Available online at www.sciencedirect.com

Journal of Organometallic Chemistry 680 (2003) 136–142

www.elsevier.com/locate/jorganchem

Synthesis and reaction of secondary and primary diorganozinc reagents using a boron–zinc exchange reaction
A useful method for the stereo- and regioselective formation of new carbon–carbon bonds

Eike Hupe, M. Isabel Calaza, Paul Knochel *

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13, D-81377 München, Germany

Received 13 February 2003; received in revised form 14 March 2003; accepted 14 March 2003

Abstract

Applications of the boron–zinc exchange reaction to make new carbon–carbon bonds are reviewed. Functionalized chiral secondary alkylzinc reagents can be prepared by this exchange reaction and allows to perform formal enantioselective Michael-additions with umpolung of reactivity. The scope of substrate controlled diastereoselective hydroborations can be considerably enhanced by this methodology. A chemoselective approach to difunctionalized arylsilanes is also described.

Keywords: Diastereoselective synthesis; Hydroboration; Transmetallation; Zinc organometallics; C–C coupling

1. Introduction

Organometallic reagents are useful intermediates for the formation of new carbon–carbon bonds [1]. The *stereoselective* formation of new carbon–carbon bonds implies the availability of Csp^3-hybridized organometallic compounds having a defined configuration [2]. Whereas chiral organolithium or organomagnesium compounds require chelating heteroatoms in an alpha-position or low temperature to ensure a configurational stability [3,4], chiral diorganozinc compounds have shown to be configurationally stable over a wide temperature range without the need of any stabilizing heteroatoms [5]. Furthermore, these chiral diorganozinc reagents have shown to be highly compatible with various functional groups [5]. This high configurational stability is due to the covalent nature of the C–Zn bond. Chiral diorganozinc reagents can be easily obtained by a one-pot sequence of hydroboration and subsequent boron–zinc exchange reaction [6]. Thus, starting from a trisubstituted olefin such as **1**, hydroboration with diethylborane leads to the triorganoborane **2**, which can be easily converted into the corresponding zinc reagent **3** by addition of $i\mathrm{Pr}_2\mathrm{Zn}$. This diorganozinc reagent can then be trapped, after transmetallation to Cu(I) or by Pd(0) catalysis [6d], with a broad range of electrophiles, giving the desired products of type **4** in satisfactory overall yields and excellent stereochemical control. All reaction steps in this sequence proceed with retention of stereochemistry (Scheme 1) [7].

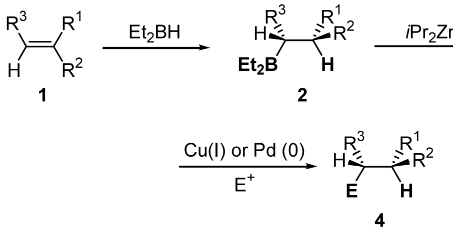
This sequence can also be applied for the synthesis of optically active diorganozinc reagents. Thus, starting from 1-phenylcyclopentene (**5**), an asymmetric hydroboration with (−)- isopinocampheylborane ((−)-IpcBH$_2$) [8] leads to the intermediate organoborane **6** in 94% *ee*. Further treatment with Et$_2$BH [9] and $i\mathrm{Pr}_2\mathrm{Zn}$ provides the optically active diorganozinc reagent **7**. After transmetallation to the corresponding copper reagent with CuCN·2LiCl [10], it was reacted with allyl bromide with retention of stereochemistry. The allylated product **8** was obtained in 94% *ee* and an overall yield of 44% as a 98:2 mixture of *trans* and *cis* isomers, showing the configurational stability of the intermediate diorganozinc reagent **7** (Scheme 2) [6e].

---

* Corresponding author. Tel.: +49-89-218077681; fax: +49-89-218077680.

E-mail address: paul.knochel@cup.uni-muenchen.de (P. Knochel).

0022-328X/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0022-328X(03)00237-7



Scheme 1.

