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Highly regioselective synthesis of chiral diamines via a Buchwald–Hartwig amination from camphoric acid and their application in the Henry reaction

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In this work the synthesis of new asymmetric diamine ligands from camphoric acid is described. The new diamines can be directly prepared in a regioselective arylation of the less hindered primary amine group of (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine via a Buchwald–Hartwig amination in high yields. The resulting diamines incorporate a secondary and primary amine group and were successfully applied as ligands in a copper-catalyzed Henry reaction. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: Buchwald–Hartwig amination; palladium; diamines; camphor; Henry reaction

Introduction

The development of new chiral ligands is an important task in the research field of asymmetric catalysis.[1] One class of asymmetric ligand that is being continuously reported is based on diamines. The latter have been studied as ligands with several different metals in a broad range of reactions.[2]

Among those transformations that have been explored is the asymmetric Henry reaction or nitro-aldol reaction, which is an important method to obtain enantiomer-enriched β-nitro alcohols from nitroalkanes and aldehydes.[3] The reaction can be catalyzed with chiral organocatalysts and metal-based systems with chiral ligands.[4] New diamine ligands for the copper-catalyzed Henry reaction are constantly being developed.[5] For several of these ligand systems (+)-camphor from the chiral pool proved to be a valuable starting material for their synthesis.[5d,5n–p]

One interesting way to utilize (+)-camphor is in the development of ligands via (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine (**2**), which can be prepared in one step from (+)-camphoric acid (**1**) via the Schmidt reaction (Scheme 1).[6] The diamine **2** has been the starting point of several attractive ligand targets over recent years.[7] Ligands **3**[7a] and **4**[7c] can be prepared by exploiting the different reactivity of the two amine groups attached to secondary and tertiary carbon atoms with carboxylic acid chlorides.

Here, we explore the possibility of differentiating between the different amine groups with a Buchwald–Hartwig amination.[8] This *N*-aryl amination has found an increased interest over the last 20 years. In the present study it gives a direct access to new diamine ligands, whose potential is explored in the copper-catalyzed asymmetric Henry reaction.

Experimental

General Remarks

Diamine **2** was prepared according to the literature[6] from (+)-camphoric acid (**1**), which was purchased from commercial sources. The diamines **18**[9] and **19**[9] were prepared according to the literature. Melting points were taken with an apparatus after Dr Tottoli and are uncorrected. IR spectra were recorded on a Bruker VERTEX 70 FT-IR spectrometer. ^{1}H NMR spectra were acquired at ambient temperature on a Bruker Avance 500 (500 MHz) in deuterated solvents as stated. ^{13}C NMR spectra were recorded at ambient temperature at 125 MHz and ^{15}N spectra at 51 Hz in deuterated solvents. Mass spectra (EI) were recorded with a Hewlett Packard 5989B at 70 eV. High-resolution mass spectra (ESI) were recorded on a Waters Quadrupole-ToF Synapt 2G. EI mass spectra were recorded on a Thermo Scientific double-focusing sector field-MS DFS. Enantiomeric excess was determined on a Merck Hitachi HPLC system. Flash column chromatography was performed on Sorbisil C-60. Reactions were monitored by TLC with Merck Silica gel 60 F254 plates. THF and diethyl ether were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. CH_2Cl_2 and acetonitrile were distilled from calcium hydride.

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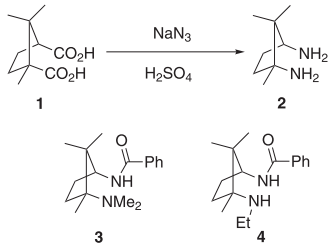


Scheme 1. Camphor diamines based on camphoric acid.

General Experimental for the Regioselective Arylation of Diamine (2)

In a dried Schlenk tube $Pd_2(dba)_3$ (2–4 mol%), (±)-BINAP (6–9 mol%) and NaO*t*Bu (3 equiv.) were dissolved in toluene under a nitrogen atmosphere and stirred for 20 min. Diamine **2** (1 equiv.) and a bromoaryl (1 equiv.) were added and the solution was stirred for 48 h at 100°C. The solution was filtered through a plug of silica and the plug was eluted with additional toluene. Thereafter, the plug was eluted with CH_2Cl_2/MeOH (9:1) until all the product was removed from the silica plug. The solvent was evaporated under reduced pressure and the crude product was dissolved in CH_2Cl_2. The organic phase was extracted with 12 M HCl. The aqueous phase was separated and washed three times with CH_2Cl_2. Thereafter, the aqueous phase was cooled to 0°C and 12 M NaOH was slowly added until the solution had a pH of 14. The basic solution was extracted five times with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed. The crude product was dissolved in pentane and the solution was filtered to remove insoluble impurities. The solvent was removed and the product was further purified via chromatography.

*(1R,3S)-1,2,2-Trimethyl-N^3-(pyridin-2-yl)cyclopentane-1,3-diamine (**5**)*

From $Pd_2(dba)_3$ (0.1 g, 0.11 mmol, 2 mol%), (±)-BINAP (0.3 g, 0.48 mmol, 6 mol%), NaO*t*Bu (2.0 g, 20.81 mmol), diamine **2** (1.0 g, 7.03 mmol), 2-bromopyridine (0.7 ml, 7.34 mmol) in toluene (100 ml). After workup, the product was purified via column chromatography (CH_2Cl_2/Et_2O, 9:1 with 4% Et_3N) and obtained as a yellow oil (1.4 g, 6.38 mmol, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 5.0 Hz, 1H, *H*-6′), 7.30–7.23 (m, 1H, *H*-4′), 6.42–6.35 (m, 1H, *H*-5′), 6.28 (dd, *J* = 8.4, 0.9 Hz, 1H, *H*-3′), 6.01 (d, *J* = 9.5 Hz, 1H, *H*-N^3), 4.03–3.94 (m, 1H, *H*-3), 2.25–2.12 (m, 1H, *H*-4), 1.78–1.65 (m, 1H, *H*-5), 1.62–1.48 (m, 2H, *H*-5, *H*-4), 1.08 (s, 3H, *H*-8), 0.88 (s, 6H, *H*-7, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.0 (*C*-2′), 148.1 (*C*-6′), 137.0 (*C*-4′), 111.6 (*C*-5′), 107.2 (*C*-3′), 61.6 (*C*-1), 60.8 (*C*-3), 47.2 (*C*-2), 38.1 (*C*-5), 29.4 (*C*-4), 26.5 (*C*-8), 24.5 (*C*-6), 17.1 (*C*-7) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 260.4 (bs, 1N, *N*-1′), 97.0 (bs, 1N, *N*^{3}), 53.2 (bs, 1N, *N*^{1}) ppm. IR (ATR) = 2962, 1621, 1584, 1471, 1435, 1315, 1249, 1207, 1162, 1018, 860, 772, 716, 617 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 219 (74) [M]$^+$, 187 (49), 149 (81), 127 (83), 126 (100), 110 (88), 96 (43), 95 (94), 93 (43), 79 (74), 70 (80), 57 (74), 42 (38). HRMS (ESI): calcd for $C_{13}H_{22}N_3$: 220.1814 [M+H]$^+$; found: 220.1813. Anal. Calcd for $C_{13}H_{21}N_3$: C, 71.19; H, 9.65; N, 19.16; found: C, 70.99; H, 9.30; N, 18.64. $[\alpha]^{20}_D$ = +71.4 (*c* = 1.2, CH_2Cl_2).

