Pergamon

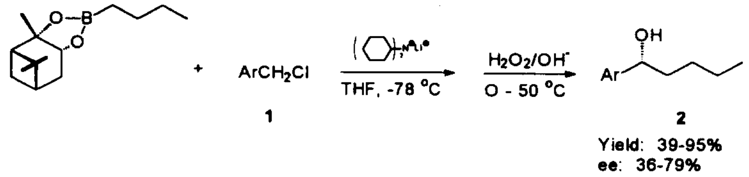
Tetrahedron: Asymmetry, Vol. 8, No. 23, pp. 3843–3846, 1997
© 1997 Elsevier Science Ltd. All rights reserved.
Printed in Great Britain
PII: S0957-4166(97)00565-X
0957-4166/97 $17.00 + 0.00

Asymmetric synthesis of alkylarylcarbinols via reaction of a chiral pinanediol alkylboronic ester with arylmethyl chlorides [†]

George W. Kabalka,* Nan-Sheng Li and Su Yu
Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, TN 37996-1600, USA

Abstract: The reaction of arylmethyl chlorides with chiral pinanediol esters of alkylboronic acids in the presence of lithium dicyclohexylamide affords chiral alkylarylcarbinols in good stereochemical yields after oxidation. © 1997 Elsevier Science Ltd. All rights reserved.

In recent years the reactions of α-haloboronate esters have been extensively investigated because of their utility in a wide variety of natural product syntheses.[1] Parallel studies involving the reaction of organoboranes with α-halomethyl anions,[2] α-substituted-α-halomethyl anions such as α-trimethylsilyl-α-chloromethyllithium,[3] and α-chloroallyl lithium reagents[4] have also proven synthetically useful. Matteson, for example, reported that the reaction of α-trimethylsilyl-α-chloromethyllithium with pinanediol phenylboronate yielded the chiral α-trimethylsilylboronic ester in 46% diastereomeric excess.[3c] In a continuation of our studies involving the reaction of (α-chloroaryl)methyl anions with organoboranes,[5] we found that (α-chloroaryl)methyl anions, generated by deprotonation of the corresponding arylmethyl chlorides, react in situ with (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol butylboronic ester to give alkylarylcarbinols in good yields after oxidation (39–95%) and with enantiomeric excesses up to 79% (Scheme 1). The enantiofacial selection on the carbanion intermediate by the chiral boronic ester is not only interesting but provides an alternate method to the synthesis of chiral alkylarylcarbinols which are often prepared by reduction of alkylarylketones[6] or by the alkylation of aryl aldehyde with alkyl organometallic reagents.[7]



Scheme 1.

The results of a study involving the reactions of (+)-pinanediol *n*-butylboronate with various arylmethyl chlorides in the presence of lithium dicyclohexylamide are presented in Table 1. The procedure is straightforward: under an argon atmosphere, lithium dicyclohexylamide (1 mmol)[8] is added to a solution of the (+)-pinanediol ester of *n*-butylboronic acid (1 mmol)[9] and the arylmethyl chloride (1 mmol) in THF (2 mL) at −78°C.[10] After the reaction has proceeded for the indicated time (Table 1) at −78°C, the mixture is allowed to warm to 0°C and then oxidized using H_2O_2/OH^- to generate the desired *n*-butylarylcarbinols. The absolute configurations of the products (**2**) were determined to be *R* by measurement of their optical rotation.

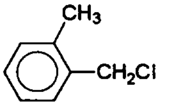
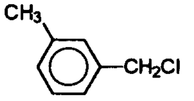
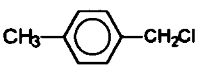
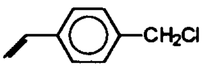
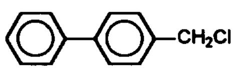
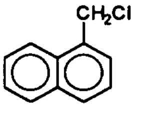
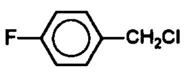
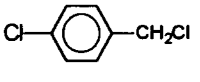
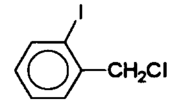
The reactions of other chiral *n*-butylboronic esters with (α-chlorophenyl)methyllithium were also studied. The reaction of (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol *n*-butylboronic ester with (α-

---

[†] Dedicated to Professor Herbert C. Brown on the occasion of his 85th birthday.

* Corresponding author. Email: Kabalka@utk.edu

Table 1. (*R*)-*n*-Butylarylcarbinols (**2**) were prepared from (1*S*,2*S*,3*R*,5*S*)-(+) pinanediol *n*-butylboronic ester and arylmethyl chlorides

Entry	Product[a]	$ArCH_2Cl$	Reaction Time[b]	Yield (%)[c]	EE(%)[d]
1	**2a**	$PhCH_2Cl$	0 min	72	71
2	**2a**	$PhCH_2Cl$	10 min	77	72
3	**2a**	$PhCH_2Cl$	60 min	73	71
4	**2b**		10 min	39	55
5	**2c**		10 min	64	79
6	**2d**		10 min	63	78
7	**2e**[e]		10 min	64	60
8	**2f**		10 min	68	45
9	**2g**		10 min	64	45
10	**2h**		10 min	69	69
11	**2i**		10 min	95	36
12	**2j**[e]		10 min	71	64

