Supporting Information

A Practical Guide for Using Lithium Halocarbenoids in Homologation Reactions

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Materials and methods

All $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker Avance spectrometers operating at 200, 300, 400 or 500 MHz and at 50, 75, 100, or 125 MHz, respectively, from CDCl$_3$ solutions. The (residual) solvent signal was used as an internal standard which was related to TMS with $\delta$ 7.26 ppm ($^1$H) and $\delta$ 77.0 ppm ($^{13}$C). Spin-spin coupling constants ($J$) are given in Hz. In some cases, full and unambiguous assignment of all $^1$H, $^{13}$C, resonances was performed by combined application of standard NMR techniques, such as APT, DEPT, HSQC, HMBC and NOESY experiments.

All melting points are uncorrected. Column chromatography purifications were conducted on silica gel 60 (40-63 μm). TLC was carried out on aluminum sheets pre-coated with silica gel 60F254; the spots were visualized under UV light ($\lambda$ = 254 nm) and/or KMnO$_4$ (aq.) was used as revealing system.

Starting materials were supplied from commercial sources otherwise indicated.

Elementary microanalyses were carried out using a Leco® CHNS 932 equipment.

General Procedures for the Chemoselective Addition of Lithium-carbenoids

2-chloro-1-phenylethan-1-ol (2a)

![OH](Cl)

To a solution of aldehyde 2 (200 mg, 1.88 mmol, 1.0 equiv), in THF (1.9 mL) cooled at -78 °C was added freshly distilled chloriodomethane (997 mg, 0.41 mL, 5.65 mmol, 3.0 equiv), followed by the addition of a solution of MeLi-LiBr complex (1.5 M, 3.52 mL, 5.28 mmol, 2.8 equiv) operated by syringe pump with flow of 0.2 ml/min. The mixture was stirred for 1 h before it was quenched with saturated aq. NH$_4$Cl (2 mL) and extracted with Et$_2$O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na$_2$SO$_4$, filtered and solvent was removed under reduced pressure to give a crude which after chromatographic purification on silica gel (eluent hexane/ethyl acetate 4:1, v/v) afforded chlorohydrin 2a (276 mg, 94% yield).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 7.38 (m, 5H, Ph), 4.81 (dd, $J$=8.5, 3.7 Hz, 1H, CH), 3.75-3.46 (m, 2H, CH$_2$), 2.74 (brs, 1H, OH).

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 139.9 (Ph C-1), 128.6 (Ph C-3,5), 128.4 (Ph C-4), 126.0 (Ph C2,6), 74.0 (CH), 50.7 (CH$_2$).

HRMS (ESI), $m/z$: calcd. For C$_8$H$_9$ClNaO 179.0234 [M+Na]; found 179.0238.
2-iodo-1-phenylethan-1-ol (2b)

![2b](image)

To a solution of aldehyde 2 (200 mg, 1.88 mmol, 1.0 equiv), in THF (1.9 mL) cooled at -78 °C was added diiodomethane (1514 mg, 0.46 mL, 5.65 mmol, 3.0 equiv), followed by the addition of a solution of MeLi-LiBr complex (1.5 M, 3.52 mL, 5.28 mmol, 2.8 equiv) operated by syringe pump with flow of 0.2 ml/min. The mixture was stirred for 1 h before it was quenched with saturated aq. NH₄Cl (2 mL) and extracted with Et₂O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and solvent was removed under reduced pressure to give a crude which after chromatographic purification on silica gel (elucent hexane/ethyl acetate 4:1, v/v) afforded iodohydrin 2b (420 mg, 90% yield).

¹H NMR (200 MHz, CDCl₃) δ: 7.37 (m, 5H, Ph), 4.84 (dd, J=8.6, 3.8 Hz, 1H, CH), 3.59-3.31 (m, 2H, CH₂), 2.44 (brs, 1H, OH).

¹³C NMR (50 MHz, CDCl₃) δ: 141.1 (Ph C-1), 128.7 (Ph C-3,5), 128.4 (Ph C-4), 125.7 (Ph C2,6), 74.1 (CH), 15.4 (CH₂).

HRMS (ESI), m/z: calcd. For C₉H₇INO 270.9590 [M+Na]; found 270.9591.

2-bromo-1-phenylethan-1-ol (2c)

![2c](image)

**Procedure A:**

To a solution of aldehyde 2 (200 mg, 1.88 mmol, 1.0 equiv), in THF (1.9 mL) cooled at -78 °C was added bromiodomethane (1247 mg, 0.43 mL, 5.65 mmol, 3.0 equiv), followed by the addition of a solution of MeLi-LiBr complex (1.5 M, 3.52 mL, 5.28 mmol, 2.8 equiv) operated by syringe pump with flow of 0.2 ml/min. The mixture was stirred for 1 h before it was quenched with saturated aq. NH₄Cl (2 mL) and extracted with Et₂O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and solvent was removed under reduced pressure to give a crude which after chromatographic purification on silica gel (elucent hexane/ethyl acetate 4:1, v/v) afforded bromohydrin 2b (294 mg, 78% yield).

