Efficient Preparation of Polyfunctional Organometallics via Directed *ortho*-Metalation

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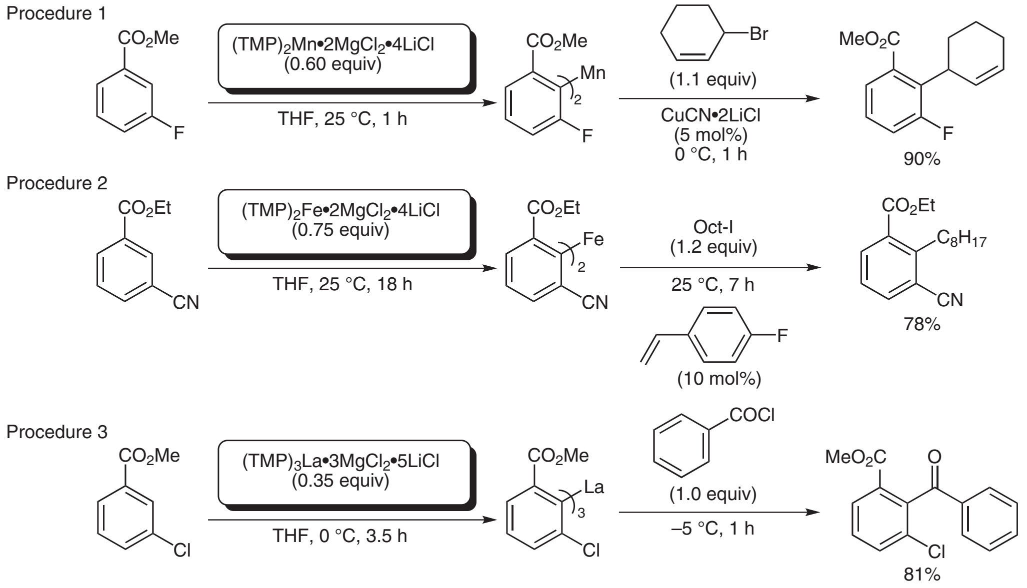
Abstract: Highly functionalized organometallics are efficiently prepared in larger quantities (up to 4 g) by directed *ortho*-metalation using the previously reported amide bases $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (TMP = 2,2,6,6-tetramethylpiperidyl), $TMP_2Fe\cdot 2MgCl_2\cdot 4LiCl$ and $TMP_3La\cdot 3MgCl_2\cdot 5LiCl$. The resulting organometallics undergo various reactions with electrophiles like acid chlorides, alkyl iodides, or aldehydes and provide the corresponding products in good to excellent yields.

Key words: directed metalation, organometallics, metal amides, catalysis, LiCl



Scheme 1 General procedures for the preparation of highly functionalized organometallics and their reactions with various electrophiles

Introduction

The metalation of functionalized unsaturated substrates provides useful intermediates in organic synthesis. Besides traditional and well-investigated lithium reagents,[1] a number of mixed ate-bases have been developed and structurally investigated.[2] Although these approaches seemed to be promising, there is still a need for neutral and easily manageable chemoselective bases for the metalation of organic substrates tolerating most functionalities at ambient temperature. Recently, we reported that the treatment of $TMPMgCl\cdot LiCl$[3] (**1**; TMP = 2,2,6,6-tetramethylpiperidyl) with metallic chlorides such as $ZnCl_2$,[4] $MnCl_2\cdot 2LiCl$,[5] $FeCl_2\cdot 2LiCl$[6] and $LaCl_3\cdot 2LiCl$[7] leads to room temperature stable and highly kinetic active metalation reagents. The metalations occur under mild conditions (usually close to 25 °C) and display a high atom economy since all TMP moieties can be used for the directed metalation. The resulting organometallics can contain a variety of functional groups and they react with a number of electrophiles (in the presence of an appropriate catalyst, if needed). In general, we have shown that changing the metal of the amide bases also changes the behavior of the corresponding organometallic reagent. Usually, the optimization of these metalation procedures was carried out in 1–2 mmol scale. Herein, we wish to report the extension of the preparation of functionalized organometallics using the new metalation reagents of Mn, Fe, and La to the experiments in larger scales (ca. 3–4 g scale) (Scheme 1).

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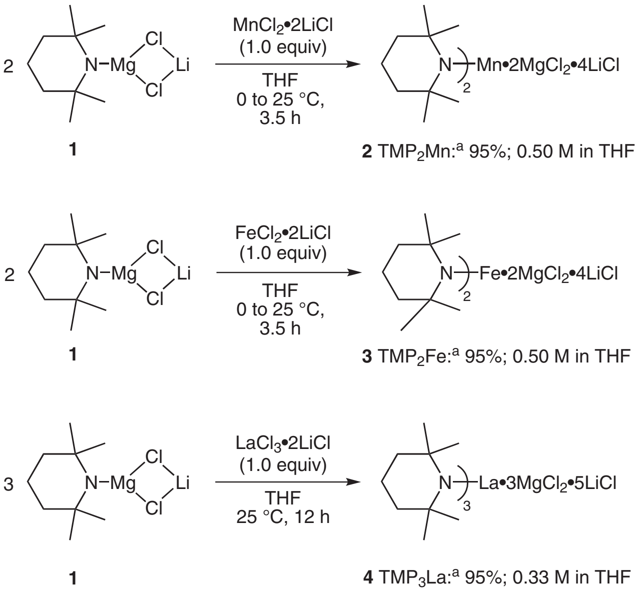
Results and Discussion

First, the amide bases **2**–**4** were efficiently prepared by the transmetalation of TMPMgCl·LiCl (**1**; Scheme 2). Thus, the reaction of TMPMgCl·LiCl[3] (**1**; 2.0 equiv) with a solution of $MnCl_2$·2LiCl[8] (1 M in THF) provides the reagent $TMP_2Mn·2MgCl_2·4LiCl$ (**2**) in >95% yield by stirring the mixture for 30 minutes at 0 °C and further for three hours at 25 °C. Similarly, the new Fe(II)-base $TMP_2Fe·2MgCl_2·4LiCl$ (**3**) is obtained by the similar reaction of TMPMgCl·LiCl (**1**; 2.0 equiv) with a solution of $FeCl_2$·2LiCl (1 M in THF). Additionally, $TMP_3La·3MgCl_2·5LiCl$ (**4**) is prepared by the reaction of TMPMgCl·LiCl (**1**; 3.0 equiv) with the THF soluble complex $LaCl_3$·2LiCl[9] in THF for 12 hours. All three bases can be stored at 25 °C under inert gas atmosphere for at least two months without decomposition.

