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

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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 non-steroidal 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.

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,g} 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.

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SUPPORTING INFORMATION

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

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 homocoupling⁹ 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 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 benzyldisulfonates.¹⁸

Initial reactions were performed with this catalyst in a 4:1 THF/H₂O 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 K₃PO₄, Cs₂CO₃, and KF were all viable options for promoting the reaction (Figure 3).

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 activity of Cs₂CO₃ in this reaction system. Although the conversion with K₃PO₄ was good, this base promoted a significant amount of homocoupled biaryl product from the trifluoroborate; therefore Cs₂CO₃ and K₂CO₃ appeared to serve as the two best bases for the reaction if it were run to completion.

Using Cs₂CO₃ and K₂CO₃ 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 Cs₂CO₃ was superior to K₂CO₃, 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 H₂O were successful, upon scaling the reactions to a 0.5 mmol scale, it was determined that a 4:1 THF/H₂O combination was superior.

Based on 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 K₂CO₃ and Cs₂CO₃ allow the reaction to go to completion, and both provide good yields for non-sterically 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 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 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 ten-fold to 5.0 mmol led to comparable yields, even with the catalyst loading cut in half (from 1 mol % 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 indolyltrifluoroborate (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.

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). Based on successful results of Deng and Duan, who successfully cross-coupled arylboronic acids with α -bromo amides using catalytic Pd in the presence of Cu₂O,^{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, Cu₂O 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 Cu₂O 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 quinoliny (entry 1), isoquinoliny (entry 6), and furyl (entry 4) trifluoroborate salts were successfully cross-coupled using these modified conditions. The addition of Cu₂O 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 ten-fold to 5.0 mmol led to comparable yields, with the catalyst loading cut in half (from 1 mol % 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

General considerations

Both THF and deionized H₂O 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 ¹³C NMR spectra were obtained at 500 and 125.8 MHz, respectively. HRMS data was obtained by ESI using a TOF mass spectrometer.

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), Cs₂CO₃ (1.5 mmol, 3 equiv),

and XPhos-Pd-G2 (3.93 mg, 5.0 μ mol, 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), H₂O (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 soln was heated at 100 °C overnight. After cooling to rt, the mixture was extracted with EtOAc (3 $\times$ 3 mL), and the combined organic layers were dried (Na₂SO₄). 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). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₆H₁₇O₃ (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). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₆H₁₆O₃Na (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). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₆H₁₆O₂Na (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). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₈H₁₆NO₂ (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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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). ^1H 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 $\text{C}_{21}\text{H}_{27}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 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. ^1H 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 $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 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). ^1H 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 $\text{C}_{13}\text{H}_{12}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 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. ^1H 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. ^1H 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). ^1H 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 $\text{C}_{18}\text{H}_{27}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 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. ^1H 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). ^1H 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 $\text{C}_{14}\text{H}_{18}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 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). ^1H 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, 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 $\text{C}_{14}\text{H}_{18}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 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. ^1H 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. ^1H 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 as an orange-brown oil in 92% yield (112 mg). Spectral data were in accordance with those published. ^1H 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). ^1H 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 $\text{C}_{15}\text{H}_{18}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ 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. ^1H 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): δ 170.1, 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. ^1H 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 $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 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). ^1H 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 $\text{C}_{15}\text{H}_{18}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ 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. ^1H 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): δ 169.4, 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). ^1H 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 $\text{C}_{10}\text{H}_{14}\text{O}_3$ (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). ^1H NMR (500 MHz, CDCl_3): δ 7.45-7.44 (m, 1H), 7.07-7.06 (m, 1H), 3.97 (s, 2H), 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 $\text{C}_{12}\text{H}_{16}\text{O}_3\text{SNa}$ ($\text{M}+\text{Na}$) $^+$, 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). ^1H 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, 2H), 1.44 (s, 9H). ^{13}C NMR (125.8 MHz, CDCl_3): δ 169.8, 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. ^1H NMR (500

MHz, CDCl₃): δ 7.37 (s, 2H), 6.34 (s, 1H), 3.70 (s, 3H), 3.45 (s, 2H). ¹³C NMR (125.8 MHz, CDCl₃): 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). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₆H₁₇NO₂ (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). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₄H₁₈NO₄ (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). ¹H NMR (500 MHz, CDCl₃): δ 7.84–7.83 (m, 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₄H₁₈NO₃ (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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₀H₁₄NO₃ (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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₁H₁₄NO₅ (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). ¹H NMR (500 MHz, CDCl₃): δ 8.02–8.00 (m, 1H), 7.88–7.87 (m, 2H), 7.55–7.53 (m, 2H), 7.45 (dt, *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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₂₀H₂₁N₂O₄S (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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₄H₁₆NO₂S (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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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), Cs₂CO₃ (1.5 mmol, 3 equiv), XPhos-Pd-G2 (3.93 mg, 5.0 μmol, 1 mol %), and Cu₂O (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), H₂O (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 soln 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 (Na₂SO₄). 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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₈H₁₇N₂O (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). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₁₂H₁₆NO (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. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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 C₉H₁₂NO₂ (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). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.8 MHz, CDCl₃): 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/EtOAc = 9:1 to 1:4) provided the title compound as a light orange solid in 62% yield (70 mg). mp 145–147 °C. ¹H NMR (500 MHz, CDCl₃): 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 $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 227.1184, found 227.1190.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Figure 2.
Structure of XPhos-Pd-G2 precatalyst

