Catalytic Enantioselective O–H Insertion Reactions

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Supporting Information

I. General

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen or argon. 1,2-Dichloroethane was purchased from Fluka (anhydrous); other solvents were purified and dried according to generally accepted procedures. 2-Trimethylsilylethanol, 2,2,2-trifluoroethanol, benzyl alcohol, *p*-methoxybenzyl alcohol, and phenol were purchased, degassed, and stored under nitrogen; all other alcohols were distilled from magnesium under an argon atmosphere. Copper(II) triflate, along with all other chemicals (including the various copper salts) were purchased, stored under inert gas, and used without further purification, unless noted otherwise. Ligand **1** was prepared according to a literature procedure.[1]

Mass spectrometric measurements were performed on an Agilent Technologies LC/MSD SL system (1100 Series). HPLC analyses were carried out on an Agilent 1100 Series system with Daicel Chiralpak® columns in hexanes/*iso*-propanol mixtures. GC analysis (chiral) was performed on a Hewlett-Packard HP 5890 Series II Plus apparatus.

II. Preparation of the Diazo Compounds

General Procedure. All of the α-diazo acetates were prepared via direct diazo transfer: Under an inert atmosphere, the α-aryl acetate was dissolved in a small amount of MeCN at room temperature. DBU (1.2-5.0 equiv) was added, and then tosyl azide (1.2-4.5 equiv) was added dropwise over 30 minutes with stirring. After 12 h, the solvent was evaporated, and the residue was dissolved in Et_2O and a 5% aqueous KOH solution. The layers were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. If a large excess of tosyl azide was employed in order to achieve an acceptable conversion (or if tosyl azide and the desired α-diazo acetate have the same R_f value in other solvent systems), the tosyl azide was removed from the crude α-diazo acetate by chromatography on deactivated silica gel (toluene/Et_3N as the eluent). Further purification was achieved by flash chromatography on deactivated silica gel (hexanes/EtOAc/Et_3N as the eluent).

All of the diazo compounds, except methyl α-diazo-α-2-fluorophenyl-acetate and ethyl α-diazo-α-2-methylphenyl-acetate have previously been reported.

Ethyl α-diazo-α-(2-methylphenyl)acetate. The general procedure was followed, using ethyl 2-(methylphenyl)acetate (1.07 g, 6.00 mmol), MeCN (10 mL), DBU (4.02 g, 3.95 mL, 26.4 mmol), and tosyl azide (4.73 g, 24.0 mmol). The excess tosyl azide was removed by flash chromatography (toluene/Et_3N 20:0.1), and the resulting residue was purified by flash chromatography (hexanes/EtOAc/Et_3N 20:1:0.1) to yield the title compound as a yellow oil: 0.87 g (4.26 mmol, 71%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.39 (m, 1H), 7.31-7.24 (m, 3H), 4.32 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 137.8, 131.01, 130.97, 129.0, 126.6, 124.4, 61.3, 20.2, 14.7. The resonance of the carbon that bears the diazo group was not detected.

IR (film) 3065, 2982, 2088, 1704, 1491, 1462, 1369, 1337, 1292, 1257, 1173, 1156, 1037, 756, 661.

Methyl α-diazo-α-(2-fluorophenyl)acetate. Under inert atmosphere methyl 2-fluorophenyl-acetate (500 mg, 2.97 mmol) is dissolved in MeCN (18 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 556 mg, 546 μl, 3.65 mmol) is added at room temperature. Then tosyl azide (710 mg, 3.60 mmol) is added dropwise with stirring at rt. After 20 h the solvent is evaporated, the residue dissolved in Et_2O and 5% aqueous KOH solution. The layers are separated and the aqueous layer is extracted twice with Et_2O. The combined org. layers are dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue is purified by flash chromatography (hexanes/EtOAc/Et_3N 19:1:0.1) to yield the title compound as a yellow oil: 524 mg (2.70 mmol, 91 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (td, J = 7.8 Hz, 1.9 Hz, 1H), 7.28-7.17 (m, 2H), 7.12-7.05 (m, 1H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 158.5 (d, J = 248 Hz), 129.6, 128.8 (d, J = 8.3 Hz), 124.8 (d, J = 3.5 Hz), 115.9 (d, J = 21.3 Hz), 113.9 (d, J = 11.9 Hz), 52.4. The resonance of the carbon that bears the diazo group was not detected.

IR (film) 3068, 3002, 2955, 2098, 1708, 1497, 1436, 1350, 1288, 1247, 1194, 1151, 1047, 1029, 756, 657.

II. Catalytic Enantioselective O–H Insertion Reactions

General Procedure for Table 2. In a glove box, $Cu(OTf)_2$ (2.9 mg, 0.0080 mmol) and ligand (+)-**1** (7.9 mg, 0.015 mmol) were dissolved in 1,2-dichloroethane (1.0 mL) that contained water (distilled and degassed; 0.016 mmol). The resulting mixture was stirred for 20 min at rt, and then it was passed through an acrodisc filter and added in one portion to a solution of the diazo compound (0.40 mmol) and the alcohol (0.42 mmol) in 1,2-dichloroethane (40 mL). The reaction mixture was stirred for 1.0 h at rt. Then, the solvent was evaporated, and the residue was purified by flash chromatography (hexane/EtOAc or pentane/Et_2O as the eluent).

