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Oxidative Coupling

Redox-Controlled Selectivity of C−H Activation in the Oxidative Cross-Coupling of Arenes**

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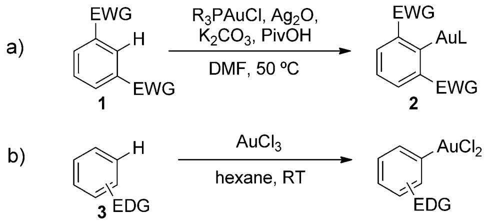
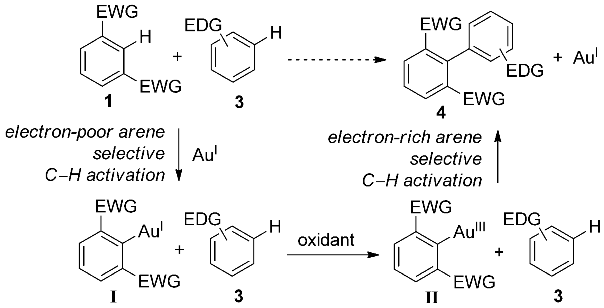
The ultimate application of C−H activation to the synthesis of biaryl compounds is a reaction in which two non-prefunctionalized arenes are cross-coupled.[1,2] Such an oxidative cross-coupling would substantially streamline synthetic strategies, resulting in greener methods. To date, these oxidative couplings have been catalyzed almost exclusively by Pd, with some recent examples using Cu.[3,4] However, several drawbacks remain to be addressed before these methods can be widely applied. First, harsh reaction conditions are commonly needed, with strong acids required as solvents and/or temperatures typically exceeding 110 °C. Second, poor regioselectivities are generally obtained with substituted arenes. Finally, in most oxidative couplings, both coupling partners are activated by Pd^{II} or Pd^{IV} species that have very similar selectivities, which results in the need for using 30–300 equiv of one of the two arenes to ensure that cross-coupling, rather than homo-coupling, is achieved.[5]

We hypothesized that a transition metal capable of presenting orthogonal C−H activation selectivities depending on its oxidation state would allow a new approach towards the rational design of oxidative cross-coupling methods with high selectivities. Herein, we demonstrate that Au species present this unique redox-controlled selectivity and highlight their potential use for the design of novel cross-couplings involving oxidative double C−H activation. These Au-mediated transformations proceed at lower temperatures than current Pd systems, and display excellent regioselectivities, high cross- versus homo-coupling selectivities (thus avoiding the need for vast excesses of the arenes), and are compatible with Pd-sensitive groups, such as I and Br.[6]

We have recently reported that Au^{I} salts are able to mediate the C−H activation of electron-poor arenes at just 50 °C (Scheme 1 a).[7] This contrasts with the well-known ability of Au^{III} salts to perform C−H activation of electron-rich arenes, even at room temperature (Scheme 1 b).[8,9] We thus hypothesized that, if Au^{I} and (III) salts are completely selective for electron-poor and -rich arenes, respectively, this interesting property of Au could be exploited to provide a completely selective double C−H activation-based cross-coupling method (Scheme 2). In our hypothetical process, a mixture of an electron-poor (**1**) and an electron-rich (**3**) arene would initially react with a Au^{I} salt, leading to selective C−H activation of **1**. Upon addition of an oxidant, aryl–Au^{I} species **I** would be oxidized to Au^{III} complex **II**, which in turn would perform selective C−H activation on the electron-rich arene, forming biaryl **4** upon reductive elimination. The development of such a process presents a number of challenges: 1) Despite the few recent methods suggested to proceed by a $Au^{I/III}$ redox cycle,[10,11] to date none involve the oxidation of aryl–Au^{I} species **I**. 2) C−H activation by aryl–Au^{III} species **II** has never been demonstrated, although it may be a step in the homocoupling of electron-rich arenes.[12] 3) Aryl–Au^{III} species have been suggested to undergo ligand scrambling by transmetalation, giving rise to homocoupling products.[9,10]



Scheme 1. Au^{I} versus Au^{III} C−H activation. EDG = electron-donating group, EWG = electron-withdrawing group.



Scheme 2. Hypothetical redox-controlled highly selective oxidative cross-coupling of electron-rich and electron-poor arenes.

