Electronic Supplementary Information (ESI)

Water opens the door to organolithium and Grignard reagents: exploring and comparing the reactivity of highly polar organometallic compounds in unconventional reaction media towards the synthesis of tetrahydrofurans

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1. General Methods

Tetrahydrofuran (THF), was freshly distilled, under a nitrogen atmosphere, over sodium/benzophenone ketyl. Eutectic mixtures of solvents [choline chloride (ChCl)--glycerol (Gly) (1:2 mol/mol); D-fructose–ChCl (2:1 mol/mol); L-tartaric acid–ChCl (1:2 mol/mol); L-lactic acid–L-alanine (9:1 mol/mol)] and the low melting mixture of D-fructose–urea (3:2 weight/weight) were prepared by heating under stirring up to 90 °C for 10–30 min the corresponding individual components until a clear solution was obtained. For 1H and 13C NMR spectra (1H NMR 400, 500 or 600 MHz; 13C NMR 100, 125 or 150 MHz), CDCl3 was used as the solvent. GC-MS spectrometry analyses were performed on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Elemental analyses were performed by using a Carlo Erba CHNS-O EA1108-Elemental Analyzer. Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying with a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 ml 17.6 % (w/v) aq. sulfuric acid and heating to 473 K for some time until blue spots appear. Some reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe-septum cap technique. The following solutions of Grignard reagents and organolithium reagents were commercially available and were used with the following concentration: MeMgCl 3.0 M in THF, EtMgCl 2.0 M in THF, i-PrMgCl 2.0 M in THF, allylMgCl 2.0 M in THF, 4-MeOC6H4MgBr 0.5 M in THF, 4-ClC6H4MgBr 1.0 M in 2-MeTHF, 4-FC6H4MgBr 2.0 M in Et2O, MeLi 1.6 M in Et2O, EtLi 0.5 M in benzene/cyclohexane, i-PrLi 0.7 M in pentane, n-BuLi 2.5 M in hexanes, PhLi 1.8 M in dibutyl ether. Spectroscopic data of compounds 3a, 3b, 3c, 3de, 3f, 3g, 3j, 3k, 3l, 3n and 4a are in agreement with the literature. γ–Chloroketones 1a–d and cyclopropyl phenyl ketone 4a are commercially available. Fully characterization data, including elemental analysis and copies of 1H and 13C NMR spectra, have been reported for the new compounds 2a, 3h, 3i and 3m.

2. Experimental Procedures

2.1 Preparation of 5-chloro-2-phenylpentan-2-ol (2a) and 2-methyl-2-phenyltetrahydrofuran (3a) in THF. Typical Procedure.

To an anhydrous THF solution (1 mL) of the ketone 1a (0.5 mmol), 0.94 mL of the commercially available MeLi (1.5 mmol in 1.6 M Et₂O solution) were added dropwise, under argon, at −40 °C. After 12 h stirring at RT, the reaction mixture was treated with 10% aq. NaOH for 3 h (or quenched with H₂O to isolate chlorohydrin 2a), and then extracted with Et₂O (3 × 20 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was concentrated in vacuo. The crude product was purified by flash-chromatography (silica gel, hexane/Et₂O 80:20, Et₃N 2%), to give 3a in 70% yield. Spectroscopic data are in accord with the literature. The chlorohydrin 2a could be purified by flash-chromatography on silica gel with hexane/AcOEt 80:20 as the eluent in 38% yield (see Table 1 of the main text).
2.2 Preparation of 2-ethyl-2-phenyltetrahydrofuran (3c) in deep eutectic solvents. Typical procedure.

To a mixture of the ketone 1a (0.5 mmol) in 1 g of ChCl–Gly (1:2), 0.75 mL of the commercially available EtMgCl (1.5 mmol in 2.0 M THF solution), handled under argon using conventional Schlenk techniques, were quickly spread out at RT, under air, and vigorous stirring. After 10 min, 10 mL of 10% aq. NaOH were added and the mixture was stirred for additional 3 h, and then extracted with Et₂O (3 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and the solvent was concentrated in vacuo. The crude product was purified by flash-chromatography to give 3c in 75% yield.
2.3 Preparation of 2-methyl-2-phenyltetrahydrofuran (3a) in water. Typical procedure.