The ee values were determined via HPLC on Daicel Chiralpak columns or via GC.

If removal of the trimethylsilylethyl group was necessary for ee analysis, an aliquot of the product was dissolved in CH_2Cl_2 and treated with an excess of $BF_3{\cdot}OEt_2$ for 15 min at rt. The reaction was quenched with a solution of sat. $NaHCO_3$, and the organic layer was dried ($MgSO_4$), filtered, concentrated, and subjected to HPLC analysis.

If reduction of the ester was necessary for ee analysis, an aliquot of the product was dissolved in Et_2O and treated with an excess of $LiAlH_4$ at rt for 45 min. The reaction was quenched with a solution of 5% H_2SO_4, and the organic layer was dried ($MgSO_4$), filtered, concentrated, and subjected to HPLC analysis.

The second runs were performed with (–)-**1**.

Methyl α-phenyl-α-methoxy-acetate (Table 2, entry 1) [26164-27-2 (*S*)]. The compound was prepared according to the General Procedure using methanol (13.5 mg, 17.1 μL). After chromatography on silica gel (pentane/Et_2O 15:1), the title compound was isolated as a colorless oil: run 1: 61 mg (85%; 72% ee); run 2: 62 mg (86%; 66% ee). The ee was determined via HPLC on an OD-H column (hexanes/*iso*-propanol 99:1, flow 1.0 mL/min) with t_r (major) 8.4 min, t_r (minor) 17.7 min.

$[\alpha]^{23}_D = 94.3$ (c = 1.01, $CHCl_3$).

(*S*)-(+)-Methyl α-phenyl-α-ethoxy-acetate (Table 2, entry 2) [65792-30-5]. The compound was prepared according to the General Procedure using ethanol (19.4 mg, 24.5 μL). After chromatography on silica gel (hexanes/Et_2O 18:1), the title compound was isolated as a colorless oil: run 1: 65 mg (84%; 86% ee); run 2: 66 mg (85%; 87% ee). The ee was determined via GC on a G-TA column with t_r(minor) 14.89 min, t_r(major) 16.02 min.

$[\alpha]^{23}_D = 87.2$ (c = 1.00, $CHCl_3$). The absolute configuration was determined by comparison with authentic material prepared by ethylation of commercially available mandelic mandelate.

Methyl α-phenyl-α-1-methylethoxy-acetate (Table 2, entry 3) [130115-06-9 (*R*)]. The compound was prepared according to the General Procedure using isopropanol (25.3 mg, 32.2 μL). After chromatography on silica gel (pentane/Et_2O 20:1), the title compound was isolated as a colorless oil: run 1: 61 mg (73%; 69% ee); run 2: 65 mg (78%;

67% ee). The ee was determined via GC on a G-TA column with t_r(minor) 30.52 min, t_r(major) 33.20 min.

$[\alpha]^{23}_D$ = 60.4 (c = 1.00, $CHCl_3$).

Methyl α-phenyl-α-1,1-dimethylethoxy-acetate (Table 2, entry 4). The General Procedure was followed, using *tert*-butanol (31.1 mg, 40.2 μL). None of the title compound could be isolated (a trace was formed, according to ^{1}H NMR spectroscopy).

(*S*)-(+)-Methyl α-phenyl-α-2-trimethylsilylethoxy-acetate (Table 2, entry 5; Table 3, entry 1). The compound was prepared according to the General Procedure using 2-trimethylsilylethanol (49.7 mg, 60.2 μL). After chromatography on silica gel (hexanes/EtOAc 20:1), the title compound was isolated as a colorless oil: run 1: 100 mg (94%; 90% ee); run 2: 99 mg (93%; 89% ee). The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min) with t_r(major) 8.3 min, t_r(minor) 13.9 min.

$[\alpha]^{23}_D$ = 68.3 (c = 1.01, $CHCl_3$). The absolute configuration was determined by deprotection and comparison with commercially available methyl mandelate.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48-7.44 (m, 2H), 7.39-7.21 (m, 3H), 4.89 (s, 1H), 3.72 (s, 3H), 3.65 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.4 Hz, 1H), 3.55 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.2 Hz, 1H), 1.07 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.4 Hz, 1H), 1.02 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.2 Hz, 1H), 0.01 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 136.9, 128.8, 128.7, 127.3, 80.8, 67.5, 52.4, 18.4, –1.2.

IR (film) 3066, 3033, 2953, 2894, 1755, 1455, 1435, 1249, 1208, 1171, 1117, 860, 839, 729, 697 cm^{-1}.

MS (ESI) calcd for $C_{14}H_{22}NaO_3Si$ (M^++Na) 289.1, found 289.0.

Methyl α-phenyl-α-2,2,2-trifluoroethoxy-acetate (Table 2, entry 6). The General Procedure was followed, using 2,2,2-trifluoroethanol (42.0 mg, 30.6 μL). None of the title compound could be isolated (a trace was formed, according to ^{1}H NMR spectroscopy).

