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Synthesis of novel carbohydrate-based valine-derived formamide organocatalysts by CuAAC click chemistry and their application in asymmetric reduction of imines with trichlorosilane

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ABSTRACT

Novel organocatalysts combining carbohydrate and *N*-formyl-L-valine derivatives were prepared by Cu^{II}-catalyzed diazo transfer and Cu^{I}-catalyzed azide–alkyne 1,3-dipolar cycloaddition CuAAC click chemistry'. It was found that the carbohydrate-based valine-derived formamide organocatalyst had high catalytic activity for the asymmetric reduction of imines with trichlorosilane. The reduction can proceed at room temperature in toluene in high yield (up to 98%) and with excellent enantioselectivity (up to 94%). 'CuAAC' click chemistry is a bridge to link *N*-formyl-L-valine derived organocatalysts with carbohydrates.

1. Introduction

Chiral amines are key building blocks for the pharmaceutical and fine chemistry industry, and are mainly prepared by the enantioselective reduction of prochiral imines.[1] In addition to transition metal-catalyzed and biocatalytic reduction, organocatalytic reduction has received much attention as a relatively easy operation and environmentally friendly method. The Lewis-basic organocatalytic reduction with trichlorosilane is an emerging organocatalytic methodology and complementary to Bronsted acid organocatalyzed-biomimetic reduction with Hantzsch esters. In 2001, *N*-formyl-L-proline anilide as a Lewis-basic organocatalyst was first reported to catalyze the reduction of imines with trichlorosilane with moderate enantioselectivity.[2] Some highly effective Lewis-basic organocatalysts were subsequently developed to catalyze the reduction of imines with trichlorosilane. In addition to *N*-formyl-L-proline anilide,[2] some other L-proline-derived organocatalysts were also developed such as *N*-picolinoyl-L-pyrrolidine,[3] L-proline derived C2-symmetric chiral tetraamide,[4] *N*-formyl proline fatty amide,[5] and N-substituted prolines.[6] *N*-Formyl-L-valine derived Lewis-basic organocatalysts were found to significantly improve the enantioselectivity.[7] *N*-Picolinoyl chiral amino acid-based organocatalysts were also considered to be highly effective organocatalysts for the reduction of imines.[3,8] Sun et al. developed pipecolinic acid derived,[9] piperazine-2-carboxylic acid derived[10] and *S*-chiral[11] catalysts to reduce imines with high enantioselectivity. In spite of these significant developments of Lewis-basic organocatalysts, the design and synthesis of organocatalysts mainly depend on the chiral scaffolds of natural compounds. Thus, it is challenging and important to develop more natural, efficient organocatalysts.

Carbohydrates have been developed as organocatalysts for application in asymmetric organic synthesis.[12] In 2007, D-glucosamine-derived bifunctional urea schiff base organocatalysts were first reported to catalyze enantioselective Strecker and Mannich reactions.[13] Subsequently, carbohydrate-derived bifunctional primary amine-thiourea catalysts showed high enantioselectivity for Michael additions of aromatic ketones with nitroolefins.[14] In our preliminary work, we developed carbohydrate-derived amino alcohols[15] and novel carbohydrate-derived prolinamides[16] to catalyze asymmetric aldol reactions. Recently, we described carbohydrate-derived pyridinecarboxylic organocatalysts for the enantioselective reduction of imines with trichlorosilane in high yield (up to 93%) and with moderate enantioselectivity (up to 75%).[17]

As part of our continued interests in carbohydrates as new organocatalysts,[15–18] novel organocatalysts combining carbohydrate and *N*-formyl-L-valine derivatives made by copper-catalyzed azide–alkyne cycloaddition CuAAC click chemistry are developed herein to catalyze the enantioselective reductions of imines with trichlorosilane.

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2. Results and discussion

2.1. Synthesis of carbohydrate-derived organocatalysts 9

N-Formyl-L-valine derived alkynes **5** were obtained by a three step reaction from *N*-BOC-valine, which had been reported in the literature.[19] Carbohydrate-based valine-derived formamide organocatalysts **9** were synthesized by Cu^{II}-catalyzed diazo transfer and Cu^{I}-catalyzed azide–alkyne 1,3-dipolar cycloaddition CuAAC click chemistry. Imidazole-1-sulfonyl azide was employed to transfer a diazo moiety onto the D-glucosamine hydrochloride catalyzed by Cu^{II}, to give 2-azido-2-deoxy-3,4,6-tri-*O*-acetyl-α,β-D-glucopyranosylacetate **8** via acetylation. *N*-Formyl-L-valine derived alkynes **5** could be linked with azidoglucopyranosylacetate with good yield. The carbohydrate-based valine-derived formamide organocatalysts **9** were in a 3:7 ratio of α- and β-isomers (Scheme 1).

