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Selective transformations mediated by main-group organometallics*

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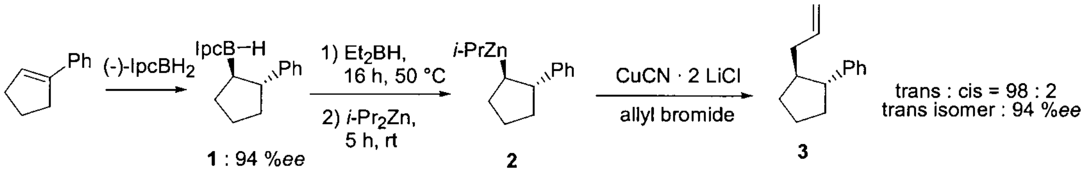
Abstract: Main-group organometallics are useful intermediates for the chemoselective and diastereoselective C–C bond formation. The boron–zinc exchange is a unique way for preparing chiral secondary alkylzinc reagents which are configurationally stable over a wide temperature scale. Coupled with the thermal rearrangement of tertiary organoboranes, a broad range of open-chain and cyclic polyfunctional molecules have been prepared. In addition, several examples of a diastereoselective remote C–H activation have been studied. The second part shows that the main-group metallic alkoxides such as *t*-BuOK can be used for the performance of catalytic reactions such as a new indole synthesis.

PREPARATION OF CHIRAL SECONDARY DIALKYLZINCS

Secondary organozincs of type **2** have a high configurational stability and are excellent regents for the preparation of chiral organometallics. The asymmetric hydroboration of 1-phenylcyclopentene with (-)-IpcBH$_2$ [1] gives the secondary organoborane **1** (94% *ee*) which, after treatment with Et$_2$BH (50 °C, 16 h), reacts with *i*-Pr$_2$Zn in tetrahydrofuran (THF) (25 °C, 5 h) furnishing the secondary mixed diorganozinc reagent **2**. The allylation of **2** in the presence of CuCN·2LiCl provides the desired product **3** with an excellent *trans:cis* ratio of 98:2. (Scheme 1) [2,3].



Scheme 1

An extension to acyclic systems is possible. *Z*- and *E*-styrenes **4** undergo the same sequence of reactions, furnishing in the first case the secondary alkylzinc reagent *anti*-**5**, whereas with *E*-styrene the *syn*-organozinc reagent (*syn*-**5**) is obtained preferentially. After allylation, the expected products *anti*-**6** and *syn*-**6** are isolated. Excellent results are also obtained with the cross coupling of the chiral organozincs with 1-bromoalkynes as shown in Scheme 2. In this case an almost perfect *anti:syn* selectivity is observed (> 99:1).

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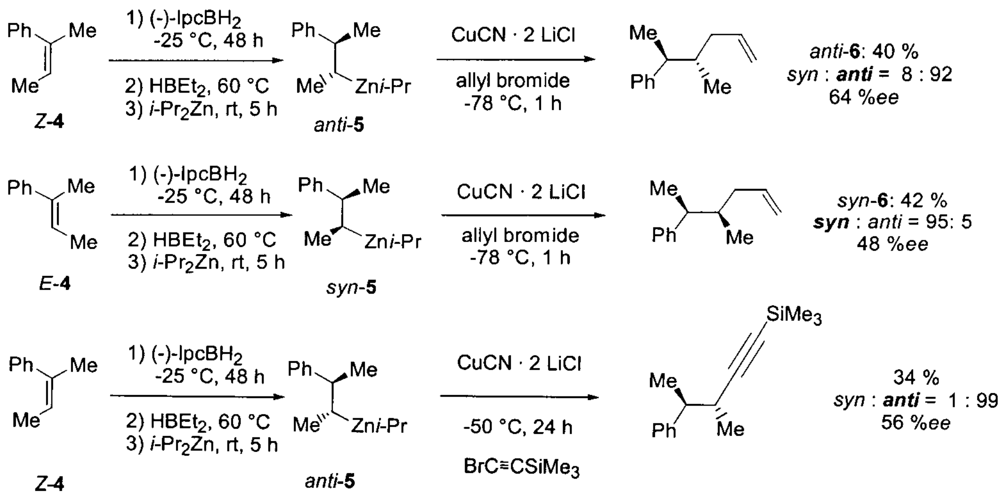
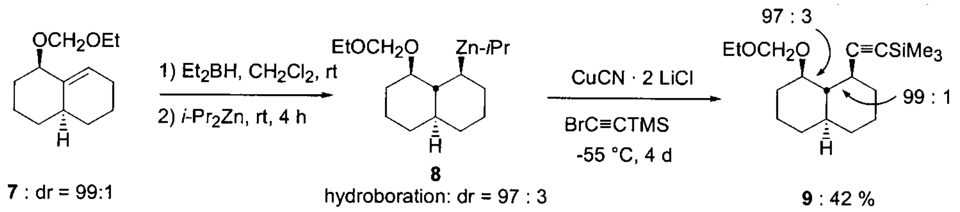


