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The First Highly Enantioselective Lewis Base Organocatalyzed Hydrosilylation of α-Imino Esters

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Novel, chiral Lewis base organocatalysts, which displayed poor enantioselection in the hydrosilylation of *N*-aryl β-enamino esters, were found to be the catalysts of choice in the hydrosilylation of α-imino esters. In the presence of 10 mol-% of the best catalyst, various α-imino esters underwent enantioselective hydrosilylation to provide a wide range of chiral α-amino esters with good yields (up to 97 %) and high enantioselectivities (up to 93 % *ee*) except for some special substrates.

Introduction

Chiral α-amino acids constitute some of the most important molecules in biological systems.[1] Natural and unnatural α-amino acids are also important tools in protein engineering and peptide-based drug discovery.[2] Therefore, intense research has been focused on the preparation of enantiomerically enriched α-amino acids.[3] Among the numerous approaches, the most straightforward one to chiral α-amino acid derivatives is the catalytic asymmetric direct reduction of α-enamides or α-imino esters. Chiral Lewis acid catalyzed hydrogenation of α-enamides has been well developed and utilized in industry.[4] Recently, chiral phosphoric acids were found to accelerate Hantzsch ester reduction of α-imino esters with excellent reactivities and enantioselectivities.[5] However, Hantzsch ester reduction occasionally suffers from difficulties in the purification of the products owing to the existence of pyridine derivatives.

In recent years, the strategy of metal-free chiral Lewis base activation of Lewis acid[6] has been widely used in asymmetric synthesis. Many efficient chiral Lewis bases have been developed to catalyze the enantioselective hydrosilylation of ketimines with trichlorosilane.[7] This new organocatalytic methodology has become a promising alternative to transition-metal catalysis in the synthesis of chiral amines. However, a very limited number of examples of chiral Lewis base catalyzed enantioselective hydrosilylation of α-imino esters has been reported, and the results are far from satisfactory.[8] Although a highly diastereoselective procedure was reported recently,[8e] a general, highly enantioselective, Lewis base catalyzed hydrosilylation of α-imino esters is still worth further exploration in view of the economy of this methodology and the great importance of chiral α-amino acids.

In this paper we report the first general, highly enantioselective hydrosilylation of α-imino esters catalyzed by novel chiral Lewis base organocatalysts derived from *trans*-4-hydroxy-L-proline. These catalysts exhibited only moderate enantioselectivities in the hydrosilylation of *N*-aryl β-enamino esters. However, they were found to catalyze the hydrosilylation of α-imino esters with high enantioselectivities (up to 93 % *ee*). It is very interesting because a poor catalyst for one kind of substrate would be the catalyst of choice for another kind of substrate. Perhaps there are no "poor" catalysts, only "unsuitable" catalysts.

Results and Discussion

During our continuing studies on chiral Lewis base catalyzed hydrosilylation of C=N double bond compounds,[8c,9] we made many efforts to search appropriate catalysts for the enantioselective hydrosilylation of α-imino esters. As can be seen in Table 1, we found that catalysts **1a** and **1b** (Figure 1), which gave good results in the enantioselective hydrosilylation of *N*-aryl β-enamino esters,[9] exhibited only moderate enantioselectivities in the hydrosilylation of ethyl 2-(4-methoxyphenylimino)-2-phenylacetate (**2a**) at –10 °C in chloroform (Table 1, Entries 1 and 2). Afterwards, we were very gratified to find that catalysts **1c** and **1d**, which delivered poor *ee* values in the enantioselective hydrosilylation of *N*-aryl β-enamino esters,[9] gave much higher enantioselectivities in this case (Table 1, Entries 3 and 4). Inversion of the configuration at C4 of the pyrrolidine ring from *R* to *S* only caused a slight drop in *ee*. Catalyst **1e** bearing a free hydroxy group at C4 of the pyrrolidine ring also gave a good result (Table 1, Entry 5).

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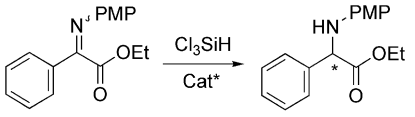
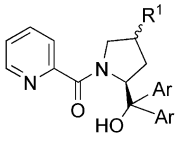
Table 1. Enantioselective hydrosilylation of α-imino ester **2a**.