*(1S,3R)-N^1-(2-Methoxyphenyl)-2,2,3-trimethylcyclo-pentane-1,3-diamine (**6**)*

From $Pd_2(dba)_3$ (0.8 g, 0.87 mmol, 4 mol%), (±)-BINAP (1.2 g, 1.93 mmol, 9 mol%), NaO*t*Bu (6.1 g, 63.48 mmol), diamine **2** (3.0 g, 21.09 mmol), 2-bromoanisole (2.6 ml, 20.88 mmol) in toluene (360 ml). After workup, the product was obtained as a yellow solid (5.2 g, 20.94 mmol, 99%).

M.p. 65°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.85 (ddd, *J* = 7.7, 6.1, 1.4 Hz, 1H, *H*-5′), 6.77 (dd, *J* = 7.9, 1.3 Hz, 1H, *H*-3′), 6.66–6.59 (m, 2H, *H*-6′, *H*-4′), 4.96 (bs, 1H, *H*-N^1), 3.85 (s, 3H, 2′-OC*H*$_3$), 3.73–3.66 (m, 1H, *H*-1), 2.24 (dddd, *J* = 13.6, 10.3, 8.5, 4.9 Hz, 1H, *H*-5), 1.76 (ddd, *J* = 13.2, 10.3, 6.1 Hz, 1H, *H*-4), 1.66 (ddd, *J* = 13.3, 11.0, 4.9 Hz, 1H, *H*-4), 1.54 (ddt, *J* = 13.7, 11.0, 6.0 Hz, 1H, *H*-5), 1.15 (s, 3H, *H*-8), 0.97 (s, 3H, *H*-6), 0.96 (s, 3H, *H*-7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.9 (*C*-2′), 138.7 (*C*-1′), 121.3 (*C*-5′), 115.5 (*C*-4′), 110.0 (*C*-6′), 109.8 (*C*-3′), 61.8 (*C*-1), 61.0 (*C*-3), 55.6 (2′-OC*H*$_3$), 47.1 (*C*-2), 38.3 (*C*-4), 29.3 (*C*-5), 26.3 (*C*-8), 23.7 (*C*-6), 17.2 (*C*-7) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 70.5 (bs, 1N, *N*^{1}), 47.7 (bs, 1N, *N*^{3}) ppm. IR (KBr) = 3435, 3062, 2961, 2869, 2284, 1601, 1515, 1454, 1428, 1368, 1341, 1311, 1223, 1179, 1119, 1026, 879, 839, 737, 551 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 248 (16) [M]$^+$, 216 (10), 123 (100), 108 (15), 70 (10). HRMS (ESI): calcd for $C_{13}H_{25}N_2O$: 249.1967 [M+H]$^+$; found: 249.1976. Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28; found: C, 72.41; H, 9.71; N, 11.21. $[\alpha]^{20}_D$ = +51 (*c* = 2.7, $CHCl_3$).

*(1R,3S)-1,2,2-Trimethyl-N^3-(o-tolyl)cyclopentane-1,3-diamine (**7**)*

From $Pd_2(dba)_3$ (0.8 g, 0.87 mmol, 4 mol%), (±)-BINAP (1.2 g, 1.93 mmol, 9 mol%), NaO*t*Bu (6.1 g, 63.48 mmol), diamine **2** (3.0 g, 21.09 mmol), 2-bromotoluene (2.5 ml, 20.79 mmol) in toluene (360 ml). After workup, the product was obtained as a yellow solid (4.0 g, 17.21 mmol, 82%).

M.p. 95°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.10–7.05 (m, 1H, *H*-4′), 7.03 (dd, *J* = 7.3, 0.6 Hz, 1H, *H*-6′), 6.61–6.55 (m, 2H, *H*-5′, *H*-3′), 5.11 (s, 1H, *H*-N^3), 3.68 (d, *J* = 4.5 Hz, 1H, *H*-3), 2.28–2.18 (m, 1H, *H*-4), 2.13 (s, 3H, 2′-C*H*$_3$), 1.86–1.77 (m, 1H, *H*-5), 1.69–1.56 (m, 2H, *H*-5, *H*-4), 1.18 (s, 3H, *H*-8), 1.02 (s, 3H, *H*-7), 0.98 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.6 (*C*-1′), 130.1 (*C*-6′), 126.9 (*C*-4′), 122.3 (*C*-2′), 115.7 (*C*-3′), 109.6 (*C*-5′), 62.6 (*C*-3), 61.7 (*C*-1), 47.2 (*C*-2), 38.2 (*C*-5), 29.4 (*C*-4), 26.5 (*C*-8), 25.0 (*C*-6), 17.9 (2′-C*H*$_3$), 17.3 (*C*-7) ppm. ^{15}N-NMR (51 MHz, $CDCl_3$) δ = 82.4 (bs, 1N, *N*^{3}), 52.1 (bs, 1N, *N*^{1}) ppm. IR (ATR) = 3288, 2967, 1602, 1580, 1502, 1448, 1386, 1364, 1314, 1262, 1227, 1144, 1049, 980, 953, 909, 856, 745, 715, 654 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 248 (16) [M]$^+$, 216 (10), 123 (100), 108 (15), 70 (10). HRMS (ESI): calcd for $C_{15}H_{25}N_2$: 233.2018 [M+H]$^+$; found: 233.2017. Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06; found: C, 77.43; H, 10.31; N, 12.00. $[\alpha]^{20}_D$ = +112 (c = 6, $CHCl_3$).

