Highly Regio- and Stereoselective Thermal Migration of Organoboranes in Acyclic Molecules

Lars O. Bromm, Hamid Laaziri, Frédéric Lhermitte, Klaus Harms, and Paul Knochel*

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

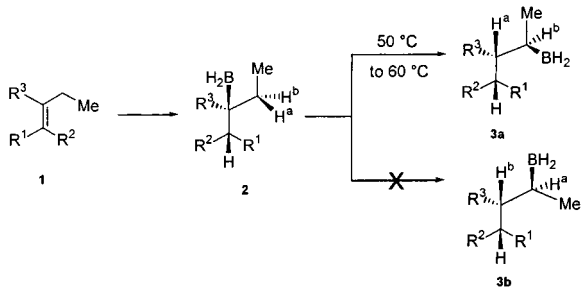
Received April 13, 2000

The stereoselective setup of adjacent chiral centers in acyclic molecules is a challenging problem.[1] Herein, we wish to report a new approach allowing the regio and stereoselective control of up to three chiral centers using a new stereoselective migration of organoboranes. In the case of organoboranes derived from disubstituted olefins by hydroboration, the thermal isomerization is known to proceed at elevated temperature (100−160 °C).[2,3] However, in the case of cyclic[4,5] and acyclic[6] *tetrasubstituted* olefins the resulting organoboranes undergo a thermal migration under far milder conditions (50 °C). For acyclic tetrasubstituted olefins with methyl groups, stereoselective migrations were observed.[6] Remote C−H activation leading to boracycles (five- and six-membered rings) has also been shown to occur with high stereoselectivity.[6]

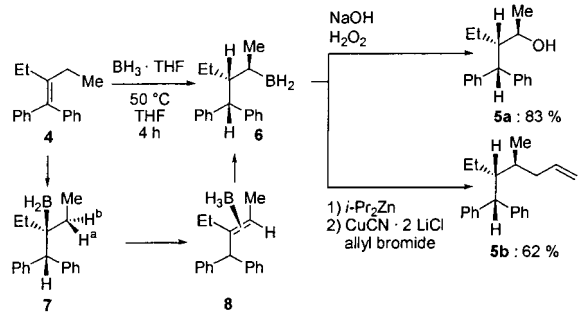
We have now found that this rearrangement allows a new preparation of more elaborated acyclic molecules with control of the relative stereochemistry of up to three adjacent centers as well as an excellent regioselectivity of the rearrangement. The migration toward higher alkyl substituents is much faster than that toward methyl groups. If the alkyl substituent is bearing diastereotopic hydrogen atoms, the migration will show high diastereoselectivity. Thus, the hydroboration of tetrasubstituted olefins of type **1** affords first the hydroboration product **2** which undergoes a highly stereoselective thermal rearrangement at 50 °C to 60 °C leading to diastereomer **3a** and not **3b** (Scheme 1).

The hydroboration of 1,3-diphenyl-2-ethyl-1-butene (**4**)[7] with $BH_3 \cdot$ THF furnishes after heating at 50 °C for 4 h and subsequent oxidation with H_2O_2/NaOH the alcohol **5a** as *only one diastereoisomer* in 87% isolated yield.[8] The allylation of the intermediate organoborane **6** [(i) *i*-Pr_2Zn, THF, room temperature; (ii) CuCN · 2 LiCl (20 mol %), −78 °C, allyl bromide] gives the diastereomerically pure product **5b** (Scheme 2).[9] This stereoselectivity can be best explained by assuming that the primary hydroboration product **7** undergoes a preferential dehydroboration with the adjacent H^a (and not H^b) resulting in the formation of the most stable olefin−borane complex **8** having the methyl group trans to the most bulky substituent of the double bond.[10] Although the dissociation of **8** has no stereochemical consequences, this type of borane−olefin complexes is a key intermediate to explain the stereoselectivity observed for **14** and **19** (Schemes 4 and 5).

Scheme 1



Scheme 2



The reaction also shows a very high regioselectivity. The unsymmetrical olefin 1,1-diphenyl-2-methyl-1-butene[7] (**9**) provides after hydroboration and thermal rearrangement (50 °C, 4 h) only the rearrangement products **10a** and **10b** where the boron migration has proceeded only in the direction of the ethyl group.[11] This regioselectivity can again be explained by the higher stability of the intermediate olefin−borane complex **11a** compared to **11b** and **11c** (Scheme 3). In this reaction also only one diastereoisomeric organoborane **12** is formed. Subsequently, after oxidation with H_2O_2/NaOH the diastereomerically pure alcohol (**10a**; 87%) is obtained. After amination [(i) BCl_3; (ii) BnN_3] the benzylamine **10b** (>99.9% one diastereoisomer, 83%) is isolated.[12]

The thermal rearrangement of acyclic organoboranes allows the preparation of diastereomerically defined molecules having three adjacent stereocenters. Thus, the reaction of (*Z*)-3,4-diphenyl-3-hexene[7] (**13a**) with $BH_3 \cdot$ THF, thermal rearrangement (65 °C, 12 h) and subsequent allylation furnishes, via the intermediate secondary organoborane (**14a**),[13] the allylated product **15a** with an excellent diastereoselectivity (>97:3) in 53% yield, showing that both the intermediate organozinc compound and

(1) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996.

