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Gold(I)-Mediated C−H Activation of Arenes

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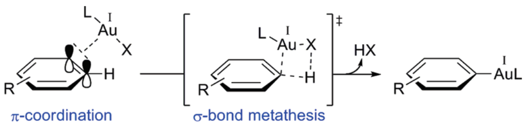
In the past decade homogeneous gold catalysis has spawned a vast array of novel transformations for C−C bond formation.[1,2] These methodologies commonly involve the use of Au(I) or Au(III) salts as powerful π acids for the activation of alkynes, alkenes, and allenes. Au(III) salts have also been shown to perform the activation of C−H bonds in electron-rich arenes, which is believed to proceed via an electrophilic aromatic substitution process.[3] In contrast with other transition metals, Au(III)-mediated activation occurs under very mild conditions, often at room temperature. Based on this mode of activation, several methods for the Au(III)-catalyzed direct functionalization of electron-rich arenes have been reported recently, including homocoupling and coupling of arenes with epoxides, alkyl triflates, imines, alkynes, and alkenes.[4]

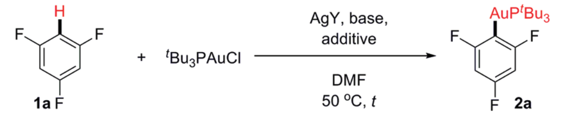
On the contrary, despite the anomalous stability of arylgold(I) complexes, Au(I) salts have never been shown to perform the direct C−H activation of aromatic compounds.[5,6] Indeed, being a late transition metal in a low oxidation state, the electrophilic substitution pathway may seem to be precluded for Au(I) complexes.[7] However, due to their uniquely strong π-coordination to unsaturated hydrocarbons including arenes,[8] other C−H activation modes may be available for Au(I). We envisaged that this strong coordination could lead to direct C−H activation of arenes via a σ-bond metathesis (SBM) pathway as depicted in Scheme 1.[9] Herein we report the first protocol for direct C−H activation of electron-poor arenes with Au(I). This new reaction mode of Au(I) has the potential to enable new mild synthetic methodologies for arene functionalization.

Scheme 1. Proposed Au(I)-Mediated C−H Activation of Arenes



We began our investigations with the electron-poor 1,3,5-trifluorobenzene (**1a**), which has previously been shown to undergo C−H activation with low-valent late transition metals via both SBM and oxidative addition pathways.[10] Initially, we examined the C−H activation of **1a** by $^t\mathrm{Bu_3PAuCl}$ at 50 °C in the presence of DBU, which led to no reaction (entry 1, Table 1). To our delight, addition of $\mathrm{AgSbF_6}$ (entry 2) led to the desired product (**2a**) with 60% yield (as determined by ^{1}H NMR analysis), presumably through the removal of Cl which provides a more cationic Au(I) center.[1] The use of CsOPiv as a base further increased the yield to 64% (entry 3). These results led us to hypothesize that the actual reactive gold species is $^t\mathrm{Bu_3PAuOPiv}$. Consequently, we speculated that the combined use of PivOH and $\mathrm{Ag_2O}$ would afford similar results. Nevertheless, initial experiments with PivOH and $\mathrm{Ag_2O}$ gave only a 37% yield of **2a** (entry 4), showing that a more profound effect was in place. Screening of the base counterion revealed that whereas NaOPiv generated *in situ* from $\mathrm{Na_2CO_3}$ and PivOH (entry 5) gave only 15% yield, KOPiv generated *in situ* from $\mathrm{K_2CO_3}$ and PivOH (entry 6) gave an excellent yield of 89%. Interestingly, further optimization revealed that in the presence of both AgOPiv and KOPiv the yield increased dramatically to 100% (entry 7). With these optimized conditions we were able to isolate via standard silica gel column chromatography the gold arene **2a** in 100% yield after only 2 h at 50 °C (entry 8). The structure of **2a** was confirmed unequivocally by means of X-ray crystallography (Figure 1). This reaction occurs under remarkably mild conditions (50 °C, mild base), in contrast with those mediated by Rh, Ir, Pd, Cu, or Li, which require high temperatures and/or the use of strong bases. Furthermore, it is operationally simple, and all reagents can be weighed under air without any special precautions.

Table 1. Optimization of Au(I)-Mediated C−H Activation of **1a**[a]



entry	AgY	base	additive	*t* (h)	yield (%)[b]
1	—	DBU	—	16	0
2	$\mathrm{AgSbF_6}$	DBU	—	16	60
3	$\mathrm{AgSbF_6}$	CsOPiv	—	16	64
4[c]	$\mathrm{Ag_2O}$	PivOH	—	16	37
5	$\mathrm{AgSbF_6}$	$\mathrm{Na_2CO_3}$	PivOH	16	15
6	$\mathrm{AgSbF_6}$	$\mathrm{K_2CO_3}$	PivOH	16	89
7[d]	$\mathrm{Ag_2O}$	$\mathrm{K_2CO_3}$	PivOH	16	100
8[d]	$\mathrm{Ag_2O}$	$\mathrm{K_2CO_3}$	PivOH	2	(100)

[a] Unless otherwise noted, all reactions were carried out under $\mathrm{N_2}$ atmosphere with AgY (1.5 equiv), base (2.5 equiv), additive (2.5 equiv), **1a** (4.5 equiv), and $^t\mathrm{Bu_3PAuCl}$ (1.0 equiv) in a 0.2 M DMF solution. [b] Yield of **2a** was determined by ^{1}H NMR analysis using an internal standard. Yields in brackets indicate isolated pure material. [c] $\mathrm{Ag_2O}$ (1.25 equiv) was used. [d] $\mathrm{Ag_2O}$ (0.75 equiv) and $\mathrm{K_2CO_3}$ (1.75 equiv) were used.

