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C–H Activation

Room Temperature C–H Activation and Cross-Coupling of Aryl Ureas in Water**

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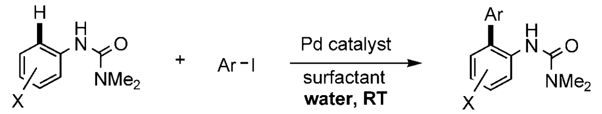
Palladium-catalyzed cross-coupling reactions of aryl halides with aromatic C–H bonds have emerged as a powerful method for the preparation of biaryls.[1,2] Despite substantially increased attention to the field, typical reaction conditions still require high temperatures (>120 °C) for insertion into aromatic C–H bonds, which can be viewed as a major drawback to this chemistry. Such forcing conditions often appear to be critical to overcoming the low reactivity of aryl C–H bonds. A much milder C–H activation reaction at ambient temperatures would, in particular, likely be more dependent on activation by the catalyst.[3]

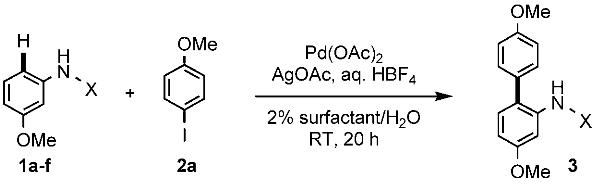
Although there are many *ortho*-directing groups for C–H activation reactions,[1] the amide residue in anilides is especially attractive as a coupling partner for the synthesis of valuable aniline derivatives. In 1984, Tremont and coworkers used acetanilides for C–H alkylation with alkyl iodides, albeit promoted by stoichiometric $Pd(OAc)_2$.[4] Both the Daugulis[5] and Sanford[6] groups have demonstrated Pd-catalyzed *ortho*-arylations of anilides with aryl iodides or iodonium salts at temperatures above 100 °C. Moreover, *ortho*-directed C–H activation can suffer from double arylations with respect to the directing group.[1,5] C–H arylations of reactive indoles have been reported at room temperature,[7] but to the best of our knowledge C–H arylation of anilide derivatives with aryl halides at ambient temperatures have not yet been achieved.[1,8] Herein, we describe the first room temperature mono-C–H activation of urea derivatives and their cross-couplings with aryl iodides in water (Scheme 1). This methodology provides a convenient route to various aniline derivatives by means of C–H activation under mild conditions.



Scheme 1. C–H activation at room temperature in water.

Optimization studies employed the combination of anilides (**1a–f**) and 4-iodoanisole (**2a**, 2 equiv) in the presence of $Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv) and aqueous HBF_4 (5 equiv) in 2 wt % surfactant/water solutions at room temperature (Table 1). The effectiveness of various directing groups was initially examined, and among a number of different anilide derivatives **1a–f** explored, only the aromatic urea **1f** smoothly underwent C–H arylation at room temperature (Table 1, runs 1–6). Recently, Lloyd-Jones and Booker-Milburn have also found aryl ureas to be more active coupling partners for C–H functionalizations than other anilides.[9] Acetanilide **1a** reacted with **2a** only upon heating to 50 °C. Pivaloylanilide **1c** has been reported as an effective directing group at 130 °C,[1,2,5] but gave a low yield under these room temperature conditions (run 3). Generally, acetic acid or trifluoroacetic acid (TFA) is required to carry out C–H activation;[1,2] in this case, HBF_4 was found to be critical for generation of biaryl **3** in good yield (run 6).