(2) (a) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1966**, *88*, 1433. (b) Brown, H. C.; Bhatt, M. V. *J. Am. Chem. Soc.* **1966**, *88*, 1433.

(3) R. Köster, W. Siebert, *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Thieme: Stuttgart, 1952; 1982; Vol. 13, part 3a, pp 1−908.

(4) (a) Wood, S. E.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 555. (b) Field, L. D.; Galagher, S. P. *Tetrahedron Lett.* **1985**, *26*, 6125.

(5) Lhermitte, F.; Knochel, P. *Angew. Chem.* **1998**, *110*, 2597; *Angew. Chem., Int. Ed.* **1998**, *37*, 2460.

(6) (a) Laaziri, H.; Bromm, L. O.; Lhermitte, F.; Gschwind, R. M.; Knochel, P. *J. Am. Chem. Soc.* **1999**, *121*, 6940. (b) Unpublished results, Munich 2000.

(7) All alkenes were prepared using *McMurry* reactions: Leimner, J.; Weyerstahl, P. *Chem. Ber.* **1982**, *115*, 3697

(8) The relative stereochemistry of the borane **6** has been established by conversion of alcohol **5a** to the 3,5-dinitrobenzoate and X-ray analysis of the obtained crystals.

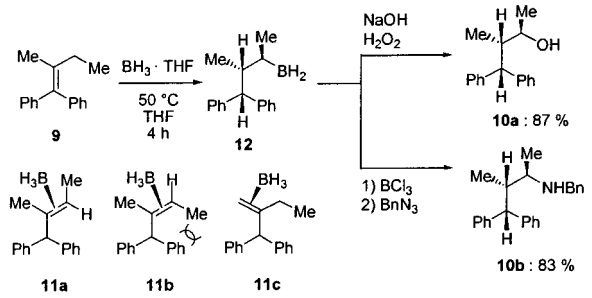
(9) **Typical procedure for a transmetalation to the zinc organometallic and allylation.** To a solution of 2-ethyl-1,1-diphenyl-1-butene (**4**) (709 mg, 3.0 mmol) in THF (25 mL) at 25 °C was added BH_3·THF (9 mL, 9 mmol, 1 M in THF). The resulting solution was stirred for 10 min at 25 °C and for 4 h at 50 °C. After the solution was cooled to 0 °C, the solvent and an excess of borane were removed under vacuum (0.1 mmHg, 60 min). *i*-Pr_2Zn (2.4 mL, 6 mmol, 2 equiv, 2.5 M in THF) was added at 25 °C. After change of color to dark gray (2 h), stirring was continued for 45 min. The excess of *i*-Pr_2Zn was removed under vacuum at 0 °C and the residue was diluted with THF (25 mL). The resulting mixture was cooled to −78 °C and a solution of CuCN·2 LiCl (0.4 mL, 0.2 equiv, 1 M in THF) was slowly added. Stirring at −78 °C was continued for 15 min. Then allyl bromide (0.8 mL, 9 mmol, 3 equiv) was added. The reaction mixture was warmed to 25 °C, stirred for 1 h, and quenched with 3 M aqueous HCl (25 mL). After typical workup, the residue obtained after evaporation of the solvents was purified by flash chromatography (pentane) affording (4*R**,5*S**)-5-benzhydryl-4-methyl-1-heptene (**5b**) (516 mg, 62%) as a clear oil.

(10) The nature of the intermediates of type **8** is currently being studied using theoretical calculations.

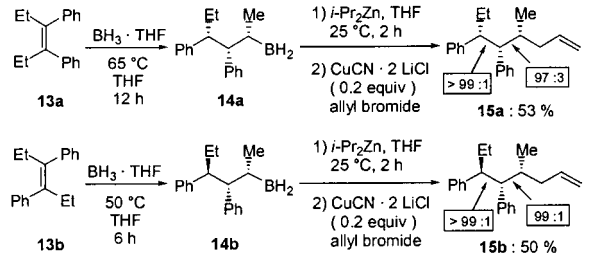
(11) The relative stereochemistry of the borane **12** has been determined by forming the alcohol **10a** and comparing its ^1H NMR with published data: (a) Zayas, J.; Platz, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 7065. (b) Dinnocenzo, J. P.; Zuilhof, H.; Lieberman, D. R.; Simpson, T. R.; McKechney, M. W. *J. Am. Chem. Soc.* **1997**, *119*, 994.

