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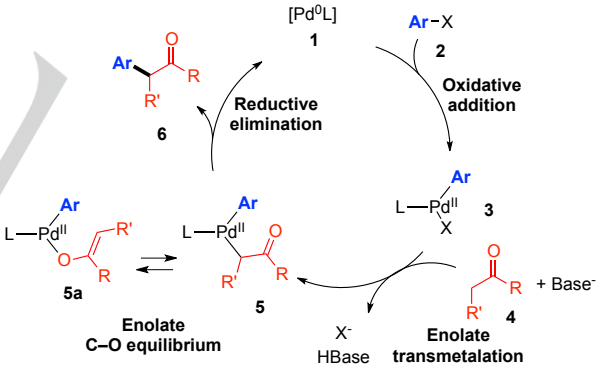
Mild, aqueous α-arylation of ketones: towards new diversification tools for halogenated metabolites and drug molecules

Enrico Marelli*,[a] Yohann Renault,[a] Sunil V. Sharma,[a] Steven P. Nolan[b,c] and Rebecca J. M. Goss*[a]

Abstract: The palladium-catalyzed aqueous α-arylation of ketones was developed and tested for a large variety of reaction partners. These mild conditions enabled the coupling of aryl/ alkyl-ketones with *N*-protected halotryptophans, heterocyclic haloarenes, and challenging base-sensitive compounds. The synthetic potential of this new methodology for the diversification of complex bioactive molecules was exemplified by derivatising prochlorperazine. The methodology is mild, aqueous and flexible, representing a means of functionalizing a wide range of halo-aromatics and therefore has the potential to be extended to complex molecule diversification.

The development of synthetic methods that are both mild and general, for modification of complex substrates, has gained increasing importance over the last decade.[1] The presence of a carbon–halogen bond represents a useful chemical handle, orthogonally enabling selective functionalization. Pd-catalyzed Cross-Coupling (CC) reactions are at the forefront as a key component within the developing toolbox of methodologies for diversification of halogenated molecules.[2] Given their excellent functional group tolerance and wide scope, CC methodologies have therefore proved a valuable tool for late-stage derivatization and labeling of biomolecules including proteins and complex natural products. So far, mild and aqueous methodologies for the Suzuki-Miyaura,[3] Mizoroki-Heck[4] Sonogashira[5] and sulfination[6] reactions have been developed. Other CCs, *e.g.* Buchwald-Hartwig and Negishi reactions, are reported in aqueous conditions,[7] although their application in complex molecule modification strategies is still unreported. The development of aqueous/partially aqueous coupling conditions enables reactions to be carried out on otherwise poorly soluble compounds such as those mentioned above, as well as permitting the use of milder bases.[8]

The α-arylation of ketones is a CC reaction between an aryl halide or pseudohalide and an enolate, formed *in situ* by deprotonation of a ketone (a pronucleophile) by a base.[9] While being a relatively recent discovery in the field,[10] the wide distribution of the α-aryl carbonyl motif in industrially relevant compounds or precursors, has driven an increasing interest towards this reaction.[11] As with many other Pd-catalyzed CC reactions, a three-step minimal mechanism involves (Scheme 1): the Pd^0 catalytic species **1** undergoes oxidative addition, activating the C–X bond of the aryl (pseudo)halide **2** to afford complex **3**, followed by enolate transmetallation (**5**) and reductive elimination generates the product **6**. Notably, despite thorough studies in this field, no aqueous procedure for the α-arylation of ketones has yet been reported. A challenging aspect of such chemistry, in aqueous condition, relates to the unfavourable equilibrium between enolates and their protonated form. This is due to the high pKa of this anionic species.[12] Other enolate reactions (for example, aldol-type) have been achieved in aqueous systems, taking into consideration the perturbation of this equilibrium and using specially developed conditions.[13] Attracted by the development of a platform for aqueous α-arylation of ketones, as it would set the stage for the late-stage functionalization of natural and new-to-nature biomolecules, such as achieved in the GenoChemetic generation of natural product analogues,[3c,h] we tackled the challenges reported above, and we disclose here the first such aqueous methodology.



