Chiral Lewis Acids

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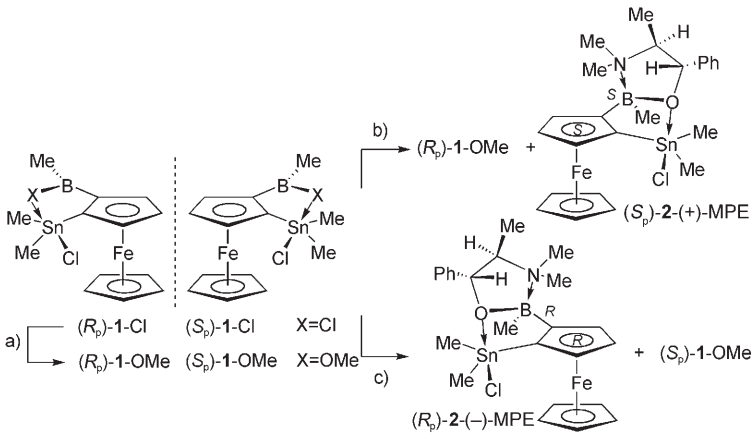
Allylation of Ketones with a Ferrocene-Based Planar Chiral Lewis Acid**

*Ramez Boshra, Ami Doshi, and Frieder Jäkle**

Owing to its rigid three-dimensional framework, ferrocene provides an excellent environment for chiral synthesis. However, most of the planar chiral ferrocene derivatives reported to date relate to the Lewis basic phosphine and amine ligands, which have found widespread use as nucleophilic catalysts[1] and as ligands in transition-metal-catalyzed chiral synthesis.[2] Surprisingly, the use of the charge-reverse complementary Lewis acids,[3] the planar chiral ferrocenylboranes, in asymmetric synthesis has not been demonstrated, although chiral organoboranes are well known to serve as highly versatile reagents and catalysts.[4] In fact, the only prior example of a planar chiral organoborane in stereoselective synthesis is the use of (η^5-1,2-azaborolyl)iron complexes in stereoselective aldol reactions and imine additions by Fu and co-workers.[5]

We have demonstrated that the heteronuclear bidentate Lewis acid 1,2-Fc(BMeCl)($SnMe_2Cl$) (**1**-Cl, Fc = ferrocenediyl) is readily available through highly regioselective *ortho* borylation of 1,1′-bis-(trimethylstannyl)ferrocene and subsequent thermal rearrangement.[6] Unusual binding phenomena are observed for **1**-Cl, including the diastereoselective coordination of pyridine from the *exo* side of ferrocene, which is aided by a bridging chlorine substituent between the neighboring boron and tin centers.[7] However, since **1**-Cl is obtained in racemic form, it has not been applied to stereoselective synthesis. We report herein a facile route for the chiral resolution of **1**-Cl and describe the application of the resulting enantiomerically pure planar chiral bidentate Lewis acids in the stereoselective allylation of ketones.

A convenient approach for the chiral resolution of organoboranes relies on the selective chelation of methoxy boranes with optically active amino alcohols.[8,9] We converted **1**-Cl to the methoxy derivative 1,2-Fc(BMe(OMe))-($SnMe_2Cl$) (**1**-OMe) and treated the latter with 0.5 equivalents of (1*R*,2*R*)-(−)-*N*-methylpseudoephedrine ((−)-MPE) or (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine ((+)-MPE, Scheme 1).[10,11] The crude product was extracted with hexanes, and the chelate complexes (R_p)-**2**-(−)-MPE and (S_p)-**2**-(+)-MPE were isolated from the corresponding solid fractions; the characteristics of the (S_p)-**2**-(+)-MPE enantiomer are described below, and similar considerations apply to the R_p isomer.



Scheme 1. a) Me_3SiOMe, CH_2Cl_2, 40 °C, 48 h; b) (+)-*N*-methylpseudoephedrine, toluene, RT, 2 h; c) (−)-*N*-methylpseudoephedrine, toluene, RT, 2 h.

Only one set of signals was observed in the ^1H, ^{11}B, and ^{119}Sn NMR spectra of (S_p)-**2**-(+)-MPE, confirming the selective conversion of only one of the enantiomers of **1**-OMe to form a single diastereomer of the chelate complex. To determine the stereochemical configuration at boron, we acquired 2D-NOESY ^1H NMR spectroscopy data. Strong cross-peaks between the BMe signal at $\delta = 0.48$ ppm and those of the unsubstituted Cp ring at $\delta = 4.23$ ppm and the Cp proton adjacent to the boryl group (Cp-H3) demonstrate that the methyl group points downward in the direction of the iron atom (Figure 1). One of the NMe signals at $\delta = 2.44$ ppm also shows a strong cross-peak with Cp-H3 but no cross-peaks with the unsubstituted Cp ring, confirming its position above the ferrocene moiety and pointing away from the Sn substituent.

