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Novel heterobimetallic catalysts for asymmetric Michael reactions

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Abstract—The newly developed chiral catalysts **1** and **2** show opposite enantioselectivity in Michael addition reactions of cyclic enones and malonates resulting in the production of both enantiomers of products in good chemical yield and enantiomeric excess. ^{27}Al NMR studies showed the formation of different types of complexes for catalysts **1** and **2** and the enantioselectivity was found to be dependent on the nature of the aluminium complex formed. Scope of the reaction was extended to other Michael donors such as nitro alkanes and thiols.

1. Introduction

Enantioselective 1,4-addition of active methylene compounds to α,β-unsaturated compounds is one of the fundamental reactions in organic synthesis for the formation of optically active compounds.[1a,b] Hence, the design of efficient chiral promoters for these processes is of current interest. Catalytic asymmetric Michael reactions have been extensively examined with chiral amines,[2a–c] alkaloids,[3a,b] polymer bound alkaloids,[4a–e] chiral crown ethers and bases,[5] optically active Co(II) complexes,[6] natural proteins[7] and amino alcohols[8] acting as catalysts. A breakthrough in catalytic asymmetric Michael addition reaction was achieved with the introduction of heterobimetallic catalysts. In a series of reports Shibasaki et al.[9a–e] elaborated the utility of such heterobimetallic catalysts of BINOL-La (Al)-alkali metals which induced high enantioselectivities.

We have already reported the syntheses of new chiral ligands, which show novel enantiomer—switching properties in asymmetric reductions of prochiral ketones[10] (Scheme 1). We report here our findings on the asymmetric Michael addition reactions promoted by the aluminate of amino ester and amino diol ligands.

The chiral ligands **1a–d** and **2a–d** were easily synthesized from readily available salicylaldehyde and amino acid esters by the previously reported procedure.[11a–c]

2. Results and discussion

Chiral ligands **1** and **2** reacted readily with $LiAlH_4$ in THF with the evolution of H_2 resulting in the formation of heterobimetallic complexes with Al as the central metal ion. Typically, reaction of cyclohexenone with diethyl malonate was studied with the newly developed heterobimetallic complexes under different reaction conditions and the results are presented in Table 1.

In the initial attempts the Michael reaction of **3** and **4** was performed with heterobimetallic catalysts **1a–d** at room temperature (entries 2, 5, 8 and 9). In all cases the (*S*)-enantiomer was obtained in excellent yield with low to satisfactory enantiomeric excess. The highest enantioselectivity was observed for the complex prepared from the ligand **1a** and $LiAlH_4$ in the ratio 1:1. However, the Al complex prepared from **1a** and $LiAlH_4$ in the ratio 2:1 resulted in 55% ee (entry 1). Therefore, other reaction parameters such as catalyst concentration and temperature were also studied to optimize the reaction conditions. The influence of the amount of catalyst on enantiomeric excess of the product was tested (entries 2–7) and it was found that 20 mol% of **1a** was optimum. Also the reaction yields high ee only at room temperature (entries 2 and 10) (Scheme 2).

Interestingly, when the Al complex, prepared from **2** and $LiAlH_4$, was used the (*R*)-isomer was obtained with 60% ee (entry 11) (Scheme 3).

