

PAPER

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Chiral phosphine-phosphoramidite ligands for highly enantioselective hydrogenation of *N*-arylimines†

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The asymmetric hydrogenation of *N*-arylimines with the chiral phosphine-phosphoramidite ligand, (*S_cS_a*)-PEAPhos 2b, has been developed. The results revealed that the presence of the substituents on the 3,3'-positions of the binaphthyl backbone significantly improved the enantioselectivity. The utility of this methodology was demonstrated in the synthesis of the chiral fungicide (*R*)-metalaxyl.

Introduction

Chiral amines are important synthetic intermediates in the synthesis of many biologically active natural and unnatural products. As a result, numerous methods are available for their preparation. Among them, catalytic asymmetric hydrogenation of imines has proven to be one of the most direct and convenient routes to chiral amines and their derivatives, due to its inherent efficiency and atom economy.¹ Although great efforts have been made during the past two decades, the development of highly efficient catalytic asymmetric hydrogenation of imines remains a challenging task, in contrast to the relative maturity of catalytic asymmetric hydrogenation of olefins and ketones, probably due to the interconversion between *E/Z* isomers of imines and the poisoning effect of the resulting amines on the catalyst. In 1975, Scorrano and co-workers² reported the first catalytic asymmetric hydrogenation of *N*-benzylimine with an Rh-diphosphine catalyst. Since then, many highly enantioselective chiral catalysts have been developed and a variety of imine frameworks including cyclic and acyclic imines have been efficiently hydrogenated in high enantioselectivities. Except for the well-known iridium-Xyliphos catalyst³ applied to the industrial production of chiral herbicide (*S*)-Metolachlor, Buchwald's titanocene catalyst,⁴ Pfaltz's iridium-PHOX catalyst,⁵ Zhang's iridium-f-Binaphane catalyst,⁶ Zhou's iridium-SIPHOX catalyst⁷ also exhibited excellent results for asymmetric hydrogenation of various imines. Despite these impressive achievements,⁸ asymmetric hydrogenation of imines still has challenges of low reactivity, narrow substrate scope and

harsh reaction conditions. Therefore, development of a new catalyst system with high reactivity and enantioselectivity as well as broad substrate scope for asymmetric hydrogenation of imines is still highly desirable.

Recently, we and other groups developed a series of unsymmetrical hybrid chiral phosphine-phosphoramidite ligands. These ligands have the advantages of easy accessibility, modularity and stability toward air and moisture, which can be exposed to air for several months without any changes in their ¹H or ³¹P NMR spectra and any loss in the catalytic activity and enantioselectivity. Therefore, these ligands have been found to display wide utility in asymmetric catalysis.⁹⁻¹⁵ However, there are few reports on the asymmetric hydrogenation of imines with chiral phosphine-phosphoramidite ligands. The only one example was reported by us recently,¹⁶ in which a new H₈-BINOL-derived phosphine-phosphoramidite ligand, (*R_cR_a*)-1, was found to be highly efficient in the enantioselective hydrogenation of sterically hindered *N*-arylimines, a class of challenging substrates. Further research disclosed that the steric effect of substituents on the 3,3'-positions of binaphthyl backbone of the ligand showed a significant influence on the enantioselectivity of the asymmetric hydrogenation of *N*-arylimines. As a result, we report herein the asymmetric hydrogenation of *N*-arylimines with a 3,3'-disubstituted binaphthyl ligand, (*S_cS_a*)-PEAPhos 2, in which high turnover numbers (up to 50 000) and excellent enantioselectivity (up to 98% ee) were obtained (Fig. 1).

