Mechanochemical Protocol Facilitates the Generation of Arylmanganese Nucleophiles from Unactivated Manganese Metal

Rina Takahashi, Pan Gao, Koji Kubota,* and Hajime Ito*

Table of Contents

1. Instrumentation and Chemicals

Materials were obtained from commercial suppliers and purified using standard procedures, unless otherwise noted. Solvents were purchased from commercial suppliers and further dried over molecular sieve (MS 4Å). Manganese powder (> 98%, product no. 130-06732) was purchased from Wako Pure Chemical Industries, Co., Ltd. All reactions were performed using grinding vessels in the Retsch MM 400 (Figure S1). Both jars and balls were made of stainless steel (SUS400B and SUS420J2, respectively, Figure S2), tungsten carbide, or zirconia. NMR spectra were recorded on JEOL JNM-ECZ400S and JNM-ECS400 spectrometers (^{1}H: 392, 399, or 401 MHz, ^{13}C: 99 or 100 MHz, ^{19}F: 375 or 377 MHz). Tetramethylsilane (^{1}H), $CDCl_3$ (^{13}C), and (Trifluoromethyl)benzene (^{19}F) were employed as internal standards, respectively. Multiplicity was recorded as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Fluorobenzene, 1,2-difluorobenzene, and hexafluorobenzene were used as an internal standard to determine the NMR yields. Thermographic images were obtained using the InfRec Thermo GEAR (NEC Avio Infrared Technologies Co., Ltd.). Recycling preparative gel permeation chromatography (GPC) was conducted with the JAI LC-9101 using $CHCl_3$ as the eluent with the JAIGEL-1H. X-Ray photoelectron spectroscopy (XPS) was performed using JEOL JPS-9200. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

Figure S1. Retsch MM400 used in this study.

Figure S2. Stainless jars and balls used in this study.

2. List of Substrates Used in This Study

Aryl halides except **1k**–**1n** were obtained from commercial suppliers and were used as received. **1k**,[1] **1l**,[2] **1m**,[3] and **1n**[4] were synthesized according to the reported procedures.

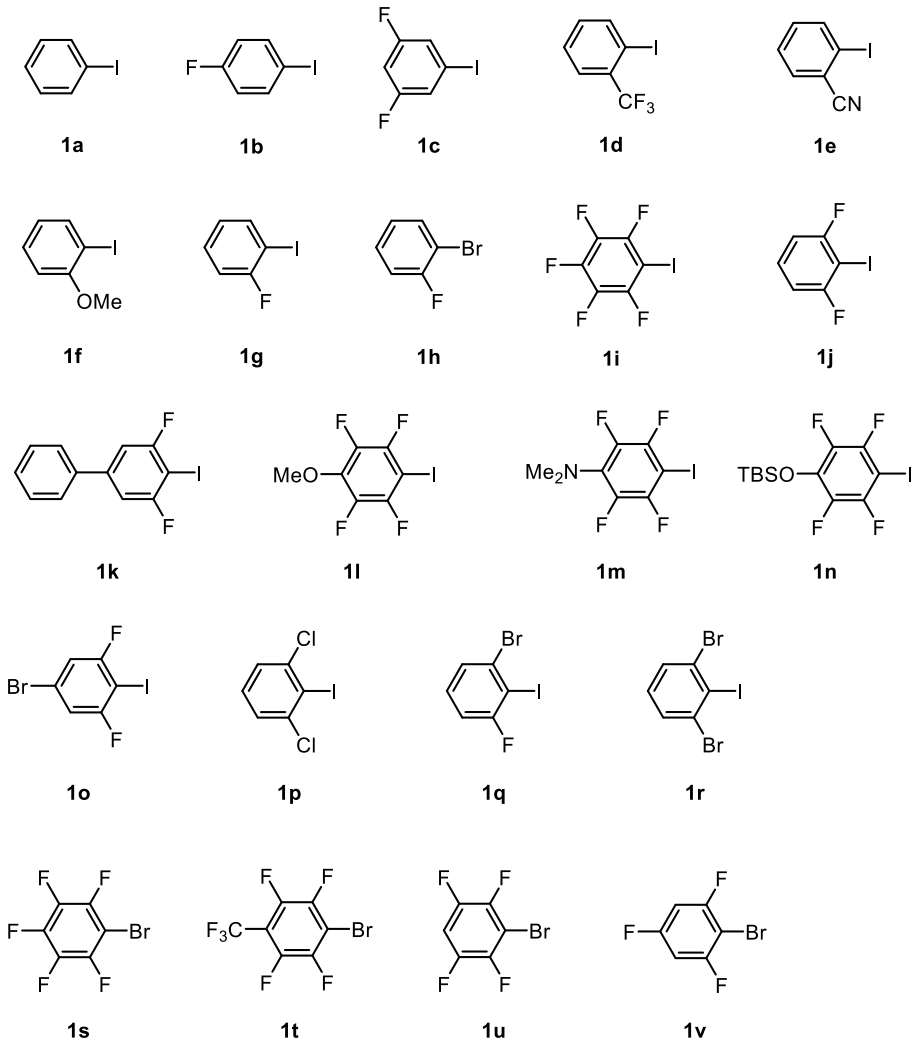


Figure S3. List of aryl halides used in this study.

All electrophiles were obtained from commercial suppliers. **2a** and **2b** were distilled before use. **2c**, **2d** and **5a**, **5b** were used as received.

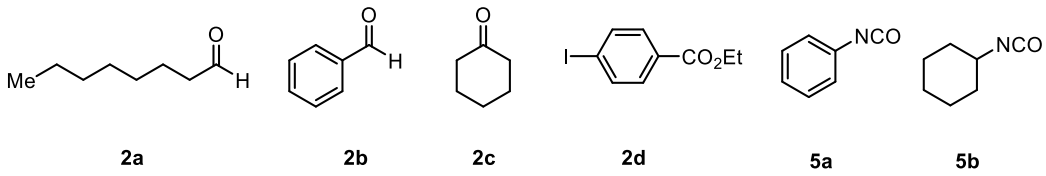
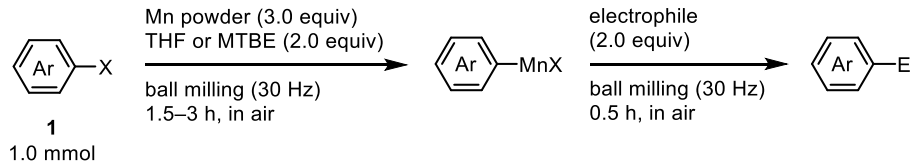


Figure S4. List of electrophiles used in this study.

