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Highly Enantioselective Lewis Base Organocatalyzed Hydrosilylation of γ-Imino Esters

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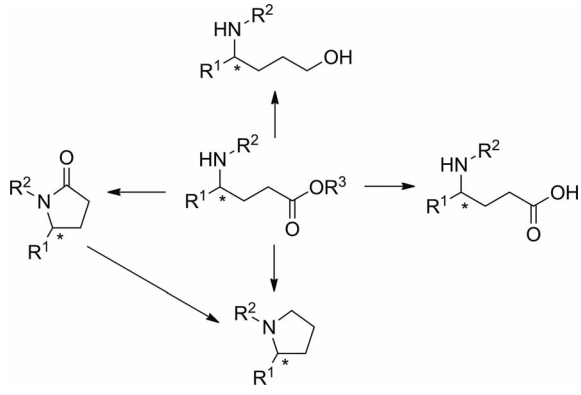
Highly enantioselective hydrosilylation of γ-imino esters with trichlorosilane promoted by a chiral Lewis base proceeded smoothly to provide various optically active γ-amino esters in good yields (up to 96 %) with excellent enantioselectivities (up to 99 % *ee*) at –10 °C in $Cl_2CHCHCl_2$. The side reactions were successfully reduced by rational modification of the substrate. The absolute configuration of one of the γ-amino esters was determined. Finally, two pharmaceutically interesting enantioenriched γ-lactams were synthesized from two γ-amino esters.

Introduction

Optically active γ-amino acids, γ-lactams, δ-amino alcohols, and α-substituted pyrrolidines are very important compounds because they are not only building blocks of γ-peptides[1,2] but also key intermediates of some pharmaceutical substances,[3–5] including compounds used in the treatment of inflammatory disorders,[3g] cannabinoid receptor 1 activity inhibitors,[3d] and protein kinase B inhibitors.[4b]

Interestingly, all of these compounds mentioned above can be readily prepared from γ-amino esters which also exist in some natural products (Scheme 1).[6] Therefore, asymmetric synthesis of optically active γ-amino esters is of great importance. However, there are very few reports on the synthesis of chiral γ-amino esters.[7] Although some progress has been achieved in the chiral transition metal complex catalyzed hydrogenation of the corresponding ketimines,[7b] the organocatalyzed asymmetric synthesis of γ-amino esters is still a great challenge.

Recently, asymmetric reactions involving the Lewis base activation of Lewis acids has attracted much attention.[8] Among these reactions, the chiral Lewis base catalyzed asymmetric hydrosilylation of C=N bonds is an important approach used to prepare enantioenriched nitrogen-containing compounds because of the mildness, economic advantage, and environmental benignancy of this transformation.[9] Several groups have achieved impressive progress in this field.[10] Malkov et al. demonstrated the first chiral Lewis base organocatalyzed enantioselective hydrosilylation of γ-imino esters.[10d] Although the reaction provided the γ-amino esters with high *ee* values, it suffered from poor yields owing to the generation of byproducts arising from ring closure of the desired γ-amino esters.



Scheme 1. Compounds that could be derived from γ-amino esters.

As an ongoing study on chiral Lewis base catalyzed asymmetric hydrosilylation of C=N bonds,[10m–10q] herein we would like to describe the chiral Lewis base organocatalyzed enantioselective hydrosilylation of γ-imino esters in which the desired optically active γ-amino esters were produced not only with excellent enantioselectivities but also in almost quantitative yield.

Results and Discussion

First, chiral picolinamide catalysts **1a**–**g** (Figure 1) were evaluated for their ability to promote the hydrosilylation of methyl 4-(4-methoxyphenylimino)-4-phenylbutanoate (**2a**)

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in dichloromethane at –10 °C. The results are summarized in Table 1.

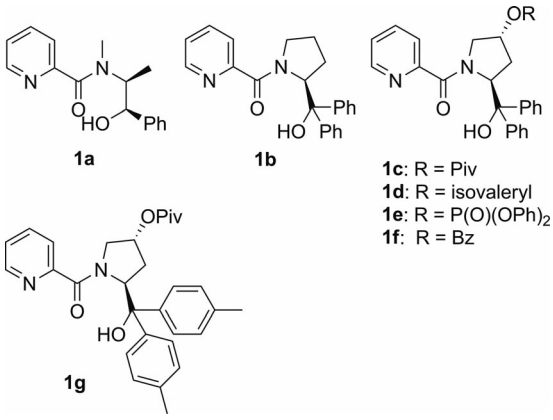
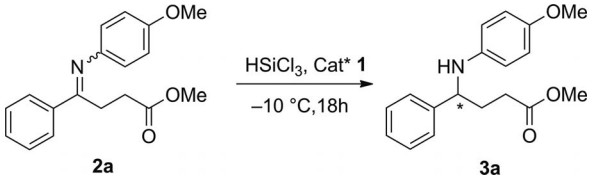


Figure 1. Chiral Lewis base organocatalysts evaluated in this study.