Methyl α-phenyl-α-benzyloxy-acetate (Table 2, entry 7) [60300-84-7]. The compound was prepared according to the General Procedure using benzyl alcohol (45.4 mg, 43.5 μL). After chromatography on silica gel (hexanes/Et_2O 12:1), the title compound was isolated as a colorless oil: run 1: 87 mg (85%; 76% ee); run 2: 89 mg (87%; 77% ee). The ee was determined after reduction of the ester via HPLC on an AS-H column (hexanes/*iso*-propanol 95:5, flow 1.0 mL/min) with t_r(major) 9.3 min, t_r(minor) 10.4 min.

$[\alpha]^{23}_D$ = 77.7 (c = 1.00, $CHCl_3$). The absolute configuration was assigned by comparison with literature data.[2]

Methyl α-phenyl-α-(4-methoxybenzyloxy)acetate (Table 2, entry 8) [641609-73-6 (*S*)]. The compound was prepared according to the General Procedure using *p*-

methoxybenzyl alcohol (58.0 mg, 52.4 μL). After chromatography on silica gel (hexanes/EtOAc 18:1), the title compound was isolated as a colorless oil: run 1: 100 mg (87%; 81% ee); run 2: 100 mg (87%; 82% ee). The ee was determined via HPLC on an OD-H column (hexanes/*iso*-propanol 99:1, flow 1.0 mL/min) with t_r(major) 12.9 min, t_r(minor) 16.3 min.

$[\alpha]^{23}_D$ = 79.4 (c = 1.00, $CHCl_3$). The absolute configuration was assigned by comparison with literature data.[3]

Methyl α-phenyl-α-allyloxy-acetate (Table 2, entry 9) [251934-74-4 (*S*)]. The compound was prepared according to the General Procedure using allyl alcohol (24.4 mg, 28.6 μL). After chromatography on silica gel (hexanes/Et_2O 20:1), the title compound was isolated as a colorless oil: run 1: 64 mg (78%; 25% ee); run 2: 62 mg (75%; 29% ee). The ee was determined via GC on a G-TA column with t_r(minor) 20.09 min, t_r (major) 21.52 min.

$[\alpha]^{23}_D$ = 25.2 (c = 1.00, $CHCl_3$).

Methyl α-phenyl-α-phenyloxy-acetate (Table 2, entry 10) [729589-62-2 (*S*)]. The compound was prepared according to the General Procedure using phenol (39.5 mg). After chromatography on silica gel (hexanes/EtOAc 18:1), the title compound was isolated as a colorless oil: run 1: 49 mg (51%; 11% ee); run 2: 58 mg (60%; 11% ee). The ee was determined via HPLC on an OD-H column (hexanes/*iso*-propanol 97:3, flow 1.2 mL/min) with t_r(minor) 6.7 min, t_r(major) 16.2 min.

$[\alpha]^{23}_D$ = –7.7 (c = 0.98, $CHCl_3$). The absolute configuration was assigned by comparison with literature data.[4]

Eq 2. $BF_3{\cdot}OEt_2$ (200 μL, 227 mg, 1.60 mmol) was added to a solution of methyl α-phenyl-α-(2-trimethylsilylethoxy)acetate (106 mg, 0.40 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred at room temperature for 40 min, and then the reaction was quenched with a solution of sat. $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc 3:1), which furnished methyl mandelate as a colorless oil: 65 mg (98%).

General Procedure for Table 3. In a glove box, $Cu(OTf)_2$ (2.9 mg, 0.0080 mmol) and ligand (+)-**1** (7.9 mg, 0.015 mmol) were dissolved in 1,2-dichloroethane (1.0 mL) that contained water (distilled and degassed; 0.016 mmol). The resulting mixture was stirred for 20 min at rt, and then it was passed through an acrodisc filter and added in one portion to a solution of the diazo compound (0.40 mmol) and 2-trimethylsilylethanol (49.7 mg, 60.2 μL, 0.42 mmol) in 1,2-dichloroethane (40 mL). The reaction mixture was stirred for 1.0 h at rt. Then, the solvent was evaporated, and the residue was purified by flash chromatography (hexane/EtOAc as the eluent).

The ee values were determined via HPLC on Daicel Chiralpak columns.

If removal of the trimethylsilylethyl group was necessary for ee analysis, an aliquot of the product was dissolved in CH_2Cl_2 and treated with an excess of $BF_3{\cdot}OEt_2$ for 15 min at rt. The reaction was quenched with a solution of sat. $NaHCO_3$, and the organic layer was dried ($MgSO_4$), filtered, concentrated, and subjected to HPLC analysis.

If reduction of the ester was necessary for ee analysis, an aliquot of the product was dissolved in Et_2O and treated with an excess of $LiAlH_4$ at rt for 45 min. The reaction was quenched with a solution of 5% H_2SO_4, and the organic layer was dried ($MgSO_4$), filtered, concentrated, and subjected to HPLC analysis.

The second runs were performed with (–)-**1**.

(*S*)-(+)-Methyl α-phenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 1); see above (Table 2, entry 5).

