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Mg- and Zn-Mediated Synthesis of Heterocycles in Solution and on the Solid Phase

von
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aus
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Erklärung

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Ehrenwörtliche Versicherung
Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe erarbeitet.
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Laurent Bérillon

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2. Gutachter	Univ.-Prof. Dr. Wolfgang Steglich
Mündliche Prüfung am	_____

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

1) L. Bérillon, R. Wagner, P. Knochel, *J. Org. Chem.* **1998**, *63*, 9117.
"Preparation and Reactions of Zincated Thymine Derivatives"

2) L. Bérillon, A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, G. Cahiez, P. Knochel, *Synlett* **1998**, 1359.
"Preparation of Highly Functionalized Pyridylmagnesium Reagents for the Synthesis of Polyfunctional Pyridines"

3) M. Rottländer, L. Boymond, L. Bérillon, A. Leprêtre, G. Varchi, S. Avolio, H. Laaziri, G. Quéguiner, A. Ricci, G. Cahiez, P. Knochel, *Chem. Eur. J.* **2000**, *6*, 767.
"New Polyfuntional Magnesium Reagents for Organic Synthesis"

4) M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618.
"Preparation of New Polyfunctional Magnesiated Heterocycles Using a Chlorine-, Bromine- or Iodine-Magnesium Exchange"

5) T. Delacroix, L. Bérillon, G. Cahiez, P. Knochel, *J. Org. Chem.* in press.
"Preparation of Functionalized Arylmagnesium Reagents Bearing an *Ortho*-Chloromethyl Group"

To Laurence

Table of contents

General Introduction

1- Overview

Heterocyclic compounds have a wide range of applications[1] and are present in many herbicides (**1a**), fungicides (**1b**), insecticides (**1c**), dyes (**1d**) or pharmaceuticals[2] (**1e**).

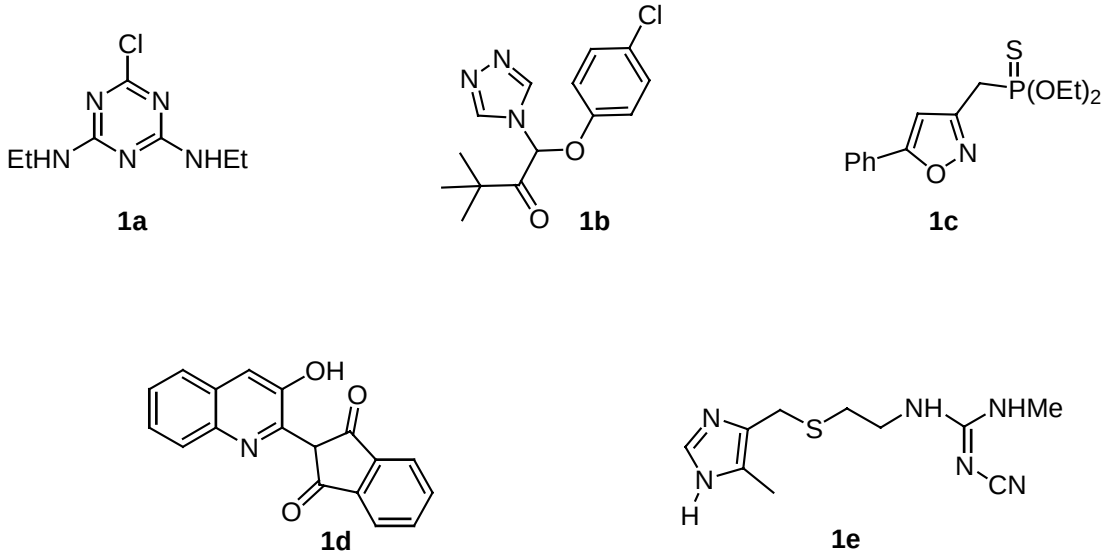
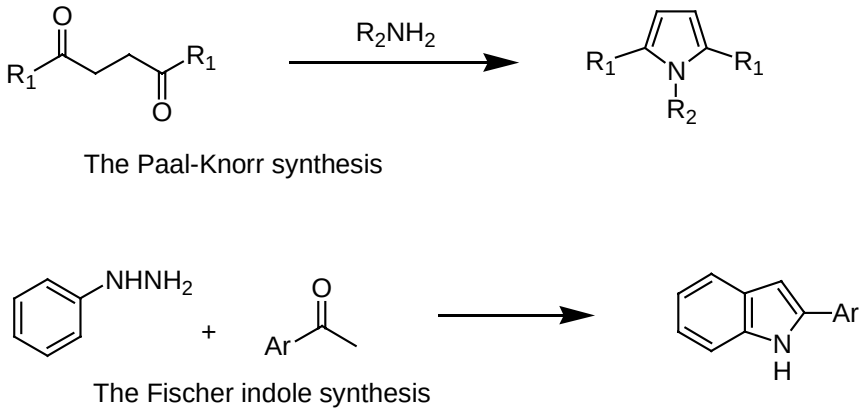


Figure 1.

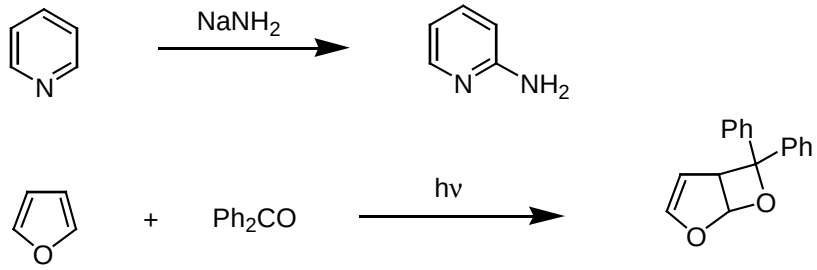
Most heterocyclic compounds with biological applications are not extracted from natural sources but are synthesized. Thus, a broad variety of methods have been developed for the preparation of heterocycles.[3] For many of the common ring systems, cyclisation reactions are available. The Paal-Knorr[4] synthesis of pyrroles from 1,4-dicarbonyl compounds or the Fischer indole synthesis[5] are typical examples which have been extensively used (scheme 1).

[1] For a review of several applications of heterocyclic compounds see: J. K. Landquist, P. J. Crowley, in *Comprehensive Heterocyclic Chemistry*; O. Meth-Cohn, Ed.; Pergamon Press: Oxford, **1984**, Vol. 1.
[2] Of the top 20 pharmaceuticals prescribed in the U.S.A. in 1994, 17 are heterocyclic compounds: A.W. Czarnik, *Acc. Chem. Res*. **1996**, *29*, 112.
[3] T.L. Gilchrist, *Heterocyclic Chemistry*, Longman Press: Harlow, **1997**. G. R. Newkome, W. W. Paudler, *Contemporary Heterocyclic Chemistry*, Wiley: New York, **1982**.
[4] C. Paal, *Chem. Ber*. **1884**, *17*, 2756. L. Knorr, *Chem. Ber*. **1884**, *17*, 2863. For a review see: R. J. Sundberg in *Comprehensive Heterocyclic Chemistry*; A. R. Katritzky, C. W. Rees, Eds.; Pergamon Press: Oxford, **1984**, Vol. 4, 329.
[5] B. Robinson, *Chem. Rev*. **1969**, *69*, 227.



Scheme 1. The Paal-Knorr and the Fischer indole synthesis as typical heterocyclic ring formation.

Another synthetic approach consists in performing the functionalization of existing heterocycles. Examples of the functionalization of pyridine (Chichibabin reaction[6]) and furan (Paterno-Büchi reaction[7]) are shown in scheme 2.



Scheme 2. Examples of available heterocycle functionalization.

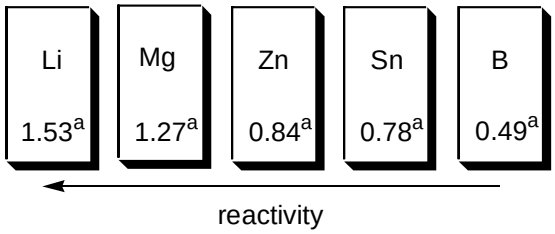
However, with all these methods difficulties are still encountered in the preparation of complex heterocycles which contain sensitive functional groups. Various protecting groups have been needed for the synthesis of these highly functionalized heterocycles.[8] Nonetheless, these protection-deprotection sequences suffer from a mediocre atom economy[9] and are expensive as well as time consuming. Radical reactions, which can often be performed under mild conditions, tolerate various functional groups but are more difficult to tune than polar reactions.[10] Another approach consists in using functionalized heterocyclic organometallics as

[6] For a review see: C. K. Mc Gill, A. Rappa, *Adv. Heterocycl. Chem.* **1988**, *44*, 1.
[7] For a review see: J. A. Porco, S. L. Schreiber in *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming Eds.; Pergamon Press: New York, **1991**, Vol. 5, 151.
[8] P. J. Kocienski, *Protecting Group*, Thieme-verlag, Stuttgart, **1994**.
[9] B. M. Trost, *Angew. Chem.* **1995**, *107*, 259; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 285.
[10] W. B. Motherwell, D. Chrich, *Free Radical Chain Reaction in Organic Synthesis*, Academic Press: London, **1992**.

building blocks. This has become a method of choice in the synthesis of complex heterocycles.

1.1- Organometallic reagents in the synthesis of heterocycles

In the last 15 years, organometallics (R-Met) of various metals (Met = Li, Mg, B, Zn, Sn, etc.) have been prepared. Their reactivity increases with the ionicity of the carbon-metal bond and thus with the difference of electronegativity[11] between the metal and carbon (figure 2).



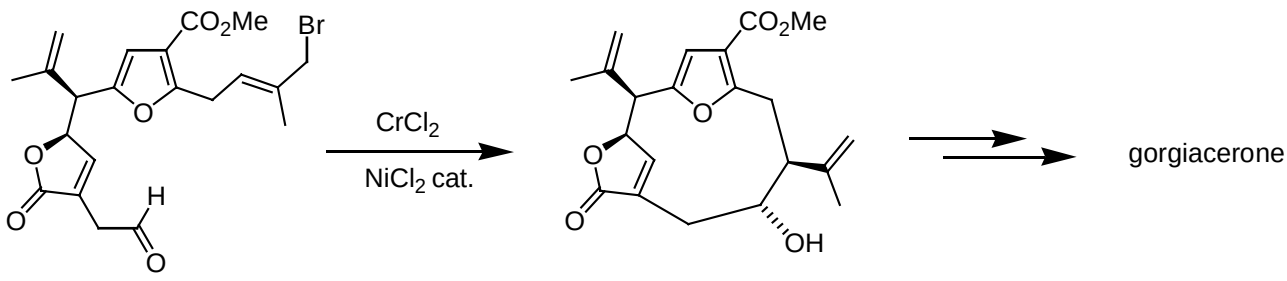
[a] difference of electronegativity with carbon

Figure 2. Difference of electronegativity of some metals with carbon.

Organolithium or organomagnesium reagents have a very polar carbon-metal bond and their high reactivity has long precluded the presence of functional groups. On the other side of the reactivity spectra are transition metals which form covalent bonds with carbon and thus tolerate sensitive functional groups such as ester, amide, nitro functions etc.

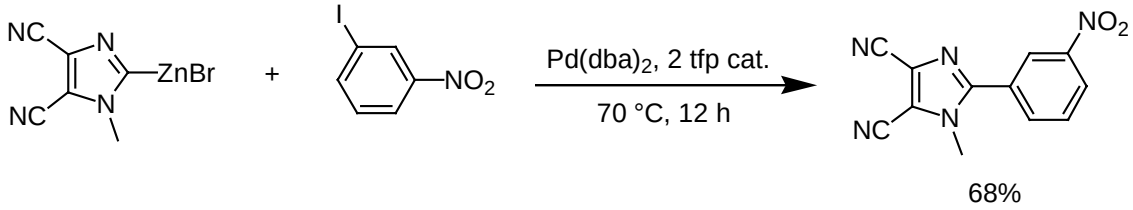
A remarkable example of functional group tolerance can be found in the Nozaki-Takai-Hiyama-Kishi reaction[12] involving a Cr intermediate as the reactive species. This reaction has been extensively used in the synthesis of complex heterocycles. Scheme 3 shows the key step in Paquette's synthesis of gorgiacerone.[13]

[11] E. Negishi, *Organometallics in Organic Synthesis*, Wiley, New York, **1980**.
[12] For reviews see: P. Cintas, *Synthesis* **1982**, *248*. N. A. Saccomano in *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, S. L. Schreiber, Eds.; Pergamon Press: New York, **1991**, Vol. 1, 173.
[13] C. M. Rayner, P. C. Astles, L. A. Paquette, *J. Am. Chem. Soc*. **1992**, *114*, 3926.



Scheme 3. Functional group tolerance in the Nozaki-Takai-Hiyama-Kishi reaction.

A main drawback of these transition metal reagents is their lack of reactivity. However, transmetalation to various transition metal salts (Pd, Ni, Cu etc.) considerably expands the scope of their application in organic synthesis. For example, cross-coupling reactions using organozinc reagents (Negishi reaction[14]), organotin reagents (Stille reaction[15]) or organoboron reagents (Suzuki reaction[16]) are well-established methods for the formation of carbon-carbon bonds. In the following example[17] where both reactants are functionalized the desired heterocycle is obtained in 68 % yield.



Scheme 4. Functional group tolerance in the Negishi reaction.

As already mentioned, main group organometallic reagents have a more polar carbon-metal bond and functionalized organolithium reagents have to be prepared at low temperature. Pioneering work by Parham[18] has shown that functionalized organolithium reagents can be prepared by a bromine-lithium exchange at -100 °C and quenched with various electrophiles. Thus a cyano function can be tolerated in this preparation as shown in scheme 5.

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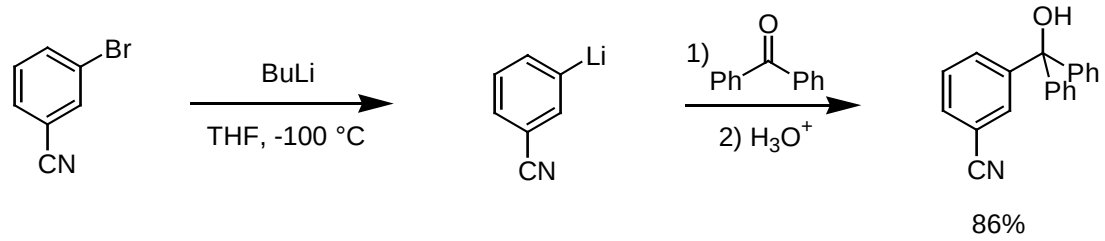
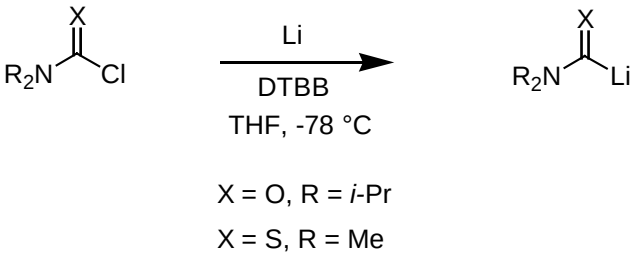
[14] E. Negishi, A. O. King, N. Okukadu, *J. Org. Chem.* **1977**, *42*, 1821. E. Negishi, T. Takahashi, A. O. King, *Org. Synth.* **1988**, *66*, 67.
[15] J. K. Stille, *Angew. Chem.* **1986**, *98*, 508; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
[16] N. Miyaura, K. Maeda, H. Suginome, A. Suzuki, *J. Org. Chem.* **1982**, *47*, 2117.
[17] A. S. B. Prasad, T. M. Stevenson, J. R. Citineni, V. Nyzam, P. Knochel, *Tetrahedron*, **1997**, *53*, 7237.
[18] W. E. Parham, L. D. Jones, Y. Sayed, *J. Org. Chem.* **1975**, *40*, 2394. W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187. W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704. W. E. Parham, D. W. Boykin, *J. Org. Chem.* **1977**, *42*, 260. W. E. Parham, R. M. Piccirilli, *J. Org. Chem.* **1977**, *42*, 257.



Scheme 5. Functionalized organolithium reagents prepared by low-temperature bromine-lithium exchange.

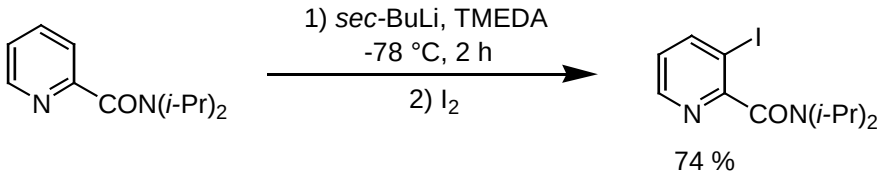
Alternatively functionalized lithium reagents can be prepared by direct lithiation with lithium powder in the presence of a catalytic amount of 4,4´-di-tert-butylbiphenyl (DTBB) as demonstrated by Yus.[19]



Scheme 6. Low temperature preparation of acyllithium reagents.

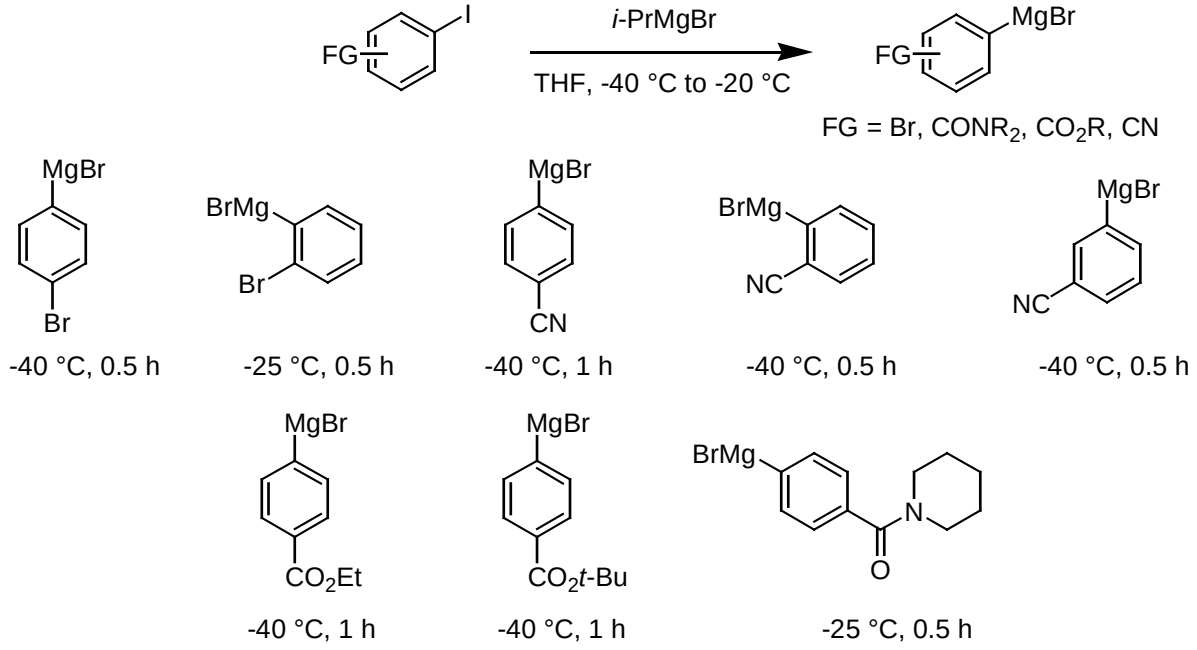
Another well-established method for the generation of functionalized lithium reagents is the so-called directed *ortho*-metalation (DoM)[20] using a strong lithium base as metalating agent. Here the presence of an *ortho*-directing functional group on the aryl or heteroaryl moiety ensures good regioselectivity. Many *ortho*-directing groups (CN, SO_2NR_2, $OCONR_2$, $CONR_2$, 2-oxazoline, CH_2NR_2, CF_3, OMe etc.) have been reported and various heterocycles such as pyridines[21] have been prepared using this reaction (scheme 7).

[19] C. Gomez, F. F. Huerta, M. Yus, *Tetrahedron Lett*. **1997**, *38*, 687. C. Gomez, F. F. Huerta, M. Yus, *Tetrahedron* **1998**, *54*, 6177. D. J. Ramon, M. Yus, *Tetrahedron Lett*. **1993**, *34*, 7115. C. Gomez, F. F. Huerta, M. Yus, *Tetrahedron* **1998**, *54*, 1853. F. Foubelo, A. Gutierrez, M. Yus, *Tetrahedron Lett*. **1997**, *38*, 4837. A. Guijarro, M. Yus, *Tetrahedron* **1995**, *51*, 231. D. Guijarro, B. Mancheno, M. Yus, *Tetrahedron Lett*. **1994**, *50*, 8551. E. Alonso, D. J. Ramon, M. Yus, *Tetrahedron Lett*. **1997**, *38*, 8903.
[20] V. Snieckus, *Chem. Rev*. **1990**, *90*, 879.
[21] G. Quéguiner, F. Marsais, V. Snieckus, J. Epsztajn, *Adv. Heterocycl. Chem*. **1992**, *52*, 187. A. Godart, F. Marsais, N. Plé, F. Trécourt, A. Turck, G. Quéguiner, *Heterocycles*, **1995**, *40*, 1055. G. Quéguiner, *Bull. Soc. Chim. Belg*. **1996**, *105*, 701.



Scheme 7. Ortho directed metalation in the synthesis of functionalized pyridines.

However, only the *ortho* position can be activated which represents a serious limitation. Moreover, all the previously described organolithium reagents are relatively unstable,[22] which makes them difficult to handle especially on industrial scale. Organomagnesium reagents, which have a more covalent carbon-metal bond, are more stable and should be more convenient to handle. However few functionalized organomagnesium reagents have been described due to the lack of a mild method for their preparation. The use of activated magnesium has been reported by Rieke[23] but lacks generality since most functional groups deactivate the surface of the magnesium and inhibit the reaction.[24] Recently, a method to generate functionalized Grignard reagents was developed in our laboratory in collaboration with Prof. G. Cahiez using a low temperature iodine-magnesium exchange (see scheme 8).[25]



Scheme 8. Synthesis of functionalized Grignard reagents by low temperature iodine-magnesium exchange.

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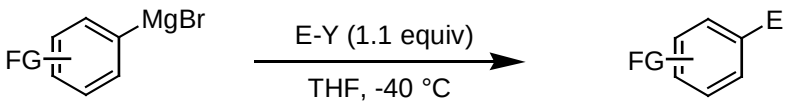
[22] For a study of the stability of common organolithium reagents see: P. Stanetty, M. Mihovilovic, *J. Org. Chem.* **1997**, *62*, 1514.
[23] R. D. Rieke, *Science* **1989**, *246*, 1260.
[24] T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674. J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.
[25] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1701.

These functionalized organometallics display the typical reactivity of Grignard reagents and can be trapped with various electrophiles (scheme 9).



FG = Br, $CONR_2$, CN, CO_2Et, CO_2tBu

E-Y = aldehydes, allyl bromide, TosCN, PhSSPh etc.

Scheme 9. Reactivity of functionalized Grignard reagent.

All the chemistry discussed so far was performed in solution. However, solid phase synthesis has recently become a powerful tool in organic synthesis. First developed for the preparation of peptides,[26] this new technique is also well suited for heterocylic synthesis and most of the reactions cited above have been transposed onto solid phase.

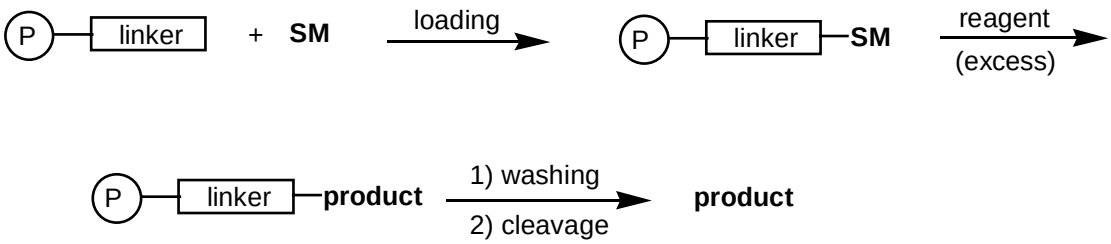
1.2- Solid phase synthesis

During the last 15 years, novel high throughput screening methods have been developed and offer the possibility to test thousands of molecules per day.[27] For this reason, high-throughput methods are also needed to generate large libraries of compounds. Solid phase synthesis,[28] with its ability to drive a reaction to completion by the use of excess reagents and the ease of purification between chemical steps, has become a powerful tool for combinatorial chemistry.[29]

The principle of solid phase synthesis is described below (figure 3). In a first step, the starting material is grafted with a suitable linker[30] to the polymeric support. An excess of reagent is

[26] R. B. Merrifield, *J. Am. Chem. Soc*. **1963**, *85*, 2149. E. Bayer, *Angew. Chem*. **1991**, *103*, 117; *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 113.
[27] R. B. Silverman, J. Seydel, *Medizinische Chemie*, VCH: Weinheim, **1994**. C. G. Wermuth, *Medicinal Chemistry for the 21st Century*, Blackwell: Oxford **1992**.
[28] D. Obrecht, J. M. Villalgordo, *Solid Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compounds*, Pergamon Press: Oxford, **1998**. B. A. Bunin, *The Combinatorial Index*, Academic Press: New York, **1998**.
[29] F. Balkenhohl, C. v. d. Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem*. **1996**, *108*, 2436; *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 2288.
[30] I. W. James, *Tetrahedron*, **1999**, *55*, 4855.

then used to ensure high conversion. A simple washing step and cleavage from the resin afford the desired product without any further purification. Such a process can easily be automated and enables the parallel synthesis of a large amount of molecules with a dramatic gain of time.

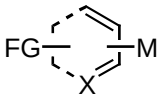


P = polystyrene, polyethylene glycol etc.
SM = starting material

Figure 3.

2- Projected work

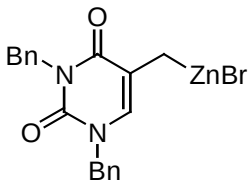
During this work, we focussed on the preparation of various functionalized heterocyclic organometallic reagents of type **A** and on their applications in heterocycle synthesis.



M = metal
FG = functional group
X = heteroatom

A

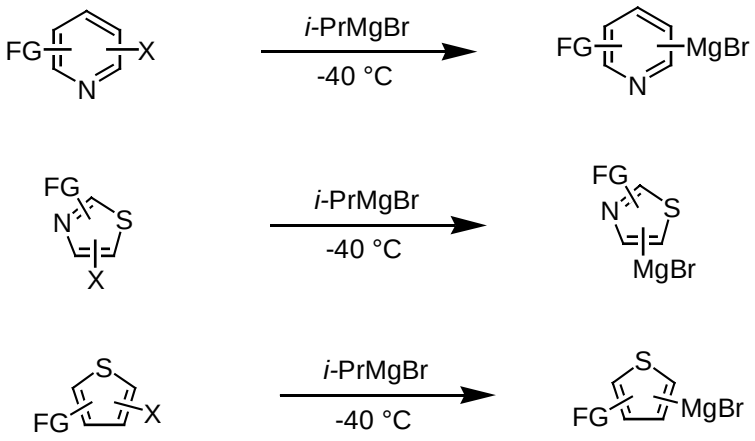
In a first part we looked at zinc derivatives. For the reasons discussed above organozinc reagents display a remarkable functional group tolerance. Thus the preparation of highly functionalized intermediates such as zincated thymine **2** seemed promising and was attempted during this work.



2

The reactivity of **2** was studied in Negishi cross-coupling reactions.

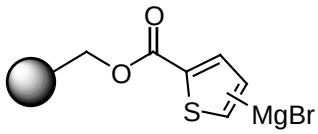
In a second part, we examined the possibility of preparing heterocyclic functionalized Grignard reagents using a low temperature halogen-magnesium exchange reaction.



X = I, Br, Cl
FG = functional group

These organomagnesium derivatives contain a very polar carbon-metal bond and should exhibit a high reactivity towards most electrophiles.

Finally, the low temperature halogen-magnesium exchange was performed on the solid phase and the synthesis of resin-attached thienyl Grignard reagents of type **B** was attempted.



B

Theoretical part

1- Preparation of zincated thymine derivatives and application in cross-coupling reactions

1.1- Introduction

Pd-catalyzed cross-coupling reactions[31] are very important for the formation of carbon-carbon bonds and are widely used, including for the synthesis of complex natural products.[32] Although many different organometallics R^2-M (R^2 = aryl, alkenyl, benzyl; M = Li,[33] MgX: Kharasch reaction,[34] M = ZnX: Negishi reaction,[14] M = $SnBu_3$: Stille reaction,[15] M = $B(OH)_2$: Suzuki reaction[16] etc.) can be used, a common mechanism can be drawn (figure 4).[35]

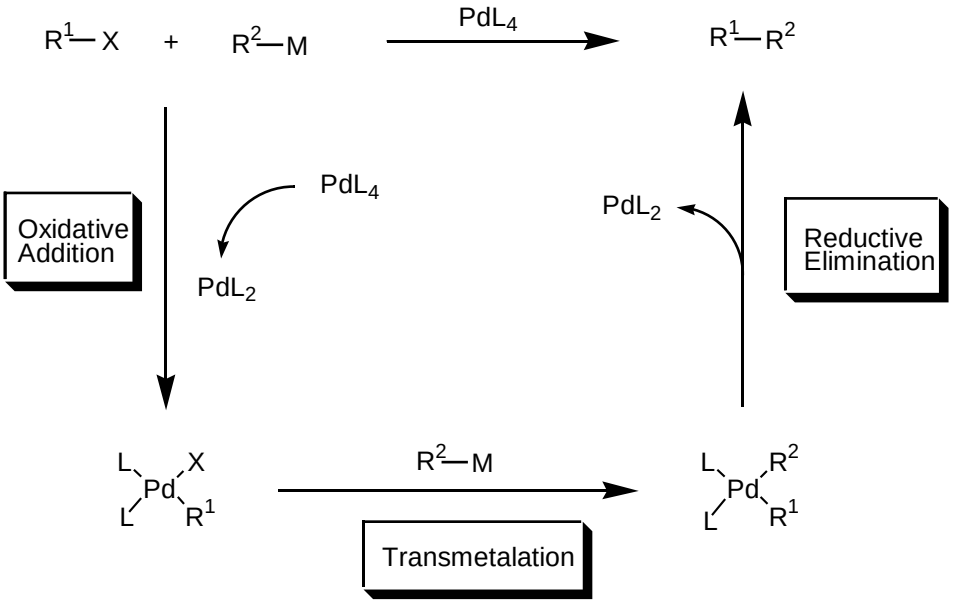


Figure 4. Mechanism of the Pd-catalysed cross-coupling reaction.

The first step is an oxidative addition of a 14 electron palladium complex into the carbon-halogen bond of the halide (RX) to produce a palladium(II) complex. Reaction with the organometallic R^2M (transmetalation step), followed by reductive elimination affords the

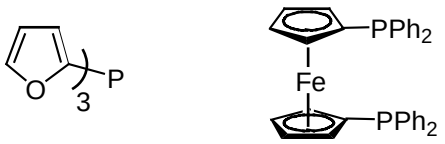
[31] J. Tsuji, *Palladium Reagents and catalyst*, Wiley: New York, 1995.
[32] K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, Verlag Chemie, Weinheim, **1996**.
[33] A. Minato, K. Tamao, T. Hayashi, K. Suzuki, M. Kumada, Tetrahedron Lett. **1981**, *22*, 5319.
[34] A. Minato, K. Tamao, T. Hayashi, K. Suzuki, M. Kumada, Tetrahedron Lett. **1980**, *21*, 845.
[35] E. Negishi, *Acc. Chem. Res*. **1982**, *15*, 340. M. Kumada, *Pure Appl. Chem*. **1980**, *52*, 669.

cross-coupling product while regenarating the palladium(0) species and closing the catalytic cycle.

Although the reactive species is a palladium(0) complex, palladium(II) complexes such as $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$ can also be used (*in situ* reduction). $Pd(PPh_3)_4$ is a common palladium(0) source but its increased air sensitivity makes $Pd(dba)_2$ much more convenient to handle (shelf stable). Another advantage of $Pd(dba)_2$ is the possibility to add two equivalents of phosphine to form directly the 14-electron complex (excess of phosphine has been shown to be deleterious[31]).

The steric as well as the electronic properties of the ligand (often phosphine) are also extremely important. The oxidative addition is facilitated by electron rich phosphines (increased electron density on the metal) whereas electron poor phosphines favor the transmetalation step as well as the reductive elimination. Thus, the choice of the ligand depends on which step is rate determining. In the case of aryl iodides oxidative addition is usually fast and electron poor ligands give better results. On the other hand, the oxidative addition is the rate determining step for aryl chlorides and electron rich ligands strongly facilitate the cross-coupling reaction in this case.

Tri-2-furylphosphine[36] (tfp) and bis-diphenylphosphinoferrocene[37] (dppf) are two ligands which were used during this work for Negishi cross-coupling reactions (figure 5).



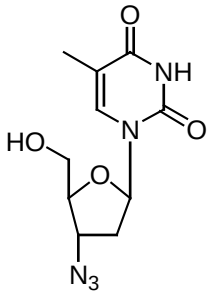
tfp dppf

Figure 5.

[36] V. J. Farina, B. Krishnan, *J. Am. Chem. Soc*. **1991**, *113*, 9585.
[37] T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc*. **1984**, *106*, 158.

1.2- Synthesis of thymine derivatives

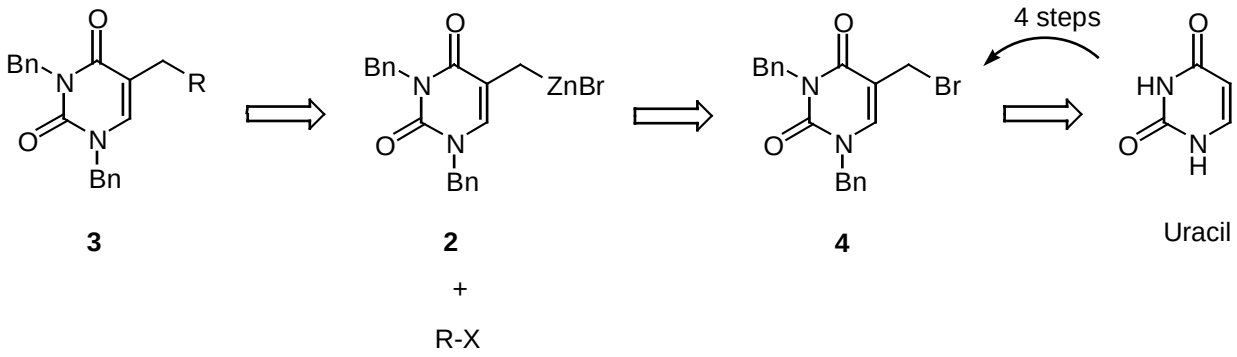
Thymine belongs to the DNA bases and as such is a logical starting point in the search for drugs against cancers and viruses. One major approach for such potential drugs in the past has been the investigation of nucleoside analogues[38] (a purine or pyrimidine base linked to a sugar). For example Zidovudine (AZT) **C** is used in the treatment of AIDS.



C: AZT

The proposed target molecules in this work were thymine derivatives with the general structure **3**.

The presence of two sensitive carbonyl groups in the thymine ring is a key feature of structure **3** and had to be taken into account in the following retrosynthesis (scheme 10).



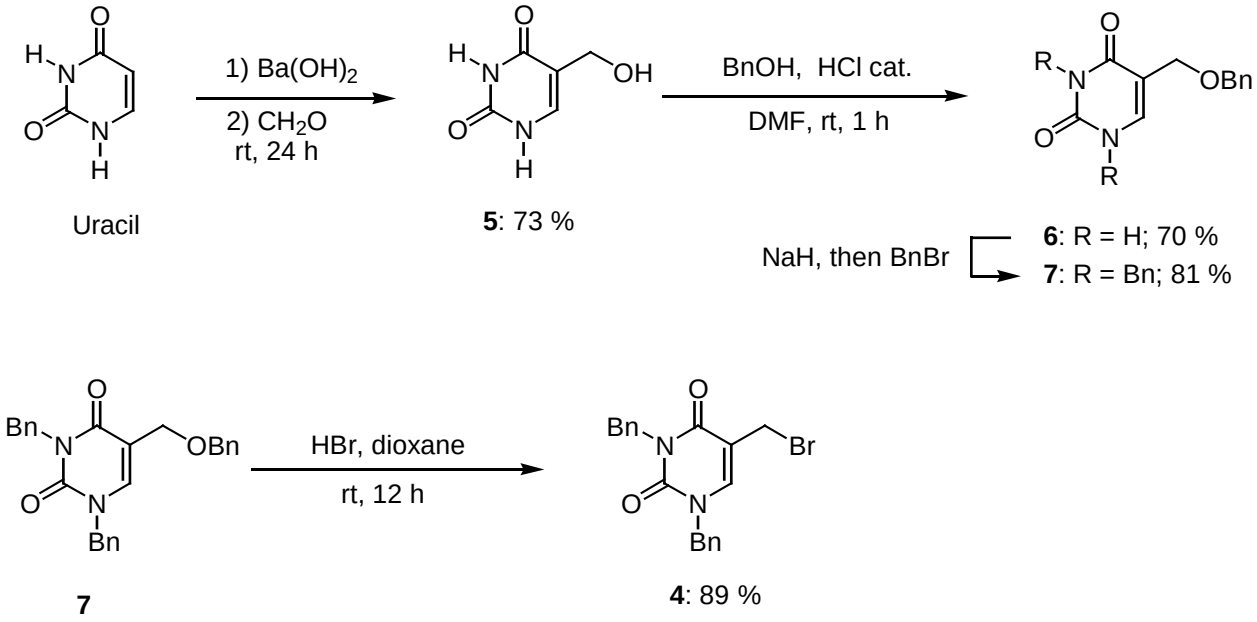
Scheme 10. Retrosynthesis of thymine derivatives of type **3**.

[38] For reviews see: M. F. Jones, *Chem. Ber*. **1988**, 1122. G. B. Elion, *Angew. Chem.* **1989**, *101*, 893; *Angew. Chem. Int. Ed. Engl*. **1989**, *28*, 870.

As already mentioned, organozinc reagents have been extensively used in Pd-catalyzed cross-coupling reaction due to their exceptional functional group tolerance.[39] Thus, zincated thymine derivative **2** was selected as potential intermediate. The corresponding heterocyclic benzylic bromide **4** should be easily available starting from uracil.

1.2.1- Synthesis in solution

The synthesis of benzylic bromide **4** was achieved starting from commercially available uracil (scheme 11).

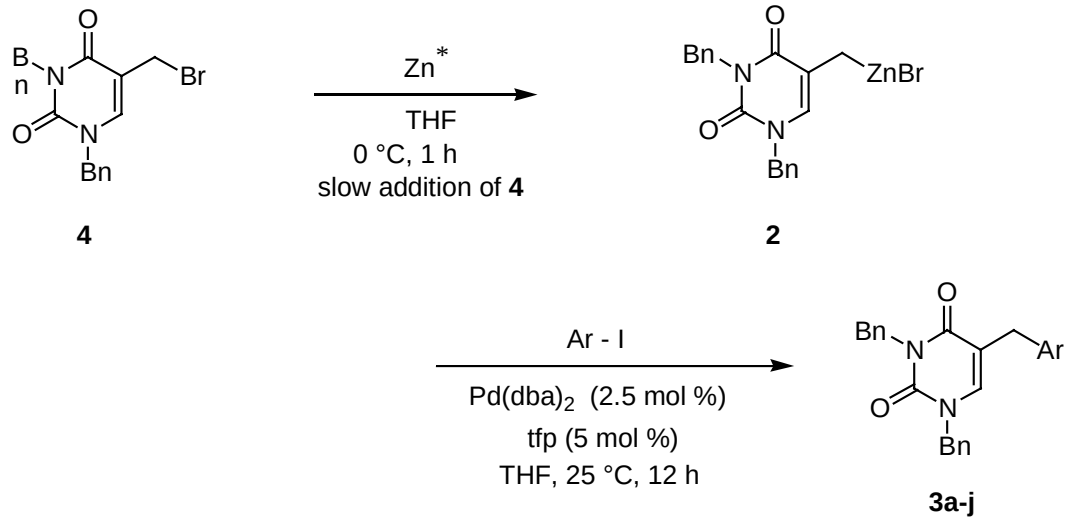


Scheme 11. Preparation of benzylic bromide **4** from uracil.

Treatment of uracil with $Ba(OH)_2$ and aqueous formaldehyde afforded after 24 h at rt the desired hydroxymethyl derivative **5** in 73 % yield following a literature procedure.[40] After two straightforward protecting steps, tribenzylated product **7** was obtained in 57 % overall yield. The conversion of **7** to 1,3-dibenzyl-5-(bromomethyl)uracil **4** was performed using a HBr solution in 1,4-dioxane. This compound was relatively unstable and underwent partial decomposition when chromatographed on silica. However, bromide **4** could be obtained in pure form by recrystallization from ether (89 % yield).

[39] P. Knochel, R. Singer, *Chem. Rev*. **1993**, *93*, 2117.

Zinc insertion in a carbon-halogen bond is especially well suited for the formation of benzylic zinc reagents.[41] Important for the success of this reaction is the activation of the zinc powder by treatment with 1,2-dibromoethane and TMSCl.[42] A slow addition at 0 °C of benzylic bromide **4** using a syringe pump (to avoid Wurz product formation) to previously activated zinc afforded the zincated thymine derivative **2** in approximately 80 % yield as estimated by titration. This zinc reagent showed good stability and could be stored without problems for up to one month at 0-5 °C.



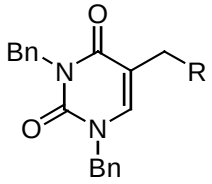
Scheme 12. Preparation of thymine derivatives **3a-j** using a Negishi cross-coupling reaction.

The utility of the zinc reagent **2** was demonstrated by performing cross-coupling reactions. Thus, Negishi cross-couplings between zincated thymine derivative **2** and various aryl iodides led after 12 h at rt using $Pd(dba)_2$/2 tfp as catalyst to products **3a-j** in moderate to good yields (scheme 12, Table1).

It is important to note that various functionalized iodides are tolerated in this reaction, such as those bearing a chloride (entry 3), bromide (entry 4), cyano (entry 8) or nonaflate group[43] (entry 10). However, in the case of 1-iodo-4-nitrobenzene (entry 11) only decomposition was observed, leading to mixture of unidentified products.

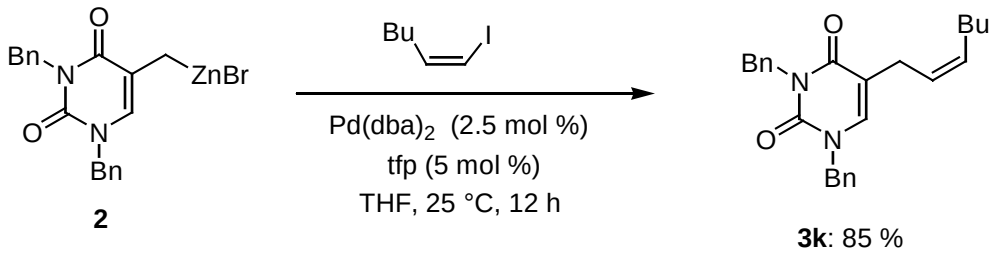
[40] R. Brossmer, E. Röhm, *Liebigs Ann. Chem.* **1966**, *692*, 119.
[41] S. C. Berk, M. C. P. Yeh, N. Yeong, P. Knochel, *Organometallics*, **1990**, *9*, 3053.
[42] C. Jubert, P. Knochel, *J. Org. Chem.* **1992**, *57*, 5431.
[43] M. Rottländer, P. Knochel, *J. Org. Chem.* **1998**, *63*, 203.

