Chemie und Pharmazie, Ludwig-Maximilians-Universität Munich.

2 Typical Procedures (TP)

2.1 Typical procedures for the nickel-catalyzed Csp^3-Csp^3 cross-coupling reaction

TP 1: Typical procedure for the nickel-catalyzed Csp^3-Csp^3 cross-coupling of alkyl iodides with alkylzinc iodides

A dried, argon-flushed 10 mL two-necked flask was charged with $Ni(acac)_2$ (77 mg, 0.3 mmol) and evacuated for 5 min. Dry THF (2 mL), NMP (1 mL), the alkyl iodide (3.0 mmol), 4-fluorostyrene (**1f**: 74 mg, 0.6 mmol) and tetrabutylammonium iodide (3.3 g, 9.0 mmol) were added successively at rt. The reaction mixture was cooled to -35 °C, whereupon a solution of pentylzinc iodide (4.5 mL, 2 M, 9.0 mmol) was added. The reaction mixture was then allowed to warm up to -5 °C. After complete conversion (approx. 16 h) the reaction was quenched with saturated, aqueous NH_4Cl (2 mL) and extracted with diethyl ether (4 x 50-75 mL). The combined organic phases were dried ($MgSO_4$) and the solvents removed *in vacuo*. Flash chromatography on silica gel furnished the cross-coupling product.

TP 2: Typical procedure for the nickel-catalyzed Csp^3-Csp^3 cross-coupling of alkyl iodides with mixed alkyl(TMSM)zincs

A dried, argon-flushed 10 mL two-necked flask was charged with $Ni(acac)_2$ (77 mg, 0.3 mmol) and evacuated for 5 min. Dry THF (2 mL), NMP (1 mL), the alkyl iodide (3.0 mmol) and 4-fluorostyrene (**1f**: 74 mg, 0.6 mmol) were added successively at rt. The reaction mixture was cooled to -60 °C before the slow addition of a solution of pentyl(TMSM)zinc iodide (4.5 mL, 2 M in THF, 9.0 mmol) was begun. When the addition was complete, the reaction mixture was allowed to warm up to -20 °C. After complete conversion (approx. 1 h) the reaction was quenched with saturated, aqueous NH_4Cl (2 mL) and extracted with diethyl ether (4 x 50-75 mL). The combined organic phases were dried ($MgSO_4$) and the solvents removed *in vacuo*. Flash chromatography on silica gel furnished the cross-coupling product.

TP 3: Typical procedure for the nickel-catalyzed Csp^3-Csp^3 cross-coupling of alkyl iodides with secondary dialkylzincs

A dried, argon-flushed 10 mL two-necked flask was charged with $Ni(acac)_2$ (26 mg, 0.1 mmol) and evacuated for 5 min. Dry THF (0.7 mL), NMP (0.3 mL), the alkyl iodide (1.0 mmol) and 4-fluorostyrene (**1f**: 25 mg, 0.2 mmol) were added successively at rt. The reaction mixture was cooled to -60 °C and a solution of dialkylzinc (4.0 mmol) was slowly added. The reaction mixture was then allowed to warm up to -15 °C. After complete conversion the reaction mixture was quenched with saturated, aqueous NH_4Cl (2 mL) and extracted with diethyl ether (4 x 50-75 mL). The combined organic phases were dried ($MgSO_4$) and the solvents removed *in vacuo*. Flash chromatography on silica gel furnished the cross-coupling product.

TP 4: Typical procedure for the nickel-catalyzed Csp^3-Csp^3 cross-coupling of alkyl iodides with benzylic zinc bromides

A dried and argon-flushed 10 mL two-necked flask was charged with $Ni(acac)_2$ (74 mg, 0.3 mmol) and evacuated for 5 min. Dry THF (2 mL), NMP (1 mL), the alkyl iodide (3.0 mmol), 4-fluorostyrene (**1f**: 74 mg, 0.6 mmol) and tetrabutylammonium iodide (3.3 g, 9.0 mmol) were added successively at rt. The reaction mixture was cooled to -35 °C then a solution of benzylic zinc bromide (7.5 mmol) in dry THF was slowly added. The reaction mixture was then allowed to warm to 0 °C, and after 1 h at 0 °C, to 10 °C. After completion (approx. 16 h) the reaction was quenched with saturated, aqueous NH_4Cl (2 mL) and extracted with diethyl ether (4 x 50-75 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were removed *in vacuo*. Flash chromatography on silica gel furnished the cross-coupling product.

2.2 Typical procedures for the cross-coupling reactions with 1,4-phenylenediamine derivatives

TP 5: Typical procedure for the palladium-catalyzed Csp^2-Csp^2 cross-coupling reaction

A dried, argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with a protected iodo-aniline derivative (1.0 mmol) in dry THF (1 mL) and cooled to -10 °C. *i*-PrMgBr (3.3 mL, 0.6 M in THF, 2.0 mmol) was then added slowly. After 1 h, the iodine-magnesium exchange was complete (checked by TLC analysis) and a $ZnBr_2$ solution (0.8 mL, 1.5 M in THF, 1.1 mmol) was added. The reaction was then allowed to warm to rt. Another dried, argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with $Pd(dba)_2$ (29 mg, 0.05 mmol) and tfp (23 mg, 0.1 mmol) in dry THF (1 mL). After formation of the active catalyst the aryl iodide (0.7 mmol) was added, followed by the zinc reagent. The reaction mixture was stirred at rt for 16 h, then quenched with saturated, aqueous NH_4Cl (2 mL), poured into water (50 mL) and extracted with diethyl ether (3 x 40 mL). The combined organic fractions were washed with brine (70 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel furnished the cross-coupling product.

TP 6: Typical procedure for the copper mediated S_N2' reaction

A dried, argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with a protected iodo-aniline derivative (1.0 mmol) in dry THF (1 mL) and cooled to -10 °C. *i*-PrMgBr (3.3 mL, 0.6 M in THF, 2.0 mmol) was then added slowly. After 1 h the exchange was complete (checked by TLC analysis) and CuCN·2LiCl (1.0 mL, 1 M in THF, 1.0 mmol) was added slowly. After 30 min an allyl bromide (3 mmol) was added and the reaction mixture was allowed to warm to rt overnight. The reaction was quenched with saturated, aqueous NH_4Cl/25 % aqueous NH_3 9:1 (3 mL), poured into water (20 mL) and extracted with diethyl ether (3 x 40 mL). The combined organic fractions were washed with brine (100 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel furnished the product.

TP 7: Typical procedure for the deprotection of N-phenylmethyleneamine derivatives

The 2-substituted N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (1 mmol) was dissolved in methanol (10 mL) and a few drops of 2 M sulfuric acid were added. The solution immediately turned dark red, then decolorized within 30 sec. The solution was concentrated *in vacuo*. The product was purified by cation exchange extraction on a Varian bond elute SCX column. The SCX column was conditioned with 10 % acetic acid in methanol, then the product was dissolved in methanol and applied to the column, which was then washed with methanol and acetonitrile. For the elution of the product, 10 % ammonia in methanol was employed. The product was obtained after concentration of the latter fraction.

TP 8: Typical procedure for the deprotection of *N,N*-diallylamine derivatives

In a dried, argon-flushed Schlenk flask $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and *N*,*N*'-dimethylbarbituric acid (936 mg, 6.0 mmol) were mixed, then the 2-substituted N^1,N^1,N^4,N^4-tetraallyl-benzene-1,4-diamine (150 mg, 0.5 mmol) was added as a solution in dry, degassed CH_2Cl_2 (3 mL). The suspension was warmed to 35 °C and stirred at this temperature for 2 h. After cooling to rt, CH_2Cl_2 was evaporated and the residue taken up in diethyl ether, then washed with $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, concentrated and purified on a SCX column as described under TP 7.

TP 9: Typical procedure for the a-iodination of aniline derivatives

A 250 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with iodine (5.0 g, 20 mmol) and silver sulfate (6.2 g, 20 mmol) in ethanol (100 mL). A 4-substituted aniline (20 mmol) was then added and the mixture was stirred vigorously at rt until the reaction was complete (approx. 1 h). The reaction mixture was filtered through a glass sinter and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (100 mL), washed twice with 5% NaOH solution (75 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel furnished the product.

3 Synthesis of Organozinc and Organomagnesium Reagents

Synthesis of primary and secondary alkylzinc iodides

A 25 mL two-necked flask equipped with a dropping funnel, a reflux condenser and a stirring bar was charged with cut zinc foil (Merck) (1.8 g, 27.0 mmol), flame dried, and flushed with argon. THF (1 mL) and 1,2-dibromoethane (51 mg, 0.3 mmol) were added and the zinc was activated by heating the solvent to reflux with a heat gun, then allowing the reaction mixture to cool. This procedure was repeated until foam no longer formed as a result of heating. The mixture was then heated to 50 °C and an alkyl iodide (9.0 mmol) was then added dropwise as a solution in THF (4 mL). The mixture was maintained at 50 °C until the zinc insertion into the alkyl iodide was complete (checked by GC analysis, approx. 4 h).

Synthesis of mixed alkyl(TMSM)zincs

A 25 mL two-necked flask equipped with a stirring bar was flame dried and flushed with argon, then charged with an alkylzinc iodide (9.0 mmol, 1-2 M in THF) and cooled to -40 °C. Trimethylsilylmethyllithium (9 mL, 1 M, 9.0 mmol) was then added dropwise over 5 min. The reaction was left for 1 h at -40 °C before it was warmed to rt. After concentrating the reagent *in vacuo*, an approx. 2 M solution was obtained, which was used directly in the cross-coupling reaction.

Synthesis of benzylic zinc bromides

A 25 mL Schlenk flask charged with cut zinc foil (1.5 g, 22.5 mmol) and a stirring bar was flame dried and flushed with argon. THF (1 mL) and 1,2-dibromoethane (402 mg, 2.3 mmol) were added and the zinc was activated by heating to reflux, then allowing to cool. This procedure was repeated until foam no longer occurred as a result of heating. The mixture was cooled to 0 °C before the benzylic bromide (7.5 mmol) was added dropwise (0.1 drop/sec) as

a solution in THF (5 mL). The temperature of the mixture was maintained at 0 °C until the reaction was complete (checked by GC, approx. 2 h). The reagent was concentrated to a 2-3 M solution under vacuum before use.

Synthesis of dipentylzinc (3a)

A dried, three-necked flask equipped with an argon inlet, a dropping funnel and a thermometer was charged with magnesium turnings (Fluka) (8.4 g, 345 mmol). A small amount of diethyl ether was added to cover the magnesium. Pentyl bromide (47.4 g, 345 mmol) was added at such a rate that the ether maintained a gentle reflux. After the addition was complete the reaction mixture was stirred at rt for an additional 3 h. It was then cooled to 0 °C and zinc(II) bromide (35.4 g, 157 mmol) in diethyl ether (150 mL) was added. The reaction mixture was then allowed to warm to rt and stirred overnight. The diethyl ether was evaporated and dipentylzinc (**3a**) was subsequently purified by distillation (Bp 60 °C, 0.1 mm Hg), yielding the neat reagent (26.5 g, 80 %). The molarity was determined by back titration of iodine with $Na_2S_2O_3$.

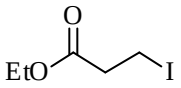
Diisopropylzinc was prepared by an analogous procedure starting from isopropyl bromide.

Synthesis of isopropylmagnesium bromide

A dried, three-necked flask equipped with an argon inlet, a dropping funnel and a thermometer was charged with magnesium turnings (Fluka) (3.7 g, 150 mmol). A small amount of THF was added to cover the magnesium, and isopropyl bromide (12.3 g, 100 mmol) in THF (150 mL) was added dropwise, keeping the temperature of the mixture below 30 °C (water bath). After the addition was complete the reaction mixture was stirred at rt for 10 h. The excess magnesium was removed by filtration and the molarity was determined by the method of Paquette.[95] Yields between 90 and 95 % were obtained.

4 Nickel-Catalyzed Csp^3-Csp^3 Cross-Coupling Reactions

Synthesis of ethyl 3-iodopropionate (2d)



A 1 L round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with ethyl 3-chloropropionate (27.3 g, 0.2 mol) and acetone (400 mL). Sodium iodide (300 g, 2.0 mol) was added to the clear solution and the mixture was refluxed for 16 h.[96] After completion of the reaction the acetone was evaporated *in vacuo*. The residue was taken up in diethyl ether (300 mL) and washed with a saturated, aqueous solution of sodium thiosulfate (3 x 100 mL). The ethereal phase was dried over $MgSO_4$, filtered and concentrated. The resulting yellow oil was purified by distillation with a membrane pump (90 °C/25 mbar) yielding **2d** as a colorless oil (37.9 g, 83%).

IR (KBr): 2981 (m), 1372 (m), 1213 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15 (q, *J* = 7.1 Hz, 2H), 3.32 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

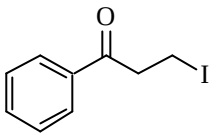
^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 61.3, 39.0, 14.6, 3.3.

MS (EI, 70 eV): 228 (33), 183 (27), 155 (67), 101 (100), 73 (49).

$C_5H_9O_2I$	Calcd.	C, 26.34	H, 3.98
	Found	C, 26.27	H, 3.96

96 Finkelstein, H. *Chem. Ber.* **1910**, *43*, 1528.

Synthesis of 3-iodo-1-phenyl-1-propanone (2f)



Prepared analogously to ethyl 3-iodopropionate *via* a Finkelstein reaction, from 3-chloro-1-phenyl-1-propanone (5.0 g, 30 mmol). Complete after 16 h reflux, isolated as above and recrystallized from pentane, to yield **2f** as white crystals (6.67 g, 85 %).

Mp 64 °C

IR (KBr): 3438 (w), 1675 (s), 1447 (m), 1338 (m) cm^{-1}.

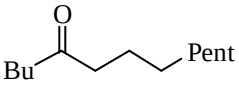
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95-7.93 (m, 2H), 7.61-7.56 (m, 1H), 7.52-7.45 (m, 2H), 3.62 (t, *J* = 5.2 Hz, 2H), 3.46 (t, *J* = 5.2 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 136.1, 133.5, 128.7, 128.0, 42.5, 4.0.

MS (EI, 70 eV): 260 (11), 133 (31), 105 (100), 77 (41).

C_9H_9OI	HRMS	Calcd.	259.9698
		Found	259.9716

Synthesis of 5-tridecanone (4a)



Prepared according to TP 1 from 1-iodo-4-octanone (229 mg, 9.0 mmol) and pentylzinc iodide (13.5 mL, 2 M in THF, 27 mmol). Reaction time: 16 h at -5 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4a** as a colorless oil (925 mg, 52 %).

IR (KBr): 2873 (s), 1716 (s), 1467 (m) cm^{-1}.

