HHS Public Access

Author manuscript

J Org Chem. Author manuscript; available in PMC 2018 December 15.

Published in final edited form as:

J Org Chem. 2017 December 15; 82(24): 13728–13734. doi:10.1021/acs.joc.7b02589.

Direct Synthesis of Secondary Benzylic Alcohols Enabled by Photoredox/Ni Dual-Catalyzed Cross-Coupling

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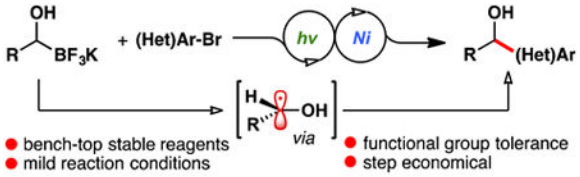
Abstract

An operationally simple, mild, redox-neutral method for the cross-coupling of α-hydroxyalkyltrifluoroborates is reported. Utilizing an Ir photocatalyst, α-hydroxyalkyl radicals are generated from the single-electron oxidation of the trifluoroborates, and these radicals are subsequently engaged in a nickel-catalyzed C-C bond-forming reaction with aryl halides. The process is highly selective, functional group tolerant, and step economical, which allows the direct synthesis of secondary benzylic alcohol motifs.

Graphical abstract



The importance of the secondary benzylic alcohol motif is clearly evident from its presence in pharmaceutically and biologically active compounds, and its application as an intermediate in numerous organic syntheses.[1] Syntheses of this class of compounds are primarily dependent on the nucleophilic addition of organometallic reagents to carbonyl compounds or the reduction of suitable ketones (Figure 1).[1b] Despite considerable advances in the addition of organometallic reagents to aldehydes, most of these methods suffer from limitations such as sensitivity to air and moisture, toxicity of the organometallic reagents, poor functional group compatibility, and/or the use of harsh reaction conditions. Moreover, the reduction of a ketone can be associated with challenging chemoselectivity issues when the target compound is furnished with multiple electrophilic functional groups.[1a]

Transition metal-catalyzed cross-coupling of an α-hydroxyalkylmetallic reagent with an aryl halide would represent an attractive alternative strategy for the direct synthesis of protected secondary benzylic alcohol derivatives. Approaches to this transformation have been

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Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental setup for gram scale reaction, cyclic voltammogram of compound 3a, and copies of ^{1}H, ^{13}C, ^{11}B, and ^{19}F spectra.

The authors declare no competing financial interest.

realized through the efforts of Falck[2] and Molander,[3] who have reported the cross-coupling of *protecting group-dependent* α-alkoxyalkylstannane and -boron nucleophiles, respectively (Figure 2A). Although these protocols are useful to synthesize secondary benzylic alkoxy compounds, *protection followed by subsequent deprotection* steps are involved for the isolation of the corresponding alcohols. In fact, very few methods permit *direct synthesis of unprotected secondary benzylic alcohols* without the intermediacy of an unprotected derivative.[4] To the best of our knowledge there is no general report in the literature regarding the direct cross-coupling of unprotected α-hydroxyalkylmetallic nucleophiles with aryl halides.

Recently, our group and others have developed powerful methods for engaging Csp^3-centered radicals in a dual-catalytic, photoredox/Ni cross-coupling system.[5] The identification of bench-top stable precursors from which radicals can be photocatalytically generated *via* single electron transfer (SET) oxidation or reduction is an underlying hurdle that must be overcome in the development of this type of catalysis. In our investigations, alkyltrifluoroborates have been employed based on favorable SET potentials under photoredox conditions.[5f, 6]

However, it remains of importance to introduce new classes of radical precursor reagents to demonstrate advantages over standard two-electron cross-coupling protocols. In this connection, we envisioned coupling α-hydroxyalkyltrifluoroborates and aryl halides, which would offer an *umpolung disconnection approach* for the direct synthesis of secondary benzylic alcohols (Figure 1).

This transformation is highly desirable because an α-hydroxyalkyl group can be directly installed through the construction of a new Csp^2–Csp^3 bond. Recently, it has been reported that the α-hydroxyalkyl radical can be generated from alcohols, with subsequent trapping of the generated radical with a Michael acceptor.[7] An alternative approach to generate the hydroxy radical would be the reduction of carbonyl compounds by a photocatalytic proton coupled electron transfer process.[8] However, the direct cross-coupling of α-hydroxyalkyl radicals with aryl halides remains unexplored to this point in time. Therefore, we set out to use α-hydroxyalkyltrifluoroborates as radical precursors, generating α-hydroxyalkyl radicals under suitable photoredox/Ni dual catalytic conditions (Figure 2B).

We initiated our study using 3a as a representative radical precursor, which was easily prepared from a commercially available aldehyde. At the outset, the ease of single electron oxidation of the reagent was evaluated. Gratifyingly, cyclic voltammetric analysis of the alkyltrifluoroborate 3a (E_{ox} = +1.22 V vs SCE) confirmed the viability of this oxidation. A mechanistic scenario was envisioned (Scheme 1) based on our previous studies,[5a, 9] in which the excited state of a suitable photocatalyst possessed a redox potential sufficiently high to induce a single-electron oxidation of the trifluoroborate 3, affording the α-hydroxyalkyl radical 4 upon fragmentation. Subsequent capture of the stabilized alkyl radical by Ni(0) species 2a would then yield Ni(I) species 2b, which could oxidatively add to aryl halides to generate the high-valent Ni(III) species 2c. Diorgano Ni(III) intermediate 2c was expected to undergo reductive elimination to give the desired cross-coupled product 6 and Ni(I) species

2d. From here, reduction of 2d by the reduced of photocatalyst (1b) would regenerate both the Ni(0) species 2a and Ir catalyst 1, closing the dual catalytic cycle.

To validate the cross-coupling of α-hydroxyalkyltrifluoroborates with aryl halides, 4-bromobenzonitrile (**5a**) and potassium trifluoroborate **3a** were chosen as model coupling partners in the presence of $\{Ir[dF(CF_3)ppy]_2(bpy)\}PF_6$ **1** ($E^*_{1/2}$= 1.32 V vs SCE)[10] as a photocatalyst. An extensive screening of various reaction parameters (e.g., solvent, Ni catalyst, ligand, and base) was carried out to determine suitable conditions for the desired cross-coupling as summarized in Table 1. A variety of photocatalysts were screened that possessed sufficiently high excited-state redox potentials to oxidize the trifluoroborate **3a**. Although 4CzIPN ($E^*_{1/2}$= 1.35 V vs SCE)[11] proved to be a viable catalyst, the Ir catalyst **1** provided superior yields (entries 1–2). MesAcr (mesitylacridinium) has a sufficiently high oxidation potential ($E^*_{1/2}$= 2.2 V vs SCE),[12] but it did not give any desired product **6a** (entry 4), likely because of its inability to reduce the putative Ni(I) (E_{red} > -1.1 V)[5a] intermediate (Scheme 1, **2d**). Other organophotocatalysts such as Eosin Y were also ineffective under these reaction conditions (entry 3), most likely because of their low redox potential ($E^*_{1/2}$= 0.79 V vs SCE).[13] The reaction was also unsuccessful in the absence of Ir photocatalyst or Ni catalyst (entries 5-6). A control experiment was run in the absence of light (entry 7) to demonstrate that the catalyst is active only in its photoexcited state. Of those additives screened, K_2HPO_4 was the best for maximizing the cross-coupling reaction. The yield was diminished in the absence of base (entry 8) indicating that BF_3 may interfere with the reaction, requiring sequestration by a base. Although different aprotic solvents were examined for the cross-coupling reaction, 1,4-dioxane was found to be superior to DME, MeCN and DMF (entries 8-10). Moreover, application of dtbbpy (4,4′-di-*tert*-butyl-2,2′-dipyridyl) ligand was the most efficient compared to other bipyridyl ligands. As anticipated, control experiments showed that all parameters were essential for the reaction to proceed.