We started these upscaling experiments with the directed manganations using the manganese amide base **2**. Thus, the metalation of methyl 3-fluorobenzoate (**5a**) is complete within one hour at 25 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**2**; 0.6 equiv). A CuCN·2LiCl catalyzed allylation[10] with 3-bromocyclohexene furnishes the 1,2,3-trisubstituted arene **6a** in 90% yield (Table 1, entry 1). Furthermore, the manganation of 4-fluorobenzonitrile (**5b**) takes place at 25°C within two hours using $TMP_2Mn·2MgCl_2·4LiCl$ (**2**; 0.6 equiv). A subsequent CuCN·2LiCl mediated acylation[10] with benzoyl chloride leads to the benzophenone **6b** in 68% yield (entry 2). Ethyl 4-cyanobenzoate (**5c**) is fully manganated within 1.25 hours at 0 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**2**; 0.6 equiv) and the ketone **6c** is obtained in 70% yield after a CuCN·2LiCl mediated acylation[10] with 2-furoyl chloride (entry 3).



Scheme 2 Preparation of the bases **2**–**4**. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity

Table 1 Preparation of the Products of Type **6** by Directed Metalation Using the TMP-Bases of Mn, Fe, and La

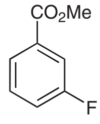
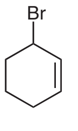
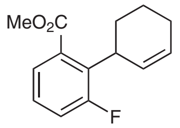
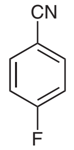
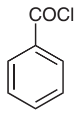
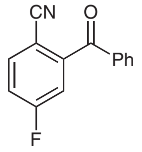
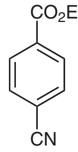
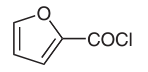
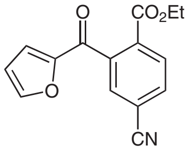
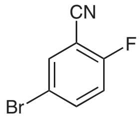
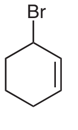
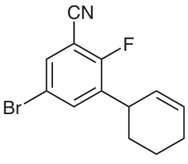
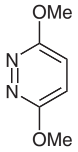
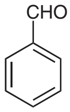
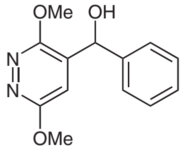
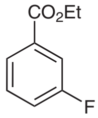
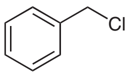
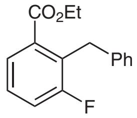
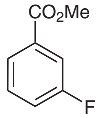
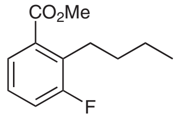
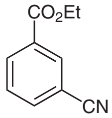
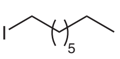
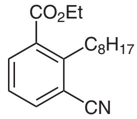
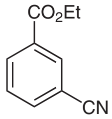
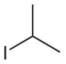
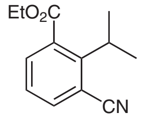
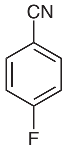
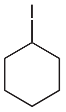
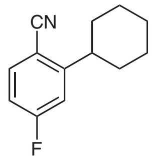
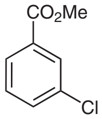
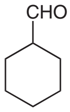
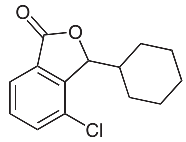
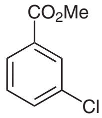
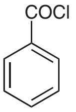
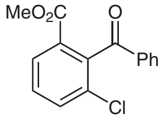
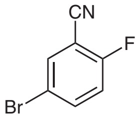
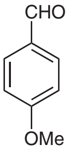
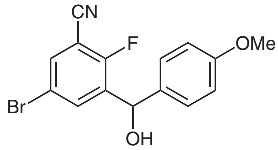
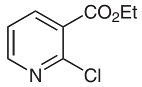
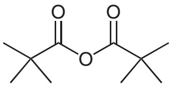
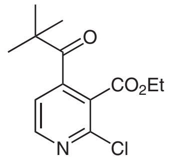
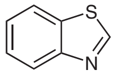
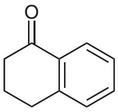
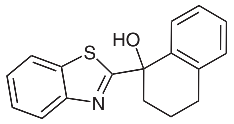
Entry	Substrate (**5**)		Base	Temp (°C), time (h)	Electrophile	Product (**6**)	Yield (%)[a]
1		**5a**	TMP_2Mn (**2**)	25, 1			**6a**: 90[b]
2		**5b**	TMP_2Mn (**2**)	25, 2			**6b**: 68[c]
3		**5c**	TMP_2Mn (**2**)	0, 1.25			**6c**: 70[c]
4		**5d**	TMP_2Mn (**2**)	0, 0.5			**6d**: 96[b]

Table 1 Preparation of the Products of Type **6** by Directed Metalation Using the TMP-Bases of Mn, Fe, and La (continued)

Entry	Substrate (**5**)		Base	Temp (°C), time (h)	Electrophile	Product (**6**)	Yield (%)[a]
5		**5e**	TMP_2Mn (**2**)	0, 0.5			**6e**: 94
6		**5f**	TMP_2Fe (**3**)	25, 3			**6f**: 85
7		**5a**	TMP_2Fe (**3**)	25, 3			**6g**: 83[d]
8		**5g**	TMP_2Fe (**3**)	25, 18			**6h**: 78[d]
9		**5g**	TMP_2Fe (**3**)	25, 18			**6i**: 78[d]
10		**5b**	TMP_2Fe (**3**)	25, 18			**6j**: 69[d]
11		**5h**	TMP_3La (**4**)	0, 3.5			**6k**: 73
12		**5h**	TMP_3La (**4**)	0, 3.5			**6l**: 75
13		**5d**	TMP_3La (**4**)	–35, 0.5			**6m**: 80
14		**5i**	TMP_3La (**4**)	–20, 0.75			**6n**: 80
15		**5j**	TMP_3La (**4**)	0, 0.5			**6o**: 87

[a] Isolated yield of analytically pure products.

[b] CuCN·2LiCl (5 mol%) was used.

[c] CuCN·2LiCl (20 mol%) was used.

[d] 4-Fluorostyrene (10 mol%) was used.

Surprisingly, the manganation of 5-bromo-2-fluorobenzonitrile (**5d**) is achieved in position adjacent to the fluorine substituent within 30 minutes at 0 °C using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**2**; 0.6 equiv). A $CuCN \cdot 2LiCl$ catalyzed allylation[10] with 3-bromocyclohexene gives the highly functionalized arene **6d** in 96% yield (entry 4). Similarly, the metalation of 3,6-dimethoxypyridazine (**5e**) is accomplished within 30 minutes at 0 °C using $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**2**; 0.6 equiv). The addition of the metalated species to benzaldehyde provides the alcohol **6e** in 94% yield (entry 5).