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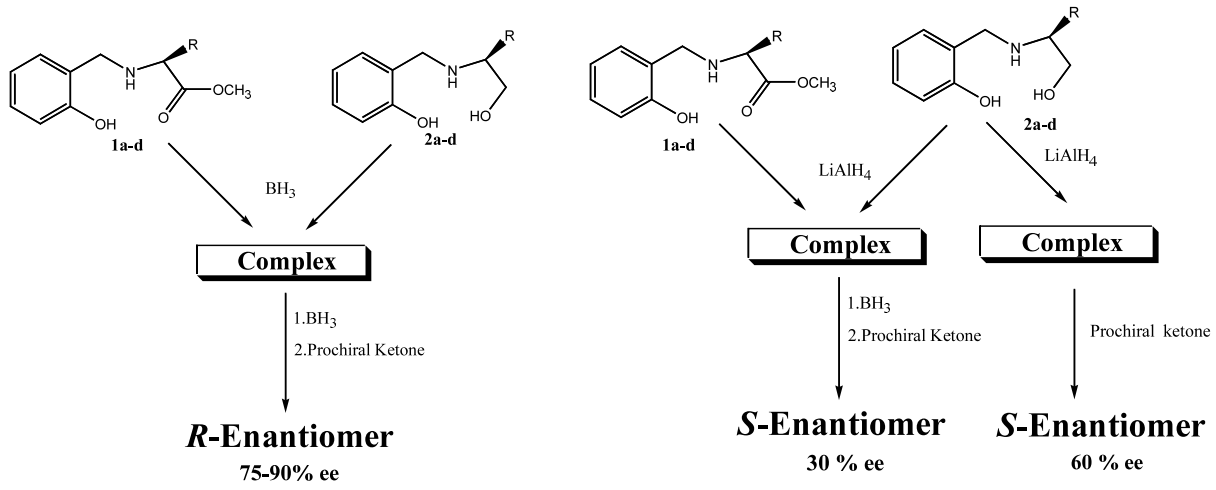


1a R = isopropyl, 1b R= iso butyl, 1c R= sec butyl, 1d R = benzyl

Scheme 1.

Table 1. Enantioselective Michael addition of cyclohexenone and diethylmalonate catalysed by heterobimetallic complexes[a]

S. no	Ligand	L:$LiAlH_4$ ratio	Reactants	Mol%	Temp. (°C)	Time (h)	Yield (%)[b]	ee[c] (%)	Abs. config.[d]
1	**1a**	2:1	**3** and **4**	20	30	4	85	55.5	*S*
2	**1a**	1:1	**3** and **4**	20	30	4	90	95[e]	*S*
3	**1a**	1:1	**3** and **4**	10	30	4	70	65	*S*
4	**1a**	1:1	**3** and **4**	50	30	4	90	81	*S*
5	**1b**	1:1	**3** and **4**	10	30	4	65	13.5	*S*
6	**1b**	1:1	**3** and **4**	20	30	4	75	22.5	*S*
7	**1b**	1:1	**3** and **4**	50	30	4	80	25	*S*
8	**1c**	1:1	**3** and **4**	20	30	4	80	17	*S*
9	**1d**	1:1	**3** and **4**	20	30	4	80	0	–
10	**1a**	1:1	**3** and **4**	20	0	4	70	47	*S*
11	**2a**	2:1	**3** and **4**	20	30	4	79	60	*R*

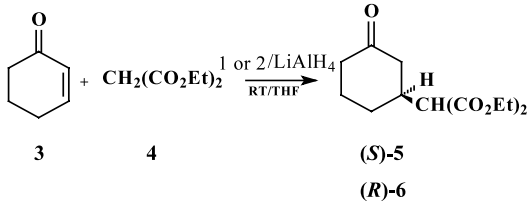
[a] All reactions were performed in THF solvent.
[b] Isolated yield.
[c] Based on specific rotation values available in the literature Ref. 9.
[d] Determined by comparison of the sign of optical rotation values with those in the literature Ref. 9.
[e] Based on HPLC analysis using Chiralcel OD (see Section 4).

The results indicate that chiral switching is occurring with cyclic enones and malonates, with **1a** producing the (*S*)- and **2a** yielding the (*R*)-enantiomer. This prompted us to study if there could be any change in the nature of the Al complex produced under the reaction conditions.

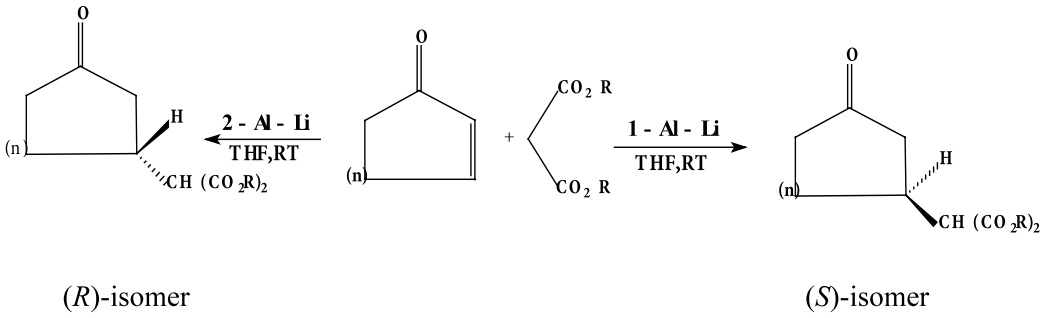
Ligand **1** when used in a stoichiometric amount reacted instantaneously with $LiAlH_4$ liberating 2 equiv. of hydrogen and the balance utilized for the reduction of the ester group presumably resulting in **7**. However, when ligand **2** was used in the ratio of 2:1, 4 equiv. of H_2 was liberated instantaneously without participation from the -NH group producing the conventional complex **8** (Scheme 4).