2. Using the boron–zinc exchange reaction for a formal enantioselective 1,4-addition with umpolung of the reactivity

The conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds has been extensively studied over the last years [11]. Especially, its enantioselective version has received much attention [12]. Although many excellent methods for conjugate additions have been described, the enantioselectivity of Michael-addition is very much dependent on the nature of the nucleophile used. Furthermore, several classes of nucleophiles, such as alkynyl [13], allenyl or allylic organometallics, still cannot be generally added enantioselectively. The hydroboration/boron–zinc exchange sequence, allows to perform conjugate additions with an umpolung [14] of the classical 1,4-addition. Whereas the usual reactivity pattern of an α,β-unsaturated carbonyl compound requires a reaction with a nucleophile, we envisioned a reaction of a protected Michael-acceptor with an electrophile [15]. Thus, the unsaturated acetal **9** was hydroborated with (−)-IpcBH_2 and converted by the addition of $i$$Pr_2Zn$ into the optically active diorganozinc reagent **10** (91% *ee*). Its reaction, after transmetallation to the corresponding copper reagent, with a variety of different electrophiles afforded the desired products **11**–**13** in excellent selectivities and 46–52% overall yields (Scheme 3) [15].

The zinc reagent **10** shows a high configurational stability after transmetallation, in the reaction with various alkynyl bromides. Reaction with allyl bromides or propargyl bromide leads to small amounts (3–6%) of the undesired *cis* product, but the alkynylated products **12a**–**b** were obtained in selectivities of ≥99:1 and acceptable overall yields.

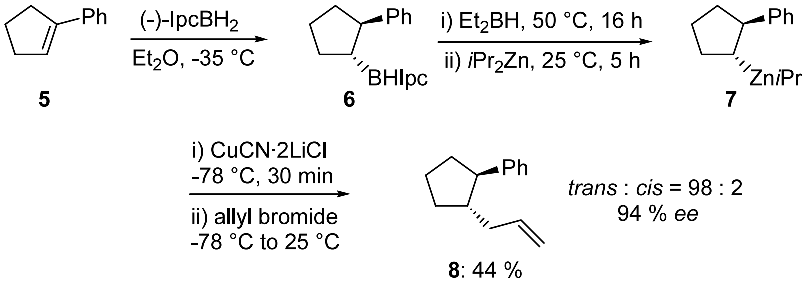
To demonstrate the validity of the umpolung procedure, the functionalized alkyne **12a** was deprotected by treatment with dilute aqueous HCl furnishing the free *trans*-aldehyde **14** as one diastereoisomer in 88% *ee* and 93% yield (42% overall yield starting from the unsaturated acetal **9**) (Scheme 4).

An extension to open chain systems was also possible. Thus, the protected *exo*-alkylidene enone **15** was hydroborated with (−)-IpcBH_2 affording, after further treatment with Et_2BH and $i$$Pr_2Zn$, the optically active secondary alkylzinc reagent **16** in 76% *ee*. After a transmetallation with Cu(I) and allylation, the desired products **17a**–**b** were obtained in excellent diastereoselectivities (≥94:6) (Scheme 5) [15].

