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Synthesis of a series of novel chiral Lewis base catalysts and their application in promoting asymmetric hydrosilylation of β-enamino esters†

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A series of novel chiral Lewis base catalysts were synthesized from L-serine and applied in the hydrosilylation of β-enamino esters, in which the optimal one promoted the reactions to afford a wide variety of β-amino esters in good yields with good enantioselectivities. It is noteworthy that several cyclic substrates were hydrosilylated under the optimal conditions to give the cyclic β-amino esters with high yields, good diastereoselectivities as well as good ee values.

Introduction

β-Amino acids are key building blocks of peptides, peptidomimetics, many natural products and other physiologically active compounds.[1] Notably, peptides based on β-amino acids have been proven to have secondary structures comparable to their α-amino acid analogues, but are not vulnerable towards proteases.[1b,2] Therefore, the asymmetric synthesis of enantiomerically pure β-amino acids has been extensively studied.[1b,3] In the past few years, the catalytic asymmetric synthesis of β-amino acid derivatives using transition metals, organocatalysts and biocatalysts has been studied intensively.[3i,j] Among various catalytic asymmetric approaches to enantioenriched β-amino acid derivatives, the most efficient and straightforward way is catalytic asymmetric reduction of β-enamino esters. Up to now, many chiral transition metal complexes have been developed to catalyze asymmetric hydrogenation of β-enamino esters with high enantioselectivities.[4]

More recently, Lewis base catalytic asymmetric hydrosilylation[5] of β-enamino esters has emerged as a powerful alternative to transition-metal-catalysis in the synthesis of chiral β-amino acids.[5e,6] Malkov and co-workers employed an L-valine derived formamide as the Lewis base catalyst to promote asymmetric hydrosilylation of β-enamino esters to afford the corresponding β-amino esters in good yields with good enantioselectivities.[6a] We demonstrated asymmetric Lewis base organocatalyzed hydrosilylation of β-enamino esters[6b] as well as α-acetoxy-β-enamino esters.[6c] Sun and co-workers reported a highly enantioselective hydrosilylation of *N*-alkyl-β-enamino esters catalyzed by an *N*-sulfinyl L-prolinamide Lewis base.[6d] Benaglia and co-workers employed an ephedrine-derived 4-chloropicolinamide and chiral phosphinamide derived from proline to accelerate hydrosilylation of β-enamino esters, respectively.[6e,f] Jones *et al.* developed a novel imidazole-based Lewis base and employed it in enantioselective hydrosilylation of β-enamino esters.[6g] Although the present methods delivered a wide variety of β-amino esters with good yields in good enantioselectivities, sometimes they suffered from some harsh conditions, such as low temperature (down to −40 °C) or long reaction time (up to 2 days). Moreover, reactions of some kinds of β-enamino esters could not provide satisfactory results. For example, some cyclic substrates resulted in very poor enantioselectivities.[6b] Therefore, it is highly desirable to develop novel catalytic systems to improve the reaction conditions and adapt them to more types of substrates.

Our group has been actively engaged in research on chiral Lewis base organocatalyzed hydrosilylation of C=N double bonds. Recently, we developed a new class of chiral Lewis base organocatalysts **1** (Fig. 1) which catalyzed asymmetric hydrosilylation of α-acetoxy-β-enamino esters to afford α-hydroxy-β-amino esters in high yields with good diastereoselectivities as well as good enantioselectivities.[6c] Herein we describe a set of newly designed analogous catalysts **2** (Fig. 1) and their application in asymmetric hydrosilylation of β-enamino esters. To our delight, the optimal one of **2** promoted asymmetric hydrosilylation of β-enamino esters successfully. Particularly, some cyclic substrates underwent the reaction to afford various cyclic β-amino esters in high yields with good diastereoselectivities as well as good enantioselectivities.

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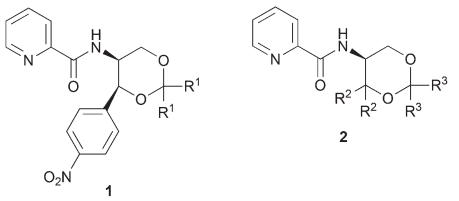
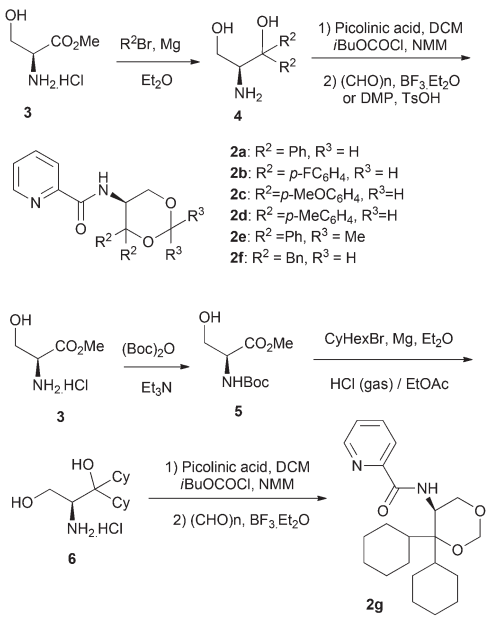


Fig. 1 Chiral Lewis base organocatalysts **1** and **2**.