[*] R. Boshra, A. Doshi, Prof. F. Jäkle
Department of Chemistry
Rutgers University Newark
73 Warren Street, Newark, NJ 07102 (USA)
Fax: (+1) 973-353-1264
E-mail: fjaekle@rutgers.edu
Homepage: http://www.andromeda.rutgers.edu/~fjaekle/

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

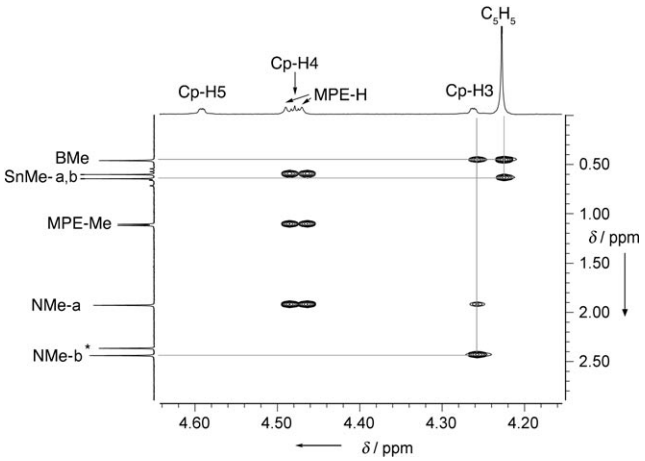


Figure 1. Methyl/Cp region of the NOESY spectrum of (S_p)-**2**-(+)-MPE ($CDCl_3$, 25 °C). Cocrystallized toluene is indicated with an asterisk.

Thus, the remaining boron substituent, the oxygen atom, must be pointing toward Sn, as also suggested by the upfield shift of the resonance in the ^{119}Sn NMR spectrum ($\delta = 22.4$ ppm vs. $\delta = 69.0$ ppm for **1**-OMe). We conclude that the S_B isomer is preferentially formed in the binding of (+)-MPE to (S_p)-**1**-OMe.

X-ray quality crystals of (S_p)-**2**-(+)-MPE were obtained from a concentrated toluene solution at −38 °C.[12] Two independent molecules are found, which are very similar; only one of them is further discussed and displayed in Figure 2. The structure confirms the stereochemical assignment to the S_p,S_B isomer as predicted from the NOESY data. The five-membered B–N heterocycle occupies the less crowded space above the plane of the substituted Cp ring and is fused to another five-membered heterocycle that is formed as a result of donation from the oxygen atom to the Lewis acidic tin atom. The short Sn1···O1 contact of 2.467(3) Å leads to a distorted trigonal bipyramidal environment at tin and is consistent with the upfield shift of the signal in the ^{119}Sn NMR spectrum in solution. The B–N bond length of 1.676(6) Å and the tetrahedral character of 71.7% for boron are similar to literature data for related chelate complexes.[13]

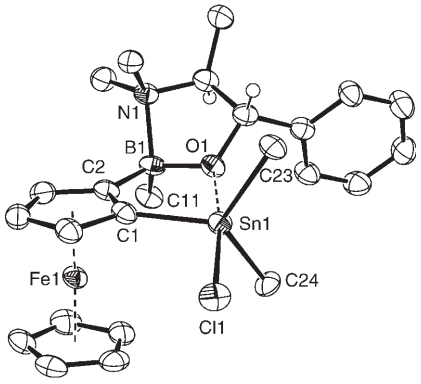
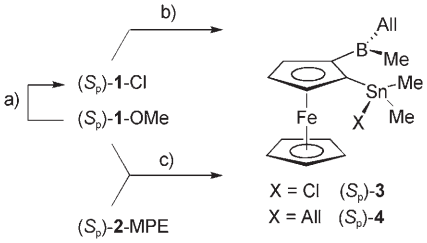


Figure 2. Molecular structure of one of the independent molecules of (S_p)-**2**-(+)-MPE (thermal ellipsoids are shown at 50% probability). A cocrystallized toluene molecule is omitted, and only hydrogen atoms attached to stereogenic carbon atoms are shown. Selected interatomic distances [Å] and angles [°]: Sn1–Cl1 2.4903(12), Sn1–C1 2.104(5), Sn1–C23 2.143(5), Sn1–C24 2.123(5), Sn1···O1 2.467(3), B1–C2 1.608(8), B1–C11 1.615(7), B1–O1 1.511(7), B1–N1 1.676(6); O1···Sn1-Cl1 172.05(9).