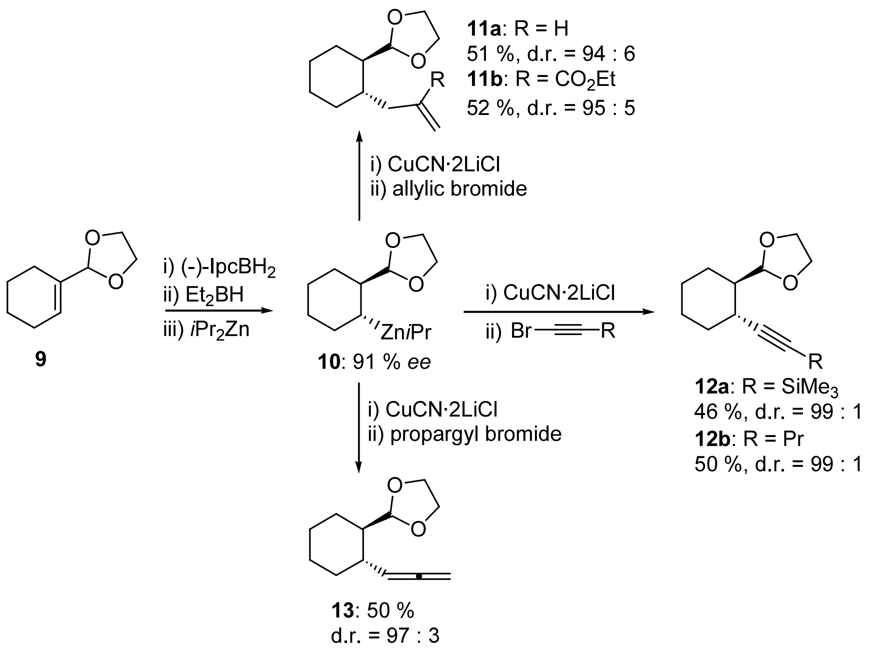
3. Substrate controlled diastereoselective synthesis of chiral diorganozinc reagents

Substrate controlled hydroboration is a useful reaction for performing diastereoselective syntheses [16]. One major drawback of these reactions is that the resulting chiral organoboranes are usually not reactive enough to participate in new carbon–carbon bond formations. The boron–zinc exchange allows to convert usually unreactive organoboranes to more reactive organozinc reagents, which in the presence of appropriate catalysts are efficiently used for the formation of new carbon–carbon bonds. Thus, the trisubstituted olefin **20**, obtained after diastereoselective Luche reduction [17] and protection of **18** [18], is diastereoselectively hydroborated (d.r. (1, 2) = 97:3) by using CH_2Cl_2 as a co-solvent. Further conversion to the corresponding diorganozinc reagent and Cu(I) mediated reaction with propionyl chloride (d.r. (2, 3) = 94:6) leads to the desired product **22** which was obtained in 59% overall yield. It was possible to generate a chiral diorganozinc reagent with the control of four stereogenic centers (Scheme 6) [19].

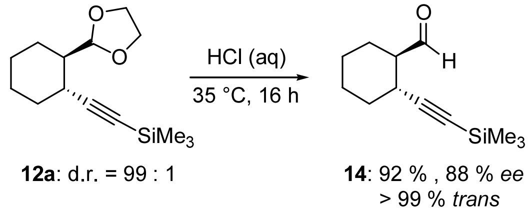
Most literature procedures for substrate controlled diastereoselective hydroborations use sterically hindered hydroborating reagents. Fleming et al. have reported excellent diastereoselectivities for the hydroboration of the chiral allylic silane **23** using 9-BBN–H [20]. The



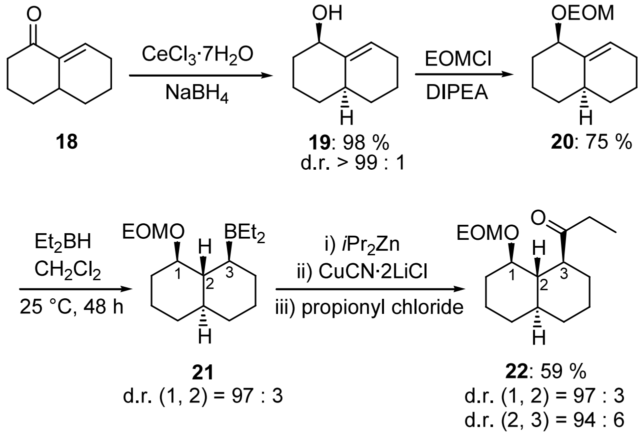
Scheme 2.



Scheme 3.



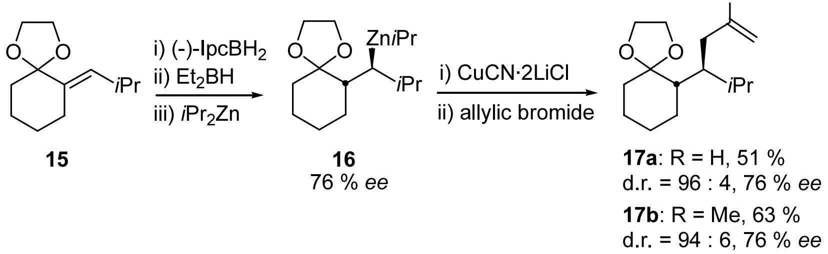
Scheme 4.