Cyclic β-amino acids are important building blocks for the construction of many natural products, biologically active molecules and β-peptides.[7] Therefore, the synthesis of enantioenriched cyclic β-amino acid derivatives has attracted much attention.[4e,k,8] However, to date, there have been only a few examples of highly efficient asymmetric catalytic synthesis of enantioenriched cyclic β-amino acid derivatives. Zhang *et al.*[4e] and Zhou *et al.*[4k] have developed transition-metal catalytic highly diastereoselective and enantioselective hydrogenation of cyclic β-enamino esters, respectively. We employed a proline derived chiral Lewis base catalyst to promote the hydrosilylation of several cyclic β-enamino esters and the reactions gave the products in very high diastereoselectivities, but in very low enantioselectivities.[6b] Gratifyingly, in this study, the newly developed catalyst **2** made a good compensation for this methodology.

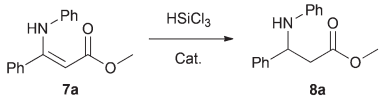
Results and discussion

The catalysts **2a–2g** were synthesized from methyl L-serinate hydrochloride **3** *via* three or five steps. As depicted in Scheme 1, first, methyl L-serinate hydrochloride **3** reacted with various Grignard reagents to afford amino dialcohols **4**.[9] Condensation of picolinic acid with **4** followed by cyclization with paraformaldehyde or 2,2-dimethoxy propane generates the novel chiral Lewis base catalysts **2a–2f**. As for the synthesis of **2g**, it was necessary to protect the amino group of **3** with Boc before reacting with Grignard reagent.



Scheme 1 Preparation of catalysts **2a–2g**.

Table 1 Screening of chiral Lewis base catalysts, solvents and temperatures in the enantioselective hydrosilylation of β-enamino ester **7a**[a]



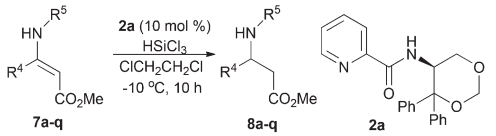
Entry	Cat.*	Solvent	T (°C)	Yield[b] (%)	ee[c] (%)
1	**2a**	$ClCH_2CH_2Cl$	−10	97	94
2	**2b**	$ClCH_2CH_2Cl$	−10	96	92
3	**2c**	$ClCH_2CH_2Cl$	−10	97	91
4	**2d**	$ClCH_2CH_2Cl$	−10	98	90
5	**2e**	$ClCH_2CH_2Cl$	−10	96	88
6	**2f**	$ClCH_2CH_2Cl$	−10	96	53
7	**2g**	$ClCH_2CH_2Cl$	−10	95	52
8	**2a**	CH_2Cl_2	−10	96	92
9	**2a**	THF	−10	95	87
10	**2a**	$CHCl_3$	−10	50	N.D.[d]
11	**2a**	CH_3CCl_3	−10	50	N.D.[d]
12	**2a**	$ClCH_2CH_2Cl$	0	96	92
13	**2a**	$ClCH_2CH_2Cl$	−20	97	93

[a] Unless specified otherwise, the reaction was carried out with **7a** (0.3 mmol), trichlorosilane (0.6 mmol), catalyst **2** (10 mol%) in 3 mL of solvent for 10 hours. [b] Isolated yield based on **7a**. [c] The ee value was determined by chiral HPLC (Chiralcel OD). [d] Not detected.

With these catalysts in hand, we initiated the hydrosilylation of β-enamino ester **7a** in 1,2-dichloroethane at −10 °C. The results are summarized in Table 1. These sets of new catalysts were found to be highly active and the reactions were completed in 10 hours to give almost quantitative yields of the product. First, several diaryl catalysts **2a–2e** were tested and they all exhibited good enantioselection. Among these catalysts, **2a** delivered the best ee value of 94% (Table 1, entry 1). Introduction of electron-donating groups or electron-withdrawing groups at the *para* positions of the phenyl groups caused no improvement in enantioselection (Table 1, entries 2–4). Meanwhile, when catalyst **2e** which bears methyl groups at C2 of the six-membered ring of the catalyst was employed, the product was obtained in excellent yield, but the ee value decreased obviously (Table 1, entry 5). When the aryl groups were replaced by alkyl groups, the enantioselectivities decreased dramatically (Table 1, entries 6 and 7). Apparently the diaryl substituents of the six-membered ring of the catalyst were crucial to obtain high enantioselectivity. It suggests that arene–arene interaction between the catalyst and the substrate could make a great contribution to the enantioselection.

