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Highly Enantioselective Synthesis of β-Amino Acid Derivatives by the Lewis Base Catalyzed Hydrosilylation of β-Enamino Esters

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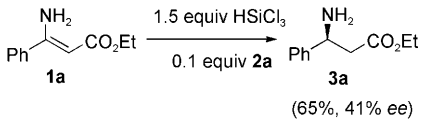
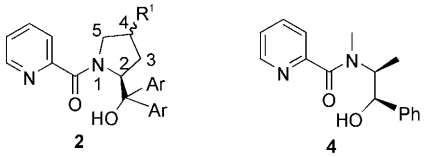
Optically active β-amino acids are very important chiral building blocks for the synthesis of β-peptides, β-lactams, natural products, and physiologically active substances.[1] Therefore, efficient methods for the synthesis of optically active β-amino acids would be of great value for drug discovery and organic synthesis. Among the approaches to chiral β-amino acids,[2] the most straightforward and atom economic one is catalytic asymmetric reduction of β-enamino esters. Pioneered by Noyori et al.,[3a] many chiral transition-metal complexes were developed to catalyze high-pressure hydrogenation of *N*-acyl β-enamino esters,[3] *N*-aryl β-enamino esters,[4] or *N*-unprotected β-enamino esters[5] with high enantioselectivities. However, transition-metal-catalyzed hydrogenation cannot get rid of the problems of metal leaching, high pressure, the cost of the catalyst, and its regeneration.

Recently, asymmetric reactions involving the strategy of Lewis base activation of Lewis acids attracted much attention.[6] Among these reactions, Lewis base catalyzed enantioselective hydrosilylation of ketimines has become an important alternative to transition-metal catalysis in synthesis of chiral amines.[7] However, there is only limited examples of enantioselective hydrosilylation of β-enamino esters.[7b,8] To our knowledge, a general, highly enantioselective Lewis base organocatalyzed hydrosilylation of β-enamino esters has not been reported, and thus remains an important challenge.

Herein, we describe the first general, highly enantioselective organocatalytic hydrosilylation of β-enamino esters. Matsumura and co-workers reported the hydrosilylation of unprotected β-enamino ester **1a** catalyzed by *N*-picolinoylpyrrolidine derivative **2a** that resulted in poor yield and enantioselectivity (Scheme 1).[7b] However, to our delight, we found that the same catalyst **2a** and its analogues displayed excellent activities and enantioselectivities in promoting hydrosilylation of *N*-aryl β-enamino esters.



Scheme 1. Enantioselective hydrosilylation of β-enamino ester **1a** reported by Matsumura et al.[7b]



2a: R^1 = H, Ar = Ph
2b: R^1 = H, Ar = *p*MeC_6H_4
2c: R^1 = H, Ar = 3, 5-$Me_2C_6H_3$
2d: R^1 = OMe (*R*), Ar = Ph
2e: R^1 = OMe (*S*), Ar = Ph

First, *N*-picolinoylpyrrolidine derivatives **2a**–**2e** and *N*-picolinoylephedrine (**4**)[7m] were evaluated in hydrosilylation of (*Z*)-methyl 3-phenyl-3-(phenylamino)acrylate.[9] As can be seen in Table 1, 10 mol% of catalysts **2a**–**2c** delivered

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Table 1. Enantioselective hydrosilylation of β-enamino ester **1b**.

