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An Air-Tolerant Approach to the Carbonylative Suzuki–Miyaura Coupling: Applications in Isotope Labeling

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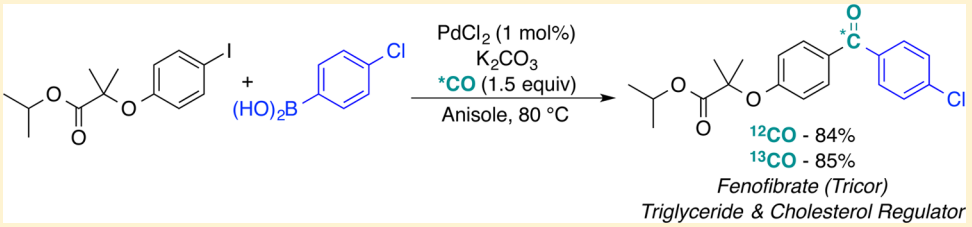
Supporting Information



ABSTRACT: Carbonylative Suzuki–Miyaura coupling conditions have been developed that proceed without the exclusion of oxygen and in the presence of nondegassed and nondried solvents. By adapting the method to a two-chamber setup, the direct handling of carbon monoxide, produced from stable CO precursors, is avoided. The protocol afforded the desired benzophenones with excellent functional group tolerance and in good yields. Substituting the CO precursor, in the CO-producing chamber, with its carbon-13 labeled version generated the corresponding carbon-13 labeled benzophenones. Finally, the developed system was applied in the synthesis and isotope labeling of two pharmaceuticals, nordazepam and Tricor.

INTRODUCTION

In principle, every palladium-catalyzed cross coupling holds a carbonylative counterpart.[1] In example, whereby the heteroatoms represent the nucleophile, this includes the direct amination with its corresponding aminocarbonylation, as well as the aryl ether formation and the alkoxycarbonylation. Reactions with carbon nucleophiles including the Sonogashira, Stille, and Suzuki–Miyaura couplings also have their carbonylative versions. Even the Mizoroki–Heck reaction can be transformed into a reaction where carbon monoxide (CO) is incorporated. In this way, it is possible to prepare a vast structural diversity based on few starting materials by performing the cross coupling reaction under conditions with and without CO integration.

The Suzuki–Miyaura cross coupling represents one of the most applied transition metal-catalyzed reaction in discovery chemistry.[2] A successful coupling results in the site-specific carbon–carbon bond formation between two activated substrates, typically an aryl boronic acid or derivative thereof and an aryl halide, to form a biaryl. Furthermore, there is literature precedence providing conditions for virtually any desirable Suzuki–Miyaura coupling, and chemical distributors provide large chemical catalogues of commercially available boronic acid and aryl halide derivatives, adding to the ever-growing popularity of this transformation.

The carbonylative version of the Suzuki–Miyaura reaction has also been studied, although not to the same extent as its direct version. One class of products obtained from successful coupling is the benzophenones. Such compounds are found in sunblockers (benzophenone 1–9), Tricor,[3] Sector,[4] Evista,[5] photoinitiators in UV-curing inks, and serve as key structural components in the benzodiazapine families (Scheme 1).[9,6] The high presence of benzophenones in target structures makes the carbonylative Suzuki–Miyaura coupling an obvious synthetic strategy for the R&D chemist. The majority of the literature covering this particular cross coupling is dominated by high-pressure protocols, and only few are found applying CO at atmospheric pressure.[7−9] However, it is interesting to note that protocols have emerged that operate without the exclusion of oxygen from the headspace or the reaction medium. This is achieved by applying air-stable ligands or even ligandless conditions. Furthermore, a few of these protocols afford the carbonylative Suzuki–Miyaura coupling product under a simple balloon pressure of CO.

One drawback that relates to all carbonylative reactions is the necessity to apply carbon monoxide as the gas itself. Because CO is a corrosive, flammable, and highly toxic gas, it must be handled with extreme caution. This statement is further strengthened since CO is colorless, odorless, and without taste. CO is typically delivered in pressurized cylinders and operated in the presence of CO detectors and in dedicated laboratories to protect the operator.

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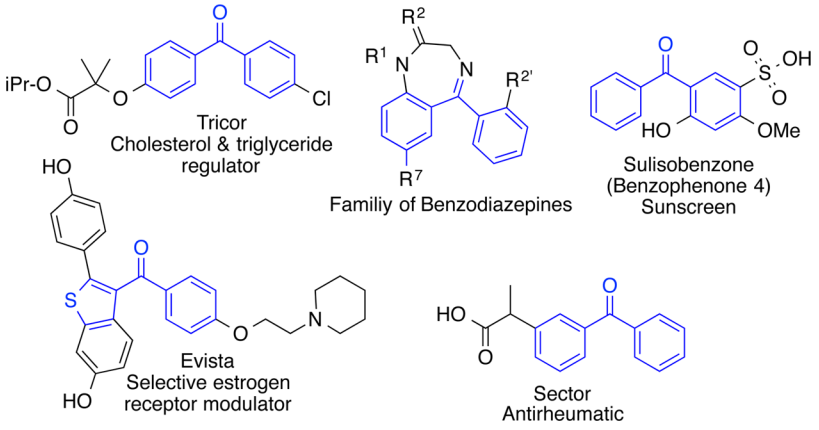
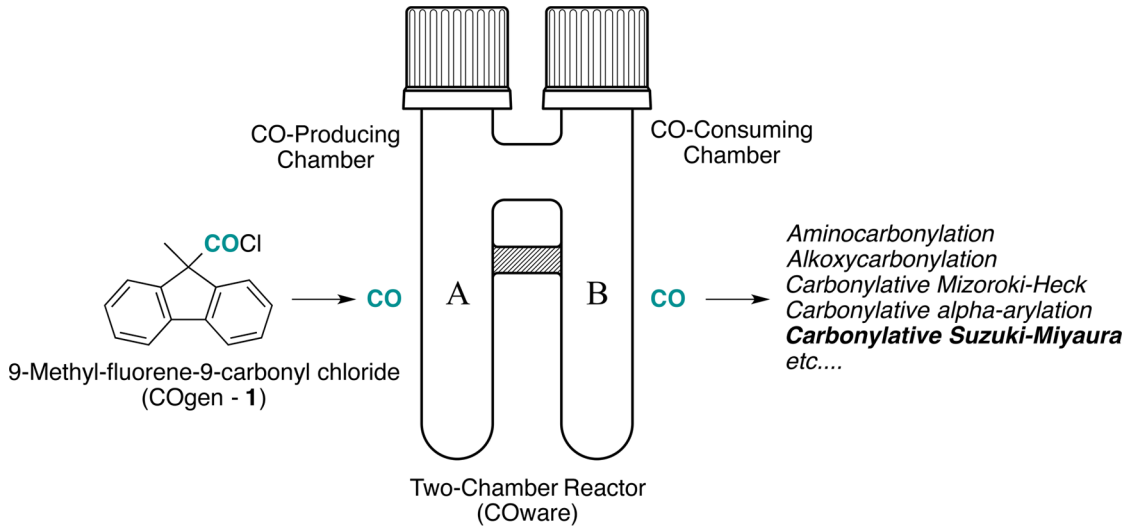
Scheme 1. Selected Examples of Benzophenone Derivatives



Scheme 2. Applications of COgen and COware



Previously, we have developed an alternative delivery method of CO.[10] This technique was based on a stable solid CO precursor (COgen) from which a predetermined amount of CO can be released. Upon combination of the CO release with a sealed two-chamber system (COware), this method has proven highly adaptable for many Pd-catalyzed carbonylations (Scheme 2).[10,11] During our work, it was realized that despite the CO release being a palladium/phosphine-catalyzed transformation, CO could efficiently be produced under noninert conditions (i.e., in the presence of air and in nondegassed and nondried solvents). Obviously, this adds to the overall applicability of the two-chamber technique by circumventing the direct handling of CO and not requiring an inert atmosphere or glovebox.

