Heterocycles

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Copper-Catalyzed Direct C Arylation of Heterocycles with Aryl Bromides: Discovery of Fluorescent Core Frameworks**

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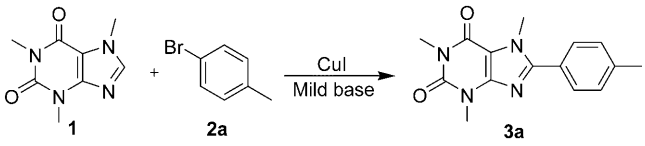
Direct C-arylation of heteroaromatic compounds has recently received considerable attention.[1] This transformation has been achieved by using Rh-, Ru-, and (more extensively) Pd-based noble metal catalysts.[2] From an academic, industrial, and economic standpoint, big challenges lie ahead in controlling selectivity and identifying inexpensive metal catalysts. At the turn of this century, the economically viable use of copper led to remarkable progress in the development of copper-catalyzed carbon–heteroatom bond-forming reactions.[3] However, few examples of C–H bond-functionalization reactions,[4] especially of direct C-arylation of heteroaromatic compounds,[5] have been reported. Recently, a significant breakthrough was made by Do and Daugulis on the copper-catalyzed C-arylation of various azole derivatives; however, this method still suffers from some limitations.[5a] Firstly, the system was only efficient with aryl iodides, secondly, the formation of *tert*-butyl aryl ether resulted in decreased conversion into the arylation products, and thirdly, the regioselectivity and functional group tolerance was significantly limited owing to the use of strong bases.[5a]

Xanthines are important biologically active alkaloids. 8-Aryl- or heteroaryl-substituted xanthines are highly potent and selective antagonists at human A_{2B} adenosine receptors.[6] Recently, our research group has developed a palladium-catalyzed direct C-arylation to afford 8-aryl xanthines.[7] However, the relatively high cost of palladium and its incompatibility with certain functional groups leave room for further improvement. Inspired by our recent work on the CuI-catalyzed N-arylation of N-heterocycles,[8] we postulated that the C-arylation of heteroaromatic compounds with aryl bromides could be performed by utilizing copper catalysts. Moreover, a subtle combination of a ligand extensively employed in the N-arylation of N-heterocycles and a commonly used mild inorganic base could suppress the benzyne mechanism, which was observed to facilitate regioselectivity in the Daugulis system,[5a,9] thus resulting in improved tolerance of functional groups and thereby extending the scope of possible substrates. Herein, we report the first copper-catalyzed direct C-arylation of heterocycles using non-activated aryl bromides as arylating reagents and a surprising discovery of a new series of fluorescent core frameworks.

Our investigation started with the coupling of caffeine (**1**) with *p*-bromotoluene (**2a**) using copper(I) iodide as the catalyst. After screening a variety of ligands, solvents, and bases (Table 1, entries 1–15), the best results were obtained in DMF/xylene (1:1) at 140 °C for 36 h using two equivalents of K_3PO_4 as the base in the presence of a catalyst system that was generated in situ from CuI (20 mol %) and 1,10-phenanthroline (Phen, 20 mol %). An attempt to lower the amount of CuI to 10 mol % resulted in the incomplete consumption of caffeine, in spite of extended reaction time (Table 1, entry 16). In addition, we also tested lithium *tert*-butoxide (*t*BuOLi) as a base, which was described as the optimal base for the C-arylation of heterocycles with aryl iodides in the Daugulis

Table 1: Optimization of the coupling of caffeine with *p*-bromotoluene.[a]