1b **3b**

Entry[a]	Cat*	Solvent	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	**2a**	$CHCl_3$	0	36	88	87
2	**2a**	CH_2Cl_2	0	36	93	80
3	**2a**	THF	0	36	trace	–
4	**2a**	toluene	0	36	90	67
5	**2b**	$CHCl_3$	0	36	92	88
6	**2c**	$CHCl_3$	0	36	84	90
7	**2d**	$CHCl_3$	0	36	96	57
8	**2e**	$CHCl_3$	0	36	94	55
9	**4**	$CHCl_3$	0	36	88	−72
10	**2a**	$CHCl_3$	−10	36	88	89
11	**2b**	$CHCl_3$	−10	36	84	90
12	**2a**	$CHCl_3$	−20	36	90	91
13	**2b**	$CHCl_3$	−20	36	88	91
14	**2a**	$CHCl_3$	−30	36	76	92
15	**2b**	$CHCl_3$	−30	36	78	92
16	**2b**	$CHCl_3$	−30	48	86	92
17	**2c**	$CHCl_3$	−30	48	94	95
18	**2a**	$CHCl_3$	−40	72	90	83

[a] Unless specified otherwise, reactions were carried out with 10 mol% of catalyst and 2.0 equiv of $HSiCl_3$ on a 0.2 mmol scale in 2.0 mL of solvent. [b] Isolated yield based on the β-enamino ester. [c] The *ee* values were determined using chiral HPLC.

satisfying yields and good enantioselectivities in chloroform at 0°C. The *ee* values (*ee* = enantiomeric excess) increased slightly along with the increase of the size of the aryl groups in the catalysts (Table 1, entries 1, 5, and 6). However, introduction of a methoxy group on C4 of pyrrolidine ring of **2a** led to dramatic drop in enantioselection, no matter what the configuration of the carbon atom is (Table 1, entries 7 and 8). Perhaps it is due to the undesired coordination of methoxy group with trichlorosilane. Compound **4** gave the opposite enantiomer with moderate *ee* value (Table 1, entry 9).

Examination of the solvents revealed that chlorinated solvents proved to be essential. Little reaction was observed in nonprotic polar media such as THF (Table 1, entry 3). Reactions performed in nonpolar solvent such as toluene gave high yield but moderate *ee* value (Table 1, entry 4). The most favorable solvent is chloroform (Table 1, entry 1). Lowering the temperature from 0°C to −30°C resulted in an evident improvement in enantioselectivities. The best yield and enantioselectivity were obtained with catalyst **2c** at −30°C for 48 h (Table 1, entry 17). Further lowering the temperature to −40°C led to decrease in both reactivity and enantioselectivity (Table 1, entry 18).

Under the optimized conditions, the generality of the Lewis base organocatalyzed hydrosilylation of various β-enamino esters were examined. In the presence of 10 mol% of **2c**, β-enamino esters **1b–1y** were reduced in chloroform at −30°C with trichlorosilane. The results were summarized in Table 2. Interestingly, this catalytic system exhibited a high sensitivity to the *N*-substituents. All of the *N*-aryl β-enamino esters underwent the hydrosilylation smoothly to give corresponding β-amino esters in good yields. However, *N*-acyl β-

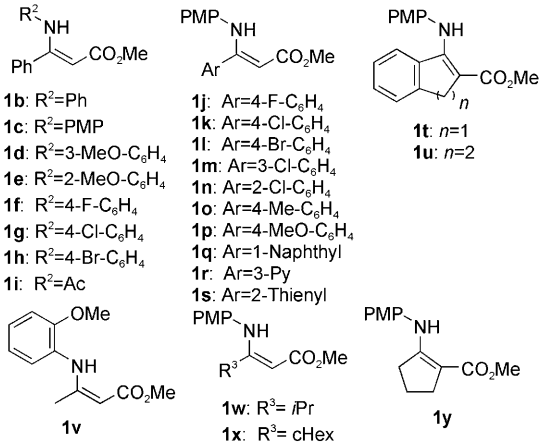


Table 2. Enantioselective hydrosilylation of β-enamino esters **1** catalyzed by **2c**.

