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Metal and organo-catalysed asymmetric hydroaminomethylation of styrenes

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ABSTRACT

A new protocol that enables asymmetric hydroaminomethylation of styrenes to afford chiral amines has been developed. Catalysed by an Rh-phosphine species and a chiral phosphoric acid, styrenes are converted into β-chiral amines with good enantioselectivities under syngas in the presence of an amine and Hantzsch ester. The reaction involves two key steps, hydroformylation and reductive amination, with the former catalysed by the Rh species whilst the latter by the phosphoric acid.

1. Introduction

We recently reported that imino bonds can be reduced highly enantioselectively under metal-organo cooperative catalysis [1–5]. Since olefins such as styrenes could be selectively hydroformylated to the corresponding α-branched aldehydes [6], which readily condense with an amine to afford imines, it became possible to us that β-chiral amines might be accessible via a similar strategy (Scheme 1). The enantioselectivity would be achieved through a dynamic kinetic resolution (DKR) process preceding the reduction. In the presence of a chiral acid catalyst, imines are expected to undergo fast racemisation by tautomerisation, and one of the enantiomers of the iminium cation could be selectively reduced, leading to chiral amines [7].

Hydroformylation of an alkene, followed by reductive amination of the resulting aldehyde intermediate with an amine, is known as hydroaminomethylation [8]. It represents a one-pot, atom-efficient reaction for the synthesis of amines, one of the most ubiquitous functionalities in chemical synthesis. A suitable catalyst for hydroaminomethylation must fulfil a number of requirements (Scheme 2). It must be highly regioselective to either the linear or branched aldehyde, depending on the desired final product. The catalyst must be active for the enamine/imine hydrogenation, as a slow hydrogenation leads to aldol-type side reactions [9]. Finally, the catalyst must be selective for enamine/imine hydrogenation over hydrogenation of aldehydes. In addition, the enamine/imine isomerisation must be faster than the subsequent hydrogenation to ensure efficient DKR.

The first example of hydroaminomethylation was reported by Reppe et al. at BASF in the early 1950s [10]. Simple alkenes, like ethene or propene, were converted to secondary and tertiary amines in low yields, with ammonia under harsh conditions of up to 390 °C and 950 bar H_2 using $[Fe(CO)_5]$ in almost stoichiometric quantity. Significant progress has been made since, with notable contributions being made by the groups of Eilbracht and Beller [8,11–13]. There are, however, few studies concerning asymmetric hydroaminomethylation, with none

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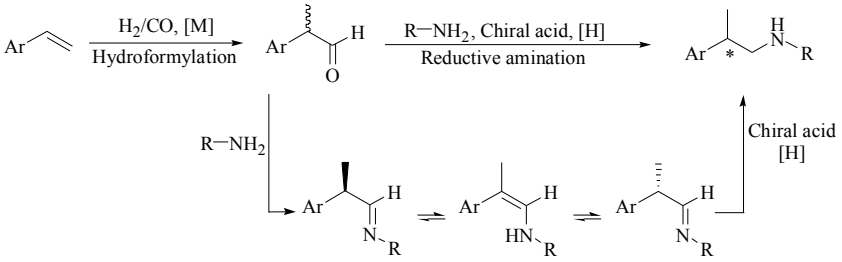
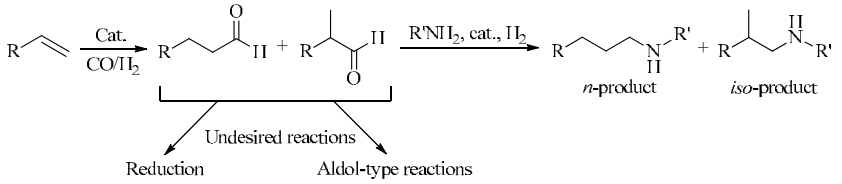


Scheme 1. Asymmetric hydroaminomethylation via tandem hydroformylation-asymmetric reductive amination.



Scheme 2. Chemo- and *i/n* regio-selectivity issues in the hydroaminomethylation sequence.

reporting significant enantioselectivities [14,15].

2. Experimental

2.1. General procedure for the synthesis of racemic mixtures of ***1a–p***

To a glass liner equipped with a stir bar was added styrene (5 mmol), [Rh(acac)(CO)$_2$] (25 μmol), (4-MeOC$_6$H$_4$)$_3$P (50 μmol), and toluene (2 mL). The glass liner was then placed into an autoclave, followed by degassing with syngas three times. The reaction was carried out at 11 bar syngas with stirring at 50 °C overnight. The stirring was then stopped, and the autoclave allowed to cool down to room temperature. The syngas was then carefully released in a fume hood and the solution was filtered through celite, transferred to a flask, and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (50/1) yielded the desired aldehyde product.

