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Halogen–Lithium Exchange of Sensitive (Hetero)aromatic Halides under Barbier Conditions in a Continuous Flow Set-Up

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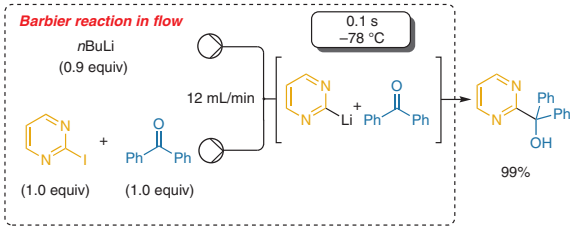
In memory of Prof. Dr. Kilian Muñiz



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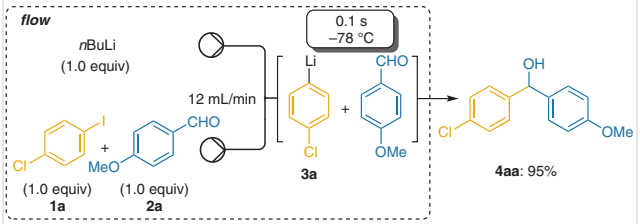
Abstract A halogen–lithium exchange reaction of (hetero)aromatic halides performed in the presence of various electrophiles such as aldehydes, ketones, Weinreb amides, and imines using BuLi as exchange reagent and a commercially available flow set-up is reported. The organolithiums generated in situ were instantaneously trapped with various electrophiles (Barbier conditions) resulting in the formation of polyfunctional (hetero)arenes. This method enables the functionalization of (hetero)arenes containing highly sensitive functional groups such as esters, which are not tolerated in batch conditions.

Key words heterocycles, flow chemistry, organolithiums, Barbier reaction, halogen–lithium exchange

Functionalized (hetero)arenes play an important role in the elaboration of pharmaceuticals and agrochemicals.[1] New strategies for the functionalization of aromatics and heteroaromatics are still needed for extending the reaction scope.[2] In the past, lithium bases have been used to produce various lithiated aromatics and heteroaromatics.[3] However, some major drawbacks, including a low functional group tolerance and moderate stability of the resulting (hetero)-aryllithiums, have been noticed.[4] To overcome these limitations, other organometallic reagents, such as organomagnesium and organozinc species with increased stability were used.[5] Nevertheless, their low reactivity towards electrophiles often requires the presence of transition metal catalysts.[5] Recently, Yoshida and others reported an increased compatibility of lithiated compounds bearing functional groups under continuous flow conditions.[6] Inspired by Yoshida's work and having in mind, that the halogen–lithium exchange is a fast reaction for the generation of lithiated (hetero)aromatics,[7] we have examined the preparation of various (hetero)aryllithium derivatives in the presence of electrophiles (Barbier conditions). In addition, the precise control of reaction parameters such as temperature, reaction time, and ultra-fast mixing using a commercial flow set-up allows convenient reaction conditions at noncryogenic temperatures and scale-ups without further optimization of the reaction conditions.[8]

Herein, we report a Barbier halogen–lithium exchange reaction of sensitive (hetero)aromatic halides of type **1** using *n*BuLi or *t*BuLi as exchange reagents in the presence of various electrophiles of type **2** using a commercially available flow set-up.[9] The resulting lithiated (hetero)aromatic species of type **3** were quenched in situ with various electrophiles resulting in a broad range of functionalized (hetero)-aromatic products of type **4**. We first screened the stoichiometry of 1-chloro-4-iodobenzene (**1a**) and *p*-anisaldehyde (**2a**, playing the role of an in situ electrophile) as well as the reaction time and temperature (Scheme 1).



Scheme 1 Halogen–lithium exchange reaction of functionalized (hetero)aryl halides of type **1** under Barbier conditions and in situ trapping with various electrophiles of type **2** affording polyfunctionalized (hetero)aryls of type **4** using a commercial continuous flow set-up

We found that by using a combined flow rate of 12 mL/min at –78 °C, arene **1a** (1.0 equiv), electrophile **2a** (1.5 equiv), and *n*BuLi (1.5 equiv) as exchange reagent, a

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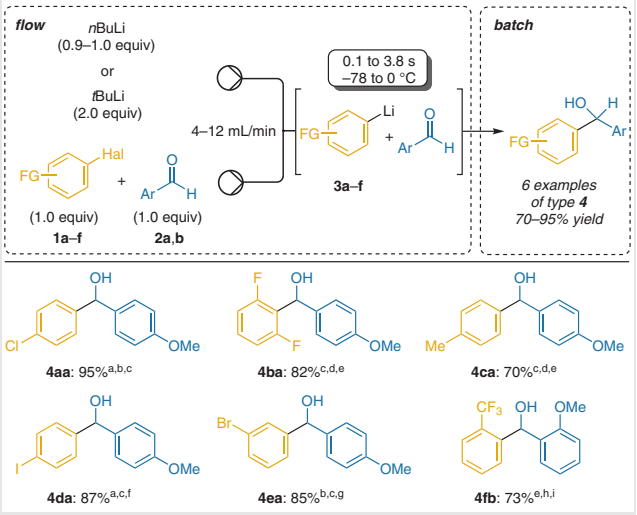
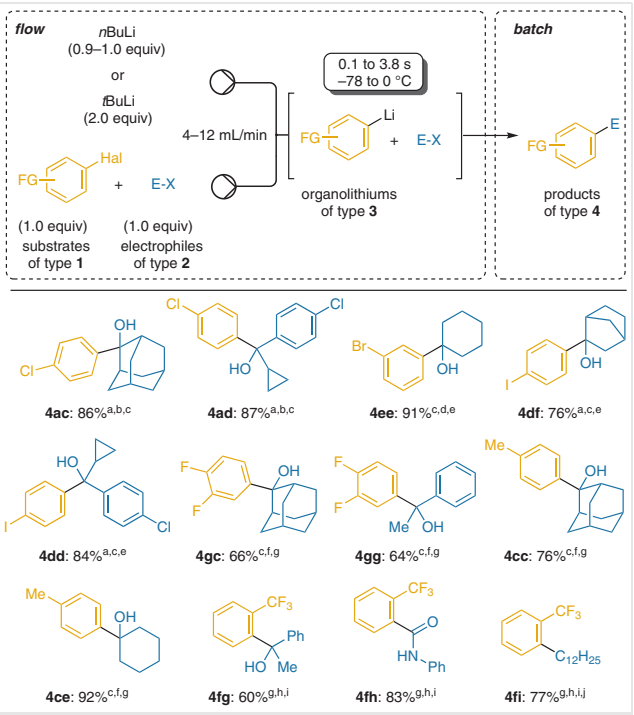
complete iodine–lithium exchange was obtained within 0.1 second and instantaneous trapping with *p*-anisaldehyde (**2a**) led to the secondary alcohol **4aa** in 72% GC-yield. Increasing the reaction time (up to 24 s) or conducting the reaction at elevated temperatures (up to 0 °C) led to a decreased GC-yield of 62–65%. Finally, optimal results were achieved using aromatic iodide **1a** (1.0 equiv), aldehyde **2a** (1.0 equiv), and *n*BuLi (1.0 equiv) as exchange reagent. The addition of *n*BuLi to *p*-anisaldehyde leading to a secondary alcohol was a negligible side-reaction and **4aa** was obtained in 95% yield (Scheme 1). Similarly, 1,3-difluoro-2-iodobenzene (**1b**) gave the organolithium reagent **3b** at –20 °C within 1.9 seconds, which was subsequently trapped with **2a** resulting in the secondary alcohol **4ba** in 82% yield (Scheme 2). The reaction of 1-methyl-4-iodobenzene (**1c**) with *p*-anisaldehyde (**2a**) afforded the desired product **4ca** in 70% yield. The method was applied to dihalogenated starting materials such as 1,4-diiodobenzene (**1d**) and 1-bromo-2-iodobenzene (**1e**). The in situ generated organolithiums **3d**,**e** were immediately trapped with **2a** resulting in the corresponding alcohols **4da** and **4ea** in 85–87% yield. As expected, using 1,4-diiodobenzene (**1d**) merely one iodine was exchanged. Additionally, 1-bromo-3-iodobenzene (**1e**) underwent a clean I–Li exchange providing the benzhydryl alcohol **4ea** in 85% yield. The exchange of 1-iodo-2-(trifluoromethyl)benzene (**1f**) using *n*BuLi only led to the undesired BuLi addition to the aldehyde, however, by using *t*BuLi (2.0 equiv), the desired organolithium **3f** was obtained. After in situ trapping with *o*-anisaldehyde (**2b**) the desired alcohol **4fb** was isolated in 73% yield.