Table 1. Arylated thymine derivatives **3a-j** obtained by the reaction of the heterocyclic benzylic zinc reagent **2** with aryl iodides in the presence of palladium(0).

Entry	ArI	Product of type **3**	yield (%)[a]
			
1	PhI	**3a**: R = Ph	89
2	3,5-$Me_2C_6H_3I$	**3b**: R = $Me_2C_6H_3$-	81
3	*p*-ClC_6H_4I	**3c**: R = *p*-ClC_6H_4-	80
4	*p*-BrC_6H_4I	**3d**: R = *p*-BrC_6H_4-	89
5	*p*-$CF_3C_6H_4I$	**3e**: R = *p*-$CF_3C_6H_4$-	86
6	*p*-$MeOC_6H_4I$	**3f**: R = *p*-$MeOC_6H_4$-	62
7	*o*-$MeOC_6H_4I$	**3g**: R = *o*-$MeOC_6H_4$-	66
8	*o*-NCC_6H_4I	**3h**: R = *o*-NCC_6H_4-	76
9	*m*-$MeOC_6H_4I$	**3i**: R = *m*-$MeOC_6H_4$-	80
10	*m*-$C_4F_9SO_3C_6H_4I$	**3j**: R = *m*-$C_4F_9SO_3C_6H_4$-	95
11	*p*-$NO_2C_6H_4I$	R = *p*-$NO_2C_6H_4$	-

[a]Isolated yield of analytically pure products.

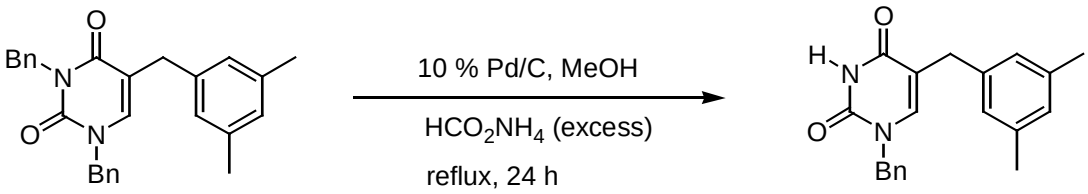
Interestingly a similar reaction was also possible with alkenyl iodides such as (*Z*)-1-iodohexene leading to the desired cross-coupling product **3k** in 85 % (scheme 13).



Scheme 13. Negishi cross coupling between (*Z*)-1-iodohexene and zincated thymine **2**.

1.2.2- Deprotection of N-benzyl protected thymine derivatives

Numerous methods are available for the deprotection of N-benzylated groups.[44] First, several conventional methods were tried. Hydrogenation[45] using $Pd(OH)_2$ under pressure of hydrogen failed. No reaction was observed with α-chloroethyl chloroformate[46] and the use of sodium[47] dissolved in liquid ammonia resulted in total decomposition of the starting material. Finally, a selective mono deprotection was realized by transfer hydrogenation[48] with ammonium formate and 10 % Pd-C (scheme 14).



3a **8**: 77 %

Scheme 14. N-Debenzylation by transfer hydrogenation.

1.2.3 - Solid phase synthesis of thymine derivatives

As already mentioned, solid phase synthesis has become a powerful tool in combinatorial chemistry and several cross-coupling reactions have been optimized on the solid phase including Negishi cross-coupling.[49]

Rink-resin-attached *p*-iodobenzamide **9a** and Wang-resin-attached *o*- *m*- or *p*- iodobenzoates **9c-d** were easily prepared using standard procedures (scheme 15).[50] The resin was treated with the appropriate iodobenzoic acid (10 equiv) in presence of DMAP (1.0 equiv) and DIC (5.0 equiv). After 12 h at rt, the resin was filtered, washed repeatedly with CH_2Cl_2 and MeOH and dried in an oven (55 °C) overnight. The HPLC-purity was checked by cleaving a small amount of the resin with TFA and was greater than 95 % in all cases.

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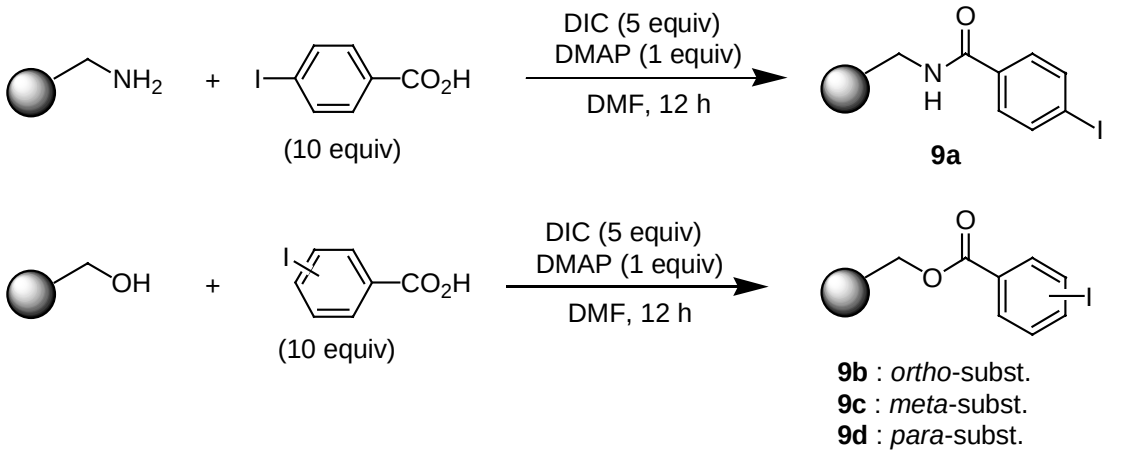
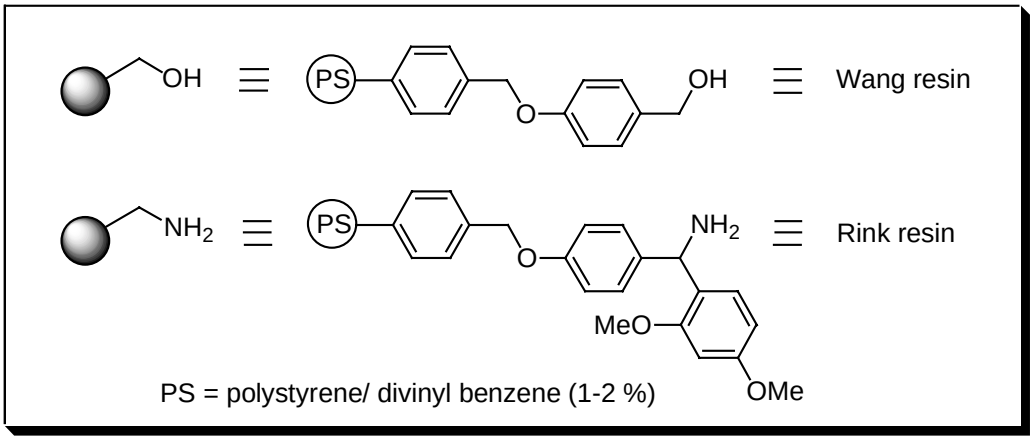
[44] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley: New York, **1999**.
[45] R. C. Bernotas, R. V. Cube, *Synth. Commun*. **1990**, *20*, 1209.
[46] R. A. Olofson, J. T. Martz, J.-P. Senet, M. Piteau, T. Malfroot, *J. Org. Chem*. **1984**, *49*, 2081.
[47] V. du Vigneaud, O. K. Behrens, *J. Biol. Chem*. **1937**, *117*, 27.
[48] S. Ram, L. D. Spicer, *Tetrahedron Lett*. **1987**, *28*, 515. S. Ram, L. D. Spicer, *Synth. Commun*. **1987**, *17*, 415.
[49] S. Marquais, M. Arlt, *Tetrahedron Lett*. **1996**, *37*, 5491.

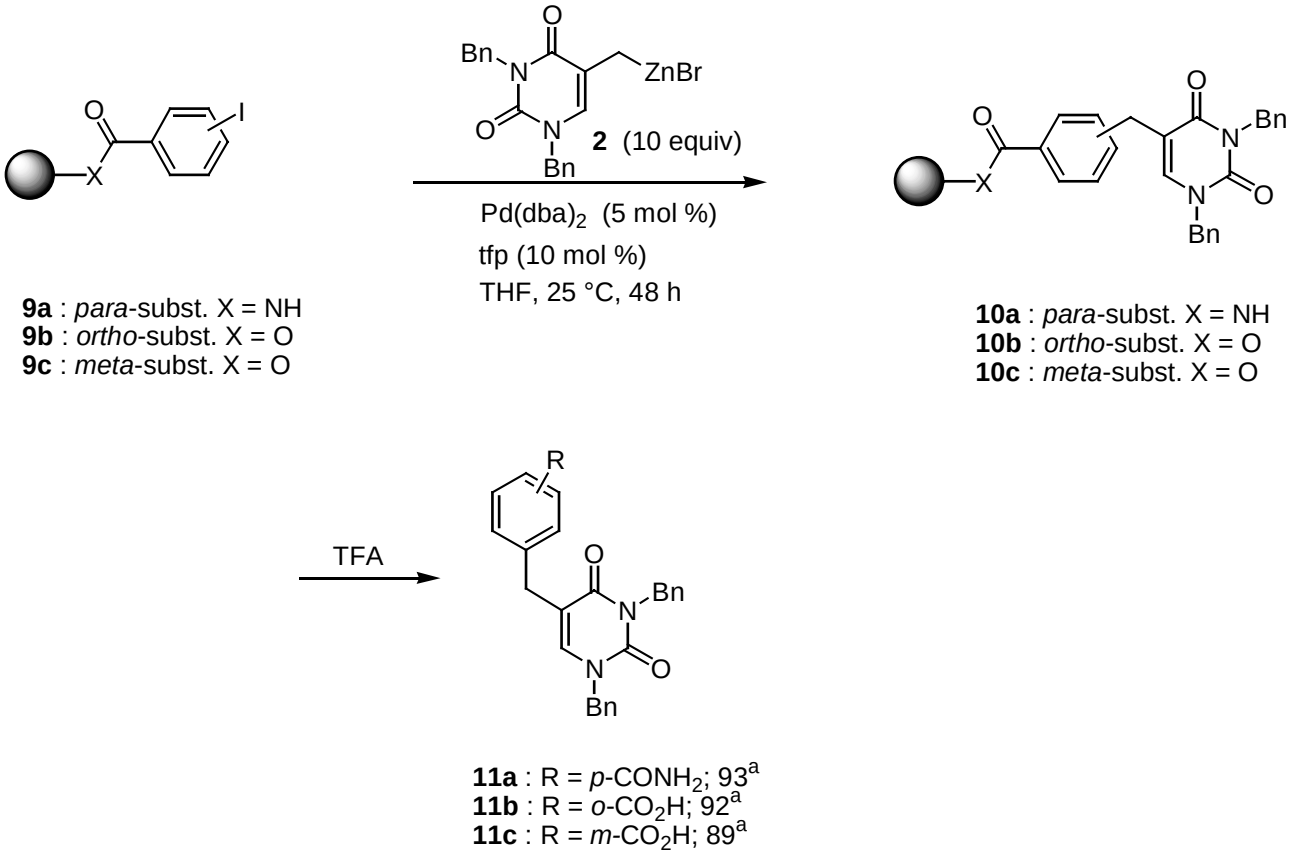




Scheme 15. Preparation of polymer-supported aryl iodides.

A Negishi cross-coupling reaction was then carried out on resin-attached aryl iodides **9a-c**. The resin was suspended in THF and treated with zincated thymine reagent **2** (10 equiv) using $Pd(dba)_2$/2 tfp as catalyst. After two days at rt the resin was filtered and washed (CH_2Cl_2 and MeOH), affording resins **10a-c**. Treatment with TFA (90 % in CH_2Cl_2) resulted in cleavage, leading to amide **11a** and carboxylic acids **11b-c** in high purity (93 %, 92 %, 89 % respectively) as indicated by HPLC analysis (UV detection at 254 nm, scheme 16).

[50] Novabiochem, *Peptide Synthesis Handbook*, **1995**.



Scheme 16. Solid phase synthesis of thymine derivatives **11a-c**. [a]HPLC-purity (UV, 254 nm).

1.3- Summary

• Zincated thymine derivative **2** was obtained by zinc insertion using the corresponding heterobenzylic bromide **4**. This latter compound could be readily prepared from uracil in 4 steps (37 % overall yield).

• Zincated thymine derivative **2** could undergo Negishi cross-couplings with aryl and alkenyl iodides affording the corresponding cross-coupling products in moderate to good yields. Various functionalized iodides were tolerated, allowing diversity in the final products.

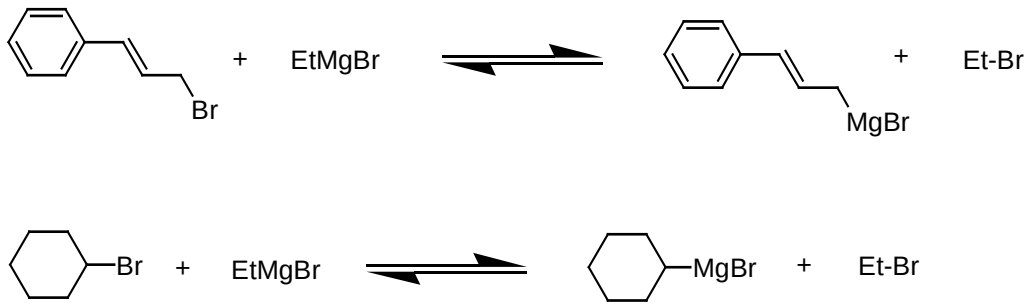
• Finally, this cross-coupling was also successfully performed on the solid phase using Wang- and Rink-resin attached aromatic iodides. After cleavage, the desired carboxylic acids and amides were obtained with high HPLC purity (89-93 %).

2- Synthesis of functionalized heterocyclic derivatives in solution using a low temperature halogen-Mg exchange

2.1- Introduction

Grignard reagents are standard carbanion reagents in organic synthesis and have found many applications in organic chemistry.[51] However, their low functional group tolerance has limited the scope of their application. The use of activated magnesium for the low temperature synthesis of functionalized Grignard reagents has recently been reported by Rieke but lacks generality since most functional groups deactivate the surface of the magnesium and inhibit the reaction.[24] Thus the halogen-magnesium exchange provides an efficient alternative when performed at low temperature.

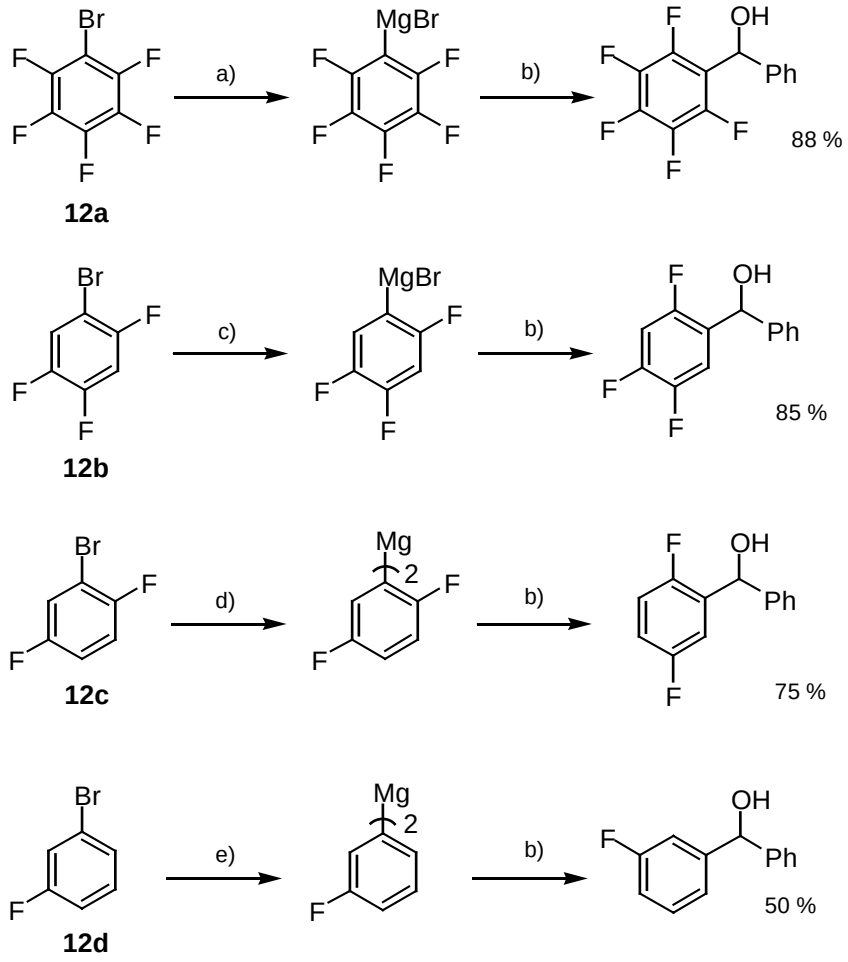
The facility with which a halogen-magnesium exchange can take place was first demonstrated in 1931 by Prevost[52] who observed the formation of cinnamylmagnesium bromide by reacting cynnamylbromide and ethylmagnesium bromide. The same observations were made by Urion[53] a few years later in the reaction beetwen cyclohexyl bromide and ethylmagnesium bromide (scheme 17).



Scheme 17.

[51] G. S. Silverman, P. E. Rakita, *Handbook of Grignard-Reagents*, Marcel Dekker: New York, **1996**.
[52] C. Prevost, *Bull. Soc. Chim. Fr*. **1931**, 1372.
[53] E. Urion, *Comptes rendus* **1934**, *198*, 1244.

Electron-withdrawing groups are often necessary for a fast bromine-magnesium exchange.[54] For example, a significant rate difference is observed for the bromine-magnesium exchange in the case of fluorinated bromobenzene derivatives **12a-d** (scheme 18).[55] Whereas bromopentafluorobenzene **12a** reacts with *i*-PrMgBr at -78 °C within 0.5 h, 1-bromo-2,4,5-trifluorobenzene **12b** requires a reaction temperature of -10 °C. For the difluoro-substituted bromobenzene **12c**, the use of more reactive *i*-Pr_2Mg at 20 °C is required. Also 1-bromo-3-fluorobenzene **12d** is converted to the corresponding magnesium reagent only by using an excess of *i*-Pr_2Mg (rt, 20 °C).

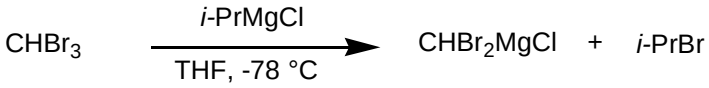


Scheme 18. Rate of the bromine-magnesium exchange. a) *i*-PrMgBr, THF, -78 °C, 0.5 h; b) PhCHO; c) *i*-PrMgBr, THF, -10 °C, 1 h; d) *i*-Pr_2Mg, THF, 20 °C, 2 h; e) *i*-Pr_2Mg, THF, 20 °C, 3 h.

[54] For bromine-magnesium exchange using magnesium ate complexes see: K. Kitagawa, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem*. **2000**, *112*, 2594.
[55] M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett*. **1999**, *40*, 7449.

Interestingly, the iodine-magnesium exchange is much faster and does not require such activating groups. Thus an unactivated aryl iodide such as 1-naphthyl iodide reacts at rt within 0.5 h using a stoichiometric amount of *i*-Pr_2Mg.[25]

Although this reaction is now well established and has served in the synthesis of many heterocyclic organomagnesium reagents[56], its real synthetic potential can be demonstrated in the synthesis of polyfunctionalized Grignard reagents. The mild conditions required for the performance of a halogen-magnesium exchange have first been shown by Villiéras in the preparation of magnesium carbenoids.[57]



Scheme 19. Low temperature carbenoid preparation by bromine-magnesium exchange.

Recently a general method for the preparation of functionalized Grignard reagents was developed in our group using a low temperature iodine-magnesium exchange (scheme 8, page 7). Its application in the synthesis of functionalized heterocycles has been studied during this work and will be described in the following chapters.

2.2- Synthesis of pyridine derivatives

2.2.1- Preparation of the starting materials

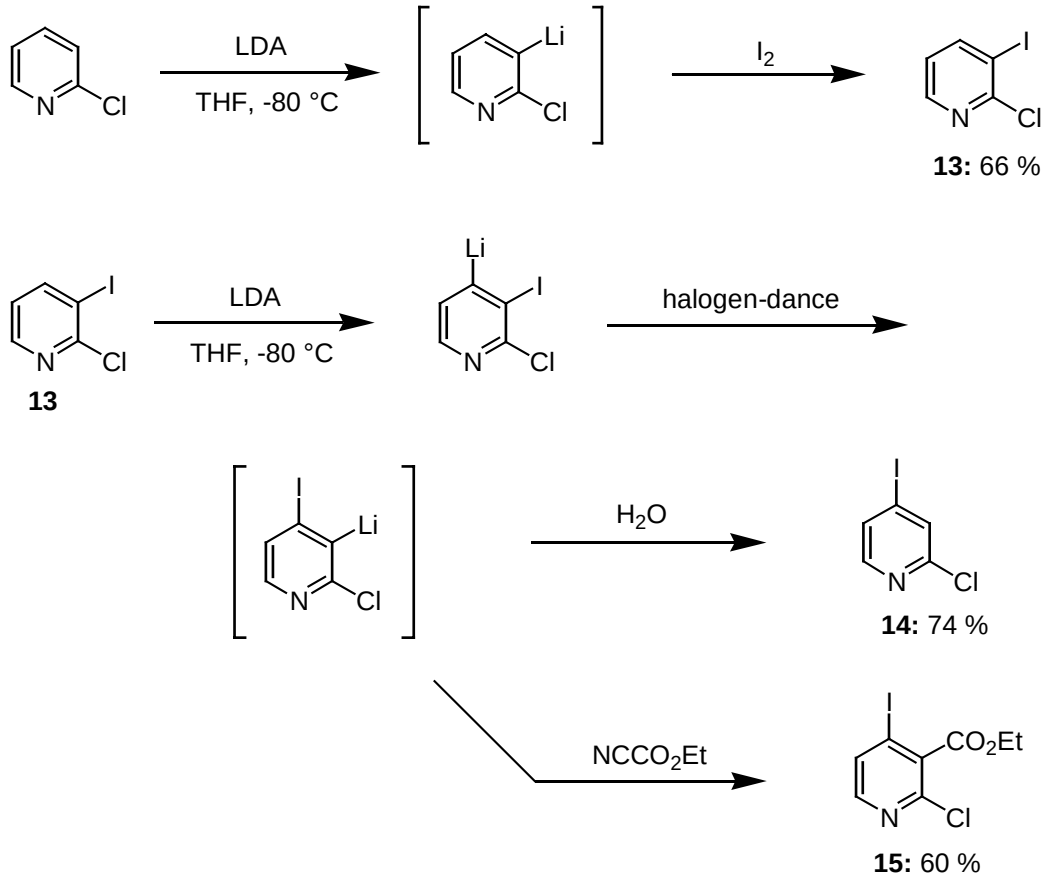
The low temperature iodine-magnesium exchange was first studied on iodopyridines in collaboration with Dr. Anne Leprêtre and Prof. Guy Quéguiner. Starting materials **13-15** were prepared according to a method[58] recently developed by Quéguiner and coworkers involving

[56] For examples of halogen-magnesium exchange see: H. Paradies, H. Görbing, *Angew. Chem.* **1969**, *81*, 293; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 279. C. F. Smith, G. J. Moore, C. Tamborski, *J. Organomet. Chem.* **1971**, *33*, C21. G. Cahiez, D. Bernard, J. F. Normant, *ibid*. **1976**, *113*, 107. D. Seyferth, R. Lambert, *ibid*. **1973**, *54*, 123. N. Redwane, P. Moreau, A. Commeyras, *J. Fluorine Chem.* **1982**, *20*, 699. N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett*. **1987**, *28*, 5845. H. Nishiyama, K. Isaka, K. Itoh, K. Ohm, H. Nagase, K. Matsumoto, H. Yoshiwara, *J. Org. Chem.* **1992**, *57*, 407. C. Bolm, D. Pupowicz, *Tetrahedron Lett*. **1997**, *38*, 7349.

[57] J. Villiéras, *Bull. Soc. Chim. Fr*. **1967**, 1520.

[58] P. Rocca, C. Cochennec, F. Marsais, L. Thomas-dit-Dumont, M. Mallet, A. Godart, G. Quéguiner, *J. Org. Chem*. **1993**, *58*, 7832.

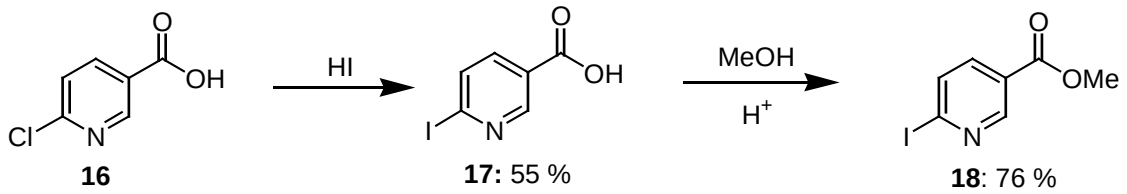
the metalation of pyridines. Lithiation of 2-chloropyridine at -80 °C followed by addition of iodine afforded 2-chloro-3-iodopyridine **13** in 66 % yield. Treatment of this compound with LDA led to the corresponding lithiated pyridine which was isomerized *via* a so-called "halogen-dance" reaction.[59] During this process a more stable lithium derivative[60] was formed by migration of the iodine atom, and quenched with water or ethyl cyanoformate affording iodopyridines **14** and **15** respectively in 74 % and 60 % yield (scheme 20).



Scheme 20. Preparation of functionalized iodopyridines **13-15** by lithiation.

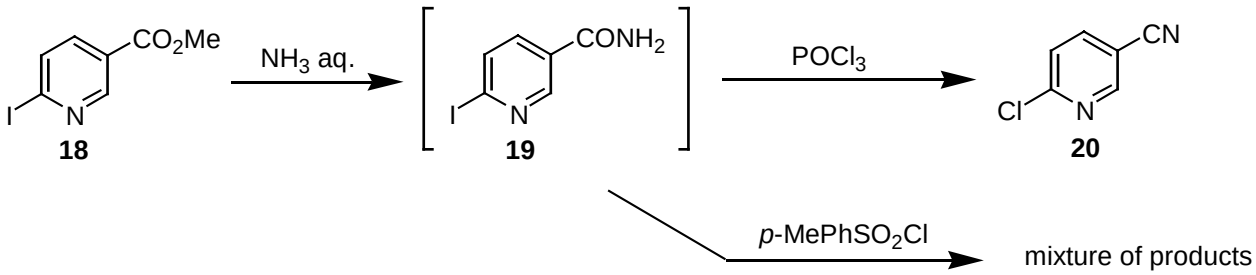
It should be noted that the corresponding organomagnesium derivatives could be directly obtained from the lithiated pyridines by transmetalation with $MgCl_2$. However, it was interesting in our case to test the viability of a low-temperature iodine-magnesium exchange. Methyl-6-iodonicotinate **18** was obtained starting from commercially available 6-chloronicotinic acid **16** (scheme 21) by treatment with hydriodic acid followed by esterification.

[59] J. F. Bunnett, *Accounts Chem. Res*. **1972**, *5*, 139.
[60] For a mechanistic study of the "halogen-dance" see: M. Mallet, G. Quéguiner, *Tetrahedron* **1982**, *38*, 3035.



Scheme 21. Preparation of methyl-2-iodonicotinate **18**.

Cyanopyridines were also interesting substrates although the preparation of only one example had been reported in very low overall yield.[61] For this reason the sequence shown in scheme 22 was attempted. Methyl 6-iodonicotinate **18** was first converted to the corresponding primary amide by treatment with aqueous ammonia. Unfortunately, conventional procedures to convert amide **19** into the corresponding nitrile failed. By refluxing in the presence of *p*-toluenesulfonyl chloride[62] a mixture of products was obtained which did not contain the desired iodopyridine. Treatment with $POCl_3$[63] resulted in displacement of the iodine atom by a chlorine atom affording chloropyridine **20**.

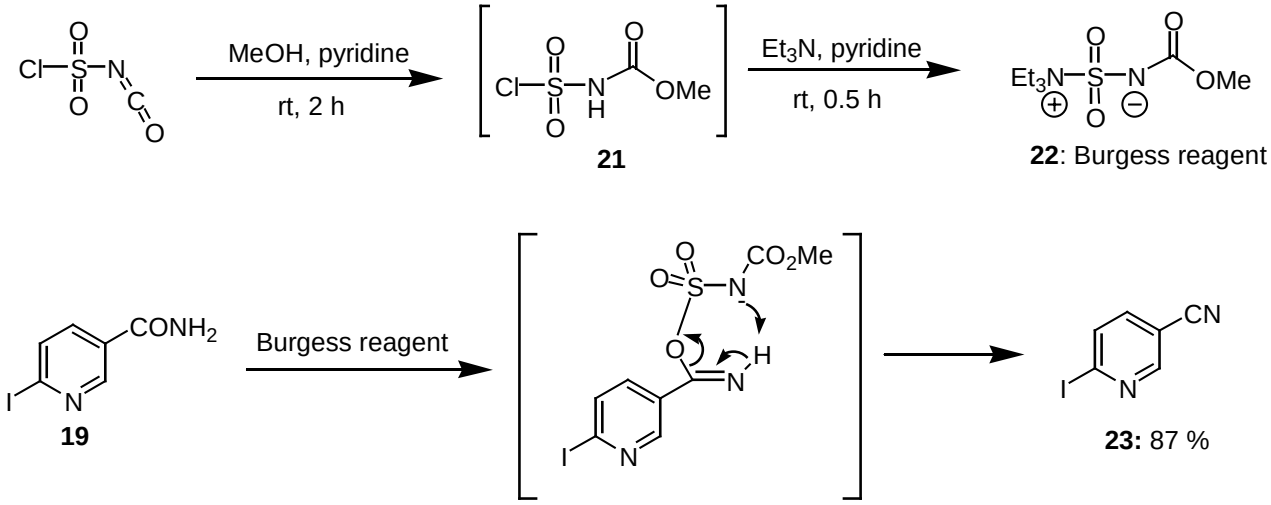


Scheme 22. Attempted preparations of 3-cyano-6-iodopyridine **23**.

These unexpected results prompted us to find milder reaction conditions. DCC (dicyclohexyl carbodiimide) unfortunately failed, giving no reaction even by heating the reaction mixture.
Recently a new dehydrating procedure has been described by Burgess.[64] This method uses very mild conditions and has found many applications including in the preparation of nitriles from primary amides.[65] The Burgess reagent **22** (methyl N-(triethylammoniumsulfonyl) carbamate) can be prepared in 2 steps from chlorosulfonyl isocyanate as shown in scheme 23.

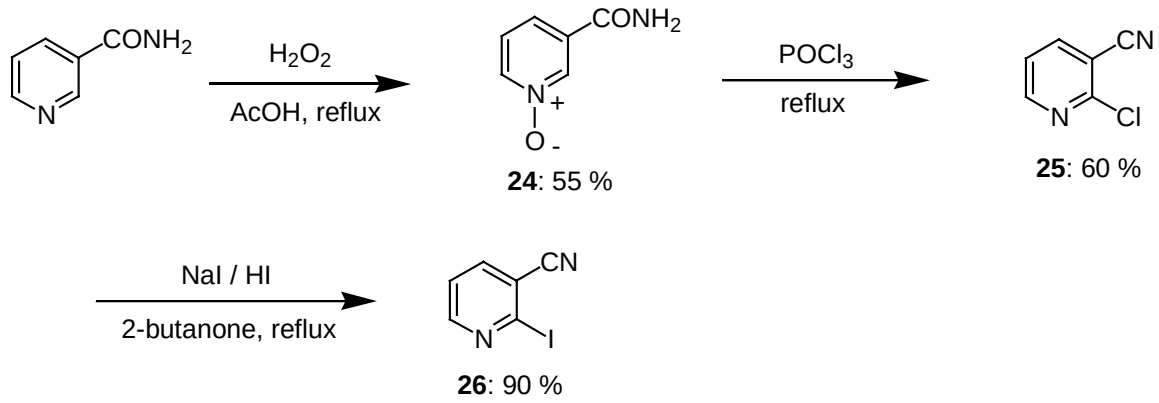
[61] M. Riley, R. N. Perham, *Biochem. J*. **1973**, *131*, 625.
[62] R. C. Stephens, E. J. Bianco, J. Pilgrim, *J. Am. Chem. Soc.* **1955**, *77*, 1701.
[63] D. M. Ketcha, G. W. Gribble, *J. Org. Chem*. **1985**, *50*, 5451.
[64] E. M. Burgess, H. R. Penton, E. A. Taylor, *J. Org. Chem*. **1973**, *38*, 26.
[65] D. A. Claremon, B. T. Phillips, *Tetrahedron Lett*. **1988**, *29*, 21552.

By treating amide **19** with this latter reagent a smooth dehydration took place at room temperature within 15 min affording nitrile **23** in 87 % yield.



Scheme 23. Preparation of 3-cyano-6-iodopyridine **23** using the Burgess reagent.

The isomeric 3-cyano-2-iodopyridine **26** was also successfully prepared from the known 2-chloro-3-cyanopyridine **25**[66] (scheme 24). Oxidation of nicotinamide with H_2O_2 affords the pyridine N-oxide **24** wich was converted to 2-chloro-3-cyanopyridine **25** in one step by refluxing in the presence of $POCl_3$. Displacement of chloride afforded 3-cyano-2-iodopyridine **26** in 90 % yield.

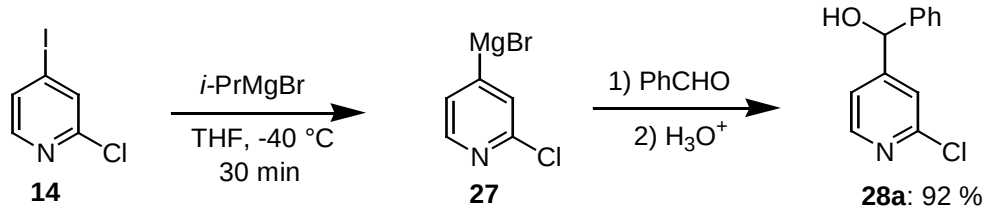


Scheme 24. Preparation of 3-cyano-2-iodopyridine **26**.

[66] E. C. Taylor, A. J. Crovetti, *J. Org. Chem.* **1954**, *19*, 1633.

2.2.2- Low temperature iodine-magnesium exchange

The low temperature iodine-magnesium exchange was first studied on 2-chloro-4-iodopyridine **14**. At -40 °C in THF, slow addition of *i*-PrMgBr (1.1 equiv) afforded the desired pyridylmagnesium bromide **27**. The exchange was complete after 30 min as indicated by GC analysis of reaction aliquots. Interestingly, Grignard reagent **27** was stable at -40 °C and no decompositon was observed at this temperature even after 1 h as indicated by GC analysis using tetradecane as internal standard. After quenching with benzaldehyde the desired alcohol **28a** was obtained in 92 % yield (scheme 25).



Scheme 25. Low temperature iodine-magnesium exchange on 2-chloro-4-iodopyridine **14**.

The exchange reaction was then performed using functionalized iodopyridines **13** and **15**. Results are summarized in Table 2. Remarkably, the presence of an ester function is compatible with the formation of a pyridylmagnesium functionality at -40 °C (entries 8-12). Various electrophiles can be used to trap these pyridylmagnesium reagents. Aldehydes such as benzaldehyde or hexanal react well, furnishing the corresponding alcohols (entries 1, 2, 5, 6, 10, 12). The reaction of the pyridylmagnesium reagent **29** an **31** with tosyl cyanide provides 2-chloro-3-cyanopyridine **30d** (entry 7) and 4-cyanonicotinate **32d** (entry 11) respectively. Allylation reactions were best performed by adding CuCN (10 mol %) prior to the addition of allyl bromide (entry 3, 4, 8) and benzoylation was achieved using a stoichiometric amount of CuCN followed by the addition of PhCOCl (entry 9) furnishing the expected ketone **32b**.

Table 2. Products **28a-c, 30a-d, 32a-d** and **34** obtained by the iodine-magnesium exchange of iodopyridines **13, 15** and **18** followed by the reaction with electrophiles.

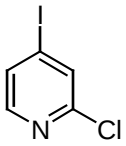
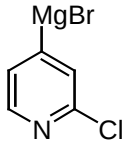
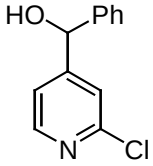
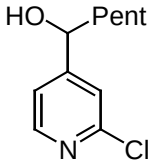
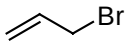
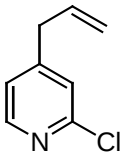
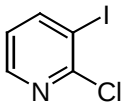
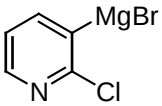
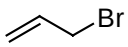
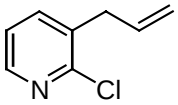
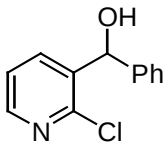
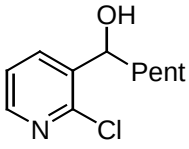
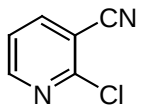
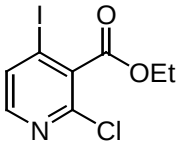
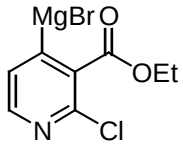
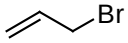
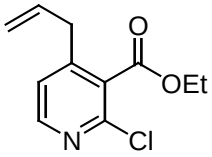
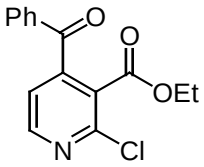
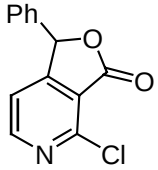
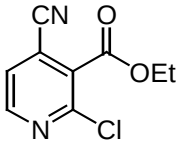
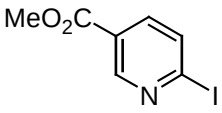
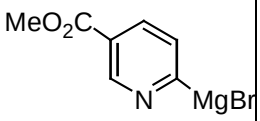
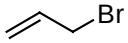
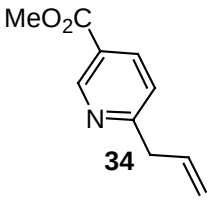
Entry	Iodopyridine	Grignard reagent	Electrophile	Product	Yield (%)
1	 **14**	 **27**	PhCHO	 **28a**	92
2	**14**	**27**	PentCHO	 **28b**	85
3	**14**	**27**		 **28c**	85[a]
4	 **13**	 **29**		 **30a**	80[a]
5	**13**	**29**	PhCHO	 **30b**	85
6	**13**	**29**	PentCHO	 **30c**	79

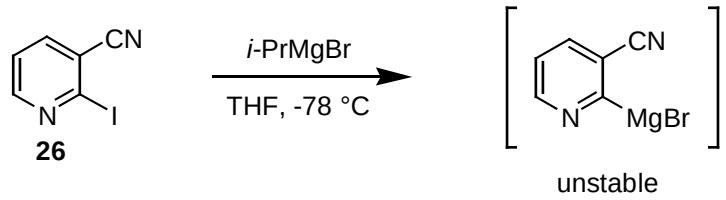
Table 2. (Continued).

7	**13**	**29**	TosCN	 **30d**	81
8	 **15**	 **31**		 **32a**	82[a]
9	**15**	**31**	PhCOCl	 **32b**	84[b]
10	**15**	**31**	PhCHO	 **32c**	56
11	**15**	**31**	TosCN	 **32d**	55
12	 **18**	 **33**		 **34**	62[a]

[a]A catalytic amount of CuCN·2 LiCl was added prior to the addition of the electrophile. [b]A stoichiometric amount of CuCN·2 LiCl was added prior to the addition of the electrophile.

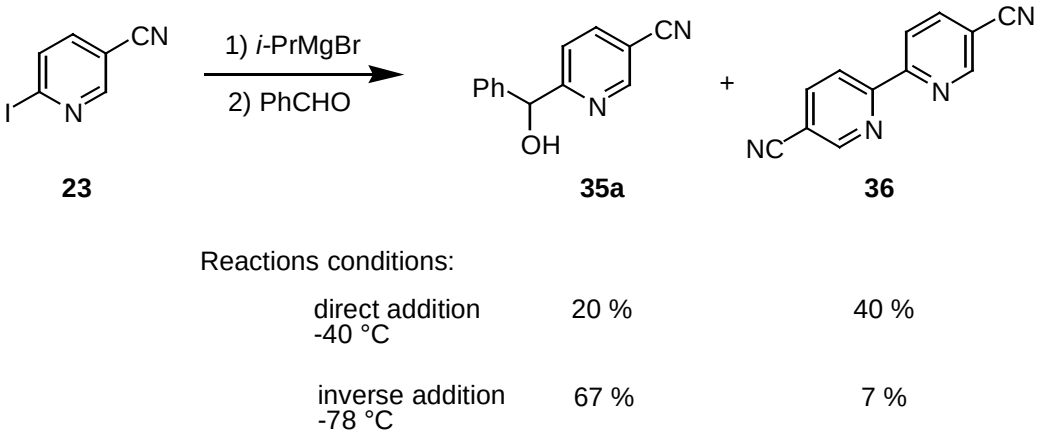
The iodine-magnesium exchange was next tried on iodopyridines bearing a cyano group. Slow addition of *i*-PrMgBr to a cooled solution of 2-iodo-3-cyanopyridine **26** in THF

resulted in partial decomposition according to GC analysis. Even at -78 °C low and irreproducible yields were obtained when quenching with allyl bromide (scheme 26).



Scheme 26. Low temperature iodine-magnesium exchange on 3-cyano-2-iodopyridine **26**.

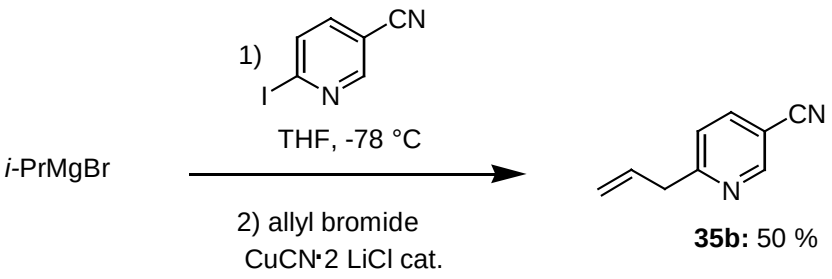
Interestingly, when 5-cyano-2-iodopyridine **23** was used, a competitive homocoupling reaction was observed. This side reaction is probably due to the high acceptor character of 2-iodopyridines which favors an addition-elimination mechanism[67] (scheme 27). Thus the iodine-magnesium exchange followed by the quenching with PhCHO afforded under our standard conditions a mixture of the desired product **35a** and the homocoupling product **36** (major product). This result could be greatly improved by performing the iodine-magnesium exchange at -78 °C and by slowly adding the iodopyridine **23** to *i*-PrMgBr (1.1 equiv) immediately followed by the addition of benzaldehyde, leading to the product **35a** (67 %) with a negligible amount of **36** (7 %).



Scheme 27. Low temperature iodine-magnesium exchange on 3-cyano-6-iodopyridine **23**.

[67] S. W. Golstein, P. J. Dambek, *Synthesis*, **1989**, 221. R. F. Francis, W. Davis, J. T. Wisserer, *J. Org. Chem.* **1974**, *39*, 59.

The use of allyl bromide as electrophile in the presence of a catalytic amount of CuCN afforded the allylated product **35b** in 50 % yield (scheme 28).

