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Double C−H Activation: The Palladium-Catalyzed Direct C-Arylation of Xanthines with Arenes

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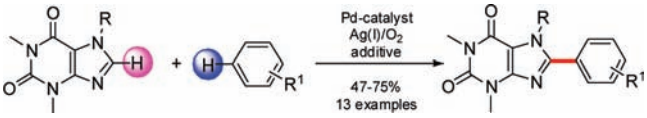
ABSTRACT

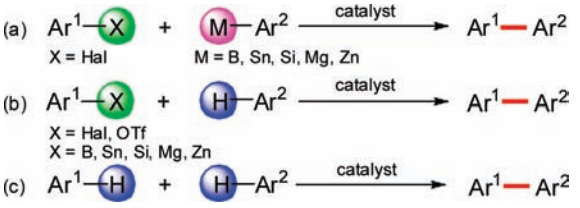


The novel Pd-catalyzed C(sp^2)−H/C(sp^2)−H cross-coupling of unactivated xanthines with unactivated arenes utilizing a combination of Ag(I) and O_2 as oxidants exclusively yields C-8 arylated xanthines in a single synthetic operation.

Many natural products and other biologically active compounds contain a bis(hetero)aryl moiety as a key structural motif. During the last decades a number of reliable transition metal-catalyzed cross-coupling reactions between (hetero)aryl halides Ar−X and stoichiometric amounts of organometallic reagents Ar−M have been developed to synthesize this kind of structure element by C(sp^2)−C(sp^2) bond formation (Scheme 1a).[1] However, many of the required organometallic reagents Ar−M cannot always be obtained commercially, and often their synthesis is difficult to achieve. Another disadvantage of this type of cross-coupling is their low step and atom economy.

This is why the concept of direct (hetero)arylation via C−H bond cleavage is highly attractive and has received considerable attention over the past few years.[2] (Hetero) arylation can either be performed by coupling of an activated (hetero)arene with an unactivated (hetero)-arene (Scheme 1b) or by reacting two unactivated (hetero)arenes (Scheme 1c). It has been shown that a number of oxidants can be employed for the dehydrogenative (hetero)arylations.[3] Using O_2 for this purpose provides an appealing option. Naturally, the C(sp^2)−C(sp^2) bonding between two unactivated (hetero)arenes is most

Scheme 1. Synthesis of Bis(hetero)aryls



challenging. Meanwhile, a number of intramolecular oxidative C−H functionalizations of this type allowing for the preparation of dibenzofurans[4] and carbazoles[5] have been developed. In addition, ample evidence exists for the intermolecular homocoupling of both arenes and heteroarenes.[6] Intermolecular cross-coupling reactions between unactivated reactants are much more difficult to achieve because the problems that need to be addressed are not limited to reactivity issues but also include regioselectivity control. Important contributions have come from

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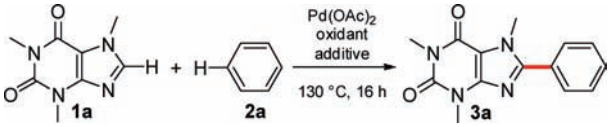
Table 1. Pd-Catalyzed C−H Activation of Caffeine (**1a**) with Benzene (**2a**)[a]



entry	$Pd(OAc)_2$ (mol %)	oxidant	PivOH (equiv)	yield of **3a** (%)
1	10	Ag_2CO_3 (3 equiv); Ar		10
2	10	Ag_2CO_3 (3 equiv); O_2		21
3	10	Ag_2CO_3 (3 equiv); O_2	3	41
4	15	Ag_2CO_3 (3 equiv); O_2	3	46
5	20	Ag_2CO_3 (3 equiv); O_2	3	56
6	30	Ag_2CO_3 (3 equiv); O_2	3	75
7		Ag_2CO_3 (3 equiv); O_2	3	
8	10		3	trace
9	2.5	$Cu(OAc)_2 \cdot H_2O$ (1.5 equiv); Ar		20[b]
10	10	$Cu(OAc)_2$ (2 equiv); Ar	1.5	17[c]
11	2.5	Ag_2CO_3 (1.5 equiv); Ar		8[d]