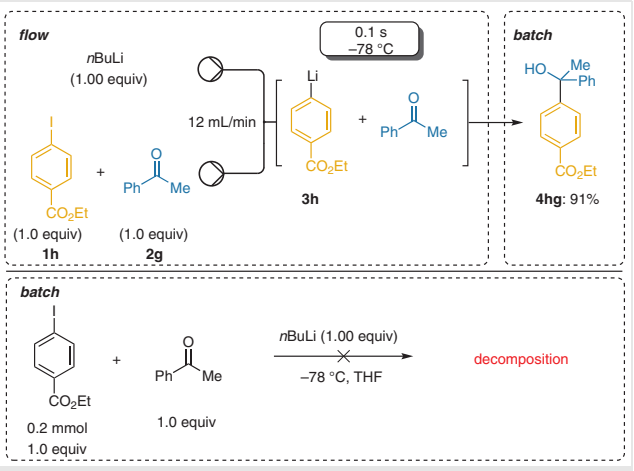
Scheme 2 Halogen–lithium exchange reaction of functionalized aryl halides under Barbier conditions and in situ trapping with aldehydes using a commercial continuous flow set-up. [a] –78 °C, 12 mL/min, 0.1 s. [b] *n*BuLi = 1.0 equiv. [c] From the corresponding iodide. [d] –20 °C, 8 mL/min, 1.9 s. [e] *t*BuLi = 2.0 equiv. [f] *n*BuLi = 0.9 equiv. [g] 0 °C, 12 mL/min, 0.1 s. [h] –20 °C, 4 mL/min, 3.8 s. [i] From the corresponding bromide.

In contrast to the less reactive magnesium or zinc species, we could trap the corresponding highly reactive lithium species in situ using Barbier conditions with various ketones resulting in tertiary alcohols. Remarkably, sterically hindered ketones, which are prone to undergo a reduction with lithium reagents,[10] such as 2-adamantanone (**2c**) and 4-chlorophenyl cyclopropyl ketone (**2d**) were satisfactorily used as trapping agents (Scheme 3). Thus, the aryllithium **3a** was quenched with **2c** and **2d** resulting in the tertiary alcohols **4ac**,**ad** in 86–87% yield. Then, arenes bearing fluoro, bromo, and iodo substituents were investigated using our optimum flow conditions. The in situ generated aryllithiums **3d**, **3e**, and **3g** were subsequently trapped by cyclohexanone (**2e**), norcamphor (**2f**), 4-chlorophenyl cyclopropyl ketone (**1d**), and adamantanone (**2c**) affording the functionalized arenes **4dd**, **4df**, **4ee**, and **4gc** in 66–91% yield. Moreover, 1,2-difluoro-4-iodobenzene (**1g**) reacted instantaneously with acetophenone (**2g**) without any detection of aldol side products affording the alcohol **4gg** in 64% yield. Similarly, 1-methyl-4-iodobenzene (**1c**) led after in situ trapping of the lithiated species **3c** with adamantanone (**2c**) and cyclohexanone (**2e**) to the corresponding tertiary alcohols **4cc** and **4ce** in 76–92% yield. Notably, lithiation of 1-iodo-2-(trifluoromethyl)benzene (**1f**) using the optimum conditions in the presence of acetophenone (**2g**) resulted in the organolithium **3f**, which after in situ trapping with acetophenone (**2g**) afforded the alcohol **4fg** in 60% yield. Extending the flow procedure to isocyanates as in situ trapping reagents was also possible. Thus, the addition of **1f** to phenyl isocyanate (**2h**) under our standard conditions afforded the corresponding amide **4fh** in 83% yield. Next, we examined a Wurtz–Fittig-type coupling[11] using dodecyl iodide (1.5 equiv) in the absence of any transition metal catalyst. To our delight, the alkylated arene **4fi** was obtained in 77% yield.[2]

We examined the behavior of ethyl 4-iodobenzoate (**1h**), bearing an ester functionality, which is not tolerated under batch conditions using lithium bases.[12] However, with a flow set-up we were able to perform an iodine–lithium exchange in the presence of acetophenone (**2g**, 1.0 equiv). The in situ trapping of the lithiated arene **3h** resulted in the desired tertiary alcohol **4hg** in 91% yield, whereas a batch reaction led to undesired side reactions and decomposition of ester **1h** (Scheme 4). Furthermore, the functionalization of heterocycles is a key synthetic task for the elaboration of pharmacological active compounds and agrochemicals.[2] To demonstrate the broad applicability of Barbier halogen–lithium exchange reactions, we investigated its compatibility with heteroaromatic halides of type **5**, affording functionalized heterocycles of type **7** via the heteroaryllithium species of type **6**. Notably, 2-bromopyridine (**5a**) was used to generate the highly reactive intermediate 2-pyridyllithium (**6a**) at –78 °C within 0.1 second.



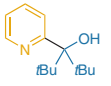
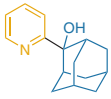
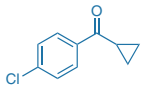
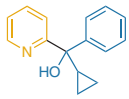
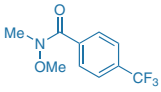
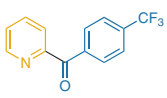
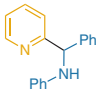
Scheme 3 Halogen–lithium exchange reaction of functionalized aryl halides under Barbier conditions and in situ trapping with sterically hindered ketones, phenyl isocyanate and dodecyl iodide using a continuous flow set-up. [a] –78 °C, 12 mL/min, 0.1 s. [b] *n*BuLi = 1.0 equiv. [c] From the corresponding iodide. [d] 0 °C, 6 mL/min, 0.1 s. [e] *n*BuLi = 0.9 equiv. [f] –20 °C, 8 mL/min, 1.9 s. [g] *t*BuLi = 2.0 equiv. [h] –20 °C, 4 mL/min, 3.8 s. [i] From the corresponding bromide. [j] Dodecyl iodide (1.5 equiv) was used.

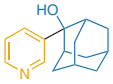
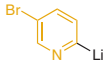
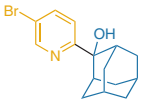
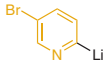
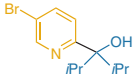
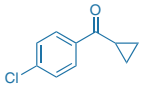
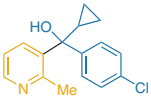
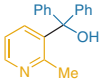
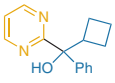
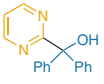


Scheme 4 In situ trapping iodine–lithium exchange reaction of highly sensitive ethyl 4-iodobenzoate (**1h**) under Barbier conditions using a commercial continuous flow set-up

Trapping of **6a** with sterically demanding ketones **2c**, **2d**, and **2j** afforded the tertiary alcohols **7ac**, **7ad**, and **7aj** in 93–99% yield (Table 1, entries 1–3). Quenching with Weinreb amide **2k** and imine **2l** led to the desired ketone **7ak** and secondary amine **7al** in 59–62% yield (entries 4, 5). The tertiary alcohol **7bc** was obtained upon in situ quenching of organolithium **6b** at 0 °C within 7.5 seconds from 3-bromopyridine (**5b**), whereas the bromine–lithium exchange under batch conditions usually was performed at –78 °C (entry 6). Further, 2,5-dibromopyridine (**5c**) was lithiated in flow with *n*BuLi (0.9 equiv) with complete regioselectivity. Upon an immediate quench of resulting lithium species **6c** with various sterically demanding ketones such as adamantanone (**2c**) and 2,4-dimethylpentan-3-one (**2m**) solely the 2-substituted pyridines **7cc** and **7cm** were obtained in 53–64% yield (entries 7, 8). Further, 3-iodo-2-methylpyridine (**5d**) was subjected to these conditions affording after in situ trapping with ketones **2d** and **2n** the desired tertiary alcohols **7dd** and **7dn** in 81–92% yield (entries 9, 10). Further, 2-iodopyrimidine (**5e**) was lithiated at –78 °C within 0.1 second affording upon Barbier trapping with ketones **2n** and **2o** the sterically demanding tertiary alcohols **7eo** and **7en** in 79–99% yield (entries 11, 12).

