

Highly Diastereoselective and Enantioselective Synthesis of α -Hydroxy β -Amino Acid Derivatives: Lewis Base Catalyzed Hydrosilylation of α -Acetoxy β -Enamino Esters**

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Chiral α -hydroxy β -amino acid moieties are important structural components in a wide variety of biologically active compounds as well as natural products, of which the side chains of Taxol and its analogues are the most famous examples.^[1] Consequently, the synthesis of chiral α -hydroxy β -amino acid derivatives has attracted considerable attention.^[2] Some syntheses include the Sharpless asymmetric aminohydroxylation,^[3] asymmetric dihydroxylation,^[4] ring opening of chiral epoxides,^[5] asymmetric nitroaldol reactions,^[6] asymmetric Mannich reaction,^[7] asymmetric 1,3-dipolar cycloaddition,^[8] and other transformations.^[9] Among the successful strategies developed for obtaining optically active α -hydroxy β -amino acid derivatives, those that lead to substrates containing certain functional groups are of great significance. Accordingly, it can be reasoned that direct asymmetric reduction of the corresponding C=N double bond in substrates would be the most straightforward way to construct chiral α -hydroxy β -amino acid derivatives. However, to the best of our knowledge, the research on the above-mentioned reaction has not yet been reported.

Recently, asymmetric reactions involving the Lewis base activation of Lewis acids has attracted much attention.^[10] Among these reactions, chiral Lewis base catalyzed asymmetric hydrosilylation of C=N double bonds has become an important approach to chiral nitrogen-containing compounds because of the mild reaction conditions, cheap reagents, and the environmentally benign nature of this transformation.^[11] Several groups have achieved impressive progress in this field.^[12] During our ongoing studies on chiral Lewis base catalyzed asymmetric hydrosilylation of C=N double bond compounds such as β -enamino esters,^[12m] we envisioned that the design and synthesis of β -enamino esters bearing various functional groups on the α position would provide a wide range of precursors to α -substituted β -amino acid derivatives.

Therefore, we first tried to introduce an acetoxy group to the α position of β -enamino esters so as to generate α -acetoxy β -enamino ester **1** in which every functional group was finely assembled as depicted in Figure 1.

(1*S*,2*S*)-2-Amino-1-(4-nitrophenyl)propane-1,3-diol (**2**) is the intermediate of chloramphenicol. It is very cheap and easily accessible. The two hydroxy groups can undergo condensation with a ketone or an aldehyde to generate a six-membered ring.^[13] Thus it occurred to us that we could make a novel chiral, rigid picolinamide Lewis base catalyst through the same transformation. We reasoned that this rigid catalyst might be highly selective in promoting asymmetric hydrosilylation of C=N double bonds. Hence we synthesized catalysts through two facile steps. As can be seen in Scheme 1, **2** was condensed with picolinic acid to give amide **3**. The two hydroxy groups of amide **3** were then condensed with formaldehyde or a ketone to generate the cyclic catalysts **4a–4d**.

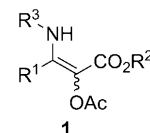
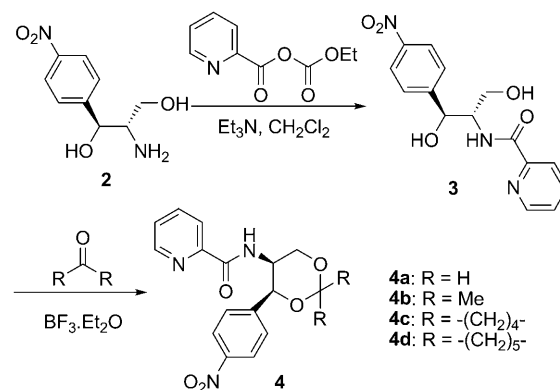


Figure 1. α -Acetoxy β -enamino esters **1** that were subjected to hydrosilylation in this study.



Scheme 1. Synthesis of the novel chiral Lewis base catalysts **4a–4d**.

First we initiated the hydrosilylation of α -acetoxy β -enamino ester **1a** by employing **4a** as the catalyst. Gratifyingly, the reaction proceeded smoothly in 1,2-dichloroethane at -10°C for 40 hours to generate the desired product in almost quantitative yield with a high diastereoselectivity of 91:9 (*syn/anti*), as well as a high enantioselectivity of 94% (Table 1, entry 1). Encouraged by this result, we then used the bulkier catalysts **4b–4d** to promote the hydrosilylation of **1a**.