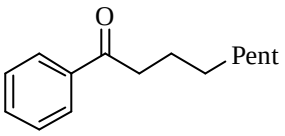
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (t, *J* = 7.4 Hz, 4H), 1.57-1.52 (m, 4H), 1.33-1.26 (m, 12H), 0.92-0.84 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 212.0, 43.2, 42.9, 32.2, 29.7, 29.6, 29.5, 26.3, 24.2, 23.0, 22.7, 14.4, 14.2.

MS (EI, 70 eV): 198 (6), 156 (10), 141 (72), 85 (85), 57 (100).

$C_{13}H_{26}O$ Calcd. C, 78.72 H, 13.21
Found C, 78.65 H, 13.31

Synthesis of 1-phenyl-1-nonanone (4b)



Prepared according to TP 1 from 4-iodo-1-phenyl-1-butanone (820 mg, 3.0 mmol) and pentylzinc iodide (6.0 mL, 1.5 M, 9.0 mmol). Reaction time: 16 h at -5 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4b** as a colorless oil (509 mg, 78 %).

IR (KBr): 2926 (s), 2855 (m), 1688 (s), 1445 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00-7.96 (m, 2H), 7.59-7.44 (m, 3H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.79-1.68 (m, 7H), 1.31-1.17 (m, 5H), 0.92 (t, *J* = 7.4 Hz, 3H).

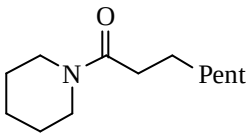
^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 137.5, 133.2, 128.9, 128.4, 39.3, 38.0, 37.5, 33.7, 33.6, 27.1, 26.8, 22.1.

MS (EI, 70 eV): 218 (6), 133 (8), 120 (73), 105 (100), 77 (18).

$C_{15}H_{22}O$ Calcd. C, 82.52 H, 10.16
Found C, 82.90 H, 10.38

Alternatively, **4b** was prepared from 4-bromo-1-phenyl-1-butanone (681 mg, 3.0 mmol). Reaction time: 24 h at -5 °C (457 mg, 70 %). **4b** was also prepared from 4-iodo-1-phenyl-1-butanone (820 mg, 3 mmol) and pentyl(TMSM)zinc iodide (4.5 mL, 2 M in THF, 9.0 mmol) (TP 2). Reaction time 1 h at -20 °C. (481 mg, 74 %).

Synthesis of 1-piperidino-1-octanone (4c)



Prepared according to TP 1 from 3-iodo-1-piperidino-1-propanone (798 mg, 3.0 mmol) and pentylzinc iodide (6 mL, 1.5 M in THF, 9.0 mmol). Reaction time: 16 h at -5 °C. Purification by flash chromatography (pentane/EtOAc 8:2) yielded **4c** as a colorless oil (392 mg, 62 %).

IR (KBr): 2930 (s), 2855 (m), 1644 (s), 1434 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (bs, 2H), 3.32 (bs, 2H), 2.27-2.21 (m, 2H), 1.60-1.48 (m, 8H), 1.25-1.21 (m, 8H), 0.81 (t, *J* = 6.6 Hz, 3H).

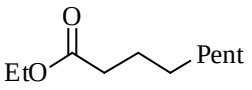
^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 47.1, 43.0, 42.7, 33.9, 32.1, 29.9, 29.5, 27.0, 25.9, 25.0, 23.0, 14.4.

MS (EI, 70 eV): 211 (7), 140 (41), 127 (100), 84 (41).

$C_{13}H_{25}ON$	Calcd.	C, 73.88	H, 11.92	N, 6.63
	Found	C, 73.94	H, 11.86	N, 6.40

Alternatively, **4c** was prepared from 3-bromo-1-piperidino-1-propanone (220 mg, 1.0 mmol). Reaction time: 16 h at 0 °C (145 mg, 69 %).

Synthesis of ethyl nonanoate (4d)



Prepared according to TP 1 from ethyl 4-iodobutanoate (726 mg, 3.0 mmol) and pentylzinc iodide (4.5 mL, 2 M in THF, 9.0 mmol). Reaction time: 16 h at -5 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4d** as a colorless oil (266 mg, 48 %).

IR (KBr): 2957 (m), 2928 (s), 2856 (m) 1739 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (q, *J* = 7.2 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.60 (q, *J* = 7.2 Hz, 2H), 1.26-1.21 (m, 13H), 0.86 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 58.8, 33.0, 30.5, 27.9, 27.8, 27.8, 21.3, 16.3, 12.9, 12.7.

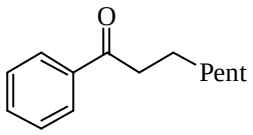
MS (EI, 70 eV): 186 (4), 141 (39), 101 (60), 88 (100).

$C_{11}H_{22}O_2$ Calcd. C, 78.72 H, 13.21

Found C, 78.65 H, 13.31

Alternatively, **4d** was prepared from ethyl 4-bromobutanoate (585 mg, 3.0 mmol) and dipentylzinc (1.2 mL, 5 M, 6.0 mmol) omitting Bu_4NI (TP 3). Reaction time: 16 h at -25 °C (102 mg, 55 %).

Synthesis of 1-phenyl-1-octanone (4e)



Prepared according to TP 1 from 3-iodo-1-phenyl-1-propanone (780 mg, 3.0 mmol) and pentylzinc iodide (4.5 mL, 2 M, 9.0 mmol). Reaction time: 16 h at -5 °C. After purification by flash chromatography (pentane/diethyl ether 20:1) product **4e** was obtained as a colorless oil (349 mg, 57 %).

IR (KBr): 2956 (s), 2856 (m), 1687 (s), 1449 (s), 1266 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.56 - 7.42 (m, 3H), 2.95 (t, *J* = 7.5 Hz, 2H), 1.76-1.20 (m, 10H), 0.89 (t, *J* = 6.6 Hz, 3H).

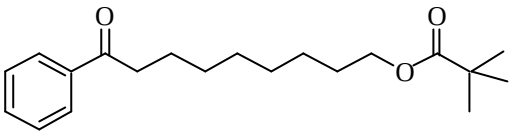
^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 137.5, 133.2, 128.9, 128.4, 39.0, 31.9, 29.7, 29.5, 24.7, 23.6, 14.4.

MS (EI, 70 eV): 204 (5), 133 (9), 120 (90), 105 (100), 77 (35).

$C_{14}H_{20}O$ Calcd. C, 82.30 H, 9.87

Found C, 82.52 H, 9.53

Synthesis of 9-oxo-9-phenyloctyl pivalate (4f)



Prepared according to TP 1 from 4-iodo-1-phenyl-1-butanone (274 mg, 1.0 mmol) and {5-[(2,2-dimethylpropanoyl)oxy]-pentyl}zinc iodide (2.5 mL, 2 M in THF, 5.0 mmol). Reaction time: 16 h at -5 °C. Purification by flash chromatography (pentane/EtOAc 95:5) yielded **4f** as a colorless oil (250 mg, 78 %).

IR (KBr): 2933 (s), 2857 (m), 1728 (s) 1688 (s) cm^{-1}.

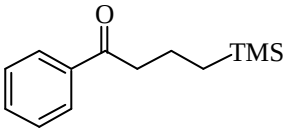
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98-7.95 (m, 2H), 7.56-7.44 (m, 3H), 4.05 (t, *J* = 6.6 Hz, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.77-1.72 (m, 2H), 1.63-1.60 (m, 2H), 1.36 (m, 8H), 1.20 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9, 179.6, 137.5, 133.2, 128.9, 128.4, 64.8, 39.1, 38.9, 29.7, 29.6, 29.5, 29.0, 27.6, 26.2, 24.7.

MS (EI, 70 eV): 318 (3), 120 (88), 105 (100), 57 (28).

$C_{20}H_{30}O_3$	Calcd. C, 75.43	H, 9.49
	Found C, 75.47	H, 9.32

Alternatively, **4f** was prepared from 4-iodo-1-phenyl-1-butanone (820 mg, 3.0 mmol) and {5-[(2,2-dimethylpropanoyl)oxy]-pentyl}(TMSM)zinc (4.5 mL, 2 M in THF, 9.0 mmol) omitting Bu_4NI (TP 2). Reaction time: 6 h at -20 °C (474 mg, 50 %). In this reaction 1-phenyl-4-(trimethylsilyl)-1-butanone was formed as a by-product (147 mg, 21 %).[92]

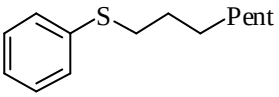


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95-7.90 (m, 2H), 7.60-7.46 (m, 3H), 2.97 (t, *J* = 7.2 Hz, 2H), 1.67-1.58 (m, 2H), 0.68 (t, *J* = 7.2 Hz, 2H), 0.00 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 198.9, 136.7, 133.2, 128.6, 127.8, 42.4, 18.7, 16.5, 2.0.

MS (EI, 70 eV): 234 (3), 219 (44), 215 (72), 144 (35), 120 (100), 105 (43), 73 (87).

Synthesis of octyl phenyl sulfide (4g)



Prepared according to TP 2 from 3-iodopropyl phenyl sulfide (556 mg, 2.0 mmol) and pentyl(TMSM)zinc iodide (2 mL, 2 M in THF, 4.0 mmol). Reaction time: 16 h at -20 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4g** as a colorless oil (300 mg, 71 %).

IR (KBr): 2957 (m), 2927 (s), 2855 (m) 1480 (w) cm^{-1}.

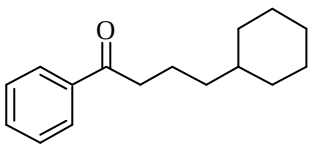
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.03 (m, 5H), 2.82 (t, *J* = 7.5 Hz, 2H), 1.59-1.51 (m, 2H), 1.35-1.31 (m, 2H), 1.21-1.10 (m, 8H), 0.80 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7, 130.6, 127.4, 125.8, 37.3, 35.3, 33.5, 31.1, 30.7, 24.3, 15.8, 15.1.

MS (EI, 70 eV): 222 (55), 126 (26), 110 (100), 77 (9).

$C_{14}H_{22}S$	Calcd.	C, 75.61	H, 9.97	S, 14.42
	Found	C, 75.82	H, 10.28	S, 14.41

Synthesis of 4-cyclohexyl-1-phenyl-1-butanone (4h)



Prepared according to TP 2 from 4-iodo-1-phenyl-1-butanone (544 mg, 2.0 mmol) and cyclohexyl(TMSM)zinc iodide (2 mL, 2 M in THF, 4.0 mmol). Reaction time: 5 h at -20 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4h** as a colorless oil (303 mg, 65 %).

IR (KBr): 2925 (s), 2849 (s), 1687 (s), 1448 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99-7.96 (m, 2H), 7.56-7.44 (m, 3H), 2.98 (t, *J* = 7.5 Hz, 2H), 1.80-1.73 (m, 3H), 1.44-1.20 (m, 9H), 0.92-0.53 (m, 3H).

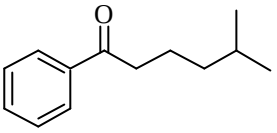
^{13}C NMR (75 MHz, $CDCl_3$): δ 202.2, 138.8, 134.5, 130.2, 129.7, 39.3, 35.0, 29.9, 28.1, 25.5, 24.0, 18.3, 17.0, 15.7.

MS (EI, 70 eV): 230 (8), 120 (100), 105 (71), 77 (28).

$C_{16}H_{22}O$ Calcd. C, 83.43 H, 9.63

Found C, 83.44 H, 9.85

Synthesis of 5-methyl-1-phenyl-1-hexanone (4i)



Prepared according to TP 1 from 4-iodo-1-phenyl-1-butanone (274 mg, 1.0 mmol) and diisopropylzinc (0.55 mL, 3.7 M in THF, 2.0 mmol). Reaction time: 3 h at -30 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4i** as a colorless oil (121 mg, 63 %).

IR (KBr): 2955 (s), 2870 (m), 1687 (s), 1449 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99-7.96 (m, 2H), 7.57-7.45 (m, 3H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.79-1.74 (m, 2H), 1.65-1.50 (m, 1H), 1.33-1.27 (m, 2H), 0.92 (d, *J* = 3.3 Hz, 6H).

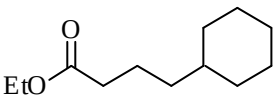
^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 137.5, 133.2, 128.9, 128.4, 39.2, 39.0, 28.3, 22.9, 22.6.

MS (EI, 70 eV): 190 (8), 133 (8), 120 (78), 105 (100), 77 (37).

$C_{13}H_{18}O$ Calcd. C, 82.06 H, 9.53

Found C, 81.92 H, 9.26

Synthesis of ethyl 4-cyclohexylbutanoate (4j)



Prepared according to TP 3 from ethyl 4-iodobutanoate (726 mg, 3.0 mmol) and dicyclohexylzinc (7.5 mL, 0.8 M in THF, 6.0 mmol). Reaction time: 16 h at -30 °C.

Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4j** as a colorless oil (351 mg, 61 %).

IR (KBr): 2955 (s), 2870 (m), 1687 (s), 1449 (m) cm^{-1}.

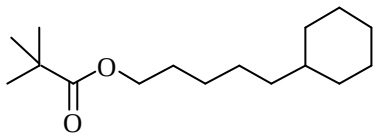
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06 (q, *J* = 7.1 Hz, 2H), 2.23-2.17 (m, 2H), 1.65-1.53 (m, 6H), 1.21-1.10 (m, 8H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.81-0.79 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 60.5, 37.7, 37.3, 35.6, 33.6, 27.0, 26.7, 22.7, 18.8, 14.6, 14.0.

MS (EI, 70 eV): 198 (3), 155 (94), 135 (37), 101 (27), 88 (100).

$C_{12}H_{22}O_2$ Calcd. C, 72.68 H, 11.18
Found C, 72.80 H, 10.96

Synthesis of 5-cyclohexylpentyl pivalate (4k)



Prepared according to TP 1 from 5-iodopentyl pivalate (894 mg, 3.0 mmol) and dicyclohexylzinc (7.5 mL, 0.8 M in THF, 6.0 mmol). Reaction time: 16 h at -20 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4k** as a colorless oil (425 mg, 56 %).

IR (KBr): 2924 (s), 2852 (m), 1731 (s), 1156 (s) cm^{-1}.

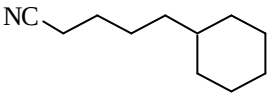
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (t, *J* = 6.6 Hz, 2H), 1.63-1.54 (m, 6H), 1.50-1.42 (m, 5H), 1.20-1.09 (m, 6H), 1.125 (s, 9H), 0.83-0.72 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 64.8, 39.1, 38.0, 37.7, 33.8, 29.1, 29.0, 27.6, 27.1, 26.8, 26.6.

MS (EI, 70 eV): 254 (0), 152 (26), 124 (13), 103 (100), 96 (62), 57 (86).

$C_{16}H_{30}O_2$ Calcd. C, 75.54 H, 11.89
Found C, 75.77 H, 11.93

Synthesis of 5-cyclohexylpentanenitrile (4l)



Prepared according to TP 1 from 5-iodopentanenitrile (624 mg, 3.0 mmol) and dicyclohexylzinc (7.5 mL, 0.8 M in THF, 6.0 mmol). Reaction time: 16 h at -20 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **4l** as a colorless oil (330 mg, 67 %).

