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New Methods for the Synthesis of Organozinc and Organocopper Reagents

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New Methods for the Synthesis of Organozinc and Organocopper Reagents

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe erarbeitet.

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Claudia Piazza

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Table of Contents

Introduction

Results and Discussion

Experimental Section

Introduction

1 Overview

Organozinc and organocopper reagents are an indispensable part of the synthetic chemist's knowledge. Nowadays, almost every synthesis of natural product has at least one step which involves the use of this kind of compounds. Therefore, there is a constant need for the development of new methods for a straightforward and efficient preparation of zinc and copper organometallics. In this work the attention was focused on a new approach for the preparation of benzylic and allylic organozincs, which are among the most reactive zinc species. Even if diorganozincs and organozinc halides display only moderate reactivity toward most organic electrophiles, the scope and synthetic application of these species were greatly extended when it was found that they can accommodate a wide range of functional groups. An important C-C bond forming reaction for the construction of nitrogen-containing molecules is the addition of carbon nucleophiles to iminium intermediates. For this reason, the use of zinc reagents with these highly reactive elctrophiles for the synthesis of functionalised amines will also be described.

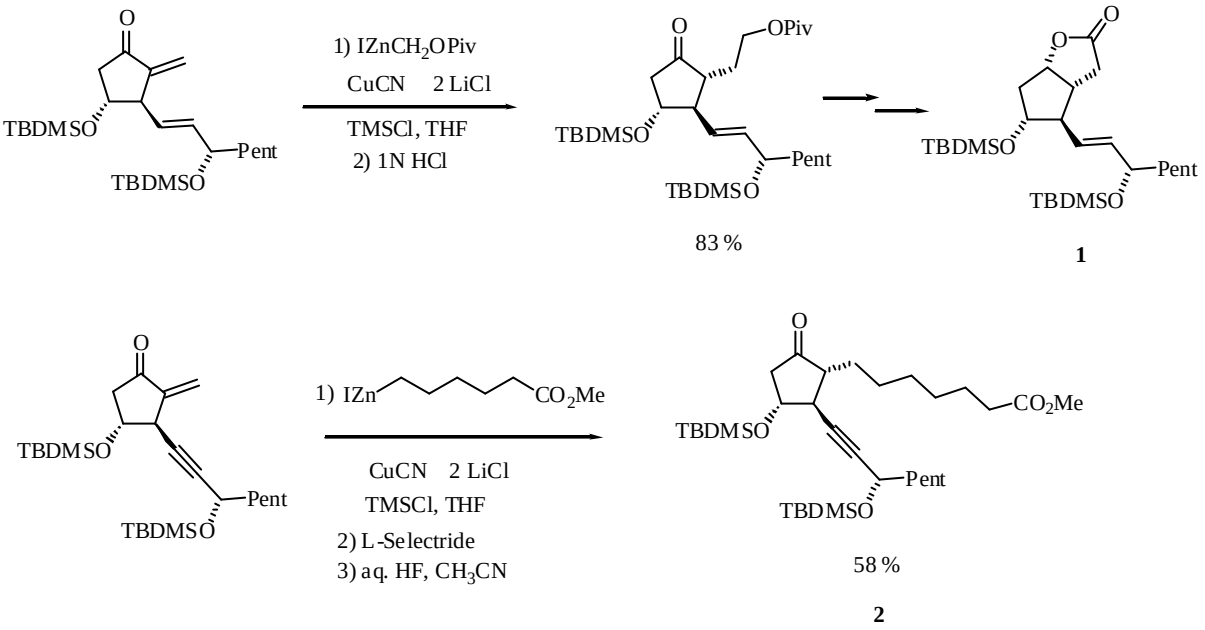
The vast majority of experimental protocols for the preparation of organocopper complexes involve the transmetalation process from other organometallic species. This places a limitation in the functional groups that can be present in the molecule, depending on the precursor of choice. The search for a method that avoids the transmetalation step, allowing the preparation of organocoppers bearing any kind of functionalities by direct halogen-copper exchange reaction, was considered to be of a remarkable synthetic utility and was therefore attempted.

1.1 Organozinc reagents

With the synthesis of diethylzinc in 1849, E. Frankland lay the foundation stone for modern organometallic chemistry.[1] However, organomagnesium[2] and organolithium[3] reagents were the first reagents to dominate this branch of organic chemistry. Although almost ignored for more than 100 years after their discovery, organozinc compounds are today one of the most useful class of organometallic reagents, due to their easy preparation and higher functional group

[1] a) Frankland, E. *Liebigs Ann. Chem.* **1848-49**, *71*, 171. b) Frankland, E. *J. Chem. Soc.* **1848-49**, *2*, 263.
[2] Grignard, V. *Compt. Rend.* **1900**, *130*, 1322.
[3] a) Schlenk, W.; Holtz, J. *Chem. Ber.* **1917**, *50*, 262. b) Ziegler, K.; Colonius, H. *Liebigs Ann. Chem.* **1930**, *479*, 135.

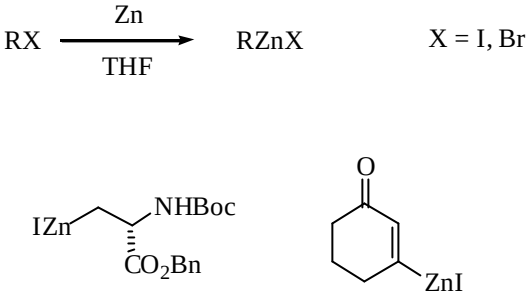
compatibility in comparison with organolithium and Grignard reagents. Furthermore, their excellent reactivity in the presence of the appropriate catalyst makes them a very powerful tool for natural product synthesis, as illustrated in the preparation of prostaglandin intermediates **1** and **2**[4] (Scheme 1).



Scheme 1

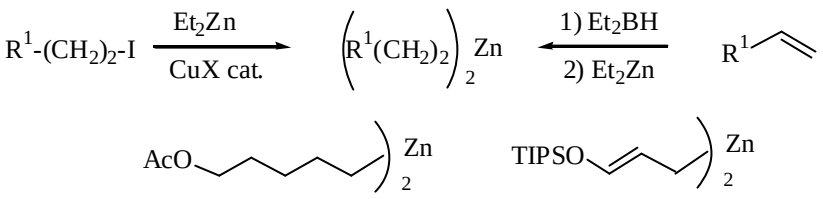
There are three main classes of organozinc compounds:[5] organozinc halides (RZnX), diorganozincs (R_2Zn) and lithium or magnesium zincates. Organozinc halides are readily available by the direct insertion of zinc dust into organic halides[6] (Scheme 2).

[4] a) Miyaji, K.; Ohara, Y.; Miyauchi, Y.; Tsuruda, T.; Arai, K. *Tetrahedron Lett*. **1993**, *34*, 5597. b) Yoshino, T.; Okamoto, S.; Sato, F. *J. Org. Chem.* **1991**, *56*, 3205. c) Koga, M.; Fujii, T.; Tanaka, T. *Tetrahedron* **1995**, *51*, 5529.
[5] Knochel, P.; Jones, P. *Organozinc Reagents. A Practical Approach*, Oxford University Press, **1999**.
[6] a) Berk, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053; b) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, A.; Reddy, C. K. *Angew. Chem.* **1997**, *109*, 1603; *Angew. Chem. Int. Ed*. **1997**, *36*, 1496. c) Rottändler, M.; Knochel, P. *Tetrahedron Lett*. **1997**, *38*, 1749. d) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.



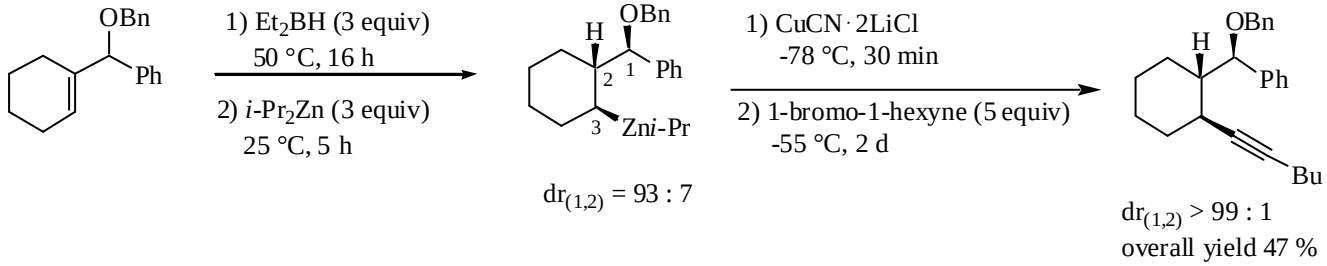
Scheme 2

Diorganozinc reagents require different methods of preparation, like iodine-zinc and boron-zinc exchange.[7] These methods are applicable to the formation of primary and secondary diorganozinc species[8] (Scheme 3).



Scheme 3

Remarkably, by using *i*-Pr_2Zn, configurationally defined secondary dialkylzinc reagents have been prepared[7c] (Scheme 4).



$dr_{(1,2)}$ = 93 : 7

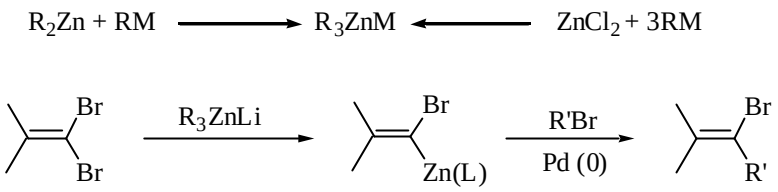
$dr_{(1,2)}$ > 99 : 1
overall yield 47 %

Scheme 4

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

[8] a) Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 9007. b) Devasagayaraj, A.; Schwink, L.; Knochel, P. *J. Org. Chem.* **1995**, *60*, 3311.

Diorganozincs display enhanced chemical reactivity compared to alkylzinc halides, but even more reactive are lithium or magnesium zincates, which are readily prepared by transmetalation reactions from the corresponding magnesium or lithium reagents and are well suited to halogen-zinc exchange reactions[9] (Scheme 5).



Scheme 5

1.2 Uncatalysed reactions of zinc organometallics

1.2.1 Aminomethylation

In contrast with organolithium and Grignard reagents, organozincs have a relatively covalent carbon-metal bond, resulting in their more moderate reactivity than that of organometallics containing a more polar carbon-metal bond. Only reactive classes of organozinc reagents like allylic zinc halides[10] and zinc enolates[11] efficiently undergo additions to carbonyl compounds. On the other hand, a few classes of highly reactive electrophilic reagents directly react with zinc organometallics, among them immonium salts. Iminium salts are important intermediates in organic synthesis[12] and aminomethylation is a transformation which has been performed with various immonium salts[13] or iminium salt precursors.[14] The reaction of these intermediates with functionalised organozinc reagents was first reported by *Saidi*,[15] who performed a three component aminoalkylation of aldehydes promoted by lithium perchlorate. In this way *N*,*N*-dialkylamino esters are obtained in good to moderate yields (Scheme 6).

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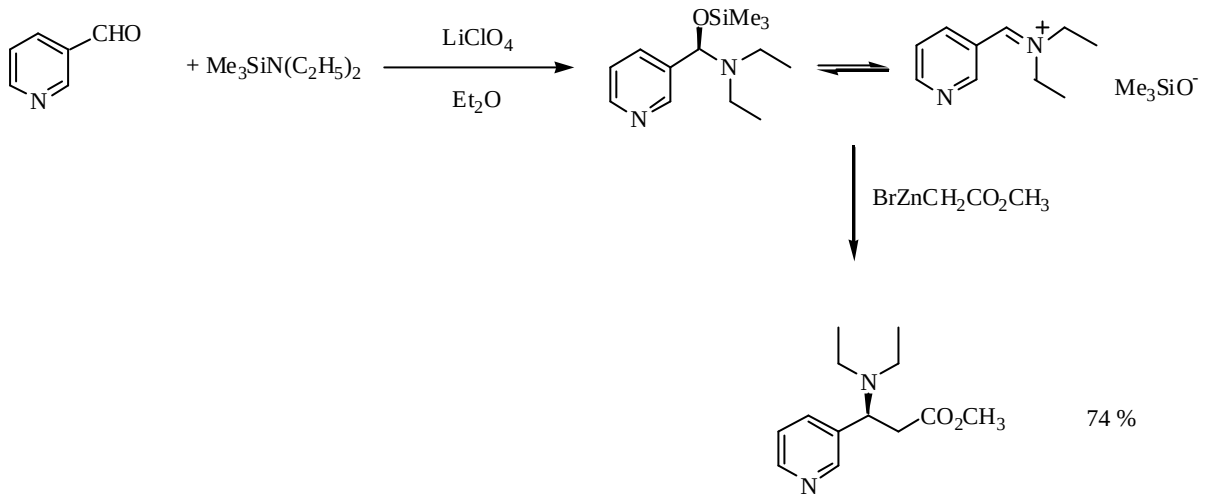
[9] Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am Chem. Soc.* **1996**, *118*, 8733.
[10] a) Miginiac, L. *The chemistry of the metal-carbon bond* (ed. F.R. Harvley and S. Patai), Wiley, New York, **1985**, Vol.3, pp. 99-141. b) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1973**, *52*, 214.
[11] Fürstner, A. *Synthesis* **1989**, 571.
[12] a) Jung, M. E. *Comprehensive Organic Synthesis* (ed. B. Trost and I. Fleming), Pergamon Press, Oxford, **1991**, Vol.2, p. 893. b) Henry, K. J. jr.; Grieco, P. A. *J. Chem. Soc. Chem.Commun.* **1993**, 510. c) Grieco, P. A.; Moher, E. D. *Tetrahedron Lett.* **1993**, *34*, 5567.
[13] For a review see : Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *110*, 1044.
[14] Katritzky, A. R.; Jiang, J.; Urogdi, L. *Tetrahedron Lett.* **1989**, *30*, 3303.
[15] Saidi, M.; Khalaji. H. R.; Ipaktschi, J. *J. Chem. Soc. Perkin Trans.1* **1997**, 1983.

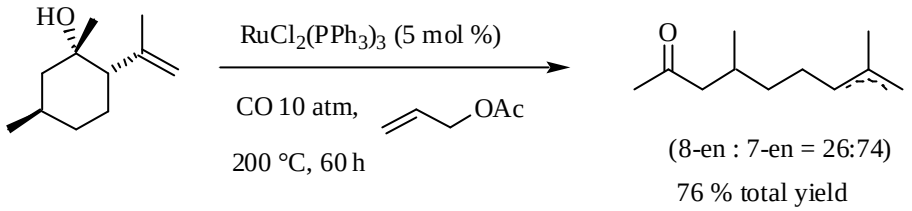


Scheme 6

1.2.2 Fragmentation of homoallylic zinc alcoholates

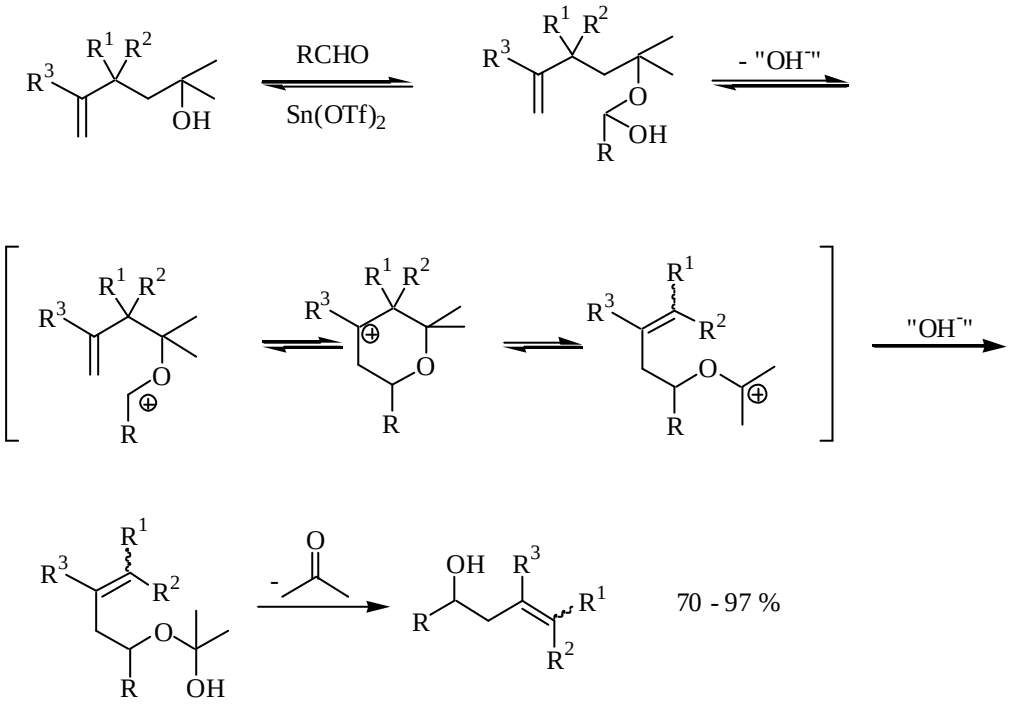
Transition metal-catalysed organic reactions involving the cleavage of C-C single bonds have recently attracted much attention.[16] Although the cleavage is energetically unfavourable, various unique catalytic transformations including ring-expansion, fragmentation and coupling with another molecule[17] can be realised when appropriately designed. Utilising the cleavage to form M–C species and ketones (or aldehydes), Pd-catalysed ring-opening reactions of cyclic allylic carbonates,[18] cyclobutanols,[19] and cyclopropanols[20] have been reported. The driving force of these reactions originates from the release of ring strain or the formation of a relatively stable π-allylmetal intermediate. *Kondo* developed a Ru-catalysed fragmentation of homoallylic alcohols[21] which constitutes the first example of catalytic deallylation of tertiary homoallylic alcohols via selective cleavage of a C-C bond (Scheme 7).

[16] For a review see: Crabtree, R. H. *Angew. Chem. Int. Ed.* **1999**, *111*, 918.
[17] Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.
[18] Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem. Int. Ed.* **1997**, *36*, 2352.
[19] Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2000**, *122*, 12049.
[20] Park, S. -B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147.
[21] Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587.



Scheme 7

The development and use of allylic organometallic reagents has been an underlying theme of modern organic synthesis.[22] *Nokami* described an allyl transfer reaction of homoallylic alcohols catalysed by tin(II) triflate[23] which corresponds to a conceptually new allylation of aldehydes. In this case tin(II) triflate does not react to form an allylic tin compound but simply assists the formation of the carbocation through hemiacetalization of the initial aldehyde (Scheme 8).

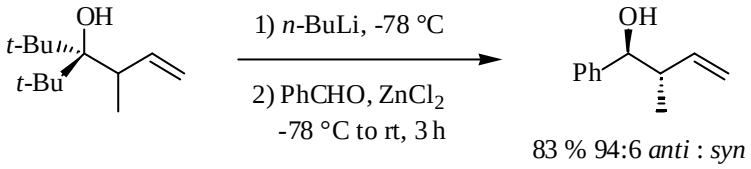


Scheme 8

Despite the plethora of methods which are currently available for the introduction of allylic moieties into complex molecules, several problems remain, especially that of contamination of the products with the Wurtz-coupling adduct. It has been shown by *Knochel* that sterically hindered homoallylic zinc alcoholates undergo a smooth fragmentation reaction providing highly

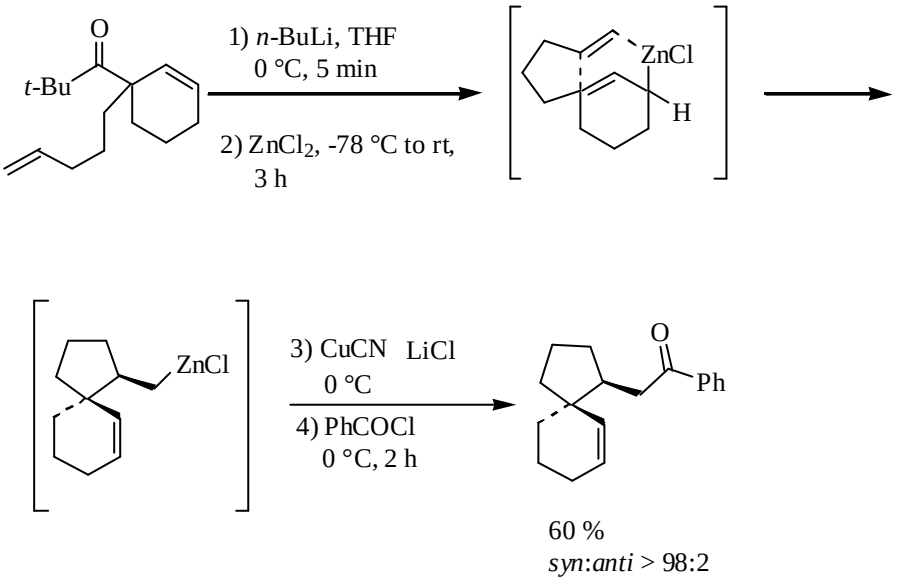
[22] Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
[23] Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609.

substituted allylic zinc compounds with the absence of formation of any homocoupling product.[24] This methodology has also revealed excellent stereocontrol in the subsequent reaction with aldehydes (Scheme 9).



Scheme 9

A new application of homoallylic zinc alcoholates for the preparation of cyclic allylzinc reagents and the performance of a zinc-mediated ene cyclisation have also been described (Scheme 10). [25]



Scheme 10

More recently, *Nokami* developed the first highly enantioselective crotylation of aldehydes via an allyl transfer reaction from a chiral crotyl donor,[26] but attempts to apply this concept to an asymmetric allylation of aldehydes gave only moderate success.

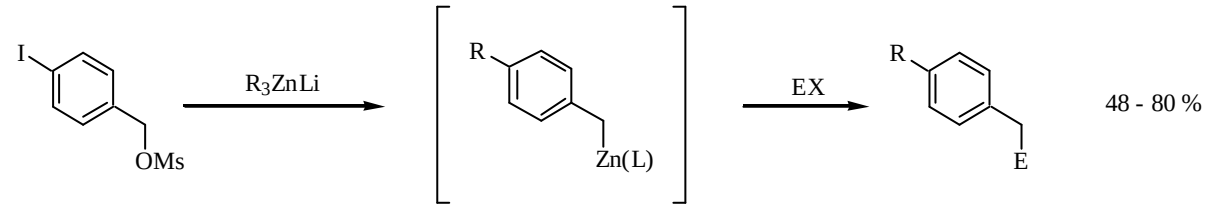
---

[24] a) Jones, P.; Knochel, P. *Chem. Commun.* **1998**, 2407. b) Jones, P.; Millot, N.; Knochel, P. *Chem. Commun.* **1998**, 2405. c) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186.
[25] Millot, N.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7779.
[26] Nokami, J.; Masanori, O.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

1.2.3 Generation of benzylic zinc reagents

Benzylic organometallics are important intermediates in the synthesis of polyfunctional molecules of pharmaceutical interest.[27] Although several methods are available for the preparation of benzylic lithium and magnesium compounds,[28] these reactions are all complicated by the formation of homocoupling products. Benzylic zinc reagents prepared by the direct insertion of zinc dust are obtained in a more straightforward fashion and the formation of Wurtz-coupling products is minimized in many cases.[6a] However, where electron-rich benzylic halides are used for the preparation of benzylic zinc reagents, the formation of Wurtz-coupling is a serious side-reaction.[29] This is due to the radical nature of the reaction of a metal like magnesium or zinc with a benzylic halide. *Knochel et al.* described the preparation of secondary alkyl and benzylic zinc bromides using activated zinc metal deposited on titanium oxide.[30] This method minimizes the amount of Wurtz-coupling side product to less than 1 %, but the study was not comprehensive and no functionalised secondary zinc compounds were reported.

A new method for preparing benzylic zinc reagents has been developed by *Harada* and is based on the homologation of triorganozincates.[31] Arylzincates undergo facile 1,2-migration at low temperatures to give benzylzinc reagents which can be utilized in reactions with a variety of electrophiles (Scheme 11).



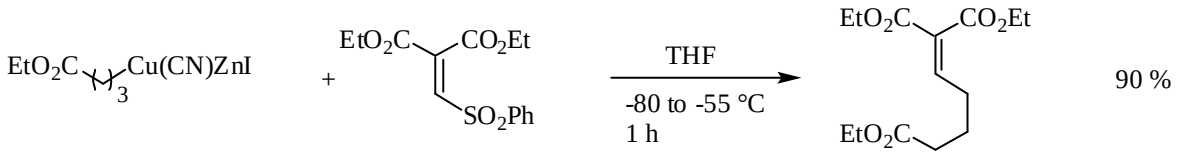
Scheme 11

[27] Lednicer, D.; Mitscher, L. A. *Organic Chemistry of Drug Synthesis* Wiley, New York, **1977**.
[28] a) Raston, C. L.; Salem, G. *J. Chem. Soc. Chem. Commun.* **1984,** 1702. b) Harvey, S.; Junk, P. C.; Raston; C. L.; Salem, G. *J. Org. Chem.* **1988**, *53*, 3134. c) Bogdanovich, B. *Acc. Chem. Res.* **1988**, *21*, 261.
[29] Knochel, P.; Singer, R. B. *Chem. Rev.* **1993**, *93*, 2117.
[30] Stadtmüller, H.; Greve, B.; Lennick, K.; Chair, A.; Knochel, P. *Synthesis* **1995**, 70.
[31] Harada, T.; Kaneko, T.; Fujiwara, T.; Oku, A. *J. Org. Chem.* **1997**, *62*, 8966.

Also in this case, due to the presence of the highly reactive triorganozincate, no investigation into functional group tolerance has been carried out.

1.3 Transition metal catalysed reactions of zinc organometallics

The low reactivity of zinc organometallic reagents can be increased by adding a transition metal catalyst. The covalent character of the zinc-carbon bond allows these reagents to undergo transmetalation reactions with a wide variety of transition metal salts,[32] producing intermediate transition metal organometallics which display enhanced reactivity towards many electrophiles due to the presence of *d*-orbitals. The moderate activity of zinc organometallics is an essential factor for the success of these transmetalations, since it prevents the transfer of several organic groups to the same metal centre and therefore reduces the possible decomposition pathways. Of special interest for synthetic application is the transmetalation of organozincs to give mixed copper-zinc reagents represented as RCu(CN)ZnX. The resulting copper species display a similar, but somewhat reduced, reactivity compared with organocuprates prepared from magnesium or lithium organometallics.[33] On the other hand the better functional group tolerance displayed by organozinc reagents, makes them particularly attractive and versatile building blocks, for example in cross-coupling reactions (Scheme 12).[34, 35]

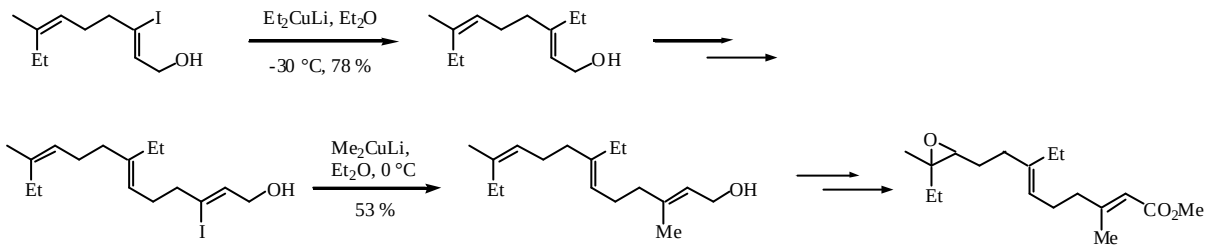


Scheme 12

[32] For reviews see: a) Erdik, E. *Tetrahedron* **1987**, *43*, 2203. b) Knochel, P.; Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
[33] a) Posner, G. *Org. React.* **1972**, *19*, 1. b) Lipshutz, B.H. *Synthesis* **1987**, 325. c) Lipshutz, B.H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. d) Posner, G. *Org. React.* **1975**, *22*, 253.
[34] Tucker, C. E.; Knochel, P. *Synthesis* **1993**, 530.
[35] Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *78*, 2387.

1.4 Organocopper reagents

Gilman and *Woods* published a synthesis of methylcopper in 1943,[36] and in 1952 *Gilman et al.* reported for the first time the preparation of organocuprates (Gilman reagents).[37] Soon after, the use of copper salts as catalysts in organometallic reactions became popular. *House et al.* demonstrated the intermediacy of organocopper species in copper-catalyzed conjugated addition reactions.[38] It was soon shown that organocuprates react in a synthetically useful manner with a range of alkyl and aryl halides.[39] In 1968 *Corey et al.* described the synthesis of *Cecropia* juvenile hormone using this methodology,[40] demonstrating the value of stoichiometric organocopper reagents for the synthesis of complex natural products (Scheme 13).

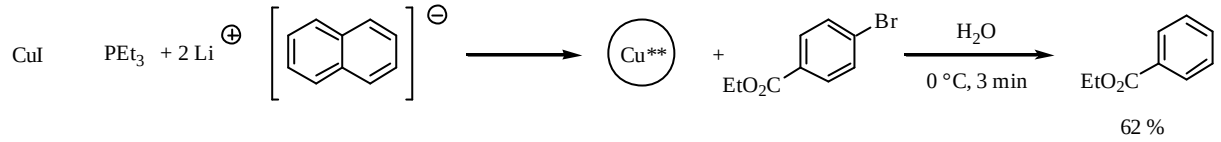


Scheme 13

Since then, the development of organocopper reagents has had an enormous impact on practically every aspect of organic synthesis.[41] Organocopper complexes are correlated with such major pathways for carbon-carbon bond formation as conjugate additions to α,β-unsaturated carbonyl compounds, nucleophilic displacement of halides,[42] sulfonates[43] and allylic acetates,[44] epoxide ring openings[45] and addition to acetylenes.[46] However, the vast majority of experimental

[36] Gilman, H.; Woods, L. A. *J. Am. Chem. Soc.* **1943**, *65*, 435.
[37] Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.
[38] House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128.
[39] a) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911. b) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615. c) Whitesides, G. M.; Fischer, W. F.; San Filippo, J.; Bashe, R. W.; House, O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.
[40] Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618.
[41] For a review see: Wipf, P. *Synthesis* **1993**, 537.
[42] a) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888. b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
[43] Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.
[44] Anderson, R. J.; Henrick, C. A.; Siddal, J. B.; Zurflüh, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 5379.
[45] Johnson, C. R.; Herr, R. W.; Wieland, D. M. *J. Org. Chem.* **1973**, *38*, 4263.
[46] Normant, J. F.; Cahiez, G.; Bourgain, M.; Chuit, C.; Villieras, J. *J. Bull. Chim. Soc. Fr.* **1974**, 1656.

protocols for the preparation of organocopper complexes involve organolithium or Grignard reagents as intermediates.[47,48] This route places an obvious limitation on the types of functionalities which are compatible with the preparative procedure. Major improvements have been achieved in the direct synthesis of copper organometallics from halides and highly activated copper metal. Most notably *Rieke* and coworkers have developed several reactive forms of zerovalent copper in combination with additives that allow the direct use of functionalised alkyl halides,[49] allylic chorides and acetates[50] and aryl, vinyl and alkynyl halides (Scheme 14).[51]



Scheme 14

Other remarkable advances have been made by means of organozinc reagents and via vinylzirconium intermediates and transmetalation using higher order cyanocuprates.[52] Quite surprisingly, the formation of functionalised organocopper reagents via halogen-metal exchange has not yet been extensively studied.

The first iodine-copper exchange was reported by *Corey* and *Posner*,[40b] who observed that lithium dialkylcuprates react with aryl iodides leading to the expected cross-coupling product and a competitive halogen-metal exchange reaction. More recently, *Kondo* and *Sakamoto* described the use of lithium dimethylcuprate, which allows the performance of an iodine-copper exchange on a functionalised aryl iodide bearing an ester group.[53] An excess of the cuprate is required to quench the methyl iodide formed during the exchange reaction (Scheme 15).

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[47] a) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents* Wiley, New York, **1980**. b) Yamamoto, Y. *Angew. Chem. Int. Ed.* **1986**, *25*, 947. c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. d) Lipshutz, B. H. *Synlett* **1991**, 119.

[48] a) Nakamura, E. *Synlett* **1991**, 539. b) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225. c) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983.

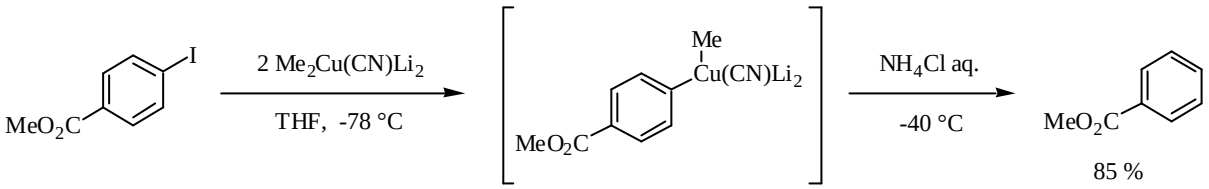
[49] a) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5280. b) Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5056. c) Wehmeyer, R. M.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 565.

[50] Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* **1992**, *114*, 5110.

[51] Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1988**, *53*, 4482.

[52] a) Lipshutz, B. H.; Keil, R. *J. Am. Chem. Soc.* **1992**, *114*, 7919. b) Venanzi, L. M.; Lehmann, R.; Keil, R.; Lipshutz, B. H. *Tetrahedron Lett.* **1992**, *33*, 5857.

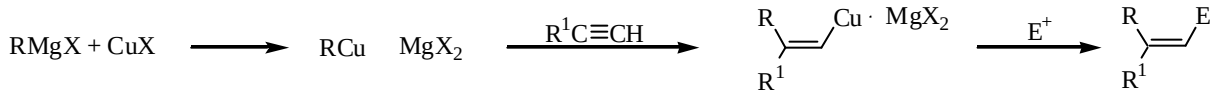
[53] Kondo, Y.; Matsudaira, T.; Sato, J.; Muraka, N.; Sakamoto, T. *Angew. Chem.* **1996**, *108*, 818; *Int. Ed.* **1996**, *35*, 736.



Scheme 15

1.4.1 Vinylic organocuprates

The addition of organocopper reagents to terminal alkynes and to acetylene represents an efficient way to synthesize vinylcopper reagents with a given geometry.[54] The addition proceeds in a Markownikov way in a *syn*-specific fashion. The organic cuprate is normally prepared from a Grignard or a lithium reagent and a copper(I) salt (Scheme 16).

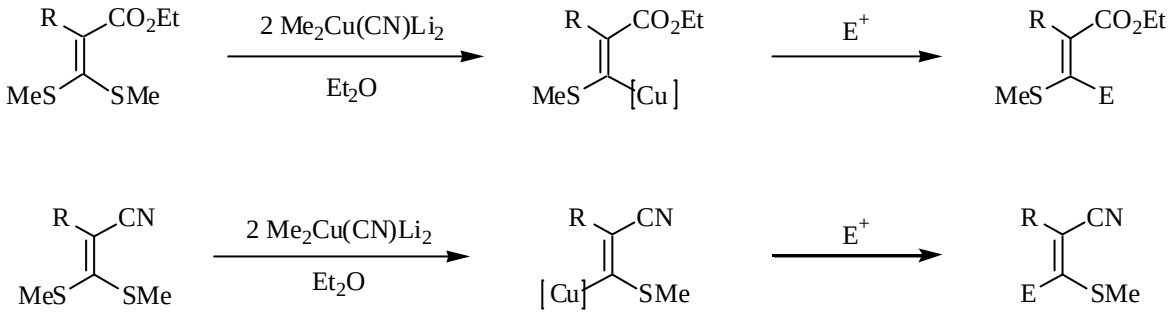


Scheme 16

Normant and *Alexakis*[55] extensively studied this methodology and its application in the synthesis of conjugated dienes, allylic thioethers and allylic amides. *Cahiez* and *Knochel* prepared polyfunctional and stereochemically pure (E) or (Z) alkenylcopper reagents by carbocupration of terminal alkynes and reacted with alkylidenemalonates.[56] More recently a variety of metalated vinylcuprate intermediates resulting from silyl- or stannylcupration of silyl- and tin-containing acetylenes were obtained, affording interesting functionalised polymetalated olefins.[57] A different approach was developed by *Hosomi*,[58] who reported the reductive cupration of ketene dithioacetals as a way to generate functionalised (Z) and (E) vinylcopper reagents (Scheme 17).

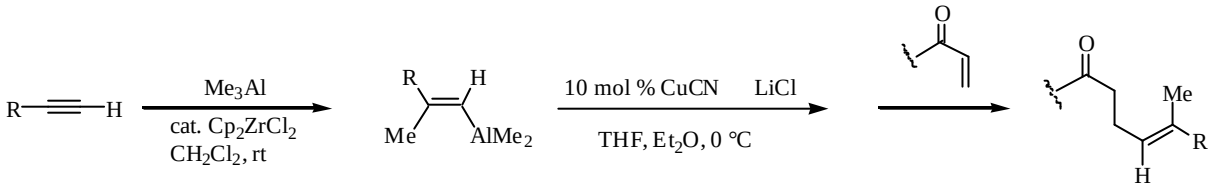
---

[54] Normant, J. F. *Organocopper Reagents. A Practical Approach* (ed. R.J.K. Taylor), Oxford Unversity Press, **1994**, cp.11, p. 237.
[55] a) Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 3851. b) Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1982**, *23*, 5151. c) Germon, C.; Alexakis, A.; Normant, J. F. *Synthesis* **1984**, 40. d) Germon, C.; Alexakis, A.; Normant, J. F. *Synthesis* **1984**, 43.
[56] Cahiez, G.; Venegas, P.; Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Chem. Soc. Chem. Commun.* **1992**, 1406.
[57] Cuadrado, P.; González-Nogal, A.; Sánchez, A. *J. Org. Chem.* **2001**, *66*, 1961.
[58] Hojo, M.; Harada, H.; Watanabe, C.; Hosomi, A. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1495.



Scheme 17

A second way of preparing vinylic cuprates involves the carbometalation of an alkyne and a subsequent transmetalation to copper. Thus, vinylic stannanes,[59] tellurides[60] and zirconates[61] readily exchange their vinylic ligands for alkyl groups on copper. Vinylic alanes, formed via a Negishi-type carbometalation with Me_3Al/catalytic Cp_2ZrCl_2[62] have also been converted into mixed higher order cyanocuprates which transfer vinylic residues in a Michael sense to enones[63] (Scheme 18).



Scheme 18

A very recent and interesting application of vinylic cuprates has been reported by *Hall*,[64] who described the carbocupration of readily available alkynoate esters for the preparation of isomerically pure tetrasubstituted allylboronates, which were then employed for the enantioselective construction of quaternary carbon centres (Scheme 19).

---

[59] Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

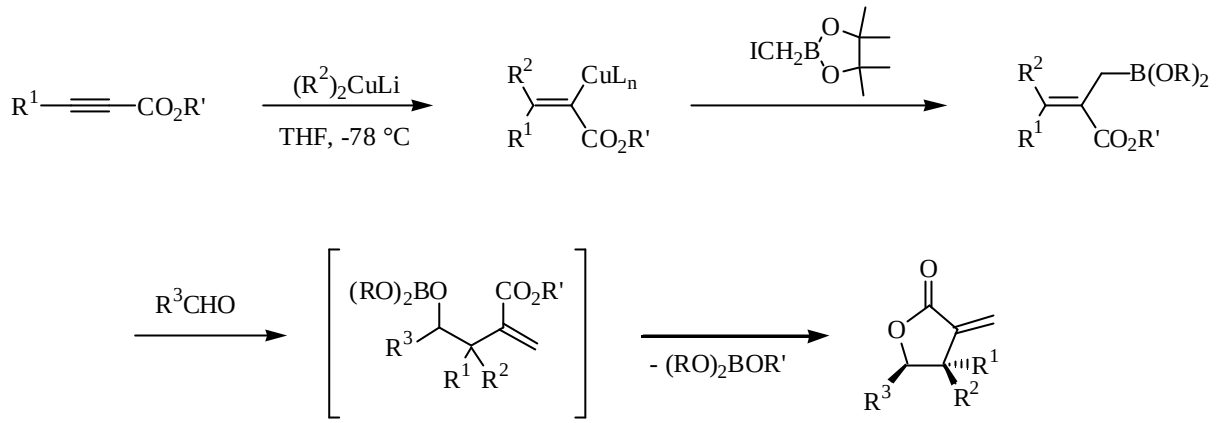
[60] a) Comasseto, J. V.; Berriel, J. N. *Synth. Commun.* **1990**, *20*, 1681. b) Moraes, D. N.; Barrientos-Astigarraga, R.E.; Castelani, P.; Comasseto, J. V *Tetrahedron* **2000**, *56*, 3327.

[61] a) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440. b) Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7741. c) Lipshutz, B. H.; Kato, K. *Tetrahedron Lett.* **1991**, *32*, 5647.

[62] Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333.

[63] a) Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425. b) Lipshutz, B. H.; Dimock, S. H. *J. Org. Chem.* **1991**, *56*, 5761.

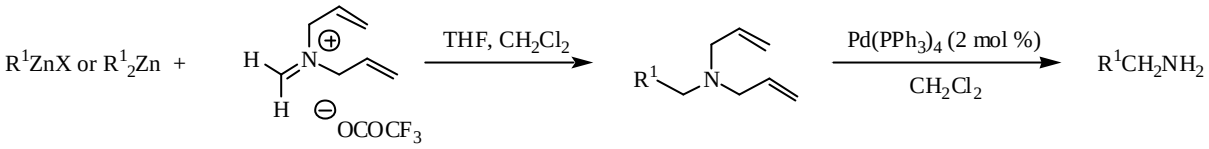
[64] Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898.