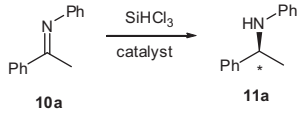
2.2. Catalytic activities of carbohydrate-derived organocatalysts in asymmetric reductions of imines with trichlorosilane

With the aforementioned organocatalysts in hand, we next evaluated their catalytic activities in the enantioselective reduction of imines with trichlorosilane. The asymmetric reduction of imine **10a** with trichlorosilane was selected as a model reaction. Initially, these new catalysts were screened in toluene and the results are shown in Table 1.

In the presence of 10 mol % catalyst **9a**, the asymmetric reduction of imine **10a** with trichlorosilane proceeded smoothly at room temperature. The desired product was obtained in excellent yield and with moderate ee value (Table 1, entry 1). Organocatalyst **9b** showed higher catalytic activity than organocatalyst **9a**, with the ee value for the (*S*)-enantiomer being improved to 88% (Table 1, entry 2). The optimization of reaction conditions was next focused on the solvent (Table 1, entries 2–5). The reaction was carried out in chloroform and dichloromethane, it gave moderate ee values. The ee value of the reduction was poor in acetonitrile. We found that toluene was the best solvent and afforded the product in 95% yield and with 88% ee. We further investigated the reaction temperature effect using toluene as the solvent (Table 1, entries 2, 6–8). Lowering the reaction temperature led to an increased ee. However, the increase of ee value was not obvious. When the reaction temperature decreased from room temperature to −20 °C, the ee value only increased from 88% to 91%. Based on the above results, we selected room temperature as the optimal temperature for this reaction.

Having established the optimal reaction conditions, we next explored the substrate scope of the asymmetric reduction. In order to investigate the generality of catalyst **9b**, we examined the asym-

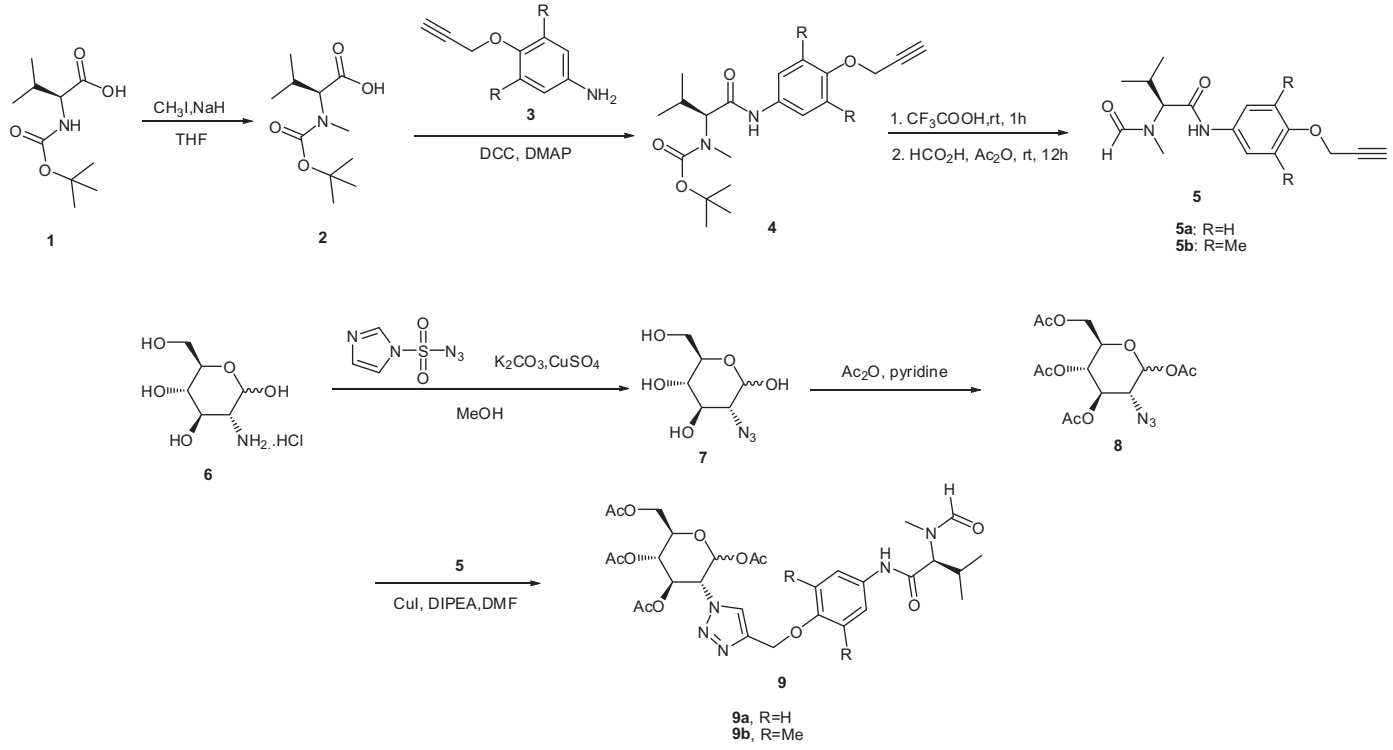
Table 1
Asymmetric reduction of imine **10a**[a]