Table 1 Halogen–Lithium Exchange Reaction of Functionalized Heteroaryl Halides of Type **5** under Barbier Conditions and in situ Trapping of Intermediate Organolithiums of Type **6** with Electrophiles of Type **2** Affording Functionalized Heteroaryls of Type **7** in Continuous Flow

Entry	Metal species Temp (°C); Time (s); Flow rate (mL/min)	Electrophile	Product
			
1	**6a** –40; 0.1; 12	**2j**	**7aj**: 93%[a]
			
2	**6a** –40; 0.1; 12	**2c**	**7ac**: 98%[b]
			
3	**6a** –40; 0.1; 12	**2d**	**7ad**: 99%[b]
			
4	**6a** –40; 0.1; 12	**2k**	**7ak**: 62%[b]
			
5	**6a** –40; 0.1; 12	**2l**	**7al**: 59%[b]

Entry	Metal species Temp (°C); Time (s); Flow rate (mL/min)	Electrophile	Product
			
6	**6b** 0; 7.5; 2	**2c**	**7bc**: 60%[a]
			
7	**6c** −78; 0.15; 8	**2c**	**7cc**: 64%[b]
			
8	**6c** −78; 0.15; 8	**2m**	**7cm**: 53%[b]
			
9	**6d** −78; 0.1; 12	**2d**	**7dd**: 81%[b]
			
10	**6d** −78; 0.1; 12	**2n**	**7dn**: 92%[b]
			
11	**6e** −78; 0.1; 12	**2o**	**7eo**: 79%[b]
			
12	**6e** −78; 0.1; 12	**2n**	**7en**: 99%[b]

[a] *t*BuLi: 2.0 equiv, prepared from the corresponding bromide.
[b] *n*BuLi: 0.9 equiv, prepared from the corresponding iodide.

In summary, we have reported a general method to functionalize (hetero)aryl halides using a halogen–lithium exchange under Barbier conditions in continuous flow. The merger of flow technology and highly reactive organolithiums enables a functional group tolerance commonly not accessible using lithium reagents under batch conditions. In situ trapping with various electrophiles such as aldehydes, ketones, imines, Weinreb amides, isocyanates, and alkyl halides led to a broad range of functionalized (hetero)arenes in good to excellent yields. Further extensions of this work are currently under way in our laboratories.

Tetradecane ($nC_{14}H_{30}$), dodecane ($nC_{12}H_{26}$), or undecane ($nC_{11}H_{24}$) were used as internal standards for GC analysis. All flasks were heat gun dried (650 °C) under vacuum and backfilled with argon after cooling. Syringes, which were used to transfer reagents and solvents, were purged with argon three times prior to use. Batch quenching reactions were carried out with magnetic stirring. Flow reactions were performed on commercially available flow systems. A Vapourtec E-series Integrated Flow Chemistry System with 3rd Pump Kit, Organometallic Kit, Collection Valve Kit, and Cryogenic Reaction Kit or an Uniqsis FlowSyn system was used. If the Vapourtec System was used, hexane solutions of *n*BuLi or *t*BuLi and THF solutions of the remaining reactants were kept in flasks with rubber septa under an argon atmosphere. If the Uniqsis system was used, carrier solvents as well as reactant solutions were stored under argon and injected to carrier solvent streams. All reactions were performed in coiled tube reactors. Coiled reactors were made from PFA or PTFE Teflon (I.D. = 0.8 mm or 0.25 mm, O.D. = 1.6 mm) tubing and T-pieces (I.D. = 0.5 mm) were used as mixers. Prior to performing reactions, the systems were dried by flushing with anhyd THF or hexane (flow rate of all pumps: 1.00 mL/min; run-time: 30 min).

Flow and Subsequent Batch Quenching Reactions; General Procedure

A *n*BuLi solution in hexane (0.20 M, 1.0 equiv) and a solution of (hetero)aryl halide (0.20 M, 1.0 equiv) and electrophile (0.20 M, 1.0 equiv) in THF were prepared. Injection loop A (vol^{inj} = 1.00 mL) was loaded with *n*BuLi as exchange reagent and injection loop B (vol^{inj} = 1.00 mL) was loaded with a solution containing (hetero)aryl halide and electrophile. The solutions were simultaneously injected into separate streams of THF, respectively (pump A: THF; pump B: THF, flow rates: 1.00–6.00 mL/min), each of which passed a pre-cooling loop (vol^{pre} = 1.00 mL, T^1 = −78 to 0 °C, residence time: 10–60 s), before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (Vol^R = 0.02–0.25 mL; residence time: t^1 = 0.1–3.4 s, T^1 = −78 to 0 °C) and was subsequently collected in a flask. The reaction mixture was quenched with sat. aq NH_4Cl solution. The aqueous phase was extracted with EtOAc and the organic phases were dried and filtered. After removal of the solvent in vacuo, flash column chromatography (silica gel, suitable isohexane:EtOAc mixture) afforded the functionalized (hetero)arenes.

Halogen–Lithium Exchange of (Hetero)aryl Halides with *n*BuLi as Exchange Reagent; Typical Procedure 1 (TP1) Using an Uniqsis Flow Setup

An *n*BuLi solution in hexane (0.18 M, 0.9 equiv) and a solution of 2-bromopyridine (**5a**; 41 mg, 0.20 M, 1.0 equiv), and 2-adamantanone (**2c**; 30 mg, 0.20 M, 1.0 equiv) in THF were prepared. Injection loop A (vol_{inj} = 1.00 mL) was loaded with *n*BuLi as exchange reagent and injection loop B (vol_{inj} = 1.00 mL) was loaded with a solution containing **5a** and **2c**. The solutions were simultaneously injected into separate streams of THF, respectively (pump A: THF; pump B: THF, flow rates: 6.00 mL/min), each of which passed a pre-cooling loop (vol_{pre} = 1.00 mL, T^1 = −78 °C, residence time: 10 s) before they were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (Vol_R = 0.02 mL; residence time: t^1 = 0.1 s, T^1 = −78 °C) and

was subsequently collected in a flask. The reaction mixture was quenched with sat. aq NH_4Cl. The aqueous phase was extracted with EtOAc and the organic phases were combined, dried, and filtered. After removal of the solvent in vacuo, flash column chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7ac** as white crystals (45 mg, 0.18 mmol, 98%). See below for full characterization of **7ac**.

Halogen–Lithium Exchange of (Hetero)aryl Halides with *t*BuLi as Exchange Reagent; Typical Procedure 2 (TP2) Using a Vapourtec E-Series Integrated Flow Chemistry System

A *t*BuLi solution in hexane (0.40 M, 2.0 equiv) and a solution of 2-bromopyridine (**5a**; 32 mg, 0.20 M, 1.0 equiv) and hexamethylacetone (**2j**; 28 mg, 0.20 M, 1.0 equiv) in THF were prepared. The solutions were pumped from their flasks through a suction needle with a flowrate of 6.00 mL/min. After passing a PTFE tube (vol_{pre} = 1.00, T^1 = –40 °C, residence time: 10 s) for precooling, the solutions were mixed in a T-mixer (PTFE, I.D. = 0.5 mm). The combined stream passed a PTFE reactor tube (Vol_R = 0.02 mL; residence time: t^1 = 0.1 s, T^1 = –40 °C) and was subsequently collected in an empty flask. The reaction mixture was quenched with sat. aq NH_4Cl solution. The aqueous phase was extracted with EtOAc and the organic phases were combined, dried, and filtered. After removal of the solvent in vacuo, flash column chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7aj** as a yellow solid (41 mg, 0.19 mmol, 93%). See below for full characterization.

