Chiral aminoborane as a chiral proton source for asymmetric protonation of lithium enolates derived from 2-arylcycloalkanones

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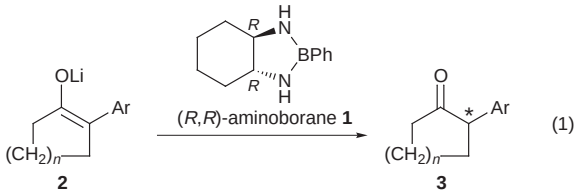
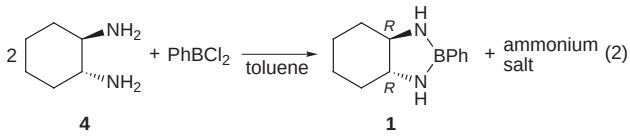
Reaction of lithium enolates of 2-arylcycloalkanones 2 with (*R*,*R*)-aminoborane 1, prepared from (1*R*,2*R*)-1,2-diaminocyclohexane 4 and $PhBCl_2$, gives the corresponding optically active ketones 3 with up to 93% ee; this is the first example of enantioselective protonation using a metal-containing chiral proton source.

Asymmetric protonation of prochiral metal enolates has proved to be an efficient method for the synthesis of chiral carbonyl compounds.[1] The success of this process depends on the structure and acidity of the chiral proton source. Several chiral acids have been developed so far, and have been applied to enantioselective protonations.[2–4] However, as far as we know, there are no reports on a proton source containing metal atoms. We describe here a new enantioselective protonation of lithium enolates **2** with chiral aminoborane **1** [eqn. (1)].

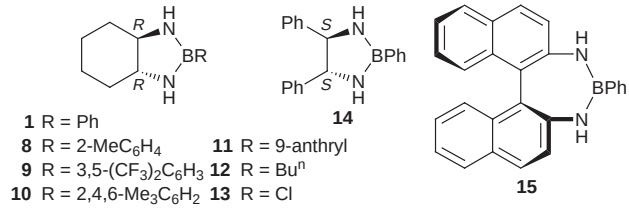


Heteroatom-substituted chiral boron compounds such as oxazaborolidines and acyloxyboranes are well-known as chiral Lewis acid catalysts for various asymmetric reactions.[5] High levels of asymmetric induction are obtained in Diels–Alder reactions or Mukaiyama aldol reactions, and the formation of a stable complex of a boron catalyst with a carbonyl compound is regarded as the key to success. We considered that if a chiral aminoborane could form a rigid cyclic transition state structure with a lithium enolate, and if the amide proton is acidic enough, a highly enantioselective protonation might occur.

Chiral aminoborane **1** was synthesized from (1*R*,2*R*)-1,2-diaminocyclohexane **4** (2 equiv.) and $PhBCl_2$ (1 equiv.) in toluene [eqn. (2)].[6] The resulting ammonium salt was filtered



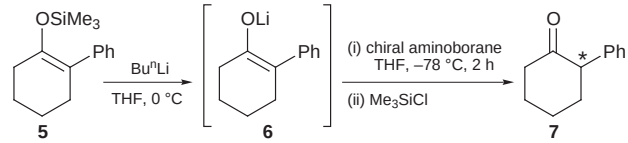
off. Treatment of lithium enolate **6**, generated from silyl enol ether **5** and Bu^nLi/hexane (1.1 equiv.) in THF at 0 °C,[7] with a solution of (*R*,*R*)-aminoborane **1** (1.5 equiv.) in toluene–THF (1:1) at −78 °C for 2 h followed by quenching with Me_3SiCl (to remove unreacted **6**) at −78 °C gave (*S*)-enriched 2-phenylcyclohexanone **7** in 94% yield and 84% ee (Table 1, entry 1).‡ Using various chiral aminoboranes, we studied the enantioselectivity of this protonation; yields and enantiomeric excesses of the product **7** obtained by reactions with other chiral aminoboranes **8**–**15** in THF at −78 °C are shown in Table 1. Substitution of the phenyl group of **1** by a chlorine atom resulted in a lower



enantioselectivity, while the chemical yield increased (entry 7). As a consequence, (*R*,*R*)-aminoborane **1** was the most effective chiral proton source for the protonation of **6**.

This asymmetric protonation was applied to a variety of lithium enolates of ketones **17**, and the results with (*R*,*R*)-aminoborane **1** are summarized in Table 2. These reactions have the following characteristics: (i) all of the reactions proceeded to give a satisfactory yield at −78 °C for 2 h, except for the lithium enolate of 2-methylindanone **22**, which gave a low yield due to concomitant side reactions (entry 5); (ii) moderate to high asymmetric induction occurred in the protonation of lithium enolates **6**, **19**–**21** and **29**, which possess an aryl group at the C-2 position (entries 1–4 and 12). The highest enantioselectivity (93% ee) was obtained with the enolate of 2-(2-naphthyl)cyclohexanone **21** (entry 4). The enolates **22**, **23**, **27** and **28** derived from 2-methylindanone, 2-methyltetralone and their derivatives also gave good optical purities (entries 5, 6, 10, and 11). However, the use of simple substrates bearing no aromatic

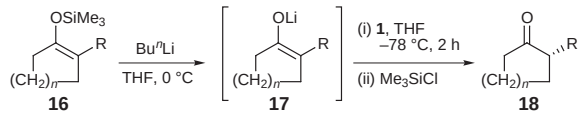
Table 1 Protonation of the lithium enolate **6** with chiral aminoboranes **1** and **8**–**15**[a]