Initially, we explored the coupling of *o*-iodoanisole with aryl–Au^{I} **2a** (Table 1), which was prepared under our standard C−H activation conditions (Scheme 1 a)[7] in 99 % yield. Oxidant optimization revealed that, whereas in the absence of oxidant no product was obtained, the desired cross-coupling product could be observed, albeit in low yields,

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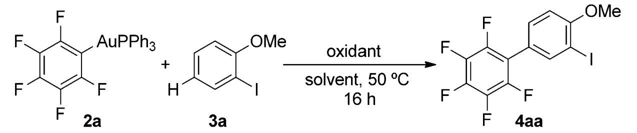
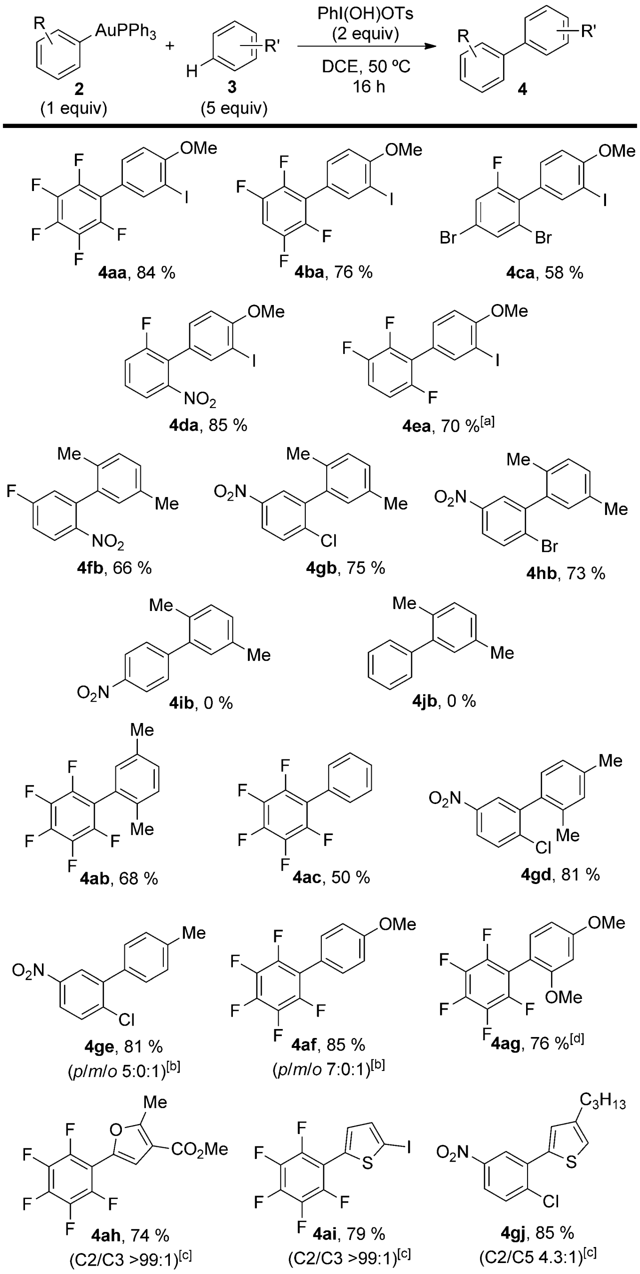
Table 1: Optimization of the oxidative cross-coupling procedure with aryl–Au^I **2a** and *o*-iodoanisole.[a]



Entry	Oxidant	Solvent	**4aa** [%]
1	–	DCE	0
2	Selectfluor	DCE	traces
3	XeF_2	DCE	12
4	$PhI(OAc)_2$	DCE	48
5	$PhI(OCOCF_3)_2$	DCE	51
6	$PhI(OPiv)_2$	DCE	81
7	**PhI(OH)OTs**	**DCE**	**91**
8	PhI(OH)OTs	dioxane	52
9	PhI(OH)OTs	DMF	0
10	PhI(OH)OTs	MeCN	34

[a] Reactions were performed under N_2 atmosphere with **2a** (1 equiv), *o*-iodoanisole (5 equiv), and oxidant (2 equiv). Yields were determined by ^1H NMR spectroscopy using an internal standard. DCE = 1,2-dichloroethane, DMF = dimethylformamide, Piv = pivaloyl, Selectfluor = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), Ts = *p*-toluenesulfonyl.

