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Palladium-Catalyzed α-Arylation of 2-Chloroacetates and 2-Chloroacetamides

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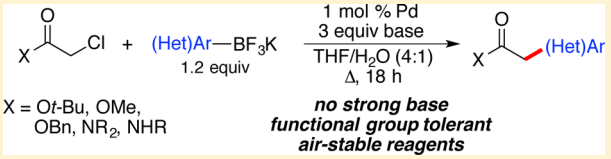
Supporting Information

ABSTRACT: A method has been developed for the Pd-catalyzed synthesis of α-(hetero)aryl esters and amides through a Suzuki–Miyaura cross-coupling reaction. This method avoids the use of strong base, does not necessitate inert or low temperature formation of reagents, and does not require the use of a large excess of organometallic reagent. Utilization of organotrifluoroborate salts as nucleophilic partners allows a variety of functional groups and heterocyclic compounds to be tolerated.



INTRODUCTION

The synthesis of α-aryl esters and amides through metal-catalyzed C–C bond-forming reactions has been extensively investigated over the past decade.[1] The α-aryl ester and amide moieties, as well as their carboxylic acid derivatives, are of biological importance and can be readily observed in the cores of numerous nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics (Figure 1).[2] Although several methods have been developed for the construction of these biologically important structures, none solve all of the challenges associated with their synthesis.

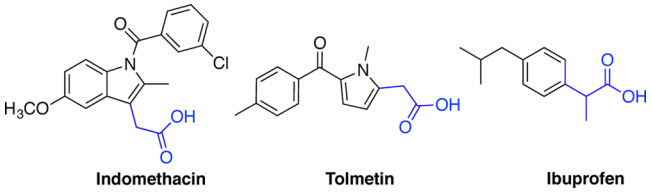


Figure 1. Examples of NSAIDS that contain the α-aryl- or heteroarylacetic acid motif.

There are two common strategies for the synthesis of α-aryl esters and amides (Scheme 1). The first involves enolate formation of an ester or amide, which is reacted with an aryl or heteroaryl halide under Pd-catalyzed conditions (Scheme 1, route a).[1a,b] In his seminal study, Buchwald illustrates this method using a strong base (LiHMDS or NaHMDS) to deprotonate a variety of esters, amides, and ketones, which are subsequently reacted with an aryl halide.[3] This method presents several limitations: (1) The use of strong base prevents the presence of many important functional groups within the aryl electrophile, including ketone, nitro, and carboxylic acid moieties.[1a] (2) Competition with a Claisen side reaction (between two molecules of the enolate) necessitates either the use of a large excess of ester or a sterically encumbered group on the ester to prevent formation of acetoacetates.[1a,b,3] (3) Mixtures of mono- and diarylated products are frequently obtained.[1b,3] In a similar manner, Hartwig has employed a Reformatsky reagent generated from an α-bromoester or amide in cross-coupling with a variety of aryl bromides.[4] Although functional group tolerance is improved by this method, the preformation of the metal enolate under low-temperature, inert conditions is required, and all coupling reactions were carried out in a glovebox or in Schlenkware.

A complementary strategy that alleviates a number of these problems reverses the polarity of the reaction, employing an α-halo ester or amide as an electrophile, which is then coupled with an arylmetallic species (Scheme 1, route b). One example of this polarity reversal employs aryl Grignard reagents in an iron-catalyzed reaction with α-bromo esters.[5] This method still requires inert, in situ formation of the organometallic reagent and has low functional group tolerance.

Although in principle Suzuki–Miyaura cross-coupling reactions can provide some improvements in these transformations in terms of functional group compatibility,[6] in fact the use of aryl 9-BBN compounds for this modified reaction suffers from many of the same limitations as methods described above.[7] Arylboronic acids, on the other hand, are advantageous in that they avoid the use of a strong base and the necessity for preformation of air- and temperature-sensitive reagents. Methods using these reagents face a different set of challenges, however, because many arylboronic acids are prone to protodeboronation,[8] and homocoupling[9] under Pd-catalyzed conditions is often inherently more prevalent in arylboronic acid cross-coupling than in organotrifluoroborates, for example.[10] To account for the instability of the boronic acids under employed conditions, either a large excess (20–50 mol %) of the arylboronic acid is required,[11] or a more stable arylboron species, such as a boronate ester, is necessary.[12] Addition of a phase transfer catalyst is required to aid quick transmetalation

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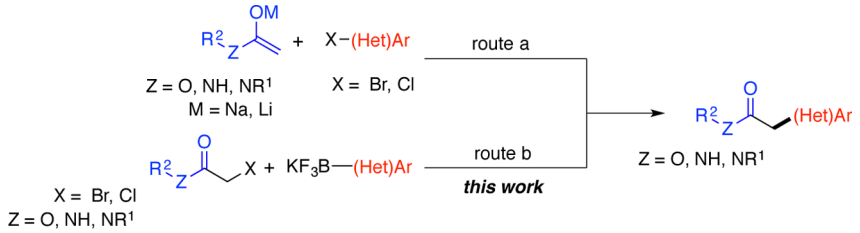
Scheme 1. Approaches to the Synthesis of α-(Hetero)aryl Esters and Amides

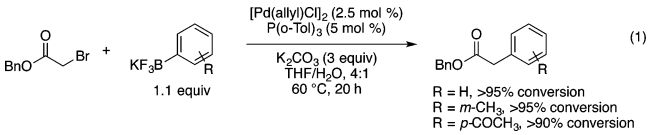


of the boronic acid if a large excess of the organoboron species is not employed.[13]

The method described herein follows the latter approach (Scheme 1, route b), but employs potassium aryl and heteroaryltrifluoroborate salts to overcome the drawbacks of previously reported approaches. Organotrifluoroborate salts, which are air and moisture stable, crystalline solids or free-flowing powders at room temperature, are less prone to protodeboronation,[14] and the presence of water in the reaction system allows the slow release of a hydrated species capable of transmetalation.[10,15] Because of their enhanced stability,[16] a large excess of the organoboron species is not required, and furthermore the materials are all bench-stable and able to be weighed in air without special considerations. Using this protocol, the substrate scope has been expanded from previous methods to include heteroaryl substrates, and the current method boasts acceptance of several functional groups that are not tolerated by other methods. It is demonstrated that a wide range of esters and amides can be employed in this reaction.

RESULTS AND DISCUSSION

Initial conditions for the general reaction of potassium aryltrifluoroborate salts with benzyl bromoacetate were developed through a limited screening process in which several Pd sources were evaluated. Using a system of $[Pd(allyl)Cl]_2$, good conversions to cross-coupled products were observed by GC−MS (eq 1).