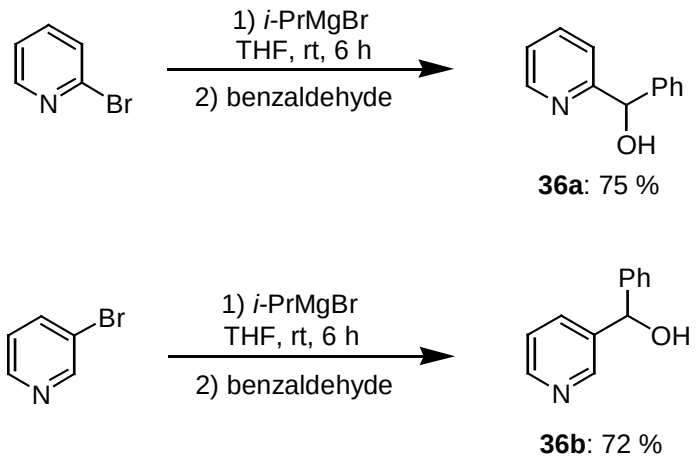


Scheme 28. Preparation of 6-allyl-3-cyanopyridine **35b**.

In summary, various functionalized pyridylmagnesium reagents could be prepared by a low temperature iodine-magnesium exchange. However, the sometimes tedious preparation of the starting materials as well as the relative instability of some 2-iodopyridines derivatives prompted us to study the reactivity of bromopyridines.

2.2.3- Low temperature bromine-magnesium exchange

As already mentioned, the bromine-magnesium exchange is a slow reaction compared to the iodine-magnesium exchange and strong electron withdrawing groups are generally needed for a fast reaction (scheme 18). Interestingly, when either 2-bromopyridine or 3-bromopyridine was treated with *i*-PrMgBr in THF at rt, the exchange reaction was complete within 6 hours. This result is due to the π deficient character of the pyridine ring which can better stabilize a negative charge than a benzene ring. Treatment of the pyridylmagnesium reagents with benzaldehyde afforded the corresponding alcohols **36a** and **36b** in 75 % and 72 % yields respectively (scheme 29).



Scheme 29. Bromine-magnesium exchange on bromopyridines.

This bromine-magnesium exchange on bromopyridines was also studied by Quéguiner and their results have been recently published.[68] Moreover it was applied in our group to various heterocycles such as bromoimidazoles or bromopyrroles.[55] The next chapter of this work will concentrate on the synthesis of thiazole derivatives

2.3- Synthesis of thiazole derivatives

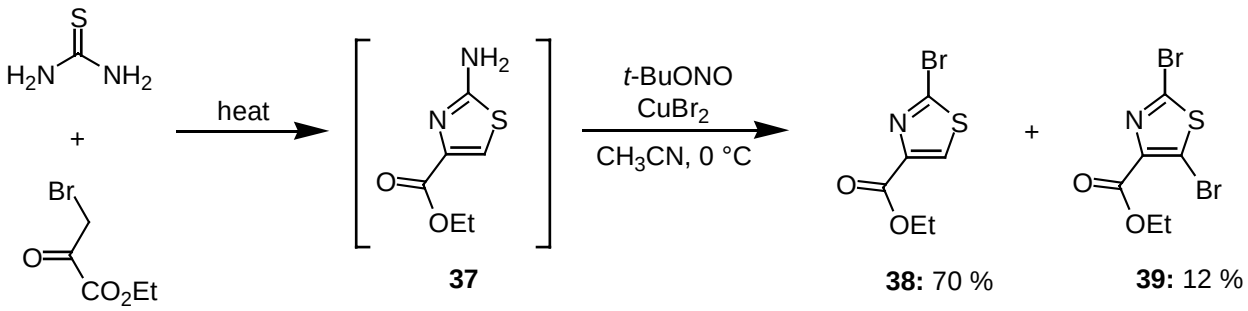
Thiazoles are electron rich heterocycles but their reactivity in the bromine-magnesium exchange can be increased by the presence of an electron withdrawing ester function. Thus monobromothiazole **38** and dibromothiazole **39** (scheme 30) were interesting starting materials, especially compound **39** where the presence of 2 bromine atoms could allow for the introduction of 2 different groups into the molecule. Moreover the ester function could serve as a useful handle for further development of the process on the solid phase.

The synthesis of starting materials **38** and **39** starts with a condensation reaction between thiourea and ethyl 3-bromopyruvate.[69] This reaction was carried out neat and affords intermediate thiazole **37** in sufficient purity for the next step. A diazotation reaction, performed with *t*-butyl nitrite, followed by conversion to the bromo derivative using

[68] F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais, G. Quéguiner, *Tetrahedron Lett*. **1999**, *40*, 4339. F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais, G. Quéguiner, *Tetrahedron* **2000**, *56*, 1349.

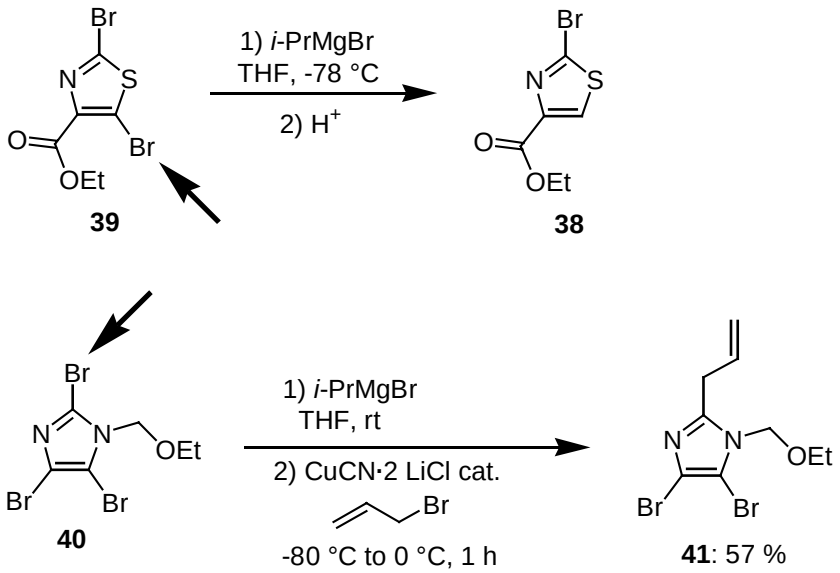
[69] A. T. Ung, S. G. Pyne, *Tetrahedron: Asymmetry* **1998**, *9*, 1395.

copper(II) bromide, gave a mixture of compounds **38** and **39** (70 % and 12 % respectively) which could easily be separated by column chromatography.



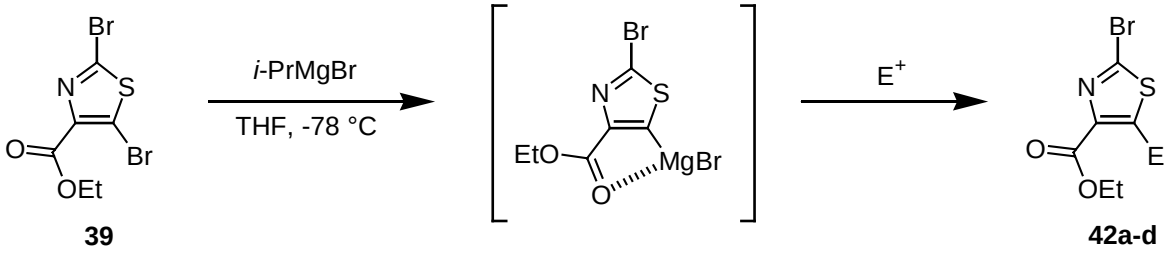
Scheme 30. Preparation of bromothiazole **38** and **39**.

The bromine-magnesium exchange was first performed on dibromothiazole **39** to study the regioselectivity of the reaction. A THF solution of **39** was cooled to -78 °C and *i*-PrMgBr was slowly added. The reaction was complete within 20 min as indicated by TLC analysis. Interestingly, when the reaction was quenched with water the product obtained showed identical ^{1}H and ^{13}C spectra to compound **38**. Thus the exchange reaction was favored at position 5. As shown in scheme 31, this regioselectivity is in strong contrast with results reported on tribromoimidazoles **40**.[55] In this latter case, exchange at position two is favored leading to imidazole **41** after allylation.



Scheme 31. Regioselectivity of the bromine-magnesium exchange on dibromothiazole **39** vs tribromoimidazole **40**.

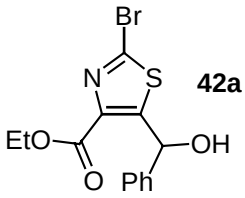
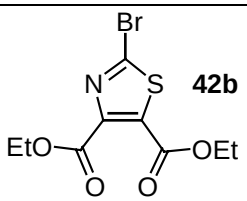
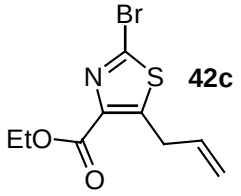
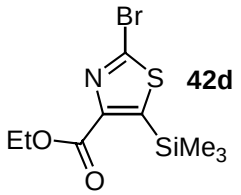
This unexpected regiochemistry can be explained by the formation of a 5-membered ring chelate as shown in scheme 32.



Scheme 32. Regioselectivity of the bromine-magnesium exchange on dibromothiazole **39**.

Thiazoles **42a-d** were prepared by using different electrophiles as shown in Table 3.

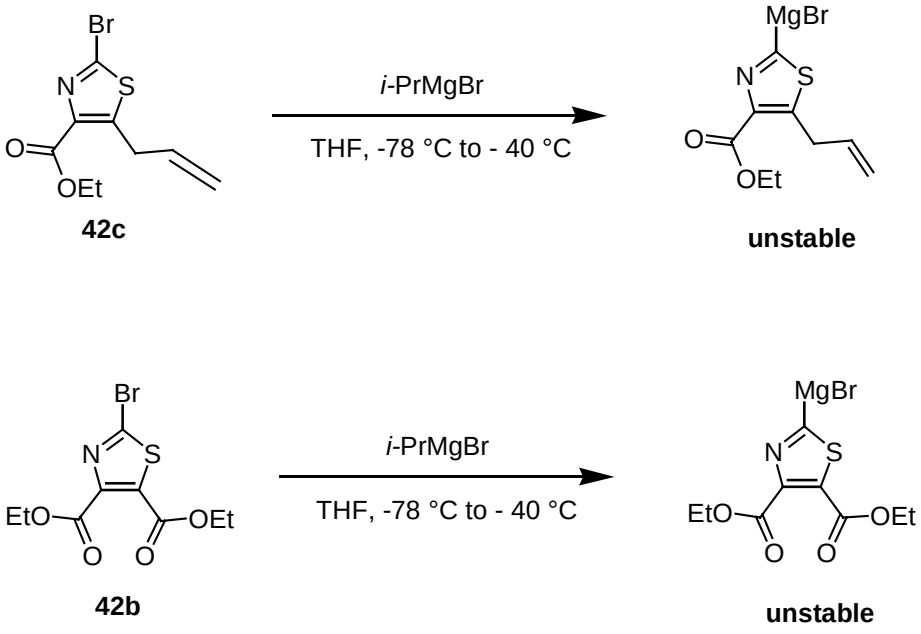
Table 3. Thiazoles **42a-d** obtained by bromine-magnesium exchange followed by the reaction with electrophiles.

Entry	Electrophile	Product **42**	Yield (%)[a]
1	Benzaldehyde	 **42a**	58
2	$NCCO_2Et$	 **42b**	67
3	Allyl bromide	 **42c**	81[b]
4	Me_3SiCl	 **42d**	67

[a]Isolated yield of analytically pure products. [b]A catalytic amount of CuCN·2 LiCl was added prior to the addition of the electrophile.

A second bromine-magnesium exchange was then attempted using bromothiazole **42c** as starting material (scheme 33). Unfortunately no exchange occured below -78 °C and decomposition was observed when the temperature was increased, leading to complex reaction mixtures. *i*-Pr_2Mg,[25] which often leads to faster exchange reactions compared to *i*-PrMgBr, also failed and changing the solvent from THF to ether did not give a cleaner reaction.

A bromine-magnesium exchange was also tried on compound **42b**. It was reasoned that the presence of two electron withdrawing ester groups would favor the exchange reaction. (scheme 33). Unfortunately, only degradation products could be isolated when quenching with different electrophiles.



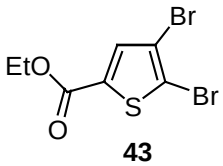
Scheme 33. Attempted bromine-magnesium exchange on bromothiazoles **42b** and **42c**.

Due to the lack of stability of the organomagnesium reagents in the thiazole series, we next turned our attention to thiophene derivatives.

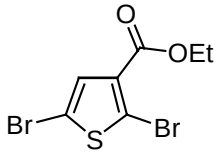
2.4- Synthesis of thiophene derivatives

2.4.1- Preparation of the starting materials

In order to study the halogen-magnesium exchange on this class of compounds, thiophenes **43** and **44** were selected.

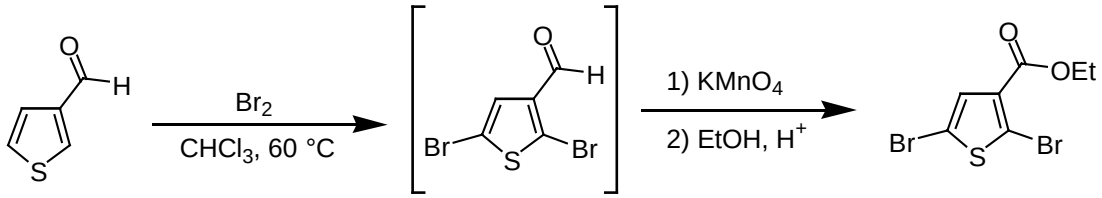


43



44

Thiophene **43** is commercially available and thiophene **44** has already been reported in the literature.[70] It was readily prepared from 3-formylthiophene (scheme 34) using a three step sequence. Bromination followed by oxidation with $KMnO_4$ and esterification afforded the desired dibromothiophene ester **44** in 24 % overall yield.



44: 24 %

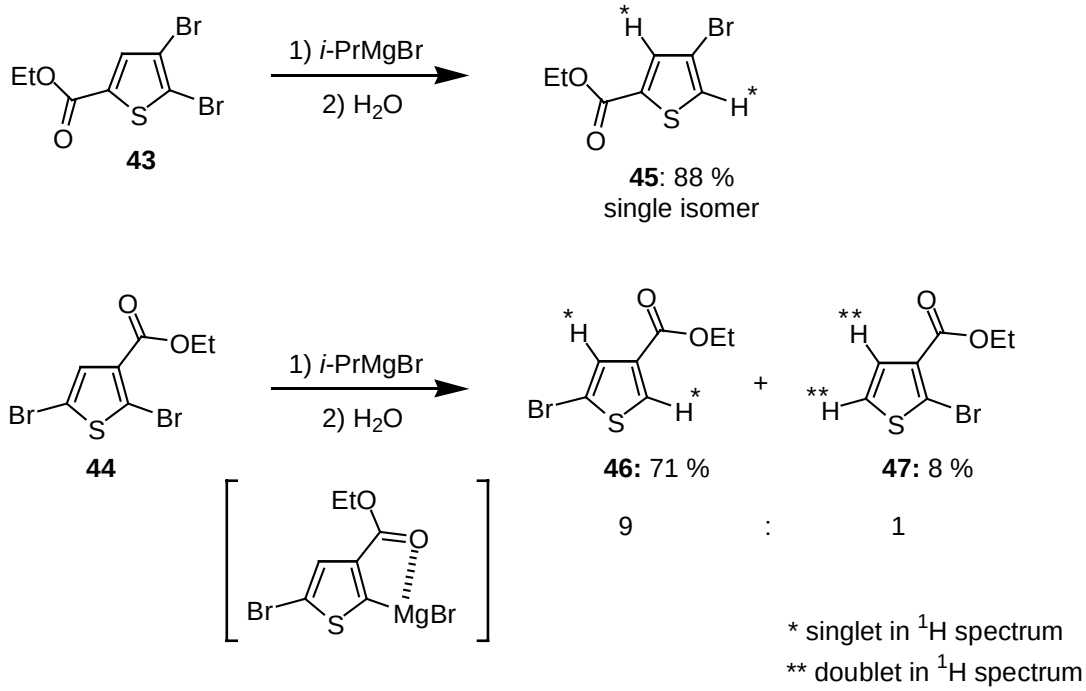
Scheme 34. Preparation of 2,5-dibromothiophene-3-carboxylic acid ethyl ester **44**.

2.4.2- Low temperature bromine-magnesium exchange

The regioselectivity of the bromine-magnesium exchange was first studied on thiophene **43**. For this purpose a THF solution of compound **43** was subjected to *i*-PrMgBr at -40 °C for 30 min. The reaction mixture was then quenched with water. After usual work-up thiophene **45** was obtained as single regioisomer. The regioselectivity was confirmed by the presence of two singlets in the ^{1}H NMR spectrum (scheme 35).

[70] P. Fournari, R. Guilard, M. Person, *Bull. Soc. Chim. Fr*. **1967**, 4115.

The same study was conducted on dibromothiophene **44**. Bromine-magnesium exchange was favored at position 2 leading to an organomagnesium compound stabilized by chelation, accompanied by minor amounts (10 %) of the regioisomeric magnesium reagents (scheme 35).

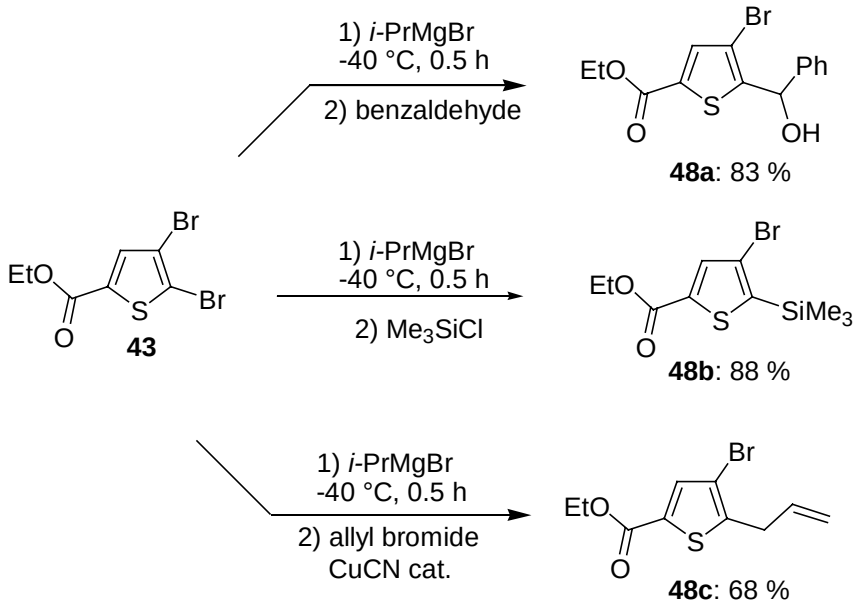


Scheme 35. Regioselectivity of the bromine-magnesium exchange on dibromothiophene **43** and **44**.

Having established the regioselectivity of the bromine-magnesium exchange, the synthesis of various thiophenes was performed in solution in collaboration with Dr. Jérome Thibonnet.

2.4.2.1- Bromine-magnesium exchange on ethyl 4,5-dibromothiophene 2-carboxylate

The halogen-magnesium exchange was performed on dibromothiophene **43** by treatment with *i*-PrMgBr (1.0 equiv) at -40 °C for 0.5 h. The Grignard reagent obtained was quenched with typical electrophiles such as benzaldehyde, allyl bromide (CuCN catalysis) and Me_3SiCl affording the expected thiophene derivatives **48a-c** in good yields.



Scheme 36. Bromine-magnesium exchange on dibromothiophene **43**.

A second bromine-magnesium exchange could not be achieved at position 4 due to an increased electron density at this position as shown in figure 6.

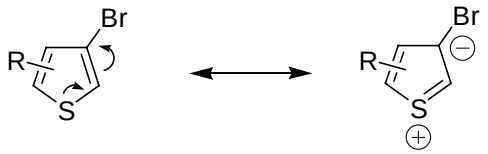
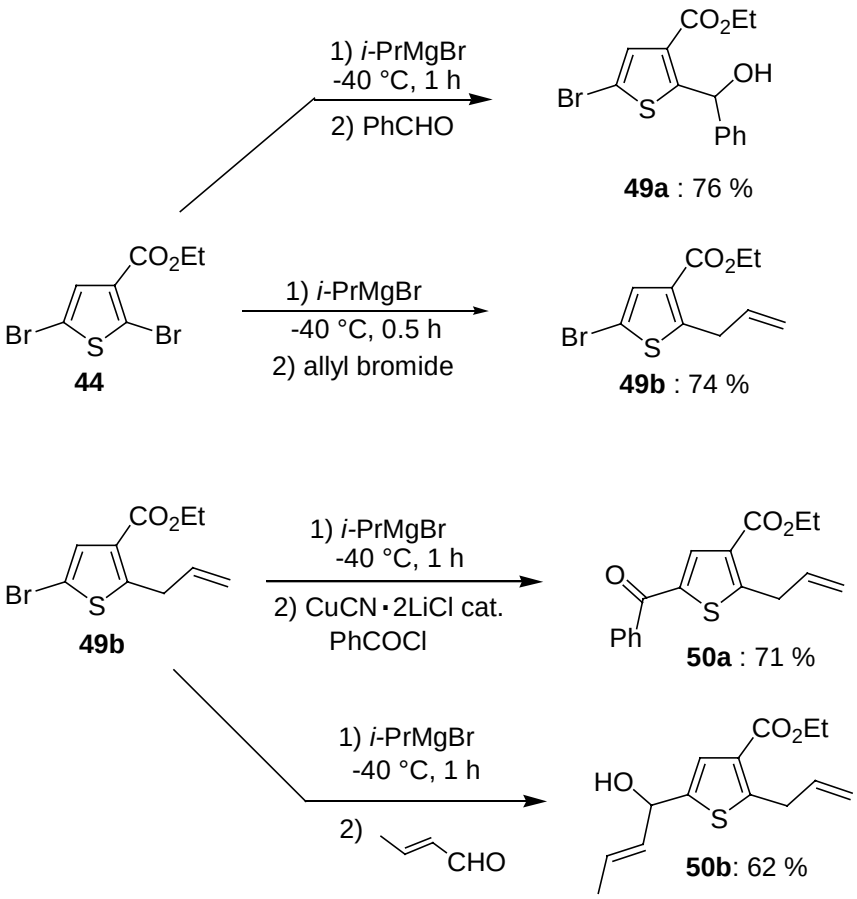


Figure 6.

For this reason functionalization at position 4 was achieved by performing a Negishi cross-coupling reaction. This reaction was carried out on the solid phase and will be discussed in chapter 3.4.3.

2.4.2.2- Bromine-magnesium exchange on ethyl 2,5-dibromothiophene 3-carboxylate

In the case of dibromothiophene **44**, two consecutive bromine-magnesium exchange reactions could be performed as shown in scheme 37. Thus treatment with *i*-PrMgBr followed by addition of benzaldehyde or allyl bromide (CuCN catalysis) led to thiophene **49a** and **49b** in 76 % and 74 % yield. A second bromine-magnesium exchange was then performed on **49b** leading to products **50a-b** in 62-71 % yields.



Scheme 37. Bromine-magnesium exchange on dibromothiophene **44**.

2.4.3- Chlorine-magnesium exchange

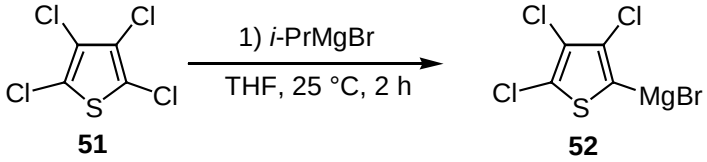
Recently, many efforts have been made to replace iodides and bromides by the less expensive and often more stable chlorinated derivatives. For example cross-coupling reactions,[71] amination reactions[72] and Heck reactions[73] have been developed using aryl chlorides. A chlorine-magnesium exchange would also be of great practical interest in our case.

[71] For recent examples of cross-coupling reactions with aryl chlorides see: W. A. Herrmann, C. P. Reisinger, M. Spiegler, *J. Organomet. Chem*. **1998**, *557*, 93. T. Weskamp, V. P. W. Böhm, W. A. Herrmann, *J. Organomet. Chem*. **1999**, *585*, 348. C. Zhang, J. Huang, M. Trudell,, S. P. Nolan, *J. Org. Chem*. **1999**, *64*, 3804. A. F. Littke, G. C. Fu, *Angew. Chem.* **1998**, *110*, 3586; *Angew. Chem. Int. Ed. Engl.* **1998**, *38*, 3387. A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc*. **2000**, *122*, 4020. J. Huang, S. P. Nolan, *J. Am. Chem. Soc*. **1999**, *121*, 9889. D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc*. **1998**, *120*, 9722. J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc*. **1999**, *121*, 9550.

[72] S. P. Nolan, *Org. Lett*. **1999**, *1*, 1307. S. R. Stauffer, S. Lee, J. P. Stambuli, S. I. Hauck, J. F. Hartwig, *Org. Lett*. **2000**, *2*, 1423.

[73] M. Beller, W. A. Herrmann, *Angew. Chem*. **1995**, *107*, 1989; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1848. A. F. Littke, G. C. Fu, *J. Org. Chem*. **1999**, *64*, 10.

As already mentioned, electron-withdrawing groups greatly facilitate the exchange reaction. Thus, tetrachlorothiophene was selected as starting material. As shown in scheme 38, tetrachlorothiophene could undergo a selective chlorine-magnesium exchange at position 2 when treated with *i*-PrMgBr at rt leading to Grignard reagent **52**. The regiochemistry of the exchange was confirmed by X-ray analysis of compound **53c** obtained by quenching with ethyl cyanoformate (Table 4, entry 3).

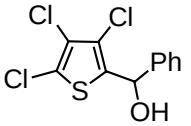
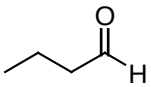
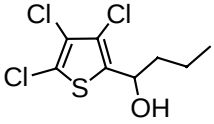
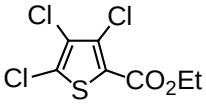
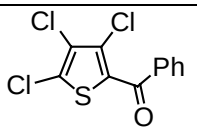
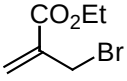
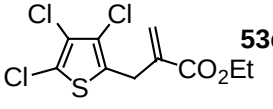


51 **52**

Scheme 38. Chlorine-magnesium exchange on tetrachlorothiophene.

Various electrophiles can be used, affording products **53a-e** in moderate to excellent yields. The results are summarized in Table 4.

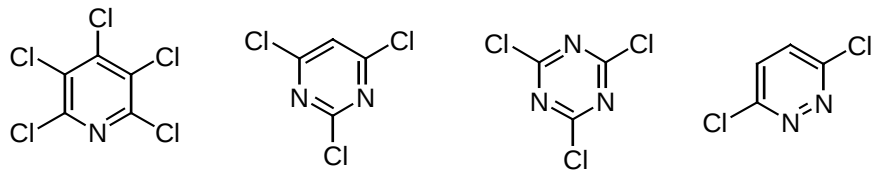
Table 4. Products **53a-e** obtained by a chlorine-magnesium exchange on tetrachlorothiophene followed by the reaction with electrophiles.

Entry	Electrophile	Product **53**	Yield (%)
1	Benzaldehyde	 **53a**	64
2		 **53b**	72
3	$NCCO_2Et$	 **53c**	78
4	PhCOCl	 **53d**	75[a]
5		 **53e**	96[b]

[a]A stoichiometric amount of CuCN·2 LiCl wad added prior to the addition of the electrophile. [b]A catalytic amount of CuCN·2 LiCl was added prior to the addition of the electrophile.

A second chlorine-magnesium exchange was attempted on compounds **53c** and **53e**. No reaction was observed in both cases. This lack of reactivity compared to tetrachlorothiophene is probably due to the absence of the fourth chlorine atom resulting in a higher electron density on the thiophene ring.

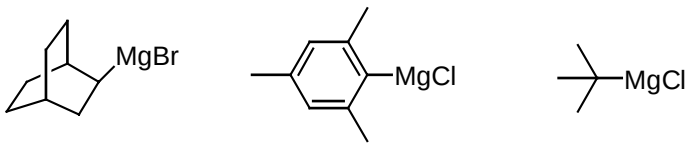
It should also be noted that pentachloropyridine **54** as well as heterocycles **55-57** also failed to undergo a chlorine-magnesium exchange. Treatment with *i*-PrMgBr at low temperature (-78 °C to 0 °C) led to complex mixtures of heavy products.



54 **55** **56** **57**

Figure 7.

Nucleophilic addition is often observed on π deficient heterocycles[67]. To avoid this side-reaction, hindered secondary and tertiary Grignard reagents **58-60** were used instead of *i*-PrMgBr.

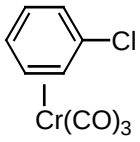


58 **59** **60**

Figure 8.

No exchange reaction was obtained with *t*-BuMgCl or Grignard reagent **58** even at rt and when Grignard reagent **59** was used, polymerisation was observed.

In summary, the chlorine-magnesium exchange could only be carried out successfully in the case of tetrachlorothiophene and could not be applied to other perhalogenated heterocycles. The high reactivity of these substrates led to polymerization. It would be interesting however in the future to test the chlorine-magnesium exchange on other activated aryl chlorides of type **61** (figure 9).



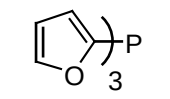
61

Figure 9.

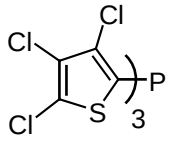
Complexation to the chromium tricarbonyl fragment would make the aromatic ring extremely electron poor and thus should favor the chlorine-magnesium exchange.

2.4.4- Application to the synthesis of phosphorous ligands

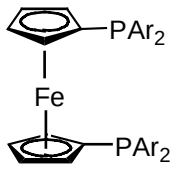
The chlorine-magnesium exchange previously described was applied to the synthesis of ligand **62** and **63** analogues of tfp and ddpf respectively (figure 10).



tfp



62



dppf: Ar = Ph

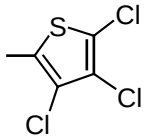
63: Ar = 

Figure 10.

As already mentioned in chapter 1.1 (figure 4) the catalytic activity of a palladium or nickel complex strongly depends on the electronic properties of the ligand. In the case of aryl iodides the rate limiting step is the transmetalation step and is greatly facilitated by electron poor ligands as shown in figure 11.[74]

[74] V. Farina, *Pure Appl. Chem.* **1996**, *68*, 73.

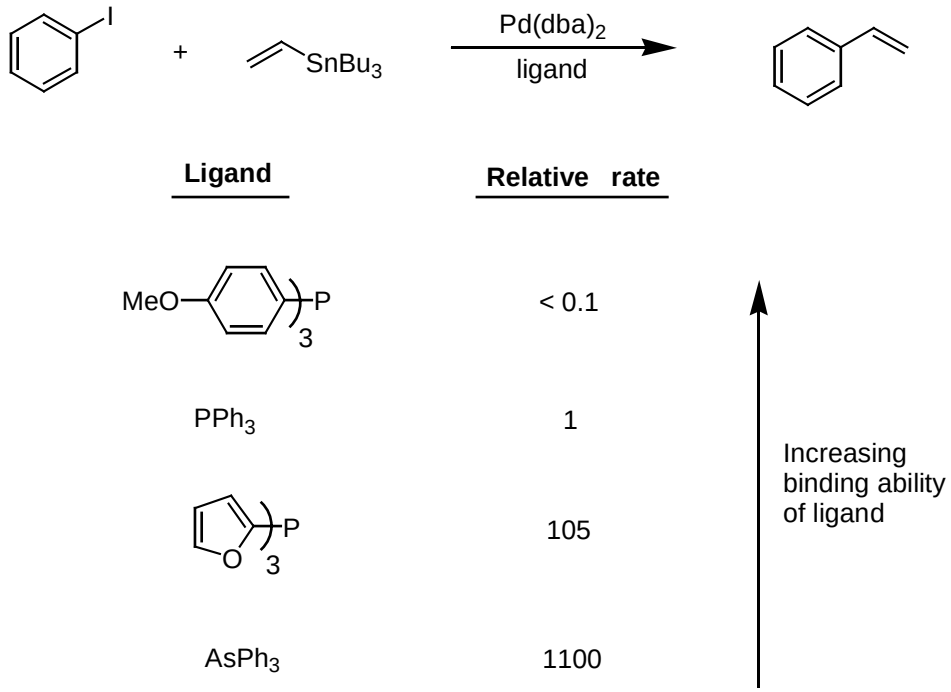
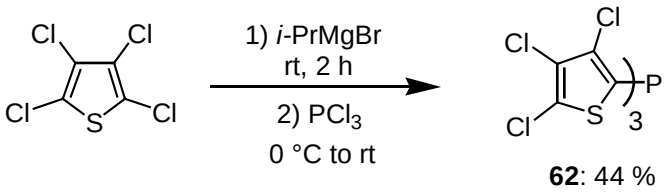


Figure 11. Ligand effect on the Stille cross-coupling reaction.

Replacement of the aryl groups of tfp or dppf by a trichlorothienyl moiety would considerably decrease the electron density on the phosphor atom and should thus facilitate the transmetalation step.

Synthesis of ligand **62** started with a chlorine-magnesium exchange of tetrachlorothiophene. The resulting Grignard reagent was trapped with PCl_3 at 0 °C. The reaction mixture was then allowed to warm to room temperature affording ligand **62** in 44 % yield.

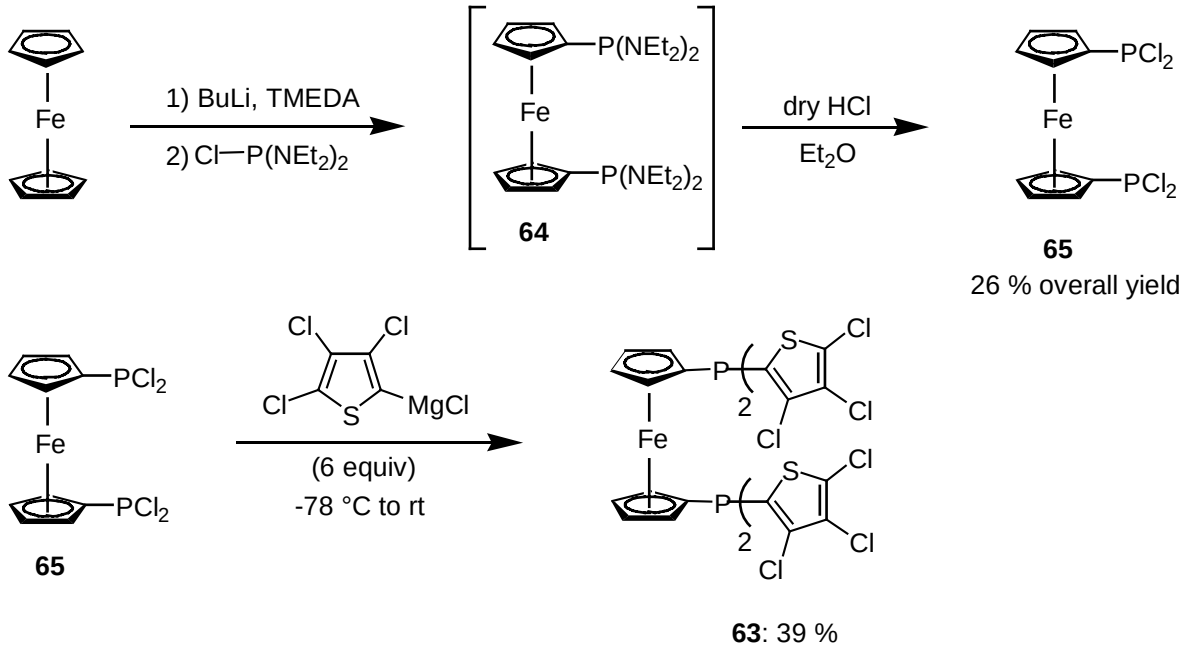


Scheme 39. Chlorine-magnesium exchange on tetrachlorothiophene.

Recently, Hartwig prepared dppf derivatives using dichlorophosphine **65**[75] as the key intermediate.[76] The same strategy was followed for the synthesis of ligand **63**.

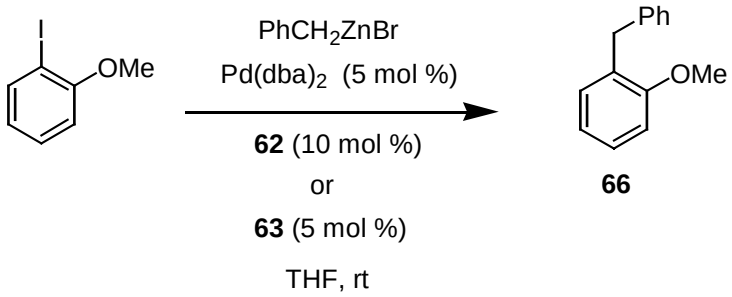
[75] I. E. Nifant'ev, A. A. Boricenko, L. F. Manzhukova, E. E. Nifant'ev, *Phosphorus, Sulfur, Silicon* **1992**, *68*, 99. M. T. Reetz, A. Gosberg, R. Goddard, S. H. Kyung, *Chem. Commun*. **1998**, 2077.
[76] B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc*. **1998**, *120*, 3694.

Dilithiation of ferrocene with BuLi/TMEDA followed by addition of bis(diethylamino)chlorophosphine afforded diethylaminophosphine **64** which was directly converted to dichlorophosphine **65** by treatment with a solution of HCl in ether. Chlorophosphine **65** was then treated with an excess of trichlorothienylmagnesium bromide affording ligand **63** in 39 % yield (scheme 40).



Scheme 40. Preparation of ligand **63**.

Ligands **62** and **63** were tested in the following Negishi cross-coupling reaction:



Scheme 41. Negishi cross-coupling reaction using ligand **62** and **63**.

Results are summarized in Table 5.

Table 5. Negishi cross-coupling reaction using ligand **62** and **63**.

Conversion (%)[a]					
Time (min)	5	10	20	40	60
tfp	32	57	66	86	100
Ligand **62**	82	90	91	95	100
Ligand **63**	0	0	0	0	0

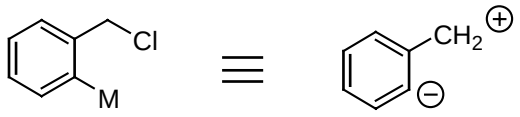
[a]Conversion of the iodide as indicated by GC-MS analysis using tetradecane as standard. Product **66** was observed accompanied by negligible amount of homocoupling products (< 10 %).

No catalytic activity was observed in the case of ligand **63**. The high steric hindrance of this ligand probably prevents oxidative addition of the palladium and thus inhibits the reaction. Interestingly the cross-coupling was very fast when ligand **62** was used with 82 % of conversion in 5 min compared to 32 % conversion in the case of tfp. The cross-coupling product **66** was obtained as the major compound accompanied with negligible amount (< 10%) of homocoupling products as indicated by GC-MS. Ligand **62** is being further tested by BASF.

2.5- Arylmagnesium reagents bearing an *ortho*-chloromethyl group

2.5.1- Introduction

Aryl organometallic reagents bearing an *o*-chloromethyl group are synthetic equivalents of the zwitterionic synthons **67** and are interesting intermediates for cylisation reactions.



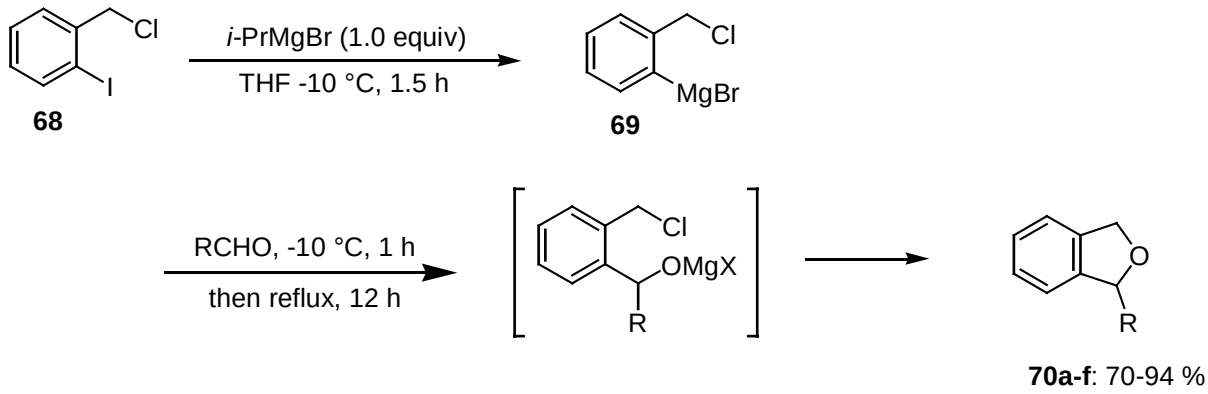
M = Li, Mg etc. **67**

Figure 12.

The lithium derivative has already been prepared by bromine-lithium exchange.[77] Very low temperatures (-100 °C) are required for this exchange reaction and the resulting organolithium reagent has to be quenched immediately with electrophiles due to its instability. On the other hand, the corresponding organomagnesium reagent should display a better stability and more convenient reaction conditions shoud be allowed. Its preparation using an iodine-magnesium exchange was thus tried in collaboration with Thomas Delacroix and applications to the synthesis of dihydrobenzofurans as well as tetrahydrobenzazepines are described below.

2.5.2- Synthesis of dihydrobenzofurans

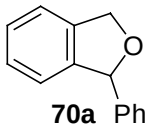
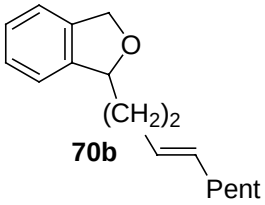
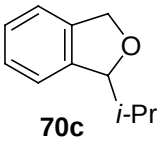
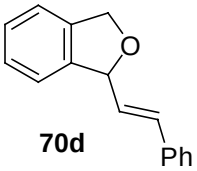
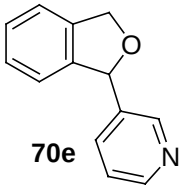
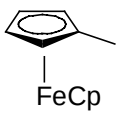
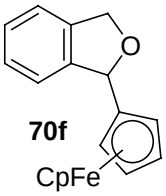
When aryl iodide **68** was treated with *i*-PrMgBr at -10 °C a smooth iodine-magnesium exchange took place affording Grignard reagent **69** in 1.5 h. This organomagnesium reagent was stable at this temperature and could be trapped by various aldehydes (scheme 42). After heating the intermediate alcoholates to reflux in THF for 12 h, the desired cyclization was observed leading to dihydrobenzofurans **70a-f** in 70-91 % yields (table 6). Aryl (entries 1, 5 and 6), alkenyl (entry 4) or aliphatic aldehydes (entries 2 and 3) can be used in this reaction.



Scheme 42. Preparation of dihydrobenzofurans **70a-f**.

[77] W. E. Parham, L. D. Jones, Y. A. Sayed, *J. Org. Chem*. **1976**, *41*, 1184.

Table 6. Heterocycles **70a-f** obtained by the reaction of organomagnesium reagents **69** with aldehydes.