*(1S,3R)-N^1-([1,1′-Biphenyl]-2-yl)-2,2,3-trimethylcyclo-pentane-1,3-diamine (**8**)*

From $Pd_2(dba)_3$ (0.8 g, 0.87 mmol, 4 mol%), (±)-BINAP (1.2 g, 1.93 mmol, 9 mol%), NaO*t*Bu (6.2 g, 64.52 mmol), diamine **2** (3.1 g, 21.79 mmol), 2-bromo-1,1′-biphenyl (3.7 ml, 20.26 mmol) in toluene (360 ml). After workup the product was obtained as a yellow oil (4.7 g, 15.96 mmol, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47–7.38 (m, 4H, *H*-6″, *H*-5″, *H*-3″, *H*-2″), 7.34–7.29 (m, 1H, *H*-4″), 7.19 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H, *H*-6′), 7.08 (dd, *J* = 7.6, 1.7 Hz, 1H, *H*-4′), 6.72–6.67 (m, 2H, *H*-5′, *H*-3′), 4.90 (s, 1H, *H*-N^1), 3.64 (s, 1H, *H*-1), 2.19 (tdt, *J* = 10.6, 8.2, 5.4 Hz, 1H, *H*-5), 1.72 (ddd, *J* = 13.4, 10.5, 6.0 Hz, 1H, *H*-4), 1.61–1.52 (m, 1H, *H*-4), 1.49–1.38 (*H*-5), 1.11 (s, 3H, *H*-8), 0.91 (s, 3H, *H*-7), 0.78 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.5 (*C*-2′), 140.0 (*C*-1″), 130.3 (*C*-4′), 129.5 (*C*-5″, *C*-3″), 128.6 (*C*-6′), 128.6 (*C*-6″, *C*-2″), 127.9 (*C*-1′), 126.9 (*C*-4″), 116.0 (*C*-5′), 110.5 (*C*-3′), 62.2 (*C*-1), 61.2 (*C*-3), 47.1 (*C*-2), 37.9 (*C*-4), 29.0 (*C*-5), 26.1 (*C*-8), 23.8 (*C*-7), 17.2 (*C*-6) ppm. ^{15}N-NMR (51 MHz, $CDCl_3$) δ = 79.6 (bs, 1N, *N*^{1}), 50.4 (bs, 1N, *N*^{3}) ppm. IR (ATR) = 3296, 3057, 2959, 2867, 1597, 1576,

1506, 1489, 1462, 1436, 1387, 1368, 1319, 1283, 1161, 1144, 1063, 1007, 994, 927, 879, 841, 769, 734, 701, 615 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 294 (9) $[M]^+$, 258 (34), 248 (15), 216 (12), 169 (99), 123 (100), 110 (70), 70 (58), 57 (65). HRMS (ESI): calcd for $C_{20}H_{27}N_2$: 295.2174 $[M+H]^+$, found: 295.2162. Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.51; found: C, 80.95; H, 8.98; N, 9.43. $[\alpha]^{20}_D = +44$ (*c* = 7, $CHCl_3$).

*(1R,3S)-1,2,2-Trimethyl-N³-(naphthalen-1-yl)cyclo-pentane-1,3-diamine (**9**)*

From $Pd_2(dba)_3$ (0.5 g, 0.55 mmol, 4 mol%), (±)-BINAP (0.5 g, 0.80 mmol, 6 mol%), NaO*t*Bu (4.1 g, 42.66 mmol), diamine **2** (2.0 g, 14.06 mmol), 1-bromonaphthalene (1.9 ml, 13.58 mmol) in toluene (180 ml). After workup, the product was further purified via column chromatography (CH_2Cl_2/MeOH, 99:1) on neutral aluminum oxide and obtained as a white solid (2.4 g, 8.94 mmol, 64%).

M.p. 126°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.0 Hz, 1H, *H*-8′), 7.81–7.74 (m, 1H, *H*-5′), 7.46–7.37 (m, 2H, *H*-7′, H-6′), 7.34 (t, *J* = 7.9 Hz, 1H, *H*-3′), 7.15 (d, *J* = 8.2 Hz, 1H, *H*-4′), 6.64–6.48 (m, 2H, *H*-N³, *H*-2′), 3.84 (d, *J* = 5.0 Hz, 1H, *H*-3), 2.37–2.25 (m, 1H, *H*-4), 1.93–1.85 (m, 1H, *H*-5), 1.85–1.76 (m, 1H, *H*-4), 1.75–1.66 (m, 1H, *H*-5), 1.23 (s, 3H, *H*-8), 1.13 (s, 3H, *H*-7), 1.05 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 144.1 (*C*-1′), 134.7 (*C*-4′a), 128.5 (*C*-5′), 126.8 (*C*-3′), 125.5 (*C*-6′), 124.2 (*C*-7′), 124.0 (*C*-8′a), 120.9 (*C*-8′), 115.7 (*C*-4′), 103.6 (*C*-2′), 63.3 (*C*-3), 62.2 (*C*-1), 47.5 (*C*-2), 38.2 (*C*-5), 29.2 (*C*-4), 26.4 (*C*-8), 25.7 (*C*-6), 17.4 (*C*-7) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 83.6 (bs, 1N, N^3), 54.4 (bs, 1N, N^1) ppm. IR (ATR) = 1258, 1227, 1153, 1028, 633, 574, 517 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 268 (34), 157 (36), 143 (100), 112 (49), 97 (44), 95 (24), 83 (66), 71 (53), 70 (58), 69 (58), 57 (84), 55 (63), 44 (42), 43 (57), 41 (56). HRMS (ESI): calcd for $C_{18}H_{24}N_2Na$: 291.1837 $[M+H+Na]^+$; found: 291.1829. Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44; found: C, 80.55; H, 9.13; N, 10.43. $[\alpha]^{20}_D = +137$ (*c* = 2.1, $CHCl_3$).