[a] All reactions were performed with 0.5 mmol of **1a** and 20 mmol of **2a** in a sealed vial, unless otherwise indicated. [b] Reaction was carried out with 1 equiv of pyridine as an additive at 120 °C for 20 h in 0.6 mL of 1,4-dioxane. [c] In a sealed vial, 0.2 mmol of **1a** was reacted with 22.4 mmol of **2a**, using 0.75 equiv of Na_2CO_3 at 110 °C for 24 h in 2 mL of DMA. [d] Reaction was carried out with 1 equiv of AcOH at 120 °C for 7 h in 2 mL of DMF and 100 μL (5%) of DMSO.

the groups of Fagnou[7] and DeBoef,[8] who demonstrated that indoles and benzofurans can be coupled with arenes. Although intermolecular cross-coupling has been extended to intermolecular (hetero)arylations of pyrrols,[7b] pyridin-*N*-oxides,[9] anilides,[10] benzo[*h*]quinolines,[11] *N*-acetyl tetrahydroquinolines,[12] and perfluoroarenes,[13] the range of substrates that can be cross-coupled remains small.

Xanthines such as caffeine, theophilline, and theobromine are important biologically active alkaloids. In the field of medicinal chemistry, C-8 (hetero)aryl-substituted xanthines are of considerable interest as they are known to act as selective antagonists of the human A_{2B} adenosine receptor.[14] By using the classic methods repertoire of heterocyclic chemistry the synthesis of C-8 arylated xanthines can only be achieved by multistep synthesis of the xanthine skeleton itself. And therefore, a modular, straightforward approach allowing for the synthesis of C-8 arylated xanthines in a single step is highly desirable, which is why considerable effort has been devoted to the arylation of xanthines over the past few years. Recently, Daugulis[15] and You[16] have developed the Pd- and the Cu-catalyzed C-8 arylation of xanthines, respectively, by using aryl halides as coupling partners, while Ackermann reported on similar reactions using the corresponding aryl tosylates as substrates.[17] The use of arylboronic acids for the arylation of xanthines has also been described.[18] Recently, the direct heteroarylation of xanthines with thiophenes and furans has been achieved.[19] The direct arylation of xanthines, however, has not been achieved so far.

Here we disclose that C-8 arylated xanthines can be efficiently synthesized via Pd-catalyzed double C−H activation of unactivated xanthines with unactivated arenes.

The starting point of our study (Table 1) was the observation that the reaction of caffeine (**1a**) and benzene (**2a**) performed in the presence of 10 mol % of $Pd(OAc)_2$ as a catalyst, Ag_2CO_3 as an oxidant, and under an atmosphere of Ar led to the exclusive isolation of the cross-coupling product 8-phenylxanthine (**3a**) with 10% yield (Table 1, entry 1). Remarkably, the yield of the product **3a** could be doubled to 21% by replacing Ar with O_2 (Table 1, entry 2). When pivalic acid was added (Table 1, entry 3) 8-phenylxanthine (**3a**) was formed in 41% yield. Other

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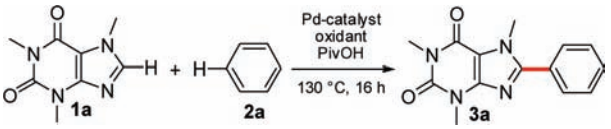
Table 2. Optimization of the Intermolecular Cross-Coupling of **1a** and **2a**[a]



