JOC The Journal of Organic Chemistry

Article

B(C6F5)3–Catalyzed Asymmetric Reductive Amination of Ketones with Ammonia Borane

Zhentao Pan, Leixin Shen, Dingguo Song, Zhen Xie, Fei Ling, and Weihui Zhong

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 29 Aug 2018

Just Accepted

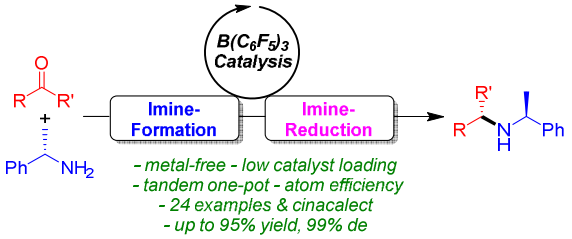
ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

$B(C_6F_5)_3$–Catalyzed Asymmetric Reductive Amination of Ketones with Ammonia Borane

Zhentao Pan, Leixin Shen, Dingguo Song, Zhen Xie, Fei Ling and Weihui Zhong *

Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China



ABSTRACT: The first example of metal–free $B(C_6F_5)_3$–catalyzed asymmetric reduction amination of ketones with chiral *α*-methylbenzylamine (*α*-MBA) using ammonia borane as the reductant is reported. This one–pot method has a broad substrate scope and provides various chiral amines in 81–95 % yield with 80–99 % de. This protocol was further applied in the total synthesis of cinacalcet.

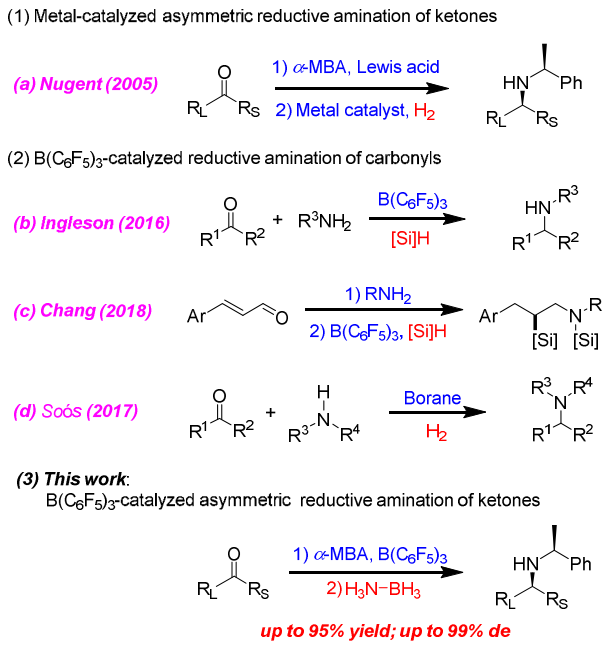
INTRODUCTION:

Chiral amines are at the central stage of the biologically relevant molecules, which include natural products, drugs and agrochemicals.[1] Various asymmetric synthetic methods have been developed to meet the increasing demand for enantiomerically pure amines. Asymmetric reductive amination using (*S*)- or (*R*)-*α*-methylbenzylamine (*α*-MBA) as the chiral auxiliary represents a powerful and widely studied method.[2] Particularly, the metal–catalyzed asymmetric reductive amination (Scheme 1a), exhibits high reactivity and diastereoselectivitiy.[3] Despite its unarguable efficiency, the use of metal catalysts and stoichiometric Lewis acids limited its further application in pharmaceuticals.[4] As a consequence, there is a continued effort to develop practical strategies to access chiral amines in a metal–free fashion.

$B(C_6F_5)_3$, reported in 1964,[5] re-emerged as a paradigm for small molecule activation in the past decade, especially as a component in frustrated Lewis pairs (FLPs) chemistry.[6] Moreover, $B(C_6F_5)_3$ has been successfully employed in various transformations.[7] One of the research hotspots is the borane–catalyzed

reductive amination. Using silanes as the hydride sources, Ingleson and co–workers disclosed an elegant reductive amination method promoted by water tolerant boranes (Scheme 1b).[8] Recently, Chang and co–workers reported a $B(C_6F_5)_3$–catalyzed reductive amination/hydrosilylation cascade of *α,β*-unsaturated aldehydes (Scheme 1c).[9] Alternatively, employing hydrogen as the reductant, Soós and co–workers developed a boron/nitrogen centered frustrated Lewis pair for the reductive amination of carbonyls (Scheme 1d).[10] Despite their great success that have been achieved, $B(C_6F_5)_3$–catalyzed asymmetric reductive amination still remains an unexploited field.

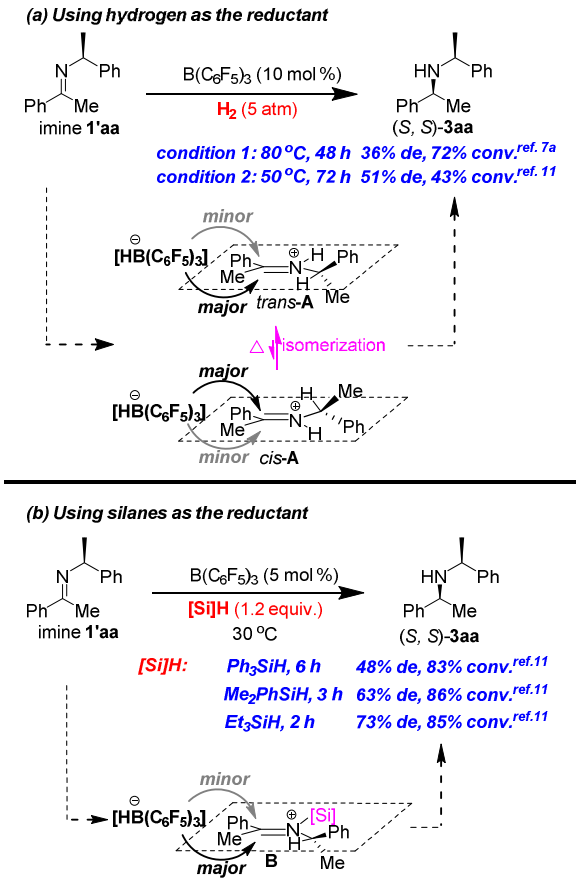
Scheme 1. Reductive Amination of Carbonyls



The greatest challenge for metal–free asymmetric reductive amination is to control the diastereoselectivity well in the step of imine–reduction. In 2011, Stephan and co–workers reported a $B(C_6F_5)_3$–catalyzed diastereoselective catalytic hydrogenation of imines using hydrogen as the reductant.[7a] Hydrogenation of imine **1'aa** with 10 mol % $B(C_6F_5)_3$ at 80 °C afforded product **3aa** in 72% conversion with 36% de (Scheme 2a, condition 1).[7a] When lowing the reaction temperature from 80 °C to 50 °C, an increased diastereoselectivity was observed, albeit in lower conversion (Scheme 2a, condition 2, 43% conv., 51% de). These results indicate that the decrease of reaction temperature could effectively suppress the *trans*-to-*cis* imine isomerization of intermediate **A**, but inhibit the reaction reactivity in turn. Subsequently, different silanes were employed as the reductant in our laboratory. Ph_3SiH, Me_2PhSiH and Et_3SiH all gave **3aa** in high conversions (83–86% conv.)

within 2–6 h at 30 °C. Notably, the de of **3aa** had increase (from 48% to 73% de) with the decrease of the steric hinderance from the silane group. However, the diastereoselectivity of product was still moderate. To explain this phenomenon, we speculated that the steric bulk of silane group minished the asymmetric bias, thus leading to a decreased diastereoselectivity. Therefore, discovering diminutive and efficient reductants for metal–free asymmetric reductive amination have remained elusive, but highly desirable.

Scheme 2. Proposed Pathway of Asymmetric Reduction of Chiral Imine using Hydrogen and Silane as the Reductant



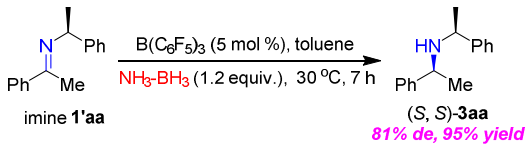
Ammonia borane is an ideal hydrogen source due to its 19.6 wt % hydrogen capacity, low molecular weight, readily available and easy in handling, which can provide both proton and hydride under mild conditions.[15] Hence, ammonia borane is a very powerful reductant widely used for $B(C_6F_5)_3$–catalyzed hydrogenations of imines,[13a] pyridines,[13b] 2,3-disubstituted quinoxalines[13c] and N-heterocycles.[13d] Based on these researches and inspired by our previous work on FLP–catalyzed hydrogenation of imines,[14] we supposed that employing

ammonia borane might improve the diastereoselectivitiy of asymmetric reductive amination of ketones catalyzed by $B(C_6F_5)_3$.

