

Au-catalyzed cross-coupling of arenes *via* double C–H activation

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Supporting Information Placeholder

ABSTRACT: The first methodology for Au(I/III)-catalyzed oxidative cross-coupling of arenes *via* double C–H activation has been developed. The reaction is fully selective for the cross-coupling between electron-rich hetero-/carbocyclic arenes and electron-poor arenes bearing relatively acidic C–H bonds. The inherently high cross-selectivity of the system obviates the need for directing groups or a large excess of one of the coupling partners.

The oxidative cross-coupling of simple arenes *via* double C–H activation has the potential to constitute an ideal tool for the synthesis of biaryls, where two fragments of the target molecule would be joined together with no pre-functionalization and with minimal waste production.¹ Besides the challenges inherent to all C–H activation-based methodologies^{1d–e} (i.e. reactivity and regioselectivity), cross-couplings proceeding *via* double C–H activation also require suppression of undesired homo-coupling reactions (Figure 1a).²

To date, several methods for oxidative cross-coupling of arenes have been reported using Cu, Rh and, most frequently, Pd catalysts.¹ Within these, common approaches to address the cross-selectivity problem involve the use of one coupling partner bearing a directing group and/or a large excess (frequently 30–100 equiv) of the other,³ with only rare exceptions.⁴ These limitations can be explained in the context of a prototypical Pd(II/0)-catalytic cycle (Figure 1b) which requires two similar Pd(II) species (A and B), differing only on the ligands around the metal center, to perform the two C–H activation steps with a complete inversion of selectivity. As an alternative, an oxidative cross-coupling mechanism in which the two metal species performing the C–H activation steps have different oxidation state could provide a way around these limitations.

Precedents on the C–H metallation of arenes with Au(I) and Au(III) complexes suggested that Au could be a suitable catalyst for the oxidative cross-coupling between electron-rich and electron-deficient arenes in the context of a redox-controlled mechanistic manifold (Figure 1c).⁵ Importantly, C–H auration shows orthogonal selectivities dependent on the electronic properties of the arene and the oxidation state of the Au center.⁶ Au(III) species (F in Figure 1c) display a well-established selectivity for C–H activation of electron-rich

arenes, with scope and regioselectivity indicative of an electrophilic aromatic substitution (S_EAr).^{7,8} On the other hand, direct C–H auration with Au(I) compounds (D in Figure 1c) is specific for electron-poor arenes and heteroarenes, with regioselectivity favoring the most acidic C–H bond, characteristic of concerted metalation-deprotonation (CMD) or deprotonation-metalation mechanisms.⁹ Furthermore, the feasibility of an oxidative cross-coupling based on these elementary steps has been recently supported by stoichiometric studies.¹⁰

A similar approach using Pd(II/IV) systems has been explored previously. Despite having great synthetic value, the resulting transformations still required directing groups and a large excess of one of the arenes,¹¹ possibly to outcompete fast carbon-heteroatom reductive elimination.¹²

Herein, we present the successful development of the Au-catalyzed cross-coupling of electron-rich and electron-deficient arenes.

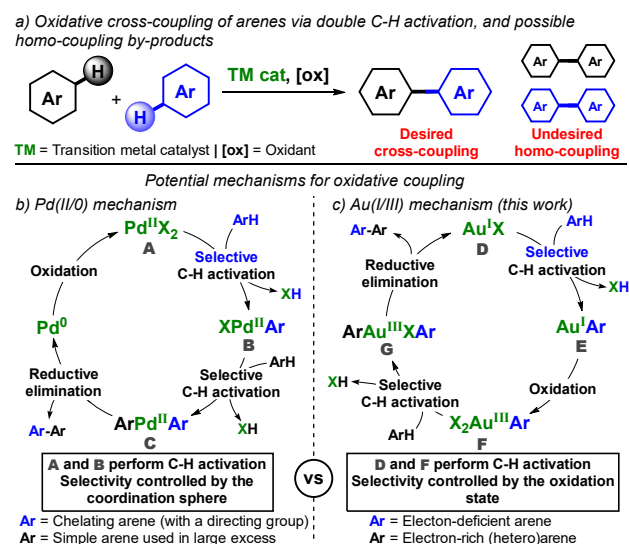


Figure 1. Oxidative cross-coupling of arenes, comparison of Pd- and Au-catalyzed putative mechanisms.

