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Graphical Abstract

With ammonia borane as hydrogen source, an asymmetric transfer hydrogenation of β-*N*-substituted enamino esters was successfully realized to give β-amino acid derivatives in 51−90% yields with up to 91% ee by using a combination of Piers' borane and (*S*)-*tert*-butylsulfinamide as a chiral catalyst.

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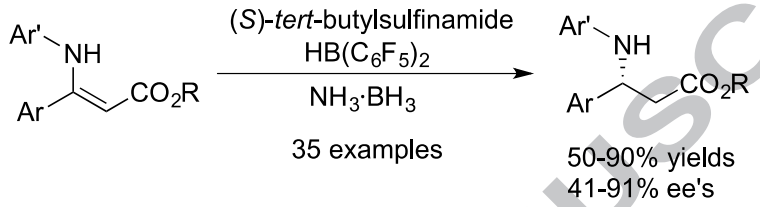

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Asymmetric Transfer Hydrogenations of β-*N*-Substituted Enamino Esters with Ammonia Borane

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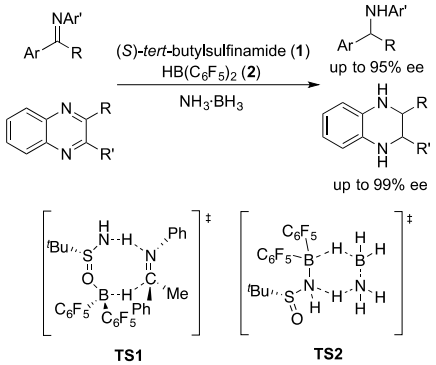
ABSTRACT

Optically active β-amino acids and their derivatives are very useful building blocks in synthetic and medicinal chemistry. The catalytic asymmetric reduction of β-enamino esters is one of the most efficient approaches for their synthesis. Ammonia borane with low molecular weight, high hydrogen capacity, and good stability, is an ideal hydrogen source for the transfer hydrogenation. However, only a few successful examples have been reported for the asymmetric reduction with ammonia borane. In this work, an asymmetric metal-free transfer hydrogenation of β-*N*-substituted enamino esters with ammoinia borane was successfully realized by using a frustrated Lewis pair of Piers' borane and (*S*)-*tert*-butylsulfinamide as a chiral catalyst. A variety of β-amino acid derivatives were obtained in 51−90% yields with up to 91% ee.

Optically active β-amino acids and their derivatives are extremely important building blocks in synthetic and medicinal chemistry.[1] Clinical medicines ezetimibe and sitagliptin are among the most representative examples.[2] Various methodologies have been established for the synthesis of optically active β-amino acids.[3] The catalytic asymmetric reduction of β-enamino esters is among the most efficient and straightforward approaches.[4] A great success has been achieved for the asymmetric hydrogenation with chiral transition-metal catalysts.[5] Alternatively, the asymmetric metal-free hydrosilylation with trichlorosilane as hydrogen source using chiral Lewis base as catalyst is also a very promising approach.[6] However, trichlorosilane is extremely flammable and moisture sensitive, and its hydrogen capacity is low. Exploring stable and easily handling hydrogen donors with high hydrogen capacities is therefore still of great importance.

Ammonia borane ($NH_3{\cdot}BH_3$, AB) with some unique features including low molecular weight, high hydrogen capacity, and good stability, has been widely studied as a potential solid hydrogen-storage material.[7] Moreover, ammonia borane has also been employed as an effective hydrogen source in transition-metal catalyzed or catalyst-free transfer hydrogenations.[8] But only a few successful examples have been reported for the asymmetric reaction.[9] For example, in 1984, Williams and co-workers realized an asymmetric reduction of ketones which the complex of ammonia borane and chiral 18-crown-6. Recently, our group developed a novel type frustrated Lewis pair (FLP)[10] by the combination of (*S*)-*tert*-butylsulfinamide (**1**)[11] and Piers' borane (**2**)[12], which was highly effective for asymmetric transfer hydrogenations of imines and 2,3-disubstituted quinoxalines (Scheme 1).[13] The hydrogen transfer between FLP and imine occurred via an 8-memberered transition state **TS1**, and the FLP catalyst was regenerated with ammonia borane through a concerted 6-membered transition state **TS2**. Very recently, our group disclosed a chiral ammonia borane by the dehydrogenation of ammonia borane with chiral phosphoric acid, which was a regenerable hydrogen donor for asymmetric transfer hydrogenations of imines and β-enamino esters.[14] As our ongoing interest in the FLP catalysis,[15] herein, we wish to report our preliminary results on the FLP-catalyzed asymmetric transfer hydrogenation of β-enamino esters for the synthesis of optically active β-amino acid derivatives.