2.1. ^{27}Al NMR studies on Michael reaction

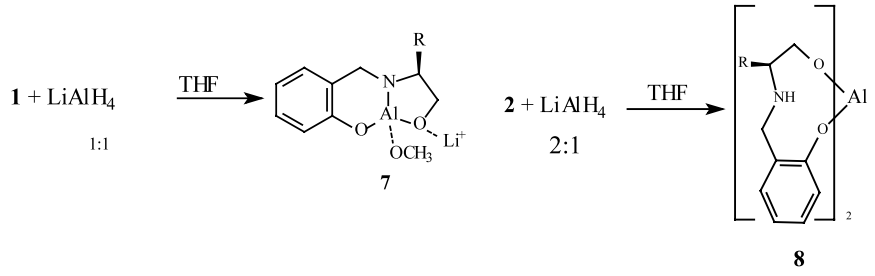
In order to explore the unique behavior of '**enantiomer-switching**' achieved with the two catalysts, **1a** and **2a**, detailed ^{27}Al NMR studies were carried out using $AlCl_3 \cdot 6H_2O$ as external reference (δ 0 ppm). Shibasaki et al.[9d] have already utilised ^{27}Al NMR to study the interaction between enone and aluminium. They have reported one broad signal at δ 75 ppm for the BINOL-Al–Li complex and upon addition of 3 equiv. of cyclohexenone two additional signals were obtained at δ 40 and δ 23 ppm. The latter signal became stronger and was a major peak under the conditions of the Michael reaction. Similar studies were made with ligands **7** and **8** and the chemical shift values are given in Table 2.



Scheme 2.



Scheme 3.



Scheme 4.

Table 2. ^{27}Al NMR values—a comparison with the other reported aluminium complexes

Ligand	Al complex (δ ppm)	Al complex + enone (δ ppm)	Al complex + enone + DEM* (δ ppm)
7	0–5	+23	0–5
8	+36	+18	+36 and +18
BINOL-Al–Li	+75[9d]	+40 and +23[a]	–

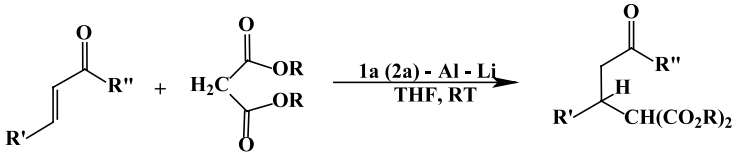
* Diethyl malonate.
[a] With 3 equiv. of enone.

In the case of ligand **8** the ^{27}Al NMR value is similar to BINOL based ligands, indicating the formation of a C_2 symmetric complex, which is expected to produce the (*R*)-enantiomer in asymmetric Michael addition reactions.

However, the value for complex **7** shows an upfield shift indicating considerable shielding of the Al atom. This could be due to the π-stacking interaction between the phenyl ring of the catalyst and the p-system of the enone. Presumably this provides a stereochemically better locking of the reactants resulting in higher ee.

Encouraged by the high enantioselectivity obtained in the Michael addition of malonic esters to cyclic enones the study was extended to Michael addition of malonic esters, nitro alkanes and thiols to cyclic and acyclic α,β-unsaturated enones and enals (Scheme 5). The results obtained are listed in Table 3.