We started our investigation by studying the oxidative coupling between *N*-pivaloylindole (**1a**) and tetrafluorobenzene (**2a**) in the presence of an aryl-Au(I) pre-catalyst (**Au-2b**) containing a pentafluorophenyl unit (Figure 2). We envisioned that this experimental design would allow us to independently monitor the two fundamental parts of our hypoth-

esized catalytic cycle. Thus, formation of **3ab** would be an indication that the oxidative part of the catalytic cycle was operating (**E**→**F**→**G**→**D** in Figure 1c), whereas formation of **3aa** would also require the C–H activation of **2a** to form a new aryl–Au(I) compound (**D**→**E** in Figure 1c). Indeed, the reaction under these conditions with dipivaloyloxyiodobenzene (DPIB) as the oxidant¹³ provided a good yield of the stoichiometric coupling product **3ab** (9% out of a possible maximum of 10%) but no trace of **3aa**, indicating that no C–H activation of **2a** was taking place, preventing catalytic turnover. Based on previously reported conditions for the C–H activation of electron-poor arenes, we studied the use of stoichiometric bases, both with or without the addition of Ag(I) salts.^{8a,c} This, however, caused complete inhibition of the cross-coupling (Figure 2 and Tables S2–3). Surprisingly, when the stoichiometric base was omitted and using AgOPiv as a sub-stoichiometric additive, catalytic turnover was obtained, providing both **3ab** and **3aa** in 5 and 16% yield, respectively. Both cross-coupled products were obtained as single regioisomers from arylation at the indole C3 position.¹⁴

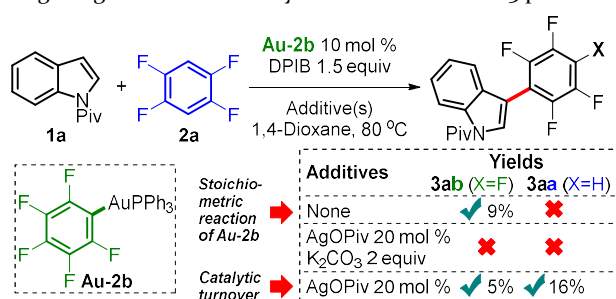


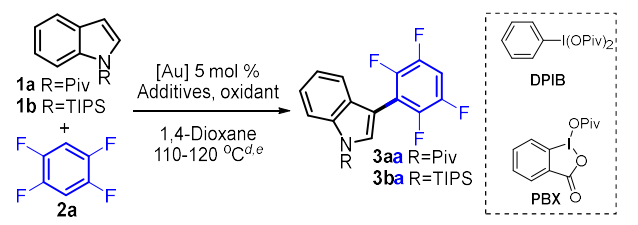
Figure 2. Initial search for conditions. Reactions run with **1a** (0.2 mmol), **2a** (5 equiv), DPIB (1.5 equiv) and **Au-2b** (10 mol %) in 1,4-dioxane (0.2 M) for 16 h.

Having found a lead for achieving catalytic turnover, we set out to optimize the cross-coupling using more practical pre-catalysts (Table 1). Thus, use of PPh₃AuCl (5 mol %) and AgOPiv (10 mol %) at 120 °C (entry 1) provided 33% yield of **3aa**, along with significant formation of iodinated by-products from both **1a** and **2a**, which increased when increasing the loading of AgOPiv. Use of the more stable oxidant 1-pivaloyloxy-1,2-benziodoxol-3(*1H*)-one (PBX) at 110 °C effectively suppressed the iodination side reactions and provided an increased 41% yield (entry 2).¹⁵ Adjusting the loading of AgOPiv resulted in a further improvement (entry 3) and the use of DMSO (0.5 equiv) as an additive provided 67% yield of product **3aa** (entry 4). Finally a screening of indole protecting groups (Table S7) showed *N*-TIPS-indole (**1b**) to be the best substrate, providing 77% yield of **3ba** (73% isolated, entry 5). Surprisingly, the addition of DMSO did not provide any improvement with **1b** (entry 6). This substrate dependence was observed also during the investigation of the substrate scope (Figure 3). Although the exact role of DMSO cannot be explained at the moment, it may be due to an increased solubility of AgOPiv and/or stabilization of low coordination number Au species in solution. The substrate dependence of its effect may be explained by a required compromise between the rates of the different steps in the mechanism, which are expected to depend on the nature of both substrates.