With suitable reaction conditions in hand, the scope of the cross-coupling reaction was explored in the context of various aryl bromides using α-hydroxyalkyltrifluoroborate **3a**. As illustrated in Table 2, different electron-poor aryl bromides provided moderate to high yields of the desired products (**6a-k**). Of note, a number of electrophilic functional groups that are intolerant of Grignard reactions[14] or even reducing conditions[15] could be employed to afford nitrile (**6a**), aldehyde (**6b**)[8a], ketone (**6c**), ester (**6f**), and lactone (**6g**)-containing secondary benzylic alcohols. Furthermore, the reaction is also scalable; on scaling the reaction 11-fold to 5.50 mmol, the coupling of 4-bromobenzonitrile (**5a**) and **3a** afforded an uncompromised yield under the same reaction time. The trifluoromethyl ketone group could also be incorporated within reaction partners as demonstrated by the transformation leading to **6e**. Aryl bromides containing multiple different substituents can also be used for the cross-coupling as demonstrated by the reaction of substrates affording **6g-h**.

A bromo sulfonamide can also be engaged in the coupling to give **6i**. Not only electron-withdrawing but also electron-donating aryl bromides can be employed for the cross-coupling. For example, 4-bromoanisole can be cross-coupled with extended reaction time (36 h) affording the compound **6I** in moderate yield. Furthermore, the pinacol ester of 4-bromophenylboronic acid reacted smoothly to afford arylboronate product **6m**, thereby permitting potentially powerful sequential cross-coupling sequences with either nucleophilic

or electrophilic partners.[16] Unfortunately, attempts to use 4-bromophenol and 4-bromobenzoic acid were not met with success (**6n-o**). At this time, we surmise that the phenol and carboxylic acid functional groups undergo rapid deprotonation in the presence of base to form the oxyanions, which may strongly coordinate the Ni catalyst and thus diminish the catalyst activity. Moreover, the desired coupling product **6a** was not observed when the aryl bromide **5a** was replaced with 4-chlorobenzonitrile, which indicates the incompatibility of aryl chlorides as coupling partner under these reaction conditions. A similar trend was observed in previously reported photoredox/Ni-dual catalyzed cross-coupling reactions.[5f, 6]

Once the versatility of the protocol was demonstrated against different aryl bromides, we turned our attention to both the alkyltrifluoroborate radical precursors and the aryl bromide partners simultaneously to show the utility of this cross-coupling in cases where both the nucleophilic and electrophilic partner present structural and/or electronic challenges (Table 3). Notably, the alkyltrifluoroborates are easily synthesized from readily available aldehydes following the previously described procedures.[3a, 17]

The developed reaction conditions were quite general, and various substitution patterns were well accommodated. A diverse range of alkylated benzylic alcohols were isolated in modest to high yields (**6p-x**). α-Hydroxyalkyltrifluoroborates containing stereocenters were cross-coupled with moderate diastereoselectivity (**6r**). Notably, the starting boryl nucleophile in this case was isolated in a 3:1 diastereomeric ratio. Isopropyl- and 3-pentyl-substituted trifluoroborates were also well suited to the reaction (**6s-w**). Compound **6v** demonstrates electronic tolerance of *meta*-substitution in the aryl ring, although the reaction was not suitable for *ortho*-substituted aryl bromides. For example, the reaction between 2-bromobenzonitrile and **3e** afforded trace product. Electron-deficient *N*-heteroaromatic halides such as 2-trifluoromethyl-5-bromopyridine could also be used under the reaction conditions, although affording a modest yield of the desired product (**6w**). Finally, *tert*-butyl-substituted trifluoroborate **3f** also reacted smoothly to afford a sterically crowded benzylic alcohol **6x** in good yield. Unfortunately, electron-neutral *N*-heteroaryl bromides were ineffective under the coupling conditions. We speculate that the nitrogen in the aromatic ring serves to ligate the metal center competitively, inhibiting the active catalyst. Similar reactivity was observed in a previously reported reaction describing cross-coupling between 3°-alkyltrifluoroborates and aryl halides under photoredox/Ni dual catalysis.[5d]

During our study, we also observed the formation of aldehyde as a side product. In particular, the coupling of trifluoroborate **3a** generated 15-20% of aldehyde. Notably, aldehyde formation was only observed in the presence of nickel catalyst. To understand the formation of aldehyde, we hypothesized two plausible pathways (**I-II**) depicted in Figure 3. According to pathway **I**, a hydroxyalkyl radical-captured Ni species **2e** could undergo β-hydride elimination to afford an enol (**7a**), which subsequently forms aldehyde **7b**. On the other hand, β-hydride elimination from the hydroxyl group would also lead to the same aldehyde **7b** (pathway **II**), which is very unlikely.[18] Pathway **II** is independent of substrates bearing β-hydrogens in the hydroxyalkyltrifluoroborates. We reasoned that trifluoroborate **3f**, which lacks β-hydrogens, might provide insight into the process by which aldehyde is generated. Indeed, aldehyde formation was not observed when **3f** was employed in the cross-coupling reaction with 4-bromoacetophenone **5c**, indicating that aldehyde formation most

likely follows pathway **I**, where the *β*-hydride elimination leads to the formation of enol, with subsequent tautomerization providing the aldehyde.[19]

Conclusions

In summary, an operationally simple, scalable, and efficient method for the direct synthesis of secondary benzyl alcohols under photoredox/Ni dual catalysis is described. To the best of our knowledge, this reaction is the first example of direct cross-coupling of α-hydroxyalkyl nucleophiles with aryl halides under transition metal catalysis. This method avoids protection-deprotection strategies and therefore offers a step-economical, direct route to a variety of secondary benzylic alcohols. The mild reaction conditions tolerate a number of electrophilically sensitive functional groups such as aldehydes, ketones, esters, lactones and boronates. Furthermore, the excellent functional group compatibility and mild reaction conditions favor employment in late-stage functionalization of complex structural motifs. The reported protocol represents a significant advance in the cross-coupling of α-hydroxyalkyl nucleophiles and enables the rapid synthesis of an important class of compounds.

