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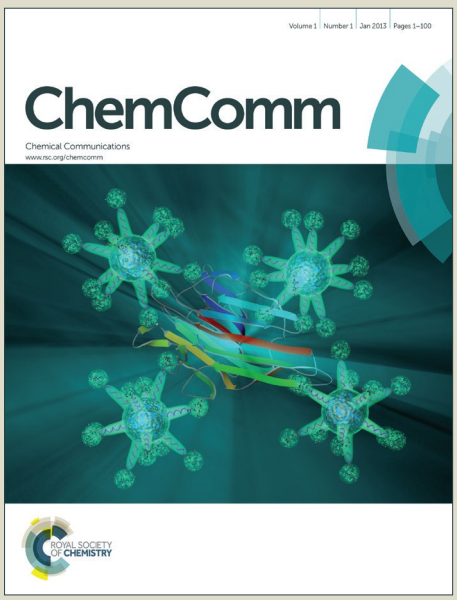

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ARTICLE TYPE

C–H Activation Dependent Pd-Catalyzed Carbonylative Coupling of (Hetero)Aryl Bromides and Polyfluoroarenes**

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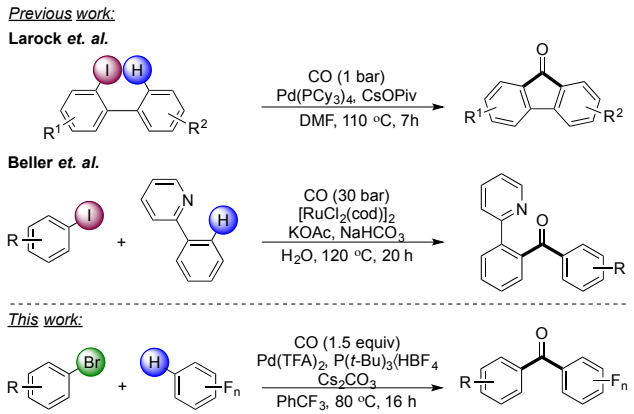
The carbonylative coupling of aryl and heteroaryl bromides with polyfluoroarenes via palladium-catalyzed C−H activation is presented. This transformation proceeds efficiently at moderate reaction temperatures and does not require strong base or reactive intermediates. A near stoichiometric amount of CO is sufficient and the methodology can thus be easily expanded to include the preparation of [^{13}C]-acyl labeled benzopolyfluorophenones.

Introduction

Fluorinated compounds occupy a special place in both material science and the medicinal industry.[1] Currently, there are more than 225 approved fluorinated pharmaceuticals, and the percentage of fluorinated small molecule drugs reaching the market is on a continuous increase.[2] At present, approximately one fifth of newly developed and approved drugs contain fluorine, while fluorinated agrochemicals account for an even larger percentage of known compounds.[3] Installation of polyfluorinated aromatic rings have been less extensively studied than *e.g.* fluorination or trifluoromethylation, which is in contrast to their intriguing chemical properties.[4,5]

In terms of atom economy and waste generation, transition metal catalyzed C−H activation is an appealing alternative to the classical cross coupling reactions, relying on stoichiometric amounts of e.g. organo-zinc, -tin, -boron or -silicon reagents for transmetallation. Consequently, over the last two decades considerable efforts have been allocated to the development of such reactions.[6] Installation of polyfluorinated aromatic rings via C−H activation is even more attractive as the corresponding polyfluorophenyl boronic acids are known to undergo fast protodeborination, rendering this coupling highly challenging.[5b,7]

The majority of the research efforts in the field of transition metal catalyzed C−H activation have been devoted to the study of direct C−C bond formation between two aromatic cores, while reports on 3-component carbonylative couplings are scarce.[8] The limited number of such procedures may be explained by their inherent difficulty as many Pd-catalyzed C−H activation coupling



Scheme 1. Carbonylative couplings relying on C(sp^2)−H activation.