(1)

Because of the significantly increased commercial availability of α-chloro esters and amides compared to the corresponding bromides, we sought to optimize the reaction for C−C bond formation between chlorinated electrophiles and (hetero)aryl trifluoroborates. Although product formation was observed from benzyl chloroacetate under the above conditions, significant amounts of undesired homocoupled biaryl product and protodeboronated starting material were prevalent. After further optimization, XPhos-Pd-G2 (Figure 2), a preformed Pd catalyst capable of rapid reductive elimination to a reactive, monoligated Pd(0) species, emerged as an ideal catalyst for the reaction of benzyl chloroacetate with aryl trifluoroborates. This species, which contains a bulky monodentate biaryl ligand, has been shown to be a model catalyst for Suzuki−Miyaura cross-coupling reactions of sensitive aryl and heteroarylboronic acids under mild conditions.[17] Recently, XPhos was found to be the ligand of choice for the enolate arylation of aryl benzylsulfonates.[18]

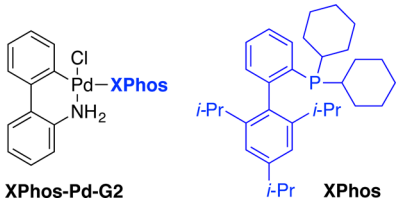


Figure 2. Structure of XPhos-Pd-G2 precatalyst.

Initial reactions were performed with this catalyst in a 4:1 THF/H_2O solvent system, and several bases were tested at two different temperatures. The results of the base screening showed that increased temperature aided the reaction and that K_3PO_4, Cs_2CO_3, and KF were all viable options for promoting the reaction (Figure 3).

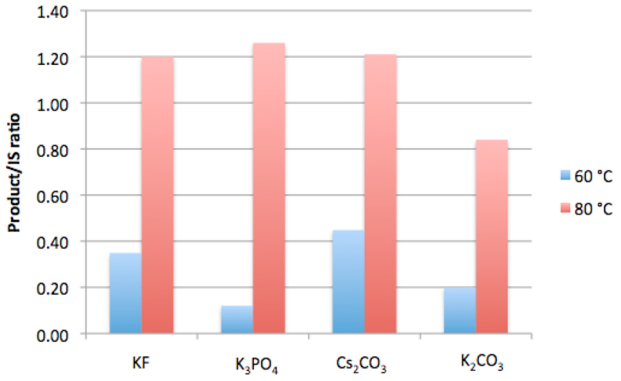


Figure 3. Screening results from the reaction of methyl chloroacetate with potassium phenyltrifluoroborate (1 mol % XPhos-Pd-G2, 0.25 M in 4:1 THF/H_2O, 18 h) in the presence of 3 equiv of each base at the shown temperature.

The four bases were tested on a 0.5 mmol scale in the reaction of benzyl chloroacetate with potassium 2-methoxyphenyltrifluoroborate at 80 °C, and the conversions were followed by GC−MS (Table 1), which pointed to the increased

Table 1. GC−MS Conversions for the Reaction of Benzyl Chloroacetate with Potassium 2-Methoxyphenyltrifluoroborate in the Presence of Four Bases[a]

base	% conversion
KF	42
K_3PO_4	81
Cs_2CO_3	92
K_2CO_3	77

[a]3 equiv of each base shown; 1 mol % XPhos-Pd-G2, 0.25 M in 4:1 THF/H_2O, 18 h, 80 °C.

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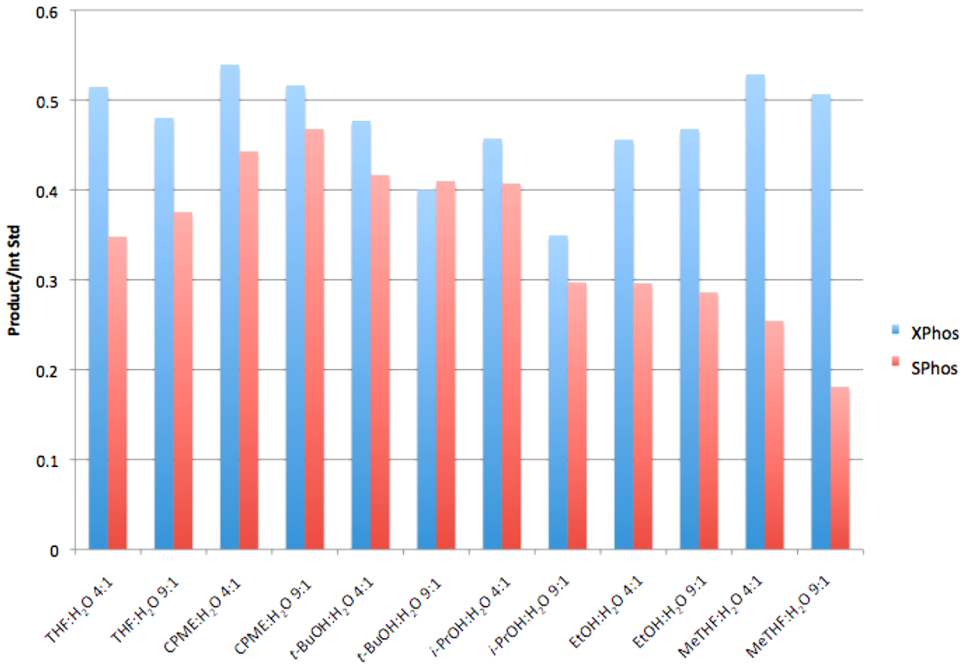


Figure 4. Screening results for the reaction of benzyl chloroacetate with potassium 3-pyridyltrifluoroborate (1 mol % XPhos-Pd-G2, 3 equiv base, 0.25 M, 80 °C, 18 h).

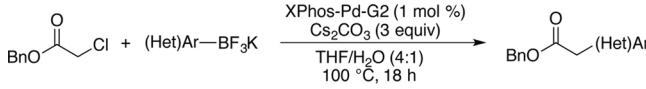
activity of Cs_2CO_3 in this reaction system. Although the conversion with K_3PO_4 was good, this base promoted a significant amount of homocoupled biaryl product from the trifluoroborate; therefore, Cs_2CO_3 and K_2CO_3 appeared to serve as the two best bases for the reaction if it was run to completion.

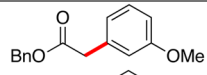
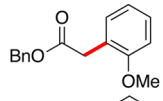
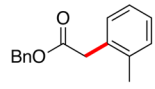
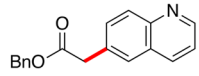
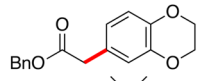
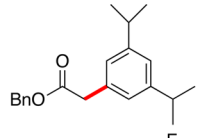
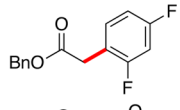
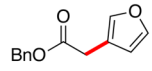
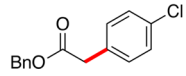
Using Cs_2CO_3 and K_2CO_3 for further optimization, several solvent systems were screened for activity in the presence of XPhos and SPhos on a more challenging system of benzyl chloroacetate with potassium 3-pyridyltrifluoroborate. It was quickly evident that Cs_2CO_3 was superior to K_2CO_3, and XPhos showed increased activity over SPhos regardless of the solvent system (Figure 4). Although within the context of screening on a small scale (25 μmol), THF, CPME, and 2-MeTHF in a 4:1 ratio with H_2O were successful, upon scaling the reactions to a 0.5 mmol scale, it was determined that a 4:1 THF/H_2O combination was superior.