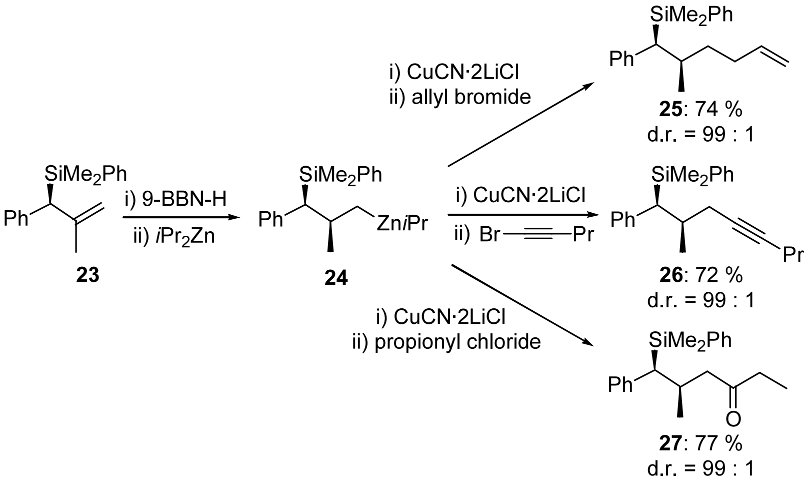
Scheme 6.

hydroboration of **23** under Fleming's conditions followed by a boron–zinc exchange affords the corresponding zinc reagent **24**, which readily reacted with a variety of different electrophiles. The desired products **25**–**27** were obtained in good yields and in excellent diastereoselectivities (Scheme 7) [21,22].

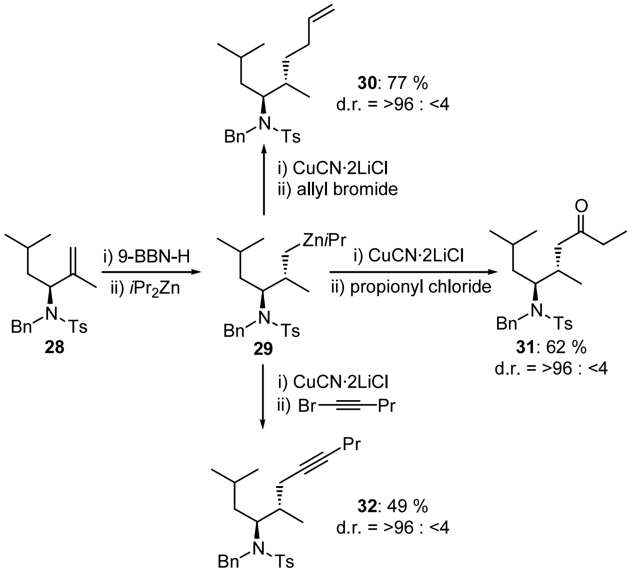
Similarly, Burgess et al. have shown that protected chiral allylic amines such as **28** can be hydroborated with 9-BBN–H yielding, after oxidative workup, the corresponding amino alcohol in a selectivity of $>96:<4$ [23]. Hydroboration of **28** under Burgess's conditions lead to a triorganoborane that was then converted to the corresponding zinc organometallic **29**, which by the reaction with different electrophiles provided the desired



Scheme 5.



Scheme 7.



Scheme 8.

functionalized amines **30**–**32** in good overall yields and excellent diastereoselectivities (Scheme 8) [22].