*(1S,3R)-N¹-Mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (**10**)*

From $Pd_2(dba)_3$ (0.8 g, 0.87 mmol, 4 mol%), (±)-BINAP (1.2 g, 1.93 mmol, 9 mol%), NaO*t*Bu (6.1 g, 63.48 mmol), diamine **2** (3.0 g, 21.09 mmol), 2-bromo-1,3,5-trimethylbenzol (3.2 ml, 20.90 mmol) in toluene (360 ml). The product was obtained as a yellow oil (5.3 g, 20.35 mmol, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.78 (s, 2H, *H*-5′, *H*-3′), 4.21 (bs, 1H, *H*-N¹), 3.42 (dd, *J* = 7.7, 4.9 Hz, 1H, *H*-1), 2.25 (s, 6H, 6′-CH_3, 2′-CH_3), 2.21 (s, 3H, 4′-CH_3), 1.90–1.81 (m, 1H, *H*-5), 1.75–1.60 (m, 2H, *H*-4), 1.54–1.45 (m, 1H, *H*-5), 1.12 (s, 3H, *H*-8), 1.09 (s, 3H, *H*-7), 0.94 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.5 (*C*-1′), 129.7 (*C*-6′, *C*-2′), 129.6 (*C*-5′, *C*-3′), 128.7 (*C*-4′), 66.4 (*C*-1), 61.2 (*C*-3), 47.0 (*C*-2), 38.2 (*C*-4), 28.6 (*C*-5), 26.8 (*C*-8), 23.9 (*C*-6), 20.5 (*C*-4′), 19.4 (*C*-6′, *C*-2′), 17.1 (*C*-7) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 68.8 (bs, 1N, N^1), 50.6 (bs, 1N, N^3) ppm. IR (ATR) = 3319, 2961, 2866, 1584, 1481, 1386, 1370, 1300, 1237, 1156, 1137, 1110, 1059, 1026, 927, 890, 851, 810, 763 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 260 (24) $[M]^+$, 228 (22), 161 (8), 146 (21), 135 (100), 120 (8), 86 (9), 70 (46), 57 (30), 41 (11). HRMS (EI): calcd for $C_{17}H_{28}N_2$: 260.2247 $[M]^+$; found: 260.2248. Anal. Calcd for $C_{17}H_{28}N_2$: C, 78.41; H, 10.84; N, 10.76; found: C, 78.39; H, 10.80; N, 10.75. $[\alpha]^{20}_D = +79$ (*c* = 4.3, $CHCl_3$).

*(1S,3R)-N¹-(2-Isopropylphenyl)-2,2,3-trimethylcyclopentane-1,3-diamine (**11**)*

From $Pd_2(dba)_3$ (0.5 g, 0.55 mmol, 4 mol%), (±)-BINAP (0.8 g, 1.29 mmol, 9 mol%), NaO*t*Bu (4.1 g, 42.66 mmol), diamine **2** (2.0 g, 14.06 mmol), 1-bromo-2-isopropylbenzene (2.2 ml, 14.37 mmol) in toluene (350 ml). After workup, the product was obtained as a brown oil (1.8 g, 6.91 mmol, 49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.13–7.03 (m, 2H, *H*-5′, *H*-3′), 6.67–6.59 (m, 2H, *H*-6′, *H*-4′), 5.41 (s, 1H, *H*-N¹), 3.66 (s, 1H, *H*-1), 2.92–2.87 (m, 1H, 2′-*CH*(CH_3)$_2$), 2.25–2.17 (m, 1H, *H*-5), 1.84–1.78 (m, 1H, *H*-4), 1.64–1.56 (m, 2H, *H*-5, *H*-4), 1.25 (t, *J* = 7.1 Hz, 6H, 2′-CH(C*H*)$_3$), 1.16 (s, 3H, *H*-8), 1.02 (s, 3H, *H*-7), 0.97 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.3 (*C*-1′), 132.5 (*C*-2′), 126.6 (*C*-4′), 124.9 (*C*-6′), 115.9 (*C*-3′), 110.1 (*C*-5′), 62.8 (*C*-3), 61.5 (*C*-1), 47.3 (*C*-2), 38.5 (*C*-5), 29.3 (2′-*CH*(CH_3)$_2$), 27.5 (*C*-4), 26.8 (2′-CH*C*H_3), 25.1 (2′-CH*C*H_3), 22.5 (*C*-8), 22.1 (*C*-7), 17.3 (*C*-6) ppm. ^{15}N-NMR (51 MHz, $CDCl_3$) δ = 80.6 (br, 1N, N^1), 51.1 (br, 1N, N^3) ppm. IR (ATR) = 3306, 2957, 2870, 1602, 1579, 1509, 1451, 1364, 1258, 1056, 886, 735 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 261 (6) $[M]^+$, 260 (26), 243 (5), 228 (16), 201 (2), 200 (6), 186 (3), 161 (4), 146 (24), 135 (100), 120 (57), 110 (71), 93 (11), 71 (15), 70 (43), 57 (56), 42 (22). HRMS (ESI): calcd for $C_{17}H_{29}N_2$: 261.2331 $[M+H]^+$, found: 261.2324. Anal. Calcd for $C_{17}H_{28}N_2$: C, 78.41; H, 10.84; N, 10.76; found: C, 78.38; H, 10.34; N, 10.90. $[\alpha]^{20}_D = +172$ (*c* = 0.55, CH_2Cl_2).

*(1S,3R)-N¹-([1,1′-Biphenyl]-3-yl)-2,2,3-trimethylcyclopentane-1,3-diamine (**12**)*