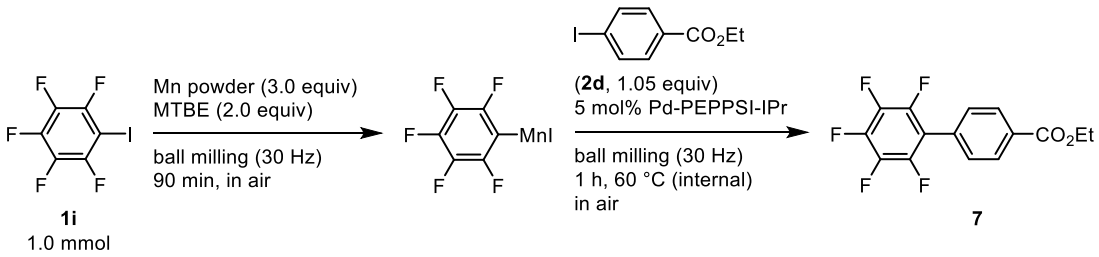
3. General Procedure for Synthesis of Organomanganese Reagents Using a Ball Mill

Procedure for the nucleophilic addition to various electrophiles (A)



All synthetic operations were carried out under atmospheric conditions. Manganese powder (3.0 mmol, 3.0 equiv) were placed in a milling jar (5 mL) with a ball (10 mm, diameter). An aryl halide (**1**, 1.0 mmol, 1.0 equiv) and liquid additive [2.0 mmol, 2.0 equiv, THF (162 μL) or MTBE (236 μL)] were added to the jar using a syringe. After the jar was closed without purging with inert gas, the jar was placed in the ball mill (Retsch MM 400, 1.5–3 h, 30 Hz). After ball milling, the jar was opened in air and charged with an electrophile (2.0 mmol, 2.0 equiv). The jar was then closed without purging with inert gas, and was placed in the ball mill (Retsch MM 400, 0.5 h, 30 Hz). After ball milling, the reaction mixture was quenched with 1 M HCl and extracted with ethyl acetate (30 mL×3). The solution was washed with brine and dried over $MgSO_4$. After the removal of the solvents under reduced pressure, the crude material was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) to give the corresponding product. In some cases, the product was further purified by recycling GPC.

Procedure for the palladium-catalyzed cross-coupling reactions (B)



The reaction was conducted based on a solution-state reaction reported by P. Knochel *et al*.[5] All synthetic operations were carried out under atmospheric conditions. Manganese powder (3.0 mmol, 3.0 equiv) were placed in a milling jar (5 mL) with a ball (10 mm, diameter). 1,2,3,4,5-Pentafluoro-6-iodobenzene (**1i**, 1.0 mmol, 1.0 equiv) and MTBE (2.0 mmol, 2.0 equiv, 236 μL) were added to the jar using a syringe. After the jar was closed without purging with inert gas, the jar was placed in the ball mill (Retsch MM 400, 90 min, 30 Hz). After ball milling, the jar was opened in air and charged with Pd-PEPPSI-IPr (0.05 mmol, 5 mol%) and ethyl 4-iodobenzoate (**2d**, 1.05 mmol, 1.05 equiv). The jar was then closed without purging with inert gas, and was placed in the ball mill (Retsch MM 400, 1 h, 30 Hz) and a heat gun (Takagi HG-1450B). After ball milling while applying heated air to the

outside of the milling jar (the preset temperature at 120 °C), the reaction mixture was quenched with 1 M HCl and extracted with ethyl acetate (30 mL×3). The solution was washed with brine and dried over $MgSO_4$. After the removal of the solvents under reduced pressure, the crude material was purified by flash column chromatography (SiO_2, hexane) and recycling GPC using $CHCl_3$ as the eluent.

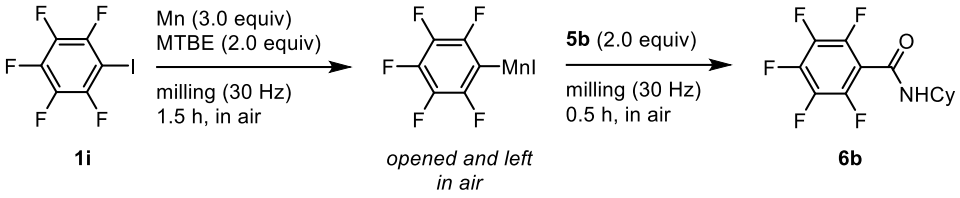
Set-up procedure for high-temperature ball-milling

The heat gun was fixed with clamps and placed directly above the ball milling jar (distance between the heat gun and ball milling jar: ca. 1 cm) (Figure S4). The mechanochemical cross-coupling reactions were conducted while applying heated air to the outside of the milling jar (the preset temperature at 120 °C). The temperature inside the milling jar after the solid-state coupling reactions was confirmed by observation with a thermography camera immediately after opening the milling jar.

Figure S5. The set-up procedure for a heat gun on MM400.

4. Air Stability of Organomanganese Reagents Prepared by Ball Milling

We conducted a number of nucleophilic addition reactions with **5b** after exposing the mechanochemically generated arylmanganese nucleophile **1i** to air for different lengths of time (10−60 min; Figure S6). The results showed that the yield of **6b** decreased when the generated arylmanganese species were exposed to air for 10 min or more.