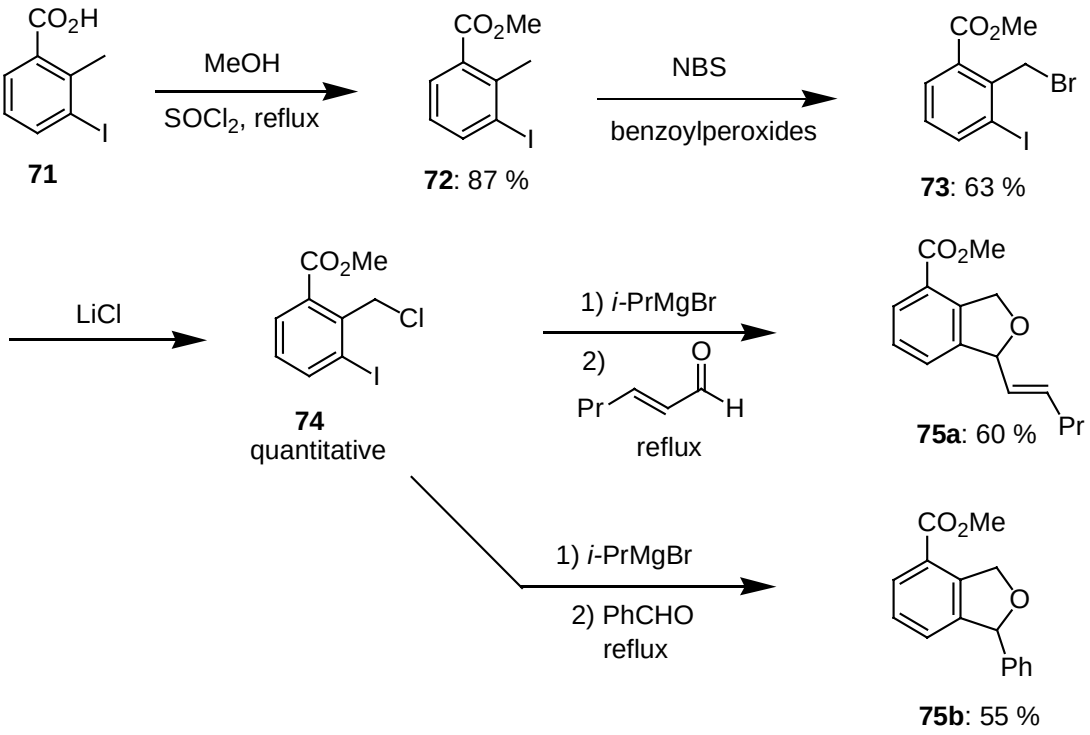
Entry	R of aldehyde RCHO	Product of type **70**	Yield (%)[a]
1	Ph	 **70a** Ph	82
2	(*E*)-Pent-CH=CH-$(CH_2)_2$-	 **70b**	70
3	*i*-Pr	 **70c**	86
4	(*E*)-Ph-CH=CH-	 **70d**	91
5	3-pyridyl	 **70e**	78
6		 **70f**	81

[a]Yield of analytically pure products.

Remarkably, an ester function could be tolerated as shown in scheme 43. Preparation of starting material **74** was performed in 3 steps from 3-iodo-2-methylbenzoic acid **71**. Esterification followed by a benzylic bromination with NBS led to benzylic bromide **73** in

55 % overall yield. The correspondind benzylic chloride **74** was obtained by performing a Finkelstein reaction using LiCl.

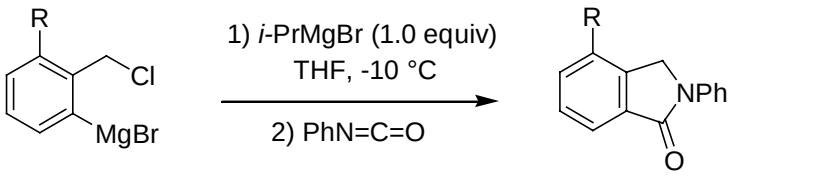
An iodine-magnesium exchange was then carried out on this substrate using the same reaction conditions as previously described. The presence of the ester function facilitates the exchange, which was complete after 1 h in this case. Addition of aldehydes led to cyclized products **75a-b** in moderate yields.



Scheme 43. Preparation of dihydrobenzofurans **75a-b**.

Interestingly, benzylic bromide **73** failed in this reaction. When treated with *i*-PrMgBr polymerization was observed due to the high reactivity of the benzylic bromide function.

Alternatively, phenyl isocyanate could be used as the electrophile, furnishing, after cyclisation, benzolactams **76** and **77** in 96 % and 75 % yield respectively (scheme 44).



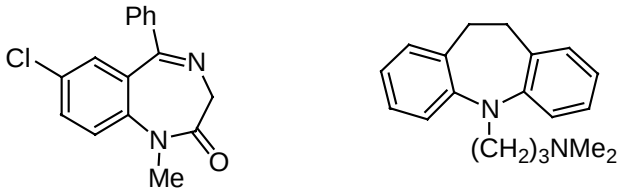
68: R = H
74: R = CO_2Me

76: R = H; 96 %
77: R = CO_2Me; 75 %

Scheme 44. Synthesis of benzolactams **76** and **77**.

2.5.3- Synthesis of tetrahydrobenzazepines

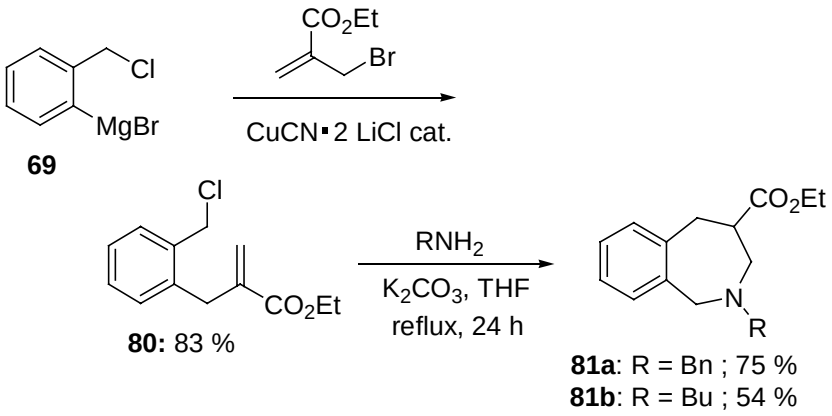
So far we have focussed on five- and six-membered heterocycles. Seven-membered heterocycles are also interesting compounds with useful biological activity. For example benzodiazepine **78** (Valium) or dibenzazepine **79** (Imipramine) are used in the relief of anxiety (figure 13).



78 **79**

Figure 13.

Tetrahydrobenzazepine derivatives were readily obtained in 2 steps, starting from the functionalized organomagnesium **69**. Thus, the reaction of **69** with ethyl (2-bromomethyl)acrylate[78] provided the allylated product **80** in 83 %. Subsequent treatment with primary amines in presence of K_2CO_3 in refluxing THF resulted in smooth cyclisation affording the tetrahydrobenzazepines **81a-b** in 54-75 % yield (Scheme 45).



Scheme 45. Synthesis of tetrahydrobenzazepines **81a** and **81b**.

[78] J. Villieras, M. Rambaud, *Synthesis*, **1982**, 924.

2.6- Summary

• The low temperature halogen-magnesium exchange could be applied to the synthesis of functionalized heterocyclic Grignard reagents. Functional groups such as ester, nitrile or amide functions are tolerated making this method highly versatile.

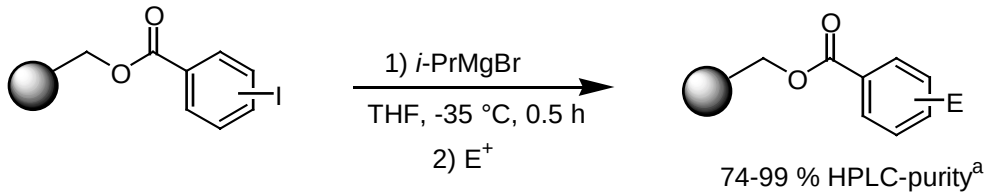
• The resulting organomagnesium reagents display the typical reactivity of Grignard reagents and could be trapped with various electrophiles. Functionalized pyridine, thiazole and thiophene derivatives could thus be prepared.

• Alternatively, arylmagnesium reagents bearing an *o*-chloromethyl group could be prepared using a low temperature halogen-magnesium exchange. These latter reagents are interesting intermediates for cyclisation strategies and a new method leading to dihydrobenzofurans, benzolactams and tetrahydrobenzazepines was developed.

3- Synthesis of functionalized heterocycle derivatives on the solid phase using a low temperature halogen-magnesium exchange

3.1- Introduction

The first part of this work has focussed on the halogen-magnesium exchange reaction and on its applications for the synthesis of heterocyclic derivatives in solution. We then turned our attention to the solid phase. Dr. Mario Rottländer has shown that an iodine-magnesium exchange could be performed on resin-attached aryl iodides using an excess of *i*-PrMgBr at -35 °C (scheme 46).[25] The resulting Grignard reagents could be trapped with various electrophiles and the products were obtained with high HPLC purities after cleavage. Remarkably, an ester function is tolerated under these reactions conditions even in the presence of a large excess of *i*-PrMgBr.



E = allyl bromide, aldehyde, Ph_2S_2, TosCN
[a]HPLC-purity (UV detection, 254 nm)

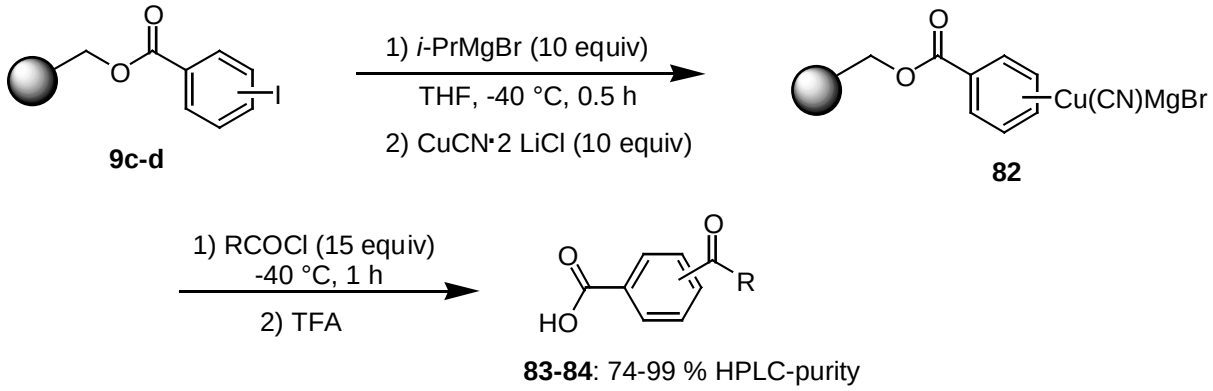
Scheme 46. Iodine-magnesium exchange on the solid phase.

During this work we first tried to broaden the scope of this reaction by performing acylation reactions. A wide range of acid chlorides are available from the corresponding carboxylic acids which would allow diversity in the final products.
Finally we applied the halogen-magnesium exchange to the synthesis of thiophene derivatives.

3.2- Acylation reaction on the solid phase

Resin-attached aromatic iodides **9a-c** were treated with *i*-PrMgBr (10 equiv) at -40 °C for 0.5 h. A THF solution of CuCN·2 LiCl (10 equiv) was then added and the resulting copper

reagents **82** were quenched with various acid chlorides. After 0.5 h at -40 °C the resin was filtered and washed repeatedly with CH_2Cl_2 and MeOH. Cleavage was performed with TFA (90 % in CH_2Cl_2) leading to the desired products **83-84** in 74-99 % HPLC purity (scheme 47, Table 7).



9c-d **82**

83-84: 74-99 % HPLC-purity

Scheme 47.

Table 7. Products **83a-f, 84a-c** obtained by the iodine-magnesium exchange on Wang-resin attached iodides **9c-9d** followed by acylation.

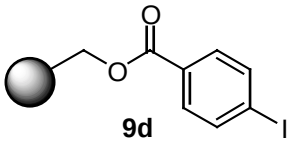
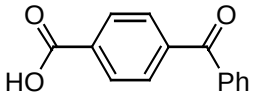
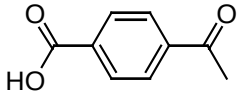
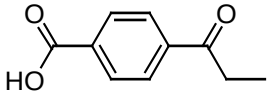
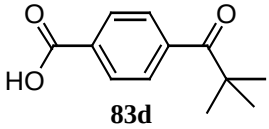
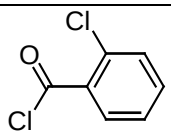
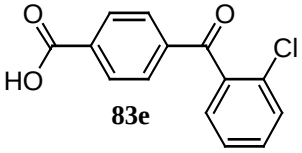
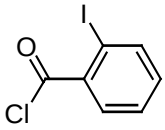
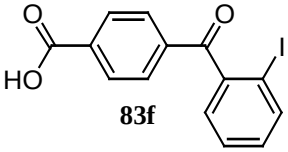
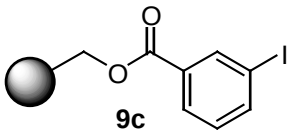
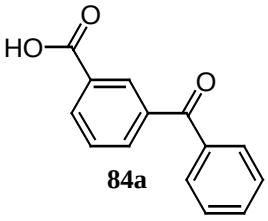
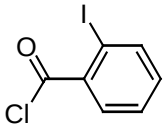
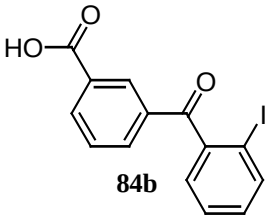
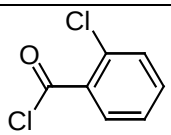
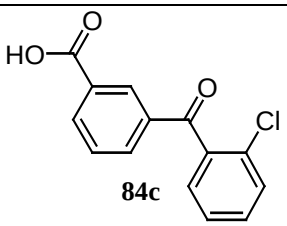
Resin	Acid chloride	Product	HPLC-purity (%)
 **9d**	PhCOCl	 **83a**	97
9d	MeCOCl	 **83b**	94
9d	EtCOCl	 **83c**	92
9d	*t*-BuCOCl	 **83d**	96

Table 7. (Continued).

9d		 **83e**	93
9d		 **83f**	86
 **9c**	PhCOCl	 **84a**	92
9c		 **84b**	89
9c		 **84c**	91

The results summarized in Table 7 show that this acylation reaction is quite general and can be performed with various acid chlorides. Interestingly, when pivaloyl chloride was used a longer reaction time was required and the reaction was complete only after 6 h. This significant rate difference can be attributed to the steric hindrance of pivaloyl chloride.

Resin-attached iodide **85** was also an interesting substrate where 2 different substituents could be introduced into the ring by performing a selective iodine-magnesium exchange followed by a Negishi cross-coupling (figure 14).

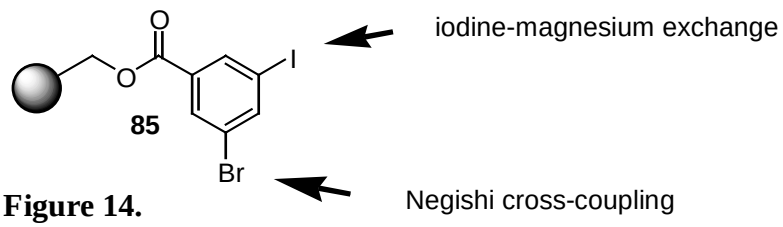
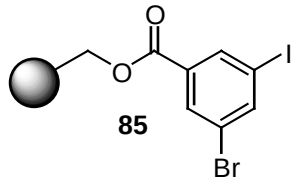
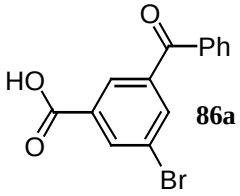
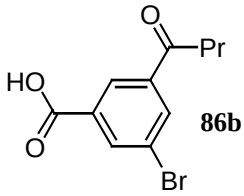
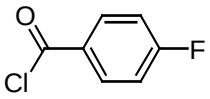
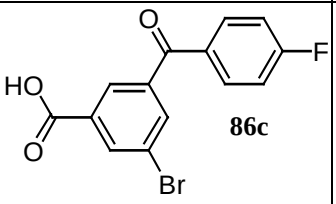
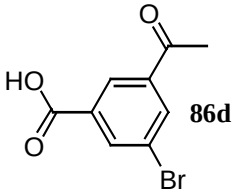
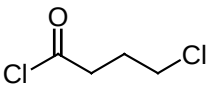
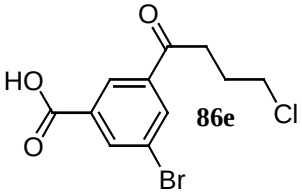


Figure 14.

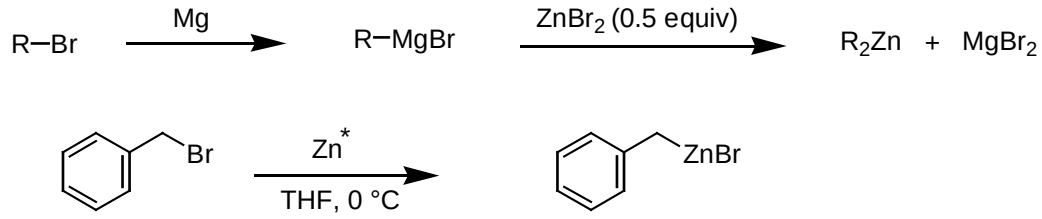
The iodine-magnesium exchange was first performed using the same conditions as previously described. However a lower reaction temperature (-78 °C) was required to avoid a competitive bromine-magnesium exchange. Addition of CuCN·2 LiCl followed by various acid chlorides afforded products **86a-e**. The results are summarized in Table 8.

Table 8. Products **86a-e** obtained by iodine-magnesium exchange on Wang-resin attached iodide **85** followed by acylation.

Resin	Acyl chloride	Product	HPLC-Purity (%)
 **85**	PhCOCl	 **86a**	93
85	PrCOCl	 **86b**	97
85		 **86c**	95
85	MeCOCl	 **86d**	86
85		 **86e**	77

3.3- Negishi cross-coupling on the solid phase

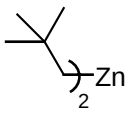
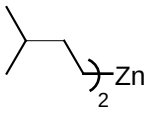
Alternatively, a Negishi cross-coupling reaction could be performed before cleavage using various zinc reagents. Diorganozinc reagents are readily prepared from the corresponding Grignard reagents by transmetalation using $ZnBr_2$ (scheme 48).[79] After distillation under vacuum they are obtained as neat compounds. Benzylzinc bromide was prepared by direct insertion of previously activated zinc.[41]



Scheme 48. Preparation of organozinc compounds

Zinc reagents **87-90** were prepared according to these procedures (Table 9).

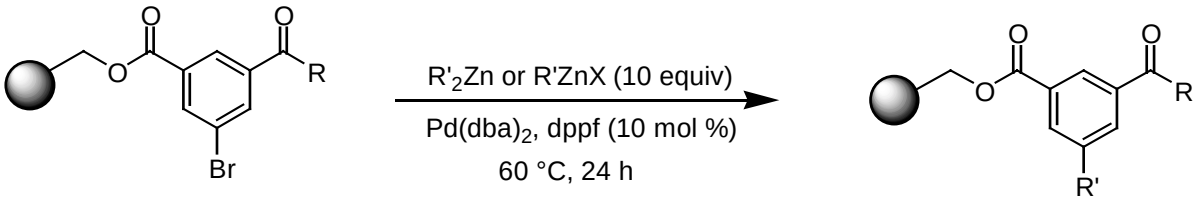
Table 9. Preparation of organozinc reagents **87-90**.

Zinc reagent	Yield (%)	Zinc reagent	Yield (%)
$Pent_2Zn$ **87**	80	 **89**	76
 **88**	70	$PhCH_2ZnBr$ **90**	85

Negishi cross-coupling reactions were performed on resin **91** and **92** using $Pd(dba)_2$ and dppf as catalyst (10 mol %) with the appropriate zinc reagent (10 equiv). At rt a very sluggish reaction was observed leading to incomplete conversion even after one day. This Negishi

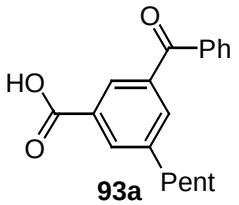
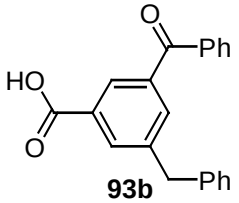
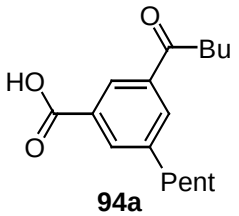
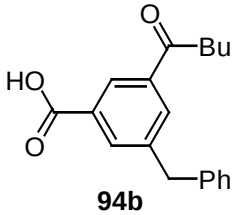
[79] *Organozinc Reagents, A Practical Approach*; P. Knochel, P. Jones, Eds.; Oxford Press: Oxford, **1999**.

cross-coupling could be greatly accelerated by heating the reaction mixture to 60 °C. At this temperature the reaction was complete after one day and disubstituted products **93a-c** and **94a-b** were obtained in moderate to good HPLC purity (scheme 49, Table 10).



Scheme 49.

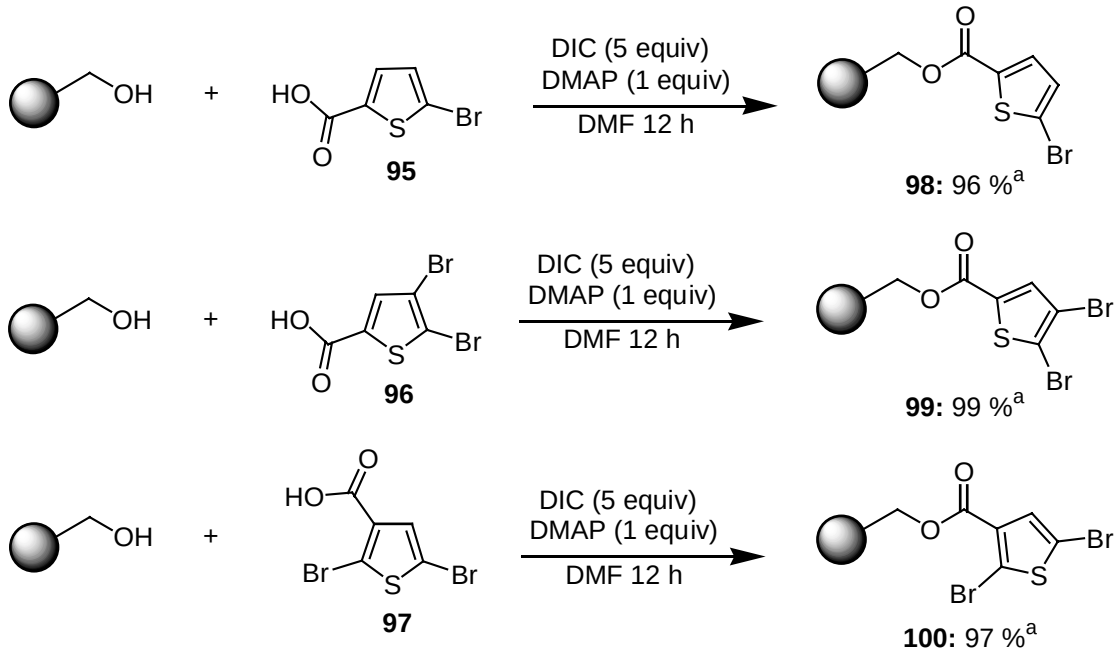
Table 10. Negishi cross-coupling reaction on the solid phase.

Resin	Zinc reagent	Product	HPLC purity (%)
91	$Pent_2Zn$	 **93a**	93
91	$PhCH_2ZnBr$	 **93b**	91
92	$Pent_2Zn$	 **94a**	93
92	$PhCH_2ZnBr$	 **94b**	95

3.4- Synthesis of thiophenes derivatives on the solid phase

3.4.1- Loading on Wang-resin

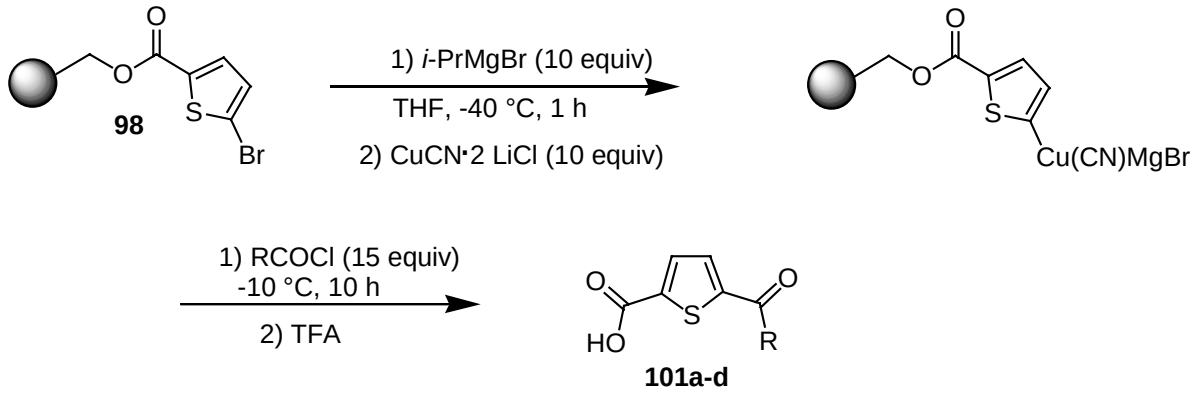
Wang resin-attached bromothiophenes **98-100** were easily prepared using carboxylic acids **95-97** according to standard procedures.[50] The Wang-resin was treated with the appropriate carboxylic acid (10 equiv) in the presence of DIC and DMAP. The resins were then washed repeatedly with CH_2Cl_2 and MeOH and dried in an oven (50 °C). The HPLC-purity was determined by cleavage of a small resin amount with TFA.



Scheme 50. [a]HPLC-purity (UV detection, 254 nm).

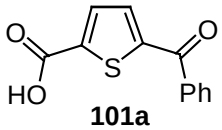
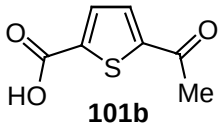
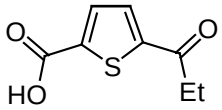
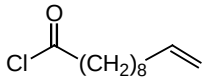
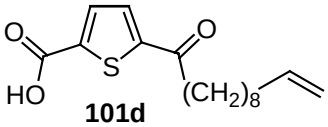
3.4.2- Acylation reaction

Acylation reactions were then performed on resin **98** (scheme 51). Treatment with *i*-PrMgBr (10 equiv) followed by addition of CuCN·2 LiCl led to the corresponding copper reagent. The reaction with acid chlorides was significantly slower than for aryl copper reagent **82** and both a higher temperature (-10 °C) as well as a longer reaction time (10 h) were required. Under these modified reaction conditions products **101a-d** were obtained in high HPLC purity. The results are summarized in Table 11.

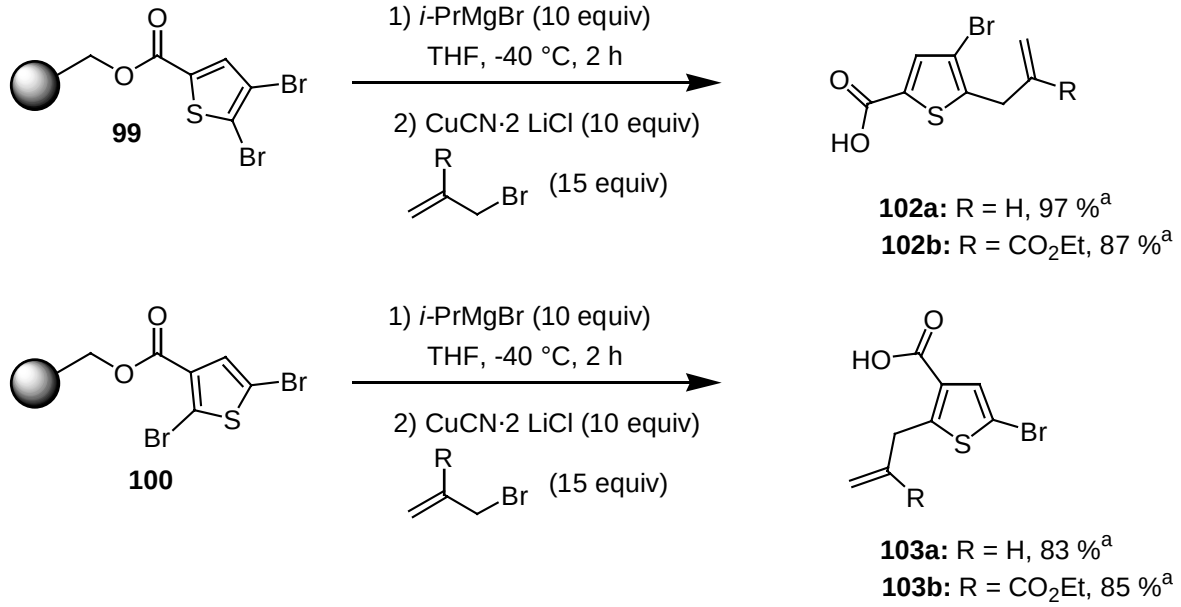


Scheme 51.

Table 11. Products **101a-d** obtained by a low temperature iodine-magnesium exchange followed by acylation.

Acid chloride	Product	HPLC purity (254 nm)
PhCOCl	 **101a**	93
AcCl	 **101b**	84
EtCOCl	 **101c**	90
	 **101d**	99

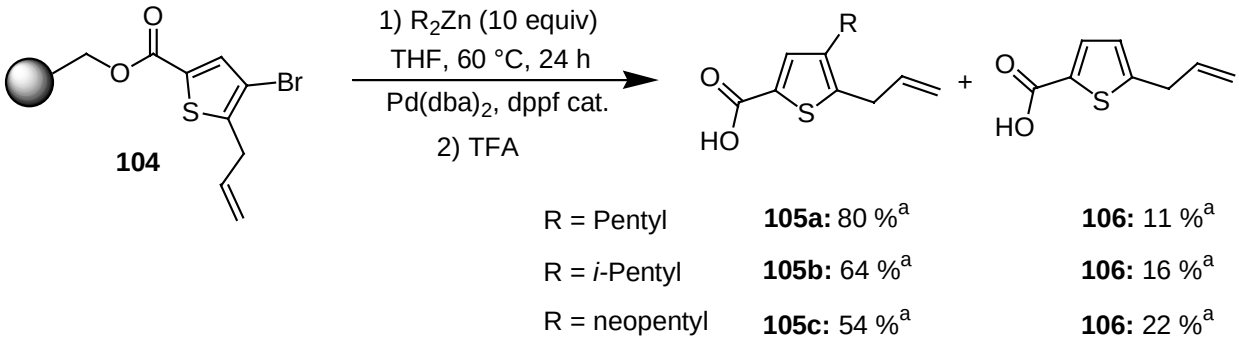
A low-temperature halogen-magnesium exchange could also be performed on Wang-resin attached bromothiophenes **99** and **100** using *i*-PrMgBr (10 equiv) as shown in scheme 52. The regioselectivities observed are identical to those observed in solution. Exchange occured exclusively at position 2 in the case of resin **99** furnishing products **102a-b** after quenching with allyl bromide and ethyl (2-bromomethyl)acrylate. The regioselectivity was slightly lower in the case of resin **100**. Products **103a-b** were obtained in 83 % and 85 % HPLC-purity accompanied by approximately 10 % of the regioisomers. Lowering of the temperature to -78 °C did not change this ratio.



Scheme 52. [a]HPLC-purity (UV detection, 254 nm).

3.4.3- Negishi cross-coupling

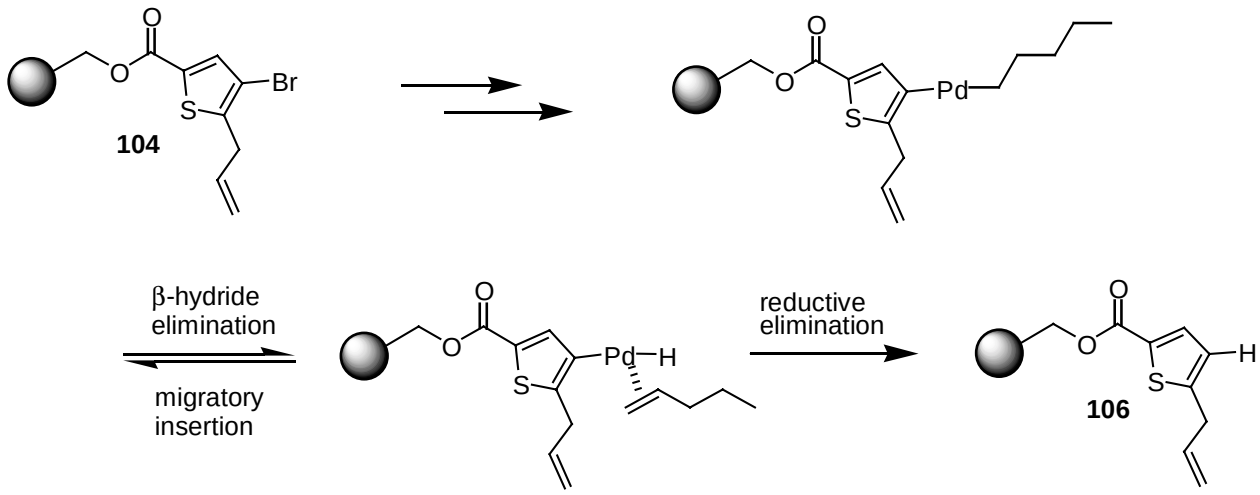
A Negishi cross-coupling was then carried out on resin **104** using various diorganozinc reagents with $Pd(dba)_2$ and dppf as catalyst. Unfortunately the cross-coupling products **105a-c** was contaminated with significant amounts of the reduction product **106** (scheme 53). In the case of dipentylzinc, 11 % of reduction product was obtained after cleavage. When more hindered diorganozinc reagents such as diisopentylzinc or dineopentylzinc were used larger amounts of reduction product were formed (16 % and 22 % respectively).



Scheme 53. [a]HPLC-purity (UV detection, 254 nm).

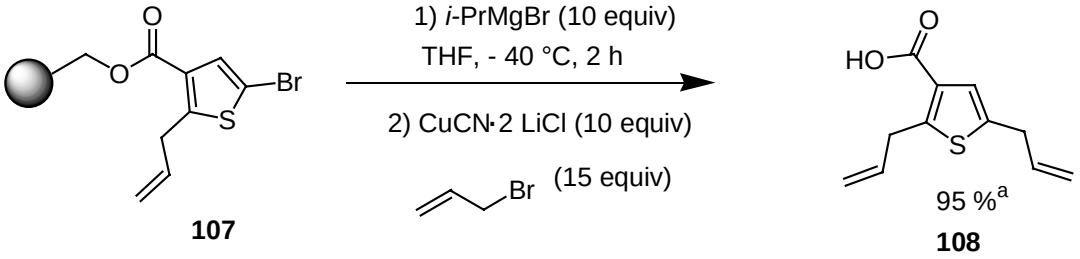
The formation of the reduction product can be explained by a β-hydride elimination process as shown in scheme 54 and could not be suppressed by lowering the reaction temperature to 40 °C.

The use of benzylzinc bromide as nucleophile also failed, leading to a complex reaction mixture.



Scheme 54.

In the case of resin **107,** a second bromine-magnesium exchange can be performed using *i*-PrMgBr. Addition of CuCN·2 LiCl and allyl bromide afforded thiophene **108** in high HPLC-purity after cleavage (scheme 55).



Scheme 55. [a]HPLC-purity (UV detection, 254 nm).

3.5- Summary

• A low temperature halogen-magnesium exchange was carried out on resin-attached aromatic iodides using an excess of *i*-PrMgBr. The Grignard reagents so obtained could be transmetalated to the corresponding copper reagents with CuCN·2 LiCl and reacted with acid

chlorides. This acylation reaction proved to be very general and could be performed with numerous acid chlorides leading to the desired products in high HPLC-purity.

• Two points of diversity could be introduced on Wang resin-attached 3-bromo-5-iodo carboxylic acid **85**. First, a selective iodine-magnesium exchange was performed, followed by a Negishi cross-coupling reaction using a palladium catalysis.

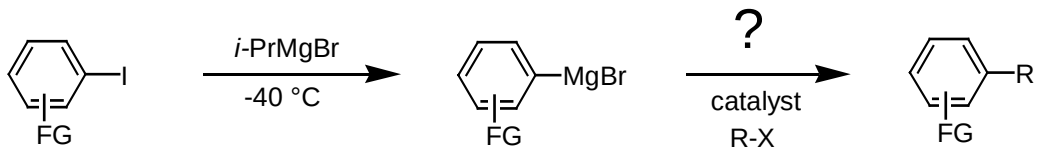
• Finally, various Wang resin-attached bromothiophenes proved to be suitable substrates for a low temperature bromine-magnesium exchange. The resulting Grignard reagents were used in acylation reactions or quenched with typical electrophiles, affording various thiophene derivatives after cleavage.

4- Functionalized Grignard reagents for low temperature cross-coupling reactions

4.1- Introduction

Since the discovery that Pd or Ni salts[80] catalyze cross-coupling reactions, various organometallics have been used.[11] As already mentioned in the introduction, main group organometallics suffer from a low functional group tolerance which has considerably limited their use in such cross-coupling reactions. An alternative consists in performing a transmetalation using transition metal salts prior to the cross-coupling reaction. However, stoichiometric amounts of transition metal salts are needed and this process suffers from a poor atom economy.[9]

We have shown that a low temperature halogen-magnesium exchange is an efficient method for the formation of functionalized Grignard reagents. As shown in scheme 56, a direct low temperature cross-coupling with these functionalized Grignard reagents would be of great interest since no transmetalation would be required.



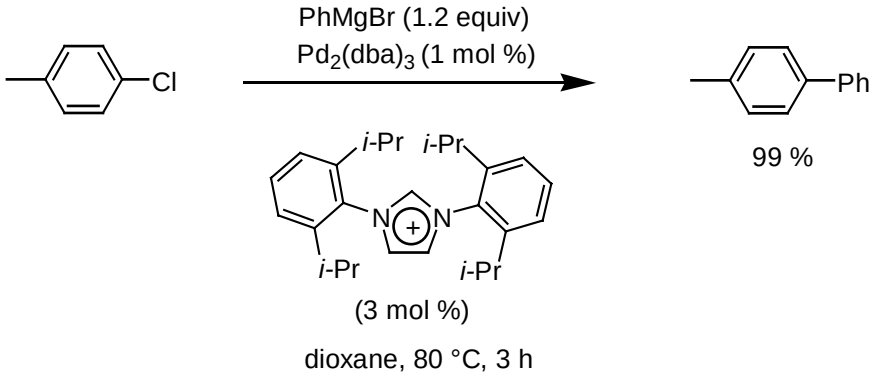
FG = functional group
RX = aryl or alkenyl halide

Scheme 56.

4.2- Low temperature aryl-aryl cross-coupling reactions

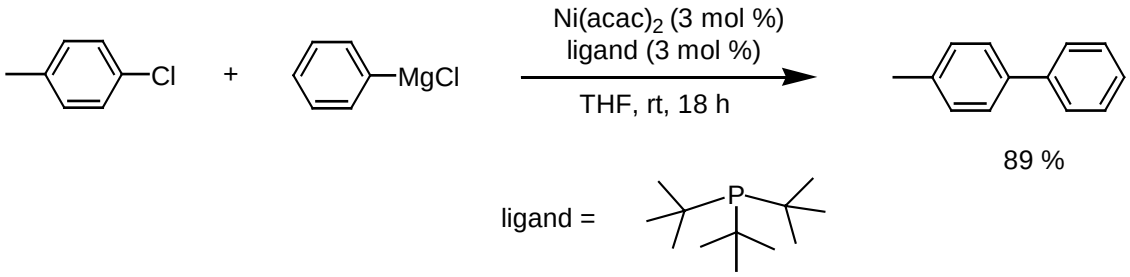
Grignard reagents are very reactive intermediates and often give side reactions such as the formation of homocoupling products. Also, many efforts have been made to find suitable reaction conditions for aryl-aryl cross-coupling reactions. For example imidazolium salts have

been used as precursors to N-heterocyclic carbene ligands for the *in situ* formation of highly active catalytic systems. [81]



Scheme 57. Cross-coupling with Grignard reagents.

The use of bulky phosphine ligand such as P(*t*-Bu)$_3$ has also successfully been used.[82]



Scheme 58. Cross-coupling with Grignard reagents.

However, very few examples of low temperature cross-coupling reactions have been reported in the literature and either activated halides, such as trichlorobenzene, or long reaction times were required (scheme 59).[83]

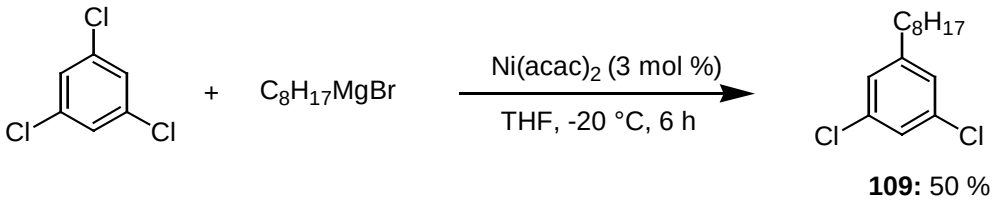
---

[80] K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc*. **1972**, *94*, 4374. R. J. P. Corriu, J. P. Masse, *J. Chem. Soc., Chem. Comm*. **1972**, 144.

[81] S. P. Nolan, *J. Am. Chem. Soc*. **1999**, *121*, 9889. For a review see: W. A. Herrmann, C. Köcher, *Angew. Chem.* **1997**, *109*, 2256; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2162.

[82] V. P. W. Böhm, T. Weskamp, C. W. K. Gstöttmayr, W. A. Herrmann, *Angew. Chem.* **2000**, *112*, 1672; *Angew. Chem. Int. Ed. Engl*. **2000**, *39*, 1602.

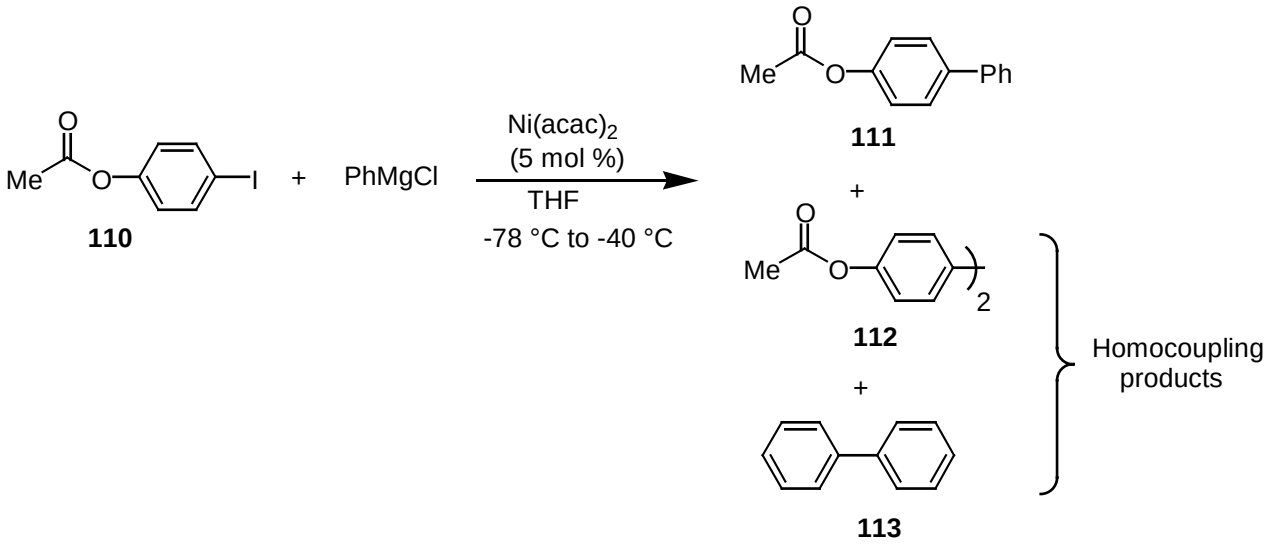
[83] For example of low temperature cross-coupling reactions with Grignard reagents see: K. C. Eapen, S. S. Dua, C. Tamborski, *J. Org. Chem*. **1984**, *49*, 478. T. Hayashi, K. Hayashizaki, T. Kiyoi, Y. Ito, *J. Am. Chem. Soc*. **1988**, *110*, 8153.