From $Pd_2(dba)_3$ (0.08 g, 0.09 mmol, 4 mol%), (±)-BINAP (0.1 g, 0.16 mmol, 9 mol%), NaO*t*Bu (0.6 g, 6.24 mmol), diamine **2** (0.3 g, 2.11 mmol), 3-bromobiphenyl (0.4 ml, 2.40 mmol) in toluene (60 ml). After workup, the product was obtained as a yellow oil (0.3 g, 1.02 mmol, 48%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.67-7.64 (m, 2H, *H*-6″, *H*-5″), 7.50–7.45 (m, 2H, *H*-2″, *H*-3″), 7.40–7.36 (m, 1H, *H*-4″), 7.29–7.25 (m, 1H, *H*-6′), 6.93 (ddd, *J* = 7.5, 1.6, 0.9 Hz, 1H, *H*-5′), 6.90–6.87 (m, 1H, *H*-4′), 6.66 (ddd, *J* = 8.1, 2.4, 0.8 Hz, 1H, *H*-2′), 5.19 (br s, 1H, *H*-N³), 3.76 (d, *J* = 4.6 Hz, 1H, *H*-1), 2.32–2.25 (m, 1H, *H*-5), 1.87–1.80 (m, 1H, *H*-4), 1.71–1.63 (m, 2H, *H*-5, *H*-4), 1.19 (s, 3H, *H*-8), 1.04 (s, 3H, *H*-7), 1.02 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 149.1 (*C*-3′), 142.4 (*C*-1″), 142.2 (*C*-5′), 129.6 (*C*-5″, *C*-3″), 128.6 (*C*-6′), 127.3 (*C*-6″, *C*-2″), 127.1(*C*-1′), 115.6 (*C*-4″), 112.2 (*C*-5′), 112.1 (*C*-4′), 62.8 (*C*-1), 61.4 (*C*-3), 47.4 (*C*-2), 38.3 (*C*-4), 29.3 (*C*-5), 26.6 (C-8), 24.8 (C-7), 17.3 (C-6) ppm. ^{15}N-NMR (51 MHz, $CDCl_3$) δ = 84.1 (bs, 1N, N^1), 51.1 (bs, 1N, N^3) ppm. IR (ATR) = 3286, 3051, 2940, 2866, 1577, 1523, 1480, 1466, 1425, 1374, 1346, 1253, 1161, 1140, 1076, 1011, 927, 899, 845, 759, 713, 616 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 294 (15) $[M]^+$, 277 (4), 262 (9), 250 (3), 234 (8), 208 (4), 195 (8), 194 (4), 170 (17), 169 (100), 155 (13), 152 (6), 126 (11), 93 (5), 70 (5), 41 (4). HRMS (ESI): Calcd for $C_{20}H_{27}N_2$: 295.2174 $[M+H]^+$; found: 295.2172. Anal. Calcd for $C_{20}H_{28}N_2$: C, 81.59; H, 8.90; N, 9.51; found: C, 80.70; H, 9.17; N, 9.52. $[\alpha]^{20}_D = +88$ (*c* = 0.49, CH_2Cl_2).

*1,2,2-Trimethyl-N³-(2-(1-naphthyl)phenyl)cyclopentane-1,3-diamine (**13**)*

From $Pd_2(dba)_3$ (0.03 g, 0.03 mmol, 4 mol%), (±)-BINAP (0.04 g, 0.06 mmol, 9 mol%), NaO*t*Bu (0.2 g, 2.08 mmol), diamine **2** (0.1 g, 0.71 mmol), 1-(2-bromophenyl)naphthalene (0.2 mg, 0.70 mmol) in toluene (100 ml). After workup, the product was obtained as a mixture of diastereoisomers as a yellow solid (0.08 g, 0.23 mmol, 33%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.86 (dd, *J* = 16.7, 8.1 Hz, 4H, *H*-8″$_{D1}$, *H*-8″$_{D2}$, *H*-2″$_{D1}$, *H*-2″$_{D2}$), 7.72–7.62 (m, 2H, *H*-5″$_{D1}$, *H*-5″$_{D2}$), 7.58–7.28 (m, 10H, *H*-4″$_{D1}$, *H*-4″$_{D2}$, *H*-3″$_{D1}$, *H*-3″$_{D2}$, *H*-6′$_{D1}$, *H*-6′$_{D2}$, *H*-6″$_{D1}$, *H*-6″$_{D2}$, *H*-7‴$_{D1}$, *H*-7″$_{D2}$), 7.15 (dt, *J* = 7.5, 1.7 Hz, 2H, *H*-4′$_{D1}$, *H*-4′$_{D2}$), 6.79–6.74 (m, 4H, *H*-5′$_{D1}$, *H*-5′$_{D2}$, *H*-3′$_{D1}$, *H*-3′$_{D2}$) 4.67 (d, *J* = 9.1 Hz, 1H, *H*-N$^1_{D1}$), 4.50 (d, *J* = 9.1 Hz, 1H, *H*-N$^1_{D2}$), 3.81–3.48 (m, 2H, *H*-1$_{D1}$, *H*-1$_{D2}$), 2.24–1.90 (m, 2H, *H*-5$_{D1}$, *H*-5$_{D2}$), 1.67–1.55 (m, 2H, *H*-4$_{D1}$, *H*-4$_{D2}$), 1.42–1.20 (m, 4H, *H*-5$_{D1}$, *H*-5$_{D2}$, *H*-4$_{D1}$, *H*-4$_{D2}$), 0.96 (s, 3H, CH_3, *H*-8$_{D1}$), 0.94 (s, 3H, CH_3, *H*-8$_{D2}$), 0.82 (s, 3H, CH_3, *H*-7$_{D1}$), 0.78

(s, 3H, CH_3, H-7_{D2}), 0.53 (s, 3H, CH_3, H-6_{D1}), 0.37 (s, 3H, CH_3, H-6_{D2}) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.6 (C-$2'_{D1}$), 146.4 (C-$2'_{D2}$), 137.7 (C-$1''_{D1}$, C-$1''_{D2}$), 133.9 (C-$4''a_{D1}$), 133.7 (C-$4''a_{D2}$), 132.3 (C-$8''a_{D1}$), 132.1 (C-$8''a_{D2}$), 130.8 (C-$4'a_{D1}$, C-$4'a_{D2}$), 128.8 (C-$5''_{D1}$, C-$5''_{D2}$), 128.1 (C-$8''_{D1}$), 128.1 (C-$8''_{D2}$), 127.8 (C-$4''_{D1}$), 127.8 (C-$4''_{D2}$), 127.7 (C-$6''_{D1}$), 127.6 (C-$6''_{D2}$), 126.9 (C-$7''_{D1}$, C-$7''_{D2}$), 126.4 (C-$3''_{D1}$, C-$3''_{D2}$), 126.1 (C-$2''_{D1}$, C-$2''_{D2}$), 125.9 (C-$6'_{D1}$), 125.8 (C-$6'_{D2}$), 125.8 (C-$5'_{D1}$, C-$5'_{D2}$), 115.7 (C-$1'_{D1}$), 115.6 (C-$1'_{D2}$), 110.2 (C-$3'_{D1}$), 110.1 (C-$3'_{D2}$), 62.4 (C-1_{D1}), 62.2 (C-1_{D2}), 60.7 (C-3_{D1}), 60.6 (C-3_{D2}), 46.9 (C-2_{D1}, C-2_{D2}), 38.2 (C-4_{D1}, C-4_{D2}), 29.1 (C-5_{D1}), 28.8 (C-5_{D2}), 26.3 (C-8_{D1}), 26.2 (C-8_{D2}), 24.2 (C-6_{D1}), 23.9 (C-6_{D2}), 16.8 (C-7_{D1}), 16.7 (C-7_{D2}).

