Enantiotopic Differentiation of *pro-R* or *pro-S* Chlorides in (Dichloromethyl)borates by Chiral Lewis Acids: Enantioselective Synthesis of (α-Chloroalkyl)boronates

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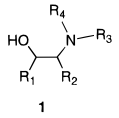
Asymmetric catalysis has been the focus of intense research for the past several years. Most asymmetric reactions depend on the enantiotopic or the diastereotopic differentiation of sp^2 center(s).[1] Diastereotopic differentiation of two leaving groups on an sp^3 center has been rarely used for controlling the stereoselectivity.[2,3] Matteson homologation is one of the known examples where the stereoselectivity is controlled by diastereotopic differentiation of the chloride groups on an sp^3 carbon.[2b] However, to the best of our knowledge the enantiopic differentiation of two leaving groups on an sp^3 center by chiral Lewis acids is hitherto unknown. Chiral (α-chloroalkyl)-boronates with excellent enantiomeric purity (>99% ee) have been prepared by the treatment of chiral diol boronates with (dichloromethyl)lithium[4] or by reaction of chiral diol (dichloromethyl)boronates with organometallics.[5] The outcome of the stereochemical preference is governed by the chirality of the diol moiety in the borate complexes. (α-Chloroalkyl)boronates are highly versatile synthetic intermediates which undergo nucleophilic displacement of chloride with a variety of nucleophiles to provide a broad spectrum of functionalized compounds[6] and are key intermediates for the synthesis of α-aminoboronic acids or boropeptides which have been extensively studied as inhibitors of serine proteases.[7] We were encouraged by the observation made by Matteson that the yield and the enantiomeric excess (ee) of the α-(chloroalkyl)boronates improved significantly by addition of Lewis acids, such as $ZnCl_2$.[4,8] We herein report the first example of enantiotopic differentiation of *pro-R* or *pro-S* chlorides in (dichloromethyl)borate complexes by chiral Lewis acid catalysts.

Initially combinations of zinc with a series of chiral amino alcohols **1** were examined as chiral Lewis acid catalysts for the 1,2-migration reaction of the borate complexes. Thus, the



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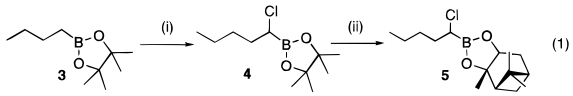
treatment of pinacol butylboronate (**3**) with (dichloromethyl)-lithium in THF at −100 °C, followed by addition of diethylzinc and amino alcohol **1**[9] provided pinacol (1-chloropentyl)boronate (**4**) in 70−75% isolated yield (eq 1). The migration product **4**

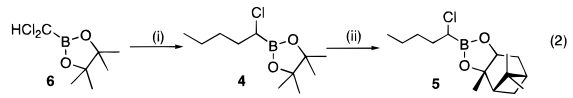


(1)

(i) n-BuLi/ CH_2Cl_2/ THF/ -100 oC; $ZnEt_2$/ **1**; rt/ 18h; (ii) NH_4Cl; (*S*)-Pinanediol

was transesterified with (*S*)-pinanediol to yield (*S*)-pinanediol (1-chloropentyl)boronate (**5**) and used for determination of the percent enantiomeric excess (% ee).[10] Among the chiral Lewis acids examined, those derived from valinol (**1a**) and phenylglycinol (**1b**), and diethylzinc, gave the product **4** in 16% and 20% ee, respectively. Catalysts derived from other amino alcohols provided **4** without any enantioselectivity.

We observed low enantioselectivity (∼20% ee) because donor solvents such as THF may be decreasing the Lewis acidity of the chiral catalyst by coordination with the zinc species.[11] In order to test this hypothesis, an experiment was designed to eliminate the use of donor solvents completely. Thus, the treatment of pinacol (dichloromethyl)boronate (**6**) with butyllithium in hexane at −40 °C, followed by addition of **1a** in methylene chloride and diethylzinc, yielded **4** in 40% ee (Table 1, entry 1; eq 2). Enantioselectivity of the product **4** was further improved to 70% ee by use of a large excess of (2*S*)-**1a** and diethylzinc (4 equiv of each) (Table 1, entry 2).