1 2a 3a

Entry	Ligand	Solvent	Base	Yield [%][b]
1	–	DMF	K_3PO_4	–
2	Hacac	DMF	K_3PO_4	40
3	L-proline	DMF	K_3PO_4	–
4	BINOL	DMF	K_3PO_4	29
5	Phen	DMF	K_3PO_4	55
6	TMEDA	DMF	K_3PO_4	15
7	DMEDA	DMF	K_3PO_4	27
8	Phen	xylene	K_3PO_4	–
9	Phen	DMF/xylene (1:1)	K_3PO_4	78
10[c]	Phen	DMF/xylene (1:1)	K_3PO_4	96
11	Phen	DMF/xylene (1:2)	K_3PO_4	69
12	Phen	DMF/xylene (2:1)	K_3PO_4	62
13	Phen	DMF/xylene (1:1)	K_2CO_3	65
14	Phen	DMF/xylene (1:1)	Cs_2CO_3	61
15	Phen	DMF/xylene (1:1)	*t*BuOLi	trace
16[d]	Phen	DMF/xylene (1:1)	K_3PO_4	76

[a] Reactions were carried out using CuI (20 mol %), base (2.0 equiv), ligand (20 mol %), caffeine (1 mmol), and *p*-bromotoluene (1.5 mmol) at a 1.2 M concentration at 140 °C for 24 hours. [b] Yield of isolated product. [c] Reaction time of 36 hours. [d] Reaction was carried out using CuI (10 mol %) for 36 hours. BINOL = 1,1′-bi-2-naphthyl, DMEDA = *N*,*N*′-dimethylethylenediamine, DMF = *N*,*N*-dimethylformamide, Hacac = acetylacetone, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

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system,[5a,9] but only a trace amount of the desired compound was produced.

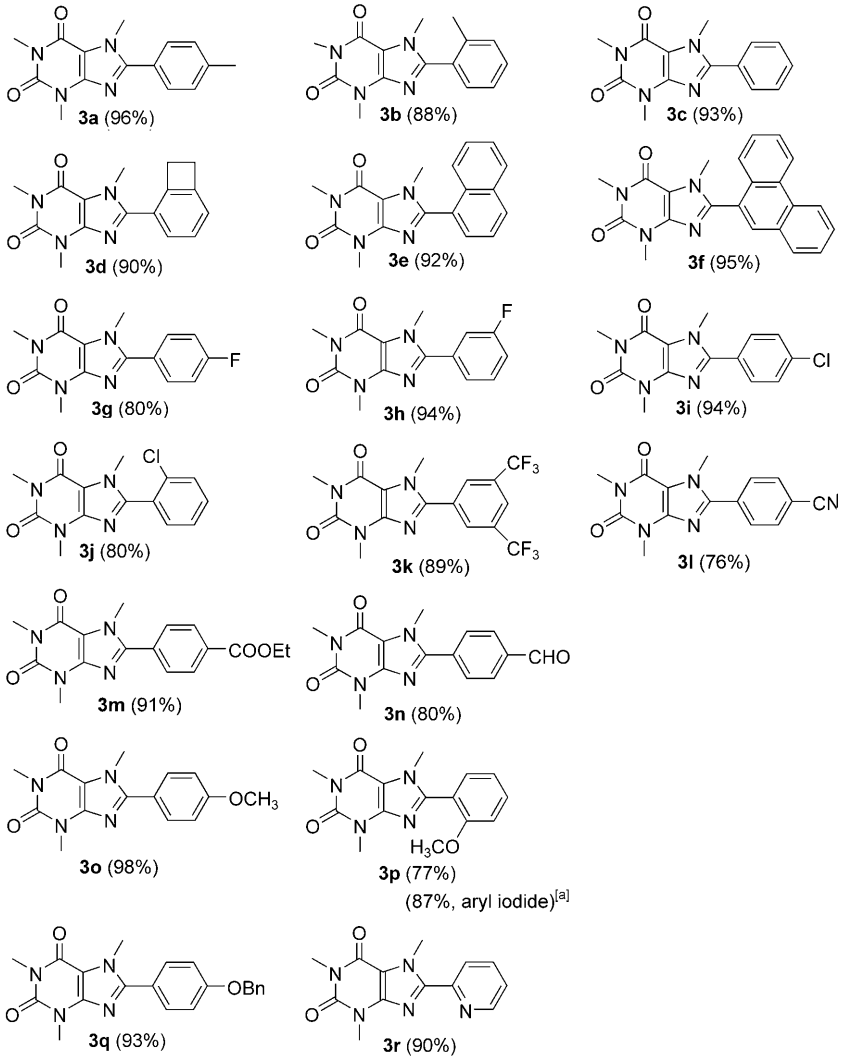
Subsequently, a variety of substituted aryl and heteroaryl halides were tested under the optimized reaction conditions using caffeine (**1**) as the heterocycle, and the results are summarized in Scheme 1. Gratifyingly, various 8-aryl caffeine derivatives were obtained with both nonactivated and activated aryl bromides. Whether aryl bromides are electron-rich, electron-poor, or sterically bulky, all of them afforded good to excellent yields (**3a–q**). The heteroaryl bromide derivative was also reactive (→**3r**). In addition, high-yielding arylation was possible with aryl iodides in a shorter time of 24 hours (→**3p**). It is important to stress that these reaction conditions were compatible with the presence of important functional groups such as ester, cyano, aldehyde, and benzyloxy groups that were positioned on the aryl bromide substrate, and which could then be subject to further synthetic transformations (**3l–q**). Notably, our catalytic system could be applied to the C-arylation of caffeine (**1**) with *o*-methoxy aryl bromide (→**3p**), whereas our previously reported palladium-catalyzed system afforded little coupling product.[7]