A boron–zinc exchange reaction was possible after rhodium-catalyzed hydroborations with catecholborane [21,22]. The protected *exo*-methylidene cyclohexanol derivative **33** was hydroborated with catecholborane and catalytic amounts of $Rh(PPh_3)_3Cl$ according to a procedure described by Evans et al. [24]. Treatment with $i$$Pr_2Zn$ leads to the diorganozinc compound **34**, which could then be allylated to yield **35a**–**b** in 52 and 46% overall yield or trapped with bromopentyne yielding the alkyne **36** in 49% overall yield (Scheme 9). The diastereoselectivities obtained in the products **35a**–**b** and **36** are the same as described by Evans for the corresponding alcohol obtained after oxidative workup of the intermediate boronic ester [24].

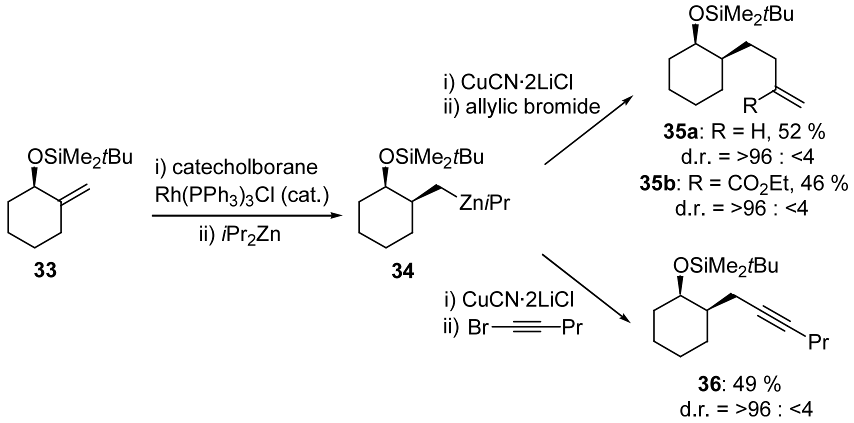
This example demonstrates that the scope of substrate controlled diastereoselective hydroborations can be considerably enhanced by performing a B–Zn exchange sequence.

4. One-pot chemoselective difunctionalization of arylsilanes using a boron–zinc exchange reaction

The use of the boron–zinc exchange reaction for the synthesis of *allyl*zincs was described by Thiele et al. [25]. Oppolzer and Srebnik have used the boron–zinc exchange reaction for the synthesis of *vinylic* organozinc reagents starting from *vinylic* organoboranes [26]. To complement the scope of the boron–zinc exchange reaction, we turned our attention to the synthesis of *aryl*zinc reagents starting from arylboranes [27].

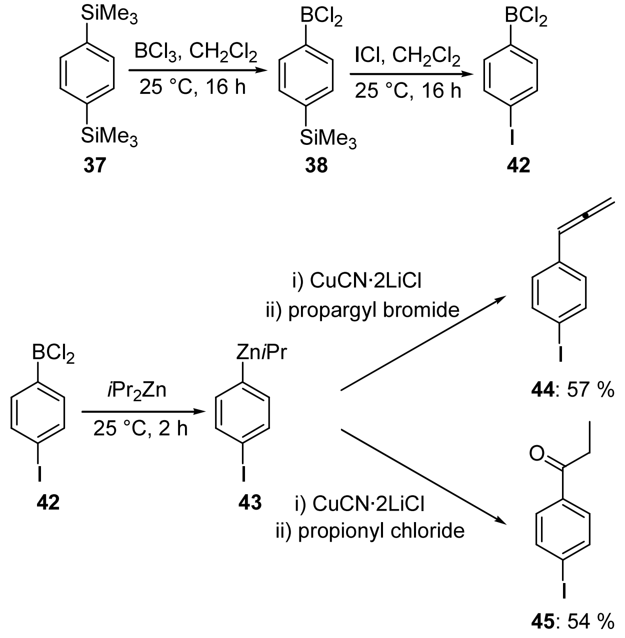
Arylboranes of the type $ArBCl_2$ are easily available by a silicon–boron exchange of arylsilanes with BCl_3 [28]. Thus, starting from the aromatic 1,4-disilane **37**, the arylborane **38** was obtained by adding BCl_3. Transmetallation of **38** to the corresponding zinc reagent **39** with $i$$Pr_2Zn$ was quantitative after 2 h at 25 °C. Further transmetallation of **39** with Cu(I) and subsequent reaction with propargyl bromide or propionyl chloride lead to the desired aromatic products **40** and **41** in 73 and 72% yield by a one-pot procedure (Scheme 10) [29].