Results and discussion

The chiral phosphine-phosphoramidite ligand (*S_cS_a*)-PEAPhos 2a-c were synthesized from commercially available (*S*)-1-phenylethylamine as we have reported previously.^{10e,u} With these ligands in hand, we then examined their efficiency in the iridium-catalyzed asymmetric hydrogenation of *N*-arylimines. *N*-(1-Phenylethylidene)benzenamine 3a was selected as a model

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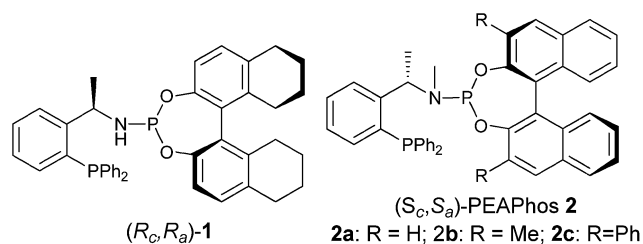


Fig. 1 Chiral phosphine-phosphoramidite ligands, (R_c, R_a) -1 and (S_c, S_a) -PEAPhos 2.

substrate for the screening process and the result are summarized in Table 1. The initial hydrogenation was carried out in the presence of 1 mol% of catalyst prepared *in situ* from $[\text{Ir}(\text{COD})\text{Cl}]_2$ and 2.2 equiv. of chiral ligand with KI as an additive. To our delight, (S_c, S_a) -PEAPhos **2a** displayed a promising performance in this reaction, affording *N*-(1-phenylethyl)benzenamine **4a** in full conversion with 80% ee (entry 1). Since the steric hindrance of a chiral ligand normally affects the catalytic activity and enantioselectivity, we then decided to investigate the ligands **2b–c** with more sterically hindered substituents on the 3,3'-positions of binaphthyl backbone. As expected, ligand **2b** with two methyl groups on 3,3'-positions provided an ee value of 93%, remarkably superior to that obtained with the parent ligand **2a** (entry 2). However, replacing methyl groups with more sterically hindered phenyl groups on the 3,3'-positions, the enantioselectivity decreased significantly (entry 3). The solvent effect was next investigated with ligand **2b**. It was found that all of CH_2Cl_2 , toluene and THF were suitable solvents for this reaction, with CH_2Cl_2 being optimal in terms of conversion and enantioselectivity (entries 4–7).

Under the optimal reaction conditions, a range of *N*-arylimines were then investigated. As can be seen from Table 2, a wide spectrum of *N*-arylimines with electron-donating and -withdrawing substituents on the phenyl ring were hydrogenated with full conversions and excellent enantioselectivities

Table 1 Asymmetric hydrogenation of imine **3a**^a

Entry	Ligand	Solvent	Conv. ^b (%)	ee ^c (%)
1	2a	CH_2Cl_2	>99	80
2	2b	CH_2Cl_2	>99	93
3	2c	CH_2Cl_2	>99	29
4	2b	Toluene	>99	90
5	2b	THF	>99	90
6	2b	AcOEt	>99	86
7	2b	MeOH	>99	62

^a Hydrogenation was carried out with 5 mol% of KI and 1 mol% of Ir-catalyst at rt for 24 h. ^b Determined by GC. ^c Determined by HPLC using a chiral stationary phase.

Table 2 Asymmetric hydrogenation of *N*-arylimines **3** to amines **4**^a

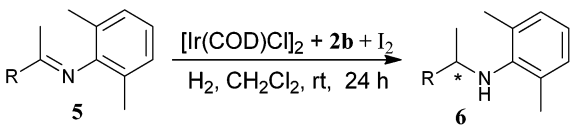
Entry	3 (R, Ar)	Yield ^b (%)	ee ^c (%)
1	3a (R = H, Ar = C_6H_5)	99	93
2	3b (R = H, Ar = 4- $\text{CH}_3\text{OC}_6\text{H}_4$)	99	92
3	3c (R = H, Ar = 4- ClC_6H_4)	98	94
4	3d (R = H, Ar = 4- $\text{NO}_2\text{C}_6\text{H}_4$)	98	93
5	3e (R = H, Ar = 3- $\text{NO}_2\text{C}_6\text{H}_4$)	98	97
6	3f (R = H, Ar = 3,4- $\text{Cl}_2\text{C}_6\text{H}_3$)	95	93
7	3g (R = 4-F, Ar = C_6H_5)	95	95
8 ^d	3h (R = H, Ar = 2- $\text{CH}_3\text{C}_6\text{H}_4$)	95	62
9 ^e	3i (R = 2- CH_3 , Ar = C_6H_5)	95	72
10 ^f	3j (R = 2- CF_3 , Ar = C_6H_5)	92	78
11	3k (R = H, Ar = 6- CH_3O -2-naphthyl)	98	83
12	3l (R = H, Ar = thienyl)	99	85

