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Novel enantiomer-switching catalysts for asymmetric reductions and Michael reactions

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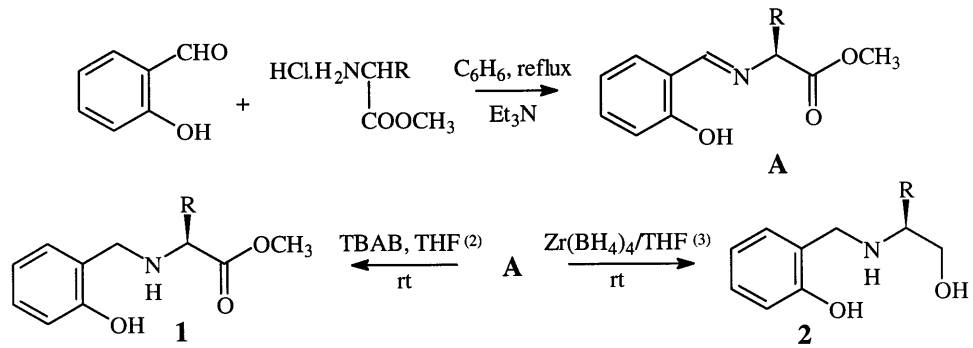
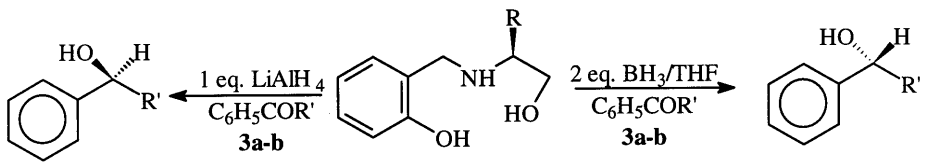
Abstract—The newly developed chiral ligands **1** and **2** show opposite enantioselectivity in prochiral ketone reduction and Michael addition reactions resulting in the production of both enantiomers of the products in good chemical and enantiomeric yield.

Asymmetric Michael reactions are amongst the most important methods for creating asymmetric centres.[1] Earlier we synthesised the new chiral reagents **1** and **2** starting from salicylaldehyde and L-valine methyl ester (Scheme 1).[2,3] We now report the unique behaviour of 'enantiomeric switching' in the asymmetric reduction of



R = isopropyl

Scheme 1.



3a, **4a**, **5a** R' = CH_3, **3b**, **4b**, **5b** R' = CH_2Cl

Scheme 2.

Keywords: Michael reaction; methyl 2-(*N*-2′-hydroxybenzyl)amino-3-methylbutanoate; 2-[*N*-2′-hydroxybenzyl]amino-3-methyl-1-butanol; Al-complex; chiral switch.

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prochiral ketones and Michael additions using ligands **1** and **2**. Thus, the bicyclic oxazaborolidines of **2** derived using BH_3–THF gave the *R*-isomer on reduction of ketone **3** in 90% *ee*, while the Al-complex generated using $LiAlH_4$ and **2** gave the *S*-isomer in 60% *ee* (Scheme 2, Table 1).

While searching for further applications of these reagents, we found that Shibasaki and co-workers had widely studied asymmetric Michael addition using heterobimetallic catalysts involving the combination of monovalent metals like Na or Li with trivalent metals like La, Gd or Al,[4] achieving excellent enantioselectivity with BINOL–Al–Li catalysts. This prompted us to form the aluminium complexes of **1** and **2** with $LiAlH_4$ (Scheme 3) and to study their effect on asymmetric induction in Michael reactions.