RESULT AND DISCUSSION

To validate our assumption, hydrogenation of imine **1'aa** with 5 mol % $B(C_6F_5)_3$ and 1.2 equiv. ammonia borane at 30 °C was performed (Scheme 3). Delightfully, desired product **3aa** was furnished in 95% yield with good diastereoselectivity (81% de). Encouraged by this result, we next devoted our efforts to realize the asymmetric reductive amination of ketones in one–pot.

Scheme 3. $B(C_6F_5)_3$–Catalyzed Hydrogenation of Imine using Ammonia Borane



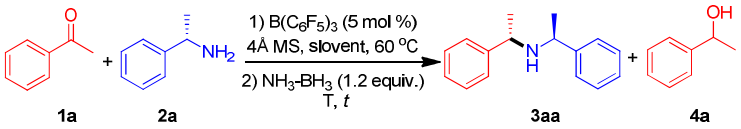
imine **1'aa**

(*S*, *S*)-**3aa**

81% de, 95% yield

Initially, the imine was formed by subjecting ketone **1a** to (*S*)-*α*-MBA **2a** (1.2 equiv.) using $B(C_6F_5)_3$ (5 mol %) as the catalyst in toluene at 60 °C for 8h. Without separation, ammonia borane (1.2 equiv.) was added at 60 °C and stirred for 4h. The desired product **3aa** was obtained in low yield with good diastereoselectivity (37% yield, 73% de), along with the formation of 1-phenylethanol (**4aa**) (Table 1, entry 1). We envisioned that the poor conversion of ketone to imine might take place, owing to the in-suit generation of H_2O. A sharp increase on yield was achieved by adding 4Å MS, affording the corresponding product **3aa** in 93% yield with 75% de. Next, the optimization of the imine–reduction step was operated. It was noteworthy that the diastereoselectivity of **3aa** was increased to 85% when the reaction temperature was reduced from 90 °C to 0 °C (Table 1, entries 2–5). Further decreasing the reaction temperature to –30 °C did not improve the diastereoselectivity (Table 1, entry 6). Additionally, the reaction solvent was also examined and toluene turned out to be the best medium for this transformation (Table 1, entries 7–9). The reaction concentration had slight influence on the diastereoselectivity, and 0.1 M was proved to be the optimal concentration to afford the expected product **3aa** in 91% yield with 91% de (Table 1, entries 10–12). Besides, decreasing the dosage of ammonia borane to 1.0 equiv. resulted lower yield of **3aa** (80% yield) (Table 1, entry 13). Satisfyingly, this process underwent smoothly without loss of efficiency in both yield and diastereoselectivity even with the reduced catalyst loading from 5 mol % to 1 mol % (Table 1, entry 14).

Table 1. Optimization of Reaction Condition[a]

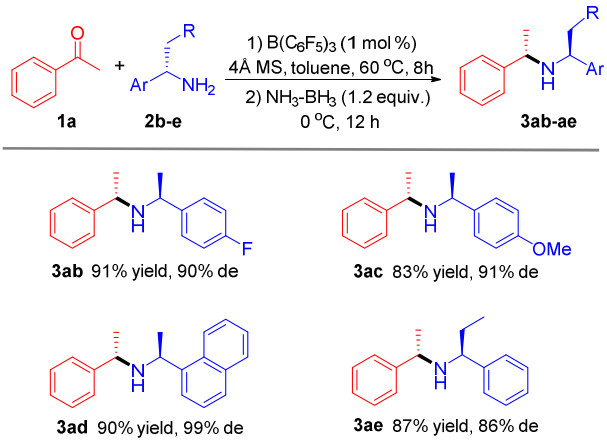


entry	solvent	T (°C)	*t* (h)	conc. (M)	yield (**3aa**, **4a**)[b] (%)	de of **3aa**[c] (%)
1[d]	toluene	60	4	0.4	37, 53	73
2	toluene	90	2	0.4	92, trace	64
3	toluene	60	4	0.4	91, trace	75
4	toluene	30	7	0.4	93, trace	81
5	toluene	0	8	0.4	92, trace	85
6	toluene	-30	10	0.4	85, 10	85
7	hexane	0	12	0.4	47, 21	65
8	THF	0	12	0.4	62, 15	78
9	$CHCl_3$	0	12	0.4	80, 13	74
10	toluene	0	9	0.2	92, trace	88
11	***toluene***	***0***	***10***	***0.1***	***91, trace***	***91***
12	toluene	0	12	0.05	90, trace	91
13[e]	Toluene	0	12	0.1	80, trace	90
14[f]	Toluene	0	12	0.1	91, trace	91

[a]Reactions were carried out with **1a** (0.5 mmol), **2a** (0.6 mmol), $B(C_6F_5)_3$ (5 mol %), 4 Å MS (200 mg) in solvent under an ambient atmosphere at 60 °C for 8 h, and then ammonia borane (1.2 equiv.) was added and stirred at desired temperature. [b]Isolated yield based on 1a. [c]Determined by GC analysis of crude product. [d]Reaction was performed without 4 Å MS. [e]1.0 equiv. of ammonia borane was used. [f]1 mol % of $B(C_6F_5)_3$ was used.

The above initial observation prompted us to examine the effect of chiral auxiliary on the diastereoselectivity of product. It was found that there was little correlation between electronic effect of the chiral auxiliary and the diastereoselectivity of product (Scheme 4, **3ab** and **3ac**). On the contrary, the steric effect of the chiral auxiliary had remarkably affected the de of **3**, and the naphthyl group produced the **3ad** with 99% de (Scheme 4, **3ad**). However, a decreased de was observed when using the 1-phenylpropan-1-amine as the chiral auxiliary, due to its diminished asymmetric bias (Scheme 4, **3ae**). In consideration of the atom economy and easy removal of the chiral auxiliary, *α*-MBA seemed to be the ideal one. Therefore, we next set out to determine the versatility of this reaction system in the tandem asymmetric reductive amination of various ketones with *α*-MBA.

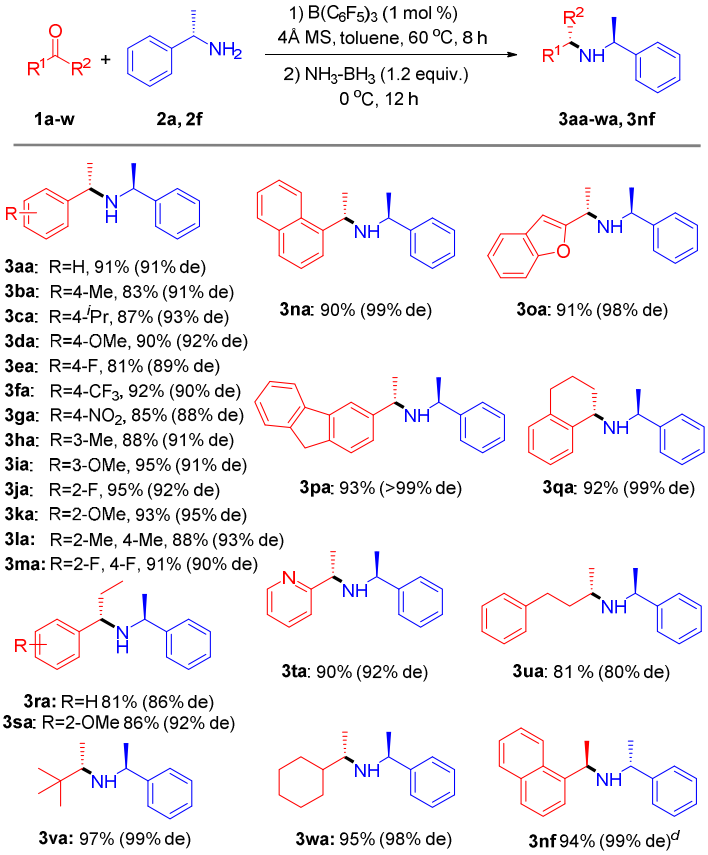
Scheme 4. Effect of Chiral Auxiliary on the Diastereoselectivity of Product[a,b]



[a]Reactions were carried out with **1a** (0.5 mmol), **2** (0.6 mmol), $B(C_6F_5)_3$ (1 mol %), 4 Å MS (200 mg) in toluene (5 mL) under an ambient atmosphere at 60 °C for 8 h, and then ammonia borane (1.2 equiv.) was added and stirred at 0 °C for additional 12 h. [b]Isolated yield based on **1a**.