With the optimal conditions established above, the scope of this reaction was investigated. In the presence of 10 mol% of catalyst **2a**, a wide variety of β-enamino esters were hydrosilylated in 1,2-dichloroethane at −10 °C. The results are summarized in Table 2. Generally, varying the *N*-aryl substituent resulted in marginal changes in enantioselectivity (Table 2, entries 1–6). In most cases, good enantioselectivities were observed with β-aryl-*N*-aryl-β-enamino esters (Table 2, entries

Table 2 Enantioselective hydrosilylation of β-enamino esters **7a–q** promoted by chiral Lewis base **2a**[a]



Entry	7	R^4	R^5	Yield[b] (%)	ee[c] (%)
1	**7a**	Ph	Ph	97	94
2	**7b**	Ph	4-FC_6H_4	97	93
3	**7c**	Ph	4-ClC_6H_4	97	91
4	**7d**	Ph	4-BrC_6H_4	97	92
5	**7e**	Ph	4-MeC_6H_4	97	98
6	**7f**	Ph	4-$MeOC_6H_4$	96	94 (*R*)[d]
7	**7g**	4-FC_6H_4	4-$MeOC_6H_4$	98	88
8	**7h**	4-BrC_6H_4	4-$MeOC_6H_4$	97	92
9	**7i**	4-MeC_6H_4	4-$MeOC_6H_4$	98	95
10	**7j**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	96	94
11	**7k**	3-ClC_6H_4	4-$MeOC_6H_4$	97	94
12	**7l**	2-ClC_6H_4	4-$MeOC_6H_4$	98	80
13	**7m**	2-Naphthyl	4-$MeOC_6H_4$	96	96
14	**7n**	4-$BnOC_6H_4$	4-FC_6H_4	96	95
15	**7o**	3-$MeOC_6H_4$	Ph	96	92
16	**7p**	Bn	4-$MeOC_6H_4$	96	45
17	**7q**	Ph	Bn	97	82

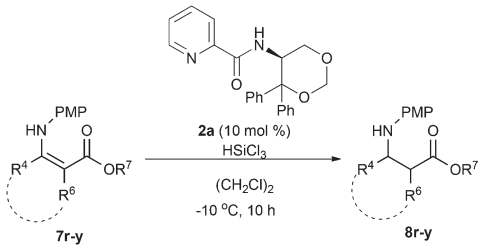
[a] Unless specified otherwise, the reaction was carried out with 7 (0.3 mmol), trichlorosilane (0.6 mmol), **2a** (10 mol%) in 3 mL of 1,2-dichloroethane at −10 °C for 10 hours. [b] Isolated yield based on 7. [c] The ee was determined by chiral HPLC (Chiralcel OD, AD or OJ). [d] The absolute configuration of the product was determined by a comparison of its optical rotation value with the literature datum.[6b]

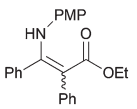
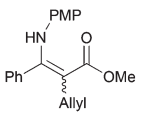
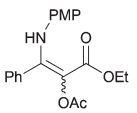
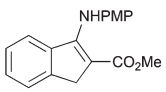
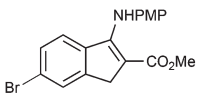
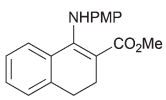
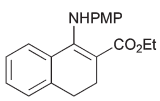
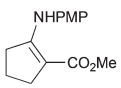
1–11 and 13–15). However, β-*ortho*-substituted-phenyl substrate **7l** gave only a moderate ee value (Table 2, entry 12). β-Alkyl-*N*-aryl-β-enamino ester **7p** afforded poor enantioselection (Table 2, entry 16). β-Aryl-*N*-alkyl-β-enamino ester **7q** also afforded rather low enantioselectivity (Table 2, entry 17).

To further extend the utility of our methodology, several kinds of α-substituted-β-enamino esters were also subjected to the titled reaction. The results are summarized in Table 3. Hydrosilylation of α-phenyl substrates **7r** afforded the desired products **8r** with high yield, high diastereoselectivity but poor enantioselectivity (Table 3, entry 1), while α-allyl substrate **7s** and α-acetyl substrate **7t** provided good enantioselectivities, but inferior diastereoselectivities (Table 3, entries 2 and 3). To our delight, several cyclic substrates **7u–x** reacted smoothy to generate the corresponding products with excellent yields in high diastereoselectivities as well as good enantioselectivities (Table 3, entries 4–7). However, cyclic substrate **7y** delivered a poor enantioselectivity (Table 3, entry 8).