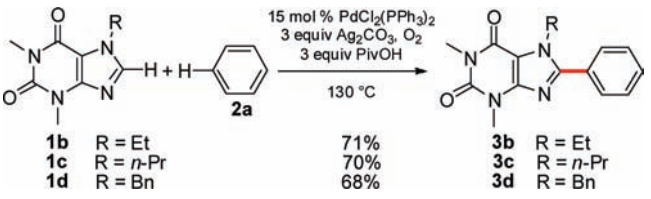
entry	Pd-source (mol %)	oxidant	yield of **3a** (%)
1	$Pd(TFA)_2$/20	Ag_2CO_3 (3 equiv); O_2	41
2	$PdCl_2(PhCN)_2$/20	Ag_2CO_3 (3 equiv); O_2	25
3	$PdCl_2(PPh_3)_2$/20	Ag_2CO_3 (3 equiv); O_2	70[b]
4	$PdCl_2(PPh_3)_2$/10	Ag_2CO_3 (3 equiv); O_2	51
5	$PdCl_2(PPh_3)_2$/15	Ag_2CO_3 (3 equiv); O_2	73
6	$PdCl_2(PPh_3)_2$/15	AgOAc (3 equiv); O_2	55
7	$PdCl_2(PPh_3)_2$/15	Ag_2CO_3 (2.2 equiv); O_2	69
8	$PdCl_2(PPh_3)_2$/15	Ag_2CO_3 (3 equiv); air	58
9	$PdCl_2(PPh_3)_2$/15	Ag_2CO_3 (3 equiv); Ar	50
10	$PdCl_2(PPh_3)_2$/15	Ag_2CO_3 (3 equiv); O_2	56[c]

[a] All reactions were performed with 0.5 mmol of **1a** and 20 mmol of **2a** in a sealed vial. [b] In addition, an unpolar product was observed that could not be identified. [c] 20 equiv of **2a**.

additives, including acetic acid and isovaleric acid, proved to be less effective in producing **3a**. However, the yields of the desired product **3a** could be improved by gradually increasing the amounts of $Pd(OAc)_2$: with 30 mol % of $Pd(OAc)_2$ the product **3a** was finally formed in 75% yield (Table 1, entries 4−6). The experiments clearly demonstrate that the best way to proceed with the selective cross-coupling of **1a** and **2a** is by using $Pd(OAc)_2$ as the catalyst, a combination of Ag_2CO_3 and O_2 as oxidants, and pivalic acid as an additive (Table 1, entries 1, 2, 7, and 8). In addition, we have also tested reaction conditions that have been reported for double C−H activations between (a) electron-deficient polyfluoroarenes and simple arenes,[13a] (b) electron-deficient polyfluoroarenes and heteroaromatic compounds,[13b] and (c) xanthines and heteroaromatic compounds.[19] The results obtained for the reaction of **1a** with **2a** clearly demonstrate that the reagents/reaction conditions employed are not suitable for the successful arylation of xanthines as the yields of the arylated xanthine **3a** did not exceed 20% (Table 1, entries 9−11).

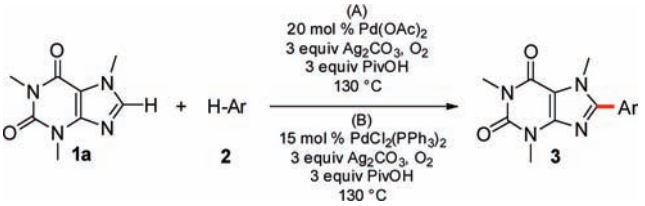
Then we found that the cross-coupling reaction of **1a** and **2a** was not restricted to using $Pd(OAc)_2$ as a catalyst,