IR (KBr): 2924 (s), 2851 (s), 2246 (w), 1448 (m) cm^{-1}.

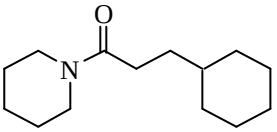
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (t, *J* = 7.1 Hz, 2H), 1.64-1.52 (m, 7H), 1.43-1.33 (m, 2H), 1.15-1.09 (m, 6H), 0.85-0.79 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 120.2, 37.8, 36.9, 33.2, 33.2, 27.0, 26.7, 26.7, 26.3, 26.0, 17.5.

MS (EI, 70 eV): 164 (12), 136 (67), 110 (100), 83 (63), 55 (79).

$C_{11}H_{19}N$	Calcd.	C, 79.94	H, 11.59	N, 8.47
	Found	C, 79.91	H, 11.08	N, 8.38

Synthesis of 1-(3-cyclohexyl-propanoyl)piperidine (4m)



Prepared according to TP 1 from 3-bromo-1-piperidino-1-propanone (801 mg, 3.0 mmol) and cyclohexylzinc iodide (4.5 mL, 2 M in THF, 9.0 mmol). Reaction time: 16 h at -5 °C. Purification by flash chromatography (pentane/EtOAc 8:2) yielded **4m** as a colorless oil (421 mg, 63 %).

IR (KBr): 2922 (s), 2851 (m), 1644 (s) 1445 (m) cm^{-1}.

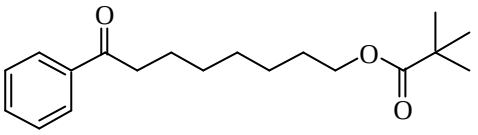
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.52-3.42 (m, 4H), 2.35-2.29 (m, 2H), 1.76-1.63 (m, 13H), 1.57-1.50 (m, 4H), 1.23-1.20 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 47.1, 43.0, 37.9, 33.5, 33.3, 31.4, 27.0, 27.0, 26.6, 26.0, 25.0.

MS (EI, 70 eV): 223 (3), 140 (25), 127 (100), 84 (18), 55 (10).

$C_{14}H_{25}ON$	Calcd.	C, 75.29	H, 11.28	N, 6.27
	Found	C, 75.31	H, 11.16	N, 6.11

Synthesis of 8-oxo-8-phenylheptyl pivalate (4n)



Prepared according to TP 1 from 4-bromo-1-phenyl-1-butanone (227 mg, 1.0 mmol) and {4-[(2,2-dimethylpropanoyl)oxy]-butyl}zinc iodide (2.5 mL, 2 M in THF, 5.0 mmol). Reaction time: 20 h at -5 °C. Purification by flash chromatography (pentane/EtOAc 95:5) yielded **4n** as a colorless oil (222 mg, 73 %).

IR (KBr): 2934 (s), 2859 (m), 1727 (s) 1688 (s), 1285 (s), 1157 (s) cm^{-1}.

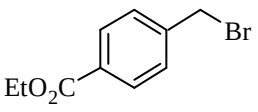
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 6.9 Hz, 2H), 7.53-7.38 (m, 3H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.80-1.25 (m, 10H), 1.12 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 179.0, 137.5, 133.3, 128.9, 128.4, 64.7, 39.1, 38.9, 29.6, 29.5, 29.0, 27.6, 26.2, 24.6.

MS (EI, 70 eV): 304 (2), 120 (94), 105 (100), 57 (23).

$C_{19}H_{28}O_3$	Calcd.	C, 74.96	H, 9.27
	Found	C, 74.99	H, 9.40

Synthesis of ethyl 4-bromomethylbenzoate



In a dried Schlenk flask equipped with a reflux condenser, 4-bromomethylbenzoic acid (5.4 g, 25 mmol) was treated with thionyl chloride (9.0 mL, 75 mmol) and heated to reflux for 5.5 h. When the reaction was complete, the excess thionyl chloride was evaporated and the resulting clear oil was dried under high vacuum. The crude product was taken up in CH_2Cl_2 (30 mL) and the solution cooled to 0 °C. A solution of ethanol (1.6 mL, 30 mmol) and pyridine (2.4

mL, 30 mmol) in CH_2Cl_2 (5 mL) was then added slowly, while maintaining the temperature of the reaction mixture below 10 °C. After the addition was complete the reaction mixture was stirred for an additional 0.5 h before saturated, aqueous NH_4Cl was added to quench. The reaction mixture was extracted three times with CH_2Cl_2 and the combined organic phases were washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded ethyl 4-bromomethylbenzoate as white crystals (3.94 g, 65 %).

Mp 35 °C.

IR (KBr): 3000 (w), 2981 (w), 1718 (s), 1463 (m), 1414 (m), 1274 (s), 1108 (s), 1091 (s), 1018 (m), 768 (m), 704 (s) cm^{-1}.

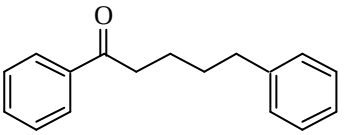
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 4.41 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 142.9, 130.8, 130.4, 129.4, 61.5, 32.6, 14.7.

MS (EI, 70 eV): 242 (4), 197 (11), 163 (100), 135 (18), 118 (15), 90 (17).

$C_{10}H_{11}O_2Br$	HRMS	Calcd.	241.9942
		Found	241.9936

Synthesis of 1,5-diphenyl-1-pentanone (6a)



Prepared according to TP 4 from 4-iodobutyrophenone (820 mg, 3.0 mmol) and benzylic zinc bromide (2.5 M, 7.5 mmol). After 1 h at 0 °C the reaction was allowed to warm to 10 °C, and was complete in 16 h. Purification by flash chromatography (pentane/diethyl ether 20:1) furnished the cross-coupling product **6a** as a colorless oil (476 mg, 67 %).

IR (KBr): 3025 (w), 2935 (m), 1686 (s), 1597 (m), 1496 (m), 1448 (s), 750 (m), 691 (s) cm^{-1}.

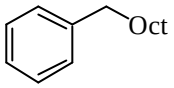
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 - 7.06 (m, 10H), 2.84 (t, *J* = 7.1 Hz, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 1.92 - 1.54 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 142.4, 137.2, 133.1, 128.7, 128.6, 128.5, 128.2, 125.9, 38.6, 36.0, 31.3, 24.2.

MS (EI, 70 eV): 238 (2), 120 (12), 105 (12), 71 (41), 42 (100).

$C_{17}H_{18}O$ HRMS Calcd. 238.1352
Found 238.1355

Synthesis of 1-phenylnonane (6b)



Prepared according to TP 4 from octyl iodide (720 mg, 3.0 mmol) and benzylic zinc bromide (3.0 mL, 2.5 M, 7.5 mmol). Reaction time: 4 h at 0 °C. Purification by flash chromatography (pentane) yielded **6b** as a colorless oil (470 mg, 77 %).

IR (KBr): 3027 (m), 2925 (s), 2854 (s), 1605 (w), 1496 (m), 1454 (m), 697 (s) cm^{-1}.

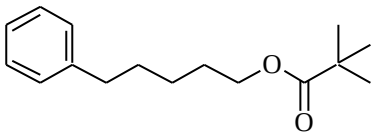
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 - 6.83 (m, 5H), 2.53 (t, *J* = 7.6 Hz, 2H), 1.54 (q, *J* = 7.6 Hz, 2H), 1.24 - 1.19 (m, 12H), 0.81 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 128.3, 128.1, 125.4, 76.5, 35.9, 31.8, 31.4, 29.5, 29.4, 29.2, 22.6, 14.0.

MS (EI, 70 eV): 204 (42), 105 (13), 91 (100), 71 (12), 57 (14), 43 (26), 41 (20), 29 (12).

$C_{15}H_{24}$ HRMS Calcd. 204.1870
Found 204.1874

Synthesis of 5-phenylpentyl pivalate (6c)



Prepared according to TP 4 from 4-iodobutyl pivalate (850 mg, 3.0 mmol) and benzylic zinc bromide (3.0 mL, 2.5 M, 7.5 mmol). Reaction time: 4 h at 0 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **6c** as a colorless oil (603 mg, 81 %).

IR (KBr): 3026 (s), 2935 (s), 2859 (s), 1728 (s), 1453 (s), 1157 (m), 1036 (m) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20 - 7.08 (m, 5H), 3.97 (t, *J* = 6.5 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.64 - 1.30 (m, 6H), 1.27 (s, 9H).

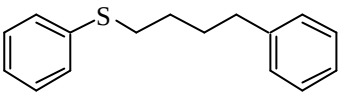
^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 142.4, 128.4, 128.3, 125.7, 64.3, 38.7, 35.8, 31.0, 28.5, 27.2, 25.5.

MS (EI, 70 eV): 146 (100), 117 (64), 104 (81), 91 (87), 57 (76), 41 (21), 28 (21).

$C_{16}H_{24}O_2$ Calcd. C, 77.38 H, 9.74

Found C, 77.70 H, 9.72

Synthesis of phenyl (4-phenylbutyl) sulfide (6d)



Prepared according to TP 4 from 3-iodopropyl phenyl sulfide (830 mg, 3.0 mmol). Reaction time: 1 h at 0 °C, followed by 10 h at rt. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **5d** as a colorless oil (457 mg, 63 %).

IR (KBr): 3060 (m), 2933 (s), 2856 (m), 1584 (m), 1480 (s), 1452 (s), 1438 (s), 1092 (m), 1025.3 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 - 7.02 (m, 10H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.69 - 1.42 (m, 4H).

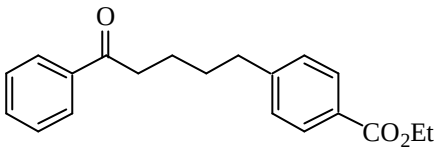
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 138.5, 129.1, 128.8, 128.5, 128.4, 128.3, 125.8, 35.4, 33.6, 30.4, 28.7.

MS (EI, 70 eV): 242 (100), 110 (53), 91 (77), 28 (20).

$C_{16}H_{18}S$ HRMS Calcd. 242.1120

Found 242.1125

Synthesis of ethyl 4-(5-phenyl-5-oxopentyl) benzoate (6e)



Prepared according to TP 4 from 4-iodobutyrophenone (820 mg, 3.0 mmol) and 4-carbethoxybenzylic zinc bromide (2.31 g, 7.5 mmol). Reaction time: 1 h at 0 °C, followed by 16 h at rt. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **6e** as white crystals (660 mg, 71 %).

Mp 69 °C.

IR (KBr): 3066 (m), 2930 (m), 1705 (s), 1682 (s), 1608 (s), 1281 (s), 1180 (m), 1109 (m), 1022 (m) cm^{-1}.

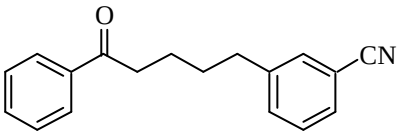
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.25 - 7.01 (m, 9H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.95 - 1.64 (m, 8H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 167.0, 147.7, 146.4, 138.1, 133.0, 129.7, 128.6, 128.5, 128.2, 60.8, 37.5, 35.9, 30.8, 23.9, 14.4.

MS (EI, 70 eV): 310 (45), 281 (20), 265 (23), 191 (49), 163 (100), 144 (45), 131 (51), 120 (74), 105 (97), 90 (33), 77 (55).

$C_{20}H_{22}O_3$ HRMS Calcd. 310.1571
Found 310.1570

Synthesis of ethyl 3-(5-phenyl-5-oxopentyl)benzonitrile (6f)



Prepared according to TP 4 from 4-iodobutyrophenone (820 mg, 3.0 mmol) and 3-cyanobenzylic zinc bromide (1.96 g, 7.5 mmol). Reaction time: 1 h at 0 °C, followed by 16 h at 10 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **6f** as white crystals (582 mg, 74 %).

Mp 68 °C.

IR (KBr): 3056 (m), 2942 (s), 2867 (m), 2226 (s), 1727 (s), 887 (m), 754 (s) cm^{-1}.

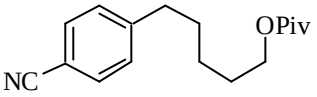
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 - 7.19 (m, 9H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 1.74 - 1.62 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 143.3, 131.2, 131.1, 127.9, 126.6, 125.2, 119.0, 109.7, 86.5, 67.6, 48.5, 37.7, 25.3.

MS (EI, 70 eV): 263 (22), 133 (23), 120 (70), 105 (100), 77 (30).

$C_{18}H_{17}NO$ HRMS Calcd. 263.1312
Found 263.1311

Synthesis of ethyl 3-(5-phenyl-5-oxopentyl)benzonitrile (6h)



Prepared according to TP 4 from 4-cyanobenzyl bromide (196 mg, 1.0 mmol) and 4-pivaloyloxy-butylzinc iodide (2.5 mL, 2 M, 5 mmol). Reaction time: 1 h at 0 °C, followed by 16 h at 25 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) yielded **6h** as a colorless oil (144 mg, 53 %).

IR (KBr):) 3020 (s), 2861 (s), 1712 (s), 1465 (s), 1157 (m) cm^{-1}.

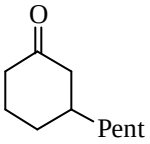
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 - 7.19 (m, 4H), 4.08 (t, *J* = 6.8 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 1.60 - 1.53 (m, 6H), 1.24 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 143.7, 131.8, 131.0, 129.1, 129.0, 117.1, 108.5, 67.9, 40.8, 37.1, 33.2, 29.8, 24.1.

MS (EI, 70 eV): 273 (41), 188 (100), 162 (30).

$C_{17}H_{23}NO_2$ HRMS Calcd. 273.1729
Found 273.1720

Synthesis of 3-pentyl-cyclohexanone (8)[97]



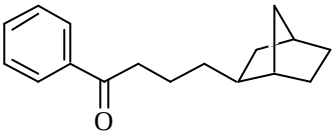
A 23 mL Schlenk flask charged with TBAI (738 mg, 2 mmol) and THF (2 mL) was cooled to -30 °C, then cyclohexenone (192 mg, 2 mmol) and TMS-Cl (200 mg, 2 mmol) were added, followed by dipentylzinc (**3a**) (0.4 mL, 5.0 M, 2 mmol). The resulting mixture was stirred for 1 h at -30 °C, then was poured into aqueous 10 % HCl solution (20 mL) in THF (20 mL), and stirred for 15 min. The mixture was then extracted with ether, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded **8** as a colorless oil (98 mg, 41 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37-1.80 (m, 9H), 1.13-1.20 (m, 8H), 0.81 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 211.0, 47.2, 40.5, 38.1, 35.6, 31.3, 30.6, 25.1, 24.3, 21.6, 13.0.

MS (EI, 70 eV): 168 (11), 88 (100), 72 (22).