It was possible to treat the disilane **37** with BCl_3 yielding the mixed B–Si-aryl derivative **38**. Its treatment in a one-pot procedure with ICl allows the regio- and chemoselective exchange of the second Si-functionality to iodine furnishing the iodoarylboron derivative **42**, which was then transmetalated, via a chemoselective boron–zinc exchange to the zinc reagent **43.** The arylzinc reagent **43** was, after transmetalation to Cu(I), trapped with a variety of different electrophiles to provide the desired products **44**–**45** in acceptable overall yields (Scheme 11) [29].



Scheme 9.

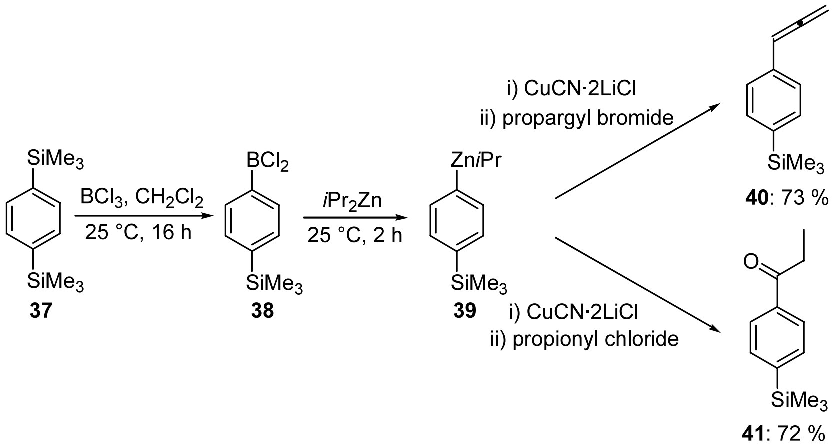
The aromatic disilane **46** was similarly functionalized twice by a double Si–B exchange yielding the aromatic diborane **47**, that was easily transfered into the corresponding bis-diorganozinc reagent **48** by addition of *i*Pr_2Zn. After Cu(I) mediated reaction with 1-bromo-2-trimethylsilylacetylene, the desired product **49** was obtained in good overall yield (68%, one-pot procedure) (Scheme 12) [29].



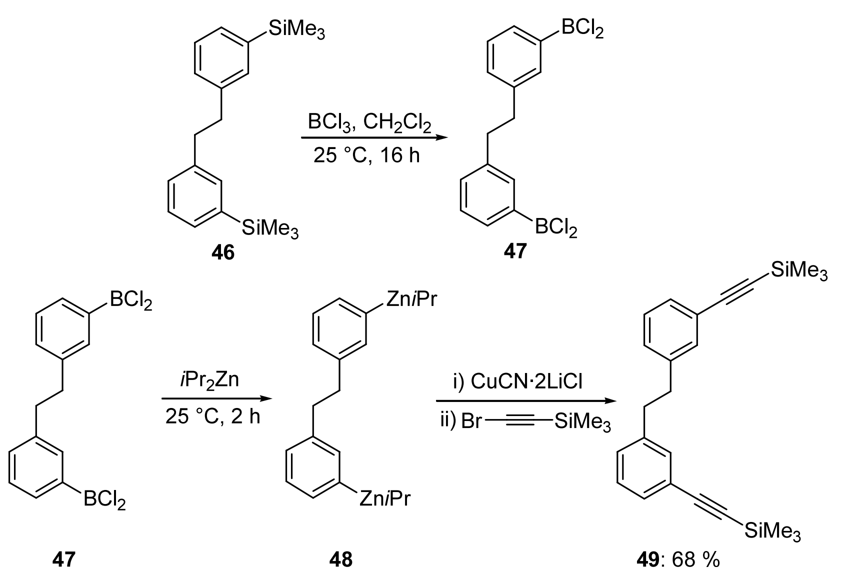
Scheme 11.