We next applied our protocol to other xanthines to prepare 8-aryl theophylline and theobromine derivatives (Scheme 2, **4a–d**). In particularly, benzylic theophylline and theobromine were arylated with *p*-bromotoluene in 81% and 90% yields, respectively (→**4a**,**b**). Further removal of the benzylic group by hydrogenation should afford important biologically active C8-arylated (NH)-xanthines.[6,10] Notably, allylic theobromine could be transformed into the target compound **4d** in 86% yield. The previous reported palladium-catalyzed methods, however, were not compatible with this substrate because of a competitive Heck reaction.[2m,n,7]

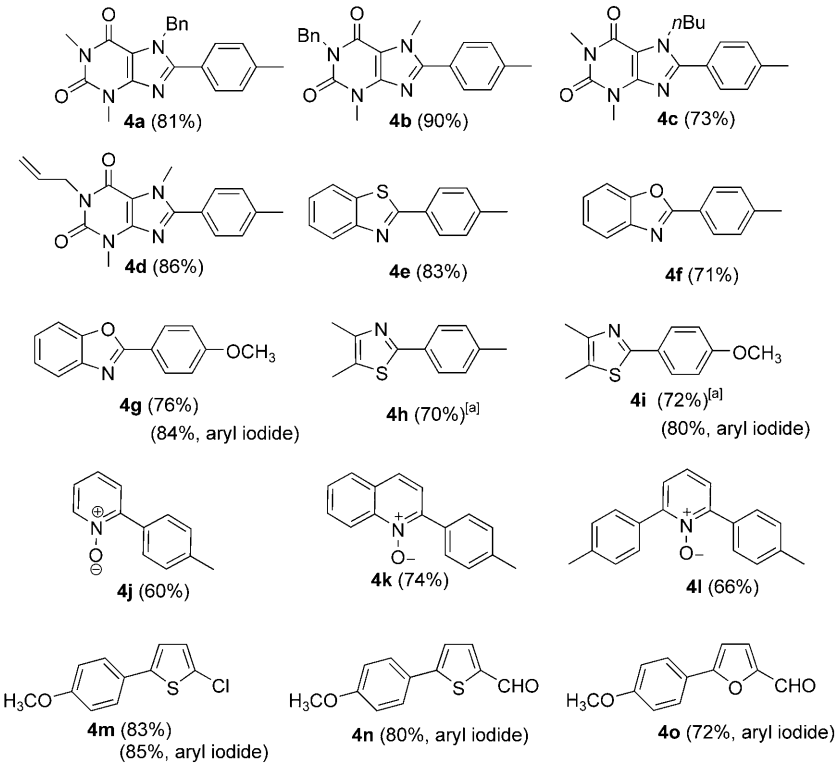
To further expand the scope of our methodology, we used this new catalytic system in the direct arylation of other heterocyclic C–H bonds (Scheme 2). Overall, we were pleased with the generality of our methodology. For example, the azole derivatives (i.e., benzothiazole, benzoxazole, and 4,5-dimethylthiazole) were arylated with aryl bromides in good yields under the optimized reaction conditions (→**4e–i**). In addition to these azoles, the direct arylation of functionalized furan and thiophene derivatives was also very successful (→**4m–o**). To our knowledge, this was the first report of copper-catalyzed direct arylation of 2-formylfuran and 2-formylthiophene, although more active aryl iodides were required.[11] Interestingly, pyridine *N*-oxide, quinoline *N*-oxide, and 2-*p*-tolylpyridine *N*-oxide smoothly underwent arylation with aryl bromide and afforded the desired products (→**4j–l**). In contrast, recent examples required the use of palladium and phosphine ligands in these reactions.[12]