^a Hydrogenation was carried out with 5.0 mol% of KI and 1.0 mol% of Ir-catalyst in 2 mL CH_2Cl_2 , 60 bar of H_2 , at rt for 24 h, unless otherwise stated. ^b Yields of isolated product. ^c Enantiomeric excesses were determined by chiral HPLC. ^d Using **2c** as ligand. ^e Using **2a** as ligand. ^f Using I_2 as additive instead of KI.

(entries 1–7). The highest enantioselectivity (97% ee) was achieved in the hydrogenation of *N*-(1-(3-nitrophenyl)ethylidene)benzenamine **3e** (entry 5). Notably, the hydrogenation appeared to be sensitive to the steric property of the substituents on the aromatic ring. For substrates **3h–j** having a *o*-substituent on the phenyl ring, a dramatic decrease of enantioselectivities (62–78% ee) was observed (entries 8–11). Hydrogenation of 2-naphthyl substrate **3k** also gave good ee-value (entry 12). Meanwhile, a heteroaromatic derivative **3l** was also suitable for this hydrogenation (entry 13). These results suggested that a variety of *N*-arylimines, which bear substituted groups such as methoxy, nitro, fluoro, chloro in the phenyl ring, as well as naphthyl and heteroaromatic derivatives, all could be hydrogenated to afford the corresponding chiral amines in good to excellent enantioselectivities.

Encouraged by these promising results, we then investigated the hydrogenation of more challenging, sterically hindered *N*-arylimines **5**. The results are summarized in Table 3. The additive was investigated because of its significant influence on the asymmetric catalysis.¹⁷ It revealed that the use of I additives could significantly increase the enantioselectivity, which was in accordance with the result reported before by us.¹⁶ I_2 and KI gave the similar results, while I_2 was slightly superior to KI with respect to enantioselectivity in the hydrogenation of sterically hindered *N*-arylimines (entries 1 and 2). Under the optimized condition, a variety of sterically hindered *N*-arylalkylarylimines and *N*-aryldialkylarylimines could be hydrogenated in good to excellent enantioselectivities. For *N*-arylalkylarylimines **5a–f**, the hydrogenation proceeded smoothly and afforded the corresponding sterically hindered chiral amines in excellent enantioselectivities (94–98% ee) (entries 1–7). The electronic

Table 3 Asymmetric hydrogenation of sterically hindered *N*-arylimines **5**^a

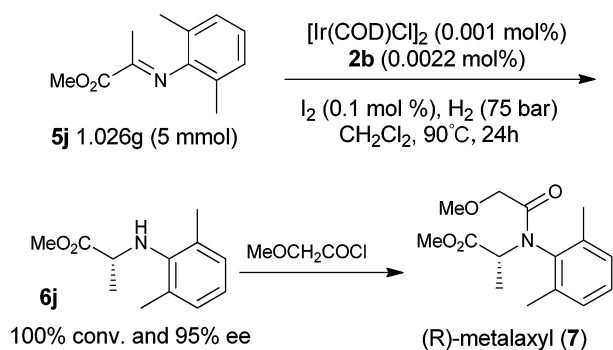


Entry	Imine (R)	Yield ^b (%)	ee ^c (%)
1	5a : R = C ₆ H ₅	98	96
2 ^d	5a : R = C ₆ H ₅	98	94
3	5b : R = 4-CH ₃ C ₆ H ₄	98	94
4	5c : R = 4-BrC ₆ H ₄	98	96
5	5d : R = 4-NO ₂ C ₆ H ₄	99	98
6	5e : R = 3-NO ₂ C ₆ H ₄	98	98
7	5f : R = 3-CH ₃ OC ₆ H ₄	98	95
8	5g : R = 6-CH ₃ O-2-naphthyl	92	92
9 ^e	5h : R = <i>i</i> -Pr	97	84
10	5i : R = MeOCH ₂	95	92