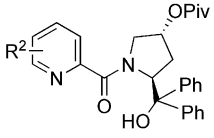
2a **3a**

Entry[a]	Cat*	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	$CHCl_3$	–10	24	92	66
2	**1b**	$CHCl_3$	–10	24	70	62
3	**1c**	$CHCl_3$	–10	24	90	79
4	**1d**	$CHCl_3$	–10	24	88	76
5	**1e**	$CHCl_3$	–10	24	84	82
6	**1f**	$CHCl_3$	–10	24	84	79
7	**1g**	$CHCl_3$	–10	24	85	81
8	**1h**	$CHCl_3$	–10	24	86	83
9	**1i**	$CHCl_3$	–10	24	98	88
10	**1j**	$CHCl_3$	–10	24	96	84
11	**1k**	$CHCl_3$	–10	24	95	78
12	**1l**	$CHCl_3$	–10	24	92	86
13	**1m**	$CHCl_3$	–10	24	95	77
14	**1n**	$CHCl_3$	–10	24	90	51
15	**1o**	$CHCl_3$	–10	24	95	65
16	**1p**	$CHCl_3$	–10	72	trace	–
17	**1i**	CH_2Cl_2	–10	24	96	88
18	**1i**	$ClCH_2CH_2Cl$	–10	24	91	82
19	**1i**	PhCl	–10	24	74	77
20	**1i**	toluene	–10	24	86	56
21	**1i**	CH_3CN	–10	24	98	32
22	**1i**	THF	–10	24	96	55
23	**1i**	diethyl ether	–10	24	54	51
24	**1i**	CH_2Cl_2	–20	41	98	90
25	**1i**	CH_2Cl_2	–30	41	96	91
26	**1i**	CH_2Cl_2	–40	67	97	92

[a] Unless specified otherwise, reactions were carried out with the catalyst (10 mol-%) and $HSiCl_3$ (2.0 equiv.) on a 0.5-mmol scale in the appropriate solvent (2.0 mL). [b] Isolated yield based on the α-imino ester. [c] The *ee* values were determined by using chiral HPLC.



1a: R^1 = H, Ar = *p*-MeC_6H_4
1b: R^1 = H, Ar = 3,5-$Me_2C_6H_3$
1c: R^1 = OMe (*R*), Ar = Ph
1d: R^1 = OMe (*S*), Ar = Ph
1e: R^1 = OH (*R*), Ar = Ph
1f: R^1 = OBn (*R*), Ar = Ph
1g: R^1 = OTMS (*R*), Ar = Ph
1h: R^1 = O-isovaleryl (*R*), Ar = Ph
1i: R^1 = OPiv (*R*), Ar = Ph
1j: R^1 = OBz (*R*), Ar = Ph
1k: R^1 = OP(O)$(OPh)_2$ (*R*), Ar = Ph
1l: R^1 = OPiv (*R*), Ar = *p*-MeC_6H_4



1m: R^2 = 5-OMe
1n: R^2 = 5-NO_2
1o: R^2 = 6-Br
1p: R^2 = 6-Me

Figure 1. Chiral Lewis base organocatalysts evaluated in this study.

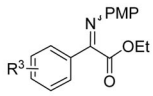
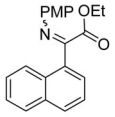
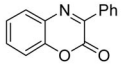
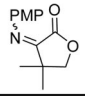
In this study, it seemed that introduction of a bulky group at C4 of the pyrrolidine ring would be beneficial to the reaction. In search of more effective catalysts, we modified the hydroxy group with various bulkier groups to generate a series of novel chiral Lewis bases. However, benzylation, trimethylsilylation, and isovalerylation of the hydroxy group only caused marginal changes in the enantioselection (Table 1, Entries 6–8). To our delight, when *O*-pivaloyl catalyst **1i** was employed, an obvious increase in enantioselectivity was observed (Table 1, Entry 9). Modification of the hydroxy group with benzoyl and diphenyl phosphoryl groups made no improvement in enantioselectivity (Table 1, Entries 10 and 11). Hence, pivoloylation of the hydroxy group at C4 of the pyrrolidine ring was regarded as the most suitable modification. An attempt to further enhance the *ee* value through enlarging the size of the aryl groups in the catalyst proved to be in vain (Table 1, Entry 12). Introduction of an electron-donating group or an electron-withdrawing group at C5 of the pyridine ring brought about dramatic decreases in the *ee* values in both cases (Table 1, Entries 13 and 14). 6-Bromo catalyst **1o** also displayed poor enantioselectivity (Table 1, Entry 15). Moreover, 6-methyl catalyst **1p** was totally inactive in the titled reaction (Table 1, Entry 16), perhaps as a result of the steric hindrance of methyl group, which made the catalyst hard to coordinate with trichlorosilane.

Hence, catalyst **1i** was determined as the most appropriate catalyst in this study. Afterwards, various solvents were screened. Chlorinated solvents were found to be superior to other kinds of solvents (Table 1, Entries 24–26). Chloroform and dichloromethane were both favorable. Lowering the temperature proved to be effective (Table 1, Entries 17–23). When the temperature was lowered to –40 °C, the reaction proceeded smoothly for 67 h to provide α-amino ester **3a** with almost quantitative yield and high enantioselectivity of 92 %*ee* (Table 1, Entry 26).