reactions are believed to rely on an initial C−H bond activation by a Pd^{II}-species, which is generally incompatible with the reducing capabilities of carbon monoxide.[9] Nevertheless, in specific cases such C−H activation dependent carbonylative couplings have been demonstrated to be viable reaction pathways. One example is the Pd-catalyzed intramolecular formation of fluorenone-derivatives from *o*-iodobiaryls disclosed by Campo and Larock (Scheme 1).[10] In a different approach, the Gaunt and Yu teams have both reported on the Pd-catalyzed alkyl C−H activation and carbonylation, via nitrogen coordination.[11] All of these transformations rely on an intramolecular C−H activation by palladium,[12] while only a single example of intermolecular carbonylative C−H activation exists. Although highly significant, Beller and coworkers rely on a Ru-catalyst at high reaction temperature and CO pressure, along with a nitrogen directing group in a biaryl system for coupling with aryl iodides.[13]

With the underdeveloped nature of C−H activation dependent carbonylative transformations in mind, we speculated whether polyfluoroarenes could serve as viable and important substrates for such a reaction. Consequently, we set out to develop the first Pd-catalyzed intermolecular carbonylative coupling relying on C−H activation. Despite the lack of precedents for the use of aryl bromides in C−H activation dependent carbonylative transformations, we preferred these substrates because of their

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higher stability, better atom economy and wider commercial availability.

Initiating our investigation starting from 4-bromoanisole (**1a**) and pentafluorobenzene (**2a**), using a catalyst generated from $Pd(OAc)_2$ and PCy_3, and with Cs_2CO_3 as base, provided an 8% NMR yield of the product **3a** (Table 1, entry 1) after 16 h at 80 °C.[14] The major side-product of this and the consecutive reactions in Table 1 was 4-methoxybenzoic acid, even if all reagents were rigorously dried and the reaction was setup in a glovebox under argon. Changing the base away from Cs_2CO_3 only resulted in trace formation of **3a** (entries 2 and 3), while cataCXium A as ligand proved marginally better than PCy_3 (entry 4). Pd-catalysts ligated by the highly bulky P(*t*-Bu)$_3$ have previously been found to perform well under carbonylative conditions.[15] This was also the case for this transformation as **3c** was formed in 17% NMR yield using this ligand (entry 5). XantPhos is a privileged ligand for carbonylation chemistry, but in this reaction no conversion into product was observed when this ligand was used (entry 6).[16]

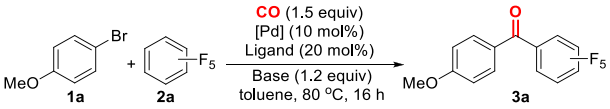
Keeping P(*t*-Bu)$_3$ as the supporting ligand, the Pd-source was next varied and found to have a profound effect. Only the corresponding acid was formed in yields ranging from 18-62% when using $Pd(dba)_2$, $Pd(acac)_2$ or $Pd(COD)Cl_2$ (entries 7-9). Pleasingly, the application of $Pd(TFA)_2$ (palladium(II) trifluoroacetate) afforded the product and in a markedly improved NMR yield of 30% (entry 10). Increasing the amount of base to 2.15 equivalents boosted the NMR yield to 48% (entry 11), while simultaneously applying 4.0 equivalents of **2a** provided a satisfactory 72% yield of **3a** (entry 12). Changing solvent to α,α,α-trifluorotoluene ensured slightly increased yield (entry 13).

With suitable reaction conditions identified for the carbonylative coupling of aryl bromides and pentafluorobenzene via C−H activation at hand, we set out to probe the scope of this transformation (Scheme 2). Initially **3a** was isolated in a 72% yield, demonstrating good correspondence with the NMR yield observed. Applying the corresponding aryl iodide as starting material for the transformation gave a similar yield, albeit under slightly altered conditions to improve the product to acid ratio. Moving the methoxy-substituent to the *meta*-position, thus creating a more electron poor aryl bromide, cause a slight reduction in yield as 61% of **3b** could be isolated. While *ortho*-functionalized substrates have often proved challenging in carbonylative couplings,[15b,16c] 2-bromoanisole reacted smoothly to provide product **3c** in an 58% isolated yield, with no observation of benzofuran-3(2H)-one arising from intramolecular C−H activation.