Other relevant observations obtained from the optimization process and additional control experiments include:

i) Au sources without a phosphine ligand also catalyzed the reaction, albeit with lower yields than PPh₃AuCl.¹⁶ (Table S1)
 ii) The presence of the Ag salt was necessary for the reaction to take place, even when PPh₃AuOPiv was used as the catalyst (Table S1), indicating a participation of Ag beyond chloride abstraction.
 iii) The reaction proceeded equally in the dark or under visible light irradiation, discarding a light-promoted transformation (Table S8).

Table 1. Optimization of the oxidative cross-coupling^a



Entry	1	Oxidant	Additives	T (°C)	Yield (%) ^b
1	1a	DPIB	AgOPiv (10)	120	33
2	1a	PBX	AgOPiv (10)	110	41
3	1a	PBX	AgOPiv (35)	110	49
4	1a	PBX	AgOPiv (35) DMSO (50)	110	67
5	1b	PBX	AgOPiv (35)	110	77 (73)
6	1b	PBX	AgOPiv (35) DMSO (50)	110	74

^a Reactions run as in Figure 2 with PPh₃AuCl (5 mol %).

^b Yields calculated by ¹H NMR with an internal standard, isolated yield in brackets.

We next explored the applicability of the optimized conditions (Figure 3a) in the coupling of *N*-TIPS-indole (**1b**) with various electron-poor arenes (Figure 3b). The oxidative coupling was compatible with a wide range of substituents –a key requirement both for the preparation of functionalized building blocks and for potential applications in late stage arylations. For example, protic, oxidizable benzylic alcohols could be used without requiring protecting groups (**3bt** and **3bu**), as well as other readily oxidizable groups such as thioether (**3be**) and benzylic aldehyde (**3bf**). While free amines were not compatible, simple masked forms such as nitro (**3bq**) and nitrile groups (**3bl**, **3bg**) –frequently troublesome in transition metal-catalyzed reactions– could be used, as well as phthalimide-protected tetrafluoroaniline (**3bj**). Benzoate ester (**3bh**) enolizable ketone (**3bp**) and fluorinated pyridines (**3br** and **3bs**) also underwent the coupling. Carbon-halogen bonds, including carbon-iodine (**3bm**, **3bn** and **3bo**), were well tolerated owing to the low tendency of Au(I) complexes to react with organohalides by oxidative addition.¹⁷ These demonstrate a complementary character of this methodology with respect to Pd-catalyzed transformations, and allow subsequent functionalizations of the products by ‘traditional’ cross-coupling reactions.

The reactivity decreased for less electron-deficient arenes, as illustrated by the polyfluorobenzene series: while pentafluorobenzene provided an excellent 85% yield of its corresponding arylindole product (**3bb**), those of 1,2,4,5- and 1,2,3,5-tetrafluorobenzene (**3ba** and **3bk**) were isolated in 73% and 62% yields, respectively. For less active substrates