Furthermore, the directed ferration and the subsequent cross-couplings catalyzed by nickel impurities can also be carried out in larger scales. Thus, the metalation of ethyl 3-fluorobenzoate (**5f**) leads to the fully ferrated arene within three hours at 25 °C. The subsequent reaction with benzyl chloride affords the substituted diphenylmethane **6f** in 85% yield (entry 6). Similarly, the ferration of methyl 3-fluorobenzoate (**5a**) using $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**3**; 0.75 equiv) is also finished within three hours at 25 °C. An adjacent alkylation with 1-iodobutane in the presence of 4-fluorostyrene[11] furnishes the alkylated arene **6g** in 83% yield (entry 7). Arenes bearing cyano groups can also be used for this ferration procedure. Thus, ethyl 3-cyanobenzoate (**5g**) is metalated regioselectively in position 2 within 18 hours at 25 °C using $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**3**; 0.75 equiv). The subsequent alkylation reactions with either 1-iodooctane or 2-iodopropane in the presence of 4-fluorostyrene provide the products **6h**,**i** in 78% yield in both cases (entries 8 and 9). Additionally, the metalation of 4-fluorobenzonitrile (**5b**) is readily finished within 18 hours at 25 °C using $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**3**; 0.75 equiv). An alkylation with iodocyclohexane in the presence of 4-fluorostyrene affords the functionalized benzonitrile **6j** in 69% yield (entry 10).

Subsequently, the lanthanations were investigated. Thus, methyl 3-chlorobenzoate (**5h**) is converted into the fully lanthanated species within 3.5 hours at 0 °C using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**4**; 0.35 equiv). The subsequent additions to electrophiles bearing carbonyl groups like cyclohexanecarbaldehyde or benzoyl chloride furnish the lactone **6k** and the benzophenone **6l** in 73 and 75% yield, respectively (entries 11,12). Furthermore, after 30 minutes at –35 °C, the metalation of 5-bromo-2-fluorobenzonitrile (**5d**) is complete using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**4**; 0.35 equiv) and the adjacent addition to 4-methoxybenzaldehyde gives the alcohol **6m** in 80% yield (entry 13). Moreover, ethyl 2-chloronicotinate (**5i**) is fully metalated after 45 minutes at –20 °C using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**4**; 0.35 equiv) and a subsequent acylation with 2,2-dimethylpropanoic anhydride provides the highly functionalized pyridine **6n** in 80% yield (entry 14). Finally, the lanthanation of benzothiazole (**5j**) is readily finished after 30 minutes at 0 °C using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**4**; 0.35 equiv) and the reaction of the metalated species with α-tetralone leads to the tertiary alcohol **6o** in 87% yield (entry 15).

In summary, we have demonstrated that the use of the bases $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**2**), $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**3**), and $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**4**) leads smoothly to the corresponding organometallics. The reactions are carried out in larger amounts and important functional groups like esters or cyano groups can be easily tolerated during the metalation protocols. Efficient and atom economical reactions with electrophiles provide the desired products in good to excellent yields. The application of these bases to more complex systems is currently underway in our laboratories.

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under N_2. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR spectroscopy (25 °C) and capillary GC analysis. NMR spectra were recorded on solutions in $CDCl_3$ with residual $CHCl_3$ ($\delta = 7.25$ for ^{1}H NMR and 77.0 for ^{13}C NMR), DMSO-d_6 ($\delta = 2.49$ for ^{1}H NMR and 39.5 for ^{13}C NMR). Column chromatographical purifications were performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck, unless otherwise indicated. TMPH, liquid acid chlorides and aldehydes were distilled prior to use. $LaCl_3 \cdot 2LiCl$ was purchased as a 0.5 M solution in THF from Chemetall GmbH, Frankfurt.

Reagent $MnCl_2 \cdot 2LiCl$ (1 M in THF)

A dry and argon-flushed 250 mL Schlenk tube, equipped with a magnetic stirring bar and a glass stopper, was charged with LiCl (6.8 g, 160 mmol) and heated up to 150 °C under high vacuum for 3 h. After cooling to r.t. under argon, $MnCl_2$ (10.1 g, 80 mmol, 99% pure) was added under inert atmosphere inside a glove box. The Schlenk flask was further heated to 130 °C for 3 h under high vacuum, cooled to r.t., and charged with freshly distilled THF (80 mL) under argon with vigorous stirring. The mixture was stirred for at least 24 h at 25 °C. The reagent $MnCl_2 \cdot 2LiCl$ (1.0 M in THF) was obtained as a yellow solution.

Reagent $FeCl_2 \cdot 2LiCl$ (1 M in THF)

A dry and argon-flushed 250 mL Schlenk tube, equipped with a magnetic stirring bar and a glass stopper, was charged with LiCl (4.7 g, 110 mmol) and heated up to 150 °C under high vacuum for 3 h. After cooling to r.t. under argon, $FeCl_2$ (6.34 g, 50 mmol, 98% pure) was added under inert atmosphere inside a glove box. The Schlenk flask was further heated to 130 °C for 5 h under high vacuum, cooled to r.t., charged with freshly distilled THF (50 mL) under argon and wrapped in an aluminum foil to protect it from light. The mixture was vigorously stirred until all solid goes in solution (ca. 6 h). The reagent $FeCl_2 \cdot 2LiCl$ (1.0 M in THF) was obtained as a brown solution.

Reagent $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (2)

In a dry and argon-flushed 250 mL Schlenk flask, freshly titrated $TMPMgCl \cdot LiCl$ (**1**; 200 mmol, 1.18 M, 170 mL) was purged and cooled to 0 °C. Then, $MnCl_2 \cdot 2LiCl$ (1 M in THF, 100 mL, 100 mmol) was added over a period of 5 min. The resulting mixture was stirred for 30 min at 0 °C, warmed to 25 °C, and stirred for another 3 h. The resulting solution of $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**2**) was concentrated in vacuo and was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of up to 0.5 M in THF was obtained.

Manganation of Functionalized Aromatics and Heteroaromatics Using $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (2); General Procedure (GP 1)

In a dry argon-flushed 100 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, the starting material was dissolved in THF (1 mL per mmol). This solution was brought to the given temperature, then $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**2**) was added dropwise and stirred at this temperature for the indicated time. Complete metalation was monitored by GC analysis of reaction aliquots, which were quenched with allyl bromide in the presence of CuCN·2LiCl in anhyd THF using tetradecane as internal standard (Table 1).

Reagent $TMP_2Fe\cdot 2MgCl_2\cdot 4LiCl$ (3)

In a dry and argon-flushed 250 mL Schlenk flask, freshly titrated TMPMgCl·LiCl (**1**; 100 mmol, 1.18 M, 85 mL) was purged and cooled to 0 °C. Then, $FeCl_2\cdot 2LiCl$ (1 M in THF, 50 mL, 50 mmol) was added over 5 min. The resulting mixture was stirred for 30 min at 0 °C, warmed to 25 °C, and stirred for another 3 h. The resulting solution of $TMP_2Fe\cdot 2MgCl_2\cdot 4LiCl$ (**3**) was concentrated in vacuo and was titrated prior to use at 0 °C with benzoic acid (0.2 M in THF) using 4-(phenylazo)diphenylamine as indicator. A concentration of up to 0.5 M in THF was obtained.