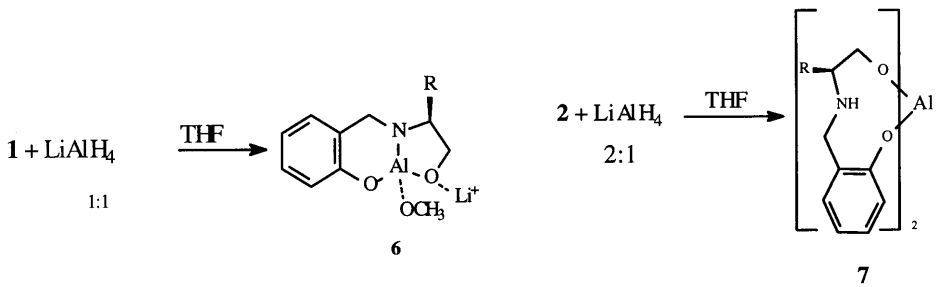
Ligand **1** when used in a stoichiometric amount reacted instantaneously with $LiAlH_4$ liberating two equivalents of hydrogen. However, when ligand **2** was used in a ratio of 2:1, 4 equivalents of H_2 were liberated instantaneously without participation from the –NH group.

The Michael reaction of cyclohexenone **8** ($n=2$) and diethyl malonate was carried out with 20 mol% of the Al-complex of **2**. A typical work-up procedure gave the Michael adduct, *ee* 60% with the *R*-isomer predominating, which is similar to the results obtained with catalysts having C_2-symmetry.[5] A similar Michael reaction was carried out with other dialkyl malonates and the results are presented in Table 2, entries 1–3. Curiously, the same reaction carried out with the Al-complex of **1** resulted in the *S*-isomer in 80% *ee*. In order to study the efficiency of this catalyst various malonates were reacted with cyclic enones **8** ($n=1$ or 2) (Scheme 4), and the results are presented in Table 2, entries 4–9.

Indeed, the results indicate a high chemical yield and good enantioselectivity for the *S*-isomer in short reaction times. The opposite enantioselectivity achieved with catalysts **1** and **2** may be attributed to the differ-

Table 1. Asymmetric reduction of ketones with boron and aluminium complexes of **2**

Substrate	Reagent	Product	Yield (%)	*ee*% (abs. confg.)	$[\alpha]_D$ 23°C $c=5$, $CHCl_3$
3a	**2**/1 equiv. $LiAlH_4$	**4a**	90	60 (*S*)	−25
3b	″	**4b**	90	55 (*R*)	−26
3a	**2**/2 equiv. BH_3/THF	**5a**	95	90 (*R*)	+38
3b	″	**5b**	90	85 (*S*)	+36

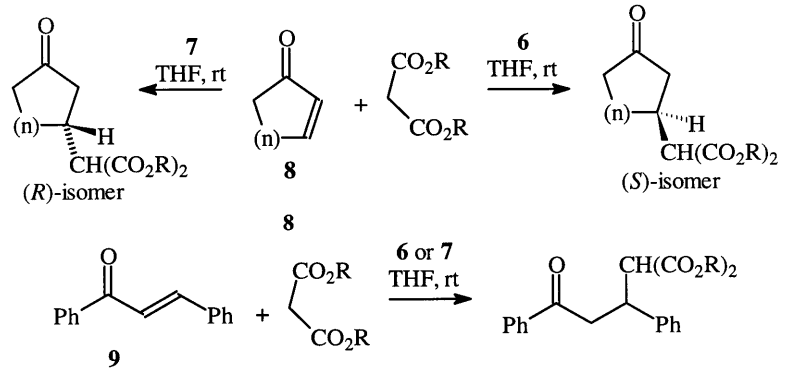


Scheme 3.

Table 2. Asymmetric Michael addition of malonates to cyclic enones with new heterobimetallic catalysts