(4-Chlorophenyl)(4-methoxyphenyl)methanol (4aa)

According to **TP1**, a solution of 1-chloro-4-iodobenzene (**1a**; 0.20 M, 48 mg, 0.20 mmol) and *p*-anisaldehyde (**2a**; 0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.00 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 7:3) afforded the title compound **4aa** as a white solid; yield: 47 mg (0.19 mmol, 95%); mp 54.2–56.7 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.34–7.29 (m, 4 H), 7.28–7.22 (m, 2 H), 6.89–6.84 (m, 2 H), 5.76 (s, 1 H), 3.77 (s, 3 H), 2.42 (s, 1 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 159.8, 143.6, 136.6, 133.4, 128.9 (2 C), 128.3 (4 C), 114.4 (2 C), 75.5, 55.8.

The spectroscopic data match the literature values.[13]

(2,6-Difluorophenyl)(4-methoxyphenyl)methanol (4ba)

According to **TP1**, a solution of 1,3-difluoro-2-iodobenzene (**1b**; 0.20 M, 50 mg, 0.20 mmol) and *p*-anisaldehyde (**2a**; 0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.3 s, 0 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 8:2) afforded the title compound **4ba** as a colorless oil; yield: 41 mg (0.16 mmol, 82%).

IR (Diamond-ATR, neat): 3415, 2838, 1510, 1303, 1231, 1169, 1064, 1010, 868 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 2 H), 7.25 (tt, *J* = 8.4, 6.4 Hz, 1 H), 6.95–6.83 (m, 4 H), 6.19 (d, *J* = 8.4 Hz, 1 H), 3.79 (s, 3 H), 2.73 (dt, *J* = 9.4, 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (dd, *J* = 248.2, 8.3 Hz, 2 C), 159.2, 134.4, 129.6 (t, *J* = 10.7 Hz), 127.1 (2 C), 119.6 (t, *J* = 16.4 Hz), 113.9 (2 C), 112.4–111.8 (m, 2 C), 67.6 (t, *J* = 3.5 Hz), 55.4.

MS (EI, 70 eV): *m*/*z* (%) = 250 (45), 233 (27), 141 (98), 137 (34), 109 (100), 108 (29), 94 (22).

HRMS (EI): *m*/*z* calcd for [$C_{14}H_{12}F_2O_2$]: 250.0805; found: 250.0799.

(4-Methoxyphenyl)(*p*-tolyl)methanol (4ca)

According to **TP2**, a solution of 1-iodo-4-methylbenzene (**1c**; 0.20 M, 44 mg, 0.20 mmol) and *p*-anisaldehyde (**2a**; 0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **4ca** as a white solid; yield: 32 mg (0.14 mmol, 70%); mp 63.8–64.7 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.31–7.19 (m, 4 H), 7.19–7.10 (m, 2 H), 6.89–6.81 (m, 2 H), 5.75 (d, *J* = 3.4 Hz, 1 H), 3.77 (s, 3 H), 2.32 (s, 3 H), 2.25 (dd, *J* = 3.5, 0.6 Hz, 1 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 159.6, 142.1, 137.7, 137.2, 129.6 (2 C), 128.2 (2 C), 126.7 (2 C), 114.3 (2 C), 76.0, 55.8, 21.3.

The spectroscopic data match the literature values.[14]

(4-Iodophenyl)(4-methoxyphenyl)methanol (4da)

According to **TP1**, a solution of 1,4-diiodobenzene (**1d**; 0.20 M, 66 mg, 0.20 mmol) and *p*-anisaldehyde (**2a**; 0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **4da** as a white solid; yield: 53 mg (0.16 mmol, 87%); mp 94.6–96.0 °C.

IR (Diamond-ATR, neat): 3253, 1741, 1510, 1392, 1249, 1217, 1110, 1019, 1000, 799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 2 H), 7.25–7.21 (m, 2 H), 7.14–7.09 (m, 2 H), 6.88–6.82 (m, 2 H), 5.72 (d, *J* = 2.9 Hz, 1 H), 3.79 (s, 3 H), 2.30 (d, *J* = 3.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 143.8, 137.5 (2 C), 135.8, 128.5 (2 C), 128.0 (2 C), 114.1 (2 C), 93.0, 75.4, 55.4.

MS (EI, 70 eV): *m*/*z* (%) = 340 (28), 231 (50), 152 (24), 137 (16), 135 (100), 109 (70), 108 (31), 94 (14).

HRMS (EI): *m*/*z* calcd for [$C_{14}H_{13}IO_2$]: 339.9960; found: 339.9955.

(3-Bromophenyl)(4-methoxyphenyl)methanol (4ea)

According to **TP1**, a solution of 1-bromo-3-iodobenzene (**1e**; 0.20 M, 57 mg, 0.20 mmol) and *p*-anisaldehyde (**2a**; 0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 9:1) afforded the title compound **4ea** as a yellow oil; yield: 45 mg (0.15 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (t, *J* = 1.8 Hz, 1 H), 7.40 (ddd, *J* = 7.9, 2.1, 1.1 Hz, 1 H), 7.32–7.25 (m, 3 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 6.92–6.87 (m, 2 H), 5.76 (s, 1 H), 3.82 (s, 3 H), 2.37 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 146.4, 135.7, 130.5, 130.1, 129.5, 128.1 (2 C), 125.1, 122.7, 114.2 (2 C), 75.3, 55.4.

The spectroscopic data match the literature values.[15]

(2-Methoxyphenyl)[2-(trifluoromethyl)phenyl]methanol (4fb)

According to **TP2**, a solution of 1-bromo-2-(trifluoromethyl)benzene (**1f**; 0.20 M, 45 mg, 0.20 mmol) and *o*-anisaldehyde (**2b**; 0.20 M, 27 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 4 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (3.8 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 85:15) afforded the title compound **4fb** as a pale yellow oil; yield: 41 mg (0.15 mmol, 73%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.9 Hz, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 6.99 (d, *J* = 1.8 Hz, 1 H), 6.95 (d, *J* = 7.7 Hz, 1 H), 6.84 (dd, *J* = 8.2, 2.6 Hz, 1 H), 6.31 (d, *J* = 3.2 Hz, 1 H), 3.81 (s, 3 H), 2.41 (d, *J* = 3.7 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.8, 144.6, 142.4, 132.5 (d, *J* = 1.0 Hz), 129.7, 129.6, 127.9, 127.8 (q, *J* = 30.1 Hz), 125.7 (q, *J* = 5.8 Hz), 124.5 (q, *J* = 274.1 Hz), 118.9, 113.0, 112.3, 70.8 (q, *J* = 2.4 Hz), 55.3.

The spectroscopic data match the literature values.[16]

Adamant-2-yl(4-chlorophenyl)methanol (4ac)

According to **TP1**, a solution of 1-chloro-4-iodobenzene (**1a**; 0.20 M, 48 mg, 0.20 mmol) and 2-adamantanone (**2c**; 0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 100:0 → 95:5) afforded the title compound **4ac** as a white solid; yield: 45 mg (0.17 mmol, 86%); mp 84.2–85.7 °C.