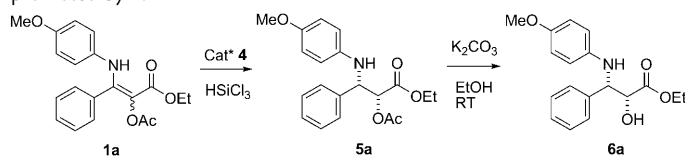
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Table 1: Asymmetric hydrosilylation of α -acetoxy β -enamino ester **1a** promoted by **4**.



Entry ^[a]	Cat* (mol %)	Solvent	T [°C]	t [h]	Yield [%] ^[b]	syn/ anti ^[c]	ee [%] ^[d]
1	4a (10%)	ClCH ₂ CH ₂ Cl	−10	40	95	91:9	94
2	4b (10%)	ClCH ₂ CH ₂ Cl	−10	40	99	60:40	80
3	4c (10%)	ClCH ₂ CH ₂ Cl	−10	40	96	63:37	87
4	4d (10%)	ClCH ₂ CH ₂ Cl	−10	40	93	62:38	80
5	4a (10%)	CH ₂ Cl ₂	−10	30	90	84:16	86
6	4a (10%)	Cl ₂ CHCHCl ₂	−10	60	47	77:23	88
7	4a (10%)	CHCl ₃	−10	40	54	89:11	84
8	4a (10%)	THF	−10	15	98	82:18	91
9	4a (15%)	ClCH ₂ CH ₂ Cl	−10	24	98	91:9	93
10	4a (20%)	ClCH ₂ CH ₂ Cl	−10	24	99	91:9	93
11	4a (10%)	ClCH ₂ CH ₂ Cl	0	24	97	91:9	90
12	4a (10%)	ClCH ₂ CH ₂ Cl	−20	60	96	91:9	93

[a] Unless otherwise specified, the reactions were carried out on a 0.15 mmol scale with 2.0 equiv of HSiCl₃ in 1.5 mL of solvent. [b] Yield of isolated **5a**. [c] The d.r. values of **6a** were determined by HPLC analysis using a chiral stationary phase. [d] The ee values of the major diastereomer of **6a** were determined by HPLC analysis using a chiral stationary phase.

These catalysts proved to be highly active, however, the diastereoselectivity and enantioselectivity were lower (Table 1, entries 2–4).

Therefore, **4a** was determined to be the optimal catalyst and was employed in the subsequent investigations. Several solvents were tested for the reaction. Dichloromethane gave a good yield but lower diastereoselectivity and enantioselectivity (Table 1, entry 5). To our surprise, 1,1,2,2-tetrachloroethane and chloroform resulted in very poor yields (Table 1, entries 6 and 7). The reaction in THF was complete in only 15 hours; however, it suffered from an evident decrease in diastereoselectivity and a little erosion in enantioselectivity (Table 1, entry 8). Hence, 1,2-dichloroethane was determined to be the most appropriate solvent for this study. In addition, we found that the reaction proceeded sluggishly in dehydrated solvent to give very little product, whereas the reaction proceeded smoothly in commercially available solvent without any pretreatment. We reasoned that trace acid arising from the reaction of trichlorosilane with traces of water in the solvent promoted the isomerization of the substrate from the enamine tautomer to the imine tautomer, which is the species involved in the hydrosilylation. Further attempts to enhance the d.r. and ee values by increasing the catalyst loading did not prove to be successful (Table 1, entries 9 and 10). When the reaction was conducted at a higher temperature (0°C), the diastereoselectivity remained at the same level and the ee value decreased slightly (Table 1, entry 11). However, when the temperature fell to −20°C, no improvement in either the d.r. or ee values were observed (Table 1, entry 12).

Having established the optimal reaction conditions, the generality of this reaction was examined. In the presence of

10 mol % of catalyst **4a**, a wide variety of α -acetoxy β -enamino esters were hydrosilylated in 1,2-dichloroethane at −10°C using trichlorosilane. The results are summarized in Table 2. Generally, most of the β -aryl- α -acetoxy β -enamino esters underwent the reaction smoothly to give the desired products in high yields with good diastereoselectivities and enantioselectivities (Table 2, entries 1–9, 11 and 15). The electronic nature of the substituents on the

Table 2: Asymmetric hydrosilylation of α -acetoxy β -enamino esters **1a–1n** promoted by **4a**.