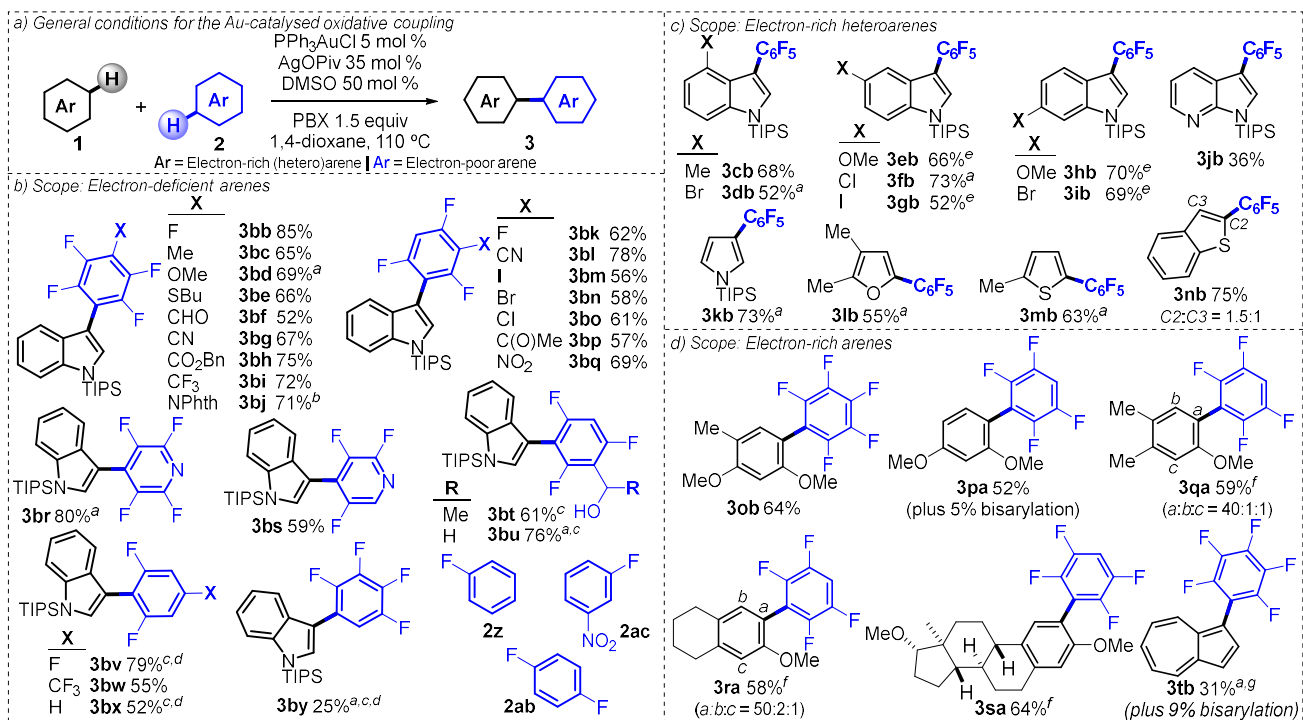


Figure 3. General optimized conditions for the Au-catalyzed oxidative cross-coupling (a) and scope for electron-poor arenes (b), electron-rich heteroarenes (c) and electron-rich carbocyclic arenes (d). Reactions run using arene or heteroarene **1** (0.2 mmol), **2** (1 mmol), PBX (0.3 mmol), PPh₃AuCl (0.01 mmol) and AgOPiv (0.07 mmol) in dioxane (0.2 M concentration of **1**) at 110 °C. ^a No DMSO added. ^b Isolated as the corresponding NH indole after deprotection with TBAF. ^c 10 equiv of **2** and 70 mol % AgOPiv. ^d 5 mol % phenanthroline used. ^e At 95 °C. ^f 10 mol % PPh₃AuCl, 40 mol % AgOPiv, 120 °C. ^g Isolated as an inseparable 10:1 mixture with 1-iodo-3-(perfluorophenyl)azulene.

such as 1,3,5-tri- and 1,3-difluorobenzene (**3bv** and **3bx**) the yields could be improved by using phenanthroline (5 mol %) as an additive, combined with increased loadings of both the fluoroarene (10 equiv) and AgOPiv (0.7 equiv). The presence of two fluorine substituents *ortho* to the position being activated was essential for good performance. Thus, 1,2,3,4-tetrafluorobenzene gave place to cross-coupling product **3by** in only 25% yield. Less electron-poor substrates such as fluorobenzene (**2z**) and 1,4-difluorobenzene (**2ab**) provided only traces, as well as 1-fluoro-3-nitrobenzene (**2ac**). 3,5-difluorobenzotrifluoride gave place exclusively to arylation in between the two fluorine substituents (**3bw**).