With a simple CO technique in hand and with existing literature on air-tolerant carbonylative Suzuki–Miyaura coupling conditions, we decided to investigate the potential combination of these two areas into a new tool for the general organic chemists. Not only would this represent a simple method for the preparation of benzophenones, but also at the same time it would provide a facile entry point for carbon isotope labeling, applying isotopically labeled CO generated from ^{13}COgen or even ^{14}COgen. CO is an ideal source for isotope labeling, as the conditions applied for its introduction, typically transition metal catalysis, ensure a high functional group tolerance. This in turn allows this particular isotope-labeled building block to be installed in the final steps of the linear sequence toward the target structure. This ensures a high isotope efficiency and reduces the number of overall steps in which the labeled material needs to be handled, a fact which is especially important when working with radioactive isotopes such as carbon-14.[3] Furthermore, CO is typically introduced by the formation of a stable carbon–carbon bond, which is important, if the final compound is to be applied in drug metabolism studies. Being able to apply an identical synthetic approach for the preparation of the test substrates and even their isotopically labeled counterparts could significantly reduce downstream processes in the pharmaceutical and agrochemical industry.

Here, we report on our findings on a simple and air-tolerant carbonylative Suzuki–Miyaura coupling. CO was generated in parallel to the carbonylative coupling based on a two-chamber technique, and the conditions developed allowed for high functional group tolerance in the synthesized benzophenones. This approach allows the carbonylative Suzuki–Miyaura coupling to be performed without the direct handling of CO, and it avoids the elaborate drying and deoxygenation of both solvents and the reaction vessel. Finally, the method was applied for the synthesis and carbon isotope labeling of the two pharmaceuticals, Tricor and nordazepam, clearly illustrating the usefulness of this simple and straightforward protocol.

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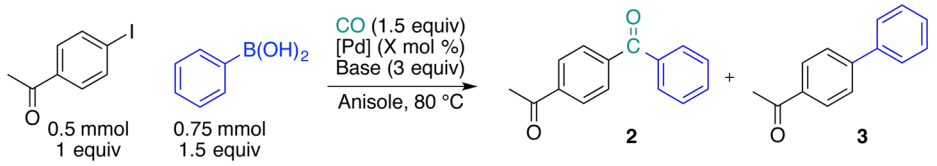
Table 1. Optimization of the Carbonlytative Suzuki–Miyaura Coupling[a]



entry	Pd cat (mol %)	base	conversion (%)	ratio 2:3[b] [yield][c]
1	$Pd(OAc)_2$ (5)	K_2CO_3	100	25:75
2	$Pd(OAc)_2$ (1)	K_2CO_3	100	69:31 [67%]
3	$PdCl_2COD$ (1)	K_2CO_3	100	71:29
4	$PdBr_2$ (1)	K_2CO_3	100	84:16
5	$Pd(dba)_2$ (1)	K_2CO_3	100	71:29
6	$Pd(TFA)_2$ (1)	K_2CO_3	100	58:42
7	$PdCl_2$ (1)	K_2CO_3	100	94:6 [81%]
8	Pd/C (1)	K_2CO_3	100	89:11
9	none	K_2CO_3	0	–
10	$PdCl_2$ (1)	Na_2CO_3	13	>95:5
11	$PdCl_2$ (1)	K_3PO_4	87	83:17
12	$PdCl_2$ (1)	KF	100	83:17
13	$PdCl_2$ (1)	NaOAc	15	>95:5

[a]Conditions: Chamber A, COgen (0.75 mmol), $Pd(dba)_2$ (5 mol %), $HBF_4P(tBu)_3$ (5 mol %), DIPEA (2.0 equiv) in anisole (3 mL). Chamber B, 4-iodoacetophenone (0.5 mmol), [Pd] (*x* mol %), Base (3 equiv) in anisole (3 mL). Both chambers were heated to 80 °C. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yields of **2** are reported in square brackets.

RESULTS AND DISCUSSION

The previously developed CO-delivery system consisting of the acid chloride **1** (COgen), $Pd(dba)_2$, $HBF_4P(tBu)_3$, and *N*,*N*-diisopropyl-*N*-ethylamine (DIPEA) as the stoichiometric base proved able to deliver CO even in presence of an ambient atmosphere applying nondried solvents.[10] With this source of CO in our hands and inspired by the work of Yang and Xue et al., who reported a benzophenone protocol applying $Pd(dba)_2$ as the catalyst with K_2CO_3 as the base in anisole delivering CO by a balloon, we set forth to develop an equally oxygen-compatible carbonylative Suzuki–Miyaura coupling protocol.[8a] Several groups have reported that the combination of $Pd(OAc)_2$ with K_2CO_3 effectively promotes the carbonylated Suzuki–Miyaura coupling reaction. Importantly, the use of anisole as the solvent proved essential in order to secure high yields, whereas solvents like DMF, toluene, and THF afforded mainly the direct biaryl coupling products without CO insertion.[7a,8a–c,9] As a model system, we chose the coupling of 4-iodoacetophenone and phenylboronic acid with anisole as the solvent (Table 1). 1.5 equiv of CO was applied using the two-chamber setup. All reactions were set up using nondried solvents and with no exchange of the headspace atmosphere with inert N_2 or Ar. The crude reaction mixtures were analyzed for the desired benzophenone **2**, the direct coupling product 4-phenyl acetophenone (**3**), and the overall conversion.

Applying the conditions tested by Yang and Xue, however, using $Pd(OAc)_2$ instead of $Pd_2(dba)_3$, afforded a clean reaction with full conversion but with a nonideal 25:75 ratio of **2**:**3** (entry 1).[8a] Lowering the $Pd(OAc)_2$ loading to 1 mol % afforded the same conversion rate while increasing the formation of **2** (entry 2). This increase in the formation of **2** could be explained by the higher CO/Pd ratio. Setting the reaction temperature to 60 °C resulted in incomplete conversion (result not shown). Other Pd sources were screened as shown in entries 3–8. For all of the tested Pd sources, completion of the reactions were observed, and gratifyingly, we found that $PdCl_2$ afforded an excellent 94:6 ratio of **2**:**3** as measured by ^{1}H NMR analysis of the crude reaction mixture (entry 7). Furthermore, an 81% isolated yield of **2** (entry 7) was shown.[12] Even Pd/C was able to catalyze the carbonylative coupling with a 89:11 selectivity for CO insertion (entry 8).[13] Omitting the Pd catalyst led to an inactive catalytic system (entry 9).[14] Finally, different bases were tested as alternatives to K_2CO_3 (entries 10–13). Only KF afforded the same high reactivity as K_2CO_3 but with a lowered **2**:**3** ratio of 83:17.[2a,b] Finally, by carefully mixing the $PdCl_2$ with K_2CO_3 in a mortar, a pale brown powder was obtained, which proved simple to handle and to weigh out. This catalyst/base mixture afforded the same results as when the two reagents were added separately, and hence, this mixture was therefore used in the rest of the carbonylative couplings.[15] Attempts to include aryl bromides as electrophiles did afford the desired benzophenones; however, only low yields were obtained because of competing formation of the benzoic acid derivatives.