The chiral methoxy derivatives (S_p)-**1**-OMe and (R_p)-**1**-OMe were isolated from the hexanes extracts of the reactions of racemic **1**-OMe with 0.5 equivalents (−)-MPE and (+)-MPE, respectively. They were readily converted back to the corresponding chlorine-substituted, but now enantiomerically pure, bidentate Lewis acids (S_p)-**1**-Cl and (R_p)-**1**-Cl by treatment with $PhBCl_2$ in hexanes (Scheme 2). The optical



Scheme 2. a) $PhBCl_2$, hexanes, RT, 30 min; b) for conversion of (S_p)-**1**-Cl into (S_p)-**3**: Me_3SnAll, CH_2Cl_2, RT, 24 h; c) for conversion of (S_p)-**1**-OMe or (S_p)-**2**-(−)-MPE into (S_p)-**4**: AllMgBr (1.95 equiv), Et_2O, RT, 2 h. All = allyl.

purity of the Lewis acids was assessed by complexation with the chiral donor (4*S*,5*S*)-(−)-4,5-dihydro-4-methoxymethyl-2-methyl-5-phenyl-oxazole. The ^{119}Sn NMR spectra show individual, well-resolved signals at 58.9 ppm for (S_p)-**1**-Cl and at $\delta = 56.5$ ppm for (R_p)-**1**-Cl. On the basis of ^{119}Sn and ^{1}H NMR spectroscopic analysis, the optical purity of each enantiomer was estimated to be greater than 97% (see the Supporting Information).

To examine the novel planar chiral bidentate Lewis acids in asymmetric synthesis, we chose the boron-induced asymmetric allylation of aldehydes and ketones as a model reaction.[9,14] The boron-allylated compounds (R_p)-**3** and (S_p)-**3** are obtained selectively from (R_p)-**1**-Cl and (S_p)-**1**-Cl, respectively, by metathesis with Me_3SnAll (Scheme 2, All = allyl). Alternatively, the bis-allyl compounds (R_p)-**4** and (S_p)-**4** can be generated by reaction of the methoxy derivatives (R_p)-**1**-OMe/(S_p)-**1**-OMe or the ephedrine complexes (R_p)-**2**-(−)-MPE/(S_p)-**2**-(+)-MPE with 1.95 equivalents AllMgBr, as illustrated in Scheme 2 for the S_p enantiomer.[15]

The allylborane reagents were isolated as oily materials and used without further purification in the allylation of the chosen aldehyde or ketone in CH_2Cl_2. Enantioselectivities were similar at −78 °C and RT; the data in Table 1 are reported for RT reactions. The planar chiral allylboranes did not give any significant asymmetric induction in the allylation of typical aldehydes (e.g. 8% *ee* with benzaldehyde). However, when applied to ketones, the reaction resulted in chiral homoallylic alcohols in up to 80% *ee* in less than 30 minutes (Table 1). This result contrasts most other boron-based allylating agents, for which asymmetric allylation of ketones is generally more difficult to achieve than with aldehydes.[16]

Table 1: Allylboration of ketones R^1R^2CO.

Entry	R^1	R^2	Reagent	Yield [%][a]	$S:R$[b,c]
1	pentyl	Me	(R_p)-**3**	80	70:30
2	Ph	Me	(S_p)-**3**	96	20:80[d]
3	Ph	Me	(R_p)-**4**	86	90:10[e]
4	Ph	pentyl	(R_p)-**4**	97	90:10[e]

[a] Yields of corresponding homoallylic alcohol determined by GC. [b] Determined by chiral GC analysis. [c] Absolute configuration determined by measurement of the optical rotation of the product with R^1 = Ph and R^2 = Me; other compounds were assigned based on their relative order in the GC trace. [d] Duplicate run with (R_p)-**3**. [e] Duplicate run with (S_p)-**4**.

Finally, the enantioselectivity can be tuned by suitable substitution at tin, as evident from an increase of the *ee* value for the allylation of acetophenone from 60% for (R_p)/(S_p)-**3** to 80% for (R_p)/(S_p)-**4** (entries 2 and 3 in Table 1).[17] The following considerations provide a possible rational for the observed enantioselectivity enhancement. Compound (R_p)/(S_p)-**3**, with a chlorine substituent attached to tin, can easily extend its coordination sphere from tetrahedral to trigonal bipyramidal through coordination of a nucleophile *trans* to chlorine. This feature is found, for example, in the structure of (S_p)-**2**-(+)-MPE (Figure 2), where the ephedrine oxygen atom adopts a bridging position between boron and tin.[18] Hence, the intermediate complex formed upon allylation of acetophenone likely features the carbonyl oxygen atom in a bridging position between the Sn and B centers with a favorable Sn···O interaction similar to that in the structure of (S_p)-**2**-(+)-MPE.[19] In such a trigonal-bipyramidal Sn complex, the Me groups are placed in equatorial positions, and thus the space between the tin and boron centers is opened up. In contrast, with an allyl group in place of the chlorine substituent on tin, a tetraorganotin species is present, for which hyper-coordination to form a trigonal-bipyramidal tin environment is unfavorable. Hence, the Sn-Me groups more closely approach the adjacent boryl group, which should effectively reduce the space available in the chiral pocket and lead to increased stereoselectivity.