Scheme 1. The mechanism of Pd-catalyzed α-arylation of ketones according to Hartwig.[9, 15a]

We particularly wished to achieve the diversification of halotryptophans.[14] Tryptophan, an essential amino acid, is a key component in many natural products and its presence in proteins/peptides is crucial to their structural integrity and fluorescence properties, which makes it a very exciting target for derivatization.[3b,c] To this aim, we initiated our studies on a model reaction comprising 5-Br-indole **2a** and propiophenone **4a** in aqueous media. While propiophenone represents a common model compound for this reaction,[15] heterocyclic electrophiles, *i.e.* haloindoles, are generally more challenging reactants for CC chemistry, because the intrinsic reactivity of heteroatom can lead to Pd-poisoning and *N*-arylation.[1f] Initially, we screened a number of phosphine and *N*-heterocyclic carbenes based

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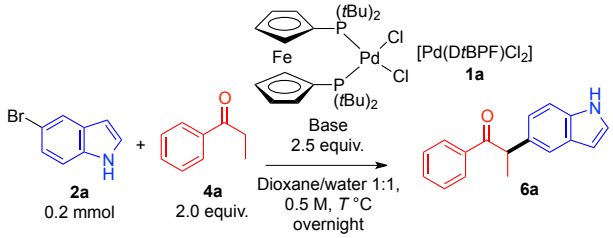
complexes in our model reaction (see supporting information for details). Of all the pre-catalysts tested, only **1a**,[16] [Pd(D*t*BPF)Cl_2] (D*t*BPF= 1,1'-*bis*(di-tert-butylphosphino)ferrocene), was found to be active in water/co-solvent mixtures. The use of **1a** in the α-arylation of ketones is well known: its utility and limitations have been proven by Colacot between 2007 and 2008, using temperatures between R.T. and 100 °C, in THF or dioxane, and *t*-butoxide as base.[17] Its commercial availability and high activity make it one of the most used catalysts in this reaction.[15g-i] Once the pre-catalyst was identified, we systematically screened for the optimum base/solvent system, which play a crucial role in this CC.[17,18]

Table 1. Optimization of the conditions.

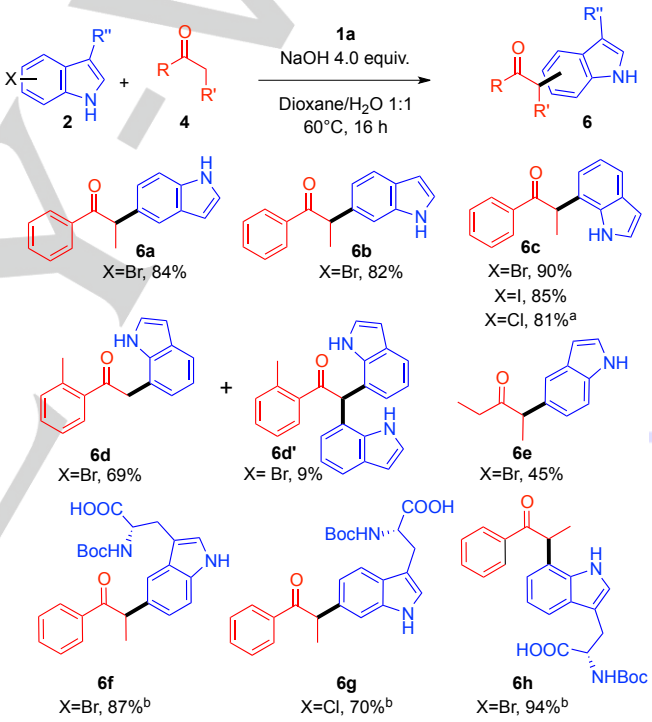


Entry	[Pd] (mol%)	Base	T (°C)	GC Conversion%[a] (NMR Yield %[b])
1	2	NaOH	60	>99 (65)
2	2	K_3PO_4	60	>99 (22)
3	2	Na_2CO_3	60	>99 (41)
4	2	NaOH	80	>99 (70)
5	5	NaOH	60	>99 (66)
6	5	NaOH	80	>99 (70)
7[c]	2	NaOH	60	>99 (90)

