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Asymmetric, Catalytic Phenyl Transfer to Imines:
Highly Enantioselective Synthesis of Diarylmethylamines

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1 General

^{1}H and ^{13}C NMR-spectra were recorded on a Varian VXR 300 (300/75 MHz) or Varian Inova (400/100 MHz) instrument. Chemical shifts are reported with tetramethyl silane (TMS) as internal standard. Abbreviations for ^{1}H NMR: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad, Ar=aromatic. Preparative liquid chromatography was performed on straight phase silica gel (Merck 60, 230-400 mesh, 0.040 – 0.063 mm) with the eluent indicated. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1750. Mass spectra were recorded on a Finnigan SSQ 7000, high resolution mass spectra were recorded on a Finnigan MAT 95, both with EI ionization. Optical rotations were measured with a Perkin Elmer P241 polarimeter in a 10 cm cell with the solvent indicated. Melting points were measured on a Büchi B-540 and are uncorrected. Elemental analyses were carried out in the "Mikroanalytisches Labor des Instituts für Organische Chemie der RWTH Aachen" on a Elementar Vario EL. Chiral HPLC analyses were performed on Gynkotek (Dionex)-HPLC using Chiralcel OD or OD-H columns.

All reactions were conducted in dried glassware under an atmosphere of dry argon. All chemicals and solvents were used as received unless otherwise stated. Toluene was distilled under argon from Na/benzophenone. The *N*-formyl-α-(*p*-tolylsulfonyl)benzylamine starting materials were prepared according to literature procedures.[1]

2 Phenylzinc additions to imines (general protocol)

In a glovebox, a well-dried Schlenk-flask was charged with diphenylzinc (83 mg, 0.375 mmol). The flask was sealed and removed from the glovebox. Freshly distilled toluene (3 mL) was added followed by diethylzinc (39 µL, 0.375 mmol). After stirring of the mixture for 30 min at room temperature, (R_p,S)-**6** (11 mg, 0.025 mmol) was added, and stirring at room temperature was continued until deprotonation of the ligand was complete (change of color from orange to bright yellow). The resulting solution was then cooled to –20 °C and stirred for additional 10 min at this temperature, before the substrate (0.25 mmol) was added directly in one portion. The Schlenk flask was sealed, and the reaction mixture was stirred at –20 °C for 12 h. The reaction was then quenched by addition of 1 N HCl followed by extraction with dichloromethane. The combined organic layers were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Concentration and purification by column chromatography (silicagel; hexanes/ethyl acetate = 3:1) gave the pure products **9** in 75-89% yield. The *ee* was determined by HPLC on a chiral stationary phase.

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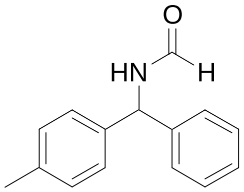
[1] J. Sisko, M. Mellinger, P. W. Sheldrake, N. H. Baine, *Tetrahedron Lett.* **1996**, *37*, 8113.

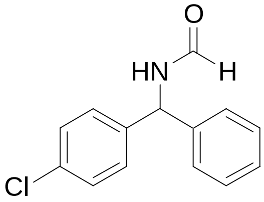
3 Analytical data for phenylation products

N-(Phenyl-*p*-tolyl-methyl)-formamide (9a)



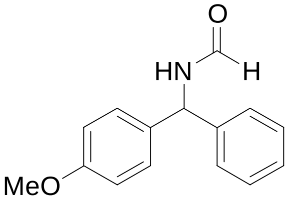
According to the general protocol, *N*-[(toluene-4-sulfonyl)-*p*-tolylmethyl]-formamide (76 mg, 0.25 mmol), (R_p,S)-**6** (11 mg, 0.025 mmol, 10 mol%), diphenylzinc (83 mg, 0.375 mmol) and diethylzinc (39 µL, 0.375 mmol) afforded **9a** within 12 h at –20 °C as a white solid. HPLC: Chiralcel OD-H, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 20 °C, 230 nm, R_t = 32.7 min minor, 45.6 min major enantiomer, 97% *ee*. $[\alpha]_D^{20}$ = + 23.9 (c = 1.0; $CHCl_3$). Mp: 82 °C. The NMR shows a 4:1 mixture of two rotamers (rotation of the *N*-formyl group), major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 6.26 (d, J = 8.0 Hz, 1H, C*H*), 6.36 (s, br, 1H, N*H*), 7.02-7.37 (m, 9 H, H_{Ar}), 8.23 (s, 1H, C*H*O) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.44, 55.76, 127.51, 127.53, 127.76, 128.90, 129.63, 137.56, 138.22, 141.29, 160.37 ppm. MS (EI, 70 eV), *m/z* (rel. intensity) = 225 (100) [M^+], 210 (25), 165 (44). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3308, 1655, 1527, 1384, 700. Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.65; H, 6.65; N, 6.14.