On the basis of these results, benzyl chloroacetate was successfully cross-coupled with a wide range of aryl trifluoroborate salts in good yields (Table 2). Although hydrolysis of the benzyl ester was observed in the presence of most nitrogen-containing heterocyclic substrates, 6-quinolinyltrifluoroborate was successfully cross-coupled in good yield (entry 4). The conditions allowed successful cross-coupling of electron-rich (entry 6) and ortho-substituted trifluoroborates (entries 2 and 3). Electron-deficient, fluorinated substrates (entry 7) could be isolated in moderate yield. In the cross-coupling of benzyl esters, both K_2CO_3 and Cs_2CO_3 allow the reaction to go to completion, and both provide good yields for nonsterically hindered substrates (entries 8 and 9). Under the optimized conditions, formation of the desired cross-coupled product was not observed when α-chloro ketones or secondary α-haloesters were employed, and protodehalogenated products were observed in these reactions.

Although cross-couplings with benzyl chloroacetate were accompanied by a noticeable amount of hydrolyzed ester, alkyl esters did not suffer from this fate and could be employed as

Table 2. Cross-Coupling of Benzyl Chloroacetate with Aryl and Heteroaryl Trifluoroborates[a]



Entry	Product		Yield (%)
1		**2a**	80
2		**2b**	66
3		**2c**	87
4		**2d**	80
5		**2e**	84
6		**2f**	63
7		**2g**	58
8		**2h**	84[b]
9		**2i**	84[b]

[a]General conditions: Benzyl ester (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cs_2CO_3 (1.50 mmol) in THF (1.6 mL)/H_2O (0.40 mL) at 100 °C for 18 h. [b]K_2CO_3 used as base.

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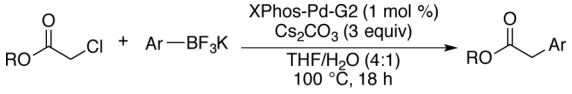
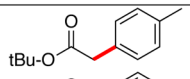
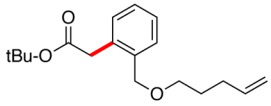
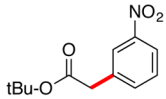
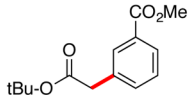
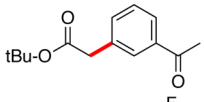
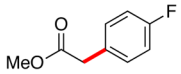
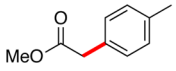
more effective substrates. Thus, under the same conditions, *tert*-butyl chloroacetate and methyl chloroacetate were successfully cross-coupled with a variety of aryl (Table 3) and heteroaryl

Table 3. Cross-Coupling of Alkyl Chloroacetates with Aryltrifluoroborates[a]



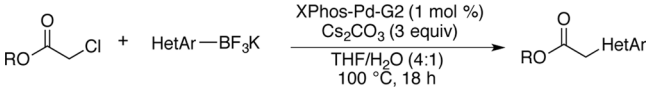
Entry	Product		Yield (%)
1		**3a**	95, 96[b]
2		**3b**	63
3		**3c**	60
4		**3d**	82
5		**3e**	98
6		**3f**	67
7		**3g**	80

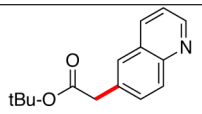
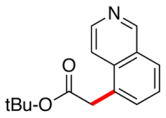
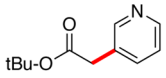
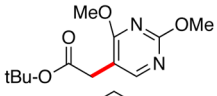
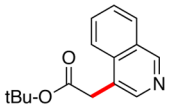
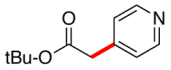
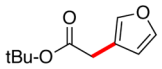
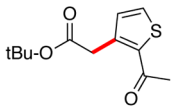
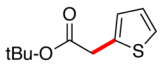
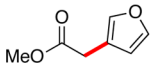
[a]General conditions: Ester (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cs_2CO_3 (1.50 mmol) in THF (1.6 mL)/H_2O (0.40 mL) at 100 °C for 18 h. [b]Isolated on 5.0 mmol scale using 0.5 mol % XPhos-Pd-G2.

(Table 4) partners. It was illustrated that ester (Table 3, entry 4), ketone (Table 3, entry 5 and Table 4, entry 8), and terminal alkenyl (Table 3, entry 2) functional groups remain intact under the employed conditions. Electron-deficient groups (Table 3, entries 3–6) were tolerated, although in some cases the desired products were isolated in lower yields. For challenging substrates, an increase to 2 mol % Pd was attempted, but yields did not dramatically increase (Table 4, entry 3). However, we were able to demonstrate that increasing the scale 10-fold to 5.0 mmol led to comparable yields, even with the catalyst loading cut in half (from 1 to 0.5 mol %, Table 3, entry 1).

The scope of the reaction was next broadened to include α-chloro amides as electrophilic coupling partners (Table 5). A variety of α-chloro tertiary amides were successfully cross-coupled under the same conditions, and both aryl and heteroaryl nucleophilic partners were employed. Both furyl (entries 6 and 7) and benzothienyltrifluoroborates (entry 9) were successful coupling partners, as was an indolinyltrifluoroborate (entry 8). Neither unprotected indoles nor those with base-labile protecting groups (Boc) were successful under these conditions. Somewhat surprisingly, this method allowed the cross coupling of a furyltrifluoroborate bearing a free carboxylic acid (entry 7). Electron-poor functional groups (entries 4 and 5) were cross-coupled in moderate yields.

Table 4. Cross-Coupling of Alkyl Chloroacetates with Heteroaryltrifluoroborates[a]



Entry	Product		Yield (%)
1		**4a**	92
2		**4b**	94
3		**4c**	50, 57[b]
4		**4d**	93
5		**4e**	80
6		**4f**	40
7		**4g**	88
8		**4h**	76
9		**4i**	75
10		**4j**	79

[a]General conditions: Ester (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cs_2CO_3 (1.50 mmol) in THF (1.6 mL)/H_2O (0.40 mL) at 100 °C for 18 h. [b]2 mol % XPhos-Pd-G2 (0.010 mmol).