Experimental Section

General Consideration

NMR Spectra (^{1}H, ^{13}C, ^{19}F, ^{11}B) were performed at 298 K. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (internal standard: 7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C), DMSO-d_6 (internal standard: 2.50 ppm, ^{1}H) and MeCN-d_6 (internal standard: 1.32 ppm, ^{13}C) using 500 MHz spectrometers. Accurate mass measurement analyses were conducted on either a time-of-flight GCMS with electron ionization (EI), or a time-of-flight LCMS with electrospray ionization (ESI). Samples were taken up in a suitable solvent for analysis. The signals were mass measured against an internal lock mass reference of perfluorotributylamine (PFTBA) for EI-GCMS, and leucine enkephalin for ESI-LCMS. The software calibrates the instruments and reports measurements by use of neutral atomic masses. The mass of the electron is not included. IR spectra were recorded using FTIR-ATR of the neat oil or solid products. Reactions were monitored by ^{1}H NMR, and/or by TLC on silica gel plates (60 Å porosity, 250 μm thickness). TLC analysis was performed using hexanes/EtOAc as the eluent and visualized using UV light. Silica plugs utilized flash silica gel (60 Å porosity, 32–63 μm). Flash chromatography was accomplished using an automated system (visualizing at 254 nm, monitoring at 280 nm) with silica cartridges (60 Å porosity, 20–40 μm). Solvents were purified by use of drying cartridges through a solvent delivery system. Melting points (°C) are uncorrected. Deuterated NMR solvents were either used as purchased or were stored over 4Å molecular sieves. $NiBr_2$•dme, 4,4′-di-*tert*-butyl-2,2′-dipyridine (dtbbpy), K_2HPO_4 and 1,4-dioxane were used as purchased. Aryl bromides were purchased from commercial suppliers and used without further purification. Aldehydes were distilled and freshly used. Cu catalyst (ICyCuCl) and NaO^{t}Bu were stored in a N_2 filled glovebox. Before use, dioxane was degassed thoroughly with N_2 and stored under N_2 and molecular sieves. The Ir photocatalyst and 4CzIPN were synthesized according to the described procedure.[5a, 11, 20]

Synthesis of α-hydroxyalkyltrifluoroborate compounds (3a-f)

Potassium α-hydroxyalkyltrifluoroborate compounds (3a-f) were synthesized according to previously described methods.[3, 21] Compounds were bench-top stable and stored under ambient conditions.

General procedure for the cross-Coupling of α-hydroxyalkyltrifluoroborate and Ar-Br (Table 2-3)

To a two dram (8 mL) borosilicate glass vial equipped with a Teflon-coated magnetic stir bar was added $NiBr_2$•dme (8.0 mg, 0.025 mmol), the corresponding Ar-Br (0.5 mmol), dtbbpy (7.0 mg, 0.025 mmol), $Ir[dFCF_3ppy]_2(bpy)PF_6$ **1** (10.0 mg, 0.01 mmol), potassium hydroxyalkyltrifluoroborate (0.65 mmol, 1.3 equiv) and K_2HPO_4 (175.0 mg, 1.0 mmol, 2 equiv). The vial was sealed with a cap containing a TFE-lined silicone septa and placed under an N_2 atmosphere through evacuating and purging with nitrogen three times *via* an inlet needle. The vial was then charged with anhydrous and degassed 1,4-dioxane (2.5 mL) *via* a syringe. The cap was sealed with Parafilm®, and the solution was irradiated with blue LEDs. The temperature of the reaction was maintained at approximately 25-27° *via* a fan. The solution was stirred vigorously while being irradiated. After completion, the crude reaction mixture was filtered through a plug of Celite and rinsed with EtOAc. The resulting solution was concentrated, and the residue was purified by silica gel column chromatography using EtOAc/hexane mixtures as the eluent to obtain products in pure form.

Gram scale reaction for the synthesis of 6a

To a ~125 mL Schlenk tube equipped with a Teflon-coated magnetic stir bar was added $NiBr_2$•dme (0.24 mmol, 77.0 mg), $Ir[dFCF_3ppy]_2(bpy)PF_6$ **1** (0.11 mmol, 109.0 mg), dtbbpy (0.24 mmol, 66.0 mg), 4-bromobenzonitrile **5a** (5.5 mmol, 1.00 g), hydroxyalkyltrifluoroborate **3a** (7.14 mmol, 1.73 g, 1.3 equiv), and K_2HPO_4 (11 mmol, 1.9 g, 2 equiv). The vial was sealed and subsequently purged and evacuated three times with N_2. Anhydrous and degassed 1,4-dioxane (28 mL) was then added by syringe under N_2. The resulting mixture was stirred vigorously for 5-7 min. The Schlenk tube was then placed in a blue LEDs chamber (Supporting Information, Figure-A3), and the mixture was stirred for 24 h. A fan was blown across the reaction setup to maintain an ambient temperature. After completion, the crude reaction mixture was filtered through a plug of Celite and rinsed with EtO Ac (8-10 mL). The resulting solution was concentrated, and the residue was purified by automated column chromatography on silica gel with EtOAc/hexane mixtures as the eluent, to obtain 73% (950 mg, 4.0 mmol) product in pure form (Supporting Information, Figure-A5).

4-(1-Hydroxy-3-phenylpropyl) benzonitrile (6a)—The compound was prepared according to the general procedure. Product **6a** was isolated in 72% yield (85.0 mg, 0.36 mmol) as a light-yellow oil using a gradient of 0 to 20% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.64 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.30-7.27 (m, 2H), 7.22-7.17 (m, 3H), 4.78-4.74 (m, 1H), 2.79-2.68 (m, 2H), 2.12-1.98 (m, 2H), 1.94 (d, J = 4.0 Hz, ^{1}H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 150.1, 141.3, 132.5, 128.7, 128.5, 126.7, 126.3, 118.9, 111.4, 73.1, 40.7, 31.9; **FT-IR** (cm^{-1}, neat, ATR)

3431, 2228, 1608, 1496; **HRMS** (pos. ESI) m/z: Calcd for $C1_6H_{16}NO$ $[M+H]^+$ 238.1226. Found, 238.1237.

4-(1-Hydroxy-3-phenylpropyl) benzaldehyde (6b)—The compound was prepared according to the general procedure. Product **6b** was isolated in 65% yield (78.0 mg, 0.32 mmol) as a light-yellow oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.87 (d, J = 8.20 Hz, 2H), 7.52 (d, J = 8.11 Hz, 2H), 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 4.80-4.78 (m, 1H), 2.80-2.68 (m, 2H), 2.16-2.00 (m, 2H), 1.97 (bs, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 191.1, 150.7, 140.4, 134.9, 129.1, 127.6, 127.5, 125.5, 125.2, 72.4, 39.7, 31.0; **FT-IR** (cm^{-1}, neat, ATR) 3400, 1694, 1606, 1577, 1209; **HRMS** (EI^+) m/z: Calcd for $C_{16}H_{16}O_2$ [M] 240.1150. Found, 240.1153.

