ClCH₂MgCl·LiCl: A Chemoselective Reagent for the Synthesis of Functionalized Aromatic Chlorohydrins.

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Supporting Information

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1. General Information

Commercially available starting material were used without further purification, all syntheses were performed with distilled solvents under an atmosphere of nitrogen, and using flame-dried glassware with standard vacuum line techniques. Flash chromatography was performed on silica gel (230–400 mesh) under pressure with eluents listed. The infrared (IR) spectra were measured as films on KBr using a Shimadzu IR-Prestige-21 spectrometer. All the products were analyzed by gas chromatography–mass spectrometry (GC–MS) using a Shimadzu GC (model 2010) coupled to a Shimadzu QP 2010 Ultra MS operated in the electron impact ionization mode (70 eV). HRMS spectra were measured with a Bruker Daltonics microTOF II – ESI-TOF Mass Spectrometer. 1H-NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 MHz) in a CDCl3 solution. Chemical shifts were expressed in ppm from tetramethylsilane (TMS) as the internal standard (CDCl3 δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet), and coupling constants (Hz), integration. 13C-NMR spectra were recorded on a Bruker DPX-400 spectrometer (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl3 δ 77.26 ppm).


Methyl 2-formylbenzoate (4c): To a solution of 2-formybenzoic acid (7 mmol, 1.0 g) in 10 mL of N,N-dimethylformamide (DMF) and potassium carbonate (3.78 mmol, 0.52 g) was added iodomethane (13.02 mmol, 0.81 mL). The reaction mixture was allowed stir under reflux for 60 min. After completion of reaction, water was added (30 mL) and compound was extracted in ethyl acetate (3 × 30 mL). The combined organic layer was washed with aqueous HCl 10% (20 mL), saturated NaHCO3 (20 mL) and

1 Gaenzler, F.C., Guo, C.L., Zhang, Y.-W.; Azab, M.E.; Salem, M.A.I.; Fan, D.P.; Smith, M.B. Tetrahedron 2009, 65, 8781
dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford the residue. The residue was purified by flash column chromatography using hexane-ethyl acetate as an eluent to provide the compound 4c (0.94 g, 82%) as yellow oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{, ppm) } \delta: 10.6 \text{ (s, 1H), 7.99-7.92 (m, 2H), 7.68-7.64 (m, 2H), 3.98 (s, 3H); 13C NMR (CDCl}_3\text{, 100 MHz) } \delta: 192.0, 166.6, 136.9, 132.8, 132.3, 131.8, 130.2, 128.3, 52.7; \text{ LRMS (m/z, %): 164 (1), 149 (14), 133 (28), 105 (79), 92 (43), 77(100).} \]

2-formylphenyl acetate (4d)\(^2\) To a solution of 2-hydroxybenzaldehyde (3 mmol, 0.37 g) in 5 mL of tetrahydrofuran (THF) was added acetic anhydride (5.82 mmol, 0.55 mL) and potassium carbonate (3.99 mmol, 0.55 g). The reaction mixture was allowed to stir at room temperature for 3 h. After completion of reaction, water was added and compound was extracted in ethyl acetate (3 \times 50 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford the residue. The residue was purified by flash column chromatography using hexane-ethyl acetate as an eluent, compound 4d was obtained in 87% yield as a white solid.

\[ \text{1H NMR (300 MHz, CDCl}_3\text{, ppm) } \delta: 10.1 \text{ (s, 1H), 7.88 (dd, } J = 7.8 \text{ Hz, } J = 1.8 \text{ Hz, 1H), 7.63 (td, } J = 7.8 \text{ Hz, } J = 1.8 \text{ Hz, 1H), 7.39 (t, } J = 7.5 \text{ Hz, 1H), 7.18 (d, } J = 8.2 \text{ Hz, 1H), 2.39 (s, 3H); 13C NMR (75 MHz, CDCl}_3\text{, ppm) } \delta: 188.7, 169.1, 151.4, 135.2, 131.2, 127.9, 126.3, 123.4, 20.7; \text{ LRMS (m/z, %): 164 (1), 122 (100), 104 (10), 77(10), 65(23).} \]