109: 50 %

Scheme 59. Low-temperature cross-coupling reaction with Grignard reagents.

In order to find more general reaction conditions the following reaction was studied:



Scheme 60.

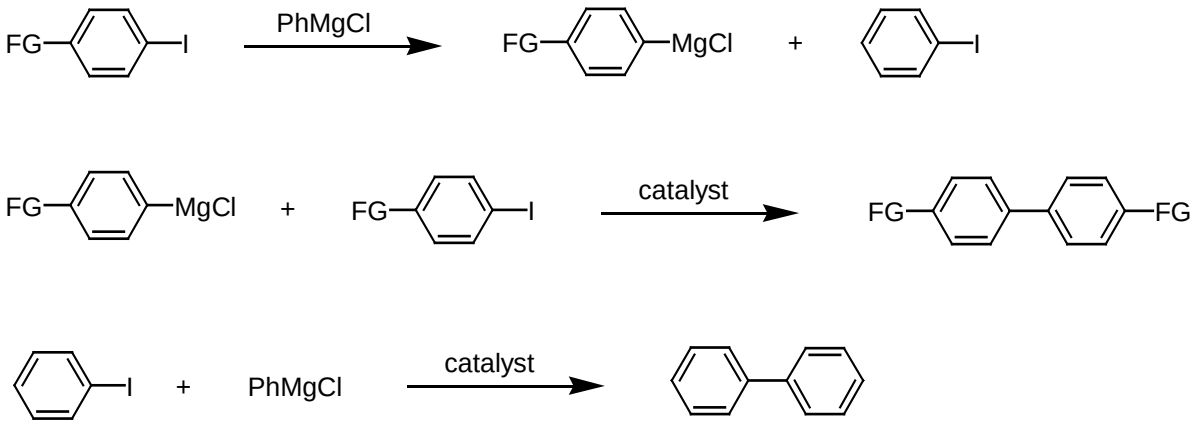
Functionalized aryl iodide **110** was treated with phenylmagnesium chloride in THF using $Ni(acac)_2$ (5 mol %) as catalyst. The reaction was carried out at different temperatures.
As shown in Table 12, no reaction occured below -40 °C. When the temperature was raised to -40 °C the reaction was complete after 30 min and the cross-coupling product **111** was obtained in 54 % yield. Both homocoupling products **112** and **113** were formed as indicated by GC-MS, which accounts for the relatively low yield obtained. Higher reaction temperature resulted in lower yield (entry 4) and addition of a cosolvent such as DME (4 equiv; entry 5)[84] did not improve the reaction.

[84] For cross-coupling reactions with Grignard reagents using DME as cosolvent see: E. Riguet, PhD thesis, Paris, **1998**.

Table 12 Yield of cross-coupling product **111**.

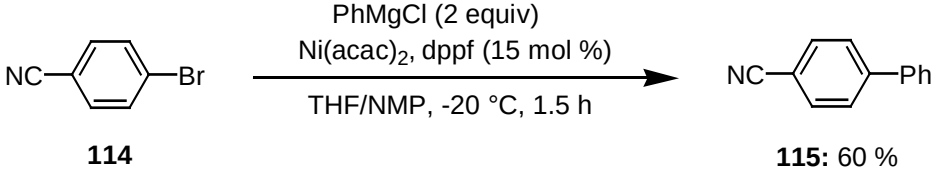
Entry	Temperature (°C)	Cosolvent	Yield (%)
1	-78	-	No reaction
2	-60	-	No reaction
3	-40	-	54
4	-20	-	40
5	-40	DME	57

The formation of homocoupling products can be explained by an iodine-magnesium exchange as shown in scheme 61. Both products formed during this exchange reaction then enter the catalytic cycle.



Scheme 61.

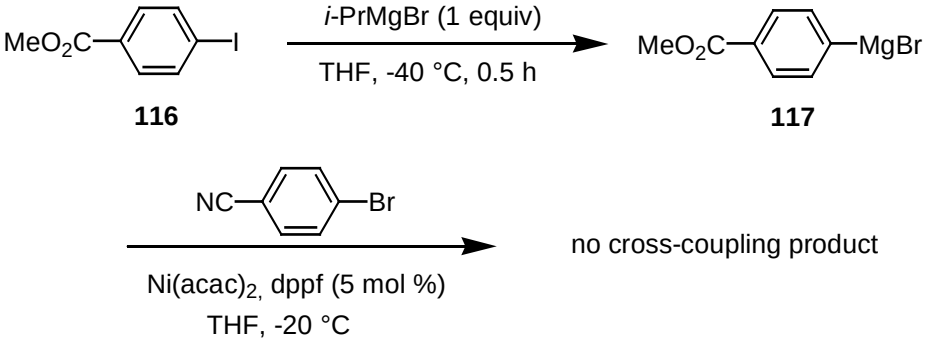
To reduce the amount of cross-coupling products, a less reactive substrate would be favorable. Thus aryl bromide **114** was selected as starting material (scheme 62).



114 **115:** 60 %

Scheme 62.

When $Ni(acac)_2$ was used as catalyst no reaction was observed even at -20 °C, which is probably due to a slow oxidative addition. Addition of dppf as ligand resulted in a faster reaction, affording the cross-coupling product in 60 % yield after 1.5 h. Importantly, the Grignard reagent had to be added in 2 portions to drive the reaction to completion. Again the formation of both homocoupling products were responsible for the moderate yield obtained.
These reactions conditions were next applied to functionalized Grignard reagent prepared by an iodine-magnesium exchange at -40 °C (scheme 63).

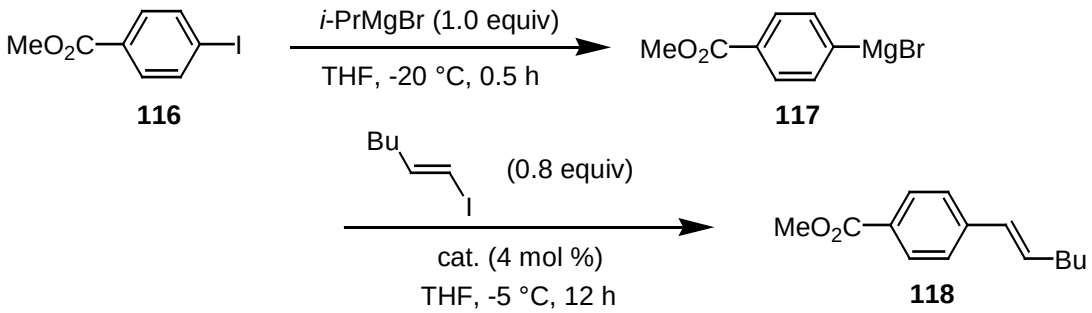


Scheme 63.

Unfortunately, no cross-coupling product was formed at -20 °C. At higher temperatures only degradation was observed leading to complex reaction mixtures. This unexpected lack of reactivity compared to phenylmagnesium chloride can be explained by the presence of the ester function which stabilizes Grignard reagent **117** and prevents the transmetalation step. The formation of aggregates due to the higher polarity of these functionalized Grignard reagents could also result in a decreased reactivity.

4.3- Low temperature aryl-alkenyl cross-coupling reactions

Alkenyl iodides such as (*E*)-1-iodohexene are very reactive substrates for cross-coupling reactions and the following reaction was attempted:



Scheme 64.

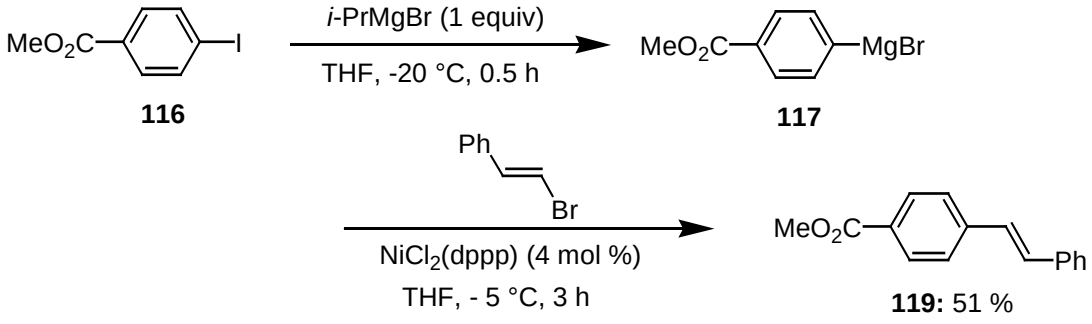
Various catalysts were tested as shown in Table 13.

Table 13. Yield of cross-coupling product **118**.

Catalyst	Yield (%)
$PdCl_2$(dppf)	-
$Ni(acac)_2$ dppf	-
$Ni(acac)_2$ 2 P(*t*-Bu)$_3$	-
$NiCl_2$(dppp)	62 %

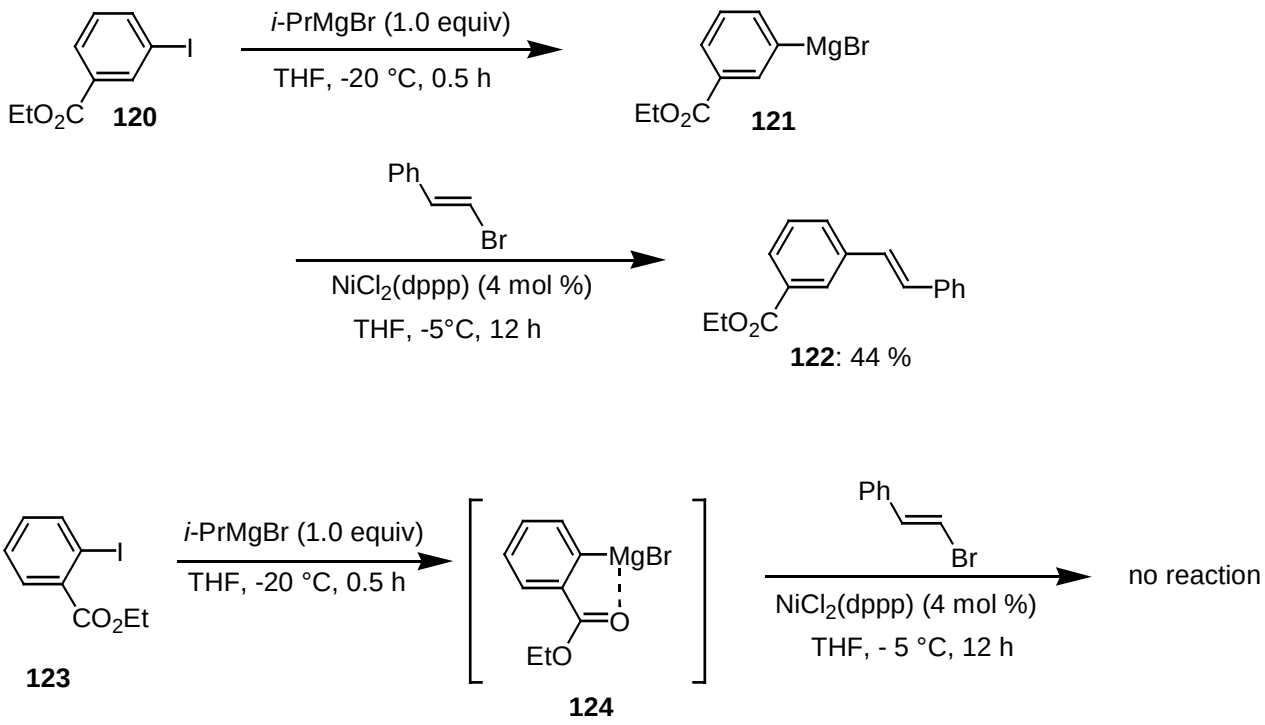
When $PdCl_2$(dppf) was used no reaction was observed at -5 °C. $Ni(acac)_2$ dppf was not a suitable catalyst either, affording homocoupling materials as major products according to GC-MS analysis. This is in strong contrast with results obtained using 4-benzonitrile. The use of P(*t*-Bu)$_3$[82] as ligand resulted in decomposition of the Grignard reagent. Finally, cross-coupling product **118** could be obtained in 62 % yield when $NiCl_2$(dppp) (4 mol %) was used as catalyst. Very low amounts of homocoupling products (< 10 %) were formed as indicated by GC-MS.

Interestingly, this low-temperature cross-coupling reaction could also be applied to *trans*-β-bromostyrene as shown in scheme 65. A fast reaction took place in this case leading to product **119** after 3 h in 51 % yield.



Scheme 65.

We then tried to broaden the scope of the reaction starting with different functionalized aromatic iodides (scheme 66).



Scheme 66.

When *meta*-substituted aromatic iodide **120** was used as starting material, the cross-coupling product was obtained in a slightly lower yield (44 %) whereas no reaction occured with the *ortho*-substituted aromatic iodide **123**. A plausible explanation for this latter result could be the formation of a five membered ring chelate **124** resulting in a stabilized organomagnesium species.

4.4- Summary

Suitable conditions were found to perform a cross-coupling reaction between functionalized Grignard reagents and vinylic halides such as (*E*)-1-iodohexene and *trans*-β-bromostyrene at –5 °C. However, the yields are moderate, probably due to partial decomposition of the functionalized Grignard reagents. A solution to this problem would be to find an efficient

catalytic system at a temperature lower than -5 °C. Nickel salts which allow an oxidative addition at low temperatures seem especially promising for this purpose.

Low temperature aryl-aryl cross-couplings could also be performed using phenylmagnesium chloride as the organometallic reagent. However, functionalized Grignard reagents failed in this reaction. The higher polarity of these reagents is probably responsible for this low reactivity due to the formation of aggregates. Thus addition of polar cosolvents to the reaction mixture should be beneficial.

5- Summary and outlook

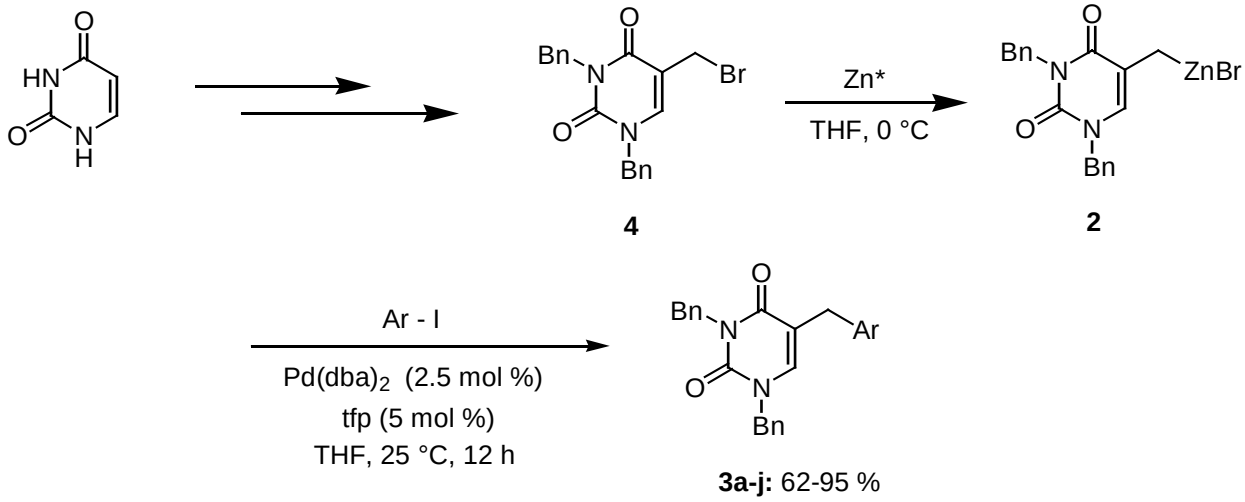
This work has focussed on the preparation of functionalized heterocyclic organometallics. In the first part, functionalized zinc derivatives were used due to their high functional group tolerance. Thus various thymine derivatives have been prepared both in solution and on the solid phase.

Alternatively, a new route to functionalized heterocyclic Grignard reagents was developed using a low-temperature halogen-magnesium exchange. Ester, amide and nitrile functions are tolerated and the resulting organomagnesium derivatives could be reacted with various electrophiles.

Finally, we have attempted to perform low-temperature cross-coupling reactions using these functionalized Grignard reagents.

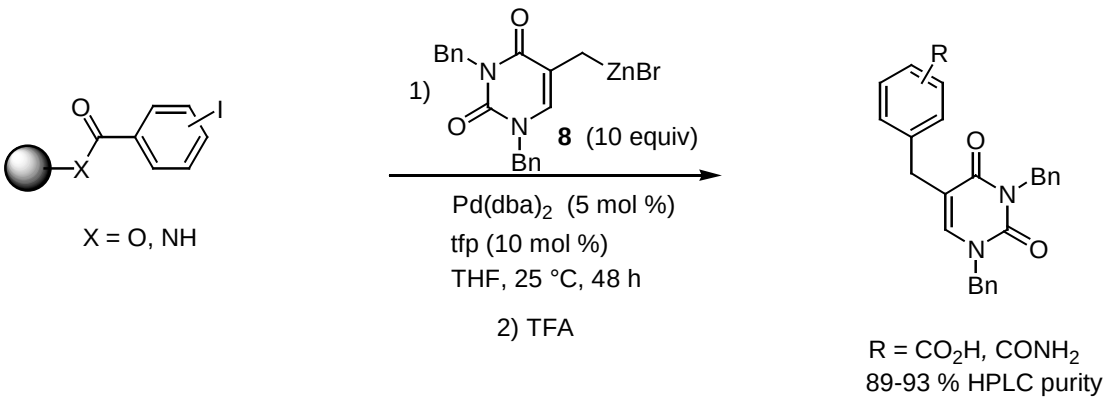
5.1- Synthesis of thymine derivatives

Zincated thymine derivative **2** was prepared by zinc insertion from the corresponding bromide **4,** readily available in four steps from uracil. Negishi cross-coupling reactions were then performed using zinc reagent **2** and various aryl iodides.



Scheme 67. Preparation of thymine derivatives **3a-j** using a Negishi cross-coupling reaction.

Resin-attached aryl iodides were also suitable substrates and solid phase synthesis of thymine derivatives could be performed with high HPLC-purities (89-93 %).

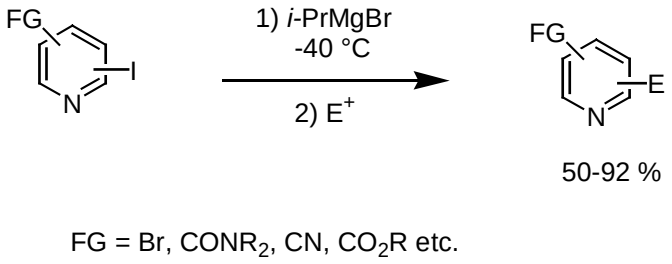


Scheme 68. Solid phase synthesis of thymine derivatives.

5.2- Synthesis of functionalized heterocyclic derivatives using a low temperature halogen-magnesium exchange

• Synthesis of pyridine derivatives

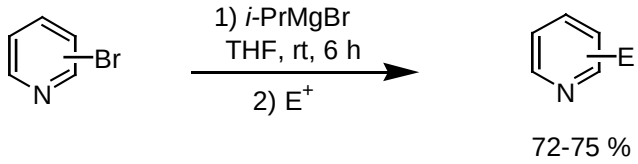
Functionalized pyridinyl Grignard reagents were prepared using a low temperature iodine-magnesium exchange and trapped with electrophiles. Functional groups such as ester, amide or nitrile functions are tolerated in this process.



Scheme 69. Preparation of functionalised pyridines using a low temperature iodine-magnesium exchange.

The bromine-magnesium exchange is less general than the iodine magnesium-exchange and electron withdrawing groups are often necessary to accelerate the exchange reaction.

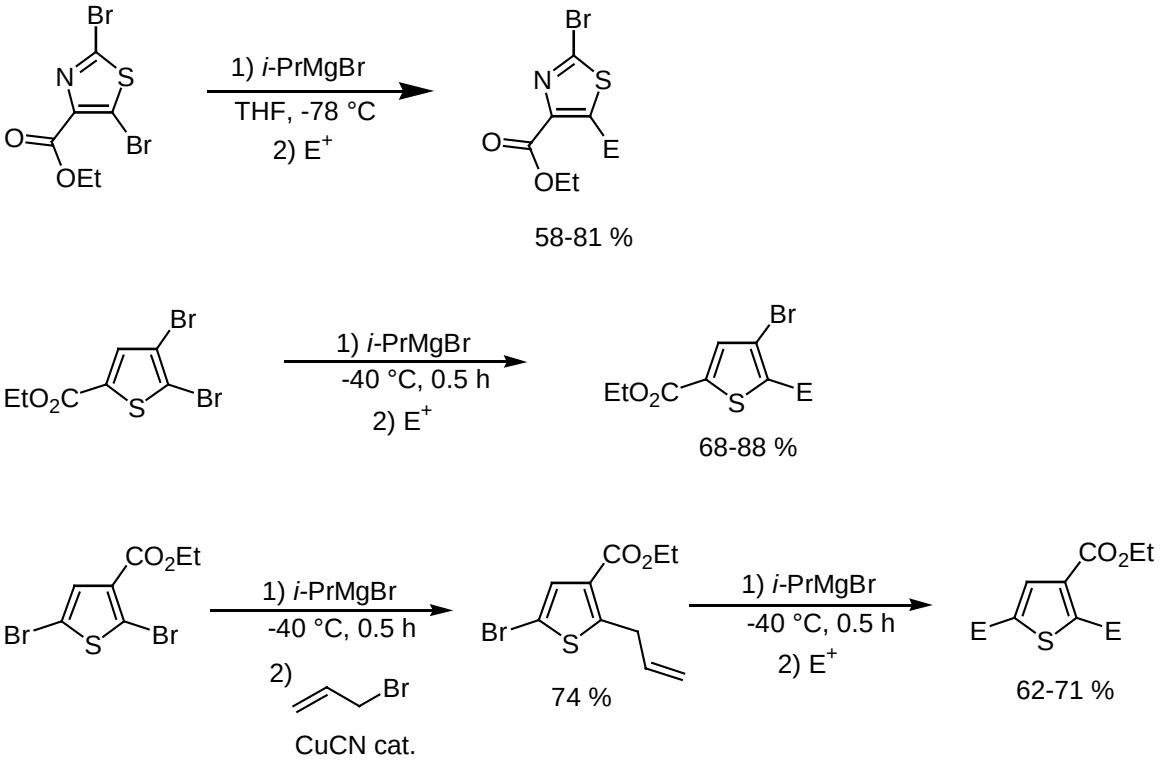
However, 2-bromo and 3-bromopyridine were suitable substrates due to the π deficient character of these heterocycles.



Scheme 70. Preparation of pyridine derivatives using a bromine-magnesium exchange.

• Synthesis of thiazole and thiophene derivatives

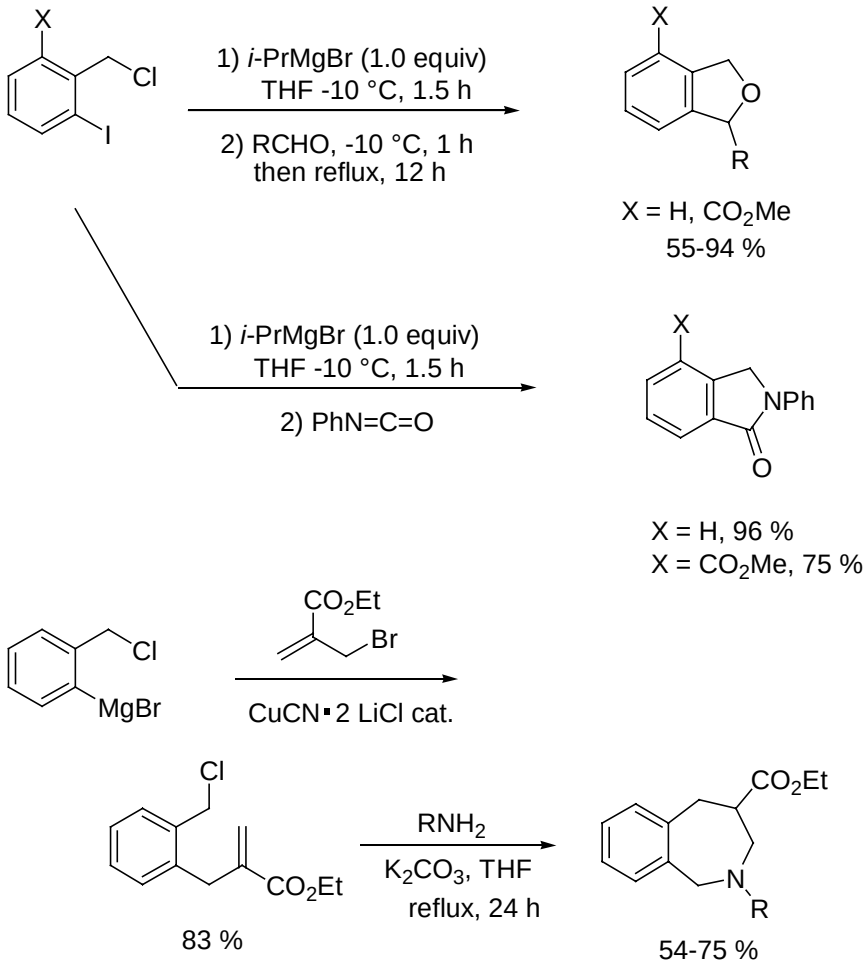
A low temperature bromine-magnesium exchange was then used in the synthesis of functionalized thiazole and thiophene derivatives.



Scheme 71. Preparation of thiazole and thiophene derivatives using a bromine-magnesium exchange.

• Synthesis of dihydrobenzofurans and tetrahydrobenzazepines

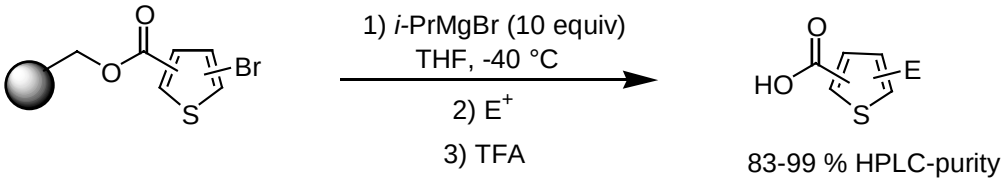
An access to dihydrobenzofurans, benzolactams and tetrahydrobenzazepines was developed using arylmagnesium reagents bearing an *o*-chloromethyl group.



Scheme 72. Preparation of dihydrobenzofurans and tetrahydrobenzazepines using a low temperature iodine-magnesium exchange.

- **Low-temperature halogen-magnesium exchange on the solid phase**

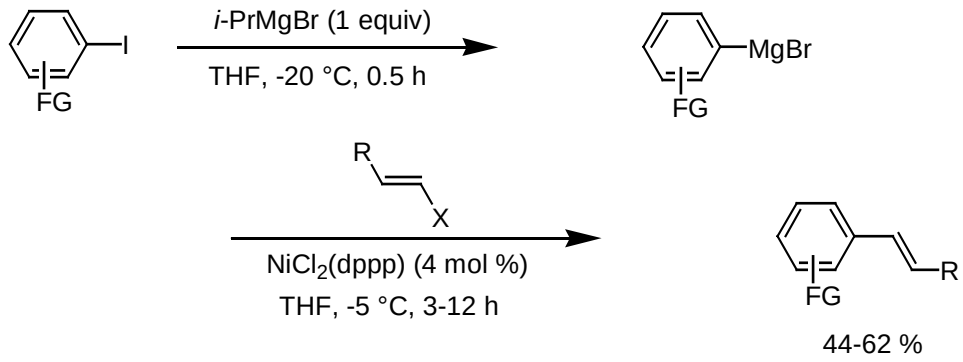
The low-temperature halogen-magnesium exchange could also be performed on the solid phase using an excess of *i*-PrMgBr and was applied to the synthesis of various thiophene derivatives.



Scheme 73. Solid phase synthesis of thiophene derivatives using a low temperature bromine-magnesium exchange.

5.3- Low temperature cross-coupling reactions using functionalized Grignard reagents

In the course of this work, low temperature cross-coupling reactions using functionalized Grignard reagents were studied. It was found that $NiCl_2$(dppp) was a suitable catalyst when alkenyl halides such as (*E*)-1-iodohexene and *trans*-β-bromostyrene where used.



Scheme 74. Low-temperature cross-coupling reactions using functionalized Grignard reagents.

So far only moderate yields have been obtained and other catalysts are being tested in our group. The extension of this reaction to functionalized heterocyclic Grignard reagents is also being investigated.

Experimental part

1- General considerations

All reactions were carried out with magnetical stirring and, if oxygen or moisture sensitive under argon. Syringes were used to transfer the reagents and were purged with argon before use. Organomagnesium solutions were titrated using Paquette' s method[85] and organozinc solutions were titrated by iodolysis.

Solvents

Solvents were dried by distillation over drying agents as follows: acetonitrile (Phosphor(V)oxide), dichloromethane, dimethylformamide and pentane (CaH_2), diethyl ether, THF and DME (Na/benzophenone), isopropanol (Mg), pyridine and triethylamine (KOH), toluene (Na).

Reagents

- Reagents of > 98 % purity were used directly.
- 1 M CuCN·2 LiCl solution was prepared by drying CuCN (8.96 g, 0.1 mol) and LiCl (8.48 g, 0.2 mol) in a Schlenk-tube under vacuum during 2 h at 120 °C. After cooling to rt, dry THF (100 mL) was added and stirring was continued until the salts were dissolved.
- $ZnBr_2$ was dried 2 h at 130 °C under vacuum.
- Wang-resin[86] and Rink resin[87] were purchased from Novabiochem with a loading of 0.75 mmol/g and 0.54 mmol/g respectively.
- The following reagents were prepared according to literature procedures: palladium(II) *bis* (dibenzylideneacetone),[88] tri-*o*-furylphosphine,[89] 1,1´-bis(diphenylphosphino)ferrocene,[90] ethyl (2-bromomethyl)acrylate,[78] (*Z*)-1-iodohexene,[91] (*E*)-1-iodohexene,[92] 2-chloro-3-iodopyridine (**13**),[58] 2-chloro-4-iodopyridine (**14**),[58] ethyl 2-chloro-4-iodonicotinate (**15**),[58] 6-iodonicotinic acid (**17**),[93] methyl-6-iodonicotinate (**18**),[94] Burgess reagent: (methyl N-

[85] H. -S. Lin, L. A. Paquette, *Synth. Commun*. **1994**, *24*, 2503.
[86] H. Rink, *Tetrahedron Lett*. **1987**, *28*, 3787.
[87] S.-S. Wang, *J. Am. Chem. Soc*. **1973**, *95*, 1328.
[88] Y. Takahashi, T. Ito, S. Sakai, *Chem. Comm*. **1970**, 1065.
[89] D. W. Allen, B. G. Hutley, M. T. J. Mellor, *J. Chem. Soc. Perkin II* **1972**, 63.
[90] R.-J. de Lang, J. van Soolingen, H. D. Verkruijsse, L. Brandsma, *Synth. Commun*. **1995**, *25*, 2989.
[91] A. Alexakis, G. Cahiez, J. F. Normant, *Org. Synth*. **1984**, *62*, 1.
[92] J. K. Stille, J. H. Simpson, *J. Am. Chem. Soc*. **1987**, *109*, 2138.
[93] G. R. Newkome, C. N. Moorfield, B. Sabbaghian, *J. Org. Chem.* **1986**, *51*, 953.

(triethylammoniumsulfonyl)carbamate) (**22**),[64] nicotinamide-1-oxyde (**24**),[66] 2-chloro-3-cyanopyridine (**25**),[66] ethyl 2-bromothiazole-4-carboxylate (**38**),[69] ethyl 2,5-dibromothiazole-4-carboxylate (**39**),[69] ethyl 2,5-dibromothiophene-3-carboxylate (**44**),[70] bis(dichlorophosphino)ferrocene (**65**),[75] 3-iodo-2-methylbenzoic acid (**71**)[95] methyl 3-iodo-2-methylbenzoate (**72**),[95] methyl 2-(bromomethyl)-3-iodobenzoate (**73**),[96] 2,5-dibromothiophene-3-carboxylic acid (**97**).[70]

Chromatography

- Thin layer chromatography (TLC) was performed using aluminium coated with SiO_2 (Merck 60, F-254). The spots were visualized by UV-light or by treating the plate with different solutions:
  - $KMnO_4$ (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), H_2SO_4 conc. (12 mL) in water (230 mL).
- Column chromatography was performed using SiO_2 60 (0.063-0.200 mm).
- Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm).
- Gas chromatography (GC): Hewlett-Packart 5890 series II.
  - Column A (Hewlett Packart): methylpolysiloxane (HP 1), 5 m x 0.53 mm.
  - Column B (Megabore): 5 % phenylmethylpolysiloxane (DB 5), 15 m x 0.53 mm.
- High performance liquid chromatography: Ginkotek-HPLC with a diode-array-detector (DAD) 215-280 nm. Reverse phase column (RP-18), 125 mm x 3 mm. Eluent: acetonitrile/water. Gradient: 5-100 % acetonitrile in 20 min.

Analytic

- Melting points were uncorrected and were measured on a Dr Tottoli (Büchi) apparatus.
- NMR spectra were recorded on a Bruker ARX 200, AC 300 or WH 400 instruments. Chemical shifts were given relative to the residual solvent peaks: $CDCl_3$ by 7.25 ppm (^{1}H NMR) and 77.00 ppm (^{13}C NMR). For ^{31}P NMR, phosphoric acid was used as external standard.

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[94] R. L. Beard, D. F. Colon, T. K. Song, P. J. A. Davies, D. M. Kochhar, R. A. S. Chandraratna, *J. Med. Chem.* **1996**, *39*, 3556.
[95] J. I. Degraw, V. H. Brown, W. T. Colwell, *J. Med. Chem.* **1974**, 762.
[96] E. C. Taylor, L. D. Jennings, Z. Mao, B. Hu, J. G. Jun, P. Zhou, *J. Org. Chem.* **1997**, *62*, 5392.

- IR spectra were recorded on a Nicolet 510 or a Perkin-Elmer 281 spectrometer.
- Electron impact mass (EI) spectra were recorded on a Varian MAT CH 7A. High resolution mass spectra (HRMS) were recorded on a Varian MAT 711.

2- Typical procedures (TP)

TP 1- Typical procedure for the palladium(0) catalyzed cross-coupling between the zincated thymine derivative (2) and aryl or alkenyl iodides in solution

A dry three-necked flask equipped with an argon inlet, septum and thermometer was charged with $Pd(dba)_2$ (11.5 mg, 2.5 mol %) and tfp (9.2 mg, 5 mmol %) followed by THF (1 mL). The initial red color disappeared after 1 min leading to a yellow solution. The iodide (0.8 mmol) was added followed by the zincated thymine **2** (6.0 mL, 1.92 mmol, 0.32 M in THF). The reaction mixture was stirred for 12 h at rt, worked up by pouring in aq. sat. NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and the residual oil obtained after evaporation of the solvent was purified by flash chromatography.

TP 2- Typical procedure for loading on resin

To a suspension of Wang resin (2.0 g, 1.5 mmol) or Rink resin (2.7 g, 1.5 mmol) in DMF (20 mL) was added the carboxylic acid (15 mmol), DIC (947 mg, 7.5 mmol) and DMAP (183 mg, 1.5 mmol). The reaction mixture was stirred 10 h at rt. The resin was then filtered, washed with DMF and repeatedly with MeOH and CH_2Cl_2 (4 times). The resin was then dried overnight in an oven (50 °C). Loading and HPLC purity of the resin were determined by cleaving 50 mg of resin using a TFA/CH_2Cl_2 (9/1) solution for Wang resin or a TFA/CH_2Cl_2 (1/1) solution for Rink resin (20 min).

TP 3-Typical procedure for the Pd(0) catalyzed cross-coupling between the zincated thymine derivative (2) and resin-attached aromatic iodides

Resin (50 µmol) was placed into a Schlenk-flask under argon. THF (2 mL) containing $Pd(dba)_2$ (1.4 mg, 2.5 µmol), tfp (1.2 mg, 5.0 µmol) and zinc reagent **2** (1.7 mL, 0.5 mmol, 0.30 M in THF) were added and the reaction mixture was stirred 48 h at rt. The resin was then treated with MeOH, filtered, washed with DMF and repeatedly with MeOH and CH_2Cl_2 (4 times). The desired compound was cleaved from the resin by treatment with a TFA/CH_2Cl_2 (9/1) solution for Wang resin or a TFA/CH_2Cl_2 (1/1) solution for Rink resin (20 mn). Excess TFA was removed under vacuum affording the desired product.

TP 4-Typical procedure for the halogen-magnesium exchange in solution

A solution of *i*-PrMgBr (1.05 mmol) in THF (0.8 M, 1.31 mL) was added dropwise over 5 min to a stirred solution of the aryl halide (1 mmol) in THF (3 mL) at -40 °C under argon. The resulting solution was then stirred until the exchange reaction was complete (GC monitoring) and the electrophile (1.20 mmol) was added. The reaction mixture was allowed to warm up to rt, quenched with brine (20 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography.

TP 5-Typical procedure for the preparation of dihydrobenzofurans

A solution of *i*-PrMgBr (1.1 mmol) in THF (0.88 M, 1.25 mL) was added dropwise to a stirred solution of aryl iodide **68** (253 mg, 1.0 mmol) in THF (3 mL) at –10 °C under argon. The resulting solution was then stirred for 1.5 h and the aldehyde (1.5 mmol) was added. The reaction mixture was slowly allowed to warm up to rt, heated at reflux for 12 h quenched with brine (20 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography.

TP 6-Typical procedure for the halogen-magnesium exchange on the solid phase

A solution of *i*-PrMgBr (0.75 mmol) in THF (0.80 M, 0.94 mL) was added dropwise to a stirred suspension of the resin (75 μmol) in THF (4 mL) at –40 °C under argon. The reaction mixture was then stirred for 1 h and the electrophile (1.13 mmol) was added. The reaction mixture was stirred for an additional 1 h at -40 °C and quenched with methanol. The resin was filtered, washed with DMF and repeatedly with MeOH and CH_2Cl_2 (4 times). Cleavage from the resin was performed by treatment with a TFA/CH_2Cl_2 (9/1) solution (20 mn at rt). Excess TFA was removed under vacuum affording the desired product.

TP 7-Typical procedure for cross-coupling reactions on the solid phase

A solution of $Pd(dba)_2$/dppf (7.5 μmol) in THF (0.015 M, 0.5 mL) was added dropwise to a stirred suspension of the resin (0.75 mmol) in THF (4 mL) at rt under argon. A THF solution of the zinc reagent was added and the reaction mixture was heated to 60 °C for 24 h. The resin was then filtered, washed with DMF and repeatedly with MeOH and CH_2Cl_2 (4 times). Cleavage from the resin was performed by treatment with a TFA/CH_2Cl_2 (9/1) solution (20 mn at rt). Excess TFA was removed under vacuum affording the desired product.

3- Synthesis of organomagnesium and organozinc reagents

Synthesis of isopropylmagnesium bromide

A dry three-necked flask equipped with an argon inlet a dropping funnel and a thermometer was charged with magnesium (3.65 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 while keeping the temperature under 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 under argon. Titration was performed using Paquette's method.[85] Yields between 90 and 95 % were obtained.

Synthesis of diisopropylmagnesium

A dry three-necked flask equipped with an argon inlet, a dropping funnel and a thermometer was charged with magnesium (3.65 g, 150 mmol) and a small amount of *t*-butylmethylether was added to cover the magnesium. The reaction mixture was heated to 50 °C and isopropyl bromide (12.3 g, 0.1 mol) in *t*-butylmethylether (100 mL) was added dropwise. Stirring was continued at 50 °C for 5 h. The reaction mixture was then cooled to rt and left overnight. The magnesium(II) bromide salts formed were removed by filtration under argon and washed with *t*-butylmethylether. Yields between 85 % and 95 % were obtained.

2-Norbornylmagnesium bromide **58** and 2-bromomesitylmagnesium bromide **59** were prepared following the same procedure as for isopropylmagnesium bromide using 2-norbornyl bromide and 2-bromomesitylene respectively.

Synthesis of dipentylzinc (87)

A dry three-necked flask equipped with an argon inlet a dropping funnel and a thermometer was charged with magnesium (8.40 g, 345 mmol). A small amount of ether was added to cover the magnesium and pentyl bromide (47.4 g, 314 mmol) was added at such a rate that the ether is gently refluxing. Stirring was continued for 3 h at room temperature. The reaction mixture was cooled to 0 °C and zinc(II) bromide (35.4 g, 157 mmol) in ether (150 mL) was added. The reaction mixture was then warmed to rt and stirred overnight. The ether was removed by heating under argon and dipentylzinc was distilled under vacuum (b.p. 60 °C, 0.1 mm Hg). 26.5 g (80 %) of dipentylzinc are obtained.

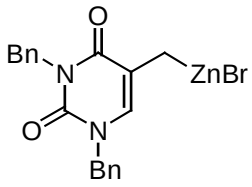
Dineopentylzinc (**89**) and diisopentylzinc (**88**) were prepared following the same procedure as for dipentylzinc using neopentyl bromide and isopentyl bromide respectively.

Synthesis of benzylzinc bromide (90)

A dry three-necked flask equipped with an argon inlet a dropping funnel and a thermometer was charged with zinc dust (2.68 g, 42 mmol). A small amount of THF was added to cover the zinc and the mixture was cooled to 5 °C (ice bath). A solution of benzyl bromide (2.39 g, 14 mmol) in 15 mL of THF was added dropwise (1 drop/5 s). The reaction mixture was stirred at 5 °C for 3 h. Titration was performed by iodolysis (85 %).

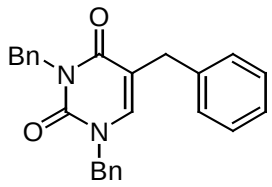
4- Synthesis of thymine derivatives

Synthesis of zincated thymine reagent (2)



A dry 50 mL three-necked flask equipped with an argon inlet, a magnetic stirring bar and a thermometer was charged with zinc dust (Aldrich, 325 mesh, 1.96 g, 30 mmol). The flask was flushed with argon and 1,2-dibromoethane (ca. 200 mg, 0.1 mmol) in THF (2 mL) was added. The zinc suspension was heated three times to reflux with a heat gun for ca. 30 s and was allowed to cool to rt. TMSCl (ca. 0.3 mL) was added and the reaction mixture was stirred for 5 min and cooled to 0 °C with an ice-bath. The bromide **4** (3.84 g, 10 mmol) in THF (14 mL) was slowly added using a syringe pump (1 drop each 5 s) and the reaction mixture was stirred for further 30 min at rt after the end of the addition. The excess of zinc was removed by filtration under argon. Titration was performed by iodolysis (80 %).

Synthesis of 1,3,5-tribenzyluracil (3a)



Prepared according to TP 1 starting from iodobenzene (163 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6 mL, 1.9 mmol, 0.32 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane/EtOAc 2:1), the product **3a** was obtained as a pale yellow solid (270 mg, 89 %).

Mp: 101 °C.

IR (KBr): 1697 (s), 1659 (s), 1450 (s), 1337 (m), 1215 (m) cm^{-1}.

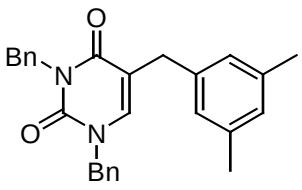
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55-7.46 (m, 2H), 7.29-7.16 (m, 13 H), 6.72 (s, 1H), 5.13 (s, 2H), 4.78 (s, 2H), 3.16 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0, 151.4, 139.0, 138.2, 136.9, 135.5, 129.0, 128.9 (2), 128.6, 128.4, 128.3, 127.8, 127.5, 126.6, 114.3, 52.2, 44.7, 33.2.

MS (EI): 383 (18), 382 (43), 291 (57), 91 (100).