Ferration of Functionalized Aromatics Using $TMP_2Fe\cdot 2MgCl_2\cdot 4LiCl$ (3); General Procedure (GP 2)

In a dry argon-flushed 100 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, the starting material was dissolved in THF (1 mL per mmol). Then, $TMP_2Fe\cdot 2MgCl_2\cdot 4LiCl$ (**3**) was added dropwise at 25 °C and stirred at this temperature for the indicated time. The metalation progress was monitored by GC analysis of the reaction aliquots, which were quenched with allyl bromide in the presence of CuCN·2LiCl in anhyd THF using tetradecane as internal standard (Table 1).

Reagent $TMP_3La\cdot 3MgCl_2\cdot 5LiCl$ (4)

In a dry and argon-flushed 250 mL Schlenk flask, freshly titrated TMPMgCl·LiCl (**1**; 100 mmol, 1.18 M, 85 mL) was purged with N_2 and cooled to 0 °C. Then, freshly titrated $LaCl_3\cdot 2LiCl$ (0.5 M in THF, 66 mL, 33 mmol) was added over 5 min. The resulting mixture was stirred for 30 min at 0 °C, warmed to 25 °C and stirred for another 12 h. The resulting solution of $TMP_3La\cdot 3MgCl_2\cdot 5LiCl$ (**4**) was concentrated in vacuo and was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of up to 0.35 M in THF was obtained.

Lanthanation of Functionalized Aromatics and Heteroaromatics Using $TMP_3La\cdot 3MgCl_2\cdot 5LiCl$ (4); General Procedure (GP 3)

In a dry argon-flushed 100 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, the starting material (1 equiv) was dissolved in THF (1 mL per mmol). This solution was brought to the given temperature, then $TMP_3La\cdot 3MgCl_2\cdot 5LiCl$ (**4**; 0.75 equiv) was added dropwise and stirred at this temperature for the indicated time. The metalation progress was monitored by GC analysis of reaction aliquots, which were quenched with allyl bromide in the presence of CuCN·2LiCl in anhyd THF using tetradecane as internal standard (Table 1).

Methyl 2-Cyclohex-2-en-1-yl-3-fluorobenzoate (6a)

According to GP 1, the metalation of methyl 3-fluorbenzoate (**5a**; 2.46 g, 16.0 mmol) was complete within 1 h at 25 °C using $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**2**; 0.52 M in THF, 16.2 mL, 8.4 mmol). The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 0.8 mL) and 3-bromocyclohexene (2.7 g, 16.8 mmol) were then added dropwise and the mixture was allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with a sat. aq NH_4Cl (60 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 9:1) to give **6a** (2.96 g, 90%) as a colorless oil.

IR (Diamond-ATR, neat): 3021, 2933, 2860, 2837, 1722, 1651, 1609, 1576, 1452, 1432, 1283, 1254, 1240, 1192, 1169, 1140, 1130, 1072, 1049, 999, 932, 903, 871, 812, 802, 794, 770, 734, 719, 693, 684, 622 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.39 (m, 1 H), 7.28–7.10 (m, 2 H), 5.85–5.77 (m, 1 H), 5.66–5.60 (m, 1 H), 4.12–4.01 (m, 1 H), 3.88 (s, 3 H), 2.22–2.00 (m, 3 H), 1.96–1.83 (m, 2 H), 1.80–1.63 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5 (d, *J* = 3.9 Hz), 161.9 (d, *J* = 245 Hz), 133.4 (dd, *J* = 5.2 Hz, *J* = 44.3 Hz), 129.3 (d, *J* = 1.3 Hz), 127.2 (d, *J* = 9.3 Hz), 126.8 (d, *J* = 2.3 Hz), 124.9 (d, *J* = 3.4 Hz), 118.5 (d, *J* = 23.5 Hz), 52.1, 36.2 (d, *J* = 1.3 Hz), 29.1 (d, *J* = 1.6 Hz), 24.6, 22.9.

MS (EI, 70 eV): *m/z* (%) = 234 (16, [M^+]), 202 (100), 184 (34), 159 (16), 146 (23), 133 (21), 73 (16), 69 (17), 40 (18).

HRMS (EI): *m/z* calcd for $C_{14}H_{15}FO_2$: 234.1056; found: 234.1058.

2-Benzoyl-4-fluorobenzonitrile (6b)

According to GP 1, the metalation of 4-fluorobenzonitrile (**5b**; 1.94 g, 16 mmol) was complete within 1 h at 25 °C using $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**2**; 0.52 M in THF, 16.2 mL, 8.4 mmol). The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 3.2 mL) and benzoyl chloride (2.92 g, 20.8 mmol) were then added dropwise and was allowed to warm up slowly to 20 °C and stirred at this temperature for 3 h. The resulting mixture was then quenched with sat. aq NH_4Cl (60 mL), extracted with Et_2O (3 × 100 mL), and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 5:1) to give **6b** (2.48 g, 68%) as a colorless solid; mp 77.8–88.9 °C.

IR (Diamond-ATR, neat): 3348, 3103, 1066, 1049, 2921, 2229, 1963, 1908, 1733, 1652, 1637, 1597, 1578, 1533, 1484, 1449, 1404, 1363, 1316, 1302, 1280, 1230, 1198, 1178, 1134, 1106, 1072, 1024, 1000, 974, 922, 881, 853, 830, 807, 740, 728, 714, 696, 672, 645, 623 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.77 (m, 4 H), 7.67–7.62 (m, 1 H), 7.52–7.17 (m, 2 H), 7.30 (t, *J* = 8.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.8, 161.4 (d, *J* = 245 Hz), 136.6 (d, *J* = 9.8 Hz), 136.3, 135.5 (d, *J* = 4.6 Hz), 134.2, 129.8 (d, *J* = 0.8 Hz), 128.8, 117.9 (d, *J* = 23.5 Hz), 117.2, 109.2 (d, *J* = 3.9 Hz).

MS (EI, 70 eV): *m/z* (%) = 225 (29, [M^+]), 148 (14), 105 (100), 77 (30), 74 (16), 59 (22), 45 (15)

HRMS (EI): *m/z* calcd for $C_{14}H_8FNO$: 225.0590; found: 225.0589.

4-Cyano-2-(furan-2-carbonyl)benzoic Acid Ethyl Ester (6c)

According to GP 1, the metalation of ethyl 4-cyanobenzoate (**5c**; 2.45 g, 14.0 mmol) was complete within 75 min at 0 °C using $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**2**; 0.48 M in THF, 17.5 mL, 8.4 mmol). The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 15.4 mL, 15.4 mmol) and 2-furoyl chloride (2.19 g, 16.8 mmol) were then added dropwise and allowed to warm up slowly to 20 °C and stirred at this temperature for 3 h. The resulting mixture was then quenched with sat. aq NH_4Cl (60 mL), extracted with Et_2O (3 × 100 mL), and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 65:35) to give **6c** (2.64 g, 70%) as a yellowish solid; mp 115.9–117.4 °C.