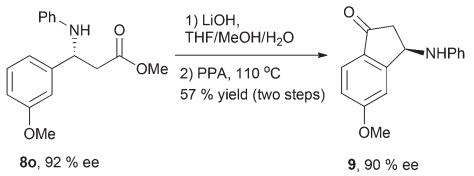
In order to demonstrate the synthetic utility of this transformation, product **8o** was hydrolyzed with LiOH followed by cyclization by PPA to generate the 3-aminoindan-1-one derivative **9** (Scheme 2). 3-Aminoindan-1-one derivatives are versatile synthetic intermediates toward the 1-aminoindane moiety embedded in many biologically important compounds including HIV protease inhibitors,[10] neuroprotective agents,[11] and the drugs used for cocaine abuse treatments.[12]

Table 3 Asymmetric hydrosilylation of α-substituted-β-enamino esters **7r–y** under the optimal conditions[a]

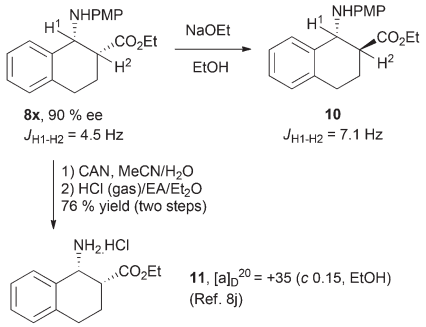


Entry	7	Yield[b] (%)	dr[c]	ee[d] (%)
1	 **7r**	97	*anti* : *syn* 21 : 1	34 (*anti*)
2[e]	 **7s**	90	*anti* : *syn* 3.2 : 1	90 (*anti*) 42 (*syn*)
3[f]	 **7t**	82	*syn* : *anti* 10 : 1	90 (*syn*) (2*R*,3*S*)[g]
4	 **7u**	98	*syn* : *anti* >99 : 1	95 (*syn*)
5	 **7v**	97	*syn* : *anti* >99 : 1	96 (*syn*)
6	 **7w**	95	*syn* : *anti* >99 : 1	92 (*syn*)
7	 **7x**	98	*syn* : *anti* >99 : 1	90 (*syn*)
8[e]	 **7y**	95	*syn* : *anti* >99 : 1	18 (*syn*)

[a] Unless specified otherwise, the reaction was carried out with 7 (0.3 mmol), trichlorosilane (0.6 mmol), **2a** (10 mol%) in 3 mL of 1,2-dichloroethane for 10 hours. [b] Isolated yield based on 7. [c] The dr values were determined by ^{1}H NMR. [d] The ee values were determined by chiral HPLC (Chiralcel OD, AD or OJ). [e] The reaction time is 24 hours. [f] The yield, dr and ee values were measured after the product was hydrolyzed by K_2CO_3 in MeOH. [g] The absolute configuration of the product was determined by comparison of its optical rotation value and chiral HPLC with the literature data.[6c]



Scheme 2 Synthesis of chiral 3-aminoindan-1-one derivative **9**.



Scheme 3 Isomerization of **8x** and determination of its configuration.

Furthermore, isomerization of cyclic product **8x** was performed. Treatment of **8x** with NaOEt provided the corresponding epimer **10**. The coupling constant of H^1–H^2 of **8x** is 4.5 Hz and the coupling constant of H^1–H^2 of **10** is 7.1 Hz. It reveals that the relative configuration of **8x** is *syn*. In addition, **8x** was deprotected with CAN followed by treatment with HCl to give a known compound **11**. Thus the absolute configuration of compound **8x** was determined as (1*R*,2*R*) by a comparison of the optical rotation value of **11** with the literature data (Scheme 3).[8j]

Conclusions

In summary, we have developed a highly enantioselective hydrosilylation of β-enamino esters catalyzed by a novel Lewis base derived from L-serine. This transformation enables us to prepare various enantioenriched β-amino esters in good yields as well as good enantioselectivities under rather moderate conditions. Notably, several cyclic substrates underwent reaction to provide cyclic β-amino esters in high yields with excellent diastereoselectivities as well as good enantioselectivities. Afterwards, one of the products was employed in the construction of a 3-aminoindan-1-one derivative. The absolute configurations of the products were determined by a comparison of their optical rotation values with the literature data. Further work is in progress to explore new applications of this novel Lewis base organocatalyst.

Acknowledgements

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