4-((tert-butyldimethylsilyloxy)benzaldehyde (4k):\(^3\) To a solution of 4-hydroxybenzaldehyde (6 mmol, 0.73 g) in DMF (10 mL), was added imidazole (14.52 mmol, 0.98 g) followed by tert-butyldimethylsilyl chloride (TBDMSCI) (7.2 mmol, 1.08 g) at 0°C under N\(_2\). The resulting solution was stirred for 2 h at room temperature, thus diluted with diethyl ether (40 mL), washed with water (3 \times 5 mL) and brine (10 mL), dried (MgSO\(_4\)), filtered,

\[ \text{Kang, J.; Zhao, G.; Xu, J.; Yang, W. Chem. Commun. 2010, 46, 2868} \]

\[ \text{MuranaKa, K.J.; Ichikawa, S.; Matsuda, A. J. Org. Chem. 2011, 76, 9278.} \]
and concentrated in vacuo. Purification of the residue by flash chromatography eluting with EtOAc/hexane, afforded 4K in 60 % yield as a yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$, ppm) $\delta$: 9.88 (s, 1H), 7.79 (d, $J = 8.5$ Hz, 2H), 6.94 (d, $J = 8.5$ Hz, 2H), 0.99 (s, 9H), 0.25 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$, ppm) $\delta$: 190.8, 161.4, 131.8, 130.4, 120.4, 25.5, 18.2, -4.3; LRMS (m/z, %): 236 (13), 179 (100), 151 (54), 95 (9), 77 (8).

(5-formylfuran-2-yl)methyl acetate (9):$^4$ Anhydride acetic (29.5 mmol, 2.8 mL) was added dropwise to a stirred mixture of 5-hydroxymethyl-2-furfural (11.8 mmol, 1.48 g) and NaOAc (24.8 mmol, 2.0 g) maintained at 80°C. The mixture was stirred for 2.5 h, the cooled at room temperature and distilled water (45 mL) was added. The resulting solution was extracted with diethyl ether (5x20 mL), the organic layer was combined and dried with MgSO$_4$, filtered, and concentrated. Purification of the residue by flash chromatography eluting with EtOAc/hexane, afforded the product 9 in 84 % yield as a yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$, ppm) $\delta$: 9.64 (s, 1H), 7.23 (d, $J = 3.6$ Hz, 1H), 6.60 (d, $J = 3.6$ Hz, 1H), 5.13 (s, 2H), 2.11 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, ppm) $\delta$: 177.6, 170.1, 155.3, 152.7, 121.5, 112.4, 57.6, 20.5; LRMS (m/z, %): 168 (1), 126 (100), 109 (27), 79 (40) 43 (65).

4-benzoylbenzaldehyde (4e)$^5$

An anhydrous THF solution (5 mL) of 4-benzoylbenzoic acid (5 mmol, 1.13g) was slowly added to a suspension of LiAlH$_4$ (60 mmol, 2.27g) in THF (40 mL) cooled at 0°C under N$_2$. The mixture was stirred for 20 h at room temperature, then cooled at 0°C,
hydrolyzed with an NaOH aqueous solution (15 %) (10 mL), and extracted several times with ethyl ether. The combined ether extracts were washed with water, dried over MgSO₄ and concentrated. The product was used in the next step without purification.

Pyridinium chlorochromate (PCC) (30 mmol, 6.47 g), celite (3.0 g) and sodium acetate (6.10 mmol, 0.5 g) were suspended in dry DCM (30 mL) at 25 °C. The product obtained in the previous step in DCM (5 mL) was added slowly to the stirred suspension. After 3 h, the black reaction mixture was filtered through a short pad of silica and celite and wash with dry diethyl ether. The solvent was removed under reduced pressure and was purified by column chromatography on silica gel (hexane – ethyl acetate) yielding 0.82 g (78 % to two steps) as a white solid.

1H NMR (300 MHz, CDCl₃, ppm) δ: 10.1 (s, 1H), 8.0 (d, J = 8.1 Hz, 2H), 7.93 (d, J = 8.1 Hz, 2H), 7.82-7.48 (m, 5H); 13C NMR (75 MHz, CDCl₃, ppm) δ: 195.7, 191.5, 142.5, 138.4, 136.7, 133.0, 130.2, 130.0, 129.4, 128.5; LRMS (m/z, %): 210 (30), 133 (30), 105 (100), 77 (74), 51 (38).

**N,N-diethyl-4-formylbenzamide (4h)**

Thionyl chloride (20 mmol, 1.45 mL) was added to a mixture of 4-formylbenzoic acid (5 mmol, 0.75 g) in DCM (20 mL). The mixture was stirred under reflux for approximately 4 h. After completion of the reaction, the excess of thionyl chloride and DCM were removed by distillation. To this mixture was added diethylaniline (7.5 mmol, 0.78 mL), triethylamine (6.25 mmol, 0.87 mL) and 20 mL of DCM, the reaction mixture was stirred for 2 h at 25°C. Distilled water was added, the aqueous layer was extracted with DCM (3 × 30 mL). The organic layer was combined and was successively washed with aqueous HCl (1mol/L), dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography using hexane- ethyl acetate as an eluent to provide the compound 4h (0.81 g, 79 %) as yellow oil.