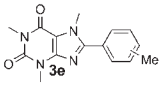
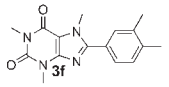
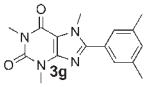
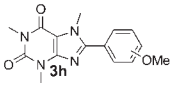
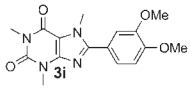
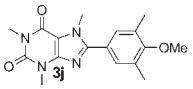
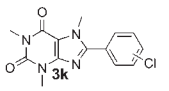
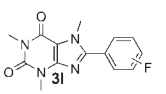
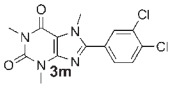
Scheme 2. Pd-Catalyzed C−H Arylation of *N*-Substituted Xanthines **1b−d** with **2a**



but could also be catalyzed by other Pd complexes as well, including $Pd(TFA)_2$, $PdCl_2(PhCN)_2$, or $PdCl_2(PPh_3)_2$ (Table 2, entries 1−5). The best results were achieved with 15 mol % of $PdCl_2(PPh_3)_2$. Further experiments with $PdCl_2(PPh_3)_2$ revealed that Ag_2CO_3 could be replaced with AgOAc and that the amount of Ag_2CO_3 could also be decreased to 2.2 equiv (Table 2, entries 6 and 7). However, avoidance of silver salts has so far not been possible. Replacing O_2 by air or Ar is possible but only at the cost of decreasing the yield of **3a**; the same holds true when the excess of benzene is substantially reduced (Table 2, entries 8−10). The best yield of **3a** (73%) was

Table 3. Pd-Catalyzed C−H Arylation of **1a** with Substituted Arenes **2b−j**[a]



entry	**2**	A/B	product	*t* (h)	yield **3** (%)
1		A		16	73[b]
		B		16	45[b]
2		A		16	70
3		A		16	69
4		A		16	41[c]
		B		16	65[c]
5		A		18	71
6		A		16	58
7		A		16	56[d]
8		A		20	47[e]
9		A		16	56

[a] All reactions were performed with 0.5 mmol of **1a** and 20 mmol of **2a** in a sealed vial. [b] *m*/*p* = 1.25:1. [c] *o*/*p* = 1:4. [d] *m*/*p* = 3:2. [e] *m*/*p* = 2.5:1.

obtained when the reaction was performed with 15 mol % of $PdCl_2(PPh_3)_2$ and 3 equiv of each Ag_2CO_3 and pivalic acid under an atmosphere of O_2 (Table 2, entry 5). In summary, two efficient catalytic systems based on Pd catalysts have been identified which can be used for further cross-coupling reactions.

The next goal was to explore the scope of the method. We started off with the application of the $PdCl_2(PPh_3)_2$-based protocol to the cross-coupling of various *N*-substituted xanthines **1b**−**d** with benzene (**2a**) (Scheme 2). The arylated xanthines (**3b**−**d**) were isolated in yields ranging from 68% to 71%. As with all other transformations presented no homocoupling products could be detected.

Then we focused on the reactions of **1a** with different substituted arenes **2b**−**j** and found that a number of mono-, di-, and trisubstituted arenes carrying methyl-, methoxy-, chloro-, and fluoro-groups can be used to arylate caffeine (**1a**). The arylated xanthines **3e**−**m** could be isolated with yields ranging from 47% to 73% (Table 3). These results clearly demonstrate that the method easily tolerates both electron-donating and electron-withdrawing groups. It should be noted that most of these couplings were carried out with $Pd(OAc)_2$ as a catalyst after preliminary experiments revealed that the use of the $PdCl_2(PPh_3)_2$-based protocol produced lower yields of **3e**−**m**. The formation of the arylated xanthenes is notable for its excellent regioselectivity. This holds true for the selectivity toward both the caffeine and the arenes. The only exceptions observed were the transformations with the monosubstituted arenes toluene (**2b**), anisole (**2e**), chlorobenzene (**2h**), and fluorobenzene (**2i**).

To summarize, the Pd-catalyzed direct C−H arylation of unactivated xanthines with unactivated arenes has been reported for the first time. This method allows for a highly regioselective preparation of C-8 arylated xanthines in a single step without previously activating the substrates. The arylation of xanthines is not restricted to benzene itself but may also be conducted with mono-, di-, and trisubstituted arenes.

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Supporting Information Available. Experimental details and spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.