To an oven-dried Schlenk tube equipped with a stir bar was added the aldehyde prepared (0.5 mmol), amine (0.5 mmol) and an Iridicycle catalyst (5 μmol) [25]. The tube was degassed with nitrogen three times. MeOH (4 mL) was then added with syringe, followed by HCOOH/Et$_3$N (5:2, 1 mL). The resulting mixture was stirred at 80 °C for 3 h. The stirring was then stopped, and the reaction mixture allowed to cool down to room temperature. The reaction was then quenched with water and basified with saturated KOH$_{aq}$ solution, extracted with ethyl acetate and dried over MgSO$_4$. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (15/1) yielded the racemic mixtures of **1a**–**p**.

2.2. General procedure for asymmetric hydroaminomethylation

To a glass liner equipped with a stir bar was added 4 Å MS (100 mg), alkene (0.4 mmol), amine (0.25 mmol), [Rh(acac)(CO)$_2$] (1.25 μmol), (4-MeO-C$_6$H$_4$)$_3$P (2.5 μmol), Et-HEH (0.6 mol), TRIP (12.5 μmol), and toluene (2 mL). The glass liner was then placed into an autoclave, followed by degassing with syngas three times. The reaction was carried out at 11 bar syngas with stirring at 50 °C for 3 d. The stirring was then stopped, and the autoclave allowed to cool down to room temperature. The syngas was then carefully released in a fume hood and the solution was filtered through celite, transferred to a flask, and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (40/1 to 30/1) yielded the desired amine product.

2.3. Analytical data

4-Methoxy-*N*-(2-*p*-tolylpropyl)aniline, **1a** [17]. The product (50 mg, 79% yield, 80% ee) was obtained as a colourless oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.30 (d, J = 7.0 Hz, 3H), 2.33 (s, 3H), 2.98–3.05 (m, 1H), 3.16 (dd, A of ABX, J_{AB} = 12.1 Hz, J_{AX} = 8.4 Hz, 1H), 3.28 (dd, B of ABX, J_{AB} = 12.1 Hz, J_{BX} = 6.2 Hz, 1H), 3.74 (s, 3H), 3.53–6.57 (m, 2H), 6.74–6.78 (m, 2H), 7.10–7.15 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.0, 21.1, 38.8, 52.1, 55.8, 114.4, 114.9, 127.2, 129.4, 136.1, 141.6, 142.4, 152.1; C$_{17}$H$_{22}$NO [M+H]$^+$: *m/z* Calcd.: 256.1701; Found: 256.1706; HPLC (Chiralcel OJ, hexane:isopropanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm): t_R = 16.5 min (minor), t_R = 18.7 min (major).

3-Methoxy-*N*-(2-*p*-tolylpropyl)aniline, **1b**. The product (53 mg, 83% yield, 84% ee) was obtained as a colourless oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.31 (d, J = 6.9 Hz, 3H), 2.33 (s, 3H), 2.97–3.06 (m, 1H), 3.19 (dd, A of ABX, J_{AB} = 12.2 Hz, J_{AX} = 8.3 Hz, 1H), 3.30 (dd, B of ABX, J_{AB} = 12.2 Hz, J_{BX} = 6.2 Hz, 1H), 3.75 (s, 3H), 6.13 (t, J = 2.1 Hz, 1H), 6.18 (dd, J = 8.1, 2.1 Hz, 1H), 8.25 (dd, J = 8.1, 2.1 Hz, 1H), 7.05 (t, J = 8.1 Hz, 1H), 7.10–7.15 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.5, 21.0, 38.8, 50.9, 55.1, 98.8, 102.4, 106.1, 127.1, 129.3, 129.9, 136.1, 141.4, 149.5, 160.8; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 30.1 min (minor), t_R = 37.2 min (major).

3-Methyl-*N*-(2-*p*-tolylpropyl)aniline, **1c**. The product (52

mg, 87% yield, 78% ee) was obtained as a clear yellow oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 7.0 Hz, 3H), 2.26 (s, 3H), 2.34 (s, 3H), 2.97–3.05 (m, 1H), 3.19 (dd, A of ABX, J_{AB} = 12.2 Hz, J_{AX} = 8.3 Hz, 1H), 3.31 (dd, B of ABX, J_{AB} = 12.2 Hz, J_{BX} = 6.2 Hz, 1H), 3.52 (brs, 1H), 6.38–6.39 (m, 2H), 6.51 (d, J = 7.4 Hz, 1H), 7.02–7.06 (m, 1H), 7.11–7.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.2, 21.8, 39.0, 51.1, 110.2, 113.9, 118.4, 127.3, 129.2, 129.5, 136.2, 139.0, 141.7, 148.4; HRMS for $C_{17}H_{22}N$ $[M+H]^+$: *m/z* Calcd.: 240.1747; Found: 240.1744; HPLC (Chiralcel OD-H, hexane: isopropanol = 99.8:0.2, flow rate 1 mL/min, λ = 254 nm): t_R = 20.2 min (minor), t_R = 20.9 min (major).