A methyl-substituent is also well tolerated, with only minor variations in yield over the *para*-, *meta*- and *ortho*-substituted products **3d**, **3e** and **3f**, respectively. Coupling simple bromobenzene afforded **3g** in only a 34% yield, with significant formation of benzoic acid, while reducing the reaction temperature to 70 °C raised the yield to a synthetically useful 43%. This effect was also observed in the formation of **3h**, which was generated in 37% yield after 16 h at a slightly reduced reaction temperature. With a phenoxy-substituent in the *para*-position, the product **3i** could be isolated in a 53% yield, while the more electron donating *N*,*N*-dimethylamine-substituent ensured the isolation of **3j** in a 71% yield. Di- and tri-substituted aryl bromide also coupled efficiently under the optimized conditions to afford **3k** and **3l** in 55% and 50% yield, respectively.

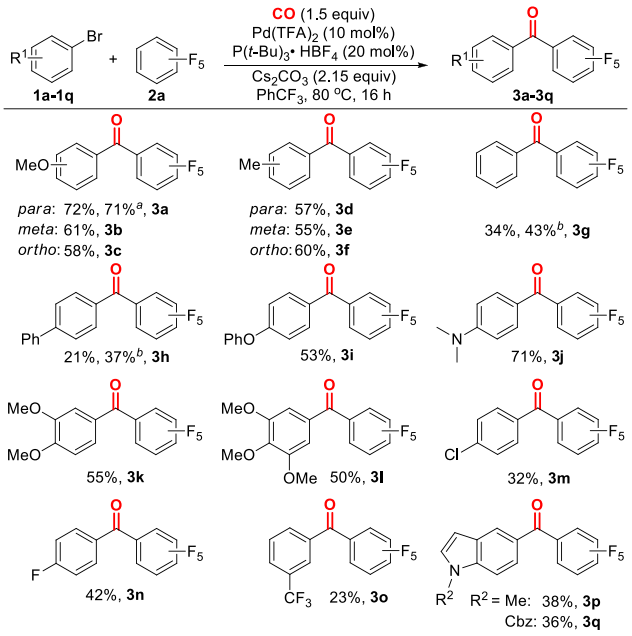
Tolerance towards other halides on the aryl bromide ring was demonstrated by the synthesis of compound **3m** and **3n**, the former allowing for post coupling modification by e.g. Suzuki or Buchwald-Hartwig coupling of the aryl chloride.[17] Electron deficient aryl bromides also participate in this carbonylative coupling, albeit generally in reduced yields, as exemplified by **3o**.

Table 1. Optimization of the Pd-catalyzed carbonylative coupling of aryl bromides and pentafluorobenzene via C-H activation.

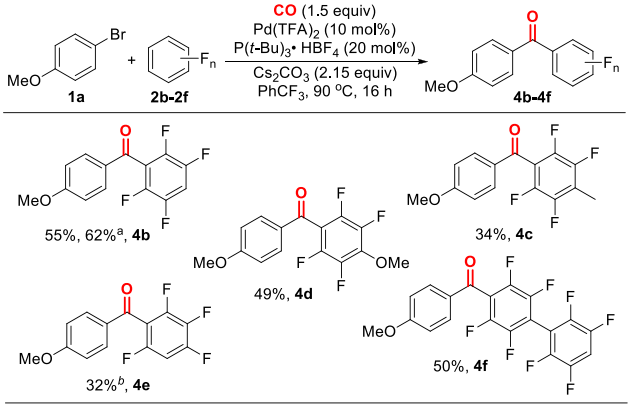


Entry	[Pd]-catalyst	Ligand	Base	Yield[a](%)
1	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	8
2	$Pd(OAc)_2$	PCy_3	K_2CO_3	trace
3	$Pd(OAc)_2$	PCy_3	K_3PO_4	trace
4	$Pd(OAc)_2$	cataCXium A	Cs_2CO_3	9
5	$Pd(OAc)_2$	(*t*-Bu)$_3$P•HBF$_4$	Cs_2CO_3	17
6[b]	$Pd(OAc)_2$	XantPhos	Cs_2CO_3	0
7	$Pd(dba)_2$	(*t*-Bu)$_3$P•HBF$_4$	Cs_2CO_3	0
8	$Pd(acac)_2$	(*t*-Bu)$_3$P•HBF$_4$	Cs_2CO_3	0
9	$Pd(COD)Cl_2$	(*t*-Bu)$_3$P•HBF$_4$	Cs_2CO_3	0
10	$Pd(TFA)_2$	(*t*-Bu)$_3$P•HBF$_4$	Cs_2CO_3	30
11[c]	$Pd(TFA)_2$	(*t*-Bu)$_3$P•HBF$_4$	Cs_2CO_3	48
12[c,d]	$Pd(TFA)_2$	(*t*-Bu)$_3$P•HBF$_4$	Cs_2CO_3	72
13[c,d,e]	$Pd(TFA)_2$	(*t*-Bu)$_3$P•HBF$_4$	Cs_2CO_3	75