Scheme 1. Our previous work on the FLP-catalyzed transfer hydrogenation with ammonia borane.

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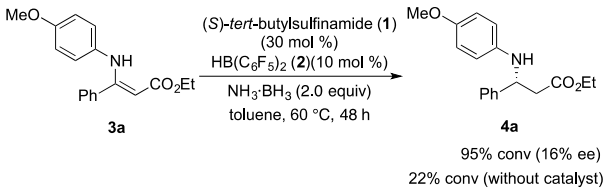
The initial study was conducted by subjecting ethyl (*Z*)-3-(4-methoxyphenyl)amino)-3-phenylacrylate (**3a**) to the asymmetric hydrogenation with $NH_3{\cdot}BH_3$ (2.0 equiv) in toluene at 60 °C for 48 h by using (*S*)-*tert*-butylsulfinamide (**1**) (30 mol %) and $HB(C_6F_5)_2$ (**2**) (10 mol %) as a FLP catalyst (Scheme 2). Despite the excess of (*S*)-*tert*-butylsulfinamide (**1**), product **4a** was obtained with a disappointing enantioselectivity. A control experiment indicates the reaction between ammonia borane and **3a** without catalyst was not very fast under the same condition (Scheme 2).



Scheme 2. Initial study on transfer hydrogenation of **3a**.

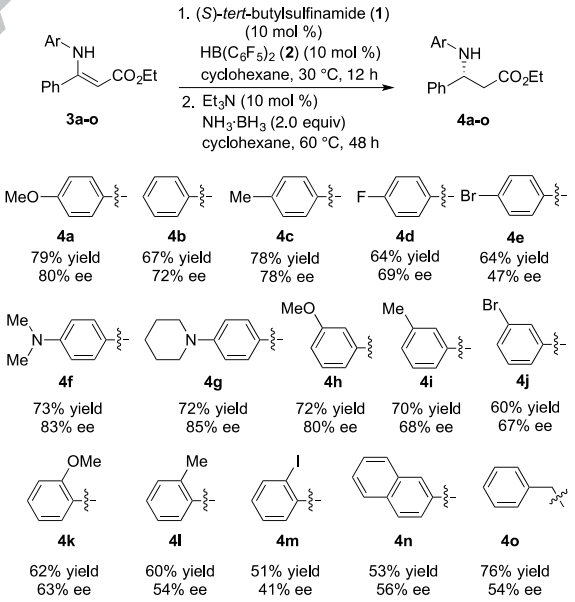
Table 1. Optimization of reaction conditions[a]

Entry	Additive (10 mol %)	Solvent	Conv. (%)[b]	Ee (%)[c]
1	--	Toluene	95	16
2	--	*p*-Xylene	78	19
3	--	Chloroform	93	38
4	--	Dichloromethane	99	10
5	--	*n*-Hexane	89	73
6	--	*n*-Heptane	88	76
7	--	*n*-Decane	85	71
8	--	Cyclohexane	90	78
9[d]	--	Cyclohexane	60	76
10	Pyridine	Cyclohexane	50	64
11	2-Phenylpyridine	Cyclohexane	88	73
12	Diethylamine	Cyclohexane	71	68
13	Triethylamine	Cyclohexane	89	85
14[e]	Triethylamine	Cyclohexane	89	73
15[f]	Triethylamine	Cyclohexane	88	84
16[g]	--	Cyclohexane	33	61