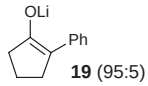
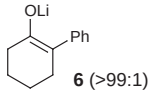
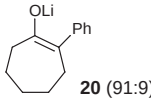
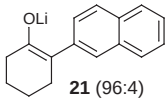
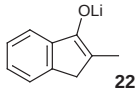
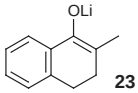
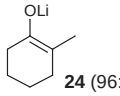
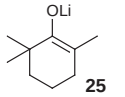
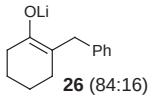
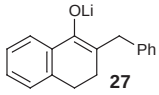
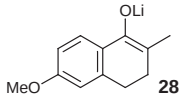
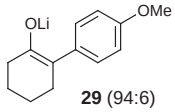


Entry	Chiral aminoborane	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	**1**	94	84	*S*
2	**8**	83	60	*S*
3	**9**	65	47	*S*
4	**10**	17	5	*S*
5	**11**	14	3	*R*
6	**12**	74	20	*S*
7	**13**	> 99	44	*S*
8	**14**	20	32	*R*
9	**15**	19	6	*S*

[a] The lithium enolate **6** was generated from the corresponding silyl enol ether **5** (1 equiv.) and a solution of Bu^nLi/hexane (1.1 equiv.) in THF at 0 °C for 2 h. The following protonation was carried out using a chiral aminoborane (1.5 equiv.) in THF at −78 °C for 2 h. The reaction was quenched by TMSCl at −78 °C to exclude the unreacted enolate **6**. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). [d] The absolute configuration was determined by comparison of the $[\alpha]_D$ value with reported data [ref. 3(*c*)].

Table 2 Enantioselective protonation of various enolates with (*R*,*R*)-aminoborane **1**[a]



Entry	Lithium enolate[b]	Yield (%)[c]	Ee (%)[d]	Configuration[e]
1	 **19** (95:5)	70	34[f] (36)[f,g]	—
2	 **6** (>99:1)	94	84	*S*[h]
3	 **20** (91:9)	69	70[f] (77)[f,g]	—
4	 **21** (96:4)	84	89 (93)[g]	—
5	 **22**	26	60	—
6	 **23**	80	70	*S*[i]
7	 **24** (96:4)	69	1[j]	*S*[i]
8	 **25**	>99	16[k]	*S*[l]
9	 **26** (84:16)	93	8[m] (10)[g,m]	*R*[i]
10	 **27**	64	47	—
11	 **28**	88	78	—
12	 **29** (94:6)	92	81 (86)[g]	—

[a] All conditions are the same as in Table 1. [b] Parentheses indicate the regioisomeric ratio of the starting silyl enol ethers **16**. [c] Isolated yield. [d] Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). [e] The absolute configuration was determined by comparison of the $[\alpha]_D$ value with reported data. [f] Determined by HPLC analysis (Chiralpak AS, Daicel Chemical Industries, Ltd.). [g] Corrected value based on the regioisomeric ratio of the starting silyl enol ether **16**. [h] Ref. 3(*c*). [i] Ref. 8. [j] Determined by GC analysis with chiral column (ChiraldexTM B-TA, astec). [k] Determined by GC analysis with chiral column (ChiraldexTM G-TA, astec). [l] Ref. 4(*b*). [m] Determined by HPLC analysis (Chiralcel OJ, Daicel Chemical Industries, Ltd.).

groups gave unsatisfactory results (entries 7 and 8); (iii) a lithium enolate of 2-phenylcyclohexanone is superior to that of 2-phenylcyclopentanone or 2-phenylcycloheptanone with respect to enantioselectivity (compare entries 1–3); and (iv) introduction of an electron-donating group to the aromatic ring improved the enantiomeric ratios to some extent (entries 11 and 12).

Notes and References

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‡ Procedure for protonation of lithium enolate **6** with (*R*,*R*)-aminoborane **1**: To a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (172 mg, 1.5 mmol) in dry toluene (4 ml) was added $PhBCl_2$ (97 µl, 0.75 mmol) at −78 °C. The mixture was warmed to room temperature and again stirred for 2.5 h at this temperature. The resulting ammonium salt was filtered off under an argon atmosphere and washed with dry THF (2 ml). To the filtrate was added at −78 °C a solution of lithium enolate **6**, prepared from trimethylsilyl enol ether **5** (123 mg, 0.5 mmol) and BunLi (1.67 M hexane solution, 0.33 ml, 0.55 mmol) in dry THF (2.3 ml) at 0 °C, through a stainless steel cannula under an argon stream. After being stirred for 2 h at −78 °C, TMSCl (65 µl, 0.5 mmol) was added, and stirring continued for another 30 min at this temperature. The reaction mixture was treated with saturated aqueous NH_4Cl, extracted with Et_2O , dried (Na_2SO_4), and finally purified by column chromatography on silica gel to give (*S*)-enriched 2-phenylcyclohexanone [(*S*)-**7**, 94% yield] with 84% ee. The enantiomeric ratio was determined by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). The absolute configuration was determined by comparison of its optical rotation with published data; (*S*)-isomer (87% ee): $[\alpha]_D^{29}$ −88.9 (*c* 1.0, $CHCl_3$) [ref. 3(*c*)]. Observed value of (*S*)-isomer (84% ee): $[\alpha]_D^{28}$ −94.1 (*c* 1.1, $CHCl_3$).

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