1-(4-(1-Hydroxy-3-phenylpropyl) phenyl) ethan-1-one (6c)—The compound was prepared according to the general procedure. Product **6c** was isolated in 71% yield (91.0 mg, 0.035 mmol) as a pale-yellow oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.94 (d, J = 8.21 Hz, 2H), 7.45 (d, J = 8.61 Hz, 2H), 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 4.78-4.75 (m, 1H), 2.79-2.65 (m, 2H), 2.60 (s, 3H), 2.16-2.00 (m, 2H), 1.93 (d, J = 3.20 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 198.0, 150.1, 141.5, 136.6, 128.7, 128.6, 128.5, 126.1(4), 126.1(2), 73.4, 40.7, 32.0, 26.8; **FT-IR** (cm^{-1}, neat, ATR) 3450, 1673, 1607, 1496, 1267; **HRMS** (pos. ESI) m/z: Calcd for $C_{17}H_{19}O_2$ $[M+H]^+$ 255.1380. Found, 255.1380.

3-Chloro-1-(4-(1-hydroxy-3-phenylpropyl) phenyl) propan-1-one (6d)—The compound was prepared according to the general procedure. Product **6d** was isolated in 69% yield (106.0 mg, 0.35 mmol) as a pale-yellow oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.94 (d, J = 8.26 Hz, 2H), 7.46 (d, J = 8.36 Hz, 2H), 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 4.79-4.76 (m, 1H), 3.92 (t, J = 6.81 Hz, 2H), 3.45 (t, J = 6.81 Hz, 2H), 2.79-2.67 (m, 2H), 2.15-2.00 (m, 2H), 1.94 (d, J = 4.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 196.5, 150.6, 141.5, 135.7, 128.6, 128.5, 128.5, 126.3, 126.2, 73.3, 41.4, 40.6, 38.8, 32.0; **FT-IR** (cm^{-1}, neat, ATR) 3450, 1679, 1606, 699; HRMS (pos. ESI) m/z: Calcd for $C_{18}H_{20}ClO_2$ $[M+H]^+$ 303.1146. Found, 303.1162.

2,2,2-Trifluoro-1-(4-(1-hydroxy-3-phenylpropyl) phenyl) ethan-1-one (6e)—The compound was prepared according to the general procedure. Product **6e** was isolated in 47% yield (73.0 mg, 0.24 mmol) as a colorless oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.31-7.28 (m, 2H), 7.22-7.19 (m, 3H), 4.83-4.79 (m, 1H), 2.81-2.70 (m, 2H), 2.15-2.00 (m, 2H), 1.97 (d, J = 4.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 180.3 (q, J = 35.1 Hz), 152.9, 141.3, 130.6, 129.2, 128.7, 128.5, 126.6, 126.3, 116.8 (q, J = 290.9 Hz), 73.2, 40.7, 31.9; **^{19}F NMR** (470 MHz, $CDCl_3$): δ -71.39; **FT-IR** (cm^{-1}, neat, ATR) 3341, 1716, 1607, 1196, 942; **HRMS** (EI^+) m/z: Calcd for $C_{17}H_{15}F_3O_2$ [M] 308.1024. Found, 308.1025.

Methyl 4-(1-Hydroxy-3-phenylpropyl) benzoate (6f)—The compound was prepared according to the general procedure. Product **6f** was isolated in 74% yield (100.0 mg, 0.37 mmol) as a light-yellow oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.01 (d, J = 8.41 Hz, 2H), 7.41 (d, J = 8.21 Hz, 2H), 7.30-7.27 (m, 2H), 7.20-7.17 (m, 3H), 4.77-4.74 (m, 1H), 3.91 (s, 3H), 2.78-2.66 (m, 2H), 2.15-2.00 (m, 2H), 1.98 (bs, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.1, 149.9, 141.6, 129.9, 129.4, 128.6, 128.5, 126.1, 125.9, 73.4, 52.2, 40.6, 32.0; **FT-IR** (cm^{-1}, neat, ATR) 3450, 1720, 1703, 1611, 1276; **HRMS** (EI^+) m/z: Calcd for $C_{17}H_{18}O_3$ [M] 270.1256. Found, 270.1266

5-(1-Hydroxy-3-phenylpropyl) isobenzofuran-1(3H)-one (6g)—The compound was prepared according to the general procedure. Product **6g** was isolated in 68% yield (91.0 mg, 0.34 mmol) as a light-yellow oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.88 (d, J = 7.86 Hz, 1H), 7.51 (s, 1H), 7.49 (d, J = 7.91 Hz, 1H), 7.31-7.28 (m, 2H), 7.22-7.19 (m, 3H), 5.30 (s, 2H), 4.86-4.83 (m, 1H), 2.82-2.70 (m, 2H), 2.16-2.02 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.1, 152.0, 147.2, 141.3, 128.7, 128.5, 127.1, 126.2, 125.9, 125.0, 119.4, 73.4, 69.8, 41.0, 32.0; **FT-IR** (cm^{-1}, neat, ATR) 3444, 1745, 1619, 1048; **HRMS** (EI^+) m/z: Calcd for $C_{17}H_{16}O_3$ [M] 268.1099. Found, 268.1097.

Methyl 4-(1-Hydroxy-3-phenylpropyl)-2-methoxybenzoate (6h)—The compound was prepared according to the general procedure. Product **6h** was isolated in 64% yield (96.0 mg, 0.32 mmol) as a light-yellow oil using a gradient of 0 to 40% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.77 (d, J = 7.96 Hz, 1H), 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 7.00 (s, 1H), 6.93-6.91 (m, 1H), 4.73-4.70 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.79-2.67 (m, 2H), 2.15-2.00 (m, 2H), 1.98 (d, J = 4.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.6, 159.6, 151.0, 141.6, 132.0, 128.6, 128.5(6), 126.1, 119.1, 117.7, 109.5, 73.5, 56.2, 52.1, 40.6, 32.0; **FT-IR** (cm^{-1}, neat, ATR) 3450, 1708, 1610, 1496, 1245, 1085; **HRMS** (EI^+) m/z: Calcd for $C_{18}H_{20}O_4$ [M] 300.1362. Found, 300.1359.

4-(1-Hydroxy-3-phenylpropyl) benzenesulfonamide (6i)—The compound was prepared according to the general procedure. Product **6i** was isolated in 48% yield (70.0 mg, 0.24 mmol) as a light yellow solid (mp: 98-100 °C) using a gradient of 0 to 50% EtOAc/ hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, DMSO): δ 7.78 (d, J = 8.30 Hz, 2H), 7.51 (d, J = 8.31 Hz, 2H), 7.28-7.25 (m, 4H), 7.19-7.15 (m, 3H), 5.44 (d, J = 4.30 Hz, 1H), 4.62 (bs, 1H), 2.69-2.57 (m, 2H), 1.91-1.87 (m, 2H); **^{13}C NMR** (125 MHz, CD_3CN): δ 151.9, 143.6, 143.3, 129.8(4), 129.8(1), 127.9, 127.4, 127.2, 73.5, 42.2, 33.0; **FT-IR** (cm^{-1}, neat, ATR) 3264, 3086, 1495, 1326, 1157,; **HRMS** (EI^+) m/z: Calcd for $C_{15}H_{15}NO_2S$ [M-H_2O] 273.0819. Found, 273.0823.