10a **11a**

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Yield[b] (%)	ee[c] (%) (config)[d]
1	**9a** (10)	Toluene	rt	94	73 (*S*)
2	**9b** (10)	Toluene	rt	95	88 (*S*)
3	**9b** (10)	CH_2Cl_2	rt	93	61 (*S*)
4	**9b** (10)	$CHCl_3$	rt	91	43 (*S*)
5	**9b** (10)	CH_3CN	rt	87	12 (*S*)
6	**9b** (10)	Toluene	0	87	89 (*S*)
7	**9b** (10)	Toluene	−20	73	92 (*S*)
8[e]	**9b** (10)	Toluene	−20	92	91 (*S*)

[a] The reactions were carried out with catalyst **9b** and 1.5 equiv of $SiHCl_3$ on a 0.5 mmol scale in 2.0 mL of solvent for 24 h.
[b] Isolated yield based on the imine.
[c] Determined by chiral HPLC.
[d] The absolute configuration was determined by comparison of the specific rotation with that of the literature value.[10]
[e] This reaction was carried out for 48 h.

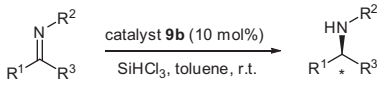


Scheme 1. Synthesis of carbohydrate-derived organocatalysts **9**.

metric reduction of some ordinary *N*-aryl imines with trichlorosilane under the optimal reaction conditions. The results are summarized in Table 2. As the substrate of the model reaction, imine **10a** could be reduced in 95% yield and with 88% ee (Table 2, entry 1). For aromatic *N*-Ph imines **10b**–**10e**, the desired products **11b**–**11e** were obtained with satisfactory yields and enantioselectivities. When the aromatic *N*-Ph imines with electron-withdrawing groups **10b**–**10d** were reduced, the yields increased (97–98%, entries 2–4, Table 2) with excellent enantioselectivities (92–94%). Imines **10e** with an electron-donating group led to a yield and ee that were lower than those of **10a** (Table 2, entry 5). Phenyl *N*-aryl imines were somewhat different from the aromatic *N*-Ph imines, and only afforded the 34-86% ee values (Table 2, entries 6–11). In the case of imine **10h**, phenyl *N*-aryl imines with electron-withdrawing groups **10f**, **10g**, and **10i** could be reduced in high yields (92–96%) and with moderate enantioselectivities (83–86% ee values). On the other hand, the yields and enantioselectivities of phenyl *N*-aryl imines with electron-donating groups **10j**–**10k** were not satisfactory with 69–84% yields and only 34–53% ee (Table 2, entries 10–11). Overall, for organocatalyst **9b**, the catalytic effect of imines with electron-withdrawing groups was better than that of imines with electron-donating groups. For valine-derived organocatalysts, arene–arene interactions between the catalyst and substrate have a great influence on the catalytic activity.[7a] As *N*-alkyl acetophenone ketimines, ketimine **10l** was different from **10a** and gave nearly racemic products (Table 2, entries 12). For aliphatic imines, good yields and low enantioselectivities were obtained (Table 2, entries 14 and 15). It is noteworthy that **10m** could also be reduced in good yield and with moderate enantioselectivity (Table 2, entries 13).

In order to determine whether organocatalyst **9b** could be recovered and reused, we carried out a recycling test of **9b** to catalyze the asymmetric reduction of imine **10a** with trichlorosilane (Fig. 1). When the reaction was completed, organocatalyst **9b** was recovered by separation from the product. By using column chromatography on silica gel with a petroleum ether/ethyl acetate mixture (99:1), the crude product eluted the pure amine and continued elution with pure ethyl acetate, then released the organocatalyst. The recovered organocatalyst was directly reused to catalyze the reduction. Generally, the catalyst recycling had a slight loss of activity. Therefore, the catalyst used in every new cycle was less than the previous one, which in turn led to a slight decrease in the yield and enantioselectivity. After five cycles, a marginal effect of the reactivity and selectivity was observed, indicating that organocatalyst **9b** could be reused. Thus it is possible that *N*-formyl-L-valine derived organocatalysts can be linked with carbohydrates by CuAAC.

