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Lewis base-catalyzed conjugate reduction and reductive aldol reaction of α,β-unsaturated ketones using trichlorosilane†

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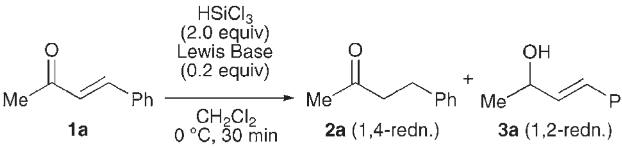
Lewis bases such as $Ph_3P{=}O$ and HMPA catalyze the 1,4-reduction of α,β-unsaturated ketones with trichlorosilane, and because the 1,2-reduction of aldehydes scarcely proceeded under the conditions, one-pot reductive aldol reactions with aldehydes were successfully achieved; preliminary studies using a chiral Lewis base revealed a high potential for enantioselective catalysis.

Conjugate reduction of α,β-unsaturated carbonyl compounds and subsequent one-pot reactions with electrophiles such as aldehydes are efficient synthetic tactics in organic synthesis. In these processes, transition metals are typically utilized as catalysts with silane or borane reductants.[1] Recently, organocatalytic variants of conjugate reduction (chiral secondary amines as catalysts and Hantzsch esters as stoichiometric reducing agents) have been reported,[2] but subsequent reactions with electrophiles have yet to be fully explored.[3] Herein, we report an alternative methodology for organocatalytic conjugate reduction of enones and subsequent reactions with aldehydes (reductive aldol reactions). The method employs phosphorus oxide (P=O) compounds as Lewis base-catalysts and trichlorosilane as a reductant.[4–6]

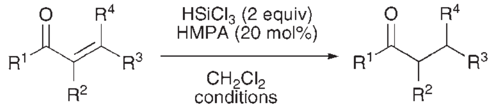
We hypothesized that if a suitable Lewis base activates the silane, the 1,4-reduction may proceed selectively *via* a six-membered transition state, and with the assistance of the same Lewis base, the generated trichlorosilyl enolate should react with coexisting aldehyde electrophile.[7] Therefore, we investigated the reduction of benzalacetone (**1a**) with trichlorosilane in the presence of a catalytic amount of various Lewis bases (Scheme 1).[8] Reduction was not observed in the absence of catalyst, but 1,2-reduction mainly occurred upon the addition of DMF [**2a** (2%), **3a** (43%)]. On the other hand, 1,4-reduction proceeded selectively when DMPU [**2a** (11%), **3a** (<1%)], $Ph_3P{=}O$ [**2a** (64%), **3a** (0%)], or HMPA [**2a** (99%), **3a** (0%)] was used as the Lewis base-catalyst. *N*,*N*-Dimethylacetamide, isoquinoline *N*-oxide and DMSO showed a negligible catalytic activity.

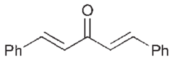
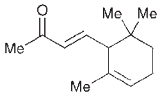
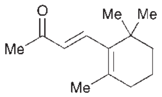
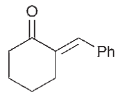
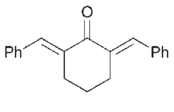
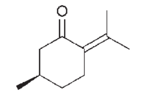


Scheme 1 Lewis base-catalyzed reduction of benzalacetone.

Thus, with effective catalysts in hand, conjugate reduction of various α,β-unsaturated ketones was examined (Table 1). The reactions were performed in the presence of HMPA (20 mol%) at 0 °C or rt. Acyclic β-monosubstituted enones

Table 1 HMPA-catalyzed conjugate reduction of various enones[a]



Entry	Enone	R^1, R^2, R^3, R^4	Conditions	Yield (%)
1	**1a**	Me, H, Ph, H	0 °C, 30 min	87
2	**1b**	Ph, H, Ph, H	0 °C, 30 min	91
3	**1c**	Ph, H, Me, H	0 °C, 30 min	72
4	**1d**		0 °C, 60 min	80
5	**1e**		0 °C, 4 h then rt, 2 h	93
6	**1f**		0 °C, 30 min	94
7	**1g**	Ph, H, Ph, Me	0 °C, 5 h then rt, 19 h	74
8	**1h**	Ph, Me, H, H	0 °C, 9 h then rt, 17 h	60
9	**1i**		0 °C, 30 min	89
10	**1j**		0 °C, 40 min	82
11	**1k**		0 °C, 4 h then rt, 16 h	84[b]

[a] All reactions were carried out by addition of trichlorosilane (2.0 mmol) to a solution of an enone (1.0 mmol) and HMPA (0.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C or rt. [b] *trans* : *cis* = 1.7 : 1.