*(1R,3S)-1,2,2-Trimethyl-N^3-phenylcyclopentane-1,3-diamine (**14**)*

From $Pd_2(dba)_3$ (0.3 g, 0.33 mmol, 2.5 mol%), (±)-BINAP (0.5 g, 0.80 mmol, 6 mol%), NaO*t*Bu (1.7 g, 17.69 mmol), diamine **2** (2.5 g, 17.57 mmol), bromobenzene (1.8 mL, 17.14 mmol) in toluene (180 ml). After workup, the product was obtained as a brown oil (2.3 g, 10.53 mmol, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.15 (dd, J = 8.6 Hz, H-6′, H-2′), 6.62 (m, 3H, H-3′, H-4′, H-5′), 5.2-4.7 (s (br), 1H, H-N^1), 3.65 (m, 1H, H-3), 2.21 (m, 1H, H-4), 1.77 (m, 1H, H-5), 1.59 (m, 2H, H-5, H-4), 1.38–1.20 (s (br), 2H, H-N^3), 1.14 (s, 3H, H-8), 0.96 (s, 3H, H-7), 0.95 (s, 3H, H-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 148.7 (C-1′), 129.2 (C-6′, C-2′), 116.3 (C-4′), 113.1 (C-5′, C-33), 62.6 (C-3), 61.3 (C-1), 47.2 (C-2), 38.2 (C-5), 29.1 (C-4), 26.5 (C-8), 24.5 (C-6), 17.2 (C-7) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 83.8 (bs, 1N, N^3), 51.0 (bs, 1N, N^1) ppm. IR (ATR) = 3401, 3360, 3300, 3083, 3052, 3020, 2959, 2867, 1909, 1595, 1500, 1468, 1312, 854, 742, 690, 502 cm^{-1}. MS (EI, 70 eV): m/z (%) = 218 (85) [M]$^+$, 201 (27), 186 (77), 132 (40), 126 (97), 119 (72), 109 (68), 93 (100), 77 (32), 70 (72), 57 (65), 41 (30). HRMS (ESI): calcd for $C_{14}H_{23}N_2$: 219.1861 [M+H]$^+$; found: 219.1854. Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83; found: C, 76.86; H, 10.11; N, 12.69. $[\alpha]^{20}_D$ = +112.2 (c = 1.05, CH_2Cl_2).

*(1R,3S)-1,2,2-Trimethyl-N^3-(quinolin-2-yl)cyclopentane-1,3-diamine (**15**)*

From $Pd_2(dba)_3$ (0.3 g, 0.33 mmol, 4 mol%), (±)-BINAP (0.4 g, 0.64 mmol, 9 mol%), NaO*t*Bu (2.0 g, 20.81 mmol), diamine **2** (1.0 g, 7.03 mmol), 2-chloroquinoline (1.2 g, 7.34 mmol) in toluene (180 ml). After workup, the product was obtained as a yellow solid (1.0 g, 3.71 mmol, 53%).

M.p. 81°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.9 Hz, 1H, H-4′), 7.61 (d, J = 8.4 Hz, 1H, H-8′), 7.52 (dd, J = 7.9, 1.3 Hz, 1H, H-5′), 7.47 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, H-7′), 7.13 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H, H-6′), 6.57 (d, J = 8.9 Hz, 1H, H-3′), 6.41 (bs, 1H, H-N^3), 4.44 (s, 1H, H-3), 2.38–2.26 (m, 1H, H-4), 1.87–1.76 (m, 1H, H-5), 1.70–1.58 (m, 2H, H-5, H-4), 1.16 (s, 3H, H-8), 0.99 (s, 3H, H-7), 0.95 (s, 3H, H-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 157.0 (C-2′), 148.5 (C-8′a), 136.6 (C-4′), 129.2 (C-7′), 127.3 (C-5′), 126.1 (C-8′), 123.3 (C-4′a), 121.3 (C-6′), 112.2 (C-3′), 61.8 (C-1), 60.4 (C-3), 47.6 (C-2), 38.2 (C-5), 29.7 (C-4), 26.6 (C-8), 24.7 (C-7), 17.3 (C-6) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 237.8 (bs, 1N, N-1′), 105.1 (bs, 1N, N^3), 52.5 (bs, 1N, N^1) ppm. IR (ATR) = 3308, 2961, 2868, 1658, 1615, 1563, 1515, 1487, 1421, 1398, 1367, 1307, 1255, 1211, 1140, 1119, 1062, 1021, 928, 885, 814, 779, 752, 618 cm^{-1}. MS (EI, 70 eV): m/z (%) = 269 (11) [M]$^+$, 252 (21), 237 (5), 199 (21), 183 (12), 169 (21), 144 (100), 128 (24), 117 (14), 101 (5), 70 (8), 57 (10), 41 (7). HRMS (EI): calcd for $C_{17}H_{23}N_3$: 269.1886 [M]$^+$; found: 269.1877. $[\alpha]^{20}_D$ = +19 (c = 2.7, $CHCl_3$).

General Procedure for the Henry Reaction

The appropriate ligand (1–1.5 equiv.) and Lewis acid (0–1.5 equiv.) were dissolved in a solvent (1 ml) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. A solution of aldehyde (10 equiv.) and base (0.2 equiv.) in a solvent (0.5 ml) was added and the reaction mixture was stirred at various temperatures over 15 min. Nitroalkane (100–200 equiv.) was added and the solution was stirred for the specific time at various temperatures. The resulting mixture was filtered through a silica gel column (10 cm^3) with EtOAc (100 ml) to remove the catalyst. The solvent was removed under reduced pressure at <30°C and the crude product was purified by silica gel flash column chromatography to give the corresponding β-nitro alcohol. The enantiomeric excess was determined by chiral HPLC analysis. The absolute configuration was assigned by comparison to literature values (for yields and enantiomeric excess see Tables 3 and 4).