Table 2
Asymmetric reduction of imine **10** with catalyst **9b**[a]



10 11

Entry	Imine	R^1	R^2	R^3	Yield[b] (%)	ee[c] (%)
1	**10a**	C_6H_5	C_6H_5	Me	95	88
2	**10b**	4-FC_6H_4	C_6H_5	Me	97	92
3	**10c**	4-ClC_6H_4	C_6H_5	Me	97	94
4	**10d**	4-$NO_2C_6H_4$	C_6H_5	Me	98	93
5	**10e**	4-$CH_3C_6H_4$	C_6H_5	Me	72	67
6	**10f**	C_6H_5	4-FC_6H_4	Me	96	84
7	**10g**	C_6H_5	4-ClC_6H_4	Me	96	83
8	**10h**	C_6H_5	3-ClC_6H_4	Me	85	76
9	**10i**	C_6H_5	3-BrC_6H_4	Me	92	86
10	**10j**	C_6H_5	4-$CH_3C_6H_4$	Me	84	53
11	**10k**	C_6H_5	2-$CH_3C_6H_4$	Me	69	34
12	**10l**	C_6H_5	$C_6H_4CH_2$	Me	56	5
13	**10m**	C_6H_5	C_6H_5	Et	89	79
14	**10n**	*c*-C_6H_{11}	C_6H_5	Me	85	28
15	**10o**	3-Me-*i*-Bu	C_6H_5	Me	95	21

[a] The reactions were carried out with 10 mol % catalyst **9b** and 1.5 equiv of $SiHCl_3$ on a 0.5 mmol scale in 2.0 mL of toluene for 24 h.
[b] Isolated yield based on the imine.
[c] Determined by chiral HPLC.

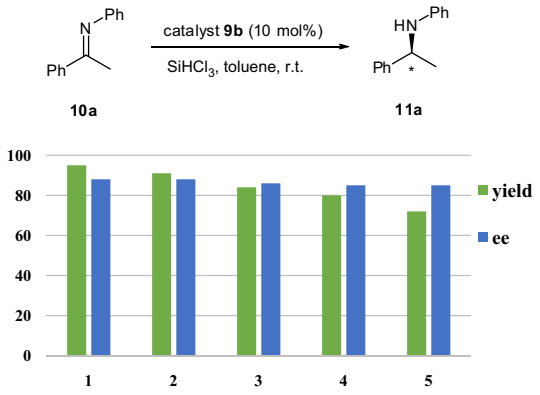


Figure 1. Recycling and reuse of catalyst **9b**[a,b,c]. [a]The reactions were carried out with 10 mol % catalyst **9a** and 1.5 equiv of $SiHCl_3$ on a 0.5 mmol scale in 2.0 mL of toluene for 24 h. [b]Isolated yield based on the imine. [c]Determined by chiral HPLC.

3. Conclusion

In conclusion, we have described a novel carbohydrate-based valine-derived formamide organocatalyst and its application in the asymmetric reduction of imines with trichlorosilane. The carbohydrate-based valine-derived formamide organocatalyst can promote the asymmetric reduction of imines with trichlorosilane in high yield (up to 98%) and with excellent enantioselectivity (up to 94%). The organocatalyst can be reused by a relatively undemanding recovery process. Thus, CuAAC click chemistry is a potential method to link *N*-formyl-L-valine derived organocatalysts with carbohydrates such as chitosan, polysaccharides, and so on. Further investigations into the application of valine-derived formamide organocatalyst immobilization in asymmetric reduction of imines with trichlorosilane are currently underway.

4. Experimental

4.1. General

Nuclear magnetic resonance (NMR) spectra were measured at 400 MHz (^1H) or at 100 MHz (^{13}C) on a Bruker Avance DRX-400 spectrometer. Enantiomeric excesses (% ee) were determined by HPLC (Agilent 1100) analysis using Chiral OD column. All reactions were monitored by analytical thin-layer chromatography (TLC) from Merck with detection by spraying with 5% (w/v) phosphomolybdic acid in ethanol and subsequent heating or UV. All reagents and solvents were of general reagent grade unless otherwise stated. All reactions were carried out in predried glassware (150 °C, 5 h) cooled under vacuum.