Scheme 2

The diastereoselective hydroboration of allylic ethers is also possible. Starting with the bicyclic compound **7**, it is possible to control four chiral centers. The hydroboration of **7** with Et_2BH furnishes selectively the corresponding organoborane which, after boron–zinc exchange, results in the organozinc derivative **8**. A copper-mediated cross-coupling with a bromoalkyne furnishes compound **9** as one major diastereomer (Scheme 3) [4].

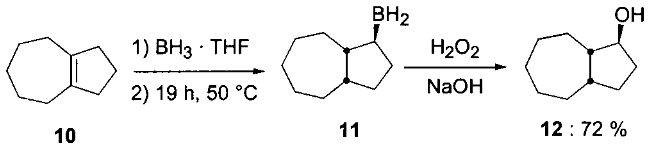


Scheme 3

DIASTEREOSELECTIVE THERMAL MIGRATION OF ORGANOBORANES

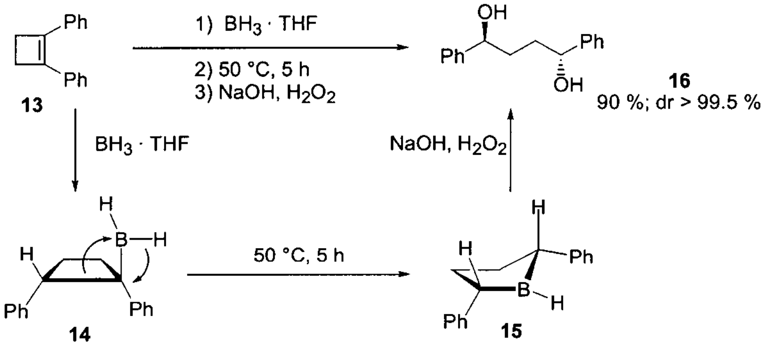
The activation of nonactivated C–H bonds is an important research field [5]. In most cases, transition-metal complexes have been used for this purpose. In this chapter, we wish to describe a stereoselective allylic C–H activation involving the thermal rearrangement of organoboranes [1,7]. The observed stereochemistry may be best explained by a dehydroboration–rehydroboration mechanism, but mechanistic studies indicate that the reaction may proceed via a more complex pathway involving a second molecule of BH_3.

Thus, the hydroboration of the tetrasubstituted olefin **10** first produces the normal hydroboration product which undergoes a 1,2-migration at 50 °C due to the steric hindrance of the resulting tertiary organoborane. A new secondary organoborane **11** is formed, which can be oxidized to the alcohol **12** (Scheme 4).