^a Hydrogenation was carried out with 5.0 mol% of I₂ and 1.0 mol% of Ir-catalyst in 2 mL CH₂Cl₂, 60 bar of H₂, at rt for 24 h, unless otherwise stated. ^b Yields of isolated product. ^c Enantiomeric excesses were determined by chiral HPLC or by chiral GC. ^d Using KI as additive. ^e Hydrogenation was performed at 60 °C under a H₂ pressure of 70 bar.

property of substituents on the phenyl ring showed no apparent influence on the enantioselectivity. For the hydrogenation of 2-naphthyl substrate **5g**, a slight decrease of enantioselectivity (92% ee) was obtained (entry 8). It is noteworthy that the hydrogenation of more challenging *N*-aryldialkylimines **5h** and **5i** were conducted smoothly with good enantioselectivities (84% and 92% ee, respectively) (entries 9 and 10). These results demonstrated the high efficiency of the present catalytic system in the enantioselective hydrogenation of a broad scope of sterically hindered *N*-arylimines.

To explore the synthetic utility of the current method, we attempted this methodology as the key step in the enantioselective synthesis of the chiral fungicide (*R*)-metalaxyl as shown in Scheme 1. With the present catalytic system, hydrogenation of imine **5j** afforded the corresponding chiral amine **6j** in 95% ee with full conversion, even when the catalyst loading was lowered to 0.002 mol% (*S*/*C* = 50 000/1). It should be noted that the asymmetric hydrogenation of **5j** can be carried out on a



Scheme 1 Synthesis of chiral fungicide (*R*)-metalaxyl on gram scale.

gram scale and operated in air without loss of the enantioselectivity and activity. The resulting product **6j** can easily be converted to herbicide (*R*)-metalaxyl **7**,¹⁸ demonstrating the potential utility of this method in the synthesis of chiral pesticides.

Conclusions

In conclusion, we have demonstrated the asymmetric hydrogenation of *N*-arylimines with chiral phosphine-phosphoramidite ligand, (*S*_c,*S*_a)-PEAPhos **2b**, in which high turnover numbers (up to 50 000) and excellent enantioselectivity (up to 98% ee) were achieved. The results revealed that the presence of the substituents on the 3,3'-positions of the binaphthyl backbone significantly improved the enantioselectivity. The utility of this methodology was demonstrated by the synthesis of chiral fungicide (*R*)-metalaxyl at a catalyst loading of 0.002 mol%. Further applications of chiral phosphine-phosphoramidite ligand in asymmetric catalysis are in progress.

Experimental section

General method

All reactions were carried out under a nitrogen atmosphere. Solvents were purified by standard procedure before use. Commercial reagents were used without further purification. ¹H NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts for protons are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and are referenced to residual protium in the NMR solvent (CHCl₃ = δ 7.26). Enantiomeric ratios were determined by chiral HPLC with *n*-hexane and *i*-PrOH as solvents.

General procedure for the synthesis of phosphine-phosphoramidite ligands **2a–2c**

Chiral phosphine-phosphoramidite ligands were synthesized according to literature.^{10e,u} To a stirred solution of (*S*_a)-chlorophosphite (1.0 mmol) in dried toluene (4.0 mL) at 0 °C was added a solution of (*S*_c)-DPPNHMe (1.0 mmol) and Et₃N (3.0 mmol) in dried toluene (4.0 mL) within 30 min. The resulting mixture was stirred overnight at room temperature. The precipitate was filtered, and the solid was washed with toluene. The filtrate was collected, and concentrated under reduced pressure to give the crude product which was further purified by column chromatography.

(*S*_c,*S*_a)-PEAPhos **2a**. ¹H NMR (400 MHz, CDCl₃) δ 1.59–1.65 (m, 3H), 1.99 (d, *J* = 3.1 Hz, 3H), 5.37–5.46 (m, 1H), 6.97–7.02 (m, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 7.18–7.16 (m, 4H), 7.27–7.45 (m, 14H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.57–7.60 (m, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 30.1, 56.7, 122.1, 124.5, 125.9, 127.0, 127.5, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 129.2, 130.1, 130.6, 131.4, 132.7, 133.7, 133.9, 134.1, 134.5, 136.1, 136.7, 137.2, 147.4, 149.7, 150.7; ³¹P NMR

(162 MHz, CDCl₃) δ -18.5, 148.4; HRMS calcd for C₄₁H₃₃NO₂P₂: 633.1987, found: 633.1992.