Satisfied with these simple-to-perform carbonylative Suzuki–Miyaura coupling conditions, these were then tested against a series of different aryl iodides and aryl boronic acids, the results of which are depicted in Table 2.[16]

Full conversion of the aryl iodide starting material was typically observed, and drops in yields are ascribed to competing biaryl coupling as observed by ^{1}H NMR analysis of the crude reaction mixture. Aryl iodides carrying electron-withdrawing groups such as nitro or and amide underwent successful coupling with phenylboronic acid providing the corresponding benzophenones with isolated yields of 72, 93, and 59% (entries 1–3).[17] The presence of a free phenolic alcohol only afforded low conversion, but upon its MOM or tosyl protection, the desired benzophenones could be obtained in reasonable yields (entries 4, 5 and 15). A slight decrease in isolated yield was observed by the introduction of a substituent in *ortho*-position of the aryl iodide (entries 6, 8, 9 and 15). The presence of both protected and free anilines did not seem to interfere with the catalytic system, and the corresponding benzophenones were secured in yields ranging from 71–79% (entries 9, 11–13). Even the acetylated phenyldiazenyl iodophenol provided the desired

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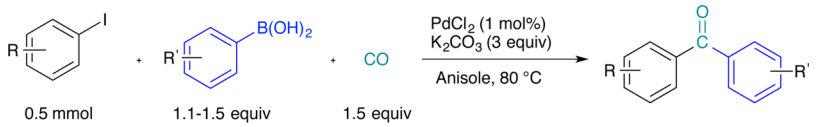
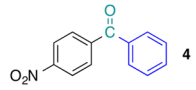
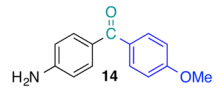
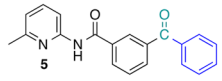
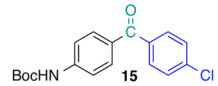
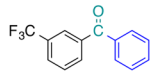
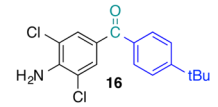
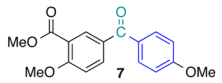
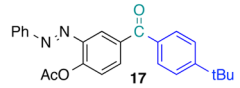
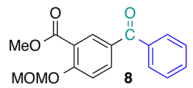
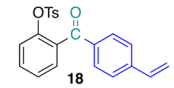
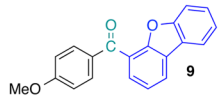
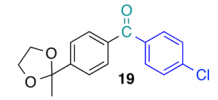
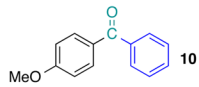
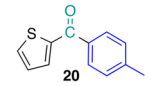
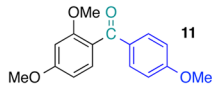
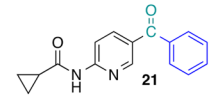
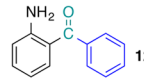
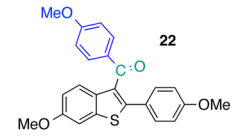
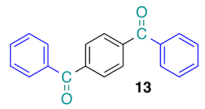
Table 2. Carbonylative Suzuki–Miyaura Couplings[a]



Entry	Product	Yield[b]	Entry	Product	Yield[b]
1	 **4**	72	11	 **14**	68
2	 **5**	93	12	 **15**	79
3	 **6**	59	13	 **16**	74
4	 **7**	52	14	 **17**	50
5	 **8**	68	15	 **18**	52
6	 **9**	58	16	 **19**	80
7	 **10**	93	17	 **20**	71
8	 **11**	79	18	 **21**	70
9	 **12**	71 (82)[c]	19	 **22**	67
10	 **13**	70			

[a]For specific reaction conditions, see Supporting Information. [b]Isolated yields after column chromatography. [c]Reaction repeated on 3 mmol scale (yield in brackets).

benzophenone, although only in a 50% isolated yield after column chromatography (entry 14). Acetal protection of the ketone moiety in 4-iodoacetophenone prior to coupling generated the benzophenone coupling product in 80% isolated yield (entry 16). Also heteroaromatic aryl iodides underwent successful coupling with isolated yields of 71, 70, and 67% (entries 17–19). A double coupling was attempted using 1,4-diiodobenzene as substrate affording the 1,4-dibenzoyl benzene in 70% isolated yield (entry 10). Finally, performing the reaction of *o*-iodoaniline with phenylboronic acid on a 3 mmol scale afforded a slight increase in isolated yield to 82% (entry 9, results in brackets).

Next, a few examples of the benzophenones depicted in Table 2 were selected for carbon-13 labeling (Scheme 3). By simply exchanging COgen for ^{13}COgen, applying the exact coupling conditions as in Table 2, the desired ^{13}C-labeled benzophenones were obtained in yields similar to those of the unlabeled version (Table 2, entries 3, 6, 15 and 17). Again, these couplings are performed without careful drying or deoxygenation of solvents, nor was oxygen excluded from the reaction vessel headspace.

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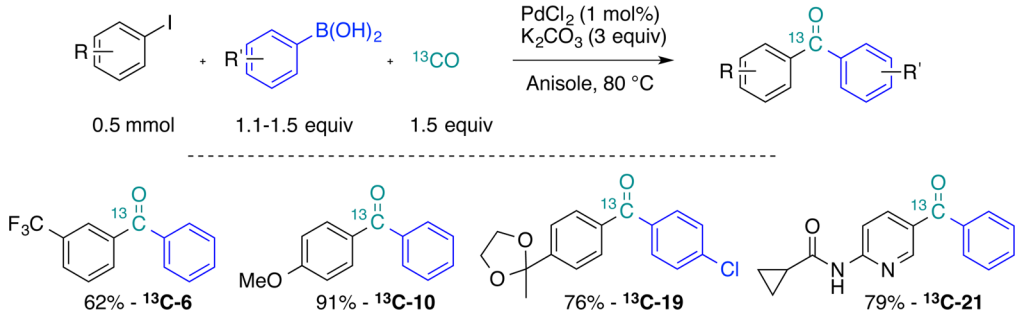
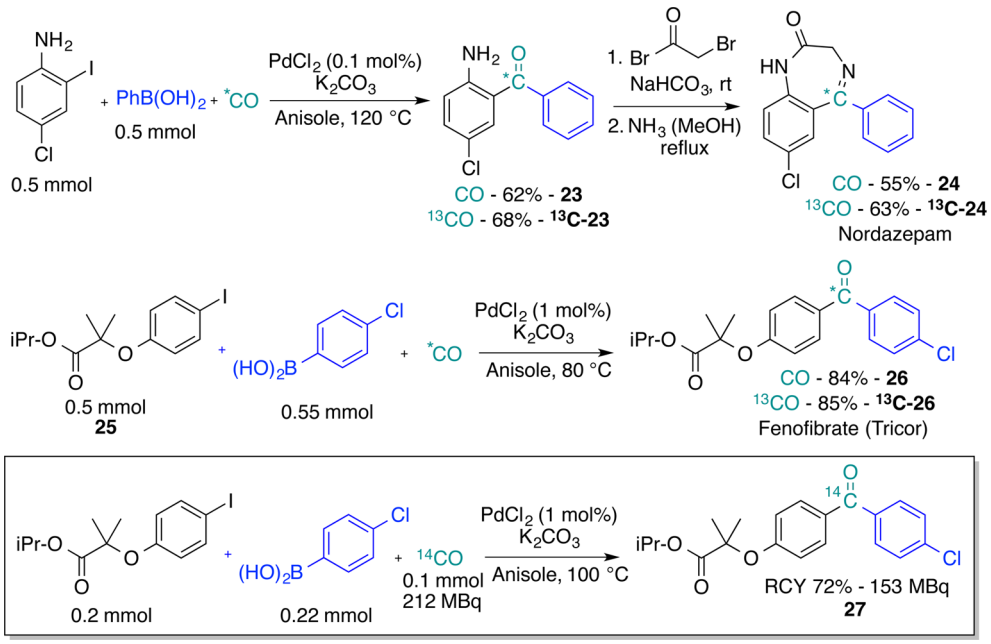
Scheme 3. Synthesis of ^{13}C-Isotope Labeled Benzophenones