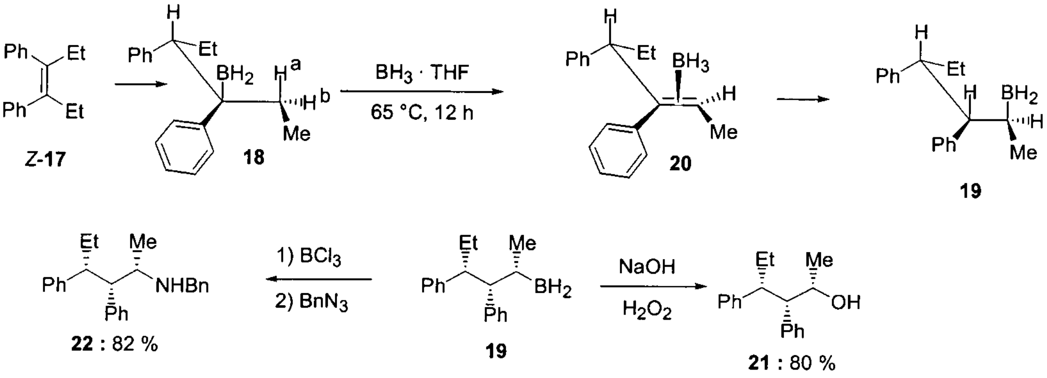
Scheme 4

Remarkably, in the case of four-membered rings such as **13** (Scheme 5), a new rearrangement of the intermediate tertiary organoborane **14** occurs affording the boracycle **15**. After alkaline oxidation with hydrogen peroxide the *meso*-1,4-diol **16** has one isomer [8]. This reaction has some generality and allows the preparation of various 1,4-diols with excellent diastereoselectivity.



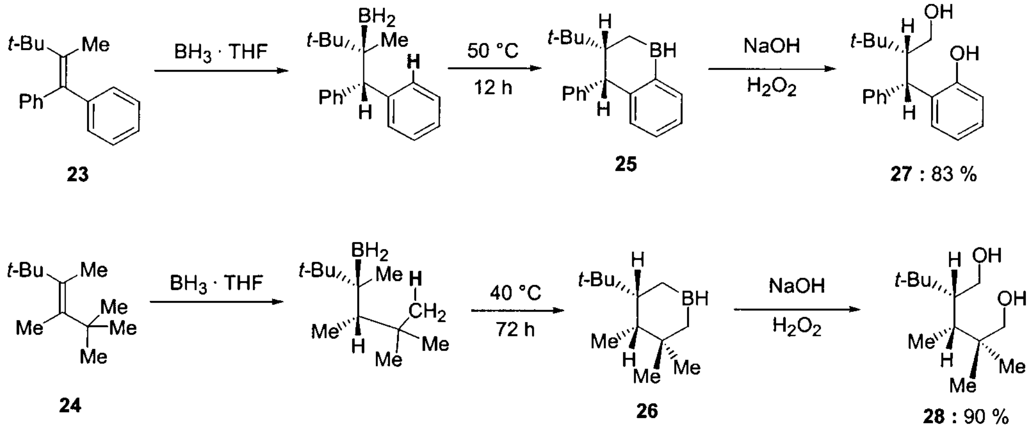
Scheme 5

Starting with the ethyl-substituted olefin **17**, there are two possibilities for the migration since two diastereotopic hydrogen atoms H^a and H^b of **18** are available for the migration. Only one of these two hydrogens undergoes selectively the rearrangement leading to the secondary organoborane **19**. This may be explained by assuming that the most stable borane-olefin complex **20** is formed having the bulky benzyl and the methyl group in a *trans*-arrangement. After oxidative workup (NaOH, H_2O_2) or amination, the expected products **21** and **22** are obtained as only one diastereomer (Scheme 6; dr > 99.5%).



Scheme 6

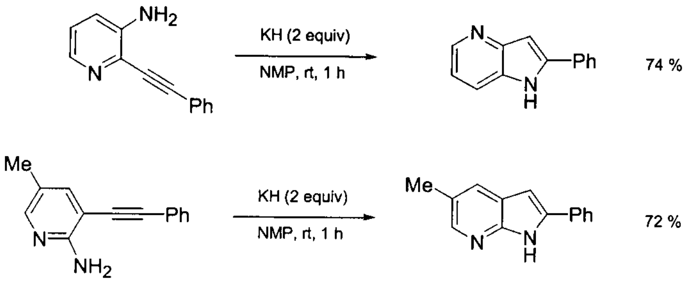
The remote activation of C–H bonds is an important synthetic. Some especially crowded tetra-substituted olefins undergo such a reaction. Furthermore, in all the examples studied, this activation proceeds with high diastereoselectivity. Thus, the two *tert*-butyl substituted olefins **23** and **24** undergo, after the initial hydroboration and migration [9], an insertion into a remote C–H bond forming the boracycles **25** and **26**, which, after oxidation, furnish the two diols **27** and **28** as one diastereoisomer. The control of up to three centers is possible (Scheme 7) [10].