R1
CO2R'
(R2)2CuLi
THF, -78 °C
R2
CuLn
R1
CO2R'
ICH2B
O
O
R2
B(OR)2
R1
CO2R'
R3CHO
(RO)2BO
CO2R'
R3
R1
R2
- (RO)2BOR'
O
O
R1
R3
R2

Scheme 19

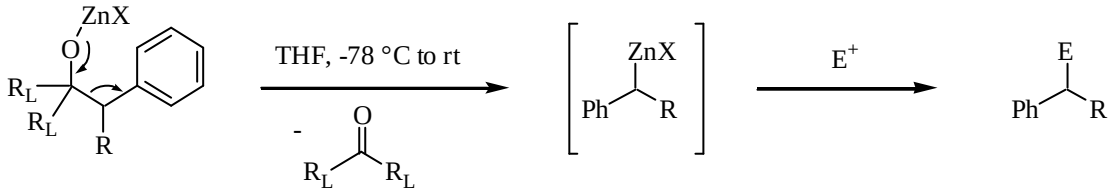
2. Objectives

The first project studied concerned the preparation of functionalised primary amines via aminomethylation of organozinc and Grignard reagents using immonium trifluoroacetates (Scheme 20).



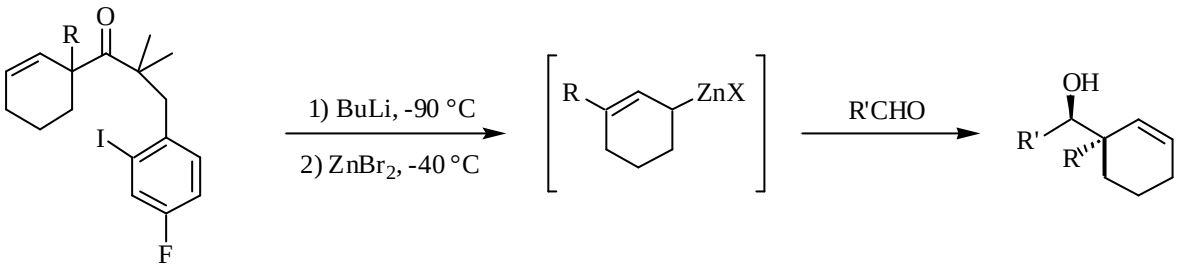
Scheme 20

Following the successful development of a new approach for the preparation of allylic zinc reagents based on the fragmentation of sterically hindered homoallylic alcohols[·], it was of interest to study a similar protocol for the generation of secondary benzylic zinc reagents via a fragmentation reaction (Scheme 21).



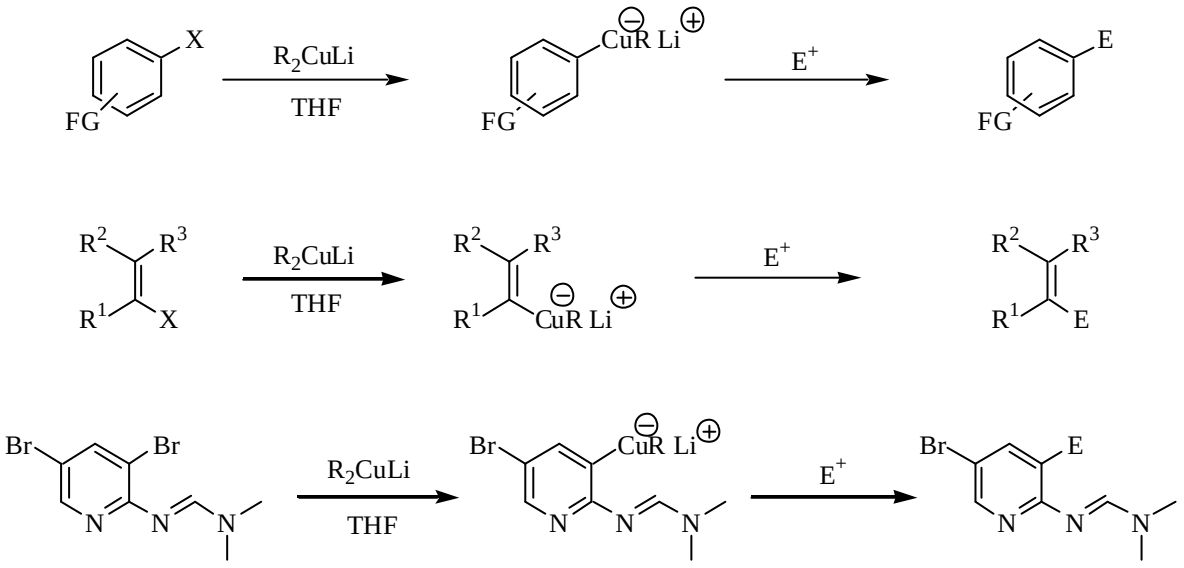
Scheme 21

The possibility of preparing allylic zinc reagents (eventually functionalised) via a cyclization-fragmentation reaction, and reacting these in a diastereoselective manner with aldehydes, was also explored (Scheme 22).



Scheme 22

A second project of particular interest was the generation of highly functionalised mixed cuprates via a halogen-copper exchange. Following the preparation of two new sterically hindered lithium dialkylcuprates (neopentyl and neophylcuprate), the halogen-copper exchange on functionalised arylic, vinylic and heterocyclic substrates was studied, in order to determine its range of applicability and in particular its functional group compatibility (Scheme 23).

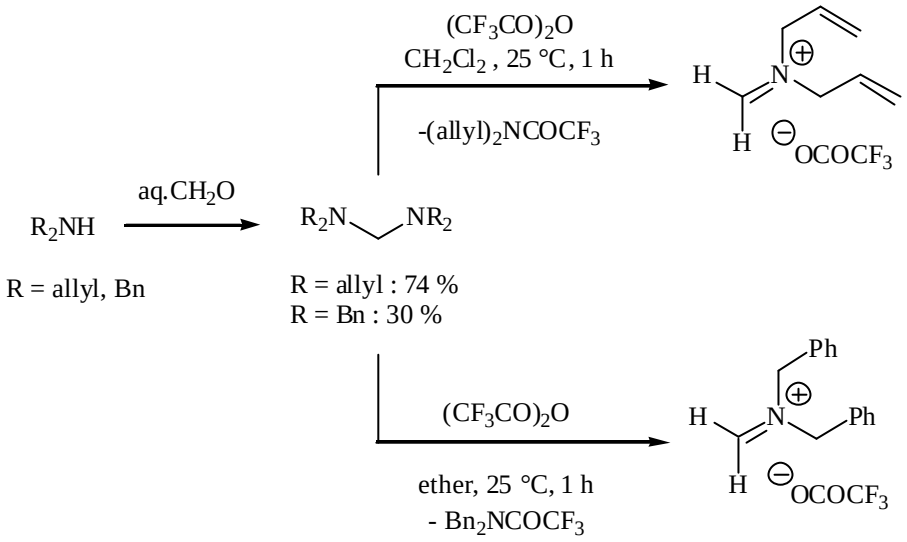


Scheme 23

Results and Discussion

1 Aminomethylation of Functionalised Organozinc Reagents and Grignard Reagents

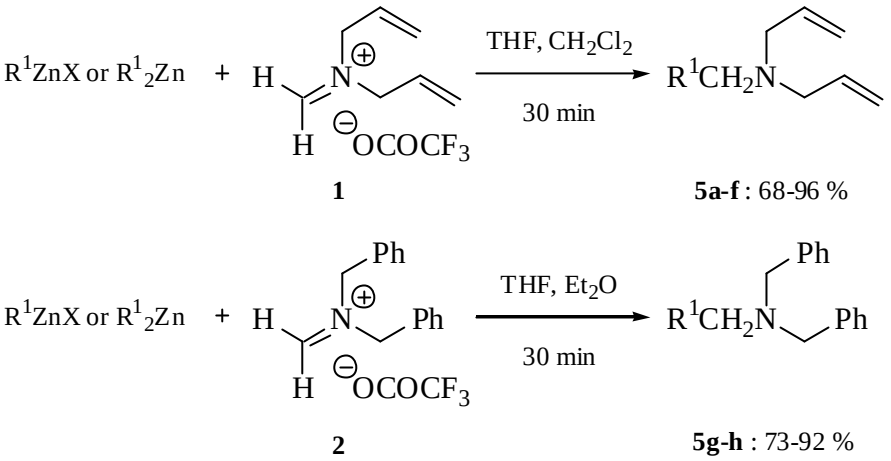
Among the various iminium salts known,[13,14] the allyl and benzyl moieties were chosen, as they could be removed to afford the desired aminomethylated products. The preparation of the immonium trifluoroacetates was based on the work of Tietze.[65] Thus, heating an aqueous solution of formaldehyde with diallylamine or dibenzylamine resulted in the formation of the aminals 3 and 4, in 74 % and 30 % yield respectively. The treatment of 3 in CH_2Cl_2 (25 °C, 1 h) or 4 in ether (25 °C, 1 h) with trifluoroacetic anhydride provided solutions of the immonium trifluorocetates 1 or 2 in essentially quantitative yields (Scheme 24).



Scheme 24

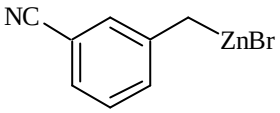
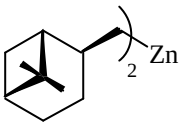
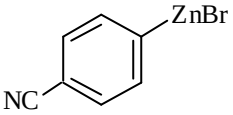
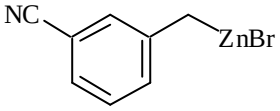
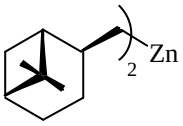
The immonium salts **1** and **2** were readily soluble in CH_2Cl_2/THF and ether/THF mixtures and rapidly reacted with various functionalised organozinc reagents (R^1ZnX or $R^1{}_2Zn$) providing the aminomethylated products **5a-h** (Scheme 25 and Table 1).

[65] Kinast, G. Tietze, L.-F. *Angew. Chem.* **1976**, *88*, 261; *Angew. Chem. Int. Ed.* **1976**, *15*, 239.


R1ZnX or R1 2Zn
+
H
N
H
OCOCF3
THF, CH2Cl2
30 min
R1CH2N
1
5a-f : 68-96 %
R1ZnX or R1 2Zn
+
Ph
H
N
Ph
H
OCOCF3
THF, Et2O
30 min
R1CH2N
Ph
2
5g-h : 73-92 %

Scheme 25

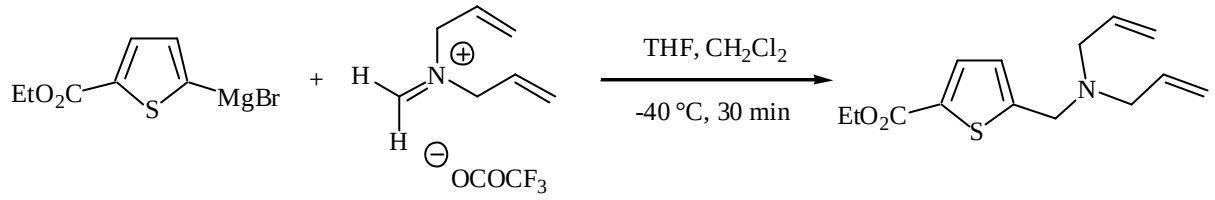
Table 1. Aminomethylated products **5a-h** obtained by reaction of organozinc halides or diorganozincs with the immonium salts **1** or **2**.

Entry	Organozinc reagent	Immonium salts **1** or **2**	Temperature (°C)	Product of type **5**	Yield (%)[a]
1		**1**	-78	**5a**	96
2	$NC(CH_2)_3ZnI$	**1**	25	**5b**	68
3	$EtO_2C(CH_2)_3ZnI$	**1**	25	**5c**	73
4	*c*-HexZnI	**1**	25	**5d**	83
5		**1**	25	**5e**	91
6		**1**	-78	**5f**	72
7		**2**	-78	**5g**	92
8		**2**	25	**5h**	73

[a]Isolated yield of analytically pure product.

Whereas arylzinc halides and benzylic zinc halides already underwent addition at -78 °C (entries 1 and 6), best results using alkylzinc halides were obtained when they were added at 25 °C. The reactions were always complete within 30 min. Ester group (entry 3) and cyano groups (entries 1, 2 and 6) were perfectly tolerated.

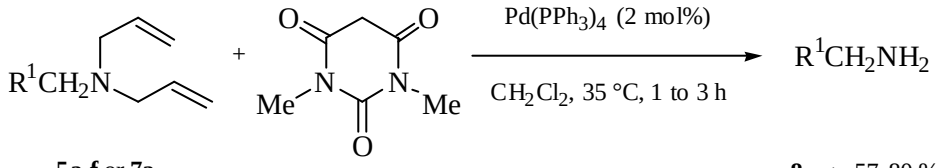
Interestingly, functionalised organomagnesium compounds like ethyl 5-bromo-2-thiophenecarboxylate, prepared by iodine-magnesium exchange,[66] reacted at low temperature with the immonium salt **1**, smoothly undergoing addition at -40 °C (Scheme 26).



6a **1** **7a** : 77 %

Scheme 26

The resulting *bis*-allylated amines could be deprotected according to the method of Guibé.[67] Thus, the reaction of diallylamines of type **7** with N,N´-dimethylbarbituric acid in presence of $Pd(PPh_3)_4$ (2 mol %) in CH_2Cl_2 at 35 °C produced within 1 to 3 h the primary amines **8a-g** in satisfactory yields (Scheme 4 and Table 2). Debenzylations of the amines **5g-h** were unsuccessful under a variety of hydrogenation conditions using Pearlman's catalyst and no other efficient deprotection was found.[68]

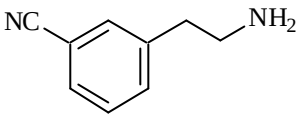
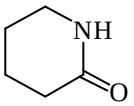
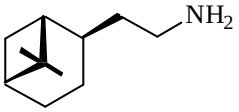
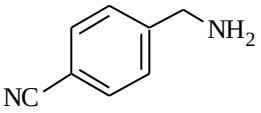
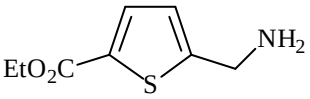


5a-f or **7a** **8a-g** : 57-80 %

Scheme 27

[66] Boymond, L; Rottändler, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *110*, 1801.
[67] Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109.
[68] Greene, T.W. *Protective Groups in Organic Synthesis, Third Edition*, Wiley, New York, **1999**.

Table 2. Deallylation of *bis*-allylamines **5** or **7a** using N,N´-dimethylbarbituric acid leading to primary amines **8a-g**.

Amine	Product of type **8**	Yield (%)[a]
5a	 **8a**	63
5b	$NC(CH_2)_4NH_2$ **8b**	59
5c	 **8c**	57
5e	 **8e**	74
5f	 **8f**	80
7a	 **8g**	60

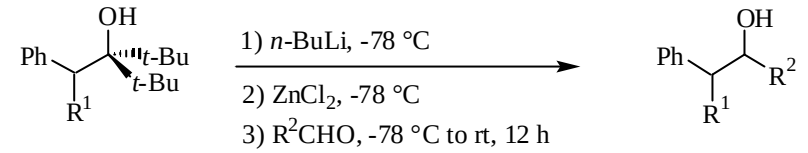
[a]Isolated yield of analytically pure product.

1.1 Summary

In summary, a range of functionalised primary amines were prepared in a two step sequence from organozinc and magnesium reagents via aminomethylation and selective desallylation.

2 Preparation of Benzylic Zinc Reagents via a Fragmentation Reaction

Based on the method recently developed by *Knochel et al.* for the preparation of allylic zinc reagents via a fragmentation reaction, a similar concept was applied to benzylic substrates. It was rationalized that the generation of a zinc alkoxide of a sterically hindered tertiary homobenzylic alcohol would result in decomposition to the ketone and a benzylic zinc reagent, which in the presence of a suitable electrophile could be utilized synthetically (Scheme 28).

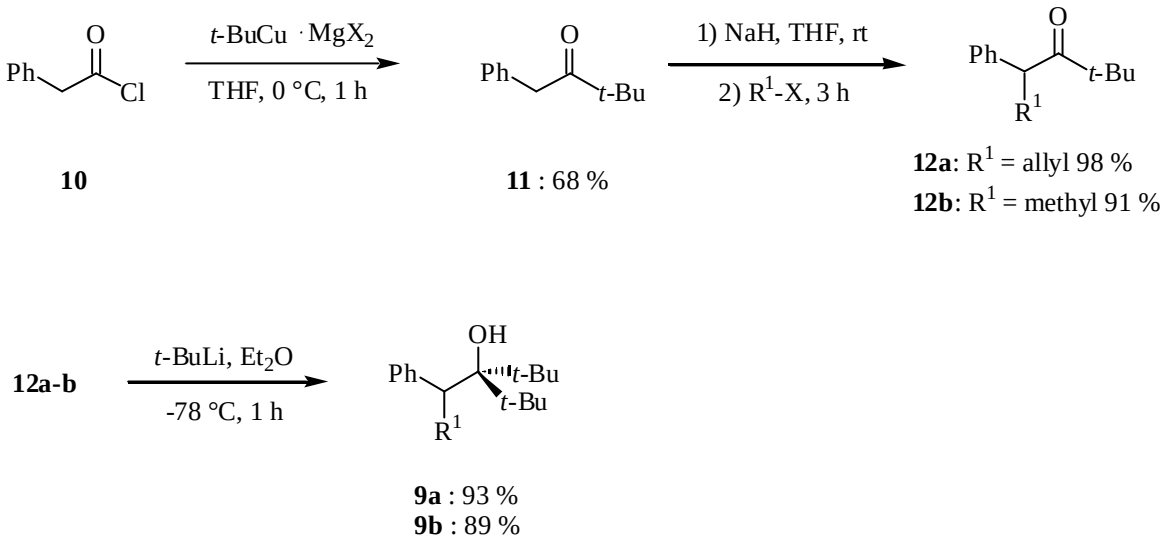


9a : R^1 = allyl
9b : R^1 = methyl

13a-i : 46-80 %

Scheme 28

The required homobenzylic alcohols **9** were readily prepared starting from commercially available phenylacetyl chloride **10**. First, reaction of the acid chloride **10** with *t*-$BuCuMgX_2$[33c] provided the ketone **11** in 68 % yield. Treatment of the ketone **11** with sodium hydride (rt, 1 h), followed by the addition of an electrophile (allyl bromide or methyl iodide), furnished, after a reaction time of 3 h, the expected alkylated products **12a** and **12b** in 98 % and 91 % yield respectively (Scheme 29). The ketones **12a** and **12b** were treated with *t*-BuLi at -78 °C for 1 h in diethyl ether, leading to the desired alcohols **9a** and **9b** in 93 % and 89 % yield. These alcohols were treated at -78 °C with *n*-BuLi (1.1 equiv) followed by the addition of a THF solution of zinc chloride (1.1 equiv) and subsequent addition of an aldehyde (1.1 equiv). The reaction mixture was allowed to reach rt within 12 h, leading to the expected homobenzylic alcohols **13a-i** in 46-80 % yield (Scheme 28 and Table 3).



10

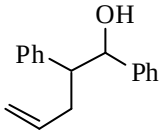
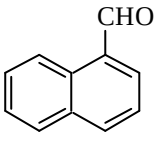
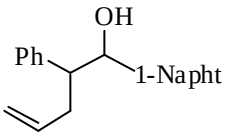
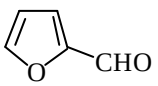
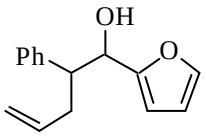
11 : 68 %

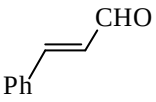
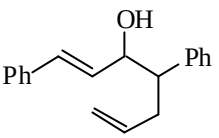
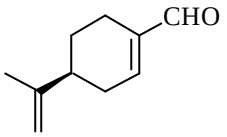
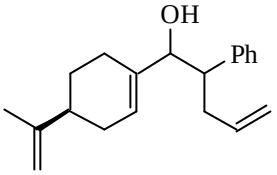
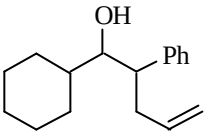
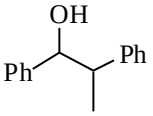
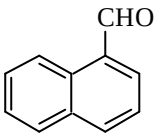
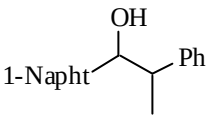
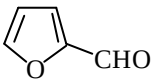
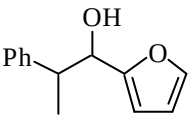
12a: R^1 = allyl 98 %
12b: R^1 = methyl 91 %

9a : 93 %
9b : 89 %

Scheme 29

Table 3. Homobenzylic alcohols **13a-j** prepared by the fragmentation of zinc alcoholates obtained from the corresponding homobenzylic alcohols **9a-b** and subsequent reaction with an aldehyde.

Entry	Alcohol of type **9**	Aldehyde	Product of type **13**	Diastereomeric ratio *syn* : *anti*	Yield (%)[a]
1	**9a**	PhCHO	 **13a**	48 : 52	74
2	**9a**		 **13b**	48 : 52	63
3	**9a**		 **13c**	32 : 68	73

4	**9a**		 **13d**	45 : 55	46
5	**9a**		 **13e**	40 : 60	70
6	**9a**	*c*-HexCHO	 **13f**	45 : 55	60
7	**9b**	PhCHO	 **13g**	43 : 57	73
8	**9b**		 **13h**	36 : 64	80
9	**9b**		 **13j**	40 : 60	66

[a]Isolated yield of analytically pure product.

Aromatic aldehydes like benzaldehyde (entries 1 and 7), 1-naphthaldehyde (entries 2 and 8) and furfural (entries 3 and 9) reacted rapidly, to give the alcohols as a mixture of diastereoisomers. The reaction also proceeded with α,β-unsaturated aldehydes such as *trans*-cinnamaldehyde (entry 4) and perillaldehyde (entry 5). Finally, the aliphatic aldehyde cyclohexanecarboxaldehyde also gave the expected alcohol **13f** in 60 % yield (entry 6).

All the products were obtained as an almost 1:1 mixture of the *syn* and *anti* diastereomers, indicating that little sterochemical control is involved in the reaction mechanism.

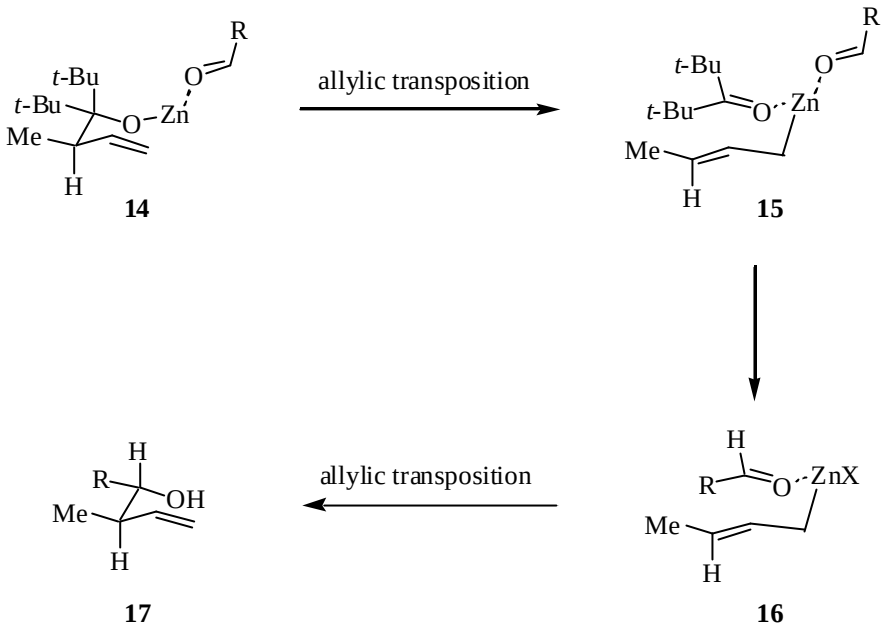
2.1 Summary

A new preparation of benzylic zinc reagents via the fragmentation of sterically hindered homobenzylic zinc alcoholates was developed. This method completely avoids the formation of Wurtz byproducts. The starting homobenzylic alcohols are readily prepared, making this an efficient method, complementary to other known procedures.

3 Preparation of Allylic Zinc Reagents via a Cyclization-Fragmentation Reaction

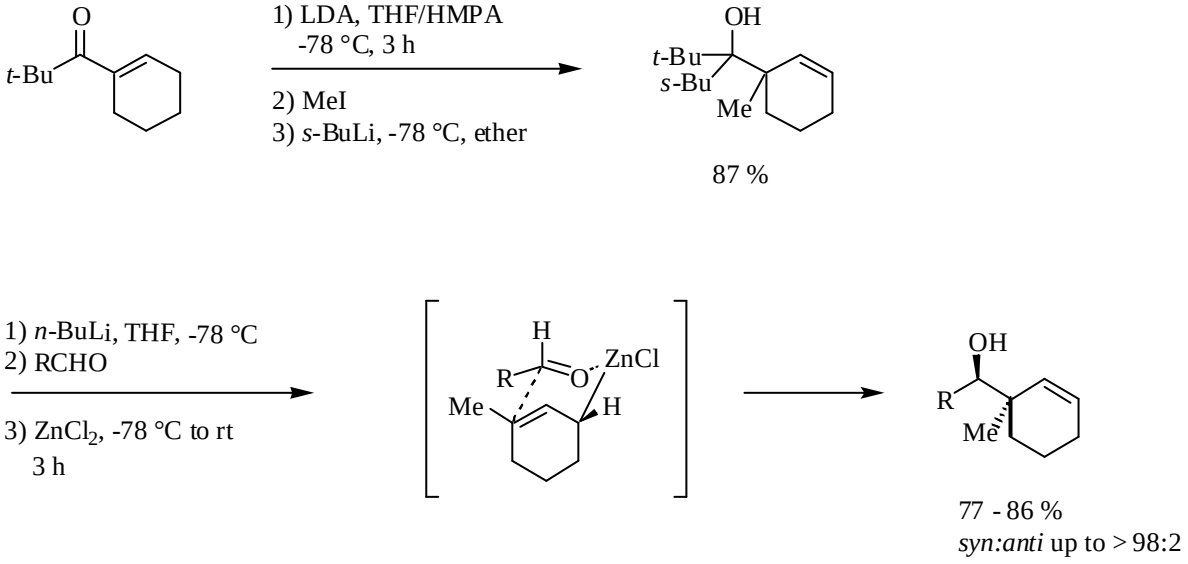
Although the use of allylic organometallics for carbon-carbon bond formation in stereoselective synthesis has received much attention over the past decades,[22] several problems associated with the generation of allyl organometallic reagents still remain unresolved and the search for new methodologies continues to be a matter of investigation. According to the method for the preparation of masked allylic zinc reagents developed by *Knochel et al.*, treatment of a sterically hindered homoallylic alcohol first with *n*-BuLi and then with zinc chloride was known to give the zinc alkoxide which fragmented *in situ* to generate an allyl zinc reagent.[24b] Addition of an electrophile such as a ketone or an aldehyde led to the expected addition products in very good yields and, in the case of substituted allylic organozincs, with excellent regio- and diastereoselectivities. The proposed mechanism involves a double allylic transposition: generation of the zinc alkoxide **14** results in a cyclic six-member ring intermediate where the zinc is complexed to the reacting carbonyl compound (Scheme 30). Allylic transposition gives rise to a zinc reagent **15** complexed to the parent di(*tert*-butyl)ketone and the carbonyl oxygen atom of the aldehyde, the zinc reagent bearing solely a *trans*-configuration. At -78 °C this species is stable and undergoes no isomerisation.[69] Owing to the complexation of the reacting partner with the zinc, the formation of a new six-centred intermediate **16** is possible, whereby all the substituents lie in a pseudo-equatorial position; allylic transposition then gives rise to the product **17**, predominantly as the *anti*-diastereomer.

[69] Bis (3-Methylallyl)zinc is known to be a rapidly isomering system at room temperature, hence explaining the 1:1 *anti*:*syn* selectivity in addition to aldehydes. See Benn, R.; Hoffmann, E. G.; Lehmkuhl, H.; Nehl, H. *J. Organomet. Chem.* **1978**, *146*, 103.



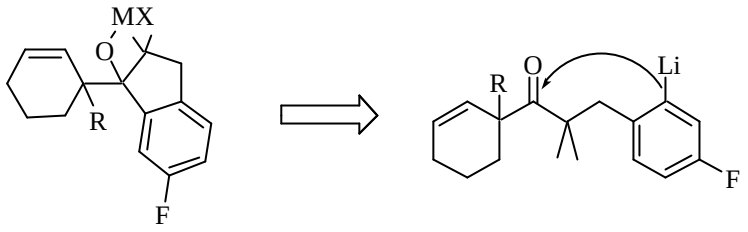
Scheme 30

In a similar way, cyclic homoallylic zinc alcoholates underwent a fragmentation reaction in the presence of zinc salts affording highly substituted cyclic allylzinc reagents which could be trapped with a range of aldehydes in satisfactory yields and excellent diastereoselectivities (up to > 98:2, Scheme 31).



Scheme 31

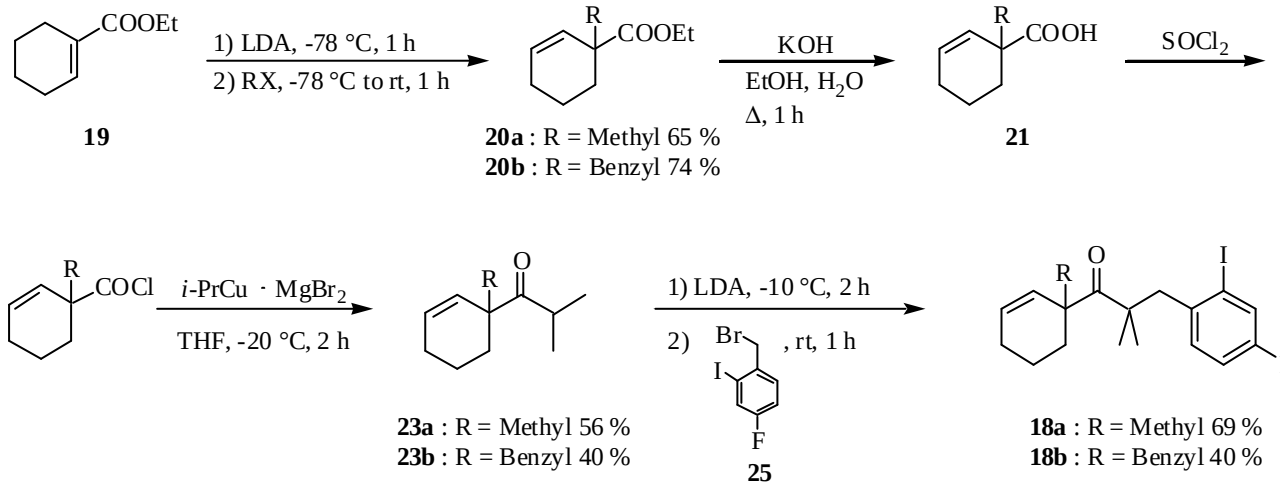
In order to explore the possibility of generating functionalised substituted allylic zinc reagents, addition of *s*- or *t*-BuLi had to be avoided. Therefore, a new sterically hindered cyclic homoallylic alcoholate such as **26** had to be formed, which can be obtained by a rapid exchange reaction of *n*-BuLi with an aryl iodide and subsequent intramolecular attack to the carbonyl group (Scheme 32).



26

Scheme 32

To facilitate the iodine-lithium exchange a fluorine atom is present in the benzene ring and two methyl groups are placed alpha to the ketone to help the cyclization step. The required compound was then identified in the ketone **18** which was obtained in five steps from commercially available starting materials (Scheme 33).

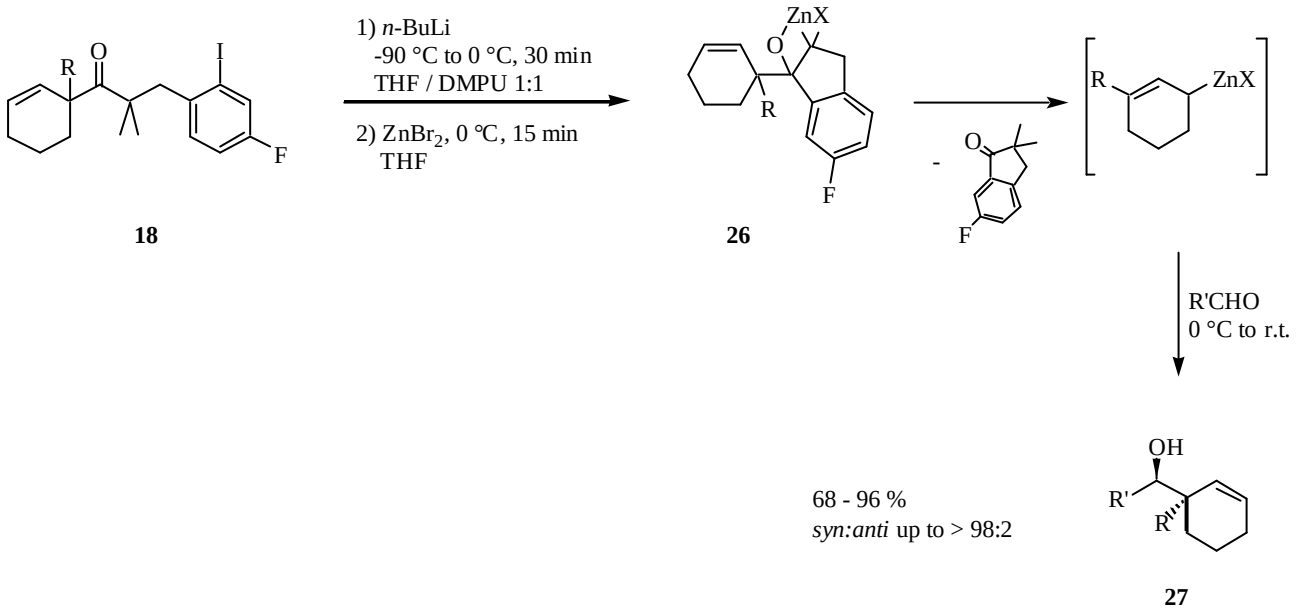


Scheme 33

The γ-deprotonation of **19** with LDA in THF led to the expected lithium dienolate. Its methylation or benzylation at the α-position afforded an intermediate β,γ-unsaturated ester **20** in 65 and 74 % yield respectively. Saponification and treatment with thionyl chloride gave the

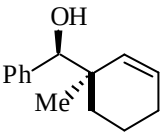
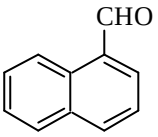
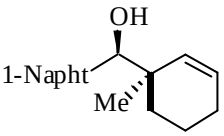
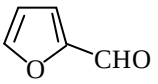
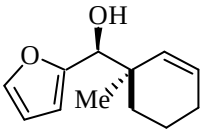
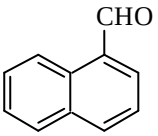
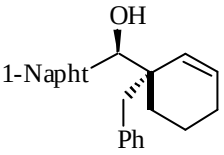
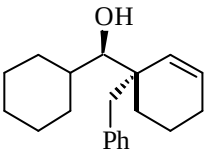
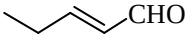
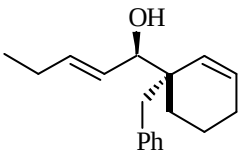
corresponding unsaturated acid chloride which was converted into the ketone **23** by cuprate addition. Finally, alkylation at the α-position with a previously prepared benzyl bromide derivative led to the desired ketones **18a** and **18b** in 69 % and 40 % yield respectively.

Upon addition of *n*-BuLi at -90 °C to a 1:1 THF/DMPU solution of the ketone **18**, a fast iodine-lithium exchange took place and, upon warming to 0 °C, a subsequent cyclization occurred, leading to the formation of a five-member cyclic lithium alcoholate. Transmetalation to zinc by addition of a THF solution of zinc bromide generated the alcoholate **26** which, upon addition of an aldehyde, led to a rapid fragmentation reaction to afford the *syn* γ-adduct **27** in good yield and very good selectivity (Scheme 34 and Table 4).



Scheme 34

Table 4. Homoallylic alcohols **27a-f** prepared by the fragmentation of zinc alcoholates obtained from the ketones **18a-b** in the presence of an aldehyde.

Entry	Ketone of type **18**	Aldehyde	Product of type **27**	Diastereomeric ratio[a] *syn* : *anti* [c]	Yield[b] (%)
1	**18a**	PhCHO	 **27a**	97:3	68
2	**18a**		 **27b**	88:12	80
3	**18a**		 **27c**	97:3	96
4	**18b**		 **27d**	> 2:98	87
5	**18b**	*c*-HexCHO	 **27e**	> 2:98	80
6	**18b**		 **27f**	9:91	79

[a]^{1}H NMR determined ratio

[b]Isolated yield of analytically pure product.

[c]The relative diastereoselectivity of compounds **27** was assigned according to the previously published NMR data (see footnote 25).

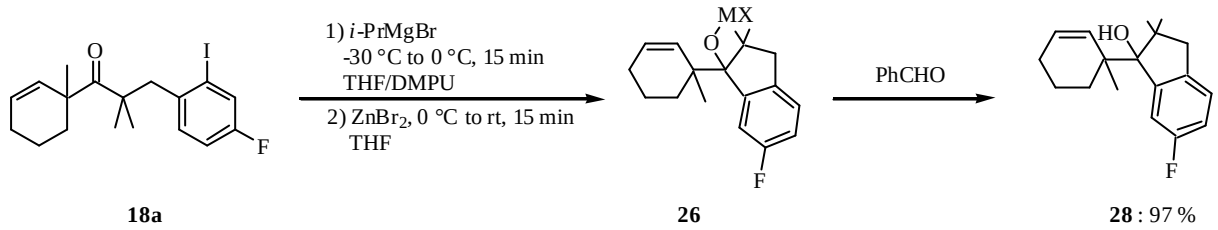
As illustrated in Table 4, both aromatic and aliphatic aldehydes reacted well with the *in situ* allylic zinc reagents. The reaction was usually complete within 45 min and led to the expected products in good to excellent yield. The rate of fragmentation depends on the steric hindrance of the alcoholate. When R is methyl the reaction was slower and sometimes stopped at the cyclic alcoholate **26**. Thus, from reaction of **18a** in the presence of aliphatic aldehydes like cyclohexane carboxaldehyde or *n*-butanal, only aldol-condensation products were isolated. On the other hand, if the steric hindrance was increased (R = Benzyl), fragmentation occurred within 30 min and quenching with an aliphatic aldehyde (entry 5) afforded the desired product in good yield. An α,β-unsaturated aldehyde was also tolerated, giving exclusively the 1,2-addition product in 79 % yield (entry 6).

The diastereoselectivity is influenced by the size of the substituent R in the cyclic alcoholate and, to a minor extent, by the steric hindrance of the R' group of the aldehyde. Reaction of the ketone **18a** with 1-naphthaldehyde gave the expected product with a diastereomeric ratio of 88:12 (entry 2), while the fragmentation of the alcoholate derived from the ketone **18b** in presence of the same electrophile, led only to the *anti* diastereoisomer (entry 4). The role of the R' group in determining the diastereomeric ratio can be elucidated by entries 4, 5 and 6: as expected, moving from arylic or cyclic to linear substituents causes a significant decrease of diastereoselectivity.

The role of DMPU as a polar cosolvent has proved to be quite important in terms of yield and reaction rate. When the reaction was performed in pure THF, the mixture needed to be heated to 70 °C in order for the fragmentation to take place, and after addition of benzaldehyde the expected homoallylic alcohol was isolated in just 51 % yield. In a more polar solvent system like THF/DMPU 2:1, cyclisation occurred at room temperature but no migration of the allylic group was observed. Finally, in a 1:1 THF/DMPU mixture the reaction proceeded smoothly to give the desired product in 68 % yield (Table 4, entry 1).

Attempts to perform the cyclization and fragmentation step with a Grignard reagent were unsuccessful. *i*-PrMgBr was added at -30 °C to a THF solution of the ketone **18a** and after 15

min a THF solution of zinc bromide was added and the mixture was allowed to warm to room temperature. After addition of benzaldehyde the only product isolated was the cyclic alcohol **28** (Scheme 35). The use of a polar cosolvent (THF/HMPA 2:1, THF/DMPU 1:1) did not bring any improvement, indicating that the transmetalation process probably did not proceed. The use of different zinc salts was then considered, upon the addition of THF solutions of zinc chloride or zinc triflate, however no improvement was detected.