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$^{1}$H NMR (500 MHz, CDCl$_3$, ppm) δ: 10.0 (s, 1H), 7.93 (d, $J = 8.2$ Hz, 2H), 7.53 (d, $J = 8.2$ Hz, 2H), 3.57 (q, $J = 6.7$ Hz, 2H), 3.22 (q, $J = 6.7$ Hz, 2H), 1.27 (t, $J = 6.7$ Hz, 3H), 1.16 (t, $J = 6.7$ Hz, 3H); RMN de $^{13}$C (125 MHz, CDCl$_3$, ppm) δ: 191.6, 169.9, 143.0, 136.5, 129.9 126.9, 43.3, 39.4, 14.2, 12.9; LRMS (m/z, %): 205 (22), 133 (100), 105 (28), 77(34), 51 (19).
3. NMR Spectra

$^1$H NMR (400 MHz, CDCl$_3$) of methyl 4-(2-chloro-1-hydroxyethyl)benzoate (5a)

$^{13}$C NMR (100 MHz, CDCl$_3$) of methyl 4-(2-chloro-1-hydroxyethyl)benzoate (5a)
$^1$H NMR (400 MHz, CDCl$_3$) of methyl 3-(2-chloro-1-hydroxyethyl)benzoate (5b)

$^{13}$C NMR (100 MHz, CDCl$_3$) of methyl 3-(2-chloro-1-hydroxyethyl)benzoate (5b)
\[^1\text{H} \text{NMR (500 MHz, CDCl}_3\text{)}\) of 3-(chloromethyl)isobenzofuran-1(3\text{H})-one (5c)\]

\[^{13}\text{C} \text{NMR (125 MHz, CDCl}_3\text{)}\) of 3-(chloromethyl)isobenzofuran-1(3\text{H})-one (5c)\]
$^1$H NMR (400 MHz, CDCl$_3$) of 2-(2-chloro-1-hydroxyethyl)phenyl acetate (5d)

$^{13}$C NMR (100 MHz, CDCl$_3$) of 2-(2-chloro-1-hydroxyethyl)phenyl acetate (5d)
$^1$H NMR (500 MHz, CDCl$_3$) of (4-(2-chloro-1-hydroxyethyl)phenyl)methanone (5e)

$^{13}$C NMR (125 MHz, CDCl$_3$) of (4-(2-chloro-1-hydroxyethyl)phenyl)methanone (5e)
$^{1}$H NMR (500 MHz, CDCl$_3$) of 1-(4-(2-chloro-1-hydroxyethyl)phenyl)ethan-1-one (5f)

$^{13}$C NMR (125 MHz, CDCl$_3$) of 1-(4-(2-chloro-1-hydroxyethyl)phenyl)ethan-1-one (5f)
$^{1}H$ NMR (300 MHz, CDCl$_3$) of 2-chloro-1-(3-chlorophenyl)ethan-1-ol (5g)

$^{13}$C NMR (75 MHz, CDCl$_3$) of 2-chloro-1-(3-chlorophenyl)ethan-1-ol (5g)
$^1$H NMR (400 MHz, CDCl$_3$) of 4-(2-chloro-1-hydroxyethyl)-$N,N$-diethylbenzamide (5h)

$^{13}$C NMR (100 MHz, CDCl$_3$) of 4-(2-chloro-1-hydroxyethyl)-$N,N$-diethylbenzamide (5h)
$^1$H NMR (400 MHz, CDCl$_3$) of 3-(2-chloro-1-hydroxyethyl)benzonitrile (5i)

$^{13}$C NMR (100 MHz, CDCl$_3$) of 3-(2-chloro-1-hydroxyethyl)benzonitrile (5i)
$^1$H NMR (400 MHz, CDCl$_3$) of 4-(2-chloro-1-hydroxyethyl)benzonitrile (5j)

$^{13}$C NMR (100 MHz, CDCl$_3$) of 4-(2-chloro-1-hydroxyethyl)benzonitrile (5j)
$^1$H NMR (500 MHz, CDCl$_3$) of 1-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-chloroethan-1-ol (5k)

$^{13}$C NMR (75 MHz, CDCl$_3$) of 1-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-chloroethan-1-ol (5k)
$^1$H NMR (500 MHz, CDCl$_3$) of 2-(2-chloro-1-hydroxyethyl)phenol (51)

$^{13}$C NMR (75 MHz, CDCl$_3$) of 2-(2-chloro-1-hydroxyethyl)phenol (51)
$^1$H NMR (400 MHz, CDCl$_3$) of 1-(benzo[$d$][1,3]dioxol-5-yl)-2-chloroethan-1-ol (7)

$^{13}$C NMR (100 MHz, CDCl$_3$) of 1-(benzo[$d$][1,3]dioxol-5-yl)-2-chloroethan-1-ol (7)
\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \text{ of (5-(2-chloro-1-hydroxyethyl)furan-2-yl)methyl acetate (10)} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \text{ of (5-(2-chloro-1-hydroxyethyl)furan-2-yl)methyl acetate (10)} \]