Table 1: Optimization of C–H arylations at room temperature.[a]



Run	X		Surfactant	Yield [%]
1	COMe	**1a**	PTS	trace
2	CO*i*Pr	**1b**	PTS	trace
3	CO*t*Bu	**1c**	PTS	24
4	$CSNMe_2$	**1d**	PTS	0
5	$COCF_3$	**1e**	PTS	trace
6	$CONMe_2$	**1f**	PTS	67(0,[b] 0,[c] 0,[d] 60[e])
7	$CONMe_2$	**1f**	Triton X-100	73 (47,[f] 20[g])
8	$CONMe_2$	**1f**	Solutol	65
9	**$CONMe_2$**	**1f**	**Brij 35**	**76**
10	$CONMe_2$	**1f**	Brij 30	72
11	$CONMe_2$	**1f**	TPGS	73
12	$CONMe_2$	**1f**	Cremophor EL	40
13	$CONMe_2$	**1f**	none	35

[a] Conducted at room temperature for 20 h in 2 wt% surfactant/water with 10 mol% $Pd(OAc)_2$, AgOAc (2 equiv), aq. HBF_4 (5 equiv), **1** (0.25 mmol), and **2** (2 equiv). [b] AcOH (instead of HBF_4). [c] HCl. [d] TFA. [e] TsOH. [f] 1.2 equiv AgOAc. [g] 3 mol% catalyst.

Although use of the surfactant PTS[10] gave good yields, comparable results were realized with several commercially available amphiphiles. Best yields were obtained using 2 wt % Brij 35 in water (Table 1, runs 7–13). Reduced amounts of HBF_4, silver salt, or palladium catalyst led to lower yields. A

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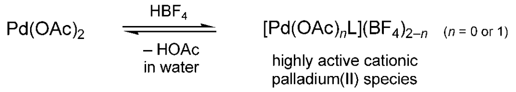


Scheme 2. Generation of a cationic palladium(II) species.

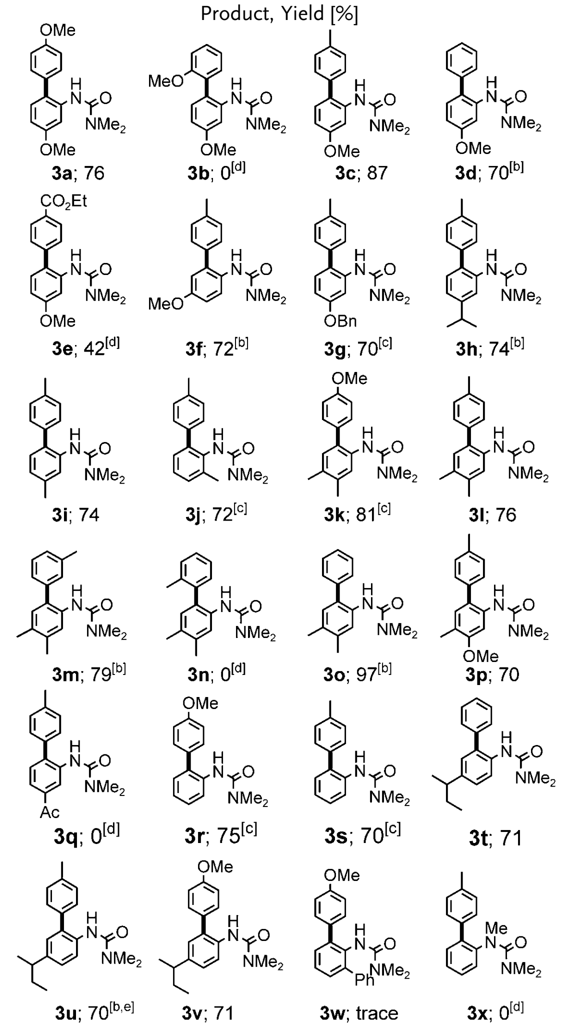
plausible rationale for these results involves generation of a highly active cationic palladium species (Scheme 2).[7c,11]

As illustrated by several representative examples in Table 2, the scope of this transformation is broad, applying to aryl urea derivatives and aryl iodides bearing a variety of functional groups with yields in the 70–97 % range, all done in water at room temperature. Under these mild conditions, only mono-arylated products of net substitution were typically obtained.