Scheme 7

POTASSIUM *TERT*-BUTOXIDE CATALYZED INDOLE SYNTHESIS

The performance of catalytic activation of N–H bonds is also possible using *t*-BuOK in *N*-methylpyrrolidinone (NMP) as base. Under these conditions a broad range of polyfunctional indoles and aza-indoles can be prepared (Scheme 8) [11]. Remarkably, these cyclizations are performed under mild conditions and can be applied to the solid-phase synthesis of indoles.



Scheme 8

CONCLUSION

The boron-zinc exchange is an excellent method for activating the C–B bond and allows the transition-metal-catalyzed reactions with many types of electrophiles. Furthermore, it is a unique way for preparing chiral secondary alkylzinc organometallics, without the need of any stabilizing, neighboring heteroatom. The thermal rearrangement of organoboranes is a powerful method for controlling stereocenters in cyclic and acyclic molecules. With appropriate substrates, diastereoselective remote C–H activation reaction can be accomplished. Also, the use of potassium alkoxides allow the performance of catalytic C–N bond formation.

REFERENCES AND NOTES

1. a) H. C. Brown. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, New York, pp. 301–446, (1972); b) H. C. Brown, G. W. Kramer, A. B. Levy, M. M. Midland. *Organic Synthesis*

via Organoboranes, Wiley-Interscience, New York (1975); c) D. S. Matteson. *Stereodirected Synthesis with Organoboranes*, Springer-Verlag, Berlin (1995).

2. P. Knochel and P. Jones (Eds.). In *Organozinc Reagents: A Practical Approach*, Oxford Press, Oxford (1999).
3. a) F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel. *J. Org. Chem.* **61**, 8229 (1996); b) P. Knochel and R. D. Singer. *Chem. Rev.* **93**, 2117 (1993); c) P. Knochel. *Synlett.* 393 (1995); d) A. Boudier, F. Flachsmann, P. Knochel. *Synlett.* **39**, 1438 (1998); e) M. C. P. Yeh and P. Knochel. *Tetrahedron Lett.* **30**, 4799 (1989); f) A. Boudier and P. Knochel. *Tetrahedron Lett.* **40**, 687 (1999).
4. A. Boudier, E. Hupe, P. Knochel. *Angew. Chem.* **39**, 2294 (2000).
5. a) J. C. W. Lohrenz and H. Jacobsen. *Angew. Chem.* **108**, 1403 (1996); *Angew. Chem. Int. Ed. Engl.* **35**, 1305 (1996); b) B. A. Arndtsen and R. G. Bergmann. *Science* 270, 1970 (1995).
6. a) N. A. Williams, Y. Uchimaru, M. Tanaka. *J. Chem. Soc. Chem. Commun.* 1129 (1995); b) F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, S. Murai. *Bull. Chem. Soc. Jpn.* **68**, 62 (1995); c) Y.-G. Lim, Y. H. Kim, J.-B. Kang. *J. Chem. Soc. Chem. Commun.* 2267 (1994).
7. a) L. D. Field, A. V. George, B. A. Messerle. *J. Chem. Soc. Chem. Commun.* 1339 (1991); b) R. Köster, W. Siebert. *Methoden Org. Chem*, 4th ed., Vol. 13, Part 3a, pp. 1–908 Houben-Weyl (1982); c) S. E. Wood and B. Rickborn. *J. Org. Chem.* **48**, 555 (1983); d) A. Suzuki, S. Sono, M. Itoh, H. C. Brown, M. M. Midland. *J. Am. Chem. Soc.*, **93**, 4329 (1971).
8. F. Lhermitte and P. Knochel. *Angew. Chem.* **110**, 2598 (1998); *Angew. Chem. Int. Ed. Engl.* **37**, 1305 (1998).
9. H. Laaziri, L. O. Bromm, F. Lhermitte, R. M. Gschwind, P. Knochel. *J. Am. Chem. Soc.* **121**, 6940 (1999).
10. L. O. Bromm, H. Laaziri, F. Lhermitte, K. Harms, P. Knochel. *J. Am. Chem. Soc*. **122**, 10218 (2000).
11. A. Rodriguez, C. Koradin, W. Dohle, P. Knochel. *Angew. Chem. Int. Ed*. **39**, 2488 (2000).