S.No	Enone **8**/**9**	Malonate (*R*)	Catalyst	Time (h)	Yield (%)[a]	*ee* (%)[a]	Abs. confg.	$[\alpha]_D$ ($c=5$ in $CHCl_3$)
1	**8**, $n=2$	Ethyl	**7**	4	79	60	*R*	+2
2	**8**, $n=2$	Isopropyl	**7**	6	75	37	*R*	+2
3	**8**, $n=2$	Benzyl	**7**	5	80	55	*R*	+1
4	**8**, $n=1$	Ethyl	**6**	4	80 (84)	73 (91)	*S*	−24
5	**8**, $n=1$	Isopropyl	**6**	6	74	–	*S*	−3
6	**8**, $n=1$	Benzyl	**6**	5	85 (93)	82 (91)	*S*	−27
7	**8**, $n=2$	Ethyl	**6**	4	82 (87)	80 (95)	*S*	−3
8	**8**, $n=2$	Isopropyl	**6**	5	70 (72)	43 (49)[b]	*S*	−2
9	**8**, $n=2$	Benzyl	**6**	4	86 (88)	84 (99)	*S*	−1
10	**9**	Ethyl	**6** or **7**	6	70	–	–	–
11	**9**	Isopropyl	**6** or **7**	7	65	–	–	–
12	**9**	Benzyl	**6** or **7**	5	75	–	–	–

[a] Values in parentheses indicate the reported yield and *ee* with (*R*)-BINOL–Al–Li catalyst (Ref. 4c).
[b] Literature reported *ee* using L-proline rubidium salt (see Ref. 6).



Scheme 4.

ences in the nature of the complexes involved in the reactions.

However, when the reaction was extended to acyclic α,β-unsaturated ketones (*trans*-chalcone **9**), the Michael addition was smoother but the expected enantioselectivity was not achieved (entries 10–12). This may be due to the loss of rigidity in the acyclic system. Thus, the newly developed heterobimetallic catalysts can behave as a chiral switch producing either *R* or *S* isomers.

General experimental procedure for reduction

*Reduction of **3a** using the Al complex of **2***: To **2** (1.45 g, 5 mmol), $LiAlH_4$ (190 mg, 5 mmol) was added and stirred. Acetophenone (0.6 mL, 5 mmol) was added and the mixture stirred for 1 h at 0°C. The reaction was then quenched with dil. HCl. The reaction mixture was extracted with chloroform and washed with water. The chloroform layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Purification using column chromatography with hexane:ethyl acetate (98:2) as eluant gave (*S*)-(−)-*sec*-phenethylalcohol (0.54 g, 90%) with an ee of 60%.

*Reduction of **3a** using the boron complex of **2***: To a freshly prepared solution of **2** (5 mmol), 1 M borane–THF solution, (10 mL, 10 mmol) was added and the mixture stirred at room temperature for 30 min. Acetophenone (0.6 mL, 5 mmol) was added and the mixture stirred for 10 min at room temperature, then quenched with methanol. The reaction mixture was worked up and purified as above to give (*R*)-(+)-*sec*-phenethylalcohol (0.56 g, 95%) with an *ee* of 90%.

General experimental procedure for Michael addition reaction

Typically, the chiral ligand **1** (237 mg, 1 mmol) in dry THF was added to a solution of $LiAlH_4$ (38 mg, 1 mmol) in dry THF. The mixture was stirred for 1 h at room temperature, then 2-cyclohexenone (490 mg, 5 mmol) and diethyl malonate (800 mg, 5 mmol) were added. The mixture was stirred for 4 h. The reaction was quenched with 1N HCl and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a syrupy mass which on flash column chromatography gave the product as a colourless oil (1.1 g, 90% yield), $[\alpha]_D$ −2.86 ($c=5$ in $CHCl_3$).

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References

1. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Syntheses*; Pergamon Press: 1992. (b) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis*, *Tetrahedron Organic Chemistry Series*; Pergamon Press: Oxford, 1996; Vol. 14, p. 161.
2. Narasimhan, S.; Swarnalakshmi, S.; Balakumar, R.; Velmathi, S. *Synlett* **1998**, *12*, 1321.
3. Narasimhan, S.; Balakumar, R. *Synth. Commun.* **2000**, *30*, accepted for publication.
4. (a) Shibasaki, M.; Sasai, H.; Arai, T. *J. Am. Chem. Soc.* **1994**, *116*, 1571. (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (c) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104. (d) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236–1256.
5. Manickam, G.; Sundararajan, G. *Tetrahedron* **1999**, *55*, 2721.
6. Yamaguchi, M. et al. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176.