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. Besides the challenges inherent to all C–H activation-based methodologies (i.e. reactivity and regioselectivity), cross-couplings proceeding via double C–H activation also require suppression of undesired homo-coupling reactions (Figure 1a).

To date, several methods for oxidative cross-coupling of arenes have been reported using Cu, Rh and, most frequently, Pd catalysts. 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, with only rare exceptions. 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). Importantly, C–H auration shows orthogonal selectivities dependent on the electronic properties of the arene and the oxidation state of the Au center. 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 (SAr). 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 metatation-deprotonation (CMD) or deprotonation-metatation mechanisms. Furthermore, the feasibility of an oxidative cross-coupling based on these elementary steps has been recently supported by stoichiometric studies. 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, possibly to outcompete fast carbon-heteroatom reductive elimination.

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 (Au2b) containing a pentafluorophenyl unit (Figure 2). We envisioned that this experimental design would allow us to independently monitor the two fundamental parts of our hypo-
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(II) compound (D→E in Figure 1c). Indeed, the reaction under these conditions with dipivaloyloxyiodobenzene (DPIB) as the oxidant 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. 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.44

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).55 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 the precatalyst (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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Additives</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>DPIB</td>
<td>120</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>AgOPiv</td>
<td>110</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>PBX</td>
<td>110</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>PBX</td>
<td>110</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>AgOPiv</td>
<td>110</td>
<td>77 (73)</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>AgOPiv</td>
<td>110</td>
<td>74</td>
</tr>
</tbody>
</table>

* Reactions run as in Figure 2 with PPh₃AuCl (5 mol %).
* 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—key requirement both for the preparation of functionalized building blocks and for potential applications in late stage arylations. For example, protoxidic benzylalcohol could be used without requiring protecting groups (3bt and 3bu), as well as other readily oxidizable groups such as thiocarbonyl (3be) and benzylaldehyde (3bf). While free amines were not compatible, simple masked forms such as nitro (3bh) and nitrile groups (3bl, 3bg) – frequently troublesome in transition metal-catalyzed reactions—could be used, as well as phthalimide-protected tetrafluoroaniline (3bi). Benzoeate ester (3bb) 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(III) complexes to react with organohalides by oxidative addition.7 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 pentfluorobenzene 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 carboxylic arenes (d). Reactions run using arene or heteroarene (0.2 mmol), 2 (1 mmol), PBX (0.3 mmol), PPh3AuCl (0.01 mmol) and AgOPiv (0.07 mmol) in 1,4-dioxane (0.2 M concentration of 1) at 110 °C. *No DMSO added. † Isolated as the corresponding NH indole after deprotection with TBAF. ‡ 10 equiv of 2 and 70 mol % AgOPiv. ‡ 5 mol % phenanthroline used. * At 95 °C / 10 mol % PPh3AuCl, 40 mol % AgOPiv, 120 °C. † Isolated as an inseparable 1:2 mixture with trans-1,3,5-tris-(perfluorophenyl)azulene.

such as 1,3,5-tri- and 1,3,4-difluorobenzene (3bw 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 (2x) and 1,4-difluorobenzene (2ab) provided only traces, as well as 1-fluoro-3-nitrobenzene (2ac). 1,3,5-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-Azaazidole, 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 aryalted. 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 carboxylic arenes (Figure 3d) such as 1,3-dimethylurea (3ob), 1,3-dimethoxybenzene (3pa), 3,4-dimethylaniline (3qa) and a tetrahydroanaphol derivative (3ra). Phenol and anisole derivatives are important motifs in organic chemistry, being present in many natural products. When arylation of dimethylstilbene 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 meta functionalization 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 65% 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.†‡ Through 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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REFERENCES


(5) For other results with 1-1.5 equiv of fluoroarene, see Table S9.

(6) For a Cu-catalyzed oxidative coupling between electronically differentiated arenes, see ref. 4b. For a single example of oxidative coupling between indole and pentafluorobenzene, see ref. 3d.
Electron rich Ar

Metalation at nucleophilic C

Electron-poor Ar

Metalation at acidic C-H

Au Ar complex

 oxidative cross-coupling

Selectivity for cross-coupling

No directing groups needed

Down to 1:1.5 Ar:Ar ratio

Hetero- and carbonylic Ar

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