$C_{25}H_{22}N_2O_2$	Calcd:	C	78.51	H	5.80	H 7.32
	Found:	C	78.70	H	5.95	N 7.15

Synthesis of 1,3-dibenzyl-5-(3,5-dimethylbenzyl)uracil (3b)



Prepared according to TP 1 starting from 3,5-dimethyl-1-iodobenzene (186 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol) and zinc reagent **2** (6.2 mL, 2.4 mmol, 0.39 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography

(pentane/EtOAc 6:1), the product **3b** was obtained as a yellow oil (262 mg, 80 %).

IR (neat): 1705 (m), 1664 (s), 1452 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.47 (m, 2H), 7.33-7.17 (m, 8 H), 6.84 (s, 1H), 6.74-6.72 (m, 3H), 5.15 (s, 2H), 4,.83 (s, 2H), 3.55 (s, 2H), 2.25 (s, 6H).

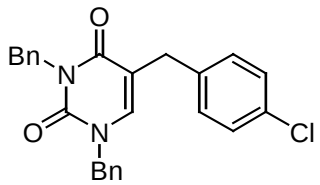
^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 151.6, 139.1, 138.1 (2), 137.1, 135.7, 129.1, 129.0, 128.4 (2), 128.3, 127.9, 127.6, 126.8, 114.7, 52.2, 44.8, 33.0, 21.3.

MS (EI): 411 (20), 410 (33), 319 (45), 91 (100).

$C_{27}H_{26}N_2O_2$ HRMS: Calcd: 410.1994

Found: 410.1990

Synthesis of 1,3-dibenzyl-5-(4-chlorobenzyl)uracil (3c)



Prepared according to TP 1 starting from 1-chloro-4-iodobenzene (191 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6 mL, 1.9 mmol, 0.32 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane/EtOAc 4:1), the product **3c** was obtained as a white solid (266 mg, 80 %).

Mp: 110 °C.

IR (KBr): 1695 (s), 1659 (s), 1489 (m), 1452 (s), 1366 (m), 1348 (m) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46-7.06 (m, 14H), 6.74 (s, 1H), 5.13 (s, 2H), 4.84 (s, 2H), 3.57 (s, 2H).

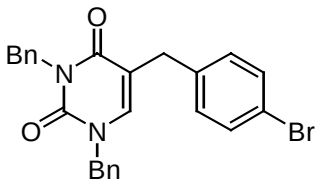
^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8, 151.4, 139.0, 136.8, 135.3, 132.4, 130.2, 129.0, 128.7, 128.4, 127.8, 127.6, 113.8, 52.2, 44.7, 32.7.

MS (EI): 418 (11), 416 (28), 327 (12), 325 (38), 91 (100).

$C_{25}H_{21}ClN_2O_2$ HRMS: Calcd: 416.1292

Found: 416.1287

Synthesis of 1,3-dibenzyl-5-(4-bromobenzyl)uracil (3d)



Prepared according to TP 1 starting from 1-bromo-4-iodobenzene (226 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol) and zinc reagent **2** (6.2 mL, 2.4 mmol, 0.39 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane/EtOAc 5:1), the product **3d** was obtained as a white solid (327 mg, 89 %).

Mp: 90 °C.

IR (KBr): 1709 (m), 1656 (s), 1452 (m), 1367 (m) cm^{-1}.

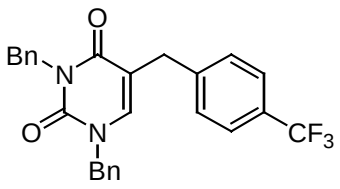
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46-7.20 (m, 12H), 7.04-7.00 (m, 2H), 6.74 (s, 1H), 5.13 (s, 2H), 4.84 (s, 2H), 3.56 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8, 151.4, 139.0, 137.3, 136.8, 135.3, 131.6, 130.5, 129.0, 128.3, 127.8, 127.6, 120.4, 113.6, 52.1, 44.7, 32.7.

MS (EI): 462 (21), 460 (20), 371 (20), 369 (2), 91 (100).

$C_{25}H_{21}BrN_2O_2$	Calcd:	C	65.08	H	4.59	N 6.07
	Found:	C	64.81	H	4.55	N 5.90

Synthesis of 1,3-dibenzyl-5-(4-trifluoromethylbenzyl)uracil (3e)



Prepared according to TP 1 starting from 4-iodobenzotrifluoride (272 mg, 1.0 mmol), $Pd(dba)_2$ (115 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol) and zinc reagent **2** (11.4 mL, 4.0 mmol, 0.35 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane/EtOAc 3:1), the product **3e** was obtained as a yellow oil (388 mg, 86 %).

IR (neat): 1699 (s), 1664 (s), 1453 (s), 1324 (s), 1160 (m), 1119 (s), 1065 (m) cm^{-1}.

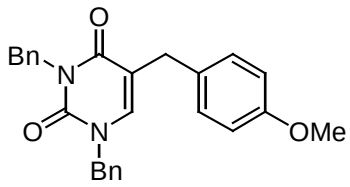
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41-7.08 (m, 14H), 6.70 (s, 1H) 5.04 (s, 2H), 4.74 (s, 2H), 3.55 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8, 151.5, 142.7, 139.2, 136.8, 135.3, 129.1, 128.5, 124.2 (q, J_{F-C} = 272 Hz), 127.9, 127.7, 125.6, 113.3, 52.2, 44.8, 33.2.

MS (EI): 450 (31), 360 (12), 359 (35), 316 (16), 91 (100).

$C_{26}H_{21}F_3N_2O_2$	Calcd:	C	69.33	H	4.70	N 6.22
	Found:	C	68.89	H	4.62	N 6.13

Synthesis of 1,3-dibenzyl-5-(4-methoxybenzyl)uracil (3f)



Prepared according to typical prodecure 1 starting from 4-iodoanisole (187 mg, 0.8 mmol) $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mol) and zinc reagent **2** (6 mL, 1.94 mmol, 0.32 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane/EtOAc 4:1) the product **3f** was obtained as a white solid (330 mg, 62 %).

Mp: 95 °C.

IR (KBr): 1709 (s), 1665 (s), 1510 (m), 1461 (m), 1243 (m) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47-7.05 (m, 12H), 6.82-6.78 (m, 2H), 6.71 (s, 1H), 5.14 (s, 2H), 4.80 (s, 2H), 3.76 (s, 3H), 3.56 (2H).

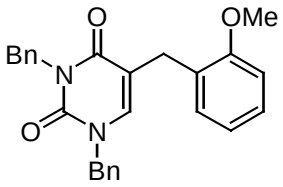
^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0, 158.3, 151.5, 138.9, 136.9, 135.5, 130.0, 129.0, 128.4,

127.8, 127.5, 114.8, 114.0, 55.2, 52.2, 44.7, 32.4.

MS (EI): 413 (11), 412 (57), 321 (29), 278 (10), 91 (100).

$C_{26}H_{24}N_2O_3$	Calcd:	C	75.71	H	5.86	N 6.79
	Found:	C	75.50	H	5.80	N 6.44

Synthesis of 1,3-dibenzyl-5-(2-methoxybenzyl)uracil (3g)



Prepared according to TP 1 starting from 2-iodoanisole (187 mg, 0.8 mmol), $Pd(dba)_2$ (11,5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6.2 mL, 2.4 mmol, 0.39 M in THF). Reaction time: 12 h at rt. After purification by flash chromatrography (pentane/EtOAc 5:1) the product **3g** was obtained as a colorless solid (219 mg, 66 %).

Mp: 80 °C.

IR (KBr): 1696 (s), 1656 (s), 1450 (s), 1246 (m) cm^{-1}.

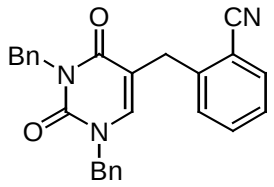
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.48 (m, 12H), 6.88-6.79 (m, 3H), 5.14 (s, 2H), 4.82 (s, 2H), 3.60 (s, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 163.1, 157.3, 151.5, 139.0, 137.0, 135.7, 131.0, 129.1, 128.9, 128.3, 128.2, 128.0, 127.9, 127.5, 126.2, 120.6, 113.0, 110.2, 54.9, 51.9, 44.6, 28.0.

MS (EI): 413 (11), 412 (57), 321 (29), 278 (10), 91 (100).

$C_{26}H_{24}N_2O_3$	HRMS:	Calcd:	412.1787
		Found:	412.1789

Synthesis of 1,3-dibenzyl-5-(2-cyanobenzyl)uracil (3h)



Prepared according to TP 1 starting from 2-iodobenzonitrile (206 mg, 0.9 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (7.4 mL, 2.3 mmol, 0.31 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane/EtOAc 4:1) the product **3h** was obtained as a white solid (278 mg, 76 %).

Mp: 131 °C.

IR (KBr): 1700 (m), 1661 (s), 1452 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.25 (m, 15H), 5.10 (s, 2H), 4.89 (s, 2H), 3.82 (s, 2H).

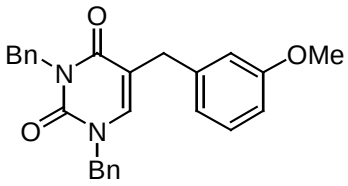
^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 151.4, 142.5, 140.3, 136.8, 135.3, 132.9 (2), 131.1, 129.1, 129.0, 128.4 (2), 128.3, 127.6, 127.2, 119.0, 112.2, 111.6, 52.6, 44.8, 32.4.

MS (EI): 408 (14), 407 (38), 317 (20), 316 (68), 273 (13), 91 (100).

$C_{26}H_{21}N_3O_2$ HRMS: Calcd: 407.1634

Found: 407.1639

Synthesis of 1,3-dibenzyl-5-(3-methoxy)uracil (3i)



Prepared according to TP 1 starting from 3-iodoanisole (187 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6.3 mL, 2.4 mmol, 0.33 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane/EtOAc 4:1), the product **3i** was obtained as a colorless oil (265 mg, 80 %).

IR (neat): 1699 (s), 1642 (s), 1602 (m), 1452 (s) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60-7.47 (m, 2H), 7.32-7.18 (m, 9H), 6.75-6.72 (m, 4H), 5.14 (s, 2H), 4.80 (s, 2H), 3.71 (s, 3H), 3.59 (s, 2H).

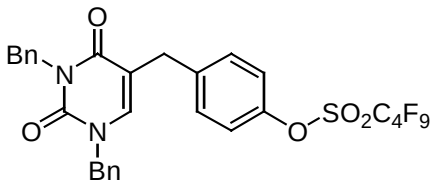
^{13}C NMR (50 MHz, $CDCl_3$): δ 162.9, 159.8, 151.4, 139.8, 139.1, 136.9, 135.5, 129.6, 129.0 (2), 128.4, 128.3, 127.8, 127.5, 121.2, 114.3, 112.2, 55.1, 52.2, 44.7, 33.2.

MS (EI): 413 (16), 412 (533), 321 (53), 91 (100).

$C_{26}H_{24}N_2O_3$ HRMS: Calcd: 412.1787

Found: 412.1780

Synthesis of 1,3-dibenzyl-5-[3-(nonafluorobutylsulfonyl)benzyl]uracil (3j)



Prepared according to TP 1 starting from 4-(nonafluorobutylsulfonyl)iodobenzene (351 mg, 0.7 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (5.8 mL, 1.8 mmol, 0.31 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane/EtOAc 4:1) the product **3j** was obtained as a colorless oil (450 mg, 95 %).

IR (neat): 1699 (m), 1663 (m), 1643 (s), 1458 (m), 1450 (m), 1430 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.11 (m, 14H), 6.83 (s, 1H), 5.14 (s, 2H), 4.87 (s, 2H), 3.66 (s, 2H).

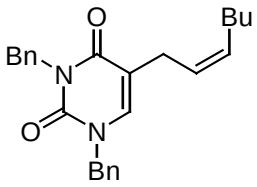
^{13}C NMR (50 MHz, $CDCl_3$): δ 162.9, 151.5, 149.9, 141.7, 139.4, 136.9, 135.4, 130.4, 129.1, 128.5, 128.0, 127.7, 121.8, 119.5, 113.1, 52.3, 44.9, 33.1.

MS (EI): 680 (40), 590 (13), 589 (39), 91 (100).

$C_{29}H_{21}F_9N_2O_5S$ HRMS Calcd: 680.1028

Found: 680.1039

Synthesis of 1,3-dibenzyl-5-[(2)-2-heptenyl]uracil (3k)



Prepared according to TP 1 starting from (*Z*)-1-iodohexene (210 mg, 1.0 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (11.4 mL, 4 mmol, 0.35 M in THF). Reaction time: 12 h at rt. After purification by flash chromatography (pentane EtOAc 5:1), the product **3k** was obtained as a yellow oil (330 mg, 85 %).

IR (neat): 2956 (s), 2929 (s), 1701 (s), 1665 (s), 1452 (s), 1382 (s), 1350 (s) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70-7.25 (m, 10H), 6.88 (s, 1H), 5.59-5.32 (m, 2H), 5.16 (s, 2H), 4.89 (s, 2H), 3.07 (d, *J* = 7.2, 2H), 1.97 (m, 2H), 1.23 (m, 4H), 0.85 (tr, *J* = 6.8 Hz, 3H).

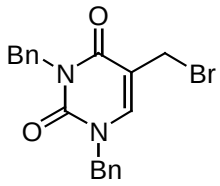
^{13}C NMR (50 MHz, $CDCl_3$): δ 163.2, 151.6, 137.9, 137.0, 135.6, 133.6, 129.1, 128.4, 127.8, 127.5, 124.2, 113.3, 112.9, 52.2, 44.7, 31.6, 26.8, 24.6, 22.3, 13.9.

MS (EI): 388 (15), 305 (22), 91 (100).

$C_{25}H_{28}N_2O_2$ HRMS: Calcd: 388.2151

Found: 388.2157

Synthesis of 1,3-dibenzyl-5-bromomethyluracil (4)



A solution of HBr in dry 1,4-dioxane (30 mL, ca. 44 mmol) was added to 5-benzyloxy-1,3-dibenzyluracil **7** (9 g, 22 mmol) resulting in the formation of a clear solution. The reaction mixture was stirred 12 h at rt and then quenched with water. The precipitate was filtered and washed with ether affording bromide **3** (7.5 g, 89 % yield) as a white powder.

Mp: 133 °C.

IR (KBr): 1704 (s), 1657 (s), 1459 (s), 1452 (s), 1384 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.37-7.24 (m, 9H), 5.15 (s, 2H), 4.91 (s, 2H), 4.22 (s, 2H).

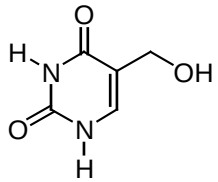
^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 151.3, 141.5, 136.5, 134.9, 129.2, 129.1, 128.7, 128.4, 128.1, 127.7, 111.1, 52.5, 44.9, 25.9.

MS (EI): 384 (0.1), 306 (17), 305 (52), 92 (16), 91 (100).

$C_{19}H_{17}BrN_2O_2$ HRMS: Calcd: 384.0474

Found: 384.0480

Synthesis of 5-hydroxymethyluracil (5)[40]



Uracil (25 g, 223 mmol) was added to a filtered solution of $Ba(OH)_2 \cdot 8\ H_2O$ (15 g, 480 mmol) in water (500 mL). A solution of 37 % aq. formaldehyde (54 mL, 720 mmol) was added and the reaction mixture was refluxed a few minutes in order to dissolve uracil. The reaction mixture was allowed to stand 12 h at rt and CO_2 (g) was bubbled into the reaction mixture in order to precipitate Ba_2CO_3. After filtration, the water was evaporated and the crude residue was recrystallized in hot ethanol affording alcohol **5** (23 g, 73 % yield) as a colorless solid.

Mp: 220-230 °C.

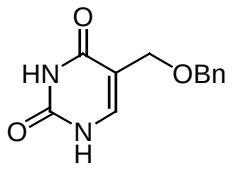
IR (KBr): 3371 (m), 3190 (m), 3037 (m), 1706 (s), 1678 (s), 1432 (m) cm^{-1}.

^{1}H NMR (200 MHz, D_2O): δ 7.60 (s, 1H), 4.37 (s, 2H).

^{13}C NMR (125 MHz, D_2O): δ 163.9, 150.9, 139.2, 110.2, 54.2.

MS (EI): 142 (100), 141 (35), 124 (26), 113 (41).

Synthesis of 5-benzyloxymethyluracil (6)[97]



A suspension of 5-hydroxymethyluracil **5** (12.0 g, 84 mmol) and conc. aq. HCl (6 mL) in benzyl alcohol (300 mL) was refluxed for 1 h resulting in the formation of a clear solution. After cooling to rt, the reaction mixture was poured into ether (1.6 L). The resulting fine precipitate was filtered and washed several times with ether affording product **6** (15.4 g, 79 % yield).

Mp: 199-202 °C.

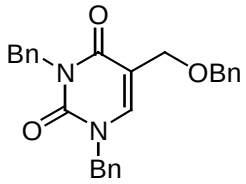
IR (KBr): 3209 (br), 1751 (s), 1719 (s), 1669 (s), 1445 (m), 1431 (m) cm^{-1}.

^{1}H NMR (200 MHz, DMSO): δ 10.82 (s, 2H), 7.38 (s, 1H), 7.25 (s, 5H), 4.41 (s, 2H), 4.01 (s, 2H).

^{13}C NMR (50 MHz, DMSO): δ 164.2, 151.7, 141.1, 138.8, 128.6, 127.7, 109.4, 71.7, 64.6.

MS (EI): 126 (100), 108 (24), 107 (30), 91 (39).

Synthesis of 1,3-dibenzyl-5-benzyloxyuracil (7)



A suspension of 5-benzyloxymethyluracil **6** (8 g, 34 mmol) in dry DMF (70 mL) was treated portionwise with sodium hydride (2.08 g, 69 mmol, 80 % in oil). After the end of gas evolution, the reaction mixture was stirred for 1 h at rt, benzyl bromide (10 mL, 84 mmol) was slowly added and the reaction mixture was stirred 1 h at rt. The solvent was evaporated using a rotatory evaporator and then a vacuum pump (0.1 mmHg). The residue was dissolved

[97] R. Brossmer, E. Z. Röhm, *Physiolog. Chem.* **1967**, *348*, 1431.

in ethyl acetate (100 mL) and was washed with water (150 mL). The aqueous phase was washed with ethyl acetate (2 x 25 mL) and the combined organic phase was washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the crude residue was purified by chromatography (EtOAc/pentane 1:4) providing the desired product **7** (11.1 g, 79 % yield) as a colorless oil.

IR (neat): 1701 (s), 1663 (s), 1642 (s), 1454 (s), 1060 (m) cm^{-1}.

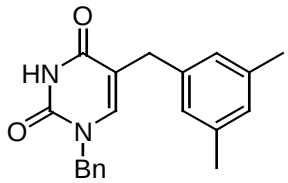
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.15 (m, 16H), 5.07 (s, 2H), 4.83 (s, 2H), 4.48 (s, 2H), 4.22 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 150.6, 138.5, 136.7, 135.8, 134.4, 128.1, 127.4, 127.0, 126.8, 126.6, 110.3, 72.2, 64.0, 51.4, 43.6.

MS (EI): 412 (0.1), 306 (66), 215 (41), 91 (100).

$C_{26}H_{24}N_2O_3$	Calcd:	C	75.64	H	5.86	N 6.79
	Found:	C	75.40	H	5.46	N 6.74

Synthesis of 3-benzyl-5-(3,5-dimethylbenzyl)uracil (8)



To a stirred suspension of thymine derivative **3b** (140 mg, 0.34 mmol) and an equal weight of 10 % Pd-C in dry methanol (2 mL), anhydrous ammonium formate (108 mg, 1.7 mmol) was added in a single portion under argon. The resulting mixture was stirred at reflux and the reaction was monitored by TLC. After completion of the reaction (24 h), the catalyst was removed by filtration through a celite pad, which was washed with chloroform (20 mL). The filtrate after evaporation under reduced pressure, afforded the pure uracil derivative **8** as a colorless solid (84 mg, 77 %).

Mp: 149-152 °C.

IR (KBr): 3217 (m), 3076 (m), 2944 (m), 1713 (s), 1648 (s), 1447 (m) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.21 (s, 1H), 7.36-7.17 (m, 5H), 6.79-6.63 (m, 4H), 5.02 (s, 2H), 3.48 (s, 2H), 2.20 (s, 6H).

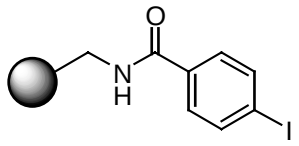
^{13}C NMR (50 MHz, $CDCl_3$): δ 163.5, 153.3, 138.3, 138.0, 136.7, 135.8, 128.8, 128.5, 127.7, 127.0, 114.7, 44.1, 33.0, 21.4.

MS (EI) : 321 (10), 320 (40), 229 (56), 186 (40), 143 (11), 91 (100).

$C_{20}H_{20}N_2O_2$ HRMS: Calcd: 320.1525

Found: 320.1523

Synthesis of Rink-resin attached *p*-iodobenzamide (9a)

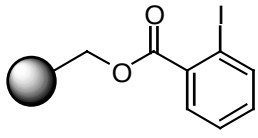


The reaction was carried out according to TP 2 using *p*-iodobenzamide (3.7 g, 15 mmol).

HPLC purity (UV 254 nm): 98 %.

Loading : 0.55 mmol/g.

Synthesis of Wang-resin attached *o*-iodobenzoic acid (9b)

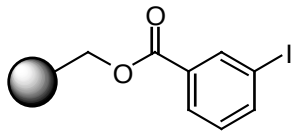


The reaction was carried out according to TP 2 using *o*-iodobenzoic acid (3.7 g, 15 mmol).

HPLC purity (UV 254 nm): 98 %.

Loading : 0.74 mmol/g.

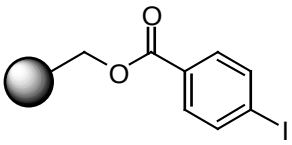
Synthesis of Wang-resin attached *m*-iodobenzoic acid (9c)



The reaction was carried out according to TP 2 using *m*-iodobenzoic acid (3.7 g, 15 mmol).

HPLC purity (UV 254 nm): 99 %.
Loading : 0.75 mmol/g.

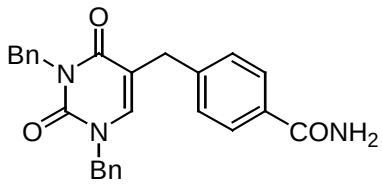
Synthesis of Wang resin attached *p*-iodobenzoic acid (9d)



The reaction was carried out according to TP 2 using *p*-iodobenzoic acid (3.7 g, 15 mmol).

HPLC purity (UV 254 nm): 98 %.
Loading : 0.75 mmol/g.

Synthesis of 4-(3-benzyl-2,4-dioxo-1-phenethyl-1,2,3,4-tetrahydro-5-pyrimidinylmethyl) benzamide (11a)



Preparation according to TP 3 starting from Rink-resin attached *p*-iodobenzamide **9a** (100 mg, 55 µmol). Thymine derivative **11a** was obtained as a colorless solid (19 mg, 81 %).

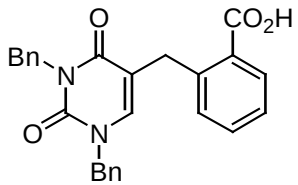
HPLC purity (UV 254 nm): 93 %.

^{1}H NMR (300 MHz, DMSO): δ 7.81-7.09 (m, 15H), 4.90 (s, 2H), 4.87 (s, 2H), 3.55 (s, 2H).

^{13}C NMR (75 MHz, DMSO): δ 167.3, 162.0, 150.6, 142.6, 141.3, 136.7, 136.3, 131.8, 111.1, 51.1, 43.4, 31.9.

MS (EI): 279 (11), 167 (38), 150 (12), 149 (82), 113 (20), 112 (17), 97 (12), 83 (23), 71 (46), 57 (100), 43 (71), 41 (28), 32 (23), 29 (11), 28 (97).

Synthesis of 2-(3-benzyl-2,4-dioxo-1-phenethyl-1,2,3,4-tetrahydro-5-pyrimidinylmethyl) benzoic acid (11b)



Preparation according to TP 3 starting from Wang-resin attached *o*-iodobenzoate **9b** (70 mg, 50 µmol). Thymine derivative **11b** was obtained as a colorless solid (17 mg, 80 %).

HPLC purity (UV 254 nm): 92 %.

^{1}H NMR (300 MHz, DMSO): δ 7.64-7.00 (m, 15H), 4.79 (s, 2H), 4.71 (s, 2H), 3.77 (s, 2H).

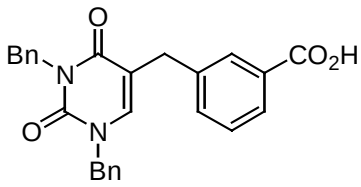
^{13}C NMR (75 MHz, DMSO): δ 167.9, 161.8, 150.2, 140.75, 139.0, 136.4, 135.9, 130.9, 129.6, 129.5, 127.9, 127.6, 126.9, 126.7, 126.6, 126.4, 125.6, 111.1, 50.9, 43.1, 29.8.

MS (EI): 426 (31), 408 (30), 335 (13), 317 (24), 132 (16), 91 (100), 28 (44).

$C_{26}H_{22}N_2O_4$ HRMS: Calcd: 426.1579

Found: 426.1582

Synthesis of 3-(3-benzyl-2,4-dioxo-1-phenethyl-1,2,3,4-tetrahydro-5-pyrimidinylmethyl) acid (11c)



Preparation according to TP 3 starting from Wang-resin attached *m*-iodobenzoate **9c** (70 mg, 50 μmol). Thymine derivative **11c** was obtained as a colorless solid (15 mg, 70 %).

HPLC purity: (UV 254 nm): 88%.

^{1}H NMR (300 MHz, DMSO): δ 8.01-7.28 (m, 15H), 5.03 (s, 2H), 5.00 (s, 2H), 3.71 (s, 2H).

^{13}C NMR (75 MHz, DMSO): δ 167.1, 162.0, 150.0, 141.4, 139.7, 136.7, 136.3, 132.4, 130.5, 128.7, 128.2, 128.0, 127.9, 127.3, 127.0, 126.9, 126.7 (2), 111.2, 51.1, 43.4, 31.9.

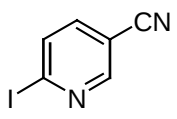
MS (EI): 426.0 (27), 380 (15), 335 (47), 292 (13), 91 (100).

$C_{26}H_{22}N_2O_4$ HRMS Calcd: 426.1579

Found: 426.1581

5- Synthesis of pyridine derivatives

Synthesis of 3-cyano-6-iodopyridine (23)



Methyl-6-iodonicotinate[94] **18** (1.47 g, 5.6 mmol) was dissolved in aqueous ammonia (29 %;

20 mL). The reaction mixture was stirred for 14 h. The precipitate was filtered, washed with ether and dissolved in THF/CH_2Cl_2 (1/1; 20 mL) mixture. Burgess reagent (2.42 g, 10.2 mmol) freshly prepared according to litterature procedure[64] was added. The reaction was complete after 15 mn as indicated by GC. After removal of the solvent, water was added and the reaction mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography (pentane/Et_2O 5/1) affording iodopyridine **23** (1.13 g, 87 %) as a colorless solid.

Mp: 100 °C.

IR (KBr) : 2236 (m), 1578 (m), 1408 (w), 1146 (m), 1133 (w).

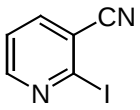
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.71 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.8, 138.7, 134.4, 122.0, 115.1, 108.6.

MS (EI): 230 (54), 103 (100), 76 (34).

$C_{12}H_{10}ClNO$	HRMS:	Calcd:	229.9341
		Found:	229.9344

Synthesis of 2-iodo-3-cyanopyridine (26)



2-Chloro-3-cyanopyridine **25**[66] (0.92 g, 4.0 mmol), sodium iodide (3.0 g, 20.0 mmol), and HI (0.4 mL) in 2-butanone (10 mL) were refuxed for 24 h. After removal of the solvent, water was added and the reaction mixture extracted with dichloromethane. The organic layer was washed with an aq. solution of sodium thiosulfate, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was washed with pentane affording iodopyridine **26** (8.30 g, 90 %) as a colorless solid.

Mp: 105 °C.

IR (KBr): 2245 cm^{-1}.

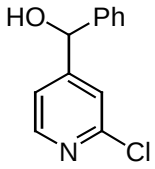
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.56 (dd, *J* = 4.9 Hz, *J* = 2.0 Hz 1H), 7.63 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz 1H), 7.44 (dd, *J* = 8.0 Hz, *J* = 4.9 Hz 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.7, 141.0, 122.3, 120.7, 119.6, 117.5.

MS (EI): 230 (68), 103 (100), 76 (27).

$C_{12}H_{10}ClNO$	Calcd:	C	31.30	H	12.17	N 1.30
	Found:	C	31.20	H	12.07	N 1.23

Synthesis of (2-chloro-pyridin-4-yl)(phenyl)methanol (28a)



The reaction was carried out according to TP 4 using iodopyridine **14** (718 mg, 3.0 mmol), *i*-PrMgBr (4.74 mL, 3.6 mmol, 0.76 M in THF), (exchange at -40 °C, 30 min) and benzaldehyde (413 mg, 3.9 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 1:1) affording alcohol **28a** (606 mg, 92 %) as a colorless oil.

IR (neat): 3236 (vs), 1593 (m), 1457 (m), 1384 (m), 1081 (w), 1053 (w) cm^{-1}.

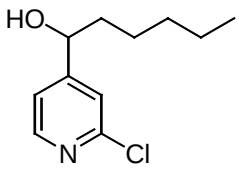
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.02 (d, *J* = 5.1 Hz, 1H), 7.37 (s, 1H), 7.26 (m, 5H), 7.15 (d, *J* = 5.1 Hz, 1H), 5.69 (s, 1H), 4.55 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 151.4, 149.1, 142.1, 128.8, 128.5, 127.0, 121.8, 120.3, 74.3.

MS (EI): 221 (30), 220 (17), 219 (98), 218 (15), 140 (20), 113 (53), 107 (70), 79 (100), 77 (53).

$C_{12}H_{10}ClNO$	Calcd:	C	65.61	H	4.58	N 6.38
	Found:	C	65.74	H	4.71	N 6.25

Synthesis of 1-(2-chloropyridin-4-yl)hexan-1-ol (28b)



The reaction was carried out according to TP 4 using iodopyridine **14** (718 mg, 3.0 mmol), *i*-PrMgBr (4.74 mL, 3.6 mmol, 0.76 M in THF), (exchange at -40 °C, 30 min) and hexanal (390 mg, 3.9 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 1:1) affording alcohol **28b** (544 mg, 85 %) as a yellow oil.

IR (neat): 3370 (vs), 2955 (s), 2932 (s), 1596 (s), 1549 (m), 1466 (m), cm^{-1}.

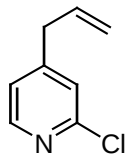
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18 (d, *J* = 4.8 Hz, 1H), 7.32-7.34 (m, 1H), 7.19 (dd, *J* = 4.8 Hz, *J* = 1.0 Hz, 1H), 4.69 (m, 1H), 4.25 (bs, 1H), 1.73-1.62 (m, 2H), 1.37-1.25 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.4, 151.4, 149.1, 121.6, 119.9, 72.2, 38.8, 31.6, 25.1, 22.5, 14.0.

MS (EI): 213 (6), 144 (26), 143 (27), 142 (100), 78 (25), 43 (15).

$C_{11}H_{16}ClNO$	Calcd:	C	61.82	H	7.55	N 6.55
	Found:	C	61.63	H	7.58	N 6.68

Synthesis of 4-allyl-2-chloropyridine (28c)



The reaction was carried out according to TP 4 using **14** (718 mg, 3.0 mmol), *i*-PrMgBr (4.74 mL, 3.6 mmol, 0.76 M in THF), (exchange at -40 °C, 30 min), CuCN (10 % mol, 27 mg) and allyl bromide (472 mg, 3.9 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 9:1) affording pyridine **28c** (391 mg, 85 %) as an orange oil.

IR (neat): 1592 (m), 1458 (w), 1382 (m), 1087 (w) cm^{-1}.

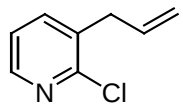
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.15 (s, 1H), 7.05 (d, *J* = 5.0 Hz, 1H), 5.94-5.91 (m, 1H), 5.19-4.97 (m, 2H), 3.36 (d, *J* = 6.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.5, 151.6, 149.5, 134.3, 124.2, 122.8, 118.1, 38.9.

MS (EI): 153 (37), 152 (30), 118 (100), 91 (47), 39 (20).

C_8H_8ClN	Calcd:	C	62.55	H	5.25	N 9.12
	Found:	C	62.78	H	5.45	N 8.98

Synthesis of 3-allyl-2-chloropyridine (30a)[98]



The reaction was carried out according to TP 4 using iodopyridine **13** (240 mg, 1.0 mmol), *i*-PrMgBr (1.60 mL, 1.1 mmol, 0.70 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.1 mL, 0.1 mmol, 1 M in THF) and allyl bromide (133 mg, 1.1 mmol) to give a crude residue, which was purified by column chromatography on silica affording **30a** (123 mg, 80 %) as a colorless oil.

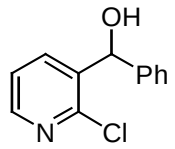
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (dd, *J* = 5.0 Hz, *J* = 1.6 Hz, 1H), 7.45 (dd, *J* = 7.4 Hz, *J* = 1.6 Hz, 1H), 7.11 (dd, *J* = 7.4 Hz, *J* = 5.0 Hz, 1H), 5.85 (m, 1H), 5.05 (m, 2H), 3.40 (d, *J* = 6.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.3, 147.5, 138.8, 134.4, 134.1, 122.6, 117.6, 37.1.

C_8H_8ClN	Calcd:	C	62.55	H	5.25	N 9.12
	Found:	C	62.78	H	5.59	N 9.33

[98] M. Mallet *J. Organomet. Chem.* **1991**, *406*, 49.

Synthesis of (2-chloropyridin-3-yl)(phenyl)methanol (30b)



The reaction was carried out according to TP 4 using iodopyridine **13** (239 mg, 1.0 mmol), *i*-PrMgBr (1.60 mL, 1.1 mmol, 0.70 M in THF), (exchange at -40 °C, 1 h), benzaldehyde (0.11 mL, 1.1 mmol) to give a crude residue, which was purified by column chromatography on silica affording the alcohol **30b** (187 mg, 85 %) as a colorless solid.

Mp: 95 °C.

IR (KBr): 3338 (s), 1582 (m), 1569 (w), 1413 (m), 1089 (w), 1042 (w), 761 (m) cm^{-1}.

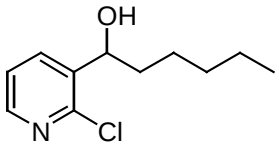
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.16 (dd, *J* = 5.0 Hz, *J* = 1.5 Hz, 1H), 7.92 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 7.26 (m, 6H), 6.05 (s, 1H), 3.00 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.00, 145.9, 139.2, 136.4, 135.2, 128.0, 126.4, 125.8, 120.7, 69.6.

MS (EI): 219.

$C_{12}H_{10}ClNO$	Calcd:	C	65.61	H	4.59	N 6.38
	Found:	C	65.41	H	4.60	N 6.22

Synthesis of 1-(2-chloropyridin-3-yl)hexan-1-ol (30c)



The reaction was carried out according to TP 4 using iodopyridine **13** (240 mg, 1.0 mmol), *i*-PrMgBr (1.60 mL, 1.1 mmol, 0.70 M in THF), (exchange at -40 °C, 1 h), hexanal (0.13 mL, 1.1 mmol) to give a crude residue, which was purified by column chromatography on silica affording the alcohol **30c** (169 mg, 79 %) as a colorless oil.

IR (neat): 3366 (s), 2955 (m), 2932 (w), 1580 (m), 1569 (w), 1409 (w), 1116 (m), 1058 (m), 751 (m) cm^{-1}.

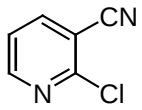
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.10 (dd, *J* = 4.8 Hz, *J* = 1.3 Hz, 1H), 7.88 (dd, *J* = 7.4 Hz, *J* = 1.3 Hz, 1H), 7.17 (dd, *J* = 7.4 Hz, *J* = 4.8 Hz, 1H), 4.95 (m, 1H), 3.55 (s, 1H), 1.60 (m, 2H), 1.21 (m, 6H), 0.81 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.4, 148.6, 140.6, 137.4, 123.8, 70.6, 38.3, 32.37, 26.2, 23.4, 14.9.

MS (EI): 213.

$C_{11}H_{16}ClNO$	Calcd:	C	61.82	H	7.55	N 6.55
	Found:	C	61.55	H	7.60	N 6.65

Synthesis of 2-chloro-3-cyanopyridine (30d)



The reaction was carried out according to TP 4 using iodopyridine **13** (240 mg, 1.0 mmol), *i*-PrMgBr (1.60 mL, 1.1 mmol, 0.70 M in THF), (exchange at -40 °C, 1 h), tosyl cyanide (200 mg, 1.1 mmol) to give a crude residue, which was purified by column chromatography on silica affording **30d** (112 mg, 81 %) as yellow cristals.

Mp: 108 °C.

IR (KBr): 3476 (s), 3082 (m), 3065 (w), 2924 (m), 2236 (w), 1578 (w), 1554 (m), 1408 (m), 1399 (m), 1133 (w), 1071 (m) cm^{-1}.

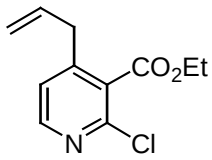
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.62 (dd, *J* = 5.1 Hz, *J* = 1.8 Hz, 1H), 8.03 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 1H), 7.45 (dd, *J* = 8.0 Hz, *J* = 5.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.3, 153.1, 143.1, 122.8, 115.0, 111.2.

MS (EI): 138.

C_6H_3ClN2	Calcd:	C	52.01	H	2.18	N 20.22
	Found:	C	51.78	H	1.96	N 20.00

Synthesis of ethyl 4-allyl-2-chloronicotinate (32a)



The reaction was carried out according to TP 4 using iodopyridine **15** (467 mg, 1.50 mmol), *i*-PrMgBr (1.74 mL, 1.50 mmol, 0.86 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (1.70 mL, 1.70 mmol, 1M in THF) and allyl bromide (273 mg, 2.25 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 1:1) affording **32a** (278 mg, 82 %) as an orange oil.

IR (neat): 1735 (s), 1582 (m), 1382 (w), 1278 (m), 1123 (w), 1061 (w) cm^{-1}.

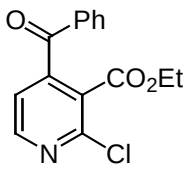
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.33 (d, *J* = 5.0 Hz, 1H), 7.16 (d, *J* = 5.0 Hz, 1H), 5.88-5.80 (m, 1H), 5.20-5.09 (m, 2H), 4.44 (q, *J* = 7.0 Hz, 2H), 3.41 (d, *J* = 6.6 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.6, 149.8, 149.5, 147.7, 133.6, 130.0, 123.3, 118.4, 62.2, 37.2, 14.0.

MS (EI): 225 (46), 197 (19), 182 (100), 180 (89), 116 (30), 89 (37).

$C_{11}H_{12}ClNO_2$ HRMS: Calcd: 225.0557
Found: 225.0555

Synthesis of ethyl 4-benzoyl-2-chloronicotinate (32b)



The reaction was carried out according to TP 4 using **15** (467 mg, 1.5 mmol), *i*-PrMgBr (1.94 mL, 1.65 mmol, 0.86 M in THF), (exchange at -40 °C, 30 min), CuCN·2LiCl (1.65 mL, 1.65 mmol, 1 M in THF) and benzoyl chloride (274 mg, 1.95 mmol) to give a crude residue, which

was purified by column chromatography on silica (pentane/Et_2O 7:3) affording the product **32b** (364 mg, 84 %) as a yellow oil.

IR (neat): 1742 (s), 1675 (s), 1450 (w), 1382 (w), 1282 (s), 1174 (w), 1121 (w) cm^{-1}.

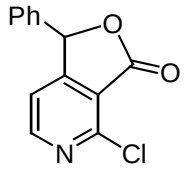
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.45 (d, *J* = 5.0 Hz, 1H), 7.71-7.41 (m, 5H), 7.24 (d, *J* = 5.0 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δϖ 192.9, 164.0, 150.5, 149.3, 148.5, 134.9, 134.2, 129.8, 128.7, 127.4, 120.9, 62.3, 13.3.

MS (EI): 289 (5), 105 (100), 77 (33).

$C_{15}H_{12}ClNO_3$	Calcd:	C	62.18	H	4.18	N 4.84
	Found:	C	62.11	H	4.33	N 4.94

Synthesis of 4-chloro-1-phenyl-1*H*-furo[3,4-*c*]pyridin-3-one (32c)



The reaction was carried out according to TP 4 using iodopyridine **15** (467 mg, 1.50 mmol), *i*-PrMgBr (2.0 mL, 1.50 mmol, 0.76 M in THF), (exchange at -40 °C, 1 h) and benzaldehyde (240 mg, 2.25 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 1:1) affording the product **2d** (206 mg, 56 %) as an orange oil.

IR (neat): 1756 (s), 1660 (w), 1592 (w), 1405 (w), 1254 (w) cm^{-1}.

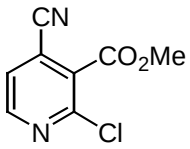
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.58 (d, *J* = 4.8 Hz, 1H), 7.53-7.25 (m, 6H), 6.42 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7, 161.1, 153.5, 149.3, 134.0, 129.8, 129.5, 126.6, 119.1, 117.2, 80.8.

MS (EI): 245 (100), 167 (36), 166 (22), 139 (88), 105 (49), 77 (33), 51 (26).

$C_{13}H_8ClNO_2$	HRMS:	Calcd:	245.0244
		Found:	245.0245

Synthesis of ethyl 2-chloro-4-cyanonicotinate (32d)

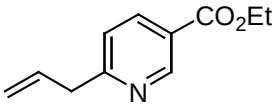


The reaction was carried out according to TP 4 using iodopyridine **15** (467 mg, 1.5 mmol), *i*-PrMgBr (1.94 mL, 1.65 mmol, 0.86 M in THF), (exchange at -40 °C, 45 min) and *p*-toluenesulfonyl cyanide (353 mg, 1.95 mmol, 0 °C, 10 h) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 9:1) affording **32d** (173 mg, 55 %) as a colorless oil.

IR (neat): 1740 (s), 1573 (m), 1384 (m), 1273 (s), 1124 (m) cm^{-1}.
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, *J* = 5.0 Hz, 1H), 7.61 (d, *J* = 5.0 Hz, 1H), 4.55 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.5, 151.3, 149.6, 130.6, 124.6, 121.7, 113.8, 63.5, 13.8.
MS (EI): 210 (30), 184 (21), 182 (65), 167 (38), 165 (100), 140 (19), 138 (34), 137 (29), 76 (24).

$C_9H_7ClN_2O_2$	Calcd:	C	51.32	H	3.35	N 13.30
	Found:	C	51.05	H	3.52	N 12.80

Synthesis of ethyl 6-allylnicotinate (34)



The reaction was carried out according to TP 4 using iodopyridine **18** (230 mg, 0.87 mmol), *i*-PrMgBr (1.23 mL, 0.96 mmol, 0.78 M in THF), (exchange at -40 °C, 20 min) CuCN·2LiCl (0.1 mL, 0.1 mmol, 1 M in THF) and allyl bromide (133 mg, 1.1 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 8:1) affording the product **34** (95 mg, 62 %) as a yellow oil.