1-(4-(Methylsulfonyl) phenyl)-3-phenylpropan-1-ol (6j)—The compound was prepared according to the general procedure. Product **6j** was isolated in 72% yield (104.0 mg, 0.36 mmol) as a light-yellow oil using a gradient of 0 to 50% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.90 (d, J = 8.40 Hz, 2H), 7.55 (d, J = 8.30 Hz, 2H), 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 4.81-4.79 (m, 1H), 3.04 (s, 3H),

2.80-2.69 (m, 2H), 2.14-2.00 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.3, 141.3, 139.5, 128.6, 128.5, 127.6, 126.9, 126.2, 73.0, 44.6, 40.7, 31.9; **FT-IR** (cm^{-1}, neat, ATR) 3492, 1600, 1300, 1143, 1088; **HRMS** (EI^+) m/z: Calcd for $C_{16}H_{18}O_3S$ [M] 290.0977. Found, 290.0967.

3-Phenyl-1-(4-(trifluoromethyl) phenyl) propan-1-ol (6k)—The compound was prepared according to the general procedure. Product **6k** was isolated in 71% yield (99.0 mg, 0.35 mmol) as a colorless oil using a gradient of 0 to 20% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.61 (d, J = 8.20 Hz, 2H), 7.46 (d, J = 8.10 Hz, 2H), 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 4.78-4.75 (m, 1H), 2.79-2.67 (m, 2H), 2.15-2.00 (m, 2H), 1.91 (d, J = 4.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 148.7, 141.5, 129.9 (q, J = 32.4 Hz), 128.6, 128.5, 126.3, 126.2, 125.6, 124.3 (q, J = 271.9), 73.3, 40.7, 32.0; **^{19}F NMR** (470 MHz, $CDCl_3$): δ -62.46; **FT-IR** (cm^{-1}, neat, ATR) 3369, 1323, 1110, 1066; **HRMS** (EI^+) m/z: Calcd for $C_{16}H_{15}F_3O$ [M] 280.1075. Found, 280.1093.

1-(4-Methoxyphenyl)-3-phenylpropan-1-ol (6l)—The compound was prepared according to the general procedure. Product **6l** was isolated in 54% yield (65.0 mg, 0.27 mmol) as a colorless oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.29-7.25 (m, 4H), 7.19-7.16 (m, 3H), 6.89-6.87 (d, J = 8.66 Hz, 2H), 4.65-4.61 (m, 1H), 3.80 (s, 3H), 2.75-2.69 (m, 1H), 2.66-2.61 (m, 1H), 2.17-2.09 (m, 1H), 2.03-1.96 (m, 1H), 1.81 (d, J = 3.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.2, 142.0, 136.8, 128.6, 128.5, 127.3, 126.0, 114.0, 73.6, 55.4, 40.5, 32.3; **FT-IR** (cm^{-1}, neat, ATR) 3350, 1610, 1496, 1244; **HRMS** (EI^+) m/z: Calcd for $C_{16}H_{18}O_2$ [M] 242.1307. Found, 242.1295.

3-Phenyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) propan-1-ol (6m)—The compound was prepared according to the general procedure. Product **6m** was isolated in 52% yield (88.0 mg, 0.26 mmol) as a light-yellow oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.29-7.25 (m, 2H), 7.19-7.16 (m, 3H), 4.70 (bs, 1H), 2.76-2.63 (m, 2H), 2.16-2.08 (m, 1H), 2.06-1.99 (m, 1H), 1.85 (bs, 1H), 1.34 (s, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 147.8, 141.9, 135.2, 128.6, 128.5, 126.0, 125.4, 83.9, 73.9, 40.5, 32.1, 25.0; **^{11}B NMR** (160 MHz, $CDCl_3$): 30.94; **FT-IR** (cm^{-1}, neat, ATR) 3450, 1612, 1398, 1358, 1187, 1142; **HRMS** (pos. ESI) m/z: Calcd for $C_{21}H_{27}BO_3Na$ [M +Na]$^+$ 361.1945. Found, 361.1964.

4-(1-Hydroxy-2-phenylethyl) benzonitrile (6p)—The compound was prepared according to the general procedure. Product **6p** was isolated in 54% yield (60.0 mg, 0.27 mmol) as a light-yellow oil using a gradient of 0 to 20% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.16 Hz, 2H), 7.45 (d, J = 8.36 Hz, 2H), 7.33-7.30 (m, 2H), 7.28-7.25 (m, 1H), 7.16-7.15 (m, 2H), 4.98-4.95 (m, 1H), 3.04 (dd, J = 13.64, 4.73 Hz, 1H), 2.94 (dd, J = 13.59, 8.53 Hz, 1H), 2.06 (d, J = 3.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 149.1, 137.0, 132.3, 129.6, 128.8, 127.1, 126.7, 119.0, 111.3, 74.6, 46.2; **FT-IR** (cm^{-1}, neat, ATR) 3433, 2228, 1608, 1495; **HRMS** (EI^+) m/z: Calcd for$C_{15}H_{13}NO$ [M] 223.0997. Found, 223.1000.

Methyl 4-(1-Hydroxy-2-phenylethyl) benzoate (6q)—The compound was prepared according to the general procedure. Product **6q** was isolated in 58% yield (74.0 mg, 0.29 mmol) as a light-yellow oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.00 (d, J = 8.21 Hz, 2H), 7.40 (d, J = 8.16 Hz, 2H), 7.31-7.28 (m, 2H), 7.25-7.23 (m, 1H), 7.17-7.15 (m, 2H), 4.98-4.95 (m, 1H), 3.91 (s, 3H), 3.06-2.94 (m, 2H), 2.11 (bs, 1H); **FT-IR** (cm^{-1}, neat, ATR) 3512, 1724, 1699, 1282; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.1, 149.0, 137.5, 129.8, 129.6, 129.4, 128.7, 126.9, 126.0, 75.0, 52.2, 46.2; **HRMS** (EI^+) m/z: Calcd for $C_{16}H_{16}O_3$ [M] 256.1099.Found, 256.1089.

4-(1-Hydroxy-2-phenylpropyl) benzonitrile (6r)—The compound was prepared according to above general procedure. The crude product was purified by silica gel chromatography eluting with a gradient of 0 to 20% EtOAc/hexane, and **6r** was isolated in 80% yield (95.0 mg, 0.4 mmol) as a light-yellow oil with a dr = 70:30 as determined by ^{1}H NMR of the crude mixture. **^{1}H NMR** (500 MHz, $CDCl_3$): (**major isomer**) δ 7.54 (d, J = 8.36 Hz, 2H), 7.37-7.34 (m, 1H), 7.32-7.26 (m, 4H), 7.13-7.11 (m, 2H), 4.85-4.83 (m, 1H), 3.10-3.05 (m, 1H), 2.02 (d, J = 3.4 Hz, 1H), 1.29 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): (**major isomer**) δ 148.3, 142.7, 131.9, 128.9, 128.1, 127.8, 127.1, 119.0, 111.1, 78.2, 47.3, 14.8; (**minor isomer**) δ 147.9, 142.1, 132.1, 128.6, 128.2, 127.4, 119.0, 111.6, 79.0, 48.2, 18.0; FT-IR (cm^{-1}, neat, ATR) 3468, 2228, 1608; **HRMS** (EI^+) m/z: Calcd for $C_{16}H_{15}NO$ [M] 237.1154. Found, 237.1156.