IR (Diamond-ATR, neat): 2931, 2896, 1493, 1093, 1014, 970, 932, 911, 822, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.44 (m, 2 H), 7.36–7.31 (m, 2 H), 2.50 (s, 2 H), 2.38 (d, *J* = 12.5 Hz, 2 H), 1.90 (t, *J* = 2.9 Hz, 1 H), 1.73 (d, *J* = 12.9 Hz, 7 H), 1.64 (d, *J* = 13.4 Hz, 2 H), 1.55 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 133.1, 128.9 (2 C), 127.2 (2 C), 75.4, 37.7, 35.8 (2 C), 34.9 (2 C), 33.0 (2 C), 27.5, 26.9.

MS (EI, 70 eV): *m*/*z* (%) = 253 (21), 141 (33), 139 (100), 91 (25), 81 (20), 80 (19), 79 (45).

HRMS (EI): *m*/*z* calcd for [$C_{16}H_{19}ClO$]: 262.1124; found: 262.1121.

Bis(4-chlorophenyl)(cyclopropyl)methanol (4ad)

According to **TP1**, a solution of 1-chloro-4-iodobenzene (**1a**; 0.20 M, 48 mg, 0.20 mmol) and (4-chlorophenyl)(cyclopropyl)methanone (**2d**; 0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 100:0 → 95:5) afforded the title compound **4ad** as a colorless oil; yield: 51 mg (0.17 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 4 H), 7.30–7.26 (m, 4 H), 1.87 (s, 1 H), 1.60–1.51 (m, 1 H), 0.63–0.58 (m, 2 H), 0.47–0.42 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4 (2 C), 133.3 (2 C), 128.4 (4 C), 128.3 (4 C), 76.6, 21.7, 1.9 (2 C).

The spectroscopic data match the literature values.[17]

1-(3-Bromophenyl)cyclohexanol (4ee)

According to **TP1**, a solution of 1-bromo-3-iodobenzene (**1e**; 0.20 M, 57 mg, 0.20 mmol) and cyclohexanone (**2e**; 0.20 M, 20 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 6 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (2.5 s, 0 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 100:0 → 95:5 → 9:1) afforded the title compound **4ee** as a colorless oil; yield: 42 mg (0.16 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (t, *J* = 1.9 Hz, 1 H), 7.42 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1 H), 7.37 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1 H), 7.21 (t, *J* = 7.9 Hz, 1 H), 1.85–1.62 (m, 11 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0, 129.9, 129.8, 128.2, 123.4, 122.6, 73.1, 38.9 (2 C), 25.5, 22.2 (2 C).

The spectroscopic data match the literature values.[18]

2-(4-Iodophenyl)bicyclo[2.2.1]heptan-2-ol (4df)

According to **TP1**, a solution of 1,4-diiodobenzene (**1d**; 0.20 M, 66 mg, 0.20 mmol) and norcamphor (**2f**; 0.20 M, 22 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **4df** as white crystals; yield: 43 mg (0.14 mmol, 76%); mp 92.8–94.9 °C.

IR (Diamond-ATR, neat): 3336, 2941, 2865, 1579, 1449, 1309, 1142, 1019, 1000, 958 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 2 H), 7.29–7.24 (m, 2 H), 2.54–2.51 (m, 1 H), 2.31 (td, *J* = 5.9, 5.3, 2.5 Hz, 1 H), 2.23 (ddd, *J* = 13.2, 4.9, 2.8 Hz, 1 H), 2.19–2.10 (m, 1 H), 1.68 (s, 1 H), 1.66–1.60 (m, 1 H), 1.55–1.41 (m, 4 H), 1.34 (ddt, *J* = 10.1, 3.4, 1.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 137.4 (2 C), 128.2 (2 C), 92.5, 80.7, 47.4, 46.9, 38.9, 37.7, 29.1, 22.4.

MS (EI, 70 eV): *m*/*z* (%) = 259 (11), 246 (55), 231 (100), 187 (57), 169 (14), 141 (14), 132 (23).

HRMS (EI): *m*/*z* calcd for [$C_{13}H_{15}IO$]: 314.0168; found: 314.0163.

(4-Chlorophenyl)(cyclopropyl)(4-iodophenyl)methanol (4dd)

According to **TP1**, a solution of 1,4-diiodobenzene (**1d**; 0.20 M, 66 mg, 0.20 mmol) and (4-chlorophenyl)(cyclopropyl)methanone (**2d**; 0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **4dd** as a pale yellow oil; yield: 58 mg (0.15 mmol, 84%).

IR (Diamond-ATR, neat): 3575, 3476, 3079, 1902, 1593, 1483, 1390, 1367, 1296, 1144, 1060, 982 cm^{-1}.

^1H NMR (400 MHz, CD_2Cl_2): δ = 7.67–7.63 (m, 2 H), 7.40–7.35 (m, 2 H), 7.32–7.27 (m, 2 H), 7.21–7.16 (m, 2 H), 2.00 (s, 1 H), 1.56 (tt, *J* = 8.3, 5.5 Hz, 1 H), 0.62–0.55 (m, 2 H), 0.43 (tdd, *J* = 5.2, 4.2, 1.7 Hz, 2 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 147.3, 146.0, 137.6 (2 C), 133.5, 129.4 (2 C), 128.9 (2 C), 128.6 (2 C), 93.3, 77.0, 21.8, 2.2, 2.1.

MS (EI, 70 eV): *m*/*z* (%) = 358 (32), 356 (100), 343 (19), 231 (36), 165 (16), 141 (15), 139 (46).

HRMS (EI): *m*/*z* calcd for [$C_{16}H_{14}ClIO$]: 383.9778; found: 383.9775.

2-(3,4-Difluorophenyl)adamantan-2-ol (4gc)

According to **TP2**, a solution of 4-bromo-1,2-difluorobenzene (**1c**; 0.20 M, 39 mg, 0.20 mmol) and 2-adamantanone (**2g**; 0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **4gc** as a white solid; yield: 35 mg (0.13 mmol, 66%); mp 89.9–90.4 °C.

IR (Diamond-ATR, neat): 3320, 1605, 1520, 1449, 1389, 1276, 1148, 1045, 945 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (ddd, *J* = 12.5, 7.7, 2.3 Hz, 1 H), 7.29–7.22 (m, 1 H), 7.15 (dt, *J* = 10.1, 8.4 Hz, 1 H), 2.46 (t, *J* = 2.9 Hz, 2 H), 2.41–2.31 (m, 2 H), 1.90 (h, *J* = 3.1 Hz, 1 H), 1.80–1.68 (m, 7 H), 1.64 (dt, *J* = 13.6, 2.5 Hz, 2 H), 1.53 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3 (dd, *J* = 120.5, 12.6 Hz), 148.8 (dd, *J* = 121.6, 12.6 Hz), 142.8 (t, *J* = 4.2 Hz), 121.8 (dd, *J* = 6.1, 3.5 Hz), 117.4 (d, *J* = 16.9 Hz), 115.1 (d, *J* = 17.8 Hz), 75.3, 37.6, 35.9 (2 C), 34.9 (2 C), 33.0 (2 C), 27.4, 26.8.

MS (EI, 70 eV): *m*/*z* (%) = 264 (13), 247 (15), 246 (100), 221 (15), 204 (13), 141 (43), 91 (10).

HRMS (EI): *m*/*z* calcd for [$C_{16}H_{18}F_2O$]: 264.1326; found: 264.1313.

1-(3,4-Difluorophenyl)-1-phenylethan-1-ol (4gg)

According to **TP2**, a solution of 4-bromo-1,2-difluorobenzene (**1g**; 0.20 M, 39 mg, 0.20 mmol) and acetophenone (**2g**; 0.20 M, 24 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **4gg** as a pale yellow oil; yield: 30 mg (0.13 mmol, 64%).

IR (Diamond-ATR, neat): 3417, 3060, 1510, 1446, 1373, 1298, 1275, 1157, 1101, 917, 875 cm^{-1}.