A challenge was observed in coupling of secondary α-chloro amides, which under the developed conditions showed very low conversions. Attempts were made to increase catalyst loading, but this only led to the production of homocoupled trifluoroborate (biaryl product). On the basis of successful results of Deng and Duan, who successfully cross-coupled arylboronic acids with α-bromo amides using catalytic Pd in the presence of Cu_2O,[6a] it was hypothesized that the addition of a catalytic source of Cu(I) could aid in the cross-coupling of secondary amides. After conducting a small screen to examine the addition of several Cu(I) salts to the reaction conditions, Cu_2O was determined to be superior to CuCl and CuI, and XPhos worked better in the reaction than other structurally similar ligands (e.g., SPhos and RuPhos, Figure 5). Increasing the amount of base did not aid the reaction. The addition of 5 mol % of Cu_2O to the originally developed conditions allowed these reactions to proceed in moderate to good yields with aryl or heteroaryl coupling partners (Table 6). Aryl (entries 2 and 3) as well as quinolinyl (entry 1), isoquinolinyl (entry 6), and

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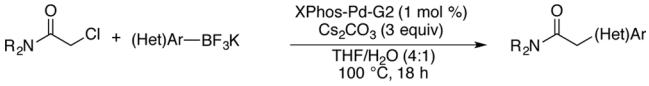
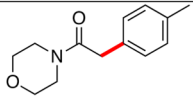
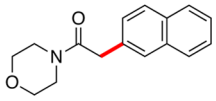
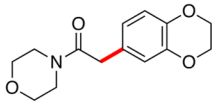
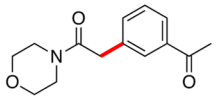
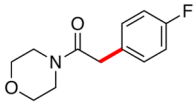
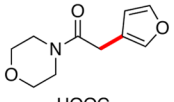
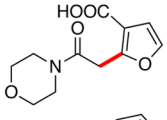
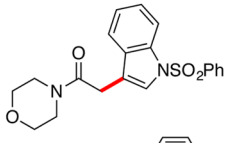
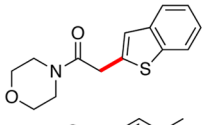
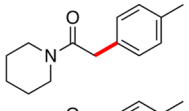
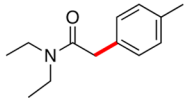
Table 5. Cross-Coupling of Tertiary Amides with Aryl and Heteroaryltrifluoroborates[a]



Entry	Product		Yield (%)
1		**5a**	81
2		**5b**	88
3		**5c**	98
4		**5d**	70
5		**5e**	68
6		**5f**	85
7		**5g**	71
8		**5h**	85
9		**5i**	62
10		**5j**	86
11		**5k**	72

[a]General conditions: Amide (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cs_2CO_3 (1.50 mmol) in THF (1.6 mL)/H_2O (0.40 mL) at 100 °C for 18 h.

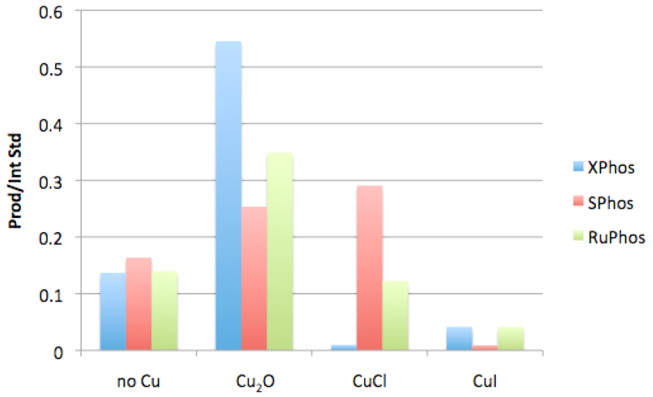
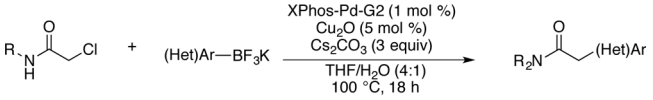
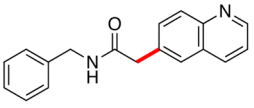
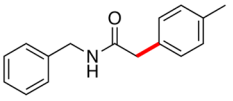
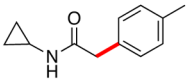
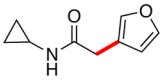
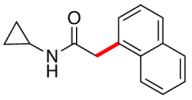
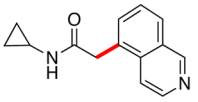


Figure 5. Screen results of the addition of Cu(I) sources to the reaction of *N*-benzyl chloroacetamide with potassium 4-methylphenyltrifluoroborate (1 mol % XPhos-Pd-G2, 3 equiv of Cs_2CO_3, 0.25 M 4:1 THF/H_2O, 100 °C, 18 h).

Table 6. Cross-Coupling of Secondary Amides with Aryl and Heteroaryltrifluoroborates[a]



Entry	Product		Yield (%)
1		**6a**	70
2		**6b**	75, 69[b]
3		**6c**	67
4		**6d**	70
5		**6e**	71
6		**6f**	62

[a]General conditions: Amide (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cu_2O (0.025 mmol), Cs_2CO_3 (1.50 mmol) in THF (1.6 mL)/H_2O (0.40 mL) at 100 °C for 18 h. [b]Isolated on 5.0 mmol scale using 0.5 mol % XPhos-Pd-G2.

furyl (entry 4) trifluoroborate salts were successfully cross-coupled using these modified conditions. The addition of Cu_2O to a sampling of reactions performed with esters and tertiary amides did not increase the yields of those reactions. Finally, because the reactions were optimized on a 0.5 mmol scale, we showed that increasing the scale 10-fold to 5.0 mmol led to comparable yields, with the catalyst loading cut in half (from 1 to 0.5 mol %, entry 2).

In conclusion, we have developed a versatile, scalable reaction system in which potassium aryl and heteroaryltrifluoroborate salts can be cross-coupled with α-chloroesters and amides. Although limited in some respects by the availability and structure of the α-halo carbonyl substrates, this method nevertheless avoids many of the limitations of current methods for the synthesis of α-aryl esters and amides through the use of air-stable reagents and reaction conditions that tolerate common functional groups as well as heteroaryl substrates.

EXPERIMENTAL SECTION

General Considerations. Both THF and deionized H_2O were thoroughly degassed with Ar prior to use. All solids were weighed out in the air, and the reactions were conducted under an Ar atmosphere. All 2-chloroacetates and 2-chloroacetamides were purchased from commercial sources and used without further purification. ^1H and ^{13}C NMR spectra were obtained at 500 and 125.8 MHz, respectively. HRMS data was obtained by ESI using a TOF mass spectrometer.

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General Procedure A for Cross-Coupling of (Hetero)-aryltrifluoroborates with 2-Chloroacetates and Tertiary 2-Chloroacetamides. An oven-dried Biotage 10 mL microwave vial equipped with a magnetic stirbar was charged with the (hetero)aryl trifluoroborate (0.525 mmol, 1.05 equiv), Cs_2CO_3 (1.5 mmol, 3 equiv), and XPhos-Pd-G2 (3.93 mg, 5.0 μmol, 1 mol %). A disposable Teflon septum cap was used to seal the vial, which was evacuated and purged with Ar three times. THF (1.6 mL), H_2O (0.4 mL), and the electrophile (0.5 mmol, 1 equiv) were added via syringe with stirring under Ar. In cases where the electrophile was a solid, it was added along with the solid materials before sealing the vial. The solution was heated at 100 °C overnight. After cooling to rt, the mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers were dried (Na_2SO_4). The crude products were purified by flash column chromatography, eluting with a gradient of EtOAc in hexanes.