4-(1-Hydroxy-2-methylpropyl) benzonitrile (6s)—The compound was prepared according to the general procedure. Product **6s** was isolated in 75% yield (66.0 mg, 0.37 mmol) as a colorless oil using a gradient of 0 to 20% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.16 Hz, 2H), 7.43 (d, J = 8.26 Hz, 2H), 4.49 (dd, J = 5.91, 3.50 Hz, 1H), 2.05 (d, J = 3.40 Hz, 1H), 1.98-1.91 (m, 1H), 0.94 (d, J = 6.71 Hz, 3H), 0.85 (d, J = 6.81 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 149.1, 132.1, 127.3, 119.0, 111.2, 74.0, 35.4, 19.0, 17.6; **FT-IR** (cm^{-1}, neat, ATR) 3454, 2963, 2229, 1016; **HRMS** (EI^+) m/z: Calcd for $C_{11}H_{13}NO$ [M] 175.0997. Found, 175.0996.

Methyl 4-(1-Hydroxy-2-methylpropyl) benzoate (6t)—The compound was prepared according to the general procedure. Product **6t** was isolated in 64% yield (56.0 mg, 0.32 mmol) as a colorless oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.00 (d, J = 8.36 Hz, 2H), 7.38 (d, J = 8.16 Hz, 2H), 4.46 (dd, J = 6.30, 3.25 Hz, 1H), 3.91 (s, 3H), 2.00-1.93 (m, 2H), 0.97 (d, J = 6.71 Hz, 3H), 0.83 (d, J = 6.86 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.1, 148.9, 129.6, 129.4, 126.6, 79.5, 52.2, 35.5, 19.0, 17.9; **FT-IR** (cm^{-1}, neat, ATR) 3348, 1722, 1706, 1436; **HRMS** (EI^+) m/z: Calcd for $C_{12}H_{16}O_3$ [M] 208.1099. Found, 208.1104.

4-(2-Ethyl-1-hydroxybutyl) benzonitrile (6u)—The compound was prepared according to the general procedure. Product 6u was isolated in 61% yield (62.0 mg, 0.31 mmol) as a colorless oil using a gradient of 0 to 20% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.40 Hz, 2H), 7.45 (d, J = 8.11 Hz, 2H), 4.77-4.75 (m, 1H), 1.85 (d, J = 4.0 Hz 1H), 1.56-1.49 (m, 1H), 1.42-1.35 (m, 2H), 1.34-1.22 (m, 2H),

0.90 (t, *J* = 7.46 Hz, 3H), 0.85 (t, *J* = 7.50 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 149.7, 132.1, 127.2, 119.1, 110.9, 74.9, 48.2, 22.0, 20.5, 11.6, 11.3; **FT-IR** (cm^{-1}, neat, ATR) 3454, 2228, 1462, 1017; **HRMS** (EI^+) m/z: Calcd for $C_{13}H_{17}NO$ [M] 203.1310 Found, 203.1301.

3-(2-Ethyl-1-hydroxybutyl) benzonitrile (6v)—The compound was prepared according to the general procedure. Product **6v** was isolated in 65% yield (66.0 mg, 0.33 mmol) as a colorless oil using a gradient of 0 to 20% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.65 (s, 1H), 7.58-7.55 (m, 2H), 7.45 (t, *J* = 7.76 Hz, 1H), 7.67 (d, *J* = 8.10 Hz, 2H), 4.75-4.73 (m, 1H), 1.82 (d, *J* = 4.0 Hz 1H), 1.54-1.49 (m, 1H), 1.43-1.37 (m, 2H), 1.35-1.20 (m, 2H), 0.91-0.85 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 145.7, 131.0, 131.0, 130.2, 129.1, 119.1, 112.3, 74.7, 48.2, 22.0, 20.5, 11.6, 11.2; **FT-IR** (cm-1, neat, ATR) 3454, 2230, 1461, 801, 695; **HRMS** (EI^+) m/z: Calcd for $C_{13}H_{15}N$ [M-H_2O] 185.1204. Found, 185.1209.

2-Ethyl-1-(6-(trifluoromethyl) pyridin-3-yl) butan-1-ol (6w)—The compound was prepared according to the general procedure. Product **6w** was isolated in 45% yield (55.0 mg, 0.22 mmol) as a light-yellow oil using a gradient of 0 to 30% EtOAc/hexane with Et_3N (1%) for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 8.66 (s, 1H), 7.87 (d, *J* = 8.10 Hz, 1H), 7.67 (d, *J* = 8.10 Hz, 1H), 4.85 (bs, 1H), 1.95 (bs, 1H), 1.59-1.54 (s, 1H), 1.45-1.38 (m, 2H), 1.36-1.23 (m, 2H), 0.94-0.87 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 148.5, 147.1 (q, *J*=34.8 Hz), 142.8, 135.5, 121.7 (q, *J*=273.7 Hz), 120.2, 73.1, 48.2, 21.9, 20.5, 11.5, 11.2; **^{19}F NMR** (470 MHz, $CDCl_3$): *δ* -67.75; **FT-IR** (cm^{-1}, neat, ATR) 3372, 1335, 1136, 1085; **HRMS** (EI^+) m/z: Calcd for $C_{12}H_{16}F_3NO$ [M] 247.1184. Found, 247.1189.

1-(4-(1-Hydroxy-2, 2-dimethylpropyl) phenyl) ethan-1-one (6x)—The compound was prepared according to the general procedure. Product **6x** was isolated in 60% yield (62.0 mg, 0.3 mmol) as a colorless oil using a gradient of 0 to 30% EtOAc/hexane for silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.91 (d, *J* 8.31 Hz, 2H), 7.41 (d, *J* 8.26 Hz, 2H), 4.46 (d, *J* 3.10 Hz, 1H), 2.60 (s, 3H), 1.92 (d, *J* 3.20 Hz, 1H), 0.93 (s, 9H); **^{13}C NMR** (125 MHz, CDCl3): *δ* 198.1, 147.7, 136.4, 128.0, 127.8, 82.1, 35.9, 26.7, 26.0; **FT-IR** (cm^{-1}, neat, ATR) 3473, 2954, 1675, 1361, 1270; **HRMS** (EI^+) m/z: Calcd for $C_{12}H_{15}O_2$ $[M\text{-}CH_3]^+$ 191.1067. Found, 191.1053

Supplementary Material

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Acknowledgments

The authors are grateful for the financial support provided by NIGMS (R01 GM 113878). R.A. is thankful to Swedish Chemical Society for a postdoctoral fellowship. We thank J. K. Matsui of the University of Pennsylvania for helpful input. We thank Dr. Charles W. Ross, III (UPenn) for assistance in obtaining HRMS.

