Nitrogen Heterocycles

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Combining Gold(I)/Gold(III) Catalysis and C–H Functionalization: A Formal Intramolecular [3+2] Annulation towards Tricyclic Indolines and Mechanistic Studies**

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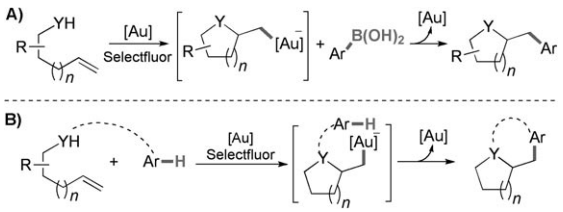
Homogeneous gold catalysis involving gold(I)/gold(III) catalytic cycles[1] has recently attracted much attention and is poised to ignite the next round of "gold rush" because of its mechanistic resemblance to versatile reactions catalyzed by transition metals such as palladium, nickel, copper, and rhodium. Before 2009, several notable reports of oxidative homocoupling[2] using catalytic[3] or stoichiometric amounts[4] of gold complexes or salts suggested that a gold(I)/gold(III) catalytic cycle is feasible, albeit with limited mechanistic proof. The first examples of homogeneous gold-catalyzed oxidative cross-coupling reactions were reported by us in 2009,[5] where C_{sp^2}–C_{sp^2}[5a] and C_{sp^2}–O[5b] bonds were formed. In these studies along with a homocoupling reaction,[6] Selectfluor [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate)][7] was found to be a uniquely versatile oxidant for promoting these oxidative processes.

To expand the bond types[4c,8] that could be formed, we recently reported an oxidative coupling between alkyl gold compounds and arylboronic acids, thus resulting in the efficient functionalization of vinyl groups (Scheme 1 A).[9] Our deuterium-labeling studies established that the C_{sp^3}–C_{sp^2} bond formation was highly stereoselective. Toste and coworkers later reported the use of a different gold catalyst for this chemistry[10] and extended it to a three-component coupling reaction.[11] Lately, arylsilanes[12] have been used instead of arylboronic acids in the three-component reaction.



Scheme 1. A) The oxidative coupling of an alkyl gold compound with a C–B bond[9,10] and B) the oxidative coupling of an alkyl gold compound with a C–H bond (this work).

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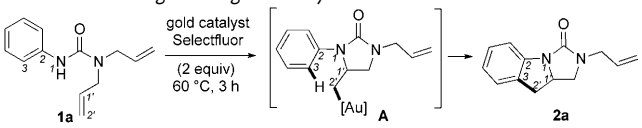
Transition-metal-catalyzed C–H activation/functionalization[13] and gold catalysis are contemporary research topics of immense interest. The combination of these two areas[4c,14] offers an increasing number of exciting opportunities for the development of efficient synthetic methods. Notably, C_{sp^2}–H bonds have so far been coupled with alkynyl[8a,b,d] or alkenyl gold compounds[15] but not alkyl gold compounds through oxidative gold catalysis. During our studies of gold(I)/gold(III) catalysis, we decided to examine whether C_{sp^2}–H bonds could replace the aforementioned C_{sp^2}–M bonds (M = Si or B) in the coupling with alkyl gold compounds (Scheme 1 B). This C–H functionalization would employ simple and economical substrates and, moreover, offer a valuable opportunity to probe the mechanism of gold-mediated C_{sp^3}–C_{sp^2} bond formations in the absence of any potential F–M (M = Si or B) interaction.[10,12b] Herein we report a convenient synthesis of tricyclic indolines in a formal intramolecular [3+2] manner by oxidative gold catalysis. Mechanistic studies suggest that the C_{sp^2}–H bond is activated by electrophilic aromatic auration and the C_{sp^3}–C_{sp^2} bond formation proceeds through an inner-sphere reductive elimination on a gold(III) center.

Although our attempt to use benzene and toluene, as either the solvent[16] or an excess reagent, to achieve intermolecular cross-coupling of C–H bonds with in situ generated alkyl gold compounds had failed, we turned to the intramolecular coupling reaction of *N*,*N*-diallyl-*N*′-phenylurea (**1a**).[8c] We anticipated that this reaction would proceed through a selective cyclization by the urea nitrogen atom and the subsequent desired oxidative coupling of the formed alkyl gold moiety with the *ortho* C–H bond on the tethered phenyl group (Table 1). Notably, this reaction constitutes a formal [3+2] annulation[17] between the aniline moiety and the C–C double bond, and the first formal C–H functionalization by alkyl gold intermediates; moreover, the tricyclic indoline motif has been studied in the search for inhibitors of 11B-HSD1.[18]