Especially noteworthy are aniline derivatives lacking *ortho*- or *meta*-substitution, which have previously been shown to be prone to double arylation. Under these conditions, couplings are selective for singly arylated products (**3f**, **3r**, **3s**, **3v**). Only reactions of the aryl urea bearing a 4-*sec*-butyl group with phenyliodide and 4-tolyl iodide produced small amounts (10–15 % yields) of doubly arylated products. Reduced aryl iodide loading or reaction time, however, suppressed double arylation to less than 3 % (**3t**, **3u**).

Table 2: Products from reactions of aryl ureas with aryl iodides.[a]

Product, Yield [%]

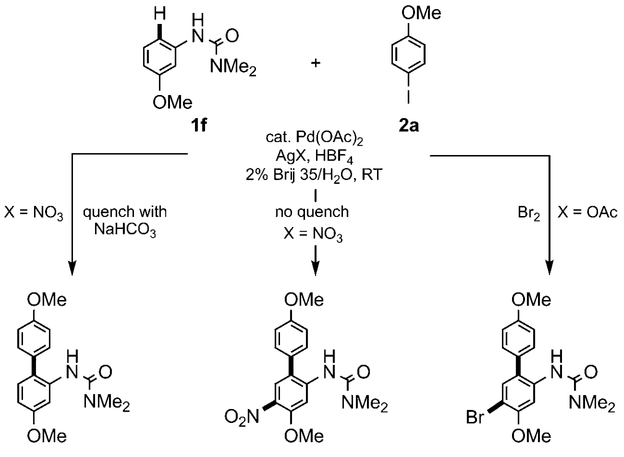


3a; 76	**3b**; 0[d]	**3c**; 87	**3d**; 70[b]
3e; 42[d]	**3f**; 72[b]	**3g**; 70[c]	**3h**; 74[b]
3i; 74	**3j**; 72[c]	**3k**; 81[c]	**3l**; 76
3m; 79[b]	**3n**; 0[d]	**3o**; 97[b]	**3p**; 70
3q; 0[d]	**3r**; 75[c]	**3s**; 70[c]	**3t**; 71
3u; 70[b,e]	**3v**; 71	**3w**; trace	**3x**; 0[d]

[a] Conducted at room temperature for 20 h in 2 wt% Brij 35/water with 10 mol% $Pd(OAc)_2$, AgOAc (2 equiv), aq. HBF_4 (5 equiv), **1** (0.25 mmol), and **2** (2 equiv). [b] Run for 48 h. [c] Run for 72 h. [d] Run for 96 h. [e] 1.2 equiv of ArI.

While current reaction conditions were effective for a variety of substrates, products resulting from sterically hindered aryl iodides having *ortho*-substituents, such as 2-anisyl iodide and 2-tolyl iodide, were not formed (**3b**, **3n**). The reactivity of *N*-methyl substituted ureas (e.g., **3x**) appears to be much lower than that of their non-*N*-methyl-substituted analogues, possibly due to palladium coordination in the initial C–H activation step. Electron-deficient ureas (e.g., **3q**) were also inert, suggesting that electrophilic attack of cationic palladium may be critical for activating aromatic C–H bonds. The reactivity of aryl iodides possessing electron-rich groups is also much higher than that of more electron-withdrawing aryl iodides (**3a** vs. **3e**).

Further advantage can also be taken of the reaction conditions associated with these cross-couplings to allow for tandem processes. Thus, in the presence of silver nitrate, arylation afforded a product of type **3** exclusively, following standard treatment with hydrogen carbonate (Scheme 3).



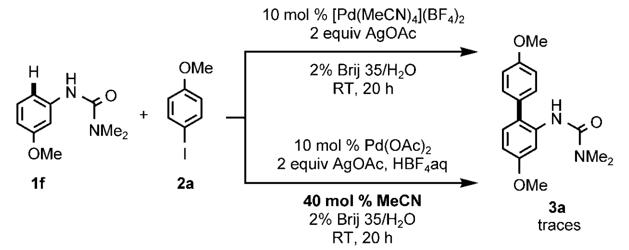
3a (73%) **4** (48%) **5** (70%)

Scheme 3. Tandem C–H arylation–electrophilic trapping.