This method showed a broad substrate scope and wide tolerance towards different functionalities (Scheme 5). Both electron-withdrawing and donating substituents on benzene rings were well tolerated (**3aa–wa**). To our delight, the 2–benzofuran **1o** and 2–acetylpyridine **1t** also proceeded to afford the corresponding products **3oa** and **3ta** in 91% and 90% yield, with 98% and 92% de, respectively. Significantly, an increase in diastereoselectivity was observed when more steric-hindered ketones were used. For example, a methoxy substituent at the *ortho* position of acetophenone (**1k**) resulted with a slight higher de than the *para* (**1d**) and *meta* (**1i**) position. Moreover, excellent diastereoselectivities could be achieved when employing more steric congested ketones **1n**, **1p**, and **1q**. Additionally, propiophenone derivatives were compatible with this progress to afford the desired products **3ra** and **3sa** in good yield and de. Subsequently, the scope of this process with respect to dialkyl ketones was evaluated with the formation of the desired products in 81–97% yield with 80–99% de. Notably, straight–chain ketone furnished product **3ua** with relatively lower diastereoselectivity (80% de) than sterically encumbered ketones (**3va** and **3wa**, 99% and 98% de). It was delight that replacing (*S*)-*α*-MBA **2a** with (*R*)-*α*-MBA **2f** for the reductive amination of 1-acetonaphthone **1n** led to the generation of the expected product (*R,R*)-**3nf** in 91% yield with 99% de.

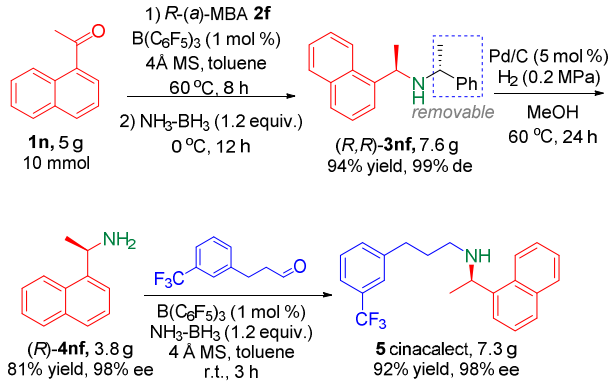
Scheme 5. Substrate Scope of Ketones[a,b,c]



[a]Reactions were carried out with **1** (0.5 mmol), **2a** (0.6 mmol), $B(C_6F_5)_3$ (1 mol %), 4 Å MS (200 mg) in toluene (5 mL) under an ambient atmosphere at 60 °C for 8 h, and then ammonia borane (1.2 equiv.) was added and stirred at 0 °C for additional 12 h. [b]Isolated yield based on **1**. [c]De of crude product. [d](*R*)-*α*-MBA **2f** was used.

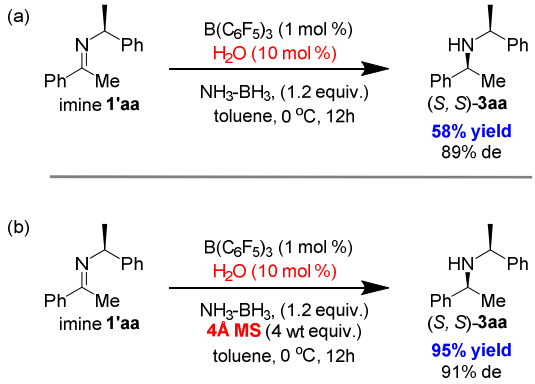
Furthermore, the methodology was applied for the total synthesis of the calcimimetic drug cinacalcet on gram scale (Scheme 6). Firstly, the $B(C_6F_5)_3$–catalyzed asymmetric reductive amination of **1n** with (*R*)-*α*-MBA **2f** afforded **3nf**, which was converted to the primary amine **4nf**. Subsequently, **4nf** was reacted with 3-(trifluoromethyl)benzenepropanal in the presence of $B(C_6F_5)_3$ as the catalyst and ammonia borane as the reductant to afford cinacalcet (**5**) in 92% yield with 98% ee.

Scheme 6. Total Synthesis of Cinacalcet



To shed light on the details of the reaction pathway, two control experiments were designed. Adding 10 mol % of water significantly reduced the reaction reactivity, providing **3aa** in moderate yield (58%) with a slight reduced diastereoselectivity (89% de) after 12 h (Scheme 7a). In contrast, the reaction with 4 Å molecular sieves smoothly furnished 95% yield of **3aa** with 91% de (Scheme 7b). These results indicate that the drying of the reaction mixture by 4 Å molecular sieves is crucial to this reduction reaction.

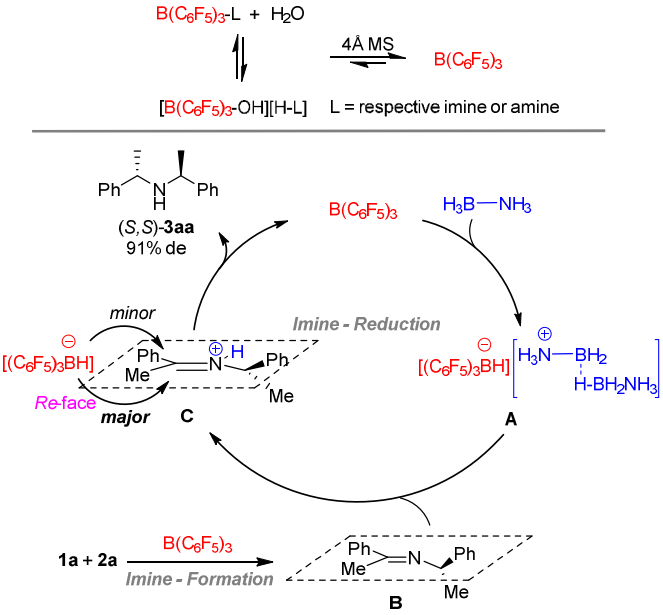
Scheme 7. Control Experiments



Based on the above control experiments and related references[8,15], a plausible catalytic pathway for the present $B(C_6F_5)_3$–catalyzed asymmetric reductive amination is depicted in Scheme 8. Initially, $B(C_6F_5)_3$ could convert to $[B(C_6F_5)_3\text{-OH}][H\text{-L}]$ in the presence of L (respective imine or amine) and water derived from the imine formation[8a]. Due to the drying of the reaction mixture by 4 Å molecular sieves, a critical concentration of $B(C_6F_5)_3$ is formed from $[B(C_6F_5)_3\text{-OH}][H\text{-L}]$. Subsequently, $B(C_6F_5)_3$ promotes ketone-amine condensation resulted in the formation of *trans*-imine **B** via a B···O interaction. Simultaneously, $B(C_6F_5)_3$ activates ammonia borane to generate species **A** with an ion–pair,[15] followed by the protonation of the imine to furnish

intermediate **C**. Owing to the low reduction temperature, the *trans*-to-*cis* imine isomerization of **C** rarely takes place, which is the key requirement for the high diastereoselectivity of product. Finally, the borohydride attacks at the iminium carbon from the less encumbered *Re*-face to afford product (*S*,*S*)-**3aa** in 91% de along with the release of $B(C_6F_5)_3$.

Scheme 8. Plausible Catalytic Pathway



CONCLUSION

In conclusion, a $B(C_6F_5)_3$-catalyzed asymmetric reductive amination of ketones with *α*-MBA and ammonia borane has been developed to afford the chiral secondary amines in high yields with up to 99% de. This protocol has a broad scope covering a wide range of aryl, alkyl and dialkyl ketones, and is used for the synthesis of cinacalcet. Mechanism study on this reaction as well as those for other $B(C_6F_5)_3$-catalyzed transformations will be reported in due course.