2-Methyl-*N*-(2-*p*-tolylpropyl)aniline, **1d**. The product (36 mg, 61% yield, 86% ee) was obtained as a colourless oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.9 Hz, 3H), 1.93 (s, 3H), 2.33 (s, 3H), 3.04–3.09 (m, 1H), 3.19 (dd, A of ABX, J_{AB} = 11.9 Hz, J_{AX} = 8.4 Hz, 1H), 3.37 (dd, B of ABX, J_{AB} = 12.2 Hz, J_{BX} = 5.8 Hz, 1H), 3.43 (brs, 1H), 6.64 (d, J = 7.7 Hz, 2H), 7.00, (d, J = 7.4 Hz, 1H), 7.10–7.12 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 19.6, 21.0, 38.7, 51.0, 109.9, 116.8, 122.1, 127.1, 129.4, 129.5, 130.0, 136.2, 141.4, 146.1; HRMS for $C_{17}H_{22}N$ $[M+H]^+$: *m/z* Calcd.: 240.1747; Found: 240.1746; HPLC (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 1 mL/min, λ = 254 nm): t_R = 7.2 min (major), t_R = 7.9 min (minor).

4-Bromo-*N*-(2-*p*-tolylpropyl)aniline, **1e**. The product (34 mg, 45% yield, 79% ee) was obtained as a clear oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 7.0 Hz, 3H), 2.33 (s, 3H), 2.95–3.03 (m, 1H), 3.15 (dd, A of ABX, J_{AB} = 12.3 Hz, J_{AX} = 8.5 Hz, 1H), 3.28 (dd, B of ABX, J_{AB} = 12.3 Hz, J_{BX} = 6.0 Hz, 1H), 3.57 (brs, 1H), 6.41–6.44 (m, 2H), 7.08–7.14 (m, 4H), 7.19–7.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 21.0, 38.7, 50.9, 108.8, 114.5, 127.5, 129.4, 131.9, 136.3, 141.1, 147.1; $C_{16}H_{19}{}^{79}BrN$ $[M+H]^+$: *m/z* Calcd.: 304.0701; Found: 304.0704; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 14.7 min (minor), t_R = 15.3 min (major).

4-Methoxy-*N*-(2-phenylpropyl)aniline, **1f** [17]. The product (45 mg, 74% yield, 83% ee) was obtained as a colourless oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 7.0 Hz, 3H), 3.00–3.08 (m, 1H), 3.19 (dd, A of ABX, J_{AB} = 12.2 Hz, J_{AX} = 8.3 Hz, 1H), 3.30 (dd, B of ABX, J_{AB} = 12.2 Hz, J_{BX} = 6.1 Hz, 1H), 3.74 (s, 3H), 6.52–6.56 (m, 2H), 6.74–6.77 (m, 2H), 7.21–7.25 (m, 3H), 7.30–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 39.2, 52.0, 55.8, 114.4, 114.9, 126.6, 127.3, 128.7, 142.4, 144.6, 152.1; $C_{16}H_{20}NO$ $[M+H]^+$: *m/z* Calcd.: 242.1539; Found: 242.1537; HPLC (Chiralcel OJ, hexane :isopropanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm): t_R = 19.6 min (minor), t_R = 23.1 min (major).

3-Methoxy-*N*-(2-(*o*-tolyl)propyl)aniline, **1g**. The product (31 mg, 49% yield, 91% ee) was obtained a pale yellow oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.4 Hz, 3H), 2.24 (s, 3H), 3.18–3.32 (m, 3H), 3.54 (brs, 1H), 3.68 (s, 3H), 6.06 (t, J = 2.2 Hz, 1H), 6.11 (dd, J = 8.0, 1.5 Hz, 1H), 6.18 (dd, J = 8.0, 2.2 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 7.04–7.11 (m, 2H), 7.13–7.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (2C), 34.2, 50.2, 55.1, 98.8, 102.5, 106.0, 125.3, 126.2, 126.5, 129.9, 130.5, 136.2, 142.6, 149.6, 160.9; $C_{17}H_{22}NO$ $[M+H]^+$: *m/z* Calcd.: 256.1701; Found: 256.1703; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 41.3 min (minor), t_R = 52.7 min (major).