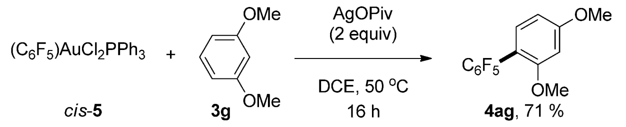


Scheme 3. Scope of the Au$^{I/III}$-mediated oxidative cross-coupling. Yields shown are of isolated products. [a] Reaction performed at 70 °C with **3a** (10 equiv). [b] Determined by ^1H NMR analysis. [c] Determined by GC-MS analysis. [d] 1,3-dimethoxybenzene was added after stirring all the other reagents at 50 °C for 10 min.

when using Selectfluor or XeF_2, which are known to oxidize Au^I to Au^{III} (Table 1, entries 1–3). Gratifyingly, the use of iodonium species, PhI(OH)OTs in particular, afforded **4aa** in high yield (entry 7). Aryl–Au^I complexes have previously been used to form biaryls in Pd- and Ni-catalyzed cross-couplings with (pseudo)haloarenes,[13] but, to the best of our knowledge, this is the first example of a direct C–H arylation using these species.

These optimized conditions were then applied to a number of *ortho*-disubstituted aryl–Au^I compounds **2** (Scheme 3a). We were pleased to observe that the desired cross-coupling products (**4aa**–**4ea**) were isolated in good yields. Furthermore, as we had hypothesized, the procedure affords excellent selectivity, with the cross-coupling products almost exclusively obtained in preference to their potential homo-coupling counterparts,[14] and with no detection of a second arylation onto the anisole unit of the biaryls. Remarkably, this oxidative coupling tolerates both I (**4aa**–**4ea**) and Br (**4ca**) substituents, which are generally not compatible with Pd-mediated couplings. This provides a valuable highly reactive handle for subsequent Pd-based transformations and illustrates the unique reactivity of this system. Ar–Au^I compounds bearing only one *ortho* electron-withdrawing group (Cl, NO_2, and Br) were also found to undergo the C–H arylation process (**4fb**–**4hb**).[15] On the contrary, when the electron-withdrawing substituent (NO_2) is in the *para* position (**4ib**), or absent altogether (**4jb**), no reaction is observed.

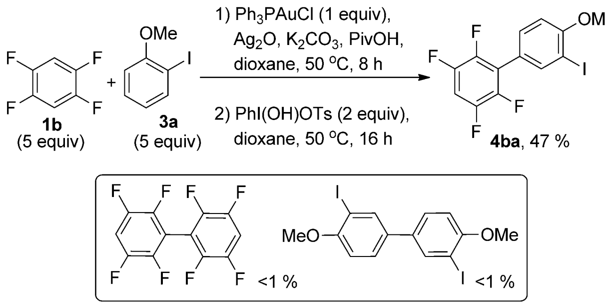
To further explore the potential of the Au$^{I/III}$ redox couple in oxidative couplings, we tested the reaction with electron-rich arenes **3b**–**j** (Scheme 3b). Even benzene reacts at 50 °C (**4ac**) with an excess of only 5 equiv, in contrast to the much more forcing conditions required for analogous processes with Pd.[16] The regioselectivities of the arylation are clearly suggestive of an S_EAr-type process (**4gd**–**e** and **4af**–**g**). Thus, monosubstituted toluene (**4ge**) and anisole (**4af**) display very high *para*-selectivity (*para*/*ortho* 5:1 and 7:1, respectively), again in contrast to Pd systems, which often provide mixtures of the *para*, *meta*, and *ortho* products in non-useful ratios.[2,17] Similarly, 1,3-xylene and 1,3-dimethoxybenzene afforded exclusively 1,3,4-substituted adducts **4gd** and **4ag**, in contrast to the mixtures commonly obtained with Pd, where 1,3,5-arylation predominates.[1,2] Heteroarenes can also be used as coupling partners (**4ah**–**i**, **4gj**) with good regioselectivities.



Scheme 4. Mechanistic studies to test the intermediacy of Au^{III} species.