5. Summary

In summary, we have shown that the boron–zinc exchange reaction is an useful method for the formation of new carbon–carbon bonds. An asymmetric hydroboration and subsequent boron–zinc exchange reaction on protected α,β-unsaturated ketones or aldehydes lead to products of a formal enantioselective Michael-addition with umpolung of the reactivity. Furthermore, we have shown that chiral triorganoboranes, obtained after substrate controlled diastereoselective hydroborations on chiral, protected allylic alcohols, leads to chiral diorganozinc reagents that can be trapped with different electrophiles. The scope of substrate controlled diastereoselective hydroborations can be considerably enhanced by the method presented herein. Finally, we



Scheme 10.



Scheme 12.

have shown that arylsilanes can be easily difunctionalized by the boron–zinc exchange reaction on arylboranes, leading to functionalized aromatic systems in good overall yields.

Acknowledgements

We thank the DFG (Leibniz-Program) for financial support. E.H. thanks the Fonds der Chemischen Industrie for a Kekulé-fellowship. M.I.C. thanks the European Community for a Marie Curie fellowship (HPMF-CT-2000-01024). We thank also the BASF AG, Bayer AG, Chemetall GmbH and Degussa AG for the generous gift of chemicals.

References

[1] (a) K.C. Nicolaou, E.J. Sorensen, Classics in Total Synthesis, Verlag Chemie, Weinheim, 1996;
(b) E. Negishi, Organometallics in Organic Synthesis, Wiley, New York, 1980.
[2] (a) G.-Q. Lin, Y.-M. Li, A.S.C. Chan, Principles and Applications of Asymmetric Synthesis, Wiley-Interscience, New York, 2001;
(b) R.E. Gawley, J. Aubé, Principles of Asymmetric Synthesis, Pergamon, Oxford, 1996;
(c) R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley, New York, 1994.
[3] (a) W.C. Still, C. Sreekumar, J. Am. Chem. Soc. 102 (1980) 1201;
(b) D. Hoppe, O. Zschage, Angew. Chem. Int. Ed. 28 (1989) 67;
(c) P. Beak, H. Du, J. Am. Chem. Soc. 115 (1993) 2516;
(d) S.T. Kerrick, P. Beak, J. Am. Chem. Soc. 113 (1991) 9708.
[4] (a) R.W. Hoffmann, P.G. Nell, Angew. Chem. Int. Ed. 38 (1999) 338;
(b) R.W. Hoffmann, B. Hölzer, O. Knopff, K. Harms, Angew. Chem. Int. Ed. 39 (2000) 3072;
(c) R.W. Hoffmann, B. Hölzer, O. Knopff, Org. Lett. 3 (2001) 1945.
[5] (a) P. Knochel, N. Millot, A.L. Rodriguez, C.E. Tucker, Org. React., vol. 58, 2001, p. 417;
(b) R. Duddu, M. Eckhardt, M. Furlong, H.P. Knoess, S. Berger, P. Knochel, Tetrahedron 50 (1994) 2415.
[6] (a) L. Micouin, M. Oestreich, P. Knochel, Angew. Chem. Int. Ed. 36 (1997) 245;
(b) C. Darcel, F. Flachsmann, P. Knochel, J. Chem. Soc. Chem. Commun. (1998) 205;
(c) A. Boudier, F. Flachsmann, P. Knochel, Synlett (1998) 1438;
(d) A. Boudier, P. Knochel, Tetrahedron Lett. 40 (1999) 687;
(e) A. Boudier, C. Darcel, F. Flachsmann, L. Micouin, M. Oestreich, P. Knochel, Chem. Eur. J. 6 (2000) 2748.
[7] E. Hupe, P. Knochel, K.J. Szabó, Organometallics 21 (2002) 2203.
[8] H.C. Brown, A.K. Mandal, N.M. Yoon, B. Singaram, J.R. Schwiez, P.K. Jadhav, J. Org. Chem. 47 (1982) 5069.
[9] The purpose of the treatment with Et_2BH is to replace the bulky isopinocampheyl ligand by an ethyl group or a hydrogen atom.
[10] P. Knochel, M.C.P. Yeh, S.C. Berk, J. Talbert, J. Org. Chem. 53 (1988) 2390.
[11] P. Perlmutter, Conjugate addition reactions in organic synthesis, in: J.E. Baldwin, P.D. Magnus (Eds.), Tetrahedron Organic Chemistry Series, vol. 9, Pergamon Press, Oxford, 1992.
[12] (a) K. Tomioka, Y. Nagaoka, in: E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis III, Springer, Berlin, 1999, p. 1105;
(b) B.L. Feringa, Acc. Chem. Res. 33 (2000) 346;
(c) A. Alexakis, Chimia 54 (2000) 55;
(d) G. Helmchen, A. Pfaltz, Acc. Chem. Res. 33 (2000) 336.
[13] J.M. Chong, L. Shen, N.J. Taylor, J. Am. Chem. Soc. 122 (2000) 1822.
[14] D. Seebach, Angew. Chem. 91 (1979) 259.
[15] E. Hupe, P. Knochel, Angew. Chem. Int. Ed. 40 (2001) 3022.
[16] For reviews about substrate controlled diastereoselective hydroborations see:
(a) K. Burgess, M.J. Ohlmeyer, Chem. Rev. 91 (1991) 1179.
(b) R.W. Hoffmann, Chem. Rev. 89 (1989) 1841.
(c) A.H. Hoveyda, D.A. Evans, G.C. Fu, Chem. Rev. 93 (1993) 1307.
[17] J.-L. Luche, J. Am. Chem. Soc. 100 (1978) 2226.
[18] S.A. Bal, A. Marfat, P. Helquist, J. Org. Chem. 47 (1982) 5045.
[19] A. Boudier, E. Hupe, P. Knochel, Angew. Chem. Int. Ed. 39 (2000) 2294.