(2)

(i) n-BuLi/ hexane/ -40 oC; Lewis acid/ **1** or **2**/ CH_2Cl_2; rt/ 18h; (ii) NH_4Cl; (*S*)-Pinanediol

Similar experiments were also carried out by using bisoxazolines **2a**−**e** and metal triflates including $Yb(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, and $Lu(OTf)_3$) as Lewis acids.[12] As summarized in

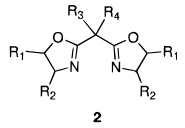


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Table 2, ytterbium is the metal of choice and provides the product **4** in 71% ee. A stoichiometric amount of **2b**·$Yb(OTf)_3$ complex (see Table 2, entry 8) was needed to yield **4** in 71% ee. After identifying the optimum combination of chiral ligand and Lewis acid, we turned our attention to varying the stoichiometry of the Lewis acid with the chiral ligand. The best result (88% ee; Table 3, entry 7) was obtained by the use

(1) For a general overview of recent advances in this area, see: (a) Noyori, R. *Assymmetric Catalysis in Organic Synthesis;* Wiley: New York, 1994. (b) *Catalytic Assymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, Weinheim, 1993.

(2) For a general review of the Matteson homologation see: (a) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201. (b) Matteson D. S. *Pure Appl. Chem.* **1991**, *63*, 339 and references cited therein.

(3) For a general review of the chemistry of chiral acetals, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

(4) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077.

(5) Sadhu, K. M.; Matteson, D. S.; Hurst, G. D.; Kurosky, J. M. *Organometallics* **1984**, *3*, 804.

(6) (a) Matteson, D. S.; Man, H. W. *J. Org. Chem.* **1994**, *59*, 5734. (b) Matteson, D. S.; Michnick T. J. *Organometallics* **1990**, *9*, 3171. (c) Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 3286. (d) Matteson, D. S.; Peterson, M. L. *J. Org. Chem.* **1987**, *52*, 5116.

(7) (a) Bone, R.; Shenvi, A. B.; Kettner, C. A.; Agard, D. A. *Biochemistry* **1987**, *26*, 7609. (b) Weber, P. C.; Lee, S.; Lewandowski, F. A.; Schadt, M. C.; Chang, C.-H.; Kettner, C. A. *Biochemistry* **1995**, *34*, 3750.

(8) The yield and ee increased from 15−30% to 90%, and 77% to 99%, respectively, for the homologation of (*S*)-pinanediol isobutylboronate.

(9) There were no differences in ee and yield when the ligands and metal salts were mixed at room temperature and stirred for 1 h before being added to the reaction mixture.

(10) (a) The ee of **5** was determined by measuring the peak height in the ^1H NMR ((1*R*) δ 1.129 and 1.093 via (1*S*) δ 1.121 and 1.084) and ^{13}C NMR ((1*S*) δ 35.182 via (1*R*) δ 35.164). (b) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810.

(11) The ee dropped from 45% to 35% using (2*R*)-**2b**·$Cu(OTf)_2$·**6** (1:1:1), even in the presence of 1% ether.

(12) A typical procedure: To a solution of **6** (211 mg, 1 mmol) in hexane (1.5 mL) was added *n*-butyllithium (0.75 mL, 1.6 M, 1.2 mmol) at −40 °C. After 5 min, to the mixture was added CH_2Cl_2 (20 mL), followed by (2*R*)-**2b** (167 mg, 0.5 mmol) and $Yb(OTf)_3$ (132 mg, 0.21 mmol) as solids. The mixture was allowed to warm to room temperature and kept overnight. NH_4Cl (20 mL) and ether (25 mL) were added, followed by (*S*)-pinanediol (275 mg, 1.62 mmol). After 15 min, the organic layer was separated and dried over $MgSO_4$. Removal of solvent and chromatography (silica gel, CH_2Cl_2) gave **5** (276 mg, 86% yield). The ee of **5** was determined as 55% (*R*) by ^1H NMR. Caution: all solvents must be removed under vacuum at >200 Torr to avoid loss of **5** by evaporation under high vaccum.

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Table 1. Reaction of **6** with Butyllithium Catalyzed by **1** and $ZnEt_2$

entry	ligands **1**	R_1	R_2	R_3	R_4	molar ratio **1**:$ZnEt_2$:**6**	% ee[a]	config
1	(2*S*)-**1a**	H	*i*-Pr	H	H	1:1:1	40	(*S*)
2	(2*S*)-**1a**					4:4:1	70	(*S*)