Methyl α-2-methoxyphenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 2). The compound was prepared according to the General Procedure using methyl α-diazo-α-2-(methoxyphenyl)acetate (82.5 mg). After chromatography on silica gel (hexanes/EtOAc 15:1), the title compound was isolated as a colorless oil: run 1: 108 mg (91%; 97% ee); run 2: 106 mg (89%; 94% ee).

The ee was determined after reduction of the ester via HPLC on an OD-H column (hexanes/*iso*-propanol 95:5, flow 1.0 mL/min) with t_r(major) 5.7 min, t_r(minor) 7.4 min.

$[\alpha]^{23}_D = 80.1$ (c = 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (dd, *J* = 7.5 Hz, 1.8 Hz, 1H), 7.31 (ddd, *J* = 8.3 Hz, 7.5 Hz, 1.8 Hz, 1H), 6.98 (ddd, *J* = 7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 6.90 (dd, *J* = 8.3 Hz, 1.1 Hz, 1H), 5.32 (s, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.66 (ddd, *J* = 10.4 Hz, 9.3 Hz, 6.2 Hz, 1H), 3.56 (ddd, *J* = 10.4 Hz, 9.3 Hz, 6.2 Hz, 1H), 1.05 (ddd, *J* = 13.8 Hz, 10.4 Hz, 6.2 Hz, 1H), 1.01 (ddd, *J* = 13.8 Hz, 10.4 Hz, 6.2 Hz, 1H), 0.00 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 157.1, 129.9, 128.6, 125.7, 121.0, 111.0, 74.4, 67.5, 55.9, 52.3, 18.3, –1.2.

IR (film) 3002, 2952, 2896, 1751, 1602, 1494, 1465, 1249, 1204, 1094, 1029, 860, 839, 755 cm^{-1}.

MS (ESI) calcd for $C_{15}H_{24}NaO_4Si$ (M^++Na) 319.1, found 319.0.

Ethyl α-2-methylphenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 3). The compound was prepared according to the General Procedure using methyl α-diazo-α-2-(methylphenyl)acetate (81.7 mg). After chromatography on silica gel (hexanes/EtOAc 20:1), the title compound was isolated as a colorless oil: run 1: 111 mg (94%; 80% ee); run 2: 111 mg (94%; 78% ee).

The ee was determined via HPLC on an AD-H column (hexanes/*iso*-propanol 99:1, flow 1.0 mL/min) with t_r(major) 4.1 min, t_r(minor) 5.0 min.

$[\alpha]^{23}_D = 72.6$ (c = 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48-7.43 (m, 1H), 7.24-7.15 (m, 3H), 5.08 (s, 1H), 4.21 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 4.16 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 3.65 (ddd, *J* = 10.3 Hz, 9.2 Hz, 6.3 Hz, 1H), 3.54 (ddd, *J* = 10.3 Hz, 9.2 Hz, 6.1 Hz, 1H), 2.44 (s, 3H), 1.22 (t, *J* = 7.1 Hz,

3H), 1.06 (ddd, *J* = 13.9 Hz, 10.3 Hz, 6.3 Hz, 1H), 1.02 (ddd, *J* = 13.9 Hz, 10.3 Hz, 6.1 Hz, 1H), 0.02 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 136.4, 135.6, 130.7, 128.5, 127.6, 126.4, 77.9, 67.4, 61.2, 19.6, 18.4, 14.3, –1.2.

IR (film) 3025, 2954, 2897, 1751, 1464, 1391, 1249, 1094, 1029, 860, 839, 742 cm^{-1}.

MS (ESI) calcd for $C_{16}H_{26}NaO_3Si$ (M^++Na) 317.2, found 317.1.

Methyl α-2-chlorophenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 4). The compound was prepared according to the General Procedure using methyl α-diazo-α-2-(chlorophenyl)acetate (84.3 mg). After chromatography on silica gel (hexanes/EtOAc 20:1), the title compound was isolated as a colorless oil: run 1: 115 mg (96%; 95% ee); run 2: 115 mg (96%; 96% ee).

The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min) with t_r(major) 8.1 min, t_r(minor) 9.2 min.

$[\alpha]^{23}_D$ = 82.7 (c = 1.01, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56-7.53 (m, 1H), 7.40-7.37 (m, 1H), 7.32-7.25 (m, 2H), 5.38 (s, 1H), 3.73 (s, 3H), 3.69 (ddd, *J* = 10.4 Hz, 9.3 Hz, 6.2 Hz, 1H), 3.57 (ddd, *J* = 10.5 Hz, 9.3 Hz, 6.1 Hz, 1H), 1.07 (ddd, *J* = 13.8 Hz, 10.5 Hz, 6.2 Hz, 1H), 1.01 (ddd, *J* = 13.8 Hz, 10.4 Hz, 6.1 Hz, 1H), 0.01 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 135.1, 133.8, 129.9, 129.7, 128.9, 127.4, 76.9, 67.9, 52.5, 18.4, –1.2.

IR (film) 3068, 2953, 2896, 1754, 1474, 1436, 1250, 1209, 1106, 860, 839 cm^{-1}.

MS (ESI) calcd for $C_{14}H_{21}ClNaO_3Si$ (M^++Na) 323.1, found 323.0.