Without exposure to this aqueous workup, nitrated biaryl **4** was isolated. Since use of silver acetate gave only arylated product **3a** regardless of quenching conditions, the potential for carrying out secondary electrophilic aromatic substitution could readily be demonstrated. Simple introduction of bromine prior to workup afforded the C-arylated, regiospecifically brominated adduct **5** in good overall isolated yield (70 %). The identities of products **3a** and **4** were confirmed by X-ray analyses (see Supporting Information).

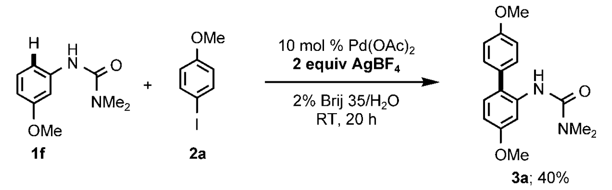
While the exact reaction mechanism is currently unclear, one possibility involves a cationic Pd^{II} complex-catalyzed electrophilic C–H activation step.[7,11] Nevertheless, the reaction of **1f** and **2a** (see Table 2) in the presence of

$[Pd(MeCN)_4](BF_4)_2$, a commercially available cationic palladium(II) complex, did not result in the formation of product (Scheme 4, top). It was found, however, that adding 40 mol% MeCN under the standard, optimized, and otherwise successful conditions (cf. Table 2, product **3a**; 76% yield), only traces of product formation was observed (Scheme 4, bottom). This suggests that the low reactivity of the pre-formed cationic palladium complex may actually be due to suppression of the reaction by MeCN coordination to the Lewis acidic Pd^{II}.



Scheme 4. Effect of cationic palladium species.

With the goal of generating a highly active cationic Pd^{II} complex without the aid of strong acid, and in the absence of coordinating ligands, the combination of $Pd(OAc)_2$ and $AgBF_4$ was examined (Scheme 5). As expected, these conditions led to C–H activation. Unlike the reaction with AgOAc, the reaction with $AgBF_4$ produced the corresponding C–H arylated product **3a** without assistance of external acid at room temperature. This result, under such mild conditions, is indicative of the potential for highly active cationic palladium species to serve as especially effective catalysts for C–H arylation reactions. The silver salt may not only weaken the C–I bond and/or function as halogen scavenger, but may also play an important role in the generation of cationic palladium(II) species.



Scheme 5. C–H activation without acids at room temperature in water.

In summary, the first room temperature C–H arylation of anilides with aryl iodides to give biaryl derivatives in good yields is described. These are accomplished using aryl urea derivatives, and are all done in water in the absence of phosphine ligands. Further studies of metal-catalyzed C–H activation reactions at room temperature, including both Heck couplings and mechanistic studies, are currently under investigation.

Experimental Section

General procedure: Aryl urea **1** (0.25 mmol), aryl iodide **2** (0.5 mmol), AgOAc (0.5 mmol, 83 mg), and $Pd(OAc)_2$ (0.025 mmol, 5.6 mg) were sequentially added in air to a reaction tube equipped with a stir bar and a septum. The aqueous solution containing the surfactant (1.0 mL, 2 wt%), and 48 wt% HBF_4 solution (1.25 mmol, 0.16 mL) were added by syringe and vigorously stirred for 20 h. After completion, the contents of the flask were quenched with $NaHCO_3$ and extracted with EtOAc. The solution obtained was filtered through a plug of silica gel and anhydrous $MgSO_4$, and concentrated by rotary evaporation. The residue was purified by flash chromatography eluting with hexane/EtOAc to afford the product.

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