Scheme 4. Synthesis and ^{13}C-Labeling of Nordazepam and Tricor



Attention was then turned toward more advanced applications of this method in order to prove its utility in the synthesis of biologically relevant structures. The basic idea was to apply a carbonylative coupling in which CO was incorporated into the core of the final structure. From the family of benzodiazepines and used in the treatment of anxiety, nordazepam was chosen as the first target structure. To this end, 4-chloro-2-iodoaniline was attempted coupled with phenyl boronic acid. Using the developed conditions from Table 1 only afforded the target benzophenone **23** in low yield. ^{1}H NMR analysis of the crude reaction mixture showed full consumtion of the aryl iodide with the formation of the biaryl without CO insertion. Lowering the amount of phenyl boronic acid to an equimolar amount (0.5 mmol) increased the selectivity toward the benzophenone moiety. Decreasing the palladium loading further improved the selectivity toward **23** but at the expence of an incomplete reaction. Finally, increasing the temperature of the reaction to 120 °C in combination with 0.1 mol % of $PdCl_2$ catalyst allowed for a 62% isolated yield of **23** after column chromatography. In a similar manner **^{13}C-23** could be obtained in 68% isolated yield. Acetylation of both **23** and **^{13}C-23** applying 2-bromoacetyl bromide in the presence of sodium bicarbonate followed by treatment with aqueous ammonia in a one-pot manner affoded nordazepam (**24**) and ^{13}C-labeled nordazepam (**^{13}C-24**) in 55 and 63% isolated yields, respectively (Scheme 4).[18]

As a final example, the synthesis of Tricor, a cholesterol and triglyceride regulator, was chosen. The starting iodide **25** for the carbonylative coupling was obtained from iodophenol via a Barganelli reaction (acetone, KOH, and chloroform), followed by Fischer esterification in isopropyl alcohol. Gratifyingly, the coupling of **25** with 4-chlorophenyl boronic acid, applying the developed conditions, afforded Tricor (**26**) and ^{13}C-labeled Tricor (**^{13}C-26**) in 84 and 85% isolated yields, respectively (Scheme 4). We have previously reported the synthesis of ^{14}C-Tricor (**27**) using the same conditions introducing this radioactive label in the final step of the synthesis, however, applying ^{14}CO as the limiting reagent on a 0.1 mmol scale (Scheme 4, bottom reaction).[3,19] The successful synthesis and labeling of Tricor under near identical conditions, only substituting the CO precursor, applying the same two-chamber reaction vessel for all transformations proves the overall strength and simplicity of the developed carbonylative Suzuki–Miyaura protocol.

■ CONCLUSION

In conclusion, carbonylative Suzuki–Miyaura coupling conditions have been developed in combination with CO being delivered from a CO precursor in a two-chamber system. All reactions were performed using nondried solvents and with no exclusion of air from the reactor headspace significantly

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simplifying the reaction setup. Several benzophenones were synthesized with high functional group tolerance and good to excellent isolated yields. The method was further extrapolated to include isotope labeling using ^{13}CO simply by exchanging the carbon monoxide precursor to its carbon-13 labeled counterpart. Finally, the synthesis of both nordazepam and Tricor and their labeled versions was performed using the developed method on key transformations introducing the carbonyl moiety onto advanced reaction intermediates. The simplicity of the developed approach will provide the synthetic chemistry community with a straightforward tool for performing carbonylative Suzuki–Miyaura couplings without the need of handling CO or drying/degassing solvents and reactor headspace.

EXPERIMENTAL SECTION

General Materials and Methods. All purchased chemicals were used as received without further purification. Flash chromatography was carried out on silica gel 60 (230–400 mesh). The chemical shifts are reported in ppm relative to solvent residual peak.[20] ^1H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz, and ^{19}F NMR were recorded at 376.8 MHz. MS spectra were recorded on a LC TOF (ES) apparatus.

General Method. Aryl halide (0.50 mmol, 1.0 equiv), arylboronic acid (0.55–0.75 mmol, 1.1–1.5 equiv), K_2CO_3 (1.5 mmol, 3 equiv), and $PdCl_2$ (0.005 mmol, 0.01 equiv) were added to chamber A of a COware system. 9-Methyl-fluorene-9-carbonyl chloride (0.75 mmol, 1.5 equiv), $P(tBu)_3HBF_4$ (0.0375 mmol, 0.075 equiv), and $Pd(dba)_2$ or $PdCl_2(cod)$ (0.0375 mmol, 0.075 equiv) were added to chamber B. To both chambers was added anisole (3.0 mL). Finally, DIPEA (1.5 mmol, 3 equiv) was added to chamber B, and both chambers were fitted with a Teflon-sealed screwcap. Both reaction chambers were heated overnight at 80 °C. The crude of chamber A was evaporated onto silica gel and purified with flash column chromatography to yield the desired product.

1-(4-Benzoylphenyl)ethanone[21] (2). General method with 1-(4-iodophenyl)ethanone (123.0 mg, 0.50 mmol) and phenylboronic acid (91.0 mg, 0.75 mmol). Flash column chromatography (10% EtOAc in pentane). This gave 91.2 mg (81% yield) of the title compound as a colorless solid: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05–8.02 (m, 2H), 7.86–7.83 (m, 2H), 7.80–7.77 (m, 2H), 7.62–7.58 (m, 1H), 7.50–7.46 (m, 2H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.6, 196.0, 141.4, 139.6, 137.0, 133.1, 130.2, 130.1, 128.5, 128.2, 27.0; HRMS m/z calculated for $C_{15}H_{12}O_2H^+$ [M + H$^+$] 225.0910, found 225.0911.

(4-Nitrophenyl)(phenyl)methanone[22] (4). General method with 1-iodo-4-nitrobenzene (124.5 mg, 0.50 mmol) and phenylboronic acid (67.1 mg, 0.55 mmol). Flash column chromatography (50% CH_2Cl_2/pentane) gave 81.6 mg (72% yield) of the title compound as a colorless solid: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (d, 2H, J = 8.6 Hz), 7.94 (d, 2H, J = 8.5 Hz), 7.80 (d, 2H, J = 7.1 Hz), 7.68–7.63 (m, 1H), 7.55–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.9, 149.9, 143.0, 136.4, 133.6, 130.8, 130.2, 128.8, 123.7; HRMS m/z calculated for $C_{13}H_{10}NO_3H^+$ [M + H$^+$] 228.0655, found 228.0654.

3-Benzoyl-*N*-(6-methylpyridin-2-yl)benzamide (5). General method with 3-methyl-*N*-(6-methylpyridin-2-yl)benzamide (169.1 mg, 0.50 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol). Flash column chromatography (25% EtOAc/pentane) gave 147.5 mg (93% yield) of the title compound as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.01 (s, 1H), 8.30–8.29 (m, 1H), 8.15–8.10 (m, 2H), 7.95–7.92 (m, 1H), 7.76–7.74 (m, 2H), 7.61–7.54 (m, 3H), 7.47–7.43 (m, 2H), 6.87 (d, 1H, J = 7.4 Hz), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.6, 164.9, 156.9, 150.7, 138.8, 138.1, 136.9, 134.7, 133.3, 132.9, 131.1, 130.0, 128.9, 128.6, 128.5, 119.7, 111.2, 23.9; HRMS m/z calculated for $C_{20}H_{16}N_2O_2Na^+$ [M + Na$^+$] 339.1104, found 339.1107.