[a] All reaction products exhibited physical and spectral characteristics in accord with literature values. [b] Reaction time at -78°C after adding lithium dicyclohexylamide. [c] Isolated yield. [d] Determined by ^1H NMR analysis of the corresponding Mosher's esters. [e] Confirmed by HRMS.

chlorophenyl)methyllithium at −78°C for 10 min gave (*S*)-1-phenyl-1-pentanol in 75% chemical yield and 70% optical purity after oxidation; the reaction using (1*R*,2*R*)-(−)-1,2-dicyclohexyl-1,2-ethanediol *n*-butylboronic ester gave (*R*)-1-phenyl-1-pentanol in 70% optical purity. None of the desired 1-phenyl-1-pentanol was formed in reactions using the chiral boronic ester prepared from diethyl L-tartrate, presumably due to the higher acidity of the α-proton in the tartrate ester compared to the benzylic proton in benzyl chloride which precluded the formation of the prerequisite (α-chlorophenyl)methyllithium reagent.

Zinc chloride enhances both the chemical yield and the stereoselectivity of reactions involving chiral boronic esters with dichloromethyllithium reagents by influencing which of the two chlorines is displaced.[1] Not surprisingly, since there is only a single chlorine available, no improvement was noted in the present case upon the addition of zinc chloride.

The enantioface selectivity brought about by the chiral boronic ester provides a useful degree of enantioselectivity and is applicable to systems which might not tolerate the organometallic reagents required in the Matteson reaction sequence (Table 1, entries 11 and 12).[11] In addition, it offers the intriguing possibility that boronic esters containing chirality in both the alkyl group and in the ester might lead to enhanced diastereoselectivities via matched (versus mismatched) diastereochemical pairings.[12]

Acknowledgements

We wish to thank the Department of Energy and the Robert H. Cole Foundation for support of this research.

References

1. For reviews see: (a) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer, Berlin, 1995, pp. 162–220. (b) Matteson D. S. *Chem. Rev.* **1989**, *89*, 1535. (c) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294.
2. (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795. (c) Brown, H. C.; Phadke, A. S.; Rangaishenvi, M. V. *J. Am. Chem. Soc.* **1988**, *110*, 6263. (d) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8957. (e) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8961. (f) Brown, H. C.; Phadke, A. S.; Bhat, N. G. *Tetrahedron Lett.* **1993**, *34*, 7845.
3. (a) Matteson, D. S.; Majumdar, D. *J. Organomet. Chem.* **1980**, *184*, C41. (b) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230. (c) Tsai, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236.
4. (a) Brown, H. C.; Ragaishenvi, M. V. *Tetrahedron Lett.* **1990**, *31*, 7113. (b) Brown, H. C.; Jayaraman, S. *J. Org. Chem.* **1993**, *58*, 6791.
5. (a) Kabalka, G. W.; Li, N.-S.; Yu, S. *Tetrahedron Lett.* **1995**, *36*, 8545. (b) Li, N.-S.; Yu, S.; Kabalka, G. W. *Organometallics* **1997**, *16*, 709. (c) Li, N.-S.; Yu, S.; Kabalka, G. W. *J. Organomet. Chem.* **1997**, *531*, 101.
6. (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Rawson, D.; Meyer, A. I. *J. Chem. Soc., Chem. Commun.* **1992**, 494. (c) Zhang, X.; Kumobayashi, H.; Takaya, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1179.
7. (a) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans 1* **1991**, 2717. (b) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 9751. (c) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691. (d) Urabe, H.; Yamakawa, T.; Sato, F. *Tetrahedron: Asymmetry* **1992**, *3*, 5. (e) Chibale, K.; Greeves, N.; Lyford, L.; Pease, J. E. *Tetrahedron: Asymmetry* **1993**, *4*, 2407.
8. Lithium dicylohexylamide (1 mmol) was prepared in situ by metallating dicyclohexylamine (0.18 g, 0.20 mL, 1 mmol) in THF (1 mL) with *n*-BuLi (1 mmol; 0.63 mL, 1.6 M solution in hexane) at 0°C and was used immediately.
9. (+)-Pinanediol *n*-butylboronic ester (1 mmol) was prepared in situ by the reaction of *n*-butyldiisopropoxyborane (1 mmol) with (+)-pinanediol (1mmol) in THF (1 mL) at rt for 30 min. After removing the solvent and isopropanol under reduced pressure, the residue was used without further purification. The ^1H NMR of the crude boronic ester [250 MHz NMR ($CDCl_3$) δ: 0.77 to 2.41 (*m*, 24 H, pinanyl with methyl resonance at δ 0.84, 1.29, 1.38 *n*-butyl), 4.25 (*dd*, 1H, J=1.87,

J=8.70. CHOB] is consistent with that reported in the literature: Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics* **1983**, *2*, 1536.

10. Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585.
11. Benzylic chlorides containing strongly electron-withdrawing substituents (e.g. $-NO_2$ and $-CO_2CH_3$) generate significant amounts of coupling products, presumably due to the stability of the intermediate carbanions.
12. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. F. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.

(Received 10 April 1997; accepted 13 June 1997)