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Carbonylative Suzuki Couplings of Aryl Bromides with Boronic Acid Derivatives under Base-Free Conditions

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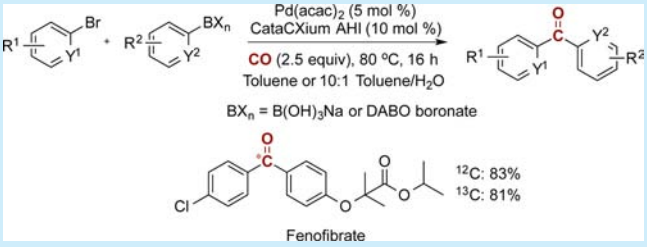
Supporting Information

ABSTRACT: The carbonylative Suzuki–Miyaura reaction between aryl bromides and arylboronic acid equivalents is herein reported, using base-free conditions and a limited excess of carbon monoxide generated *ex situ* from stable CO-precursors. Under these conditions, unsymmetrical biaryl ketones were obtained in modest to excellent yields. This method was adapted to the synthesis of the triglyceride and cholesterol regulator drug, fenofibrate, and its ^{13}C-labeled derivative in good yields from the appropriate CO-precursor.



The palladium-catalyzed carbonylative Suzuki–Miyaura reaction represents a viable three-component coupling protocol for rapid access to unsymmetrical benzophenones.[1,2] Such structures are key components in a variety of important pharmaceuticals including Tricor,[3] Sector,[4] and Evistor,[5] in addition to being a masked but essential fragment in the benzodiazepine family. Furthermore, benzophenones have other useful applications such as sun blockers and photo-initiators in UV-curing inks.

Although there is now considerable literature precedence for this carbonylative transformation, the majority of the work has been carried out with iodides. Only a handful of reports focus on the use of the more challenging aryl bromides as viable substrates,[6] and in all cases these transformations were carried out with boronic acids as the nucleophilic coupling partner and in the presence of an organic or inorganic base. With the considerable advances in the development and application of stable, crystalline borate salts and boronic acid derivatives,[7] we considered whether these would be useful coupling partners for this carbonylation reaction with aryl bromides. In this report, we demonstrate the successful identification of a catalytic system that promotes the coupling of (hetero)aryl bromides with (hetero)aryl trihydroxyborates or DABO boronates (2,8-dioxa-5-aza-1-borabicyclo[3.3.0]octanes). The process was performed in a two-chamber reactor with *ex situ* generated carbon monoxide, thereby avoiding the handling of this toxic but useful diatomic gas. Furthermore, all the carbonylation reactions were carried out in the absence of base.

In previous work, we described a simple, alternative setup for performing Pd-catalyzed carbonylation reactions without the need of a CO cylinder.[8] The method relies on the use of carbon monoxide releasing molecules (CORMs), which upon activation provide a desired quantity of CO from one chamber into another in which the actual carbonylation reaction takes place. The experimental outline illustrated in Scheme 1 relies on the use of the acid chloride, **COgen** (9-methyl-9*H*-fluorene-9-carbonyl chloride), as a solid CO precursor. This setup was also applied to the development of an air-tolerant carbonylative Suzuki coupling, although the method was only adaptable for aryl iodides.[9]

In our examination of the usefulness of aryl bromides for this carbonylative coupling, preliminary experiments were carried out between potassium phenyltrifluoroborate[10] and *p*-bromoacetophenone. Although a range of experimental conditions were tested, including numerous Pd(0) and Pd(II) sources, phosphine ligands, and solvents, poor conversions, precipitation of palladium black, and competitive diaryl formation were observed for all cases. More successful were alternative aryl borate salts such as sodium phenyltrihydroxyborate.[11] With these borate derivatives, neither base nor water was required for cross-coupling. Initial studies had already demonstrated the usefulness of $Pd(acac)_2$ as the palladium source, and a small ligand screening was therefore undertaken as depicted in Table 1. Tricyclohexylphosphine, which was previously shown to be the ligand of choice in the reductive carbonylation of aryl iodides and bromides using the two-chamber system,[12] also provided some carbonylative coupling to benzophenone **A** (entries 1–3). The conversion was nevertheless low, and a considerable amount of the corresponding biphenyl was produced as a side product. Increasing the catalyst loading from 2 to 5 mol % or the ligand/Pd ratio only had a modest effect.