Time (min)	0	5	10	30	60
Yield (%)	91	61	51	38	18

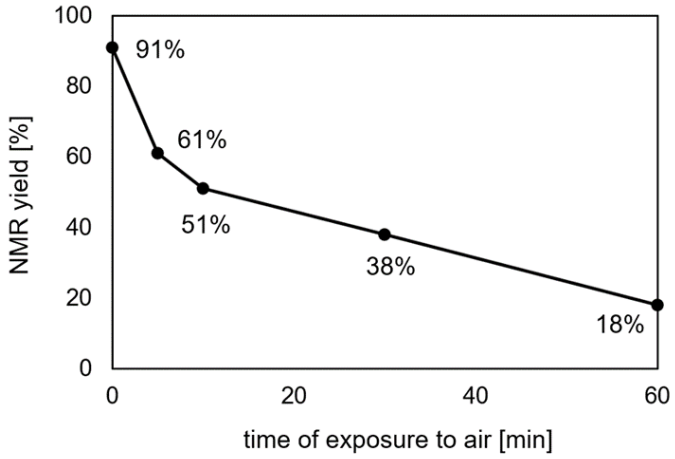
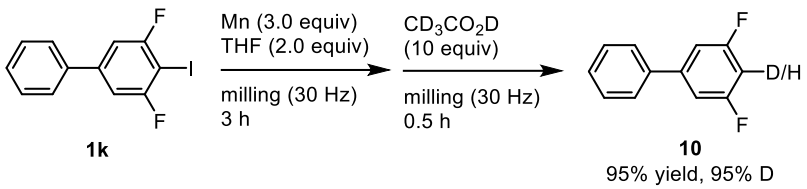


Figure S6. Stability of the mechanochemically generated organomanganese reagent in air.

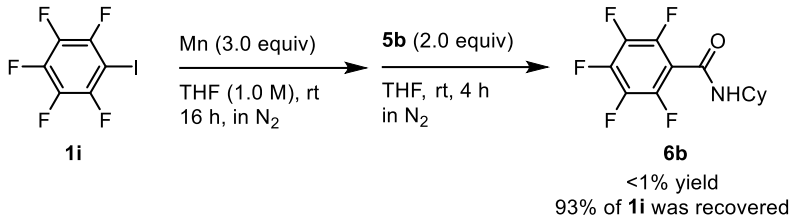
5. Deuteration Experiments



All synthetic operations were carried out under atmospheric conditions. Manganese powder (3.0 mmol, 3.0 equiv) and 3,5-difluoro-4-iodo-1,1'-biphenyl (**1k**) were placed in a milling jar (5 mL) with a ball (10 mm, diameter). THF (2.0 mmol, 2.0 equiv, 162 μL) were added to the jar using a syringe. After the jar was closed without purging with inert gas, the jar was placed in the ball mill (Retsch MM 400, 3 h, 30 Hz). After ball milling, the jar was opened in air and charged with acetic acid-d_4 (10 mmol, 10 equiv). The jar was then closed without purging with inert gas, and was placed in the ball mill (Retsch MM 400, 0.5 h, 30 Hz). After grinding, the reaction mixture was quenched with 1 M HCl, extracted with ethyl acetate (30 mL×3), washed with saturated aqueous Na_2CO_3, and dried over $MgSO_4$. After the removal of the solvents under reduced pressure, the resulting crude mixture was analyzed by ^{1}H NMR with dibromomethane as an internal standard to determine the NMR yield of 3,5-difluoro-1,1'-biphenyl (**10**, 95% yield, 95% D).

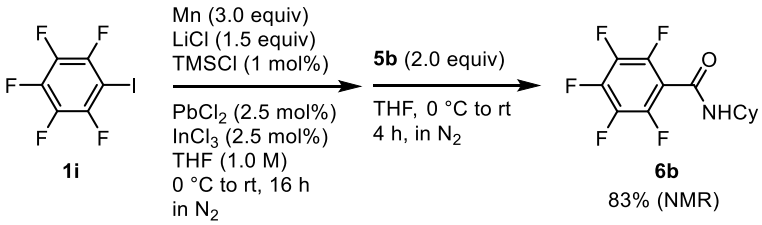
6. Details of Solution-based Reactions

Solution-based reaction without activation of manganese



An oven-dried reaction vial was charged with manganese powder (3.0 equiv) in air. After the vial was sealed with a screw cap containing a Teflon®-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (1.0 mL) was added to the vial via syringe. **1i** was then added dropwise and the reaction mixture was stirred for 16 h. After 16 h, cyclohexyl isocyanate (**5b**, 249.8 mg, 2.0 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 16 h followed by quenching with 1M HCl. The aqueous layer was extracted with ethyl acetate (30 mL×3). The combined organic phases were dried over $MgSO_4$, the solvent was removed in vacuo. The resulting crude mixture was analyzed by ^{19}F NMR with fluorobenzene as internal standards to determine the NMR yield of **6b** and the conversion of **1i**.

Solution-based reaction under the conditions reported by P. Knochel *et al.*



The reaction was conducted according to the reported procedure.[5] Mn powder (≧99.9%, product No. 463728, purchased from Aldrich), LiCl (99.9%, product No. 125-03322, purchased from Wako), $PbCl_2$ (−10 mesh, 99.999%, product No. 203440, purchased from Aldrich) and $InCl_3$ (99.999%, product No. 203440, purchased from Aldrich) were used for this reaction. An oven-dried reaction vial was charged with manganese powder (3.0 equiv), LiCl (1.5 equiv), $InCl_3$ (2.5 mol %) and $PbCl_2$ (2.5 mol %) in a glovebox under argon atmosphere. After the reaction vial was removed from the glove box, the mixture was dried for 5 min with a heat gun under high vacuum. The vial was then evacuated and backfilled with nitrogen three times and THF (4.0 mL) and TMSCl (1 mol%) were added to the mixture via syringe. **1i** (579.5 mg, 2.0 mmol) was then added dropwise at 0 °C and the reaction mixture was stirred for 16 h to give the solution of arylmanganese(II) iodide. This solution was added to a THF solution of cyclohexyl isocyanate (**5b**, 249.4 mg, 2.0 mmol, 1.3 M) at 0 °C. The reaction mixture was

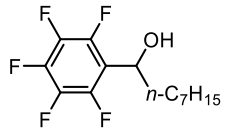
allowed to warm to room temperature and continuously stirred for 4 h, followed by quenching with brine. The aqueous layer was extracted with CH_2Cl_2 (30 mL×3). The combined organic phases were dried over $MgSO_4$, the solvent was removed in vacuo. The resulting crude mixture was analyzed by ^{19}F NMR with fluorobenzene as an internal standard to determine the NMR yield of **6b**.