**Procedure B:**

To a solution of aldehyde 2 (200 mg, 1.88 mmol, 1.0 equiv), in THF (1.9 mL) cooled at -78 °C was added dibromomethane (983 mg, 0.40 mL, 5.65 mmol, 3.0 equiv), followed by the addition of a solution of MeLi-LiBr complex (1.5 M, 3.52 mL, 5.28 mmol, 2.8 equiv) operated by syringe pump with flow of 0.2 ml/min. The mixture was stirred for 1 h before it was quenched with saturated aq. NH₄Cl (2 mL) and extracted with Et₂O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and solvent was removed under reduced pressure to give a crude which after chromatographic...
purification on silica gel (eluent hexane/ethyl acetate 4:1, v/v) afforded bromohydrin 2b (294 mg, 78% yield).

1H NMR (200 MHz, CDCl3) δ: 7.37 (m, 5H, Ph), 4.84 (dd, J=8.6, 3.8 Hz, 1H, CH), 3.59-3.31 (m, 2H, CH2), 2.44 (brs, 1H, OH).

13C NMR (50 MHz, CDCl3) δ: 141.1 (Ph C-1), 128.7 (Ph C-3,5), 128.4 (Ph C-4), 125.7 (Ph C2,6), 74.1 (CH), 15.4 (CH2).

HRMS (ESI), m/z: calcd. For C8H9BrNaO 222.9729 [M+Na]; found 222.9730.

2-phenyloxirane (3)

1H NMR (400 MHz, CDCl3) δ: 7.33 (m, 5H, Ph), 3.86 (dd, 1H, CH), 3.15 (dd, 1H, CH), 2.81 (dd, 1H, CH).

13C NMR (100 MHz, CDCl3) δ: 137.5 (Ph C-1), 128.3 (Ph C-4), 128.0 (Ph C2,6), 125.3 (Ph C-3,5), 52.1 (CH), 51.0 (CH2).

1-phenylethanol-1-ol (4)

1H NMR (400 MHz, CDCl3) δ: 7.23-7.47 (m, 5H, Ph), 4.90 (q, J=6.5 Hz, 1H, CH), 1.93 (brs, 1H, OH), 1.50 (d, J=6. 4 Hz, 1H, CH3).

13C NMR (100 MHz, CDCl3) δ: 145.8 (Ph C-1), 128.5 (Ph C-4), 127.4 (Ph C2,6), 125.4 (Ph C-3,5), 70.4 (CH), 25.1 (CH3).

1-chloro-3-phenylpropan-2-ol (5a)

To a solution of aldehyde 5 (200 mg, 1.66 mmol, 1.0 equiv), in THF (1.9 mL) cooled at -78 °C was added freshly distilled chloroiodomethane (881 mg, 0.36 mL, 5.0 mmol, 3.0 equiv), followed by the addition of a solution of MeLi-LiBr complex (1.5 M, 3.11 mL, 4.66 mmol, 2.8 equiv) operated by syringe pump with flow of 0.2 ml/min. The mixture was stirred for 1 h before it was quenched with saturated aq. NH4Cl (2 mL) and extracted with Et2O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na2SO4, filtered and solvent was removed under reduced pressure to give a crude which after chromatographic purification on silica gel (eluent hexane/ethyl acetate 4:1, v/v) afforded chlorohydrin 2a (180 mg, 64% yield).

1H NMR (200 MHz, CDCl3) δ: 7.14-7.30 (m, 5H, Ph), 3.99 (m, 1H, CH), 3.38-3.59 (m, 2H, CH2Cl), 2.82 (d, 2H, CH2Ph), 2.09 (brd, 1H, OH).
2-chloro-1-phenylethan-1-one (6a)

![structure_6a](image)

To a solution of Weinreb amide 6 (200 mg, 1.21 mmol, 1.0 equiv), in THF (1.2 mL) cooled at -78 °C was added freshly distilled chloroiodomethane (641 mg, 0.26 mL, 3.63 mmol, 3.0 equiv), followed by the addition of a solution of MeLi-LiBr complex (1.5 M, 2.26 mL, 3.39 mmol, 2.8 equiv) operated by syringe pump with flow of 0.2 ml/min. The mixture was stirred for 1 h before it was quenched with saturated aq. NH₄Cl (2 mL) and extracted with Et₂O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and solvent was removed under reduced pressure to give a crude which after chromatographic purification on silica gel (eluent hexane/ethyl acetate 4:1, v/v) afforded chloroketone 6a (153 mg, 82% yield).

1H NMR (400 MHz, CDCl₃) δ: 7.92 (m, 2H, Ph H-2,6), 7.57 (m, 1H, Ph H-4), 7.47 (m, 2H, Ph H-3,5), 4.70 (s, 2H, CH₂).

13C NMR (100 MHz, CDCl₃) δ: 190.8 (C=O), 134.0 (Ph C-1), 133.7 (Ph C-4), 128.6 (Ph C2,6), 128.2 (Ph C-3,5), 46.0 (CH₂).

IR (NaCl, νmax, cm⁻¹): 3062, 1691, 1589.