(S_c,S_a)-PEAphos 2b. ¹H NMR (400 MHz, CDCl₃) δ 1.56–1.64 (m, 3H), 2.06 (d, *J* = 2.2 Hz, 3H), 2.61 (s, 3H), 2.45 (s, 3H), 5.24–5.35 (m, 1H), 6.91–6.97 (m, 1H), 7.10–7.20 (m, 4H), 7.23–7.39 (m, 14H), 7.63–7.66 (m, 1H), 7.68 (s, 1H), 7.75–7.82 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 17.9, 21.8, 29.4, 56.5, 122.0, 124.3, 124.9, 126.9, 127.1, 127.2, 127.5, 128.5, 128.6, 128.7, 128.9, 129.0, 129.3, 129.6, 130.4, 130.9, 131.2, 131.6, 133.8, 134.0, 136.2, 136.7, 137.2, 146.6, 146.9, 148.9, 150.1; ³¹P NMR (162 MHz, CDCl₃) δ -17.4, 144.7; HRMS calcd for C₄₃H₃₇NO₂P₂: 661.2300, found: 661.2310.

(S_c,S_a)-PEAphos 2c. ¹H NMR (400 MHz, CDCl₃) δ 0.82–0.90 (m, 3H), 1.80 (s, 3H), 4.74–4.82 (m, 1H), 6.72–6.81 (m, 2H), 6.96–7.03 (m, 2H), 7.04–7.09 (m, 2H), 7.11–7.17 (m, 2H), 7.19–7.35 (m, 12H), 7.35–7.44 (m, 6H), 7.69–7.77 (m, 4H), 7.86–7.95 (m, 3H), 7.99 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 30.6, 57.1, 123.6, 124.9, 125.9, 126.8, 127.0, 127.1, 127.3, 127.5, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.7, 130.0, 130.1, 130.4, 130.7, 131.1, 132.5, 133.6, 133.8, 134.0, 134.8, 135.3, 136.7, 137.3, 138.5, 147.3, 147.5, 147.8, 148.1; ³¹P NMR (162 MHz, CDCl₃) δ -17.5, 148.2; HRMS calcd for C₅₃H₄₁NO₂P₂: 785.2613, found: 785.2619.

General procedure for asymmetric hydrogenation

In a nitrogen-filled glovebox, a stainless steel autoclave was charged with [Ir(COD)Cl]₂ (0.0025 mmol), (S_c,S_a)-**2b** (0.0055 mmol) and KI or I₂ (0.025 mmol) in 1.0 mL of a degassed CH₂Cl₂. After stirring for 10 min at room temperature, a solution of the imine substrates **3** or **5** (0.5 mmol) in 1.0 mL of CH₂Cl₂ was added to the reaction mixture, and then the hydrogenation was performed at room temperature under an H₂ pressure of 60 bar for 24 hours. The solvent was then evaporated and the residue was purified by flash column chromatography to give the corresponding hydrogenation product **4** or **6**, which was analysed by chiral GC or chiral HPLC to determine the enantiomeric excesses.

N-(1-Phenylethyl)benzenamine 4a. 99% yield. 93% ee was determined by chiral HPLC (chiralcel OJ-H, *n*-hexane/*i*-PrOH = 97/3, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 20.9, 25.5 min. ¹H NMR (400 MHz, CDCl₃): δ 1.49 (d, *J* = 8.0 Hz, 3H), 4.02 (br, 1H), 4.46 (q, *J* = 8.0 Hz, 1H), 6.48–6.50 (m, 2H), 6.61–6.65 (m, 1H), 7.05–7.09 (m, 2H), 7.20–7.36 (m, 5H).