Synthesis of 4-bicyclo[2.2.1]hept-2-yl-1-phenyl-1-butanone (10)



A 25 mL Schlenk flask equipped with a stirring bar was flame dried and flushed with argon. 2-Norbornene (376 mg, 4 mmol) was added, the flask was degassed three times and then diethylborane (1.6 mL, 7 M, 12 mmol) was added dropwise at rt. The reaction mixture was stirred for 16 h at 50 °C, then excess diethylborane was distilled off (25 °C, 1 mmHg, 3 h) and *i*-Pr_2Zn was added *via* syringe at rt. The resulting mixture was stirred at rt for 5 h, then the

97 Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425.

excess *i*-Pr_2Zn was distilled off (25 °C, 1 mmHg, 2 h). The dinorbornylzinc (**3d**) was taken up in THF (7 mL) and transferred to a dried and argon-flushed Schlenk flask. After centrifugation, the supernatant was concentrated *in vacuo* and used directly in the cross-coupling reaction.

The subsequent cross-coupling reaction was performed according to TP 3 from 4-iodo-1-phenyl-1-butanone (274 mg, 1.0 mmol) and dinorbornylzinc (**3d**) (2 mL, 2 M in THF, 4.0 mmol). Reaction time: 16 h at -15 °C. Purification by flash chromatography (pentane/diethyl ether 20:1) furnished the cross-coupling product **10** as a colorless oil (146 mg, 61 %, d.r. >95:5).

IR (KBr): 2947 (s), 2868 (m), 1687 (s), 1449 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.84 (m, 2H), 7.47-7.32 (m, 3H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.10 (bs, 1H), 1.88 (bs, 1H), 1.64-1.59 (m, 2H), 1.39-0.94 (m, 11H).

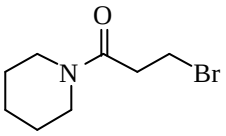
^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 136.1, 131.8, 127.5, 127.0, 41.1, 40.9, 37.8, 37.6, 36.2, 35.5, 34.3, 29.1, 27.8, 22.6.

MS (EI, 70 eV): 242 (9), 133 (13), 120 (100), 105 (53).

$C_{17}H_{22}O$	Calcd.	C, 84.25	H, 9.15
	Found	C, 83.98	H, 9.24

The stereochemistry of the product was determined by NOESY, HMBC, HMQC, COSY, ^{1}H and ^{13}C NMR experiments. The observation of an NOE between one of the protons (1.5 ppm) of the one carbon bridge with the protons on the methylene carbon attached to the ring (1.2 ppm) clearly indicated that the *exo* product had been formed.

Synthesis of 3-bromo-1-piperidino-1-propanone (11b)



Prepared analogously to 4-bromo-1-phenyl-1-butanone from 3-chloro-1-piperidino-1-propanone (3.1 g, 18 mmol). The crude product was distilled under vacuum, to yield **11b** (3.2 g, 79 %).

Bp 97 °C, 0.1 mbar.

IR (KBr): 3488 (br), 2937 (s), 2856 (m), 1640 (s), 1444 (s), 1253 (m) cm^{-1}.

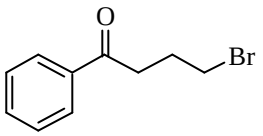
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (t, *J* = 7.2 Hz, 2H), 3.49 (t, *J* = 5.6 Hz, 2H), 3.33 (t, *J* = 5.6 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 1.61-1.46 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 46.9, 43.2, 36.8, 27.9, 26.8, 25.9, 24.8.

MS (EI, 70 eV): 221 (8), 140 (100), 126 (16), 84 (22).

$C_8H_{14}NOBr$	HRMS	Calcd.	219.0259
		Found	219.0242

Synthesis of 4-bromo-1-phenyl-1-butanone (11c)



In a round-bottomed flask equipped with a reflux condenser and a stirring bar, a mixture of 4-chloro-1-phenyl-1-butanone (5.5 g, 30 mmol), NaBr (0.6 g, 6 mmol) and ethyl bromide (22.4 mL, 300 mmol) in NMP (30 mL) was heated to 65 °C for 36 h.[98] The reaction mixture was then poured into a mixture of water/ice/brine 1:1:1 (500 mL), the organic layer was separated and washed again with water and brine, then concentrated. The crude product was distilled under vacuum using an oil pump, to yield **11c** (5.45 g, 80 %).

Bp 115 °C, 0.1 mbar

IR (KBr): 3060 (w), 2964 (w), 1685 (s), 1598 (m), 1449 (m), 1223 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.35 (m, 5H), 3.46 (d, *J* = 6.3 Hz, 2H), 3.09 (d, *J* = 6.3 Hz, 2H), 2.22 (q, *J* = 6.3 Hz, 2H).

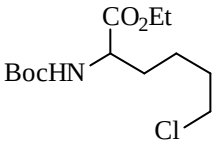
^{13}C NMR (75 MHz, $CDCl_3$): δ 199.1, 137.1, 133.6, 129.0, 128.4, 37.0, 34.0, 27.3.

MS (EI, 70 eV): 227 (0), 147 (31), 120 (34), 105 (100), 77 (42).

$C_{10}H_{11}OI$	HRMS	Calcd.	225.9993
		Found	225.9989

98 Willy, W. E.; McKean, D. R.; Garcia, B. A. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1989.

Synthesis of ethyl 2-[*t*-butoxycarbonyl)amino]-6-chlorohexanoate



A 250 mL flame-dried and argon-flushed flask containing LDA (60 mmol, 0.5 M in THF/hexane) was cooled to -78 °C, whereupon a solution of ethyl 2-[*t*-butoxycarbonyl)amino]acetate (4.0 g, 20 mmol) in THF (70 mL) was added slowly. The mixture was warmed to -60 °C and left for 1 h, then cooled again to -78 °C before slowly adding 4-chloro-1-iodobutane (17.4 g, 80 mmol). After the addition was complete, the reaction mixture was allowed to warm to rt overnight. The reaction was quenched with saturated NH_4Cl solution and extracted several times with EtOAc, then dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/EtOAc 8:2) to give ethyl 2-[*t*-butoxycarbonyl)amino]-6-chlorohexanoate as a pale yellow oil (3.16 g, 54 %).

IR (KBr): 3306 (m), 1745 (s), 1440 (m), 1403 (m), 1226 (s) cm^{-1}.

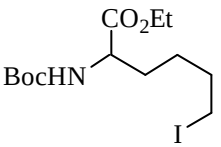
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (bd, 1H), 4.28-4.08 (m, 3H), 3.46 (t, *J* = 7.2 Hz, 2H), 1.82-1.38 (m, 6H), 1.37 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 155.7, 80.2, 61.7, 53.6, 44.9, 32.4, 32.2, 28.7, 22.9, 14.5.

MS (EI, 70 eV): 293 (2), 258 (42), 212 (76), 57 (100).

$C_{13}H_{24}O_4NCl$	Calcd.	C, 53.15	H, 8.23	N, 4.77
	Found	C, 52.92	H, 8.03	N, 4.73

Synthesis of ethyl 2-[*t*-butoxycarbonyl)amino]-6-iodohexanoate (12)



Ethyl 2-[*t*-butoxycarbonyl)amino]-6-chlorohexanoate (2.5 g, 8.5 mmol) was taken up in acetone (30 mL), NaI (12.6 g, 85 mmol) was added, and the resulting mixture was refluxed

for 16 h. The solvent was then evaporated *in vacuo* and the crude product was taken up in EtOAc, washed with aqueous $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated. The residual oil was purified by flash chromatography (pentane/EtOAc 8:2) to give the product **12** as a pale yellow oil (2.87 g, 89 %).

IR (KBr): 3306 (m), 1745 (s), 1440 (m), 1403 (m), 1226 (s) cm^{-1}.

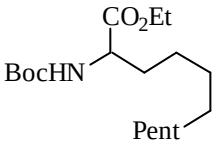
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (bd, 1H), 4.28-4.08 (m, 3H), 3.46 (t, *J* = 7.2 Hz, 2H), 1.82-1.38 (m, 6H), 1.38 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 155.7, 80.3, 61.8, 53.6, 33.2, 32.1, 28.7, 26.5, 14.5, 6.6.

MS (EI, 70 eV): 293 (2), 258 (42), 212 (76), 57 (100).

$C_{13}H_{24}O_4NI$	Calcd.	C, 40.53	H, 6.28	N, 3.64
	Found	C, 40.33	H, 6.49	N, 3.65

Synthesis of ethyl 2-[*t*-butoxycarbonyl)amino]undecanoate (14)



Prepared according to TP 3 from ethyl 2-[*t*-butoxycarbonyl)-amino]-6-iodohexanoate (385 mg, 1.0 mmol) and dipentylzinc (0.4 mL, 5 M, 2.0 mmol). Reaction time: 4 h at -30 °C. Purification by flash chromatography (pentane/EtOAc 8:1) yielded **14** as a colorless oil (184 mg, 56 %).

IR (KBr): 3306 (m), 1745 (s), 1440 (m), 1403 (m), 1226 (s) cm^{-1}.

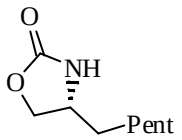
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (bd, 1H), 4.23-4.08 (m, 3H), 1.70-1.62 (m, 1H), 1.59-1.48 (m, 1H), 1.39 (s, 9H), 1.25-1.16 (m, 17H), 0.81 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 155.8, 80.1, 61.5, 53.9, 42.7, 33.2, 32.2, 29.8, 29.7, 29.6, 29.6, 28.7, 23.0, 14.6, 14.4.

MS (EI, 70 eV): 329 (2), 256 (42), 212 (76), 57 (100).

$C_{18}H_{35}O_4N$	Calcd.	C, 63.13	H, 10.06	N, 8.18
	Found	C, 63.20	H, 10.00	N, 8.12

Synthesis of 4-hexyl-1,3-oxazolidin-2-one (15)



Prepared according to TP 3 from 4-(iodomethyl)-1,3-oxazolidin-2-one (340 mg, 1.5 mmol) and dipentylzinc (0.6 mL, 5 M in THF, 3.0 mmol). Reaction time: 3 h at -30 °C. Purification by flash chromatography (pentane/EtOAc 1:1) yielded **15** as a colorless oil (143 mg, 60 %).

IR (KBr): 3272 (m), 2956 (s), 2857 (s), 1754 (s) cm^{-1}.

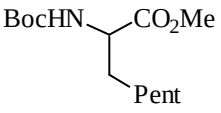
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (bs, 1H), 4.43-4.37 (dt, *J* = 8.4 and 0.9 Hz, 1H), 3.95-3.90 (m, 1H), 3.81-3.76 (m, 1H), 1.51-1.47 (m, 2H), 1.22-1.19 (m, 8H), 0.83-0.79 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 70.7, 53.1, 37.7, 31.9, 29.3, 25.2, 23.1, 14.3.

MS (EI, 70 eV): 154 (0), 86 (100), 58 (6).

$C_9H_{16}O_2N$	Calcd.	C, 63.13	H, 10.06	N, 8.18
	Found	C, 63.20	H, 10.00	N, 8.12

Synthesis of methyl 2-*N*-*t*-butoxycarbonylamino-octanoate (17)



Prepared according to TP 3 from methyl 2-*N*-*t*-butoxycarbonylamino-3-iodo-propanoate (329 mg, 1.0 mmol) and dipentylzinc (0.4 mL, 5 M in THF, 2.0 mmol). Reaction time: 3 h at -30 °C. Purification by flash chromatography (pentane/EtOAc 95:5) yielded **17** as a colorless oil (112 mg, 40 %).

IR (KBr): 3366 (br), 2956 (m), 2930 (m), 1716 (s), 1513 (m), 1166 (m) cm^{-1}.

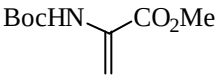
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91 (bs, 1H), 4.19 (bs, 1H), 3.67 (s, 3H), 1.75-1.48 (m, 2H), 1.38 (s, 9H), 1.27-1.09 (m, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 155.7, 53.8, 52.5, 46.5, 33.1, 31.9, 29.2, 28.7, 25.6, 22.9, 14.4, 11.5.

MS (EI, 70 eV): 274 (1), 173 (11), 140 (14), 114 (100), 55(19).

$C_{14}H_{27}O_4N$	HRMS	Calcd.	273.1940
		Found	273.1923

In this reaction methyl 2-*N*-*t*-butoxycarbonylamino-acrylate (**18**) was formed as a by-product (67 mg, 28 %).[99]

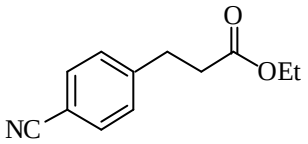


^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (bs, 1H), 6.10 (s, 1H), 5.64 (s, 1H), 3.76 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 151.5, 130.3, 104.1, 79.7, 51.8, 27.2.

MS (EI, 70 eV): 201 (1), 156 (13), 142 (12), 140 (100), 115 (32), 55(50).

Synthesis of ethyl 3-(*p*-cyanophenyl)propionate (20)



A dried 250 mL three-necked flask equipped with an argon inlet and a stirring bar was charged with 4-bromobenzonitrile (9.1 g, 50 mmol) and evacuated for 5 min. After flushing with argon, dry THF (100 mL) was added and the flask was equipped with a thermometer. The solution was cooled to -100 °C and left for 5 min before slowly adding *n*-BuLi (32 mL, 1.56 M in hexane, 50 mmol) (approx. 20 min). After complete addition the mixture was stirred at -100 °C for an additional 30 min before it was allowed to warm up to -78 °C. At this temperature, a solution of $ZnBr_2$ (36.6 mL, 1.5 M in THF, 55 mmol) was slowly added (approx. 20 min). After complete addition, the reaction mixture was kept at -78 °C for 5 min, then the flask was warmed with an ice bath to 0 °C and left 10 min at this temperature before it was allowed to warm to rt. The yield of the zinc reagent was checked by hydrolysis and iodolysis before concentrating *in vacuo* to 2.0-2.2 M (22-25 mL).

[99] Caulier, T. P.; Reisse, J. *J. Org. Chem.* **1996**, *61*, 2547.

Another dried 100 mL three-necked flask, equipped with an argon inlet and a stirring bar, was charged with $Ni(acac)_2$ (520 mg, 2 mmol) and evacuated for 10 min before flushing with argon. THF (6.7 mL), NMP (3.3 mL), **3f** (496 mg, 4 mmol) and ethyl 3-iodopropionate **1d** (4.56 g, 20 mmol) were successively added after which the flask was equipped with an internal thermometer. The reaction mixture was cooled to -60 °C before slowly adding the zinc reagent *via* syringe through a large diameter canula. After complete addition, the reaction mixture was allowed to warm to -14 °C in a cryostat. The conversion was complete within 12-15 h, after which the reaction was quenched with saturated, aqueous NH_4Cl (15 mL) and allowed to warm to rt. The mixture was then extracted with diethyl ether (7x150 mL), and the ethereal extracts were dried over $MgSO_4$ and concentrated. The resulting yellow oil was purified by flash chromatography affording **20** 3.01 g (74 %) as a pale yellow oil.