7. Sample Preparation for XPS Analysis

X-Ray photoelectron spectroscopy (XPS) was used to analyze the surface of manganese metals. The ball-milled sample was prepared via the following conditions: Manganese powder (160 mg) was placed in a milling jar (5 mL) with a ball (10 mm, diameter) under atmospheric conditions. After the jar was closed without purging with inert gas, the jar was placed in the ball mill (Retsch MM 400, 1.5 h, 30 Hz). After ball milling, the jar was opened in a glove box, and the ball-milled sample was transferred to the vessel for XPS analysis.

8. Characterization of Products

1-(Perfluorophenyl)octan-1-ol (3i).

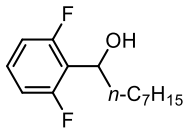


3i

The first metalation step was conducted with **1i** (293.7 mg, 1.0 mmol) and MTBE (236 μL, 2.0 mmol) for 1.5 h and the second addition step was conducted with **2a** (246.5 mg, 1.9 mmol) for 0.5 h. The product **3i** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 90:10) and GPC. The product **3i** was obtained in 54% yield (160.7 mg, 0.54 mmol) as a white solid.

^{1}H NMR (399 MHz, $CDCl_3$, δ): 0.88 (t, J = 6.6 Hz, 3H), 1.17–1.37 (m, 9H), 1.39–1.50 (m, 1H), 1.77–1.88 (m, 1H), 1.96–2.06 (m, 1H), 2.10 (d, J = 7.6 Hz, 1H), 5.04 (q, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1 (CH_3), 22.7 (CH_2), 26.0 (CH_2), 29.26 (CH_2), 29.31 (CH_2), 31.9 (CH_2), 36.9 (CH_2), 66.5 (*C*H), 117.3 (t, $J_{C–F}$ = 15.3 Hz, *C*), 137.6 (dm, $J_{C–F}$ = 252.0 Hz, *C*), 140.6 (dm, $J_{C–F}$ = 254.0 Hz, *C*), 144.8 (dm, $J_{C–F}$ = 247.3 Hz, *C*). ^{19}F NMR (375 MHz, $CDCl_3$, δ): −162.8 (t, J = 23.1 Hz, 2F), −156.4 (d, J = 23.3 Hz, 1F), −145.0 (t, J = 22.9 Hz, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{14}H_{17}F_5O$, 296.1200; found, 296.1198.

1-(2,6-Difluorophenyl)octan-1-ol (3j).

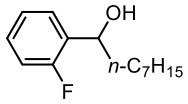


3j

The first metalation step was conducted with **1j** (240.5 mg, 1.0 mmol) and THF (165 μL, 2.0 mmol) for 3 h and the second addition step was conducted with **2a** (255.9 mg, 2.0 mmol) for 0.5 h. The product **3j** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 90:10) and GPC. The product **3j** was obtained in 67% yield (96.6 mg, 0.68 mmol) as colorless oil.

^{1}H NMR (399 MHz, $CDCl_3$, δ): 0.87 (t, J = 6.8 Hz, 3H), 1.18–1.36 (m, 9H), 1.39–1.51 (m, 1H), 1.77–1.88 (m, 1H), 1.94–2.05 (m, 1H), 2.17 (dt, J = 2.4, 9.0 Hz, 1H), 5.03 (q, J = 7.8 Hz, 1H), 6.83–6.92 (m, 2H), 7.16–7.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.2 (CH_3), 22.7 (CH_2), 26.0 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 37.4 (CH_2), 66.6 (*C*H), 111.4–112.0 (m, *C*H), 119.9 (t, $J_{C–F}$ = 16.7 Hz, *C*), 128.9 (t, $J_{C–F}$ = 11.0 Hz, *C*H), 161.1 (dd, $J_{C–F}$ = 8.7, 248.0 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −116.5 (s, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{14}H_{20}F_2O$, 242.1482; found, 242.1481.

1-(2-Fluorophenyl)octan-1-ol (3g).

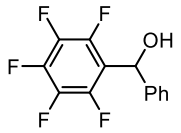


3g

The first metalation step was conducted with **1g** (222.2 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 3 h and the second addition step was conducted with **2a** (257.0 mg, 2.0 mmol) for 0.5 h. The product **3g** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 90:10) and GPC. The product **3g** was obtained in 25% yield (55.1 mg, 0.25 mmol) as colorless oil.

^{1}H NMR (399 MHz, $CDCl_3$, δ): 0.87 (t, J = 6.8 Hz, 3H), 1.18–1.37 (m, 9H), 1.39–1.50 (m, 1H), 1.69–1.82 (m, 2H), 1.85 (d, J = 4.8 Hz, 1H), 5.01 (q, J = 5.9 Hz, 1H), 7.02 (ddd, J = 1.4, 8.2, 10.4 Hz, 1H), 7.15 (td, J = 1.1, 7.5 Hz, 1H), 7.21–7.26 (m, 1H), 7.46 (td, J = 1.9, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.2 (*C*H_3), 22.8 (*C*H_2), 25.8 (*C*H_2), 29.3 (*C*H_2), 29.5 (*C*H_2), 31.9 (*C*H_2), 38.2 (*C*H_2), 68.5 (*C*H), 115.3 (d, $J_{C–F}$ = 21.9 Hz, *C*H), 124.3 (d, $J_{C–F}$ = 2.9 Hz, *C*H), 127.4 (d, $J_{C–F}$ = 4.8 Hz, *C*H), 128.8 (d, $J_{C–F}$ = 8.7 Hz, *C*H), 132.0 (d, $J_{C–F}$ = 13.3 Hz, *C*), 159.9 (d, $J_{C–F}$ = 245.2 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −120.8 (s, 1F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{14}H_{21}FO$, 224.1576; found, 224.1568.

(Perfluorophenyl)(phenyl)methanol (3d).