Reaction conditions: Propiophenone (0.4 mmol, 2.0 equiv.), 5-Br-indole (0.2 mmol, 1 equiv.), base (0.5 mmol, 2.5 equiv.), [Pd(D*t*BPF)Cl_2] 2-5 mol%, dioxane/water 1:1 mixture (0.5 M), T°C, 16h. [a] Conversion measured by GC analysis; [b] Yield measured by quantitative ^{1}H-NMR using 1,3,5-tri-*t*-butylbenzene as internal standard; [c] 4 equiv. propiophenone and 4 equiv. base used, 84% isolated yield.

Although we observed high GC conversions, based on consumption of starting material (>99%, **Table 1**), NMR yields were significantly lower (22-70%) even with increased Pd loading or temperature (entries 1-6), or using different bases. In GC analysis, no 5-Br-indole **2a** was detected in the filtered reaction mixtures. We hence postulated that a side reaction, involving intermolecular coupling between the N–H bond and the C–Br bond of **2a**, may produce insoluble oligomers and could perhaps be responsible for this discrepancy. Indeed, in accordance with this hypothesis, increasing the amount of ketone and base to 4 equiv. each forced the desired coupling by the law of mass action (according to Le Chatelier's principle), leading to an increased NMR yield of 90%, and a satisfactory 84% isolated yield (entry **7**).

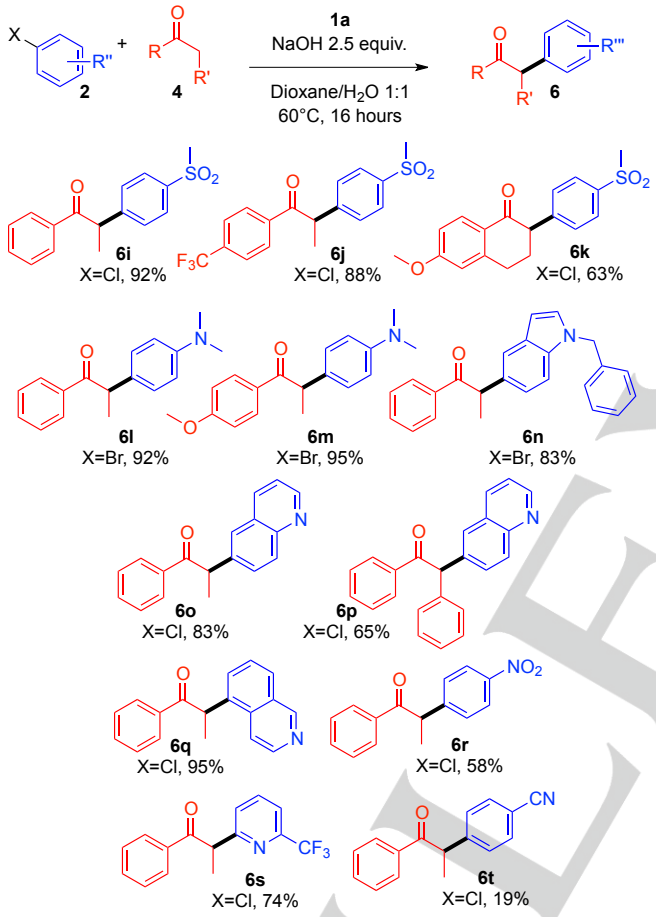
With the optimal conditions in hand, we began to explore the reaction scope and applicability to different substrates. At first, we investigated the coupling of a series of haloindoles: 5-, 6- and 7-Br-indole were all successfully coupled in high yields (**Scheme 2**, entries **6a-6c**). The effect of the halogen was verified using 7-Cl- and 7-I-indoles: while the latter gave only a slightly lower yield compared to its brominated congener, the former required an increased catalyst loading (from 2 to 5 mol%, entry **6c**) to restore full conversion and a synthetically useful yield. The use of different ketones was also tested: the CC of *o*-methylacetophenone with 7-Br-indole resulted in fair yield of the monoarylated compound **6d**, with the contemporary formation of the diarylated congener **6d'**. The lack of mono-arylation selectivity of [Pd(D*t*BPF)Cl_2], when acetophenone derivatives are used, is well known.[19] The reaction also proceeded well with 3-pentanone pronucleophile, affording moderate yield of product **6e**.