^1H NMR (400 MHz, CD_2Cl_2): δ = 7.42–7.39 (m, 2 H), 7.35–7.24 (m, 4 H), 7.13–7.09 (m, 2 H), 2.34 (s, 1 H), 1.92 (s, 3 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 150.4 (dd, *J* = 246.6, 12.7 Hz), 149.6 (dd, *J* = 246.6, 12.7 Hz), 147.9, 146.3 (dd, *J* = 4.7, 3.8 Hz), 128.9 (2 C), 127.8, 126.2 (2 C), 122.5 (dd, *J* = 6.3, 3.5 Hz), 117.2 (d, *J* = 16.9 Hz), 115.7 (d, *J* = 18.3 Hz), 76.0 (d, *J* = 1.3 Hz), 31.2.

MS (EI, 70 eV): *m*/*z* (%) = 220 (13), 219 (100).

HRMS (EI): *m*/*z* calcd for [$C_{14}H_{12}F_2O$]: 234.0856; found: 234.0844.

2-(*p*-Tolyl)adamantan-2-ol (4cc)

According to **TP2**, a solution of 1-iodo-4-methylbenzene (**1c**; 0.20 M, 44 mg, 0.20 mmol) and 2-adamantanone (**2c**; 0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4), and

filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **4cc** as a white solid; yield: 37 mg (0.15 mmol, 76%); mp 73.6–75.4 °C.

IR (Diamond-ATR, neat): 3450, 2930, 2887, 1514, 1349, 1192, 1082, 1020, 971, 934 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.2 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 2.55 (s, 2 H), 2.41 (d, *J* = 12.3 Hz, 2 H), 2.35 (s, 3 H), 1.91 (s, 1 H), 1.76–1.70 (m, 9 H), 1.48 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 137.0, 129.5 (2 C), 125.5 (2 C), 75.6, 37.8, 35.8 (2 C), 35.1 (2 C), 33.1 (2 C), 27.6, 27.1, 21.1.

MS (EI, 70 eV): *m*/*z* (%) = 242 (34), 227 (29), 224 (43), 121 (19), 119 (100), 91 (28).

HRMS (EI): *m*/*z* calcd for [$C_{17}H_{22}O$]: 242.1671; found: 242.1659.

1-(*p*-Tolyl)cyclohexan-1-ol (4ce)

According to **TP2**, a solution of 1-iodo-4-methylbenzene (**1c**; 0.20 M, 44 mg, 0.20 mmol) and cyclohexanone (**2e**, 0.20 M, 20 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.9 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **4ce** as a white solid; yield: 35 mg (0.18 mmol, 92%); mp 53.3–55.2 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 2.35 (s, 3 H), 1.86–1.71 (m, 7 H), 1.66–1.61 (m, 2 H), 1.57 (s, 1 H), 1.36–1.26 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 136.4, 129.0 (2 C), 124.6 (2 C), 73.1, 39.0 (2 C), 25.7, 22.4 (2 C), 21.1.

The spectroscopic data match the literature values.[19]

1-Phenyl-1-[2-(trifluoromethyl)phenyl]ethan-1-ol (4fg)

According to **TP2**, a solution of 1-bromo-2-(trifluoromethyl)benzene (**1f**; 0.20 M, 45 mg, 0.20 mmol) and acetophenone (**2g**; 0.20 M, 24 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 4 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (3.8 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 85:15) afforded the title compound **4fg** as a pale yellow oil; yield: 32 mg (0.12 mmol, 60%).

IR (Diamond-ATR, neat): 3455, 2983, 1494, 1374, 1270, 1163, 1095, 1070, 1032, 959 cm^{-1}.

^1H NMR (400 MHz, CD_2Cl_2): δ = 7.75 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.57 (td, *J* = 7.8, 0.9 Hz, 1 H), 7.47–7.41 (m, 1 H), 7.32–7.21 (m, 5 H), 2.52 (s, 1 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 148.8 (d, *J* = 1.3 Hz), 146.5 (d, *J* = 1.3 Hz), 132.0 (d, *J* = 1.1 Hz), 129.8, 128.8 (q, *J* = 6.8 Hz), 128.6 (2 C), 128.3 (q, *J* = 31.2 Hz), 128.1, 127.5, 125.8 (2 C), 125.2 (q, *J* = 273.9 Hz), 77.6, 33.2 (d, *J* = 1.4 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 251 (46), 232 (14), 231 (97), 212 (15), 211 (100), 183 (26).

HRMS (EI): *m*/*z* calcd for [$C_{15}H_{13}F_3O$]: 266.0918; found: 266.0906.

N-Phenyl-2-(trifluoromethyl)benzamide (4fh)

According to **TP1**, a solution of 1-iodo-2-(trifluoromethyl)benzene (**1f**; 0.20 M, 54 mg, 0.20 mmol) and phenyl isocyanate (**2h**; 0.20 M, 24 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 9:1) afforded the title compound **4fh** as white crystals; yield: 42 mg (0.15 mmol, 83%); mp 145.1–147.7 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.6 Hz, 1 H), 7.64 (dd, *J* = 4.2, 1.3 Hz, 2 H), 7.61–7.56 (m, 4 H), 7.37 (dd, *J* = 8.6, 7.3 Hz, 2 H), 7.18 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 137.5, 135.9 (q, *J* = 2.0 Hz), 132.3, 130.3, 129.3 (2 C), 128.7, 127.5 (q, *J* = 31.7 Hz), 126.6 (q, *J* = 4.9 Hz), 125.2, 123.7 (q, *J* = 273.8 Hz), 120.4 (2 C).

The spectroscopic data match the literature values.[20]

1-Dodecyl-2-(trifluoromethyl)benzene (4fi)

According to **TP2**, a solution of 1-iodo-2-(trifluoromethyl)benzene (**1f**; 0.20 M, 45 mg, 0.20 mmol) and dodecyl iodide (**2i**; 0.30 M, 89 mg, 0.30 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 4 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (3.8 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with hexane (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane) afforded the title compound **4fi** as a colorless oil; yield: 48 mg (0.15 mmol, 77%).

IR (Diamond-ATR, neat): 2955, 2853, 1466, 1312, 1167, 1122, 1060, 1035, 766, 654 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.32 (d, *J* = 7.7 Hz, 1 H), 7.26 (d, *J* = 15.3 Hz, 1 H), 3.19 (t, *J* = 7.1 Hz, 3 H), 2.80–2.71 (m, 2 H), 1.82 (pent, *J* = 7.1 Hz, 3 H), 1.66–1.51 (m, 2 H), 1.39 (dt, *J* = 9.1, 4.1 Hz, 7 H), 0.88 (t, *J* = 6.8 Hz, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8 (q, *J* = 1.6 Hz), 131.6, 130.9, 128.3 (q, *J* = 29.7 Hz), 125.8 (q, *J* = 5.8 Hz), 125.6, 124.7 (d, *J* = 273.9 Hz), 33.6, 32.8, 32.0, 30.5, 29.7, 29.6, 29.5, 29.4, 28.6, 22.7, 14.2, 7.4.

MS (EI, 70 eV): *m*/*z* (%) = 161 (10), 160 (100), 159 (43), 109 (10), 91 (21).

HRMS (EI): *m*/*z* calcd for [$C_{19}H_{29}F_3$]: 314.2221; found: 314.2213.

Ethyl 4-(1-Hydroxy-1-phenylethyl)benzoate (4hg)

According to **TP1**, a solution of ethyl 4-iodobenzoate (**1h**; 0.20 M, 55 mg, 0.20 mmol) and acetophenone (**2g**, 0.20 M, 24 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.20 M in hexane, 0.20 mmol, 1.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **4hg** as a pale yellow oil; yield: 49 mg (0.18 mmol, 91%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.98–7.93 (m, 2 H), 7.53–7.48 (m, 2 H), 7.43–7.39 (m, 2 H), 7.35–7.29 (m, 2 H), 7.27–7.22 (m, 1 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 2.40 (s, 1 H), 1.96 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 166.8, 153.7, 148.1, 129.8 (2 C), 129.7, 128.8 (2 C), 127.7, 126.3 (2 C), 126.3 (2 C), 76.5, 61.4, 31.0, 14.7.