[a] Determined by ^{1}H NMR of **5.**

Table 2. Reaction of **6** with Butyllithium Catalyzed by **2** and Metal Triflates

entry	ligands **2**	R_1	R_2	R_3	R_4	metal	molar ratio **2**:metal:**6**	% ee[a]	config
1	(2*S*)-**2a**	H	Ph	H	H	$Zn(OTf)_2$	0.8:0.8:1	44	(*S*)
2	(2*R*)-**2b**	H	Ph	Me	Me	$Zn(OTf)_2$	1:1:1	45	(*R*)
3	(2*R*)-**2b**	H	Ph	Me	Me	$Cu(OTf)_2$	1:1:1	45	(*R*)
4	(2*S*)-**2b**	H	Ph	Me	Me	$Zn(OTf)_2$	1:1:1	45	(*S*)
5	(2*S*)-**2c**	H	$PhCH_2$	Et	Et	$Cu(OTf)_2$	1:1:1	35	(*S*)
6	(2*S*)-**2d**	H	*t*-Bu	Me	Me	$Cu(OTf)_2$	1:1:1	0	
7	(1S,2*R*)-**2e**	Ph	Me	Me	Me	$Cu(OTf)_2$	1:1:1	0	
8	(2*R*)-**2b**	H	Ph	Me	Me	$Yb(OTf)_3$	1.1:0.9:1	71	(*R*)
9	(2*R*)-**2b**	H	Ph	Me	Me	$Lu(OTf)_3$	1:1:1	60	(*R*)

[a] Determined by ^{1}H NMR of **5.**

Table 3. Reaction of **6** with Butyllithium Catalyzed by (2*R*)-**2b** and $Yb(OTf)_3$

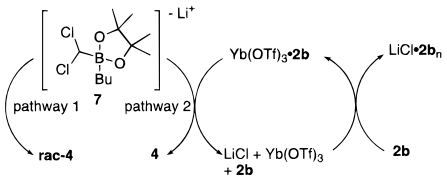
entry	molar ratio **2b**:metal:**6**	% ee[a]	config
1[b]	0.5:0.2:1	55	(*R*)
2	0.5:0.4:1	62	(*R*)
3	1.1:0.9:1	71	(*R*)
4	2.5:1:1	85	(*R*)
5	2:0.14:1	82	(*R*)
6	3.7:0.2:1	80	(*R*)
7	5:0.3:1	88	(*R*)
8	5:1:1	86	(*R*)

[a] Determined by ^{1}H NMR of **5.** [b] 86% chemical yield.[12]

of 5 equiv of the chiral ligand **2b** and 0.3 equiv of $Yb(OTf)_3$ for every 1 equiv of **6**. The amount of $Yb(OTf)_3$ was not very critical for the % ee since the product can be obtained in >80% ee with the use of only 0.14 equiv of the Lewis acid (Table 3, entry 5). Reducing the amount of chiral ligand from 5 to 0.5 equiv resulted in lowering the enantiomeric purity of **6** from 88% ee to 55% ee (Table 3, entries 1 and 7).

The % ee of the homologation product under the optimized conditions is as high as 88%. The reaction is catalytic since the use of 0.5 equiv of chiral ligand **2b** and 0.2 equiv of Lewis acid provided the product in 55% ee and 86% chemical yield (Table 3, entry 1). However, for the highest enantioselectivity (88% ee), excess **2b** was needed. The mechanism in Scheme 1 has been proposed to explain the need for excess ligand in this reaction. Treatment of (dichloromethyl)boronate **6** with butyllithium yielded the "borate" complex **7**, in which the *n*-butyl group migrates from boron to the neighboring carbon to give **4**. The rearrangement would proceed with or without Lewis acid (Scheme 1, pathway 1 or 2). A racemic mixture of chloride *rac*-**4** would be obtained by pathway 1. However, when the migration is catalyzed by the chiral Lewis acid $Yb(OTf)_3$·(**2b**), an enantiomerically enriched product (**4**) is obtained (pathway 2). During the catalytic cycle lithium chloride is produced as the undesired byproduct of the reaction. We postulated that LiCl competes with $Yb(OTf)_3$ for the chiral ligand **2b**. Catalysis by uncomplexed $Yb(OTf)_3$ would also result in the formation of a racemic product. Consequently, it is important to have sufficient chiral ligand available for complexation with $Yb(OTf)_3$ as well as with the byproduct LiCl.[13]

Scheme 1



In conclusion, we have developed a chiral Lewis acid catalyzed method for the 1,2-migration of (dichloromethyl)-borate complexes to provide synthetically useful (α-chloroalkyl)-boronates. These catalysts are capable of differentiating two enantiotopic chloride groups on an sp^3 carbon center. The highest enantioselectivity (88% ee) was observed with the chiral Lewis acid derived from bisoxazoline **2b** and $Yb(OTf)_3$.

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(13) We were unsuccessful in designing experiments that will allow scavenging of the byproduct LiCl without interfering with the chiral catalysis process. We believe that this reaction could be made even more catalytically efficient without an effect on the enantioselective process if one finds a way to remove LiCl as it is formed.