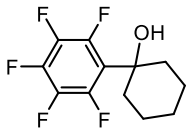


3k

The first metalation step was conducted with **1i** (293.8 mg, 1.0 mmol) and MTBE (236 μL, 2.0 mmol) for 1.5 h and the second addition step was conducted with **2b** (215.4 mg, 2.0 mmol) for 0.5 h. The product **3k** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 90:10) and obtained in 60% yield (165.0 mg, 0.60 mmol) as a white solid. ^{1}H, ^{13}C, and ^{19}F NMR of the product **3k** were in agreement with the literature.[6]

^{1}H NMR (401 MHz, $CDCl_3$, δ): 2.64 (d, J = 8.0 Hz, 1H), 6.25 (d, J = 8.0 Hz, 1H), 7.30–7.37 (m, 1H), 7.38 (d, J = 3.2 Hz, 2H), 7.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 67.6 (*C*H), 117.0 (t, $J_{C–F}$ = 13.8 Hz, *C*), 125.4 (*C*H), 128.3 (*C*H), 128.8 (*C*H), 137.7 (dm, $J_{C–F}$ = 252.7 Hz, *C*), 140.6 (*C*), 140.9 (dm, $J_{C–F}$ = 254.6 Hz, *C*), 144.7 (dm, $J_{C–F}$ = 249.8 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −162.4 (t, J = 23.0 Hz, 2F), −155.5 (d, J = 34.7 Hz, 1F), −144.0 (t, J = 23.0 Hz, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_7F_5O$, 274.0417; found, 274.0414.

1-(Perfluorophenyl)cyclohexan-1-ol (4).

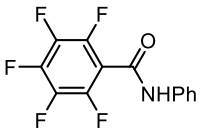


4

The first metalation step was conducted with **1i** (295.6 mg, 1.0 mmol) and MTBE (236 μL, 2.0 mmol) for 1.5 h and the second addition step was conducted with **2c** (117.0 mg, 1.2 mmol) for 0.5 h. The product **4** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 90:10) and GPC. The product **4** was obtained in 45% yield (120.1 mg, 0.45 mmol) as a white solid. ^1H, ^{13}C, and ^{19}F NMR of the product **4** were in agreement with the literature.[6]

^1H NMR (392 MHz, $CDCl_3$, δ): 1.29 (qt, J = 3.8, 12.8 Hz, 1H), 1.56–1.64 (m, 2H), 1.67–1.89 (m, 3H), 1.97–2.09 (m, 4H), 2.42 (t, J = 3.4 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 21.4 (CH_2), 25.1 (CH_2), 37.2 (t, $J_{C–F}$ = 4.3 Hz, CH_2), 75.3 (*C*), 121.3–121.7 (m, *C*), 137.5 (dm, $J_{C–F}$ = 184.9 Hz, *C*), 140.0 (dm, $J_{C–F}$ = 189.6 Hz, *C*), 145.1 (dm, $J_{C–F}$ = 248.8 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): –162.7 (t, J = 23.1 Hz, 2F), –157.1 (d, J = 23.1 Hz, 1F), –140.7 (t, J = 23.1 Hz, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{12}H_{11}F_5O$, 266.0730; found, 266.0728.

2,3,4,5,6-Pentafluoro-*N*-phenylbenzamide (6a).

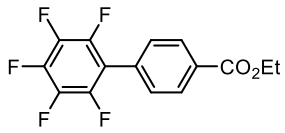


6a

The first metalation step was conducted with **1i** (293.8 mg, 1.0 mmol) and MTBE (236 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5a** (237.4 mg, 2.0 mmol) for 0.5 h. The product **6a** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 85:15) and obtained in 69% yield (197.0 mg, 0.69 mmol) as a white solid. ^1H and ^{19}F NMR of the product **6a** were in agreement with the literature.[7]

^1H NMR (401 MHz, $CDCl_3$, δ): 7.23 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.52 (brs, 1H), 7.61 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 112.5 (t, $J_{C–F}$ = 20.5 Hz, *C*), 119.6 (*C*H), 124.8 (*C*H), 129.1 (*C*H), 137.1 (dm, $J_{C–F}$ = 253.7 Hz, *C*), 138.0 (*C*), 141.5 (dm, $J_{C–F}$ = 250.9 Hz, *C*), 143.2 (dm, $J_{C–F}$ = 251.3 Hz, *C*), 154.9 (*C*). ^{19}F NMR (375 MHz, $CDCl_3$, δ): –160.4 (t, J = 23.1 Hz, 2F), –150.6 (t, J = 23.3 Hz, 1F), –140.9 (s, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_6F_5NO$, 287.0370; found, 287.0372.

Ethyl 2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-4-carboxylate (7).

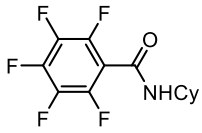


7

The reaction was conducted with **1i** (293.5 mg, 1.0 mmol) according to the general procedure B. The product **7** was purified by GPC. The product **7** was obtained in 71% yield (224.6 mg, 0.71 mmol) as a white solid. ^{1}H, ^{13}C, and ^{19}F NMR of the product **7** were in agreement with the literature.[8]

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.42 (t, J = 7.1 Hz, 3H), 4.42 (q, J = 7.0 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 8.17 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.2 (CH_3), 61.3 (CH_2), 114.7–115.2 (m, *C*), 129.7 (*C*H), 130.2 (*C*H), 130.7 (*C*), 131.2 (*C*), 137.8 (dm, $J_{C–F}$ = 252.2 Hz, *C*), 140.7 (dm, $J_{C–F}$ = 254.1 Hz, *C*), 144.0 (dm, $J_{C–F}$ = 249.3 Hz, *C*), 165.8 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): –162.2 (t, J = 23.1 Hz, 2F), –154.8 (d, J = 34.7 Hz, 1F), –143.4 (s, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{15}H_9F_5O_2$, 316.0523; found, 316.0520.

***N*-Cyclohexyl-2,3,4,5,6-pentafluorobenzamide (4a).**



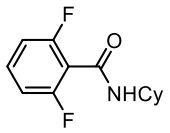
6b

For reaction with **1i**: the first metalation step was conducted with **1i** (293.3 mg, 1.0 mmol) and MTBE (236 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (246.4 mg, 2.0 mmol) for 0.5 h. The product **6b** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 72% yield (210.7 mg, 0.72 mmol) as a white solid.