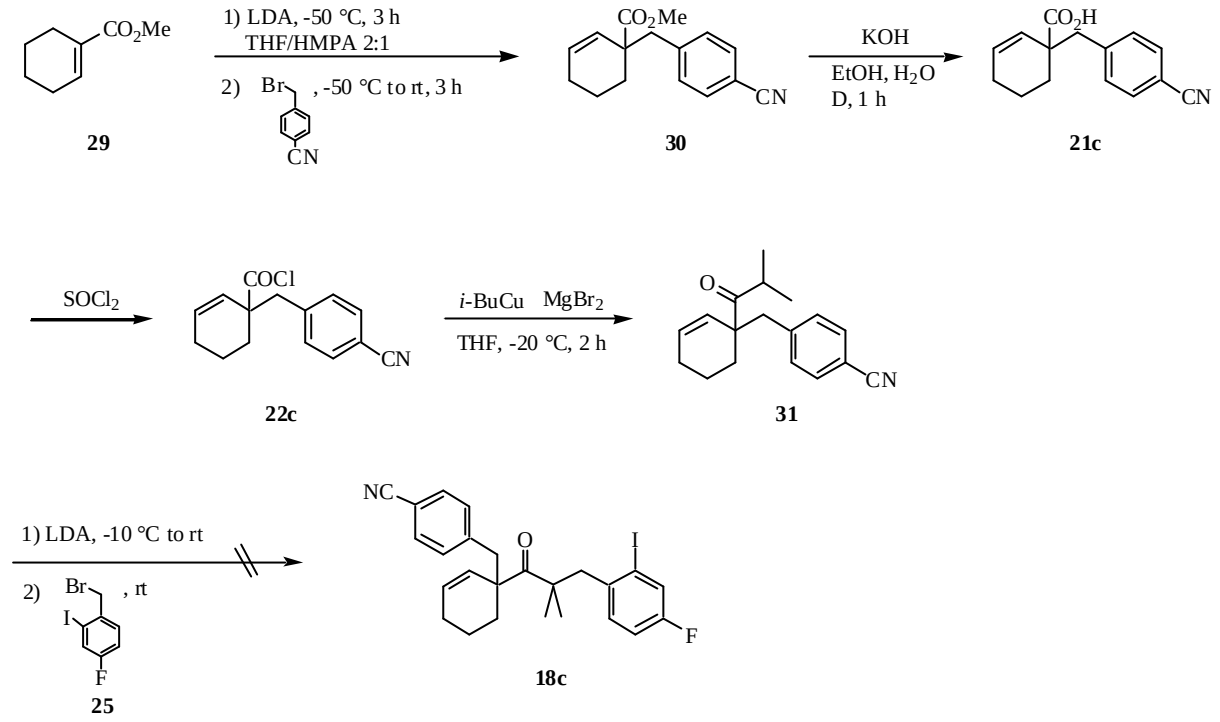


18a **26** **28** : 97 %

Scheme 35

3.1 Attempted synthesis of functionalised allylic zinc reagents via a cyclization-fragmentation reaction

Having optimised the conditions for the generation of substituted allylic zinc reagents, it was of interest to explore the functional group compatibility of such a method. In order to do so, the synthesis of functionalised analogues of the ketone **18** was attempted. The starting 1-cyclohexene-1-carboxylic acid methyl ester **29** was deprotonated with LDA and alkylated at the α-position with 4-(bromomethyl)-benzonitrile in 77 % yield (Scheme 36). Saponification and treatment with thionyl chloride afforded the corresponding acid chloride which was then reacted with *iso*-propylcuprate to give the ketone **31** in a disappointing 40 % yield, due to partial attack of the Grignard to the cyano group. Surprisingly, any attempt to obtain the desired ketone **18c** from **31** failed. LDA, lithium diethylamine and NaH were all ineffective at deprotonating **31** α to the carbonyl group and the unreacted starting material was recovered in all cases.



Scheme 36

3.2 Summary

The generation of allylic zinc reagents via a cyclization-fragmentation reaction is an efficient method for the preparation of allylic zinc species free of any Wurtz homocoupling products and allows the synthesis of a variety of homoallylic alcohols with high degree of diastereoselectivity. The reaction is influenced by the polarity of the solvent and, as regards the diastereomeric excess, by the bulkyness of the substituents R and R'. This approach could in principle allow the preparation of functionalised allylic zinc compounds and this possibility should be further explored developing a different retro synthetic pathway for the functionalised ketone of type **18**.

4 Preparation of Highly Functionalised Organocuprates via Halogen-Copper Exchange

4.1 Higher order cyanocuprates

Beginning of 1981, *Lipshutz et al.*[70,47c,d] introduced the concept of higher order mixed organocuprates. On the basis of improved yields and (where relevant) different stereochemical outcomes,[71] it was claimed that these species were different from "lower-order" or Gilman-like cuprates, R_2CuLi, in that the Cu-cluster contained an additional ligand (negatively charged). While no unambiguous structure determination work had yet been carried out, the higher order species were described as Cu(I) dianionic salts.[72] It has been unequivocally asserted that the cyano group is bonded to copper by means of a Cu-(CN) bond.[73] The higher order claim has been strongly challenged[74] and subsequently defended.[75] Computational analysis,[76] NMR[77] and EXAFS studies[78] later showed that tricovalent Cu(I) is neither obligatory nor sufficiently stable to describe the structure around the copper centre in $R_2Cu(CN)Li_2$. A recent NMR study by *Bertz*[79] showed that these very effective organocopper reagents, obtained from the reaction of two equivalents of organolithium RLi and one equivalent of CuCN, are modified Gilman reagents and not higher order cyanocuprates. Consequently, they should be called Cyano-Gilman reagents and represented as $R_2CuLi{\cdot}LiCN$.

4.2 Non-transferable ligands

[70] a) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672. b) Limited spectroscopic studies were reported: Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1984**, *49*, 3943.
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[74] Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031.
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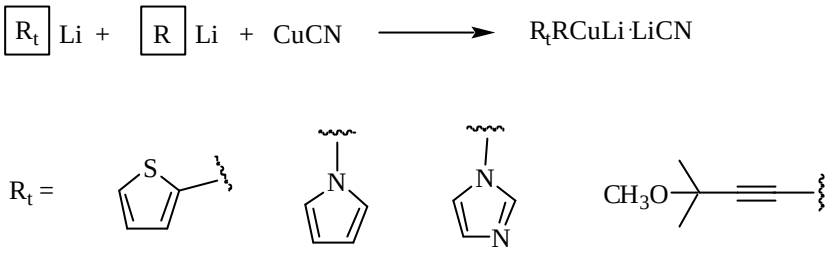
[77] Bertz, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 5470.
[78] a) Stemmler, T.; Penner-Hahn, J. E.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 348. b) Stemmler, T. L.; Barnhart, T. M.; Penner-Hahn, J. E.; Tucker, C. E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* **1995**, *117*, 12489.
[79] Bertz, S. H.; Nilsson, K.; Davidsson, Ö.; Snyder, J. P. *Angew. Chem. Int. Ed.* **1998**, *37*, 314.

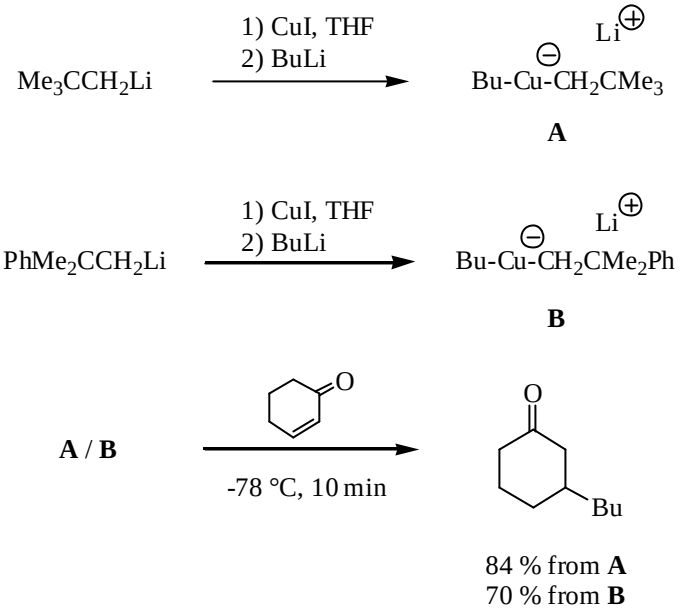
Homocuprate reagents (R_2CuLi or R_2CuMgX) are the most widely used of the organocopper reagents. Usually only one of the organic ligands is transferred to form a new C-C bond, and if the organometallic precursors are expensive or difficult to prepare, this presents a serious drawback. To overcome this problem, in 1972 *Corey* and *Beames*[80] introduced mixed homocuprates derived from pentynyl copper, having demonstrated that alkynyl ligands are transferred much more slowly than other organic groups. Since that time, a number of non-transferable ("dummy") ligands (R_t) have been proposed,[81] which combine with a valuable organolithium (RLi) and CuCN to form a mixed higher order cyanocuprate (Scheme 37).



Scheme 37

Since organozinc reagents offer higher functional group tolerance than organolithium, an interesting extension of this approach has been developed by *Knochel*,[6b, 82] who showed that mixed organozinc reagents of the type FG-R-Zn-CH_2SiMe_3, carrying one transferable alkyl group and one non-transferable trimethylsilylmethyl group, maintain the reactivity, albeit slightly less than typical diorganozincs. Further investigation[83] led to the discovery of two new cheaper non-transferable ligands, the neopentyl group (CH_2CMe_3) and the structurally similar neophyl group (CH_2CMe_2Ph) which proved to be suitable also for organocopper chemistry (Scheme 38).

[80] Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
[81] a) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437. b) Malmberg, H.; Nilsson, M.; Ullenius, C. *Tetrahedron Lett.* **1982**, *23*, 3823. c) Lipshutz, B. H.; Fatheree, P.; Hagen, W.; Stevens, K. L. *Tetrahedron Lett.* **1992**, *33*, 1041. d) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418. e) Johnson, C. R.; Dhanoa, D. S. *J. Org. Chem.* **1987**, *52*, 1885.
[82] a) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895. c) Jones, P.; Knochel, P. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3117. d) Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471.
[83] Lutz, C.; Jones, P.; Knochel, P. *Synthesis* **1999**, 312.



Scheme 38

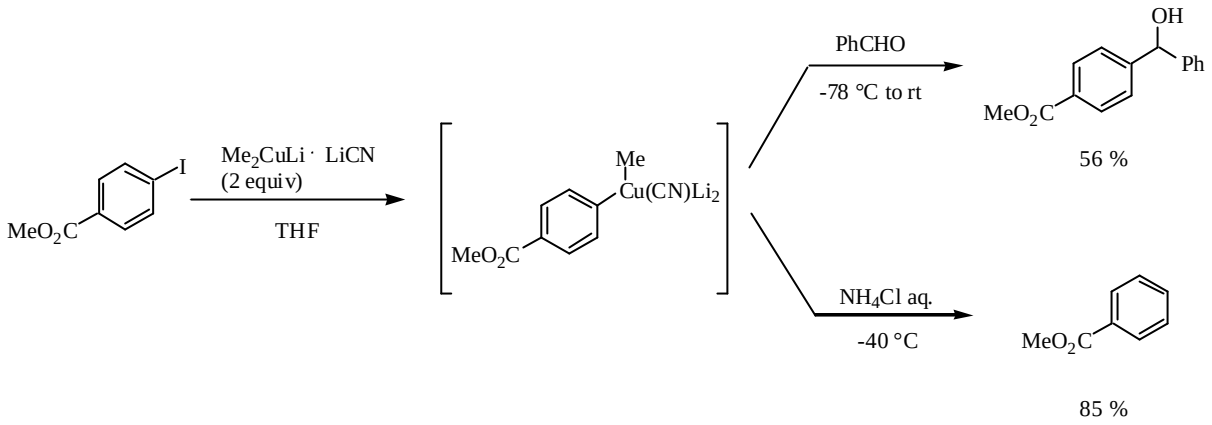
Thus, copper(I) iodide was treated with neopentyllithium and then butyllithium to yield the mixed neopentyl(butyl)cuprate A. Treatment of this reagent with 2-cyclohexen-1-one gave, within 10 min, 84 % yield of 3-butylcyclohexanone. No neopentyl migration was observed. Similarly, a mixed neophyl(butyl)cuprate B was prepared. This material was treated likewise with cyclohex-2-enone and after 10 min at -78 °C, 3-butylcyclohexanone was isolated in 70 % yield. Again, no transfer of the neophyl group was observed.

4.3 Functionalised aryl organocuprates

The halogen-metal exchange is one of the most useful methods for the preparation of metalated aryl compounds, especially lithium[84] and magnesium[85] ones. Functionalised organocuprates are usually obtained via transmetalation from the corresponding zinc reagents[6d, 86] or by direct oxidative addition of reactive copper into a carbon-halogen bond.[51] Even if the possibility of a

[84] a) Wakefield, B. J. *The Chemistry of Organolithium Compounds* Pergamon Press, Oxford, **1974**. b) Wakefield, B. J. *Organolithium Method* Academic Press, London, **1988**.
[85] Tamborski, C.; Moore, G. J. *J. Organomet. Chem.* **1971**, *26*, 153. b) Paradies, H. H.; Gorbing, M. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 279.
[86] a) Zhu, L.; Rieke, R. D. *Tetrahedron Lett.* **1991**, *32*, 2865. b) Knochel, P.; Rao, S. *J. Am. Chem. Soc.* **1990**, *112*, 6146. c) Knochel, P. *ibid*. **1990**, *112*, 6146. d) Rao, S.; Knochel, P. *ibid*. **1991**, *113*, 5735. e) Wipf, P. *Synthesis* **1993**, 537.

halogen-copper exchange has been suggested for a long time,[87] it has not so far been extensively studied. In the work of *Kondo* and *Sakamoto*,[54] the higher order cuprate $Me_2CuLi{\cdot}LiCN$ performed an iodine-copper exchange on methyl 4-iodobenzoate and, after addition of benzaldehyde, furnished the expected product in 56 % yield (Scheme 39).



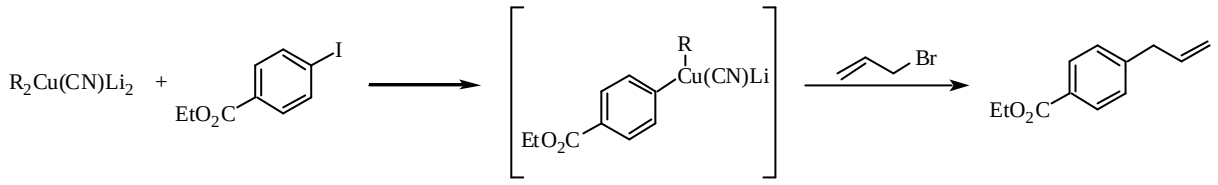
Scheme 39

An excess (2 equiv) of cuprate has to be used to quench the methyl iodide formed during the exchange reaction. In this way the MeCuLiCN obtained *in situ* is less reactive towards the electrophile than $MeArCu{\cdot}LiCN$ and does not interfere in the coupling process. Clearly, this method has some drawbacks and is not totally efficient. The formation of the mixed cuprate is not quantitative, as demonstrated by the yield of the hydrolysed product recovered after treatment with NH_4Cl, but its considerable synthetic potential makes it worth further exploration.

4.4 Screening of other non-transferable groups

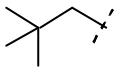
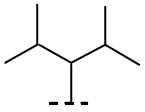
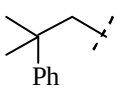
In order to find the most suitable ligand and based on the previous results obtained for organozinc chemistry, a range of lithium dialkylcuprates were prepared, including the cuprate of Sakamoto. These were then tested in the iodine-copper exchange of ethyl 4-iodobenzoate and the subsequent reaction with allyl bromide (Scheme 40 and Table 5).

[87] a) House, H. O.; Koepsell, W. J.; Campbell, W. J. *J. Org. Chem.* **1972**, *37*, 1003. b) Barri, F.; Di Nunno, L.; Florio, S.; Marchese, G.; Naso, F. *J. Organomet. Chem.* **1979**, *169*, 263.



Scheme 40

Table 5. Yields of ethyl 4-allylbenzoate obtained by iodine-copper exchange of lithium dialkylcuprates cuprates bearing different non-transferable ligands with ethyl 4-iodobenzoate.

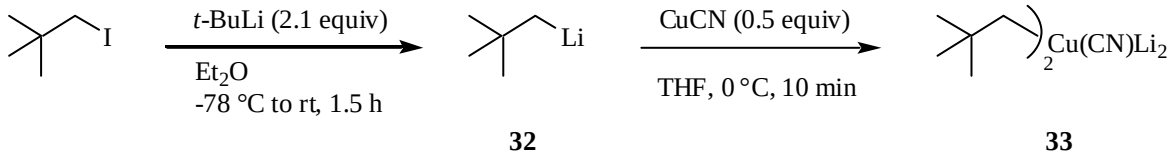
Entry	R	T (° C)	t (h)	Yield (%)[a]
1	Me (2 equiv)	- 40	1	65
2	Bu	- 78	3	58
3		- 20	3	95
4		25	10	88
5		0	3.5	90
6	$TMSCH_2$	0	5	74

[a]Isolated yield of analytically pure product

The allylated product was isolated in all cases, in moderate to excellent yield. As reported by Sakamoto, two equivalents of lithium dimethylcuprate were necessary to obtain full conversion and to isolate ethyl 4-allylbenzoate in 65 % yield (entry 1). A similar result was given by the dibutyl cuprate (entry 2) although only one equivalent of cuprate was used in this case. Much better results were observed when the steric bulk of the non-transferable group was increased. The neopentyl group proved to be the best: the exchange was complete within three hours (using 1 equiv of cuprate) and the allylated compound was recovered in 95 % yield (entry 3). The related neophyl group appeared to be slightly less reactive, requiring a longer reaction time and higher temperature (entry 5). Finally, the secondary alkyl group also furnished the expected product in good yield, but warming to rt overnight was necessary to complete the exchange (entry 4). A non-transferable ligand containing a silyl group was also tested, since it proved to be advantageous for organozinc chemistry.[6b, 19] It showed a moderate efficiency (entry 6), and its reactivity, comparable with that of other alkyl groups, suggests that no β-silyl effect[88] is present.

4.5 Neopentyl and neophyl group as non-transferable ligands

After these encouraging results, neopentyl and neophyl groups were the ligands of choice for performing an iodine-copper exchange on various functionalised substrates. Lithium dineopentylcuprate (Np_2CuLi) **33** was readily prepared starting from commercially available neopentyl iodide, which was converted into the lithium species **32** by reaction with *t*-BuLi, according to the procedure of *Negishi*,[89] and then transmetalated to copper to give the higher order cyanocuprate (Scheme 41).



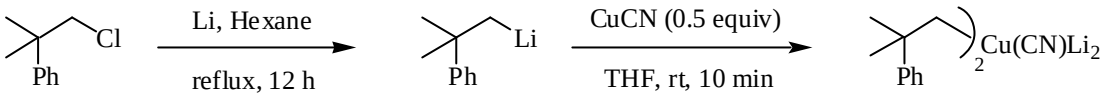
32 **33**

Scheme 41

[88] Bertz has prepared and investigated the reactivity of alkyl (trimethylsilylmethyl)cuprates and argues the involvement of β-silyl effect. Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906 and references therein.

[89] Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

Similarly, lithium dineophylcuprate was prepared from the starting chloride which, upon refluxing overnight with metallic lithium in hexane, reacted to give the lithium compound **34**. Reaction of this with CuCN at rt gave the expected cuprate **35** (Scheme 42).



34 **35**

Scheme 42

Neophyllithium is obtained as an ethereal solution, according to the procedure of *Cano et al.*,[90] and is titrated before use with menthol in the presence of *o*-phenanthroline as indicator. The solution can be stored for several days at -30 °C without loosing its reactivity.

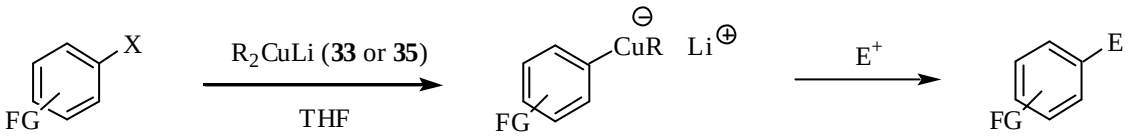
These two lithium dialkylcuprates exhibit different thermal stability:[91] dineopentylcuprate is stable at 0 °C in THF for a few hours but decomposes rapidly if warmed to rt, while dineophylcuprate retains its reactivity in the same solvent for up to three hours at rt.

4.6 Halogen-copper exchange on functionalised arylic compounds

Having established an easy method for the preparation of lthium dineopentylcuprate Np_2CuLi **33** and lithium dineophylcuprate $Nphyl_2CuLi$ **35**, these were employed to perform a chemoselective halogen-copper exchange on a variety of functionalised arylic systems. Np_2CuLi, **33** and $Nphyl_2CuLi$ **35** rapidly reacted with various fictionalized halogenides of type **36**, leading to mixed organocuprates of type **37**, which selectively transferred the aryl group in the reaction with electrophiles (E^+) leading to products of type **38** (Scheme 43).

[90] Cano, A.; Cuenca, T.; Galakov, M.; Rodríguez, G. M.; Royo, P.; Cardin, C. J.; Convery, M. A. *J. Organomet. Chem.* **1995**, *493*, 17.

[91] Higher order cuprates have a similar stability to heterocuprate reagents. Bertz, S. H.; Dabbagh, G. *J. Chem. Soc. Chem. Commun.* **1982**, *18*, 1030.



36: X= Br,I **37** **38**

FG = ester, ketone, aldehyde; R= Me_3CCH_2 (**33**) or Me_2PhCCH_2 (**35**)

Scheme 43

This approach allows a general preparation of polyfunctional organocuprates.[92] The steric hindrance at the copper centre of **33** and **35** is essential for ensuring the chemoselectivity of the iodine-copper exchange[93] and the large bulk of the non-transferable group serves to orientate the neophyl or neopentyl ligand far away from the incoming electrophile, thereby placing the second organic residue in closer proximity to the electrophilic reaction partner.

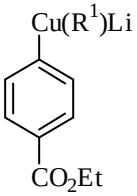
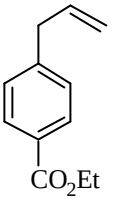
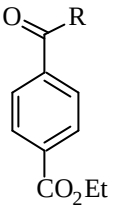
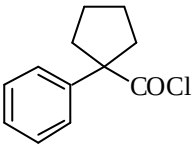
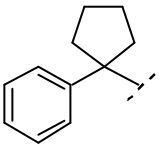
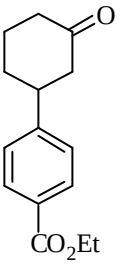
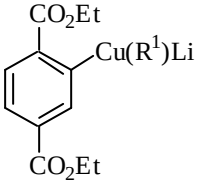
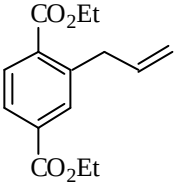
4.6.1 Reactions of lithium dineopentylcuprate

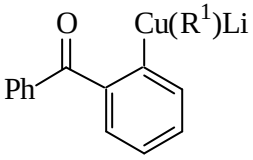
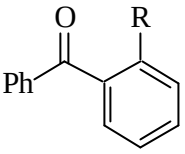
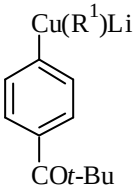
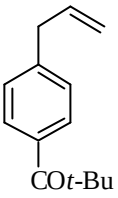
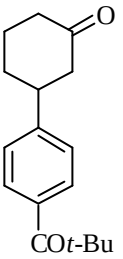
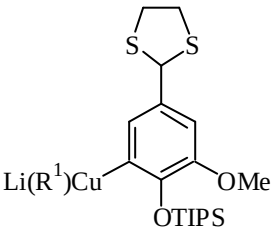
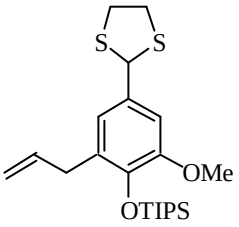
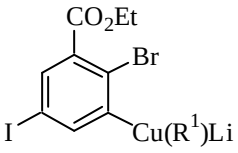
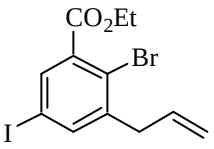
Lithium neopentylcuprate has proved to be more reactive than the neophyl reagent. Its exchange reaction with various fictionalized arylic substrates occurred in THF within 3 h at a temperature between -78 °C and -30 °C, in good to excellent yield (Table 6). Quenching with 0.9-1 equiv. of electrophile furnished the expected products normally without detection of neopentyl transfer or partial attack at the functional group present. Thus, ethyl 4-iodobenzoate **36a** underwent a smooth iodine-copper exchange with Np_2CuLi (1.1 equiv, -30 °C, 2 h), affording the desired mixed cuprate **37a**, which reacted with electrophiles like allyl bromide, acid chlorides or 2-cyclohexen-1-one to afford the desired products **38a-f** in 60 %-95 % yield (entries 1-5). Since arylic iodides are expensive and sometimes difficult to synthesize, it was interesting to observe that the functionalised aromatic bromide diethyl 2-bromoterephthalate smoothly underwent a bromine-copper exchange with Np_2CuLi (THF, -40 °C, 30 min), leading to the lithium cuprate **37b**, allylation of which furnished the diester **38e** in 76 % yield (entry 6). Remarkably, ketone functions are compatible with the iodine-copper exchange reaction. The treatment of 2-

[92] For the preparation of functionalized cuprates see: a) Taylor, R. J. K. *Organocopper Reagents*, Oxford Unversity Press, Oxford, **1994**. b) Krause, N. *Modern Organocopper Chemistry*, Wiley-VCH, Weinheim, **2002**.
[93] For a chemoselective halogen-lithium exchange, see: Kondo, Y.; Asai, M.; Uchiyama, T.; Sakamoto, T. *Org. Lett.* **2001**, *3*, 13.

iodobenzophenone with **33** (-40 °C to 0 °C, 30 min) led to the desired mixed cuprate **37c**. After allylation or methylation with methyl iodide the products **38f** and **38g** were obtained in 80 % yield (entries 7 and 8). Similarly, 4-iodophenyl *tert*-butyl ketone was converted into the cuprate **37d** and allylated in 93 % yield (entry 9), while its reaction with 2-cyclohexen-1-one gave the 1,4-adduct in 60 % yield (entry 10). Interestingly, electron-rich substrates are also susceptible to iodine-copper exchange, even if higher temperature and longer reaction times are required. Thus, [4-(1,3-dithiolan-2-yl)-2-iodo-6-methoxyphenoxy](triisopropyl)silane gave after treatment with Np_2CuLi (1.1 equiv, rt, 7 h) the expected mixed cuprate **37e** which was allylated in 61 % yield (entry 11). Finally, a halogen-copper exchange reaction was performed on a polyhalogenated system (entry 11), to investigate the selectivity of the method. Ethyl 2-bromo-3,5-diiodobenzoate was treated with Np_2CuLi and at -50 °C a rapid and selective exchange reaction took place (45 min) in 3-position, giving, after quenching with allyl bromide, ethyl 3-allyl-2-bromo-5-iodobenzoate as the sole product in 76 % yield (entry 12). No bromine-copper exchange was detected.

Table 6. Products of type **38** obtained by the reaction of mixed functionalised lithium neopentylcuprate of type **37** with electrophiles.

Entry	Cuprate of type **37** [a]	Electrophile	Product of type **38**		Yield (%)[b]
1	 **37a**	allyl bromide		**38a**	95 90[c]
2	**37a**	PhCOCl	 R = Ph	**38b**	87 95[c]
3	**37a**	*t*-BuCOCl	R = *t*-Bu	**38c**	83
4	**37a**		R = 	**38d**	60
5	**37a**	cyclohexenone		**38e**	70
6	 **37b**	allyl bromide		**38f**	76

7	 **37c**	allyl bromide	 R = allyl	**38g**	80
8	**37c**	methyl iodide	R = methyl	**38h**	80
9	 **37d**	allyl bromide		**38i**	93
11	**37d**	cyclohexenone		**38j**	60
12	 **37e**	allyl bromide		**38k**	61
11	 **37f**	allyl bromide		**38l**	76

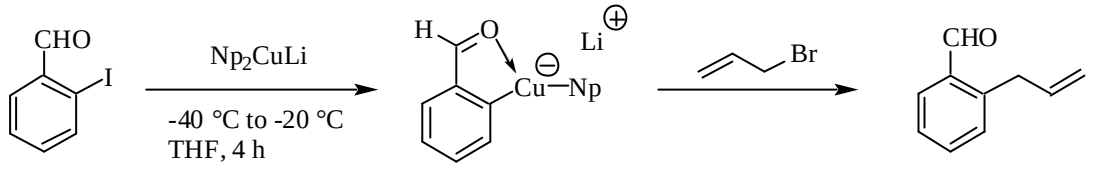
[a] R^1 = neopentyl; R^2 = neophyl.

[b] Isolated yield of analytically pure product.

[c] Yields obtained by performing the I/Cu exchange with the reagent **35**.

4.6.2 Aldehydes and ketones: reactions of neophylcuprate

Recently, *Knochel et al.* showed that iodine-magnesium exchange allows the preparation of polyfunctional arylmagnesium reagents[94] bearing ester, nitrile, amino or nitro groups, but more sensitive functionalities like a *ketone* or an *aldehyde* are not usually compatible with the presence of a carbon-magnesium bond. For this reason, a methodology that could tolerate the presence of these important moieties would mean a considerable improvement of this branch of organometallic chemistry. The performance of an iodine-copper exchange on 2-iodobenzaldehyde was therefore attempted. The treatment of this substrate with Np_2CuLi (1.1 equiv, -40 °C to -20 °C, 4 h) provided the cuprate **37g**, the allylation of which gave 2-allylbenzaldehyde **38m** in 80 % yield (Scheme 44 and Table 7).



39 **37g** **38m** : 80 %

Scheme 44

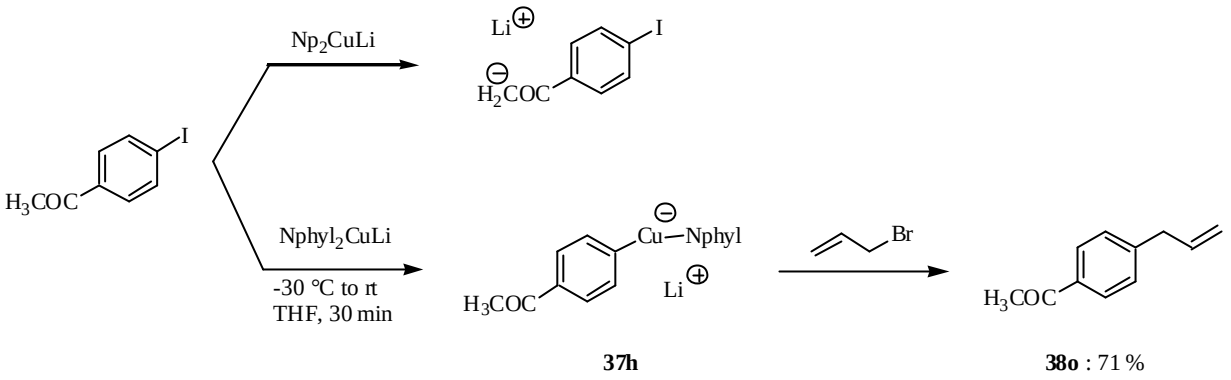
Similarly, acylation gave the expected product in 75 % yield, demonstrating that an aldehyde group is compatible with an iodine-copper exchange. The reaction is sensitive towards steric effects: quenching with bulky electrophiles like benzoyl chloride, pivaloyl chloride or ethyl propiolate did not furnish the desired products.

The proximity of the carbonyl group to the iodine seems to be essential for the success of the exchange reaction. In fact, attempts to obtain the mixed cuprate starting from *meta*- or *para*-iodobenzaldehyde did not lead to any ligand exchange product and when the temperature was increased, attack of the aldehyde was observed.

The use of Np_2CuLi for the conversion of 4-iodoacetophenone into the corresponding cuprate led to extensive deprotonation α to the carbonyl. However, the use of $Nphyl_2CuLi$ **35** allowed the preparation of the corresponding cuprate **37h**, which was allylated in 71 % yield (Scheme 45).

---

[94] Jensen, A. E.; Dohle, W.; Sapountzis, J.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565.

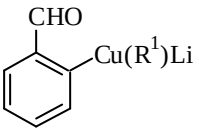
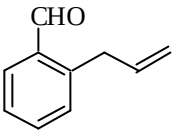
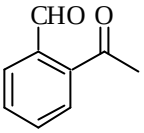
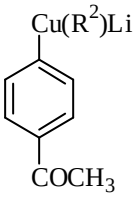
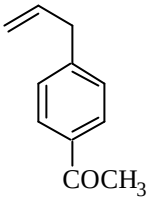
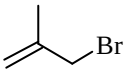
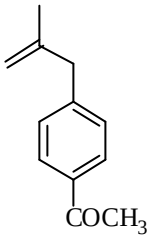
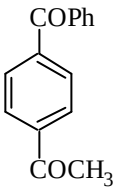
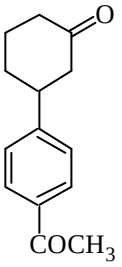


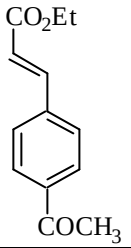
37h **38o** : 71 %

Scheme 45

The exchange reaction proceeded relatively fast, requiring just 30 min at rt for complete conversion of 4-iodoacetophenone into the mixed cuprate **37h**, which could also be acylated in 89 % yield (Table 7, entry 4) and underwent Michael additions with 2-cyclohexen-1-one and ethyl propiolate leading to the expected products in 68 and 78 % yield respectively (entries 5 and 6). In contrast to the aldehydic substrate, here the success of the exchange reaction is not dependent on the position of the carbonyl group.

Table 7. Reaction of functionalised lithium cuprates **37g-h** with electrophiles to give **38m-s**.

Entry	Cuprate of type **37**[a]	Electrophile	Product of type **38**		Yield (%)[b]
1	 **37g**	allyl bromide		**38m**	80
2	**37g**	CH_3COCl		**38n**	75
3	 **37h**	allyl bromide		**38o**	71
4	**37h**			**38p**	65
5	**37h**	PhCOCl		**38q**	77
6	**37h**	cyclohexenone		**38r**	68

7	**37h**	ethyl propiolate		**38s**	78

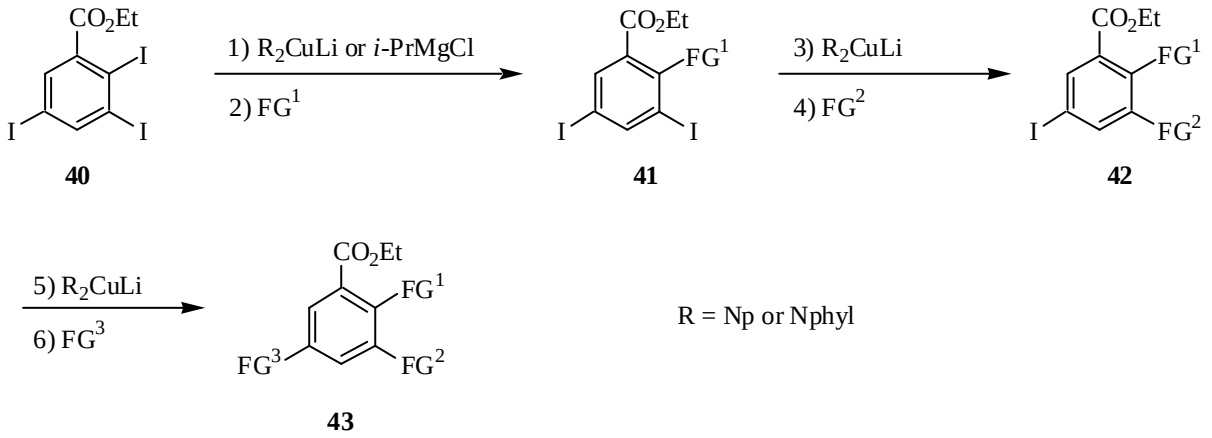
[a] R^1 = neopentyl; R^2 = neophyl.

[b] Isolated yield of analytically pure product.

As already mentioned, neophylcuprate proved to be slightly less reactive than the neopentyl reagent. On the other hand, its low reactivity becomes an advantage when very sensitive functional groups are involved in the exchange. Furthermore, its straightforward and inexpensive preparation makes it a very attractive reagent, particularly for industrial applications.

4.7 Regioselective functionalisation of polyiodinated arylic substrates

Having two lithium alkylcuprates with complementary reactivity and functional group tolerance, it should in principle be possible to perform a halogen-copper exchange on a polyiodinated system to selectively introduce different functionalities. For example, starting from the triiodoester **40** a polyfunctionalised molecule of type **43** could be synthesized (Scheme 46).

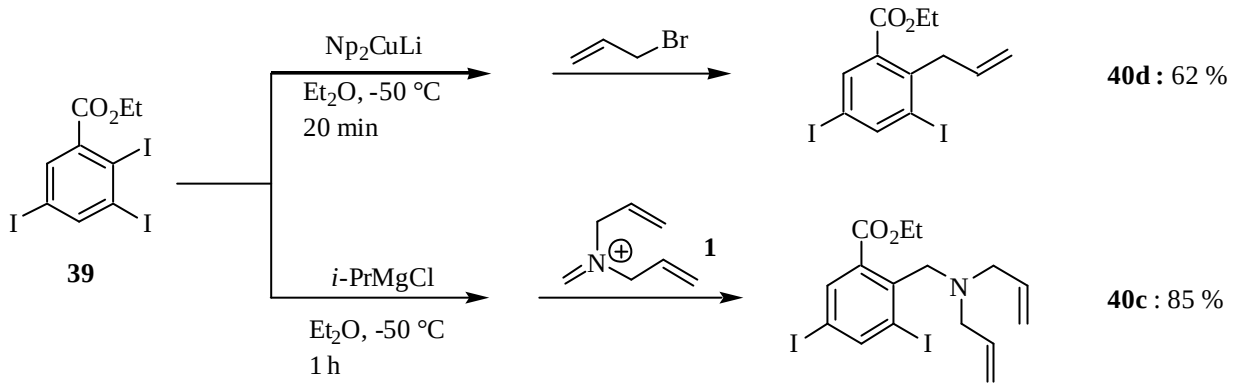


40 **41** **42** **43**

Scheme 46

Combining neopentyl and neophyl cuprates with Grignard reagents, three organometallic reagents of decreasing reactivity are now at our disposal, and a large variety of

polyfunctionalised compounds can thereby be prepared.[95] The first exchange can be performed either with Grignard or with organocopper reagents however, in order to obtain complete selectivity, the reaction conditions had to be optimised. The importance of the solvent was soon recognized. In the allylation reaction of ethyl 2,3,5-triiodobenzoate all three possible regioisomers were detected by GC-MS when THF was chosen as solvent, probably because the strong solvating medium minimizes the *ortho*-directing effect of the ester group, making all the three positions susceptible to exchange, regardless of which copper reagent was used. Switching to diethyl ether resulted in a considerable improvement, a clean and selective iodine-copper exchange took place and the desired product was isolated in 62 % yield. Similarly, a selective iodine-magnesium exchange was achieved, leading, upon reaction with immonium trifluoroacetate **1**, to the aminomethylation product **40c** in 85 % yield (Scheme 47).



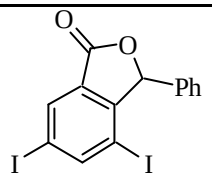
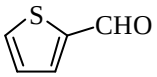
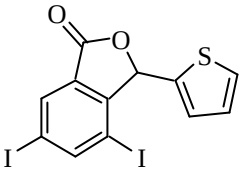
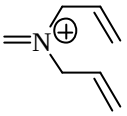
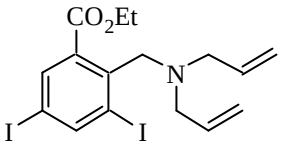
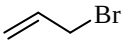
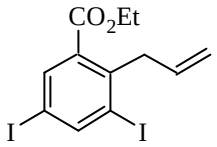
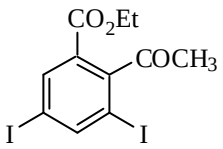
Scheme 47

The selectivity of the reaction was determined by HMBC/HSQC-NMR.

Applying these optimised conditions, a variety of products substituted in the 2-position were obtained (Table 8).

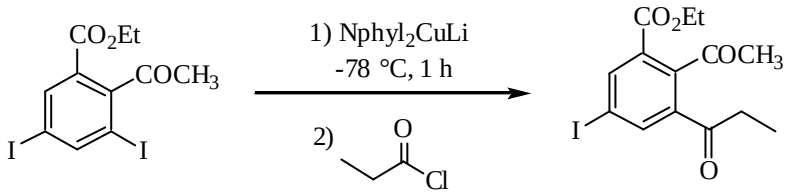
[95] Rotter, T. *Diplomarbeit*, LMU Universität München, **2002**.

Table 8. Selective iodine-metal exchange in the 2-position on ethyl 2,3,5-triiodobenzoate.

Entry	Reagent	Electrophile	Product of type **41**		Yield (%)[a]
1	*i*-PrMgCl	PhCHO		**41a**	77
2	*i*-PrMgCl			**41b**	83
3	*i*-PrMgCl			**41c**	85
4	Np_2CuLi			**41d**	62
5	Np_2CuLi			**41e**	60

[a]Isolated yield of analytically pure product

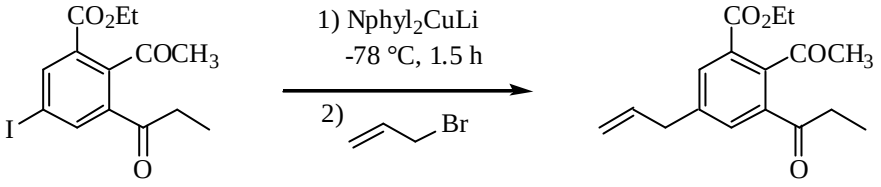
A second exchange was then performed on ethyl 2-acetyl-3,5-diiodobenzoate (Table 8, entry 5), using lithium dineophylcuprate. At -78 °C a smooth reaction with propanoyl chloride occurred in 1 hour to give the expected product 42 of acylation in position 3, in 66 % yield (Scheme 48). The regioselectivity was determined by a NOESY-NMR experiment.