Although more detailed investigations of the reaction mechanism are currently underway, we rationalize that it should be consistent with that suggested by Daugulis.[4c,5a,9] The catalytic reaction was assumed to perform through the base-assisted formation of an heteroarylcopper species, and subsequent reaction of this species with aryl halide. The ligand stabilized the arylcopper species and facilitated the halide displacement step.

The importance of fluorescent molecules has been well documented in various fields of research.[13] The use of new synthetic methodologies to discover novel fluorescent core frameworks is starting to attract interest.[14] During our investigation of the coupling of xanthines with aryl bromides, we found that 8-aryl-substituted xanthines exhibited significantly strong photonic luminescence in a



Scheme 1. Catalytic C-arylation of caffeine with a variety of aryl bromides. Reactions were carried out using CuI (20 mol%), 1,10-phenanthroline (20 mol%), K_3PO_4 (2.0 equiv), caffeine (1.0 equiv), and aryl bromides (1.5 equiv) in DMF/xylene (1:1; 1.2 M concentration) at 140°C for 36 hours. Yield of isolated product is given in parenthesis. [a] Reaction time of 24 hours.

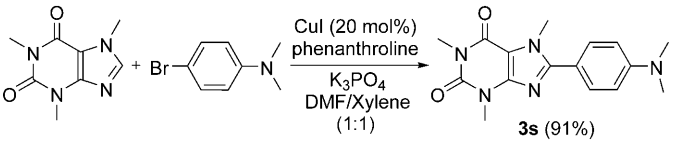


Scheme 2. Catalytic C-arylation of heteroarenes with aryl bromides. Reaction conditions: see Scheme 1 or the Supporting Information. Yield of isolated product is given in parenthesis. [a] Reaction time of 60 hours.

variety of solvents such as $CHCl_3$, DMF, CH_3CN, CH_3OH, and water. The intensity of the photonic emission was proven to be heavily depend upon the types of substitutent groups on the xanthines. As compared to non-substituted or N1/N7-substituted derivatives (i.e, caffeine, benzylic theophylline, and benzylic theobromine), C8-aryl-substituted xanthines gave rise to an obvious increase in emission (Figure S1 in the Supporting Information). Notably, the photophysical properties of 8-aryl xanthines have never been explored.

To gain insight into the remarkable photonic luminescence of C8-aryl xanthines, we synthesize the fluorophore **3s** to mimic a "push–pull" π-electron mode, in which the nitrogen atom of an *N*,*N*-dimethylaniline moiety serves as the electron donor and the electron-deficient groups of caffeine (**1**) act as the electron acceptor (Scheme 3). The fluorophore will undergo an intramolecular charge transfer from the donor to the acceptor upon excitation by light. As expected, we were delighted to find that **3s** not only exhibited strong fluorescence in $CHCl_3$, but also noteworthy solid-state fluorescence that is essential for the development of optoelectronic devices, such as organic light-emitting diodes and solid-state organic lasers (Figure 1 a–c).[15] In addition, we found that **4b** also showed strong solid-state fluorescent characteristics and produced hypsochromically shifted emission relative to **3s** in $CHCl_3$ (Figures S1 and S2 in the Supporting Information).