10.1021/ja001283y CCC: $19.00
Published on Web 10/03/2000

Scheme 3



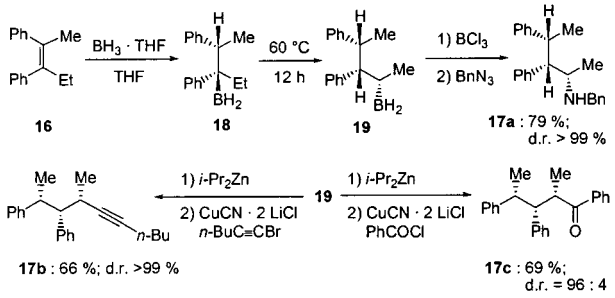
Scheme 4



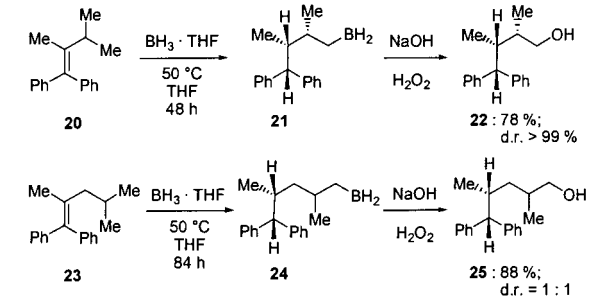
organocopper reagent have a high configurational stability.[14] By starting with the corresponding (*E*)-3,4-diphenyl-3-hexene (**13b**), the intermediate organoborane **14b** is formed and after the same allylation procedure, the diastereomerically pure product **15b** is obtained (Scheme 4).

By hydroboration of the unsymmetrical *Z*-olefin[7] **16** a preferential migration of the tertiary organoborane in compound **18** toward the ethyl group is observed. The resulting secondary organoborane **19**[15] is converted to the diastereomerically pure amine **17a** after the usual amination procedure in 79% yield. Similarly, the treatment of the organoborane **19** with *i*-Pr_2Zn followed by CuCN · 2 LiCl and 1-bromohexyne provides the alkyne **17b** in 66% yield as one diastereoisomer (Scheme 5). By the analogous reaction with PhCOCl, the ketone **17c** is obtained

Scheme 5



Scheme 6



in 69% yield (d.r. = 96:4). It should be noticed that the initial hydroboration is not regioselective, but that a rapid isomerization seems to occur between the two regioisomers under the reaction conditions. Only the product derived from regioisomer **18** is observed since migration to ethyl or higher alkyl groups has been found to be substantially faster.

A diastereoselective multiple migration has been observed in the case of 1,1-diphenyl-2,3-dimethyl-1-butene (**20**).[7] After oxidative workup of the organoborane **21** (H_2O_2/NaOH) the diastereomerically pure alcohol **22** was isolated.[16] However, for 1,1-diphenyl-2,4-dimethyl-1-pentene[7] (**23**) the migration led to the intermediate organoborane **24** and after oxidative workup (H_2O_2/NaOH) to the alcohols **25** as a 1:1 mixture of diastereoisomers (Scheme 6).

In summary, we have described that organoboranes undergo highly regio- and stereoselective thermal migrations affording acyclic molecules with relative stereocontrol of three adjacents carbon centers.

Acknowledgment. Dedicated to Henri B. Kagan on the occasion of his 70th birthday. We thank the DFG (SFB 260, Leibniz-program) and the Fonds der Chemischen Industrie for generous support. We thank the BASF AG, BAYER AG, Chemetall GmbH and PPG-SIPSY SA (France) for generous gift of chemicals.

Supporting Information Available: Spectral data for compounds **5**, **10**, **15**, **17**, **22**, and **25** and X-ray data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001283Y

(12) **Typical procedure for the amination.** To a solution of 2-methyl-1,1-diphenyl-1-butene (**9**) (667 mg, 3 mmol) in THF (25 mL) at 25 °C was added BH_3·THF (9.0 mL, 9 mmol, 1 M in THF). The resulting solution was stirred at 25 °C for 10 min and at 50 °C for 4 h. After the solution was cooled to 0 °C, the solvent and the excess of borane were removed under vacuum (0.1 mmHg, 60 min). The residue was dissolved in CH_2Cl_2 (25 mL) and BCl_3 (12 mL, 4 mmol, 1 M in CH_2Cl_2) was added at 0 °C. The mixture was warmed to 25 °C and was stirred for 3 h. The solvent and an excess of BCl_3 were removed under vacuum (0 °C, 0.1 mmHg, 60 min). The residue was dissolved in CH_2Cl_2 (25 mL) and benzyl azide (479 mg, 3.6 mmol, 1.2 equiv) was added at 0 °C. The solution was warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with 3 M aqueous NaOH (25 mL) at 0 °C and worked up as usual. Flash-chromatographic purification of the residue (pentane:ether 2:1) afforded *N*-benzyl[(1*R**,2*S**)-1,2-dimethyl-3,3-diphenylpropyl]amine (**10b**) (821 mg, 83%) as a clear oil.

(13) The relative stereochemistry of **14a** has been established by X-ray analysis of the corresponding alcohol (oxidative workup: NaOH, H_2O_2).

(14) (a) Darcel, C.; Flachsmann, F.; Knochel, P. *J. Chem. Soc., Chem. Commun.* **1998**, 205. (b) Boudier, A.; Flachsmann, F.; Knochel, P. *Synlett* **1998**, 1438. (c) Boudier, A.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 687.

(15) The relative stereochemistry of **19** has been established by X-ray analysis of the corresponding alcohol (oxidative workup: NaOH, H_2O_2).

(16) The relative stereochemistry of **21** has been established by X-ray analysis of the alcohol **22**.