41e **42** : 66 %

Scheme 48

Finally even a third exchange was achieved on the diacylated substrate **42** at -78 °C in 1.5 h. The allylated product was isolated in 61 % yield (Scheme 49).

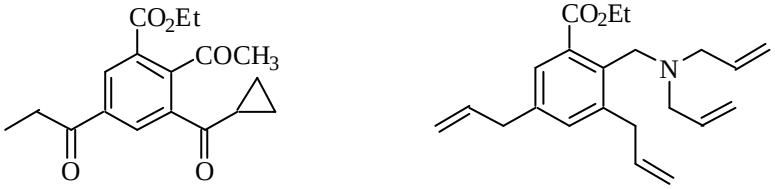


42 **43a** : 61 %

Scheme 49

The reactivity of the system decreased slightly from the first to the third exchange, depending of course also on the functional groups introduced. For the substitution in the 5-position, where no *ortho*-effect is possible, reaction times are significantly longer and sometimes an excess of cuprate is required to bring the exchange reaction to completion.

Using this efficient protocol, a variety of polysubstituted aryl compounds can be prepared. Particularly interesting are polyacylated molecules like **43b** which are not easy to obtain by other methods and can serve as useful building blocks for more complex systems (Figure 1).

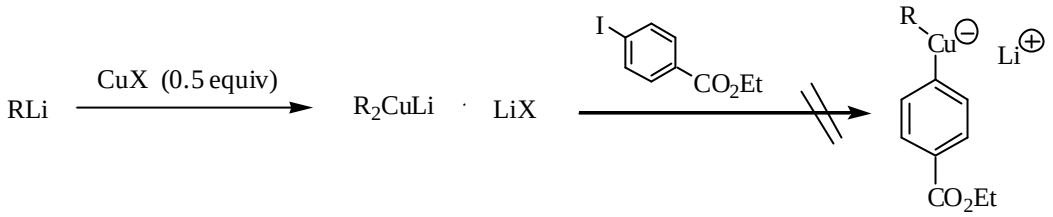


43b : 63 % **43c** : 60 %

Figure 1

4.8 The role of copper cyanide

For industrial application the use of other copper salts instead of the relatively unfriendly cyanide would be desirable. The possibility of preparing homocuprate reagents of the type R_2CuLi for use in the exchange reaction of ethyl 4-iodobenzoate was then examined (Scheme 50).



Scheme 50

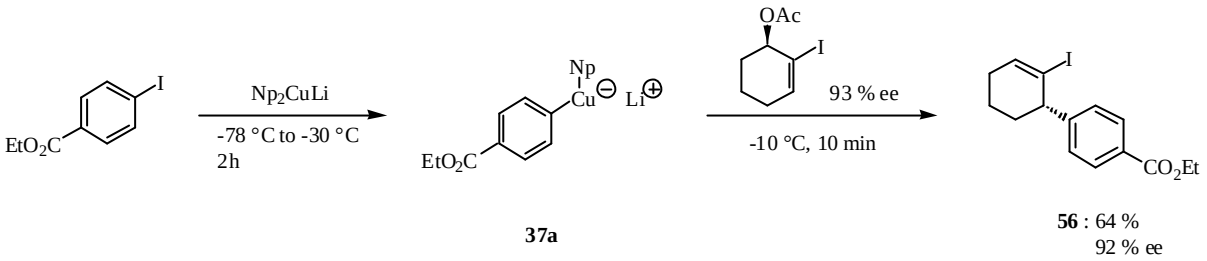
Two of the most common sources of Cu(I), the salts CuI and $CuBr{\cdot}SMe_2$, were employed in the reaction with neophyllithium. In both cases no exchange was observed and the unreacted iodobenzoate was recovered. This result underlines the different reactivity of the higher order cuprates compared to the Gilman reagents, despite the fact that the role of the cyanide is still not clearly understood.

4.9 Substitution reactions with functionalised mixed cuprates

The regio- and stereochemical outcomes of the reactions of organocopper reagents with allylic esters,[96] halides,[97] sulfonates,[98] phosphonates,[99] carbamates,[100] alcohols and ethers,[101] ammonium

[96] a) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1991**, *56*, 2563. b) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3000. c) Agami, C.; Couty, F.; Evano, G.; Mathieu, H. *Tetrahedron*, **2000**, *56*, 367.
[97] Arai, M.; Nakamura, E.; Lipshutz, B. H. *J. Org. Chem.* **1991**, *56*, 5489.
[98] a) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* 1989, *111*, 4864. b) Ibuka, T.; Akimoto, N.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 4055.
[99] a) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251. b) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 5552.
[100] Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984.
[101] Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144.

salts,[102] and oxiranes,[103] as well as with propargylic[104] and allenic[105] substrates, are well documented.[106] Organocopper-Lewis acid complexes are one of the reagents of choice in (E)-stereoselective and S_N2'-selective reactions. Preliminary experiments performed with mixed lithium neopentylcuprate showed that the reaction between the mixed organocuprate **37a** and 2-iodo-2-cyclohexen-1-yl acetate proceeded at -20 °C in 30 min to give the substitution product **56** in 64 % yield and without loss of stereochemical information (Scheme 51).



37a

56 : 64 %
92 % ee

Scheme 51

This interesting result suggests the potential for the regio- and stereoselective introduction of moieties bearing very sensitive functionalities which are normally not tolerated by magnesium or zinc cuprates.

4.10 Summary

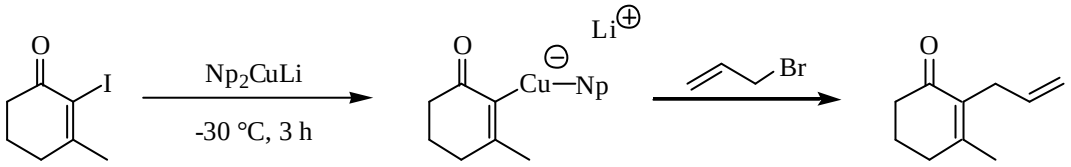
In summary, it has been shown that sterically hindered cuprates **33** and **35** allow a highly chemoselective halogen-copper exchange. With this method, new functionalised cuprates bearing ester, ketone, or even aldehyde functions can be prepared and used in synthesis. Moreover, an efficient method for the selective functionalisation of polyiodoarylic substrates was developed. The possibility of employing three different organometallic reagents allows the synthesis of a potentially vast range of complex molecules bearing very sensitive functional groups at any position of the benzene ring. Finally, preliminary experiments on the use of these mixed cuprates

[102] Pan, Y.; Hutchinson, D. K.; Nantz, M. H.; Fuchs, P. L. *Tetrahedron Lett.* **1989**, *45*, 467.
[103] Marino, J.P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389.
[104] Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2387.
[105] Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3059.
[106] Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

in substitution reactions with optically active substrates, indicated their possible application in the preparation of a broad variety of functionalised enantiomerically pure products.

5 Iodine-Copper Exchange on Vinylic Substrates

Numerous methods for the preparation of vinylic transition metal complexes are known and have been used frequently in organic synthesis.[107] An efficient method is the addition of organocopper reagents to terminal alkynes and to acetylene.[54,63] An alternative route is the transmetalation of a variety of organometallic intermediates mediated by preformed higher order cuprates. As already mentioned, vinylic stannanes,[59] tellurides,[60, 108] and zirconates[61, 109] readily exchange their vinylic ligands for alkyl groups on copper. Vinylic alanes, formed via Negishi carbometalations with Me_3Al/catalytic Cp_2ZrCl_2,[62] have also been converted into mixed higher order cyanocuprates. No example of halogen-copper exchange for the formation of vinylic cuprates has appeared until now in the literature. In order to extend the scope of our new method, its application to the selective transfer of vinylic substrates was studied. Generally, the transferability of organic ligands decreases in the order alkenyl > alkyl > methyl > alkynyl[110] but changes in this order are not unusual, depending on the type of system studied. The iodine-copper exchange was then studied on the following α,β-unsaturated ketone which possesses acidic α-hydrogens (Scheme 52).



44a **45a** : 74 %

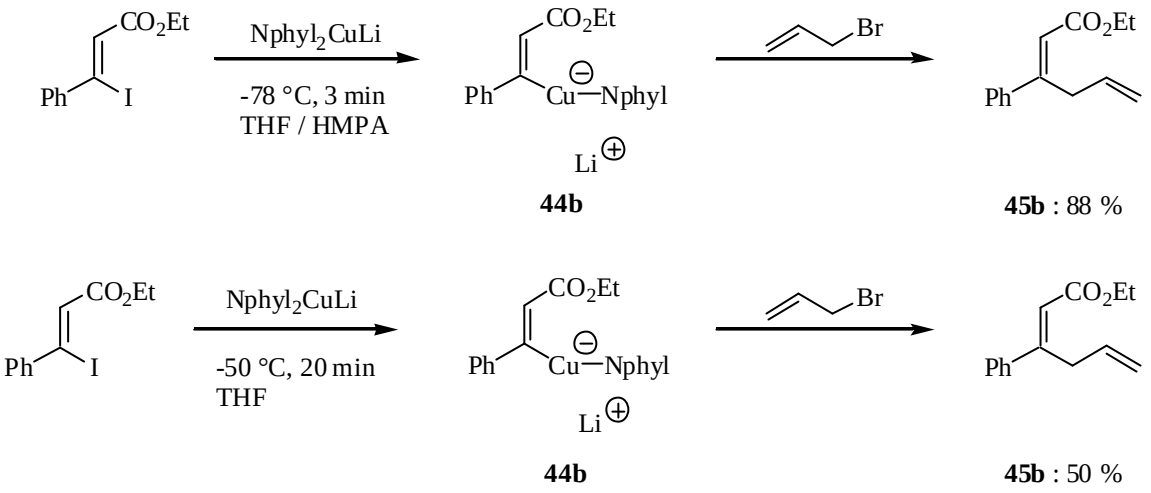
Scheme 52

Probably thanks to the chelating effect of the carbonyl group, α-deprotonation was minimized and a smooth iodine-copper exchange occurred (Np_2CuLi, -30 °C, 3 h), to give the allylated product **45a** in good yield.

---

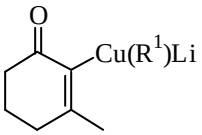
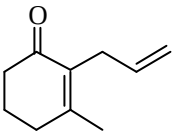
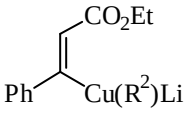
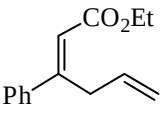
[107] For a recent review see: a) Fürstner, A. *Active Metals*, Wiley-VCH, Weinheim, **1996**. b) Negishi, E. *Organometallics in Organic Synthesis*, Wiley-Interscience, New York, **1980**.
[108] a) Tucci, F.; Chieffi, A.; Comasseto, J. V. *J. Org. Chem.* **1996**, *61*, 4975.
[109] a) Lipshutz, B. H. *Acc. Chem. Res.* **1997**, *30*, 277. b) Farhat, S.; Marek, I. *Angew. Chem. Int. Ed.* **2002**, *114*, 1468.
[110] a) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. b) Alexakis, A.; Hanaizi, J.; Jachiet, D.; Normant, J. F. *Tetrahedron Lett.* **1990**, *31*, 1271. c) Mandeville, W. H.; Whitesides,G. M. *J. Org. Chem.* **1974**, *39*, 400.

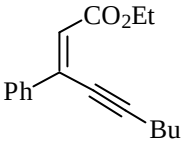
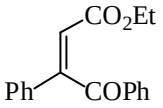
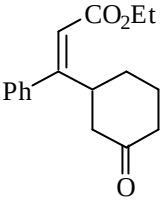
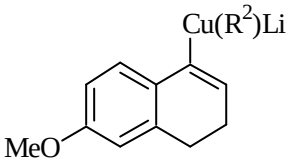
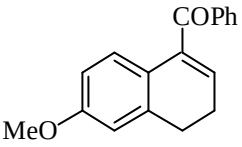
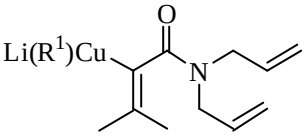
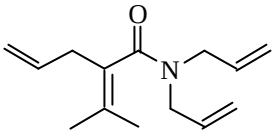
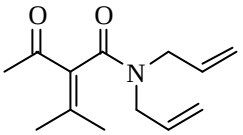
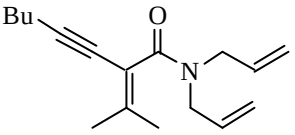
After this promising result, another two α,β-unsaturated open-chain substrates were tested. Ethyl (2Z) 3-iodo-3-phenylpropenoate was reacted with lithium dineopentylcuprate at -50 °C but the major product observed was ethyl (2*E*)-5,5-dimethyl-3-phenyl-2-hexenoate, derived from addition-elimination reaction. The use of the less reactive neophylcuprate solved the problem: a very fast exchange took place (-78 °C, 3 min) and the allylated product **45b** could be isolated in 88 % yield as a single stereoisomer (Scheme 53 and Table 9).



Scheme 53

Table 9. Reaction of functionalised lithium vinyl cuprates **44** with electrophiles to give **45**.

Entry	Cuprate of type **44**[a]	Electrophile	Product of type **45**		Yield (%)[b]
1	 **44a**	allyl bromide		**45a**	74
2	 **44b**	allyl bromide		**45b**	88 50[c] 60[d]

3	**44b**	1-Br-hexyne		**45c**	63
4	**44b**	PhCOCl		**45d**	56
5	**44b**	cyclohexenone		**45e**	48
6	 **44c**	PhCOCl		**45f**	72
7	 **44d**	allyl bromide		**45g**	55
8	**44d**	CH_3COCl		**45h**	72
9	**44d**	1-Br-hexyne		**45i**	58

[a] R^1 = neopentyl; R^2 = neophyl

[b] Isolated yield of analytically pure product.

[c] Yield in THF [d] Yield in THF/DMPU 1:1

The reaction seemed to be very sensitive to the solvent system. Poor yields and selectivities were observed in THF alone as solvent (entry 2). Addition of HMPA had a great impact on the reaction. Not only were the yields improved, but the (Z)-products were obtained exclusively in presence of nine equivalent of HMPA[64] (entry 2). The use of DMPU as cosolvent was also

effective but yields were generally lower. This result suggests that the additive stabilizes vinylcopper intermediate,[111] avoiding isomerization to the (E) cuprate.

The cuprate **44b** could be allylated (entries 2) and acylated with benzoyl chloride in reasonable yield (entry 4). Remarkably, a cross-coupling reaction with 1-bromohexyne also furnished the desired product in acceptable yield, always with complete retention of the double bond geometry (entry 3). Alkenylcopper reagents are considerably less reactive than alkylcopper derivatives and undergo 1,4-additions less efficiently than their alkyl-counterparts.[56] Vinylic copper compounds prepared by the addition of alkylcoppers to terminal alkynes in diethyl ether are especially unreactive towards Michael acceptors. On the other hand, vinyl copper reagents prepared by lithium-copper or magnesium-copper exchange react with enones to give conjugate addition products in good yields.[112] In our case, probably due also to a steric effect, the mixed vinylic cuprate **44b** underwent a 1,4-addition reaction with 2-cyclohexen-1-one (entry 5) in moderate yield.

Non-activated vinylic iodides like **44c** could also be acylated in good yield, even if the exchange reaction was slower (2.5 h at 0 °C, entry 6).

Surprisingly, functionalised vinylic bromides were also susceptible to halogen-copper exchange with neophylcuprate, although the yields of these reactions tended to be lower. Complete exchange occurred in 30 min at 0 °C and allylation, acylation and coupling products were isolated in acceptable yields (entries 7-9).

5.1 Summary

In conclusion, the halogen-copper exchange on vinylic substrates is a suitable method for the preparation of tri- or tetrasubstituted alkenes. The cuprate stability is dependent on the solvent system and best results are obtained in more polar systems. The exchange reaction occurs very fast in the case of activated vinylic substrates and leads to the desired products in good yields with no isomerisation of the double bond. The procedure is also applicable to non-activated substrates and even to vinylic bromides, although moderate yields are obtained in this case. Further studies should be made on the performance of iodine-copper exchange on linear vinylic halides bearing other functional groups such as aldehydes.

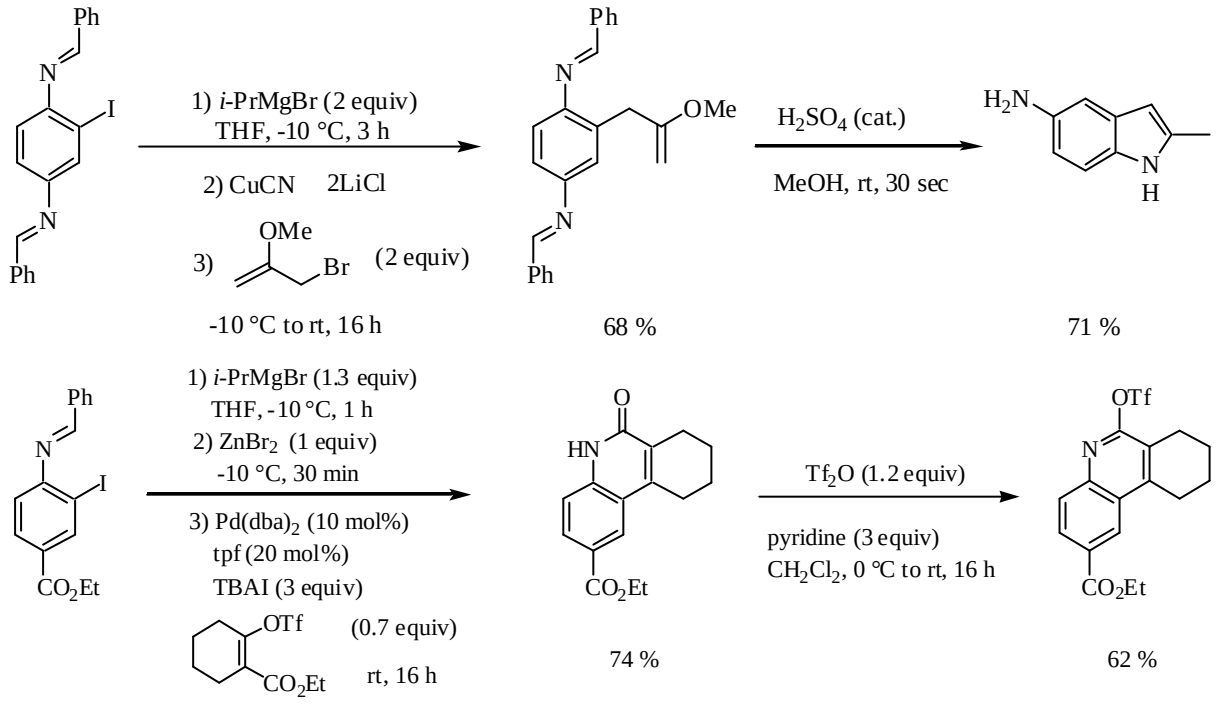
---

[111] Piers, E.; Chong, J. M.; Keay, B. A. *Tetrahedron Lett.* **1985**, *26*, 6265.

[112] a) Funk, R. L.; Vollhardt, K. P.C. *J. Am. Chem. Soc.* **1980**, *102*, 5253. b) Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525.

6 Halogen-Copper Exchange on Heterocycles

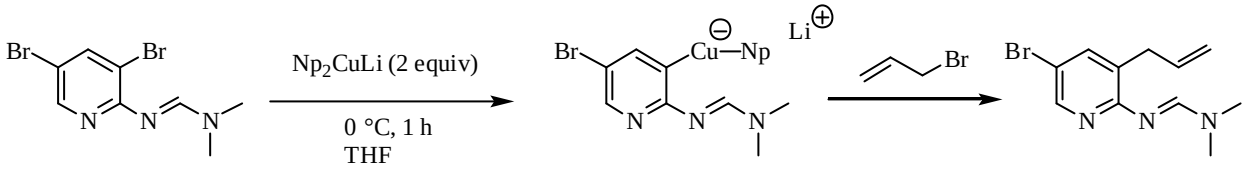
Heterocycles are fundamental constituents of most biologically active compounds. The preparation of polyfunctional heterocycles has been recently studied.[113] Moreover, the halogen-magnesium exchange has already been established as a very efficient tool for the synthesis of substituted indoles[114] or quinoline derivatives[115] (Scheme 54).



Scheme 54

A similar approach was adopted for the preparation of heterocyclic copper reagents. The readily prepared dibromopyridine **47** smoothly underwent to a bromine-copper exchange in presence of two equivalents of Np_2CuLi at 0 °C in 1 h, affording the corresponding cuprate **48a** which was allylated in 73 % yield. As in the case of magnesium exchange, the first equivalent is probably partially chelated by the amidine moiety and the second performs a selective exchange in the 3-position (Scheme 55 and Table 10, entry 1).

[113] Neumann, H.; Wangelin, A. J. v.; Gördes, D.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2001**, *123*, 8398.
[114] Dohle, W. *Ph.D. Thesis* LMU Universität München, **2002**.
[115] Jensen, A. E. *Ph.D. Thesis* LMU Universität München, **2001**.

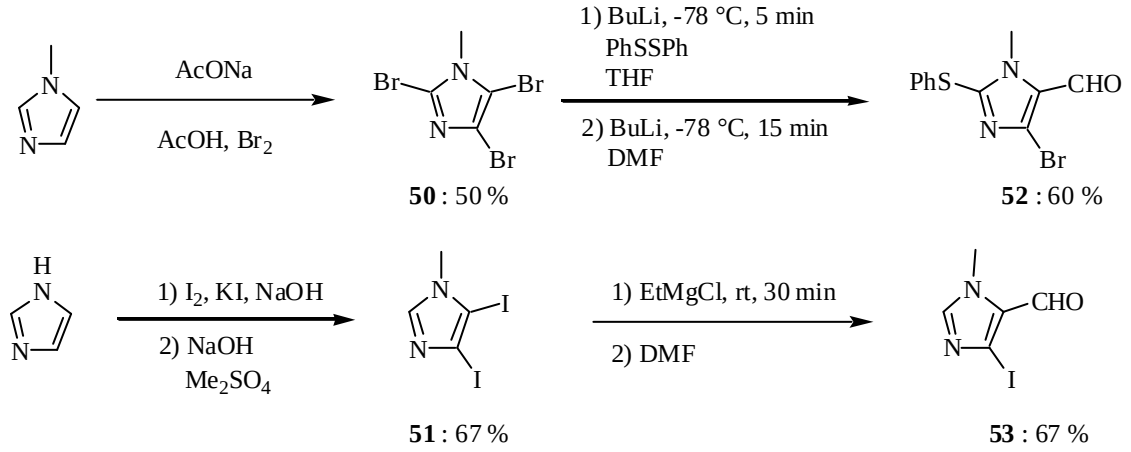


47 **48a** **49a** : 73 %

Scheme 55

Acylation of the cuprate **48a** with benzoyl chloride yielded the expected product in only 30 % yield (entry 2) and the hydrolysed bromopyridine was also recovered. This seems to indicate that the reaction is quite sensitive to steric effects, which was confirmed by the unsuccessful 1,4-addition to 2-cyclohexen-1-one (entry 3).

More interesting is the imidazole system. Generally, the acidic hydrogen in the 2-position of an imidazole ring can be abstracted by a base at low temperature.[116] For this reason, the carbon in the 2-position has to be protected if a halogen-lithium exchange is attempted, however this precaution is not necessary when magnesium reagents are used. Starting from commercially available *N*-methylimidazole, bromination furnished the imidazole derivatives **50**, which was treated with *n*-BuLi to give the protected substrate **52**. Similarly, iodination and subsequent methylation yielded the diiodomethyl imidazole **51**, which upon iodine-magnesium exchange and quenching with DMF, furnished the unprotected substrate in the 2-position **53** (Scheme 56).



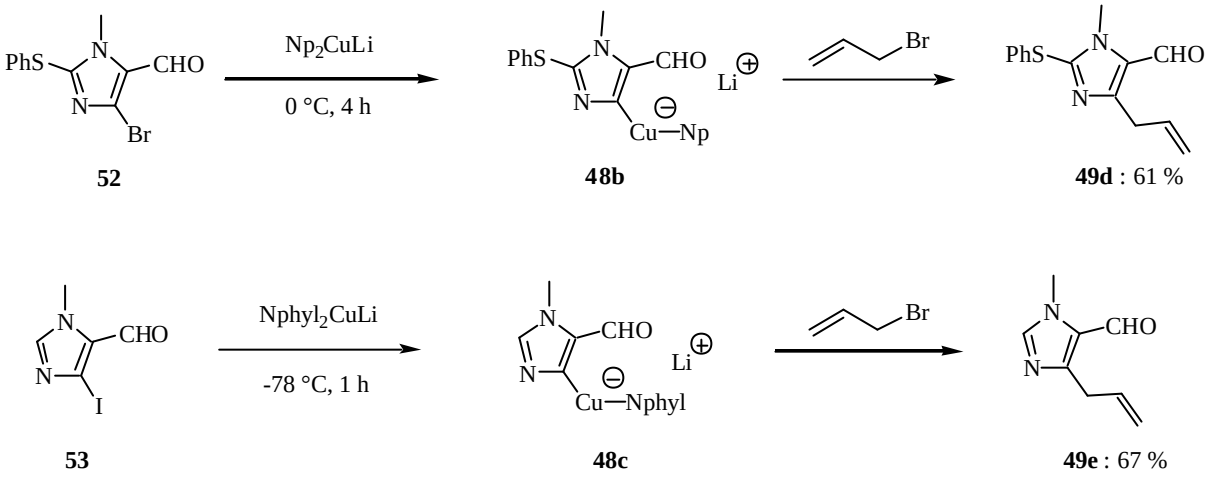
50 : 50 % **52** : 60 %

51 : 67 % **53** : 67 %

[116] For review on imidazole chemistry see: a) Grimmett, M. R. *Adv. Heterocyc. Chem.* **1980**, *27*, 241. b) Grimmett, M. R. C*omprehensive Heterocyclic Chemistry* (Ed. A. R. Katrizsky and C. W. Rees), Pergamon Press, Oxford, **1984**, Vol.4, p.345.

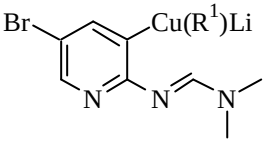
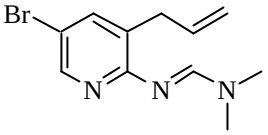
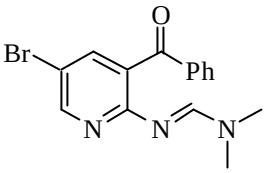
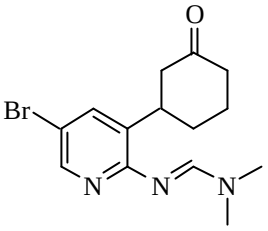
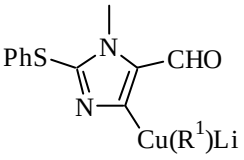
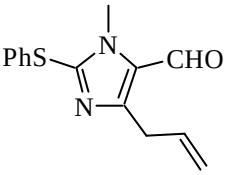
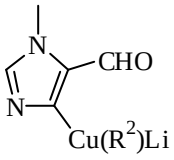
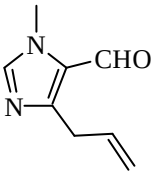
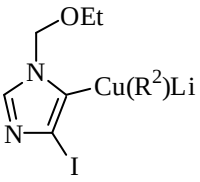
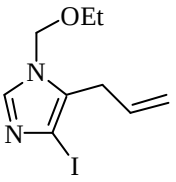
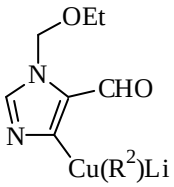
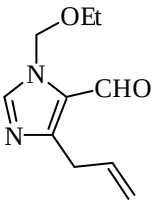
Scheme 56

For the bromine-copper exchange the more reactive Np_2CuLi was employed. In this case only one equivalent was necessary for the reaction to take place and after quenching with allyl bromide the desired product **49d** was obtained in 61 % yield. When non-protected imidazole was used, neopentyl cuprate had to be replaced by $Nphyl_2CuLi$ in order to avoid deprotonation, and the reaction proceeded smoothly at -78 °C to give 4-allyl-1-methyl-1*H*-imidazole-5-carbaldehyde **49e** in 67 % yield (Scheme 57 and Table 10).



Scheme 57

Table 10. Reaction of functionalised lithium heterocyclic cuprates **48** with electrophiles to give **49**.

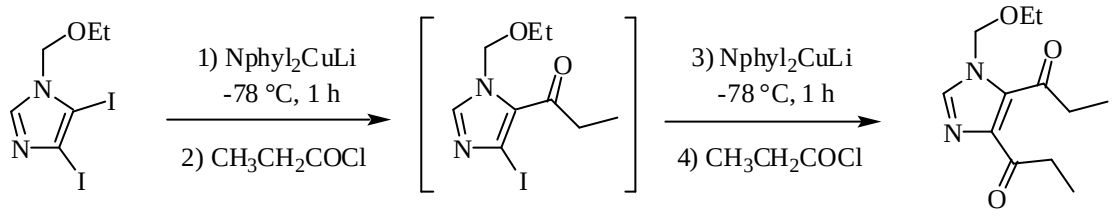
Entry	Cuprate of type **48**[a]	Electrophile	Product of type **49**		Yield (%)[b]
1	 **48a**	allyl bromide		**49a**	73
2	**48a**	PhCOCl		**49b**	30
3	**48a**	cyclohexenone		**49c**	trace
4	 **48b**	allyl bromide		**49d**	61
5	 **48c**	allyl bromide		**49e**	67
6	 **48d**	allyl bromide		**49f**	91
7	 **48e**	allyl bromide		**49g**	46

[a]R^1= neopentyl; R^2= neophyl

[b]Isolated yield of analytically pure product.

Similarly, 1-ethoxymethyl-4,5-diiodoimidazole smoothly underwent iodine-copper exchange with $Nphyl_2CuLi$ (-78 °C, 1 h), furnishing after quenching with allyl bromide the expected product in 91 % yield (entry 6).[117] The related derivative functionalised in the 5-position with an aldehyde group was allylated in 46 % yield (entry 7).

Interestingly, it was also possible to achieve a double iodine-copper exchange *in situ* in the presence of 2 equiv of $Nphyl_2CuLi$ at -78 °C, whereby the double acylated product **55** was obtained in 28 % overall yield (Scheme 58).



54 **55** : 28 %

Scheme 58

6.1 Summary

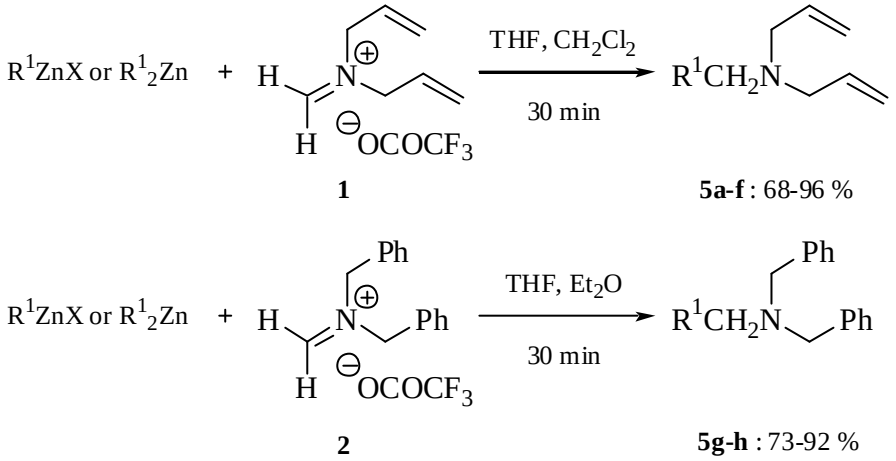
These results demonstrate that halogen-copper exchange on functionalised heterocycles is a method with a vast range of substrate applicability. Pyridine and imidazole derivatives react smoothly and furnish a variety of mono- and disubstituted products. Moreover, fast exchange rates and high functional group tolerance make it a potentially very useful tool in natural product synthesis.

[117] Matsuo, K. *Unpublished results*.

7 Summary and Outlook

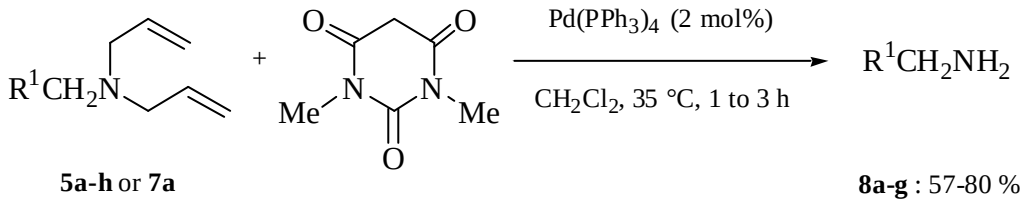
This work has been focused on new methods for the synthesis of zinc and copper reagents, and their application in the preparation of polyfunctionalised molecules.

In the first part an aminomethylation reaction of various functionalised zinc and magnesium reagents has been described. The readily prepared immonium trifluoroacetates reacted with organometallic species to give the corresponding protected amines in good to excellent yields (Scheme 59).



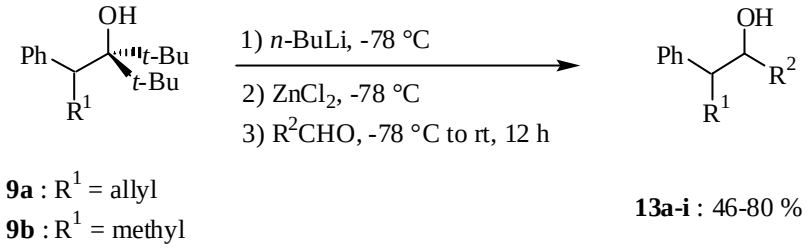
Scheme 59

The *bis*-allylated amines could then be deprotected to the primary amines. The reaction showed high tolerance towards functionalities like esters or nitriles (Scheme 60).



Scheme 60

An efficient protocol for the preparation of substituted benzylic zinc reagents has been developed. It is based on a fragmentation reaction of sterically hindered homobenzylic alcoholates and in this way avoids any formation of Wurtz-coupling side products. The fragmentation reaction leads to the formation of a benzylic zinc reagent, which reacts with various aldehydes, furnishing the desired substituted homobenzylic alcohols in good yields as a 1:1 mixture of diastereoisomers (Scheme 61).



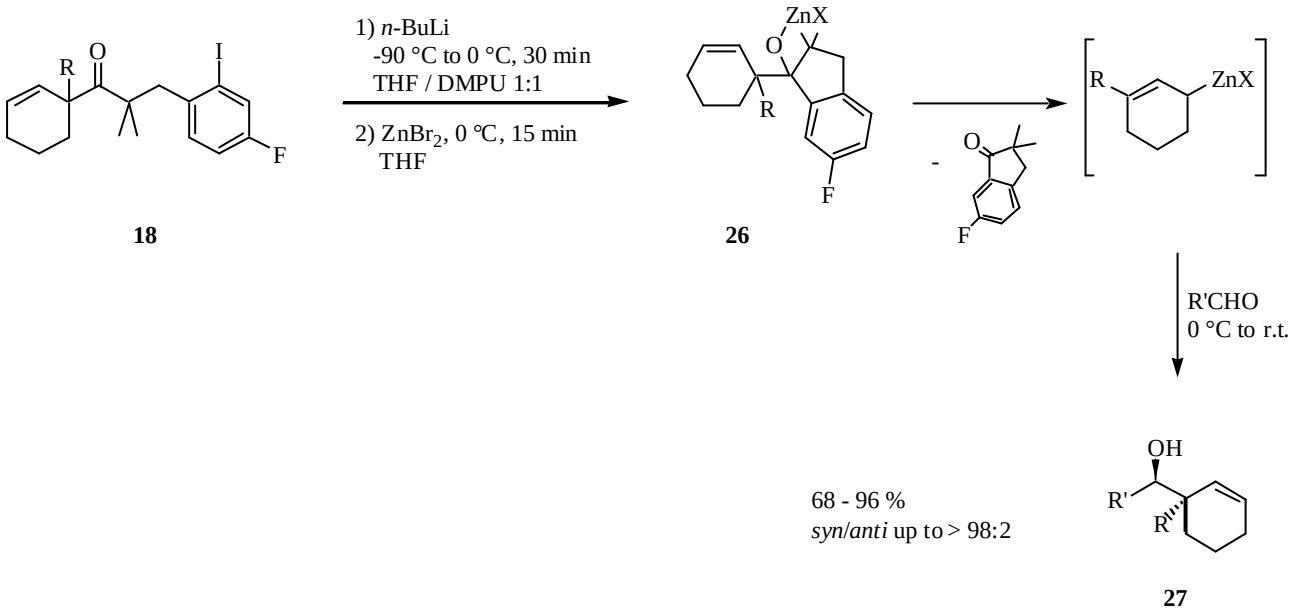
9a : R^1 = allyl
9b : R^1 = methyl

13a-i : 46-80 %

Scheme 61

Further improvements to this procedure would allow the synthesis of functionalised secondary benzylic zinc reagents, which are still difficult to obtain by other methods.

A similar concept was applied for the preparation of substituted allylic zinc reagents, obtained by a cyclization-fragmentation reaction of sterically hindered ketones. A cyclic five-membered ring alcoholate was obtained after iodine-lithium exchange at low temperature, and transmetalation to zinc followed by fragmentation led to the substituted allylic zinc reagent which, upon reaction with aldehydes, yielded the expected homoallylic alcohols in good yields and excellent diastereoselectivities (Scheme 62).

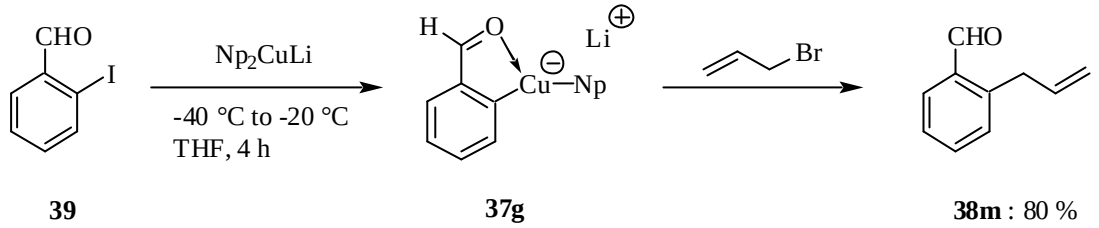


Scheme 62

The reaction proceeds *via* a six-membered ring intermediate with a fixed geometry, thereby favouring the attack of the electrophile from only one side of the molecule. It was observed that the addition of a polar cosolvent such as DMPU brought a significant improvement in yield and reaction rate and the size of the substituent R also played an important role in the diastereoselectivity of the reaction, while the steric bulk of the aldehyde had a minor influence.

A further step in the development of this elegant procedure would be the preparation of functionalised allylic zinc reagents. Even if preliminary results were not satisfactory, due to difficulties in the synthesis of the starting material, it would be of interest to develop a more general protocol that allows the formation of highly functionalised allylic zinc reagents and to investigate their diastereoselective reaction with a broader range of electrophiles.

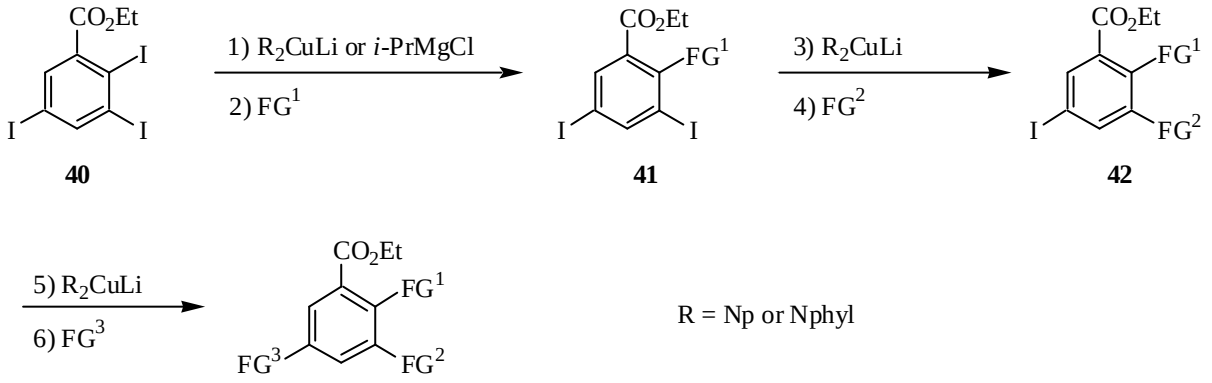
In the second part of this work the preparation of new sterically hindered lithium dialkylcuprates, Np_2CuLi and $Nphyl_2CuLi$, for the synthesis of highly functionalised mixed cuprates *via* halogen-copper exchange was developed. This method has been applied to arylic, vinylic and heterocyclic substrates and exhibited very high functional group tolerance. For the first time, sensitive functionalities such as aldehydes or enolizable ketones were compatible with a halogen-metal exchange (Scheme 63).