Entry ^[a]		t [h]	Yield [%] ^[b]	syn/ anti ^[c]	ee [%] ^[d]
1	1a : R ¹ = Ph	40	95	91:9 ^[e]	94 ^[f]
2	1b : R ¹ = 4-BrC ₆ H ₄	40	90	93:7	92
3	1c : R ¹ = 4-FC ₆ H ₄	40	94	90:10	89
4	1d : R ¹ = 4-MeOC ₆ H ₄	42	91	92:8	93
5	1e : R ¹ = 4-MeC ₆ H ₄	40	98	91:9	93
6	1f : R ¹ = 3-MeOC ₆ H ₄	40	96	91:9	87
7	1g : R ¹ = 3-ClC ₆ H ₄	40	93	92:8	91
8	1h : R ¹ = 3, 4-MeO ₂ C ₆ H ₃	40	97	92:8	93
9	1i : R ¹ = 2-naphthyl	40	92	92:8	93
10	1j : R ¹ = 2-thienyl	30	96	95:5	77
11	1k : R ¹ = 2-furanyl	24	98	88:12	96
12	1l : R ¹ = Bn	40	93	99:1	41
13	1m : R ² = Me	40	97	91:9	93
14	1n : R ² = <i>t</i> Bu	40	93	93:7	93
15	1o	42	90	95:5	93

[a] Unless otherwise specified, the reactions were carried out on a 0.15 mmol scale with 2.0 equiv of HSiCl₃ in 1.5 mL of solvent. [b] Yield of isolated **5**. [c] The d.r. values of **5** were determined by HPLC analysis using a chiral stationary phase. [d] The ee values of the major diastereomers of **5** were determined by HPLC analysis using a chiral stationary phase. [e] The d.r. value of **6a** was determined by HPLC analysis using a chiral stationary phase. [f] The ee value of the major diastereomer of **6a** was determined by HPLC analysis using a chiral stationary phase.

phenyl group showed very little influence on the results of the reaction. β -Heterocyclic aryl substrates **1j** and **1k** were found to undergo the reaction more quickly. Notably, the thienyl-derived **1j** gave a much lower ee value (Table 2, entry 10), whereas furanyl-derived **1k** resulted in excellent enantioselectivity (96% ee) albeit with a slightly lower diastereoselectivity (Table 2, entry 11). The reaction of β -benzyl- α -acetoxy β -enamino ester **1l** proceeded smoothly to generate the corresponding product in good yield with excellent diastereoselectivity (99:1), but, unfortunately with a poor ee value

(Table 2, entry 12). It is clear that the β -aryl group plays a key role in enantioselection in our asymmetric catalytic system. Variation of the ester group of the substrates led to little change in d.r. and *ee* values (Table 2, entries 13 and 14).

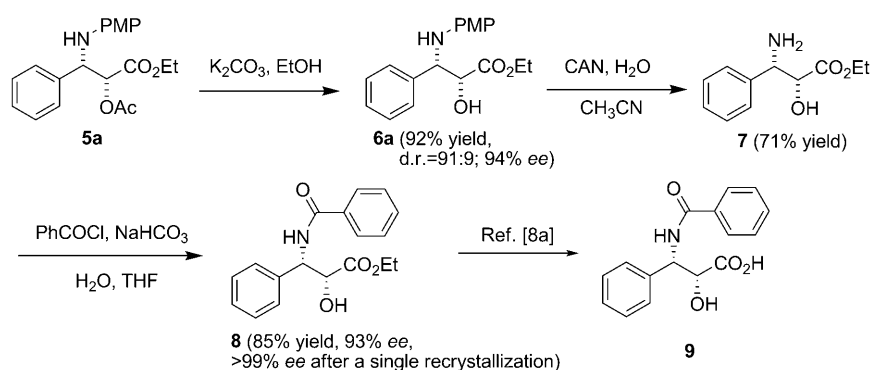
To further illustrate the synthetic potential of this methodology, the formal synthesis of the C13 side chain of taxol was performed. As shown in Scheme 2, the asymmetric hydrosilylation product **5a** was treated with K_2CO_3 to generate **6a**. Then the PMP group was removed with CAN to afford amino alcohol **7**. Finally, alcohol **7** was benzoylated to give **8**. Compound **8** was identical with the reported compound, which can be hydrolyzed to provide the C13 side chain of taxol (**9**) according to the literature.^[8a]