Phenyl-(3-(trifluoromethyl)phenyl)methanone[23] (6). General method with 3-(trifluoromethyl)-iodobenzene (136.0 mg, 0.50 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Flash column chromatography (pentane to dichloromethane). This gave 73.5 mg (59% yield) of the title compound as a colorless solid: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.07 (d, 1H, J = 0.6 Hz,), 7.98 (d, J = 7.7 Hz, 1H), 7.85 (dd, 1H, J = 7.8, 0.6 Hz), 7.81–7.79 (m, 2H), 7.63 (dt, 2H, J = 7.6, 0.6 Hz), 7.51 (dt, 2H, J = 7.7, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.2, 138.3, 136.7, 133.1, 133.0, 131.0 (q, J = 32.7 Hz), 130.0, 128.9, 128.8 (q, J = 3.6 Hz), 128.5, 126.7 (q, J = 3.8 Hz), 126.7 (q, J = 270.6 Hz); ^{19}F NMR (376.8 MHz, $CDCl_3$) δ (ppm) −62.8 (s, 3F); HRMS $C_{14}H_9F_3O$ [M + Na$^+$]; calculated 273.0498, found 273.0500, [M + H$^+$]; calculated 251.0678, found 251.0679.

[^{13}C]-Phenyl-(3-(trifluoromethyl)phenyl)methanone (^{13}C-6). General method with 3-(trifluoromethyl)-iodobenzene (136.0 mg, 0.50 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). ^{13}C-Labeled 9-methyl-fluorene-9-carbonyl chloride (182.8 mg, 0.75 mmol) in chamber B. Flash column chromatography (pentane to CH_2Cl_2). This gave 78.3 mg (62% yield) of the title compound as a colorless solid: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.07 (t, 1 H, J = 1.8 Hz), 7.98 (dd, 1 H, J = 7.7, 3.7 Hz), 7.85 (dd, 1H, J = 1.0 Hz, 0.5 Hz), 7.84–7.78 (m, 2H), 7.63 (dt, 2H, J = 7.5, 0.5 Hz), 7.52 (dt, 2H, J = 7.6, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.9 (^{13}CO), 138.3 (d, J = 50.0 Hz), 136.7 (d, J = 60.0 Hz), 133.1 (d, J = 1.0 Hz), 133.0 (d, J = 1.0 Hz), 131.3 (dd, J = 32.6, 4.1 Hz), 130.0 (d, J = 4.0 Hz), 128.9 (d, J = 5.0 Hz), 128.8 (q, J = 3.6 Hz), 128.6 (d, J = 7.0 Hz), 126.7 (q, J = 4.0 Hz), 123.8 (q, J = 270.6 Hz); HRMS [M + H$^+$]; calculated 252.0712, found 252.0709.

Methyl 2-methoxy-5-(4-methoxybenzoyl)benzoate (7). General method with methyl 5-iodo-2-methoxybeonzoate (146.0 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (67.1 mg, 0.55 mmol). Flash column chromatography (10–40% EtOAc/pentane) gave 78.5 mg (52% yield) of the title compound as a colorless solid: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24–8.24 (m, 1H), 7.97–7.94 (m, 1H), 7.80–7.76 (m, 2H), 7.07–7.05 (m, 1H), 6.99–6.95 (m, 2H), 3.98–3.98 (m, 3H), 3.88–3.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.6, 166.0, 163.2, 162.0, 135.5, 134.0, 132.3, 130.2, 130.2, 119.8, 113.7, 111.7, 56.4, 55.6, 53.3; HRMS m/z calculated for $C_{17}H_{16}O_5H^+$ [M + H$^+$] 301.1071, found 301.1072.

Methyl 5-benzoyl-2-(methoxymethoxy)benzoate (8). General method with methyl 5-iodo-2-(methoxymethoxy)benzoate (161.0 mg, 0.50 mmol) and phenylboronic acid (91.4 mg, 0.75 mmol). Flash column chromatography (0–5% EtOAc/CH_2Cl_2) gave 101.4 mg (68% yield) of the title compound as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, 1H, J = 2.3 Hz), 7.92 (dd, 1H, J = 8.7, 2.3 Hz), 7.76–7.73 (m, 2H), 7.58–7.54 (m, 1H), 7.48–7.44 (m, 2H), 7.27 (d, 1H, J = 8.8 Hz), 5.32 (s, 2H), 3.87 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.7, 165.8, 159.8, 137.5, 135.3, 133.9, 132.4, 130.6, 129.8, 128.4, 121.0, 115.2, 94.7, 56.6, 52.3; HRMS m/z calculated for $C_{17}H_{16}O_5H^+$ [M + H$^+$] 301.1071, found 301.1070.

Dibenzo[*b*,*d*]furan-4-yl(4-methoxyphenyl)methanone (9). General method with 4-iodoanisole (117.0 mg, 0.50 mmol) and dibenzo[*b*,*d*]furan-4-ylboronic acid (116.6 mg, 0.75 mmol). Flash column chromatography (5% EtOAc/pentane) gave 88.9 mg (59% yield) of the title compound as a colorless solid: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (dd, 1H, J = 7.7, 1.2 Hz), 8.00–7.97 (d, 1H), 7.92 (d, 2H, J = 9.0 Hz), 7.68 (dd, 1H, J = 7.6, 1.3 Hz), 7.54 (d, 1H, J = 8.2 Hz), 7.48–7.42 (m, 2H), 7.39–7.35 (m, 1H), 8.96 (d, 2H, J = 8.9 Hz), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 192.6, 163.9, 156.4, 153.7, 132.8, 130.4, 128.3, 127.8, 125.5, 123.9, 123.7, 123.5, 123.2, 122.6, 120.8, 113.7, 112.2, 55.6; HRMS m/z calculated for $C_{20}H_{14}O_3H^+$ [M + H$^+$] 303.1016, found 303.1018.

(4-Methoxyphenyl)(phenyl)methanone[21] (10). General method with 4-iodoanisole (117.0 mg, 0.50 mmol) and phenylboronic acid (91.4 mg, 0.75 mmol). Flash column chromatography (50% CH_2Cl_2/pentane) gave 98.3 mg (93% yield) of the title compound as a colorless solid: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (d, 2H, J = 8.9 Hz), 7.77–7.74 (m, 2H), 7.58–7.54 (m, 1H), 7.49–7.44 (m, 2H), 6.96 (d, 2H, J = 8.9 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.6, 163.3, 138.3, 132.6, 131.9, 130.2, 129.8, 128.2, 113.6, 55.5; HRMS m/z calculated for $C_{14}H_{12}O_2H^+$ [M + H$^+$] 213.0910, found 213.0911.

[^{13}C]-(4-Methoxyphenyl)(phenyl)methanone (^{13}C-10). General method with 4-iodoanisole (117.0 mg, 0.50 mmol) and phenylboronic acid (91.4 mg, 0.75 mmol). ^{13}C-labeled 9-methyl-fluorene-9-carbonyl chloride (182.8 mg, 0.75 mmol) in chamber B. Flash column

chromatography (50% CH_2Cl_2/pentane) gave 96.7 mg (91% yield) of the title compound as colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85−7.80 (m, 2H), 7.76−7.73 (m, 2H), 7.57−7.54 (m, 1H), 7.48−7.44 (m, 2H), 6.96 (d, 2H, J = 8.8 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.6 (^{13}C), 163.3, 138.4 (d, J = 54.0 Hz), 132.6 (d, J = 3.0 Hz), 132.0, 130.2 (d, J = 57.0 Hz), 129.8 (d, J = 3.0 Hz), 128.3 (d, J = 4.0 Hz), 113.6 (d, J = 4.0 Hz), 55.6; HRMS m/z calculated for $C_{13}{}^{13}CH_{12}O_2H^+$ [M + H$^+$] 214.0944, found 214.0947.