The spectroscopic data match the literature values.[21]

2,2,4,4-Tetramethyl-3-(pyridin-2-yl)pentan-3-ol (7aj)

According to **TP2**, a solution of 2-bromopyridine (**5a**; 0.20 M, 31 mg, 0.20 mmol) and 2,2,4,4-tetramethylpentan-3-one (**2j**; 0.20 M, 28 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –40 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7aj** as a yellow solid, yield: 41 mg (0.19 mmol, 93%); mp 42.7–43.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (ddd, *J* = 5.0, 1.7, 1.2 Hz, 1 H), 7.64 (ddd, *J* = 8.9, 6.9, 1.8 Hz, 1 H), 7.60 (dt, *J* = 8.2, 1.3 Hz, 1 H), 7.20 (ddd, *J* = 6.9, 5.0, 1.3 Hz, 1 H), 1.04 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 145.9, 135.1, 123.4, 121.9, 82.0, 41.5 (2 C), 29.6 (6 C).

The spectroscopic data match the literature values.[22]

2-(Pyridin-2-yl)adamantan-2-ol (7ac)

According to **TP1**, a solution of 2-iodopyridine (**5f**; 0.20 M, 41 mg, 0.20 mmol) and 2-adamantanone (**2c**; 0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7ac** as white crystals; yield: 45 mg (0.18 mmol, 98%); mp 109.6–110.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1 H), 7.68 (td, *J* = 7.8, 1.9 Hz, 1 H), 7.49 (dt, *J* = 8.0, 1.1 Hz, 1 H), 7.16 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1 H), 2.67 (q, *J* = 3.3 Hz, 2 H), 2.49–2.35 (m, 2 H), 2.16 (s, 1 H), 1.90 (pent, *J* = 3.1 Hz, 1 H), 1.83–1.60 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 149.4, 136.7, 122.2, 120.3, 37.9, 35.1 (2 C), 35.0 (2 C), 33.0 (2 C), 27.5, 27.2.

The spectroscopic data match the literature values.[23]

(4-Chlorophenyl)(cyclopropyl)(pyridin-2-yl)methanol (7ad)

According to **TP1**, a solution of 2-iodopyridine (**5f**; 0.20 M, 41 mg, 0.20 mmol) and (4-chlorophenyl)(cyclopropyl)methanone (**2d**; 0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7ad** as a colorless oil; yield: 50 mg (0.18 mmol, 99%).

IR (Diamond-ATR, neat): 3339, 1592, 1489, 1433, 1356, 1294, 1211, 1152, 1048, 994 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1 H), 7.63 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.49–7.43 (m, 2 H), 7.28–7.15 (m, 4 H), 5.74 (s, 1 H), 1.59 (tt, *J* = 8.2, 5.3 Hz, 1 H), 0.67–0.54 (m, 2 H), 0.45 (dtd, *J* = 9.5, 5.5, 4.3 Hz, 1 H), 0.35 (dddd, *J* = 9.0, 8.1, 6.1, 4.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 147.1, 145.3, 137.1, 133.1, 128.7 (2 C), 128.3 (2 C), 122.4, 121.2, 75.0, 20.5, 1.9, 0.8.

MS (EI, 70 eV): *m*/*z* (%) = 218 (23), 141 (25), 139 (78), 134 (58), 132 (20), 106 (28), 96 (54), 93 (21), 79 (37), 78 (100), 75 (28).

HRMS (EI): *m*/*z* calcd for [$C_{15}H_{14}ClNO$]: 259.0764; found 258.0680 (M – H).

Pyridin-2-yl[4-(trifluoromethyl)phenyl]methanone (7ak)

According to **TP1**, a solution of 2-iodopyridine (**5f**; 0.20 M, 41 mg, 0.20 mmol) and *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (**2k**; 0.20 M, 33 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **7ak** as a yellow oil; yield: 30 mg (0.11 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1 H), 8.23–8.09 (m, 3 H), 7.95 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.75 (d, *J* = 8.2 Hz, 2 H), 7.54 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.9, 154.2, 148.8, 139.4, 137.5, 133.9 (q, *J* = 32.6 Hz), 131.4 (2 C), 126.9, 125.2 (q, *J* = 3.7 Hz, 2 C), 124.9, 123.8 (q, *J* = 273 Hz).

The spectroscopic data match the literature values.[24]

N-[Phenyl(pyridin-2-yl)methyl]aniline (7al)

According to **TP1**, a solution of 2-iodopyridine (**5f**; 0.20 M, 41 mg, 0.20 mmol) and *N*,1-diphenylmethanimine (**2l**; 0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1) afforded the title compound **7al** as a brown oil; yield: 29 mg (0.12 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 4.3 Hz, 1 H), 7.62 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.46 (d, *J* = 7.3 Hz, 2 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.25 (d, *J* = 7.0 Hz, 1 H), 7.19–7.08 (m, 3 H), 6.68 (t, *J* = 7.3 Hz, 1 H), 6.63 (d, *J* = 7.7 Hz, 2 H), 5.59 (s, 1 H), 5.46 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 149.2, 147.0, 142.5, 136.9, 129.2 (2 C), 128.9 (2 C), 127.6, 127.4 (2 C), 122.3, 121.9, 117.5, 113.6 (2 C), 63.3.

The spectroscopic data match the literature values.[25]

2-(Pyridin-3-yl)adamantan-2-ol (7bc)

According to **TP2**, a solution of 3-bromopyridine (**5b**; 0.20 M, 31 mg, 0.20 mmol) and 2-adamantanone (**2c**; 0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *t*BuLi (0.40 M in hexane, 0.40 mmol, 2.0 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq. NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7bc** as white crystals; yield: 27 mg (0.12 mmol, 60%); mp 148.0–148.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 2.4 Hz, 1 H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.82 (dt, *J* = 8.1, 2.1 Hz, 1 H), 7.27 (dd, *J* = 8.0, 4.7 Hz, 1 H), 2.53 (q, *J* = 3.1 Hz, 2 H), 2.42 (dd, *J* = 12.8, 3.2 Hz, 2 H), 1.91 (t, *J* = 3.2 Hz, 1 H), 1.81–1.67 (m, 7 H), 1.61 (dt, *J* = 13.2, 2.7 Hz, 2 H), 1.24 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 147.5, 141.0, 133.9, 123.7, 74.6, 37.7, 35.4 (2 C), 34.7 (2 C), 32.8 (2 C), 27.5, 26.9.

The spectroscopic data match the literature values.[26]

2-(5-Bromopyridin-2-yl)adamantan-2-ol (7cc)

According to **TP1**, a solution of 5-bromo-2-iodopyridine (**5c**; 0.20 M, 47 mg, 0.20 mmol) and 2-adamantanone (**2c**; 0.20 M, 30 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL/min flowrate in a T-mixer. The combined stream passed a 0.25 mL reactor tube (1.88 s, –20 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted times with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7cc** as white crystals; yield: 37 mg (0.12 mmol, 64%); mp 115.7–117.3 °C.

IR (Diamond-ATR, neat): 3367, 2916, 2854, 1451, 1372, 1336, 1092, 1056, 1004, 975 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 2.3 Hz, 1 H), 8.59 (d, *J* = 2.4 Hz, 1 H), 7.98 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.80 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.38 (d, *J* = 8.4 Hz, 1 H), 7.28 (dd, *J* = 8.5, 0.8 Hz, 1 H), 2.61 (t, *J* = 2.9 Hz, 2 H), 2.39 (dd, *J* = 12.7, 3.1 Hz, 2 H), 2.19 (s, 1 H), 1.93–1.86 (m, 1 H), 1.81–1.66 (m, 6 H), 1.60 (dt, *J* = 13.3, 2.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 162.9, 155.2, 150.3, 145.0, 139.3, 122.4, 121.9, 119.1, 91.6, 37.7, 35.1, 35.0, 34.9, 32.9, 32.9, 27.4, 27.0.