4.2. General procedure for the synthesis of compound 5

To a solution of *N*-BOC-valine **1** (217 mg, 1 mmol) and iodomethane (1.42 g, 10 mmol) in anhydrous tetrahydrofuran (THF, 20 mL) was added neat sodium hydride (240 mg, 10 mmol). The reaction mixture was stirred at room temperature for 24 h. The

mixture was then quenched with water (30 mL). The reaction mixture was extracted with ethyl acetate (EtOAc, 2 × 15 mL) and the aqueous solution was acidified to pH 3, after which it was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated to afford the corresponding *N*-methylated product **2** (thick colorless oil, 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 4.49–3.93 (m, 1H), 2.87 (s, 3H), 2.23 (dd, *J* = 16.3, 9.9 Hz, 1H), 1.47 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H).

To a stirred solution of amine **3** (175 mg, 1 mmol) in CH_2Cl_2 (100 mL) were added **2** (231 mg, 1 mmol), dicyclohexylcarbodiimide (DCC, 226 mg, 1.1 mmol), and 4-dimethylaminopyridine (DMAP, 12 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 24 h. The organic phase was filtered and evaporated under reduced pressure to give a crude product, which was purified by column chromatography through silica gel, eluting with a 5:1 EtOAc/petroleum ether (PE) solvent mixture, to give pure product **4** (yellow oil, 44% yield). Compound **4a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.66 (d, *J* = 2.2 Hz, 2H), 4.12 (d, *J* = 7.1 Hz, 1H), 2.84 (s, 3H), 2.51 (t, *J* = 2.4 Hz, 1H), 2.43–2.27 (m, 1H), 1.48 (s, 9H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.60, 157.42, 154.07, 132.14, 121.27, 115.36, 80.65, 78.55, 75.53, 65.97, 56.14, 30.53, 28.38, 26.00, 19.85, 18.60. Compound **4b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br, 1H), 7.18 (s, 2H), 4.46 (d, *J* = 2.2 Hz, 2H), 4.12 (d, *J* = 7.1 Hz, 1H), 2.83 (s, 3H), 2.50 (t, *J* = 2.4 Hz, 1H), 2.44–2.33 (m, 1H), 2.29 (s, 6H), 1.47 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.69, 157.41, 151.63, 134.12, 131.78, 120.11, 80.64, 79.26, 75.03, 65.99, 59.90, 30.44, 28.38, 25.98, 19.85, 18.58, 16.63.

Compound **4** (388 mg, 1 mmol) was dissolved in trifluoroacetic acid (2.0 mL) at room temperature. After 1 h the reaction mixture was evaporated in vacuo, the residue was dissolved in formic acid (0.75 mL), and the resulting solution was cooled to 0 °C. Acetic anhydride (2 mL) was added dropwise and the mixture was stirred at room temperature overnight. The organic phase was evaporated under reduced pressure. Purification using column chromatography on silica gel, eluting with a 2:1 PE/EtOAc mixture afforded product **5**. Compound **5a** (yellow oil, 76% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.14 (s, 1H), 7.48 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 4.66 (d, *J* = 2.4 Hz, 2H), 4.43 (d, *J* = 11.2 Hz, 1H), 3.02 (s, 3H), 2.51 (t, *J* = 2.4 Hz, 1H), 2.48–2.41 (m, 1H), 2.09 (d, *J* = 6.3 Hz, 2H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.03, 163.99, 154.29, 131.78, 121.50, 115.34, 78.51, 75.57, 69.07, 56.13, 31.65, 25.43, 19.52, 18.57. Compound **5b** (yellow oil, 75% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.14 (s, 1H), 7.21 (s, 2H), 4.47–4.41 (m, 3H), 3.02 (s, 3H), 2.50 (t, *J* = 2.2 Hz, 1H), 2.47–2.38 (m, 1H), 2.28 (s, 6H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.18, 163.97, 151.84, 133.77, 131.79, 120.38, 79.23, 75.08, 62.97, 59.89, 31.61, 25.44, 19.50, 18.59, 16.63.