(2,4-Dimethoxyphenyl)(4-methoxyphenyl)methanone[24] (11). General method with iodo-2,4-dimethoxybenzene (132.0 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (114.0 mg, 0.75 mmol). Flash column chromatography (30% EtOAc/toluene) gave 107.1 mg (79% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (d, 2H, J = 9.0 Hz), 7.34 (d, 1H, J = 8.4 Hz), 6.90 (d, 2H, J = 9.0 Hz), 6.55−6.51 (m, 2H), 3.86−3.86 (m, 6H), 3.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.3, 163.2, 162.9, 159.1, 132.1, 131.5, 131.4, 121.9, 113.3, 104.5, 98.8, 55.6, 55.5, 55.4; HRMS m/z calculated for $C_{16}H_{16}O_4Na^+$ [M + Na$^+$] 295.0941, found 295.0946.

(2-Aminophenyl)(phenyl)methanone[25] (12). General method with 2-iodoaniline (109.5 mg, 0.50 mmol) and phenylboronic acid (67.1 mg, 0.55 mmmol). Flash column chromatography (CH_2Cl_2) gave 81.2 mg (71% yield) of the title compound as a yellow solid. Repeating this reaction on a 6 mmol scale afforded **12** in an isolated yield of 82%: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66−7.63 (m, 2H), 7.55−7.50 (m, 1H), 7.48−7.43 (m, 3H), 7.29 (ddd, 1H, J = 8.3, 7.1, 1.6 Hz), 6.74 (ddd, 1H, J = 8.2, 1.1, 0.3 Hz), 6.60 (ddd, 1H, J = 9.16, 7.1, 1.1 Hz), 6.10 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 199.2, 151.0, 140.2, 134.7, 134.3, 131.1, 129.2, 128.2, 118.3, 117.1, 115.6; HRMS m/z calculated for $C_{13}H_{11}NOH^+$ [M + H$^+$] 198.0913, found 198.0915.

1,4-Dibenzoylbenzen[26] (13). General method with 1,4-diiodobenzene (82.5 mg, 0.25 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol). Flash column chromatography (CH_2Cl_2). This gave 50.4 mg (70% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 7.89 (s, 4H), 7.86−7.83 (m, 4H), 7.65−7.60 (m, 2H), 7.53−7.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.1, 140.8, 137.0, 133.1, 130.2, 129.8, 128.6; HRMS m/z calculated for $C_{20}H_{14}O_2H^+$ [M + H$^+$] 287.1067, found 287.1068.

(4-Aminophenyl)(4-methoxyphenyl)methanone[27] (14). General method with 4-iodoaniline (109.5 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (114.0 mg, 0.75 mmol). Flash column chromatography (10% EtOAc/CH_2Cl_2) gave 76.8 mg (68% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 (d, 2H, J = 8.9 Hz), 7.67 (d, 2H, J = 8.6 Hz), 6.94 (d, 2H, J = 8.9 Hz), 6.65 (d, 2H, J = 8.7 Hz), 4.21 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.4, 162.5, 150.8, 132.7, 132.0, 131.4, 127.9, 113.7, 113.4, 55.5; HRMS m/z calculated for $C_{14}H_{13}NO_2Na^+$ [M + Na$^+$] 250.0838, found 250.0838.

***tert*-Butyl 4-(4-chlorobenzoyl)phenylcarbamate (15).** General method with *tert*-butyl 4-iodophenylcarbarbamate (159.6 mg, 0.50 mmol) and 4-chlorophenylboronic acid (86.0 mg, 0.55 mmol). Flash column chromatography (5% EtOAc/pentane) gave 130.9 mg (79% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76 (d, 2H, J = 8.8 Hz), 7.70 (d, 2H, J = 8.7 Hz), 7.49 (d, 2H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.7 Hz), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.5, 152.2, 142.8, 138.5, 136.3, 131.7, 131.4, 131.2, 128.5, 117.4, 81.4, 28.3; HRMS m/z calculated for $C_{18}H_{18}ClNO_3Na^+$ [M + Na$^+$] 354.0867, found 354.0872.

(4-Amino-3,5-dichlorophenyl)(4-*tert*-butylphenyl)-methanone (16). General method with 2,6-dichloro-4-iodoaniline (144.0 mg, 0.50 mmol) and 4-*tert*-butyl phenylboronic acid (97.9 mg, 0.55 mmol). Flash column chromatography (30% CH_2Cl_2/pentane) gave 119.1 mg (74% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 (s, 2H), 7.68 (d, 2H, J = 8.6 Hz), 7.50 (d, 2H, J = 8.6 Hz), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.1, 156.0, 143.9, 134.9, 130.5, 129.7, 127.6, 125.5, 118.7, 35.2, 31.3; HRMS m/z calculated for $C_{17}H_{17}Cl_2NOH^+$ [M + H$^+$] 322.0760, found 322.0762.

***(E)*-4-(4-*tert*-Butylbenzoyl)-2-(phenyldiazenyl)phenyl acetate (17).** General method with (*E*)-4-iodo-2-(phenyldiazenyl)phenyl acetate (183.1 mg, 0.50 mmol) and 4-*tert*-butyl phenylboronic acid (97.9 mg, 0.55 mmol). Flash column chromatography (CH_2Cl_2) gave 100.5 mg (50% yield) of the title compound as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.13−8.10 (m, 2H), 7.92−7.87 (m, 2H), 7.80−7.78 (m, 2H), 7.54−7.45 (m, 5H), 7.38−7.35 (m, 1H) 2.02 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.9, 169.1, 157.3, 152.5, 150.5, 149.8, 134.5, 132.6, 131.6, 130.1, 129.3, 125.8, 125.7, 125.3, 124.2, 123.1, 35.4, 31.2, 20.7; HRMS m/z calculated for $C_{25}H_{24}N_2O_3H^+$ [M + H$^+$] 401.1860, found 401.1865.

2-(4-Vinylbenzoyl)phenyl 4-methylbenzenesulfonate (18). General method with 2-iodophenyl 4-methylbenzenesulfonate (187.1 mg, 0.50 mmol) and 4-vinylphenylboronic acid (111.0 mg, 0.75 mmol). Flash column chromatography (CH_2Cl_2) gave 99.2 mg (52% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (d, 2H, J = 1.8 Hz), 7.55−7.50 (m, 1H), 7.46 (d, 2H, J = 8.4 Hz), 7.43−7.34 (m, 5H), 7.11 (d, 2H, J = 8.0 Hz), 6.75 (dd, 1H, J = 17.6, 10.9 Hz), 5.88 (d, 1H, J = 17.6 Hz), 5.41 (d, 1H, J = 10.9 Hz), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 192.6, 146.5, 145.6, 142.3, 136.0, 135.9, 133.2, 132.1, 132.0, 130.6, 130.5, 129.7, 128.5, 127.0, 126.0, 124.0, 117.1, 21.8; HRMS m/z calculated for $C_{22}H_{18}O_4H^+$ [M + H$^+$] 379.0999, found 379.1001.

(4-Chlorophenyl)(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)-methanone (19). General method with 2-(4-iodophenyl)-2-methyl-1,3-dioxolane (145.0 mg, 0.50 mmol) and 4-chlorophenylboronic acid (86.0 mg, 0.55 mmol). Flash column chromatography (CH_2Cl_2) gave 122.3 mg (81% yield) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76−7.72 (m, 4H), 7.59 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz), 4.10−4.01 (m, 2H), 3.82−3.74 (m, 2H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.2, 148.2, 139.0, 136.8, 135.9, 131.5, 130.1, 128.7, 125.5, 108.6, 64.7, 27.6; HRMS m/z calculated for $C_{17}H_{15}ClO_3H^+$ [M + H$^+$] 303.0782, found 303.0783.