Regarding the indole counterpart (Figure 3c), substitution at either C4 (**3cb** and **3db**), C5 (**3eb**, **3fb** and **3gb**) or C6 (**3hb** and **3ib**) provided good yields, with carbon-halogen bonds (**3db**, **3fb**, **3gb** and **3ib**) being tolerated in this coupling partner as well. 7-Azaindole, however, provided only a modest yield (**3jb**). In addition to indoles, TIPS-protected pyrrole (**3kb**), 2,3-dimethylfuran (**3lb**) and 2-methylthiophene (**3mb**) were efficiently and selectively arylated. Benzothiophene showed excellent reactivity, although the regioselectivity in this case was poor (**3nb**).

Finally, the same reaction conditions also worked well for the arylation of electron-rich carbocyclic arenes (Figure 3d) such as 1,3-dimethoxytoluene (**3ob**), 1,3-dimethoxybenzene (**3pa**), 3,4-dimethylanisole (**3qa**) and a tetrahydronaphthol derivative (**3ra**). Phenol and anisole derivatives are important motifs in organic chemistry, being present in many natural products. When arylation of dimylestradiol was performed, product **3sa** was obtained in good yield, as a single

isomer and in a single step without requiring any pre-functionalization of the substrate. Methodologies to perform this or related transformations using the valuable, electron-rich arene as the limiting reagent are scarce.¹⁸ Azulene also reacted, although in low yield (**3tb**). In all the cases, the reaction displayed good selectivity for the most nucleophilic position on the arene, consistent with an electrophilic metalation mechanism of activation.

While optimal yields were generally obtained with 1:5 ratio of substrates, the reaction took place also with lower ratios without giving place to homo-coupling by-products. Thus, the arylation of **1b** with 1.5 equiv of **2b** (Figure 4) provided only a slightly decreased 70% yield of **3bb** while maintaining complete cross-coupling selectivity. Similarly, use of 1.5 equiv of tetrafluoropyridine provided 63% yield of **3br**.¹⁹

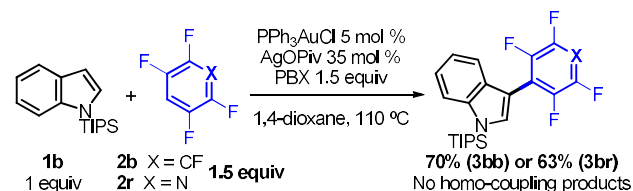


Figure 4. Cross-coupling with 1:1.5 ratio of arenes.

In conclusion, an efficient Au-catalyzed protocol for the oxidative cross-coupling of arenes has been developed. This methodology simplifies the preparation of biaryls by direct cross-coupling of simple electron-poor and electron-rich (hetero)arenes, with complete selectivity for the cross-coupling product over the two possible homo-couplings even

at close to stoichiometric ratio of arenes and without requiring the use of directing groups. We envision the general principles uncovered during this investigation will be applicable for the successful development of other new useful oxidative methodologies based on C–H activation. Although the exact mechanism is still not clear, the scope and regioselectivity of the electron-rich arenes are consistent with a Au(III) C–H activation. The required presence of Ag for catalytic turnover (Figure 2), suggests a possible involvement in the C–H activation of the electron-poor arene.^{4d,20} Thorough studies on the mechanism and the exact role of Ag in this transformation are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data of all new compounds and copies of ¹H, ¹³C and ¹⁹F NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (13) The more reactive and more electrophilic I(III) oxidant hydroxy(tosyloxy)iodobenzene (HTIB) resulted in poor mass recovery. Reaction of highly electron-rich arenes with HTIB has been previously described in a similar setting, giving place to diaryliodonium compounds which were inactive in the Au-promoted cross-coupling. See ref 10a.
- (14) Confirmed by ¹H NMR, see SI section 3.6.
- (15) With PBX as the oxidant, the reactions provided mainly product **3** and unreacted starting materials. Low yielding reactions provided also iodinated **1** and **2** in small amounts and, with substrate **1b**, deprotected indole and O-TIPS 2-iodobenzoic acid. Incomplete mass recovery is tentatively attributed to decomposition of the deprotected indole to insoluble materials.
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