4.3. General procedure for the synthesis of compound 9

Product **8** was prepared by a diazo transfer reaction of D-glucosamine hydrochloride **6** as reported in the literature.[18c,20] A solution of **8** (0.25 mmol) and CuI (5.0 mg, 0.0255 mmol, 0.1 equiv) in degassed DMF (5 mL) was stirred under nitrogen. The appropriate alkyne **5** (0.30 mmol, 1.2 equiv) was then added, following by the addition of *N*,*N*-diisopropylethylamine (DIPEA, 0.25 mmol, 32.0 mg, 1.0 equiv). The solution was stirred at 100 °C under nitrogen, and the reaction was reacted for 12 h. The mixture was cooled to room temperature and then diluted with EtOAc (80 mL). The organic layer was washed with hydrochloric acid (5%, 10 mL × 2), $NaHCO_3$ (5%, 10 mL × 2), and brine (20 mL × 1), and then dried over anhydrous Na_2SO_4. The organic phase was filtered and evaporated under reduced pressure to give a crude product, which was purified by column chromatography on silica gel, eluting with 2:1 PE/EtOAc solvent mixture, to give pure product **9**. Compound **9a** (pale yellow oil, yield 91%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.09 (s, 1H), 7.56 (s, 1H), 7.43–7.35 (m, 2H), 6.89–6.75 (m, 2H), 6.29 (d, *J* = 3.5 Hz, 0.3H), 6.13 (t, *J* = 7.8 Hz, 0.8H), 5.87 (dd, *J* = 11.3, 9.3 Hz, 0.4H), 5.79–5.64 (m, 0.8H), 5.26–5.12 (m, 2H), 5.12–5.06 (m, 2H), 4.63–4.54 (m, 1H), 4.35–4.28 (m, 2H), 4.03–3.97 (m, 1H), 2.94 (s, 3H), 2.45–2.27 (m, 1H), 2.07–1.94 (m, 12H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.52, 169.13, 168.60, 168.07, 167.05, 166.00, 162.97, 153.73, 143.46, 130.57, 121.99, 120.57, 114.15, 90.58, 71.93, 71.05, 68.05, 67.04, 61.71, 61.24, 60.35, 30.62, 24.36, 19.87, 19.67, 19.53, 19.45, 19.14, 18.50, 17.53. Compound **9b** (pale yellow oil, yield 92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.02 (s, 1H), 7.61 (s, 1H), 7.11 (d, *J* = 9.4 Hz, 2H), 6.33 (d, *J* = 3.5 Hz, 0.3H), 6.12 (d, *J* = 8.7 Hz, 0.7H), 5.92 (dd, *J* = 11.2, 9.4 Hz, 0.4H), 5.80–5.67 (m, 0.7H), 5.28–5.03 (m, 2H), 4.92–4.77 (m, 2H), 4.63 (dd, *J* = 10.5, 8.9 Hz, 1H), 4.37–4.26 (m, 2H), 4.06–3.94 (m, 1H), 2.93 (s, 3H), 2.46–2.35 (m, 1H), 2.15 (s, 6H), 2.09–1.89 (m, 12H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.52, 168.89, 168.62, 168.10, 167.06, 166.10, 163.00, 151.00, 143.80, 132.63, 130.49, 121.92, 119.42, 90.64, 89.04, 71.92, 71.11, 68.05, 67.77, 67.09, 62.11, 61.25, 60.36, 30.60, 24.28, 19.87, 19.67, 19.54, 19.52, 19.24, 18.51, 17.54, 15.42.

4.4. General experimental procedure for the asymmetric reduction of imines with trichlorosilane catalyzed by an organocat alyst

To a stirred solution of imine **10** (0.5 mmol) and organocatalyst (0.05 mmol) in toluene (2 mL) was added trichlorosilane (0.15 ml, 1.5 mmol) at room temperature and the reaction mixture was stirred at room temperature for 24 h. Next, saturated $NaHCO_3$ (2 ml) was added and extracted with ethyl acetate (3 * 10 ml). The combined organic phases were washed with brine, and dried over anhydrous $MgSO_4$. Afterward the organic phase was evaporated under reduced pressure to give the crude product, which was purified by column chromatography through silica gel, eluting with 1:99 EtOAc/PE solvent mixture, to give pure product **11**. The ee value of the reduction product was determined by HPLC on a chiral column (Daicel, Chiralpak, OD).

4.4.1. (*S*)-*N*-Phenyl-1-phenylethylamine 11a[2,17]

Yellow oil, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.18 (m, 4H), 7.14 (t, *J* = 7.1 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 2H), 6.56 (t, *J* = 7.2 Hz, 1H), 6.43 (d, *J* = 7.6 Hz, 2H), 4.41 (q, *J* = 6.6 Hz, 1H), 3.92 (br, 1H), 1.43 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.26, 144.20, 128.07, 127.60, 125.83, 124.82, 116.21, 112.29, 52.43, 23.98. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 8.81 min, t_{minor} = 10.21 min, ee: 88%.