[^{13}C]-(4-Chlorophenyl)(4-(2-methyl-1,3-dioxolan-2-yl)-phenyl)methanone (^{13}C-19). General method with 2-(4-iodophenyl)-2-methyl-1,3-dioxolane (145.0 mg, 0.50 mmol) and 4-chlorophenylboronic acid (86.0 mg, 0.55 mmol). ^{13}C-labeled 9-methyl-fluorene-9-carbonyl chloride in chamber B. Flash column chromatography (CH_2Cl_2) gave 116.0 mg (76% yield) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76−7.72 (m, 4H), 7.59 (d, 2H, J = 8.6), 7.44 (d, 2H, J = 8.6), 4.10−4.01 (m, 2H), 3.83−3.74 (m, 2H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.1 (^{13}C), 148.3, 139.0, 136.9 (d, J = 55.0 Hz), 135.9 (d, J = 55.0 Hz), 131.5 (d, J = 3.0 Hz), 130.1 (d, J = 3.0 Hz), 128.7 (d, J = 4.0 Hz), 125.5 (d, J = 4.0 Hz), 108.6, 64.7, 27.6; HRMS m/z calculated for $C_{16}{}^{13}CH_{15}ClO_3H^+$ [M + Na$^+$] 304.0816, found 304.0817.

Thiophen-2-yl (*p*-tolyl)methanone[28] (20). General method with 2-iodothiophene (105.0 mg, 0.50 mmol) and *p*-tolylboronic acid (74.8 mg, 0.55 mmol). Flash column chromatography (50% CH_2Cl_2/pentane) gave 71.5 mg (71% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.79 (d, 2h, J = 8.1 Hz), 7.70 (dd, 1H, J = 4.9, 1.1 Hz), 7.64 (dd, 1H, J = 3.8, 1.1 Hz), 7.31−7.28 (m, 2H), 7.17−7.14 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 188.1, 143.9, 143.2, 135.5, 134.6, 134.0, 129.5, 129.2, 128.0, 21.8; HRMS m/z calculated for $C_{12}H_{10}OSH^+$ [M + H$^+$] 203.0525, found 203.0524.

***N*-(5-Benzoylpyridin-2-yl)cyclopropanecarboxamide (21).** General method with *N*-(5-iodopyridin-2-yl)cyclopropanecarboxamide (144.0 mg, 0.50 mmol) and phenylboronic acid (67.1 mg, 0.55 mmol). Flash column chromatography (20% EtOAc/pentane) gave 93.5 mg (70% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.73 (d, 1H, J = 1.7 Hz), 8.62 (br, 1H), 8.32 (d, 1H, J = 8.7 Hz), 8.15 (dd, 1H, J = 8.7, 2.3 Hz), 7.79−7.77 (m, 2H), 7.62 (m, 1H), 7.53−7.49 (m, 2H), 1.64−1.58 (m, 1H), 1.17−1.13 (m, 2H), 0.97−0.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.1, 172.8, 154.1, 150.6, 140.5, 137.3, 132.9, 129.9, 129.1, 128.7, 113.0, 16.2, 9.1; HRMS m/z calculated for $C_{16}H_{14}N_2O_2Na^+$ [M + Na$^+$] 289.0947, found 289.0950.

[^{13}C]-*N*-(5-Benzoylpyridin-2-yl)cyclopropanecarboxamide (^{13}C-21). General method with *N*-(5-iodopyridin-2-yl)-cyclopropanecarboxamide (144.0 mg, 0.50 mmol) and phenylboronic acid (67.1 mg, 0.55 mmol). ^{13}C-Labeled 9-methyl-fluorene-9-carbonyl chloride in chamber B. Flash column chromatography (20% EtOAc/

pentane) gave 105.6 mg (79% yield) of the title compound as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.73 (s, 1H), 8.66 (s, 1H), 8.32 (d, 1H, J = 8.3 Hz), 8.16−8.14 (m, 1H), 7.79−7.76 (m, 2H), 7.61 (t, 1H, J = 7.4 Hz), 7.50 (t, 2H, J = 7.4 Hz), 1.66−1.58 (m, 1H), 1.17−1.13 (m, 2H), 0.97−0.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.0 (^{13}C), 172.8, 154.1, 150.4 (d, J = 4.0 Hz), 140.5 (d, J = 3.0 Hz), 137.3 (d, J = 55.0 Hz), 132.9, 129.9 (d, J = 3.0 Hz), 129.1 (d, J = 57.0 Hz), 128.7 (d, J = 4.0 Hz), 113.0 (d, J = 3.0 Hz), 16.2, 9.1; HRMS m/z calculated for $C_{15}{}^{13}CH_{14}N_2O_2Na^+$ [M + Na$^+$] 290.0981, found 290.0985.

(6-Methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)(4-methoxyphenyl)methanone[29] (22). General method with 3-iodo-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]-thiophene (198.1 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (63.6 mg, 0.55 mmol). Flash column chromatography (10−40% EtOAc/pentane) gave 139.2 mg (67% yield) of the title compound as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (d, 2H, J = 8.9 Hz), 7.53 (d, 1H, J = 8.9 Hz), 7.35 (d, 2H, J = 8.8 Hz), 7.31 (d, 1H, J = 2.4 Hz), 6.96 (dd, 1H, J = 8.9, 2.4 Hz), 6.76 (dd, 2H, J = 9, 2.5 Hz), 3.88 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.4, 163.8, 159.9, 157.8, 142.6, 140.2, 134.1, 132.5, 130.7, 130.5, 130.4, 126.2, 124.2, 114.9, 114.2, 113.8, 104.6, 55.8, 55.5, 55.4; HRMS m/z calculated for $C_{24}H_{20}O_4SNa^+$ [M + Na$^+$] 427.0975, found 427.9080.

(2-Amino-5-chlorophenyl)(phenyl)methanone[30] (23). 4-Chloro-2-iodoaniline (133.7 mg, 0.50 mmol), phenylboronic acid (67.0 mg, 0.55 mmol), $PdCl_2$ (17.7 mg, 0.1 mmol) and K_2CO_3 (207.3 mg, 1.50 mmol) were added to chamber A of a COware system. 9-Methyl-fluorene-9-carbonyl chloride (182.0 mg, 0.75 mmol), P(tBu)$_3$HBF$_4$ (10.9 mg, 0.0375 mmol) and $PdCl_2$(cod) (21.4 mg, 0.05 mmol) were added to chamber B. To both chambers anisole (3.0 mL) was added before DIPEA (260 μL, 1.5 mmol) was added to chamber B, and both chambers were fitted with a Teflon-sealed screwcap. The reaction was heated overnight at 120 °C. The crude was evaporated onto silica gel and purified by flash column chromatography (1:1 pentane/CH_2Cl_2 to dichloromethane). This gave 73.3 mg (63% yield) of the title compound as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (dd, 2H, J = 7.5, 0.6 Hz), 7.57−7.53 (m, 1H), 7.47 (t, 2H, J = 7.9 Hz,), 7.41 (d, 1H, J = 2.5 Hz), 7.23 (ddd, 1H, J = 8.8, 2.5, 0.6 Hz), 6.68 (d, 1H, J = 8.8 Hz), 6.09 (b, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.0, 149.4, 139.3, 134.2, 133.2, 131.5, 129.1, 128.3, 119.9, 118.7, 118.5; HRMS $C_{13}H_{10}ClNO$ [M + H$^+$]; calculated 232.0524, found 232.0525.