For the reaction with **1s**: the first metalation step was conducted with **1s** (246.8 mg, 1.0 mmol) and MTBE (236 μL, 2.0 mmol) for 1.5 h and the second arylation step was conducted with **5b** (248.2 mg, 2.0 mmol) for 0.5 h. The product **6b** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 85:15) and obtained in 57% yield (168.2 mg, 0.57 mmol) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.15–1.32 (m, 3H), 1.36–1.49 (m, 2H), 1.61–1.69 (m, 1H), 1.71–1.80 (m, 2H), 1.99–2.09 (m, 2H), 3.94–4.06 (m, 1H), 5.76 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (CH_2), 25.4 (CH_2), 32.7 (CH_2), 49.6 (*C*H), 112.2 (t, $J_{C–F}$ = 18.6 Hz, *C*), 137.6 (dm, $J_{C–F}$ = 255.1 Hz, *C*), 142.1 (dm, $J_{C–F}$ = 256.1 Hz, *C*), 144.0 (dm, $J_{C–F}$ = 251.7 Hz, *C*), 156.5 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): –161.1 (s, 2F), –152.1 (d, J = 23.0 Hz, 1F), –141.7 (d, J = 23.4 Hz, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{12}F_5NO$, 293.0839; found, 293.0833.

***N*-Cyclohexyl-2,6-difluorobenzamide (6c).**

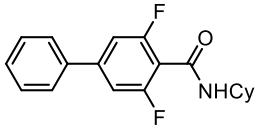


6c

The first metalation step was conducted with **1b** (242.1 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (248.9 mg, 2.0 mmol) for 0.5 h. The product **6c** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 79% yield (191.1 mg, 0.80 mmol) as a white solid. ^1H, ^{13}C, and ^{19}F NMR of the product **6c** were in agreement with the literature.[9]

^1H NMR (392 MHz, $CDCl_3$, δ): 1.18–1.32 (m, 3H), 1.36–1.50 (m, 2H), 1.59–1.69 (m, 1H), 1.70–1.80 (m, 2H), 2.01–2.10 (m, 2H), 3.97–4.07 (m, 1H), 5.77 (brs, 1H), 6.90–6.98 (m, 2H), 7.30–7.39 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (*C*H_2), 25.6 (*C*H_2), 33.0 (*C*H_2), 49.0 (*C*H), 111.9–112.1 (m, *C*H), 114.9 (t, $J_{C–F}$ = 20.5 Hz, *C*), 131.5 (t, $J_{C–F}$ = 10.1 Hz, *C*H), 159.5 (*C*), 160.0 (dd, $J_{C–F}$ = 6.7, 251.7 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −113.6 (s, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{15}F_2NO$, 239.1122; found, 239.1120.

***N*-Cyclohexyl-3,5-difluoro-[1,1'-biphenyl]-4-carboxamide (6d).**

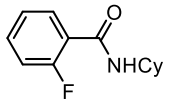


6d

The first metalation step was conducted with **1k** (316.3 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 3 h and the second amidation step was conducted with **5b** (247.6 mg, 2.0 mmol) for 0.5 h. The product **6d** was purified by flash column chromatography (SiO_2, CH_2Cl_2) and the obtained solid was washed with hexane. The product **6d** was obtained in 71% yield (224.0 mg, 0.71 mmol) as a white solid.

^1H NMR (401 MHz, $CDCl_3$, δ): 1.16–1.34 (m, 3H), 1.38–1.50 (m, 2H), 1.60–1.69 (m, 1H), 1.71–1.81 (m, 2H), 2.02–2.13 (m, 2H), 3.98–4.10 (m, 1H), 5.84 (brs, 1H), 7.14–7.20 (m, 2H), 7.40–7.50 (m, 3H), 7.52–7.57 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ): 24.5 (*C*H_2), 25.2 (*C*H_2), 32.2 (*C*H_2), 48.3 (*C*H), 109.8 (d, $J_{C–F}$ = 24.8 Hz, *C*H), 114.4 (t, $J_{C–F}$ = 6.2 Hz, *C*), 126.9 (*C*H), 128.9 (*C*H), 129.1 (*C*H), 137.2 (*C*H), 143.3 (t, $J_{C–F}$ = 9.6 Hz, *C*), 158.5 (*C*), 159.2 (dd, $J_{C–F}$ = 9.0, 247.5 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −113.1 (s, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{19}H_{19}F_2NO$, 315.1435; found, 315.1430.

***N*-Cyclohexyl-2-fluorobenzamide (6e).**

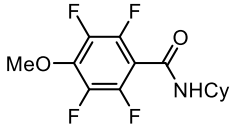


6e

The first metalation step was conducted with **1g** (221.3 mg, 1.0 mmol) and 1,2-dimethoxyethane (207 μL, 2.0 mmol) for 3 h and the second amidation step was conducted with **5b** (253 μL, 2.0 mmol) for 0.5 h. The product **6e** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 38% yield (84.1 mg, 0.38 mmol) as a white solid. ^{1}H, ^{13}C, and ^{19}F NMR of the product **6e** were in agreement with the literature.[10]

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.18–1.34 (m, 3H), 1.38–1.51 (m, 2H), 1.60–1.69 (m, 1H), 1.71–1.80 (m, 2H), 1.98–2.09 (m, 2H), 3.96–4.09 (m, 1H), 6.62 (brs, 1H), 7.10 (dd, J = 8.6, 11.4 Hz, 1H), 7.22–7.29 (m, 1H), 7.40–7.50 (m, 1H), 8.09 (dt, J = 3.9, 11.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (CH_2), 25.6 (CH_2), 33.0 (CH_2), 48.6 (*C*H), 115.9 (d, $J_{C–F}$ = 24.8 Hz, *C*H), 121.6 (d, $J_{C–F}$ = 12.3 Hz, *C*), 124.7 (d, $J_{C–F}$ = 2.8 Hz, *C*H), 132.0 (*C*H), 133.0 (d, $J_{C–F}$ = 8.7 Hz, *C*H), 160.5 (d, $J_{C–F}$ = 247.0 Hz, *C*), 162.3 (d, $J_{C–F}$ = 2.9 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −114.9 (s, 1F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{16}FNO$, 221.1216; found, 221.1216.