N-[(4-Chloro-phenyl)-phenyl-methyl]-formamide (9b):



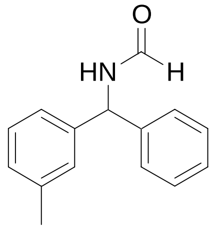
According to the general protocol, *N*-[(4-chlorophenyl)-(toluene-4-sulfonyl)]-formamide (81 mg, 0.25 mmol), (R_p,S)-**6** (11 mg, 0.025 mmol, 10 mol%), diphenylzinc (83 mg, 0.375 mmol) and diethylzinc (39 µL, 0.375 mmol) afforded **9b** within 12 h at −20 °C as a white solid. HPLC: Chiralcel OD, heptane/*i*-PrOH = 90:10, 0.9 mL/min, 25 °C, 230 nm, R_t = 15.5 min minor, 24.1 min major enantiomer, 94% *ee* (*R*). $[\alpha]_D^{20}$ = +1.0 (c = 0.6; CH_2Cl_2). Mp: 130 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.24 (d, *J* = 7.9 Hz, 1H, C*H*), 6.49 (s, br, 1H, N*H*), 7.00-7.37 (m, 9 H, H_{Ar}), 8.21 (s, 1H, C*H*O) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 55.51, 127.63, 128.14, 128.93, 129.06, 129.11, 133.66, 139.64, 140.63, 160.47 ppm. MS (EI, 70 eV), *m/z* (rel. intensity) = 245 (100) [M^+], 165 (64). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3281, 1640, 1492. Anal. Calcd. for $C_{14}H_{12}NOCl$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.37; H, 4.87; N, 5.43.

N-[(4-Methoxy-phenyl)-phenyl-methyl]-formamide (9c):



According to the general protocol, *N*-[(4-methoxyphenyl)-(toluene-4-sulfonyl)]-formamide (80 mg, 0.25 mmol), ligand (R_p,S)-**6** (11 mg, 0.025 mmol, 10 mol%), diphenylzinc (83 mg, 0.375 mmol) and diethylzinc (39 µL, 0.375 mmol) afforded **9c** within 12 h at −20 °C as a white solid. HPLC: Chiralcel OD, heptane/*i*-PrOH = 90:10, 0.9 mL/min, 25 °C, 230 nm, R_t = 26.7 min minor, 35.0 min major enantiomer, 97% *ee*. $[\alpha]_D^{20}$ = +40.4 (c = 0.9; $CHCl_3$). Mp: 89 °C The NMR shows a 6:1 mixture of two rotamers (rotation of the *N*-formyl group), major rotamer: ^{1}H-NMR (300 MHz, CDCl$_3$): δ 3.74 (s, 3H, C*H*$_3$) 6.23 (d, *J* = 8.2 Hz, 1H, C*H*), 6.62 (s, br, 1H, N*H*), 7.05-7.37 (m, 9 H, H$_{Ar}$), 8.16 (s, 1H, C*H*O) ppm. ^{13}C-NMR (75 MHz, CDCl$_3$): δ 55.49, 55.66, 114.50, 127.37, 127.72, 128.72, 128.88, 133.43, 141.40, 159.13, 160.51 ppm. MS (EI, 70 eV), *m/z* (rel. intensity) = 241 (100) [M^+], 212 (16), 196 (18), 181 (20). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3311, 1655, 1515. HRMS Calcd. for $C_{15}H_{15}NO_2$: 241.110279. Found: 241.110204.