*(S)-2-Nitro-1-phenylethanol (**16**)*

The compound was prepared according to the general procedure and purified by column chromatography (*n*-hexane/EtOAc, 8:2) to give a colorless oil (93% yield). HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85/15 v/v, 1 ml min^{-1}, 25°C, UV = 250 nm): t_{minor} = 11.76 min, t_{major} = 14.05 min; 77% ee. Spectral data were consistent with literature values.[5h,o]

*(S)-1-(2-Methoxyphenyl)-2-nitroethanol (**23**)*

The compound was prepared according to the general procedure and purified by column chromatography (*n*-hexane/EtOAc, 8:2) to give a yellow oil (65% yield). HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 1 ml min^{-1}, 25°C, UV = 250 nm): t_{minor} = 10.32 min, t_{major} = 11.55 min; 83% ee. Spectral data were consistent with literature values.[5h,o]

*(S)-2-Nitro-1-(2-nitrophenyl)ethanol (**21**)*

The compound was prepared according to the general procedure and purified by column chromatography (*n*-hexane/EtOAc, 7:3) to give an orange solid (68% yield). HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 1 ml min^{-1}, 25°C, UV = 250 nm): t_{minor} = 13.36 min, t_{major} = 14.61 min; 82% ee. Spectra data were consistent with literature values.[5h,o]

*(S)-2-Nitro-1-(3-nitrophenyl)ethanol (**22**)*

The compound was prepared according to the general procedure and purified by column chromatography (*n*-hexane/EtOAc, 8:2) to give a yellow solid (57% yield). HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 1 ml min^{-1}, 25°, UV = 250 nm): t_{minor} = 20.56 min, t_{major} = 22.72 min; 59% ee. Spectral data were consistent with literature values.[5h,o]

*(S)-1-(3-Chlorophenyl)-2-nitroethanol (**20**)*

The compound was prepared according to the general procedure and purified by column chromatography (*n*-hexane/EtOAc, 8:2) to give a yellow oil (65% yield). HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 1 ml min^{-1}, 25°C, UV = 250 nm): t_{minor} = 11.44 min, t_{major} = 13.97 min; 63% ee. Spectral data were consistent with literature values.[5h,o]

*2-Nitro-1-(2-nitrophenyl)propan-1-ol (**24**)*

The compound was prepared according to the general procedure and purified by column chromatography (*n*-hexane/EtOAc, 8:2)

to give a brown oil (73% yield as a mixture of diastereoisomers), dr (*anti*/*syn*) = 38:62 determined by ^{1}H NMR analysis. HPLC (combination of Chiralpak AD-H column + Chiralpak AS-H column, *n*-hexane/*i*-PrOH, 95/5 v/v, 0.5 ml min^{-1}, 25°C, UV = 250 nm): t_{major} = 59.65 min, t_{minor} = 63.41 min for *anti*-isomer, t_{minor} = 74.88 min, t_{major} = 81.81 min for *syn*-isomer; 53% ee for *anti*-isomer, 57% ee for *syn*-isomer. Spectra data were consistent with literature values.[5h,o]

Results and Discussion

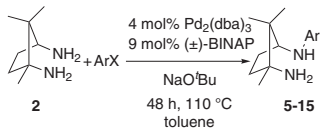
In order to explore the different reactivities of the two amine groups of **2** in a Buchwald–Hartwig amination, the diamine **2** was treated in a modified literature procedure[10] with 1 equiv. of different bromoarenes in the presence of $Pd_2(dba)_3$, BINAP and NaO^{t}Bu.

The results are summarized in Table 1. In general, good to excellent yields could be obtained of the desired regioisomers. The reaction tolerated arenes with various substitution patterns. The sterically hindered 2-bromomesitylene, for example, gave an excellent yield of 97% (Table 1, entry 6). Bromobiphenyls (Table 1, entries 4 and 8) as well as 2-bromonaphthyl (Table 1, entry 5) could be applied. Heteroaromatic compounds could be also used. 2-Bromopyridine resulted in a yield of 91% (Table 1, entry 1). In order to explore also chloroarenes in the reaction, 2-chloroquinoline was applied in the reaction and compound **15** was isolated in a yield of 53% (Table 1, entry 11). Due to the axial chirality of 1-(2-bromophenyl)naphthalene the product **13** was isolated as a mixture of diastereomers in 33% yield.

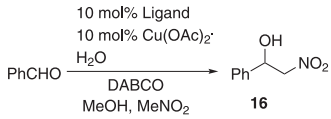
In all cases only the desired regioisomers were observed and identified by ^{1}H–^{13}C NMR-HMBC. The high regioselectivity is remarkable considering the high reaction temperature of 100°C.

With these new diamines available their potential as ligands in the copper-catalyzed asymmetric Henry reaction was explored (Scheme 2). First, different ligands were explored under the same conditions. 10 mol% $Cu(OAc)_2.H_2O$ and 10 mol% ligand were mixed in methanol and after the addition of 3 mol% DABCO,

Table 1. Regioselective arylation of diamine **2** with various bromoarenes via the Buchwald–Hartwig amination



Entry	Arene	Product	Yield (%)
1	2-Bromopyridine	**5**	91
2	2-Bromoanisole	**6**	99
3	2-Bromotoluene	**7**	82
4	2-Bromo-1,1′-biphenyl	**8**	73
5	1-Bromonaphthalene	**9**	64
6	2-Bromo-1,3,5-trimethylbenzol	**10**	97
7	1-Bromo-2-isopropylbenzene	**11**	49
8	3-Bromobiphenyl	**12**	48
9	1-(2-Bromophenyl)naphthalene	**13**	33
10	Bromobenzene	**14**	60
11	2-Chloroquinoline	**15**	53



Scheme 2. Asymmetric addition of nitromethane to benzaldehyde catalyzed by copper(II) acetate and ligands 5–11.

benzaldehyde and 10 equiv. of nitromethane the reaction was stirred at 0°C for 24 h. The results are summarized in Table 2. Next to the new prepared ligands, the diamines **18**[9] and **19**[9] with two secondary amine functions were also explored in the reaction. While **18** and **19** resulted in a small enantiomeric excess of the *R* enantiomer of the Henry product (Table 2, entries 11 and 12), the other diamines gave the *S* enantiomer in excess. The highest enantiomeric excess was obtained with diamine **8** (Table 2, entry 4). As can be seen from Table 2, in general a sterically demanding substituent at one *ortho* position of the arene ring increases the enantiomeric excess. If the aryl substituent becomes too large, as in the case of ligand **10**, the yield decreases (Table 2, entry 6).

In order to further optimize the reaction conditions with the new ligands, different influences of solvents, copper sources and bases were explored with ligand **7**. The results are summarized in Table 3. From the table it is evident that methanol is the best solvent for the presented system. The use of ethanol and isopropanol resulted in a lower yield (Table 3, entries 2 and 3). When copper chlorides were used, lower yields and enantioselectivities were obtained (Table 3, entries 4, 15 and 16). A decrease in temperature from 0 to −25°C increased the enantiomeric excess only slightly. However, the yield decreased from 82% to 39% (Table 3, entry 11).