EXPERIMENTAL SECTION

General information: All starting materials and reagents were purchased from commercial sources and used as received unless otherwise noted. Commercially available molecular sieves (4 Å) were dried in Muffle furnace at 400 °C for 5 h before use. Reactions were monitored using thin-layer chromatography(TLC) on commercial silica gel plates. Visualization of the developed plates was performed under UV light (254nm). Flash column chromatography was performed on silica gel. NMR spectra were recorded on a Bruke Avance III

spectrometer, operating at 600 MHz (^{1}H) and 150 MHz (^{13}C) respectively. Chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS (= 0) or relative to $CHCl_3$ (7.254 ppm) for **^{1}H NMR**. For **^{13}C NMR**, chemical shifts were reported in the scale relative to $CHCl_3$ (77.16 ppm) as an internal reference. Multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The coupling constants are expressed in Hz. Melting points were determined with a Büchi B-540 capillary melting point apparatus and are uncorrected. Optical rotations were determined using a AUTOPOL V polarimeter. For amine products **3**, the diastereomeric excess measurements were obtained using a Agilent 6890N GC instrument with a Agilent HP-5 column (60m*0.25mm*0.25um 19091J-436); T_{inj}= 300 °C and T_{det}= 300 °C, and carrier gas He @ 24 psi were always constant. Program: 100 °C (1 min), then 20 °C/min to 200 °C (hold 3 min), then 20 °C/min to 300 °C (hold 2 min). For amine product **4nf** and **5**, the enantiomeric excess measurements were obtained using a Agilent 1100 HPLC instrument with a CHIRALCEL OD-H column with n-heptane and isopropanol as eluents. A positive ion mass spectrum of sample was acquired on a Thermo LTQ-FT mass spectrometer with an electrospray ionization source.

General synthesis of Secondary Amine 3aa–wa and 3nf. A solution of ketone **1** (0.5 mmol), (*S*)-*α*-MBA ((*R*)-*α*-MBA for **3nf**) (0.6 mmol), $B(C_6F_5)_3$ (0.005 mmol), and 4 Å MS (4 wt equiv.) were dissolved in toluene (5 mL) under an ambient atmosphere. The mixture was stirred at 60 ^{o}C for 8 h followed by addition of ammonia borane (0.6 mmol), and was stirred for another 12 h at 0 °C. Then the reaction mixture was filtered through a bed of celite and the celite subsequently washed with EtOAc (3 x 5 mL). The filtrate was dried (Na_2SO_4), and concentrated in vacuo to afford the crude product **3** (this material is used to determine the de by GC). The diastereomeric yield was determined after silica gel flash chromatography (hexane/EtOAc). Further careful flash chromatography of the diastereomeric mixture was underwent to gain the pure (*S,S*) diastereomers **3aa**–**wa** and (*R,R*) diastereomer **3nf.**

*Bis((S)-1-Phenylethyl)amine (**3aa**)*: Colorless viscous liquid, 90% yield, 101.7 mg; 91% de. $[\alpha]_D^{20}$ = -94.0 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3aa** isomer, 9.4; minor (*R,S*)-**3aa** isomer, 9.6. The NMR data of (*S,S*)-**3aa** matches that reported in the literature.[16] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55–6.69 (m, 10H), 3.41 (m, 2H), 1.18 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 145.8 (2C), 128.4 (4C), 126.8 (2C), 126.7 (4C), 55.1 (2C), 25.0 (2C). **MS** (ESI) m/z: 226.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(4-(methyl)phenyl)ethyl)ethan-1-amine (**3ba**)*: Colorless viscous liquid, 83% yield, 99.6 mg; 91% de. $[\alpha]_D^{20}$ = -84.8 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ba** isomer, 11.1; minor (*R,S*)-**3ba** isomer, 11.2. The NMR data of (*S,S*)-**3ba** matches that reported in the literature.[17] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.2 Hz, 2H), 7.19–7.12 (m, 3H), 7.06 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 3.40 (m, 2H), 2.27 (s, 3H), 1.18 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 145.8, 142.7, 136.5, 129.1 (2C), 128.4 (2C), 126.8, 126.7 (2C), 126.6 (2C), 55.1, 54.8, 25.0 (2C), 21.1. **MS** (ESI) m/z: 240.2 $[M+H]^+$.

*(S)-1-(4-isopropylphenyl)-N-((S)-1-phenylethyl)ethan-1-amine (**3ca**)*: Colorless viscous liquid, 87% yield, 116.1 mg; 93% de. $[\alpha]_D^{20}$ = -72.0 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ca** isomer, 11.7; minor (*R,S*)-**3ca** isomer, 11.9. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 6.0 Hz, 3H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 3.46 (q, *J* = 6.6 Hz, 1H), 3.42 (q, *J* = 6.6 Hz, 1H), 2.83 (dt, *J* = 13.8, 6.6 Hz, 1H), 1.20 (dd, *J* = 11.2, 6.6 Hz, 12H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 147.3, 128.3 (2C), 126.7 (4C), 126.5 (3C), 126.3 (2C), 55.1, 54.8, 33.7, 24.8 (2C), 24.0 (2C). **HRMS** (ESI) m/z: calculated for $C_{19}H_{25}N$ 267.1987 $[M+H]^+$, found 267.1988.

*(S)-1-Phenyl-N-((S)-1-(4-(methoxyl)phenyl)ethyl)ethan-1-amine (**3da**)*: Colorless viscous liquid, 90% yield, 115.3 mg; 93% de. $[\alpha]_D^{20}$ = -50.8 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3da** isomer, 9.6; minor (*R,S*)-**3da** isomer, 9.7. The NMR data of (*S,S*)-**3da** matches that reported in the literature.[18] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.2 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 3.73 (s, 3H), 3.46 (m, 2H), 1.22 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.5, 128.4 (4C), 127.8 (2C), 126.9, 126.7 (2C),113.8 (2C), 55.3, 55.1, 54.5, 24.9, 24.9. **MS** (ESI) m/z: 256.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(4-(fluoro)phenyl)ethyl)ethan-1-amine (**3ea**)*: Colorless viscous liquid, 81% yield, 98.8 mg; 89% de. $[\alpha]_D^{20}$ = -201.6 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ea** isomer, 11.1; minor (*R,S*)-**3ea** isomer, 11.2. The NMR data of (*S,S*)-**3ea** matches that reported in the literature.[18] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.2 Hz, 2H), 7.32–7.28 (m, 1H), 7.26–7.21 (m, 4H), 7.09–7.02 (m, 2H), 3.41 (m, 2H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.7 (d, *J* = 242.6 Hz, 1C), 143.5, 141.4, 128.4 (2C), 128.1 (d, *J* = 7.8 Hz, 2C), 126.6 (2C), 126.5, 115.2, 115.1, 55.1, 54.4, 25.1, 24.9. **MS** (ESI) m/z: 244.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(4-(trifluoromethyl)phenyl)ethyl)ethan-1-amine (**3fa**)*: Colorless viscous liquid, 92% yield, 135.2 mg; 90% de. $[\alpha]_D^{20}$ = -42.4 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3fa** isomer, 9.2; minor (*R,S*)-**3fa** isomer, 9.4. The NMR data of (*S,S*)-**3fa** matches that reported in the literature.[17] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 2H), 7.31–7.26 (m, 4H), 7.21–7.17 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 3.49 (q, *J* = 6.6 Hz, 1H), 3.37 (q, *J* = 6.6 Hz, 1H), 1.21 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 150.1, 145.4, 128.5 (5C), 127.0 (2C), 126.5 (2C), 125.4 (2C), 55.3, 54.8, 24.9 (2C). **MS** (ESI) m/z: 294.3 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(4-(nitro)phenyl)ethyl)ethan-1-amine (**3ga**)*: Colorless viscous liquid, 85% yield, 115.2 mg; 88% de. $[\alpha]_D^{20}$ = -75.6 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ga** isomer, 13.0; minor (*R,S*)-**3ga** isomer, 13.1. The NMR data of (*S,S*)-**3ga** matches that reported in the literature.[17] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 2H), 7.22–7.16 (m, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 3.56 (q, *J* = 6.6 Hz, 1H), 3.35 (q, *J* = 6.6 Hz, 1H), 1.22 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 153.9, 147.1, 145.1 (2C), 128.6 (2C), 127.5 (2C), 127.1, 126.4 (2C), 123.8 (2C), 55.5, 54.8, 24.8 (2C). **MS** (ESI) m/z: 271.1 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(3-(methyl)phenyl) ethyl)ethan-1-amine (**3ha**)*: Colorless viscous liquid, 81% yield, 96.0 mg; 86% de. $[\alpha]_D^{20}$ = -70.0 (c = 0.5, ethanol). GC (program see Experimental section (general method)):