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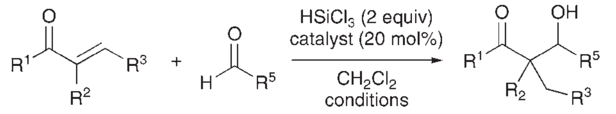
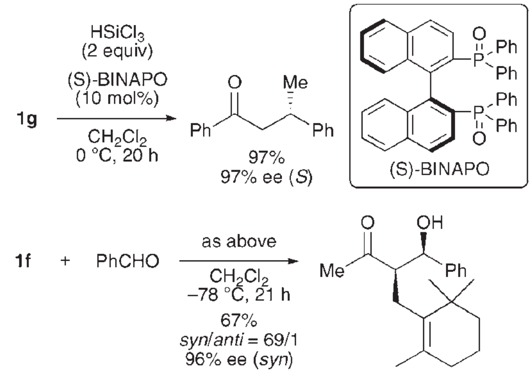
† Electronic supplementary information (ESI) available: General procedures and spectroscopic data. See DOI: 10.1039/b807529h

Table 2 Lewis base-catalyzed reductive aldol reaction[a]



Entry	Enone	R^5	Catalyst	Conditions	Yield[b] (%)
1	**1b**	Ph	HMPA	0 °C, 4 h	52
2	**1b**	Ph	$Ph_3P{=}O$	0 °C, 4 h	78
3	**1b**	p-$MeOC_6H_4$	$Ph_3P{=}O$	0 °C, 4 h	69
4	**1b**	p-$NO_2C_6H_4$	$Ph_3P{=}O$	0 °C, 4 h	72
5	**1b**	$Ph(CH_2)_2$	$Ph_3P{=}O$	rt, 24 h	19
6	**1c**	Ph	$Ph_3P{=}O$	0 °C, 4 h	70
7	**1f**	Ph	$Ph_3P{=}O$	0 °C, 5 h	65
8	**1h**	Ph	HMPA	rt, 24 h	39

[a] All reactions were carried out by addition of trichlorosilane (1.0 mmol) to a solution of an enone (0.5 mmol), an aldehyde (0.6 mmol) and a Lewis base-catalyst (0.1 mmol) in CH_2Cl_2 (2 mL) at 0 °C or rt. [b] Isolated as diastereomeric mixtures except for entry 8.



Scheme 2 Enantioselective catalysis.

gave the 1,4-reduction products in high yields with exclusive 1,4-selectivity (entries 1–6), while β- and/or α-disubstituted enones required extended reaction time (entries 7, 8 and 11). The 1,4-reduction of one enone moiety proceeded regioselectively even when substrates had an additional olefin moiety (entries 4, 5, 6 and 10). Exocyclic enones gave 1,4-reduction products smoothly (entries 9, 10 and 11), whereas an endocyclic enone, 3-phenyl-2-cyclohexenone, showed low reactivity. These observations strongly suggest the importance of the *s-cis* configuration in the transition state.[9]

HMPA or $Ph_3P{=}O$ scarcely promoted the 1,2-reduction of benzaldehyde under these conditions. Thus, three-component reactions of enones, aldehydes and trichlorosilane (reductive aldol reactions) proceeded smoothly in the presence of a Lewis base-catalyst to afford the corresponding aldol products in good yield (Table 2).[10] For the reaction of chalcone (**1b**) with benzaldehyde, $Ph_3P{=}O$ catalyst showed better activity than HMPA (entries 1 and 2). Reactions of **1b** with electron-donating and -withdrawing benzaldehyde derivatives also afforded good yields, but reaction with an aliphatic aldehyde gave a low yield (entries 3–5). Reactive enones **1c** and **1f** provided good results (entries 6 and 7), but enone **1h** having low reduction activity resulted in a low yield (entry 8).

Preliminary studies using a chiral Lewis base (BINAPO)[11] revealed a high potential for enantioselective catalysis of the reactions (Scheme 2). Although HMPA required an extended reaction time at rt for the reduction of enone **1g** (see Table 1, entry 7), the asymmetric reduction using BINAPO proceeded smoothly at 0 °C to give a high enantioselectivity. On the other hand, the asymmetric reductive aldol reaction of β-ionone (**1f**) with benzaldehyde at −78 °C provided both high diastereo- and enantioselectivities. The *syn*-diastereoselectivity can be ascribed to the formation of the (*Z*)-trichlorosilyl enolate[9] followed by Lewis base-catalyzed aldol reaction *via* a chair-like transition state.[11,12]

In summary, we have demonstrated Lewis base-catalyzed conjugate reduction of α,β-unsaturated ketones with trichlorosilane and subsequent one-pot reactions with aldehydes. Further studies on the enantioselective catalysis as well as extension to other related reactions are currently in progress.