To a suspension of the ketone 1a (0.5 mmol) in 1 mL of water, 0.94 mL of the commercially available MeLi (1.5 mmol in 1.6 M Et₂O solution), handled under argon using conventional Schlenk techniques, were quickly spread out at RT, under air, and vigorous stirring. After 10 min, 10 mL of 10% aq. NaOH were added and the mixture was stirred for additional 3 h, and then extracted with Et₂O (3 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and the solvent was concentrated in vacuo. The crude product was purified by flash-chromatography to give 3a in 75% yield.
3. Characterization Data

5-Chloro-2-phenylpentan-2-ol (2a): colourless oil. \( ^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.51 (s, 3 H); 1.54–1.61 (m, 1 H), 1.65–1.77 (m, 1 H), 1.81–1.92 (m, 2 H), 3.36–3.44 (m, 2 H); 7.15–7.19 (m, 1 H), 7.25–7.29 (m, 2 H), 7.34–7.36 (m, 2 H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 27.4, 30.6, 41.4, 45.5, 74.4, 124.7, 126.8, 128.3, 147.3; FT-IR (film, cm\(^{-1}\)): 3436, 3058, 2956, 2925, 1601, 1445, 1028, 760, 700; GC-MS (70 eV) \( m/z \) (%): 198 (M\(^+\), 5), 183 (9), 147 (11), 121 (100), 105 (19), 77 (10), 43 (15). Anal. Calcd. for C\(_{11}\)H\(_{15}\)ClO: C, 66.49; H, 7.61; Found: C, 66.84; H, 7.69.

6-Chloro-3-phenylhexan-3-ol (2c): colourless oil. \( ^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.76 (t, \( J = 7.4 \) Hz, 3 H); 1.49–1.59 (m, 1 H), 1.77–2.01 (m, 5 H), 3.46–3.50 (m, 2 H); 7.23–7.26 (m, 1 H), 7.33–7.40 (m, 4 H); \( ^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 7.6, 27.0, 35.7, 39.9, 45.7, 76.9, 125.3, 126.5, 128.2, 145.2; FT-IR (film, cm\(^{-1}\)): 3467, 3027, 2963, 2929, 1602, 1446, 1310, 760, 701; GC-MS (70 eV) \( m/z \) (%): 212 (M\(^+\), 2), 194 (6) 183 (75), 147 (61), 135 (55), 105 (100), 77 (10). HRMS calcd. for C\(_{12}\)H\(_{17}\)ClO (M + Na\(^+\)): 235.0866. Found: 235.0860.

2-Methyl-2-phenyltetrahydrofuran (3a):\(^1\) colourless oil. \( ^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.47–1.53 (m, 2 H), 1.57 (s, 3 H), 1.80–2.05 (m, 2 H), 3.55–3.65 (m, 2 H), 7.21–7.44 (m, 5 H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 26.9, 30.2, 40.9, 62.5, 74.2, 124.9, 125.8, 125.9, 126.3, 127.2, 127.2, 128.0, 128.2, 144.7, 144.8, 148.0; FT-IR (film, cm\(^{-1}\)): 3016, 2972, 2927, 2869, 1492, 1445, 1098, 1068, 1037, 763, 701; ESI-MS: 163.2 (M\(^+\) + 1).

2-Isopropyl-2-phenyltetrahydrofuran (3b):\(^2\) colourless oil. \( ^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 0.82 (d, \( J = 6.5 \) Hz, 3 H), 0.87 (d, \( J = 6.5 \) Hz, 3 H), 1.70–1.73 (m, 1 H), 1.90–1.93 (m, 1 H), 2.00–2.04 (m, 1 H), 2.06–2.10 (m, 1 H), 2.22–2.26 (m, 1 H),
2-Ethyl-2-phenyltetrahydrofuran (3c): \(^3\) colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.76 (t, \(J = 7.4\) Hz, 3 H), 1.86–1.74 (m, 3 H), 1.98–1.90 (m, 1 H), 2.07–2.00 (m, 1 H), 3.86–3.90 (m, 1 H), 3.94–4.00 (m, 1 H), 7.19–7.23 (m, 1 H), 7.37–7.29 (m, 4 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 8.7, 25.6, 35.0, 37.7, 67.4, 77.4, 87.1, 125.3, 127.8, 146.5; FT-IR (film, cm\(^{-1}\)): 3024, 2967, 2929, 1492, 1446, 1057, 758, 701; GC-MS (70 eV) \(m/z\) (%): 176 (M\(^+\), 3), 147 (100), 105 (55), 77 (16).