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/H₂O, 18 h) in the presence of 3 equiv of each base at the shown temperature.

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).

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 Cs₂CO₃, 0.25 M 4:1 THF/H₂O, 100 °C, 18 h).

Scheme 1. Approaches to the synthesis of α -(hetero)aryl esters and amides

Table 1

GC/MS Conversions for the Reaction of Benzyl Chloroacetate with Potassium 2-Methoxyphenyltrifluoroborate in the Presence of Three Bases.^a

Base	% Conversion
KF	42
K ₃ PO ₄	81
Cs ₂ CO ₃	92
K ₂ CO ₃	77

^a3 equiv of each base shown; 1 mol % XPhos-Pd-G2, 0.25 M in 4:1 THF/H₂O, 18 h, 80°C.

Table 2

Cross-Coupling of Benzyl Chloroacetate with Aryl and Heteroaryl Trifluoroborates

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 ^a

Entry	Product	Yield (%)
9	<p style="text-align: center;">2i</p>	84 ^a

General conditions: Benzyl ester (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cs₂CO₃ (1.50 mmol) in THF (1.6 mL)/H₂O (0.40 mL) at 100 °C for 18 h.

^aK₂CO₃ used as base.

Table 3

Cross-Coupling of Alkyl Chloroacetates with Aryltrifluoroborates

$$\text{RO}-\text{C}(=\text{O})-\text{CH}_2-\text{Cl} + \text{Ar}-\text{BF}_3\text{K} \xrightarrow[\text{THF/H}_2\text{O (4:1), 100 }^\circ\text{C, 18 h}]{\text{XPhos-Pd-G2 (1 mol \%), Cs}_2\text{CO}_3 \text{ (3 equiv)}} \text{RO}-\text{C}(=\text{O})-\text{CH}_2-\text{Ar}$$

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

General conditions: Ester (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cs₂CO₃ (1.50 mmol) in THF (1.6 mL)/H₂O (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

Cross-Coupling of Alkyl Chloroacetates with Heteroaryltrifluoroborates

Entry	Product	Yield (%)
1	4a	92
2	4b	94
3	4c	50, 57 ^c
4	4d	93
5	4e	80
6	4f	40
7	4g	88
8	4h	76

Entry	Product	Yield (%)
9	4i	75
10	4j	79

General conditions: Ester (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cs₂CO₃ (1.50 mmol) in THF (1.6 mL)/H₂O (0.40 mL) at 100 °C for 18 h.

^c 2 mol % XPhos-Pd-G2 (0.010 mmol).

Table 5

Cross-Coupling of Tertiary Amides with Aryl and Heteroaryltrifluoroborates

Entry	Product	Yield (%)
1	5a	81
2	5b	88
3	5c	98
4	5d	70
5	5e	68
6	5f	85
7	5g	71

Entry	Product	Yield (%)
8	5h	85
9	5i	62
10	5j	86
11	5k	72

General conditions: Amide (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cs₂CO₃ (1.50 mmol) in THF (1.6 mL)/H₂O (0.40 mL) at 100 °C for 18 h.

Table 6

Cross-Coupling of Secondary Amides with Aryl and Heteroaryltrifluoroborates

$$R_2N-CH_2-COCl + (Het)Ar-BF_3K \xrightarrow[\substack{THF/H_2O (4:1) \\ 100^\circ C, 18 h}]{\substack{XPhos-Pd-G2 (1 \text{ mol } \%) \\ Cu_2O (5 \text{ mol } \%) \\ Cs_2CO_3 (3 \text{ equiv})}} R_2N-CH_2-CO-(Het)Ar$$

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

General conditions: Amide (0.50 mmol), trifluoroborate (0.525 mmol), XPhos-Pd-G2 (0.005 mmol), Cu₂O (0.025 mmol), Cs₂CO₃ (1.50 mmol) in THF (1.6 mL)/H₂O (0.40 mL) at 100 °C for 18 h.

^b Isolated on 5.0 mmol scale using 0.5 mol % XPhos-Pd-G2.