IR (Diamond-ATR, neat): 3139, 3047, 2996, 2908, 2360, 2234, 2100, 1714, 1654, 1604, 1564, 1468, 1402, 1387, 1364, 1308, 1293, 1278, 1237, 1212, 1166, 1145, 1118, 1080, 1024, 1016, 982, 976, 914, 891, 882, 875, 858, 807, 777, 769, 750, 715, 697, 678, 632, 621 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.3 Hz, 1 H), 7.84 (dd, *J* = 6.6, 1.7 Hz, 1 H), 7.76 (d, *J* = 1.7 Hz, 1 H), 7.60 (s, 1 H), 7.07 (d, *J* = 3.6 Hz, 1 H), 6.56 (q, *J* = 1.7 Hz, 1 H), 4.16 (q, *J* = 7.0 Hz, 2 H), 1.12 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.6, 164.7, 152.1, 147.6, 140.7, 133.7, 133.6, 131.6, 130.8, 119.6, 117.1, 116.0, 112.8, 62.4, 13.6.

MS (EI, 70 eV): *m/z* (%) = 269 (44, [M^+]), 241 (45), 240 (18), 224 (99), 213 (31), 212 (91), 197 (18), 184 (22), 174 (41), 169 (15), 168 (17), 140 (61), 129 (20), 95 (100), 63 (15).

HRMS (EI): *m/z* calcd for $C_{15}H_{11}NO_4$: 269.0688; found: 269.0667.

5-Bromo-2-fluoro-1′,2′,3′,4′-tetrahydro-[1,1′-biphenyl]-3-carbonitrile (6d)

According to GP 1, the metalation of 5-bromo-2-fluorobenzonitrile (**5d**; 3.00 g, 15 mmol) was complete within 0.5 h at 0 °C using $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**2**; 0.34 M in THF, 26.4 mL, 9.0 mmol). The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 3.0 mL) and 3-bromocyclohexene (1.95 mL, 15.0 mmol) were then added dropwise and the mixture was allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with sat. aq NH_4Cl (60 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 50:1) to give **6d** (4.03 g, 96%) as a colorless oil.

IR (Diamond-ATR, neat): 2931, 2862, 2239, 1458, 1448, 1325, 1314, 1294, 1274, 1261, 1248, 1230, 1222, 1199, 952, 925, 920, 870, 775, 766, 742, 723, 700, 681, 636, 614 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.10 (m, 1 H), 7.66–7.63 (m, 1 H), 6.00–5.95 (m, 1 H), 5.59–5.55 (m, 1 H), 3.73–3.68 (m, 1 H), 2.08–1.90 (m, 3 H), 1.65–1.46 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (d, *J* = 256.4 Hz), 137.3 (d, *J* = 5.7 Hz), 136.1 (d, *J* = 14.9 Hz), 133.7, 130.3, 126.8, 116.6 (d, *J* = 3.8 Hz), 112.9, 102.3 (d, *J* = 17.3 Hz), 34.1, 29.3, 24.2, 20.2.

MS (EI, 70 eV): *m/z* (%) = 282 (11), 281 (51), 280 (9, [M^+]), 279 (49), 266 (38), 264 (32), 251 (11), 227 (14), 225 (15), 200 (22), 185 (32), 184 (12), 173 (15), 172 (100), 171 (28), 159 (43), 158 (29), 152 (23), 145 (21), 144 (10), 67 (29), 54 (69), 41 (28).

HRMS (EI): *m/z* calcd for $C_{13}H_{11}BrFN$: 279.0059; found: 279.0055.

(3,6-Dimethoxypyridazin-4-yl)phenylmethanol (6e)

According to GP 1, the metalation of 3,6-dimethoxypyridazine (**5e**; 2.10 g, 15.0 mmol) was complete within 30 min at 0 °C using $TMP_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (**2**; 0.48 M in THF, 18.8 mL, 9.0 mmol). Then, benzaldehyde (1.91 g, 18.0 mmol) was added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C and stirred at this temperature for 3 h. The resulting mixture was then quenched with sat. aq NH_4Cl (60 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 1:1) to give **6e** (3.53 g, 94%) as a white solid; mp 109.3–111.0 °C.

IR (Diamond-ATR, neat): 3262, 3102, 3057, 3026, 2995, 2951, 2889, 2866, 2590, 1956, 1936, 1885, 1819, 1758, 1700, 1662, 1626, 1600, 1551, 1492, 1468, 1453, 1380, 1302, 1257, 1217, 1191, 1180, 1154, 1136, 1077, 1046, 1029, 1008, 946, 912, 836, 806, 774, 765, 752, 726, 700, 683, 642, 620, 605 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 4 H), 7.43 (d, *J* = 5.8 Hz, 1 H), 5.99 (s, 1 H), 4.15 (s, 3 H), 4.11 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 159.4, 140.4, 137.3, 128.6, 128.3, 126.9, 117.2, 70.2, 54.6, 54.5.

MS (EI, 70 eV): *m/z* (%) = 246 (100, [M^+]), 245 (43), 231 (41), 155 (41), 153 (34), 105 (15).

HRMS (EI): *m/z* calcd for $C_{13}H_{14}N_2O_3$: 246.1004; found: 246.0981.

2-Benzyl-3-fluorobenzoic Acid Ethyl Ester (6f)

According to GP 2, the metalation of ethyl 3-fluorobenzoate (**5f**; 2.52 g, 15.0 mmol) was complete within 3 h at 25 °C using $TMP_2Fe\cdot 2MgCl_2\cdot 4LiCl$ (**3**; 0.53 M in THF, 21.2 mL, 11.25 mmol). Benzyl chloride (2.28 g, 2.1 mL, 18.0 mmol) was then added dropwise and the reaction mixture was allowed to stir at 25 °C overnight. The resulting mixture was then quenched with a mixture of sat. aq NH_4Cl (60 mL) and aq 2 M HCl (25 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 10:1) to give **6f** (3.3 g, 85%) as a colorless oil.

IR (Diamond-ATR, neat): 3030, 2982, 2938, 1718, 1604, 1583, 1496, 1452, 1391, 1367, 1259, 1215, 1182, 1172, 1159, 1132, 1112, 1096, 1075, 1025, 969, 912, 865, 843, 829, 798, 785, 755, 730, 720, 695, 640 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.72 (m, 1 H), 7.35–7.17 (m, 7 H), 4.48 (d, *J* = 1.9 Hz, 2 H), 4.34 (q, *J* = 7.3 Hz, 2 H), 1.33 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.7 (d, *J* = 3.4 Hz), 161.5 (d, *J* = 245 Hz), 139.9, 132.5 (d, *J* = 4.1 Hz), 129.0 (d, *J* = 17.0 Hz), 128.3 (d, *J* = 1.0 Hz), 128.1, 127.4 (d, *J* = 8.8 Hz), 126.1 (d, *J* = 3.6 Hz), 125.8, 118.8 (d, *J* = 23.7 Hz), 61.1, 30.9 (d, *J* = 4.6 Hz), 14.1.