N-(1-(4-Methoxyphenyl)ethyl)benzenamine 4b. 99% yield. 92% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 7.4, 8.1 min. ¹H NMR (400 MHz, CDCl₃): δ 1.54 (d, *J* = 8.0 Hz, 3H), 3.82 (s, 3H), 4.09 (br, 1H), 4.50 (q, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H).

N-(1-(4-Chlorophenyl)ethyl)benzenamine 4c. 98% yield. 94% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 8.4, 9.8 min. ¹H NMR (400 MHz, CDCl₃): δ 1.53 (d, *J* = 8.0 Hz, 3H), 4.10 (br, 1H), 4.49 (q, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 2H), 6.72 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 2H), 7.33 (s, 4H).

N-(1-(4-Nitrophenyl)ethyl)benzenamine 4d. 98% yield. 93% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 25.7, 27.9 min. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (d, *J* = 8.0 Hz, 3H), 4.30 (br, 1H), 4.57 (q, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 8.0 Hz, 2H).

N-(1-(3-Nitrophenyl)ethyl)benzenamine 4e. 98% yield. 97% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 85/15, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 18.4, 19.5 min. ¹H NMR (400 MHz, CDCl₃): δ 1.56 (d, *J* = 8.0 Hz, 3H), 4.26 (br, 1H), 4.58 (q, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 2H), 6.69 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.25 (s, 1H).

N-(1-(3,4-Dichlorophenyl)ethyl)benzenamine 4f. 95% yield. 93% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 12.2, 14.3 min. ¹H NMR (400 MHz, CDCl₃): δ 1.50 (s, 3H), 4.40–4.42 (m, 1H), 6.48 (d, *J* = 8.0 Hz, 2H), 6.69 (s, 1H), 7.11–7.25 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H).

4-Fluoro-N-(1-phenylethyl)benzenamine 4g. 95% yield. 95% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 99/1, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 12.3, 15.5 min. ¹H NMR (400 MHz, CDCl₃): δ 1.49 (d, *J* = 8.0 Hz, 3H), 3.97 (br, 1H), 4.40 (q, *J* = 8.0 Hz, 1H), 6.40–6.43 (m, 2H), 6.78 (t, *J* = 8.0 Hz, 2H), 7.19–7.24 (m, 1H), 7.28–7.35 (m, 4H).

N-(1-(*o*-Tolyl)ethyl)benzenamine 4h. 95% yield. 62% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 98/2, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 12.2, 13.5 min. ¹H NMR (400 MHz, CDCl₃): δ 1.49 (d, *J* = 6.0 Hz, 3H), 2.42 (s, 3H), 4.67 (q, *J* = 6.0 Hz, 1H), 6.47 (d, *J* = 7.2 Hz, 2H), 6.65 (d, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 2H), 7.15 (s, 3H), 7.43 (s, 1H).

2-Methyl-N-(1-phenylethyl)benzenamine 4i. 95% yield. 72% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 5.1, 7.7 min. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (d, *J* = 8.0 Hz, 3H), 2.22 (s, 3H), 3.85 (br, 1H), 4.53 (q, *J* = 20.0 Hz, 1H), 6.36 (d, *J* = 4.0 Hz, 1H), 6.59 (t, *J* = 12.0 Hz, 1H), 6.95 (t, *J* = 16.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 16.0 Hz, 1H), 7.29–7.36 (m, 4H).

N-(1-Phenylethyl)-2-(trifluoromethyl)aniline 4j. 92% yield. 78% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 99/1, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 4.5, 5.3 min. ¹H NMR (400 MHz, CDCl₃): δ 1.57 (d, *J* = 6.7 Hz, 3H), 4.57–4.59 (m, 1H), 4.73 (s, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 6.3 Hz, 1H), 7.11–7.41 (m, 4H), 7.44 (d, *J* = 7.8 Hz, 1H).

N-(1-(6-Methoxynaphthalen-2-yl)ethyl)benzenamine 4k. 98% yield. 83% ee was determined by chiral HPLC (chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, 0.5 mL min⁻¹, 254 nm, 40 °C): *t*_r = 18.8, 19.7 min. ¹H NMR (400 MHz, CDCl₃): δ 1.59 (d, *J* = 8.0 Hz, 3H), 3.91 (s, 3H), 4.60–4.62 (m, 1H), 6.57–6.65 (m, 3H), 7.06–7.14 (m, 4H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.68–7.74 (m, 3H).