Benzyl 2-(3-Methoxyphenyl)acetate (2a). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a yellow oil in 80% yield (102 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.30 (m, 5H), 7.24−7.22 (m, 1H), 6.92 (d, J =7.5 Hz, 1H), 6.87−6.85 (m, 2H), 5.12 (s, 2H), 3.76 (s, 3H), 3.63 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.4, 159.9, 136.0, 135.4, 129.7, 128.7, 128.3, 128.3, 121.8, 115.0, 113.0, 66.8, 55.3, 41.5; IR (neat) 2919, 1736, 1490, 1261, 1147 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{16}H_{17}O_3$ (M + H)$^+$, 257.1178, found 257.1171.

Benzyl 2-(2-Methoxyphenyl)acetate (2b). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a yellow oil in 66% yield (84 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.34 (m, 5H), 7.29−7.26 (m, 1H), 7.22−7.20 (m, 1H), 6.95−6.93 (m, 1H), 6.87−6.86 (m, 1H), 5.16 (s, 2H), 3.75 (s, 3H), 3.68 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.9, 157.7, 136.4, 131.1, 128.8, 128.7, 128.6, 128.2, 128.2, 123.1, 120.6, 110.5, 66.4, 55.5, 36.2; IR (neat) 2924, 1737, 1495, 1247, 1148 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{16}H_{16}O_3Na$ (M + Na)$^+$ 279.0997, found 279.0997.

Benzyl 2-(*o*-Tolyl)acetate (2c). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a light yellow oil in 87% yield (104 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.29 (m, 5H), 7.18−7.16 (m, 4H), 5.12 (s, 2H), 3.67 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.4, 137.0, 136.1, 132.8, 130.5, 130.3, 128.7, 128.3, 128.2, 127.6, 126.3, 66.7, 39.3, 19.7; IR (neat) 1734, 1498, 1455, 1257, 1146 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{16}H_{16}O_2Na$ (M + Na)$^+$ 263.1048, found 263.1048.

Benzyl 2-(Quinolin-6-yl)acetate (2d). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a brown oil in 80% yield (111 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 8.12−8.07 (m, 2H), 7.72 (s, 1H), 7.69−7.67 (m, 1H), 7.43−7.42 (m, 1H), 7.37−7.34 (m, 5H), 5.16 (s, 2H), 3.86 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.2, 150.4, 147.6, 136.0, 135.8, 132.5, 131.3, 129.9, 128.7, 128.5, 128.4, 128.1, 121.5, 67.0, 41.3; IR (neat) 2980, 1732, 1500, 1152 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{18}H_{16}NO_2$ (M + H)$^+$ 278.1181, found 278.1182.

Benzyl 2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)acetate (2e).[19] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a yellow oil in 84% yield (119 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.32 (m, 5H), 6.84 (t, J = 4.0 Hz, 2H), 6.78−6.76 (m, 1H), 5.13 (s, 2H), 4.24 (s, 4H), 3.55 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.7, 143.6, 142.9, 136.0, 128.7, 128.4, 128.3, 127.1, 122.4, 118.3, 117.4, 66.7, 64.5, 40.7.

Benzyl 2-(3,5-Diisopropylphenyl)acetate (2f). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a yellow oil in 63% yield (98 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.39 (m, 1H), 7.36−7.31 (m, 5H), 7.01−6.99 (m, 2H), 5.14 (s, 2H), 3.64 (s, 2H), 2.89−2.85 (m, 2H), 1.24 (d, J = 6.9 Hz, 12 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.8, 149.3, 136.1, 135.1, 133.8, 128.9, 128.7, 128.3, 128.2, 125.0, 123.7, 68.1, 66.6, 41.7, 34.3, 24.2; IR (neat) 2959, 1737, 1601, 1455, 1146 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{21}H_{27}O_2$ (M + H)$^+$ 311.2011, found 311.2011.

Benzyl 2-(2,4-Difluorophenyl)acetate (2g). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a white solid in 58% yield (76 mg): mp 33−34 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.31 (m, 5H), 7.21 (dd, J = 8.2, 6.6 Hz, 1H), 6.84−6.79 (m, 2H), 5.14 (s, 2H), 3.67 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.5, 162.7 (dd, J = 158.5, 12.0 Hz), 160.7 (dd, J = 159.0, 11.9 Hz), 135.8, 132.1 (dd J = 9.9, 5.5 Hz), 128.7, 128.5, 128.3, 117.3 (dd, J = 16.3, 3.7 Hz), 111.3 (dd, J = 21.2, 3.6 Hz), 103.9 (t, J = 25.7 Hz), 67.0, 33.9 (d, J = 2.5 Hz); IR (neat) 2920, 1739, 1507, 1137, 970 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{15}H_{12}F_2O_2Na$ (M + Na)$^+$ 285.0703, found 285.0702.

Benzyl 2-(Furan-3-yl)acetate (2h). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as an orange oil in 84% yield (91 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 2H), 7.35−7.33 (m, 5H), 6.29 (s, 1H), 5.15 (s, 2H), 3.52 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.3, 143.2, 140.6, 135.9, 128.8, 128.5, 128.4, 117.3, 111.5, 66.9, 31.0; IR (neat) 3034, 1736, 1455, 1163 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{13}H_{12}O_3Na$ (M + Na)$^+$ 239.0684, found 239.0685.

Benzyl 2-(4-Chlorophenyl)acetate (2i).[20] General procedure A was employed, with the only modification being the use of K_2CO_3 (3 equiv, 1.5 mmol) rather than Cs_2CO_3. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a white, opaque oil in 84% yield (110 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.29 (m, 7H), 7.23 (d, J = 8.4 Hz, 2H), 5.14 (s, 2H), 3.64 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.1, 135.9, 133.3, 132.5, 130.9, 128.9, 128.8, 128.5, 128.4, 67.0, 40.8.

***tert*-Butyl 2-(*p*-Tolyl)acetate (3a).**[21] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a light brown oil in 95% yield (98 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17−7.11 (m, 4H), 3.47 (s, 2H), 2.32 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.1, 136.3, 131.6, 129.1, 129.0, 80.6, 42.1, 28.0, 21.0.

***tert*-Butyl 2-[2-{(Pent-4-en-1-yloxy)methyl}phenyl]acetate (3b).** General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a colorless oil in 63% yield (92 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.1 Hz, 1H), 7.28−7.22 (m, 3H), 5.82−5.81 (m, 1H), 5.02−4.98 (m, 2H), 4.53 (s, 2H), 3.65 (s, 2H), 3.51 (q, J = 6.3 Hz, 2H), 2.17 (q, J = 7.3 Hz, 2H), 1.74−1.71 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.1, 138.4, 136.9, 133.8, 130.8, 129.3, 128.1, 127.2, 114.9, 80.9, 71.4, 70.0, 39.6, 30.5, 29.1, 28.2; IR (neat) 2979, 1731, 1641, 1150, 1093, 913 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{18}H_{27}O_3$ (M + H)$^+$ 291.1960, found 291.1952.

