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Diastereo- and Enantioselective Reductive Aldol Reaction with Trichlorosilane Using Chiral Lewis Bases as Organocatalysts

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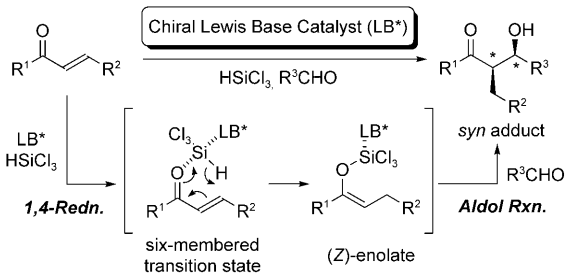
Dedicated to the 150th anniversary of Japan–UK diplomatic relations

The catalytic enantioselective tandem reaction is an efficient synthetic methodology in which optically active compounds are assembled from simple prochiral substrates via two (or more) distinct catalytic processes taking place under the same conditions.[1] The synthetic efficiency is enhanced by avoiding the time-intensive and yield-reducing isolation and purification of synthetic intermediates and by decreasing the amounts of chemicals and solvents used. The asymmetric catalytic reductive aldol reaction is an efficient tandem transformation involving conjugate reduction of α,β-unsaturated carbonyl compounds followed by aldol reaction of the enolate intermediate with aldehydes or ketones. Chiral transition-metal catalysts have been used to control the stereochemistry of these transformations.[2,3] We recently reported that achiral phosphorus oxides function as Lewis base organocatalysts[4] to promote both the conjugate reduction of enones with trichlorosilane and the reductive aldol reaction of enones with aldehydes.[5] Herein we report that enantioselective catalysis of this tandem reaction by chiral Lewis bases provides good to high diastereo- and enantioselectivities.



Scheme 1. The enantioselective reductive aldol reaction with trichlorosilane catalyzed by a chiral Lewis base catalyst.

Scheme 1 outlines the current catalytic method. Our previous study had shown that the Lewis base catalyzed conjugate reduction with trichlorosilane proceeds via a six-membered transition state with an enone in the s-*cis* conformation to give the (*Z*)-trichlorosilyl enolate exclusively.[5] Therefore, high *syn* selectivity is expected for the subsequent aldol process, assuming that the reaction proceeds through a chair-like cyclic transition state. Moreover, high enantioselectivity could also be achieved by judicious selection of chiral Lewis base catalysts (LB*).[6,7]

We first examined various chiral Lewis base catalysts (Figure 1) for the reductive aldol reaction of chalcone (**1a**) and benzaldehyde (**2a**) with trichlorosilane at −78 °C (Table 1). With (*S*)-BINAPO, the reaction in dichloromethane gave aldol adduct **3a** with respectable stereoselectivities (Table 1, entry 1). By simply changing the solvent from dichloromethane to propionitrile, both the stereoselectivities and chemical yield dramatically improved (Table 1, entry 2). Other Lewis base catalysts were then examined using this solvent (Table 1, entries 3–6). (*R*,*R*)-DIOPO showed a comparable activity to BINAPO to afford similar enantioselectivity with a slight loss of diastereoselectivity (Table 1, entry 3). Although structurally similar to BINAPO, (*S*)-

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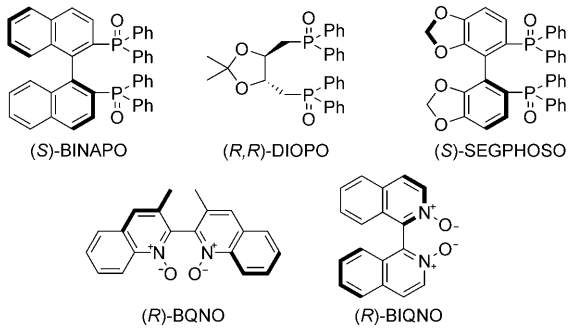
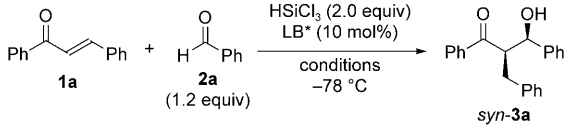


Figure 1. Chiral Lewis base catalysts used in this study.