2-(4-Methoxyphenyl)-2-phenyltetrahydrofuran (3d): \(^4\) colourless oil: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.91–1.98 (m, 2 H), 2.50–2.57 (m, 2 H), 3.76 (s, 3 H), 4.02–4.06 (m, 2 H), 6.81–6.84 (m, 2 H), 7.16–7.20 (m, 1 H), 7.27–7.36 (m, 4 H), 7.41–7.42 (m, 2 H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\): 25.5, 38.7, 55.5, 67.3, 87.8, 113.5, 125.8, 126.6, 127.1, 128.1, 138.5, 146.7, 158.4; FT-IR (film, cm\(^{-1}\)): 3059, 2953, 2876, 1610, 1509, 1250, 1055, 829; GC-MS (70eV), \(m/z\) (%): 254 (M\(^+\), 25), 223 (10), 177 (100), 135 (50).

2-(4-Chlorophenyl)-2-phenyltetrahydrofuran (3e): \(^4\) colourless oil. \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 1.95–2.03 (m, 1 H), 2.07–2.14 (m, 1 H), 2.55–2.60 (m, 1 H), 3.03–3.07 (m, 1 H), 3.96–4.05 (m, 2 H), 7.20–7.23 (m, 2 H), 7.27–7.33 (m, 6 H), 7.92–7.93 (m, 1 H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\): 26.6, 36.3, 67.6, 87.6, 126.5, 126.8, 127.1, 127.6, 127.9, 128.4, 131.0, 132.0, 143.6, 143.8; FT-IR (film, cm\(^{-1}\)): 2918, 1492, 1459, 758, 697; GC-MS (70 eV) \(m/z\) (%): 258 (M\(^+\), 22), 223 (28), 181 (80), 147 (100), 105 (57).

2-Butyl-2-phenyltetrahydrofuran (3f): \(^5\) colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.81 (t, \(J = 7.2\) Hz, 3 H), 0.92–1.08 (m, 1 H), 1.18–1.29 (m, 3 H), 3.76–3.82 (m, 1 H), 3.93–3.97 (m, 1 H), 7.21–7.38 (m, 5 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 17.5, 18.5, 25.7, 35.5, 37.9, 67.1, 89.5, 126.2, 126.3, 127.5, 145.0; FT-IR (film, cm\(^{-1}\)): 2965, 2873, 1489, 1469, 1445, 1382, 1364, 1055, 760, 703; ESI-MS: 189.1 (M\(^−\)– 1).
1.73–2.18 (m, 6 H), 3.85–3.97 (m, 2 H), 7.20–7.37 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.0, 23.1, 25.5, 26.6, 30.3, 67.4, 86.8, 125.2, 126.1, 127.9, 146.9; FT-IR (film, cm$^{-1}$): 2957, 2933, 2871, 1458, 1446, 1118, 1048, 763, 702; ESI-MS: 205 (M$^+$ + 1).

2- Allyl-2-phenyltetrahydrofuran (3g): colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.66–1.77 (m, 1 H), 1.85–1.92 (m, 1 H), 2.04–2.10 (m, 2 H), 2.43–2.48 (m, 1 H), 2.52–2.56 (m, 1 H), 3.81–3.85 (m, 1 H), 3.90–3.95 (m, 1 H), 4.91–4.96 (m, 2 H), 5.58–5.67 (m, 1 H), 7.12–7.17 (m, 1 H), 7.23–7.34 (m, 4 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 25.5, 37.2, 46.9, 67.7, 86.2, 117.4, 125.2, 126.3, 127.9, 134.3, 146.6; FT-IR (film, cm$^{-1}$): 2976, 2872, 1446, 1055, 914, 762, 703; GC-MS (70 eV) m/z (%): 188 (M$^+$, 2), 147 (100), 105 (70), 77 (21).