39 **37g** **38m** : 80 %

Scheme 63

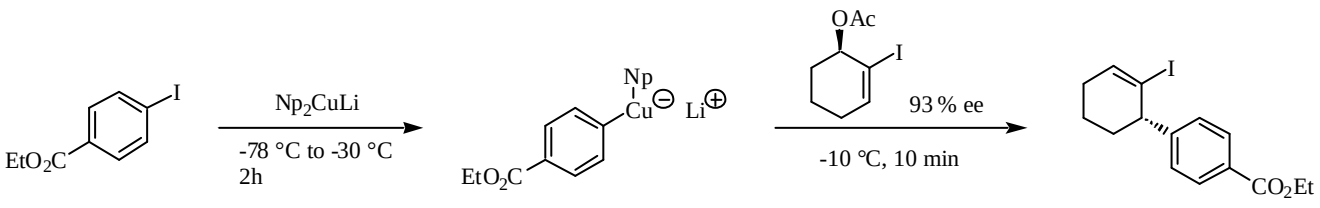
Polyiodinated aryl reagents could be regioselectively functionalised combining the use of the two cuprates which possess different reactivity and, consequently, complementary functional group tolerance (Scheme 64).



40 **41** **42** **43**

Scheme 64

Preliminary studies on substitution reactions with mixed cuprates have shown that the reaction proceeds with high stereoselectivity (Scheme 65).



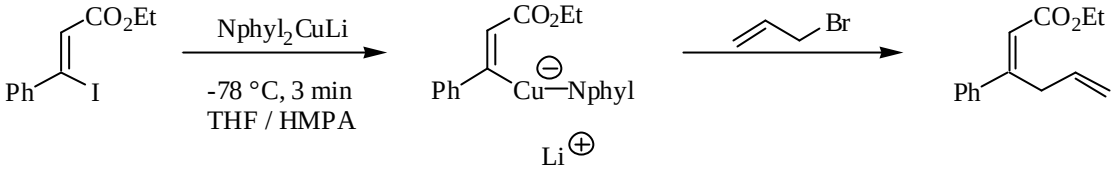
37a

56 : 64 %
92 % ee

Scheme 65

Further investigations in this field could lead to very interesting applications, for example in the synthesis of ligands.

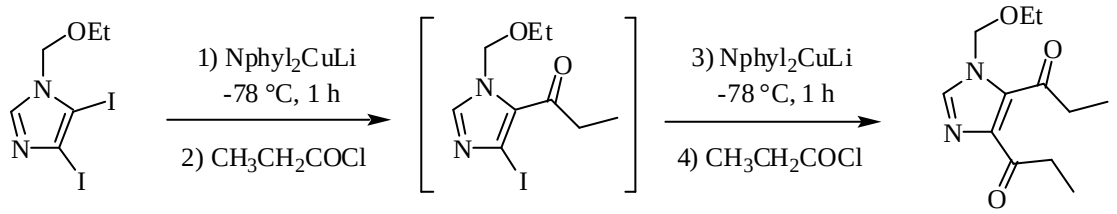
Vinylic substrates underwent halogen-copper exchange with retention of the configuration of the double bond. The exchange rate was very fast and allowed the preparation of various functionalised tri- and tetrasubstituted alkenes (Scheme 66).



44b **45b** : 88 %

Scheme 66

Finally, heterocycles have also proved to be suitable reagents for the halogen-copper exchange. Pyridine and imidazole systems bearing aldehydes or ketones were reacted with Np_2CuLi or $Nphyl_2CuLi$ affording the expected products in reasonable to very good yield (Scheme 67).



54 **55** : 28 %

Scheme 67

The important role of heterocycles in biologically active compounds makes them especially interesting substrates that should be further investigated. A particularly stimulating task would be the application of this new and quite successful methodology in the synthesis of natural products.

Experimental Section

1 General Conditions

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

Solvents

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

Reagents

- Reagents of >98 % purity were used as obtained.
- *n*-Butyllithium was used as 1.5 M solution in hexane.
- *t*-Butyllithium was used as 1.5 M solution in pentane.
- The following reagents were prepared according to literature procedures: ethyl α-bromomethylacrylate,[118] ethyl(Z)-3-iodo-3-phenylpropenoate,[119] 2-iodo-3-methyl-2-cyclohexen-1-one,[120] 4-iodo-7-methoxy-1,2-dihydronaphtalene, [121] 3-chloro-2,4-dimethylpentane. [122]

Content determination of organometallic reagent

Organolitium and organomagnesium solution were titrated using the method of Paquette.[123]

The concentrations of organozinc solutions were determined by back titration of iodine with an aqueous $Na_2S_2O_3$ solution.

---

[118] Villieras, J.; Rambaud, M. *Synthesis* **1982**, 925.
[119] Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816.
[120] Johnson, C. R.; Sakaguchi, H. *Synlett*, **1992**, 813.
[121] Lee, K.; Wiemer, D. E. *Tetrahedron Lett.* **1993**, *34*, 2433.
[122] Metveeva, E. D. ;Yaloskaya, A. I.; Cherepanov, I. A.; Bundel, Y. G.; Kurts, A. L. *J. Org. Chem. URSS* **1989**, *25*, 587.
[123] Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.

Chromatography

- Thin layer chromatography (TLC) was performed using aluminium plates covered with SiO_2 (Merck 60, F-254). The chromatograms were viewed under UV light and /or by treatment of the TLC plate with one of the solutions below followed by heating with a heat gun:
  - $KMnO_4$ (0.3 g), K_2CO_3(20 g), KOH (0.3 g) in water (300 mL).
  - Phosphormolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g), conc. H_2SO_4 (12 mL) in water (230 mL).
- Flash column chromatography was performed using SiO_2 60 (0.040-0.063 mm) from Merck.
- Gas chromatography (GC): Hewlett-Packard 6890
  - Column A: 5 % phenylmethylpolysiloxane (HP Ultra 2) 12 m x 0.2 mm
  - Column B: 5 % phenylmethylpolysiloxane (HP %) 5 m x 0.25 mm

The compounds were detected with a flame ionisation detector.

Analytical data

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

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

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

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

  - Column C: 5% phenylmethylpolysiloxane (HP 5) 30m x 250 µm x 0.25 µm

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

2 Typical Procedures (TP)

TP 1: Typical procedure for the aminomethylation of functionalised organozinc and Grignard reagents

A dried, argon flushed 100 mL flask was charged with the starting aminal (5.3 mmol) and CH_2Cl_2 (10 mL), was added. The solution was cooled to 0 °C and trifluoroaceticanhydride (0.74 mL, 5.3 mmol) was added dropwise. The mixture was kept at 0 °C for 10 min and at rt for 0.5 h. Development of a yellow colour indicates the formation of the iminium. The immonium trifluoroacetate was then cooled to -78 °C and a solution of the functionalised organometallic reagent (7.5 mmol) in THF was added. After stirring for the required time, the reaction was quenched with saturated, aqueous NH_4Cl and extracted with CH_2Cl_2 or diethyl ether (4 x 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography yielded the desired product.

TP 2: Typical procedure for palladium-catalysed deprotection of allylamines

A solution of the allylamine (2.0 mmol) in dry degassed CH_2Cl_2 (5 mL), was added with a syringe in a Schlenk tube containing the catalyst ($Pd(PPh_3)_4$, 69 mg, $5.9x10^{-5}$ mmol) and NDMBA (1.9 g, 11.9 mmol) under argon. The homogeneous mixture was stirred at 35 °C for the required time. After cooling, the CH_2Cl_2 was removed under vacuum and the residue dissolved in diethyl ether. Water was added and the mixture was acidified with 1 N HCl to pH 2, then the organic layer was separated. The aqueous layer was basified to pH 9 with saturated, aqueous Na_2CO_3 and extracted with CH_2Cl_2 (9 x 20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography yielded the desired deprotected amine.

TP 3: Typical procedure for the preparation of benzylic alcohols via a fragmentation reaction

A solution of *n*-BuLi (8.4 mL, 12.3 mmol) was added at -78 °C to a solution of the tertiary alcohol (1.1 mmol) in THF (3 mL). The reaction mixture was stirred at this temperature for 30

min and a solution of zinc chloride (115 mg, 0.8 mmol) in THF (2 mL) was added, followed by the aldehyde (0.67 mmol). The reaction was slowly warmed to rt overnight and quenched with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3 x 15 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography yielded the desired product.

TP 4: Typical procedure for the generation of homoallylic zinc reagents via a cyclization-fragmentation reaction

A solution of *n*-BuLi (0.55 mL, 0.8 mmol) was added at -90 °C to a solution of the starting ketone (0.8 mmol) in THF/DMPU 1:1 (2 mL). The reaction mixture was quickly warmed up to 0 °C and after 30 min a 1.5 M solution of zinc bromide in THF (0.74 mL, 1.1 mmol) was added. After 15 min the aldehyde was added and the mixture was let warm up to rt overnight. The reaction mixture was then quenched with saturated, aqueous NH_4Cl and the aqueous phase was extracted with diethyl ether (3 x 15 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography yielded the desired product.

TP 5: Typical procedure for the halogen-copper exchange on arylic substrates

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with the aryl halide (1.0 mmol). Dry THF (2 mL) was added and the solution was added slowly into a dry and argon flushed 25 mL flask, containing the dialkyllithiumcuprate **33** or **35**, previously prepared (1.2 mmol) and cooled to -78 °C. The mixture was warmed quickly to the required temperature. The halogen-copper exchange was complete within 1-3 h (checked by GC analysis of reaction aliquots) and the electrophile (0.9 mmol) was added to the mixed organocuprate (**4**), then the mixture was let warm up to rt. After 0.5 h of stirring at rt, the reaction mixture was quenched with saturated, aqueous NH_4Cl (2 mL) and poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 x 30 mL). The organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography yielded the desired product.

TP 6: Typical procedure for the iodine-copper exchange on ethyl (2Z)-3-iodo-3-phenylpropenoate

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with ethyl (2Z)-3-iodo-3-phenylpropenoate (302 mg, 1.0 mmol). THF (1 mL) and HMPA (1.6 mL, 9.0 mmol) were added and the solution was added slowly into a dry and argon flushed 25 mL flask, containing the dineophyllithiumcuprate **35**, previously prepared (1.2 mmol) and cooled to -78 °C. The iodine-copper exchange was complete within 3 min (checked by GC analysis of reaction aliquots) and the electrophile (0.9 mmol) was added to the mixed organocuprate, then the mixture was let warm up to rt. After 0.5 h of stirring at rt, the reaction mixture was quenched with saturated, aqueous NH_4Cl (2 mL) and poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL). The organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography yielded the desired product.

TP 7: Typical procedure for the bromine-copper exchange on *N*,*N*-diallyl-2-bromo-3-methyl-butenamide

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with *N*,*N*-diallyl-2-bromo-3-methyl-butenamide (258 mg, 1.0 mmol). THF (1 mL) was added and the solution was added slowly into a dry and argon flushed 25 mL flask, containing the dineophyllithiumcuprate **35**, previously prepared (1.2 mmol) and cooled to -78 °C. The reaction mixture was quickly warmed to 0° C. The bromine-copper exchange was complete within 30 min (checked by GC analysis of reaction aliquots) and the electrophile (2.0 mmol) was added to the mixed organocuprate, then the mixture was let warm up to rt. After 0.5 h of stirring at rt, the reaction mixture was quenched with saturated, aqueous NH_4Cl (2 mL) and poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL). The organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography yielded the desired product.

TP 8: Typical procedure for the iodine-copper exchange on imidazole derivatives

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with 4-iodo-1-methyl-1*H*-imidazole-5-carbaldehyde **53** (236 mg, 1.0 mmol). THF (1 mL) was added and the solution was added slowly into a dry and argon flushed 25 mL flask, containing the dineophyllithiumcuprate **35**, previously prepared (1.2 mmol) and cooled to -78 °C. The iodine-copper exchange was complete within 1 h (checked by GC analysis of reaction aliquots) and the electrophile (1.0 mmol) was added to the mixed organocuprate, then the mixture was let warm up to rt. After 0.5 h of stirring at rt, the reaction mixture was quenched with saturated, aqueous NH_4Cl (2 mL) and poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL). The organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography yielded the desired product.

3 Synthesis of Organozinc and Organocopper Reagents

Synthesis of primary and secondary alkylzinc iodides[29]

A 250 mL two-necked flask equipped with a dropping funnel, a reflux condenser and a stirring bar was charged with zinc dust (8.6 g, 132 mmol, Aldrich, 325 mesh), flame dried, and flushed with argon. THF (40 mL) and 1,2-dibromoethane (2.5 g, 13.3 mmol) were added and the zinc was activated by heating the solvent to reflux with a heat gun, then allowing the reaction mixture to cool. This procedure was repeated three times, then TMSCl (2.4 mL, 26.3 mmol) was added. The mixture was then heated to 50 °C and an alkyl iodide (45.0 mmol) was added dropwise as a solution in THF (20 mL). The mixture was maintained at 50 °C until the zinc insertion into the alkyl iodide was complete (checked bi GC analysis, approx. 4 h). The reagent was concentrated *in vacuo* and titrated before use.

Synthesis of benzylic zinc bromides[124]

A 250 mL two-necked flask equipped with a dropping funnel, a reflux condenser and a stirring bar was charged with zinc dust (8.6 g, 132 mmol, Aldrich, 325 mesh), flame dried, and flushed with argon. THF (40 mL) and 1,2-dibromoethane (2.5 g, 13.3 mmol) were added and the zinc was activated by heating the solvent to reflux with a heat gun, then allowing the reaction mixture to cool. This procedure was repeated three times, then TMSCl (2.4 mL, 26.3 mmol) was added. The mixture was cooled to 0 °C before the benzylic zinc bromide (44.0 mmol) was added dropwise (1 drop/sec) as a solution in THF (20 ml). The temperature was maintained at 0 °C until the reaction was complete (checked by GC, approx. 2 h). The reagent was concentrated *in vacuo* and titrated before use.

[124] Berk, S. C.; Yeh, M. C. P.; Jeong, N., Knochel, P. *Organometallics* **1990**, *9*, 3053

Synthesis of lithium dimethylcuprate[125]

MeLi (2.25 mL, 4.0 mmol, 1.79 M in Et_2O) was added dropwise to a suspension of CuCN (0.2 g, 2.2 mmol) in THF (2 mL) at -78 °C. The mixture was warmed quickly to -40 °C till a clear colourless solution was obtained.
Lithium dibutylcuprate and lithium trimethylsilylmethylcuprate were prepared by an analogous procedure.

Synthesis of lithium bis(1-isopropyl-2-methylpropyl)cuprate[126]

A mixture of lithium metal (56 mg, 8.0 mmol) and 4,4' Di-*tert*-butylbiphenyl (2.4 g, 9.2 mmol) in THF (6 mL) was cooled to -4 °C and stirred overnight at this temperature. In the morning the reaction mixture was cooled to -78 °C and a solution of 3-chloro-2,4-dimethylpentane (540 mg, 4.0 mmol) in THF (4 mL) was added. The dark red solution obtained was then cannulated into a suspension of CuCN (190 mg, 2.1 mmol) in THF (2 mL). The mixture was then warmed to -20 °C and stirred for 20 min, furnishing the expected dialkylcuprate ready to use.

Synthesis of lithium dineopentylcuprate[127]

A 10 mL round-bottomed flask, flame dried and flushed with argon was charged with neopentyl iodide (0.3 mL, 2.2 mmol) and the compound dissolved in 2 mL of diethyl ether. The solution was cooled to -78 °C and *t*-BuLi (3.1 mL, 4.6 mmol) was added dropwise. The reaction mixture was stirred for 1 h at -78 °C and warmed to rt. After stirring for another hour the mixture was then cannulated into a suspension of CuCN (110 mg, 1.2 mmol) in THF (1 mL) cooled to -78 °C. the reaction mixture was allowed to warm to 0 °C, furnishing the expected dialkylcuprate ready to use.

[125] Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1983**, *48*, 546.
[126] Freeman, P. K.; Hutchinson, L. L.; *J. Org. Chem.* **1980**, *45*, 1924.
[127] Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

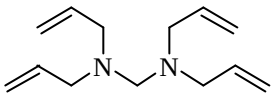
Synthesis of lithium dineophylcuprate[89]

A 500 mL round-bottomed flask, flame dried and flushed with argon was charged with lithium metal (3.0 g, 432 mmol) and neophylchloride (14.0 mL, 86.9 mmol) in hexane (75 mL). The reaction mixture was heated under reflux overnight. After cooling to rt the mixture was cannulated into a flame dried Schlenk tube and the hexane removed *in vacuo*. Dry diethyl ether was added and the mixture was centrifuged (2000 rpm, 30 min). The clear solution of neophyllithium thus obtained was titrated before use with menthol using *o*-phenantroline as indicator and could be stored at -30 °C for several days.

A 25 mL round-bottomed flask, flame dried and flushed with argon was charged with CuCN (110 mg, 1.2 mmol). THF (1 mL) was added and the suspension cooled to 0 °C. The freshly titrated solution of neophyllithium was then slowly added and the mixture quickly warmed to rt and stirred for 10 min, till a clear yellow solution of the desired cuprate was obtained.

4 Aminomethylation of Functionalised Organozinc Reagents and Grignard Reagent Using Immonium Trifluoroacetates

Synthesis of *N,N,N,N*-tetraallylmethanediamine (3)



A 100 mL round bottomed flask was charged with diallylamine (30 mL, 240 mmol). A solution of formaldehyde (12 mL, 320 mmol), was added slowly at 0 °C and the mixture was heated at 100 °C for 2 h. The formation of a biphasic system was observed, the upper layer was separated and dried over KOH pellets. After filtration the crude mixture was distilled under vacuum to give the desired product **3** as a colourless oil (18.3 g, 74 %).

Bp 90 °C, 7 mbar

IR (film, cm^{-1}): $\tilde{n}$ 3077 (w), 2805 (m), 1643 (m), 1417 (m), 1399 (m), 1161 (m), 994 (s), 916 (vs).

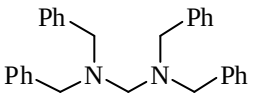
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.82-5.68 (m, 4H), 5.09-4.98 (m, 8H), 3.09-3.06 (m, 8H), 3.03 (s, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 136.6, 117.5, 72.7, 54.7.

MS (EI, 70 eV): 205 ($[M–H]^+$, 1), 110 (100), 81 (4), 68 (3), 41 (13).

$C_{13}H_{22}N_2$	HRMS	Calcd.	205.1705 $[M–H]^+$
		Found	205.1691 $[M–H]^+$

Synthesis of *N,N,N,N*-tetrabenzylmethanediamine (4)



A 100 mL round bottomed flask was charged with dibenzylamine (46 mL, 239 mmol). A solution of formaldehyde (13 mL, 350 mmol), was added slowly at 0 °C and the mixture heated at 100 °C for 2 h. The formation of a biphasic system was observed, the upper layer was

separated and dried over KOH pellets. After filtration and concentration *in vacuo* a yellow solid was obtained. Recrystallization from *n*-Hexane yielded the desired product **4** as a white crystalline solid (29.0 g, 30 %).

Mp 105 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 3067 (w), 2815 (m), 1629 (m), 1427 (m), 1153 (m), 963 (s), 916 (vs), 791 (s), 750 (vs), 734 (vs), 696 (vs), 470 (m).

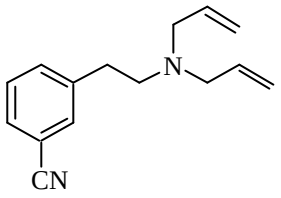
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.47-7.36 (m, 20H), 3.77 (s, 8H), 3.26 (s, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 140.3, 129.5, 129.4, 129.1, 128.9, 128.7, 127.5, 127.3, 72.8, 56.7.

MS (EI, 70 eV): 406 ($[M–H]^+$,10), 210 (100), 91 (41).

$C_{29}H_{30}N_2$	Calcd.	C, 85.67	H, 7.43	N, 6.89
	Found	C, 85.28	H, 7.36	N, 6.88

Synthesis of 3-[2-diallylamino)ethyl]benzonitrile (5a)



Prepared according to TP 1 from the corresponding benzylic zinc reagent (20.3 mL, 11.3 mmol, 0.56 M solution in THF) and immonium trifluoroacetate **1** (7.6 mmol) at -78 °C. Reaction time: 30 min. Purification by flash chromatography (CH_2Cl_2/MeOH 99:1) yielded **5a** as a colourless oil (1.6 g, 96 %).

IR (film, cm^{-1}): $\tilde{n}$ 3077 (m), 2977 (m), 2927 (m), 2807 (s), 2229 (vs), 1642 (m), 1483 (m), 1418 (m), 1151 (m), 115 (m), 996 (s), 920 (vs), 797 (s), 691 (s).

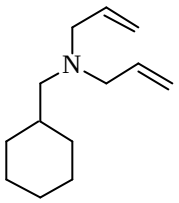
^{1}H NMR ($CDCl_3$, 300MHz): d 7.28-7.41 (m, 4H), 5.67-5.78 (m, 2H), 5.05-5.13 (m, 4H), 3.07 (d, *J* = 6,4 Hz, 4H), 2.70 (t, *J* = 29.1 and 6.5 Hz, 2H), 2.61 (t, *J* = 29.1 and 6.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 142.5, 135.8, 133.8, 132.7, 130.1, 129.4, 119.4, 118.0, 112.6 57.3, 54.7,33.4.

MS (EI, 70 eV): 226 (M^+, 30), 199 (90), 110 (100), 41 (31).

$C_{15}H_{18}N_2$	Calcd.	C, 79.21	H, 7.88	N, 12.26
	Found	C, 79.61	H, 8.01	N, 12.38

Synthesis of *N*-allyl-*N*-(cyclohexylmethyl)-2-propen-1-amine (5d)



Prepared according to TP 1 from the corresponding zinc reagent (30.0 mL, 30.7 mmol, 1 M solution in THF) and immonium trifluoroacetate **1** (20.0 mmol) at rt. Reaction time: 2 h. Purification by flash chromatography (CH_2Cl_2/MeOH 98:2) yielded **5d** as a light yellow oil (3.2 g, 83 %).

IR (film, cm^{-1}): $\tilde{n}$ 3400 (s, br), 2931 (vs), 2858 (vs), 1643 (w), 1448 (m), 1372 (m), 113 (vs), 952 (m).

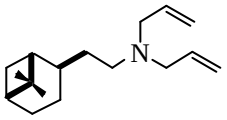
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.71-5.84 (m, 2H), 5.02-5.12 (m, 4H), 2.98 (d, *J* = 6.3 Hz, 4H), 2.12 (d, *J* = 6.9 Hz, 2H), 0.74-1.72 (m, 11H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 135.2, 115.9, 59.5, 56.4, 34.9, 30.8, 26.2, 24.3.

MS (EI, 70 eV): 193 (M^+, 3), 135 (12), 110 (100), 73 (59), 55 (75).

$C_{13}H_{23}N$	Calcd.	C, 80.57	H, 11.66	N, 7.23
	Found	C, 80.76	H, 11.99	N, 7.24

Synthesis of *N*-ally-*N*-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)ethyl]-2-propen-1-amine (5e)



Prepared according to TP 1 from the corresponding zinc reagent (3.0 mL, 3.4 mmol, 1.2 M solution in THF) and immonium trifluoroacetate **1** (2.0 mmol) at rt. Reaction time: 1 h. Purification by flash chromatography (CH_2Cl_2/MeOH 98:2) yielded **5e** as a light yellow oil (435 mg, 88 %).

IR (film, cm^{-1}): $\tilde{n}$ 3077 (w), 2980 (m), 2934 (vs), 2799 (m), 1730 (w), 1642 (w), 1468 (m), 1270 (m), 995 (m9, 917 (vs).

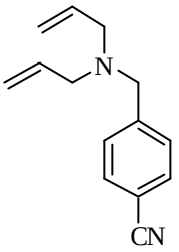
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.74-5.83 (m, 2H), 5.02-5.12 (m, 4H), 3.00 (d, *J* = 6.3 Hz, 4H), 1.10 (s, 3H), 0.93 (s, 3H), 0.74-2.37 (m, 13H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 136.2, 117.6, 57.3, 52.4, 46.5, 41.4, 39.9, 35.0, 34.1, 28.6, 27.2, 23.4, 22.9.

MS (EI, 70 eV): 247 (M^+, 3) 206 (4), 178 (9), 110 (100), 81 (4), 41 (10).

$C_{17}H_{29}N$	Calcd.	C, 81.52	H, 11.81	N, 5.66
	Found	C, 81.32	H, 11.34	N, 5.56

Synthesis of 4-[2-(diallylamino)methyl]benzonitrile (5f)



Prepared according to TP 1 from the corresponding zinc reagent (17.0 mL, 13.4 mmol, 0.79 M solution in THF) and immonium trifluoroacetate **1** (5.2 mmol) at -78 °C. Reaction time: 1 h. Purification by flash chromatography (CH_2Cl_2/MeOH 98:2) yielded **5f** as a light yellow oil (0.8 g, 72 %).

IR (film, cm^{-1}): $\tilde{n}$ 3400 (w, br), 2920 (m), 2810 (s), 2228 (vs), 1643 (s), 1608 (vs), 1447 (m), 1415 (s), 1366 (m), 1257 (m), 989 (s), 922 (vs), 816 (s), 548 (m).

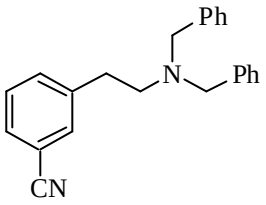
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.49 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 5.68-5.79 (m, 2H), 5.03-5.12 (m, 4H), 3.51 (s, 2H), 2.97 (d, *J* = 6.3 Hz, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 146.1, 132.4, 135.7, 129.2, 119.4, 118.1, 111.0, 57.5, 57.0.

MS (EI, 70 eV): 212 (M^+, 24), 185 (52), 171 (24), 116 (100), 89 (23), 41 (26).

$C_{14}H_{16}N_2$	Calcd.	C, 79.20	H, 7.59	N, 13.19
	Found	C, 78.73	H, 7.37	N, 12.74

Synthesis of 3-[2-(dibenzylamino)ethyl]benzonitrile (5g)

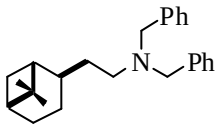


Prepared according to TP 1 from the corresponding zinc reagent (16.0 mL, 11.2 mmol., 0.69 M in THF) and immonium trifluoroacetate **2** (9.9 mmol) at -78 °C. Reaction time: 1 h. Purification by flash chromatography (CH_2Cl_2) yielded **5g** as white crystalline solid (3.0 g, 92 %).

Mp 60 °C
IR (KBr, cm^{-1}): $\tilde{n}$ 3436 (w, br), 2790 (vs), 2227 (s), 1492 (s), 1448 (s), 1374 (s), 1234 (m), 1128 (m), 1115 (m), 1026 (m), 791 (s), 750 (vs), 734 (vs), 696 (vs), 470 (m).
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.38-7.13 (m, 14H), 3.52 (s, 4H), 2.69 (t, *J* = 6.9 Hz, 2H), 2.61 (t, *J* = 6.9 Hz, 2H).
^{13}C NMR ($CDCl_3$, 75 MHz): d 141.0, 138.2, 126-132, 118.0, 111.1, 57.4, 53.1,32.1.
MS (EI, 70 eV): 324 (38), 233 (40), 210 (92), 91 (100), 65 (10), 39 (2).

$C_{23}H_{22}N_2$	Calcd.	C, 84.62	H, 6.79	N, 8.58
	Found	C, 84.28	H, 6.75	N, 8.51

Synthesis of *N*,*N*-dibenzyl-2-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)ethanamine (5h)



Prepared according to TP 1 from the corresponding zinc reagent (4.6 mL, 4.1 mmol, 0.88 M in THF) and immonium trifluoroacetate **2** (3.6 mmol) at rt. Reaction time: 3 h. Purification by flash chromatography (pentane/diethyl ether 98:2) yielded **5h** as a colourless oil (1.1 g, 86 %).

IR (film, cm^{-1}): $\tilde{n}$ 3026 (s), 2936 (vs), 2793 (s), 1601 (w), 1494 (vs), 1452 (vs), 1382 (s), 1365 (vs), 1125 (m), 1028 (s), 744 (vs), 698 (vs).

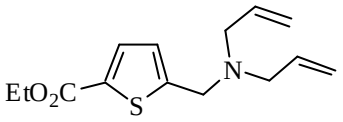
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.08-7.24 (m, 10H), 3.44 (s, 4H), 2.31 (t, *J* = 7.5 Hz, 4H), 1.04 (s, 3H), 0.89 (s, 3H), 0.69-2.15 (m, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 140.5, 129.3, 128.6, 127.2, 58.8, 52.4, 46.8, 42.0, 41.5, 39.5, 35.3, 34.1, 28.7, 27.1, 23.8, 23.0.

MS (EI, 70 eV): 347 (M^+, 4), 278 (20), 210 (100), 181 (1), 91 (75).

$C_{25}H_{33}N$	Calcd.	C, 86.39	H, 9.57	N, 4.03
	Found	C, 86.11	H, 9.49	N, 3.99

Synthesis of ethyl 5-[(diallylamino)methyl]-2-thiophenecarboxylate (7a)



Ethyl 5-bromo-2-thiophenecarboxylate (1.8 g, 7.7 mmol) was dissolved in THF (10 mL) and cooled to -40 °C. *i*-PrMgBr (11.0 mL, 8.8 mmol, 0.8 M solution in THF) was added dropwise over 15 min. After 1 h the solution of immonium trifluoroacetate **1** (4.9 mmol) in CH_2Cl_2 was added at -40 °C. After 3 h the reaction was quenched with saturated, aqueous Na_2CO_3. The aqueous phase was extracted with diethyl eher (3 x 30 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) yielded **7a** as a light yellow oil (1.0 g, 77 %).

IR (film, cm^{-1}): $\tilde{n}$ 2979 (m), 1710 (vs), 1541 (m), 1466 (s), 1366 (m), 1280 (vs), 1092 (vs), 922 (m), 751 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.55 (d, *J* = 3.8 Hz, 1H), 6.8 (d, *J* = 3.6 Hz, 1H), 5.73-5.82 (m, 2H), 5.05-5.20 (m, 4H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 2H), 3.04 (d, *J* = 6.3 Hz, 4H), 1.28 (t, *J* = 10.9 Hz, 3H).

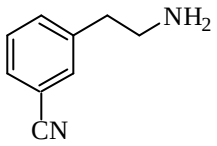
^{13}C NMR ($CDCl_3$, 75 MHz): d 162.8, 152.0, 135.7, 133.5, 131.3, 126.1, 118.2, 61.3, 56.7, 52.3, 14.7.

MS (EI, 70 eV): 265 (M^+, 23), 238 (15), 169 (100), 141 (34), 96 (21), 41 (18).

$C_{14}H_{19}NO_2S$

Calcd.	C, 63.36	H, 7.21	N, 5.28	S, 12.08
Found	C, 63.03	H, 6.97	N, 5.13	S, 12.43

Synthesis of 3-(2-aminoethyl)benzonitrile (8a)



Prepared according to TP 2 from **5a** (0.45 g, 2.0 mmol), $Pd(PPh_3)_4$ (69 mg, $5.9x10^{-5}$ mmol) and NDMBA (1.86 g, 11.9 mmol). Reaction time: 1.5 h. Purification by flash chromatography (CH_2Cl_2/MeOH 99:1) yielded **8a** as a red oil (182 mg, 63 %).

IR (film, cm^{-1}): $\tilde{n}$ 3400 (vs, br), 2228 (vs), 1676 (vs), 1582 (vs), 1379 (s), 1119 (m), 798 (s), 722 (m), 691 (s), 541 (s).

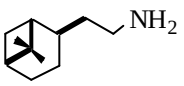
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.54-7.39 (m, 4H), 3.01 (t, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 6.5 Hz, 2H), 1.47 (s, br, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 140.4, 132.4, 131.3, 129.0, 128.2, 117.9, 111.4, 41.7, 38.5.

MS (EI, 70 eV): 145 ($[M–H]^+$, 10), 128 (21), 117 (100), 89 (85), 75 (17), 63 (39), 51 (22), 39 (36).

$C_9H_{10}N_2$	Calcd.	C, 73.94	H, 6.89	N, 19.16
	Found	C, 73.87	H, 6.46	N, 19.17

Synthesis of 2-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)ethanamine (8d)



Prepared according to TP 2 from **5e** (395 mg, 1.6 mmol), $Pd(PPh_3)_4$ (50 mg, $4.3x10^{-5}$ mmol) and NDMBA (1.6 g, 10.0 mmol). Reaction time: 3 h. Purification by flash chromatography (CH_2Cl_2/MeOH 98:2) yielded **8d** as a light yellow oil (200 mg, 74 %).

IR (film, cm^{-1}): $\tilde{n}$ 3271 (m, br), 2931 (vs), 2869 (vs), 1726 (vs), 1658 (vs), 1466 (s), 1383 (s), 1271 (vs), 1122 (vs), 1073 (s), 797 (m).

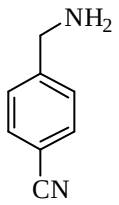
^{1}H NMR ($CDCl_3$, 300 MHz): d 2.63 (m, 4H), 1.11 (s, 3H), 0.94 (s, 3H), 0.80-2.37 (m, 13H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 131.5, 117.6, 67.1, 45.5, 40.5, 40.0, 39.6, 37.8, 37.7, 32.7, 29.4, 27.2, 23.4, 22.9.

MS (EI, 70 eV): 167 (M^+, 30), 135 (36), 107 (42), 82 (100), 69 (40).

$C_{11}H_{21}N$	Calcd.	C, 78.48	H, 12.69	N, 8.37
	Found	C, 78.32	H, 12.36	N, 8.29

Synthesis of 4-(aminomethyl)benzonitrile (8e)



Prepared according to TP 2 from **5f** (0.4 g, 1.9 mmol), $Pd(PPh_3)_4$ (46 mg, $3.9x10^{-5}$ mmol) and NDMBA (1.9 g, 11.9 mmol). Reaction time: 3 h. Purification by flash chromatography (CH_2Cl_2/MeOH 9:1) yielded **8e** as a yellow oil (200 mg, 80 %).

IR (film, cm^{-1}): $\tilde{n}$ 3380 (vs, br), 2230 (vs), 1668 (vs), 1575 (vs), 1344 (s), 1122 (m), 799 (s), 719 (m), 690 (s), 540 (s).

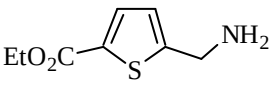
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.55-7.36 (m, 4H), 3.88 (s, 2H), 2.21 (s, br, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 147.3, 130.9, 126.7, 117.9, 109.6, 44.9.

MS (EI, 70 eV): 132 (M^+, 100), 104 (44), 77 (15).

$C_8H_8N_2$	Calcd.	C, 72.70	H, 6.10	N, 21.19
	Found	C, 72.22	H, 5.84	N, 20.61

Synthesis of ethyl 5-(aminomethyl)-2-thiphenecarboxylate (8f)



Prepared according to TP 2 from **8a** (290 mg, 1.1 mmol), $Pd(PPh_3)_4$ (30 mg, $2.6x10^{-5}$ mmol) and NDMBA (1.06 g, 6.8 mmol). Reaction time: 3 h. Purification by flash chromatography (CH_2Cl_2/MeOH 99:1) yielded **8f** as a light yellow oil (122 mg, 60 %).

IR (film, cm^{-1}): $\tilde{n}$ 3269 (m, br), 2979 (m), 1710 (vs), 1541 (m), 1466 (s), 1366 (m), 1280 (vs), 1092 (vs), 922 (m), 751 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.46 (d, *J* = 3.7 Hz, 1H), 6.83 (d, *J* = 3.7 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.00 (s, 2H), 1.31 (t, *J* = 10.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 161.3, 154.0, 133.9, 131.3, 129.2, 60.0, 14.7.

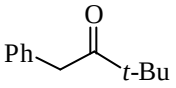
MS (EI, 70 eV): 185 (M^+, 42), 155 (29), 140 (15), 112 (100), 78 (24).

$C_8H_{11}NO_2S$

Calcd.	C, 51.96	H, 5.99	N, 7.57	S, 17.30
Found	C, 51.63	H, 5.46	N, 7.17	S, 16.85

5 Preparation of Benzylic Zinc Reagents via a Fragmentation Reaction

Synthesis of 3,3-dimethyl-1-phenyl-butan-2-one (11)[128]

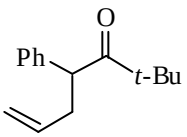


A solution of *t*-BuMgCl (65 mL, 0.11 mol, 1.7 M in THF was added dropwise over 1 h at 0 °C to a stirred suspension of copper(I) bromide (14.3 g, 0.10 mol) in THF (30 mL) containing phenylacetyl chloride (15.5 g, 0.10 mol). After complete addition the black reaction mixture was stirred at rt for 1 h and poured into ice (200 mL). The mixture was then filtered over celite and acidified with 1N HCl. The yellow solution was extracted with diethyl ether (3 x 30 mL), and the combined organic layer was washed with water (2 x 30 mL) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was distilled under vacuum to give 3,3-dimethyl-1-phenyl-butan-2-one (11.9 g, 68 %) as a light yellow oil.

Bp 115 °C, 0.1 mbar.
IR (film, cm^{-1}): $\tilde{n}$ 2967 (m), 1711 (s), 1477 (m), 1060 (m), 724 (m).
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.24-7.08 (m, 5H), 3.71 (s, 2H), 1.11 (s, 9H).
^{13}C NMR ($CDCl_3$, 75 MHz): d 212.8, 135.1, 129.7, 128.5.
MS (EI, 70 eV): 91 (48), 85 (62), 57 (100).

$C_{12}H_{16}O$	HRMS	Calcd.	176.1201
		Found	176.1199

Synthesis of 2,2-dimethyl-4-phenylhept-6-en-3-one (12a)[129]



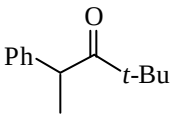
[128] Chen, K.; Koser, F. *J. Org. Chem.* **1991**, *56*, 5764.
[129] De las Heras ; M. A., Vaquero, J. J. ; Garcia-Navio, J. L. ; Alvarez-Builla J. *Tetrahedron* **1996**, *52*, 14297.

A solution of **11** (6.3 g, 35.7 mmol) and allyl bromide (3.7 mL, 42.7 mmol) in THF (10 mL) was added at rt to a suspension of sodium hydride (2.7 g, 67.0 mmol, 60 % suspension in oil) in THF (40 mL). The reaction mixture was stirred for 3 h and a saturated aqueous solution of NH_4Cl was carefully added at 0 °C. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layer was washed with water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (pentane/diethyl ether 9:1) to afford **12a** as a colourless oil (7.6 g, 98 %).

IR (film, cm^{-1}): $\tilde{n}$ 2967 (m), 1702 (s), 1477 (m), 1073 (m), 700 (s).
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.24-7.10 (m, 5H), 5.61-5.47 (m, 1H), 4.96-4.84 (m, 2H), 4.08-4.04 (m, 1H), 2.68-2.58 (m, 1H), 2.38-2.28 (m, 1H), 0.99 (s, 9H).
^{13}C NMR ($CDCl_3$, 75 MHz): d 214.9, 139.6, 136.4, 129.0, 128.6, 127.3, 117.1, 53.3, 45.4, 40.2, 26.9.
MS (EI, 70 eV): 216 (M^+, 1), 159 (17), 131 (84), 115 (19), 103 (8), 91 (52), 85 (45), 77 (11), 57 (100).

$C_{15}H_{20}O$	Calcd.	C, 83.28	H, 9.32
	Found	C, 83.16	H, 9.43

Synthesis of 2,2-dimethyl-4-phenylpentan-3-one (12b)[130]



A solution of **11** (1.0 g, 5.7 mmol) and methyl iodide (0.8 mL, 12.0 mmol) in THF (5 mL) was added at rt to a suspension of sodium hydride (480 mg, 12.0 mmol, 60 % suspension in oil) in THF (5 mL). The reaction mixture was stirred for 3 h and a saturated aqueous solution of NH_4Cl was carefully added at 0 °C. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layer was washed with water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (pentane/diethyl ether 125:1) to afford **12b** as a light yellow oil (980 mg, 91 %).

[130] Zushi, S.; Kodama, Y.; Nishihata, K.; Umomura, K.; Nishio, M.; Uzawa, J.; Hirota, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3631.

IR (film, cm^{-1}): $\tilde{n}$ 2969 (m), 1703 (m), 1477 (m), 1367 (m).

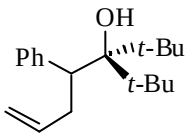
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.21-7.17 (m, 5H), 4.18 (q, *J* = 6.9 Hz, 1H), 1.02 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 216.1, 141.6, 128.7, 128.0, 126.9, 46.5, 45.3, 26.7, 21.2.

MS (EI, 70 eV): 190 (M^+, 14), 105 (93), 85 (69), 77 (35), 57 (100).

$C_{13}H_{18}O$	Calcd.	C, 82.06	H, 9.53
	Found	C, 81.76	H, 9.63

Synthesis of 3-tert-butyl-2,2-dimethyl-4-phenylhept-6-en-3-ol (9a)



A solution of *t*-BuLi (18.5 mL, 27.7 mmol) was added at -78 °C to a solution of the ketone **12a** (5.0 g, 23.1 mmol) in diethyl ether (35 mL). The reaction mixture was stirred at this temperature for 1 h and quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layer was washed with brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (pentane/diethyl ether 9:1) to afford **9a** as a colourless oil (5.9 g, 93 %).