IR (KBr): 2983 (m), 2228 (m), 1732 (s), 1688 (m), 1186 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 3.85 (q, *J* = 7.1 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H).

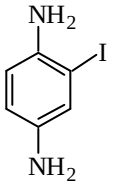
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 146.6, 132.6, 129.6, 119.2, 110.6, 61.0, 35.4, 31.3, 14.5.

MS (EI, 70 eV): 203 (26), 129 (100), 116 (39), 103 (12).

$C_{12}H_{13}O_2N$	Calcd.	C, 70.92	H, 6.45	N, 6.89
	Found	C, 70.61	H, 6.20	N, 6.74

5 Synthesis of 1,4-Phenylenediamine Derivatives

Synthesis of 2-iodo-*p*-phenylenediamine (21)



2-Iodo-4-nitroaniline (8.0 g, 30 mmol) was suspended in concentrated HCl (40 mL) and warmed to 50 °C before a solution of $SnCl_2 \cdot 2H_2O$ (25.0 g, 125 mmol) in concentrated HCl (40 mL) was slowly added. The reaction was stirred for 3 h at this temperature before being

cooled to 0 °C in an ice bath and made basic by addition of a 50 % NaOH solution. The precipitate was filtered and dried in a dessicator, then extracted several times with hot CH_2Cl_2. After concentration, recrystallization from CH_2Cl_2 afforded **21** as yellow crystals (4.7 g, 68 %).

Mp 112 °C.

IR (KBr): 3395 (m), 3284 (m), 3183 (m), 1607 (m), 1492 (s) cm^{-1}.

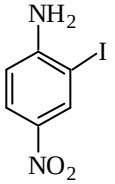
^{1}H NMR (MeOD, 200 MHz): δ 8.55 (d, *J* = 2.4 Hz, 1H), 8.04 (dd, *J* = 2.4 Hz and 8.8 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR (MeOD, 75 MHz): δ 141.8, 141.4, 127.5, 119.5, 117.9, 86.5.

MS (EI, 70 eV): 234 (100), 107 (33), 80 (18), 53 (10).

$C_6H_7N_2I$	Calcd.	C, 30.79	H, 3.02	N, 11.97
	Found	C, 30.86	H, 2.97	N, 11.85

Synthesis of 2-iodo-4-nitroaniline (23)



Prepared according to TP 9 from 4-nitroaniline (13.8 g, 100 mmol). Reaction time: 30 min at rt. Flash chromatography (pentane/EtOAc 9:1) yielded the product **23** as yellow crystals (25.3 g, 95 %).

Mp 107 °C.

IR (KBr): 3480 (m), 3373 (s), 1609 (s), 1581 (m), 1491 (s), 1303 (s) cm^{-1}.

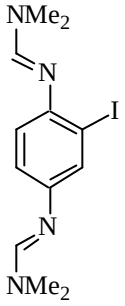
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.48 (d, *J* = 2.4 Hz, 1H), 7.99 (dd, *J* = 2.4 Hz and 9.2 Hz, 1H) 6.77 (d, *J* = 9.2 Hz, 1H), 4.86 (bs, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.3, 150.3, 132.0, 124.3, 117.8, 88.7.

MS (EI, 70 eV): 264 (100), 234 (47), 218 (13), 91 (56).

$C_6H_5O_2N_2I$	Calcd.	C, 27.29	H, 1.90	N, 10.61
	Found	C, 27.08	H, 1.61	N, 10.48

Synthesis of N^1,N^4-(2-iodophenyl)-bis-*N*,*N*-dimethylimidoformamide (24)



2-Iodo-*p*-phenylenediamine (3.5 g, 15 mmol) was dissolved in toluene (20 mL) and dimethoxy-*N*,*N*-dimethylmethanamine (10.7 g, 90 mmol) was added. The reaction mixture was heated under reflux for 2 h. After cooling to rt, the toluene and excess reagent were distilled *in vacuo*. Purification by flash chromatography (pentane/EtOAc 8:2) furnished **24** as a yellow oil (4.9 g, 95 %).

IR (KBr): 3342 (br), 2916 (w), 1634 (s), 1472 (m), 1398 (m), 1366 (m), 1101 (s) cm^{-1}.

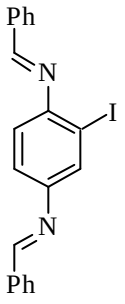
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.41 (s, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.32 (s, 1H), 6.80 (dd, *J* = 2.4 and 5.4 Hz, 1H), 6.65 (d, *J* = 5.4 Hz, 1H), 2.95 (s, 6H), 2.91 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.4, 153.1, 148.3, 148.0, 130.9, 122.7, 119.0, 97.0, 40.4, 34.9.

MS (EI, 70 eV): 344 (100), 329 (16), 302 (17), 217 (8), 176 (10).

$C_{18}H_{23}N_2I$	Calcd.	C, 41.87	H, 4.98	N, 16.28
	Found	C, 41.70	H, 4.79	N, 15.99

Synthesis of 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (25)



2-Iodo-*p*-phenylenediamine (3.5 g, 15 mmol) was dissolved in dry toluene (15 mL), then benzaldehyde (3.8 g, 36 mmol), H_2SO_4 (conc., a few drops) and molecular sieves (4Å, 400

mg) were added and the mixture was heated to reflux for 2 h. The solution was filtered and concentrated *in vacuo*. The yellow oil crystallized upon addition of diethyl ether. Recrystallization from diethyl ether yielded **25** as yellow needles (4.9 g, 79 %).

Mp 118 °C.

IR (KBr): 3436 (w), 1622 (s), 1577 (w), 1469 (w) cm^{-1}.

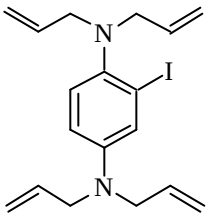
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.49 (s, 1H), 8.37 (s, 1H), 8.01-7.90 (m, 4H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.52-7.48 (m, 6H), 7.32 (dd, *J* = 2.4 Hz and 8.8 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 166.0, 150.4, 146.5, 135.3, 135.0, 131.5, 131.3, 131.2, 129.5, 129.4, 129.3, 128.4, 125.9, 122.8, 101.3.

MS (EI, 70 eV): 410 (100), 281 (10), 178 (18), 152 (16), 89 (10).

$C_{20}H_{15}N_2I$	Calcd.	C, 58.55	H, 3.69	N, 6.83
	Found	C, 58.54	H, 3.67	N, 6.75

Synthesis of N^1,N^1,N^4,N^4-tetraallyl-1-iodobenzene-1,4-diamine (26)



2-Iodo-*p*-phenylenediamine (2.6 g, 11 mmol) was dissolved in dry DMF (100 mL). Allyl bromide (16 mL, 185 mmol) and Na_2CO_3 (9.3 g, 87 mmol) were added and the mixture was heated to 100 °C for 3 h. The solution was filtered after cooling to rt, the filter cake was washed with diethyl ether and the combined organic phases were poured into water (200 mL). The water was extracted three times with diethyl ether (3 x 100 mL), then the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by bulb to bulb distillation to give **26** as an orange oil (3.2 g, 74 %).

Bp 200 °C, 10^{-2} mbar.

IR (KBr): 3077 (w), 2979 (w), 2810 (w), 1596 (s), 1496 (s), 1229 (m), 919 (m) cm^{-1}.

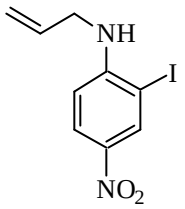
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.09 (d, *J* = 3.0 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.54 (dd, *J* = 3.0 Hz and 8.7 Hz, 1H), 5.77-5.69 (m, 4H), 5.12-4.97 (m, 8H), 3.77-3.75 (m, 4H), 3.44-3.42 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.1, 141.4, 135.9, 124.6, 123.1, 117.6, 116.8, 113.1, 103.4, 57.4, 53.3.

MS (EI, 70 eV): 394 (100), 353 (81), 225 (39), 183 (24), 157 (27), 130 (30).

$C_{18}H_{23}N_2I$	Calcd.	C, 54.83	H, 5.88	N, 7.10
	Found	C, 54.36	H, 6.24	N, 7.10

Synthesis of 1-allylamino-2-iodo-4-nitrobenzene (27)



2-Iodo-4-nitroaniline (7.9 g, 30 mmol) was dissolved in dry DMF (100 mL). Allyl bromide (20.6 mL, 240 mmol) and Na_2CO_3 (12.7 g, 120 mmol) were added and the mixture was heated at 100 °C overnight. After cooling to rt the solution was filtered, the filter cake was washed with diethyl ether and the combined organic phases were poured into water (200 mL). The aqueous phase was extracted three times with diethyl ether (3 x 100 mL), then the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (pentane/EtOAc 95:5), yielding **27** as orange crystals (6.5 g, 71 %). Only the monoallylated product was observed.

Mp 67 °C.

IR (KBr): 3380 (m), 1583 (s), 1523 (m), 1486 (s), 1318 (s), 1296 (s), 1264 (s), 1113 (s) cm^{-1}.

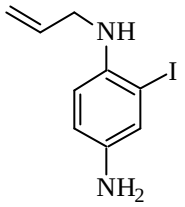
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.46 (d, *J* = 2.4 Hz, 1H), 7.99 (dd, *J* = 2.4 and 9.3 Hz, 1H), 6.39 (d, *J* = 9.3 Hz, 1H), 5.91-5.80 (m, 1H), 5.24-5.16 (m, 2H), 5.03 (bs, 1H), 3.88-3.84 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.2, 138.6, 135.6, 133.1, 126.4, 117.9, 108.7, 82.7, 46.7.

MS (EI, 70 eV): 304 (100), 277 (28), 231 (11), 177 (11), 130 (56).

$C_9H_9N_2O_2I$	Calcd.	C, 35.55	H, 2.98	N, 9.21
	Found	C, 35.53	H, 2.90	N, 9.22

Synthesis of N^1-allyl-2-iodo-1,4-benzenediamine (28)



1-Allylamino-2-iodo-4-nitrobenzene (5.8 g, 18 mmol) was suspended in concentrated HCl (25 mL) and warmed to 50 °C, whereupon a solution of $SnCl_2 \cdot 2H_2O$ (14.2 g, 63 mmol) in concentrated HCl (25 mL) was added slowly. The reaction mixture was stirred for 5 h at this temperature, then it was cooled to 0 °C in an ice bath and made basic by addition of a 50 % NaOH solution. The mixture was then extracted several times with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane/EtOAc/TEA 20:2:1) furnished **28** (3.4 g, 61 %).

IR (KBr): 3431 (br), 1486 (s), 1315 (s), 1286 (s), 1264 (s), 1107 (s) cm^{-1}.

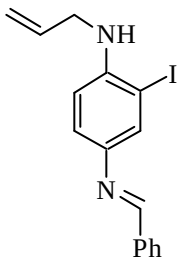
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 2.4 and 8.7 Hz, 1H), 6.47 (d, *J* = 8.7 Hz, 1H), 6.04-5.91 (m, 1H), 5.32-5.17 (m, 2H), 3.79-3.76 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9, 135.7, 126.6, 117.6, 117.2, 116.6, 112.7, 86.9, 48.0.

MS (EI, 70 eV): 274 (23), 273 (100), 258 (23), 233 (13), 145 (14), 130 (29).

$C_9H_{11}N_2I$ HRMS: Calcd. 273.9963
Found 273.9971

Synthesis of N^1-allyl-2-iodo-N^4-[(*E*)-phenylmethylidene]-1,4-benzenediamine (29)



N^1-allyl-2-iodo-1,4-benzenediamine (5.0 g, 16 mmol) was dissolved in dry toluene (20 mL), then benzaldehyde (1.9 g, 18 mmol), H_2SO_4 (conc., a few drops) and molecular sieves (4Å, 1.0 g) were added and the mixture was heated to reflux for 3 h The solution was filtered and

concentrated *in vacuo*, and the resulting brown oil was purified by flash chromatography (pentane/EtOAc/TEA 20:1:2), yielding **29** as a yellow oil (4.1 g, 64 %).

IR (KBr): 3394 (m), 2867 (br), 1621 (s), 1586 (s), 1506 (s), 1450 (m), 1314 (s) cm^{-1}.

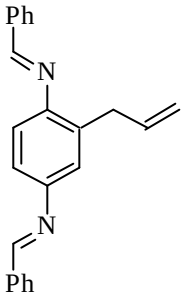
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.32 (s, 1H), 7.76-7.73 (m, 2H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.34-7.31 (m, 3H), 7.12 (dd, *J* = 2.4 Hz and 8.7 Hz, 1H), 6.45 (d, *J* = 8.7 Hz, 1H), 5.89-5.80 (m, 1H), 5.22-5.08 (m, 2H), 4.27 (bs, 1H), 3.74-3.70 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.3, 146.2, 142.8, 136.9, 134.9, 132.3, 131.3, 129.4, 129.1, 123.4, 117.0, 111.1, 85.8, 47.2.

MS (EI, 70 eV): 362 (100), 321 (94), 233 (11), 193 (14), 130 (9).

$C_{16}H_{15}N_2I$	Calcd.	C, 53.06	H, 4.17	N, 7.73
	Found	C, 53.47	H, 4.26	N, 7.74

Synthesis of 2-allyl-N^1,N^4-di[(E)-phenylmethylidene]-benzene-1,4-diamine (30a)



Prepared according to TP 6 from 2-iodo-N^1,N^4-di[(E)-phenylmethylidene]-benzene-1,4-diamine (1.2 g, 3.0 mmol) and allyl bromide (1.1 g, 9.0 mmol). Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:5) yielded **30a** as a yellow powder (812 mg, 83 %).

Mp 57 °C.

IR (KBr): 3059 (w), 2874 (w), 1623 (s), 1576 (m), 756 (s), 691 (s) cm^{-1}.

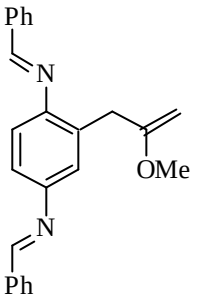
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (s, 1H), 8.35 (s, 1H), 7.86-7.82 (m, 4H), 7.43-7.39 (m, 6H), 7.09 (s, 1H), 7.01 (d, *J* = 6.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.8, 159.4, 150.3, 148.9, 137.6, 136.9, 136.7, 135.7, 131.6, 129.2, 122.6, 120.1, 118.8, 116.1, 18.1.

MS (EI, 70 eV): 324 (44), 323 (100), 220 (16), 115 (18).

$C_{23}H_{20}N_2$	Calcd.	C, 85.15	H, 6.21	N, 8.64
	Found	C, 84.75	H, 6.38	N, 8.52

Synthesis of 2-(2-methoxy-2-propenyl)-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (30b)



Prepared according to TP 6 from 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and 2-methoxyallyl bromide (60% in a mixture with 1-bromo-2-methoxy-propene and 1-bromoacetone) (750 mg, 3.0 mmol). Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **30b** as a yellow oil (242 mg, 68 %).