[a] ^{1}H-NMR yield using internal standard (1,3,5-trimethoxybenzene). [b] Ligand (10 mol%). [c] Cs_2CO_3(2.13 equiv). [d] **2a** (4.0 equiv). [e] $PhCF_3$ as solvent in both chambers.



Scheme 2. Palladium-catalyzed carbonylative coupling of pentafluorobenzene with various (hetero)aryl bromides, see Supporting Information for details. [a] 4-Iodoanisole (0.50 mmol), **2a** (2.00 mmol), $Pd(OPiv)_2$ (10 mol%), PCy_3 (20 mol%), Cs_2CO_3 (1.08 mmol) and $PhCF_3$(0.5 mL). [b] 70 °C.

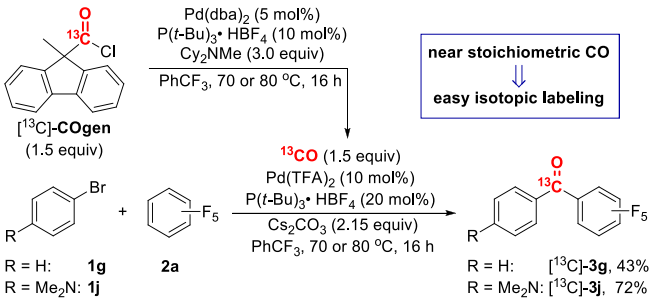


Scheme 3. Palladium-catalyzed carbonylative coupling of 4-bromoanisole with various polyfluoroarenes, see Supporting Information for details. [a] **2** (8.0 equiv). [b] 80 °C.

Nitrogen heterocycles are generally omnipresent in medicinal chemistry, and so the ability of such ring systems to participate in new catalytic reactions is of high importance.[18] To this end, the optimized conditions for this carbonylative coupling reaction did indeed furnish synthetically useful yields of both **3p** and **3q**, displaying an indole ring-system.

We nexted turned our attention towards investigating the scope of the polyfluoroarenes in this reaction (Scheme 3). Generally, these reactions were conducted at 90 °C as conversion of these less fluorinated substrates was more sluggish. Simply substituting the fluorine *para* to the hydrogen for another hydrogen atom caused a moderate drop in the coupling yield (55% yield) to provide **4b**, which could easily be improved to 62% by increasing the amount of polyfluoroarene to 8.0 equivalents. With a methyl- or methoxy-substituent *para* to the reaction site, the reaction provided both **4c** and **4d**, albeit in moderate yields as would be expected from the electron donating properties of the substituents. Applying 1,2,3,5-tetrafluorobenzene to the optimized reaction conditions at 80 °C furnished product **4e** in 32% isolated yield, while elevating the temperature only served to produce more of the corresponding carboxylic acid. Lastly, a polyfluorinated biaryl was subjected to reaction with **1a** to supply benzophenone **4f** in a 50% isolated yield.

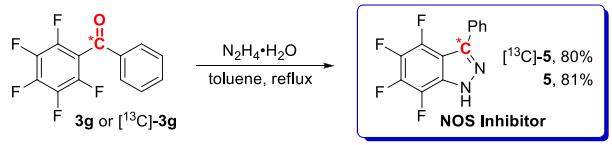
With the slight excess of CO required by this transformation, isotopic carbonyl labeling should be feasible. Applying only 1.5 equivalents of ^{13}[C]-CO generated efficiently from [^{13}C]-COgen, **3g** and **3j** were routinely prepared as their carbonyl isotopically



Scheme 4. Carbonyl labeling of benzopolyfluorophenones via C−H activation of pentafluorobenzene, applying a near stoichiometric amount of ^{13}CO, generated from [^{13}C]-COgen.

labeled version in yields comparable to the unlabeled products (Scheme 4). This isotopic labeling could easily be extended to carbon-14, as radioactive [^{14}C]-COgen has previously been demonstrated to be a viable reagent for carbonyl radiolabeling in a procedure equivalent to the one used for [^{13}C]-COgen.[20]