IR (film, cm^{-1}): $\tilde{n}$ 3592 (m), 2923 (s), 1491 (m), 1393 (m), 994 (m), 705 (s).

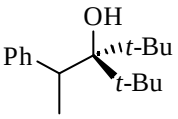
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.33-7.08 (m, 5H), 5.49-5.37 (m, 1H), 4.90 (d, *J* = 17.0 Hz, 1H), 4.83 (d, *J* = 14.1 Hz, 1H), 3.42 (d, *J* = 7.4 Hz, 1H), 3.10-2.87 (m,2H), 1.21 (s, 9H), 1.07 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 140.0, 138.4, 132.5, 127.8, 126.7, 115.6, 81.9, 52.4, 44.2, 44.0, 35.6, 31.1, 30.0.

MS (EI, 70 eV): 217 (5), 161 (2), 143 (21), 131 (39), 87 (54), 57 (100).

$C_{19}H_{30}O$	Calcd.	C, 83.15	H, 11.02
	Found	C, 83.28	H, 11.21

Synthesis of 2,2,4,4-tetramethyl-3-(1-phenylethyl)-pentan-3-ol (9b)



A solution of *t*-BuLi (2.2 mL, 3.3 mmol) was added at -78 °C to a solution of the ketone **8b** (0.3 g, 1.6 mmol) in diethyl ether (2.5 mL). The reaction mixture was stirred at this temperature for 45 min and quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layer was washed with brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (pentane/diethyl ether 99:1) to afford **9b** as a colourless oil (340 mg, 89 %).

IR (film, cm^{-1}): $\tilde{n}$ 3595 (m), 2963 (s), 1393 (m), 988 (m).

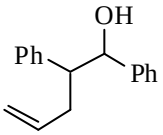
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.37-7.33 (m, 2H), 7.20-7.10 (m, 3H), 3.55 (q, *J* = 7.4 Hz, 1H), 1.65 (d, *J* = 7.4 Hz, 3H), 1.20 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 144.0, 131.6, 127.8, 126.5, 81.9, 45.7, 44.3, 43.8, 30.8, 30.4, 27.0, 19.6.

MS (EI, 70 eV): 191 (2), 143 (13), 105 (72), 87 (49), 57 (100).

$C_{17}H_{28}O$	Calcd.	C, 82.20	H, 11.36
	Found	C, 81.94	H, 11.42

Synthesis of 1,2-diphenylpent-4-en-1-ol (13a)



Prepared according to TP 3 from **9a** (270 mg, 1.1 mmol), *n*-BuLi (0.56 mL, 0.84 mmol), zinc chloride (115 mg, 0.84 mmol) and benzaldehyde (68 µL, 0.67 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 92:8) yielded **13a** as a colourless oil (118 mg, 74 %).

IR (film, cm^{-1}): $\tilde{n}$ 3436 (m), 1680 (s), 1494 (m), 698 (m).

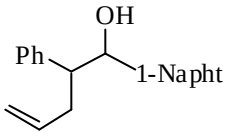
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.33-7.05 (m, 10H), 5.72-5.41 (m, 1H), 4.99-4.77 (m, 3H), 3.13-2.95 (m, 1H), 2.75-2.58 (m, 1H), 2.35-2.18 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 143.0, 142.9, 141.3, 140.8, 137.3, 136.6, 130.6, 129.4, 129.3, 128.9, 128.7, 128.5, 128.4, 128.2, 127.7, 127.4, 127.3, 126.9, 126.2, 116.7, 116.5, 78.5, 78.3, 54.4, 53.7, 36.8, 34.8.

MS (EI, 70 eV): 178 (5), 132 (62), 107 (100), 91 (55).

$C_{17}H_{16}$	HRMS	Calcd.	220.1247 $[M-H_2O]^+$
		Found	220.1252

Synthesis of 1-(2-naphthyl)-2-phenylpent-4-en-1-ol (13b)



Prepared according to TP 3 from **9a** (0.3 g, 1.1 mmol), *n*-BuLi (0.57 mL, 0.84 mmol), zinc chloride (115 mg, 0.84 mmol) and 1-naphthaldehyde (0.12 mL, 0.87 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **13b** as a light yellow oil (158 mg, 63 %).

IR (film, cm^{-1}): $\tilde{n}$ 3436 (m), 1730 (s), 1383 (s), 1112 (s), 911 (s), 734(s).

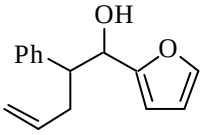
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.95-6.97 (m, 12H), 5.44-5.36 (m, 2H), 4.78-4.64 (m, 2H), 3.34-3.31 (m, 1H), 3.19-3.16 (m, 2H), 2.70-2.25 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 141.2, 137.3, 135.9, 132.7, 129.3, 128.1, 127.9, 127.5, 127.3, 127.1, 127.0, 126.8, 125.8, 125.5, 124.9, 124.4, 124.3, 124.0, 123.8, 123.4, 123.3, 122.2, 122.1, 115.5, 114.9, 73.9, 72.7, 52.7, 51.6, 35.7, 31.8.

MS (EI, 70 eV): 288 (M^+, 5), 270 (7), 229 (8), 158 (29), 129 (100).

$C_{21}H_{20}O$	Calcd.	C, 86.99	H, 6.91
	Found	C, 86.88	H, 7.07

Synthesis of 1-(2-furyl)-2-phenylpent-4-en-1-ol (13c)



Prepared according to TP 3 from **9a** (1.3 g, 4.7 mmol), *n*-BuLi (2.9 mL, 4.3 mmol), zinc chloride (600 mg, 4.4 mmol) and furfural (0.3 mL, 3.6 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **13c** as a colourless oil (600 mg, 73 %).

IR (film, cm^{-1}): $\tilde{n}$ 3398 (m), 1668 (s), 1475 (s), 703 (s).

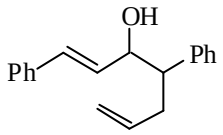
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.30-7.01 (m, 6H), 6.22 (d, *J* = 3.1 Hz, 1H), 6.11 (d, *J* = 3.4 Hz, 1H), 5.70-5.30 (m, 1H), 4.85-4.72 (m, 3H), 3.15-3.08 (m, 1H), 2.60-2.40 (m, 1H), 2.97-2.24 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 155.5, 142.3, 141.9, 141.1, 140.6, 137.0, 136.3, 129.2, 129, 128.9, 128.5, 127.5, 127.0, 126.2, 116.8, 116.7, 110.5, 107.9, 107.3, 72.3, 71.6, 66.2, 51.6, 51.4, 36.8, 35.5, 15.6.

MS (EI, 70 eV): 228 (M^+, 6), 210 (6), 170 (4), 141 (8), 132 (100), 115 (32), 104 (12).

$C_{15}H_{16}O_2$	Calcd.	C, 78.92	H, 7.06
	Found	C, 78.82	H, 6.99

Synthesis of (1E)-1,4-diphenylhepta-1,6-dien-3-ol (13d)



Prepared according to TP 3 from **9a** (0.3 g, 1.1 mmol), *n*-BuLi (0.56 mL, 0.84 mmol), zinc chloride (115 mg, 0.84 mmol) and 3-phenyl-2-propenal (85 µL, 0.67 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 88:12) yielded **13d** as a colourless oil (80 mg, 46 %).

IR (film, cm^{-1}): $\tilde{n}$ 3027 (s), 1640 (s), 1494 (s), 700 (m).

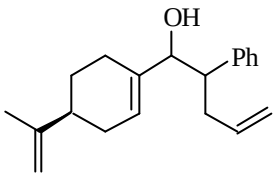
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.36-7.20 (m, 10H), 6.51 and 6.57 (2d, *J* = 21.0 Hz, 1H), 6.15 (dd, *J* = 21.0 and 6.6 Hz, 1H), 6.08 (dd, *J* = 21.0 and 6.6 Hz, 1H), 5.78-5.55 (m, 1H), 5.06-4.85 (m, 2H), 4.52-4.40 (m, 1H), 3.02-2.83 (m, 1H), 2.73-2.38 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 141.0, 140.8, 137.2, 137.1, 136.8, 134.9, 132.4, 131.4, 130.8, 130.5, 129.4, 129.0, 128.8, 128.7, 128.2, 128.0, 127.4, 127.2, 127.0, 126.9, 126.2, 125.9, 116.8, 116.7, 76.5, 76.3, 52.8, 52.4, 36.6, 35.6.

MS (EI, 70 eV): 205 (2), 133 (100), 115 (23), 91 (32), 77 (14).

$C_{19}H_{18}$	HRMS	Calcd.	246.1409 $[M-H_2O]^+$
		Found	246.1402

Synthesis of 1-(4-isopropenylcyclohex-1-en-1-yl)-2-phenylpent-4-en-1-ol (13e)



Prepared according to TP 3 from **9a** (1.3 g, 4.6 mmol), *n*-BuLi (3.3 mL, 4.9 mmol,), zinc chloride (690 mg, 5.0 mmol) and L-perillaldehyde (0.26 mL, 1.7 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded **13e** as a colourless oil (340 mg, 70 %).

IR (film, cm^{-1}): $\tilde{n}$ 3435 (s), 2921 (s), 1642 (s), 1453 (m), 700 (s).

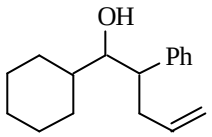
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.26-7.06 (m, 5H), 5.70-5.46 (m, 2H), 4.87-4.56 (m, 4H), 4.06-4.02 (m, 1H), 2.80-1.97 (m, 7H), 1.68 (s, 3H), 1.60 (s, 3H), 1.44 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 150.2, 149.9, 142.3, 141.3, 138.5, 138.0, 137.6, 136.9, 136.8, 129.2, 128.5, 127.3, 126.2, 116.4, 109.1, 80.5, 50.2, 41.4, 37.3, 31.1, 27.9, 25.4, 24.8, 23.9, 21.3, 21.1.

MS (EI, 70 eV): 282 (M^+, 1), 241 (37), 223 (12), 157 (16), 131 (45), 117 (19), 91 (100).

$C_{20}H_{26}O$	Calcd.	C, 85.86	H, 9.28
	Found	C, 85.85	H, 9.33

Synthesis of 1-cyclohexyl-2-phenylpent-4-en-1-ol (13f)



Prepared according to TP 3 from **9a** (1.5 g, 5.4 mmol), *n*-BuLi (3.4 mL, 5.1 mmol), zinc chloride (700 mg, 5.1 mmol) and cyclohexanecarboxaldehyde (0.49 mL, 4.1 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/ diethyl ether 95:5) yielded **13f** as a light yellow oil (600 mg, 60 %).

IR (film, cm^{-1}): $\tilde{n}$ 3400 (m), 2913 (s), 1640 (s), 701 (m).

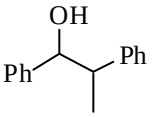
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.23-7.06 (m, 5H), 5.52 (m, 1H), 4.94-4.80 (m, 2H), 3.42-3.38 (m, 1H), 2.3-2.40 (m, 2H), 1.64-0.97 (m, 11H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 143.1, 141.6, 137.7, 137.3, 129.5, 128.8, 127.0, 126.7, 116.5, 116.2, 80.4, 78.6, 66.2, 49.1, 48.2, 40.9, 40.4, 37.7, 35.5, 30.8, 30.6, 27.9, 27.0, 26.9, 26.7, 26.6, 26.4, 15.7.

MS (EI, 70 eV): 226 (M^+-H_2O, 4), 185 (4), 132 (100), 117 (37), 91 (74).

$C_{17}H_{24}O$	Calcd.	C, 83.55	H, 9.89
	Found	C, 83.53	H, 9.99

Synthesis of 1,2-diphenylpropan-1-ol (13g)[131]



Prepared according to TP 3 from **9b** (250 mg, 1.0 mmol) *n*-BuLi (0.6 mL, 0.9 mmol), zinc chloride (115 mg, 0.8 mmol) and benzaldehyde (0.068 mL, 0.7 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 88:12) yielded **13g** as a colourless oil (104 mg, 73 %).

IR (film, cm^{-1}): $\tilde{n}$ 3436 (m), 2259 (s), 1681 (s), 1494 (m), 700 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.30-7.05 (m, 10H), 4.73 (d, J = 6.0 Hz, 1H), 2.97 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H).

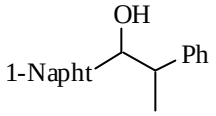
[131] Diaz, A. F.; Cheng, Y. Y.; Ochoa, M. *J. Am. Chem. Soc.* **1977**, *99*, 6319.

^{13}C NMR ($CDCl_3$, 75 MHz): d 143.7, 143.6, 143.1, 142.7, 128.8, 128.4, 128.2, 128.1, 128.0, 127.4, 127.2, 127.1, 126.6, 126.5, 79.9, 78.9, 48.3, 47.4, 18.5, 15.1.

MS (EI, 70 eV): 107 (100), 106 (81), 105 (38), 91 (45), 79 (54).

$C_{15}H_{16}O$	Calcd.	C, 84.87	H, 7.60
	Found	C, 84.67	H, 7.65

Synthesis of 1-(2-naphthyl)-2-phenylpropan-1-ol (13h)



Prepared according to TP 3 from **9b** (0.3 g, 1.1 mmol), *n*-BuLi (0.56 mL, 0.84 mmol), zinc chloride (115 mg, 0.84 mmol) and benzaldehyde (68 µL, 0.67 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 92:8) yielded **13h** as a light yellow oil (140 mg, 80 %).

IR (film, cm^{-1}): $\tilde{n}$ 3428 (m), 2919 (s), 1678 (s), 1489 (m), 700 (s).

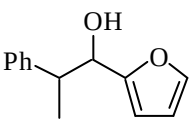
^{1}H NMR ($CDCl_3$, 300 MHz): d 8.03-7.12 (m, 12H), 5.55 (d, *J* = 5.7 Hz, 1H), 5.45 (d, *J* = 8.7 Hz, 1H), 3.30 (m, 2H), 1.85 (s, 2H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 143.7, 137.4, 132.7, 129.2, 128.0, 127.5, 126.7, 125.5, 124.9, 124.3, 124. 2, 123.0, 122.0, 75.6, 73.9, 44.1, 43.8, 12.6, 11.5.

MS (EI, 70 eV): 262 (M^+, 4), 233 (7), 158 (45), 128 (100), 105 (23).

$C_{19}H_{18}O$	Calcd.	C, 86.99	H, 6.91
	Found	C, 86.78	H, 7.17

Synthesis of 1-(2-furyl)-2-phenylpropan-1-ol (13i)[132]



[132] Molander, G. A.; Estevez-Braun, A. M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 275.

Prepared according to TP 3 from **9b** (0.3 g, 1.1 mmol), *n*-BuLi (0.73 mL, 1.1 mmol), zinc chloride (180 mg, 1.3 mmol) and furfural (75 µl, 0.9 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **13i** as a red oil (120 mg, 66 %).

IR (film, cm^{-1}): $\tilde{n}$ 3400 (m), 2963 (s), 1675 (s), 1478 (s), 711 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.32-7.06 (m, 6H), 6.18-6.14 (dt, *J* = 3.1 and 0.8 Hz, 1H), 5.96 (dd, *J* = 3.1 and 2.6 Hz, 1H), 4.15 (d, *J* = 4.8, 1H), 3.18 (q, *J* = 4.8 Hz, 1H), 1.9 (bs, 1H), 1.29 (d, *J* = 13.1 Hz, 3H).

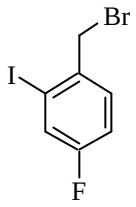
^{13}C NMR ($CDCl_3$, 75 MHz): d 155.8, 155.4, 147.7, 143.6, 143.2, 142.4, 141.9, 129.1, 128.7, 128.3, 128.8, 127.4, 126.9, 110.6, 110.5, 107.9, 107.0, 77.9, 77.4, 77.0, 73.3, 73.2, 46.0, 45.3, 18.5, 16.4.

MS (EI, 70 eV): 202 (M^+, 3), 185 (2), 105 (21), 97 (100), 91 (25), 77 (19).

$C_{13}H_{14}O_2$	Calcd.	C, 77.72	H, 6.97
	Found	C, 77.67	H, 7.10

6 Preparation of Allylic Zinc Reagents via a Cyclization-Fragmentation Reaction

Synthesis of 1-(bromomethyl)-4-fluoro-2-iodobenzene (25)[133]



A mixture of N-bromosuccinimide (2.2 g, 12.4 mmol), 4-fluoro-2-iodotoluene (5 g, 20.8 mmol), and benzoyl peroxide (0.1 g, 0.4 mmol), in tetrachloromethane (200 mL), was refluxed overnight. After cooling to rt, the succinimide was filtered and the resulting light red solution was concentrated *in vacuo*. Purification by flash chromatography (hexane) yielded **25** as a white solid (3.5 g, 90 %).

Mp 75 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 3067 (br, s,), 1694 (vs), 1590 (vs), 1479 (vs), 1415 (m), 1291 (s), 1228 (vs), 1028 (s), 866 (vs), 822 (m), 713 (s), 608 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.50 (dd, *J* = 8.7 and 2.7 Hz, 1H), 7.37 (dd, *J* = 8.7 and 5.7 Hz, 1H) 6.98 (td, *J* = 8.2 and 2.6 Hz, 1H), 4.5 (s, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 163.6, 160.3, 136.8, 131.7, 131.6, 127.5, 127.2, 116.5, 116.2, 99.9, 99.8, 38.0.

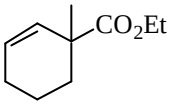
MS (EI, 70 eV): 314 (M^+, 2), 235 (100), 108 (29), 81 (4).

C_7H_5BrFI

Calcd.	C, 26.69	H, 1.78	Br, 25.37	F, 6.03	I, 40.30
Found	C, 26.59	H, 1.75	Br, 25.33	F, 5.99	I, 40.22

[133] Kesteleyn, B.; De Kimpe, N.; Van Puyvelde, L. *Synthesis* **1999**, *11*, 1881.

Synthesis of ethyl-1-methyl-2-cyclohexene-1-carboxylate (20a)[134]



n-BuLi (150 mL, 225 mmol) was added dropwise to a solution of diisopropylamine (33.0 mL, 230 mmol) in THF (200 mL), at -78 °C. The mixture was stirred at 0 °C for 5 min, then cooled back to -78 °C. HMPA (44.0 mL, 252 mmol) was added and after 30 min ethyl 1-cyclohexene-1carboxylate (35.0 g, 230 mmol). The mixture was stirred at this temperature for 1 h and then methyliodide (17.2 mL, 276 mmol) was added. After 1 h the reaction was quenched with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (4 x 200 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Distillation under reduced pressure yielded **20a** as a light yellow oil (25.0 g, 65 %).

Bp 89 °C, 18 mbar

IR (film, cm^{-1}): $\tilde{n}$ 2935 (s), 1730 (vs), 1453 (m), 1224 (s), 1181 (s), 1110 (s), 1033 (m), 727 (m).

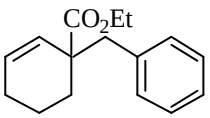
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.66-5.62 (m, 2H), 4.05 (qd, *J* = 7.2 and 2.3 Hz, 2H), 2.02-1.55 (m, 6H), 1.2 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 177.3, 131.2, 128.1, 60.8, 43.3, 33.3, 26.7, 24.5, 20.0, 14.5.

MS (EI, 70 eV): 168 (M^+, 10), 122 (15), 95 (100), 79 (11), 67 (20).

$C_{10}H_{16}O_2$	Calcd.	C, 71.39	H, 9.59
	Found	C, 71.42	H, 9.48

Synthesis of ethyl 1-benzyl-2-cyclohexene-1-carboxylate (20b)



n-BuLi (150 mL, 225 mmol) was added dropwise to a solution of diisopropylamine (17.0 mL, 120 mmol) in THF (50 mL), at -78 °C. The mixture was stirred at 0 °C for 5 min, then cooled to -50 °C. DMPU (30 mL) was added and after 30 min ethyl 1-cyclohexene-1carboxylate (35.0 g, 230 mmol). The mixture was stirred at this temperature for 2 h and then benzyl bromide (18.0

[134] Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett*. **1973**, *26*, 2436.

mL, 150 mmol) was addded. After 1 h the reaction was quenched with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (4 x 200 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Distillation under reduced pressure yielded **20b** as a yellow oil (18 g, 74 %).

Bp 99 °C, 6 mbar

IR (film, cm^{-1}): $\tilde{n}$ 2936 (s), 1727 (vs), 1495 (m), 1454, (m), 1220 (s), 1182 (vs), 1089 (s), 1029 (m), 730 (m), 701 (vs).

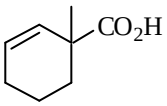
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.64 (m, 2H), 5.96 (dd, *J* = 3.1 and 2.6 Hz, 1H), 4.15 (d, *J* = 4.8, 1H), 3.18 (q, *J* = 4.8 Hz, 1H), 1.9 (s, br, 1H), 1.29 (d, *J* = 13.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 175.9, 139.6, 131.4, 130.9, 130.4, 126.9, 126.3, 61.0, 48.6, 46.4, 31.4, 26.8, 21.4, 14.5.

MS (EI, 70 eV): 244 (M^+, 25), 171 (27), 152 (50), 140 (11), 91 (100), 79 (28).

$C_{16}H_{20}O_2$	Calcd.	C, 78.65	H, 8.25
	Found	C, 78.45	H, 8.70

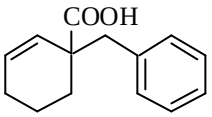
Synthesis of 1-methyl-2-cyclohexene-1-carboxylic acid (21a)[135]



A solution of **20a** (1.7 g, 10.0 mmol) and KOH (850 mg, 15.0 mmol) in ethanol (21 mL) and water (7 mL), was heated to reflux for 1 h, concentrated *in vacuo* and the residue dissolved in diethyl ether (50 mL). The mixture was acidified with 1N HCl solution at 0 °C and the aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*, to give 1.4 g of **21a** as a yellow oil, used for the next step without further purification.

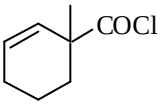
Synthesis of 1-benzyl-2-cyclohexene-1-carboxylic acid (21b)

[135] Schultz, A. G.; Macielag, M.; Podhorez, D. E.; Suhadolnik, J. C.; Kullnig, R. K. *J. Org. Chem.* **1988**, *53*, 2456.



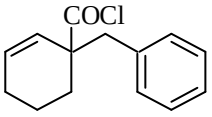
A solution of **20b** (4.6 g, 19.0 mmol) and KOH (4.5 g, 80.0 mmol) in ethanol (30 mL) and water (5 mL), was heated to reflux for 1 h, concentrated *in vacuo* and the residue dissolved in diethyl ether (70 mL). The mixture was acidified with 1N HCl solution at 0 °C and the aqueous phase was extracted with diethyl ether (3 x 40 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*, to give 3.9 g of **21b** as a yellow oil, used for the next step without further purification.

Synthesis of 1-methyl-2-cyclohexene-1-carbonyl chloride (22a)[136]



Thionly chloride (3.6 mL, 50.0 mmol) was added slowly to **21a** and the mixture stirred overnight at rt. Distillation of the thionyl chloride yielded 11.4 g of the desired product as a dark yellow oil, used for the next step without further purification.

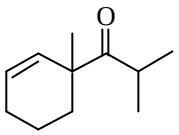
Synthesis of 1-benzyl-2-cyclohexene-1-carbonyl chloride (22b)



Thionly chloride (8 mL, 100 mmol) was added slowly to **21b** and the mixture stirred overnight at rt. Distillation of the thionyl chloride yielded 3.5 g of the desired crude product as a dark yellow oil, used for the next step without further purification.

[136] Klein, J. *Tetrahedron* **1964**, *20*, 465.

Synthesis of 2-methyl-1-(1-methyl-2-cyclohexen-1-yl)-1-propanone (23a)



To a suspension of the starting **22a** (1.4 g, 8.4 mmol) and CuBr (1.4 g, 9.5 mmol) in THF (10 mL), *i*-PrMgBr (16.6 mL, 9.5 mmol, 0.57 M solution in THF), was added slowly at -20 °C. After 1 h the reaction was quenched with with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (4 x 20 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Distillation under reduced pressure yielded the desired product as a light yellow oil (7.0 g, 56 %).

Bp 107 °C, 23 mbar

IR (film, cm^{-1}): $\tilde{n}$ 2965 (s), 2934 (vs), 1707 (vs), 1460 (m), 1006 (m), 727 (m).

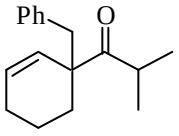
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.75 (dt, *J* = 10.1 and 3.5 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 3.00 (h, *J* = 6.7 Hz, 1H), 1.94-1.30 (m, 6H), 1.23 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 217.0, 129.4, 128.2, 48.5, 36.5, 33.5, 30.8, 24.0, 18.5, 17.9.

MS (EI, 70 eV): 166 (M^+, 3), 95 (100), 67 (20).

$C_{11}H_{18}O_2$	Calcd.	C, 79.46	H, 10.91
	Found	C, 79.19	H, 10.84

Synthesis of 1-(1-benzyl-2-cyclohexen-1-yl)-2-methyl-1-propanone (23b)



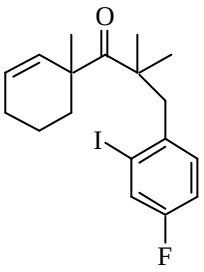
To a suspension of the starting **22b** (12.1 g, 51.4 mmol) and CuBr (9.0 g, 62.7 mmol) in THF (30 mL), *i*-PrMgBr (45.0 mL, 58.0 mmol, 1.3 M solution in THF), was added slowly at -20 °C. After 2 h the reaction was quenched with with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (4 x 30 mL). The organic fractions were washed with brine, dried

over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 99:1) yielded **23b** as a yellow oil (5.0 g, 40 %).

IR (film, cm^{-1}): $\tilde{n}$ 2932 (s), 1702 (vs), 1495 (w), 1454 (m), 1380 (w), 736 (m), 702 (s).
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.14-6.98 (m, 5H), 5.77-5.74 (m, 2H), 2.96 (d, *J* = 12.8 Hz, 1H), 2.75 (h, *J* = 6.7 Hz, 1H), 2.56 (d, *J* = 12.9 Hz, 1H), 1.95-1.30 (m, 6H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz): d 218.0, 137.8, 130.9, 130.5, 129.4, 128.7, 128.2, 126.7, 121.3, 54.5, 45.0, 37.2, 31.8, 25.4, 23.5, 20.3, 19.1.
MS (EI, 70 eV): 242 (M^+, 2), 199 (2), 171 (95), 129 (24), 91 (100), 71 (20), 67 (22), 42 (34).

$C_{17}H_{22}O$	Calcd.	C, 84.25	H, 9.15
	Found	C, 84.45	H, 9.41

Synthesis of 3-(4-fluoro-2-iodophenyl)-2,2-dimethyl-1-(1-methyl-2-cyclohexen-1-yl)-1-propanone (18a)



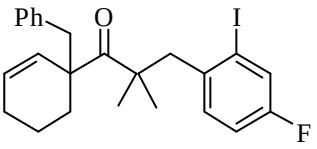
n-BuLi (8 mL, 12 mmol) was added dropwise to a solution of diisopropylamine (1.7 mL, 12.0 mmol) in THF (15 mL), at -78 °C. The mixture was stirred at 0 °C for 5 min, then cooled to -10 °C. **23a** (16.6 g, 10.0 mmol) was added and after 2 h at -10 °C a solution of **25** (3.5 g, 11.0 mmol) in THF (10 mL) was added and the mixture was let warm up to rt. After 1 h the reaction was quenched with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (4 x 25 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 99:1) yielded **18a** as a yellow oil (2.4 g, 69 %).

IR (film, cm^{-1}): $\tilde{n}$ 3067 (s, br), 2965 (s), 2934 (vs), 1707 (vs), 1590 (s), 1479 (s), 1415 (m), 1291 (s), 1228 (vs), 1028 (s), 1006 (m), 866 (vs), 822 (m), 727 (m), 713 (s), 608 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.46 (dd, *J* = 8.7 and 2.6 Hz, 1H), 7.00 (dd, *J* = 8.8 and 6.2 Hz, 1H), 6.87 (td, *J* = 8.4 and 2.8 Hz, 1H), 5.79 (d, *J* = 10.4 Hz, 1H), 5.66 (dt, *J* = 10.1 and 3.8 Hz, 1H), 3.06 (d, *J* = 2.7 Hz, 2H), 2.18-1.31 (m, 6H), 1.20 (d, *J* = 3.9 Hz, 6H), 1.10 (s, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz): d 220.3, 162.4, 159.1, 138.2, 131.9, 131.7, 131.6, 128.5, .127.0, 126.7, 115.3, 115.1, 102.7, 102.6, 52.1, 50.9, 47.9, 34.2, 27.3, 25.1, 25.1, 20.0.
MS (EI, 70 eV): 305 (25), 277 (100), 235 (80), 133 (20), 95 (50).

$C_{18}H_{22}FIO$	HRMS	Calcd.	400.0699
		Found	400.0695

Synthesis of 1-(1-benzyl-2-cyclohexen-1-yl)-3-(4-fluoro-2-iodophenyl)-2,2-dimethyl-1-propanone (18b)



n-BuLi (16.0 mL, 24.0 mmol) was added dropwise to a solution of diisopropylamine (3.5 mL, 25.0 mmol) in THF (20 mL), at -78 °C. The mixture was stirred at 0 °C for 5 min, then **23b** (4.8 g, 20.0 mmol) was added. After 1.5 h at 0 °C a solution of **25** (8.8 g, 28.0 mmol) in THF (10 mL) was added and the mixture was let warm to rt overnight. The reaction was quenched with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (4 x 25 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 98:2) yielded **18b** as a yellow oil (3.8 g, 40 %).

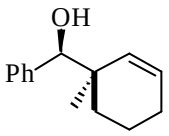
IR (film, cm^{-1}): $\tilde{n}$ 3067 (s, br), 2932 (s), 1702 (vs), 1590 (vs), 1495 (w), 1479 (vs), 1454 (m), 1415 (m), 1380 (w), 1291 (s), 1228 (vs), 1028 (s), 866 (vs), 736 (m), 713 (s), 702 (s), 608 (s).
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.46 (dd, *J* = 8.7 and 2.6 Hz, 1H), 7.14-6.98 (m, 5H), 7.00 (dd, *J* = 8.8 and 6.2 Hz, 1H), 6.87 (td, *J* = 8.4 and 2.8 Hz, 1H), 5.79 (d, *J* = 10.4 Hz, 1H), 5.66 (dt, *J* = 10.1 and 3.8 Hz, 1H), 3.06 (d, *J* = 2.7 Hz, 2H), 2.96 (d, *J* = 12.8 Hz, 1H), 2.56 (d, *J* = 12.9 Hz, 1H), 2.18-1.31 (m, 6H), 1.20 (d, *J* = 3.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 220.3, 162.4, 159.1, 139.4, 138.2, 131.9, 131.7, 131.6, 128.5, 128.3, 127.0, 126.7, 125.7, 115.3, 115.1, 102.7, 102.6, 52.1, 50.9, 47.9, 38.1, 34.2, 27.3, 25.1, 25.1.

MS (EI, 70 eV): 305 (25), 277 (100), 235 (80), 133 (20), 95 (50), 91 (85).

$C_{24}H_{26}FIO$	HRMS	Calcd.	476.1012
		Found	476.1009

Synthesis of benzenemethanol, a **-(1-methyl-2-cyclohexen-1-yl) (27a)**



Prepared according to TP 4 from **18a** (331 mg, 0.8 mmol), *n*-BuLi (0.6 mL, 0.9 mmol), zinc bromide (0.6 mL, 0.9 mmol, 1.5 M solution in THF) and benzaldehyde (0.1 mL, 1.0 mmol). Reaction time: 45 min. Purification by flash chromatography (pentane/diethyl ether 97:3) yielded **27a** as a light yellow oil (114 mg, 68 %). dr: 97:3

IR (film, cm^{-1}): $\tilde{n}$ 3390 (m), 2972 (s), 1668 (s), 1448 (s), 700 (s).

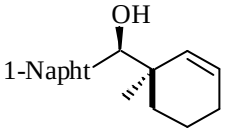
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.38-7.18 (m, 5H), 5.78 (dt, *J* = 10.1 and 4.2 Hz, 1H), 5.33 (dd, *J* = 10.1 and 1.0 Hz, 1H), 4.39 (s, 1H), 1.9 (s, br, 1H), 1.89 (m, 2H), 1.78 (td, *J* = 12.1 and 3.3 Hz, 2H), (1,60-0.90, m, 2H), 0.85 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 139.6, 132.8, 128.5, 127.0, 126.5, 126.3, 79.9, 73.3, 73.2, 39.5, 28.7, 24.1, 22.8, 17.8.

MS (EI, 70 eV): 107 (100), 96 (53), 79 (26), 67 (9), 55 (4).

$C_{14}H_{18}O$	Calcd.	C, 83.12	H, 8.97
	Found	C, 82.91	H, 9.01

Synthesis of 1-naphthalenemethanol, a **-(1-methyl-2-cyclohexen-1-yl) (27b)**



Prepared according to TP 4 from **18a** (400 mg, 1.0 mmol), *n*-BuLi (0.6 mL, 0.9 mmol), zinc bromide (0.8 mL, 1.2 mmol, 1.5 M solution in THF) and 1-naphtylaldehyde (0.2 mL, 1.4 mmol). Reaction time: 45 min. Purification by flash chromatography (pentane/diethyl ether 92:8) yielded **27b** as a yellow oil (201 mg, 80 %). dr: 88:12

IR (film, cm^{-1}): $\tilde{n}$ 3436 (m), 1730 (s), 1383 (s), 1112 (s), 911 (s), 734(s).

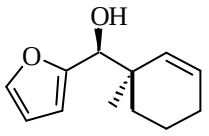
^{1}H NMR ($CDCl_3$, 300 MHz): d 9.30-7.49 (m, 7H), 5.82 (dt, *J* = 10.1 and 4.2 Hz, 1H), 5.55 (s, 1H), 5.43 (d, *J* = 10.1 Hz, 1H), 2.04-1.64 (m, 6H), 1.04 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 136.4, 133.0, 132.4, 130.9, 127.7, 127.0, 126.9, 126.5, 124.8, 124.6, 124.4, 123.1, 79.9, 40.4, 32.6, 24.2, 22.8, 18.0, 14.2.

MS (EI, 70 eV): 252 (M^+, 14), 157 (100), 129 (33), 101 (21).

$C_{18}H_{20}O$	Calcd.	C, 85.67	H, 7.99
	Found	C, 85.74	H, 8.02

Synthesis of 2-furanmethanol, a **-(1-methyl-2-cyclohexen-1-yl) (27c)**



Prepared according to TP 4 from **18a** (400 mg, 1.0 mmol), *n*-BuLi (0.6 mL, 0.9 mmol), zinc bromide (0.8 mL, 1.2 mmol, 1.5 M solution in THF) and furfural (0.12 mL, 1.4 mmol). Reaction time: 45 min. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded **27c** as a yellow oil (184 mg, 96 %). dr: 97:3

IR (film, cm^{-1}): $\tilde{n}$ 3398 (m), 1668 (s), 1475 (s), 703 (s).

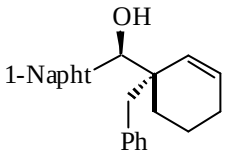
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.19 (m, 1H), 6.27 (m, 1H), 6.19 (m, 1H), 5.78 (dt, *J* = 10.1 and 4.2 Hz, 1H), 5.33 (d, *J* = 10.1 Hz, 1H), 4.42 (s, 1H), 2.09 (s (br), 1H), 1.90 (td, *J* = 12.2 and 3.1 Hz, 2H), 1.78-1.50 (m, 4H), 0.93 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 153.6, 140.5, 131.9, 128.5, 109.0, 106.6, 74.0, 39.4, 29.2, 24.0, 17.9.

MS (EI, 70 eV): 192 (M^+, 10), 159 (12), 115 (30), 97 (100).

$C_{12}H_{16}O_2$	Calcd.	C, 74.97	H, 8.39
	Found	C, 74.83	H, 8.25

Synthesis of 1-naphthalenemethanol, a **-[1-(phenylmethyl)-2-cyclohexen-1-yl] (27d)**



Prepared according to TP 4 from **18b** (370 mg, 0.8 mmol), *n*-BuLi (0.54 mL, 0.8 mmol), zinc bromide (0.7 mL, 1.0 mmol, 1.5 M solution in THF) and 1-naphthaldehyde (0.12 mL, 0.9 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 96:4) yielded **27d** as a white solid (220 mg, 87 %). dr > 98:2

Mp 50 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 3436 (br, m), 2933 (vs), 2865 (s), 1689 (vs), 1632 (vs), 1450 (vs), 1403 (s), 1317 (vs), 1217 (vs), 1170 (m), 1056 (s), 885 (m), 806 (vs), 774 (vs).

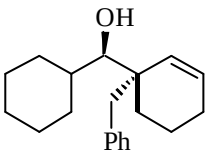
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.74-7.13 (m, 12H), 5.71 (m, 2H), 5.46 (s, 1H), 2.99 (d, *J* = 13.1 Hz, 1H), 2.73 (d, *J* = 13.0 Hz, 1H), 1.63 (s, br, 1H), 1.43-1.19 (m, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 137.8, 137.1, 132.3, 131.0, 130.5, 129.8, 128.7, 128.0, 127.7, 126.9, 126.8, 125.1, 125.0, 124.6, 124.1, 122.6, 71.1, 44.2, 41.0, 26.9, 23.8, 17.4.

MS (EI, 70 eV): 310 (M^+-H_2O, 16), 219 (15), 172 (20), 157 (100), 129 (70), 115 (12), 91 (30).

$C_{24}H_{24}O$	Calcd.	C, 87.76	H, 7.37
	Found	C, 87.73	H, 7.16

Synthesis of 2-cyclohexene-1-methanol, a **-cyclohexyl-1-(phenylmethyl)- (27e)**



Prepared according to TP 4 from **18b** (470 mg, 1.0 mmol), *n*-BuLi (0.8 mL, 1.0 mmol), zinc bromide (0.9 mL, 1.3 mmol, 1.5 M solution in THF) and cyclohexancarboxaldehyde (0.13 mL,

1.2 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 93:7) yielded **27e** as a colourless oil (227 mg, 80 %). dr > 98:2

IR (film, cm^{-1}): $\tilde{n}$ 3495 (m, br), 2925 (vs), 2851 (vs), 1667 (w), 1494 (m), 1450 (s), 1261 (w), 1079 (m), 701 (s).

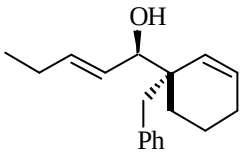
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.20-7.09 (m, 5H), 5.77 (dt, *J* = 10 and 4 Hz, 1H), 5.46 (d, *J* = 10 Hz, 1H), 3.10 (s, 1H), 2.77 (d, *J* = 14 Hz, 1H), 2.60 (d, *J* = 14 Hz, 1H), 1.83-1.14 (m, 17H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 139.1, 133.0, 131.1, 129.8, 128.1, 126.3, 79.8, 53.8, 45.0, 43.6, 39.2, 34.0, 28.4, 27.7, 27.4, 26.9, 26.8,. 25.3, 19.3.

MS (EI, 70 eV): 284 (M^+, 1), 267 (1), 193 (4), 172 (100), 143 (3), 129 (10), 111 (35), 91 (50), 82 (60).

$C_{20}H_{20}O$	HRMS	Calcd.	284.2140
		Found	284.2114

Synthesis of 2-cyclohexene-1-methanol, a **-[(1E)-1-butenyl]-1-(phenylmethyl)- (27f)**



Prepared according to TP 4 from **18b** (470 mg, 1.0 mmol), *n*-BuLi (0.8 mL, 1.0 mmol), zinc bromide (0.9 mL, 1.3 mmol, 1.5 M solution in THF) and trans-2-penten-1-al (0.1 mL, 1.0 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 96:4) yielded **27f** as a colourless oil (198 mg, 79 %). dr: 91:9

IR (film, cm^{-1}): $\tilde{n}$ 3485 (m, br), 2913 (vs), 2860 (vs), 1672 (w), 1484 (m), 1447 (s), 1260 (w), 1069 (m), 700 (s).

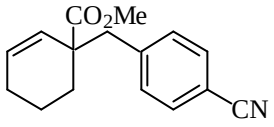
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.18-7.09 (m, 5H), 5.83 (dt, *J* = 3.1 and 2.6 Hz, 1H), 5.67 (dt, *J* = 15.2 and 7.0 Hz, 1H), 5.52-5.42 (m, 2H), 3.75 (d, *J* = 8.1 Hz, 1H), 2.74 (d, *J* = 13.1 Hz, 1H), 2.53 (d, *J* = 13.2 Hz, 1H), 2.03 (qd, *J* = 8.1 and 1.0 Hz, 2H), 1.83-1.49 (m, 6H), 0.95 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 139.0, 137.4, 132.1, 131.2, 130.9, 128.6, 128.2, 126.3, 43.9, 42.9, 27.8, 25.9, 25.3, 19.1, 14.0.