Elemental Analysis (%) for C₈H₇ClO. Calcd: C, 62.16; H, 4.56. Found: C, 62.31; H, 4.72.

1-(chloromethyl)cyclohex-2-en-1-ol (7a)

![structure_7a](image)

Procedure A:

To a solution of ketone 7 (200 mg, 2.08 mmol, 1.0 equiv) in THF (2 mL) cooled at -78 °C was added freshly distilled chloroiodomethane (997 mg, 0.41 mL, 5.65 mmol, 3.0 equiv), followed by the addition of a solution of MeLi-LiBr complex (1.5 M, 3.52 mL, 5.28 mmol, 2.8 equiv) operated by syringe pump with flow of 0.2 ml/min. The mixture was stirred for 1 hour before it was quenched with saturated aq. NH₄Cl (2 mL) and extracted with Et₂O (3 x 5 mL). The organic layer was washed with brine (5 mL),
dried over Na$_2$SO$_4$, filtered and after removing the solvent under reduced pressure, analytically pure chlorohydrin 7a (260 mg, 85% yield) was obtained as a colourless oil.

**Procedure B:**

To a solution of ketone 7 (200 mg, 2.08 mmol, 1.0 equiv) and an additive (3.0 equiv) in THF (2 mL) cooled at -35 °C was added freshly distilled chloroiodomethane (997 mg, 0.41 mL, 5.65 mmol, 3.0 equiv), followed by the addition of a solution of MeLi-LiBr complex (1.5 M, 3.52 mL, 5.28 mmol, 2.8 equiv) operated by syringe pump with flow of 0.2 ml/min. The mixture was stirred for 1 hour before it was quenched with saturated aq. NH$_4$Cl (2 mL) and extracted with Et$_2$O (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na$_2$SO$_4$, filtered and after removing the solvent under reduced pressure, analytically pure chlorohydrin 7a was obtained as a colourless oil.

$^1$H NMR (300 MHz, CDCl$_3$) δ: 5.94 (dt, J = 10.2, 3.7 Hz, 1H), 5.64 (dt, J = 10.1, 2.3 Hz, 1H), 3.55 (d, J = 2.3 Hz, 2H), 2.21 (s, 1H), 2.15 – 1.42 (m, 7H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 132.6, 128.5, 69.1, 53.8, 33.3, 25.2, 18.8.

**Elemental Analysis (%) for C$_7$H$_{11}$ClO. Calcd: C, 57.35; H, 7.56. Found: C, 57.51; H, 7.70.**

1-methyl-2-cyclohexene-1-carbaldehyde (7b)

![1-methyl-2-cyclohexene-1-carbaldehyde](image)

$^1$H NMR (400 MHz, C$_6$D$_6$) δ: 9.24 (s, 1H, CHO), 5.67 (td, $^3$J$_{H3,H2}$ = 10.0 Hz, $^3$J$_{H3,H4}$ = 3.8 Hz, 1H, H-3), 5.26 (td, $^3$J$_{H2,H3}$ = 10.0 Hz, $^3$J$_{H2,H4}$ = 2.1 Hz, 1H, H-2), 1.74 (m, 1H, H-6), 1.68 – 1.63 (m, 2H, H-4), 1.44 – 1.26 (m, 2H, H-5), 1.07 (m, 1H, H-6), 0.87 (s, 3H, 1-CH$_3$).

$^{13}$C NMR (100 MHz, C$_6$D$_6$) δ: 201.7 (CHO), 130.7 (C-3), 128.2 (C-2), 47.5 (C-1), 30.0 (C-6), 24.9 (C-4), 22.1 (1-CH$_3$), 19.1 (C-5).

HRMS (ESI), m/z: calcd. for C$_8$H$_{13}$O+: 125.0961 [M+H]$^+$; found: 125.0964.
Copies of NMR spectra

$^1$H-NMR, 200 MHz, CDCl$_3$
$^{1}H$-NMR, 200 MHz, CDCl$_3$)

$^{13}C$-NMR, 50 MHz, CDCl$_3$)
$\text{2c}$

($^1\text{H-NMR, 200 MHz, CDCl}_3$)

$\text{2c}$

($^{13}\text{C-NMR, 50 MHz, CDCl}_3$)
\( ^1H\text{-NMR, 200 MHz, CDCl}_3 \)

\( \begin{align*}
\text{3} \\
(\text{H-NMR, 200 MHz, CDCl}_3)
\end{align*} \)

\( \begin{align*}
\text{3} \\
(\text{C-NMR, 50 MHz, CDCl}_3)
\end{align*} \)
$5a$  
($^1$H-NMR, 200 MHz, CDCl$_3$)

$5a$  
($^{13}$C-NMR, 50 MHz, CDCl$_3$)
\[ \text{6a} \]

\((^1\text{H-NMR, 200 MHz, CDCl}_3)\)

\[ \text{13C-NMR, 50 MHz, CDCl}_3 \]
7b
\[(^1H-NMR, 400 MHz, C_6D_6)\]

7b
\[(^13C-NMR, 100 MHz, C_6D_6)\]