4.4.2. (*S*)-*N*-Phenyl-*N*-[1-(4-fluorophenyl)ethyl]amine 11b[21]

Yellow oil, 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 2H), 7.08 (t, *J* = 7.9 Hz, 2H), 7.01–6.90 (m, 2H), 6.64 (t, *J* = 7.3 Hz, 1H), 6.47 (d, *J* = 7.9 Hz, 2H), 4.43 (d, *J* = 6.7 Hz, 1H), 4.01 (br, 1H), 1.46 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.82 (d, *J* = 244.3 Hz), 147.13, 140.97, 140.94, 129.22, 127.41 (d, *J* = 8.0 Hz), 117.54, 115.50 (d, *J* = 21.3 Hz), 113.44, 52.98, 25.22. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 7.304 min, t_{minor} = 8.064 min, ee: 92%.

4.4.3. (*S*)-*N*-Phenyl-*N*-[1-(4-chlorophenyl)ethyl]amine 11c[21]

Yellow oil, 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 4H), 7.12–7.00 (m, 2H), 6.64 (t, *J* = 7.3 Hz, 1H), 6.52–6.36 (m, 2H), 4.42 (q, *J* = 6.7 Hz, 1H), 4.01 (br, 1H), 1.45 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.03, 143.90, 132.45, 129.23, 128.87,

127.35, 117.61, 113.43, 53.06, 25.14. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 7.795 min, t_{minor} = 8.939 min, ee: 94%.

4.4.4. (*S*)-*N*-Phenyl-*N*-[1-(4-nitrophenyl)ethyl]amine 11d[10]

Yellow oil, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–7.95 (m, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.01 (dd, J = 8.5, 7.4 Hz, 2H), 6.61 (d, J = 7.3 Hz, 1H), 6.47–6.20 (m, 2H), 4.48 (q, J = 6.8 Hz, 1H), 4.02 (br, 1H), 1.46 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.21, 147.08, 146.55, 129.26, 126.73, 124.09, 117.99, 113.32, 53.33, 24.94. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 85/15, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 15.38 min, t_{minor} = 17.349 min, ee: 93%.

4.4.5. (*S*)-*N*-phenyl-*N*-[1-(4-methylphenyl)ethyl]amine 11e[10]

Yellow oil, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.1 Hz, 2H), 7.12–7.00 (m, 4H), 6.61 (tt, J = 7.4, 1.0 Hz, 1H), 6.51–6.44 (m, 2H), 4.42 (q, J = 6.7 Hz, 1H), 3.95 (br, 1H), 2.28 (s, 3H), 1.45 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.26, 141.14, 135.27, 128.13 (d, J = 23.1 Hz), 124.69, 116.09, 112.24, 52.05, 23.92, 19.99. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 6.806 min, t_{minor} = 7.236 min, ee: 67%.

4.4.6. (*S*)-4-Fluoro-*N*-(1-phenylethyl)aniline 11f[22]

Yellow oil, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.19 (m, 4H), 7.17–7.10 (m, 1H), 6.76–6.65 (m, 2H), 6.39–6.27 (m, 2H), 4.36–4.27 (m, 1H), 3.83 (br, 1H), 1.41 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.63 (d, J = 234.7 Hz), 144.01, 142.59, 127.64, 125.92, 124.78, 114.46 (d, J = 22.2 Hz), 113.06 (d, J = 7.3 Hz), 113.02, 53.03, 24.03. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 8.956 - min, t_{major} = 9.419 min, ee: 84%.

4.4.7. (*S*)-4-Chloro-*N*-(1-phenylethyl)aniline 11g[9a]

Yellow oil, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.19 (m, 4H), 7.19–7.11 (m, 1H), 6.99–6.88 (m, 2H), 6.39–6.29 (m, 2H), 4.35 (q, J = 6.7 Hz, 1H), 4.01 (br, 1H), 1.42 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.57, 143.53, 127.79 (d, J = 19.7 Hz). 126.03, 124.77, 120.96, 113.50, 52.70, 23.86. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 7.440 min, t_{major} = 8.252 min, ee: 83%.

4.4.8. (*S*)-3-Chloro-*N*-(1-phenylethyl)aniline 11h[17]

Yellow oil, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.19 (m, 4H), 7.18–7.10 (m, 1H), 6.88 (t, J = 8.0 Hz, 1H), 6.51 (ddd, J = 7.9, 1.9, 0.8 Hz, 1H), 6.40 (t, J = 2.1 Hz, 1H), 6.27 (ddd, J = 8.2, 2.3, 0.8 Hz, 1H), 4.36 (q, J = 6.7 Hz, 1H), 4.04 (br, 1H), 1.41 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.41, 144.57, 134.83, 130.13, 128.80, 127.14, 125.81, 117.17, 113.10, 111.52, 53.38, 24.89. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 7.645 min, t_{minor} = 9.277 min, ee: 76%.