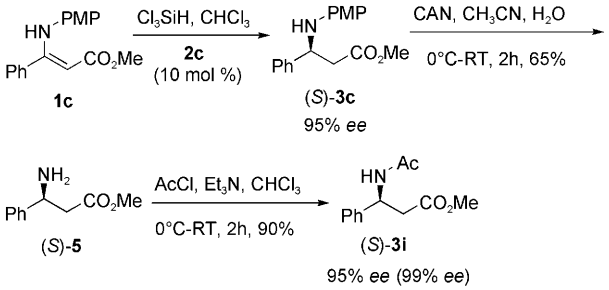
Entry[a]	β-Enamino ester	Yield [%][b]	*ee* [%][c]	Conf.
1	**1b**	94	95	(−)
2	**1c**	82	95	*S* (−)[d]
3	**1d**	86	96	(−)
4	**1e**	92	92	(+)
5	**1f**	96	92	(+)
6	**1g**	97	93	(+)
7	**1h**	97	92	(−)
8	**1i**	NR	-	–
9	**1j**	93	94	(+)
10	**1k**	91	92	(−)
11	**1l**	92	92	(+)
12	**1m**	95	91	(−)
13	**1n**	84	90	(+)
14	**1o**	95	94	(−)
15	**1p**	95	95	(−)
16	**1q**	96	95	(+)
17	**1r**	84	70	(−)
18	**1s**	96	88	(−)
19	**1t**	93	28 (dr > 99:1)	(+)
20	**1u**	84	54 (dr > 99:1)	(−)
21	**1v**	91	17	(+)
22	**1w**	92	66	(+)
23	**1x**	96	80	(+)
24	**1y**	90	28 (dr > 99:1)	(+)

[a] Unless specified otherwise, reactions were carried out with 10 mol% of catalyst and 2.0 equiv of $HSiCl_3$ on a 0.2 mmol scale in 2.0 mL of $CHCl_3$ at −30°C for 48 h. [b] Isolated yield based on the β-enamino ester. [c] The *ee* values were determined using chiral HPLC. [d] determined by comparison of the optical rotation value of derivative of **3c** with literature data.[3n]

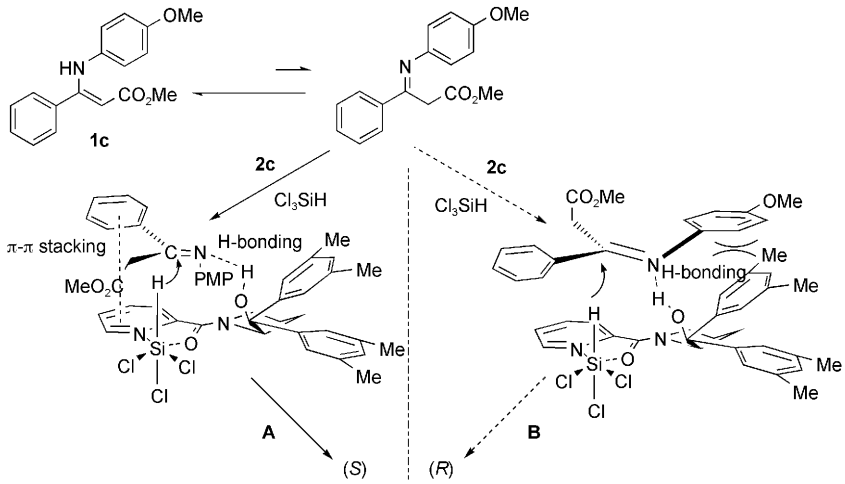
enamino ester **1i** was totally inactive in this catalytic system (Table 2, entry 8). Perhaps it is due to the difficulty for **1i** to isomerize from enamine tautomer to imine tautomer. Varying the *N*-aryl substituent resulted in marginal changes in enantioselectivity (Table 2, entries 1–7). In most cases, high enantioselectivities (≥90% *ee*) were observed with β-aryl-*N*-aryl β-enamino esters (Table 2, entries 9–16). However, pyridinyl-derived **1r** and thienyl-derived **1s** gave lower *ee* values (Table 2, entries 17 and 18), suggesting a competing coordination of the heteroatom in the substrate with trichlorosilane. As to β-alkyl-*N*-aryl β-enamino esters, the *ee*

values increased along with the increase of the size of the alkyl groups in the substrates (Table 2, entries 21–23). Besides, cyclic substrates **1t**, **1u**, and **1y** provided poor enantioselectivities but very high diastereoselectivities (Table 2, entries 19, 20, and 24). It seems that the rigidity of the substrate is very unfavorable to the coordination between catalyst and substrate.