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Scheme 1. *Ex Situ* Generation of CO in a Two-Chamber System and Application in Pd-Catalyzed Tranformations

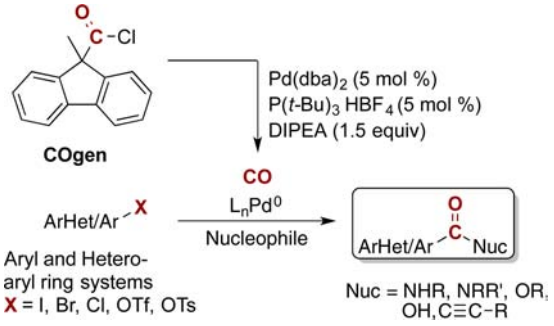
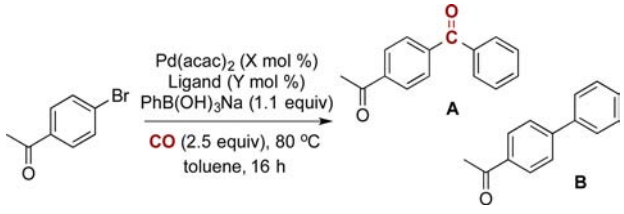


Table 1. Optimization of the Carbonylative Suzuki–Miyaura Reaction with 4-Bromoacetophenone[a]



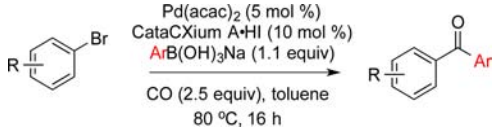
entry	$Pd(acac)_2$ (mol %)	ligand (mol %)	distribution[b] bromide/**A**/**B**
1	2	$Cy_3P{\cdot}HBF_4$ (2)	45:26:29
2	5	$Cy_3P{\cdot}HBF_4$ (5)	38:36:25
3	5	$Cy_3P{\cdot}HBF_4$ (10)	32:45:24
4	5	*i*-$Pr_3P{\cdot}HBF_4$ (10)	19:46:35
5	5	*n*-$Butyl_3P{\cdot}HBF_4$ (10)	85:0:15
6	5	*t*-$Bu_2MeP{\cdot}HBF_4$ (10)	24:46:30
7	5	CataCXium A·HI (10)	**16:82:2**

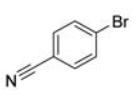
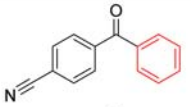
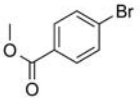
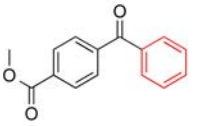
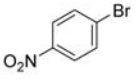
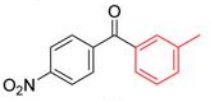
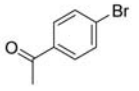
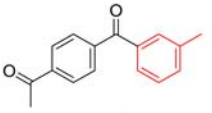
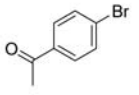
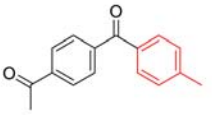
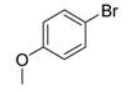
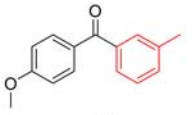
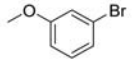
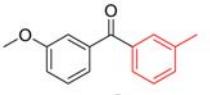
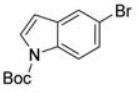
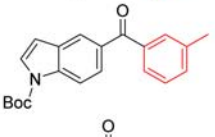
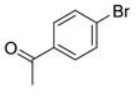
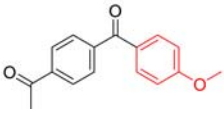
[a]Chamber A: **COgen** (1.25 mmol), $Pd(dba)_2$ (5 mol %), $(t\text{-}Bu)_3P{\cdot}HBF_4$ (5 mol %), DIPEA (1.5 equiv) in toluene (3 mL). Chamber B: *p*-bromoacetophenone (0.5 mmol), potassium phenyl trihydroxyborate (0.55 mmol), $Pd(acac)_2$ (X mol %), ligand (Y mol %), toluene (3 mL). [b]Determined by ^1H NMR.