2-Isopropyl-2-(4-methoxyphenyl)tetrahydrofuran (3h): colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.81 (d, $J = 6.5$ Hz, 3 H), 0.82 (d, $J = 6.5$ Hz, 3 H), 1.66–1.72 (m, 1 H), 1.85–1.91 (m, 1 H), 1.93–2.05 (m, 2 H), 2.19–2.24 (m, 1 H), 3.72–3.77 (m, 1 H), 3.80 (s, 3 H), 3.89–3.94 (m, 1 H), 6.83–6.86 (m, 2 H), 7.25–7.28 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 17.6, 18.5, 25.6, 35.3, 38.1, 55.2, 67.0, 89.3, 112.9, 127.5, 136.7, 158.1; FT-IR (film, cm$^{-1}$): 2962, 2874, 1610, 1508, 1464, 1294, 1246, 1176, 1058, 1039, 826, 799; GC-MS (70 eV) m/z (%): 220 (M$^+$, 13), 177 (100), 135 (30), 92 (23), 77 (14). Anal. Calcd. for C$_{14}$H$_{20}$O$_2$: C, 76.33; H, 9.15; Found: C, 76.40; H, 9.28.

2-Butyl-2-(4-methoxyphenyl)tetrahydrofuran (3i): colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.79 (t, $J = 6.9$ Hz, 3 H), 1.14–1.30 (m, 4 H), 1.67–1.79 (m, 3 H), 1.84–1.99 (m, 2 H), 2.10–2.16 (m, 1 H), 3.77 (s, 3 H), 3.80–3.85 (m, 1 H), 3.89–3.95 (m, 1 H), 6.81–6.84 (m, 2 H), 7.22–7.25 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.0, 23.1, 25.5, 26.7, 38.1, 42.4, 55.2, 67.2, 86.5, 113.2, 126.3, 138.8, 157.9; FT-IR (film, cm$^{-1}$): 2932, 1611, 1509, 1463, 1298, 1246, 1175, 1039, 830; GC-MS (70 eV) m/z (%): 234 (M$^+$, 15), 177 (100), 135 (43), 128 (12), 92 (14), 77 (5). Anal. Calcd. for C$_{15}$H$_{22}$O$_2$: C, 76.88; H, 9.46; Found: C, 77.11; H, 9.69.
2-Ethyl-2-(4-methoxyphenyl)tetrahydrofuran (3j): colourless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ 0.77 (t, $J$ = 7.5 Hz, 3 H), 1.76–1.84 (m, 3 H), 1.92–2.05 (m, 2 H), 2.13–2.18 (m, 1 H), 3.81 (s, 3 H), 3.86–3.90 (m, 1 H), 3.94–3.98 (m, 1 H), 6.87 (d, $J$ = 8.5 Hz, 2 H), 7.28 (d, $J$ = 8.5 Hz, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 9.1, 25.8, 35.4, 37.9, 55.5, 67.6, 87.2, 113.5, 126.7, 138.8, 158.2; FT-IR (film, cm$^{-1}$): 2966, 2934, 2875, 1610, 1582, 1510, 1442, 1299, 1176, 1037, 911, 830; ESI-MS: 207 (M$^+$ + 1).

2-(4-Methoxyphenyl)-2-methyltetrahydrofuran (3k): colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.42 (s, 3 H), 1.87–1.93 (m, 1 H), 2.05–2.12 (m, 1 H), 3.80 (s, 3 H), 3.81–3.84 (m, 1 H), 3.89–3.94 (m, 1 H), 6.77–6.80 (m, 2H), 7.22–7.25 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 27.2, 30.4, 41.1, 55.3, 67.1, 87.1, 113.3, 126.8, 140.3, 158.8; FT-IR (film, cm$^{-1}$): 2969, 2877, 1609, 1512, 1444, 1297, 1176, 1036, 910, 830; GC-MS (70 eV) m/z (%): 193 (M$^+$ + 1, 13), 177 (100), 175 (13), 151 (32), 135 (84) 77 (20).