IR (KBr): 3045 (w), 2872 (w), 1637 (s), 1575 (m), 760 (s) cm^{-1}.

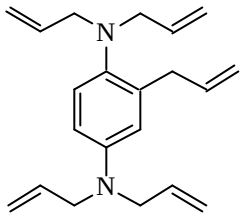
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.52 (s, 1H), 8.42 (s, 1H), 7.94-7.91 (m, 4H), 7.50-7.46 (m, 6H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.16 (dd, *J* = 2.4 and 8.1 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 3.96-3.95 (m, 1H), 3.90-3.89 (m, 1H), 3.67 (s, 2H), 3.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.7, 162.1, 152.4, 151.6, 132.5, 131.2, 130.8, 129.0, 128.6, 124.0, 123.2, 120.3, 79.0, 54.4, 35.5.

MS (EI, 70 eV): 354 (100), 323 (32), 297 (30); 250 (41), 235 (17), 193 (17).

$C_{24}H_{22}N_2O$	HRMS:	Calcd.	354.1732
		Found	354.1738

Synthesis of N^1,N^1,N^4,N^4,2-pentaallyl-benzyl-1,4-diamine (31a)



Prepared according to TP 6 from N^1,N^1,N^4,N^4-tetraallyl-1-iodobenzene-1,4-diamine (394 mg, 1.0 mmol) and ethyl 2-(bromomethyl)acrylate (576 mg, 3.0 mmol). Reaction time: allowed to warm to rt overnight. Purification by flash chromatography (pentane/EtOAc 95:5) yielded **31a** as a colourless oil (270 mg, 88 %).

IR (KBr): 3077 (w), 2978 (w), 1639 (W9, 1607 (m), 1507 (s), 917 (s) cm^{-1}.

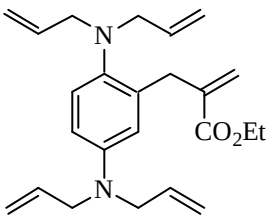
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.86 (d, *J* = 6.0 Hz, 1H), 6.48-6.43 (m, 2H), 5.79-5.71 (m, 5H), 5.13-4.95 (m, 10H), 3.80-3.77 (m, 5H), 3.40-3.38 (m, 5H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.6, 138.7, 137.3, 136.4, 135.0, 133.6, 122.8, 115.6, 115.1, 114.1, 113.0, 109.7, 56.3, 52.0, 34.3.

MS (EI, 70 eV): 308 (88), 267 (64), 226 (100), 185 (48), 170 (50), 157 (42), 143 (26), 130 (30).

$C_{21}H_{28}N_2$	Calcd.	C, 81.77	H, 9.15	N, 9.08
	Found	C, 81.78	H, 9.19	N, 8.96

Synthesis of ethyl 2-[2,5-bis(diallylamino)benzyl]acrylate (31b)



Prepared according to TP 6 from N^1,N^1,N^4,N^4-tetraallyl-1-iodobenzene-1,4-diamine (394 mg, 1.0 mmol) and ethyl 2-(bromomethyl)acrylate (576 mg, 3.0 mmol). Reaction time: allowed to warm to rt overnight. Purification by flash chromatography (pentane/EtOAc 95:5) yielded **31b** as a pale yellow oil (309 mg, 81%).

IR (KBr): 3078 (w), 2980 (m), 1717 (s), 1607 (m), 1508 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.88 (d, *J* = 8.7 Hz, 1H), 6.48 (dd, *J* = 3.3 and 8.7 Hz, 1H), 6.40 (d, *J* = 3.3 Hz, 1H), 6.12 (s, 1H), 5.77-5.71 (m, 4H), 5.24 (s, 1H), 5.11-4.94 (m, 8H), 4.13(q, *J* = 7.2 Hz, 2H), 3.77 (d, *J* = 6 Hz, 4H), 3.64 (s, 2H), 3.36 (d, *J* = 6 Hz, 4H), 1.20 (t, *J* = 7.2 Hz, 3H).

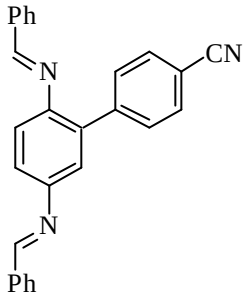
^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.9, 145.9, 141.3, 140.2, 136.7, 136.4, 134.8, 125.8, 124.5, 117.0, 116.5, 114.8, 111.4, 60.6, 57.7, 53.4, 33.4, 14.6.

MS (EI, 70 eV): 380 (100), 339 (30), 297 (17), 265 (18).

$C_{24}H_{32}N_2O_2$ Calcd. C, 75.75 H, 8.48 N, 7.36

Found C, 75.94 H, 7.98 N, 6.98

Synthesis of 2',5'-Bis{[(*E*)-phenylmethylidene]amino}[1,1'-biphenyl]-4-carbonitrile (33a)



Prepared according to TP 5 from 2-iodo-N^1,N^4-di[(E)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and 4-iodobenzonitrile (160 mg, 0.7 mmol). Reaction time: 16 h at rt. Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **33a** as a yellow oil (162 mg, 60 %).

IR (KBr): 3407 (m), 2960 (m), 2225(m), 1618 (s), 1603 (s), 1495 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.35 (s, 1H), 8.31 (s, 1H), 7.63-7.61 (m, 2H), 7.54 (d, *J* = 9 Hz, 2H), 7.41 (d, *J* = 9 Hz, 2H), 7.33-7.24 (m, 6H), 7.18-7.16 (m, 5H).

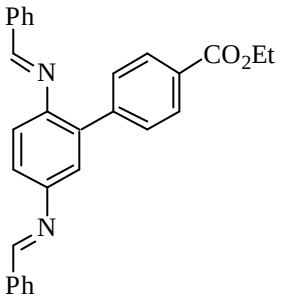
^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.4, 145.5, 144.0, 141.1, 137.9, 135.8, 134.8, 130.1, 129.9, 127.7, 126.9, 126.2, 118.0, 113.6, 113.1, 109.1.

MS (EI, 70 eV): 386 (83), 296 (9), 154 (17), 133 (30), 91 (100).

$C_{27}H_{19}N_3$ HRMS: Calcd. 385.1579

Found 385.1568

Synthesis of ethyl 2',5'-bis{[(*E*)-phenylmethylidene]amino}[1,1'-biphenyl]-4-carboxylate (33b)



Prepared according to TP 5 from 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and ethyl 4-iodobenzoate (191 mg, 0.7 mmol). Reaction time: 16 h at rt. Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **33b** as a pale yellow oil (868 mg, 81%).

IR (KBr): 3430 (br), 1712 (w), 1622(s), 1576 (m), 755 (m), 691 (s) cm^{-1}.

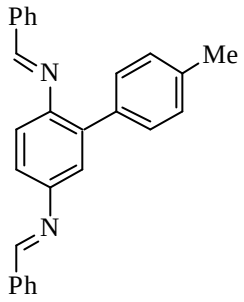
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.33 (s, 1H), 8.21 (s, 1H), 7.88-7.84 (m, 2H), 7.80-7.76 (m, 2H), 7.68 (d, *J* = 2.1 Hz, 1H), 7.38-7.22 (m, 10H), 7.15 (dd, *J* = 2.1 and 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 2.43 (q, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.3, 160.8, 160.7, 151.0, 150.8, 136.3, 132.0, 130.9, 130.0, 129.5, 129.3, 127.9, 127.4, 123.0, 118.8, 96.5, 46.7, 11.9.

MS (EI, 70 eV): 432 (100), 355 (48), 327 (47), 281 (13), 254 (22), 77 (9).

$C_{29}H_{24}N_2O_2$ HRMS: Calcd. 432.1838
Found 432.1851

Synthesis of 4'-methyl-N^2,N^5-Bis[(*E*)-phenylmethylidene][1,1'-biphenyl]-2,5-diamine (33c)



Prepared according to TP 5 from 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and 4-iodotoluene (153 mg, 0.7 mmol). Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **33c** as a yellow oil (188 mg, 71 %).

IR (KBr): 3419 (br), 3026 (w), 2960 (s), 1594 (m), 1495 (s), 1451 (m) cm^{-1}.

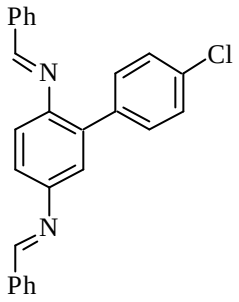
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.32 (s, 1H), 8.30 (s, 1H), 7.64-7.63 (m, 2H), 7.35-7.04 (m, 12H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 2.7 Hz, 1H), 6.40 (dd, *J* = 2.7 and 8.4 Hz, 1H), 2.28 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.6, 130.7, 130.6, 130.5, 129.1, 128.9, 128.8, 128.7, 128.6, 127.7, 127.3, 121.3, 119.3, 115.6, 113.1, 35.3.

MS (EI, 70 eV): 375 (45), 281 (11), 253 (8), 207 (100).

$C_{27}H_{22}N_2$ HRMS: Calcd. 374.1783
Found 374.1799

Synthesis of 4'-chloro-N^2,N^5-Bis[(*E*)-phenylmethylidene][1,1'-biphenyl]-2,5-diamine (33d)



Prepared according to TP 5 from 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and 1-chloro-4-iodobenzene (167 mg, 0.7 mmol). Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **33d** as a yellow oil (170 mg, 62 %).

IR (KBr): 3436 (br), 2869 (w), 1619 (s), 1577 (m), 1494 (m), 1473 (m), 1450 (m), 688 (s) cm^{-1}.

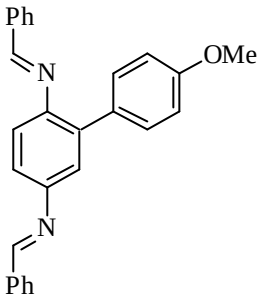
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.43 (s, 1H), 8.39 (s, 1H), 7.82-7.80 (m, 2H), 7.70-7.67 (m, 2H), 7.39-7.12 (m, 12H), 7.03 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.1, 150.4, 147.8, 138.2, 136.8, 136.7, 135.8, 133.5, 132.0, 129.3, 129.0, 123.2, 122.3, 121.6, 120.0.

MS (EI, 70 eV): 394 (21), 317 (25), 207 (100), 191 (9), 133 (8).

$C_{26}H_{19}N_2Cl$	Calcd.	C, 79.08	H, 4.85	N,7.09
	Found	C, 78.90	H, 5.19	N,6.94

Synthesis of 4'-methoxy-N^2,N^5-Bis[(*E*)-phenylmethylidene][1,1'-biphenyl]2,5-diamine (33e)



Prepared according to TP 5 from 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and 4-iodoanisol (164 mg, 0.7 mmol). Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **33e** as a yellow oil (215 mg, 79 %).

IR (KBr): 3430 (br), 3058 (w), 2957 (w), 1624 (s), 1578 (m), 1493 (m), 1451 (m), 1250 (m), 754 (s), 692 (s) cm^{-1}.

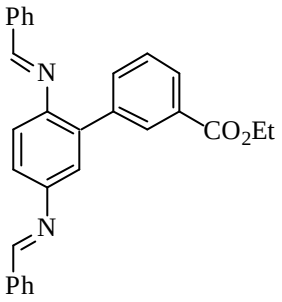
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (s, 1H), 8.29 (s, 1H), 7.81-7.79 (m, 2H), 7.60-7.57 (m, 2H), 7.36-6.75 (m, 13H), 3.51 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.1, 160.0, 132.0, 131.7, 129.3, 129.2, 129.0, 128.9, 128.7, 123.8, 122.3, 121.8, 120.7, 119.7, 111.1, 55.9.

MS (EI, 70 eV): 390 (100), 359 (71), 284 (77), 181 (36), 139 (24).

$C_{27}H_{22}N_2O$ HRMS: Calcd. 390.1732
Found 390.1718

Synthesis of ethyl 2',5'-bis{[(*E*)-phenylmethylidene]amino}[1,1'-biphenyl]-3-carboxylate (33f)



Prepared according to TP 5 from 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and ethyl 3-iodobenzoate (191 mg, 0.7 mmol). Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **33f** as a yellow oil (188 mg, 62 %).

IR (KBr): 3414 (br), 3060 (w), 2870 (w), 1714 (s), 1623 (s), 1578 (m), 1365 (s), 1270 (s), 692 (s) cm^{-1}.

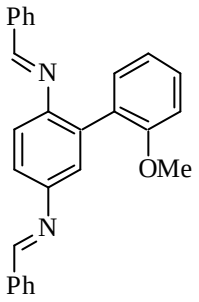
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.46 (s, 1H), 8.40 (s, 1H), 8.21 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.84-7.67 (m, 5H), 7.38-7.30 (m, 8H), 7.20 (dd, *J* = 2.1 and 8.1 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 160.4, 150.5, 147.9, 139.8, 136.8, 136.6, 136.0, 135.1, 131.9, 131.7, 130.9, 129.3, 129.2, 128.7, 128.6, 127.3, 121.8, 61.3, 14.7.

MS (EI, 70 eV): 432 (15), 147 (13), 197 (13), 133 (17), 123 (24), 109 (43), 95 (70), 83 (58), 55 (100).

$C_{29}H_{24}N_2O_2$ HRMS: Calcd. 432.1838
Found 432.1847

Synthesis of 2'-methoxy-N^2,N^5-Bis[(*E*)-phenylmethylidene][1,1'-biphenyl]-2,5-diamine (33g)



Prepared according to TP 5 from 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and 2-iodoanisole (164 mg, 0.7 mmol). Purification by flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **33g** as a yellow oil (200 mg, 74 %).

IR (KBr): 3429 (br), 2957 (w), 1623 (s), 1600 (m), 1577 (m), 1492 (m), 1452 (m) cm^{-1}.

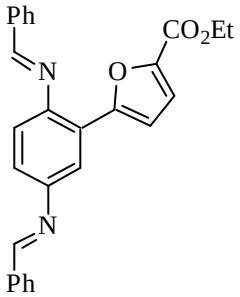
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (s, 1H), 8.29 (s, 1H), 7.81-7.79 (m, 2H), 7.60-7.57 (m, 2H), 7.36-6.75 (m, 13H), 3.51 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.1, 160.0, 152.2, 150.6, 132.0, 131.7, 129.3, 129.2, 129.0, 128.9, 128.7, 123.8, 122.3, 121.8, 120.7, 119.7, 111.1, 55.9.

MS (EI, 70 eV): 390 (100), 359 (71), 284 (77), 181 (36), 139 (24).

$C_{27}H_{22}N_2O$ HRMS: Calcd. 390.1732
Found 390.1748

Synthesis of ethyl 5-(2,5-bis{[(*E*)-phenylmethylidene]amino}-phenyl-2-furoate (33f)



Prepared according to TP 5 from 2-iodo-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (410 mg, 1.0 mmol) and ethyl 5-iodo-2-furoate (153 mg, 0.7 mmol). Purification by

flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **33h** as a yellow oil (153 mg, 52 %).