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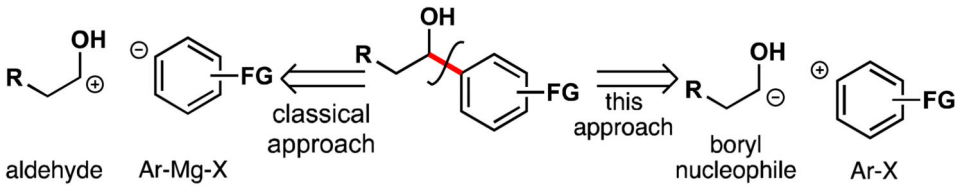


Figure 1. Disconnection approaches for the synthesis of secondary benzylic alcohols

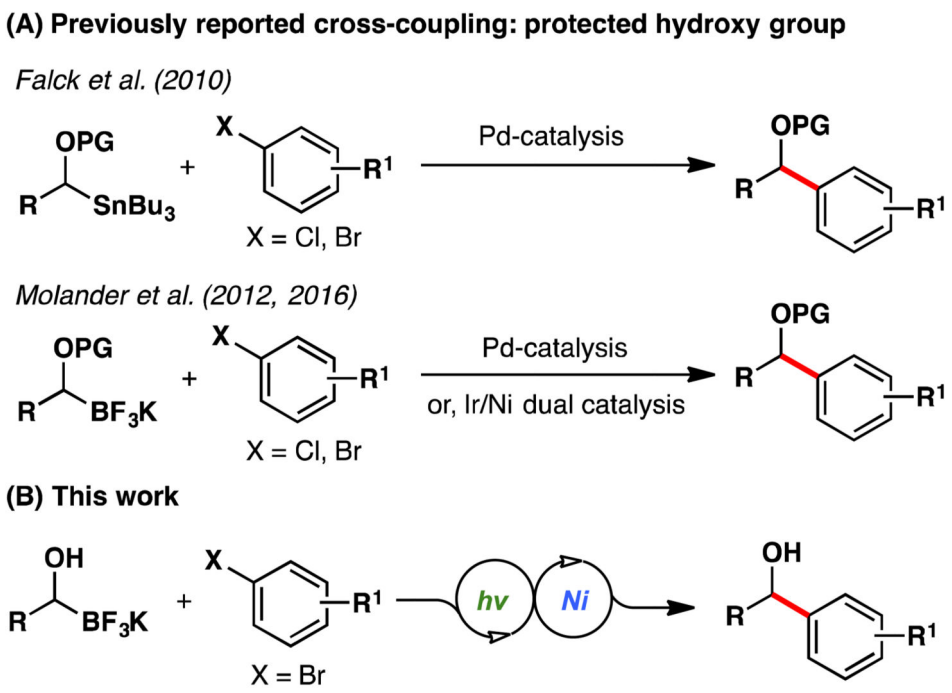


Figure 2.

(A) Previously reported methods for the cross-coupling of α-alkoxyalkylmetallic reagents *via* Pd- and Ir/Ni catalysis. (B) Presented protocol: protecting group-free, direct cross-coupling of α-hydroxyalkylmetallic reagents *via* photoredox/Ni-dual catalysis.

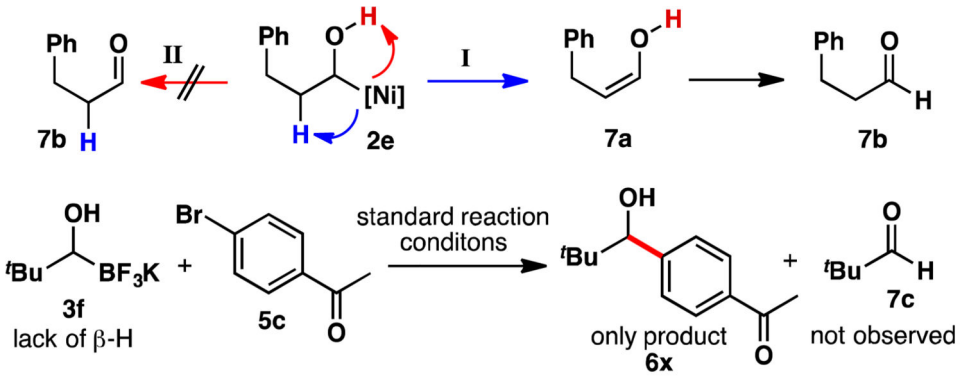
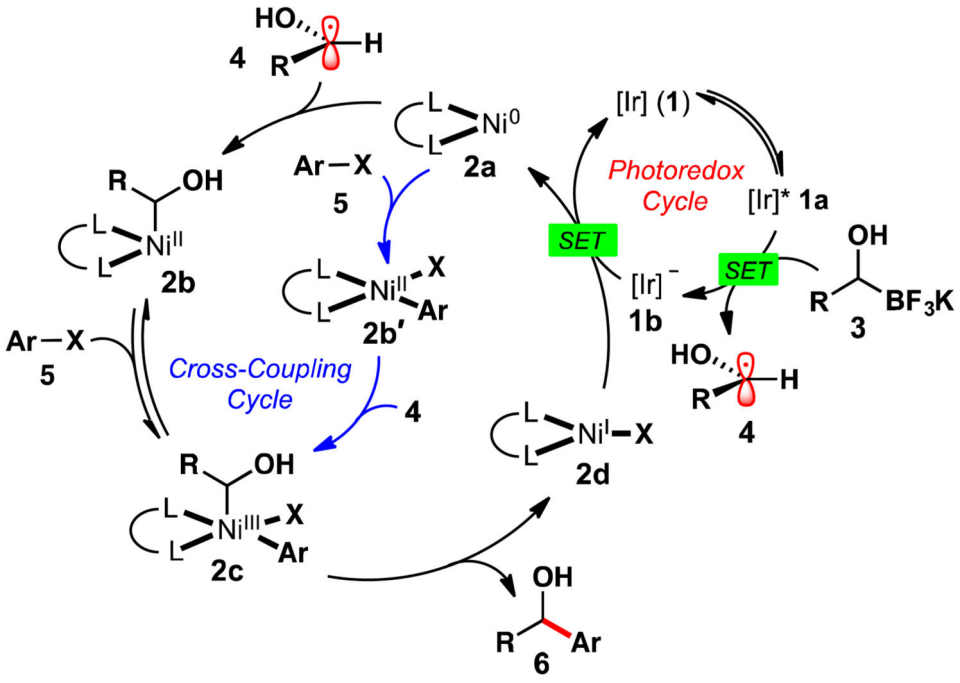


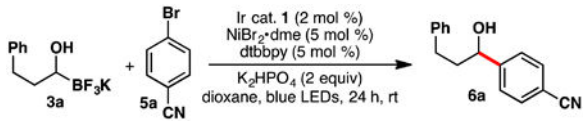
Figure 3. Plausible mechanism for the formation of aldehyde as side product



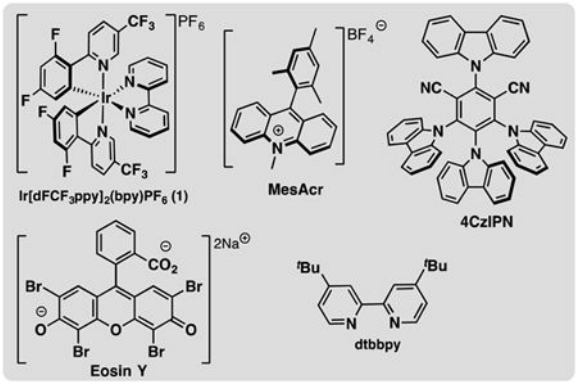
Scheme 1. Plausible mechanism

Table 1

Optimization of the Reaction Conditions[a]



entry	deviation from standard condition	yield (%)[b]
1	no change	66
2	5 mol % 4CzIPN instead of Ir cat.	22
3	5 mol % Eosin Y instead of Ir cat.	0
4	5 mol % MesAcr instead of Ir cat.	0
5	in absence of Ir cat.	0
6	in absence of nickel	0
7	in absence of light	0
8	in absence of K_2HPO_4	29
9	DME instead of dioxane	35
10	MeCN instead of dioxane	17
11	DMF-d_7 instead of dioxane	32