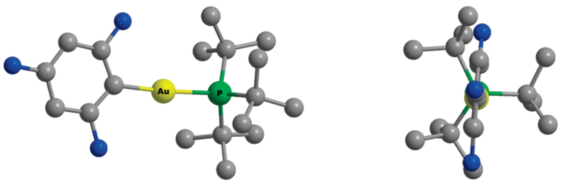


Figure 1. Structure of **2a** determined by X-ray crystallography represented in two different perspectives: (left) along the *x* axis and (right) along the *y* axis (blue is F, yellow is Au, green is P, and gray is C).

With the optimized conditions in hand, we then set out to explore the scope of this protocol with respect to other arene substrates. As shown in Scheme 2, good to excellent yields were obtained with several fluorinated benzenes to afford gold arenes **2b**−**e**.

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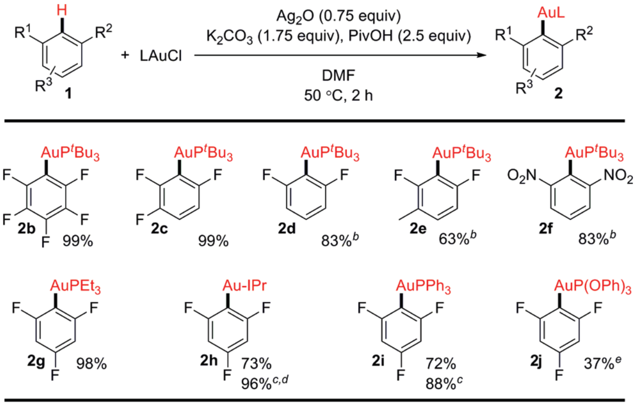
Remarkably, in every single example the Au(I)-mediated C−H activation was completely regioselective for the most electron-deficient C−H bond, in contrast to C−H activation reactions performed with Ir or Rh complexes, which generally show *meta* and *para* kinetic selectivity.[10d,e] C−H activation becomes more difficult (**2e**, 63%) or completely stops when more electron-rich arenes, such as *p*-fluoroanisole, are used. It is noteworthy that fluorine substituents are not a requirement for the reaction to proceed, as shown by the Au(I)-mediated C−H activation of 1,3-dinitrobenzene, which afforded **2f** in excellent yield.

Scheme 2. Scope of C−H Activation of Arenes with LAuCl[a]



[a] Yields are of isolated pure material. [b] These reactions were carried out for 16 h. [c] These reactions were carried out for 4 h. [d] IPr = 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene). [e] NMR yield; see ref 11.

This procedure is also compatible with a variety of ligands (L) on the Au(I) complex, such as alkyl and aryl phosphines, phosphites, and N-heterocyclic carbenes (**2g**−**j**). Interestingly, strong σ-donor ligands outperform ligands that are good π-acceptors (in the order PEt_3 (**2g**) > PPh_3 (**2i**) > $P(OPh)_3$ (**2j**)), which is consistent with a more stable gold−arene π-complex. On the other hand, cone angle does not seem to affect the reaction (compare **2a** vs **2g**; cone angles for P^tBu_3 and PEt_3 are 182° and 132°, respectively).[12] Structures of compounds **2a**−**2f**, **2h**, and **2i** were confirmed by X-ray crystallographic analysis.

The Au(I)-mediated C−H activation described here is consistent with a concerted metalation deprotonation, as first suggested for Pd(II) complexes by Fagnou, Maseras, and Echavarren, where a coordinated pivaloate ligand acts as a proton acceptor via a six-member transition state.[10a,13] Furthermore, the observation of a large primary KIE of 5 indicates that the C−H breaking step occurs during the rate-limiting step of the reaction.[14] On the other hand, an oxidative addition mechanism, where a transient Au(III) hydride species is formed, would also be consistent with these observations and for the moment cannot be discarded.[7,15]

In conclusion, we have developed the first general protocol for direct C−H activation of electron-poor arenes with Au(I) complexes. This operationally simple procedure not only provides a more straightforward alternative to the existing methods of preparing Au(I) arenes[16] but also opens the door to novel Au(I)-mediated transformations, which is especially exciting given Hashmi's recent report on the use of Au(I) arenes in Pd catalyzed cross-couplings.[17] Current investigations are directed toward the use of substoichiometric Au(I) catalysts to perform direct C−H functionalization reactions.

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Supporting Information Available: Experimental details and full characterization for all new compounds (PDF) and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See Supporting Information for experimental details.

(15) A reviewer suggested that the excess silver may be responsible for the C−H activation followed by transmetallation to gold. Reaction of **1a** as in entry 8 (Table 1) but with 0.9 equiv of $AgSbF_6$ instead of 0.75 equiv of Ag_2O afforded **2a** in 50% yield. Furthermore, a blank experiment using 1,3-difluorobenzene in the absence of LAuCl and in the presence of 20 equiv of D_2O showed no deuteration after 16 h at 50 °C. These results appear to rule out Ag-mediated C−H activation.

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