Subsequently, the generality of catalyst **1i** was examined in the hydrosilylation of various α-imino esters. However, under the optimal reaction condition for α-imino ester **2a**, the hydrosilylation of other α-imino esters proceeded sluggishly to give low yields of the desired products, whereas most of the starting materials decomposed. In order to activate the substrates, several acid additives were employed, of which pentanoic acid proved to be the most effective. Thus, in the presence of **1i** (10 mol-%), trichlorosilane (2 equiv.), and pentanoic acid (0.5 mol-%) a series of α-imino esters were reduced in dichloromethane at –40 °C. The results are summarized in Table 2. For substituted phenyl ethyl esters, *para* or *meta* substituents showed no obvious deleterious effects on reactivity and enantioselectivity, no matter whether the substituents were electron donating or electron withdrawing (Table 2, Entries 1–6, 9 and 10). However, *ortho* substitution on the phenyl group caused dramatic drops in the enantioselectivities (Table 2, Entries 7 and 8). Moreover, reaction of *ortho*-bromo substrate **2h** afforded the corresponding amino ester only in moderate yield. Apparently, *ortho* substitution on the phenyl group made the substrates sterically more hindered so that they exhibited lower reactivity and enantioselectivity. Owing to the same reason, reaction of 1-naphthyl derivative **2k** gave the product with inferior yield and *ee* value as well (Table 2, Entry 11). It should be noted that benzoxazinone **2l** underwent enantio-

selective hydrosilylation to provide the dihydrobenzoxazinone with acceptable yield and *ee* value (Table 2, Entry 12). Finally, an aliphatic and cyclic α-imino ester **2m** was reduced to give the desired product with good yield but very low *ee*.

Table 2. Enantioselective hydrosilylation of α-imino esters **2** catalyzed by **1i**.

Entry[a]	α-Imino ester		*t* [h]	Yield [%][b]	*ee* [%][c]	Conf.
		R^3=				
1		**2a**: H	67	97[d]	92	*R*(–)[e]
2		**2b**: 4-Me	94	97	93	(–)
3		**2c**: 4-MeO	94	94	91	(–)
4		**2d**: 4-F	96	96	88	(–)
5		**2e**: 4-Cl	127	90	86	(–)
6		**2f**: 4-Br	125	92	87	(–)
7		**2g**: 2-Cl	83	91	60	(–)
8		**2h**: 2-Br	72	71	51	(–)
9		**2i**: 3-Me	101	93	88	(–)
10		**2j**: 3-F	76	95	88	(–)
11		**2k**	61	76	73	(–)
12		**2l**	65	84	84	*R*(–) [f]
13		**2m**	77	90	15	(+)

[a] Unless specified otherwise, reactions were carried out with catalyst **1i** (10 mol-%), pentanoic acid (0.5 mol-%), and $HSiCl_3$ (2.0 equiv.) on a 0.5-mmol scale in CH_2Cl_2 (2.0 mL) at –40 °C. [b] Isolated yield based on the α-imino ester. [c] The *ee* values were determined by using chiral HPLC. [d] The reaction was carried out without pentanoic acid. [e] Determined by comparison of the optical rotation value of **3a** with the literature data.[5c] [f] Determined by comparison of the optical rotation value of **3l** with the literature data.[5b]

Conclusions

In summary, novel, chiral Lewis bases derived from *trans*-4-hydroxy-L-proline were developed and found to be highly enantioselective in catalyzing the hydrosilylation of α-imino esters. Thus, we have established the first general, highly enantioselective Lewis base organocatalyzed hydrosilylation of α-imino esters. Through this approach, a broad range of chiral α-amino esters were synthesized in good yields and with high levels of enantioselectivity. The absolute configurations of two of the products were determined as *R* by comparison of their rotation value with the literature data. Further work is in progress to elucidate the reaction mechanism and the utility of this reaction in the construction of complex unnatural amino acid derivatives.

Experimental Section

General Procedure for the Asymmetric Hydrosilylation of α-Imino Esters: A solution of trichlorosilane (102 μL, 1.00 mmol, 2.0 equiv.) in CH_2Cl_2 (0.5 mL) was added dropwise to a solution of the catalyst (0.05 mmol), the corresponding α-imino ester (0.50 mmol), and pentanoic acid additive (0.0025 mmol, 2.6 μL, no additive for **2a**) in dry CH_2Cl_2 (1.5 mL) at –40 °C. The reaction mixture was stirred at –40 °C until the α-imino ester disappeared (by TLC). Then, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with EtOAc, and the combined extract was washed with brine and dried with anhydrous $MgSO_4$. Concentration in vacuo followed by flash chromatography on silica gel (petroleum ether/ethyl acetate) afforded the α-amino ester. The *ee* value was determined by using established HPLC techniques with chiral stationary phases.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectral and analytical data for the catalysts, α-imino esters, and α-amino esters; HPLC chromatograms for the α-amino esters.

Acknowledgments

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