(2-Amino-5-chlorophenyl)(phenyl)methanone (^{13}C-23). 4-Chloro-2-iodoaniline (133.7 mg, 0.50 mmol), phenylboronic acid (67.0 mg, 0.55 mmol), $PdCl_2$ (17.7 mg, 0.1 mmol), and K_2CO_3 (207.3 mg, 1.50 mmol) were added to chamber A of a COware system. ^{13}C-Labeled 9-methyl-fluorene-9-carbonyl chloride (182.0 mg, 0.75 mmol), P(tBu)$_3$HBF$_4$ (10.9 mg, 0.0375 mmol) and $PdCl_2$(cod) (21.4 mg, 0.075 mmol) were added to chamber B. To both chambers anisole (3.0 mL) was added before DIPEA (260 μL, 1.5 mmol) was added to chamber B, and both chambers were fitted with a Teflon-sealed screwcap. The COware was heated overnight at 120 °C. The crude was A was evaporated on silica gel and purified by flash column chromatography (1:1 pentane/CH_2Cl_2 to CH_2Cl_2). This gave 78.9 mg (68% yield) of the title compound as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65−7.62 (m, 2H), 7.56 (t, 1H, J = 8.7 Hz), 7.48 (t, 2H, J = 7.4 Hz), 7.43−7.41 (m, 1H), 7.26−7.21 (m, 1H), 6.68 (dt, 1H, J = 8.8, 1.0 Hz), 6.09 (b, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.0 (^{13}C), 149.4, 139.4 (d, J = 54.7 Hz), 134.2, 133.2 (d, J = 5.0 Hz), 131.5, 129.1 (d, J = 3.0 Hz), 128.3 (d, J = 5.0 Hz), 119.9 (d, J = 7.0 Hz), 118.7 (d, J = 55.0 Hz), 118.5 (d, J = 3.0 Hz); HRMS $C_{12}{}^{13}C$ $H_{10}ClNO$ [M + H$^+$]; calculated 233.0557, found 233.0557.

7-Chloro-5-phenyl-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one[31] (24). Sodium bicarbonate (266.5 mg, 3.20 mmol) was added to **23** (350.0 mg, 1.50 mmol) in chloroform (5 mL). The reaction was cooled to 0 °C, and bromoacetyl bromide (160 μL, 1.81 mmol) in chloroform (0.8 mL) was added dropwise. The reaction was stirred overnight. The reaction was quenched with ice−water, separated, extracted with chloroform, washed with water and sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated in vacuo. The concentrate was dissolved in chloroform and added to saturated ammonia in methanol (0.75 mL) at 0 °C. The reaction mixture was gradually warmed to rt and heated to reflux overnight. The reaction was cooled, concentrated in vacuo, and purified by flash column chromatography (2:0.5:7.5−3:4:3 CH_2Cl_2/ethyl acetate/pentane). The solid was recrystallized in benzene. This gave 212.2 mg (55% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.62 (s, 1H), 7.54−7.51 (m, 2H), 7.49−7.44 (m, 2H), 7.42−7.36 (m, 2H), 7.30 (d, 1H, J = 2.4), 7.15 (d, 1H, J = 8.64), 4.33 (b, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.0, 169.8, 138.8, 137.4, 131.8, 130.7, 130.6, 129.6, 128.8, 128.5, 128.4, 122.7, 56.6; HRMS $C_{15}H_{11}ClN_2O$ [M + H$^+$]; calculated 271.0633, found 271.0632.

[^{13}C]-7-Chloro-5-phenyl-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (^{13}C-24). Sodium bicarbonate (30.3 mg, 0.36 mmol) was added to **^{13}C-23** (40.0 mg, 0.17 mmol) in chloroform (1 mL). The reaction was cooled to 0 °C, and bromoacetyl bromide (17.0 μL, 0.21 mmol) in chloroform (0.2 mL) was added dropwise. The reaction was stirred overnight. The reaction was quenched with ice−water, separated, extracted with chloroform, washed with water and sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated in vacuo. The concentrate was added to a closed vial and dissolved in chloroform. Saturated ammonia in methanol (0.68 mL, 4.74 mmol) taken directly from the freezer was added. The closed vial was warmed to 60 °C and left overnight. The product was purified by flash column chromatography (4:1:15−3:4:3 CH_2Cl_2/ethyl acetate/pentane) and (9:1 CH_2Cl_2/ethyl acetate/pentane to ethyl acetate). The product was again attempted to purify by flash column chromatography with Al_2O_3 (1:3:6 + 1 ‰ triethyl amine CH_2Cl_2/acetone/pentane − acetone + 1 ‰ triethylamine). This gave 29.2 mg (63% yield) of the title compound as a colorless solid. ^{13}C NMR shows two minor carbon-impurities at 198.9 and 197.5 (both unidentified): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.73 (s, 1H), 7.52−7.39 (m, 6H), 7.31 (dd, 1H, J = 2.44, 2.08 Hz), 7.10 (dd, 1H, J = 8.64, 0.68 Hz), 4.33 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 169.8 (^{13}C), 138.9 (d, J = 62.1 Hz), 137.4, 131.8, 130.7 (d, J = 2.4 Hz), 130.6, 129.6, 128.9 (d, J = 4.8 Hz), 128.6 (d, J = 50.1 Hz), 128.5 (d, J = 4.2 Hz), 122.8, 56.7; HRMS $C_{14}{}^{13}CH_{11}ClN_2O$ [M + H$^+$]; calculated 272.0666, found 272.0670.

Isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate[3] (26). General method with isopropyl 2-(4-iodophenoxy)-2-methylpropanoate (174.1 mg, 0.50 mmol) and *p*-chlorophenylboronic acid (86.0 mg, 0.55 mmol). Flash column chromatography (10−100% CH_2Cl_2/pentane) gave 153.4 mg (84% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73 (d, 2H, J = 8.9 Hz), 7.70 (d, 2H, J = 8.7 Hz), 7.45 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.9 Hz), 5.09 (hep, 1H, J = 6.3 Hz), 1.66 (s, 6H), 1.20 (d, 6H, J = 6.3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 194.5, 173.3, 160.0, 138.6, 136.7, 132.2, 131.4, 130.5, 128.8, 117.5, 79.7, 69.6, 25.7, 21.8; HRMS $C_{20}H_{21}ClO_4$ [M+Na$^+$]; calculated 383.1021, found 383.1021.

[^{13}C]-Isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (^{13}C-26). General method with isopropyl 2-(4-iodophenoxy)-2-methylpropanoate (174.1 mg, 0.50 mmol) and *p*-chlorophenylboronic acid (86.0 mg, 0.55 mmol). ^{13}C-Labeled 9-methyl-fluorene-9-carbonyl chloride in chamber B. Flash column chromatography (10−100% CH_2Cl_2/pentane) gave 155.2 mg (85% yield) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74−7.68 (m, 4H), 7.44 (d, 2H, J = 8.3 Hz), 6.86 (d, 2H, J = 8.7 Hz), 5.08 (hep, 1H, J = 6.2 Hz), 165.7 (s, 6H), 1.20 (d, 6H, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.4 (^{13}C), 173.2, 159.9, 138.5, 136.6 (d, J = 55.0 Hz), 132.1 (d, J = 3.0 Hz), 131.3 (d, J = 3.0 Hz), 130.3 (d, J = 57.0 Hz), 128.7 (d, J = 2.0 Hz), 117.4 (d, J = 4.0 Hz), 79.6, 69.5, 25.5, 21.7; HRMS $C_{19}{}^{13}CH_{21}ClO_4$ [M+Na$^+$]; calculated 384.1054, found 384.1058.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra for the Suzuki−Miyaura coupling products and nordazepam. 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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