4-Methoxy-*N*-(2-*m*-tolylpropyl)aniline, **1h**. The product (39 mg, 61% yield, 80% ee) was obtained as a pale yellow oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 7.0 Hz, 3H), 2.35 (s, 3H), 2.97–3.03 (m, 1H), 3.18 (dd, A of ABX, J_{AB} = 12.1 Hz, J_{AX} = 8.3 Hz, 1H), 3.28 (dd, B of ABX, J_{AB} = 12.1 Hz, J_{BX} = 6.1 Hz, 1H), 3.74 (s, 3H), 6.53–6.57 (m, 2H), 6.74–6.78 (m, 2H), 7.01–7.06 (m, 3H), 7.21 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.6, 39.3, 52.1, 55.9, 114.5, 115.0, 124.4, 127.5, 128.1, 128.7, 138.4, 142.5, 144.7, 152.2; HRMS for $C_{17}H_{22}NO$ $[M+H]^+$: *m/z* Calcd.: 256.1701; Found: 256.1700; HPLC (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm): t_R = 42.7 min (major), t_R = 49.9 min (minor).

3-Methoxy-*N*-(2-(*m*-tolyl)propyl)aniline, **1i**. The product (50 mg, 78% yield, 84% ee) was obtained as a pale yellow oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 7.0 Hz, 3H), 2.27 (s, 3H), 2.89–2.98 (m, 1H), 3.14 (dd, A of ABX, J_{AB} = 12.3 Hz, J_{AX} = 8.3 Hz, 1H), 3.23 (dd, B of ABX, J_{AB} = 12.3 Hz, J_{BX} = 6.2 Hz, 1H), 3.53 (brs, 1H), 3.68 (s, 3H), 6.06 (t, J = 2.3 Hz, 1H), 6.11 (dd, J = 8.1, 1.5 Hz, 1H), 6.18 (dd, J = 8.1, 2.3 Hz, 1H), 6.94–7.00 (m, 4H), 7.15 (t, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 21.4, 38.6, 50.9, 55.7, 101.9, 103.2, 124.3, 127.4, 128.0, 128.9, 129.9, 130.3, 138.3, 144.5, 149.6, 160.9; $C_{17}H_{22}NO$ $[M+H]^+$: *m/z* Calcd.: 256.1701; Found: 256.1703; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 37.8 min (minor), t_R = 47.9 min (major).

N-(2-*m*-Tolylpropyl)aniline, **1j**. The product (32 mg, 56% yield, 80% ee) was obtained as a colourless oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 7.0 Hz, 3H), 2.27 (s, 3H), 2.89–2.98 (m, 1H), 3.14 (dd, A of ABX, J_{AB} = 12.1 Hz, J_{AX} = 8.3 Hz, 1H), 3.24 (dd, B of ABX, J_{AB} = 12.2 Hz, J_{BX} = 6.2 Hz, 1H), 3.49 (brs, 1H), 6.49 (dd, J = 8.4, 0.9 Hz, 2H), 6.61 (t, J = 7.3 Hz, 1H), 6.96 (t, J = 8.4 Hz, 3H), 7.08–7.12 (m, 2H), 7.14–7.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 21.5, 39.2, 50.9, 113.0, 117.3, 124.3, 127.4, 128.0, 128.6, 129.3, 138.3, 144.5, 148.2; MS (CI) for $C_{16}H_{20}N$ $[M+H]^+$: *m/z* 226 (100%); Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 84.71; H, 8.83; N, 6.42. HPLC (Chiralcel OD-H, hexane:isopropanol = 99.5:0.5, flow rate 4 mL/min, λ = 254 nm): t_R = 11.3 min (minor), t_R = 12.3 min (major).

N-(2-(4-Methoxyphenyl)propyl)-4-methylaniline, **1k**. The product (39 mg, 61% yield, 82% ee) was obtained as a colourless oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 6.9 Hz, 3H), 2.23 (s, 3H), 2.96–3.04 (m, 1H), 3.15 (dd, A of ABX, J_{AB} = 12.2 Hz, J_{AX} = 8.4 Hz, 1H), 3.29 (dd, B of ABX, J_{AB} = 12.2 Hz, J_{BX} = 6.0 Hz, 1H), 3.80 (s, 3H), 6.48–6.51 (m, 2H), 6.85–6.88 (m, 2H), 6.97 (d, J = 8.4 Hz, 2H), 7.12–7.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.2, 38.9, 51.5, 55.9, 114.0, 114.1, 126.5, 128.2, 129.8, 136.6, 145.9, 158.2, 158.3; HRMS for $C_{17}H_{22}NO$ $[M+H]^+$: *m/z* Calcd.: 256.1701; Found: 256.1700; HPLC (Chiralcel OD-H,

hexane:isopropanol = 98.5:1.5, flow rate 0.5 mL/min, λ = 254 nm): t_R = 19.9 min (minor), t_R = 22.2 min (major).