Table 1. Screening of chiral Lewis base catalysts in the enantioselective hydrosilylation of γ-imino ester **2a**.[a]



Entry	Cat*	Conversion[b] [%]	Yield [%][c]	*ee* [%][d]
1	**1a**	100	67	46
2	**1b**	100	62	78
3	**1c**	100	56	95
4	**1d**	100	51	92
5	**1e**	100	53	90
6	**1f**	100	64	95
7	**1g**	100	59	97
8[e]	**1g**	100	60	95
9[f]	**1g**	100	65	96
10[g]	**1g**	100	67	94

[a] Unless specified otherwise, the reactions were carried out with the catalyst (10 mol-%) and $HSiCl_3$ (2.0 equiv.) on a 0.5-mmol scale in dichloromethane (2.2 mL) at –10 °C for 18 h. [b] Monitored by TLC. [c] Isolated yield. [d] The *ee* values were determined by chiral HPLC (Chiralcel OD). [e] The reaction was carried out under an argon atmosphere. [f] The reaction was conducted on a 0.2-mmol scale in 2.2 mL of dichloromethane. [g] The reaction was conducted on a 0.1-mmol scale in 2.2 mL of dichloromethane.

In the presence of 10 mol-% of these catalysts, although all of the reactions gave full conversions within 18 h, only moderate yields of desired product **3a** were obtained (Table 1). Ephedrine-derived catalyst **1a**[10o,10q] delivered poor enantioselectivity (Table 1, Entry 1). Proline-derived catalyst **1b**[10i,10n] displayed much higher but still unsatisfactory enantioselection (Table 1, Entry 2). Afterwards, catalysts **1c**–**f**[10p] bearing bulky substituents at the C4 position of the pyrrolidine ring were tested. To our delight, remarkable increases in the *ee* values were observed (Table 1, Entries 3–6), in which *O*-pivoloyl catalyst **1c** and *O*-benzoyl catalyst **1f** both exhibited excellent enantioselectivity of 95% (Table 1, Entries 3 and 6). Replacement of the two phenyl groups in **1c** with more sterically hindered *p*-tolyl groups resulted in a slight increase in the *ee* value (97%*ee*; Table 1, Entry 7). Thus, **1g** was determined as the most appropriate catalyst in this study.

It is worth noting that the reactions always provided poor yields of the desired product while accompanied by some side products. Cyclized γ-lactam **4** was the main side product, which was mixed with some unidentified impurities and could not be isolated in pure form. To our surprise, besides expected γ-lactam **4**, about 6% of unexpected α,β-unsaturated ketimine **5** was also detected (Figure 2). We reasoned that oxygen might cause the oxidation of substrate **2a** to generate **5**. Therefore, we tried to conduct the reaction under an argon atmosphere. However, compound **5** still arose (Table 1, Entry 8). It suggested that a small amount of **2a** underwent self-dehydrogenation in the reaction system. Then, we tried to perform the reaction in a more dilute solution. This attempt only led to a small increase in the yield of **3a** (Table 1, Entries 9 and 10). The problem of low yield still remained unresolved.

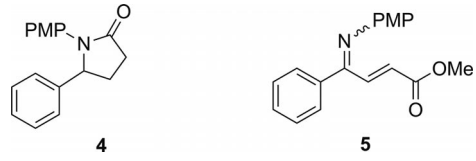
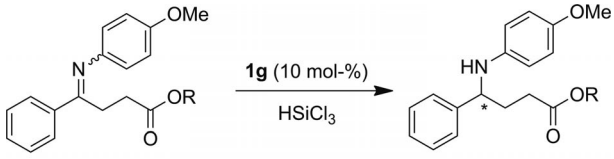


Figure 2. Main side products of the asymmetric hydrosilylation of **2a**.