N-(1-(Thiophen-2-yl)ethyl)benzenamine 4l. 99% yield. 85% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL min⁻¹, 254 nm, 40 °C): *t*_r = 7.8, 8.3 min. ¹H NMR (400 MHz, CDCl₃): δ 1.61–1.68 (m, 3H), 4.04 (br, 1H),

4.81–4.89 (m, 1H), 6.64–6.74 (m, 3H), 6.98 (d, $J = 16.0$ Hz, 2H), 7.18 (s, 3H).

***N*-(1-Phenylethyl)-2,6-dimethylbenzenamine 6a.** 98% yield. 96% ee was determined by chiral HPLC (chiralcel OJ-H, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL min⁻¹, 254 nm, 40 °C): $t_r = 4.9, 5.4$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.54 (d, $J = 8.0$ Hz, 3H), 2.19 (s, 6H), 3.22 (br, 1H), 4.34 (q, $J = 6.8$ Hz, 1H), 6.81 (t, $J = 8.0$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 2H), 7.25–7.27 (m, 1H), 7.31–7.32 (m, 4H).

***N*-[1-(4-Methylphenyl)ethyl]-2,6-dimethylbenzenamine 6b.** 98% yield. 94% ee was determined by chiral HPLC (chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL min⁻¹, 254 nm, 40 °C): $t_r = 14.5, 16.6$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.48 (d, $J = 6.8$ Hz, 3H), 2.18 (s, 6H), 2.32 (s, 3H), 3.19 (br, 1H), 4.30 (q, $J = 6.8$ Hz, 1H), 6.78 (t, $J = 7.6$ Hz, 1H), 6.94 (d, $J = 7.6$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H).

***N*-[1-(4-Bromophenyl)ethyl]-2,6-dimethylbenzenamine 6c.** 98% yield. 96% ee was determined by chiral HPLC (chiralpak AD-H, *n*-hexane/*i*-PrOH = 99.5/0.5, 0.3 mL min⁻¹, 254 nm, 40 °C): $t_r = 9.0, 10.5$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.51 (d, $J = 6.8$ Hz, 3H), 2.18 (s, 6H), 3.17 (br, 1H), 4.29 (q, $J = 6.8$ Hz, 1H), 6.81 (t, $J = 7.6$ Hz, 1H), 6.97 (d, $J = 7.6$ Hz, 2H), 7.18 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H).

***N*-[1-(4-Nitrophenyl)ethyl]-2,6-dimethylbenzenamine 6d.** 99% yield. 98% ee was determined by chiral HPLC (chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, 1.0 mL min⁻¹, 254 nm, 40 °C): $t_r = 5.6, 7.8$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.57 (d, $J = 6.8$ Hz, 3H), 2.16 (s, 6H), 3.13 (br, 1H), 4.40 (q, $J = 6.8$ Hz, 1H), 6.81 (t, $J = 7.2$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 8.15 (d, $J = 8.8$ Hz, 2H).

***N*-[1-(3-Nitrophenyl)ethyl]-2,6-dimethylbenzenamine 6e.** 98% yield. 98% ee was determined by chiral HPLC (chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, 1.0 mL min⁻¹, 254 nm, 40 °C): $t_r = 12.0, 12.4$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.58 (d, $J = 6.8$ Hz, 3H), 2.19 (s, 6H), 3.20 (br, 1H), 4.43 (q, $J = 6.8$ Hz, 1H), 6.82 (t, $J = 7.6$ Hz, 1H), 6.97 (d, $J = 7.6$ Hz, 2H), 7.45 (t, $J = 7.6$ Hz, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 8.10 (d, $J = 7.6$ Hz, 1H), 8.24 (s, 1H).