The applicability of this carbonylative C−H activation methodology was underlined by the synthesis of a biologically relevant compound (Scheme 5). The potent Nitric Oxide Synthases (NOS) inhibitor **5** was easily realized in an unlabeled, as well as, a carbon-13 labeled version through this carbonylative C−H activation dependent procedure, and subsequent reaction with hydrazine monohydrate; thus affording **5** and [^{13}C]-**5** in good isolated yields.[4b,20]



Scheme 5. Application of the methodology in the preparation of NOS inhibitor **5**.

Speculating whether this transformation did indeed proceed through a palladium assisted C−H activation, we set out to probe if this was a mere case of base induced deprotonation and subsequent acyl substitution.[21] Subjecting pentafluorobenzene to Cs_2CO_3 and 4-methoxybenzoyl chloride, in α,α,α-trifluorotoluene at 80 °C for 16 h provided none of the desired product, as only the corresponding carboxylic acid was observed in a 95% NMR yield.[22]

With this in mind, a plausible mechanism for this palladium catalyzed carbonylative transformation relying on the C−H activation of polyfluoroarenes is proposed (Figure 1). After the initial reduction of palladium(II) to palladium(0), possibly by phosphine oxidation, oxidative addition into the (hetero)aryl bromide bond occurs. Subsequent coordination and insertion

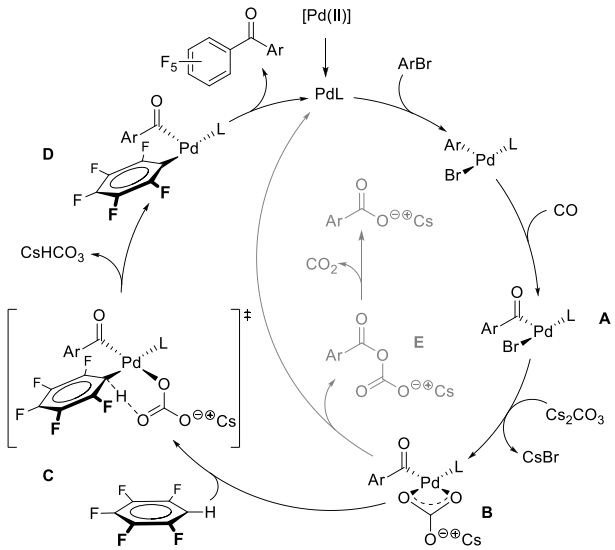


Figure 1. Plausible reaction mechanism for the palladium catalyzed carbonylative cross coupling of aryl bromides and polyfluoroarenes via C−H activation.

of carbon monoxide provides palladium acyl complex **A**. Exchange of the bromide counterion for a carbonate with simultaneous formation of CsBr affords intermediate **B**. This complex can then either participate in C−H bond activation of the polyfluoroarene, through transitionstate **C** or undergo reductive elimination forming acylcarbonate **E**. Subsequent decarboxylation of **E**, would form the carboxylic acid observed as the major side-product, thus explaining its formation even under strictly anhydrous conditions. On the other hand, if C−H activation resulting in intermediate **D** is faster than reductive elimination from **B**, then **D** only needs to undergo reductive elimination to form the desired product and regenerate the palladium(0) catalyst. Alternatively, trifluoroacetate may affect the deprotonative palladation with subsequent deprotonation by the base, thus acting as a proton shuttle.[23]

Conclusions

In summary, the first intermolecular Pd-catalyzed carbonylative coupling of aryl bromides relying on C−H activation has been presented. The transformation proceeds under relatively mild conditions and does not require an additional transition metal to furnish an organometallic species for transmetallation.[24] The methodology successfully transforms a variety of aryl- and heteroaryl bromides into their corresponding benzopolyfluorophenones. Similarly, it was shown that a number of other polyfluoroarenes are also competent substrates for this transformation. Isotopic labeling was demonstrate to be efficient, by simply applying [^{13}C]-COgen, while the synthetic usefulness of this reaction was underlined by the synthesis of a NOS inhibitor. Lastly, a mechanistic scenario, which also accounts for the experimentally observed byproduct, was proposed.

Acknowledgements

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