2,2-Bis(4-fluorophenyl)tetrahydrofuran (3l): colourless oil. $^1$H NMR (600 MHz; CDCl$_3$): δ 1.93–2.00 (m, 2 H), 2.50–2.54 (m, 2 H), 4.03–4.06 (m, 2 H), 6.96–7.01 (m, 4 H), 7.36–7.40 (m, 4 H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 25.4, 38.8, 67.4, 87.2, 114.9 (d, $^2$J$_{C-F}$ = 21.2 Hz), 127.4 (d, $^3$J$_{C-F}$ = 8.0 Hz), 141.9 (d, $^4$J$_{C-F}$ = 3.3 Hz), 161.6 (d, $^1$J$_{C-F}$ = 240 Hz); FT-IR (film, cm$^{-1}$): 3055, 2959, 1598, 1506, 1266, 743; GC-MS (70 eV), m/z (%): 260 (3), 219 (100), 123 (60). Anal. Calcd. for C$_{16}$H$_{14}$F$_2$O: C, 73.83; H, 5.42. Found: C, 74.02; H, 5.55.

2-(4-Fluorophenyl)-2-methyltetrahydrofuran (3m): colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.47 (s, 3 H), 1.72–1.80 (m, 1 H), 1.91–2.01 (m, 2 H), 2.08–2.15 (m, 1 H), 3.83–3.89 (m, 1 H), 3.94–3.99 (m, 1 H), 6.93–6.98 (m, 2 H), 7.08–7.13 (m, 1 H), 7.30–7.33 (m, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ: 17.0, 25.7, 39.5, 67.5, 83.9, 115.5 (d, $^2$J$_{C-F}$ = 21.4 Hz), 126.2 (d, $^3$J$_{C-F}$ = 7.5 Hz), 141.8, 161.3 (d, $^1$J$_{C-F}$ = 243.0 Hz); FT-IR (film, cm$^{-1}$): 3055, 2959, 1600, 1590, 1266, 1176, 912, 831; GC-MS (70 eV) m/z (%): 180 (M$^+$,6), 165 (100), 135 (7), 123 (77). Anal. Calcd. for C$_{11}$H$_{15}$FO: C, 73.31; H, 7.27. Found: C, 73.58; H, 7.51.
**2,2-Dimethyltetrahydrofuran (3n):** Colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.24 (s, 6 H), 1.71 (t, $J$ = 7.7 Hz, 2 H), 1.91–2.00 (m, 2 H), 3.84 (t, $J$ = 6.9 Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 25.9, 27.7, 38.1, 67.1, 81.4; FT-IR (film, cm$^{-1}$): 2962, 1467, 1140, 609; ESI-MS: 100 ($M^+$).

**Cyclopropyl(phenyl)methanone (4a):** Colourless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.02 (ddd, $J$ = 8.0, 7.0, 3.5 Hz, 2 H), 1.22 (ddd, $J$ = 7.0, 4.5, 3.5 Hz, 2 H), 2.60–2.70 (m, 1 H), 7.43–7.47 (m, 2 H), 7.49–7.55 (m, 1 H), 7.96–8.02 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 11.6, 17.1, 127.9, 128.3, 132.7, 138.0, 200.5; FT-IR (film, cm$^{-1}$): 3031, 2960, 1668, 1597, 1579, 752, 700; ESI-MS: 146 ($M^+$).
$^1$H and $^{13}$C NMR spectra of 2a
$^1$H and $^{13}$C NMR spectra of 2c
$^1$H and $^{13}$C NMR spectra of 3h
$^{1}$H and $^{13}$C NMR spectra of 3i

$^{1}$H NMR 400 MHz, CDCl$_3$

$^{13}$C NMR 100 MHz, CDCl$_3$
$^1$H and $^{13}$C NMR spectra of 3m