Notes and references

1 For leading references on metal-catalyzed reductive aldol reactions, see: (*a*) A. Revis and T. K. Hilty, *Tetrahedron Lett.*, 1987, **28**, 4809; (*b*) S. Isayama and T. Mukaiyama, *Chem. Lett.*, 1989, 2005; (*c*) S. Kiyooka, A. Shimizu and S. Torii, *Tetrahedron Lett.*, 1998, **39**, 5237; (*d*) T. Ooi, K. Doda, D. Sakai and K. Maruoka, *Tetrahedron Lett.*, 1999, **40**, 2133; (*e*) C.-X. Zhao, M. O. Duffey, S. J. Taylor and J. P. Morken, *Org. Lett.*, 2001, **3**, 1829; (*f*) H.-Y. Jang, R. R. Huddleston and M. J. Krische, *J. Am. Chem. Soc.*, 2002, **124**, 15156; (*g*) I. Shibata, H. Kato, T. Ishida, M. Yasuda and A. Baba, *Angew. Chem., Int. Ed.*, 2004, **43**, 711.

2 (*a*) J. W. Yang, M. T. H. Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 6660; (*b*) J. W. Yang, M. T. H. Fonseca, N. Vignola and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 108; (*c*) S. G. Ouellet, J. B. Tuttle and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 32; (*d*) N. J. A. Matrin and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13368; For related reactions based on non-metal-catalyzed hydrostannation, see: (*e*) T. Kawakami, M. Miyatake, I. Shibata and A. Baba, *J. Org. Chem.*, 1996, **61**, 376; (*f*) D. S. Hays, M. Scholl and G. C. Fu, *J. Org. Chem.*, 1996, **61**, 6751.

3 A catalytic asymmetric reductive Michael cyclization has been reported, see: J. W. Yang, M. T. H. Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036.

4 Trichlorosilane has been utilized for (asymmetric) 1,2-reduction of aldehydes, ketones, aldimines and ketimines in combination with (chiral) Lewis base-catalysts. For leading references, see: (*a*) S. Kobayashi, M. Yasuda and I. Hachiya, *Chem. Lett.*, 1996, 407; (*b*) F. Iwasaki, O. Onomura, K. Mishima, T. Maki and Y. Matsumura, *Tetrahedron Lett.*, 1999, **40**, 7507; (*c*) Y. Matsumura, K. Ogura, Y. Kouchi, F. Iwasaki and O. Onomura, *Org. Lett.*, 2006, **8**, 3789; (*d*) A. V. Malkov, A. Mariani, K. N. MacDougall and P. Kočovský, *Org. Lett.*, 2004, **6**, 2253; (*e*) A. V. Malkov, A. J. P. Stewart Liddon, P. Ramírez-López, L. Bendová, D. Haigh and P. Kočovský, *Angew. Chem., Int. Ed.*, 2006, **45**, 1432; (*f*) L. Zhou, Z. Wang, S. Wei and J. Sun, *Chem. Commun.*, 2007, 2977.

5 Cobalt(II) chloride-catalyzed 1,4-reduction of enones or acryl esters with trichlorosilane has been reported, see: M. Chauhan and P. Boudjouk, *Can. J. Chem.*, 2000, **78**, 1396. For a palladium-catalyzed reductive aldol reaction with trichlorosilane, see ref. 1*c*.

6 A patent that describes a formamide-catalyzed conjugate reduction of enones with the silane has been reported, see: Y. Matsumira and F. Iwasaki, *Jpn. Pat.*, JP 2003171334 A. However, this patent does not describe the effect of Lewis bases other than formamides. Formamides are generally effective in the reduction of aldehydes with trichlorosilane, see ref. 4.

7 For a pioneering study on aldol reaction of trichlorosilyl enolates, see: S. E. Denmark, K.-T. Wong and R. A. Stavenger, *J. Am. Chem. Soc.*, 1997, **119**, 2333.

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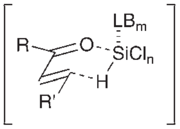
8 Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using dibenzyl ether as an internal standard.

9 ^{1}H NMR study of the reaction of benzalacetone with trichlorosilane in deuterated dichloromethane confirmed the formation of the corresponding (*Z*)-trichlorosilyl enolate (assigned by a NOESY experiment), which supports a six-membered cyclic transition state with the *s-cis* conformation of enones (Figure).



LB: Lewis Base

A similar mechanism has been suggested for borane reduction, see: G. P. Boldrini, M. Bortolotti, F. Mancini, E. Tagliavini, C. Trombini and A. Umani-Ronchi, *J. Org. Chem.*, 1991, **56** 5820.

10 Low diastereoselectivities (dr = 50 : 50 to 78 : 22) were observed in each case probably due to contributions of both catalyzed and non-catalyzed aldol processes, see ref. 7.

11 We have employed BINAPO as a chiral Lewis base catalyst for enantioselective allylation, aldol reaction and epoxide ring-opening reaction, see: S. Kotani, S. Hashimoto and M. Nakajima, *Tetrahedron*, 2007, **63**, 3122.

12 The minor *anti*-isomer is racemic, which is consistent with the fact that the non-catalyzed aldol process favors the *anti*-product in a similar system, see ref. 7.