Of the other trialkylphosphines tested (entries 4–7), only CataCXium A·HI demonstrated its worth, providing a good conversion for the coupling reaction as well as high selectivity for the benzophenone (entry 7), leading to **A** in an 82% isolated yield.[13]

With the reaction conditions for the carbonylative Suzuki reaction with bromides and trihydroxyaryl borates at hand, the generality of the reaction was tested next, the results of which are illustrated in Table 2. The four aryl bromides containing electron-withdrawing groups all furnished acceptable to good yields (entries 1–4). The obtained yields were particularly satisfying considering that CO insertion is generally slow with the electrophilic aromatic ring systems.[14] *Meta*- and *para*-substituents were tolerated on the trihydroxyaryl borate, leading to good yields of the benzophenones (entries 4 and 5). A similar attempt with an *o*-methyl substituent proved troublesome and resulted in a low conversion of 27% (result not shown). Using *m*- or *p*-methoxyphenyl bromide gave good to excellent yields of the benzophenone (entries 6 and 7). A Boc-protected indole bromide was also a good substrate for this carbonylative coupling, yielding an 81% yield of the desired product (entry 8). Lastly, an acceptable yield was obtained with

Table 2. Carbonylative Suzuki–Miyaura Reaction of Aryl Bromides with Aryl Trihydroxyborates[a]



entry	aryl bromide	product	yield (%)[b]
1			64%
2			71%
3			63%
4			83%
5			72%
6			85%
7			90%
8			81%
9			62%

[a]Chamber A: **COgen** (1.25 mmol), $Pd(dba)_2$ (5 mol %), $(t\text{-}Bu)_3P{\cdot}HBF_4$ (5 mol %), DIPEA (1.5 equiv) in toluene (3 mL). Chamber B: *p*-bromoacetophenone (0.5 mmol), potassium phenyltrifluoroborate (0.55 mmol), $Pd(acac)_2$ (0.025 mmol), CataCXium A·HI (0.05 mmol), toluene (3 mL). Prior to addition of solvent the reaction chamber was evacuated three times and placed under an argon atmosphere. [b]Isolated by flash column chromatography.

an electron-donating substituent present on the trihydroxyaryl borate (entry 9).

Unfortunately, the procedure for preparing the trihydroxyarylboronic acid derivatives required dissolving the boronic acids in hot toluene and precipitation with sat. NaOH (aq),[11] a protocol that was not compatible with a range of boronic acids. In particular, heteroarylboronic acids, which were insoluble in hot toluene, led to decomposition. Other boronic acid derivatives were therefore desired, and a search in the literature suggested that DABO boronates could represent viable substrates for this carbonylative coupling. Following the Rychnovsky protocol for the preparation of DABO boronates,

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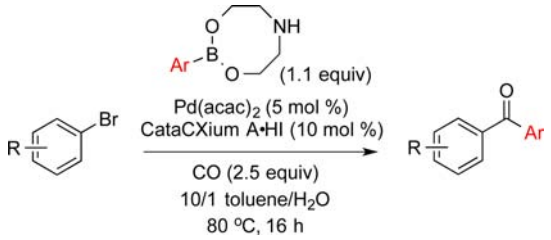
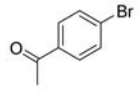
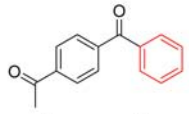
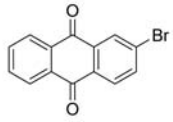
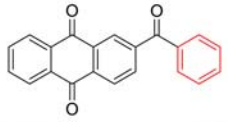
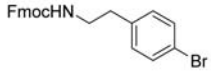
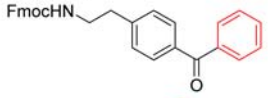
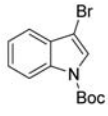
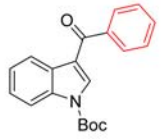
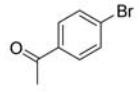
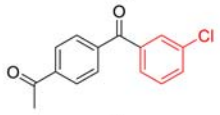
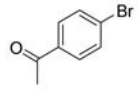
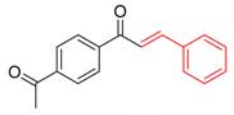
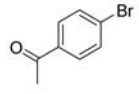
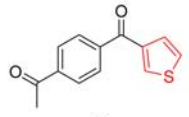
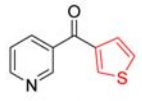
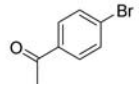
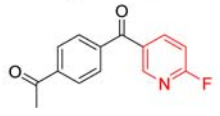
Table 3. Carbonylative Suzuki–Miyaura Reaction of Aryl Bromides with Aryl DABO Boronates[a]