MS (EI, 70 eV): 238 (M^+-H_2O, 5), 172 (25), 147 (48), 129 (30), 105 (40), 91 (100), 79 (35).

$C_{18}H_{24}O$	HRMS	Calcd.	256.1827
		Found	256.1824

Synthesis of methyl 1-(4-cyanobenzyl)-2-cyclohexene-1-carboxylate (20c)



n-BuLi (150 mL, 225 mmol) was added dropwise to a solution of diisopropylamine (17.0 mL, 120 mmol) in THF (50 mL), at -78 °C. The mixture was stirred at 0 °C for 5 min, then cooled to -50 °C. HMPA (11 mL) was added and after 30 min methyl 1-cyclohexene-1-carboxylate (7.7 g, 55.0 mmol). The mixture was stirred at this temperature for 3 h, then 4-(bromomethyl)benzonitrile (10.0 g, 51.0 mmol) was addded and the mixture was let warm to rt. After 3 h the reaction was quenched with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (4 x 200 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded **20c** as a light yellow oil (10.0 g, 77 %).

IR (film, cm^{-1}): $\tilde{n}$ 3435 (s), 2933 (s), 2228 (s), 1493 (m), 1451, (m), 1261 (m), 1043 (m), 801 (s), 780 (vs), 713 (m), 702 (s).

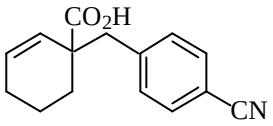
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.48 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 5.77 (m, 1H), 5.59 (d, *J* = 10.3 Hz, 1H), 3.57 (s, 3H), 2.91 (s, 2H), 1.98-1.35 (m, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 174.4, 141.9, 130.8, 129.7, 128.7, 127.4, 117.9, 109.6, 50.9, 47.2, 44.8, 30.1, 23.8, 18.4.

MS (EI, 70 eV): 256 ($[M+H]^+$, 4), 196 (26), 154 (9), 139 (100), 116 (31), 106 (20).

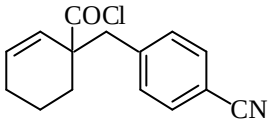
$C_{16}H_{17}NO_2$	HRMS	Calcd.	256.1338 $[M+H]^+$
		Found	256.1334

Synthesis of 1-(4-cyanobenzyl)-2-cyclohexene-1-carboxylic acid (21c)



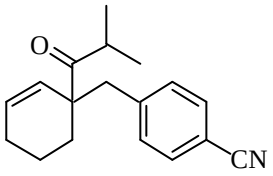
A solution of **20c** (4.8 g, 19.0 mmol) and KOH (4.5 g, 80.0 mmol) in ethanol (30 mL) and water (5 mL), was heated to reflux for 1 h, concentrated *in vacuo* and the residue dissolved in diethyl ether (70 mL). The mixture was acidified with 1N HCl solution at 0 °C and the aqueous phase was extracted with diethyl ether (3 x 40 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*, to give 3.9 g of **21b** as a yellow oil, used for the next step without further purification.

Synthesis of 1-(4-cyanobenzyl)-2-cyclohexene-1-carbonyl chloride (22c)



Thionly chloride (4 mL, 50 mmol) was added slowly to **21c** and the mixture stirred overnight at rt. Distillation of the thionyl chloride yielded 3.5 g of the desired crude product as a dark yellow oil, used for the next step without further purification.

Synthesis of 4-[(1-isobutyryl-2-cyclohexen-1-yl)methyl]benzonitrile (23c)



To a suspension of **22c** (240 mg, 0.9 mmol) and CuI (300 mg, 2.0 mmol) in THF (2 mL), *i*-PrMgBr (0.9 mL, 1.2 mmol, 1.3 M in THF), was added slowly at -20 °C. After 2 h the reaction was quenched with with saturated, aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (4 x 30 mL). The organic fractions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 98:2) yielded **23c** as a yellow oil (96 mg, 40 %).

IR (film, cm^{-1}): $\tilde{n}$ 2966 (s), 2933 (vs), 2228 (s), 1702 (vs), 1607 (m), 1447 (m), 1095 (m), 1022 (w), 854 (w).

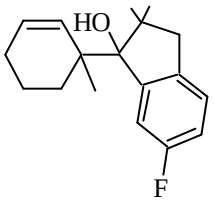
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.45 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.87 (m, 1H), 5.58 (d, *J* = 10.3 Hz, 1H), 3.11 (d, *J* = 12.8 Hz, 1H), 2.83 (h, *J* = 6.7 Hz, 1H), 2.65 (d, *J* = 12.8 Hz, 1H), 1.95-1.39 (m, 6H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): d 216.2, 142.5, 130.6, 130.4, 130.1, 128.7, 128.1, 126.9, 118.0, 109.2, 53.2, 42.8, 38.9, 35.4, 30.3, 25.7, 18.8, 18.1, 17.8.

MS (EI, 70 eV): 268 (M^+, 46), 196 (100), 168 (9), 154 (29), 142 (13), 116 (66).

$C_{18}H_{21}NO$	HRMS	Calcd.	267.1623
		Found	267.1621

Synthesis of 6-fluoro-2,2-dimethyl-1-(1-methyl-2-cyclohexen-1-yl)-1-indanol (28)



The starting ketone **18a** (400 mg, 1.0 mmol) was dissolved in THF (1 mL) and DMPU (1 mL) and cooled to -30 °C. *i*-PrMgBr (3.3 mL, 2.0 mmol, 0.6 M solution in THF) was added dropwise and the mixture was let warm to 0 °C. A solution of $ZnBr_2$ (1.2 mL, 1.7 mmol, 1.5 M in THF) was added and the mixture was let warm to rt and stirred for 15 min. Benzaldehyde (0.15 mL, 2.0 mmol) was then added and the mixture was stirred for 1 h and quenched with saturated, aqueous NH_4Cl and extracted with diethyl ether (4 x 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded the cyclized alcohol **28** as a colourless oil (265 mg, 97 %).

IR (film, cm^{-1}): $\tilde{n}$ 3390 (m), 2972 (s), 1668 (s), 1448 (s), 700 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): d 6.99-6.81 (m, 3H), 5.55 (m, br, 2H), 2.98 (d, br, *J* = 1.2 Hz, 1H), 2.30 (d, br, *J* = 1.2 Hz, 1H), 1.77 (s, br, 1H), 1.72-0.86 (m, 6H), 1.33 (s, 6H), 0.81 (s, 3H).

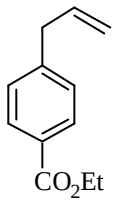
^{13}C NMR ($CDCl_3$, 75 MHz): d 161.9, 158.7, 147.4, 136.3, 131.6, 124.4, 124.3, 113.5, 113.2, 113.1, 112.8, 87.9, 49.7, 44.9, 43.4, 29.2, 27.4, 23.6, 21.3, 18.4, 13.0.

MS (EI, 70 eV): 274 (M^+, 1), 256 (26), 213 (36), 179 (100), 161 (18), 146 (6), 133 (3), 95 (3), 67 (1), 42 (3).

$C_{18}H_{23}FO$	Calcd.	C, 78.80	H, 8.45	F, 6.92
	Found	C, 78.73	H, 8.39	F, 6.87

7 Preparation of Highly Functionalized Organocuprates via Halogen-Copper Exchange

Synthesis of ethyl 4-allylbenzoate (38a)



Prepared according to TP 5 from ethyl 4-iodobenzoate (276 mg, 1.0 mmol), lithium neopentylcuprate **33** (1.2 mmol) and allyl bromide (110 mg, 0.9 mmol). Reaction time: 2.5 h at -50 °C. Purification by flash chromatography (pentane/diethyl ether 99:1) yielded **38a** as a colourless oil (180 mg, 95 %).

IR (film, cm^{-1}): $\tilde{n}$ 2980 (s), 1716 (vs), 1640 (m), 1611 (vs), 1575 (m), 1433 (s), 1367 (s), 1316 (s), 1276 (vs), 1177 (vs), 1105 (vs), 1022 (s), 917 (m), 758 (s).

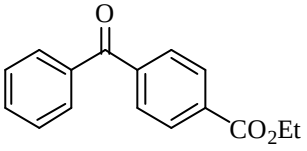
^{1}H NMR ($CDCl_3$, 300 MHz,): d 7.90 (dd, *J* = 8.3 and 1.7 Hz, 2H), 7.79 (dd, *J* = 8.0 and 1.7 Hz, 2H), 5.95-5.82 (m, 1H), 5.05-4.99 (m, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.60 (d, *J* = 6.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 165.6, 144.3, 135.4, 128.7, 127.6, 115.5, 59.8, 39.1, 13.3.

MS (EI, 70 eV): 190 (M^+, 26), 162 (14), 145 (100), 117 (51), 115 (29), 101 (1).

$C_{12}H_{14}O_2$	Calcd.	C, 75.46	H, 7.42
	Found	C, 76.10	H, 7.55

Synthesis of ethyl 4-benzoyl-benzoate (38b)



Prepared according to TP 5 from ethyl 4-iodobenzoate (276 mg, 1.0 mmol), lithium neopentylcuprate **33** (1.2 mmol) and benzoyl chloride (0.1 mL, 0.9 mmol). Reaction time: 2.5 h at -50 °C. Purification by flash chromatography (pentane/diethyl ether 95:5) **38b** as a light yellow oil (400 mg, 87 %).

IR (film, cm^{-1}): $\tilde{n}$ 3402 (m, br), 2982 (m), 1720 (vs), 1661 (vs), 1597 (m), 1579 (w), 1448 (m), 1405 (s), 1356 (s), 1369 (s), 1317 (s), 1275 (vs), 1105 (vs), 1020 (m), 939 (m), 927 (m), 851 (w), 769 (w), 715 (s), 698 (m), 657 (m).

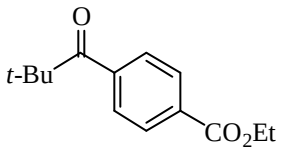
^{1}H NMR ($CDCl_3$, 300 MHz,): d 8.07 (dd, *J* = 8.4 and 1.8 Hz, 2H), 7.74 (dd, *J* = 8.1 and 1.8 Hz, 2H), 7.73 (m, 2H), 7.53 (dt, *J* = 8.0 and 1.4 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 195.0, 164.8, 140.2, 136.0, 132.6, 131.9, 129.1, 128.7, 128.4, 127.4, 126.2, 60.4, 13.3.

MS (EI, 70 eV): 254 (M^+, 48), 226 (14), 209 (45), 181 (18), 177 (57), 152 (10), 149 (14), 130 (20), 118 (17), 104 (100).

$C_{16}H_{14}O_3$	Calcd.	C, 75.57	H, 5.55
	Found	C, 75.41	H, 5.54

Synthesis of ethyl 4-(2,2-dimethyl-1-oxopropyl)-benzoate (38c)



Prepared according to TP 5 from ethyl 4-iodobenzoate (276 mg, 1.0 mmol), lithium neopentylcuprate **33** (1.2 mmol) and pivaloyl chloride (108 mg, 0.9 mmol). Reaction time: 1.5 h at -50 °C Purification by flash chromatography (pentane/diethyl ether 95:5) yielded **38c** as a light yellow oil (350 mg, 83 %).

IR (film, cm^{-1}): $\tilde{n}$ 3435 (vs, br), 1689 (vs), 1657 (vs), 1597 (m), 1579 (w), 1447 (s), 1402 (s), 1356 (s), 1316 (s), 1277 (vs), 1180 (w), 1072 (s), 939 (m), 928 (m), 850 (m), 794 (m), 736 (m), 699 (vs), 674 (m).

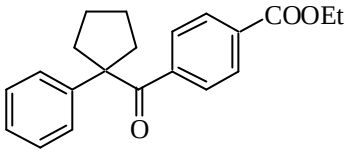
^{1}H NMR ($CDCl_3$, 300 MHz,): d 7.99 (dd, *J* = 8.7 and 1.8 Hz, 2H), 7.58 (dd, *J* = 8.7 and 1.8 Hz, 2H), 4.32 (q, *J* = 11.0 and 7.1 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.26 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 209.8, 166.2, 143.2, 132.4, 129.6, 127.7, 61.6, 44.7, 28.0, 14.6.

MS (EI, 70 eV): 235 ($[M+H]^+$, 3), 189 (8), 177 (100), 149 (20), 121 (5), 103 (6).

$C_{14}H_{18}O_3$	HRMS	Calcd.	235.1334 $[M+H]^+$
		Found	235.1352 $[M+H]^+$

Synthesis of 4-[(1-phenylcyclopentyl)carbonyl]benzoate (38d)



Prepared according to TP 5 from ethyl 4-iodobenzoate (552 mg, 2.0 mmol), lithium neopentylcuprate **33** (2.2 mmol) and 1-phenylcyclopentanecarbonylchloride (375 mg, 1.8 mmol). Reaction time: 1.5 h at -50 °C. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded **38d** as a colourless oil (350 mg, 60 %).

IR (film, cm^{-1}): $\tilde{n}$ 3432 (m, br), 2956 (m), 1715 (vs), 1667 (s), 1366 (w), 1282 (vs), 1235 (s), 1129 (m), 1110 (s), 1019 (w), 724 (w), 705 (w).

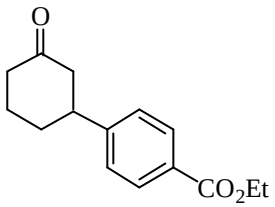
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.84 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.25-7.15 (m, 5H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.42 (m, 2H), 2.03 (m, 2H), 1.66 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d202.2, 166.2, 144.3, 140.3, 133.2, 129.9, 129.5, 127.2, 126.5, 64.0, 31.6, 37.5, 25.0, 14.6.

MS (EI, 70 eV): 323 (M^+, 1), 177 (24), 145 (100), 115 (2).

$C_{21}H_{22}O_3$	HRMS	Calcd.	322.1569 $[M-H]^+$
		Found	322.1565

Synthesis of ethyl 4-(3-oxocyclohexyl)-benzoate (38e)



Prepared according to TP 5 from ethyl 4-iodobenzoate (552 mg, 2.0 mmol), lithium neopentylcuprate **33** (2.2 mmol), 2-cyclohexen-1-one (0.16 mL, 1.6 mmol) and trimethylsilyl chloride (0.4 mL, 3.2 mmol). Reaction time: 1.5 h at -50 °C. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded ethyl 4-(3-oxocyclohexyl)-benzoate **5d** as a light yellow oil (113 mg, 70 %).

IR (film, cm^{-1}): $\tilde{n}$ 2977 (vs), 2934 (s), 2864 (vs), 1719 (m), 1444 (m), 1382 (s), 1350 (m), 1277 (m), 1261 (m), 1123 (vs), 1077 (s), 1043 (m), 1023 (m), 845 (w), 797 (m).

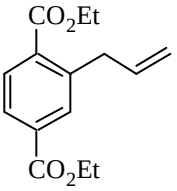
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.93 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.30 (q, *J* = 11.1 and 7.2 Hz, 2H), 3.05-2.95 (m, 1H), 2.56-1.50 (m, 8H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 209.3, 165.4, 148.3, 129.0, 128.1, 125.6, 59.9, 47.5, 43.7, 40.1, 31.5, 24.4, 13.3.

MS (EI, 70 eV): 246 (M^+, 94), 218 (2), 201 (100), 189 (9), 177 (17), 148 (14), 145 (49), 131 (89), 117 (50), 102 (22).

$C_{15}H_{18}O_3$	Calcd.	C, 73.15	H, 7.37
	Found	C, 73.44	H, 7.40

Synthesis of diethyl 2-allylterephtalate (38f)



Prepared according to TP 5 from diethyl 2-bromoterephtalate (630 mg, 2.1 mmol), lithium neopentylcuprate **33** (2.2 mmol) and allyl bromide (242 mg, 2.0 mmol). Reaction time: 1h at -40

°C. Purification by flash chromatography (pentane/diethyl ether 99:1) yielded **38f** as a light yellow oil (400 mg, 76 %).

IR (film, cm^{-1}): $\tilde{n}$ 2980 (s), 2907 (m), 1722 (vs), 1638 (w), 1477 (m), 1407 (m), 1366 (s), 1269 (vs), 1188 (m), 1110 (vs), 1070 (m), 1021 (m), 915 (m), 753 (m), 732 (m).

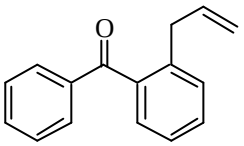
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.87-7.82 (m, 3H), 5.99-5.86 (m, 1H), 5.00-4.97 (m, 2H), 4.36-4.27 (m, 4H), 3.60 (d, *J* = 6.6 Hz, 2H), 1.37-1.30 (m, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d167.5, 166.3, 141.7, 137.1, 134.5, 133.6, 132.3, 130.8, 128.7, 116.5, 62.0, 61.7, 38.6, 14.7, 14.6.

MS (EI, 70 eV): 262 (M^+, 62), 247 (91), 217 (100), 205 (14), 189 (20), 177 (34), 171 (25), 161 (9), 143 (22), 117 (49), 115 (62).

$C_{15}H_{18}O_4$	HRMS	Calcd.	262.1205
		Found	262.1210

Synthesis of 2-allylbenzophenone (38g)



Prepared according to TP 5 from 2-iodobenzophenone (830 mg, 2.7 mmol), lithium neopentylcuprate **33** (2.8 mmol) and allyl bromide (302 mg, 2.5 mmol). Reaction time: 1h at -60 °C. Purification by flash chromatography (pentane) yielded **38g** as a light yellow oil (480 mg, 80 %).

IR (film, cm^{-1}): $\tilde{n}$ 3511 (w, br), 3062 (m), 2956(vs), 2926 (vs), 2855 (s), 1666 (vs), 1598 (vs), 1580 (s), 1477 (s), 1465 (s), 1448 (vs), 1364 (s), 1315 (vs), 1269 (vs), 1154 (m), 999 (m), 928 (vs), 762 (vs), 702 (vs), 639 (s).

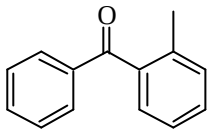
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.88-7.80 (m, 3H), 7.60-7.28 (m, 6H), 6.01-5.81 (m, 1H), 5.06-4.96 (m, 2H), 4.36-4.27 (m, 4H), 3.46 (d, *J* = 6.6 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d196.9, 136.6, 136.2, 134.5, 132.5, 131.6, 130.4, 129.6, 128.3, 127.9, 116.0, 39.6.

MS (EI, 70 eV): 222 (40), 207 (100), 178 (10), 165 (15), 145 (22), 115 (30), 105 (9), 91 (5), 77 (27).

$C_{16}H_{14}O$	HRMS	Calcd.	222.1045
		Found	224.1036

Synthesis of 2-methylbenzophenone (38h)



Prepared according to TP 5 from 2-iodobenzophenone (620 mg, 2.0 mmol), lithium neopentylcuprate **33** (2.2 mmol) and methyl iodide (0.12 mL, 1.9 mmol). Reaction time: 1 h at -60 °C. Purification by flash chromatography (pentane/diethyl ether gradient) yielded **38h** as a light yellow oil (300 mg, 80 %).

IR (film, cm^{-1}): $\tilde{n}$ 3511 (w, br), 3062 (m), 2936(vs), 2855 (w), 1676 (vs), 1562 (s), 1470 (s), 1458 (s), 1384 (m), 1315 (s), 1134 (w), 1902 (m), 757 (vs), 701 (s).

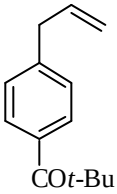
^{1}H NMR ($CDCl_3$, 300 MHz,): d 7.74-7.71 (m, 3H), 7.50 (tt, J = 7.3 and 1.3 Hz, 1H), 7.40-7.14 (m, 5H), 2.25 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 199.0, 139.0, 138.1, 137.1, 133.5, 130.6, 130.5, 128.9, 128.8, 125.8, 113.9, 20.4.

MS (EI, 70 eV): 195 (M^+, 100), 178 (15), 165 (10), 152 (8), 119 (34), 105 (30), 91 (55), 77 (45), 65 (20), 51 (15), 39 (10).

$C_{14}H_{12}O$	HRMS	Calcd.	196.0888
		Found	196.0881

Synthesis of 2,2-dimethyl-1-[4-(2-propenyl)phenyl]-1-propanone (38i):



Prepared according to TP 5 from 4-iodophenyl *t*-butyl ketone (290 mg, 1.0 mmol), lithium neopentylcuprate **33** (1.2 mmol) and allyl bromide (109 mg , 0.9 mmol). Reaction time: 1.5 h at 0 °C. Purification by flash chromatography (pentane/diethyl ether 100:1) yielded **38i** as a light yellow oil (170 mg, 93 %).

IR (film, cm^{-1}): $\tilde{n}$ 2968 (s), 2906 (s), 1672 (vs), 1606 (vs), 1477 (m), 1402 (s), 1366 (m), 1277 (s), 1171 (s), 962 (s), 916 (m), 824 (m), 759 (m), 560 (w).

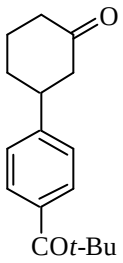
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.60 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 5.94-5.80 (m, 1H), 5.04-4.98 (m, 2H), 3.33 (d, *J* = 6.6 Hz, 2H), 1.26 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz,): d 208.7, 143.8, 136.9, 136.5, 128.8, 128.6, 116.8, 44.5, 40.4, 28.5.

MS (EI, 70 eV): 202 (M^+, 1), 145 (100), 115 (18), 101 (2).

$C_{14}H_{18}O$	HRMS	Calcd.	202.1358
		Found	202.1330

Synthesis of 3-[4-(2,2-dimethylpropanoyl)phenyl]cyclohexanone (38j)



Prepared according to TP 5 from 4-iodophenyl *t*-butyl ketone (290 mg, 1.0 mmol), lithium neopentylcuprate **33** (1.2 mmol), 2-cyclohexen-1-one (0.12 mL, 1.2 mmol) and trimethylsilyl chloride (0.3 mL, 2.4 mmol). Reaction time: 2 h at 0 °C. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **38j** as a light yellow oil (150 mg, 60 %).

IR (film, cm^{-1}): $\tilde{n}$ 3413 (m, br), 2935 (vs), 2870 (s), 1712 (vs), 1671 (vs), 1606 (s), 1477 (s), 1448 (m), 1414 (m), 1395 (m), 1366 (s), 1276 (s), 1198 (m), 1172 (vs), 962 (vs), 842 (m), 768 (m), 710 (w).

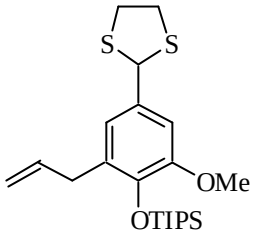
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.63 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 3.03-2.93 (m, 1H), 2.56-1.49 (m, 8H), 1.27 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz) d 210.8, 208.7, 147.7, 137.1, 129.0, 127.4, 126.7, 48.9, 44.9, 44.5, 41.5, 32.9, 28.5, 25.8.

MS (EI, 70 eV): 258 (M^+, 1), 201 (100), 144 (1), 131 (3), 115 (4), 103 (2).

$C_{17}H_{22}O_2$	HRMS	Calcd.	258.1620
		Found	258.1629

Synthesis of [2-allyl-4-(1,3-dithiolan-2-yl)-6-methoxyphenoxy](triisopropyl)silane (38k)



Prepared according to TP 5 from [4-(1,3-dithiolan-2-yl)-2-iodo-6-methoxyphenoxy](triisopropyl)silane (505 mg, 0.9 mmol), lithium neopentylcuprate **33** (12.1 mmol) and allyl bromide (490 mg, 4.0 mmol). Reaction time: 7h at rt. Purification by flash chromatography (pentane/diethyl ether 98:2) yielded **38k** as a yellow oil (250 mg, 60 %).

IR (film, cm^{-1}): $\tilde{n}$ 2945 (vs), 2865 (vs), 1585 (m), 1490 (vs), 1465 (vs), 1423 (m), 1311 (s), 1150 (s), 1077 (m), 917 (s), 884 (s), 680 (s).

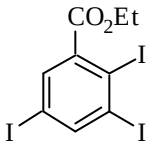
^{1}H NMR ($CDCl_3$, 300 MHz): d 6.88 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 5.88 (m, 1H), 5.54 (s, 1H), 5.01 (m, 2H), 3.71 (s, 3H), 3.41 (m, 2H), 3.31 (d, *J* = 6.6 Hz, 2H), 3.25 (m, 2H), 1.18 (m, 3H), 0.99 (d, *J* = 7.1 Hz, 18H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 148.4, 142.2, 133.3, 129.8, 129.3, 120.5, 116.2, 107.6, 55.9, 53.7, 39.1, 33.8, 17.2, 13.2.

MS (EI, 70 eV): 401 (4), 381 (100), 366 (45), 338 (24), 297 (51), 235 (9), 207 (27), 193 (12), 73 (13).

$C_{22}H_{36}O_2S_2Si$	HRMS	Calcd.	424.1926
		Found	424.1920

Synthesis of ethyl 2,3,5-triiodobenzoate (40)



A mixture of 2,3,5-triiodobenzoic acid (10.0 g, 20.0 mmol), EtOH (60 mL), and conc. H_2SO_4 (3 mL), was heated to reflux for 14 h. After cooling to rt, the reaction mixture was dissolved in CH_2Cl_2 (300 mL) and washed with saturated, aqueous $NaHCO_3$ (till pH 5) and with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was recrystallized from pentane to give the desired product **40** as a white crystalline solid (9.8 g, 93 %).

Mp 92 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 2978 (w), 1736 (vs), 1271 (vs), 1184 (vs), 774 (w).

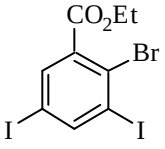
^{1}H NMR ($CDCl_3$, 300 MHz): d 8.29 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 166.1, 148.6, 141.8, 136.8, 113.2, 106.5, 93.6, 62.5, 14.1.

MS (EI, 70 eV): 528 (M^+, 100), 500 (23), 483 (54), 455 (18), 373 (10), 218 (16), 201 (32), 74 (35).

$C_9H_7I_3O_2$	Calcd.	C, 20.48	H, 1.34	I, 72.12
	Found	C, 20.43	H, 1.40	I, 72.05

Synthesis of ethyl 2-bromo-3,5-diiodobenzoate (41f)



i-PrMgCl (1.1 mL, 2.2 mmol, 2 M solution in THF) was added slowly to a solution of **40** (1.1 g, 2.1 mmol) in THF (2 mL), at -78 °C. The reaction mixture was warmed to -50 °C and after 1 h a solution of 1,2-dibromotetrachloroethane (0.8 g, 2.4 mmol) in THF (2 mL) was added. After 1 h the reaction was quenched with saturated, aqueous NH_4Cl. The aqueous phase was extracted with

diethyl ether (3 x 15 mL). The organic fractions were washed with brine, dried over and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 96:4) yielded **41f** as a light red oil (850 mg, 85 %).

IR (film, cm^{-1}): $\tilde{n}$ 3436 (s, br), 1731 (vs), 1527 (m), 1402 (m), 1374 (m), 1275 (vs), 1237 (s), 1191 (vs), 1108 (m), 1012 (m), 775 (w).

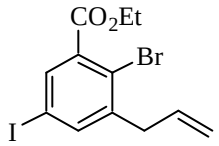
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.95 (d, *J* = 2.0 Hz, 2H), 7.65 (d, *J* = 2.0 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 166.2, 150.2, 138.6, 132.9, 128.0, 106.2, 93.7, 62.9, 14.6.

MS (EI, 70 eV): 479 (M^+, 100), 453 (27), 436 (59), 406 (9), 352 (4), 279 (6), 152 (7).

$C_9H_7BrI_2O_2$	HRMS	Calcd.	479.7719
		Found	479.7745

Synthesis of ethyl 3-allyl-2-bromo-5-iodobenzoate (38l)



Prepared according to TP 5 from 41f (400 mg, 0.8 mmol), lithium neopentylcuprate **33** (2.1 mmol) and allyl bromide (0.1 mL, 1.1 mmol). Reaction time: 45 min. Purification by flash chromatography (pentane/diethyl ether 100:1) yielded **38l** as a colourless oil (250 mg, 76 %).

IR (film, cm^{-1}): $\tilde{n}$ 2980 (m), 2925 (m), 1732 (vs), 1422 (m), 1281 (vs), 1155 (s), 1024 (vs), 919 (m), 775 (m).

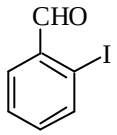
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.69 (d, *J* = 2.1 Hz, 2H), 7.56 (d, *J* = 2.1 Hz, 2H), 5.83 (m, 1H), 5.12-5.01 (m, 2H), 4.31 (q, *J* = 7.5 Hz, 2H), 3.44 (d, *J* = 6.5 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 166.1, 143.7, 141.4, 136.8, 134.7, 123.0, 118.1, 92.3, 62.5, 40.7, 14.5.

MS (EI, 70 eV): 393 (M^+, 100), 350 (60), 287 (6), 241 (4), 160 (15), 115 (45).

$C_{12}H_{12}BrIO_2$	HRMS	Calcd.	393.9065
		Found	393.9074

Synthesis of 2-iodobenzaldehyde[137] **(39)**



A solution of oxalyl chloride (1.0 mL, 11.0 mmol) in dichloromethane (25 mL), was placed in a 100 mL two-necked argon flask equipped with two dropping funnels containing DMSO (1.7 mL, 22.0 mmol) dissolved in dichloromethane (5 mL), and 2-iodobenzylalcohol (2.34 g, 10.0 mmol) dissolved in 10 mL dichloromethane respectively. The DMSO was added to the stirred oxalyl chloride solution at -50 °C. The reaction mixture was stirred for 2 min and the alcohol was added within 5 min; stirring was continued for additional 15 min.TEA (7.0 mL, 50.0 mmol) was added and the reaction mixture was stirred for 5 min and then allowed to warm to rt. Water (50 mL), was then added and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid obtained was recrystallized from pentane to give **39** as a light yellow solid (1.9 g, 82 %).

Mp 36 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 2851 (w), 1696 (vs), 1580 (s), 1437 (m), 1261 (s), 1199 (s), 1014 (s), 820 (m), 752 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): d 9.98 (s, 1H), 7.87 (dd, *J* = 7.9 and 1.0 Hz, 1H), 7.80 (dd, *J* = 7.9 amd 1.8 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.23-7.18 (m, 1H).

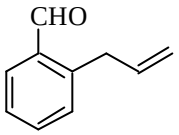
^{13}C-NMR ($CDCl_3$, 75 MHz): d 196.1, 141.0, 135.9, 135.5, 130.7, 129.1, 101.1.

MS (EI, 70 eV): 232 (M^+, 100), 203 (16), 104 (78), 76 (31), 50 (16).

C_7H_5IO	HRMS	Calcd.	231.9385
		Found	231.9387

[137] Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.*, **1978**, *43*, 2480.

Synthesis of 2-allylbenzaldehyde (38m)



Prepared according to TP 5 from 39 (210 mg, 0.9 mmol), lithium neopentylcuprate **33** (1.2 mmol) and allyl bromide (110 mg, 0.9 mmol). Reaction time: 4.5 h at -40 °C. Purification by flash chromatography (pentane/diethyl ether 98:2) yielded **38m** as a colourless oil (100 mg, 80 %).

IR (film, cm^{-1}): $\tilde{n}$ 2934 (vs, br), 2859 (vs, br), 1732 (vs), 1694 (vs), 1584 (w), 1579 (w), 1434 (m), 1368 (s), 1240 (vs), 1175 (w), 1112 (s), 1015 (s), 957 (m), 758 (s), 714 (m), 648 (w).

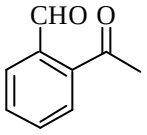
^{1}H NMR ($CDCl_3$, 300 MHz): d 10.20 (s, 1H), 7.77 (dd, J = 7.6 and 1.3 Hz, 1H), 7.46 (td, J = 7.5 and 1.4 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.03-5.90 (m, 1H), 5.04-4.88 (m, 2H), 3.75 (d, ^{3}J = 6.2 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 191.3, 141.2, 135.9, 132.9, 130.6, 130.1, 125.9, 115.4, 35.5.

MS (EI, 70 eV): 146 (M^+, 19), 131 (100), 128 (39), 118 (47), 117 (63), 155 (80), 103 (48).

$C_{10}H_{10}O$	HRMS	Calcd.	146.0732
		Found	146.0729

Synthesis of 2-acetylbenzaldehyde (38n)



Prepared according to TP 5 from 39 (230 mg, 1.0 mmol), lithium neopentylcuprate **33** (1.2 mmol) and acetyl chloride (70 µL, 1.1 mmol). Reaction time: 4.5 h at -40 °C. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **38n** as a colourless oil (111 mg, 75 %).

IR (film, cm^{-1}): $\tilde{n}$ 3379 (m, br), 2924 (m), 2856 (m), 1732 (vs), 1696 (vs), 1637 (w), 1599 (m), 1574 (w), 1434 (w), 1407 (w), 1286 (m), 1209 (m), 1175 (w), 1079 (w), 996 (m), 917 (m), 754 (s), 636 (w).

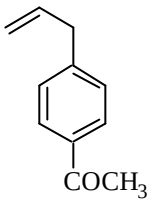
^{1}H NMR ($CDCl_3$, 300 MHz): d 10.19 (s, 1H), 7.92-7.72 (m, 2H), 7.64-7.55 (m, 2H), 2.69 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 193.9, 190.3, 140.0, 137.3, 133.4, 130.5, 130.4, 128.9, 28.3.

MS (EI, 70 eV): 148 (M^+, 3), 133 (4), 120 (2), 111 (1), 105 (100), 91 (8), 85 (3).

$C_9H_8O_2$	HRMS	Calcd.	148.0524
		Found	148.0538

Synthesis of 4-allylacetophenone (38o)



Prepared according to TP 5 from 4-iodoacetophenone (240 mg, 1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and allyl bromide (0.1 mL, 1.1 mmol). Reaction time: 30 min at rt.. Purification by flash chromatography (pentane/diethyl ether 99:1) yielded **38o** as a colourless oil (112 mg, 71 %).

IR (film, cm^{-1}): $\tilde{n}$ 2918 (w), 1682 (vs), 1605 (m), 1582 (m), 1357 (m), 1267 (vs), 1181 (m), 1005 (m), 917 (m).

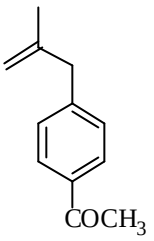
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.81 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.87 (m, 1H), 5.05-4.98 (m, 2H), 3.35 (d, *J* = 6.6 Hz, 2H), 2.49 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 198.5, 146.1, 137.5, 136.7, 129.2, 129.0, 128.7, 128.4, 117.0, 40.5, 15.7.

MS (EI, 70 eV): 160 (M^+, 15), 145 (100), 117 (21), 115 (38).

$C_{11}H_{12}O$	Calcd.	C, 82.46	H, 7.55
	Found	C, 82.69	H, 7.72

Synthesis of 1-[4-(2-methyl-2-propenyl)phenyl]ethanone (38p)



Prepared according to TP 5 from 4-iodoacetophenone (240 mg, 1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and 3-bromo-2-methyl-1-propene (0.1 mL, 1.0 mmol). Reaction time: 1 h at rt. Purification by flash chromatography (pentane/diethyl ether 97:3) yielded **38p** as a light yellow oil (110 mg, 65 %).

IR (film, cm^{-1}): $\tilde{n}$ 2919 (w), 1683 (vs), 1606 (m), 1430 (w), 1412 (w), 1357 (m), 1267 (vs), 1181 (w), 799 (w).

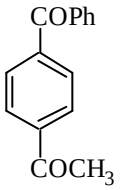
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.82 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 5.86 (s, 1H), 5.65 (s, 1H), 3.29 (s, 2H), 2.50 (s, 3H), 1.60 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 198.2, 145.9, 144.5, 135.7, 129.5, 128.9, 113.1, 44.9, 26.9, 22.5.

MS (EI, 70 eV): 174 (M^+, 11),159 (100), 131 (20), 116 (12), 105 (2).

$C_{12}H_{14}O$	HRMS	Calcd.	174.1045
		Found	174.1038

Synthesis of 4-acetylbenzophenone (38q)



Prepared according to TP 5 from 4-iodoacetophenone (240 mg, 1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and benzoyl chloride (0.1 mL, 0.9 mmol). Reaction time: 1.5 h at rt. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **38q** as a light yellow oil (155 mg, 77 %).

IR (film, cm^{-1}): $\tilde{n}$ 3435 (vs, br), 1689 (vs), 1657 (vs), 1597 (m), 1579 (w), 1447 (s), 1402 (s), 1356 (s), 1316 (s), 1277 (vs), 1180 (w), 1072 (s), 939 (m), 928 (m), 850 (m), 794 (m), 736 (m), 699 (vs), 674 (m).

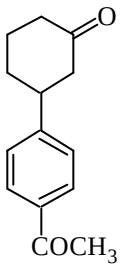
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.98 (dd, *J* = 8.0 and 1.8 Hz, 2H), 7.79 (dd, *J* = 8.1 and 1.8 Hz, 2H), 7.73 (m, 2H), 7.55 (dt, *J* = 8.1 and 1.4 Hz, 1H), 7.43 (t, *J* = 8.2 Hz, 2H), 2.59 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 197.9, 196.3, 141.7, 140.0, 137.3, 133.4, 130.5, 130.4, 129.2, 128.9, 128.5, 27.3.

MS (EI, 70 eV): 224 (M^+, 29), 209 (90), 181 (8), 167 (100), 153 (11), 147 (20), 119 (3), 105 (34).

$C_{15}H_{12}O_2$	HRMS	Calcd.	224.0837
		Found	224.0829

Synthesis of 3-(4-acetylphenyl)cyclohexanone (38r)



Prepared according to TP 5 from 4-iodoacetophenone (240 mg, 1.0 mmol), lithium neophylcuprate **35** (1.2 mmol), 2-cyclohexen-1-one (0.12 mL, 1.2 mmol) and trimethylsilyl chloride (0.3 mL, 2.4 mmol). Reaction time: 2 h at rt. Purification by flash chromatography (pentane/diethyl ether 6:4) yielded **38r** as a colourless oil (140 mg, 68 %).

IR (film, cm^{-1}): $\tilde{n}$ 3430 (m, br), 2935 (vs), 2870 (s), 1712 (vs), 1657 (vs), 1606 (s), 1477 (s), 1448 (m), 1414 (m), 1395 (m), 1366 (s), 1276 (s), 1198 (m), 1172 (vs), 962 (vs), 842 (m), 768 (m), 710 (w).

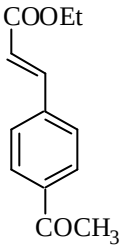
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.85 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 3.06-2.96 (m, 1H), 2.50 (s, 3H), 2.46-1.66 (m, 8H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 228.5, 210.6, 150.0, 136.2, 129.3, 127.2, 48.8, 45.0, 41.5, 32.8, 27.0, 25.8.

MS (EI, 70 eV): 216 (M^+, 27), 201 (100), 181 (11), 173 (8), 147 (3), 131 (16), 115 (4), 103 (4).

$C_{14}H_{16}O_2$	Calcd.	C, 77.75	H, 7.46
	Found	C, 77.76	H, 7.40

Synthesis of ethyl (2E)-3-(4-acetylphenyl)-2-propenoate (38s)



Prepared according to TP 5 from 4-iodoacetophenone (246 mg, 1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and ethyl propiolate (0.1 g, 1.0 mmol). Reaction time: 1.5 h at rt. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **38s** as a light yellow oil (170 mg, 78 %).

IR (film, cm^{-1}): $\tilde{n}$ 3487 (m, br), 2978 (m), 1717 (vs), 1683 (vs), 1637 (m), 1605 (m), 1365 (m), 1267 (vs), 1206 (s), 1177 (vs), 1031 (m), 828 (m), 700 (m).

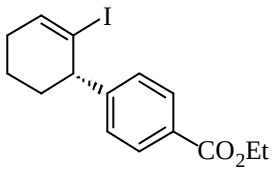
^{1}H NMR ($CDCl_3$, 300 MHz): d 8.03 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 16.0 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 6.59 (d, *J* = 15.9 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.67 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 197.7, 166.9, 143.4, 139.2, 138.4, 130.0, 129.2, 128.5, 128.3, 121.2, 61.1, 27.0, 14.7.

MS (EI, 70 eV): 218 (M^+, 24), 203 (100), 175 (16), 147 (7), 131 (10), 115 (3), 102 (12).

$C_{13}H_{14}O_3$	HRMS	Calcd.	218.0943
		Found	218.0936

Synthesis of ethyl 4-(2-iodo-2-cyclohexen-1-yl)benzoate (56)



Prepared according to TP 5 from ethyl 4-iodobenzoate (265 mg, 1.0 mmol), lithium neopentylcuprate **33** (1.2 mmol) and 2-iodo-2-cyclohexen-1-yl acetate (300 mg, 1.1 mmol, 93 % ee). Reaction time: 1 h at -40 °C. Purification by flash chromatography (pentane/diethyl ether 95:5) yielded **56** as a light yellow oil (220 mg, 64 %). ee: 92 %

IR (film, cm^{-1}): $\tilde{n}$ 2936 (vs), 1714 (vs), 1609 (s), 1416 (m), 1308 (s), 1275 (vs), 1178 (s), 1102 (vs), 1021 (s), 985 (m), 769 (m), 707 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.95 (dt, *J* = 8.4 and 1.9 Hz, 2H), 7.20 (dt, *J* = 8.4 and 1.9 Hz, 2H), 6.62 (td, *J* = 4.2 and 1.9 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.14-2.05 (m, 3H), 1.57-1.53 (m, 3H), 1.31 (t, *J* = 7.2 Hz, 3H).