***N*-[1-(3-Methoxyphenyl)ethyl]-2,6-dimethylbenzenamine 6f.** 98% yield. 95% ee was determined by chiral HPLC (chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL min⁻¹, 254 nm, 40 °C): $t_r = 19.2, 23.4$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.50 (d, $J = 6.4$ Hz, 3H), 2.18 (s, 6H), 3.21 (br, 1H), 3.75 (s, 3H), 4.29 (q, $J = 6.4$ Hz, 1H), 6.76–6.80 (m, 2H), 6.80–6.83 (m, 1H), 6.89 (d, $J = 7.2$ Hz, 1H), 6.95 (d, $J = 7.2$ Hz, 2H), 7.20–7.25 (m, 1H).

***N*-[1-(6-Methoxynaphthalen-2-yl)ethyl]-2,6-dimethylbenzenamine 6g.** 92% yield. 92% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 99/1, 1.0 mL min⁻¹, 254 nm, 40 °C): $t_r = 16.3, 17.3$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.62 (d, $J = 6.8$ Hz, 3H), 2.24 (s, 6H), 3.33 (br, 1H), 3.93 (s, 1H), 4.50 (q, $J = 6.8$ Hz, 1H), 6.83 (t, $J = 7.6$ Hz, 1H), 6.99 (d, $J = 7.6$ Hz, 2H), 7.15–7.18 (m, 2H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.71–7.73 (m, 3H).

***N*-(3-Methylbutan-2-yl)-2,6-dimethylbenzenamine 6h.** 97% yield. 84% ee was determined by chiral GC (chiral β -DEX 120 column, column temp.: 100 °C, carrier gas: N₂): $t_r = 27.9, 29.0$ min. ¹H NMR (400 MHz, CDCl₃): δ 0.97–1.05 (m, 9H), 1.76–1.84

(m, 1H), 2.29 (s, 6H), 2.97 (br, 1H), 3.18–3.24 (m, 1H), 6.79 (t, $J = 7.6$ Hz, 1H), 6.99 (d, $J = 7.6$ Hz, 2H).

***N*-(1-Methoxypropan-2-yl)-2,6-dimethylbenzenamine 6i.** 95% yield. 92% ee was determined by chiral GC (chiral β -DEX 120 column, column temp.: 85 °C, carrier gas: N₂): $t_r = 72.0, 73.7$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.20 (d, $J = 6.0$ Hz, 3H), 2.30 (s, 6H), 3.35–3.80 (m, 7H), 6.82 (t, $J = 7.2$ Hz, 1H), 6.99 (d, $J = 7.2$ Hz, 2H).

Methyl-2-(2,6-dimethylphenylamino)propanoate 6j. 96% yield. 95% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 99/1, 1.0 mL min⁻¹, 254 nm, 40 °C): $t_r = 7.6, 8.3$ min. ¹H NMR (400 MHz, CDCl₃): δ 1.38 (d, $J = 7.2$ Hz, 3H), 2.31 (s, 6H), 3.68 (s, 3H), 4.00 (q, $J = 7.2$ Hz, 1H), 6.81 (t, $J = 7.6$ Hz, 1H), 6.97 (d, $J = 7.6$ Hz, 2H).

Synthesis of (*R*)-metalaxyl 7. To a stirred solution of **6j** (20 mmol) in toluene was added NaHCO₃ (24 mmol, 1.2 eq.) at 0 °C. Methoxyacetyl chloride (24 mmol, 1.2 eq.) was then slowly added and the mixture was stirred at room temperature for 1 h. The resulted mixture was washed with 5% Na₂CO₃ and water. The layer was separated and the organic phase was dried over Na₂SO₄. It was filtered and concentrated under reduced pressure to give the crude product which was further purified by column chromatography.

(*R*)-Methyl-2-(*N*-(2,6-dimethylphenyl)-2-methoxyacetamido)propanoate 7. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.89 (d, $J = 7.4$ Hz, 3H), 2.13 (s, 3H), 2.38 (s, 3H), 3.17 (s, 3H), 3.35–3.53 (m, 2H), 3.68 (s, 3H), 4.40 (q, $J = 7.4$ Hz, 1H), 7.17–7.28 (m, 3H).

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