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Novel chiral gallium Lewis acid catalysts with semi-crown ligands for aqueous asymmetric Mukaiyama aldol reactions

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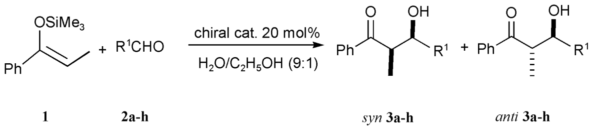
Asymmetric Mukaiyama aldol reactions in aqueous media (water–ethanol = 9:1) were catalyzed by chiral gallium catalysts with semi-crown ligands to give aldol products with good yields, *syn*-diastereoselectivities and enantioselectivities.

Among the Lewis acid catalyzed carbon–carbon bond-forming reactions, the aldol-type reaction of silyl enol ethers with carbonyl compounds (the Mukaiyama reaction)[1] has been recognized as one of the most important. Although several successful examples of catalytic asymmetric Mukaiyama aldol reaction have been developed since 1990,[2] most of these reactions must be conducted at low reaction temperatures in aprotic anhydrous solvents. Recently, interest has been growing in the development of asymmetric Mukaiyama-type reactions in aqueous media.[3] Compared with typical Lewis acids such as $TiCl_4$, $SnCl_4$, BF_3 and $AlCl_3$, certain metal triflates possess stronger Lewis acidities, and they are also water soluble or water-tolerant, air-stable and easy to handle (not requiring anhydrous treatment).[4] Recently, Kobayashi and co-workers developed the combinations of $Cu(OTf)_2$ with a chiral bis(oxazoline) ligand,[5] $Pb(OTf)_2$ with a chiral crown ether,[6] and $Ln(OTf)_3$ [*e.g.* $Nb(OTf)_3$, $Ce(OTf)_3$ and $Pr(OTf)_3$] with chiral bis-pyridino-18-crown-6[7] for asymmetric Mukaiyama aldol reactions in aqueous ethanol (ethanol–water = 9 : 1). However, when the amount of water in the mixture was increased, yields and selectivities of the reaction decreased remarkably and in water alone both low yield (4%) and selectivity (ee 15%) were observed.[6] Furthermore, the use of 'light,' main-group metal catalysts has environmental benefits (compared to heavy metals). A successful catalytic aqueous asymmetric reaction depends on high binding affinities of chiral ligands to the metal center and the catalytic ability of the complex in water. For catalysis, turnover at a reasonable rate must accompany the molecular recognition events. To satisfy both requirements, a semi-crown design would provide the opportunity for good chiral recognition and catalytic ability.[8] Herein, we wish to report novel chiral gallium catalysts with chiral semi-crown ligands for an aqueous catalytic asymmetric Mukaiyama reaction.

Chiral Lewis acids were prepared by stirring a mixture of metal salt and chiral ligands (1 : 1.2) in dichloromethane at room temperature for 2 h, then employing the mixture in the aldol reaction after evaporation of the solvent without further purification. Initially, the reaction of 1-phenyl-1-trimethylsiloxypropene **1** with benzaldehyde **2a** in the presence of Lewis acids, such as $Sc(OTf)_3$, $Nd(OTf)_3$, $Pb(ClO_4)_2$, $Cu(OTf)_2$, $Zn(OTf)_2$ and $In(OTf)_3$, with Trost's chiral semi-crown ligand (*S,S*)-**5b**[8] was carried out in a mixture solvent of ethanol–water (9 : 1) (Scheme 1). Although all reactions proceeded smoothly to give the aldol product **3a** in good yields (75–90%) and diastereoselectivities (*syn*/*anti* > 80 : 20), the enantioselectivities of *syn*-**3a** were very poor (0–5 ee%). Fortunately, the ee of *syn*-**3a** increased remarkably by using a catalytic amount of $Ga(OTf)_3$ (**4**, 20 mol%) under the same reaction conditions. Although extensive research on chiral aluminium Lewis acid in asymmetric reactions has been reported,[9] there are few examples of research on chiral gallium Lewis acid-catalyzed asymmetric reactions.[10] The combination of $Ga(OTf)_3$ and **5b** is able to make the aqueous reaction proceed smoothly with good yield (89%), diastereoselectivity (*syn*/*anti* 89 : 11) and enantioselectivity of *syn*-**3a** (ee 87%) (Table 1, entry 3).† It was noticed that the use of semi-crown ligand **5b** is essential to carry out the aldol reaction in aqueous media. If $Ga(OTf)_3$ was used alone without **5b**, the silyl enol ether **1** in the reaction mixture disappeared (as shown by TLC) after 10 min of the reaction, but no aldol product was observed and the hydrolyzed product, phenylethyl ketone, was obtained (yield 95%) (Table 1, entry 1). In the absence of the aldehyde, the enol silyl ethers also hydrolyzed under the reaction conditions. When the semi-crown ligand was used, the side-reactions could be suppressed. Similarly, as shown in Table 1 (entries 11 and 12), with gallium trichloride alone ($GaCl_3$, **9**) only a trace amount of the aldol product was obtained, whereas the combination of **9** with **5b** could not only catalyze the aldol reaction (61% yield), but also provide a good enantioselectivity (78% ee of *syn*-**3a**).