The lower rigidity of acyclic α,β-unsaturated carbonyl compounds accounts for the nucleophilic attack of the enolate from both the faces (*Re* and *Si*) thus resulting in the racemic product. Even though Michael reactions carried out with nitro alkanes gave racemic product, the Michael adducts were formed in moderate yield of 60–75% in a short period of 10 h, when compared to the existing catalysts which require 43–62 h for the completion of the reaction.[12] Similar to nitro alkanes, even thiols gave racemic products when subjected to the Michael reaction. In most cases the Michael adducts were obtained in good yield in less than 2 min. However no enantioselectivity was achieved in these reactions. The lower probability of sulfur coordinating to



Scheme 5.

Table 3. Michael additions of malonic esters, nitro alkanes and thiols to acyclic α,β-unsaturated enones and enals using catalyst **7** or **8***

S. no	Enone	Malonate (R)	Catalyst	Time (h)	Yield (%)
1	R′=R″=Ph	Ethyl	**7** or **8**	6	70
2	R′=R″=Ph	Isopropyl	**7** or **8**	7	65
3	R′=R″=Ph	Benzyl	**7** or **8**	5	75
4	R′=Ph, R″=H	Ethyl	**7** or **8**	7	75
5	R′=Ph, R″=H	Isopropyl	**7** or **8**	8	70
6	R′=Ph, R″=H	Benzyl	**7** or **8**	7	72
7	R′=CH_3, R″=H	Ethyl	**7** or **8**	4	80
8	R′=CH_3, R″=H	Isopropyl	**7** or **8**	5	70
9	R′=CH_3, R″=H	Benzyl	**7** or **8**	3	75
		Nitro alkane			
10	R′=R″=Ph	CH_3NO_2	**7** or **8**	8	75
11	R′=R″=Ph	$CH_3CH_2NO_2$	**7** or **8**	9	70
12	Cyclohexenone	CH_3NO_2	**7** or **8**	9	65
13	Cyclohexenone	$CH_3CH_2NO_2$	**7** or **8**	10	60
		Thiols			
14	R′=R″=Ph	C_6H_5SH	**7** or **8**	2	90
15	R′=R″=Ph	CH_3-C_6H_4SH	**7** or **8**	2	88
16	R′=R″=Ph	CH_3COSH	**7** or **8**	30	95
17	R′=Ph, R″=H	C_6H_5SH	**7** or **8**	5	770
18	R′=Ph, R″=H	CH_3-C_6H_4SH	**7** or **8**	5	65
19	R′=CH_3, R″=H	C_6H_5SH	**7** or **8**	3	80
20	R′=CH_3, R″=H	CH_3-C_6H_4SH	**7** or **8**	3	75
21	Cyclohexenone	C_6H_5SH	7 or 8	1	92
22	Cyclohexenone	CH_3-C_6H_4SH	**7** or **8**	2	90

* All the products were characterized through ^1H and ^{13}C NMR spectroscopy.

lithium (hard and soft acid base principle) allows only weak coordination between them, leaving a very reactive sulfur anion to attack the stacked enone from both the faces, resulting in racemic product. This also accounts for the much less reaction time (30 s–5 min/rt).

3. Conclusion

In conclusion, we have developed new heterobimetallic complexes, which show novel enantiomer switching behavior in the asymmetric Michael addition reactions of cyclic enones with dialkyl malonates resulting in the production of both enantiomers with excellent enantioselectivity. The ligands also promote 1,4-Michael additions of nitro alkanes and thio phenols to acyclic enones and enals but resulted in no enantioselectivity. Thus, complexes **7** and **8** are excellent chiral catalysts for asymmetric Michael addition reactions of malonate derivatives.

4. Experimental

4.1. General experimental procedure for Michael addition reaction

Typically, the chiral ligand **1a** (237 mg, 1 mmol) in dry THF (3 mL) was added to a solution of $LiAlH_4$ (38 mg, 1 mmol) in dry THF (2 mL). 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 (3×10 mL). The organic layer was washed successively with saturated $NaHCO_3$ solution and water 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 $CHCl_3$).

HPLC analyses were carried out using a Chiralcel OD column with hexane/isopropanol (99:1) as eluent (flow rate 0.5 ml/min, UV detection λ 230 nm: retention time for the (*R*)-enantiomer 14.9 min and retention time for the (*S*)-enantiomer 15.9 min).

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