4-Bromo-*N*-(2-(4-methoxyphenyl)propyl)aniline, **1l**. The product (41 mg, 51% yield, 84% ee) was obtained as a pale yellow oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.9 Hz, 3H), 2.94–3.03 (m, 1H), 3.13 (dd, A of ABX, J_{AB} = 12.2 Hz, J_{AX} = 8.6 Hz, 1H), 3.28 (dd, B of ABX, J_{AB} = 12.2 Hz, J_{BX} = 6.0 Hz, 1H), 3.80 (s, 3H), 6.41–6.45 (m, 2H), 6.86–6.88 (m, 2H), 7.11–7.14 (m, 2H), 7.20–7.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 38.7, 51.4, 55.7, 109.2, 114.5, 114.9, 128.5, 132.3, 136.6, 147.5, 158.8; HRMS for $C_{16}H_{19}BrNO$ $[M+H]^+$: *m/z* Calcd.: 320.0650; Found: 320.0659; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 23.0 min (minor), t_R = 27.3 min (major).

4-Methoxy-*N*-(2-(4-(trifluoromethyl)phenyl)propyl)aniline, **1m**. The product (54 mg, 70% yield, 81% ee) was obtained as a colourless oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.9 Hz, 3H), 3.08–3.17 (m, 1H), 3.22 (dd, A of ABX, J_{AB} = 12.4 Hz, J_{AX} = 8.2 Hz, 1H), 3.33 (dd, B of ABX, J_{AB} = 12.4 Hz, J_{BX} = 6.0 Hz, 1H), 3.75 (s, 3H), 6.52–6.56 (m, 2H), 6.75–6.79 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 39.2, 51.8, 55.8, 114.5, 115.0, 124.3 (q, J_{CF} = 268.9 Hz) 125.6 (q, J_{CF} = 3.6 Hz), 127.8, 128.9 (q, J_{CF} = 21.1 Hz), 141.9, 148.9, 152.3; HRMS for $C_{16}H_{19}BrNO$ $[M+H]^+$: *m/z* Calcd.: 310.1419; Found: 310.1419; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 27.1 min (major), t_R = 29.9 min (minor).

N-(2-(4-(Trifluoromethyl)phenyl)propyl)aniline, **1n**. The product (39 mg, 56% yield, 79% ee) was obtained as a colourless oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.9 Hz, 3H), 3.09–3.18 (m, 1H), 3.26 (dd, A of ABX, J_{AB} = 12.6 Hz, J_{AX} = 8.3 Hz, 1H), 3.37 (dd, B of ABX, J_{AB} = 12.6 Hz, J_{BX} = 6.2 Hz, 1H), 3.52 (brs, 1H), 6.56–6.59 (m, 2H), 6.64–6.72 (m, 1H), 7.14–7.19 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 38.6, 50.7, 112.9, 117.6, 125.6 (q, J_{CF} = 3.8 Hz), 127.6, 129.0 (q, J_{CF} = 30.6 Hz), 129.3, 147.7, 148.7 (The carbon resonance *C*F_3 was not observed, possibly due to overlap with other aromatic carbon resonances); $C_{16}H_{17}F_3N$ $[M+H]^+$: *m/z* Calcd.: 280.1313; Found: 280.1307; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 29.3 min (minor), t_R = 33.7 min (major).

4-Methoxy-*N*-(2-(naphthalen-2-yl)propyl)aniline, **1p** [17]. The product (59 mg, 81% yield, 83% ee) was obtained as a pale yellow oil according to the general procedure in 3 d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, J = 6.8 Hz, 3H), 3.18–3.26 (m, 1H), 3.29 (dd, A of ABX, J_{AB} = 12.0 Hz, J_{AX} = 8.4 Hz, 1H), 3.39 (dd, B of ABX, J_{AB} = 12.0 Hz, J_{BX} = 5.7 Hz, 1H), 3.74 (s, 3H), 6.52–6.56 (m, 2H), 6.74–6.78 (m, 2H), 7.37 (dd, J = 8.5, 1.7 Hz, 1H), 7.43–7.50 (m, 2H), 7.66 (s, 1H), 7.81 (t, J = 8.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 39.4, 51.8, 55.8, 114.4, 114.9, 125.5, 125.9, 126.1, 127.6(2), 127.6(4), 128.4, 130.2, 132.5, 133.6, 142.0, 142.3, 152.1; HRMS for $C_{20}H_{22}NO$ $[M+H]^+$: *m/z* Calcd: 292.1701; Found: 292.1711; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 36.4 min (major), t_R = 39.3 min (minor).

