Highly enantioselective synthesis of tertiary alcohols: C_2-symmetric *N*,*N*′-dioxide-Sc(III) complex promoted direct aldol reaction of α-ketoesters and diazoacetate esters†

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A C_2-symmetric *N*,*N*′-dioxide-Sc(III) complex has been developed to promote the asymmetric catalytic aldol reaction of α-ketoesters and diazoacetate esters to afford tertiary alcohols in good yields with excellent enantioselectivities.

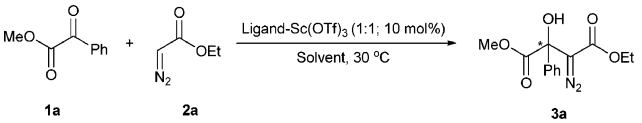
Asymmetric synthesis, especially the synthesis of certain classes of chiral compounds, has attracted growing attention over the past half century. Chiral tertiary alcohols are important building blocks of naturally occurring and pharmaceutical drugs.[1] Till now, many synthetic methodologies towards chiral tertiary alcohols have been developed through the asymmetric catalytic nucleophilic addition reactions of ketones and their derivatives, such as the addition of organometallics on ketones,[2] alkylation and arylation reactions,[3] Henry-type reactions,[4] carbonyl-ene reactions,[5] Mukaiyama-type aldol reactions[6] and direct aldol reactions of ketones and functional ketones.[7] Despite these impressive contributions, the development of new and efficient synthetic methodologies is still challenging and in high demand.

As aldol donors, the higher pK_a values of α-protons of diazoacetate esters relative to aldehydes or ketones makes them less reactive substrates. Despite the significant progress made in the development of the direct aldol reaction of aldehydes and diazoacetate esters,[8] there are no reports of catalytic enantioselective aldol reactions between a diazoacetate ester as a nucleophile and an α-ketoester as an electrophile. In this communication, we focus on the enantioselective synthesis of tertiary alcohols by the reaction of α-ketoesters and diazoacetate esters using a C_2-symmetric *N*,*N*′-dioxide-Sc(III) complex catalyst.

Owing to their tunable electronic and steric chiral environments, *N*,*N*′-dioxide complexes have emerged as a new class of effective catalysts for many asymmetric reactions.[4f,9] Encouraged by our previous study, we initially examined the aldol reaction of phenylglyoxylate **1a** and ethyl diazoacetate **2a**, promoted by *N*,*N*′-dioxide-Sc(III) complexes (Table 1) in 1 mL CH_2Cl_2 at 30 °C. *N*,*N*′-Dioxide **L3** (Fig. 1), derived from an aromatic amine, exhibited a superior result to **L1**, based on an aliphatic amine, with moderate enantioselectivity (Table 1, entry 1 *vs.* 3). To further improve the enantioselectivity of the reaction, the steric and electronic effects of the ligand were examined (Table 1, entries 2–6). As shown in Table 1, ligand **L4**, with a bulkier group at the *ortho* position of aniline, such as isopropyl, could be used to obtain the aldol adduct with higher enantioselectivity (up to 92% ee; Table 1, entry 4 *vs.* entries 2 and 3). As for the chiral backbone moiety, the (*S*)-pipecolic acid derived *N*,*N*′-dioxide exhibited its superiority in both yield and enantioselectivity toward this reaction compared with the L-proline and (*S*)-ramipril derived ones (Table 1, entry 4 *vs.* entries 5 and 6). Moreover, when amide ligand **L5** was employed, the reaction did not take place, which revealed that the *N*-oxide group was essential for the reaction (Table 1, entry 9).

Using the **L4**-Sc(III) complex as catalyst, the reaction conditions were further optimized. Solvent screening did not give any improvement in both enantioselectivity and yield, CH_2Cl_2 was still the best solvent for this reaction (Table 1, entry 4 *vs.* entries 7 and 8). When the molar ratio of ligand to central metal was changed to 1.5 : 1, the reactivity was increased and enantioselectivity was maintained (Table 1, entry 10). Remarkable progress in reactivity was

Table 1 Optimization of the reaction conditions



1a **2a** **3a**

Entry[a]	Ligand	Solvent	Yield[b] (%)	Ee[c] (%)
1	**L1**	CH_2Cl_2	32	36
2	**L2**	CH_2Cl_2	45	52
3	**L3**	CH_2Cl_2	52	56
4	**L4**	CH_2Cl_2	54	92
5	**L6**	CH_2Cl_2	54	87
6	**L7**	CH_2Cl_2	42	80
7	**L4**	DCE	50	90
8	**L4**	$CHCl_3$	46	87
9	**L5**	CH_2Cl_2	n.r.	n.d.
10[d]	**L4**	CH_2Cl_2	60	93
11[e]	**L4**	CH_2Cl_2	70	93
12[f]	**L4**	CH_2Cl_2	76	93

[a] Unless otherwise noted, reactions were carried out with phenylglyoxylate (0.1 mmol) and ethyl diazoacetate (0.2 mmol) in solvent (1.0 mL) at 30 °C for 48 h. [b] Isolated yield; n.r. = no reaction. [c] Determined by chiral HPLC; n.d. = not determined. [d] Reaction was performed with *N*,*N*′-dioxide-Sc(III) (1.5 : 1; 10 mol%) complex. [e] Reaction was carried out by using 0.2 mL of CH_2Cl_2 as solvent. [f] Reaction was performed for 72 h.