Methyl α-2-fluorophenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 5). The compound was prepared according to the General Procedure using methyl α-diazo-α-2-(fluorophenyl)acetate (77.7 mg). After chromatography on silica gel (hexanes/EtOAc 18:1), the title compound was isolated as a colorless oil: run 1: 111 mg (98%; 97% ee); run 2: 110 mg (97%; 98% ee).

The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min) with t_r(major) 7.7 min, t_r(minor) 9.0 min.

$[\alpha]^{23}_D$ = 87.0 (c = 1.02, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52-7.47 (m, 1H), 7.35-7.29 (m, 1H), 7.19-7.14 (m, 1H), 7.10-7.05 (m, 1H), 5.24 (s, 1H), 3.73 (s, 3H), 3.69 (ddd, *J* = 10.3 Hz, 9.2 Hz, 6.2 Hz, 1H), 3.56 (ddd, *J* = 10.4 Hz, 9.2 Hz, 6.1 Hz, 1H), 1.06 (ddd, *J* = 13.8 Hz, 10.3 Hz, 6.2 Hz, 1H), 1.00 (ddd, *J* = 13.8 Hz, 10.4 Hz, 6.1 Hz, 1H), 0.01 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 160.5 (d, *J* = 248 Hz), 130.4 (d, *J* = 8.1 Hz), 128.9 (d, *J* = 3.2 Hz), 124.7 (d, *J* = 3.7 Hz), 124.5 (d, *J* = 14.4 Hz), 115.7 (d, *J* = 21.8 Hz), 73.6 (d, *J* = 3.0 Hz), 67.8, 52.5, 18.3, –1.2.

IR (film) 3052, 2954, 2896, 1755, 1491, 1458, 1249, 1207, 1114, 860, 839, 757 cm^{-1}.

MS (ESI) calcd for $C_{14}H_{21}FNaO_3Si$ (M^++Na) 307.1, found 307.0.

Ethyl α-3-methoxyphenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 6). The compound was prepared according to the General Procedure using ethyl α-diazo-α-3-(methoxyphenyl)acetate (88.1 mg). After chromatography on silica gel (hexanes/EtOAc 18:1), the title compound was isolated as a colorless oil: run 1: 119 mg (97%; 90% ee); run 2: 118 mg (95%; 88% ee).

The ee was determined via HPLC on an AS-H column (hexanes/*iso*-propanol 99.8:0.2, flow 0.8 mL/min) with t_r(major) 6.6 min, t_r(minor) 7.1 min.

$[\alpha]^{23}_D$ = 49.9 (c = 0.98, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.24 (m, 1H), 7.05-7.02 (m, 2H), 6.88-6.85 (m, 1H), 4.84 (s, 1H), 4.21 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 4.16 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 3.81 (s, 3H), 3.65 (ddd, *J* = 9.9 Hz, 9.2 Hz, 6.5 Hz, 1H), 3.56 (ddd, *J* = 10.0 Hz, 9.2 Hz, 6.3 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.07 (ddd, *J* = 13.9 Hz, 10.0 Hz, 6.5 Hz, 1H), 1.02 (ddd, *J* = 13.9 Hz, 9.9 Hz, 6.3 Hz, 1H), 0.02 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 159.9, 138.6, 129.7, 119.7, 114.6, 112.3, 80.8, 67.4, 61.3, 55.5, 18.3, 14.3, –1.2.

IR (film) 2954, 2896, 1751, 1601, 1490, 1250, 1183, 1156, 1114, 1044, 860, 839 cm^{-1}.

MS (ESI) calcd for $C_{16}H_{26}NaO_4Si$ (M^++Na) 333.2, found 333.0.

Methyl α-3-chlorophenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 7). The compound was prepared according to the General Procedure using methyl α-diazo-α-3-(chlorophenyl)acetate (84.3 mg). After chromatography on silica gel (hexanes/EtOAc 20:1), the title compound was isolated as a colorless oil: run 1: 112 mg (93%; 64% ee); run 2: 109 mg (91%; 65% ee).

The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min) with t_r(major) 7.6 min, t_r(minor) 9.1 min.

$[\alpha]^{23}_D$ = 43.1 (c = 1.02, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48-7.46 (m, 1H), 7.36-7.28 (m, 3H), 4.85 (s, 1H), 3.73 (s, 3H), 3.65 (ddd, *J* = 10.2 Hz, 9.1 Hz, 6.4 Hz, 1H), 3.54 (ddd, *J* = 10.3 Hz, 9.1 Hz, 6.2 Hz, 1H), 1.07 (ddd, *J* = 13.9 Hz, 10.3 Hz, 6.4 Hz, 1H), 1.02 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.2 Hz, 1H), 0.02 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 138.9, 134.7, 130.0, 128.9, 127.4, 125.4, 80.1, 67.8, 52.6, 18.4, –1.2.

IR (film) 3058, 2954, 2895, 1756, 1434, 1250, 1208, 1173, 1118, 860, 839 cm^{-1}.

MS (ESI) calcd for $C_{14}H_{21}ClNaO_3Si$ (M^++Na) 323.1, found 323.0.