IR (KBr): 3421 (br), 1711 (s), 1624 (s), 1578 (m), 1495 (m), 1300 (s), 1208 (m), 1141 (m) cm^{-1}.

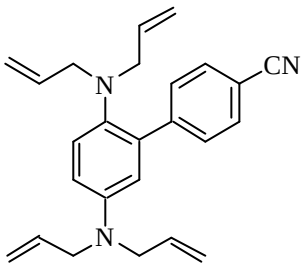
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.50 (s, 1H), 8.38 (s, 1H), 7.88-7.84 (m, 4H), 7.45-7.39 (m, 6H), 7.19-7.13 (m, 3H), 6.96 (d, *J* = 9 Hz, 1H), 6.87 (d, *J* = 3 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.8, 160.8, 160.5, 155.1, 150.4, 147.6, 143.7, 136.5, 132.1, 131.9, 129.1, 129.0, 123.1, 119.6, 118.6, 114.1, 61.3, 14.8.

MS (EI, 70 eV): 422 (12), 281 (13), 207 (100), 191 (11), 133 (8), 96 (9).

$C_{27}H_{22}N_2O_3$ HRMS: Calcd. 422.1630
Found 422.1647

Synthesis of N^2,N^2,N^5,N^5-tetraallyl-1,1'-biphenyl-4'-carbonitrile (34)



Prepared according to TP 5 from N^1,N^1,N^4,N^4-tetraallyl-2-iodobenzene-1,4-diamine (394 mg, 1.0 mmol) and 4-iodobenzonitrile (160 mg, 0.7 mmol). Purification by flash chromatography (pentane/EtOAc 95:5) yielded **34** as a yellow oil (114 mg, 31 %).

IR (KBr): 3078 (w), 2920 (m), 2228 (m), 1606 (m), 1495 (s), 1228 (m), 926 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58 (s, 4H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.58 (dd, *J* = 3.3 and 8.7 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 5.15-5.07 (m, 4H), 4.98-4.97 (m, 8H), 3.83-3.82 (m, 8H).

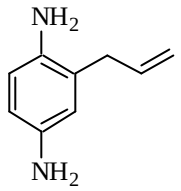
^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.2, 145.6, 138.8, 136.5, 135.5, 134.6, 132.1, 130.6, 123.8, 119.7, 117.5, 116.6, 115.1, 113.2, 110.3, 56.4, 53.4.

MS (EI, 70 eV): 369 (100), 328 (17), 286 (40), 259 (24), 231 (54).

$C_{25}H_{27}N_3$ Calcd. C, 85.15 H, 6.21 N, 8.64

Found C, 84.75 H, 6.38 N, 8.52

Synthesis of 2-allyl-1,4-phenylenediamine (35)



Prepared according to TP 7 from 2-allyl-N^1,N^4-di[(*E*)-phenylmethylidene]-benzene-1,4-diamine (324 mg, 1.0 mmol). Purification on a Varian bond elute SCX column yielded **35** as a brown oil (140 mg, 95 %).

IR (KBr): 3338 (br), 1620 (m), 1506 (s), 1453 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.48-6.38 (m, 3H), 5.90-5.79 (m, 1H), 5.05-4.97 (m, 2H), 3.18-3.15 (m, 6H).

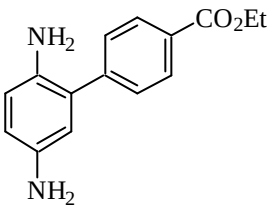
^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.2, 137.4, 136.4, 126.2, 118.2, 117.8, 116.4, 115.3, 36.8.

MS (EI, 70 eV): 148 (100), 133 (47), 121 (24), 77 (15).

$C_9H_{12}N_2$ HRMS: Calcd. 148.1000
Found 148.1003

Alternatively, **35** was obtained from N^1,N^1,N^4,N^4-tetraallyl-1-allylbenzene-1,4-diamine (150 mg, 0.5 mmol) employing TP 8. Purification on a Varian bond elute SCX column yielded **35** (63 mg, 85 %).

Synthesis of ethyl 2',5'-diamino(1,1'-biphenyl)-4-carboxylate (36)



Prepared according to TP 7 from ethyl 2',5'-bis{[(*E*)-phenylmethylidene]amino}[1,1'-biphenyl]-4-carboxylate (100 mg, 0.23 mmol). Purification on a Varian bond elute SCX column yielded **36** as a yellow oil (54 mg, 93 %).

IR (KBr): 3348 (br), 2981 (w), 1708 (s), 1608 (s), 1513 (m), 1498 (s), 1284 (s), 1103 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (dd, *J* = 2.1 and 6.6 Hz, 2H), 7.43 (dd, *J* = 2.1 and 6.6 Hz, 2H), 6.58-6.46 (m, 3H), 4.3 (q, *J* = 7.2 Hz, 2H), 3.16 (br, 4H), 1.42 (t, *J* = 7.2 Hz, 3H).

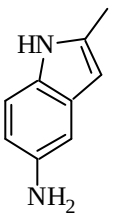
^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 144.9, 139.1, 130.3, 129.5, 128.2, 117.9, 117.3, 61.4, 14.7.

MS (EI, 70 eV): 256 (100), 228 (82), 211 (6), 183 (49), 154 (9), 91 (22).

$C_{15}H_{16}N_2O_2$ HRMS: Calcd. 256.1212
Found 256.1209

6 Synthesis of Nitrogen-Containing Heterocycles

Synthesis of 2-methyl-1*H*-indole-5-amine (37)



Prepared according to TP 7 from **30b** (531 mg, 1.5 mmol). Purification on a Varian bond elute SCX column yielded **37** as a brown oil (156 mg, 71 %).

IR (KBr): 3380 (m), 3281 (m), 1617 (m), 1491 (s) cm^{-1}.

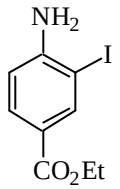
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.96 (d, *J* = 8.7 Hz, 1H), 6.50 (s, 1H), 6.38 (d, *J* = 8.7 Hz, 1H), 6.21 (s, 1H), 3.48 (s, 3H), 2.76 (bs, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9, 133.0, 129.5, 128.4, 117.2, 111.6, 110.7, 105.4, 12.9.

MS (EI, 70 eV): 146 (100), 118 (10), 91 (2), 73 (7).

$C_9H_{10}N_2$ HRMS: Calcd. 146.0844
Found 146.0834

Synthesis of ethyl 4-amino-3-iodobenzoate



Prepared according to TP 9 from ethyl 4-aminobenzoate (3.30 g, 20 mmol). Reaction time: 30 min at rt. Flash chromatography (pentane/diethyl ether 9:1) yielded ethyl 4-amino-3-iodobenzoate as an off-white powder (5.48 g, 94%).

Mp 83 °C.

IR (KBr): 3661 (m), 1687, (s), 1612 (s), 1590 (m), 1286 (s), 1248 (s) cm^{-1}.

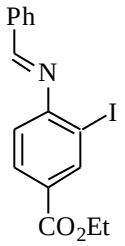
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J* = 1.8 and 8.4 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.43 (bs, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 151.0, 141.3, 131.3, 121.9, 113.5, 82.5, 61.1, 14.8.

MS (EI, 70 eV): 291 (80), 263 (31), 246 (100), 218 (9), 91 (16).

$C_9H_{10}O_2NI$ Calcd. C, 37.14 H, 3.46 N, 4.81
Found C, 37.11 H, 3.45 N, 4.81

Synthesis of ethyl 3-iodo{[(*E*)-phenylmethylidene]amino}benzoate (38)



Ethyl 4-amino-3-iodobenzoate (8.7 g, 30 mmol) was dissolved in dry toluene (60 mL), then benzaldehyde (3.8 g, 36 mmol) and H_2SO_4 (conc., a few drops) were added and the mixture was heated under reflux with a Dean-Stark trap until no more water was formed (approx. 2 h). The solution was filtered and concentrated *in vacuo*. The excess benzaldehyde was distilled at 100 °C under vacuum using an oil pump, and the resulting yellow oil crystallized upon standing. Recrystallization from diethyl ether yielded **38** as yellow needles (10.0 g, 87 %).

Mp 73 °C.

IR (KBr): 3436 (m), 1702 (s), 1626 (s), 1578 (s), 1290 (s), 1252 (s) cm^{-1}.

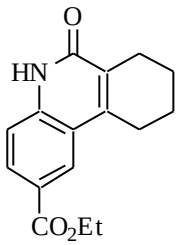
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.46 (d, *J* = 1.8 Hz, 1H), 8.19 (s, 1H), 7.94 (dd, *J* = 1.8 and 8.1 Hz, 1H), 7.89-7.86 (m, 2H), 7.44-7.40 (m, 3H), 6.89 (d, *J* = 8.1 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.3, 163.9, 155.9, 139.2, 135.4, 131.2, 129.9, 128.3, 117.0, 92.6, 60.2, 13.3.

MS (EI, 70 eV): 379 (100), 350 (19), 334 (40), 178 (17).

$C_{16}H_{14}O_2NI$	Calcd.	C, 50.68	H, 3.72	N, 3.69
	Found	C, 50.60	H, 3.76	N, 3.65

Synthesis of ethyl 6-oxo-5,6,7,8,9,10-hexahydro-2-phenanthridinecarboxylate (39)



A dried, argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with **38** (569 mg, 1.5 mmol) in dry THF (1 mL) and cooled to -20 °C. *i*-PrMgBr (1.4 mL, 1.3 M in THF, 1.8 mmol) was then added slowly. After 1 h the iodine-magnesium exchange was complete (checked by TLC analysis). $ZnBr_2$ (1.0 mL, 1.5 M in THF, 1.5 mmol) was added, and the reaction was allowed to warm to rt. Another dried, argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with $Pd(dba)_2$ (29 mg, 0.05 mmol) and tfp (23 mg, 0.10 mmol) in dry THF (1 mL). After formation of the active catalyst, ethyl 2-{[(trifluoromethyl)sulfonyl]oxy}-1-cyclohexene-1-carboxylate (302 mg, 1.0 mmol) was added, followed by the zinc reagent. The reaction mixture was stirred at rt for 16 h, then quenched with saturated, aqueous NH_4Cl (3 mL), poured into water (20 mL) and extracted with diethyl ether (3 x 70 mL). The combined organic fractions were washed with brine (70 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2/diethyl ether 9:1) to yield **39** as a pale yellow powder (200 mg, 74 %).

Mp 246 °C.

IR (KBr): 3436 (m), 2936 (w), 1709 (m), 1654 (s), 1257 (m), 1234 (m) cm^{-1}.

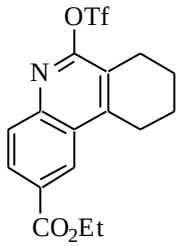
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.19 (d, *J* = 1.8 Hz, 1H), 7.91 (dd, *J* = 1.8 and 8.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.75-2.73 (m, 2H), 2.54-2.50 (m, 2H), 1.74-1.65 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7, 164.5, 145.0, 139.9, 130.1, 129.4, 125.9, 124.7, 120.4, 116.5, 61.4, 26.0, 24.2, 22.2, 22.1, 14.8.

MS (EI, 70 eV): 271 (100), 256 (58), 242 (22), 226 (19), 198 (12).

$C_{16}H_{17}O_3N$	Calcd.	C, 70.83	H, 6.32	N, 5.16
	Found	C, 70.87	H, 6.37	N, 5.11

Synthesis of ethyl 6-trifluoromethylsulfoxy-7,8,9,10-tetrahydro-2-phenanthridine-carboxylate (40)



A dried, argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with **39** (350 mg, 1.3 mmol) and pyridine (306 mg, 3.9 mmol) in dry CH_2Cl_2 (5 mL) and cooled to 0 °C. Triflic anhydride (440 mg, 1.6 mmol) was added slowly and the reaction mixture was warmed to rt overnight. The solution was partitioned between diethyl ether (20 mL) and saturated, aqueous $NaHCO_3$ (15 mL), the mixture was shaken well and the organic layer separated and washed with brine (15 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (pentane/EtOAc 95:5) to yield **40** as a pale yellow powder (324 mg, 62 %).

Mp 151 °C.

IR (KBr): 3437 (br), 2944 (w), 1720 (m), 1414 (m), 1229 (m), 1210 (s) cm^{-1}.

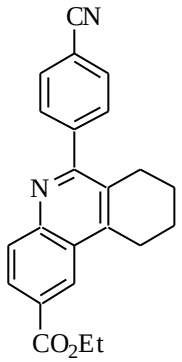
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.59 (d, *J* = 1.5 Hz, 1H), 8.17 (dd, *J* = 1.5 and 8.7 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.15-3.11 (m, 2H), 2.77-2.73 (m, 2H), 1.92-1.83 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 155.2, 150.3, 146.0, 129.7, 129.3, 127.2, 126.0, 122.8, 121.1, 116.8, 61.9, 26.2, 24.0, 21.8, 21.7, 14.7.

MS (EI, 70 eV): 403 (46), 358 (44), 270 (73), 253 (100), 224 (11), 197 (21), 180 (25).

$C_{17}H_{16}O_5NF_3S$	Calcd.	C, 50.62	H, 4.00	N, 3.47
	Found	C, 50.44	H, 3.68	N, 3.44

Synthesis of ethyl 6-(4-cyanophenyl)-7,8,9,10-tetrahydro-2-phenanthridinecarboxylate (41)



Prepared according to TP 5 from 4-iodobenzonitrile (230 mg, 1.0 mmol) and **40** (200 mg, 0.5 mmol). Purification by flash chromatography (pentane/EtOAc 9:1) yielded **41** as a pale yellow powder (126 mg, 71 %).

Mp 184 °C.

IR (KBr): 3430 (br), 2946 (m), 2226 (m), 1768 (s), 1267 (s), 1231 (m) cm^{-1}.

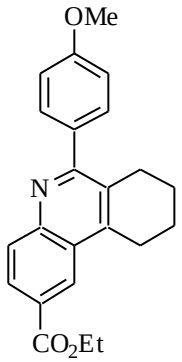
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.70 (d, *J* = 1.5 Hz, 1H), 8.20 (dd, *J* = 1.5 and 8.7 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.73-7.60 (m, 4H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.24 (d, *J* = 6.5 Hz, 2H), 2.64 (d, *J* = 6.2 Hz, 2H), 1.97-1.93 (m, 2H), 1.79-1.73 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.4, 159.5, 146.5, 144.2, 143.6, 131.9, 131.2, 129.2, 128.6, 127.8, 127.4, 125.5, 124.8, 117.7, 111.2, 60.4, 27.6, 24.8, 21.5, 20.9, 13.4.

MS (EI, 70 eV): 361 (69), 360 (100), 332 (23), 191 (9), 96 (10).