MS (EI, 70 eV): *m/z* (%) = 258 (3, [M^+]), 213 (22), 212 (100), 183 (21), 151 (10).

HRMS (EI): *m/z* calcd for $C_{16}H_{15}FO_2$: 258.1056; found: 258.1059.

Methyl 2-Butyl-3-fluorobenzoate (6g)

According to GP 2, the metalation of methyl 3-fluorobenzoate (**5a**; 2.46 g, 16.0 mmol) was complete within 3 h at 25 °C using $TMP_2Fe\cdot 2MgCl_2\cdot 4LiCl$ (**3**; 0.43 M in THF, 28.0 mL, 12.0 mmol). 1-Iodobutane (3.53 g, 19.2 mmol) and 4-fluorostyrene (370 mg) were then added dropwise and the reaction mixture was allowed to stir at 25 °C overnight. The resulting mixture was then quenched with a mixture of sat. aq NH_4Cl (60 mL) and aq 2 M HCl (25 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 80:1) to give **6g** (2.79 g, 83%) as a colorless oil.

IR (Diamond-ATR, neat): 2956, 2931, 2873, 1724, 1610, 1579, 1456, 1433, 1379, 1360, 1199, 1166, 1141, 1091, 999, 931, 879, 832, 812, 773, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.6 (m, 1 H), 7.22–7.11 (m, 2 H), 3.88 (s, 3 H), 2.97–2.92 (m, 2 H), 1.60–1.50 (m, 2 H), 1.46–1.33 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (d, *J* = 3.6 Hz), 161.5 (d, *J* = 245 Hz), 157.8, 132.0, 126.3 (d, *J* = 8.8 Hz), 126.0 (d, *J* = 3.6 Hz), 118.5 (d, *J* = 24.0 Hz), 52.1, 32.7, 25.7 (d, *J* = 4.1 Hz), 22.8, 13.8.

MS (EI, 70 eV): *m/z* (%) = 210 (15, [M^+]), 181 (20), 179 (57), 168 (35), 149 (100), 136 (64), 109 (63), 83 (12), 41 (12).

HRMS (EI): *m/z* calcd for $C_{12}H_{15}FO_2$: 210.1056; found: 210.1043.

3-Cyano-2-octylbenzoic Acid Ethyl Ester (6h)

According to GP 2, the metalation of ethyl 3-cyanobenzoate (**5g**; 2.45 g, 14.0 mmol) was complete within 18 h at 25 °C using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**3**; 0.48 M in THF, 21.9 mL, 10.5 mmol). 1-Iodooctane (3.70 g, 15.4 mmol) and 4-fluorostyrene (171 mg) were then added dropwise and the reaction mixture was allowed to stir at 25 °C overnight. The resulting mixture was then quenched with a mixture of sat. aq NH_4Cl (60 mL) and aq 2 M HCl (25 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 98:2) to give **6h** (3.19 g, 78%) as a brown oil.

IR (Diamond-ATR, neat): 3428, 3079, 2955, 2926, 2856, 2359, 2228, 2180, 2165, 2100, 1964, 1952, 1918, 1723, 1582, 1461, 1445, 1390, 1367, 1271, 1259, 1203, 1176, 1142, 1100, 1084, 1044, 1021, 949, 910, 864, 835, 820, 761, 723, 661, 640 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.70 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 3.16–3.11 (m, 2 H), 1.64–1.56 (m, 2 H), 1.43–1.35 (m, 6 H), 1.33–1.25 (m, 7 H), 0.84 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 148.0, 135.9, 134.6, 131.7, 126.3, 117.6, 114.7, 61.5, 32.7, 31.8, 31.5, 29.8, 29.3, 29.2, 22.6, 14.2, 14.1.

MS (EI, 70 eV): *m/z* (%) = 287 (39, [M^+]), 242 (83), 189 (100),184 (17), 174 (64), 170 (32), 161 (55), 160 (37), 157 (30), 156 (73), 143 (32), 142 (16), 129 (19), 128 (21), 117 (22), 116 (20), 115 (25), 77 (15), 57 (39), 55 (20), 43 (50), 41 (70).

HRMS (EI): *m/z* calcd for $C_{18}H_{25}NO_2$: 287.1885; found: 287.1878.

3-Cyano-2-isopropylbenzoic Acid Ethyl Ester (6i)

According to GP 2, the metalation of ethyl 3-cyanobenzoate (**5g**; 2.45 g, 14.0 mmol) was complete within 18 h at 25 °C using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**3**; 0.48 M in THF, 21.9 mL, 10.5 mmol). 2-Iodopropane (2.62 g, 15.4 mmol) and 4-fluorostyrene (171 mg) were then added dropwise and the reaction mixture was allowed to stir at 25 °C overnight. The resulting mixture was then quenched with a mixture of sat. aq NH_4Cl (60 mL) and aq 2 M HCl (25 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 90:10) to give **6i** (2.35 g, 78%) as a brown oil.

IR (Diamond-ATR, neat): 3636, 3546, 3436, 3079, 2970, 2938, 2906, 2878, 2732, 2360, 2226, 2165, 2154, 2086, 2042, 1960, 1918, 1721, 1582, 1460, 1442, 1388, 1367, 1285, 1259, 1210, 1178, 1146, 1136, 1107, 1095, 1054, 1017, 962, 929, 915, 891, 864, 820, 799, 765, 728, 682, 641, 634 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (q, *J* = 1.5 Hz, 1 H), 7.69 (q, *J* = 1.7 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 3.65–3.55 (m, 1 H), 1.47 (q, *J* = 7.3 Hz, 6 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0, 150.9, 136.8, 133.8, 133.1, 126.2, 118.5, 112.2, 61.8, 31.6, 21.2, 14.1.

MS (EI, 70 eV): *m/z* (%) = 217 (20, [M^+]), 189 (28), 174 (24), 172 (60), 171 (40), 170 (51), 156 (100), 154 (16), 142 (17), 130 (20), 116 (17), 115 (25), 59 (27), 44 (18), 43 (55), 43 (18), 41 (50).

HRMS (EI): *m/z* calcd for $C_{13}H_{15}NO_2$: 217.1103; found: 217.1109.

2-Cyclohexyl-4-fluorobenzonitrile (6j)

According to GP 2, the metalation 4-fluorobenzonitrile (**5b**; 2.1 g, 17 mmol) was complete within 3 h at 25 °C using $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**3**; 0.43 M in THF, 28.0 mL, 12.0 mmol). Iodocyclohexane (4.28 g, 20.4 mmol) and 4-fluorostyrene (370 mg) were then added dropwise and the reaction mixture was allowed to stir at 25 °C for 2 h. The resulting mixture was then quenched with a mixture of sat. aq NH_4Cl (60 mL) and aq 2 M HCl (25 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 80:1) to give **6j** (2.4 g, 69%) as a colorless solid; mp 56.4–58.7 °C.