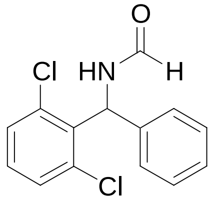
N-(Phenyl-m-tolyl-methyl)-formamide (9d):



According to the general protocol, *N*-[(toluene-4-sulfonyl)-*m*-tolylmethyl]-formamide (76 mg, 0.25 mmol), (*R*$_p$,*S*)-**6** (11 mg, 0.025 mmol, 10 mol%), diphenylzinc (83 mg, 0.375 mmol) and diethylzinc (39 µL, 0.375 mmol) afforded **9d** within 12 h at –20 °C as a white solid. HPLC: Chiralcel OD-H, heptane/*i*-PrOH = 95:5, 0.5 mL/min, 20 °C, 230 nm, R$_t$ = 76.5 min major, 88.7 min minor enantiomer, 89% *ee*. $[\alpha]_D^{20}$ = +6.5 (c = 1.0; CHCl$_3$). Mp: 81 °C. The NMR shows a 4:1 mixture of two rotamers (rotation of the *N*-formyl group), major rotamer: ^{1}H-NMR (300 MHz, CDCl$_3$): δ 2.31 (s, 3H, C*H*$_3$), 6.27 (br, 2H, C*H*, N*H*), 6.97-7.37 (m, 9 H, H$_{Ar}$), 8.26 (s, 1H, C*H*O) ppm. ^{13}C-NMR (75 MHz, CDCl$_3$): δ 21.87, 56.04, 124.60, 127.56, 127.80, 128.33, 128.65, 128.87, 128.93, 138.67, 141.04, 141.20, 160.32 ppm. MS (EI, 70 eV), *m/z* (rel. intensity) = 225 (100) [M^+], 210 (19), 165 (37).

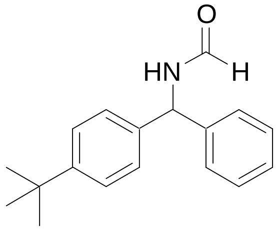
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3229, 1681, 1653, 1382, 702. HRMS: Calcd. for $C_{15}H_{15}NO$: 225.115401. Found: 225.115401.

***N*-[(2.6-Dichloro-phenyl)-phenyl-methyl]-formamide (9e):**



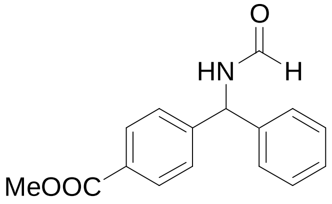
According to the general protocol, *N*-[(2,6-dichlorophenyl)-(toluene-4-sulfonyl)]-formamide (90 mg, 0.25 mmol), (R_p,S)-**6** (11 mg, 0.025 mmol, 10 mol%), diphenylzinc (83 mg, 0.375 mmol) and diethylzinc (39 µL, 0.375 mmol) afforded **9e** within 18 h at −20°C as a white solid. HPLC: Chiralcel OD, heptane/*i*-PrOH = 95:5, 1.0 mL/min, 30°C, 230 nm, R_t = 24.4 min major, 35.1 min minor enantiomer, 95% *ee*. $[\alpha]_D^{20}$ = +59.5 (c = 1.0; $CHCl_3$). Mp: 148 °C. The NMR shows a 4.5:1 mixture of two rotamers (rotation of the *N*-formyl group), major rotamer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.08-7.15 (m, 2H, C*H*, N*H*), 7.17-7.42 (m, 8 H, H_{Ar}), 8.37 (s, 1H, C*H*O) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 51.09, 126.03, 127.57, 128.80, 129.63, 129.88, 135.86, 136.11, 138.38, 160.76 ppm. MS (EI, 70 eV), *m/z* (rel. intensity) = 279 (50) [M^+], 244 (100), 199 (40). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3362, 1684, 1496, 698. Anal. Calcd. for $C_{14}H_{11}NOCl_2$: C, 60.02; H, 3.96; N, 5.00. Found: C, 59.75; H, 4.15; N, 4.85.