***tert*-Butyl 2-(3-Nitrophenyl)acetate (3c).**[22] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a yellow oil in 60% yield (71 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.54−7.51 (m, 1H), 3.64 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 161.5, 148.2, 136.5, 135.5, 129.2, 124.2, 122.0, 81.6, 41.9, 27.9.

Methyl 3-{2-(*tert*-Butoxy)-2-oxoethyl}benzoate (3d). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a colorless oil in 82% yield (103 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97−7.95 (m, 2H), 7.48 (d, J = 7.7 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 3.91 (s, 3H), 3.57 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.2, 166.8, 135.0, 133.7, 130.3, 130.3, 128.4, 128.0, 81.0, 51.9, 42.2, 27.9; IR (neat) 2977.68, 1723.06, 1284.86, 1144.00 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{14}H_{18}O_4Na$ (M + Na)$^+$ 273.1103, found 273.1098.

***tert*-Butyl 2-(3-Acetylphenyl)acetate (3e).** General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a brown oil in 98% yield (115 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.84 (m, 2H), 7.49 (t, J = 5.6 Hz, 1H), 7.44−7.41 (m, 1H), 3.59 (s, 2H), 2.61 (s, 3H), 1.44 (s,

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9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 198.0, 170.5, 137.4, 135.4, 134.1, 129.3, 128.8, 127.1, 81.2, 42.4, 28.1, 26.8; IR (neat) 2979.63, 1729.22, 1685.75, 1367.15, 1275.50, 1144.21 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{14}H_{18}O_3Na$ $(M + Na)^+$ 257.1154, found 257.1161.

Methyl 2-(4-Fluorophenyl)acetate (3f).[23] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a yellow oil in 67% yield (56 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.21 (m, 2H), 7.01−6.98 (m, 2H), 3.68 (s, 3H), 3.58 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.0, 162.0 (d, J = 244.8 Hz), 130.9 (d, J = 8.2 Hz), 129.8, 115.5 (d, J = 21.5 Hz), 52.3, 40.4.

Methyl 2-(*p*-Tolyl)acetate (3g).[24] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a yellow oil in 80% yield (66 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14−7.12 (m, 4H), 3.66 (s, 3H), 3.57 (s, 2H), 2.31 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.4, 136.9, 131.1, 129.5, 129.3, 52.2, 40.9, 21.2.

***tert*-Butyl 2-(Quinolin-6-yl)acetate (4a).**[20] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound an orange-brown oil in 92% yield (112 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89−8.87 (m, 1H), 8.16 (dd, J = 8.1, 4.6 Hz, 1H), 8.10−8.08 (m, 1H), 7.69 (s, 1H), 7.68−7.66 (m, 1H), 7.42−7.40 (m, 1H), 3.70 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.7, 150.3, 147.6, 135.9, 133.3, 131.3, 129.6, 128.3, 127.8, 121.4, 81.3, 42.7, 28.2.

***tert*-Butyl 2-(Isoquinolin-5-yl)acetate (4b).** General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as an orange-brown oil in 94% yield (114 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.60 (t, J = 5.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.77−7.76 (m, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.58−7.56 (m, 1H), 3.94 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.4, 153.2, 143.3, 135.0, 132.1, 130.8, 129.1, 127.4, 127.1, 117.1, 81.6, 39.8, 28.1; IR (neat) 2977, 1728, 1367, 1253, 1145 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{15}H_{18}NO_2$ $(M + H)^+$ 244.1338, found 244.1338.

***tert*-Butyl 2-(Pyridin-3-yl)acetate (4c).**[25] General procedure A was employed, with the only modification being that 2 mol % of XPhos-Pd-G2 was used. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a brown oil in 57% yield (55 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51−8.50 (m, 2H), 7.64−7.62 (m, 1H), 7.26−7.24 (m, 1H), 3.53 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ170.1, 150.5, 148.5, 136.9, 130.5, 123.5, 81.6, 39.9, 28.1.

***tert*-Butyl 2-(2,4-Dimethoxypyrimidin-5-yl)acetate (4d).** General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a yellow solid in 93% yield (118 mg): mp 40−42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 3.96 (s, 6H), 3.36 (s, 2H), 1.41 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.9, 169.5, 164.8, 158.0, 109.3, 81.2, 54.8, 54.0, 33.5, 28.1; IR (neat) 2985, 1730, 1569, 1470, 1380, 1227, 1147 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{12}H_{19}N_2O_4$ $(M + H)^+$ 255.1345, found 255.1347.

***tert*-Butyl 2-(Isoquinolin-4-yl)acetate (4e).** General procedure A was employed, with the only modification being that 2 mol % of XPhos-Pd-G2 was used. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as an orange-brown oil in 80% yield (97 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19−9.18 (m, 1H), 8.43−8.42 (m, 1H), 8.00−7.97 (m, 2H), 7.75−7.72 (m, 1H), 7.62−7.61 (m, 1H), 3.93 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.1, 151.9, 147.3, 135.8, 129.3, 129.3, 128.0, 127.7, 126.9, 81.6, 40.1, 28.1; IR (neat) 2977, 1728, 1367, 1141 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{15}H_{18}NO_2$ $(M + H)^+$ 244.1338, found 244.1336.

***tert*-Butyl 2-(Pyridin-4-yl)acetate (4f).**[26] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a brown oil in 40% yield (39 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56−8.54 (m, 2H), 7.21−7.20 (m, 2H), 3.53 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ169.4, 150.0, 143.6, 124.6, 81.7, 42.1, 28.1.

***tert*-Butyl 2-(Furan-3-yl)acetate (4g).** General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a dark brown oil in 88% yield (80 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, J = 6.1, 1.0 Hz, 2H), 6.36 (s, 1H), 3.32 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.4, 142.7, 140.1, 117.8, 111.3, 80.8, 32.1, 27.9; IR (neat) 2977, 1729, 1149 cm^{-1}; HRMS (CI) m/z calcd. For $C_{10}H_{14}O_3$ $(M)^+$, 182.0943 found 182.0945.

***tert*-Butyl 2-(2-Acetylthiophen-3-yl)acetate (4h).** General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a brown oil in 76% yield (91 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.44 (m, 1H), 7.07−7.06 (m, 1H), 3.97 (s, 2 H), 2.53 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 191.0, 170.0, 141.1, 136.8, 132.3, 129.7, 81.1, 36.8, 29.6, 28.2; IR (neat) 2981, 1731, 1665, 1148 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{12}H_{16}O_3SNa$ $(M + Na)^+$, 263.0718, found 263.0715.

***tert*-Butyl 2-(2-Acetylthiophen-3-yl)acetate (4i).** General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a yellow oil in 75% yield (74 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19−7.17 (m, 1H), 6.94−6.92 (m, 1H), 6.90−6.89 (m, 1H), 3.72 (s, 2 H), 1.44 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.8.0, 136.0, 126.8, 126.6, 125.0, 81.5, 37.0, 28.1.

Methyl 2-(Furan-3-yl)acetate (4j).[27] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 3:1) provided the title compound as a yellow oil in 79% yield (55 mg). Spectral data were in accordance with those published: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 2H), 6.34 (s, 1H), 3.70 (s, 3H), 3.45 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.8, 143.2, 140.5, 117.4, 111.5, 52.2, 30.8.