IR (Diamond-ATR, neat): 2929, 2852, 2226, 1605, 1585, 1489, 1448, 1409, 1372, 1289, 1238, 1183, 1135, 1097, 1011, 945, 926, 914, 890, 811, 778, 735, 687, 607 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 6.7, 4.5 Hz, 1 H), 7.49–7.44 (m, 1 H), 7.11–7.04 (m, 1 H), 2.92–2.80 (m, 1 H), 1.93–1.71 (m, 5 H), 1.49–1.17 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0 (d, *J* = 245.0 Hz), 136.4 (d, *J* = 16.2 Hz), 132.3 (d, *J* = 6.7 Hz), 131.6 (d, *J* = 9.8 Hz), 118.5, 116.5 (d, *J* = 25 Hz), 108.4 (d, *J* = 3.9 Hz), 36.9, 32.7, 26.5, 25.9.

MS (EI, 70 eV): *m/z* (%) = 203 (32, [M^+]), 160 (13), 148 (19), 147 (100), 135 (12), 134 (33), 41 (15).

HRMS (EI): *m/z* calcd for $C_{13}H_{14}FN$: 203.1110; found: 203.1099.

4-Chloro-3-cyclohexyl-2-benzofuran-1(3*H*)-one (6k)

According to GP 3, the metalation of methyl 3-chlorobenzoate (**5h**; 2.56 g, 15 mmol) was complete within 3.5 h at 0 °C using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**4**; 0.35 M in THF, 15 mL, 5.3 mmol). Cyclohexanecarbaldehyde (2.24 g, 20.0 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C for 2 h. The resulting mixture was then quenched with brine (60 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (Al_2O_3; pentane–Et_2O, 9:1) to give **6k** (2.74 g, 73%) as a colorless solid; mp 114.3–119.1 °C.

IR (Diamond-ATR, neat): 3503, 3073, 2927, 2856, 1757, 1601, 1585, 1459, 1450, 1373, 1344, 1317, 1307, 1280, 1253, 1205, 1135, 1066, 1050, 976, 958, 925, 897, 862, 844, 819, 790, 769, 741, 689, 658, 619, 603 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.7 Hz, 1 H), 7.57 (dt, *J* = 7.7 Hz, *J* = 1.2 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 1 H), 5.4 (s, 1 H), 2.47–2.33 (m, 1 H), 1.95–1.75 (m, 2 H), 1.69–1.53 (m, 3 H), 1.37–0.98 (m, 3 H), 0.95–0.74 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 145.6, 134.3, 130.5, 128.9, 128.6, 123.8, 84.9, 38.9, 30.4, 26.4, 25.8, 25.6, 23.9.

MS (EI, 70 eV): *m/z* (%) = 250 (1, [M^+]), 170 (27), 168 (100), 83 (4), 41 (2).

HRMS (EI): *m/z* calcd for $C_{14}H_{15}Cl_2O$: 250.0761; found: 250.0768.

2-Benzoyl-3-chlorobenzoic Acid Methyl Ester (6l)

According to GP 3, the metalation of methyl 3-chlorobenzoate (**5h**; 2.39 g, 14.0 mmol) was complete within 3.5 h at 0 °C using $TMP_3La{\cdot}3MgCl_2{\cdot}5LiCl$ (**4**; 0.35 M in THF, 15.0 mL, 5.3 mmol). Benzoyl chloride (2.16 g, 15.4 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with sat. aq NH_4Cl (60 mL), extracted with Et_2O (3 × 100 mL) and the combined Et_2O layers were dried (Na_2SO_4). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et_2O, 17:2) to give **6l** (2.88 g, 75%) as a white solid; mp 133.9–135.7 °C.

IR (Diamond-ATR, neat): 3068, 3009, 2951, 1920, 1721, 1678, 1674, 1597, 1582, 1567, 1449, 1432, 1313, 1295, 1267, 1205, 1184, 1154, 1111, 1070, 1024, 1001, 996, 978, 972, 939, 927, 850, 820, 794, 766, 746, 733, 727, 717, 705, 668, 654 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.03 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.79–7.76 (m, 2 H), 7.64 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.59–7.54 (m, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.47–7.42 (m, 2 H), 3.69 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 194.4, 165.0, 140.7, 136.6, 134.0, 133.4, 131.8, 130.3, 129.9, 128.9, 128.8, 128.7, 52.5.

MS (EI, 70 eV): *m/z* (%) = 274 (30, [^{35}Cl – M$^+$]), 242 (18), 198 (35), 197 (100), 105 (75), 77 (29).

HRMS (EI): *m/z* calcd for $C_{15}H_{11}ClO_3$: 274.0397; found: 274.0387.

5-Bromo-2-fluoro-3-[hydroxy(4-methoxyphenyl)methyl]benzonitrile (6m)

According to GP 3, the metalation of 5-bromo-2-fluorobenzonitrile (**5d**; 3.00 g, 15 mmol) was complete within 0.5 h at –35 °C using TMP$_3$La·3MgCl$_2$·5LiCl (**4**; 0.35 M in THF, 13 mL, 4.6 mmol). 4-Methoxybenzaldehyde (1.77 g, 1.6 mL, 13.0 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with brine (60 mL), extracted with Et$_2$O (3 × 100 mL) and the combined Et$_2$O layers were dried (Na$_2$SO$_4$). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et$_2$O, 5:1) to give **6m** (4.03 g, 80%) as a colorless solid; mp 124.5–126.1 °C.

IR (Diamond-ATR, neat): 3513, 2241, 1608, 1511, 1460, 1440, 1368, 1304, 1284, 1246, 1208, 1191, 1177, 1058, 1024, 866, 843, 829, 820, 786, 758, 718, 665, 644, 634, 627, 614 cm$^{–1}$.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 8.10–8.04 (m, 2 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.30 (d, *J* = 4.5 Hz, 1 H), 5.90 (d, *J* = 4.5 Hz, 1 H), 3.70 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 158.7, 158.6 (d, *J* = 257.2 Hz), 136.3 (d, *J* = 13.8 Hz), 135.5 (d, *J* = 5.4 Hz), 134.6, 134.3, 127.7, 116.7 (d, *J* = 3.5 Hz), 113.8, 112.7, 102.3 (d, *J* = 16.9 Hz), 67.4 (d, *J* = 1.9 Hz), 55.0.

MS (EI, 70 eV): *m/z* (%) = 337 (39), 336 (14, [M$^+$]), 335 (41), 228 (16), 226 (18), 137 (63), 135 (11), 109 (100), 77 (10).