4.4.9. (*S*)-3-Bromo-*N*-(1-phenylethyl)aniline 11i[17]

Yellow oil, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.19 (m, 4H), 7.19–7.10 (m, 1H), 6.83 (t, J = 8.0 Hz, 1H), 6.65 (dddd, J = 8.3, 6.4, 2.5, 1.3 Hz, 1H), 6.58 (t, J = 2.1 Hz, 1H), 6.34–6.27 (m, 1H), 4.43–4.28 (m, 1H), 4.04 (br, 1H), 1.42 (t, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.43, 143.40, 129.34, 127.71, 126.06, 124.72, 122.01, 119.01, 114.97, 110.79, 52.28, 23.76. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 8.303 min, t_{minor} = 10.118 min, ee: 86%.

4.4.10. (*S*)-4-Methyl-*N*-(1-phenylethyl)aniline 11j[17]

Yellow oil, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.16 (m, 4H), 7.15–7.08 (m, 1H), 6.80 (d, J = 8.1 Hz, 2H), 6.37–6.28 (m, 2H), 4.35 (q, J = 6.7 Hz, 1H), 3.77 (br, 1H), 2.09 (s, 3H), 1.39 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.37, 143.97, 128.54, 127.55, 125.73, 125.27, 124.80, 112.38, 52.61, 23.98, 19.30. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 9.004 min, t_{major} = 9.678 min, ee: 53%.

4.4.11. (*S*)-2-Methyl-*N*-(1-phenylethyl)aniline 11k[22]

Yellow oil, 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 8.2, 1.2 Hz, 2H), 7.24–7.18 (m, 2H), 7.12 (ddd, J = 12.1, 6.4, 3.2 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.90–6.81 (m, 1H), 6.51 (td, J = 7.4, 0.9 Hz, 1H), 6.28 (d, J = 7.9 Hz, 1H), 4.44 (q, J = 6.7 Hz, 1H), 3.75 (br, 1H), 2.13 (s, 3H), 1.46 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.17 (d, J = 12.5 Hz), 128.92, 127.59, 125.87 (d, J = 15.1 Hz), 124.73, 120.49, 115.79, 109.99, 52.25, 24.20, 16.57. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 5.837 min, t_{minor} = 8.211 min, ee: 34%.

4.4.12. (*S*)-*N*-Benzyl-1-phenylethanamine 11l[7b]

Yellow oil, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.21 (m, 10H), 4.57 (d, J = 9.0 Hz, 1H), 3.81–3.62 (m, 2H), 2.00 (d, J = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.61, 140.53, 128.57, 128.40, 127.31, 127.09, 127.04, 60.04, 51.43, 16.43. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 6.142 min, t_{major} = 7.357 min, ee: 5%.

4.4.13. (*S*)-*N*-(1-Phenylpropyl)aniline 11m[8a]

Yellow oil, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.21 (m, 10H), 4.57 (d, J = 9.0 Hz, 1H), 3.81–3.62 (m, 2H), 2.00 (d, J = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.48, 142.88, 128.03, 127.44, 125.82, 125.44, 116.08, 112.22, 58.67, 30.59, 9.77. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 8.572 min, t_{minor} = 10.207 min, ee: 79%.

4.4.14. (*S*)-*N*-(1-Cyclohexylethyl)aniline 11n[11b]

Yellow oil, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (t, J = 7.7 Hz, 2H), 6.55 (t, J = 7.3 Hz, 1H), 6.47 (d, J = 8.3 Hz, 2H), 3.38 (s, 1H), 3.30–3.09 (m, 1H), 1.67 (ddd, J = 45.0, 27.7, 14.1 Hz, 5H), 1.44–1.30 (m, 1H), 1.28–1.06 (m, 3H), 1.02 (d, J = 6.5 Hz, 3H), 1.00–0.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.03, 129.31, 116.56, 113.01, 53.03, 43.05, 29.84, 28.48, 26.71, 26.56, 26.42, 17.48. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 5.059 min, t_{major} = 5.232 min, ee: 28%.

4.4.15. (*S*)-*N*-(3-Methylbutan-2-yl)aniline 11o[11b]

Yellow oil, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, J = 11.7, 4.1 Hz, 1H), 6.56 (td, J = 7.3, 0.8 Hz, 1H), 6.52–6.46 (m, 1H), 3.38 (s, 1H), 3.26 (dt, J = 11.8, 6.0 Hz, 1H), 1.75 (tt, J = 13.4, 6.5 Hz, 1H), 1.02 (d, J = 6.4 Hz, 1H), 0.89 (d, J = 6.9 Hz, 1H), 0.83 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.89, 129.29, 116.66, 113.10, 53.47, 32.28, 19.21, 17.54, 16.61. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 4.796 min, t_{major} = 5.097 min, ee: 21%.

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