Scheme 2. Aqueous arylation of ketones using *N*-unprotected haloindoles and halotryptophan derivatives. Typical conditions: ketone (0.8 mmol, 4.0 equiv.), haloindole (0.2 mmol, 1.0 equiv.), NaOH (0.8 mmol, 4.0 equiv.), [Pd(D*t*BPF)Cl_2] 2 mol%, dioxane/water 1:1 (0.5 M), 60°C, 16h. [a] 5 mol% catalyst; [b] propiophenone (0.25 mmol, 5 equiv.) 0.05 mmol Halo-Tryptophan; NaOH (0.2 mmol, 4 equiv.), [Pd(D*t*BPF)Cl_2] 10 mol%; dioxane/water 1:1 (0.25 M), 60°C, 16h. Reactions are performed in triplicate, average isolated yields are given after purification and errors are reported in Supporting Information.

The Pd-mediated modification of halotryptophans can often be more demanding due to solubility issues as well as the chelation of the catalyst.[20] Our attempts to perform the reaction on fully unprotected 5-Br-tryptophan failed. To achieve the desired CC with such a challenging system, we explored *N*-protection of the halotryptophans. Employing *N*-Boc protected

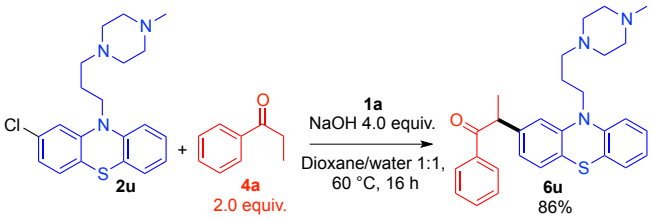
Br- and Cl-tryptophans, to our delight, this protocol was successful in providing good yields in all the three cases (70-94%, entries **6f-6h**). Excitingly, the first example of α-arylation of ketones using amino acid-derived aryl halides was achieved under Pd-catalysis. Although Itami *et.al.* reported two examples of such a reaction under Ni-catalysis, their protocol required harsher conditions (150 °C in toluene) and was limited to fully protected tyrosine derivatives.[21] To verify the retention of the *S*-configuration at the amino acid stereocenter under the reaction conditions, product **6h** was derivatized and analyzed following Marfey's procedure.[22] Satisfyingly, no racemization was observed (see Supporting Information for further details)



Scheme 3. Aqueous ketone arylation using other haloarenes. Typical conditions: ketone (0.8 mmol, 4.0 equiv.), haloindole (0.2 mmol, 1.0 equiv.), NaOH (0.8 mmol, 4.0 equiv.), [Pd(D*t*BPF)Cl$_2$] 2 mol%, dioxane/water 1:1 (0.5 M), T°C, 16h..Reactions are performed in triplicate, average isolated yields are after purification and errors are reported in Supporting Information.