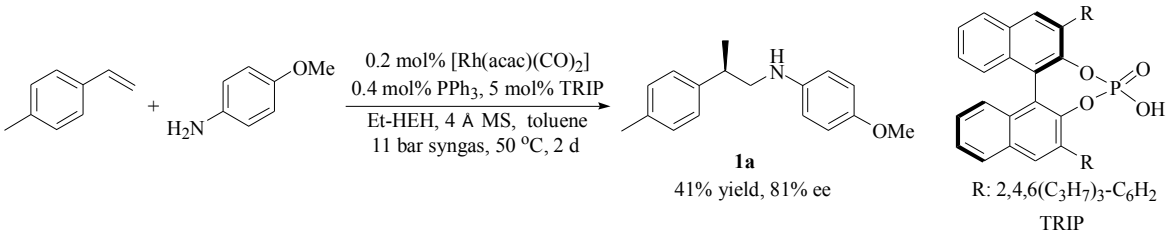
3. Results and discussion

Hydroformylation usually affords a linear aldehyde. However, it is the branched aldehyde that could lead to a chiral amine. Hence, in order to turn the product of hydroaminomethylation into highly optically active, one must first maximise the *i/n* selectivity of the transformation (Scheme 2). Li and co-workers [16] reported the selective hydroformylation of styrene to the corresponding α-branched aldehyde with a Rh catalyst containing a triarylphosphine ligand possessing a long-chain alkoxy group. The reaction takes place in toluene, with 0.2 mol% $[Rh(acac)(CO)_2]$ and 0.4 mol% phosphine ligand at 15 bar syngas and 50 °C. As a starting point, we decided to use these conditions for our hydroaminomethylation sequence, with *p*-anisidine as the model amine. A range of phosphine ligands were initially tested. Disappointedly, we quickly found that although the Rh-phosphine catalyst promoted the hydroformylation of styrene and the enamine was formed, hydrogenation of the latter was never observed, even in the presence of an acid (Scheme 1). This may not be surprising as one of the main problems with the hydroaminomethylation protocols is the slow hydrogenation of the enamine/imine intermediate [9].

Knowing that the imine hydrogenation could be effected by other catalysts, we then focused on the idea of using two different catalysts, one for the hydroformylation and the other for the hydrogenation step. In particular, List et al. [17] had developed a protocol on asymmetric reductive amination of α-branched aldehydes via DKR, in which a chiral phosphoric acid acted as the organocatalyst and a Hantzsch ester (HEH) as the hydrogen source. This became our choice to effect the reductive amination step.

We combined the $[Rh(acac)(CO)_2]$ catalyst precursor with PPh_3, Et-HEH and the phosphoric acid TRIP in toluene to examine the reaction of *p*-methylstyrene with *p*-anisidine at 11 bar syngas and 50 °C (Scheme 3). The reaction mixture was left stirring for 2 d. Delightfully, after flash chromatography purification, a promising 41% isolated yield was obtained for the desired product **1a** with a good enantioselectivity of 81% ee.

Encouraged by this result, optimisation of the conditions was then undertaken, aiming to improve the yield and enantioselectivity. First, the effect of the HEH was studied. The results are shown in Table 1. The reaction takes place under a syngas pressure; therefore H_2 could act as the reductant for the hydrogenation step. However, the presence of HEH is essential in this reaction, suggesting that the hydrogen source for the reductive amination or more precisely the reduction of the imino bond comes from the HEH (entry 1). An excess of Et-HEH provides a positive effect on the yield (entry 2 vs entry 3). Whilst a bulkier *t*Bu-HEH afforded an increase in the enantioselectivity of the reductive amination of α-branched aldehydes [17], very low yield was obtained in our case (entry 5). A decrease in the activity with bulkier HEH's was also observed by List et al. [17]. The effect of the temperature was next examined. Although better enantioselectivities were obtained at a low temperature of 6 °C for the reductive amination step [17], the hydroam-



Scheme 3. Preliminary study of the metal- and organo-catalysed asymmetric hydroaminomethylation.

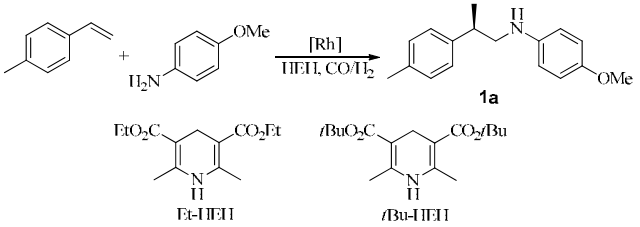
inomethylation in question became much slower when the temperature was dropped to 25 °C (3 d, 24% yield, 83% ee). As maybe expected, a higher temperature of 80 °C led to a higher yield but a slight decrease in enantioselectivity (2 d, 55% yield, 79% ee). Thus, a temperature of 50 °C was chosen which offered good enantioselectivities whilst maintaining a reasonable rate of reaction.