$C_{23}H_{20}O_2N_2$ HRMS: Calcd. 356.1525
Found 356.1512

Synthesis of ethyl 6-(4-methoxyphenyl)-7,8,9,10-tetrahydro-2-phenanthridine-carboxylate (42)



Prepared according to TP 5 from 4-iodoanisole (234 mg, 1.0 mmol), **40** (201 mg, 0.5 mmol) and TBAI (554 mg, 1.5 mmol). Purification by flash chromatography (pentane/EtOAc 9:1) yielded **42** as a pale yellow powder (161 mg, 89 %).

Mp 130 °C.

IR (KBr): 3435 (w), 2938 (w), 1706 (s), 1607 (s), 1516 (m), 1253 (s), 1233 (s), 1177 (s) cm^{-1}.

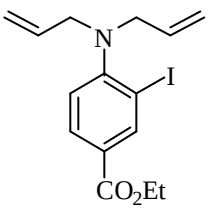
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.66 (d, *J* = 1.5 Hz, 1H), 8.14 (dd, *J* = 1.5 and 8.7 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 12 Hz, 2H), 6.92 (d, *J* = 12 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.19 (m, 2H), 2.70 (m, 2H), 1.88 (m, 2H), 1.67 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.6, 161.4, 158.8, 146.6, 142.6, 132.1, 129.2, 129.0, 128.5, 126.8, 126.6, 125.1, 124.7, 112.7, 60.2, 54.4, 27.9, 24.8, 21.7, 21.1, 13.4.

MS (EI, 70 eV): 361 (69), 360 (100), 332 (23), 191 (9), 96 (10).

$C_{23}H_{23}O_3N$	Calcd.	C, 76.43	H, 6.41	N, 3.88
	Found	C, 76.28	H, 6.72	N, 3.64

Synthesis of ethyl 4-(diallylamino)-3-iodobenzoate (43)



A 250 mL round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser, was charged with ethyl 4-amino-3-iodobenzoate (5.82 g, 20 mmol), allyl bromide (14.3 mL, 160 mmol) and sodium carbonate (8.48 g, 80 mmol). DMF (150 mL) was added and the reaction mixture was heated at 100 °C for 6 h. It was then cooled to rt and poured into water (100 mL), then extracted with diethyl ether (3 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (pentane/diethyl ether 20:1) to yield **43** as a pale yellow oil (5.60 g, 76 %).

IR (KBr): 3661.7 (m), 1687.6, (s), 1612.9 (s), 1590.3 (m), 1286.8 (s), 1248.6 (s) cm^{-1}.

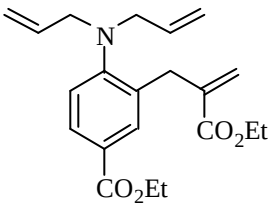
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J* = 1.8 and 8.4 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.43 (bs, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 151.0, 141.3, 131.3, 121.9, 113.5, 82.5, 61.1, 14.8.

MS (EI, 70 eV): 371 (41), 326 (21), 244 (100), 130 (44).

$C_9H_{10}O_2NI$	Calcd.	C, 37.14	H, 3.46	N, 4.81
	Found	C, 31.11	H, 3.46	N, 4.81

Synthesis of ethyl 4-(diallylamino)-3-[2-(ethoxycarbonyl)-2-propenyl]benzoate (44)



A dried, argon-flushed, 25 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with **43** (1.11 g, 3.0 mmol) in dry THF (3 mL) and cooled to -20 °C. *i*PrMgBr (3 mL,

1.3 M in THF, 3.9 mmol) was then added slowly. After 1 h at -20 °C the iodine-magnesium exchange was complete (checked by TLC analysis) and CuCN·2LiCl (3.0 mL, 1 M in THF, 3 mmol) was added slowly. After a further 30 min ethyl 2-(bromomethyl)acrylate (1.15 g, 6 mmol) was added and the reaction mixture was allowed to warm to rt overnight. The reaction was quenched with saturated, aqueous NH_4Cl/25 % aqueous NH_3 9:1 (3 mL), poured into water (50 mL) and extracted with diethyl ether (3 x 70 mL). The combined organic fractions were washed with brine (100 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (pentane/EtOAc 95:5) to yield **44** as a pale yellow oil (868 mg, 81%).

IR (KBr): 3661.7 (m), 1687.6, (s), 1612.9 (s), 1590.3 (m), 1286.8 (s), 1248.6 (s) cm^{-1}.

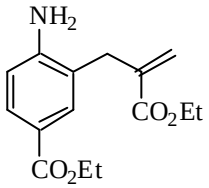
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J* = 1.8 and 8.4 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.43 (bs, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 151.0, 141.3, 131.3, 121.9, 113.5, 82.5, 61.1, 14.8.

MS (EI, 70 eV): 357 (4), 316 (100), 286 (79), 242 (44), 168 (25), 115 (18).

$C_9H_{10}O_2NI$	Calcd.	C, 37.14	H, 3.46	N, 4.81
	Found	C, 31.11	H, 3.46	N, 4.81

Synthesis of ethyl 3-(2-ethoxycarbonyl-2-propenyl)-4-[(*E*)-phenylmethylidene] aminobenzoate



Prepared according to TP 7 from **44** (365 mg, 1.0 mmol). Reaction time 2 h at 35 °C. After concentration *in vacuo* the product was purified by cation exchange extraction on a Varian bond elute SCX column. The SCX column was conditioned with 10 % acetic acid in methanol, then the product was applied in methanol and the column washed with methanol and acetonitrile. For the elution of the product, 10 % ammonia in methanol was employed. Concentration of the latter fraction yielded the product (260 mg, 94 %).

Mp 241 °C.

IR (KBr): 3201 (br), 2981 (w), 1714 (s), 1677 (s), 1614 (m), 1365 (m), 1256 (m) cm^{-1}.

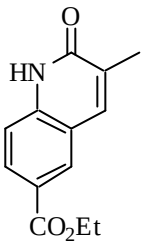
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.78 (m, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.27 (s, 1H), 5.56 (s, 1H), 4.35-4.25 (m, 4H), 3.81 (s, 2H), 1.37-1.29 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 165.8, 140.8, 134.9, 129.8, 125.6, 125.2, 122.3, 115.6, 61.5, 61.3, 33.9, 14.8, 14.7

MS (EI, 70 eV): 277 (55), 232 (86), 203 (58), 186 (55), 158 (57), 130 (100), 77 (22).

$C_{15}H_{19}O_4N$ HRMS: Calcd. 277.1314
Found 277.1319

Synthesis of ethyl 3-methyl-2-oxo-1,2-dihydro-6-quinolinecarboxylate (45)



Compound **44** (130 mg, 0.5 mmol) was taken up in dry ethanol (3 mL) and KOEt (126 mg, 1.5 mmol) was added. The reaction mixture was stirred at rt overnight, then the product was concentrated and purified by flash chromatography (pentane/EtOAc 8:2) yielding **45** as white crystals (110 mg, 96 %).

Mp 231 °C.

IR (KBr): 3434 (br), 1716 (m), 1663 (s), 1582 (m), 1259 (m), 1210 (m) cm^{-1}.

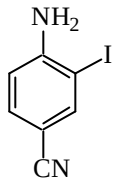
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 1.8 Hz, 1H), 8.04 (dd, *J* = 1.8 and 8.4 Hz, 1H), 7.64 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 1.75 (bs, 1H), 1.35 (t, *J* = 7.2, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 165.2, 140.8, 138.0, 131.4, 130.5, 129.6, 125.2, 120.1, 115.9, 61.5, 17.2, 14.8.

MS (EI, 70 eV): 231 (58), 186 (100), 158 (10), 130 (20).

$C_{13}H_{13}O_3N$ Calcd. C, 67.52 H, 5.67 N, 6.06
Found C, 67.22 H, 5.73 N, 5.80

Synthesis of 4-amino-3-iodobenzonitrile



Prepared according to TP 9 from 4-aminobenzonitrile (2.36 g, 20 mmol). Reaction time: 1 h at rt. Purification by flash chromatography (pentane/EtOAc 9:1) yielded ethyl 4-amino-3-iodobenzoate as a pale white powder (4.31 g, 88 %).

Mp 108 °C.

IR (KBr): 3457 (m), 3348 (s), 2116 (s), 1621 (s), 1590 (m), 1498 (s) cm^{-1}.

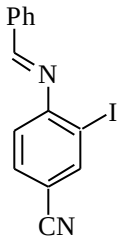
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 1.8 Hz, 1H), 7.30 (dd, *J* = 1.8 and 8.4 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.43 (bs, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 151.1, 143.1, 133.6, 118.8, 113.9, 102.0, 82.2.

MS (EI, 70 eV): 244 (100), 117 (20), 90 (12), 63 (6).

$C_7H_5N_2I$	Calcd.	C, 34.45	H, 2.07	N, 11.48
	Found	C, 34.47	H, 1.92	N, 11.48

Synthesis of 3-iodo{[(*E*)-phenylmethylidene]amino}benzonitrile (47)



Prepared analogously to **38** from 4-amino-3-iodobenzonitrile (3.8 g, 15 mmol). Reaction time: 2 h at 110 °C. Flash chromatography (pentane/diethyl ether/TEA 20:1:2) yielded **47** as yellow crystals (3.7 g, 72 %).

Mp 80 °C.

IR (KBr): 3436 (m), 1702 (s), 1626 (s), 1578 (s), 1290 (s), 1252 (s).

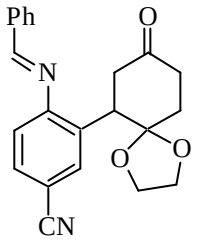
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18 (s, 1H), 8.05 (d, *J* = 1.8 Hz, 1H), 7.90-7.87 (m, 2H), 7.56 (dd, *J* = 1.8 and 7.8 Hz, 1H), 7.45-7.40 (m, 3H), 6.91 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.9, 157.6, 142.6, 135.5, 133.7, 133.0, 129.9, 129.4, 119.1, 117.8, 110.5, 94.3.

MS (EI, 70 eV): 332 (100), 228 (10), 205 (22), 177 (8), 101 (9).

$C_{14}H_9N_2I$	Calcd.	C, 50.63	H, 2.73	N,8.43
	Found	C, 50.65	H, 2.74	N, 8.41

Synthesis of 3-(8-oxo-1,4-dioxaspiro[4.5]dec-6-yl)-4-[(*E*)-phenylmethylideneamino]-benzonitrile (48)



A dried, argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with dry LiCl (16 mg, 0.4 mmol) and CuI (38 mg, 0.2 mmol) in dry THF (6 mL). To the resulting solution $(CH_3)_3SiCl$ (0.25 mL, 1.9 mmol) and 1,4-dioxaspiro[4.5]dec-6-en-8-one were added. A second dried, argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar, was charged with **47** (664 mg, 2.0 mmol) in dry THF (1.5 mL) and cooled to -40 °C. *i*-PrMgBr (2 mL, 1.3 M in THF, 2.6 mmol) was then added slowly and the mixture was stirred at -40 °C for 1 h, by which tilme the exchange was complete (checked by TLC analysis) and the solution of the first flask was added. The resulting mixture was stirred for an additional 1 h before quenching with saturated, aqueous NH_4Cl (3 mL). The aqueous phase was extracted several times with diethyl ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane/EtOAc/TEA 8:2:0.1) yielded **48** as a pale yellow powder (386 mg, 56 %).

Mp 204 °C.

IR (KBr): 3414 (br), 3339 (m), 2217 (m), 1708 (m), 1609 (s), 1517 (m) cm^{-1}.

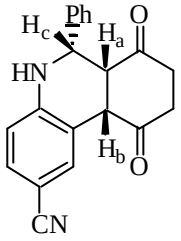
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (s, 1H), 7.78-7.14 (m, 6H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.10 (d, *J* = 6.9 Hz, 1H), 3.99-3.84 (m, 3H), 3.69-3.64 (m, 2H), 3.16-2.95 (m, 2H), 2.11-1.93 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.1, 148.1, 141.4, 135.5, 132.5, 129.3, 128.7, 127.0, 121.0, 117.0, 114.2, 109.1, 98.8, 66.1, 64.8, 54.0, 52.9, 43.7, 37.8, 33.2.

MS (EI, 70 eV): 360 (20), 231 (71), 155 (47), 100 (100).

$C_{22}H_{20}O_3N_2$ Calcd. C, 76.43 H, 6.41 N, 3.88
Found C, 76.28 H, 6.72 N, 3.64

Synthesis of 7,10-dioxo-6-phenyl-5,6,6a,7,8,9,10,10a-octahydro-2-phenanthridine-carbonitrile (49)



Compound **48** (100 mg, 0.28 mmol) was dissolved in CH_2Cl_2/TFA/water 9:1:1 (3 mL) and stirred for 12 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed several times with $NaHCO_3$, then dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (DCM) yielded **49** as a pale white powder (63 mg, 72 %, 1 steroeisomer).

Mp 179 °C.

IR (KBr): 3038 (m), 2218 (m), 1713 (s), 1609 (s), 1520 (s), 1314 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32-7.07 (m, 7H), 6.59 (d, *J* = 2.4 Hz, 1H), 5.21 (bs, 1H), 4.92 (bs, 1H), 3.63 (d, *J* = 5.7 Hz, 1H), 3.07 (dd, *J* = 2.7 and 5.7 Hz, 1H), 2.78-2.41 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 206.3, 205.5, 146.7, 141.9, 133.4, 132.1, 129.5, 128.5, 126.0, 120.1, 114.9, 113.9, 100.1, 53.2, 50.3, 45.6, 36.3, 36.2.

MS (EI, 70 eV): 316 (9), 310 (100); 282 (57), 235 (19), 155 (14).

$C_{20}H_{16}O_2N_2$ HRMS: Calcd. 316.1212
Found 316.1217

The stereochemistry of the product was determined by NOESY, ^{1}H and ^{13}C NMR experiments. The observation of a NOE between H_a (3.07 ppm) and H_b (3.63 ppm) as well as between H_a and H_c (6.59 ppm) clearly indicated that the protons are on the same face of the molecule.

Abbreviations

Ac	acetyl
acac	acetylacetonate
approx.	approximately
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bp	boiling point
br	broad
Bu	butyl
c	concentration
Calcd.	calculated
cat.	Catalytic
conc.	concentrated
d	doublet
dba	dibenzylideneacetone
DBE	1,2-dibromoethane
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
equiv	equivalent
EI electron	ionisation
Et	ethyl
EtOAc	ethyl acetate
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
i-Pr	isopropyl
IR	infra-red
J	coupling constant
M	molar
Me	methyl
min	minute
Mp	melting point
MS	mass spectroscopy
NMP	*N*-methyl-pyrrolidone
NMR	nuclear magnetig resonance
Pent	pentyl
PG	protecting group
Ph	phenyl
Piv	pivaloyl
q	quartet
quant.	quantitative
rt	room temperature
s	singlet
sec	seconds
t	triplet
TBAI	tetrabutylammonium iodide
TEA	triethyl amine
TFA	trifluoroacetic acid
TLC	thin layer chromatography
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
TMS	trimethylsilyl
TMS-Cl	chlorotrimethylsilane
TP	typical procedure
UV	ultra-violet

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