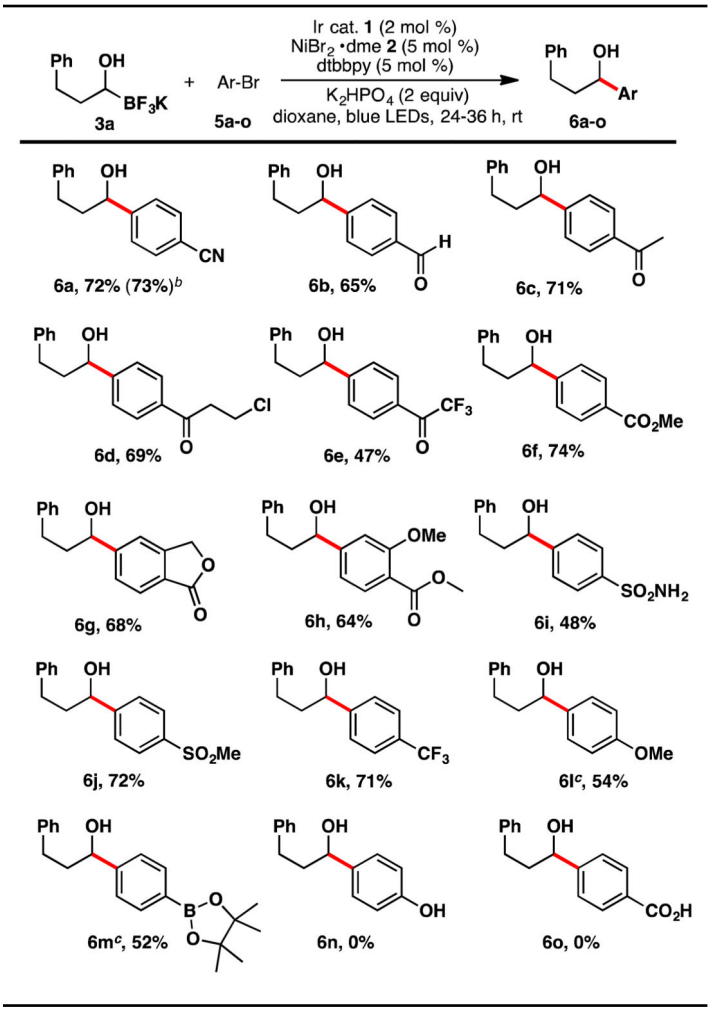


[a]General reaction conditions: Ar-Br (1.0 equiv, 0.1 mmol), trifluoroborate (1.3 equiv, 0.13 mmol), Ir catalyst (2 mol %), 1,4-dioxane (0.2 M), rt, 24 h.

[b]Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 2

Evaluation of Aryl Bromides Under Photoredox Conditions Using 3a[a]



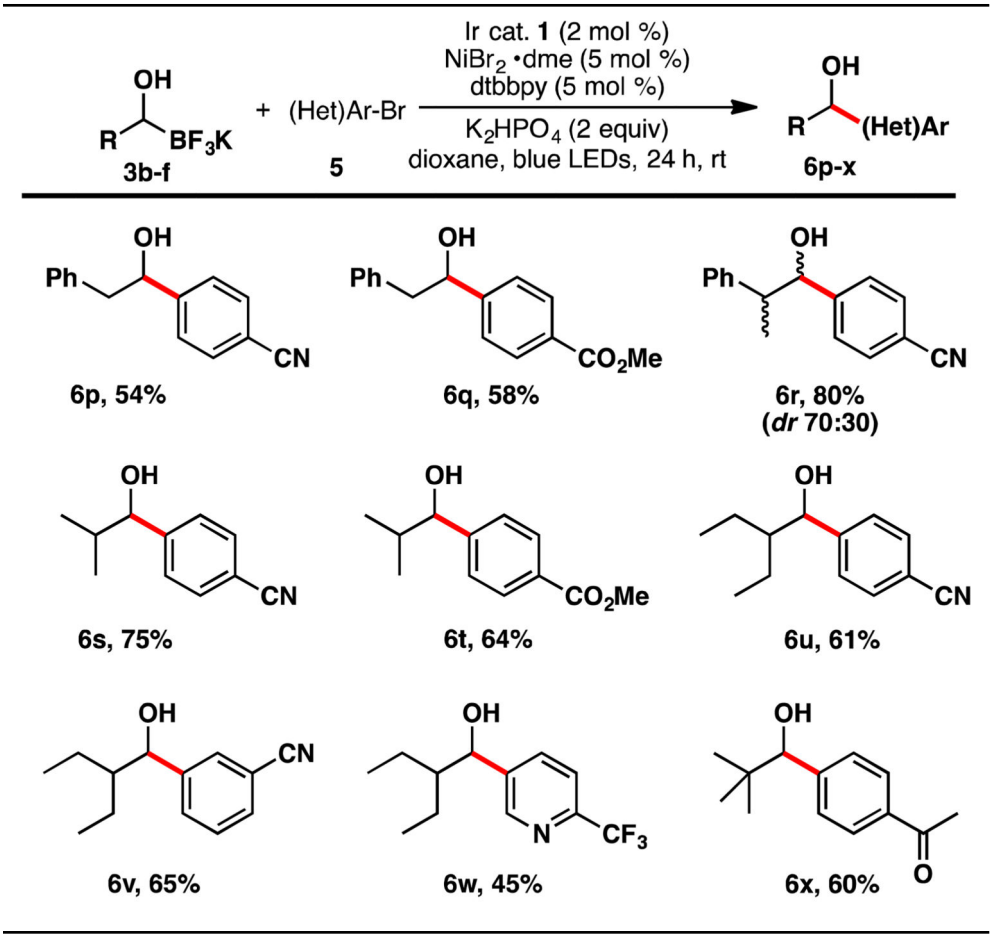
[a]General reaction conditions: Ar-Br (1.0 equiv, 0.5 mmol), trifluoroborate (1.3 equiv, 0.65 mmol), Ir catalyst (2 mol %), 1,4-dioxane (0.2 M), rt, 24-36 h.

[b]Yield in parentheses indicates yield on a 5.5 mmol scale.

[c]Reaction time 36 h.

Table 3

Photoredox Cross-Coupling Using Various Hydroxyalkyltrifluoroborates[a]



[a]General reaction conditions: Ar-Br (1.0 equiv, 0.5 mmol), trifluoroborate (1.3 equiv, 0.65 mmol), Ir catalyst (2 mol %), 1,4-dioxane (0.2 M), rt, 24 h.