Furthermore, product **5o** was converted into oxazolidinone **12**, which shows promising activity in the inhibition of cholesterol transporter NPC1L1 and is thus, a potent hypocholesterolemic agent.^[14] As seen in Scheme 3, the asymmetric hydrosilylation product **5o** was treated with K_2CO_3 to make **6o**, which was then cyclized with triphosgene to afford oxazolidinone **10**. Subsequent reaction of **10** with benzyl amine in dichloromethane, followed by hydrogenation with Pd/C and hydrogen yielded oxazolidinone **12**. Notably, the N-aryl group is an exact fragment found in the final product and therefore does not need to be removed in this case.

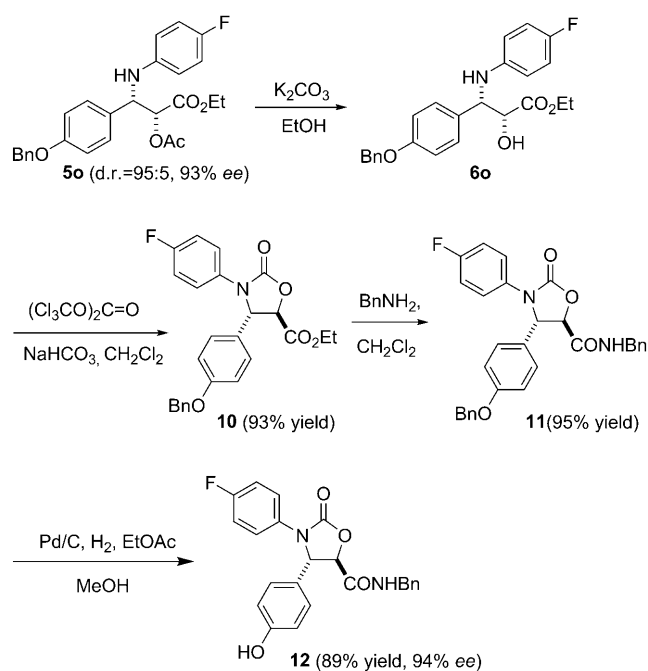
In conclusion, various α -acetoxy β -enamino esters were designed and synthesized, and a set of novel chiral Lewis base catalysts were prepared from readily available chiral sources. One of the catalysts was found to accelerate the asymmetric hydrosilylation of α -acetoxy β -enamino esters efficiently. This methodology was used to prepare a wide range of chiral α -acetoxy β -amino acid derivatives in high yields with good diastereoselectivities and enantioselectivities. The reactions were conducted under very mild reaction conditions and the removal of water and oxygen from the reaction system was not necessary. This methodology was additionally applied successfully in synthesis of the taxol C13 side chain and an oxazolidinone which is a potent hypocholesterolemic agent. Investigations of the mechanism and further application of this transformation to the construction of other complex natural products or pharmaceutically active substances are in progress. In addition, the catalytic asymmetric hydrosilylation of other α -substituted β -enamino esters is in progress.

Experimental Section

General procedure for asymmetric hydrosilylation of α -acetoxy β -enamino esters: A solution of trichlorosilane (31 μ L, 0.3 mmol, 2.0 equiv) in 120 μ L of $ClCH_2CH_2Cl$ was added to a stirred solution of the corresponding α -acetoxy β -enamino ester (0.15 mmol) and the catalyst (0.015 mmol) in $ClCH_2CH_2Cl$ (1.5 mL) at $-10^\circ C$. The mixture was stirred at the same temperature until the reaction was complete as determined by TLC. The reaction mixture was then quenched with a saturated aqueous solution of $NaHCO_3$ and was extracted with EtOAc. The combined extracts were washed with



Scheme 2. Synthesis of the taxol C13 side chain. PMP = *para*-methoxyphenyl, CAN = ceric ammonium nitrate.



Scheme 3. Synthesis of oxazolidinone **12**. Bn = benzyl.

brine and dried over anhydrous Na_2SO_4 . The solvents were removed under vacuum. Purification of the reaction mixture by column chromatography (silica gel, hexanes/EtOAc = 10:1) afforded pure product. The *ee* values were determined using established HPLC techniques with chiral stationary phases.

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