[20] I. Fleming, N.J. Lawrence, J. Chem. Soc. Perkin Trans. 1 24 (1992) 3309.
[21] E. Hupe, M.I. Calaza, P. Knochel, Tetrahedron Lett. 42 (2001) 8829.
[22] E. Hupe, M.I. Calaza, P. Knochel, in press
[23] K. Burgess, M.J. Ohlmeyer, J. Org. Chem. 56 (1991) 1027.
[24] (a) D.A. Evans, G.C. Fu, A.H. Hoveyda, J. Am. Chem. Soc. 110 (1988) 6917;
(b) K. Burgess, M.J. Ohlmeyer, Tetrahedron Lett. 30 (1989) 395.
[25] (a) K.H. Thiele, P. Zdunneck, J. Organomet. Chem. 4 (1965) 10;
(b) K.H. Thiele, J. Köhler, J. Prakt. Chem. 32 (1966) 54;
(c) K.H. Thiele, G. Engelhardt, J. Köhler, M. Arnstedt, J. Organomet. Chem. 9 (1967) 385;
(d) G.A. Molander, P.W. Zinke, Organometallics 5 (1986) 2161.
[26] (a) M. Srebnik, Tetrahedron Lett. 32 (1991) 2449;
(b) W. Oppolzer, R.N. Radinov, Helv. Chim. Acta 75 (1992) 170;
(c) W. Oppolzer, R.N. Radinov, J. Am. Chem. Soc. 115 (1993) 1593.
[27] M. Rottländer, N. Palmer, P. Knochel, Synlett (1996) 573.
[28] (a) D. Kaufmann, Chem. Ber. 120 (1987) 853;
(b) D. Kaufmann, Chem. Ber. 120 (1987) 901;
(c) U. Gross, D. Kaufmann, Chem. Ber. 120 (1987) 991.
[29] E. Hupe, M.I. Calaza, P. Knochel, Chem. Commun. (2002) 1390.