Table 1. Optimization of reaction conditions for the enantioselective reductive aldol reaction of chalcone (**1a**) and benzaldehyde (**2a**).[a]



Entry	LB*	Conditions	Yield [%]	*syn*/*anti*	*ee* [%] (*syn*[b])
1	(*S*)-BINAPO	CH_2Cl_2, 30 h	68	85:15	84
2	(*S*)-BINAPO	EtCN, 24 h	87	96:4	92
3	(*R,R*)-DIOPO	EtCN, 5 h	80	92:8	92
4	(*S*)-SEGPHOSO	EtCN, 24 h	17	72:28	61
5	(*R*)-BQNO	EtCN, 24 h	68	94:6	80[c]
6	(*R*)-BIQNO	EtCN, 24 h	75	95:5	4

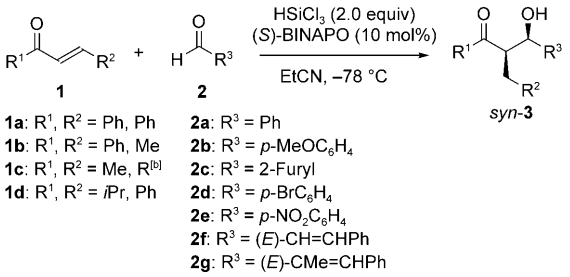
[a] All reactions were carried out by addition of trichlorosilane (1.0 mmol, ca. 3 M solution in CH_2Cl_2) to a solution of chalcone (0.5 mmol), benzaldehyde (0.6 mmol), and a Lewis base catalyst (10 mol%) in a solvent (2 mL) at −78 °C. [b] 2*R*,3*R* configuration. [c] 2*S*,3*S* configuration.

SEGPHOSO was found to significantly lower the reactivity and selectivities (Table 1, entry 4). On the other hand, (*R*)-BQNO, a bisquinoline *N,N'*-dioxide developed in our laboratory[8] exhibited good activity and selectivity, while (*R*)-BIQNO, a bisisoquinoline *N,N'*-dioxide,[9] afforded low enantioselectivity (Table 1, entries 5 and 6).[10,11]

Having discovered several effective catalysts, we next investigated the reductive aldol reaction of a variety of substrates (Table 2). The reactions of several β-monosubstituted enones (**1b-d**) with benzaldehyde (**2a**) were smoothly catalyzed by (*S*)-BINAPO to afford the corresponding adducts in good yields with high *syn* diastereo- and enantioselectivities (Table 2, entries 1–4).[11] Dichloromethane was found to provide a higher yield and enantioselectivity than did propionitrile in the reaction of β-ionone, although diastereoselectivities were comparable in the two solvents (Table 2, entries 2 vs. 3). The rapid transformation of enone **1d**, which bears a bulky isopropyl group, presumably results from the substrate's preference for the s-*cis* conformation, which is favorable for the conjugate reduction (Table 2, entry 4).[12,13]

Using chalcone (**1a**) as the enone component, (*S*)-BINAPO-catalyzed reactions with other aldehydes were investigated (Table 2, entries 5–10).[10,11] *p*-Anisaldehyde (**2b**) and 2-furaldehyde (**2c**) having electron-rich aromatic rings showed higher reactivity than benzaldehyde (**2a**; see Table 1, entry 2), but the enantioselectivity was slightly decreased (Table 2, entries 5 and 6). On the other hand, an opposite tendency was observed for *p*-bromobenzaldehyde (**2d**) and *p*-nitrobenzaldehyde (**2e**) having electron-withdrawing substituents, which resulted in higher enantioselectivity (Table 2, entries 7 and 8). In all cases, high *syn* diastereoselectivities were observed. The reaction tolerated α,β-unsaturated aldehydes to give the corresponding adducts in good yields with high *syn* diastereoselectivity and moderate enantioselectivity (Table 2, entries 9 and 10). For the reaction of these enals, significantly improved enantioselectivity was obtained by using (*R,R*)-DIOPO instead of (*S*)-BINAPO (Table 2, entries 11 and 12). It is noteworthy that the enone was chemoselectively reduced with trichlorosilane in the presence of enals. The low reactivity of α,β-unsaturated aldehydes in the conjugate reduction might be attributed to unfavorable conformations of enals in the reaction (see Figure 2).[13] As shown in Figure 2a, the s-*trans* conformer predominates for enals. Furthermore, the trichlorosilane–Lewis base complex predominantly coordinates to the sterically less hindered lone pair of the carbonyl oxygen leading to *anti* complex **B**, even in the s-*cis* conformation (Figure 2b). Both the s-*trans* conformation and *anti* complex **B**

Table 2. Enantioselective reductive aldol reaction of various enones and aldehydes.[a]