In conclusion, the novel planar chiral bidentate Lewis acids (S_p)-**1**-Cl and (R_p)-**1**-Cl are readily accessible by chiral resolution with *N*-methylpseudoephedrine and serve as versatile precursors to other chiral organoboranes. The corresponding allylboranes were successfully employed in the allylation reaction of ketones, which occurs rapidly and especially selectively with ketones that are typically difficult to convert selectively. This is the first successful application of organoborane-functionalized metallocenes as chiral reagents. The results also indicate the potential of this class of compounds as chiral Lewis acid catalysts in stereoselective synthesis.

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[10] Initial attempts to resolve **1**-OMe by employing 0.5 equivalents (1*S*,2*S*)-(+)-pseudoephedrine resulted in a 1:1 mixture of the diastereomeric complexes together with unreacted racemic **1**-OMe.
[11] For large-scale preparations, we used a slight excess of (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine (0.55 equiv) to ensure the optical purity of (R_p)-**1**-OMe, which was isolated in 75% yield. The residual material can then be converted to (S_p)-**2**-(+)-MPE (93% yield of isolated product) by simple addition of a slight excess of racemic **1**-OMe.
[12] X-ray structure analysis for (S_p)-**2**-(+)-MPE: $C_{31}H_{41}BClFeNOSn$, $M_r = 664.45$, monoclinic, space group $P2_1$, $a = 10.5287(2)$, $b = 13.8844(2)$, $c = 21.2409(3)$ Å, $\beta = 102.9250(10)°$, $V = 3026.42(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.458$ g cm^{-3}, λ-($Cu_{K\alpha}$) = 1.54178 Å, $T = 100(2)$ K, crystal dimensions $0.40 \times 0.38 \times 0.37$ mm^3, $\mu(Cu_{K\alpha}) = 11.389$ mm^{-1}, range from 2.13 to 67.98, 23 803 measured reflections, 9844 independent reflections ($R_{int} = 0.0468$), $R1$ [$I > 2(I)$] = 0.0444, $wR2$ [$I > 2(I)$] = 0.1058, GOF = 1.043, 682 parameters, final difference map within 1.875 and −0.734 e Å^{-3}. The structure was solved using direct methods, completed by subsequent difference Fourier syntheses, and refined by full-matrix least-squares procedures on $F2$. Numerical absorption corrections were applied (G. M. Sheldrick SHELXTL (6.14), Bruker ACS Inc.: Madison, WI, 2004). Non-hydrogen atoms were refined with anisotropic displacement coefficients, and hydrogen atoms were treated as idealized contributions. CCDC-66331 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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[15] In these reactions a small amount of another product is formed, which is tentatively assigned to a cyclic species that results from intramolecular 1,2-allylboration of the allyl moiety on tin. For related literature reports, see: a) J. M. Blackwell, W. E. Piers, R. McDonald, *J. Am. Chem. Soc.* **2002**, *124*, 1295; b) Y. N. Bubnov,

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[17] A reviewer suggested that in the case of the diallylated species $(R_p)/(S_p)$-**4**, allyl transfer may occur from Sn rather than B. NMR spectroscopic analysis of the intermediate obtained upon reaction of $(R_p)/(S_p)$-**4** with acetophenone shows an ^{11}B NMR spectroscopy signal shifted to 48.9 ppm ($(R_p)/(S_p)$-**4**, $\delta = 71$ ppm) and a ^{119}Sn NMR spectroscopy signal at $\delta = -14.4$ ppm, which is similar to that of $(R_p)/(S_p)$-**4** ($\delta = -14.3$ ppm). Moreover, quenching of the reaction mixture with MeOH gave NMR spectra consistent with formation of 1,2-Fc(BMe(OMe))-($SnMe_2$All).

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[19] We were unable to detect the complex of $(R_p)/(S_p)$-**3** and acetophenone directly by NMR spectroscopy even at −80 °C, where the reaction with acetophenone proceeds relatively slowly. At this temperature only the unshifted signals for the starting material and those of the allylated product were observed. However, when **1**-Cl (0.02 M solution in CD_2Cl_2) was treated with a fivefold excess of anisic aldehyde at −80 °C, a clear shift of both the ^{11}B ($\delta = 15$ ppm) and ^{119}Sn ($\delta = 71$ ppm) NMR spectroscopy signals relative to free **1**-Cl (^{11}B NMR $\delta = 61.5$ ppm; ^{119}Sn NMR $\delta = 95$ ppm) was observed.