chiral catalyst: L*/$Ga(OTf)_3$ or $GaCl_3$ (1.2:1)

Scheme 1

On the basis of these preliminary results, various chiral ligands and reaction conditions were selected and investigated. More recently, Trost developed a chiral semi-crown ligand (**5a**)–dinuclear zinc catalyst system, which has been successfully applied in direct catalytic enantioselective aldol reactions[8,11] and nitroaldol (Henry) reactions.[12] We examined chiral

Table 1 Aldol reactions of silyl enol ether **1** with **2a**

Entry	Catalyst[a]	Solvent	Reaction time[b]	Yield of **3a**(%)[c] (*syn*/*anti*)	Ee of *syn*-**3a** (%)
1	**4**	H_2O/C_2H_5OH (1 : 9)	15 min	—	
2	**5a** + **4**	H_2O/C_2H_5OH (1 : 9)	36 h	80 (87/13)	80
3	**5b** + **4**	H_2O/C_2H_5OH (1 : 9)	36 h	89 (89/11)	87
4	**6** + **4**	H_2O/C_2H_5OH (1 : 9)	36 h	72 (89/11)	5
5	**7** + **4**	H_2O/C_2H_5OH (1 : 9)	36 h	78 (85/15)	44
6	**8** + **4**	H_2O/C_2H_5OH (1 : 9)	36 h	60 (90/10)	2
7	**5b** + **4**	H_2O/THF (1 : 4)	36 h	80 (88/12)	80
8	**5b** + **4**	H_2O/C_2H_5OH (1 : 1)	36 h	84 (82/18)	82
9	**5b** + **4**	H_2O/C_2H_5OH (9 : 1)	36 h	85 (85/15)	85
10	**5b** + **4**	H_2O	3 d	41 (90/10)	84
11	**5b+9**	H_2O/C_2H_5OH (9 : 1)	36 h	61 (84/16)	78
12	**9**	H_2O/C_2H_5OH (9 : 1)	36 h	trace	
13	**5b** + **4**	C_2H_5OH	36 h	75 (88/12)	58
14	**5b** + **4**	CH_2Cl_2	3 d	trace	

[a] Catalyst loading: 20 mol%. [b] Reaction temperature: 0–5 °C. [c] Isolated yield.

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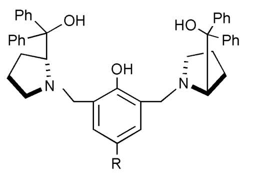
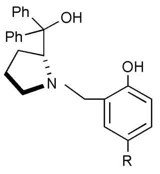
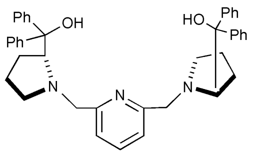


5a, R: CH_3
5b: R: $(CH_3)_3C$



6, R: $(CH_3)_3C$



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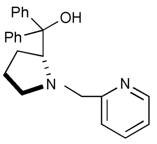