1-Morpholino-2-(*p*-tolyl)ethan-1-one (5a).[28] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as an orange solid in 81% yield (89 mg). Spectral data were in accordance with those published: mp 77−78 °C (lit. 80−81.5 °C) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12−7.11 (m, 4H), 3.69 (s, 2H), 3.64−3.63 (m, 4H), 3.50 (d, J = 5.1 Hz, 2H), 3.46 (d, J = 5.1 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.0, 136.6, 131.8, 129.6, 128.5, 66.9, 66.6, 46.6, 42.5, 40.6, 21.2.

1-Morpholino-2-(naphthalen-2-yl)ethan-1-one (5b). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a white solid in 88% yield (112 mg): mp 118−119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 7.7 Hz, 1H), 7.71 (s, 1H), 7.50−7.48 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 3.88 (d, J = 1.4 Hz, 2H), 3.65−3.64 (m, 4H), 3.45 (d, J = 2.2 Hz, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.5, 133.5, 132.3, 132.2, 128.5, 127.6, 127.5, 127.0, 126.7, 126.2, 125.7, 66.7, 66.4, 46.5, 42.1, 41.0; IR (neat) 2860, 1643, 1428, 1115 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{16}H_{17}NO_2$ $(M + H)^+$ 256.1338, found 256.1337.

2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-morpholinoethan-1-one (5c). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as an orange oil in 98% yield (129 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, J = 9.6 Hz, 1H), 6.71 (d, J = 1.8 Hz, 1H), 6.65 (dd, J = 8.2, 1.8 Hz, 1H), 4.21 (s, 4H), 3.63−3.61 (m, 6H), 3.48 (t, J = 4.7 Hz, 2H), 3.41 (t, J = 4.7 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.7, 143.5, 142.4, 127.8, 121.3, 117.4, 117.2, 66.7, 66.4, 64.2, 64.2, 46.4, 42.0, 40.0; IR (neat) 2979, 1639, 1507, 1285, 1067 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{14}H_{18}NO_4$ $(M + H)^+$, 264.1236, found 264.1235.

2-(3-Acetylphenyl)-1-morpholinoethan-1-one (5d). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a yellow oil in 70% yield (86 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.83 (m,

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1H), 7.49−7.48 (m, 1H), 7.40−7.38 (m, 1H), 7.29−7.28 (m, 1H), 4.04 (s, 2H), 3.74−3.69 (m, 8H), 2.63 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 201.7, 169.9, 137.1, 135.7, 132.5, 132.1, 130.1, 127.2, 66.7, 46.3, 42.4, 40.8, 38.8, 29.1; IR (neat) 2980, 1676, 1646, 1435, 1113 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{14}H_{18}NO_3$ (M + H)$^+$, 248.1287, found 248.1283.

2-(4-Fluorophenyl)-1-morpholinoethan-1-one (5e).[27] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a white solid in 68% yield (76 mg). Spectral data were in accordance with those published: mp 79−81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.18 (m, 2H), 7.02 (t, J = 8.7 Hz, 2H), 3.67 (s, 2H), 3.63 (s, 4H), 3.51 (t, J = 4.7 Hz, 2H), 3.42 (d, J = 4.9 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.6, 161.9 (d, J =245.2 Hz), 130.4 (d, J =3.3 Hz), 130.3 (d, J =7.7 Hz), 115.7 (d, J =21.6), 66.9, 66.6, 46.6, 42.3, 39.0.

2-(Furan-3-yl)-1-morpholinoethan-1-one (5f). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a light brown solid in 85% yield (83 mg): mp 75−77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, J = 1.2 Hz, 1H), 7.34 (s, 1H), 6.35 (s, 1H), 3.65−3.63 (m, 4H), 3.59−3.58 (m, 2H), 3.52 (d, J = 1.9 Hz, 2H), 3.47 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.1, 143.2, 139.8, 118.1, 111.0, 66.7, 66.4, 46.4, 42.0, 30.3; IR (neat) 2855, 1645, 1634, 1439., 1229, 1112 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{10}H_{14}NO_3$ (M + H)$^+$, 196.0974, found 196.0972.

2-(2-Morpholino-2-oxoethyl)furan-3-carboxylic acid (5g). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a light orange solid in 71% yield (85 mg): mp 108−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.44 (t, J = 1.6 Hz, 1H), 6.78 (t, J = 0.9 Hz, 1H), 4.88 (s, 2H), 3.71 (d, J = 4.4 Hz, 4H), 3.64 (d, J = 3.9 Hz, 2H), 3.44 (d, J = 3.8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.0, 162.4, 148.3, 143.8, 118.4, 109.8, 66.7, 66.3, 61.1, 45.0, 42.1; IR (neat) 2961, 1733, 1667, 1469, 1311, 1144 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{11}H_{14}NO_5$ (M + H)$^+$, 240.0872, found 240.0875.

1-Morpholino-2-{1-(phenylsulfonyl)-1*H*-indol-3-yl}ethan-1-one (5h). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as an orange oil in 85% yield (157 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02−8.00 (m, 1H), 7.88−7.87 (m, 2H), 7.55−7.53 (m, 2H), 7.45 (dt, J=J = 12.5, 6.4 Hz, 3H), 7.35−7.34 (m, 1H), 7.27−7.26 (m, 1H), 3.74 (s, 2H), 3.65−3.64 (m, 4H), 3.43−3.40 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.3, 138.0, 135.1, 133.8, 130.2, 129.2, 126.6, 125.1, 123.8, 123.4, 119.6, 116.2, 113.6, 66.7, 66.3, 46.4, 42.1, 30.7; IR (neat) 2979, 1643, 1446, 1365, 1174, 1115 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{20}H_{21}N_2O_4S$ (M + H)$^+$, 385.1222, found 385.1215.

2-(Benzothiophen-2-yl)-1-morpholinoethan-1-one (5i). General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a light orange solid in 62% yield (81 mg): mp 118−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.33−7.29 (m, 3H), 3.98 (s, 2H), 3.68−3.67 (m, 4H), 3.59 (t, J = 4.3 Hz, 2H), 3.54−3.53 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 167.9, 139.7, 139.6, 137.3, 124.3, 124.0, 123.1, 122.6, 122.1, 66.6, 66.4, 46.6, 42.2, 35.7; IR (neat) 2920, 1644, 1436, 1229, 1113 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{14}H_{16}NO_2S$ (M + H)$^+$, 262.0902, found 262.0898.

1-(Piperidin-1-yl)-2-(*p*-tolyl)ethan-1-one (5j).[29] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a white solid in 86% yield (93 mg). Spectral data were in accordance with those published: mp 59−60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11−7.10 (m, 4H), 3.66 (s, 2H), 3.54 (t, J = 5.4 Hz, 2H), 3.33 (t, J = 5.5 Hz, 2H), 2.29 (s, 3H), 1.57−1.55 (m, 2H), 1.50−1.49 (m, 2H), 1.32 (qt, J = 5.2 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.6, 136.3, 132.4, 129.5, 128.5, 47.4, 43.0, 41.0, 26.3, 25.6, 24.6, 21.2.