To further explore the scope of this reaction, the arylation of functionalized haloarenes was investigated using the optimised method. Pleasingly, substrates with medicinally relevant functional groups, *i.e.* sulphones and tertiary amines, were well tolerated (entries **6i-6m**). Both electron-poor and electron-rich propiophenone derivatives were well suited and afforded high yields (entries **6j**, **6m**), while cyclic ketone derivatives proved less efficient and a significantly lower yield was obtained (entry **6k**). The effect of *N*-protection of 5-Br-indole was also studied: functionalization of the *N*-benzylated derivative was possible, again with a lower amount of ketone (2.0 equiv.), confirming the operation of a side-reaction involving the unprotected indole N–H bond (entry **6n**). The compatibility with functional groups such as nitro and nitrile (entries **6r** and **6t** respectively), that cannot generally withstand the excess of strong base usually employed in this reaction,[23] is a striking highlight of the synthetic potential of the conditions we developed. Other heterocyclic cores, *e.g.* quinoline, isoquinoline and pyridine, were also suitable substrates (entries **6o**-**6q**, **6s**). The suitability of aryl-benzylketone (entry **6p**) was also tested, and a satisfactory yield of the desired product **6p** was obtained using 6-Cl-quinoline as electrophilic coupling partner. Notably, lower amounts of ketone and base were required in all of these cases (2.0 and 2.5 equiv. respectively). The conditions we developed are comparable with the current state-of-the-art: a catalyst loading of 2 mol% was used for the general protocol developed by Colacot using **1a**;[17] while other authors needed an excess of ketone (2 equiv. or more) and higher catalyst loadings to achieve reactivity, when dealing with more challenging substrates, when using the same catalyst.[24] Considering the challenges posed by an aqueous system when working with anionic enolates (*vide supra*), our system is remarkably efficient.

To test the suitability of the protocol to real-world bioactive molecules, we examined the chlorinated drug, prochlorperazine **2u**, as a substrate (**Scheme 4**). Prochlorperazine, originally developed as an antipsychotic, is currently used as an antiemetic.[25] More recently, its antimicrobial activity has been demonstrated.[26] **2u** was reacted with propiophenone as pronucleophile, obtaining high yield of the desired product **6u** (86%, **Scheme 4**). In this case, 4 equiv. of base and 5 mol% catalyst loading were required. **2u** was used as free amine, obtained by basic extraction of the dimaleate salt which constitutes its commercial formulation. This result, together with those obtained with protected amino acids (entries **6f**-**6h**), highlights the potential of this methodology for the late-stage functionalization of complex bioactive compounds.



Scheme 4. Coupling of prochlorperazine with propiophenone under aquous conditions. Isolated yield is reported after purification. Reaction performed in triplicate.

In summary, the first protocol for the aqueous α-arylation of ketones is reported. The conditions employed are relatively mild and allow the coupling of a wide range of coupling partners including those bearing sensitive functional groups that can not tolerate strong bases usually required for this reaction. We have

also demonstrated the applicability of the conditions to challenging substrates including *N*-protected halotryptophan derivatives and a halogenated drug. This work paves the way for the employment of this vertsatile derivatisation chemistry in a GenoChemetic late-stage functionalization of engineered, halogenated natural products. These studies are currently ongoing in our laboratories.

Acknowledgements

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Keywords: Palladium • Aqueous coupling• Halogenated compounds • Ketone arylation • Amino acids

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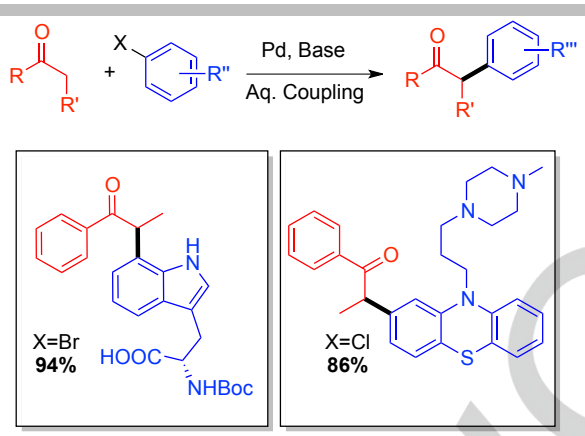
Don't leave me dry: The first aqueous α-arylation of ketones is reported. The reaction shows wide functional group compatibility, coupling alkyl- and aryl-ketones with heterocyclic and functionalized haloarenes in fair to excellent yields. The reaction scope includes chloro- and bromotryptophan derivatives, representing a potential platform for derivatization of complex molecules.



+ 23 more examples

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Page No. – Page No.

Mild, aqueous α-arylation of ketones: towards new diversification tools for halogenated metabolites and drug molecules