To probe the intermediacy of the aryl–Au^{III} species **II** suggested in Scheme 2, we prepared well-defined aryl–Au^{III} species *cis*-**5** (Scheme 4),[18] which proved unreactive when treated with 1,3-dimethoxybenzene (**3k**) at 50 °C. Interestingly, the addition of AgOPiv to replace the Cl ligands with OPiv (Piv = pivaloyl) allowed the formation of the cross-coupling adduct **4ag** in 71 % yield. This result closely matches the yield obtained using PhI(OH)OTs as an oxidant (Scheme 3), and can be explained by the formation of more electrophilic Au^{III}–pivalate species similar to those that would result upon oxidation of **2a** with $PhI(OPiv)_2$ (Table 1, entry 6), which confirms that aryl–Au^{III} species are likely to be involved in this highly selective process.[19] Alternative additional mechanisms for the processes detailed in Scheme 3 that involve direct reaction of the I^{III} species with the starting arenes were also considered and discarded.[20]

Having demonstrated the high selectivity of the aryl–Au^{I}/electron-rich arene cross-coupling, it remained to examine the overall selectivity of the process, starting from a 1:1 mixture of both initial arenes. Thus, a combined procedure where both C–H activations occur in the presence of both arenes was investigated. This presented a number of challenges: 1) the optimal solvent for Au^{I}-mediated C–H activation (DMF) was incompatible with the Au^{III} process, and conversely, DCE prevented Au^{I}-mediated C–H activation; 2) the Au^{III}-mediated process is incompatible with the presence of bases, which are required for the Au^{I} process. After solvent screening, it was found that a mixture of 1,2,4,5-tetrafluorobenzene (**1b**, 5 equiv) and 2-iodoanisole (**3a**, 5 equiv) treated with Ph_3PAuCl (1 equiv) under our standard C–H activation conditions, but using dioxane as the solvent (Scheme 5) led to exclusive formation of aryl–Au^{I} **2b** (> 99 %) and left **3a** untouched, as shown by ^1H and ^{31}P NMR analysis. Filtration of the mixture of **1b**, **3a**, and **2b** through Celite followed by the addition of PhI(OH)OTs (2 equiv) led to selective arylation of **3a**, leaving the remaining **1b** untouched, with formation of cross-coupling product **4ba** in 47 % yield (comparable to Table 1, entry 8). Only traces of the homo-coupling products of both starting arenes were detected by GC-MS analysis (< 1 %). This experiment demonstrates the powerful selectivity achievable by applying redox selectivity control and opens the door to its application in the design of novel dehydrogenative oxidative cross-couplings.



Scheme 5. Completely selective cross-coupling in the presence of an excess of both arenes.

In conclusion, we have demonstrated that the selectivity of C–H activation between electron-rich and -poor arenes can be completely controlled by switching the oxidation state of Au species. These experiments provide a new approach towards the rational design of highly selective systems for the C–H activation of arenes. This process has important advantages compared to current Pd-based methods, such as cross- versus homo-coupling selectivity, higher or complementary regioselectivity, and reactions that proceed at lower temperatures. Future development in this area will involve the development of dehydrogenative cross-coupling processes that are catalytic in gold. This will require addressing the challenge of developing mutually compatible conditions for each C–H activation step and an oxidant that selectively oxidizes aryl-Au^{I} species in the presence of other Au^{I} intermediates.

Experimental Section

General procedure for biaryl synthesis via oxidative cross-coupling: A mixture of PhI(OH)OTs (118.0 mg, 0.30 mmol), arylgold(I) compound **2** (0.15 mmol), and the arene coupling partner (0.75 mmol) in 1,2-dichloroethane (0.75 mL, 0.20 M) was stirred at 50 °C for 16 h. After this time, the resulting mixture was purified by column chromatography to afford the desired coupling products **4**. The ratio of regioisomers was evaluated by GC-MS analysis of the crude mixture.

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[20] Some of the possibilities considered were: 1) A transmetallation from Ar–Au$^{\mathrm{I}}$ **2** to PhI(OH)OTs to form (ArIPh)OTs followed by reaction with the electron-rich arene could occur; the compound (C$_6$H$_5$IPh)OTs was synthesized, but all attempts to couple it with 1,3-dimethoxybenzene, both with and without the addition of Au$^{\mathrm{I}}$ salts, failed. 2) Alternatively, the initial reaction of the electron-rich arene **3** with PhI(OH)OTs to form (Ar′IPh)OTs, could be followed by reaction with the Ar–Au$^{\mathrm{I}}$ species **2**; several (Ar′IPh)OTs were prepared and their coupling with Ar–Au$^{\mathrm{I}}$ under a variety of conditions was attempted without success. See the Supporting Information for details on these and other experiments.