IR (neat): 2981 (m), 2925 (m), 1735 (s), 1582 (w), 1382 (m), 1278 (w).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.07 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 6.05-5.91 (m, 1H), 5.18-5.07 (m, 2H), 3.87 (s, 3H), 3.57 (d, *J* = 6.5 Hz, 2H).

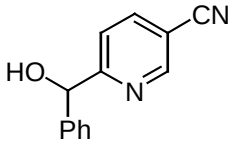
^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.3, 165.0, 151.0, 137.9, 135.1, 124.2, 122.8, 118.0, 52.7, 43.2.

MS (EI): 176 (100), 117 (23).

$C_{10}H_{10}NO_2$ HRMS: Calcd: 176.0712

Found: 176.0711

Synthesis of 6-[(hydroxy(phenyl)methyl)]nicotinonitrile (35a)



The reaction was carried out using an inverse addition. A solution of iodopyridine **23** (230 mg, 1 mmol) in THF (2 mL) was added over 1 min to a stirred solution of *i*-PrMgBr (1.16 mL, 1.1 mmol, 0.87 M in THF) at -78 °C under argon. The resulting solution was then stirred for 1 min and benzaldehyde (159 mg, 1.5 mmol) was added. The reaction mixture was then quenched with brine and the reaction worked up as usual. The crude residue was purified by column chromatography on silica (pentane/Et_2O 2:1) affording the alcohol **35a** (141 mg, 67 %) as a colorless oil.

IR (neat): 3236 (vs), 2926 (m), 2854 (m), 2244 (m), 1593 (m), 1547 (m), 1384 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.71 (d, *J* = 2.1 Hz, 1H), 7.80 (dd, *J* = 8.2 Hz, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.27-7.03 (m, 5H), 5.73 (s, 1H), 4.73 (bs, 1H).

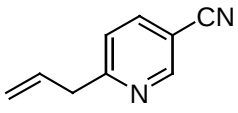
^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7, 151.2, 141.8, 139.9, 128.8, 128.4, 126.9, 121.2, 116.4, 108.6, 75.6.

MS (EI): 210 (47), 107 (29), 105 (29), 104 (31), 86 (69), 84 (100), 79 (23), 77 (40).

$C_{13}H_{10}N_2O_2$ HRMS: Calcd: 210.0793

Found: 210.0790

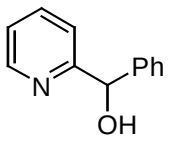
Synthesis of 6-allylnicotinonitrile (35b)



The reaction was carried out using an inverse addition. A solution of iodopyridine **23** (230 mg, 1 mmol) in THF (2 mL) was added over 1 min to a stirred solution of *i*-PrMgBr (1.16 mL, 1.1 mmol, 0.87 M in THF) at -78 °C under argon. The resulting solution was then stirred for 1 min, CuCN (10 % mol, 9 mg) and allyl bromide (181 mg, 1.5 mmol) were added. The crude residue was purified by column chromatography on silica (pentane/Et_2O 5:1) affording **35b** (71 mg, 50 %) as a colorless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.82 (d, *J* = 3.0 Hz, 1H), 7.90 (dd, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.10-5.96 (m, 1H), 5.26-5.16 (m, 2H), 3.67 (d, *J* = 7.0 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz): δ 165.1, 152.6, 139.9, 134.4, 123.2, 118.6, 117.2, 107.9, 43.3.
MS (EI): 144 (39), 143 (100), 142 (20), 118 (16).
$C_9H_8N_2$ HRMS: Calcd: 144.0687
Found: 144.0682

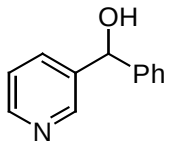
Synthesis of phenyl(pyridin-2-yl)methanol (36a)[68]



The reaction was carried out according to TP 4 using 2-bromopyridine (237 mg, 1.5 mmol), *i*-PrMgBr (1.83 mL, 1.65 mmol, 0.90 M in THF), (exchange at rt, 3 h), and benzaldehyde (239 mg, 2.25 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 1:2) affording alcohol **36a** (209 mg, 75 %) as a yellow solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.51 (dd, *J* = 4.7 Hz, *J* = 2.0 Hz, 1H), 7.30 (m, 8H), 5.81 (s, 1H), 3.79 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.2, 148.3, 140.1, 137.2, 128.9, 128.2, 127.4, 122.4, 121.7, 75.4.

Synthesis of phenyl(pyridin-3-yl)methanol (36b)[68]

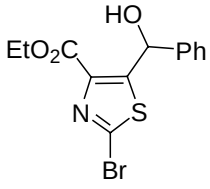


The reaction was carried out according to TP 4 using 3-bromopyridine (350 mg, 2.2 mmol), *i*-PrMgBr (3.3 mL, 2.4 mmol, 0.73 M in THF), (exchange at rt, 3 h), and benzaldehyde (238 mg, 2.5 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/Et_2O 1:2) affording alcohol **36b** (293 mg, 72 %) as a colorless solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.37 (d, *J* = 1.7 Hz, 1H), 8.20 (dd, *J* = 4.8 Hz, *J* = 1.7 Hz, 1H), 7.71 (m, 1H), 7.20 (m, 5H), 7.15 (dd, *J* = 7.9 Hz, *J* = 4.8 Hz, 1H), 5.81 (s, 1H), 5.00 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz): δ 147.7, 147.6, 143.3, 140.1, 135.4, 128.4, 127.6, 126.4, 123.4, 73.4.

6- Synthesis of thiazole derivatives

Synthesis of ethyl-2-bromo-5-[(hydroxy(phenyl)methyl)]thiazole-4-carboxylate (42a)



The reaction was carried out according to TP 4 using dibromothiazole **39** (240 mg, 0.79 mmol), *i*-PrMgBr (1.22 mL, 0.79 mmol, 0.65 M in THF), (exchange at -80 °C, 10 mn) and benzaldehyde (134 mg, 1.26 mmol, -40 °C, 1 h) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 8:2) affording **42a** (150 mg, 58 %) as a slightly yellow oil.

IR (neat): 3409 (vs), 1714 (vs), 1441 (s), 1314 (s), 1199 (s), 1031 (s), 702 (m) cm^{-1}.

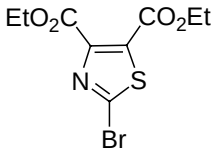
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.19 (m, 5H), 6.34 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.1, 158.7, 141.5, 140.9, 135.4, 129.1, 126.8, 69.5, 62.6, 14.6.

MS (EI): 341 (2), 296 (100), 294 (98), 216 (13), 188 (19), 162 (16), 105 (18), 77 (14).

$C_{13}H_{12}BrNO_3S$ HRMS: Calcd: 340.9765
Found: 340.9761

Synthesis of diethyl 2-bromothiazole-4,5-dicarboxylate (42b)



The reaction was carried out according to TP 4 using dibromothiazole **39** (250 mg, 0.79 mmol), *i*-PrMgBr (1.34 mL, 0.87 mmol, 0.65 M in THF), (exchange at -80 °C, 10 mn) and ethyl cyanoformate (126 mg, 1.27 mmol, -20 °C, 3 h) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 95:5) affording **42b** (165 mg, 67 %) as a yellow oil.

IR (neat): 1744 (vs), 1731 (vs), 1526 (w), 1401 (m), 1386 (m), 1323 (m), 1272 (s), 1200 (s), 1090 (s), 1040 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.36 (q, *J* = 7.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

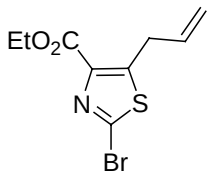
^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.6, 159.2, 149.6, 140.6, 133.4, 63.0, 14.4.

MS (EI): 309 (23), 307 (22), 264 (33), 262 (31), 236 (100), 234 (96), 209 (13), 207 (12), 193 (26), 191 (28), 165 (25), 163 (26), 130 (24).

$C_9H_{10}BrNO_4S$ HRMS: Calcd: 306.9514

Found: 306.9510

Synthesis of ethyl 5-allyl-2-bromothiazole-4-carboxylate (42c)



The reaction was carried out according to TP 4 using dibromothiazole **39** (473 mg, 1.5 mmol), *i*-PrMgBr (2.74 mL, 1.8 mmol, 0.65 M in THF), (exchange at -80 °C, 10 mn) CuCN·2 LiCl (0.15 mmol) and allyl bromide (290 mg, 2.4 mmol, -40 °C, 1 h) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 95:5) affording **42c** (335 mg, 81 %) as a yellow oil.

IR (neat) 1714 (vs), 1442 (s), 1318 (s), 1195 (s), 1031 (s), 1013 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.88-5.83 (m, 1H), 5.16-5.08 (m, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.87 (d, *J* = 6.6 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

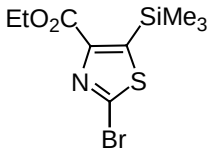
^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.0, 151.1, 139.9, 134.7, 133.1, 131.9, 117.4, 60.5, 30.8, 13.3.

MS (EI): 277 (15), 275 (14), 231 (100), 229 (97), 150 (24), 122 (26).

$C_9H_{10}BrNO_2S$ HRMS: Calcd: 274.9650

Found: 274.9652

Synthesis of ethyl 2-bromo-5-trimethylsilylthiazole-4-carboxylate (42d)



The reaction was carried out according to TP 4 using dibromothiazole **39** (810 mg, 2.57 mmol), *i*-PrMgBr (4.75 mL, 3.1 mmol, 0.65 M in THF), (exchange at -80 °C, 10 mn) and TMSCl (0.65 mL, 5.14 mmol, -40 °C, 1 h) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 9:1) affording **42d** (531 mg, 67 %) as a yellow oil.

IR (neat): 1714 (s), 1423 (s), 1303 (s), 1250 (w), 1200 (s), 1008 (s), 846 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.43 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 0.18 (s, 9H).

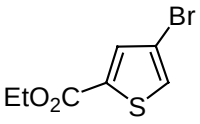
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.9, 151.5, 149.8, 139.6, 62.3, 14.9.

MS (EI): 310 (21), 308 (19), 305 (20), 291 (25), 230 (100), 151 (38), 113 (22), 85 (38), 81 (32), 71 (42).

$C_9H_{14}BrNO_2SSi$	HRMS:	Calcd:	307.9777
		Found:	307.9814

7- Synthesis of thiophene derivatives

Synthesis of ethyl 4-bromothiophene-2-carboxylate (45)



The reaction was carried out according to TP 4 using dibromothiophene **43** (314 mg, 1.0 mmol), *i*-PrMgBr (1.31 mL, 1.05 mmol, 0.8 M in THF), (exchange: -40 °C, 30 min) and

water (2 mL) to give a crude residue, which was then purified by column chromatography on silica affording **45** (206 mg, 88 %) as a colorless oil.

IR (neat): 1714 (vs), 1407 (m), 1281 (m), 1249 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43 (s, 1H), 7.25 (s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

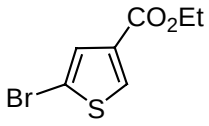
^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.7, 135.6, 135.0, 119.3, 115.3, 62.2, 14.6.

MS (EI): 236 (38), 234 (36), 208 (31), 206 (31), 191 (100), 189 (97).

$C_7H_7BrO_2S$ HRMS: Calcd: 233.9350

Found: 233.9344

Synthesis of ethyl 5-bromothiophene-3-carboxylate (46)



The reaction was carried out according to TP 4 using dibromothiophene **44** (314 mg, 1.0 mmol), *i*-PrMgBr (1.31 mL, 1.05 mmol, 0.8 M in THF), (exchange: -40 °C, 30 min) and water (2 mL) to give a crude residue, which was then purified by column chromatography on silica affording **46** (168 mg, 71 %) as a colorless oil.

IR (neat): 1724 (vs), 1525 (m), 1427 (m), 1231 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 (s 1H), 7.38 (s, 1H), 4.22 (q, *J* = 6.9 Hz, 2H), 1.27 (t, *J* = 6.9 Hz, 3H).

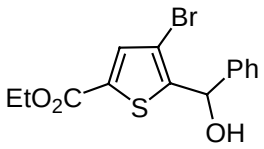
^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.9, 134.6, 134.0, 130.6, 113.2, 61.3, 14.7.

MS (EI): 236 (35), 234 (34), 208 (33), 206 (30), 191 (100), 189 (98).

$C_7H_7BrO_2S$ HRMS: Calcd: 233.9350

Found: 233.9347

Synthesis of ethyl 4-bromo-5-[(hydroxy(phenyl)methyl)]thiophene-2-carboxylate (48a)

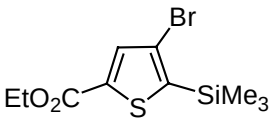


The reaction was carried out according to TP 4 using dibromothiophene **43** (314 mg, 1.0 mmol), *i*-PrMgBr (1.31 mL, 1.05 mmol, 0.8 M in THF), (exchange: -40 °C, 30 min) and benzaldehyde (0.12 mL, 1.20 mmol) to give a crude residue, which was then purified by column chromatography on silica (pentane/Et_2O 4:1) affording **48a** (283 mg, 83 %) as a colorless oil.

IR (neat): 3443 (vs), 1710 (vs), 1527 (m), 1453 (s), 1281 (vs), 1251 (vs), 1146 (vs) cm^{-1}.
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43 (s, 1H), 7.35-7.31 (m, 2H), 7.26-7.19 (m, 3H), 5.92 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.34 (bs, 1H), 1.22 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.9, 150.8, 141.4, 136.1, 132.8, 129.1, 128.7, 127.0, 108.4, 72.3, 62.1, 14.7.
MS (EI): 342 (51), 340 (50), 297 (16), 295 (16), 265 (14), 263 (23), 261 (28), 237 (86), 235 (100), 233 (12), 209 (25), 207 (25), 191 (12), 189 (13), 187 (13), 171 (17), 115 (13), 105 (78).

$C_{14}H_{13}BrO_3S$	HRMS:	Calcd:	339.9769
		Found:	339.9768

Synthesis of ethyl 4-bromo-5-trimethylsilylthiophene-2-carboxylate (48b)



The reaction was carried out according to TP 4 using dibromothiophene **43** (314 mg, 1 mmol), *i*-PrMgBr (1.31 mL, 1.05 mmol, 0.8 M in THF), (exchange: -40 °C, 30 min), TMSCl (254 µL, 2 mmol) to give a crude residue, which was then purified by column chromatography on silica (pentane/Et_2O 99:1) affording **48b** (270 mg, 88 %) as a colorless oil.

IR (neat): 1717 (vs), 1511 (s), 1403 (m), 1316 (vs), 1275 (vs), 1251 (vs) cm^{-1}.

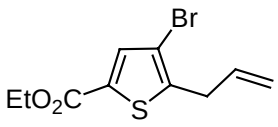
^{1}H NMR ($CDCl_3$, 300 MHz). δ 7.48 (s, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.18 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.0, 144.3, 139.2, 138.4, 118.2, 62.5, 15.3, 0.2.

MS (EI): 308 (32), 306 (30), 295 (10), 294 (18), 293 (100), 292 (18), 291 (98), 263 (13), 261 (11), 141 (15), 139 (27).

$C_{10}H_{15}BrO_2SSi$	HRMS:	Calcd:	305.9745
		Found:	305.9748

Synthesis of ethyl 5-allyl-4-bromothiophene-2-carboxylate (48c)



The reaction was carried out according to TP 4 using dibromothiophene **43** (314 mg, 1 mmol), *i*-PrMgBr (1.31 mL, 1.05 mmol, 0.8 M in THF), (exchange: -40 °C, 30 min), CuCN (10 % mol, 9 mg) and allyl bromide (173 µL, 2 mmol) to give a crude residue, which was then purified by column chromatography on silica (pentane/Et_2O 95:5) affording **48c** (187 mg, 68 %) as a colorless oil.

IR (neat): 1714 (vs), 1640 (w), 1528 (w), 1454 (s), 1336 (m), 1279 (vs), 1248 (vs), 1149 (m) cm^{-1}.

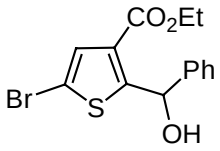
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52 (s, 1H), 5.78 (ddt, *J* = 16.3 Hz, *J* = 11.5 Hz, *J* = 6.6 Hz, 1H), 5.12-5.07 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.43 (dt, *J* = 6.6 Hz, *J* = 1.3 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.5, 145.4, 136.0, 134.0, 131.8, 118.4, 110.9, 61.7, 34.4, 14.7.

MS (EI): 274 (96), 269 (100), 248 (12), 246 (11), 231 (57), 229 (54), 123 (33), 122 (23), 121 (13).

$C_{10}H_{11}BrO_2S$	HRMS:	Calcd:	273.9663
		Found:	273.9678

Synthesis of ethyl 5-bromo-2-[hydroxy(phenyl)methyl]thiophene-3-carboxylate (49a)

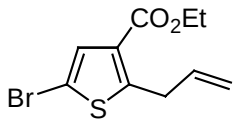


The reaction was carried out according to TP 4 using dibromothiophene **44** (314 mg, 1 mmol), *i*-PrMgBr (1.31 mL, 1.05 mmol, 0.8 M in THF), (exchange: -40°C, 1 h), benzaldehyde (122 µL, 1.2 mmol) to give a crude residue, which was then purified by column chromatography on silica (pentane/Et_2O 7:3) affording **49a** (259 mg, 76 %) as a colorless oil.

IR (neat): 1688 (vs), 1537 (m), 1454 (m), 1266 (vs), 1235 (s), 1154 (m) cm^{-1}.
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.34 (m, 2H), 7.28-7.21 (m, 4H), 6.28 (s, 1H), 4.45 (bs, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 1.23 (t, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.3, 160.0, 141.6, 132.0, 129.0, 128.9, 128.8, 127.2, 121.4, 70.7, 61.8, 14.6.
MS (EI): 342 (8), 340 (8), 313 (20), 311 (19), 296 (14), 295 (100), 294 (13), 293 (84), 105 (14), 77 (10).

$C_{14}H_{13}BrO_3S$	HRMS:	Calcd:	339.9769
		Found:	339.9769

Synthesis of ethyl 2-allyl-5-bromothiophene-3-carboxylate (49b)



The reaction was carried out according to TP 4 using dibromothiophene **44** (314 mg, 1 mmol), *i*-PrMgBr (1.31 mL, 1.05 mmol, 0.8 M in THF), (exchange: -40 °C, 30 mn), CuCN (10 % mol, 9 mg), allyl bromide (173 µL, 2 mmol) to give a crude residue, which was then purified by column chromatography on silica (pentane/Et_2O 97:3) affording **49b** (203 mg, 74 %) as a colorless oil.

IR (neat): 1715 (vs), 1537 (m), 1454 (s), 1370 (m), 1226 (vs), 1146 (m) cm^{-1}.

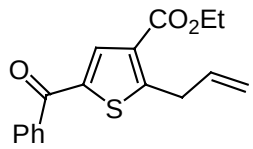
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 (s, 1H), 5.87 (ddt, *J* = 17.1 Hz, *J* = 10.5 Hz, *J* = 6.6 Hz, 1H), 5.09 (dt, *J* = 17.1 Hz, *J* = 1.5 Hz, 1H), 5.05 (dt, *J* = 10.5 Hz, *J* = 1.5 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.80 (dt, *J* = 6.6 Hz, *J* = 1.5 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.5, 154.3, 135.3, 132.1, 128.8, 118.0, 108.9, 61.0, 34.1, 14.7.

MS (EI): 276 (29), 274 (28), 261 (13), 259 (11), 247 (14), 245 (14), 235 (23), 233 (39), 231 (27), 229 (13), 219 (15), 217 (17), 203 (12), 201 (11), 122 (100).

$C_{10}H_{11}BrO_2S$	HRMS:	Calcd:	273.9663
		Found:	273.9662

Synthesis of ethyl 2-allyl-5-benzoylthiophene-3-carboxylate (50a)



The reaction was carried out according to TP 4 using bromothiophene **49b** (314 mg, 1 mmol), *i*-PrMgBr (1.31 mL, 1.20 mmol, 0.8 M in THF), (exchange: -40 °C, 1 h), CuCN·2LiCl (1.30 mL, 1.30 mmol, 1.0 M in THF), benzoyl chloride (157 µL, 1.35 mmol) to give a crude residue, which was then purified by column chromatography on silica (pentane/Et_2O 1:1) affording **50a** (213 mg, 71 %) as a colorless oil.

IR (neat): 1714 (vs), 1640 (s), 1598 (m), 1578 (m), 1374 (m), 1291 (s), 1228 (s), 1150 (m), 1028 (m) cm^{-1}.

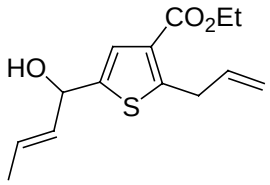
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.28-7.14 (m, 3H), 5.72 (m, 1H), 4.94-4.86 (m, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.68 (d, *J* = 6.6 Hz, 2H), 1.03 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 187.6, 162.9, 161.0, 139.9, 137.7, 136.7, 134.8, 132.8, 129.5, 128.9, 118.5, 61.1, 34.8, 14.7.

MS (EI): 300 (74), 285 (11), 257 (22), 255 (17), 227 (23), 195 (12), 105 (100), 77 (43), 44 (14).

$C_{17}H_{16}O_3S$	HRMS:	Calcd:	300.0820
		Found:	300.0792

Synthesis of ethyl 2-allyl-5-[(2*E*)-1-hydroxybut-2-enyl]thiophene-3-carboxylate (50b)



The reaction was carried out according to TP 4 using bromothiophene **49b** (314 mg, 1 mmol), *i*-PrMgBr (1.31 mL, 1.20 mmol, 0.8 M in THF), (exchange: -40 °C, 1 h), crotonaldehyde (126 µL, 1.53 mmol) to give a crude residue, which was then purified by column chromatography on silica (pentane/Et_2O 3:2) affording **50b** (180 mg, 62 %) as a colorless oil.

IR (neat): 1711 (vs), 1639 (m), 1552 (m), 1487 (m), 1376 (m), 1282 (s), 1219 (vs), 1173 (s) cm^{-1}.

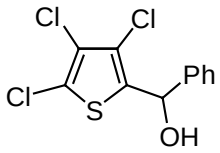
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15 (s, 1H), 5.91 (ddt, *J* = 10.2 Hz, *J* = 17 Hz, *J* = 6.6 Hz, 1H), 5.75-5.61 (m, 2H), 5.18 (d, *J* = 6.3 Hz, 1H), 5.10-5.00 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.82 (dt, *J* = 6.6 Hz, *J* = 1.2 Hz, 2H), 2.47 (bs, 1H), 1.67 (dd, *J* = 5.4 Hz, *J* = 1.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.8, 152.5, 144.3, 136.0, 132.7, 128.8, 127.7, 126.0, 117.4, 71.3, 60.7, 34.3, 18.0, 14.7.

MS (EI): 266 (100), 251 (26), 249 (11), 237 (16), 233 (11), 225 (13), 223 (15), 177 (11), 175 (19), 151 (34).

$C_{14}H_{18}O_3S$	HRMS:	Calcd:	266.0977
		Found	266.0942

Synthesis of phenyl(3,4,5-trichloro-2-thienyl)methanol (53a)[99]



The reaction was carried out according to TP 4 using tetrachlorothiophene (222 mg, 1 mmol), *i*-PrMgBr (1.51 mL, 1.1 mmol, 0.73 M in THF), (exchange at rt, 2 h) and benzaldehyde (159 mg, 1.5 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 96:4) affording **53a** (188 mg, 64 %) as a colorless oil.

IR (neat): 3306 (vs), 1454 (m), 1326 (m) cm^{-1}.

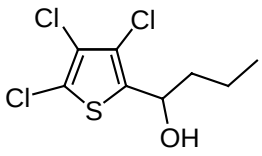
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33-7.23 (m, 5H), 5.97 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.0, 139.1, 129.2, 126.7, 124.7, 123.3, 120.2, 71.2.

MS (EI): 296 (31), 294 (100), 292 (97), 259 (47), 257 (68), 217 (37), 215 (51), 152 (23), 105 (99), 77 (27).

$C_{11}H_7Cl_3OS$	HRMS:	Calcd:	291.9250
		Found:	291.9252

Synthesis of 1-(3,4,5-trichloro-2-thienyl)pentan-1-ol (53b)



The reaction was carried out according to TP 4 using tetrachlorothiophene (222 mg, 1 mmol), *i*-PrMgBr (1.51 mL, 1.1 mmol, 0.73 M in THF), (exchange at rt, 2 h) and butanal (0.19 mL, 1.8 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 98:2) affording **53b** (188 mg, 72 %) as a colorless oil.

IR (neat): 3340 (vs), 2933 (s), 1463 (m), 1323 (m) cm^{-1}.

[99] J. Skramstad, P. Froyen, *Acta Chem. Scand*. **1993**, *472*, 131.

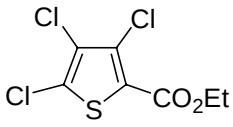
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.98 (t, *J* = 7.2 Hz, 1H), 2.60 (bs, 1H), 1.80-1.20 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.2, 123.7, 123.0, 119.4, 69.0, 40.3, 19.0, 14.5.

MS (EI): 262 (3), 260 (10), 258 (10), 219 (32), 217 (100), 215 (96).

$C_8H_9Cl_3OS$	HRMS:	Calcd:	257.9467
		Found:	257.9470

Synthesis of ethyl 3,4,5-trichlorothiophene-2-carboxylate (53c)



The reaction was carried out according to TP 4 using tetrachlorothiophene (222 mg, 1 mmol), *i*-PrMgBr (1.51 mL, 1.1 mmol, 0.73 M in THF), (exchange at rt, 2 h) and ethyl cyanoformate (0.18 mL, 1.8 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 99:1) affording **53c** (202 mg, 78 %) as colorless needles.

Mp: 53°C.

IR (KBr): 1722 (s), 1437 (s), 1325 (m), 1240 (s), 1094 (m), 1020 (w) cm^{-1}.

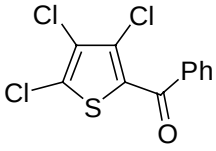
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.34 (q, *J* = 7.1 Hz, 2H), 1.35 (tr, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 131.0, 129.9, 126.2, 124.1, 62.4, 14.6.

MS (EI): 262 (14), 260 (40), 258 (39), 232 (43), 230 (41), 217 (33), 215 (100), 213 (99).

$C_7H_5Cl_3O_2S$	HRMS:	Calcd:	257.9042
		Found:	257.9054

Synthesis of 2-benzoyl-3,4,5-trichlorothiophene (53d)



The reaction was carried out according to TP 4 using tetrachlorothiophene (222 mg, 1.0 mmol), *i*-PrMgBr (1.51 mL, 1.10 mmol, 0.73 M in THF) (exchange at rt, 2 h), CuCN·2LiCl (1.10 mL, 1.10 mmol, 1 M in THF) and benzoyl chloride (274 mg, 1.95 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 99:1) affording **53d** (220 mg, 75 %) as a colorless liquid.

IR (KBr): 1657 (s), 1448 (s), 1322 (m), 1245 cm^{-1}.

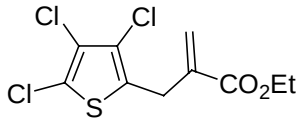
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71-7.36 (m, 5H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 186.4, 137.3, 133.8, 132.7, 131.8, 129.8, 129.0, 128.0, 126.2..

MS (EI): 294 (11), 292 (32), 290 (32), 105 (100).

$C_{11}H_5Cl_3OS$	HRMS:	Calcd:	289.9100
		Found:	289.9102

Synthesis of ethyl 2-[(3,4,5-trichloro-2-thienyl)methyl]acrylate (53e)



The reaction was carried out according to TP 4 using tetrachlorothiophene (222 mg, 1 mmol), *i*-PrMgBr (1.51 mL, 1.1 mmol, 0.73 M in THF), (exchange at rt, 2 h) and ethyl (2-bromomethyl)acrylate (348 mg, 1.8 mmol) to give a crude residue, which was purified by column chromatography on silica (pentane/EtOAc 99:1) affording the product **53e** (287 mg, 96 %) as a colorless oil.

IR (neat): 1715 (vs), 1324 (m), 1157 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.22 (s, 1H), 5.58 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 2H), 1.22 (tr, *J* = 7.1 Hz, 3H).

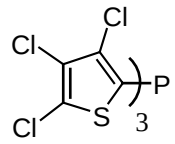
^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.2, 137.0, 132.2, 127.8, 123.1, 122.8, 122.0, 61.6, 31.3, 14.5.

MS (EI): 302 (16), 300 (47), 298 (46), 271 (47), 269 (47), 265 (58), 263 (88), 237 (65), 236 (33), 235 (100), 234 (38), 226 (68), 224 (65), 201 (34), 189 (38), 155 (30).

$C_{10}H_9Cl_3O_2S$	HRMS:	Calcd:	297.9419
		Found:	297.9424

8- Synthesis of phosphorous ligands

Synthesis of tris(3,4,5-trichloro-2-thienyl)phosphine (62)



A solution of *i*-PrMgBr (21.1 mmol) in THF (0.88 M, 24 mL) was added dropwise over 10 min to a stirred solution of tetrachlorothiophene (5 g, 22.5 mmol) in THF (10 mL) at rt under argon. The resulting solution was then stirred for 2 h and PBr_3 (0.38 mL, 4.0 mmol) was slowly added at 0 °C. The reaction mixture was stirred at rt 1 h, quenched with brine (30 mL) and extracted with CH_2Cl_2 to afford a colorless solid. After washing with pentane, the phosphine **62** was obtained (1.04 g, 44 %).

Mp: 176 °C.

IR (KBr): 1496 (w), 1397 (w), 1318 (s), 1000 (m) cm^{-1}.

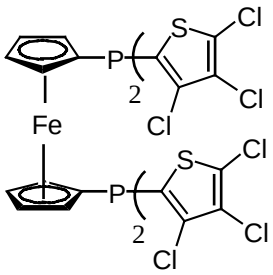
^{31}P NMR ($CDCl_3$, 81 MHz): δ -48.4.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 130.6 (d, *J* = 15.0 Hz), 124.7, 123.0, 122.6.

MS (EI): 595 (11), 593 (31), 591 (60), 590 (74), 588 (52), 586 (17), 523 (14), 403 (17), 332 (14), 220 (34), 218 (100).

$C_{12}Cl_9PS_3$	Calcd:	C	24.41	Cl	54.05	S 16.29
	Found:	C	24.49	Cl	53.81	S 15.98

Synthesis of 1,1´bis(3,4,5-trichloro-2-thienyl)phosphinoferrocene (63)



A solution of *i*-PrMgBr (12.0 mmol) in THF (0.88 M, 13.6 mL) was added dropwise over 10 min to a stirred solution of tetrachlorothiophene (2.89 g, 13 mmol) in THF (6 mL) at rt under argon. The resulting solution was then stirred for 2 h and bis(dichlorophosphino)ferrocene **65**[75] (2.0 mmol) was slowly added at 0 °C. The reaction mixture was stirred at rt 1 h, quenched with brine (30 mL) and extracted with CH_2Cl_2 to afford a colorless solid. After washing with pentane, the phosphine **63** was obtained (780 mg, 39 %).

Mp: 165 °C.

IR (KBr): 1498 (w), 1402 (w), 1314 (s), 999 (m), 794 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.52 (bs, 4H), 4.43 (bs, 4H).

^{31}P NMR ($CDCl_3$, 81 MHz): δ -47.5.

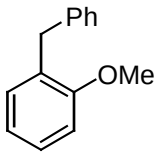
^{13}C NMR ($CDCl_3$, 75 MHz): δ 130.8 (d, *J* = 23 Hz), 129.9, 129.2, 125.2, 77.0, 74.9, 73.7, 73.1.

MS (EI): 999 (6), 995 (43),993 (78), 991 (100), 989 (88), 987 (47), 210 (29).

$C_{26}H_8Cl_{12}FeP_2S_4$ HRMS: Calcd: 985.4596

Found: 985.4569

Negishi cross-coupling reactions. Preparation of 2-benzyl anisole (66)[100]

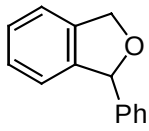


To a THF solution (2 mL) of $Pd(dba)_2$ (29 mg, 50 μmol) and ligand **62** (59 mg, 100 μmol) or **63** (50 mg, 50 μmol) was added 2-iodoanisole (234 mg, 1.0 mmol) tetradecane (2 drops) and benzylzinc bromide (1.7 mL, 1.3 mmol, 0.75 N in THF). The reaction mixture was followed by GC-MS and the conversion was determined using tetradecane as internal standard after 5, 10, 20 40 and 60 min. The reaction mixture was then quenched with brine (20 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30–6.70 (m, 9H), 3.93 (s, 2H), 3.78 (s, 3H).
GC-MS (EI): 198.

9- Synthesis of dihydrobenzofurans

Synthesis of 1-phenyl-1,3-dihydro-2-benzofuran (70a)[101]

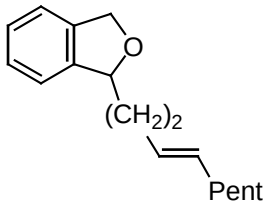


The reaction was carried out according to TP 5 affording **70a** (161 mg, 82 %) as a colorless oil.

[100] B. A. Sim, P. H. Milne, D. Griller, D. D. M. Wagner, *J. Am. Chem. Soc*. **1990**, *112*, 6635.
[101]W. Kirmse, K. Kund, *J. Org. Chem*. **1990**, *55*, 2325.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.17 (m, 8H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 1H), 5.24 (d, J_{AB} = 13.7 Hz, 1H), 5.13 (d, J_{AB} = 13.7 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 142.5, 139.6, 129.0, 128.5, 128.0, 127.9, 127.4, 122.7, 121.3, 86.7, 73.7.

Synthesis of 1-[(3*E*)-non-3-enyl]-1,3-dihydro-2-benzofuran (70b)

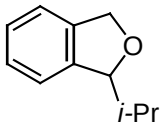


The reaction was carried out according to TP 5 affording **70b** (171 mg, 70 %) as a colorless oil.

IR (neat): 2955 (vs), 2853 (s), 1460 (w) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.07 (m, 4H), 5.36 (m, 2H), 5.16 (m, 1H), 5.02-4.98 (m, 2H), 2.08 (m, 2H), 1.89 (m, 3H), 1.74 (m, 1H), 1.21 (m, 6H), 0.80 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 139.9, 131.4, 129.8, 127.7, 127.6, 121.5, 121.3, 83.8, 72.9, 36.7, 33.0, 31.9, 29.8, 28.6, 22.9, 14.5.
MS (EI): 244 (15), 145 (55), 119 (100).

$C_{17}H_{24}O$	HRMS:	Calcd:	244.1827
		Found:	244.1837

Synthesis of 1-isopropyl-1,3-dihydro-2-benzofuran (70c)[102]

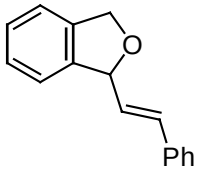


[102]P. Canonne, J. Plamondon, M. Akssira, *Tetrahedron* **1988**, *44*, 2903.

The reaction was carried out according to TP 5 affording **70c** (140 mg, 86 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.07 (m, 4H), 5.05-4.99 (m, 3H), 1.99-1.96 (m, 1H), 0.98 (d, *J* = 7.7 Hz, 3H), 0.73 (d, *J* = 7.7 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 140.3, 127.7, 127.4, 122.0, 121.2, 89.2, 73.6, 34.2, 19.4, 16.5.
MS (EI): 161 (72), 135 (100).

Synthesis of 1-[(*E*)-2-phenylethenyl]-1,3-dihydro-2-benzofuran (70d)

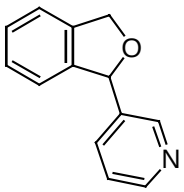


The reaction was carried out according to TP 5 affording **70d** (202 mg, 91 %) as a yellow oil.

IR (neat): 3029 (m), 2855 (m), cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.08 (m, 9H), 6.63 (d, *J* = 15.7 Hz, 1H), 6.18 (dd, *J* = 15.7 Hz, *J* = 7.6 Hz, 1H), 5.65 (d, *J* = 7.6 Hz, 1H), 5.12 (d, J_{AB} = 12.2 Hz, 1H), 5.01 (d, J_{AB} = 12.2 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 139.9, 135.4, 130.9, 128.0, 127.5, 126.8, 126.7, 126.4, 120.9, 120.0, 84.2, 71.7.
MS (EI): 222 (100), 118 (56).

$C_{16}H_{14}O$	Calcd:	C	86.45	H	6.35
	Found	C	86.09	H	6.42

Synthesis of 3-(1,3-dihydro-2-benzofuryl)pyridine (70e)



The reaction was carried out according to TP 5 affording **70e** (154 mg, 78 %) as a colorless oil.

IR (neat): 1286 (s), 1026 (vs) cm^{-1}.

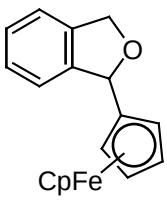
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.45 (dd, *J* = 4.9 Hz, *J* = 1.7 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.21-7.11 (m, 4H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.09 (s, 1H), 5.24 (d, J_{AB} = 12.3 Hz, 1H), 5.12 (d, J_{AB} = 12.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 148.9, 141.4, 139.4, 138.1, 135.0, 128.4, 128.1, 124.0, 122.5, 121.5, 84.2, 73.8.

MS (EI): 197 (10), 196 (49), 168 (98), 119 (82), 106 (100).

$C_{13}H_{11}NO$: HRMS: Calcd: 197.0840
Found: 197.0834

Synthesis of 1-ferrocenyl-1,3-dihydro-2-benzofuran (70f)



The reaction was carried out according to TP 5 affording **70f** (246 mg, 81 %) as an orange solid.

Mp: 107 °C.

IR (KBr): 2852 (m), 1458 (w) cm^{-1}.

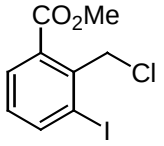
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.13 (m, 4H), 5.99 (s, 1H), 5.12 (d, J_{AB} = 12.1 Hz, 1H), 5.01 (d, J_{AB} = 12.1 Hz, 1H), 4.20-3.99 (m, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 139.9, 128.0, 127.5, 122.5, 121.4, 89.9, 82.8, 72.9, 69.1, 68.9, 68.0, 67.0, 66.9.

MS (EI): 304 (100), 208 (15).

$C_{18}H_{16}FeO$	Calcd:	C	71.08	H	5.30
	Found:	C	71.25	H	5.41

Synthesis of methyl 2-(chloromethyl)-3-iodobenzoate (**74**)



A THF solution of the known corresponding 2-bromomethylbenzoate **73**[96] (1.70 g, 4.79 mmol) and LiCl (610 mg, 14.3 mmol) was heated at reflux for 4 h. After usual work up and filtration on silica, **74** was obtained as a colorless oil in a quantitative yield.

IR (neat): 1713 (s), 1266 (s) cm^{-1}.

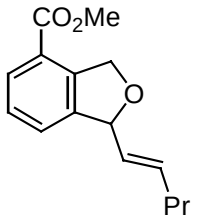
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 6.97 (t, *J* = 7.9 Hz, 1H), 5.08 (s, 2H), 3.85 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 144.2, 140.5, 132.0, 131.5, 130.3, 130.8, 53.1, 48.6.

MS (EI): 310 (6), 275 (100).

$C_9H_8ClIO_2$	HRMS:	Calcd:	309.9258
		Found:	309.9259

Synthesis of methyl 1-[(1*E*)-pent-1-enyl]-1,3-dihydro-2-benzofuran-4-carboxylate (**75a**)



The reaction was carried out according to TP 5 using **74** (350 mg, 1.13 mmol). The crude residue was dissolved in THF (2 mL). NaH (24 mg, 1.0 mmol) was added and the reaction mixture was heated at reflux for 1 h. After usual work up and purification by column chromatography on silica (hexanes/AcOEt 9:1), **75a** was obtained (167 mg, 60 %) as a colorless oil.

IR (neat): 2959 (w), 2931 (w), 1723 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.5 Hz, 1H), 7.29-7.19 (m, 2H), 5.85-5.70 (m, 1H), 5.60-5.52 (m, 2H), 5.46 (d, J_{AB} = 14.6 Hz, 1H), 5.31 (d, J_{AB} = 14.6 Hz, 1H), 3.83 (s, 3H), 2.02-1.99 (m, 2H), 1.41-1.34 (m, 2H), 0.85 (t, *J* = 7.1 Hz, 3H).

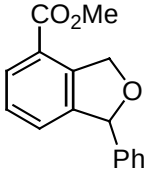
^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 142.0, 140.8, 133.8, 128.6, 128.1, 126.7, 125.4, 123.4, 83.9, 72.8, 51.0, 33.2, 21.2, 12.6.

MS (EI): 246 (4), 203 (100), 171 (20).

$C_{15}H_{18}O_3$ HRMS: Calcd: 246.1256

Found: 246.1246

Synthesis of methyl 1-phenyl-1,3-dihydro-2-benzofuran-4-carboxylate (**75b**).



The reaction was carried out according to TP 5 using **74** (245 mg, 0.79 mmol). The crude residue was dissolved in THF (2 mL). NaH (24 mg, 1.0 mmol) was added and the reaction mixture was heated at reflux for 1 h. After usual work up and purification by column

chromography on silica (hexanes/AcOEt 95:5), **75b** was obtained (110 mg, 55 %) as a colorless oil.

IR (neat): 1721 (vs), 1278 (s) cm^{-1}.

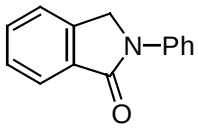
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, J = 7.6 Hz, 1H), 7.32-7.06 (m, 7H), 6.05 (s, 1H), 5.54 (d, J_{AB} = 14.6 Hz, 1H), 5.35 (d, J_{AB} = 14.6 Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 142.5, 141.0, 140.5, 128.2, 127.6, 127.2, 126.9, 125.8, 125.7, 123.4, 84.6, 73.6, 51.0.

MS (EI): 254 (64), 222 (75), 165 (100).

$C_{16}H_{14}O_3$	HRMS:	Calcd:	254.0933
		Found:	254.0928

Synthesis of 2-phenylisoindolin-1-one (**76**)



A solution of *i*-PrMgBr (1.3 mmol) in THF (0.88 M, 1.48 mL) was added dropwise to a stirred solution of **68** (300 mg, 1.2 mmol) in THF (2 mL) at –10 °C under argon. The resulting solution was then stirred for 1.5 h and phenylisocyanate (214 mg,1.8 mmol) was added. The reaction mixture was slowly allowed to warm up to rt, stirred 2 h, quenched with brine and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude product was washed with pentane affording **76** (239 mg, 96 %) as a colorless solid.

Mp:160 °C-161 °C.

IR (KBr): 1688 (s), 1502 (w), 1391 (s) cm^{-1}.

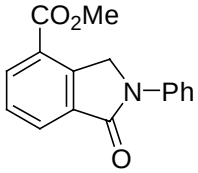
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.72 (m, 3H), 7.44-7.23 (m, 5H), 7.06-7.01 (m, 1H), 4.65 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 140.6, 139.9, 134.2, 133.6, 129.7, 128.9, 124.8, 124.4, 123.0, 119.8, 51.1.

MS (EI): 209 (100), 180 (40).

$C_{14}H_{11}NO$	HRMS:	Calcd:	209.0841
		Found:	209.0838

Synthesis of methyl 1-oxo-2-phenylisoindoline-4-carboxylate (**77**)



A solution of *i*-PrMgBr (1.1 mmol) in THF (0.88 M, 1.25 mL) was added dropwise to a stirred solution of **74** (310 mg, 1.0 mmol) in THF (4 mL) at –30 °C under argon. The resulting solution was then stirred for 1 h and phenyl isocyanate (179 mg,1.5 mmol) was added. The reaction mixture was slowly allowed to warm up to rt, stirred for 2 h, quenched with brine and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude product was recristallized (EtOAc) affording **77** (200 mg, 75 %) as a colorless needles.

Mp: 155 °C.