***N*-Cyclohexyl-2,3,5,6-tetrafluoro-4-methoxybenzamide (6f).**

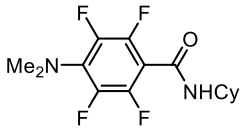


6f

The first metalation step was conducted with **1l** (308.7 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (249.4 mg, 2.0 mmol) for 0.5 h. The product **6f** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 70% yield (215.2 mg, 0.70 mmol) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.18–1.30 (m, 3H), 1.36–1.49 (m, 2H), 1.60–1.68 (m, 1H), 1.70–1.79 (m, 2H), 1.98–2.09 (m, 2H), 3.94–4.04 (m, 1H), 4.11 (t, J = 1.6 Hz), 5.77 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.7 (CH_2), 25.4 (CH_2), 32.5 (CH_2), 49.3 (*C*H), 62.0 (t, $J_{C–F}$ = 3.8 Hz, CH_3), 110.0 (t, $J_{C–F}$ = 19.6 Hz, *C*), 138.9–139.5 (m, *C*), 140.4 (dm, $J_{C–F}$ = 239.9 Hz, *C*), 143.9 (dm, $J_{C–F}$ = 249.8 Hz, *C*), 157.3 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −157.9 (s, 2F), −143.6 (d, J = 23.4 Hz, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{14}H_{15}F_4NO_2$, 305.1039; found, 305.1039.

***N*-Cyclohexyl-4-(dimethylamino)-2,3,5,6-tetrafluorobenzamide (6g).**

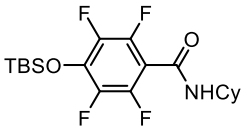


6g

The first metalation step was conducted with **1m** (318.1 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (249.2 mg, 2.0 mmol) for 0.5 h. The product **6g** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 69% yield (220.5 mg, 0.69 mmol) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.16–1.30 (m, 3H), 1.35–1.48 (m, 2H), 1.59–1.68 (m, 1H), 1.69–1.79 (m, 2H), 1.98–2.08 (m, 2H), 2.99 (t, J = 2.2 Hz, 6H), 3.93–4.05 (m, 1H), 5.78 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (*C*H_2), 25.5 (*C*H_2), 32.8 (*C*H_2), 43.1 (*C*H_3), 49.1 (*C*H), 107.1 (t, $J_{C–F}$ = 18.1 Hz, *C*), 132.9 (t, $J_{C–F}$ = 8.6 Hz, *C*), 141.2 (dm, $J_{C–F}$ = 244.1 Hz, *C*), 144.8 (dm, $J_{C–F}$ = 245.1 Hz, *C*), 158.0 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −152.5 (d, J = 23.0 Hz, 2F), −144.6 (s, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{15}H_{18}F_4N_2O_1$, 318.1355; found, 318.1346.

4-[(*tert*-Butyldimethylsilyl)oxy]-*N*-cyclohexyl-2,3,5,6-tetrafluorobenzamide (6h).

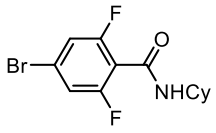


6h

The first metalation step was conducted with **1n** (406.6 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 90 min and the second amidation step was conducted with **5b** (248.7 mg, 2.0 mmol) for 30 min. The product **6h** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 28% yield (113.4 mg, 0.28 mmol) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$, δ): 0.23 (s, 6H), 1.01 (s, 9H), 1.15–1.31 (m, 3H), 1.36–1.49 (m, 2H), 1.60–1.68 (m, 1H), 1.70–1.79 (m, 2H), 2.00–2.08 (m, 2H), 3.94–4.06 (m, 1H), 5.78 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −4.9 (*C*H_3), 18.5 (*C*), 24.8 (*C*H_2), 25.3 (*C*H_3), 25.5 (*C*H_2), 32.8 (*C*H_2), 49.3 (*C*H), 108.6 (t, $J_{C–F}$ = 18.6 Hz, *C*), 136.1–136.5 (m, *C*), 140.7 (dm, $J_{C–F}$ = 248.4 Hz, *C*), 144.3 (dm, $J_{C–F}$ = 251.7 Hz, *C*), 157.7 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −157.6 (d, J = 23.0 Hz, 2F), −144.4 (s, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{19}H_{27}F_4NO_2Si$, 405.1747; found, 405.1740.

4-Bromo-*N*-cyclohexyl-2,6-difluorobenzamide (6i).

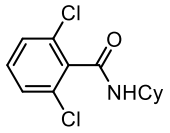


6i

The first step was conducted with **1o** (319.1 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (247.6 mg, 2.0 mmol) for 0.5 h. The product **6i** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 75% yield (219.9 mg, 0.75 mmol) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.14–1.30 (m, 3H), 1.35–1.49 (m, 2H), 1.60–1.69 (m, 1H), 1.70–1.79 (m, 2H), 1.98–2.10 (m, 2H), 3.93–4.06 (m, 1H), 5.73 (brs, 1H), 7.11–7.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (*C*H_2), 25.5 (*C*H_2), 32.9 (*C*H_2), 49.1 (*C*H), 114.2 (t, $J_{C–F}$ = 21.0 Hz, *C*), 116.0 (d, $J_{C–F}$ = 28.6 Hz, *C*H), 123.8 (t, $J_{C–F}$ = 11.9 Hz, *C*), 158.6 (*C*), 159.8 (dd, $J_{C–F}$ = 8.6, 255.6 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −111.7 (s, 2F). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{14}BrF_2NONa$, 340.0119; found, 340.0122.

2,6-Dichloro-*N*-cyclohexylbenzamide (6j).

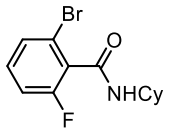


6j

The first metalation step was conducted with **1p** (273.3 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (248.5 mg, 2.0 mmol) for 0.5 h. The product **6j** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 55% yield (149.4 mg, 0.55 mmol) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.13–1.33 (m, 3H), 1.37–1.51 (m, 2H), 1.61–1.69 (m, 1H), 1.71–1.82 (m, 2H), 2.01–2.16 (m, 2H), 3.98–4.12 (m, 1H), 5.60 (brs, 1H), 7.21–7.26 (m, 1H), 7.29–7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (*C*H_2), 25.4 (*C*H_2), 32.6 (*C*H_2), 48.7 (*C*H), 127.8 (*C*H), 130.3 (*C*H), 132.1 (*C*), 136.2 (*C*), 163.4 (*C*). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{15}Cl_2NO$, 271.0531; found, 271.0531.

2-Bromo-*N*-cyclohexyl-6-fluorobenzamide (6k).