Table 2 shows the effect of phosphine ligands in this asymmetric hydroaminomethylation. Monophosphine ligands are in general superior compared to diphosphines (entries 1–3 vs 4–8). Within the derivatives of PPh_3, a more electron-donating substituent in the ligand leads to an increase in yield (entry 8), whilst an electron-deficient substituent has a negative effect on the yield (entry 7). The increase in yield stems from a higher selectivity for the branched aldehyde in the hydroformylation step. Moser and co-workers [18] showed that *p*-electron-donating groups in the phosphine increase the basicity of the phosphine and the selectivity for α-branched aldehydes.

With the outcome of optimisation in hand, we then explored the scope of the methodology using a range of styrenes and anilines. Table 3 shows the effect of substituents at the aniline on the hydroaminomethylation of *p*-methylstyrene. All the products **1a–e** were obtained with good enantioselectivity (78%–86% ee). Better enantioselectivities were obtained when more sterically-hindered anilines were used (entry 1 vs 2, entry 3 vs 4), and this observation was previously noted in the asymmetric reductive amination of ketones [19,20]. Lower yield was obtained when using electron-deficient *p*-bromoaniline (entry 5), reflecting presumably the difficulty encountered in the aldehyde-amine condensation step. This was also observed by List et al. [17] in the organocatalytic reductive amination of *α*-branched aldehydes via DKR and in transition metal- [2] and organo-catalysed [21,22] asymmetric reductive amination of ketones.

We next investigated the asymmetric hydroaminomethylation of different derivatives of styrene with aniline and its analogues (Table 4). Good yields and enantioselectivities were obtained in general. A lower yield was obtained when using an *ortho*-substituted styrene (entry 2). This is due to the *i/n* selectivity in the hydroformylation step being lower as a result of steric effects, with the *ortho* substituent inhibiting the formation of the benzylic Rh species that would favour producing the branched aldehyde [23,24]. In fact, when hydroformylation of *p*-methyl and *o*-methylstyrene was compared, the *i/n* selectivity decreased from 13:1 to 7:1. Similar to what is shown in Table 3, electron-deficient groups in the aniline ring have a detrimental effect on the yield (Table 4, entries 7 and 10). As mentioned, this is likely to result from an inefficient condensation step [17,22]. The same could be expected from electron-deficient groups in the styrene ring (entries 8–10) [17].

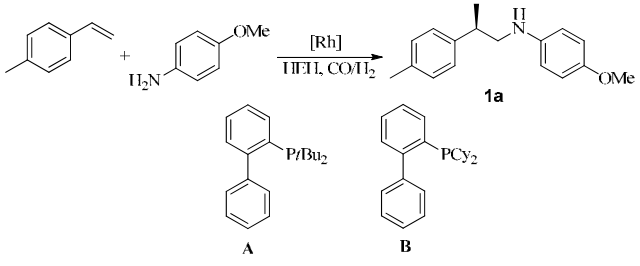
Table 1
Effect of Hantzsch esters on the model asymmetric hydroaminomethylation.



Entry	Eqs. Et-HEH	Isolated yield	ee [a] (%)
1	—	N.R. [b]	N.D. [c]
2	1.2	40	81
3	2.2	67	80
4	4.0	64	80
5	1.2 [d]	< 10	N.D. [c]

Reaction conditions: 0.4 mmol *p*-methylstyrene, 0.25 mmol *p*-anisidine, 1.25 μmol $[Rh(acac)(CO)_2]$, 2.5 μmol PPh_3, Et-HEH (unless otherwise specified), 12.5 μmol TRIP, 100 mg 4 Å MS, 4 mL toluene, 11 bar CO/H_2 1:1, 50 °C, 2 d.
[a] Determined by HPLC. [b] No reaction. [c] Not determined. [d] *t*Bu-HEH used.

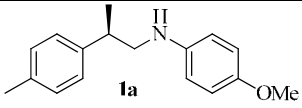
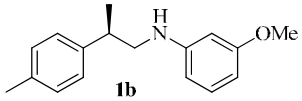
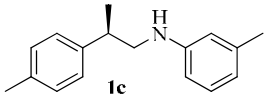
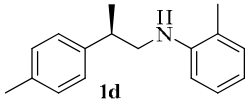
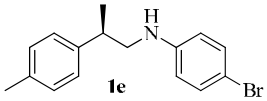
Table 2
Effect of ligands on the model asymmetric hydroaminomethylation.



Entry	Ligand	Isolated yield (%)
1	DPPP	N.R. [a]
2	DPPB	N.R. [a]
3	XANTPHOS	20
4	**A**	<5
5	**B**	43
6	PPh_3	30
7	$P(4\text{-}CF_3C_6H_4)_3$	25
8	$P(4\text{-}MeOC_6H_4)_3$	48

Reactions conditions: the same as those in Table 1 except with different phosphine ligand, 0.6 mmol Et-HEH and 17 h reaction time.
[a] No desired reaction; only linear product observed.