IR (KBr): 1709 (s), 1697 (s), 1492 (m), 1380 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.9 Hz, 1H), 5.08 (s, 2H), 3.91 (s, 3H).

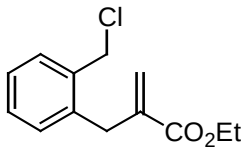
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 166.2, 142.4, 139.6, 135.0, 133.8, 129.6, 129.1, 128.9, 125.5, 125.1, 120.0, 52.7.

MS (EI): 266 (87), 252 (100).

$C_{16}H_{13}NO_3$	Calcd:	C	71.90	H	4.90	N 5.24
	Found:	C	71.40	H	4.86	N 5.25

10- Synthesis of tetrahydrobenzazepines

Synthesis of ethyl 2-[2-(chloromethyl)benzyl]acrylate (80)



A solution of *i*-PrMgBr (3.25 mmol) in THF (0.88 M, 3.7 mL) was added dropwise to a stirred solution of **68** (780 mg, 3.1 mmol) in THF (4 mL) at –10° C under argon. After 1.5 h, CuCN·2 LiCl (3.25 mL, 3.25 mmol, 1 M in THF) and ethyl (2-bromomethyl)acrylate (890 mg, 4.6 mmol) were added. The reaction mixture was stirred 1 h at –10 °C and quenched with brine. After usual work up and purification by column chromatography (pentane/AcOEt 98:2) **80** (610 mg, 83 %) was obtained as a colorless oil.

IR (neat): 2982 (s), 1715 (s), 1137 (w) cm^{-1}.

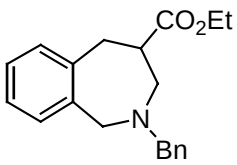
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.08 (m, 4H), 6.18 (s, 1H), 5.22 (s, 1H), 4.53 (s, 2H), 4.13 (q, *J* = 6.9 Hz, 2H), 3.69 (s, 2H), 1.20 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 140.1, 137.8, 136.2, 130.9, 130.7, 129.4, 127.6, 126.6, 61.3, 44.6, 34.8, 14.5.

MS (EI): 238 (0.1), 129 (100).

$C_{13}H_{15}ClO_2$ HRMS: Calcd: 238.0753
Found: 238.0761

Synthesis of ethyl 2-benzyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine-4-carboxylate (81a)



To a solution of **80** (173 mg, 0.72 mmol) in THF (3 mL) was added benzylamine (93 mg, 0.87 mmol) and K_2CO_3 (152 mg, 1.1 mmol). The reaction mixture was refluxed 24 h, quenched with brine and extracted with Et_2O. The crude product was purified by column chromatography on silica (pentane/AcOEt 92:8) affording **81a** (167 mg, 75 %) as a colorless oil.

IR (neat): 1728 (s), 1454 (w) cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.02 (m, 8H), 6.80 (d, *J* = 7.2 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.98 (d, J_{AB} = 14.7 Hz, 1H), 3.65 (d, J_{AB} = 14.7 Hz, 1H), 3.47-2.76 (m, 7H), 1.15 (t, *J* = 7.2 Hz, 3H).

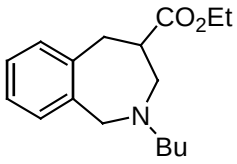
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 140.3, 139.4, 139.2, 130.4, 129.9, 129.3, 128.7, 127.8, 127.5, 126.8, 61.3, 60.9, 58.4, 57.1, 40.9, 38.5, 14.6.

MS (EI): 308 ($M\text{-}H^+$ 13), 218 (100).

$C_{20}H_{23}NO_2$ HRMS: Calcd: 308.1650

Found: 308.1618

Synthesis of ethyl 2-butyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine-4-carboxylate (**81b**)



To a solution of **80** (287 mg, 1.2 mmol) in THF (3 mL) was added butylamine (105 mg, 1.44 mmol) and K_2CO_3 (248 mg, 1.8 mmol). The reaction mixture was refluxed 24 h, quenched with brine and extracted with Et_2O. The crude product was purified by column chromatography on silica (pentane/AcOEt 92:8) affording **81b** (150 mg, 75 %) as a colorless oil.

IR (neat): 2956 (m), 2931 (m), 1729 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08-7.01 (m, 4H), 4.06 (q, *J* = 7.3 Hz, 2H), 3.99 (d, J_{AB} = 14.7 Hz, 1H), 3.73 (d, J_{AB} = 14.7 Hz, 1H), 3.44-2.61 (m, 5H), 2.31-213 (m, 2H), 1.44-1.31 (m, 2H), 1.25-1.14 (m, 5H), 0.80 (t, *J* = 7.3 Hz, 3H).

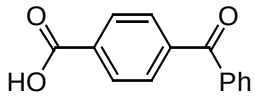
^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 138.7, 137.9, 128.6, 128.5, 126.3, 125.3, 59.8, 59.5, 57.4, 50.6, 39.0, 37.1, 28.5, 19.4, 13.2, 13.0.

MS (EI): 275 (7), 232 (100).

$C_{17}H_{25}NO_2$	HRMS:	Calcd:	275.1885
		Found:	275.1879

11- The halogen-magnesium exchange on the solid phase

Synthesis of 4-benzoylbenzoic acid (83a)



The reaction was carried out according to TP 6 using resin **9d** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), benzoyl chloride (0.16 mL, 1.41 mmol, 1 h at -40 °C) to give product **83a** (16 mg, 75 %) as a colorless solid.

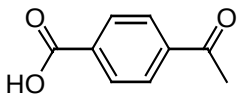
HPLC purity (254 nm): 97 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24-7.60 (m, 9 H).

MS (EI): 226 (57), 149 (52), 105 (100), 77 (61).

$C_{14}H_{10}O_3$	HRMS:	Calcd:	226.0630
		Found:	226.0631

Synthesis of 4-acetylbenzoic acid (83b)



The reaction was carried out according to TP 6 using resin **9d** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), acetyl chloride (0.10 mL, 1.41 mmol, 1 h at -40 °C) to give product **83b** (14 mg, 91 %) as a colorless solid.

HPLC purity (254 nm): 94 %.

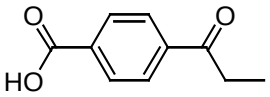
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 4H), 2.63 (s, 3 H).

MS (EI): 164 (21), 149 (100), 121 (30), 65 (44), 43 (43).

$C_9H_8O_3$ HRMS: Calcd: 164.0473

Found: 164.0476

Synthesis of 4-propionylbenzoic acid (83c)



The reaction was carried out according to TP 6 using resin **9d** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), propionyl chloride (0.12 mL, 1.41 mmol, 1 h at -40 °C) to give product **83c** (13 mg, 80 %) as a colorless solid.

HPLC purity (254 nm): 92 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 4H), 3.09 (q, *J* = 6.9 Hz, 2H), 1.10 (t, *J* = 6.9 Hz, 3H).

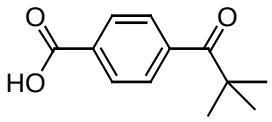
^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 166.6, 139.6, 134.4, 129.5, 127.9, 31.6, 14.0.

MS (EI): 178 (100), 149 (85), 121 (99), 65 (50).

$C_{10}H_{10}O_3$ HRMS: Calcd: 178.0630

Found: 178.0637

Synthesis of 4-(2,2-dimethylpropanoyl)benzoic acid (83d)



The reaction was carried out according to TP 6 using resin **9d** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), pivaloyl chloride (0.17 mL, 1.41 mmol, 6 h at -40 °C) to give product **83d** (16 mg, 83 %) as a colorless solid.

HPLC purity (254 nm): 96 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 1.25 (s, 9H).

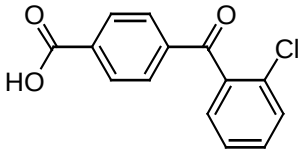
^{13}C-NMR (100 MHz, CDCl3): δ 208.9, 166.7, 142.1, 132.7, 129.1, 127.3, 43.7, 27.2.

MS (EI): 206 (5), 149 (100), 122 (23), 57 (78).

$C_{12}H_{14}O_3$ HRMS: Calcd: 206.0943

Found: 206.0945

Synthesis of 4-(2-chlorobenzoyl)benzoic acid (83e)



The reaction was carried out according to TP 6 using resin **9d** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), 2-chlorobenzoyl chloride (0.18 mL, 1.41 mmol, 1 h at -40 °C) to give product **83e** (14 mg, 58 %) as a colorless solid.

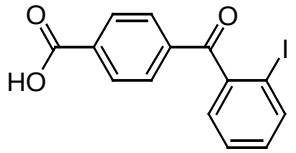
HPLC purity (254 nm): 93 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20-7.20 (m, 8H).

MS (EI): 260 (37), 149 (84), 139 (100), 111 (53), 65 (57).

$C_{14}H_9ClO_3$ HRMS: Calcd: 260.0240
Found: 260.0231

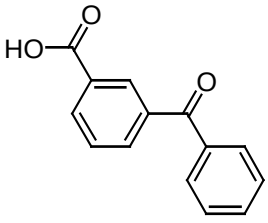
Synthesis of 4-(2-iodobenzoyl)benzoic acid (83f)



The reaction was carried out according to TP 6 using resin **9d** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), 2-iodobenzoyl chloride (375 mg, 1.41 mmol, 1 h at -40 °C) to give product **83f** (18 mg, 55 %) as a colorless solid.

HPLC purity (254 nm): 86 %.
^{1}H NMR (300 MHz, $CDCl_3$): δ 810-7.80 (m, 4H), 7.60-7.25 (m, 4H).
MS (EI): 352 (4), 122 (97), 105 (100), 77 (97).
$C_{14}H_9IO_3$ HRMS: Calcd: 351.9597
Found: 351.9602

Synthesis of 3-benzoylbenzoic acid (84a)



The reaction was carried out according to TP 6 using resin **9c** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), benzoyl chloride (0.16 mL, 1.41 mmol, 1 h at -40 °C) to give product **84a** (17 mg, 80 %) as a colorless solid.

HPLC purity (254 nm): 92 %.

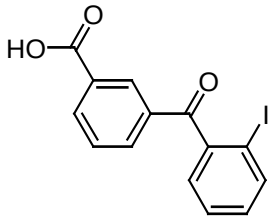
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26-8.18 (m, 2H), 7.97-7.66 (m, 5H), 7.61-7.54 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1, 166.5, 137.2, 136.6, 133.5, 133.1, 132.9, 131.3, 130.2, 129.6, 129.1, 128.6.

MS (EI): 226 (57), 149 (57), 105 (100), 65 (27).

$C_{14}H_{10}O_3$	HRMS:	Calcd:	226.0630
		Found:	226.0624

Synthesis of 3-(2-iodobenzoyl)benzoic acid (84b)



The reaction was carried out according to TP 6 using resin **9c** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), 2-iodobenzoyl chloride (375 mg, 1.41 mmol, 1 h at -40 °C) to give product **84b** (18 mg, 55 %) as a colorless solid.

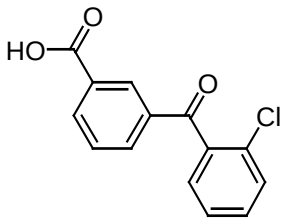
HPLC purity (254 nm): 89 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20-7.80 (m, 4H), 7.60-7.30 (m, 4H).

MS (EI): 352 (100), 231 (85), 149 (99), 65 (50).

$C_{14}H_9IO_3$	HRMS:	Calcd:	351.9596
		Found:	351.9598

Synthesis of 3-(2-chlorobenzoyl)benzoic acid (84c)



The reaction was carried out according to TP 6 using resin **9c** (125 mg, 94 µmol), *i*-PrMgBr (1.15 mL, 0.94 mmol, 0.82 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.94 mL, 0.94 mmol, 1 M in THF), 2-chlorobenzoyl chloride (0.18 mL, 1.41 mmol, 1 h at -40 °C) to give product **84c** (19 mg, 78 %) as a colorless solid.

HPLC purity (254 nm): 91 %.

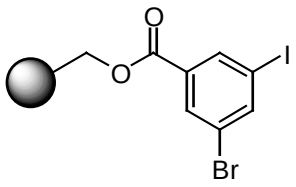
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22-7.50 (m, 3H), 7.72-7.50 (m, 5H).

MS (EI): 260 (66), 149 (14), 139 (25), 111 (53), 65 (67).

$C_{14}H_9ClO_3$ HRMS: Calcd: 260.0240

Found: 260.0238

Synthesis of Wang resin attached 3-bromo-5-iodocarboxylic acid (85)

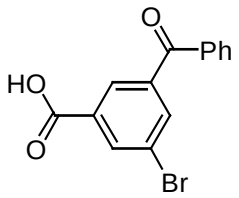


The reaction was carried out according to TP 2 using 3-bromo-5-iodocarboxylic acid (4.90 g, 15 mmol).

HPLC purity (UV 254 nm): 95 %.

Loading : 0.75 mmol/g.

Synthesis of 3-benzoyl-5-bromobenzoic acid (86a)



The reaction was carried out according to TP 6 using resin **85** (100 mg, 75 µmol), *i*-PrMgBr (1.23 mL, 0.75 mmol, 0.61 M in THF), (exchange at -78 °C, 1 h), CuCN·2LiCl (0.75 mL, 0.75 mmol, 1 M in THF), benzoyl chloride (0.13 mL, 1.13 mmol, 1 h at -40 °C) to give product **86a** (19 mg, 80 %) as a colorless solid.

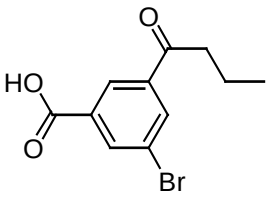
HPLC purity (UV 254 nm): 93 %.

^{1}H NMR (DMSO, 400 MHz): δ 8.30 (s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 7.79-7.73 (m, 3H), 7.63-7.58 (m, 2H).

MS (EI): 306 (23), 304 (24), 105 (100).

$C_{14}H_9BrO_3$	HRMS:	Calcd:	303.9735
		Found	303.9775

Synthesis of 3-bromo-5-butyrylbenzoic acid (86b)



The reaction was carried out according to TP 6 using resin **85** (100 mg, 75 µmol), *i*-PrMgBr (1.23 mL, 0.75 mmol, 0.61 M in THF), (exchange at -78 °C, 1 h), CuCN·2LiCl (0.75 mL, 0.75 mmol, 1 M in THF), butyryl chloride (0.11 mL, 1.13 mmol, 1 h at -40 °C) to give product **86b** (16 mg, 80 %) as a colorless solid.

HPLC purity (UV 254 nm): 97 %.

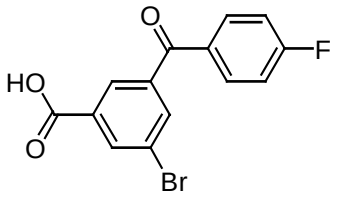
^{1}H NMR (CD_3CN, 400 MHz): δ 8.44 (s, 1H), 8.30 (s, 1H), 8.28 (s, 1H), 3.00 (t, *J* = 7.1 Hz, 2H), 1.72-1.67 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

MS (EI): 272 (4), 270 (4), 244 (22), 242 (23), 229 (98), 227 (100), 191(27).

$C_{11}H_{11}BrO_3$ HRMS: Calcd: 269.9892

Found 269.9882

Synthesis of 3-bromo-5-(4-fluorobenzoyl)benzoic acid (86c)



The reaction was carried out according to TP 6 using resin **85** (100 mg, 75 µmol), *i*-PrMgBr (1.23 mL, 0.75 mmol, 0.61 M in THF), (exchange at -40 °C, 1 h), CuCN·2LiCl (0.75 mL, 0.75 mmol, 1 M in THF), 4-fluorobenzoyl chloride (179 mg, 1.13 mmol, 1 h at -40 °C) to give product **86c** (22 mg, 90 %) as a colorless solid.

HPLC purity (UV 254 nm): 95 %.

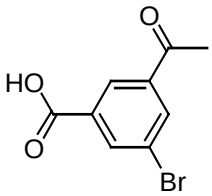
^{1}H NMR (CD_3CN, 400 MHz): δ 8.34 (m, 1H), 8.21 (m, 1H), 8.14-7.76 (m, 5H).

MS (EI): 324(36), 322 (36), 123 (100), 95 (43).

$C_{14}H_8BrFO_3$ HRMS: Calcd: 321.9618

Found 321.9624

Synthesis of 3-acetyl-5-bromobenzoic acid (86d)



The reaction was carried out according to TP 6 using resin **85** (100 mg, 75 µmol), *i*-PrMgBr (1.23 mL, 0.75 mmol, 0.61 M in THF), (exchange at -78 °C, 1 h), CuCN·2LiCl (0.75 mL, 0.75 mmol, 1 M in THF), acetyl chloride (80 µL, 1.13 mmol, 1 h at -40 °C) to give product **86d** (18 mg, 99 %) as a colorless solid.

HPLC purity (UV 254 nm): 86 %.

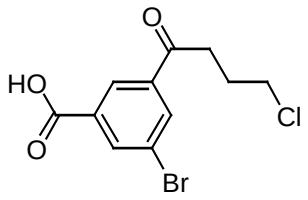
^{1}H NMR (CD_3CN, 300 MHz): δ 8.48 (s, 1H), 8.34 (s, 1H), 8.32 (s, 1H), 2.63 (s, 3H).

MS (EI): 244 (58), 242 (59), 229 (99), 227 (100), 201 (33), 199 (32).

$C_9H_7BrO_3$ HRMS: Calcd: 241.9579

Found: 241.9609

Synthesis of 3-bromo-5-(4-chlorobutanoyl)benzoic acid (86e)



The reaction was carried out according to TP 6 using resin **85** (100 mg, 75 µmol), *i*-PrMgBr (1.23 mL, 0.75 mmol, 0.61 M in THF), (exchange at -78 °C, 1 h), CuCN·2LiCl (0.75 mL, 0.75 mmol, 1 M in THF), 4-chlorobutyryl chloride (0.13 mL, 1.13 mmol, 1 h at -40 °C) to give product **86e** (19 mg, 85 %) as a colorless solid.

HPLC purity (UV 254 nm): 77 %.

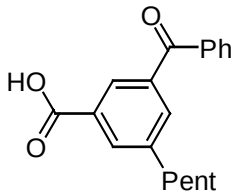
^{1}H NMR (CD_3CN, 400 MHz): δ 8.45 (s, 1H), 8.30 (s, 1H), 8.29 (s, 1H), 3.66 (t, *J* = 7.3 Hz, 2H), 3.21 (t, *J* = 7.1 Hz, 2H), 2.19 (m, 2H).

MS (EI): 306 (3), 304 (2), 270 (27), 268 (28), 244 (34), 242 (35), 229 (98), 227(100).

$C_{11}H_{10}ClBrO_3$ HRMS: Calcd: 303.9532

Found: 303.9545

Synthesis of 3-benzoyl-5-pentylbenzoic acid (93a)

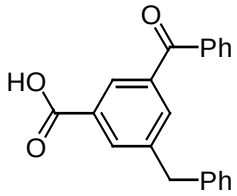


The reaction was carried out according to TP 7 using Wang-resin attached 3-benzoyl-5-bromobenzoic acid **91** (100 mg, 75 µmol), and dipentylzinc (0.75 mmol) affording product **93a** (16 mg, 70 %) as a colorless solid.

HPLC purity (UV 254 nm): 93 %.
^{1}H NMR (DMSO, 300 MHz): 8.06 (s, 1H), 7.80-7.46 (m, 5H), 7.39-7.25 (m, 2H), 2.73 (t, *J* = 7.1 Hz, 2H), 1.61-1.58 (m, 2H), 1.40-1.29 (m, 4H), 1.09 (t, *J* = 7.1 Hz, 3H).
MS (EI): 296 (2), 192 (52), 136 (100).

$C_{19}H_{20}O_3$	HRMS:	Calcd:	296.1412
		Found:	296.1413

Synthesis of 3-benzoyl-5-benzylbenzoic acid (93b)

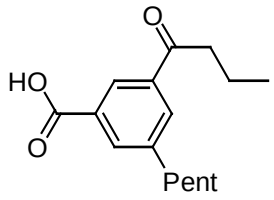


The reaction was carried out according to TP 7 using Wang-resin attached 3-benzoyl-5-bromobenzoic acid **91** (100 mg, 75 µmol), and benzylzinc bromide (0.75 mmol) affording product **93b** (15 mg, 65 %) as a colorless solid.

HPLC purity (UV 254 nm): 91 %.
^{1}H NMR (CD_3CN, 400 MHz): δ 8.12 (s, 1H), 8.08 (s, 1H), 7.85-7.20 (m, 11H), 4.11 (s, 2H).
MS (EI): 316 (66), 239 (46), 165 (50), 105 (100).

$C_{21}H_{16}O_3$	HRMS:	Calcd:	316.1099
		Found:	316.1102

Synthesis of 3-butyryl-5-pentylbenzoic acid (94a)



The reaction was carried out according to TP 7 using Wang-resin attached 3-benzoyl-5-bromobenzoic acid **91** (100 mg, 75 µmol), and benzylzinc bromide (0.75 mmol) affording product **93c** (14 mg, 70 %) as a colorless solid.

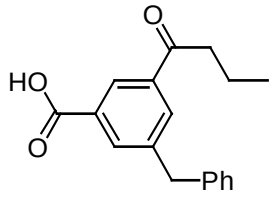
HPLC purity (UV 254 nm): 93 %.

^{1}H NMR (CD_3CN, 400 MHz): δ 8.33 (s, 1H), 8.04 (s, 1H), 7.98 (s, 1H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 1.70-1.50 (m, 4H), 1.40-1.30 (m, 4H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H).

MS (EI): 262 (7), 219 (100).

$C_{16}H_{22}O_3$	HRMS:	Calcd:	262.1569
		Found:	262.1579

Synthesis of 5-benzyl-3-butyrylbenzoic acid (94b)



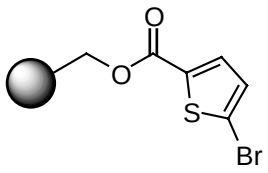
The reaction was carried out according to TP 7 using Wang-resin attached 3-bromo-5-butyrylbenzoic acid **92** (100 mg, 75 µmol), and dipentylzinc (0.75 mmol) affording product **94a** (13 mg, 60 %) as a colorless solid.

HPLC purity (UV 254 nm): 95 %.

MS (EI): 282 (4), 265 (23), 239 (100), 165 (40).

$C_{18}H_{18}O_3$	HRMS:	Calcd:	282.1256
		Found:	282.1262

Synthesis of Wang resin attached 5-bromothiophene-2-carboxylic acid (98)

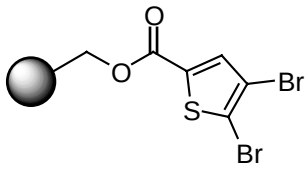


The reaction was carried out according to TP 2 using 5-bromothiophene-2-carboxylic acid (3.10 g, 15 mmol).

HPLC purity (UV 254 nm): 96 %.

Loading : 0.70 mmol/g.

Synthesis of Wang resin attached 4,5-dibromothiophene-2-carboxylic acid (99)

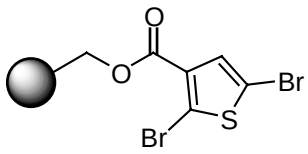


The reaction was carried out according to TP 2 using 4,5-dibromothiophene-2-carboxylic acid (4.30 g, 15 mmol).

HPLC purity (UV 254 nm): 100 %.

Loading : 0.70 mmol/g.

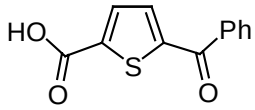
Synthesis of Wang resin attached 2,5-dibromothiophene-3-carboxylic acid (100)



The reaction was carried out according to TP 2 using 2,5-dibromothiophe-3-necarboxylic acid (4.30 g, 15 mmol).

HPLC purity (UV 254 nm): 97 %.
Loading : 0.73 mmol/g.

Synthesis of 5-benzoylthiophene-2-carboxylic acid (101a)

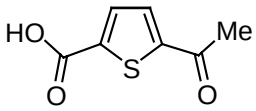


The reaction was carried out according to TP 6 using resin **98** (90 mg, 65 µmol), *i*-PrMgBr (1.0 mL, 0.65 mmol, 0.65 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.65 mL, 0.65 mmol, 1 M in THF), benzoyl chloride (0.12 mL, 1.0 mmol, 10 h at -10 °C) to give product **101a** (14 mg, 93 %) as a colorless solid.

HPLC purity (UV 254 nm): 93 %.
^{1}H NMR (DMSO, 400 MHz): δ 7.94-7.52 (m, 7H).
MS (EI): 232 (91), 187 (36), 155 (92), 105 (100), 77 (92), 51 (82).

$C_{12}H_8O_3S$	HRMS:	Calcd:	232.0194
		Found:	232.0187

Synthesis of 5-acetylthiophene-2-carboxylic acid (101b)



The reaction was carried out according to TP 6 using resin **98** (125 mg, 90 µmol), *i*-PrMgBr (1.40 mL, 0.90 mmol, 0.65 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.90 mL, 0.90 mmol, 1 M in THF), acetyl chloride (0.10 mL, 1.4 mmol, 10 h at -10 °C) to give product **101b** (14 mg, 90 %) as a colorless solid.

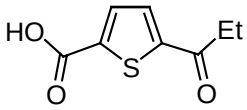
HPLC purity (UV 254 nm): 84 %.

^{1}H NMR (DMSO, 400 MHz): δ 7.92 (d, *J* = 4.0 Hz, 1H), 7.74 (d, *J* = 4.0 Hz, 1H), 2.60 (s, 3H).

MS (EI): 170 (41), 155 (100), 111 (15).

$C_7H_6O_3S$	HRMS:	Calcd:	170.0038
		Found:	170.0019

Synthesis of 5-propionylthiophene-2-carboxylic acid (101c)



The reaction was carried out according to TP 6 using resin **98** (90 mg, 65 µmol), *i*-PrMgBr (0.72 mL, 0.65 mmol, 0.9 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.65 mL, 0.65 mmol, 1 M in THF), propionyl chloride (0.09 mL, 1.0 mmol, 10 h at -10 °C) to give product **101c** (12 mg, 95 %) as a colorless solid.

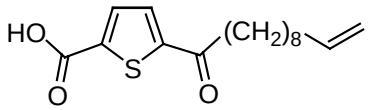
HPLC purity (UV 254 nm): 90 %.

^{1}H NMR (DMSO, 400 MHz): δ 7.91 (d, *J* = 4.0 Hz, 1H), 7.74 (d, *J* = 4.0 Hz, 1H), 3.02 (q, *J* = 7.1 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H).

MS (EI): 184 (20), 155 (100), 111 (11), 39 (13).

$C_8H_8O_3S$	HRMS:	Calcd:	184.0194
		Found	184.0188

Synthesis of 5-undecen-10-enoylthiophene-2-carboxylic acid (101d)



The reaction was carried out according to TP 6 using resin **98** (125 mg, 90 µmol), *i*-PrMgBr (1.4 mL, 0.90 mmol, 0.65 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.90 mL, 0.90 mmol, 1 M in THF), 5-undec-10-enoyl chloride (0.30 mL, 1.4 mmol, 10 h at -10 °C) to give product **101d** (14 mg, 90 %) as a colorless solid.

HPLC purity (UV 254 nm): 99 %.

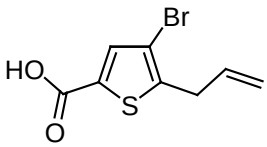
^{1}H NMR (DMSO, 400 MHz): δ 7.91 (d, *J* = 4.0 Hz, 1H), 7.75 (d, *J* = 4.0 Hz, 1H), 5.82-5.68 (m, 1H), 5.05-4.88 (m, 2H), 2.92 (t, *J* = 7.1 Hz, 2H), 1.98 (m, 2H), 1.20 (m, 12H).

^{13}C NMR (DMSO, 100 MHz): δ 194.4, 174.9, 162.9, 148.4, 139.3, 133.9, 133.3, 108.6, 38.8, 33.6, 29.2, 29.0, 28.9, 28.7, 24.4.

MS (EI): 294 (3), 183 (33), 170 (100), 155 (63), 55 (30), 41 (37).

$C_{16}H_{22}O_3S$	HRMS:	Calcd:	294.1290
		Found	294.1292

Synthesis of 5-allyl-4-bromothiophene-2-carboxylic acid (102a)



The reaction was carried out according to TP **6** using resin **99** (90 mg, 65 µmol), *i*-PrMgBr (1.1 mL, 0.65 mmol, 0.61 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.65 mL, 0.65

mmol, 1 M in THF), allyl bromide (121 mg, 1.0 mmol, 1 h at -40 °C) to give product **102a** (18 mg, 80 %) as a colorless solid.

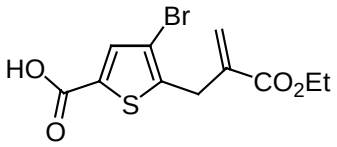
HPLC purity (UV 254 nm): 97 %.

^{1}H NMR (CD_3CN, 300 MHz): δ 7.66 (s, 1H), 6.09-5.93 (m, 1H), 5.24-5.18 (m, 2H), 3.59 (dd, *J* = 6.5 Hz, *J* = 1.2 Hz, 2H).

MS (EI): 248 (66), 246 (64), 123 (100), 122 (34), 121 (29), 79 (24), 45 (38).

$C_8H_7BrO_2S$	HRMS:	Calcd:	245.9350
		Found:	245.9342

Synthesis of 4-bromo-5-[2-(ethoxycarbonyl)prop-2-enyl]thiophene-2-carboxylic acid (102b).



The reaction was carried out according to TP 6 using resin **99** (100 mg, 70 µmol), *i*-PrMgBr (1.15 mL, 0.70 mmol, 0.61 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.70 mL, 0.70 mmol, 1 M in THF), ethyl (2-bromomethyl)acrylate (203 mg, 1.05 mmol, 90 min at -40 °C) to give product **102b** (20 mg, 90 %) as a colorless solid.

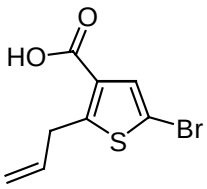
HPLC purity (UV 254 nm): 87 %.

^{1}H NMR (CD_3CN, 400 MHz): δ 7.61 (s, 1H), 6.26 (s, 1H), 5.67 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

MS (EI): 318 (10), 316 (10), 303 (20), 301 (19), 267 (100), 239 (60), 238 (32), 211 (24), 195 (39), 167 (26), 166 (26), 149 (26), 121 (35), 44 (65).

$C_{11}H_{11}BrO_4S$	HRMS:	Calcd:	317.9561
		Found	317.9543

Synthesis of 2-allyl-5-bromothiophene-3-carboxylic acid (103a)



The reaction was carried out according to TP 6 using resin **100** (80 mg, 58 µmol), *i*-PrMgBr (1.1 mL, 0.6 mmol, 0.55 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.6 mL, 0.6 mmol, 1 M in THF), allyl bromide (109 mg, 0.9 mmol, 2 h at -40 °C) to give product **103a** (11 mg, 80 %) as a colorless solid.

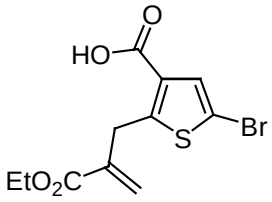
HPLC purity (UV 254 nm): 83 %.

^{1}H NMR (CD_3CN, 300 MHz): δ 7.40 (s, 1H), 6.09-5.96 (m, 1H), 5.22-5.13 (m, 2H), 3.91 (d, *J* = 6.6 Hz, 2H).

MS (EI): 248 (100), 246 (98), 233 (97), 231 (98), 168 (21), 149 (34), 123 (33), 122 (95), 121 (85), 77 (36), 44 (50).

$C_8H_7BrO_2S$	HRMS:	Calcd:	245.9350
		Found:	245.9347

Synthesis of 5-bromo-2-[2-(ethoxycarbonyl)prop-2-enyl]thiophene-3-carboxylic acid (103b)



The reaction was carried out according to TP 6 using resin **100** (80 mg, 58 µmol), *i*-PrMgBr (1.1 mL, 0.6 mmol, 0.55 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.6 mL, 0.6 mmol, 1 M in THF), ethyl (2-bromomethyl)acrylate (174 mg, 0.9 mmol, 2 h at -40 °C) to give product **103b** (17 mg, 90 %) as a colorless solid.

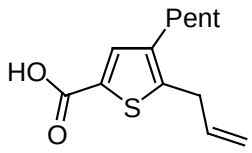
HPLC purity (UV 254 nm): 85 %.

^{1}H NMR (CD_3CN, 300 MHz): δ 7.40 (s, 1H), 6.25 (s, 1H), 5.68 (s, 1H), 4.23-4.16 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H).

MS (EI): 320 (21), 318 (21), 274 (68), 272 (63), 247 (60), 246 (100), 245 (64), 244 (92), 166 (49), 137 (30), 122 (39), 121 (32).

$C_{11}H_{11}BrO_4S$ HRMS: Calcd: 317.9562
Found: 317.9566

Synthesis of 5-allyl-4-pentylthiophene-2-carboxylic acid (105a)



The reaction was carried out according to TP 7 using Wang-resin attached 5-allyl-4-bromo-thiophene-2-carboxylic acid **104** (100 mg, 75 µmol) and dipentylzinc (0.75 mmol) affording product **105a** (14 mg, 80 %) as a colorless solid.

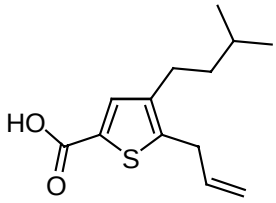
HPLC purity (UV 254 nm): 80 %.

^{1}H NMR (DMSO, 300 MHz): δ 7.37 (s, 1H), 6.00-5.85 (m, 1H), 5.13-5.08 (m, 2H), 3.48 (d, *J* = 6.6 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 1.51-1.48 (m, 2H), 1.32-1.26 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H).

MS (EI): 238 (49), 181 (53), 168 (93), 141 (75), 123 (100).

$C_{13}H_{18}O_2S$ HRMS: Calcd: 238.1028
Found: 238.1029

Synthesis of 5-allyl-4-isopentylthiophene-2-carboxylic acid (105b)



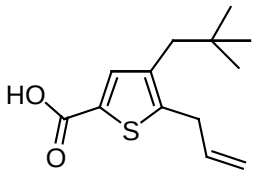
The reaction was carried out according to TP 7 using Wang-resin attached 5-allyl-4-bromo-thiophene-2-carboxylic acid **104** (100 mg, 75 µmol) and diisopentylzinc (0.75 mmol) affording product **105b** (14 mg, 80 %) as a colorless solid.

HPLC purity (UV 254 nm): 64 %.

MS (EI): 238 (3).

$C_{13}H_{18}O_2S$	HRMS:	Calcd:	238.1028
		Found:	238.1035

Synthesis of 5-allyl-4-neopentylthiophene-2-carboxylic acid (105c)



The reaction was carried out according to TP 7 using Wang-resin attached 5-allyl-4-bromo-thiophene-2-carboxylic acid **104** (100 mg, 75 µmol) and dineopentylzinc (0.75 mmol) affording product **105c** (12 mg, 70 %) as a colorless solid.

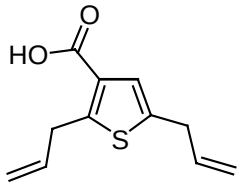
HPLC purity (UV 254 nm): 54 %.

^{1}H NMR (DMSO, 300 MHz): δ 7.48 (s, 1H), 6.02-5.92 (m, 1H), 5.19-5.10 (m, 2H), 3.55 (d, *J* = 6.6 Hz, 2H), 2.48 (s, 1 H), 0.91 (s, 9H).

MS (EI): 238 (44), 182 (100), 137 (67), 57 (83).

$C_{13}H_{18}O_2S$	HRMS:	Calcd:	238.1028
		Found:	238.1030

Synthesis of 2,5-diallylthiophene-3-carboxylic acid (108)



The reaction was carried out according to TP 6 using Wang-resin attached 2-allyl-5-bromo-thiophene-3-carboxylic acid **107** (80mg, 58 µmol), *i*-PrMgBr (0.83 mL, 0.6 mmol, 0.72 M in THF), (exchange at -40 °C, 2 h), CuCN·2LiCl (0.6 mL, 0.6 mmol, 1 M in THF), allyl bromide (80 µL, 0.9 mmol, 2 h at -40 °C) to give product **108** (10 mg, 91 %) as a colorless solid.

HPLC purity (UV 254 nm): 95 %.

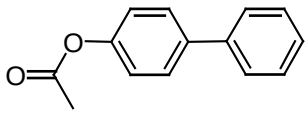
^{1}H NMR (CD_3CN, 300 MHz): δ 7.09 (s, 1H), 6.09-5.94 (m, 2H), 5.21-5.08 (m, 4H), 3.90 (d, *J* = 6.6 Hz, 2H), 3.52 (d, *J* = 6.6 Hz, 2H).

MS (EI): 208 (100), 193 (30), 181 (17), 163 (31), 135 (14).

$C_{11}H_{12}O_2S$	HRMS:	Calcd:	208.0558
		Found:	208.0554

12- Low temperature cross-coupling reactions

Synthesis of 4-acetoxybiphenyl (111)[103]



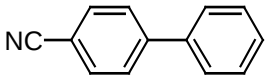
A dry three necked flask under an argon atmosphere was charged with iodide **110** (314 mg, 1.2 mmol) and $Ni(acac)_2$ (15 mg, 0.06 mmol, 5 mol %) in THF (3 mL). The reaction mixture was cooled to -40 °C and phenylmagnesium chloride (0.90 mL, 1.32 mmol, 1.5 M in THF) was added dropwise. After 30 min the reaction mixture was quenched with brine (20 mL) and

[103] M. E. Movery, P. Deshong, *J. Org. Chem.* **1999**, *64*, 3266.

extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography on silica (pentane/Et_2O 9:1) affording **111** (137 mg, 54 %) as a colorless solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84-7.04 (m, 9H), 2.18 (s, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.6, 150.3, 140.5, 139.1, 128.9, 128.3, 127.5, 127.3, 122.0, 21.2.
MS (EI): 212 (43), 170 (100), 141 (56), 115 (61), 43 (55).

Synthesis of [1,1'-biphenyl]-4-carbonitrile (115)[104]

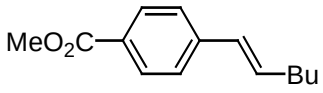


A dry three necked flask under an argon atmosphere was charged with 4-bromobenzonitrile (364 mg, 2.0 mmol), $Ni(acac)_2$ (77 mg, 0.30 mmol) and dppf (167 mg, 0.30 mmol) in THF (3 mL). The reaction mixture was cooled to -20 °C and phenylmagnesium chloride (1.33 mL, 2.0 mmol, 1.5 M in THF) was added dropwise. After 45 min a second equivallent of phenylmagnesium chloride (1.33 mL, 2.0 mmol, 1.5 M in THF) was added. After 45 min the reaction mixture was quenched with brine and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography on silica (pentane/Et_2O 95:5) affording **115** (211 mg, 60 %) as a colorless solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74-7.28 (m, 9H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.0, 139.5, 133.0, 129.6, 129.4, 128.1, 127.7, 119.4, 111.3.
MS (EI): 179 (100), 151 (27), 76 (19).

[104] I. Klement, M. Rottländer, C. E. Tucker, T. N. Majid, P. Knochel, *Tetrahedron* **1996**, *52*, 7201.

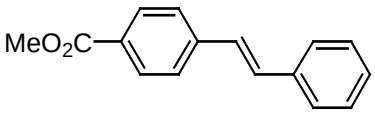
Synthesis of methyl 4-[(1*E*)-hex-1-enyl]benzoate (118)[105]



A dry three necked flask under an argon atmosphere was charged with methyl-4-iodobenzoate (393 mg, 1.5 mmol) in THF (1 mL). The reaction mixture was cooled to -20 °C and *i*-PrMgBr (2.7 mL, 1.58 mmol, 0.59 M in THF) was added dropwise. After 30 min $NiCl_2$(dppp) (25 mg, 0.046 mmol) and (*E*)-1-iodohexene (252 mg, 1.2 mmol) were added. The reaction mixture was stirred at -5 °C for 12 h, quenched with brine and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography on silica (pentane/AcOEt 98:2) affording **118** (162 mg, 62 %) as a colorless solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.30-6.28 (m, 2H), 3.81 (s, 3H), 2.16-2.11 (m, 2H), 1.38-1.28 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 142.9, 134.6, 130.3, 129.4, 128.7, 126.1, 52.6, 33.2, 31.7, 22.7, 14.3.
MS (EI): 218 (100), 162 (96), 131 (59), 115 (28).

Synthesis of *trans*-4-carbomethoxystilbene (119)[106]



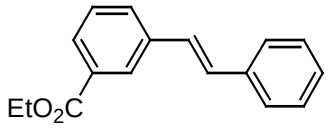
A dry three necked flask under an argon atmosphere was charged with methyl-4-iodobenzoate (655 mg, 2.5 mmol) in THF (2 mL). The reaction mixture was cooled to -20 °C and *i*-PrMgBr (3.42 mL, 2.63 mmol, 0.77 M in THF) was added dropwise. After 30 min $NiCl_2$(dppp) (36 mg, 0.067 mmol) and 2-bromostyrene (307 mg, 1.68 mmol) were added. The reaction mixture

[105] H. A. Dieck, R. F. Heck, *J. Am. Chem. Soc*. **1974**, *96*, 1133.
[106] D. H. Wadsworth, O. E. Schupp, E. J. Seus, J. A. Ford, *J. Org. Chem*. **1965**, *30*, 680.

was stirred at -5 °C for 3 h, quenched with brine and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography on silica (pentane/AcOEt 98:2) affording the product **119** (203 mg, 51 %) as a colorless solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (d, *J* = 8.4 Hz, 2 H), 7.46-7.03 (m, 9 H), 3.81 (s, 3 H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.3, 142.2, 137.2, 131.6, 130.4, 129.3, 129.2, 128.6, 128.0, 127.2, 126.7, 52.4.

Synthesis of *trans*-3-carbethoxystilbene (122)[107]



A dry three necked flask under an argon atmosphere was charged with ethyl-3-iodobenzoate (626 mg, 2.3 mmol) in THF (2 mL). The reaction mixture was cooled to -20 °C and *i*-PrMgBr (3.30 mL, 2.53 mmol, 0.77 M in THF) was added dropwise. After 30 min $NiCl_2$(dppp) (33 mg, 0.061 mmol) and 2-bromostyrene (275 mg, 1.50 mmol) were added. The reaction mixture was stirred at -5 °C for 3 h, quenched with brine and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography on silica (pentane/AcOEt 98:2) affording the product **122** (165 mg, 44 %) as a colorless solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, *J* = 7.5 Hz, 2H), 7.40-6.92 (m, 9H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.3, 140.6, 135.7, 130.0, 128.9, 128.2, 127.7, 127.3, 127.1, 126.0, 125.2, 59.8, 13.3.

[107] J. Kochi, G. S. Hammond, *J. Am. Chem. Soc*. **1953**, *75*, 3452.

Abreviations

Ac	acetyl
acac	acetylacetonate
Bn	benzyl
Calcd	calculated
cat.	Catalytic
dba	dibenzylideneacetone
d	day
DIC	diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis-diphenylphosphinoferrocene
dppp	1,3-bis-diphenylphosphinopropane
equiv	equivalent
E	electrophile
EI	electron ionisation
FG	functional group
GC	gas chromatography
h	hour
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
i-Pr	isopropyl
IR	infra-red
LDA	lithium diisopropylamide
M	molar
min	minute
Mp	melting point
MS	mass spectroscopy
TBME	*t*-butylmethylether
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
pent	pentyl
rt	room temperature
TFA	trifluoroacetic acid
TLC	thin layer chromatography
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
Ts	tosyl
UV	ultra-violet

Lebenslauf

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