[a] All reactions were carried out with **3a** (0.10 mmol), (*S*)-*tert*-butylsulfinamide (**1**) (0.03 mmol, 30 mol %), $HB(C_6F_5)_2$ (**2**) (0.01 mmol, 10 mol %), $NH_3{\cdot}BH_3$ (0.20 mmol) in solvent (1.5 mL) at 60 °C for 48 h unless other noted.
[b] The conversion was determined by crude ^1H NMR.
[c] The ee was determined by chiral HPLC.
[d] $NH_3{\cdot}BH_3$ (1.0 equiv) was used.
[e] (*S*)-*tert*-butylsulfinamide (**1**) (0.01 mmol, 10 mol %) was used.
[f] Treating **3a** (0.1 mmol) with **1** (10 mol %) and **2** (10 mol %) at 30 °C for 12 h before addition of $NH_3{\cdot}BH_3$ and triethylamine, and the mixture was stirred at 60 °C for 48 h.
[g] $NEt_3{\cdot}BH_3$ was used instead of $NH_3{\cdot}BH_3$.

Solvents were next optimized to reduce the background reaction and improve the enantioselectivity. As shown in Table 1, solvents were found to have a large impact on the enantioselectivity (entries 1-8). Alkane solvents gave much higher ee's, and cyclohexane gave the optimal result (Table 1, entries 5-8). When 1.0 equivalent of ammonia borane was used, an obvious drop of conversion was observed (Table 1, entry 9). Various Lewis bases were further studied as additives for the asymmetric transfer hydrogenation in cyclohexane to inhibit the possible racemic reaction catalyzed by free Piers' borane.[13a] Pyridines and diethylamine slowed down the reaction and lowered the ee (Table 1, entries 10-12). While, triethylamine can give 85% ee without loss of reactivity (Table 1, entry 13). With triethylamine as additive, reducing the loading of (*S*)-*tert*-butylsulfinamide (**1**) to 10 mol % resulted in a slight drop of ee (Table 1, entry 14). Adjusting the addition sequence by treating **3a** with (*S*)-*tert*-butylsulfinamide (10 mol %) and Piers' borane at 30°C for 12 h before the addition of triethylamine and ammonia borane afforded product **4a** in 88% conversion with 84% ee (Table 1, entry 15). In contrast to adding in one portion, the two-step addition sequence possibly inhibited the racemic background reaction with ammonia borane catalyzed by Piers' borane more effectively, which resulted in a higher ee.[13a] Moreover, when $NEt_3{\cdot}BH_3$ instead of $NH_3{\cdot}BH_3$ was used, much lower conversion and ee were obtained (Table 1, entry 16).

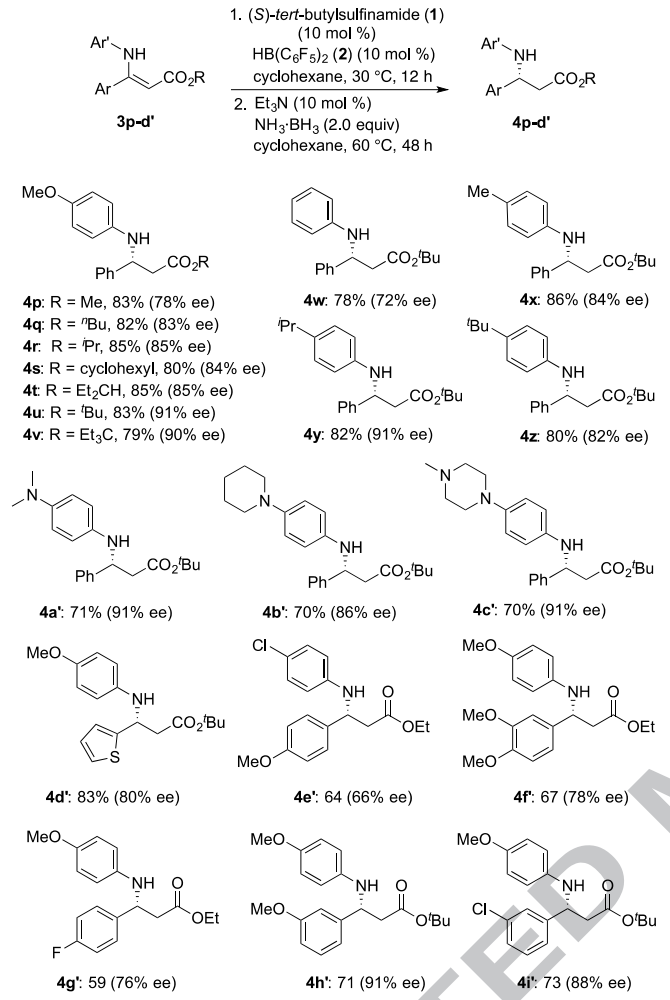
Subsequently, a variety of ethyl (*Z*)-3-amino-3-phenylacrylates **3a-o** with diverse *N*-substituents were subjected to the asymmetric transfer hydrogenation under the optimal reaction condition. As shown in Scheme 3, all the reactions proceeded smoothly to furnish the desired products **4a-o** in 51-79% yields with 41-85% ee's. Both electron-donating and withdrawing substituents on the phenyl group were well tolerated for this reaction. β-Enamino ethyl esters **3k-m** with the *ortho*-substituted phenyl group were also effective substrates, but gave relatively lower yields and ee's. When using benzyl group as the *N*-substituent, product **4o** was obtained in 76% yield with 54% ee.