***N*,*N*-Diethyl-2-(*p*-tolyl)acetamide (5k).**[30] General procedure A was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:3) provided the title compound as a white solid in 72% yield (74 mg). Spectral data were in accordance with those published: mp 103−105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17−7.12 (m, 4H), 3.67 (s, 2H), 3.41 (q, J = 6.8 Hz, 2H), 3.31 (q, J = 7.1 Hz, 2H), 2.34 (s, 3H), 1.12 (dt, J = 14.8, 7.3 Hz, 6H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.4, 136.3, 132.5, 129.4, 128.6, 42.4, 40.6, 40.2, 21.2, 14.3, 13.1.

General Procedure B for Cross-Coupling of (Hetero)-aryltrifluoroborates with Secondary 2-Chloroacetamides. An oven-dried Biotage 10 mL microwave vial equipped with a magnetic stirbar was charged with the (hetero)aryl trifluoroborate (0.525 mmol, 1.05 equiv), Cs_2CO_3 (1.5 mmol, 3 equiv), XPhos-Pd-G2 (3.93 mg, 5.0 μmol, 1 mol %), and Cu_2O (3.6 mg, 25 μmol, 5 mol %). A disposable Teflon septum cap was used to seal the vial, which was evacuated and purged with Ar three times. THF (1.6 mL), H_2O (0.4 mL), and the electrophile (0.5 mmol, 1 equiv) were added via syringe with stirring under Ar. In cases where the electrophile was a solid, it was added along with the solid materials before sealing the vial. The solution was heated at 100 °C overnight. After cooling to rt, the mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers were dried (Na_2SO_4). The crude products were purified by flash column chromatography, eluting with a gradient of EtOAc in hexanes.

***N*-Benzyl-2-(quinolin-6-yl)acetamide (6a).** General procedure B was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:4) provided the title compound as a light orange solid in 55% yield (76 mg): mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89−8.88 (m, 1H), 8.10−8.06 (m, 2H), 7.75 (s, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.41 (ddd, J = 8.2, 4.2, 1.0 Hz 1H), 7.29−7.26 (m, 3H), 7.22 (t, J = 5.7 Hz, 2H), 5.84 (br s, 1H), 4.43 (d, J = 5.8 Hz, 2H), 3.79 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.4, 150.6, 138.1, 136.5, 136.0, 133.4, 131.1, 130.3, 129.3, 128.8, 128.4, 128.2, 127.8, 127.7, 126.2, 121.7, 43.9, 43.8; IR (neat) 3229, 2361, 1628, 1554, 1328 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{18}H_{17}N_2O$ (M + H)$^+$ 277.1341, found 277.1339.

***N*-Benzyl-2-(*p*-tolyl)acetamide (6b).**[31] General procedure B was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:4) provided the title compound as a white solid in 75% yield (90 mg). Spectral data were in accordance with those published: mp 134−135 °C (lit. 136); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.2 Hz, 2H), 7.27−7.26 (m, 1H), 7.21 (d, J = 7.2 Hz, 2H), 7.18 (s, 4H), 5.67 (br s, 1H), 4.41 (d, J = 5.6 Hz, 2H), 3.60 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.3, 138.4, 137.2, 131.8, 129.9, 129.5, 128.8, 127.6, 127.5, 43.7, 43.6, 21.2.

***N*-Cyclopropyl-2-(*p*-tolyl)acetamide (6c).** General procedure B was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:4) provided the title compound as a white solid in 67% yield (63 mg): mp 117−118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16−7.14 (m, 4H), 5.43 (br s, 1H), 3.50 (s, 2H), 2.67−2.63 (m, 1H), 2.34 (s, 3H), 0.71 (dd, J =7.0, 1.3 Hz, 2H), 0.39−0.38 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.9, 137.0, 132.0, 129.7, 129.3, 43.3, 22.9, 21.2, 6.6; IR (neat) 3280, 1644, 1545, 1266 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{12}H_{16}NO$ (M + H)$^+$ 190.1232, found 190.1238.

***N*-Cyclopropyl-2-(furan-3-yl)acetamide (6d).** General procedure B was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:4) provided the title compound as a white solid in 70% yield (58 mg): mp 60−62 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 1.3 Hz, 1H), 7.37 (s, 1H), 6.33 (s, 1H), 5.77 (br s, 1H), 3.37 (s, 2H), 2.71−2.68 (m, 1H), 0.77 (q, J = 6.9 Hz, 2H), 0.45 (dd, J = 2.2, 1.1 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.1, 143.7, 140.8, 118.4, 111.3, 32.9, 22.8, 6.6; IR (neat) 3287, 1650, 1539, 1022 cm^{-1}; HRMS (ESI) m/z calcd. For $C_9H_{12}NO_2$ (M + H)$^+$ 166.0868, found 166.0870.

***N*-Cyclopropyl-2-(naphthalen-1-yl)acetamide (6e).**[32] General procedure B was employed. Column chromatography (hexanes/EtOAc = 9:1 to 1:4) provided the title compound as a white solid in 71% yield (80 mg). Spectral data were in accordance with those published: mp 134−136 °C (lit. 140−141); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (t, J = 6.1 Hz, 1H), 7.91 (q, J = 6.7 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.55−7.52 (m, 2H), 7.46−7.43 (m, 1H), 7.38−7.36 (m, 1H), 5.38 (br s, 1H), 3.99 (s, 2H), 2.60−2.57 (m, 1H), 0.65 (q, J = 6.3 Hz, 2H), 0.26−0.25 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.2, 133.9, 131.9, 131.1, 128.7, 128.4, 128.1, 126.7, 126.1, 125.5, 123.7, 41.7, 22.6, 6.4.

***N*-Cyclopropyl-2-(isoquinolin-5-yl)acetamide (6f).** General procedure B was employed. Column chromatography (hexanes/

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EtOAc = 9:1 to 1:4) provided the title compound as a light orange solid in 62% yield (70 mg): mp 145−147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.57−8.56 (m, 1H), 7.94−7.92 (m, 1H), 7.78 (t, J = 4.5 Hz, 1H), 7.58−7.57 (m, 2H), 5.49 (br s, 1H), 3.94 (s, 2H), 2.63−2.61 (m, 1H), 0.68 (dd, J = 7.0, 1.4 Hz, 2H), 0.31 (td, J = 2.5, 1.1 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.7, 153.2, 143.7, 135.0, 132.2, 130.9, 129.1, 127.8, 127.2, 117.0, 40.7, 23.0, 6.6; IR (neat) 3281, 1648, 1544 cm^{-1}; HRMS (ESI) m/z calcd. For $C_{14}H_{15}N_2O$ $(M + H)^+$ 227.1184, found 227.1190.

■ ASSOCIATED CONTENT

Supporting Information

Figures of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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