retention time [min]: major (*S,S*)-**3ha** isomer, 10.2; minor (*R,S*)-**3ha** isomer, 10.4. The NMR data of (*S,S*)-**3ha** matches that reported in the literature.[17] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.2 Hz, 2H), 7.17–7.12 (m, 4H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.95 (s, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 3.57 (q, *J* = 6.6 Hz, 1H), 3.52 (q, *J* = 6.6 Hz, 1H), 2.41 (s, 3H), 1.19 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 145.7 (2C), 137.9, 128.4 (2C), 128.2, 127.6, 127.3, 126.8, 126.7 (2C), 123.7, 55.1, 55.1, 25.0, 24.9, 21.5. **MS** (ESI) m/z: 240.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(3-(methoxyl)phenyl)ethyl)ethan-1-amine (**3ia**)*: Colorless viscous liquid, 95% yield, 121.6 mg; 91% de. $[\alpha]_D^{20}$ = -37.2 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ia** isomer, 11.6; minor (*R,S*)-**3ia** isomer, 11.8. The NMR data of (*S,S*)-**3ia** matches that reported in the literature.[17] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.2 Hz, 2H), 7.19–7.11 (m, 4H), 6.75–6.67 (m, 3H), 3.74 (s, 3H), 3.45 (q, *J* = 6.6 Hz, 1H), 3.40 (q, *J* = 6.6 Hz, 1H), 1.20 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.7, 129.4 (2C), 128.4 (2C), 126.8, 126.7, 126.6, 119.1, 112.3 (2C), 112.1, 55.2, 55.1 (2C), 29.7, 24.9. **MS** (ESI) m/z: 256.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(2-(fluoro)phenyl)ethyl)ethan-1-amine (**3ja**)*: Colorless viscous liquid, 95% yield, 116.0 mg; 92% de. $[\alpha]_D^{20}$ = -310.4 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ja** isomer, 8.2; minor (*R,S*)-**3ja** isomer, 8.4. The NMR data of (*S,S*)-**3ja** matches that reported in the literature.[19] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.2 Hz, 2H), 7.34–7.24 (m, 5H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.11–7.01 (m, 1H), 3.70–3.67 (q, *J* = 6.6 Hz, 1H), 3.43 (q, *J* = 6.6 Hz, 1H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.35 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.11 (d, *J* = 243.8 Hz, 1C), 145.6, 132.4 (d, *J* = 13.0 Hz, 1C), 128.4 (2C), 128.4, 128.09 (d, *J* = 8.3 Hz, 1C), 126.9, 126.8 (2C), 124.2 (d, *J* = 3.3 Hz, 1C), 115.6 (d, *J* = 22.3 Hz, 1C), 55.5, 50.1 (d, *J* = 1.3 Hz, 1C), 25.1, 23.4. **MS** (ESI) m/z: 244.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(2-(methoxyl)phenyl)ethyl)ethan-1-amine (**3ka**)*: Colorless viscous liquid, 93% yield, 119.1 mg; 95% de. $[\alpha]_D^{20}$ = -52.4 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ka** isomer, 10.1; minor (*R,S*)-**3ka** isomer, 10.3. The NMR data of (*S,S*)-**3ka** matches that reported in the literature.[19] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40–7.32 (m, 2H), 7.32–7.23 (m, 4H), 7.21–7.14 (m, 1H), 6.97 (dd, *J* = 10.8, 3.6 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.81 (m, 2H), 1.22 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.5, 145.5, 132.8, 128.3 (2C), 128.1, 127.7, 127.0 (2C), 126.8, 120.7, 110.8, 55.5, 55.2, 51.7, 25.0, 22.7. **MS** (ESI) m/z: 256.2 $[M+H]^+$.

*(S)-1-(2,4-dimethylphenyl)-N-((S)-1-phenylethyl)ethan-1-amine (**3la**)*: Colorless viscous liquid, 88% yield, 119.1 mg; 93% de. $[\alpha]_D^{20}$ = -62.4 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3la** isomer, 11.0; minor (*R,S*)-**3la** isomer, 11.4. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 10.2, 4.8 Hz, 2H), 7.16–7.11 (m, 1H), 7.11–7.06 (m, 2H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.82 (s, 1H), 3.66 (q, *J* = 6.6 Hz, 1H), 3.43 (q, *J* = 6.6 Hz, 1H), 2.23 (s, 3H), 1.83 (s, 3H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.6, 140.3, 135.7, 135.3, 131.1, 128.4, 127.1, 126.8 (2C), 126.7, 126.7, 125.0, 55.1, 50.1, 24.7, 24.1, 21.0, 18.8. **HRMS** (ESI) m/z: calculated for $C_{18}H_{23}N$ 253.1830 $[M+H]^+$, found 253.1833.

*(S)-1-(2,4-difluorophenyl)-N-((S)-1-phenylethyl)ethan-1-amine (**3ma**)*: Colorless viscous liquid, 91% yield, 118.8 mg; 90% de. $[\alpha]_D^{20}$ = -387.2 (c = 0.5, ethanol). GC (program see Experimental section (general method)):

retention time [min]: major (*S,S*)-**3ma** isomer, 8.9; minor (*R,S*)-**3ma** isomer, 9.1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 11.2, 4.3 Hz, 1H), 7.32 – 7.25 (m, 2H), 6.94 – 6.86 (m, 1H), 6.84 – 6.77 (m, 1H), 3.81 (q, *J* = 6.8 Hz, 1H), 3.55 (q, *J* = 6.6 Hz, 1H), 1.35 (s, 1H), 1.33 (s, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.5 (dd, *J* = 78.8, 12.0 Hz), 160.0 (dd, *J* = 79.9, 12.0 Hz), 145.3, 129.1 (dd, *J* = 9.4, 7.1 Hz)., 128.4 (2C), 128.1 (dd, *J* = 13.2, 3.6 Hz), 126.9, 126.6 (2C), 111.1 (dd, *J* = 20.4, 3.6 Hz), 103.8 (dd, *J* = 26.4, 25.2 Hz), 55.4, 49.4 (d, *J* = 1.2 Hz), 24.9, 23.4. **HRMS** (ESI) m/z: calculated for $C_{16}H_{17}F_2N$ 261.1329 $[M+H]^+$, found 261.1328.

*(S)-1-Phenyl-N-((S)-1-(naphthalen-1-yl)ethyl)ethan-1-amine (**3na**)*: White solid, m.p.: 85.8 – 86.9 °C, 90% yield, 124.2 mg; 99% de. $[\alpha]_D^{20}$ = -58.8 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3na** isomer, 13.9; minor (*R,S*)-**3na** isomer, 14.1. The NMR data of (*S,S*)-**3na** matches that reported in the literature.[20] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.95–7.90 (m, 1H), 7.86–7.81 (m, 1H), 7.76 (s, 1H), 7.62–7.56 (m, 1H), 7.51 (t, *J* = 6.6, 1H), 7.45 (m, 1H), 7.35 (m, 2H), 7.33–7.29 (m, 1H), 7.26–7.19 (m, 2H), 4.44 (q, *J* = 6.6 Hz, 1H), 3.76 (q, *J* = 6.6 Hz, 1H), 1.81 (s, 3H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.41 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.0, 141.7, 134.0, 131.5, 128.8, 128.4 (2C), 127.1, 126.8, 126.7 (2C), 125.7, 125.5, 125.3, 123.1, 122.8, 55.4, 50.8, 24.8, 24.7. **MS** (ESI) m/z: 276.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(2,3-dihydrobenzofuran-2-yl)ethyl)ethan-1-amine (**3oa**)*: White solid, mp 92.6–93.9 °C, 91% yield, 121 mg; 98% de. $[\alpha]_D^{20}$ = -294.0 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3oa** isomer, 11.9; minor (*R,S*)-**3oa** isomer, 12.0. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48–7.40 (m, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.24 (dt, *J* = 14.4, 7.2 Hz, 4H), 7.20–7.08 (m, 3H), 6.30 (s, 1H), 3.60 (m, 2H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.6, 154.8, 145.4, 128.5 (2C), 128.4, 127.0, 126.9 (2C), 123.6, 122.6, 120.7, 111.2, 102.7, 55.5, 49.2, 25.2, 21.5. **HRMS** (ESI) m/z: calculated for $C_{18}H_{20}NO$ 266.1539 $[M+H]^+$, found 266.1539.