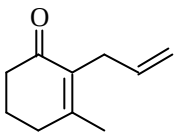
^{13}C-NMR ($CDCl_3$, 75 MHz): d 166.9, 149.8, 141.2, 130.1, 129.4, 128.7, 100.2, 61.2, 53.0, 33.9, 30.4, 19.1, 14.8.

MS (EI, 70 eV): 356 (M^+, 82), 229 (82), 206 (47), 201 (21), 163 (41), 155 (53), 129 (100), 115 (53).

$C_{15}H_{17}IO_2$	HRMS	Calcd.	356.0273
		Found	356.0265

8 Iodine-Copper Exchange on Vinylic Substrates

Synthesis of 2-allyl-3-methyl-2-cyclohexen-1-one (45a)

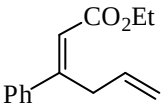


Prepared according to TP 5 from 2-iodo-3-methyl-cyclohexen-1-one (240 mg, 1 mmol), lithium neopentylcuprate **33** (1.2 mmol) and allyl bromide (110 mg, 0.9 mmol). Reaction time: 3.5 h at -30 °C. Purification by flash chromatography (pentane/diethyl ether 96:4) yielded **45a** as a colourless oil (100 mg, 74 %).

IR (film, cm^{-1}): $\tilde{n}$ 2924 (m), 2868 (m), 1666 (vs), 1636 (s), 1430 (m), 1379 (m), 1360 (w), 1261 (w), 1191 (w), 1016 (w), 996 (w), 910 (m), 799 (w).
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.73-5.64 (m, 1H), 4.90-4.84 (m, 2H), 2.99 (d, *J* = 6.2 Hz, 2H), 2.63-1.90 (m, 6H), 1.86 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): d 198.6, 157.2, 136.2, 126.7, 114.7, 38.1, 33.3, 29.6, 22.6, 21.6.
MS (EI, 70 eV): 150 (M^+, 43), 135 (100), 131 (4), 122 (9), 119 (14), 117 (22), 107 (20).

$C_{10}H_{14}O$	HRMS	Calcd.	150.1045
		Found	150.1062

Synthesis of ethyl (2E)-3-phenyl-2,5-hexadienoate (45b)



Prepared according to TP 6 from ethyl (2Z)-3-iodo-3-phenylpropenoate (1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and allyl bromide (110 mg, 0.9 mmol). Reaction time: 20 min. Purification by flash chromatography (pentane/diethyl ether 99:1) yielded **45b** as a light yellow oil (190 mg, 88 %).

IR (film, cm^{-1}): $\tilde{n}$ 2976 (m), 1733 (vs), 1638 (w), 1445 (m), 1367 (m), 1253 (s), 1157 (s), 1032 (m), 907 (m), 764 (m), 699 (s).

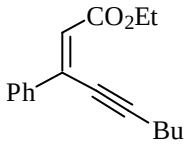
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.42-7.17 (m, 5H), 5.78 (m, 1H), 5.06-4.92 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.79 (d, *J* = 6.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d173.2, 166.7, 141.5, 139.7, 135.9, 134.4, 128.3, 118.6, 116.6, 60.3, 35.9, 14.7.

MS (EI, 70 eV): 216 (M^+, 3), 187 (1), 170 (11), 141 (79), 128 (100), 115 (18), 102 (3).

$C_{14}H_{16}O_2$	HRMS	Calcd.	216.1150
		Found	216.1128

Synthesis of ethyl (2Z)-3-phenyl-2-nonen-4-ynoate (45c)



Prepared according to TP 6 from ethyl (2Z)-3-iodo-3-phenylpropenoate (1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and benzoyl chloride (0.15 mL mg, 1.2 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 99:1) yielded **45c** as a light yellow oil (161 mg, 63 %).

IR (film, cm^{-1}): $\tilde{n}$ 2961 (s), 2873 (s), 1735 (vs), 1448 (m), 1370 (m), 1178 (s), 1098 (s), 1030 (m), 765 (w), 700 (m).

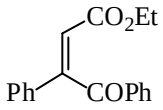
^{1}H NMR ($CDCl_3$, 300 MHz): d7.62 (m, 2H), 7.31 (m, 3H), 6.42 (s, 1H), 5.29 (q, *J* = 7.1 Hz, 2H), 2.49 (t, *J* = 7.1 Hz, 2H), 1.62-1.33 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d166.0, 138.3, 137.6, 130.0, 129.2, 128.6, 126.6, 118.5, 105.4, 60.6, 38.7, 26.3, 22.5, 20.2, 14.7, 14.0.

MS (EI, 70 eV): 256 (M^+, 10), 227 (100), 211 (64), 199 (40), 186 (99), 168 (60), 159 (61), 141 (95), 129 (76), 115 (83), 102 (25).

$C_{17}H_{20}O_2$	HRMS	Calcd.	256.1463
		Found	256.1469

Synthesis of ethyl (2Z)-4-oxo-3,4-diphenyl-2-butenoate (45d)



Prepared according to TP 6 from ethyl (2Z)-3-iodo-3-phenylpropenoate (1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and benzoyl chloride (0.15 mL mg, 1.2 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 92:8) yielded **45d** as a light yellow solid (186 mg, 69 %).

Mp 90 °C

IR (film, cm^{-1}): $\tilde{n}$ 3061 (m), 2980 (s), 1714 (vs), 1615 (vs), 1598 (vs), 1577 (vs), 1494 (s), 1448 (vs), 1369 (vs), 1346 (vs), 1276 (vs), 1218 (vs), 1182 (vs), 1096 (s), 1019 (s), 770 (vs), 698 (vs), 590 (s).

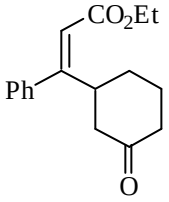
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.87 (m, 2H), 7.46-7.27 (m, 8H), 6.42 (s, 1H), 3.98 (q, J = 7.1 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d196.8, 165.4, 155.9, 136.5, 134.7, 133.9, 130.8, 129.5, 129.3, 129.1, 128.4, 127.3, 118.3, 61.3, 14.2.

MS (EI, 70 eV): 280 (M^+, 26), 252 (100), 235 (25), 206 (22), 111 (4), 105 (11).

$C_{18}H_{16}O_3$	Calcd.	C, 77.12	H, 5.75
	Found	C, 76.92	H, 5.71

Synthesis of 3-[(1E)-3-oxo-1-phenyl-1-hexenyl]cyclohexanone (45e)



Prepared according to TP 6 from ethyl (2Z)-3-iodo-3-phenylpropenoate (1.0 mmol), lithium neophylcuprate **35** (1.2 mmol), cyclohexen-1-one (0.15 mL, 1.5 mmol) and TMSCl (0.4 mL, 3.0

mmol). Reaction time: 3 min. Purification by flash chromatography (pentane/diethyl ether 1:1) yielded **45e** as a light yellow oil (130 mg, 48 %).

IR (film, cm^{-1}): $\tilde{n}$ 3443 (m, br), 2962 (s), 1713 (vs), 1630 (m), 1444 (m), 1371 (m), 1246 (m), 1176 (vs), 1030 (s), 765 (m), 700 (s).

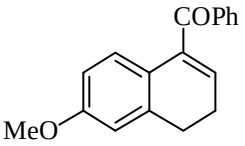
^{1}H NMR ($CDCl_3$, 300 MHz): d7.28 (m, 2H), 7.11 (m, 3H), 5.69 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.30-1.52 (m, 9H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 210.6, 166.2, 162.4, 140.4, 128.5, 128.0, 120.4, 60.6, 46.2, 41.4, 40.7, 30.4 ,25.9, 14.6.

MS (EI, 70 eV): 272 (M^+, 96), 243 (100), 226 (79), 199 (86), 171 (25), 141 (19), 128 (21), 85 (21), 71 (11), 44 (11).

$C_{17}H_{20}O_3$	HRMS	Calcd.	272.1412
		Found	272.1421

Synthesis of (6-methoxy-3,4-dihydro-1-naphtalenyl)(phenyl)methanone (45f)



A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with 4-iodo-7-methoxy-1,2-dihydronaphtalene (260 mg, 0.9 mmol). THF (1 mL) was added and the solution was added slowly into a dry and argon flushed 25 mL flask, containing the lithium neophylcuprate **35**, previously prepared (1.2 mmol) and cooled to -78 °C. The reaction mixture was warmed to 0 °C. The iodine-copper exchange was complete within 3 h (checked by GC analysis of reaction aliquots) and the mixture was cooled to -20 °C. Benzoyl chloride (0.4 mL, 3.4 mmol) was added to the mixed organocuprate 44c. After 0.5 h of stirring at -20 °C, the reaction mixture was quenched with saturated, aqueous NH_4Cl (2 mL) and poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL). The organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 96:4) yielded **45f** as a yellow oil (190 mg, 72 %).

IR (film, cm^{-1}): $\tilde{n}$ 3057 (m), 2935 (s), 2834 (m), 1720 (m), 1657 (vs), 1605 (vs), 1499 (s), 1499 (vs), 1448 (s), 1304 (s), 1268 (vs), 1252 (vs), 1160 (m), 1136 (s), 1044 (s), 1029 (s), 779 (s), 708 (s).

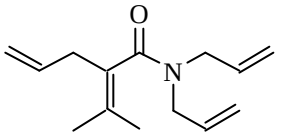
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.79 (dt, *J* = 7.0 and 1.4 Hz, 2H), 7.47 (tt, *J* = 7.4 and 1.3 Hz, 1H), 7.35 (tt, *J* = 7.3 and 1.2 Hz, 2H), 7.14 (m, 1H), 6.69-6.58 (m, 2H), 6.29 (t, *J* = 4.6 Hz, 1H), 3.72 (s, 3H), 2.78 (7, *J* = 8.1 Hz, 2H), 2.40 (m, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d197.4, 159.3, 138.5, 138.3, 137.9, 134.5, 132.9, 131.1, 128.4, 127.2, 125.2, 114.1, 111.4, 55.4, 28.2, 23.4.

MS (EI, 70 eV): 264 (M^+, 100), 236 (27), 221 (16), 159 (57), 144 (30), 105 (45), 77 (16).

$C_{18}H_{16}O_2$	HRMS	Calcd.	264.1150
		Found	264.1162

Synthesis of *N*,*N*-diallyl-2-(1-methylethylidene)-4-pentenamide (45g)



Prepared according to TP 7 from *N*,*N*-diallyl-2-bromo-3-methyl-butenamide (1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and allyl bromide (0.2 mL, 2.3 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **45g** as a colourless oil (120 mg, 55 %).

IR (film, cm^{-1}): $\tilde{n}$ 3078 (w), 2921 (m), 1651 (vs), 1640 (vs), 1436 (m), 1413 (m), 1192 (m), 993 (w), 916 (m).

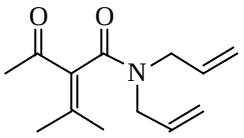
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.66 (m, 1H), 5.14-4.84 (m, 2H), 4.25 (dd, *J* = 2.7 and 1.2 Hz, 2H), 4.20 (dd, *J* = 2.8 and 1.1 Hz, 2H), 3.69-3.53 (m, 2H), 2.56 (m, 2H), 2.24 (m, 2H), 1.67 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 172.3, 143.7, 136.9, 133.7, 117.3, 117.0, 116.5, 114.1, 50.9, 49.2, 48.3, 35.9, 20.3.

MS (EI, 70 eV): 219 (M^+, 2), 204 (15), 190 (11), 178 (100), 164 (5), 150 (5), 136 (10), 124 (39), 108 (4).

$C_{14}H_{21}NO$	HRMS	Calcd.	219.1623
		Found	219.1608

Synthesis of 2-acetyl-*N*,*N*-diallyl-3-methyl-2-butenamide (45h)



Prepared according to TP 7 from *N*,*N*-diallyl-2-bromo-3-methyl-butenamide (1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and acetyl chloride (0.1 mL, 1.4 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **45h** as a colourless oil (160 mg, 72 %).

IR (film, cm^{-1}): $\tilde{n}$ 2927 (s), 1715 (s), 1681 (vs), 1657 (vs), 1439 (vs), 1414 (vs), 1368 (s), 1282 (s), 1245 (m), 927 (m), 702 (w).

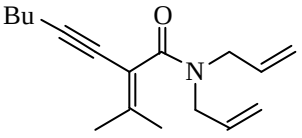
^{1}H NMR ($CDCl_3$, 300 MHz): d 5.73 (m, 2H), 5.19 (m, 4H), 3.90 (m, 4H), 2.27 (s, 3H), 2.17 s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 206.8, 167.6, 142.0, 131.9, 127.2, 117.4, 49.2, 47.9, 44.9, 30.6, 22.4, 18.6.

MS (EI, 70 eV): 221 (M^+, 16), 178 (7), 164 (100), 123 (10), 81 (12), 43 (18).

$C_{13}H_{19}NO_2$	HRMS	Calcd.	221.1416
		Found	221.1404

Synthesis of *N*,*N*-diallyl-2-(1-methylethylidene)-3-octynamide (45i)



Prepared according to TP 7 from *N*,*N*-diallyl-2-bromo-3-methyl-butenamide (1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and 1-bromohexyne (270 mg, 1.7 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **45i** as a colourless oil (150 mg, 58 %).

IR (film, cm^{-1}): $\tilde{n}$ 3400 (s, br), 2959 (vs), 2930 (vs), 1677 (vs), 1650 (vs), 1442 (vs), 1415 (s), 1283 (s), 1048 (s), 1029 (s), 925 (m), 799 (m), 778 (s), 763 (s), 700 (s).

^{1}H NMR ($CDCl_3$, 300 MHz): d 5.74-5.60 (m, 2H), 5.17-5.02 (m, 4H), 3.86 (m, 4H), 2.49 (t, *J* = 7.1 Hz, 2H), 1.80 (s, 6H), 1.62-1.33 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H).

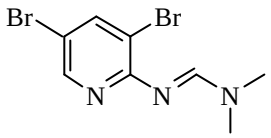
^{13}C-NMR ($CDCl_3$, 75 MHz): d 168.5, 143.6, 133.2, 128.4, 118.1, 81.8, 66.23, 48.9, 45.8, 31.4, 24.7, 23.4, 19.6, 18.7, 15.64, 13.9.

MS (EI, 70 eV): 259 (M^+, 3), 231 (7), 216 (9), 190 (21), 164 (100), 136 (8), 94 (4), 81 (8), 41 (25)

$C_{17}H_{25}NO$	HRMS	Calcd.	259.1936
		Found	259.1934

9 Halogen-Copper Exchange on Heterocycles

Synthesis of *N'*-(3,5-dibromo-2-pyridinyl)-*N*,*N*-dimethylimidoformamide (47)



3,5-dibromo-2-pyridinamine (15.0 g, 60.0 mmol) was dissolved in toluene (15 mL) and dimethoxy-*N*, *N*-dimethylmethanamine (15.9 mL, 120 mmol) was added. The reaction mixture was heated under reflux for 1 h. After cooling to rt, the toluene and excess reagent were distilled *in vacuo*. The crude product was recrystallized from EtOH to give **47** as a yellow crystalline solid (14.5 g, 78 %).

Mp 76 °C

IR (film, cm^{-1}): $\tilde{n}$ 3435 (s, br), 1485 (vs), 1470 (s), 1438 (m), 1237 (vs), 1167 (s), 1083 (s), 942 (vs), 657 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): d 8.39 (s, 1H), 8.18 (d, *J* = 2.2 Hz 1H), 7.72 (d, *J* = 2.2 Hz 1H), 3.15 (s, 3H), 3.11 (s, 3H).

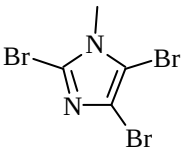
^{13}C-NMR ($CDCl_3$, 75 MHz): d 158.4, 156.0, 147.1, 143.1, 116.0, 112.0, 41.2, 35.2.

MS (EI, 70 eV): 305 (M^+, 100), 291 (48), 251 (56), 228 (74), 155 (16), 57 (40).

$C_8H_9Br_2N_3$

Calcd.	C, 31.30	H, 2.96	N, 13.69	Br, 52.06
Found	C, 31.44	H, 2.93	N, 13.76	Br, 51.84

Synthesis of 1-methyl-2,4,5-tribromoimidazole[138] (50)



[138] O' Connell, J.; Parquette, J.; Yelle, W. E.; Wang, W.; Rapoport, H. *Synthesis* **1988**, 767.

To a mixture of 1-methylimidazole (24.6 g, 300 mmol) and NaOAc (102 g, 1.2 mol) in glacial AcOH (500 mL), a solution of Br_2 (146.0 g, 900 mmol) in glacial AcOH (50 mL) was added dropwise with vigorous stirring, and cooling to maintain the temperature below 60 °C. After the addition the mixture was stirred at rt for 2 h, the poured into ice, stirred and filtered. Crystallization from AcOH/water afforded **50** as a light brown solid (48.7g, 50 %)

Mp 89 °C (lit. 94 °)

IR (film, cm^{-1}): $\tilde{n}$ 2960 (s, br), 1500 (vs), 1458 (m), 1366 (m), 1316 (s), 1221 (vs), 1134 (s), 1090 (s), 975 (vs).

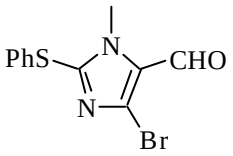
^{1}H NMR ($CDCl_3$, 300 MHz): d 3.64 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 150.7, 146.2, 106.9, 31.4.

$C_4H_3Br_3N_2$

Calcd.	C, 15.07	H, 0.95	Br, 75.19	N, 8.79
Found	C, 14.97	H, 0.92	Br, 75, 12	N, 8.73

Synthesis of 4-bromo-1-methyl-2-(phenylsulfanyl)-1*H*-imidazole-5-carbaldehyde (52)



Methyliodide (0.68 mL, 11.0 mmol) was added at rt to a solution of diphenylsufide (2.4 g, 11.0 mmol) in THF (10 mL) and the mixture was stirred for 1 h. *n*-BuLi (6.7 mL, 10.0 mmol) was added dropwise to a solution of **50** (3.2 g 10.0 mmol) in THF (10 mL) at -78 °C. After 5 min the solution of the disulfide was cannulated into the mixture and stirring was continued for further 5 min. A second equivalent of *n*-BuLi (6.7 mL, 10.0 mmol) was then added and after 15 min DMF (0.8 mL, 10.0 mmol) was added to the mixture. After 20 min the reaction was quenched with saturated, aqueous NH_4Cl (2 mL). The aqueous phase was extracted with diethyl ether (3 x 30 mL). The organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 85:15) yielded **52** as a yellow crystalline solid (1.8 g, 60 %).

Mp 114 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 3435 (w, br), 1665 (vs), 1631 (m), 1496 (s), 1457 (s), 1395 (s), 1327 (vs), 1265 (vs), 814 (s), 749 (s), 719 (s), 701 (m), 685 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): d 9.60 (s, 1H), 7.26 (m, 5H), 3.80 (s, 3H).

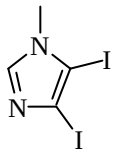
^{13}C-NMR ($CDCl_3$, 75 MHz): d179.2, 149.0, 131.9, 131.6, 130.5, 130.2, 130.1, 129.2, 129.1, 34.1.

MS (EI, 70 eV): 297 (M^+, 100), 270 (12), 217 (15), 133 (9), 121 (26), 109 (14), 91 (52), 77 (21).

$C_{11}H_9BrN_2OS$

Calcd.	C, 44.46	H, 3.05	N, 9.43	S, 10.79
Found	C, 44.39	H, 3.18	N, 9.35	S, 10.96

Synthesis of 4,5-diiodo-1-methyl-1*H*-imidazole (51)



Iodine (46.0 g, 181 mmol) and potassium iodide (30.0 g, 181 mmol) were dissolved in water (250 mL) and added with a dropping funnel to a solution of imidazole (3.4 g, 50.0 mmol) and sodium hydroxide (24 g, 600 mmol) in water (50 mL) at rt. After 3 h diluted acetic acid (200 mL) was added and the precipitate was filtered and washed many times with water and with 10 % sodiumthiosulfate aqueous solution. The light yellow solid obtained was dissolved in water (300 mL) and sodium hydroxide (ca 10.0 g) was added till a clear solution was obtained. Dimethyl sulfate (14.2 mL, 150 mmol) was added to the solution with a dropping funnel and in few minutes a white precipitate was formed. After stirring at rt for 30 min, the solid was filtered, washed with water and dried in the oven. The desired product **51** was obtained as a pale yellow solid (22.3 g, 67 %).

Mp 136 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 3101 (w), 1485 (vs), 1470 (s), 1437 (m), 1237 (vs), 1167 (s), 1083 (s), 941 (vs), 657 (m).

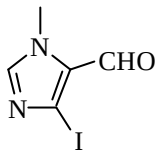
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.66 (s, 1H), 3.63 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 141.8, 95.3, 84.7, 36.6.

MS (EI, 70 eV): 333 (M^+, 100), 206 (19), 166 (7), 126 (3), 79 (4).

$C_4H_4I_2N_2$	HRMS	Calcd.	333.8464
		Found	333.8474

Synthesis of 4-iodo-1-methyl-1*H*-imidazole-5-carbaldehyde (53)



In a dried and argon flushed two necked 100 mL flask, equipped with a reflux condenser, 51 (5.0 g, 15.0 mmol) was dissolved in THF (50 mL) at rt. EtMgCl (9.0 mL, 18.0 mmol, 2 M solution in THF) was added slowly and the mixture was heated to reflux for 1 h. Dry DMF (2.2 mL, 22.0 mmol) was then added and after one additional hour the reaction was quenched with saturated, aqueous NH_4Cl (30 mL). The aqueous phase was extracted with EtOAc (6 x 30 mL). The organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **53** as a pale yellow solid (1.4 g, 40 %).

Mp 129 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 3099 (m), 1690 (vs), 1508 (w), 1449 (m), 1418 (s), 1387 (vs), 1334 (s), 944 (m), 784 (vs).

^{1}H NMR ($CDCl_3$, 300 MHz): d 9.74 (s, 1H), 7.19 (s, 1H), 4.01 (s, 3H).

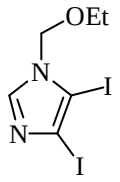
^{13}C-NMR ($CDCl_3$, 75 MHz): d 181.4, 145.9, 133.0, 85.0, 35.4.

MS (EI, 70 eV): 236 (M^+, 100), 208 (36), 165 (4), 127 (9), 81(9), 66 (7), 54 (19), 42 (22).

$C_5H_5IN_2O$

Calcd.	C, 25.45	H, 2.14	N, 11.87	I, 53.77
Found	C, 25.56	H, 2.13	N, 11.83	I, 53.76

Synthesis of 4,5-diiodo-1-ethoxymethyl-1*H*-imidazole (54)



Iodine (46.0 g, 181 mmol) and potassium iodide (30.0 g, 181 mmol) were dissolved in water (250 mL) and added with a dropping funnel to a solution of imidazole (3.4 g, 50.0 mmol) and sodium hydroxide (24.0 g, 600 mmol) in water (50 mL) at rt. After 3 h diluted AcOH (200 mL) was added and the precipitate was filtered and washed many times with water and with 10 % sodiumthiosulfate aqueous solution. The light yellow solid obtained (9.5 g, 29.7 mmol) was dissolved in DMF (89 mL) and NaH (1.25 g, 31.2 mmol) was added. The mixture was stirred at 0 °C for 1 h, then chloromethyl ethyl ether (2.9 mL, 31.2 mmol) was added and the mixture was let warm to rt and stirred for additional 4 h. The reaction was quenched with brine and the aqueous phase extracted with EtOAc (6 x 30 mL). The organic fractions were washed with with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude solid was recrystallized from pentane to give **54** as a light yellow solid (7.6 g, 78 %).

Mp 108 °C

IR (KBr, cm^{-1}): $\tilde{n}$ 3131 (w), 1495 (vs), 1478 (s), 1437 (m), 1250 (vs), 1171 (s), 1080 (s), 940 (vs), 655 (m).

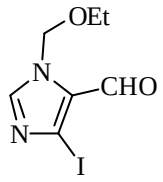
^{1}H NMR ($CDCl_3$, 300 MHz): d 7.74 (s, 1H), 5.33 (s, 2H), 3.51 (q, *J* = 7.0 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 142.0, 97.5, 82.2, 78.4, 65.0, 15.1.

MS (EI, 70 eV): 378 (M^+, 100), 334, (18), 207 (40), 59 (55).

$C_6H_8I_2N_2O$	HRMS	Calcd.	377.8726
		Found	377.8706

Synthesis of 1-(ethoxymethyl)-4-iodo-1*H*-imidazole-5-carbaldehyde (56)



In a dried and argon flushed two necked 100 mL flask, equipped with a reflux condenser, **54** (3.5 g, 9.3 mmol) was dissolved in THF (10 mL) at rt. EtMgCl (5.4 mL, 10.7 mmol, 2 M solution in THF) was added slowly and the mixture was heated to reflux for 1 h. Dry DMF (1.0 mL, 11.0 mmol) was then added and after one additional hour the reaction was quenched with saturated, aqueous NH_4Cl (60 mL). The aqueous phase was extracted with EtOAc (6 x 30 mL). The organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (penatne/diethyl ether 1:1) yielded **56** as a pale yellow oil (1.7 g, 66 %).

IR (film, cm^{-1}): $\tilde{n}$ 3112 (m), 1698 (vs), 1528 (w), 1455 (m), 1427 (s), 1399 (vs), 1345 (s), 954 (m), 790 (vs).

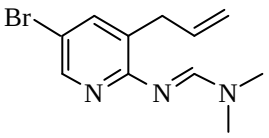
^{1}H NMR ($CDCl_3$, 300 MHz): d 9.60 (s, 1H), 7.75 (s, 1H), 5.62 (s, 2H), 3.51 (q, *J* = 7.2 Hz, 1H), 3.41 (q, *J* = 7.2 Hz, 1H), 1.14 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 181.5, 144.7, 129.7, 101.5, 76.2, 65.8, 15.2.

MS (EI, 70 eV): 280 (M^+, 30), 251 (100), 221 (10), 59 (25).

$C_7H_9IN_2O_2$	HRMS	Calcd.	279.9709
		Found	279.9685

Synthesis of *N'*-(3-allyl-5-bromo-2-pyridinyl)-*N*,*N*-dimethylimidoformamide (49a)



Prepared according to TP 5 from **47** (0.3 g, 1.0 mmol), lithium neopentylcuprate **33** (2.2 mmol), and allyl bromide (0.2 mL, 2.3 mmol). Reaction time: 1 h at 0 °C. Purification by flash chromatography (pentane/diethyl ether 1:1) yielded **49a** as a yellow oil (190 mg, 73 %).

IR (film, cm^{-1}): $\tilde{n}$ 2909 (m), 1624 (vs), 1563 (vs), 1441 (vs), 1415 (vs), 1384 (vs), 1347 (s), 1286 (m), 1239 (m), 1103 (vs), 913 (m).

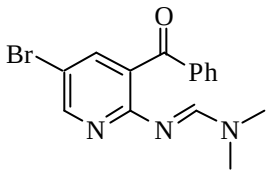
^{1}H NMR ($CDCl_3$, 300 MHz): d 8.26 (s, 1H), 8.03 (d, *J* = 2.3 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 5.88 (m, 1H), 5.01 (m, 2H), 3.37 (d, *J* = 6.7 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 159.1, 154.8, 146.6, 139.6, 136.7, 130.7, 116.6, 113.3, 40.9, 35.8, 34.9.

MS (EI, 70 eV): 267 (M^+, 92), 252 (100), 225 (38), 211 (16), 196 (22), 144 (48), 117 (26).

$C_{11}H_{14}BrN_3$	HRMS	Calcd.	267.0371
		Found	267.0347

Synthesis of *N'*-(3-benzoyl-5-bromo-2-pyridinyl)-*N*,*N*-dimethylimidoformamide (49b)



Prepared according to TP 3 from **47** (0.3 g, 1.0 mmol), lithium neopentylcuprate **33** (2.2 mmol), and benzoyl chloride (0.4 mL, 3.4 mmol). Reaction time : 30 min at 0 °C. Purification by flash chromatography (pentane/diethyl ether 1:1) yielded **49b** as a yellow crystalline solid (100 mg, 30 %).

Mp 110 °C

IR (film, cm^{-1}): $\tilde{n}$ 3434 (m, br), 1666 (s), 1619 (vs), 1561 (vs), 1538 (s), 1448 (s), 1411 (s), 1374 (vs), 1338 (s), 1105 (vs), 955 (m), 709 (s).

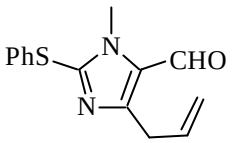
^{1}H NMR ($CDCl_3$, 300 MHz): d 8.29 (d, *J* = 2.5 Hz, 1H), 8.26 (s, 1H), 7.71 (d, *J* = 2.5 Hz, 1H), 7.44-7.30 (m, 5H), 2.89 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d196.7, 158.5, 154.5, 151.1, 139.9, 138.5, 132.9, 130.0, 129.2, 128.4, 112.7, 34.6

MS (EI, 70 eV): 331 (M^+, 5), 304 (100), 259 (7), 193 (13), 153 (9), 105 (20), 77 (37).

$C_{15}H_{14}BrN_3O$	HRMS	Calcd.	331.0320
		Found	331.0290

Synthesis of 4-allyl-1-methyl-2-(phenylsulfanyl)-1*H*-imidazole-5-carbaldehyde (49d)



Prepared according to TP 3 from **52** (296 mg, 1.0 mmol), lithium neopentylcuprate **33** (1.2 mmol) and allyl bromide (0.2 mL, 2.3 mmol). Reaction time: 3.5 h at -40 °C. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded **49d** as a light yellow oil (157 mg, 61 %).

IR (film, cm^{-1}): $\tilde{n}$ 3425 (w, br), 1659 (vs), 1633 (m), 1485 (s), 1461 (s), 1399 (s), 1330 (vs), 1270 (vs), 811 (s), 744 (s), 729 (s), 701 (m), 675 (m).

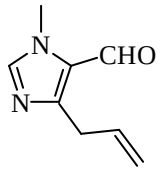
^{1}H NMR ($CDCl_3$, 300 MHz): d9.60 (s, 1H), 7.26 (m, 5H), 6.40 (m, 1H), 5.17 (m, 2H), 3.80 (s, 3H), 3.37 (d, *J* = 6.7 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d180.1, 149.0, 131.9, 131.6, 131.1, 130.5, 130.2, 130.1, 129.2, 129.1, 120.5, 34.1, 33.2.

MS (EI, 70 eV): 258 (M^+, 100), 241 (47), 229 (26), 181 (17), 150 (10), 121 (15), 94 (16).

$C_{14}H_{14}N_2OS$	HRMS	Calcd.	258.0827
		Found	258.0822

Synthesis of 4-allyl-1-methyl-1*H*-imidazole-5-carbaldehyde (49e)



Prepared according to TP 8 from **53** (236 mg, 1 mmol), lithium neophylcuprate **35** (1.2 mmol) and allyl bromide (0.2 mL, 2.3 mmol). Reaction time: 1 h at -78 °C. Purification by flash chromatography (CH_2Cl_2) yielded **49e** as a light yellow oil (100 mg, 67 %).

IR (film, cm^{-1}): $\tilde{n}$ 3089 (m), 1688 (vs), 1513 (w), 1454 (m), 1411 (s), 1373 (vs), 1342 (s), 954 (m), 783 (vs).

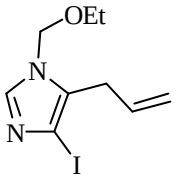
^{1}H NMR ($CDCl_3$, 300 MHz): d 9.80 (s, 1H), 7.44 (s, 1H), 5.95 (m, 1H), 5.12-5.04 (m, 2H), 3.74 (s, 3H), 3.56 (dt, *J* = 6.2and 1.3 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 179.4, 155.0, 143.1, 135.4, 126.2, 120.5, 34.8, 30.1.

MS (EI, 70 eV): 150 (M^+, 88), 133 (49), 122 (100), 94 (45), 81 (56), 67 (16), 53 (16), 41 (23).

$C_8H_{10}N_2O$	HRMS	Calcd.	150.0793
		Found	150.0779

Synthesis of 5-allyl-1-(ethoxymethyl)-4-iodo-1*H*-imidazole (49f)



Prepared according to TP 8 from **54** (280 mg, 1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and allyl bromide (0.2 mL, 2.3 mmol). Reaction time: 20 min at -78 °C. Purification by flash chromatography (pentane/diethyl ether 1:1) yielded **49f** as a light yellow oil (266 mg, 91 %).

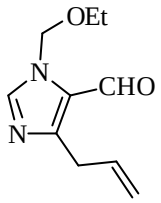
IR (film, cm^{-1}): $\tilde{n}$ 3077 (m), 1509 (w), 1434 (m), 1411 (s), 1237 (vs), 1167 (s), 954 (m), 683 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.48 (s, 1H), 5.82-5.59 (m, 1H), 5.16 (s, 2H), 5.04-4.91 (m, 2H), 3.39 (d, *J* = 6.5 Hz, 2H), 3.35 (q, *J* = 7.0 Hz, 2H), 1.11 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 138.4, 132.5, 131.0, 115.7, 84.8, 74.1, 63.1, 27.8, 13.7.

$C_9H_{13}IN_2O$	HRMS	Calcd.	292.0073
		Found	292.0063

Synthesis of 4-allyl-1-(ethoxymethyl)-1*H*-imidazole-5-carbaldehyde (49g)



Prepared according to TP 8 from **56** (280 mg, 1.0 mmol), lithium neophylcuprate **35** (1.2 mmol) and allyl bromide (0.2 mL, 2.3 mmol). Reaction time: 1 h at -78 °C. Purification by flash chromatography (pentane/diethyl ether 1:1) yielded **49g** as a light yellow oil (90 mg, 46 %).

IR (film, cm^{-1}): $\tilde{n}$ 3083 (m), 1672 (vs), 1520 (w), 1463 (m), 1420 (s), 1385 (vs), 1350 (s), 966 (m), 790 (vs).

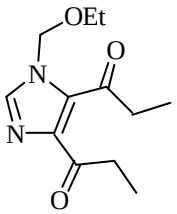
^{1}H NMR ($CDCl_3$, 300 MHz): d 9.83 (s, 1H), 7.70 (s, 1H), 6.03-5.90 (m, 1H), 5.66 (s, 2H), 5.10 (m, 2H), 3.59 (d, *J* = 6.2 Hz, 2H), 3.49 (q, *J* = 6.9 Hz, 2H), 1.13 (t, *J* = 6.9 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 179.4, 155.0, 143.1, 135.4, 126.2, 121.2, 74.1, 64.0, 34.8, 13.9.

MS (EI, 70 eV): 194 (M^+, 33), 165 (30), 149 (27), 135 (70), 120 (100), 107 (18), 80 (30), 59 (88), 53 (28).

$C_{10}H_{14}N_2O_2$	HRMS	Calcd.	194.1055
		Found	194.1050

Synthesis of 1-[1-(ethoxymethyl)-4-propanoyl-1*H*-imidazol-5-yl]-1-propanone (55)



Prepared according to TP 3 from **54** (280 mg, 1.0 mmol), lithium neophylcuprate **35** (2.2 mmol) and propionyl chloride (0.2 mL, 2.3 mmol). Reaction time: 1 h at -78 °C. Purification by flash chromatography (pentane/EtOAc 1:1) yielded **55** as a light yellow oil (67 mg, 28 %).

IR (film, cm^{-1}): $\tilde{n}$ 3083 (m), 1730 (vs), 1725 (vs), 1580 (w), 1485 (m), 1434 (s), 1385 (vs), 1353 (s), 966 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): d 7.58 (s, 1H), 5.36 (s, 2H), 3.42 (q, *J* = 7.2 Hz, 2H), 3.03 (q, *J* = 6.9 Hz, 2H), 2.96 (q, *J* = 6.9 Hz, 2H), 1.19-1.09 (m, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): d 197.4, 197.3, 141.3, 137.2, 137.1, 75.1, 64.1, 35.3, 32.2, 13.8, 7.2, 6.8.

MS (EI, 70 eV): 238 (M^+, 5), 209 (12), 192 (13), 181 (22), 151 (8), 95 (8), 59 (100), 41 (13).

$C_{12}H_{18}N_2O_3$	HRMS	Calcd.	194.1317
		Found	194.1322

Abbreviations

Ac	acetyl
approx.	approximately
Bn	benzyl
Bp	boiling point
br	broad
Bu	butyl
c	concentration
Calcd.	calculated
cat.	catalytic
conc.	concentrated
d	doublet
dr	diastereomeric ratio
DBE	dibromoethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulphoxide
ee	enantiomeric excess
equiv	equivalent
EI	electron ionisation
Et	ethyl
EtOAc	ethyl acetate
FG	functional group
GC	gas chromatography
h	hour
HMPA	hexamethylphosphorous triamide
HRMS	high resolution mass spectroscopy
i-Bu	*iso*butyl
IR	infrared spectroscopy
J	coupling constant
LDA	lithiumdiisopropylamine
LDE	lithiumdiethylamine
M	molar
Me	methyl
min	minute
Mp	melting point
MS	mass spectroscopy
NDMBA	*N*,*N*'-dimethylbarbituric acid
NMP	*N*-methyl-pyrrolidone
NMR	nuclear magnetic resonance
Ph	phenyl
q	quartet
quant.	quantitative
rt	room temperature
s	singlet
s-Bu	*sec*butyl
sec	seconds
t	triplet
t-Bu	*ter*butyl

TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
TP	typical procedure
UV	ultra-violet

Curriculum Vitae

Surname	: Piazza
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Education

1986-1991	: Liceo Ginnasio "A. Canova"; Treviso (I). Certificate: July 1991. Mark: 60/60
1991-1997	: University of Padova, Biopolymer Research Centre, CNR; Padova (I). Chemistry Degree: December 1997. Mark:108/110. Specialization: Organic and Biological Chemistry. Thesis subject: "Analogues of lipopeptaibol antibiotics Trikoningins KBI and KBII" (Prof. C. Toniolo)
1999-2002	: LMU University, Chemistry Department, Munich (D) Ph.D. in the group of Prof. P. Knochel Thesis subject: " New Methods for the Synthesis of Organozinc and Organocopper Reagents"

Work Experience

June 1998-June 1999	: DSM Research, Section Fine Chemical-Organic Chemistry Biotechnology; Geleen (NL) (Dr. B. Kaptein). Stage, subject: "Synthesis and enzymatic resolution of α,α-disubstituted amino acid amides"
2000-2002	: Assistant at the Ludwig-Maximilians Universität München: assistance of the students in organic chemistry laboratory courses.

Languages	: Italian English (fluent, written and spoken) German (Deutsche Zertifikat)

Publications

1. Piazza, C, Formaggio, F., Crisma, M., Toniolo, C., Kamphius, J. and Broxterman, Q.B. "Total synthesis and membrane modifying properties of the lipopeptaibol Trikoningin KBII and its analogues with acyl chains of different length at the N- anc C-termini" *J. Peptide Sci.* **1999**, *5*, 96.

2. Peggion, C., Piazza, C., Formaggio., F., Crisma, M., Toniolo, C., Kaptein, B., Broxterman, Q.B. "Total synthesis and membrane modifying properties of the Trikoningins KB lipopeptaibols: effect of hydrophobicity and chirality in position 1" *Letters in Peptide Science* **2000**, *7*, 9.

3. Moretto, A., Peggion, C., Formaggio, F., Crisma, M., Toniolo, C., Piazza, C., Kaptein, B., Broxterman, Q.B., Ruiz, I., Diaz-De-Villegas, M.D., Galvez, J.A., Cativiela, C. "(αMe)Nva: stereoselective synthesis and preferred conformations of selected model peptides" *Journal of Peptide Research* 2000, *56*, 283.

4. Millot, N., Piazza, C., Avolio, S., Knochel, P. "Aminomethylation of Functionalized Organozinc Reagents and Grignard Reagents using Imonium Trifluoroacetates" *Synthesis* **2000**, *7*, 941.

5. Piazza, C., Millot, N., Knochel, P. "New preparation of Benzylic Zinc Reagents via a Fragmentation Reaction" *J. Organomet. Chem.* **2001**, *624*, 88.

6. Piazza, C., Knochel, P. "New Sterically Hindered Lithium Dialkylcuprates for the Generation of Highly Functionalized Mixed Cuprates via a Halogen-Copper Exchange" *Angewandte Chem. Int. Ed.* **2002**, *41*, 3263.

Posters and Seminars

June 2002	
BASF A.-G. (Ludwigshafen, D)	"The Halogen-Copper Exchange for the Synthesis of Functionalized Organocopper Reagents" seminar
July 2002	
XX ICOMC Corfu (G)	"New Synthesis of Functionalized Organocopper Reagents Via a Halogen-Copper Exchange" poster
October 2002	
ISMOC Dortmund (G)	"Iodine-Copper Exchange for the Synthesis of Functionalized Organometallics" seminar
October 2002	
Roche Symposium Basel (CH)	"New Lithium Dialkylcuprates for the Generation of Highly Functionalized Mixed Cuprates" seminar