To restrict side reactions, substrates **2b**–**d** bearing bulkier ester groups were subjected to the reaction. We were very gratified to find that this strategy worked much more efficiently. The yields increased as the size of the ester increased (Table 2, Entries 2–4). When *tert*-butyl substrate **2d** was subjected to the reaction, the yield of corresponding γ-amino ester **3d** reached 85% and almost no γ-lactam **4** and dehydrogenated product were produced (Table 2, Entry 4). It could be easily understood why no cyclized γ-lactam **4** was detected in the reaction of **2d**, although it was somewhat puzzling that no dehydrogenated product was observed. This was a promising result, although the enantioselectivity did drop significantly (Table 2, Entry 4). Accordingly, the *tert*-butyl group was determined as the most favorable ester group in the substrates and **2d** was employed in the following investigations. Subsequently, several chlorinated solvents were examined. All of these solvents provided the product in high yields (Table 2, Entries 4–9). To our delight, we found that the reaction performed in 1,1,2,2-tetrachloroethane proceeded smoothly to give γ-amino ester **3d** in high yield with an excellent *ee* value (Table 2, Entry 7). In addition, the reaction was complete within only 12 h in this solvent. Thus, 1,1,2,2-tetrachloroethane was selected as the optimal solvent. Further variation of the reaction temperature caused little change in the yield and enantioselection (Table 2, Entries 8 and 9).

Table 2. Enantioselective hydrosilylation of γ-imino esters **2a**–**d**.[a]



2a: R = Me
2b: R = Et
2c: R = *i*Pr
2d: R = *t*Bu

3a: R = Me
3b: R = Et
3c: R = *i*Pr
3d: R = *t*Bu

Entry	R	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Me	CH_2Cl_2	–10	18	65	96
2	Et	CH_2Cl_2	–10	18	70	97
3	*i*Pr	CH_2Cl_2	–10	18	77	96
4	*t*Bu	CH_2Cl_2	–10	18	85	90
5	*t*Bu	$ClCH_2CH_2Cl$	–10	18	95	94
6	*t*Bu	Cl_3CCH_3	–10	16	93	92
7	*t*Bu	$Cl_2CHCHCl_2$	–10	12	94	96
8	*t*Bu	$Cl_2CHCHCl_2$	0	11	92	94
9	*t*Bu	$Cl_2CHCHCl_2$	–20	18	94	95

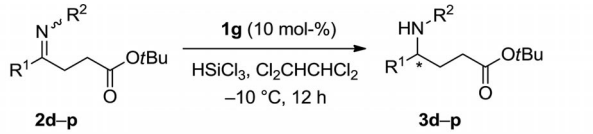
[a] Unless specified otherwise, the reactions were carried out with catalyst **1g** (10 mol-%) and $HSiCl_3$ (2.0 equiv.) on a 0.2-mmol scale in the corresponding solvent (2.2 mL). [b] Isolated yield. [c] The *ee* values were determined by chiral HPLC.

With the optimized conditions in hand, we examined the scope of the reaction with a variety of γ-imino esters in the presence of 10 mol-% of catalyst **1g** in 1,1,2,2-tetrachloroethane at –10 °C. The results are summarized in Table 3. Not only almost quantitative yields but also excellent *ee* values were observed with all of these γ-aryl-*N*-aryl-γ-imino esters, including γ-heterocyclic aryl substrate **2o** (Table 3, Entries 1–14). The reaction system exhibited good tolerance for *para* or *meta* substituents at the γ-phenyl group. The electronic nature of the substituents had little effect on the results (Table 3, Entries 2–12). The highest enantioselectivity of 99%*ee* was obtained with γ-imino ester **2n** (Table 3, Entry 12). We also tried to extend the reaction to γ-*ortho*-substituted phenyl-γ-imino esters and γ-alkyl-γ-imino esters. However, we failed to prepare these two kinds of substrates.

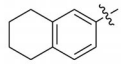
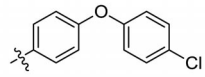
Moreover, a gram-scale reaction was performed with γ-imino ester **2l**, and the reaction reached full completion in 12 h without a decrease in the yield or enantioselectivity (Table 3, Entry 10). Consequently the absolute configuration of γ-amino ester **3l** was determined to be (*S*) by X-ray crystallographic analysis.[11]

In order to further demonstrate the synthetic utility of this transformation and the possibility of employing it in diversity-oriented synthesis, we treated product **3p** with potassium *tert*-butoxide in dry THF to generate γ-lactam **6** (Scheme 2), which can be employed to treat or prevent diseases or disorders associated with the activity of cannabinoid receptor 1 (CB1).[3d] To date, the only way to prepare optically active **6** is to separate the racemate by chiral HPLC.[3d] Now this compound can be synthesized in high enantiomeric purity through easy procedures.