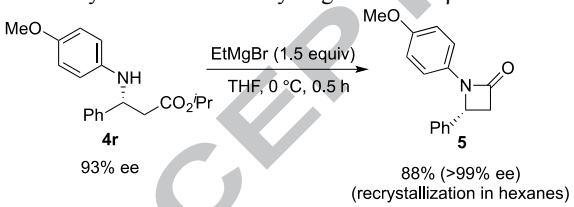
Scheme 3. Asymmetric transfer hydrogenations of β-enamino esters with diverse *N*-substituents.

The effect of ester group was investigated by subjecting β-enamino esters **3p-v** to the transfer hydrogenation. It was found that the size of alkyl groups influenced the enantioselectivity obviously, the ee values were varied from 78% to 91% (Scheme 4). The bulky *tert*-butyl group gave the highest enantioselectivity. A variety of β-enamino *tert*-butyl esters **3w-c'** were therefore employed as substrates for the asymmetric transfer hydrogenation to afford the corresponding products **4w-c'** in 70-86% yields with 72-91% ee's (Scheme 4). Moreover, β-enamino esters **3d'-f'** with different aryl groups at the β-positions were also effective substrates for this reaction to furnish the corresponding products **4d'-f'** in 59-83% yields with 66-91% ee's (Scheme 4). According to the reported methods,[16] β-lactam **5** can be easily accessed in 88% yields with >99% ee

after a recrystallization in hexanes by treating compound **4r** (93% ee after recrystallization in hexanes) with Grignard reagent in THF for 0.5 h (Scheme 5).



Scheme 4. Asymmetric transfer hydrogenations of β-enamino esters.



Scheme 5. Synthesis of β-lactam **5**.

In summary, a metal-free asymmetric transfer hydrogenation of β-*N*-substituted enamino esters with ammonia borane as a hydrogen source and a frustrated Lewis pair of $HB(C_6F_5)_2$ and (*S*)-*tert*-butylsulfinamide as a chiral catalyst has been successfully realized. A variety of optically active β-amino acid derivatives were obtained in 51−90% yields with 41-91% ee's. Enantiomer-pure β-lactam was easily prepared via a single step reaction. Further efforts on searching for novel chiral FLPs and expanding their applications in asymmetric reactions are underway in our laboratory.

Acknowledgments

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Supplementary Material

Supplementary data (the procedures for the synthesis of substrates and metal-free transfer hydrogenation of β-*N*-substituted enamino esters, the characterization of the substrates and products and data for the determination of ee's along with the NMR spectra) associated with this article can be found, in the online version.

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Highlights

1. Asymmetric transfer hydrogenations with ammonia borane were realized.
2. β-Amino acid derivatives were obtained in high yields with up to 91% ee.
3. A frustrated Lewis pair was used as an effective chiral catalyst.