Molecular fluorescent imaging techniques aid in understanding biological processes at the molecular level, and are particularly useful for the early detection of cancer.[16] Although many luminescent probes such as organic dyes, inorganic nanoparticles, lanthanide coordination complexes, fluorescent and bioluminescent proteins have been used in cell imaging, the exploitation of small fluorescent labeling molecules is still new.[17] Owing to their low cytotoxicity and excellent biocompatibility, it is reasonable to assume that these biologically active C8-aryl-substituted xanthines can be developed into new types of bright, highly stable fluorescent probes for optical imaging of living cells by convenient modification of core frameworks. Herein, Lewis lung cancer cells (LL2) and human embryo kidney 293 cells (HEK 293) were incubated with **3s** in DMEM Dulbecco's mimimum essential medium for 1 hour at 37 °C. As shown in Figure 1 d–f and Figure S3 (in the Supporting Information), **3s** successfully marked LL2 and HEK 293 cells, thus suggesting that the new fluorophore is a potentially useful reagents for biological imaging. The further modification of this fluorescent core frameworks, investigation of the fluorescent properties of 8-aryl xanthines, and their application in biological imaging are currently in progress.



Scheme 3. Arylation of caffeine with *p*-bromo-*N*,*N*-dimethylaniline.

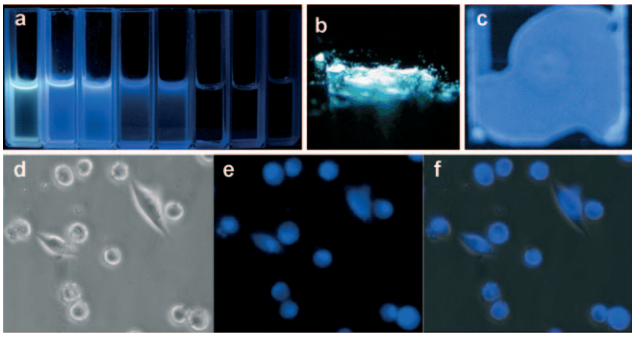


Figure 1. a) Fluorescence images of selected xanthines (λ_{ex} = 365 nm, 5×10^{-4} M) in $CHCl_3$: from left to right; **3n**, **3s**, **3f**, **3c**, **4b**, benzylic theophylline, benzylic theobromine, and caffeine. b) Fluorescence image of **3s** (powder, λ_{ex} = 365 nm). c) Fluorescence image of **3s** (thin-film prepared by spin-coating with a solution of $CHCl_3$, λ_{ex} = 365 nm). d) Bright-field transmission image of LL2 cells incubated with **3s** (40 μM). e) Fluorescence image of LL2 cells incubated with **3s** (40 μM). f) Overlay of the fluorescence and bright-field transmission images of LL2 cells incubated with **3s** (40 μM).

In summary, we have developed a copper-catalyzed C–H bond-activation path that allows, for the first time, the arylation of a relatively wide range of heterocycles (at a relatively acidic $C(sp^2)$ position) with a variety of aryl bromides to give excellent regioselectivity and good functional group tolerance. More importantly, the new approach has led to the discovery of a library of fluorophores that show intense emissions. These "push–pull" fluorophores can accommodate tunable photophysical properties by changing the substituents at the N1-, N7-, and/or C8-positions. Finally, 8-aryl xanthines have proven to be potentially useful bioimaging fluorescence probes. As 8-arylated xanthines feature significant fluorescent emission, we believe that pharmacokinetics could be conveniently monitored with these compounds through fluorescence imaging techniques, thus giving new insight into the pathophysiological processes of human A_{2B} adenosine receptors.

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