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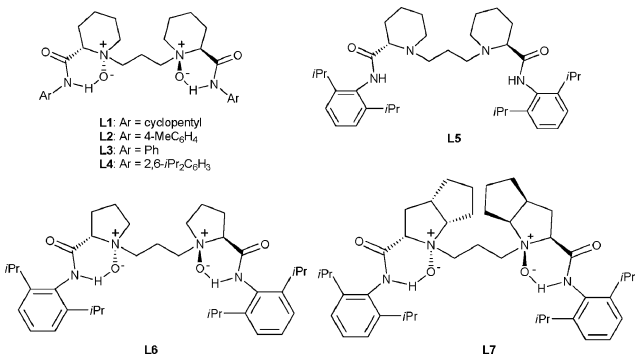

Fig. 1 Chiral ligands used in the study.

made by enhancing the substrate concentration from 0.1 M to 0.5 M (Table 1, entry 11). Meanwhile, prolonging the reaction time to 72 h gave the same level of enantioselectivity and favourable yield (93% ee, 76% yield) (Table 1, entry 12). Thus, the optimal reaction conditions were 15 mol% **L4**, 10 mol% $Sc(OTf)_3$, α-ketoester (0.1 mmol), and diazoacetate ester (0.2 mmol) in CH_2Cl_2 (0.2 mL) at 30 °C.

Under the optimized conditions, the reaction generally provided the corresponding tertiary alcohol **3** in good yields with excellent enantioselectivities (Table 2). α-Ketoesters with both electron-donating and electron-withdrawing groups at *meta* or *para* positions were well tolerated in terms of yields and enantioselectivities, up to 85% yield and 97% ee were obtained (Table 2, entries 1–16). A fused ring α-ketoester was also a suitable substrate for the reaction, giving the corresponding products with up to 92% ee (Table 2, entries 17 and 18). Moreover, a heteroaromatic substrate delivered the aldol adduct in good yield and enantioselectivity (Table 2, entry 19). Unfortunately, both yield and enantioselectivity with an aliphatic α-ketoester[10] were inferior to those with aromatic ones. (Table 2, entry 20).

In addition, as shown in Scheme 1, when the reaction of ethyl 2-oxo-2-phenylacetate with ethyl diazoacetate **2a** was performed under the optimal reaction conditions, the desired product **4** was obtained in 75% yield with 94% ee. Notably, the absolute configuration of **4** could be determined after converting to known compound **5** (Scheme 1). The hydrogenation of **4** following a literature procedure[8c] did not result in any loss of enantioselectivity. Thereby, assigning the absolute configuration of **4** to be *S* by comparing the optical rotation of **5** with that given in the literature.[11]

In conclusion, we have developed a C_2-symmetric *N*,*N*′-dioxide-Sc(III) complex for the asymmetric direct aldol reaction of α-ketoesters and diazoacetate esters. Aromatic and heteroaromatic α-ketoesters were converted into the desired products in good yields (up to 85%) with excellent enantioselectivities (up to 97% ee). The operational simplicity, practicability, and mild reaction conditions rendered it an efficient approach for the synthesis of optically active tertiary alcohols. Further efforts are being devoted to elucidate the reaction mechanism and the application of this catalyst to other reactions.

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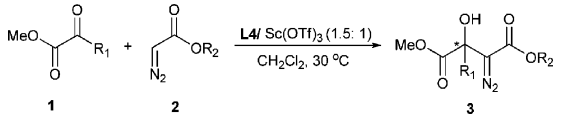
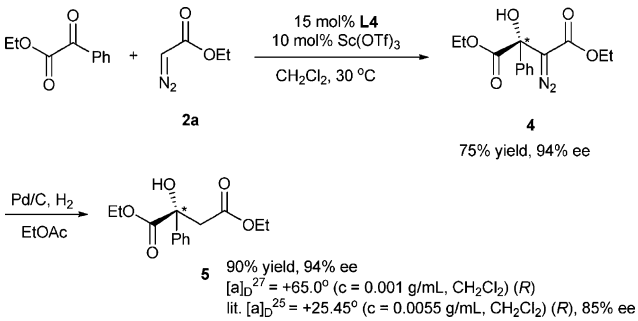
Table 2 Substrate scope for the catalytic asymmetric aldol reaction



Entry[a]	R_1	R_2	Yield[b] (%)	Ee[c] (%)
1	C_6H_5	Et	76	93
2	C_6H_5	Me	78	95
3	3-$CH_3C_6H_4$	Et	68	96
4	3-$CH_3C_6H_4$	Me	70	97
5	4-$CH_3C_6H_4$	Et	70	93
6	4-$CH_3C_6H_4$	Me	75	92
7	4-$CH_3OC_6H_4$	Et	62	90
8	4-$CH_3OC_6H_4$	Me	68	91
9	3-FC_6H_4	Et	62	94
10	3-FC_6H_4	Me	75	95
11	4-FC_6H_4	Et	66	93
12	4-FC_6H_4	Me	67	95
13	4-BrC_6H_4	Et	78	94
14	4-BrC_6H_4	Me	85	94
15	4-ClC_6H_4	Et	80	90
16	4-ClC_6H_4	Me	84	94
17	2-Naphthyl	Et	64	92
18	2-Naphthyl	Me	61	91
19	2-Thienyl	Me	65	87
20	Cyclohexyl	Et	35	52

[a] Unless noted otherwise, the reaction was carried out with α-ketoester (0.1 mmol) and diazoacetate ester (0.2 mmol) in the presence of $Sc(OTf)_3$ (10 mol%) and **L4** (15 mol%) in CH_2Cl_2 (0.2 mL) at 30 °C for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC.



Scheme 1 Conversion to known compound **5** for assignment of the absolute configuration.

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10 We also tested the other aliphatic α-ketoesters such as α-ketoesters **3** (R_1 = methyl) and methyl cinnamate **6**. The treatment of α-ketoesters **3** (R_1 = methyl) and diazoacetate ester gave lower reactivity (20% yield) and enantioselectivity (13% ee). When using methyl cinnamate **6** as substrate, 93% yield was obtained, but only with 3% ee.

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