Table 3
Asymmetric hydroaminomethylation of *p*-methylstyrene with different anilines.

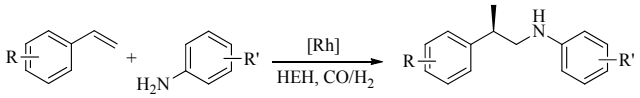
Entry	R	Product	Isolated yield (%)	ee [a] (%)
1	*p*-OMe	 **1a**	79	80
2	*m*-OMe	 **1b**	83	84
3	*m*-Me	 **1c**	87	78
4	*o*-Me	 **1d**	61	86
5	*p*-Br	 **1e**	45	79

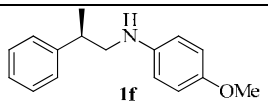
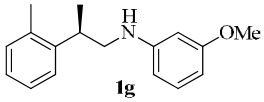
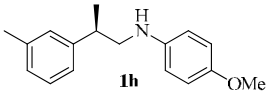
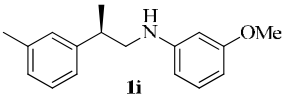
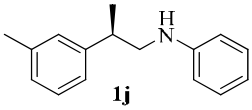
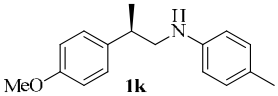
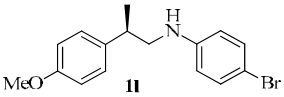
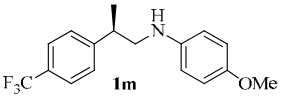
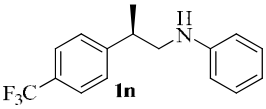
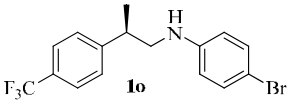
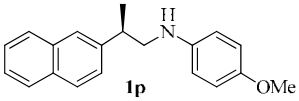
Reactions conditions: the same as those in Table 1 except with 0.25 mmol aniline derivative, 2.5 μmol P(4-$CH_3OC_6H_4$)$_3$, 0.6 mmol Et-HEH and 3 d reaction time.
[a] Determined by HPLC.

4. Conclusions

We have developed a new protocol that enables asymmetric hydroaminomethylation of styrenes, affording *β*-chiral amines with good yields and enantioselectivities. To the best of our knowledge, this is the first example of an asymmetric version of this tandem reaction where significant enantioselectivities have been achieved. The transformation is made possible by combining metal- and organo-catalysis, with the former catalysing the hydroformylation while the latter reductive amination via DKR. The protocol provides an attractive pathway for the synthesis of β-chiral amines, as they can be obtained in one step from easily available starting materials. The main drawback of the protocol is the use of HEH as hydrogen source. A single chiral metal complex to catalyse both steps will be more desirable, and lead to a greener procedure with H_2 as the only hydrogen source.

Table 4
Asymmetric hydroaminomethylation of different derivatives of styrene.



Entry	R	R'	Product	Isolated yield (%)	ee [a] (%)
1	H	*p*-OMe	 **1f**	80	83
2	*o*-Me	*m*-OMe	 **1g**	49	91
3	*m*-Me	*p*-OMe	 **1h**	61	80
4	*m*-Me	*m*-OMe	 **1i**	78	84
5	*m*-Me	H	 **1j**	56	80
6	*p*-OMe	*p*-Me	 **1k**	61	82
7	*p*-OMe	*p*-Br	 **1l**	51	84
8	*p*-CF_3	*p*-OMe	 **1m**	70	81
9	*p*-CF_3	H	 **1n**	56	79
10	*p*-CF_3	*p*-Br	 **1o**	<5	N.D. [b]
11	R [c]	*p*-OMe	 **1p**	81	83

Reaction conditions: the same as those in Table 1 except with 0.4 mmol styrene derivative, 0.25 mmol aniline derivative, 2.5 μmol P(4-$CH_3OC_6H_4$)$_3$, 0.6 mmol Et-HEH and 3 d reaction time.
[a] Determined by HPLC.
[b] Not determined.
[c] 2-Vinylnaphthalene (R: 3,4-C_4H_4) used.

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Graphical Abstract

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Metal and organo-catalysed asymmetric hydroaminomethylation of styrenes

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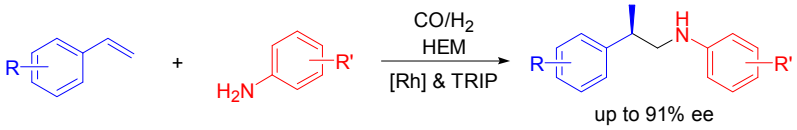

Combining metal-catalysed hydroformylation with a chiral organo-acid-catalysed reductive amination allows for asymmetric hydroaminomethylation to be realised.

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