N-[(4-*tert*-butyl-phenyl)-phenyl-methyl]-formamide (9f):



According to the general protocol, *N*-[(4-*tert*-butylphenyl)-(toluene-4-sulfonyl)]-formamide (87 mg, 0.25 mmol), (R_p,*S*)-**6** (11 mg, 0.025 mmol, 10 mol%), diphenylzinc (83 mg, 0.375 mmol) and diethylzinc (39 μL, 0.375 mmol) afforded **9f** within 12 h at –20 °C as a colorless oil. HPLC: Chiralcel OD-H, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 20 °C, 230 nm, R_t = 21.8 min minor, 37.5 min major enantiomer, 96% *ee*. $[\alpha]_D^{20}$ = +37.6 (c = 0.5; $CHCl_3$). The NMR shows a 4:1 mixture of two rotamers (rotation of the *N*-formyl group), major rotamer: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 9H, CH_3) 6.27 (d, *J* = 8.2 Hz, 1H, C*H*), 6.38 (s, br, 1H, N*H*), 7.07-7.39 (m, 9 H, H_{Ar}), 8.23 (s, 1H, C*H*O) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 31.73, 34.91, 55.73, 125.86, 127.34, 127.54, 127.74, 129.11, 138.13, 141.255, 150.77, 160.40 ppm. MS (EI, 70 eV), *m/z* (rel. intensity) = 267 (100) [M^+], 210 (92), 182 (34), 104 (17). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2963, 1660, 757, 701. HRMS Calcd. for $C_{18}H_{21}NO$: 267.162314. Found: 267.162267.

4-(Formylamino-phenyl-methyl)-benzoic acid methyl ester (9g):



According to the general protocol, 4-[Formylamino-(toluene-4-sulfonyl)-methyl]-benzoic acid methyl ester (87 mg, 0.25 mmol), ligand (R_p,S)-**6** (11 mg, 0.025 mmol, 10 mol%), diphenylzinc (83 mg, 0.375 mmol) and diethylzinc (39 µL, 0.375 mmol) afforded **9f** within 12 h at −20 °C as a white solid. HPLC: Chiralcel OD, heptane/*i*-PrOH = 95:5, 0.9 mL/min, 20 °C, 230 nm, R_t = 27.2 min minor, 39.2 min major enantiomer**,** 95% *ee*. $[\alpha]_D^{20}$ = −7.5 (c = 1.0; $CHCl_3$). Mp: 117 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, $COOCH_3$), 6.29 (d, J = 7.9 Hz, 1H, C*H*), 6.92 (d, J = 7.9 Hz, 1H, N*H*), 7.15 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.22-7.32 (m, 5 H, H_{Ar}), 7.93 (d, J = 8.3 Hz, 2H, H_{Ar}), 8.26 (s, 1H, C*H*O) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ: 52.53, 55.87, 127.53, 127.74, 128.17, 129.11, 129.53, 130.16, 140.52, 146, 23, 160.70, 166.93 ppm. MS (EI, 70 eV), *m/z* (rel. intensity) = 269 (100) [M^+], 254 (33), 165 (43). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3313, 1720, 1658, 1281, 702. HRMS. Calcd. for $C_{16}H_{15}NO_3$:269.105193. Found: 269.105159.

Deprotection of *N*-[(4-Chloro-phenyl)-phenyl-methyl]-formamide (9b):

N-[(4-Chloro-phenyl)-phenyl-methyl]-formamide (**9b**) (145 mg, 0.6 mmol, 94% *ee*) was dissolved in methanol (5 mL), conc. HCl (1 mL) was added and the solution was stirred at 50 °C for 4 h. The reaction mixture was poured into water (30 mL) and extracted with diethylether. Under ice-cooling, the aqueous layer was basified with NaOH (pH 13-14) and extracted with diethylether (2 x 20 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo to give *C*-(4-chloro-phenyl)-*C*-phenyl-methylamine (**10b**, 127 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ = −7.4 (c = 0.4; EtOH). The literature value for

(*S*)-*C*-(4-chloro-phenyl)-*C*-phenyl-methylamine (**10b**) is given as $[\alpha]_D^{20}$ = +10.8 (c = 2.18; EtOH).[2] The determination of the enantiomeric excess of the free amine by means of HPLC remained unsuccessful and was therefore determined indirectly by HPLC analysis of *N*-[(4-chloro-phenyl)-phenyl-methyl]acetamide (**11b**) obtained by treatment of **10b** with acetic anhydride and triethylamine. HPLC: Chiralcel OD-H, heptane/*i*-PrOH = 90:10, 0.5 mL/min, 20 °C, 230 nm, R_t = 17.3min minor, 25.1 min major enantiomer, 94% *ee* (*R*).

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[2] G. R. Clemo, C. Gardner, R. Raper, *J. Chem. Soc.* **1939**, 1958.