Entry	Enone	Aldehyde	*t* [h]	Product	Yield [%]	*syn*/*anti*	*ee* [%] (*syn*)
1	**1b**	**2a**	24	**3b**	70	94:6	91
2	**1c**	**2a**	24	**3c**	37	99:1	91
3[c]	**1c**	**2a**	21	**3c**	67	99:1	96
4	**1d**	**2a**	1.5	**3d**	74	99:1	97
5	**1a**	**2b**	8	**3e**	72	95:5	85
6	**1a**	**2c**	6	**3f**	84	99:1	90
7	**1a**	**2d**	24	**3g**	78	97:3	94
8	**1a**	**2e**	24	**3h**	58	95:5	96
9	**1a**	**2f**	24	**3i**	91	95:5	51
10	**1a**	**2g**	8	**3j**	71	98:2	50
11[d]	**1a**	**2f**	4.5	**3i**	71	95:5	85
12[d]	**1a**	**2g**	24	**3j**	92	99:1	98

[a] Unless otherwise noted, reactions were carried out by addition of trichlorosilane (1.0 mmol, ca. 3 M solution in CH_2Cl_2) to a solution of an enone (0.5 mmol), an aldehyde (0.6 mmol), and (*S*)-BINAPO (10 mol%) in EtCN (2 mL) at −78 °C. [b] R = 2,6,6-trimethyl-1-cyclohexenyl (β-ionone). [c] With benzaldehyde (2 equiv) in CH_2Cl_2 instead of EtCN. [d] With (*R,R*)-DIOPO (10 mol%) instead of (*S*)-BINAPO.

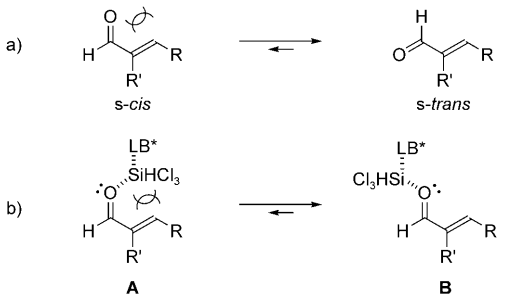
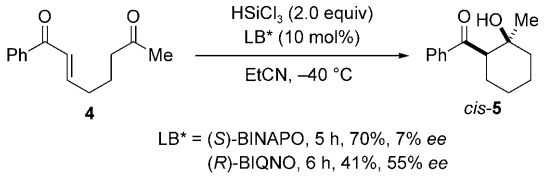


Figure 2. Conformational preference of α,β-unsaturated aldehydes and their trichlorosilane complexes.



Scheme 2. Intramolecular enantioselective reductive aldol reaction.

are unfavorable for the six-membered transition state required for the conjugate reduction.

Preliminary investigation has indicated that the current method can be applied to an intramolecular process (Scheme 2).[14] The (*S*)-BINAPO-catalyzed reaction of ketoenone **4**[14c] with trichlorosilane proceeded smoothly at −40 °C to give the expected cyclized product *cis*-**5** in a good yield, but with low enantioselectivity. The enantioselectivity was improved when (*R*)-BIQNO was used instead of BINAPO, although the yield was moderate.[15] Further improvement of the intramolecular transformation is under investigation.

In summary, we have demonstrated that the reductive aldol reaction of enones and aldehydes with trichlorosilane is catalyzed by chiral Lewis base organocatalysts to afford optically active β-hydroxy ketones with good to high diastereo- and enantioselectivities. Further investigations including extension of the scope of the reaction and application to natural product synthesis are currently underway.

Experimental Section

General procedure for enantioselective reductive aldol reaction with trichlorosilane: To a solution of a chiral Lewis base (10 mol%), an enone (0.5 mmol), and an aldehyde (0.6 mmol, 1.2 equiv) in dry propionitrile (2 mL) was added dropwise trichlorosilane (ca. 3 M CH_2Cl_2 solution, 2 equiv) at −78 °C. The reaction was monitored by TLC analysis. After the enone was consumed or no significant change was observed, the reaction was quenched with sat. aqueous $NaHCO_3$ (3 mL). After addition of ethyl acetate (10 mL), the mixture was stirred for 1 h, filtered through a celite pad and extracted with ethyl acetate (3×). The combined organic layers were washed with brine (1×), dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1–3:1) to give the corresponding aldol product.

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Keywords: aldol reaction · Lewis bases · organocatalysis · reduction · silanes

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