To test the practicality of the current method for the synthesis of β-amino esters, the asymmetric hydrosilylation of β-enamino esters **1c** in a gram-scale was carried out using 10 mol% of **2c**. The reaction proceeded smoothly to provide **3c** in 82% yield and 95% *ee* (1.0 g, 3.5 mmol of **1c)**. Furthermore, the *N*-PMP (PMP=*p*-methoxyphenyl) group of product **3c** was deprotected with CAN (CAN=ceric ammonium nitrate) to give β-amino ester **5** in 65% yield without racemization (Scheme 2). Following acetylation of the amino group of **5** generated the known compound *N*-acetyl β-aminoester **3i**.[3n] The absolute configuration of **3c** was determined as *S* by measurement of the optical rotation value of compound **3i**.



Scheme 2. Gram-scale asymmetric hydrosilylation of **1c**, deprotection of the *N*-PMP group in product **3c** and following protection of the amino group with acetic group. *ee* for **3i** given in parentheses is after a single recrystallization; determined by HPLC with a chiral AD-H column. $[\alpha]_D^{20}=-79.5$ ($c=0.6$ in $CHCl_3$, 99% *ee*); literature:[3n] $[\alpha]_D^{20}=-79.9$ ($c=1.0$ in $CHCl_3$, *S*, 99% *ee*).



Scheme 3. A plausible reaction mechanism for hydrosilylation of **1c** catalyzed by **2c**.

Although detailed structural and mechanistic studies remain to be carried out, based on these facts, we propose a mechanism shown in Scheme 3. First, it is supposed that the reaction proceeds through the imine tautomer rather than the enamine tautomer. The nitrogen atom of the pyridine ring and the carbonyl oxygen atom of catalyst **2c** are coordinated to Cl_3SiH. Meanwhile, the imine is activated by the hydroxy group of **2c** through hydrogen bonding. The less hindered transition state **A** is consistent with the experimentally observed *si*-facial selectivity of the reaction. It can also be hypothesized that **A** will be stabilized by arene–arene interactions between the aromatic systems of the catalyst and the substrate.

In summary, we have demonstrated the first general, highly enantioselective Lewis base organocatalyzed hydrosilylation of β-enamino esters that enables the straightforward and mild synthesis of a broad range of β-amino acid derivatives in high yields (up to 97%) and enantioselectivities (up to 96% *ee*). The absolute configuration of product **3c** has been determined as *S*. Finally, a plausible mechanism has been proposed. Detailed investigations of the mechanism are in progress.

Experimental Section

General procedure for asymmetric hydrosilylation of *N*-aryl β-enamino esters: Trichlorosilane (41 μL, 0.40 mmol, 2.0 equiv) was added dropwise to a solution of the catalyst (0.02 mmol) and the corresponding β-enamino ester (0.20 mmol) in dry $CHCl_3$ (2 mL) at −30 °C. The reaction mixture was stirred at −30 °C for 48 h. Then the reaction was quenched with saturated aqueous solution of $NaHCO_3$. The mixture was extracted with EtOAc, and the combined extracts was washed with brine and dried over anhydrous $MgSO_4$. Concentration in vacuo followed by flash chromatography on silica gel with petroleum ether/ethyl acetate as the eluent afforded the β-amino esters. The *ee* values were determined using established HPLC techniques with chiral stationary phases.

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Keywords: amino acids · asymmetric synthesis · hydrosilylation · lactams · organocatalysis

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