HRMS (EI): *m/z* calcd for $C_{15}H_{11}BrFNO_2$: 334.9957; found: 334.9954.

2-Chloro-4-(2,2-dimethylpropionyl)nicotinic Acid Ethyl Ester (6n)

According to GP 3, the metalation of ethyl 2-chloronicotinate (**5i**; 2.79 g, 15 mmol) was complete within 0.75 h at –20 °C using TMP$_3$La·3MgCl$_2$·5LiCl (**4**; 0.35 M in THF, 15 mL, 5.3 mmol). 2,2-Dimethylpropanoic anhydride (3.04 mL, 15.0 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with brine (60 mL), extracted with Et$_2$O (3 × 100 mL) and the combined Et$_2$O layers were dried (Na$_2$SO$_4$). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et$_2$O 5:1) to give **6n** (3.24 g, 80%) as a yellow oil.

IR (Diamond-ATR, neat): 2977, 727, 1696, 1574, 1538, 1479, 1463, 1449, 1394, 1380, 1364, 1271, 1222, 1185, 1127, 1096, 1065, 1042, 999, 854, 832, 796, 777, 768, 744, 705, 626 cm$^{–1}$.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 8.59 (d, *J* = 5.07 Hz, 1 H), 7.67 (d, *J* = 5.07 Hz, 1 H), 4.27 (q, *J* = 7.21 Hz, 2 H), 1.24 (t, *J* = 7.21 Hz, 3 H), 1.19 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 209.3, 164.6, 152.6, 151.7, 150.1, 126.0, 119.8, 62.8, 44.4, 27.2, 14.1.

MS (EI, 70 eV): *m/z* (%) = 213 (16), 212 (20), 186 (27), 183 (100), 113 (11), 57 (21).

HRMS (EI): *m/z* calcd for $C_{13}H_{16}ClNO_3$: 269.0819; found: 269.0808.

1-(1,3-Benzothiazol-2-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (6o)

According to GP 3, the metalation benzothiazole (**5j**; 1.88 g, 14 mmol) was complete within 0.5 h at 0 °C using TMP$_3$La·3MgCl$_2$·5LiCl (**4**; 0.35 M in THF, 15 mL, 5.3 mmol). α-Tetralone (2.46 g, 16.8 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C for 2 h. The resulting mixture was then quenched with a mixture of sat. aq NH$_4$Cl (60 mL) and aq 2 M HCl (25 mL), extracted with Et$_2$O (3 × 100 mL) and the combined Et$_2$O layers were dried (Na$_2$SO$_4$). After filtration, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (pentane–Et$_2$O, 5:1) to give **6o** (3.43 g, 87%) as a yellowish solid; mp 107.8–111.1 °C.

IR (Diamond-ATR, neat): 3319, 3063, 2932, 2873, 2832, 1895, 1595, 1499, 1491, 1455, 1439, 1393, 1333, 1316, 1276, 1238, 1221, 1180, 1168, 1117, 1094, 1042, 1015, 913, 875, 860, 777, 730, 724, 702, 648 cm$^{–1}$.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.01–7.87 (m, 2 H), 7.51–7.37 (m, 2 H), 7.28–7.13 (m, 4 H), 3.98–3.93 (m, 1 H), 3.06–2.90 (m, 2 H), 2.57–2.48 (m, 1 H), 2.39–2.31 (m, 1 H), 2.21–1.98 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 180.1, 139.0, 137.3, 135.5, 129.2, 128.6, 128.3, 126.5, 125.9, 124.8, 123.9, 121.6, 75.3, 39.4, 29.4, 19.3.

MS (EI, 70 eV): *m/z* (%) = 281 (15, [M$^+$]), 263 (81), 262 (100), 136 (24), 135 (14), 91 (15).

HRMS (EI): *m/z* calcd for $C_{17}H_{15}NOS$: 281.0874; found: 281.0876.

References

(1) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Whisler, M. C.; MacNeil, S.; Beak, P.; Snieckus, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206. (c) Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376. (d) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. (e) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. (f) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (g) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667.

(2) (a) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatley, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921. (b) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. (c) Naka, H.; Morey, J. V.; Haywood, J.; Eisler, D. J.; McPartlin, M.; Garcia, F.; Kudo, H.; Kondo, Y.; Uchiyama, M.; Wheatley, A. E. H. *J. Am. Chem. Soc.* **2008**, *130*, 16193. (d) Uchiyama, M.; Kobayashi, Y.; Furuyama, T.; Nakamura, S.; Kajihara, Z.; Miyoshi, T.; Sakamoto, T.; Kondo, Y.; Morokuma, K. *J. Am. Chem. Soc.* **2008**, *130*, 472. (e) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102. (f) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595. (g) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602. (h) L'Helgoual'ch, J.-M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177. (i) Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E.; O'Hara, C. T.; Russo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 731. (j) Alborés, P.; Carrella, L.; Clegg, W.; García-Álvarez, P.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; Rentschler, E.; Russo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 3317. (k) Mulvey, R. E. *Acc. Chem. Res.* **2009**, *42*, 743. (l) Carrella, L. M.; Clegg, W.; Graham, D. V.; Hogg, L. M.; Kennedy, A. R.; Klett, J.;

Mulvey, R. E.; Rentschler, E.; Russo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 4662. (m) Blair, V. L.; Clegg, W.; Conway, B.; Hevia, E.; Kennedy, A.; Klett, J.; Mulvey, R. E.; Russo, L. *Chem. Eur. J.* **2008**, *14*, 65. (n) Blair, V. L.; Carrella, L. M.; Clegg, W.; Conway, B.; Harrington, R. W.; Hogg, L. M.; Klett, J.; Mulvey, R. E.; Rentschler, E.; Russo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6208. (o) Blair, V. L.; Carrella, L. M.; Clegg, W.; Klett, J.; Mulvey, R. E.; Rentschler, E.; Russo, L. *Chem. Eur. J.* **2009**, *15*, 856.

(3) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett.* **2007**, *9*, 5525. (d) Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, *10*, 1715. (e) Stoll, A. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 113. (f) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497.

(4) (a) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. (b) Wunderlich, S. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705. (c) Wunderlich, S. H.; Knochel, P. *Chem. Commun.* **2008**, 6387.

(5) Wunderlich, S. H.; Kienle, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.

(6) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.

(7) Wunderlich, S. H.; Knochel, P. *Chem. Eur. J.* **2010**, *16*, 3304.

(8) Solinas, I.; Lutz, H. D. *J. Solid State Chem.* **1995**, *117*, 34.

(9) (a) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497. (b) Metzger, A.; Gavryushin, A.; Knochel, P. *Synlett* **2009**, 1433.

(10) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Knochel, P.; Rao, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 6146.

(11) (a) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1995**, *34*, 2723. (b) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387. (c) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544. (d) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79. (e) Korn, T. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 2947.