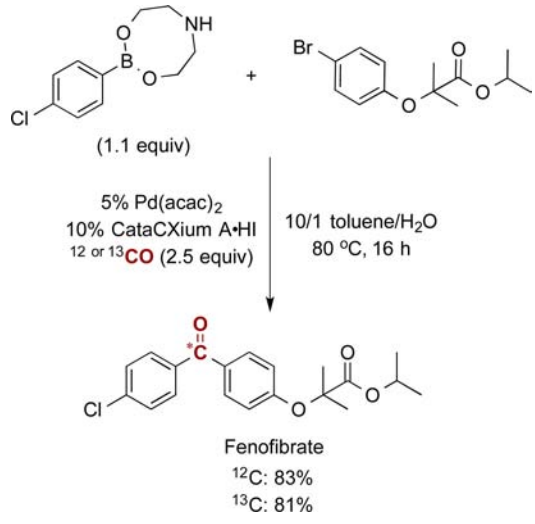


entry	aryl bromide	product	yield (%)[b]
1			95
2			44
3			75
4			77
5			74
6			95
7			74
8			73
9			29

[a]Chamber A: **COgen** (1.25 mmol), $Pd(dba)_2$ (5 mol %), $(t\text{-}Bu)_3P\cdot HBF_4$ (10 mol %), Cy_2NMe (1.5 equiv) in DMF (3 mL). Chamber B: *p*-bromoacetophenone (0.5 mmol), potassium phenyltrifluoroborate (0.55 mmol), $Pd(acac)_2$ (0.025 mmol), CataCXium A·HI (0.05 mmol), toluene (3 mL), H_2O (0.3 mL). CO release for 10 min before heating to 80 °C. [b]Isolated by flash column chromatography.

these coupling partners were readily accessed.[15] Applying the optimized coupling conditions from Table 2 in the reaction of the phenyl DABO boronate with *p*-bromoacetophenone resulted in only trace amounts of product. Nevertheless, the addition of a small quantity of water to the reaction (see Supporting Information) led to a significant improvement, resulting in the formation of the benzophenone in an 81% yield.[16] On the other hand, release of CO at 20 °C and stirring for 10 min prior to heating increased the yield to 95% (Table 3, entry 1).

Scheme 2. Synthesis of Fenofibrate from an Aryl DABO Boronate



Coupling of phenyl DABO boronate with 2-bromoanthracene-9,10-dione furnished a 44% yield of the desired ketone (entry 2), even though the corresponding bromide is relatively electron poor. Because these reaction conditions are base-free, coupling of an aryl bromide carrying the Fmoc-protecting group was possible (entry 3). A Boc-protected 3-bromoindole yielded a similar result, with the ketone being obtained in a 77% isolated yield (entry 4). Three other DABO boronates could equally be coupled successfully to *p*-bromoacetophenone, including a *m*-chlorophenyl, a *trans*-2-styryl, and a thienyl derivative (Table 3, entries 5–7). The 3-thienyl DABO boronate reacted well with 3-bromopyridine, yielding a 73% yield of the diheteroaromatic ketone (entry 8). Finally, the mild conditions used for synthesizing the DABO boronates allowed access to another heteroaromatic boronic derivative with a pyridine core (entry 9), although its coupling with the bromoacetophenone requires further optimization (entry 9).

To highlight the applicability of the developed carbonylative system, we prepared a pharmaceutically relevant benzophenone, fenofibrate (Tricor by Abbott), a triglyceride and cholesterol regulator. As depicted in Scheme 2, coupling of the *p*-chlorophenyl DABO boronate to the appropriately functionalized aryl bromide led to fenofibrate in an 83% yield. Gratifyingly, the ^{13}C-labeled version could be prepared in a similar yield simply by using the readily available ^{13}C-labeled **COgen**.

In summary, two methods have been developed for the synthesis of unsymmetrical aryl ketones by a carbonylative Suzuki–Miyaura cross-coupling with a two-chamber system. Particularly noteworthy, the reaction conditions are suitable for a range of aryl bromides, and the use of either the trihydroxy or the DABO boronates allows these couplings to proceed under base-free conditions. The method has also been demonstrated to be adaptable to the synthesis and site specific isotope labeling of fenofibrate.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data of new compounds. 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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(16) Other boronic acid derivatives were evaluated such as phenyl MIDA boronate, phenyl iminodiacetic acid boronate, and the cyclic sodium phenyl triolborate from 1,1,1-tris(hydroxymethyl)ethane. The latter was the only other derivative to display any reactivity in the presence of water, although only a 30% conversion to product was observed.