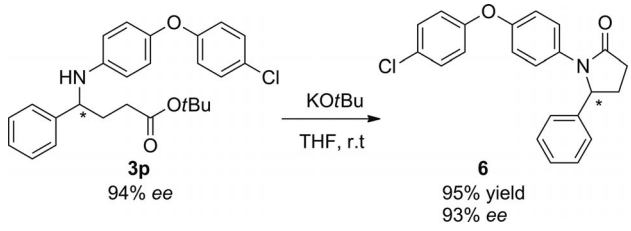
Table 3. Enantioselective hydrosilylation of γ-imino esters **2d**–**p** promoted by **1g**.[a]



2d–p **3d–p**

Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	Ph	PMP	94	96
2	4-MeC_6H_4	PMP	93	96
3	4-EtC_6H_4	PMP	94	97
4	3,4-diMeC_6H_3	PMP	96	95
5	4-$MeOC_6H_4$	PMP	92	96
6	3-$MeOC_6H_4$	PMP	91	96
7	4-FC_6H_4	PMP	95	95
8	3-FC_6H_4	PMP	91	94
9	4-ClC_6H_4	PMP	94	95 (*S*)[d]
10[e]	4-ClC_6H_4	PMP	96	95
11	4-BrC_6H_4	PMP	95	95
12		PMP	95	99
13	2-thienyl	PMP	95	95
14	Ph		96	94

[a] Unless specified otherwise, the reactions were carried out with catalyst **1g** (10 mol-%) and $HSiCl_3$ (2.0 equiv.) on a 0.2-mmol scale in 1,1,2,2-tetrachloroethane (2.2 mL) at –10 °C for 12 h. [b] Isolated yield. [c] The *ee* values were determined by chiral HPLC. [d] The absolute configuration of product **3l** was determined by X-ray crystallographic analysis.[11] [e] The reaction was conducted on a gram-scale.

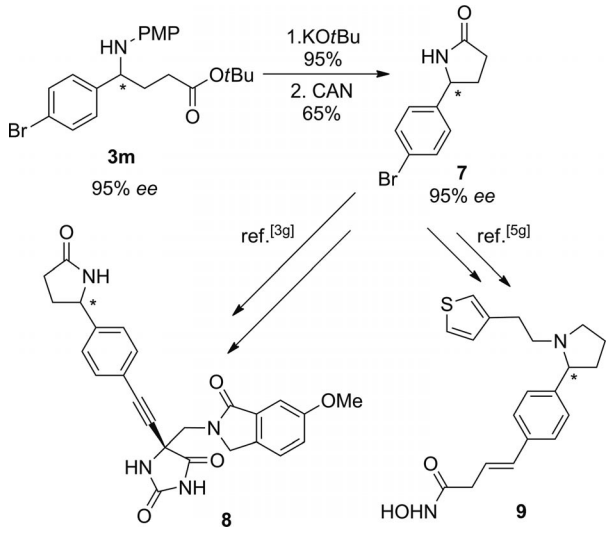


3p
94% *ee*

6
95% yield
93% *ee*

Scheme 2. Synthesis of chiral γ-lactam **6**.

Furthermore, γ-amino ester **3m** was subjected to the same cyclization with potassium *tert*-butoxide followed by deprotection of PMP with CAN (CAN = ceric ammonium nitrate) to provide γ-lactam **7**, which can be converted into potent candidate **8** for the treatment of inflammatory disorders[3g] or into pyrrolidine **9**, which is a hydroxamate-based inhibitor of deacetylases B,[5g] according to the literature (Scheme 3).



Scheme 3. Synthesis of chiral γ-lactam **7** and its synthetic potential in the construction of pharmaceutically active agents.

Conclusions

In conclusion, we have developed a general, highly enantioselective hydrosilylation of γ-imino esters promoted by chiral Lewis base organocatalysts. This transformation enables the straightforward, mild, and highly effective synthesis of various chiral γ-amino esters in high yield (96%) with excellent enantioselectivities (99%). The problem of low yield was successfully resolved by rational modification of the substrate. The absolute configuration of γ-amino ester **3l** was determined to be (*S*) by X-ray crystallographic analysis. Finally, γ-amino esters **3p** and **3m** were employed in the synthesis of two optically active γ-lactams that are important in the construction of pharmaceutically active agents.

Experimental Section

General Procedure for the Asymmetric Hydrosilylation of γ-Imino Esters: A solution of trichlorosilane (41 μL, 0.4 mmol, 2.0 equiv.) in dry $Cl_2CHCHCl_2$ (0.2 mL) was added to a stirred solution of the corresponding γ-imino ester (0.2 mmol) and the catalyst (0.02 mmol) in dry $Cl_2CHCHCl_2$ (2 mL) at –10 °C. The mixture was stirred at –10 °C for 12 h. Then, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4; the solvents were evaporated. Purification by column chromatography (silica gel, petroleum ether/EtOAc) afforded the pure product. The *ee* values were 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 γ-imino esters and γ-amino esters, HPLC chromatograms for γ-amino esters, X-ray crystal structure of **3l**·HCl.

Acknowledgments

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