Table 2. Asymmetric Henry reaction of benzaldehyde with nitromethane in the presence of various diamine ligands, 10 mol% $Cu(OAc)_2.H_2O$ and DABCO in methanol at 0°C for 24 h

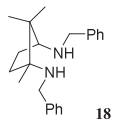
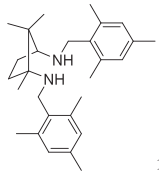
Entry	Ligand	Yield (%)	ee (%)	Config.
1	**5**	18	4	*S*
2	**6**	60	38	*S*
3	**7**	82	45	*S*
4	**8**	56	69	*S*
5	**9**	41	37	*S*
6	**10**	34	47	*S*
7	**11**	64	45	*S*
8	**12**	32	30	*S*
9	**13**	84	48	*S*
10	**14**	78	31	*S*
11	 **18**	57	7	*R*
12	 **19**	26	11	*R*

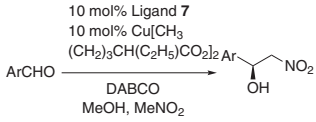
Table 3. Asymmetric Henry reaction of benzaldehyde with nitromethane in the presence of 10 mol% diamine ligand **7**, 10 mol % copper salt, and 3 mol% DABCO under different reaction conditions for 24 h

Entry	Solvent	Copper salt	*T* (°C)	Yield (%)	ee (%)
1	MeOH	$Cu(OAc)_2.H_2O$	0	82	45
2	EtOH	$Cu(OAc)_2.H_2O$	0	53	49
3	*i*PrOH	$Cu(OAc)_2.H_2O$	0	47	46
4	MeOH	CuCl	0	65	34
5[a]	MeOH	$Cu(OAc)_2.H_2O$	0	69	47
6[b]	MeOH	$Cu(OAc)_2.H_2O$	0	75	41
7[c]	MeOH	$Cu(OAc)_2.H_2O$	0	60	47
8	MeOH	—	0	68	0
9	MeOH	$Cu(OAc)_2.H_2O$	r.t.	63	38
10	MeOH	—	0	59	0
11	MeOH	$Cu(OAc)_2.H_2O$	−25	39	53
12[d]	MeOH	$Cu(OAc)_2.H_2O$	−25	42	54
13	THF	$Cu(OAc)_2.H_2O$	−25	11	73
14	H_2O	$Cu(OAc)_2.H_2O$	r.t.	21	31
15	THF	CuCl	0	56	36
16	MeOH	$CuCl_2$	0	60	16
17	MeOH	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	92	52
18	THF	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	26	72
19	CH_2Cl_2	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	9	56
20	MeOH	$Cu[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2$	0	93	77
21[e]	MeOH	$Cu(OAc)_2.H_2O$	0	69	46
22[f]	MeOH	$Cu(OAc)_2.H_2O$	0	56	69
23[f]	THF	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	21	84
24[f]	MeOH	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	74	72
25[f]	CH_2Cl_2	$Cu[C_6H_{11}(CH_2)_3CO_2]_2$	0	5	76
26[f]	MeOH	$Cu[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2$	0	59	74

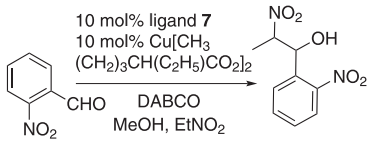
[a] 3 mol% Et_3N.
[b] 15 mol% diamine **7**.
[c] $Cu(OAc)_2.H_2O$ 15 mol%.
[d] reaction time 48 h.
[e] 200 equiv. $MeNO_2$.
[f] reaction was carried out with ligand **8**.

A longer reaction time of 48 h did not increase the yield (Table 3, entry 12). The use of THF could increase the enantiomeric excess but resulted in a lower yield (Table 3, entry 13). Next, the influence of different carboxylate counter-anions was investigated. With copper(II)-cyclohexanebutyrate a slight increase in the yield and enantioselectivity was found (Table 3, entry 17) compared to copper(II)-acetate. Interestingly, copper(II)-2-ethylhexanoate resulted in the same increase in yield but the enantioselectivity increased even further to 77% ee. Obviously, the presence of a racemic stereocenter in the ethylhexanoate would result in the formation of two diastereomeric complexes in the case where one carboxylate ligand is replaced with the diamine ligand. Whether both diastereomeric complexes have the same catalytic reactivity and selectivity cannot be determined. Finally, ligand **8** was investigated under different reaction conditions (Table 3, entries 22–26). Although the obtained enantioselectivities were slightly higher, the obtained yields were lower than with ligand **7**. Hence, ligand **7** was further used in the reaction of nitromethane with different aldehydes, as show in Table 4.

Table 4. Asymmetric Henry reaction of aryl aldehydes with nitromethane in the presence of 10 mol% diamine ligand **7**, 10 mol% copper(II)-2-ethylhexanoate and 3 mol% DABCO for 24 h



Entry	Ar	*T* (°C)	Product	Yield (%)	ee (%)
1	Ph	0	**16**	93	77
2	3-Cl-C_6H_4	0	**20**	65	63
3	2-NO_2-C_6H_4	0	**21**	68	82
4	3-NO_2-C_6H_4	0	**22**	57	59
5	2-MeO-C_6H_4	0	**23**	65	83



Scheme 3. Asymmetric Henry reaction of 2-nitrobenzene with nitroethane.

Electron-rich and electron-poor benzaldehydes were explored. While the yield decreased slightly, the enantioselectivities increased with substituents in the *ortho* position up to 83% (Table 4, entries 3 and 5).

Finally, a reaction was carried out with nitroethane and *ortho*-nitrobenzaldehyde as depicted in Scheme 3 and the desired product was isolated in 73% yield. The resulting *syn*/*anti* selectivity of the diastereomers was 34/66. The *syn* diastereomer had an enantiomeric excess of 57% and the *anti* diastereomer had an enantiomeric excess of 53%.

Conclusion

A highly regioselective arylation of diamine **2**, via a Buchwald–Hartwig amination, gave new chiral diamine ligands incorporating a primary and arylated secondary amine function. The resulting ligands were explored first in an asymmetric Henry reaction. Enantiomeric excesses of up to 84% could be obtained. In the case of ligands incorporating two secondary amine functions the opposite enantiomer was obtained, although in low excess.

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