MS (EI, 70 eV): *m*/*z* (%) = 307 (19), 206 (11), 205 (10), 158 (10), 88 (22), 61 (36), 45 (11), 43 (100).

HRMS (EI): *m*/*z* calcd for [$C_{15}H_{18}BrNO$]: 307.0572; found: 307.0576.

3-(5-Bromopyridin-2-yl)-2,4-dimethylpentan-3-ol (7cm)

According to **TP1**, a solution of 5-bromo-2-iodopyridine (**5c**; 0.20 M, 47 mg, 0.20 mmol) and 2,4-dimethylpentan-3-one (**2m**; 0.20 M, 23 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 8 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.15 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7cm** as a yellow oil; yield: 27 mg (0.11 mmol, 53%).

IR (Diamond-ATR, neat): 3417, 2933, 1464, 1381, 1318, 1237, 1209, 1128, 1092, 1017 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (dd, *J* = 2.1, 0.8 Hz, 1 H), 8.60 (dd, *J* = 2.3, 0.8 Hz, 1 H), 8.45 (dd, *J* = 2.6, 0.7 Hz, 1 H), 7.96 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.79 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.60 (dd, *J* = 8.3, 0.7 Hz, 1 H), 7.45 (dd, *J* = 8.3, 2.6 Hz, 1 H), 7.19 (dd, *J* = 8.5, 0.8 Hz, 1 H), 7.09 (dd, *J* = 8.4, 0.9 Hz, 1 H), 4.98 (s, 1 H), 2.33–2.24 (m, 2 H), 0.80 (d, *J* = 6.7 Hz, 6 H), 0.76 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 153.2, 152.0, 148.3, 144.2, 140.5, 138.7, 136.2, 122.7, 122.1, 118.9, 91.0, 80.1, 34.4, 17.6, 16.8.

MS (EI, 70 eV): *m*/*z* (%) = 61 (15), 45 (12), 43 (100).

HRMS (EI): *m*/*z* calcd for [$C_{12}H_{18}BrNO$]: 271.0572; found: 229.9995 (M – C_3H_8).

(4-Chlorophenyl)(cyclopropyl)(2-methylpyridin-3-yl)methanol (7dd)

According to **TP1**, a solution of 3-iodo-2-methylpyridine (**5d**; 0.20 M, 44 mg, 0.20 mmol) and (4-chlorophenyl)(cyclopropyl)methanone (**2d**; 0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted times with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the

solvent, flash chromatography (silica gel, isohexane:EtOAc = 6:4) afforded the title compound **7dd** as a white solid; yield: 42 mg (0.15 mmol, 81%); mp 173.3–174.1 °C.

IR (Diamond-ATR, neat): 1494, 1456, 1194, 1144, 1092, 1013, 988, 963 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (dd, *J* = 4.8, 1.7 Hz, 1 H), 8.32 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.35–7.29 (m, 2 H), 7.29–7.21 (m, 3 H), 2.57 (s, 1 H), 2.19 (s, 3 H), 1.59 (tt, *J* = 8.0, 5.6 Hz, 1 H), 0.73–0.58 (m, 3 H), 0.49–0.40 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 147.9, 144.0, 140.1, 134.8, 133.0, 128.3 (2 C), 127.7 (2 C), 120.6, 76.1, 24.5, 22.1, 2.2, 2.0.

MS (EI, 70 eV): *m*/*z* (%) = 247 (29), 245 (88), 232 (23), 139 (31), 120 (32), 61 (23), 43 (100).

HRMS (EI): *m*/*z* calcd for [$C_{16}H_{16}ClNO$]: 273.0920; found: 273.0909.

(2-Methylpyridin-3-yl)diphenylmethanol (7dn)

According to **TP1**, a solution of 3-iodo-2-methylpyridine (**5d**; 0.20 M, 44 mg, 0.20 mmol) and benzophenone (**2n**; 0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 6:4) afforded the title compound **7dn** as white crystals; yield: 49 mg (0.17 mmol, 92%); mp 146.1–148.1 °C.

IR (Diamond-ATR, neat): 3079, 1575, 1434, 1266, 1159, 1047, 1026, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (dt, *J* = 4.9, 1.6 Hz, 1 H), 7.39–7.28 (m, 6 H), 7.25–7.18 (m, 4 H), 7.10–6.94 (m, 2 H), 3.20 (dd, *J* = 10.0, 3.6 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 148.0, 145.8 (2 C), 140.3, 136.9 (2 C), 128.4 (4 C), 127.7 (5 C), 120.1, 82.2, 25.5.

MS (EI, 70 eV): *m*/*z* (%) = 198 (35), 183 (100), 155 (15), 154 (24), 120 (37), 105 (75), 93 (64), 92 (23), 77 (25).

HRMS (EI): *m*/*z* calcd for [$C_{19}H_{17}NO$]: 275.1310; found: 275.1306.

Cyclobutyl(phenyl)(pyrimidin-2-yl)methanol (7eo)

According to **TP1**, a solution of 2-iodopyrimidine (**5e**; 0.20 M, 41 mg, 0.20 mmol) and cyclobutyl(phenyl)methanone (**2o**; 0.20 M, 32 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7eo** as a white solid; yield: 37 mg (0.14 mmol, 79%); mp 84.8–85.6 °C.

IR (Diamond-ATR, neat): 3441, 2937, 1562, 1320, 1214, 1189, 1092, 1031, 996, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, *J* = 4.8 Hz, 2 H), 7.75–7.66 (m, 2 H), 7.29 (ddd, *J* = 7.7, 6.9, 1.2 Hz, 2 H), 7.22–7.17 (m, 1 H), 7.15 (t, *J* = 4.9 Hz, 1 H), 5.50 (d, *J* = 0.7 Hz, 1 H), 3.85–3.66 (m, 1 H), 2.21–2.08 (m, 1 H), 2.02–1.88 (m, 1 H), 1.88–1.71 (m, 3 H), 1.64–1.52 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 156.8 (2 C), 144.3, 128.0 (2 C), 127.0, 126.4 (2 C), 119.2, 78.7, 44.1, 22.4, 21.7, 17.4.

MS (EI, 70 eV): *m*/*z* (%) = 186 (13), 185 (100), 107 (14), 105 (12), 97 (10), 79 (10), 77 (10).

HRMS (EI): *m*/*z* calcd for [$C_{15}H_{16}N_2O$]: 240.1263; found: 240.1256.

Diphenyl(pyrimidin-2-yl)methanol (7en)

According to **TP1**, a solution of 2-iodopyrimidine (**5e**; 0.20 M, 41 mg, 0.20 mmol) and benzophenone (**2n**; 0.20 M, 36 mg, 0.20 mmol) in THF (total volume: 1.00 mL) and a solution of *n*BuLi (0.18 M in hexane, 0.18 mmol, 0.9 equiv) were prepared. The precooled solutions were mixed with an overall 12 mL/min flowrate in a T-mixer. The combined stream passed a 0.02 mL reactor tube (0.1 s, –78 °C) and was subsequently injected into an empty flask. Stirring was continued for 10 min at 25 °C before sat. aq NH_4Cl solution was added to quench the reaction. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried (anhyd Na_2SO_4) and filtered. After removal of the solvent, flash chromatography (silica gel, isohexane:EtOAc = 95:5 → 9:1 → 8:2) afforded the title compound **7en** as a white solid; yield: 51 mg (0.18 mmol, 99%).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.78 (d, *J* = 4.9 Hz, 2 H), 7.48–7.43 (m, 4 H), 7.34–7.26 (m, 6 H), 7.24 (d, *J* = 4.9 Hz, 1 H), 6.05 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 156.8 (3 C), 145.3, 128.1 (4 C), 128.0 (4 C), 127.5 (2 C), 119.4, 81.2.

The spectroscopic data match the literature values.[27]

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Supporting Information

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