*(S)-1-Phenyl-N-((S)-1-(9H-fluoren-2-yl)ethyl)ethan-1-amine (**3pa**)*: white solid, mp 166.3–168.1 °C, 93% yield, 146.1 mg; >99% de. $[\alpha]_D^{20}$ = -76.8 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3pa** isomer, 16.4. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.20–7.13 (m, 9H), 3.82 (s, 2H), 3.51 (m, 2H), 1.25 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.7, 143.3, 141.6, 128.5 (2C), 126.9(3C), 126.7 (2C), 126.5 (2C), 125.7, 125.0 (2C), 123.4, 119.8, 119.7, 55.4 (2C), 36.9, 29.7 (2C). **HRMS** (ESI) m/z: calculated for $C_{23}H_{24}N$ 314.1905 $[M+H]^+$, found: 314.1903.

*(S)-N-((S)-1-phenylethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (**3qa**)*: Colorless viscous liquid, 92% yield, 106.3 mg; 99% de. $[\alpha]_D^{20}$ = -72.8 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3qa** isomer, 12.9; minor (*R,S*)-**3qa** isomer, 13.5. The NMR data of (*S,S*)-**3qa** matches that reported in the literature.[16] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37–7.34 (m, 2H), 7.29–7.22 (m, 3H), 7.16–7.15 (m, 1H), 7.08–6.92 (m, 3H), 3.95 (q, *J* = 6.6 Hz, 1H), 3.62 (t, *J* = 4.8 Hz, 1H), 2.80–2.65 (m, 1H), 2.62–2.60 (m, 1H), 1.90–1.80 (m, 1H), 1.78–1.50 (m, 3H), 1.28–1.27 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.7, 139.9, 137.2, 129.2, 128.9, 128.5 (2C), 126.8 (2C), 126.7, 125.6 (2C), 56.2, 53.2, 29.5, 29.1, 24.8, 18.7. **MS** (ESI) m/z: 231.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-phenyl)ethyl)propan-1-amine (**3ra**)*: Colorless viscous liquid, 81% yield, 97.2 mg; 86% de. $[\alpha]_D^{20}$ = -119.2 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ra** isomer, 8.9; minor (*R,S*)-**3ra** isomer, 9.2. The NMR data of (*S,S*)-**3ra** matches that reported in the literature.[21] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29–7.22 (m, 4H), 7.21–7.07 (m, 6H), 3.41 (q, *J* = 6.6 Hz, 1H), 3.13 (t, *J* = 6.6 Hz, 1H), 1.53–1.51 (m, 2H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.66 (t, *J* = 6.6Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 128.4 (2C), 128.3 (4C), 127.4 (2C), 126.8 (4C), 61.7, 55.0, 31.4, 25.1, 11.0. **MS** (ESI) /z: 240.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(2-(propyl)phenyl)ethyl)propan-1-amine (**3sa**)*: Colorless viscous liquid, 86% yield, 116.1 mg; 92% de. $[\alpha]_D^{20}$ = -131.2 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3sa** isomer, 11.5; minor (*R,S*)-**3sa** isomer, 11.7. The NMR data of (*S,S*)-**3sa** matches that reported in the literature.[20] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 6.6 Hz, 2H), 7.15 (ddd, *J* = 9.6, 6.0, 2.4 Hz, 2H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 3.68 (s, 3H), 3.47–3.42 (m, 1H), 3.40 (q, *J* = 6.6 Hz, 1H), 1.71–1.53 (m, 2H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.67 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.9, 146.1, 129.0, 128.2 (2C), 127.6, 127.0 (2C), 126.7, 125.6, 120.4, 110.7, 58.2, 55.3, 55.1, 29.3, 25.3, 11.2. **MS** (ESI) m/z: 270.2 $[M+H]^+$.

*(S)-1-Phenyl-N-((S)-1-(2-(2-pyridinyl)ethyl)ethan-1-amine (**3ta**)*: Colorless viscous liquid, 90% yield, 102.2 mg; 88% de. $[\alpha]_D^{20}$ = -158.0 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: major (*S,S*)-**3ta** isomer, 8.6; minor (*R,S*)-**3ta** isomer, 8.9. The NMR data of (*S,S*)-**3ta** matches that reported in the literature.[22] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.52–8.51 (m, 1H), 7.52–7.50 (m, 1H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.20–7.13 (m, 3H), 7.07–7.06 (m, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 3.52 (q, *J* = 6.6 Hz, 1H), 3.37 (q, *J* = 6.6 Hz, 1H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 164.8, 149.7, 145.6, 136.2, 128.4 (2C), 126.9, 126.8 (2C), 121.9, 121.7, 56.2, 55.6, 25.1, 23.4. **MS** (ESI) m/z: 227.3 $[M+H]^+$.

*(S)-4-Phenyl-N-((S)-1-phenylethyl)butan-2-amine **(3ua)***: Colorless viscous liquid, 82% yield, 104.1 mg; 86% de. $[\alpha]_D^{20}$ = -69.9 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: minor (*R,S*)-**3ua** isomer, 10.9; major (*S,S*)-**3ua** isomer, 11.1. The NMR data of (*S,S*)-**3ua** matches that reported in the literature.[23] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25–7.09 (m, 10H), 3.85 (q, *J* = 6.6 Hz, 1H), 2.60–2.45 (m, 4H), 1.79 (dd, *J* = 12.0, 6.6 Hz, 1H), 1.59 (dd, *J* = 6.6, 3.6 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.3, 128.5 (2C), 128.4 (2C), 128.3 (2C), 127.1 (2C), 126.7 (2C), 125.8, 61.6, 54.9, 31.4, 25.1, 10.9. **MS** (ESI) m/z: 254.2 $[M+H]^+$.

*(2S)-3,3-Dimethyl-N-((S)-1-phenylethyl)butan-2-amine (**3va**)*: Colorless viscous liquid, 97% yield, 99.9 mg; 99% de. $[\alpha]_D^{20}$ = -2.4 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: minor (*R,S*)-**3va** isomer, 5.8; major (*S,S*)-**3va** isomer, 6.0. The NMR data of (*S,S*)-**3va** matches that reported in the literature.[16] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.8 Hz, 2H), 7.25–7.22 (m, 2H), 7.17–7.11 (m, 1H), 3.70 (q, *J* = 6.6 Hz, 1H), 2.23–2.21 (m, 1H), 1.20 (d, *J* = 6.6, 3H), 0.82 (s, 9H), 0.78 (d, *J* = 6.6, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 147.6, 128.3 (2C), 126.7 (2C), 126.7, 59.6, 57.1, 34.8, 26.6, 23.7, 16.0. **MS** (ESI) m/z: 206.2 $[M+H]^+$.

*(S)-1-Cyclohexyl-N-((S)-1-phenylethyl)ethan-1-amine (**3wa**)*: Colorless viscous liquid, 97% yield, 112.5 mg, 99% de. $[\alpha]_D^{20}$ = -37.2 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min]: minor (*R,S*)-**3wa** isomer, 8.7; major (*S,S*)-**3wa** isomer, 9.0. The NMR data of (*S,S*)-**3wa** matches that reported in the literature.[23] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28–7.21 (m, 4H), 7.14 (t, *J* = 6.6 Hz, 1H), 3.79 (q, *J* = 6.6 Hz, 1H), 2.56–2.17 (m, 1H), 1.75–1.57 (m, 4H), 1.49 (d, *J* = 12.4 Hz, 1H), 1.37–1.28 (m, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.16–1.54 (m, 2H), 1.10–1.01 (m, 1H), 0.99–0.89 (m, 2H), 0.81 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.5, 128.3 (2C), 126.7, 126.6 (2C), 55.5, 54.8, 42.1, 30.3, 27.3, 26.9, 26.8, 26.6, 24.4, 17.5. **MS** (ESI) m/z: 232.4 $[M+H]^+$.

*(R)-1-Phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)ethan-1-amine (**3nf**)*: White solid, mp 85.8–86.9 °C, 94% yield, 129.7 mg; 99% de. $[\alpha]_D^{20}$ = +61.4 (c = 0.5, ethanol). GC (program see Experimental section (general method)): retention time [min] : major (*R,R*)-**3nf** isomer, 13.9; minor (*R,S*)-**3nf** isomer, 14.1. The NMR data of (*S,S*)-**3nf** matches that reported in the literature.[20] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.95–7.90 (m, 1H), 7.86–7.81 (m, 1H), 7.76 (s, 1H), 7.62–7.56 (m, 1H), 7.51 (td, *J* = 6.6, 1.8 Hz, 1H), 7.45 (dd, *J* = 10.4, 4.8 Hz, 1H), 7.35 (dd, *J* = 8.4, 2.4 Hz, 2H), 7.33–7.29 (m, 1H), 7.26–7.19 (m, 2H), 4.44 (q, *J* = 6.0 Hz, 1H), 3.76 (q, *J* = 6.0 Hz, 1H), 1.81 (s, 3H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.41 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.0, 141.6, 134.0, 131.5, 128.8, 128.4 (2C), 127.1, 126.8, 126.7 (2C), 125.7, 125.5, 125.3, 123.1, 122.8, 55.4, 50.8, 24.8, 24.7. **MS** (ESI) m/z: 276.2 $[M+H]^+$.