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ligands **5**–**8** together with $Ga(OTf)_3$ for a catalytic asymmetric aldol reaction in water–ethanol (1 : 9). It was found that chiral gallium catalysts based on ligands (*S*,*S*)-**5a** and (*S*,*S*)-**5b** had similar asymmetric inductions and catalytic abilities (Table 1, entries 2 and 3). Phenol derivatives **5a**–**b** as chiral ligands exhibited higher enantioselectivities than the use of pyridinol derivative (*S*,*S*)-**7**,[13] although similar yields and diastereoselectivities (entries 2, 3, 5) were observed. Non-C_2-symmetrical mono-prolinol ligands [(*S*)-**6** and (*S*)-**8**[13]] did not show any significant enantioinductive ability (entries 4, 6). It is noteworthy that both diastereo- and enantioselectivities remained high with an increased amount of water in the mixture solvent and even with only water as the solvent (entries 8, 9, 10). However, in water alone the reaction was slow and gave a lower yield of the aldol product. The addition of a surfactant did not improve the yield of the reaction. On the other hand, in ethanol the enantioselectivity of *syn*-**3a** decreased noticeably (entry 13) and only a trace amount of the aldol product was detected when dichloromethane was used as the solvent (entry 14). Thus, water is essential to give a good enantioselectivity in the chiral gallium catalyzed aqueous Mukaiyama aldol reaction.

Subsequently, various aromatic aldehydes **2b**–**g** were employed in the asymmetric aldol reaction in water–ethanol (9 : 1) under the same reaction conditions catalyzed by chiral gallium Lewis acid derived from $Ga(OTf)_3$ and (*S*,*S*)-**5b**. All the reactions provided good yields (77–90%), diastereoselectivities (*syn*/*anti* = 80/20–90/10) and enantioselectivities of *syn*-**3b**–**f** (78–88% ee), except the case of *p*-nitrobenzaldehyde **2g** which gave a relatively low ee of aldol product **3f** (62%) (Table 2). An aliphatic aldehyde (**2h**) gave a lower ee (30%) (entry 8). No reaction was observed with simple ketones under the current conditions. The configuration of *syn*-**3a** and its analogues produced were determined as 2*R*, 3*R* by comparison with the optical rotation of authentic compounds (see ref. 14).

Table 2 Asymmetric aldol reaction of **1** with **2** catalyzed by $Ga(OTf)_3$/**5b**[a]

Entry	Aldehyde (R^1)	Product (R^1)	Yield of **3** (%)[b](*syn*/*anti*)	Ee of *syn*-**3** (%)
1	**2a**, Ph	**3a**, Ph	85 (85/15)	85
2	**2b**, *p*-CH_3Ph	**3b**, *p*-CH_3Ph	89 (90/10)	88
3	**2c**, *p*-CH_3OPh	**3c**, *p*-CH_3OPh	80 (88/12)	84
4	**2d**, *p*-ClPh	**3d**, *p*-ClPh	77 (82/18)	78
5	**2e**, PhCH=CH	**3e**, PhCH=CH	90 (90/10)	86
6	**2f** 1-naphthyl	**3f**, 1-naphthyl	87 (80/20)	82
7	**2g**, *p*-NO_2Ph	**3g**, *p*-NO_2Ph	82 (77/23)	62
8	**2h**, $CH_3(CH_2)_4$	**3h**, $CH_3(CH_2)_4$	82 (89/11)	30

[a] Reaction conditions: catalyst loading: 20 mol%, solvent: H_2O/C_2H_5OH (9 : 1), time: 36 h, temperature: 0–5 °C. [b] Isolated yield.

In conclusion, the combinations of $Ga(OTf)_3$ or $GaCl_3$ with chiral semi-crown ligands were highly effective chiral Lewis acid catalysts for catalytic aqueous Mukaiyama aldol reactions that give good yields, diastereo- and enantioselectivities. The application of these chiral gallium catalysts in other Lewis acid catalyzed reactions in aqueous media is in process.

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Notes and references

† *General procedure for the reaction*: $Ga(OTf)_3$ (0.1 mmol) and chiral ligand **5b** (0.12 mmol) were dissolved in 1 mL dichloromethane, followed by stirring for 2 h at room temperature. Then, the solvent was evaporated *in vacuo* to give a yellow solid (catalyst complex). Benzaldehyde **2a** (0.5 mmol) and silyl enol ether **1** (0.75 mmol) were added to a solution of the catalyst complex in a mixture solvent (water–ethanol = 9 : 1) at 0–5 °C, followed by stirring for 36 h at the same temperature. The reaction was quenched with aq. $NaHCO_3$. The mixture was extracted with ether (3×), and the combined organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate–petroleum ether (30–60 °C) = 1 : 10) to give a mixture of *syn*- and *anti*-**3a**. *Syn*-**3a** was obtained from flash chromatography purification of the mixture. The ratio of *syn*/*anti* and the ee of *syn*-**3a** were determined by ^1H NMR and chiral HPLC (column Chiracel OD-H).

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