Methyl α-4-methoxyphenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 8). The compound was prepared according to the General Procedure using methyl α-diazo-α-4-(methoxyphenyl)acetate (82.5 mg). After chromatography on silica gel (hexanes/EtOAc 18:1), the title compound was isolated as a colorless oil: run 1: 102 mg (86%; 87% ee); run 2: 99 mg (83%; 84% ee).

The ee was determined after reduction of the ester via HPLC on an OD-H column (hexanes/*iso*-propanol 99.4:0.6, flow 1.2 mL/min) with t_r(minor) 10.2 min, t_r(major) 11.4 min.

$[\alpha]^{23}_D$ = 81.3 (c = 0.99, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.35 (m, 2H), 6.91-6.87 (m, 2H), 4.83 (s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.61 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.4 Hz, 1H), 3.52 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.2 Hz, 1H), 1.05 (ddd, *J* = 13.8 Hz, 10.2 Hz, 6.4 Hz, 1H), 1.01 (ddd, *J* = 13.8 Hz, 10.2 Hz, 6.2 Hz, 1H), 0.01 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 160.0, 129.1, 128.7, 114.2, 80.3, 67.2, 55.5, 52.4, 18.3, –1.2.

IR (film) 3001, 2953, 2896, 1753, 1611, 1513, 1249, 1172, 1100, 1035, 860, 837 cm^{-1}.

MS (ESI) calcd for $C_{15}H_{24}NaO_4Si$ (M^++Na) 319.1, found 319.0.

Methyl α-4-acetaminophenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 9). The compound was prepared according to the General Procedure using methyl α-diazo-α-4-(acetaminophenyl)acetate (93.3 mg). After chromatography on silica gel (hexanes/EtOAc/Et_3N 66:34:0.3), the title compound was isolated as a colorless solid: run 1: 116 mg (90%; 89% ee); run 2: 111 mg (88%; 85% ee).

The ee was determined via HPLC on an OD-H column (hexanes/*iso*-propanol 93:7, flow 1.0 mL/min) with t_r(major) 15.6 min, t_r(minor) 18.6 min.

After a single crystalization from hexanes/EtOAc the title compound could be obtained in 99% ee.

mp: 135 °C;

$[\alpha]^{23}_D$ = 77.4 (c = 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, *J* = 8.6 Hz, 2H), 7.47 (s, 1H), 7.39 (d, *J* = 8.6 Hz, 2H), 4.85 (s, 1H), 3.70 (s, 3H), 3.61 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.3 Hz, 1H), 3.52 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.3 Hz, 1H), 2.17 (s, 3H), 1.04 (ddd, *J* = 13.8 Hz, 10.2 Hz, 6.3 Hz, 1H), 1.00 (ddd, *J* = 13.8 Hz, 10.2 Hz, 6.3 Hz, 1H), 0.00 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 168.6, 138.4, 132.7, 128.1, 120.1, 80.3, 67.4, 52.4, 24.8, 18.3, –1.2.

IR (film) 3304, 3066, 2953, 2896, 1746, 1670, 1605, 1555, 1411, 1249, 1211, 1173, 1105, 862, 835 cm^{-1}.

MS (ESI) calcd for $C_{16}H_{25}NNaO_4Si$ (M^++Na) 346.2, found 345.9.

Methyl α-biphenyl-4-yl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 10). The compound was prepared according to the General Procedure using methyl α-diazo-α-(biphenyl-4-yl)acetate (101.0 mg). After chromatography on silica gel (hexanes/EtOAc 20:1), the title compound was isolated as a colorless oil: run 1: 128 mg (93%; 86% ee); run 2: 122 mg (89%; 85% ee).

The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min) with t_r(major) 10.6 min, t_r(minor) 12.2 min.

$[\alpha]^{23}_D$ = 77.9 (c = 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63-7.58 (m, 4H), 7.56-7.52 (m, 2H), 7.48-7.42 (m, 2H), 7.39-7.34 (m, 1H), 4.95 (s, 1H), 3.75 (s, 3H), 3.69 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.4 Hz, 1H), 3.60 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.2 Hz, 1H), 1.10 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.4 Hz, 1H), 1.06 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.2 Hz, 1H), 0.04 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 141.7, 140.8, 135.9, 129.0, 127.7, 127.6, 127.5, 127.3, 80.6, 67.6, 52.5, 18.4, –1.2.

IR (film) 3058, 3031, 2952, 2894, 1754, 1488, 1249, 1212, 1171, 1102, 1009, 860, 838, 758 cm^{-1}.

MS (ESI) calcd for $C_{20}H_{26}NaO_3Si$ (M^++Na) 365.2, found 365.0.

Ethyl α-4-bromophenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 11). The compound was prepared according to the General Procedure using ethyl α-diazo-α-4-(bromophenyl)acetate (107.6 mg). After chromatography on silica gel (hexanes/EtOAc 20:1), the title compound was isolated as a colorless oil: run 1: 137 mg (97%; 78% ee); run 2: 132 mg (92%; 80% ee).

The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min) with t_r(major) 6.9 min, t_r(minor) 7.6 min.