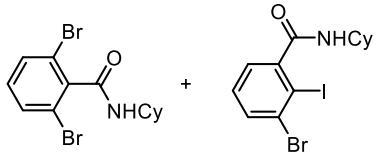


6k

The first metalation step was conducted with **1q** (299.0 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (249.7 mg, 2.0 mmol) for 0.5 h. The product **6k** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 69% yield (208.4 mg, 0.69 mmol) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.13–1.32 (m, 3H), 1.37–1.50 (m, 2H), 1.60–1.69 (m, 1H), 1.71–1.81 (m, 2H), 2.04–2.15 (m, 2H), 3.97–4.10 (m, 1H), 5.64 (brs, 1H), 7.07 (td, J = 0.8, 8.6 Hz, 1H), 7.23 (td, J = 5.9, 8.2 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.9 (*C*H_2), 25.5 (*C*H_2), 32.7 (*C*H_2), 48.9 (*C*H), 114.9 (d, $J_{C–F}$ = 22.0 Hz, *C*H), 120.6 (d, $J_{C–F}$ = 4.8 Hz, *C*), 127.8 (d, $J_{C–F}$ = 21.9 Hz, *C*), 128.5 (d, $J_{C–F}$ = 3.8 Hz, *C*H), 131.1 (d, $J_{C–F}$ = 8.6 Hz, *C*H), 159.2 (d, $J_{C–F}$ = 251.7 Hz, *C*), 162.4 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −113.4 (s, 1F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{15}BrFNO$, 299.0321; found, 299.0313.

2,6-Dibromo-*N*-cyclohexylbenzamide (6m).

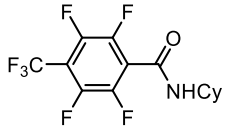


6m **6n**

The first metalation step was conducted with **1r** (379.0 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (248.5 mg, 2.0 mmol) for 0.5 h. The product **6m** and the byproduct **6n** were obtained in 54% NMR yield (**6m**:**6n** = 78:22).

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.14–1.34 (m, 3H), 1.37–1.51 (m, 2H), 1.60–1.69 (m, 1H), 1.72–1.82 (m, 2H), 2.03–2.17 (m, 2H), 3.98–4.11 (m, 1H), 5.56 (brs, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.9 (*C*H_2), 25.6 (*C*H_2), 32.8 (*C*H_2), 48.8 (*C*H), 120.5 (*C*), 131.2 (*C*H), 131.8 (*C*H), 140.0 (*C*), 165.3 (*C*). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{15}Br_2NO$, 358.9520; found, 358.9517.

***N*-Cyclohexyl-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzamide (6o).**

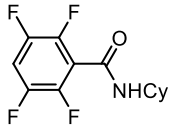


6o

The first step was conducted with **1t** (296.2 mg, 1.0 mmol) and MTBE (236 μL, 2.0 mmol) for 1.5 h and the second amidation step was conducted with **5b** (249.2 mg, 2.0 mmol) for 0.5 h. The product **6o** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 69% yield (235.1 mg, 0.68 mmol) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.18–1.32 (m, 3H), 1.37–1.50 (m, 2H), 1.62–1.70 (m, 1H), 1.72–1.80 (m, 2H), 1.99–2.10 (m, 2H), 3.95–4.07 (m, 1H), 5.80 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, δ): 24.2 (*C*H_2), 25.1 (*C*H_2), 32.0 (*C*H_2), 48.7 (*C*H), 108.0–109.3 (m, *C*), 120.4 (d, $J_{C–F}$ = 229.8 Hz, *C*), 121.9 (d, $J_{C–F}$ = 21.9 Hz, *C*), 143.3 (dm, $J_{C–F}$ = 262.3 Hz, *C*), 155.1 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −139.1 (s, 2F), −138.5 (q, *J* = 23.1 Hz, 2F), −56.6 (t, *J* = 23.2 Hz, 3F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{14}H_{12}F_7NO$, 343.0807; found, 343.0799.

***N*-Cyclohexyl-2,3,5,6-tetrafluorobenzamide (6p).**

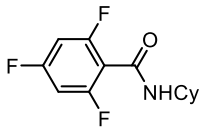


6p

The first metalation step was conducted with **1u** (299.1 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 90 min and the second amidation step was conducted with **5b** (249.7 mg, 2.0 mmol) for 30 min. The product **6p** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 80:20) and obtained in 45% yield (124.6 mg, 0.45 mmol) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.14–1.32 (m, 3H), 1.36–1.49 (m, 2H), 1.61–1.70 (m, 1H), 1.71–1.81 (m, 2H), 2.01–2.11 (m, 2H), 3.96–4.07 (m, 1H), 5.77 (brs, 1H), 7.07–7.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (*C*H_2), 25.5 (*C*H_2), 32.8 (*C*H_2), 49.4 (*C*H), 107.2 (t, $J_{C–F}$ = 22.4 Hz, *C*H), 117.7 (t, $J_{C–F}$ = 19.1 Hz, *C*), 144.6 (dm, $J_{C–F}$ = 495.4 Hz, *C*), 144.5–145.0 (m, *C*), 157.3 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −142.5 (s, 2F), −138.3 (s, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{13}F_4NO$, 275.0933; found, 275.0932.

***N*-Cyclohexyl-2,4,6-trifluorobenzamide (6q).**



6q

The first metalation step was conducted with **1v** (211.4 mg, 1.0 mmol) and THF (162 μL, 2.0 mmol) for 3 h and the second amidation step was conducted with **5b** (250.4 mg, 2.0 mmol) for 0.5 h. The product **6q** was purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 85:15) and obtained in 39% yield (101.4 mg, 0.39 mmol) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$, δ): 1.14–1.32 (m, 3H), 1.35–1.49 (m, 2H), 1.60–1.69 (m, 1H), 1.70–1.80 (m, 2H), 1.99–2.09 (m, 2H), 3.94–4.05 (m, 1H), 5.74 (brs, 1H), 6.66–6.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (*C*H_2), 25.5 (*C*H_2), 32.8 (*C*H_2), 49.1 (*C*H), 100.7 (td, $J_{C–F}$ = 3.5, 26.2 Hz, *C*H), 111.7 (td, $J_{C–F}$ = 4.1, 21.2 Hz, *C*), 158.7 (*C*), 160.4 (ddd, $J_{C–F}$ = 9.8, 15.1, 253.0 Hz, *C*), 163.2 (dt, $J_{C–F}$ = 15.3, 252.7 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −110.1 (s, 2F), −105.4 (s, 1F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{14}F_3NO$, 257.1028; found, 257.1025.

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