Synthesis of Primary Amine 4nf from 3nf. To a stainless steel autoclave, secondary amine **3nf** (7.6 g, 28 mmol), 5% Pd/C (0.5 g, 0.28 mmol) and MeOH (50 mL) were added. The autoclave was purged three times with hydrogen and finally pressurized to 0.2 MPa. The mixture was stirred at 60 °C for 24h. After the completion of the reaction, the reaction mixture was filtered through a bed of celite and the celite subsequently washed with EtOAc (3 x 20 mL).The filtrate was dried (Na_2SO_4), and concentrated in vacuo, and the residue was purified by silica gel flash chromatography to afford the desired product **4nf** as a yellow oil.

*(R)-1-(Naphthalen-1-yl)ethan-1-amine (**4nf**)*: yellow oil, 81% yield, 3.8 g; 98% ee. $[\alpha]_D^{20}$ = +50.5 (c = 0.44, ethanol); The enantiomeric excess was determined by HPLC on Chiralcel OD-H column, hexane: isopropanol = 90: 10; flow rate = 0.8 mL/min; UV detection at 285 nm; t_R = 15.1 min (minor), 17.2 min (major). The NMR data of (*S,S*)-**4nf** matches that reported in the literature.[24] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.57–7.55 (m, 1H), 7.54–7.49 (m, 2H), 4.99 (q, *J* = 6.6 Hz, 1H), 1.78 (s, 2H), 1.59 (t, *J* = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.3, 133.9, 130.7, 129.0, 127.2, 125.9, 125.6, 125.4, 122.9, 121.4, 46.5, 24.8. **MS** (ESI) m/z: 172.1 $[M+H]^+$.

Synthesis of Cinacalect. A solution of amine **4nf** (3.8 g, 22 mmol), 3-(3-(trifluoromethyl)phenyl)propanal (5.3 g, 26 mmol), $B(C_6F_5)_3$ (113 mg, 0.22 mmol), and 4 Å MS (15.2 g, 4 wt equiv.) were dissolved in toluene (50 mL) under an ambient atmosphere. The mixture was stirred at r.t. for 8 h followed by addition of ammonia borane (0.8 g, 26 mmol), and was stirred for another 12 h at r.t.. Then the reaction mixture was filtered through a bed of celite and the celite subsequently washed with EtOAc (3 x 20 mL). The filtrate was dried (Na_2SO_4), and concentrated in vacuo, and the residue was purified by silica gel flash chromatography to afford the desired product **cinacalcet (5)** as a yellow oil.

*Cinacalcet (**5**)*: yellow oil, 92% yield, 7.3 g; 98% ee. $[\alpha]_D^{20}$ = +17.7 (c = 0.52, ethanol); The enantiomeric excess was determined by HPLC on Chiralcel OD-H column, hexane: isopropanol = 97: 3; flow rate = 0.8 mL/min; UV detection at 285 nm; t_R = 9.8 min (minor), 10.8 min (major). The NMR data of (*S,S*)- **5** matches that reported in the literature.[25] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.47–7.36 (m, 3H), 7.32 (d, *J* = 6.0 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 4.52 (q, *J* = 6.6 Hz, 1H), 2.68–2.34 (m, 4H), 1.82–1.65 (m, 2H), 1.38 (t, *J* = 17.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.1, 141.2, 134.0, 131.8, 131.3, 130.6 (q, *J* = 31.9 Hz, 1C), 129.0 (2C), 128.7 (2C), 127.2 (2C), 125.8, 125.7, 125.3, 125.0 (q, *J* = 3.8 Hz, 1C), 53.8, 47.3, 33.4, 31.9, 23.6. **MS** (ESI) m/z: 358.2 $[M+H]^+$.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxxx

Copies of **^{1}H** and **^{13}C NMR** spectra and **GC** spectra of all products.

AUTHOR INFORMATION

Corresponding Author

*E-mail: weihuizhong@zjut.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21676253 and 21706234) for financial support.

REFERENCES

(1) (a) Blaser, H. U.; Burkhardt, S.; Kirner, H. J.; Mössner, T.; Studer, M. Ethyl 2,4-Dioxo-4-phenylbutyrate: A Versatile Intermediate for the Large–Scale Preparation of Enantiomerically Pure *α*-Hydroxy and *α*-Amino Acid Esters. *Synthesis.* **2003**, *11*, 1679–1682. (b) Blaser, H. U.; Schmidt, E. *Wiley-VCH: Weinheim.* **2004**, 91–103. (c) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R.Asymmetric Reductive Amination: Convenient Access to Enantioenriched Alkyl-Alkyl or Aryl-Alkyl Substituted *α*-Chiral Primary Amines. *Adv. Synth. Catal*. **2006**, *348*, 1289–1299.

(2) For recent reviews, see: (a) Xie, J. H.; Zhu, S. F.; Zhou, Q. L. Transition Metal-Catalyzed Enantioselective Hydrogenation of Enamines and Imines. *Chem. Rev*. **2011**, *111*, 1713–1760. (b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of *tert*-Butanesulfinamide. *Chem. Rev*. **2010**, *110*, 3600–3740. (c)

Nicolas, F. B.; Fuente, V. L.; Claver, S. C. Highlights of Transition Metal–Catalyzed Asymmetric Hydrogenation of Imines. *ChemCatChem*. **2010**, *2*, 1346–1371. (d) Nugent, T. C.; Shazly, M. E. Chiral Amine Synthesis-Recent Developments and Trends for Enamide Reduction, Reductive Amination, and Imine Reduction. *Adv. Synth. Catal*. **2010**, *352*, 753–819. (e) Colle, F. T.; Dodd, R. H.; Dauban, P. Catalytic C-H amination: recent progress and future directions. *Chem. Commun*. **2009**, *34*, 5061–5074. (f) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. Enantioselective Organocatalytic Transfer Hydrogenation Reactions using Hantzsch Esters. *Acc. Chem. Res*. **2007**, *40*, 1327–1339.

(3) (a) Nugent, T. C.; Wakchaure, V. N.; Ghosh, A. K. and Mohanty, R. R. Evolution of Titanium(IV) Alkoxides and Raney Nickel for Asymmetric Reductive Amination of Prochiral Aliphatic Ketones. *Org. Lett.* **2005**, *7*, 4967–4970. (b) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N. and Mohanty, R. R. Asymmetric Reductive Amination: Convenient Access to Enantioenriched Alkyl-Alkyl or Aryl-Alkyl Substituted *α*-Chiral Primary Amines.*Adv. Synth. Catal*. **2006**, *348*, 1289–1299. (c) Nugent, T. C.; El-Shazly, M.; Wakchaure, V. N. *Ytterbium Acetate Promoted Asymmetric Reductive Amination: Significantly Enhanced Stereoselectivity. J. Org. Chem*. **2008**, *73*, 1297–1305. (d) Nugent, T. C.; Negru, D. E.; El-Shazly, M.; Hu, D.; Sadiq, A.; Bibi, A.; Umar, M. N. Sequential Reductive Amination–Hydrogenolysis: A One-Pot Synthesis of Challenging Chiral Primary Amines. *Adv. Synth. Catal*. **2011**, *353*, 2085–2092.

(4) (a) Presented in part at the Pharmacopeia Forum, **2010**. (b) Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). *Angew. Chem., Int. Ed*. **2002**, *41*, 2008–2022.

(5) (a) Massey, A. G.; Park, A. J. Perfluorophenyl derivatives of the elements : I. Tris(pentafluorophenyl)boron. *J. Organomet. Chem*. **1964**, 2, 245–250.

(6) (a) Stephan, D. W. *Science*. **2016**, *354*, 1248–1257. (b) Stephan, D. W. Frustrated Lewis Pairs. *J. Am. Chem. Soc*. **2015**, *137*, 10018–10032. (c) Stephan, D. W.; Erker, G. Frustrated Lewis Pair Chemistry: Development and Perspectives. *Angew. Chem., Int. Ed*. **2015**, *54*, 6400–6441. (d) Stephan, D. W. Frustrated Lewis Pairs: From Concept to Catalysis. *Acc. Chem. Res*. **2015**, *48*, 306–316. (e) Meng, M. Feng, X. Du H. Frustrated Lewis Pairs Catalyzed Asymmetric Metal-Free Hydrogenations and Hydrosilylations. *Acc. Chem. Res.* **2018**, *51*, 191–201.