$[\alpha]^{23}_D$ = 36.3 (c = 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51-7.48 (m, 2H), 7.36-7.33 (m, 2H), 4.82 (s, 1H), 4.18 (m, 2H), 3.65 (ddd, *J* = 10.0 Hz, 9.1 Hz, 6.5 Hz, 1H), 3.54 (ddd, *J* = 10.0 Hz, 9.1 Hz, 6.3 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.06 (ddd, *J* = 13.9 Hz, 10.0 Hz, 6.5 Hz, 1H), 1.01 (ddd, *J* = 13.9 Hz, 10.0 Hz, 6.3 Hz, 1H), 0.02 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 136.3, 131.9, 128.9, 122.7, 80.3, 67.6, 61.5, 18.4, 14.3, –1.2.

IR (film) 3054, 2954, 2895, 1751, 1487, 1250, 1177, 1122, 1096, 1013, 860, 838 cm^{-1}.

MS (ESI) calcd for $C_{15}H_{23}BrNaO_3Si$ (M^++Na) 381.1, found 380.9.

Methyl α-4-fluorophenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 12). The compound was prepared according to the General Procedure using methyl α-diazo-α-4-(fluorophenyl)acetate (77.7 mg). After chromatography on silica gel (hexanes/EtOAc 20:1), the title compound was isolated as a colorless oil: run 1: 105 mg (92%; 89% ee); run 2: 103 mg (91%; 88% ee).

The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min) with t_r(major) 7.6 min, t_r(minor) 8.8 min.

$[\alpha]^{23}_D$ = 61.2 (c = 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.41 (m, 2H), 7.08-7.02 (m, 2H), 4.86 (s, 1H), 3.72 (s, 3H), 3.64 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.3 Hz, 1H), 3.53 (ddd, *J* = 10.3 Hz, 9.2 Hz, 6.1 Hz, 1H), 1.07 (ddd, *J* = 13.9 Hz, 10.3 Hz, 6.3 Hz, 1H), 1.00 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.1 Hz, 1H), 0.00 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 163.0 (d, *J* = 247 Hz), 132.8 (d, *J* = 3.1 Hz), 129.1 (d, *J* = 8.4 Hz), 115.7 (d, *J* = 21.8 Hz), 80.1, 67.6, 52.5, 18.4, –1.2.

IR (film) 3074, 2954, 2895, 1755, 1605, 1509, 1250, 1224, 1173, 1114, 1014, 860, 838 cm^{-1}.

MS (ESI) calcd for $C_{14}H_{21}FNaO_3Si$ (M^++Na) 307.1, found 307.0.

Methyl α-4-trifluoromethylphenyl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 13). The compound was prepared according to the General Procedure using

methyl α-diazo-α-4-(trifluoromethylphenyl)acetate (97.7 mg). After chromatography on silica gel (hexanes/EtOAc 20:1), the title compound was isolated as a colorless oil: run 1: 121 mg (90%; 19% ee); run 2: 119 mg (89%; 22% ee).

The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 97:3, flow 1.0 mL/min) with t_r (major) 14.0 min, t_r (minor) 15.5 min.

$[\alpha]^{23}_D$ = 10.6 (c = 1.03, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64-7.59 (m, 4H), 4.95 (s, 1H), 3.73 (s, 3H), 3.69 (ddd, *J* = 10.2 Hz, 9.1 Hz, 6.3 Hz, 1H), 3.56 (ddd, *J* = 10.2 Hz, 9.1 Hz, 6.1 Hz, 1H), 1.08 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.3 Hz, 1H), 1.03 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.1 Hz, 1H), 0.02 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 140.9, 138.9 (q, *J* = 32.5 Hz), 127.5, 125.7 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272 Hz), 80.3, 68.0, 52.6, 18.4, –1.2.

IR (film) 3053, 2956, 2896, 1758, 1419, 1327, 1251, 1168, 1128, 1068, 860, 838 cm^{-1}.

MS (ESI) calcd for $C_{15}H_{20}F_3O_3Si$ (M^+–H+Na) 333.1, found 333.0.

Methyl α-naphthalene-2-yl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 14). The compound was prepared according to the General Procedure using methyl α-diazo-α-(naphthalene-2-yl)acetate (95.5 mg). After chromatography on silica gel (hexanes/EtOAc 18:1), the title compound was isolated as a colorless oil: run 1: 119 mg (94%; 84% ee); run 2: 116 mg (92%; 83% ee).

The ee was determined after cleavage of the trimethylsilylethyl group via HPLC on an OD-H column (hexanes/*iso*-propanol 90:10, flow 1.0 mL/min) with t_r (major) 12.1 min, t_r (minor) 14.2 min.

$[\alpha]^{23}_D$ = 86.9 (c = 0.99, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95-7.93 (m, 1H), 7.89-7.82 (m, 3H), 7.61-7.58 (m, 1H), 7.53-7.47 (m, 2H), 5.07 (s, 1H), 3.73 (s, 3H), 3.70 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.3 Hz, 1H), 3.61 (ddd, *J* = 10.2 Hz, 9.2 Hz, 6.3 Hz, 1H), 1.11 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.3 Hz, 1H), 1.08 (ddd, *J* = 13.9 Hz, 10.2 Hz, 6.3 Hz, 1H), 0.03 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 134.4, 133.6, 133.3, 128.6, 128.3, 127.9, 126.8, 126.52, 126.47, 124.8, 80.9, 67.5, 52.5, 18.4, –1.2.

IR (film) 3058, 2952, 2894, 1754, 1435, 1249, 1198, 1176, 1108, 859, 839, 753 cm^{-1}.

MS (ESI) calcd for $C_{18}H_{24}NaO_3Si$ (M^++Na) 339.2, found 339.0.

Methyl α-benzo[1,3]dioxol-5-yl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 15). The compound was prepared according to the General Procedure using methyl α-diazo-α-(benzo[1,3]dioxol-5-yl)acetate (88.1 mg). After chromatography on silica gel (hexanes/EtOAc 15:1), the title compound was isolated as a colorless oil: run 1: 110 mg (89%; 89% ee); run 2: 107 mg (87%; 88% ee).

The ee was determined via HPLC on an OD-H column (hexanes/*iso*-propanol 99:1, flow 1.0 mL/min) with t_r (major) 6.1 min, t_r (minor) 7.3 min.

$[\alpha]^{23}_D$ = 73.6 (c = 1.01, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.96 (d, *J* = 1.7 Hz, 1H), 6.91 (dd, *J* = 7.9 Hz, 1.7 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 5.97 (m, 2H), 4.79 (s, 1H), 3.72 (s, 3H), 3.59 (ddd, *J* = 10.3 Hz, 9.2

Hz, 6.4 Hz, 1H), 3.52 (ddd, *J* = 10.3 Hz, 9.2 Hz, 6.2 Hz, 1H), 1.05 (ddd, *J* = 13.8 Hz, 10.3 Hz, 6.4 Hz, 1H), 1.00 (ddd, *J* = 13.8 Hz, 10.3 Hz, 6.2 Hz, 1H), 0.00 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 148.09, 148.05, 130.8, 121.2, 108.4, 107.7, 101.4, 80.5, 67.3, 52.4, 18.3, –1.2.

IR (film) 3075, 2953, 2894, 1753, 1504, 1490, 1445, 1248, 1201, 1172, 1103, 1040, 933, 861, 839 cm^{-1}.

MS (ESI) calcd for $C_{15}H_{22}NaO_5Si$ (M^++Na) 333.1, found 333.0.

Methyl α-thiophene-3-yl-α-(2-trimethylsilylethoxy)acetate (Table 3, entry 16). The compound was prepared according to the General Procedure using methyl α-diazo-α-(thiophene-3-yl)acetate (72.9 mg). After chromatography on silica gel (hexanes/EtOAc/Et_3N 25:1:0.1), the title compound was isolated as a colorless oil: run 1: 97 mg (89%; 89% ee); run 2: 95 mg (87%; 87% ee).

The ee was determined after cleavage of the trimethylsilylethylgroup via HPLC on an OD-H column (hexanes/*iso*-propanol 95:5, flow 1.0 mL/min) with t_r(major) 13.7 min, t_r(minor) 17.3 min.

$[\alpha]^{23}_D$ = 51.8 (c = 1.01, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.35 (m, 1H), 7.30 (dd, *J* = 5.0 Hz, *J* = 3.0 Hz, 1H), 7.15 (dd, *J* = 5.0 Hz, *J* = 1.3 Hz, 1H), 5.00 (s, 1H), 3.75 (s, 3H), 3.65 (ddd, *J* = 10.1 Hz, 9.1 Hz, 6.6 Hz, 1H), 3.56 (ddd, *J* = 10.1 Hz, 9.1 Hz, 6.4 Hz, 1H), 1.05 (ddd, *J* = 13.9 Hz, 10.1 Hz, 6.6 Hz, 1H), 1.02 (ddd, *J* = 13.9 Hz, 10.1 Hz, 6.4 Hz, 1H), 0.02 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 137.6, 126.4, 126.3, 123.6, 77.1, 67.6, 52.5, 18.3, –1.21.

IR (film) 3106, 2953, 2894, 1755, 1436, 1249, 1198, 1174, 1107, 860, 839, 773 cm^{-1}.

MS (ESI) calcd for $C_{12}H_{20}NaO_3SSi$ (M^++Na) 295.1, found 295.0.

Eq 3. In a glove box, $Cu(OTf)_2$ (0.6 mg, 1.6 μmol) and (+)-**1** (1.6 mg, 3.0 μmol) were dissolved in 1,2-dichloroethane (200 μL) that contained water (3.2 μmol; 50% D). The resulting mixture was stirred for 20 min at rt, and then it was passed through an acrodisc filter and added in one portion to a solution of methyl α-diazo-α-phenylacetate (14.1 mg, 0.080 mmol) and $TMSCH_2CH_2OH$(D) (46 μL, 12.2 mg, 0.32 mmol; 50% D according to ^{1}H NMR) in 1,2-dichloroethane (8 mL). The reaction mixture was stirred for 1.0 h at rt. Then, the solvent was evaporated, the residue was passed through a plug of silica gel (Et_2O as eluent), and the deuterium incorporation was determined by NMR. Run 1: 28% D (99% yield); run 2: 27% D (98% yield).

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