(7) (a) Heiden, Z. M.; Stephan, D. W. Metal-free diastereoselective catalytic hydrogenations of imines using $B(C_6F_5)_3$. *Chem. Commun*. **2011**, *47*, 5729–5731. (b) Han, Y.; Zhang, S.; He, J.; Zhang, Y. $B(C_6F_5)_3$–Catalyzed (Convergent) Disproportionation Reaction of Indoles. *J. Am. Chem. Soc.* **2017**, *139*, 7399−7407. (c) Ma, Y.; Zhang, L.; Luo, Y.; Nishiura, M.; Hou, Z. $B(C_6F_5)_3$–Catalyzed C–Si/Si–H Cross-Metathesis of Hydrosilanes. *J. Am. Chem. Soc*. **2017**, *139*, 12434–12437. (d) Zhi, Y. L.; Zhi, H. W.; Xiao, C. W. $B(C_6F_5)_3$–Catalyzed Cascade Reduction of Pyridines. *Angew. Chem., Int. Ed.* **2017**, *56*, 5817–5820. and references cited therein. (e) Meng, W.; Feng, X.; Du, H. Frustrated Lewis Pairs Catalyzed Asymmetric Metal–Free Hydrogenations and Hydrosilylations. *Acc. Chem. Res*. **2018**, *51*, 191-201. and references cited therein.

(8) (a) Fasano, V.; Radcliffe, J. E.; Ingleson, M. J. $B(C_6F_5)_3$-Catalyzed Reductive Amination using Hydrosilanes. *ACS Catal.* ***2016***, 6, 1793–1978. (b) Fasano, V.; Ingleson, M. J. Expanding Water/Base Tolerant Frustrated Lewis Pair Chemistry to Alkylamines Enables Broad Scope Reductive Aminations. *Chem. Eur. J*. ***2017***, *23*, 2217–2224.

(9) Kim, E.; Park, S.; Chang, S. Silylative Reductive Amination of *α,β*-Unsaturated Aldehydes: A Convenient Synthetic Route to *β*-Silylated Secondary Amines. *Chem. Eur. J.* **2018**, *24*, 5765–5769.

(10) Dorkó, E.; Szabó, M.; Kótai, B.; Pápai, I. Domján, A.; Soós, T. Expanding the Boundaries of Water-Tolerant Frustrated Lewis Pair Hydrogenation: Enhanced Back Strain in the Lewis Acid Enables the Reductive Amination of Carbonyls. *Angew. Chem., Int. Ed*. ***2017***, *56*, 9512–9516.

(11) Reactions were performed in our labouratroy..

(12) For leading reviews, see: (a) Marder, T. B. Will We Soon Be Fueling our Automobiles with Ammonia-Borane? *Angew. Chem., Int. Ed.* **2007**, *46*, 8116–8118. (b) Hamilton, C. W.; Baker, R. T.; Staubitz, A.; Manners, I. B–N compounds for chemical hydrogen storage. *Chem. Soc. Rev.* ***2009***, *38*, 279–293. (c) Satubitz, A.; Robertson, A. P. M. Ammonia-Borane and Related Compounds as Dihydrogen Sources. *Chem. Rev.* ***2010***, *110*, 4079–4124. (d) Huang, Z.; Autrey, T. Boron-nitrogen-hydrogen (BNH) compounds: recent developments in hydrogen storage, applications in hydrogenation and catalysis, and new syntheses. *Energy Environ. Sci.* ***2012***, *5*, 9257–9268. (e) Houghton, A. Y.; Hurmalainen, J.; Mansikkamäki, A. Piers W. E.; Tuononen, H. M. Direct observation of a borane-silane complex involved in frustrated Lewis-pair-mediated hydrosilylations. *Nat. Chem.* ***2014***, *6*, 983–988. (f) Rossin, A.; Peruzzini, M. Ammonia-Borane and Amine-Borane Dehydrogenation Mediated by Complex Metal Hydrides. *Chem. Rev*. ***2016***, *116*, 8848–8872.

(13) (a) Li, S.; Li, G.; Meng, W.; Du, H. A Frustrated Lewis Pair Catalyzed Asymmetric Transfer Hydrogenation of Imines Using Ammonia Borane. *J. Am. Chem. Soc.* **2016**, *138*, 12956–12962. (b) Li, S., Meng, W.; Du, H. Asymmetric Transfer Hydrogenations of 2,3–Disubstituted Quinoxalines with Ammonia Borane. *Org. Lett.* **2017**, *19*, 2604–2606. (c) Ding, F.; Zhang, Y.; Zhao, R.; Jiang, Y.; Bao, R. L.; Lina, K.; Shi, L. $B(C_6F_5)_3$-Promoted hydrogenations of N-heterocycles with ammonia borane. *Chem. Commun*. **2017**, *53*, 9262–9264.

(14) Wang, G.; Chen, C.; Du, T.; Zhong, W. Metal-Free Catalytic Hydrogenation of Imines with Recyclable [2.2]Paracyclophane-Derived Frustrated Lewis Pairs Catalysts. *Adv. Synth. Catal*. **2014**, *356*, 1747–1752.

(15) Stephens, F. H.; Baker, R. T.; Matus, M. H.; Grant, D. J.; Dixon, D. A. Acid Initiation of Ammonia-Borane Dehydrogenation for Hydrogen Storage. *Angew. Chem., Int. Ed*. **2007**, *46*, 746–749.

(16) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R. Asymmetric Reductive Amination: Convenient Access to Enantioenriched Alkyl-Alkyl or Aryl-Alkyl Substituted *α*-Chiral Primary Amines. *Adv. Synth. Catal.* **2006**, *348*, 1289–1299.

(17) D. Brenna, D.; Rossi, S.; Cozzi, F.; Benaglia, M. Iron catalyzed diastereoselective hydrogenation of chiral imines. *Org. Biomol. Chem.* **2017**, *15*, 5685–5688.

(18) Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. Practical Synthesis of Optically Active Fluorine-substituted *α*-Phenylethylamines by Retardation of Hydrogenolytic Cleavage at Benzylic Position. *Chemistry Letters.* **2004**, *33*, 1424-1425.

(19) Thomas, C. N.; Daniela, E. N.; Mohamed, E. S.; Dan, H.; Abdul, S.; Ahtaram, B.; Umar, M. N. Sequential Reductive Amination-Hydrogenolysis: A One‐Pot Synthesis of Challenging Chiral Primary Amines. *Adv. Synth. Catal*. **2011**, *353*, 2085–2092.

(20) T Barry, M. T.; Steven, M. S.; James, P. S. Development of an Asymmetric Trimethylenemethane Cycloaddition Reaction: Application in the Enantioselective Synthesis of Highly Substituted Carbocycles. *J. Am. Chem. Soc*. **2011**, *133*, 19483–19497.

(21) Heiden, Z. M.; Stephan, D. W. Metal-free diastereoselective catalytic hydrogenations of imines using $B(C_6F_5)_3$. *Chem. Commun*. **2011**, *47*, 5729–5731.

(22) Uenishi, J.; Masahiro, H.; Sachiko, A.; Katsuya, M.; Osamu, Y.; Hiroshi, T. Synthesis of Chiral Nonracemic 1-(2-Pyridinyl)ethylamines: Stereospecific Introduction of Amino Function onto the 2-Pyridinylmethyl Carbon Center. *J. Org. Chem*. **2004**, *69*, 6781–6789.

(23) Thomas, C. N.; Vijay, N. W.; Abhijit, K. G.; Rashmi, R. M. Evolution of Titanium(IV) Alkoxides and Raney Nickel for Asymmetric Reductive Amination of Prochiral Aliphatic Ketones. *Org. Lett.* **2005**, *7*, 4967–4970.

(24) Akihito, K.; Koichi, N.; Hikaru, M.; Hideto, N.; Tomohiro. E.; Akio, B.; Makoto, Y. C_3-Symmetric Boron Lewis Acid with a Cage-Shape for Chiral Molecular Recognition and Asymmetric Catalysis. *Chem. Eur. J.* **2017**, *23*, 1273–1277.

(25) Geoghegan, K.; Kelleher, S.; Evans, P. An Investigation into the One-Pot Heck Olefination-Hydrogenation Reaction. *J. Org. Chem.* **2011**, *76*, 2187–2194.