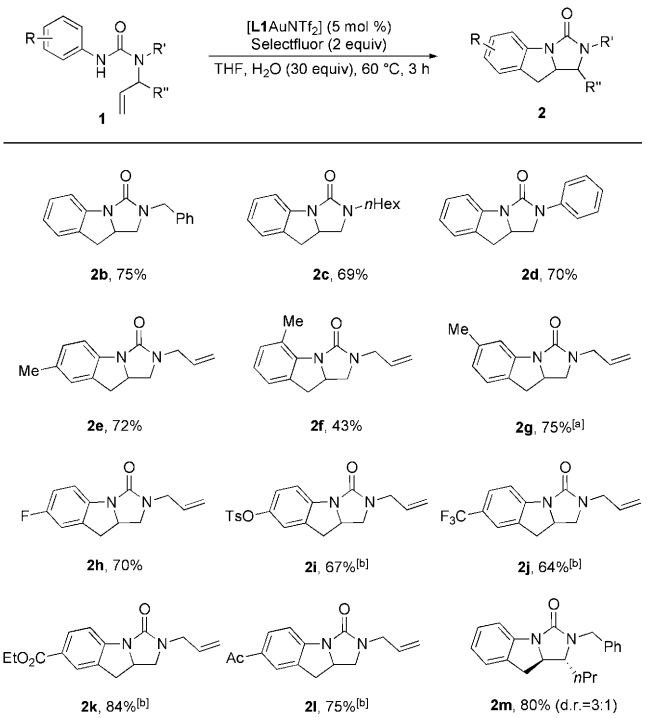
Our initial screening of various [LAuX] complexes (X = halide) included [Ph_3PAuCl] (entry 1) and [$dppm(AuBr)_2$][10] (entry 2), and cationic gold(I) complexes (entries 3 and 4), all of which led to disappointing results. However, a small amount of the desired **2a**[19] was detected when the solvent was changed from MeCN to THF and the more reactive [$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$] catalyst[20] was used (entry 5). To our delight, the reaction was significantly improved when H_2O (15 equiv) was added (entry 6); 30 equivalents of H_2O was found to be optimal and the reaction yield was improved to

Table 1: Screening of the gold catalysts and reaction conditions.[a]



Entry	Catalyst	Additive	Solvent	Yield [%][b]
1	$[Ph_3PAuCl]$	–	CH_3CN	<5%
2	$[dppm(AuBr)_2]$	–	CH_3CN	<5%
3	$[Ph_3PAuNTf_2]$	–	CH_3CN	<5%
4	[**L1**$AuNTf_2$]	–	CH_3CN	<5%
5	[**L1**$AuNTf_2$]	–	THF	9%
6	[**L1**$AuNTf_2$]	H_2O (15 equiv)	THF	60%
7	[**L1**$AuNTf_2$]	H_2O (30 equiv)	THF	80%(79%)[c]
8	[**L1**$AuNTf_2$]	Ph_3PO (2 equiv)	THF	<5%
9	[**L1**$AuNTf_2$]	TMU (2 equiv)	THF	50%
10	[**L1**AuCl]	H_2O (30 equiv)	THF	<2%
11	$[(\mathbf{L1}Au)_3O]^+ BF_4^-$	H_2O (30 equiv)	THF	65%

[a] In vial; [**1**] = 0.05 M. [b] Estimated by ^1H NMR analysis using diethyl phthalate as the internal reference. [c] Yield of isolated product. [Au] = Au**L1**, dppm = 1,1-Bis(diphenylphosphino)methane, **L1** = $(4\text{-}CF_3C_6H_4)_3P$, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMU = *N*,*N*,*N*′,*N*′-tetramethylurea.

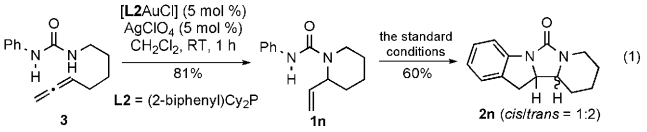


Scheme 2. Investigations into the reaction scope. The concentration of **1** is 0.05 M and the yields are of the isolated products. [a] *para*/*ortho* = 3:1. The *para* isomer is shown. [b] Reaction time is 8 h. Ts = 4-toluenesulfonyl.

80% (entry 7). Other additives such as Ph_3PO and TMU did not work well (entries 8 and 9), and when MeOH and DMSO were used they reacted with Selectfluor. The main role of the H_2O is believed to be the enhancement of the solubility of Selectfluor, which dissolves poorly in THF.[7] Compared with Selectfluor, other oxidants such as *N*-fluorobenzenesulfonimide and $PhI(OAc)_2$ were much less effective and led to yields of less than 15%. Notably, little reaction was observed when using [**L1**AuCl] as the catalyst (entry 10), but $[(\mathbf{L1}Au)_3O]^+ BF_4^-$ did catalyze this reaction with an acceptable efficiency (entry 11).

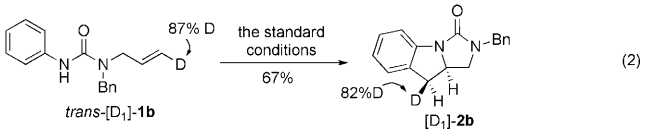
By using the optimized reaction conditions, in entry 7 of Table 1, the reaction scope was studied (Scheme 2). The additional allyl group in **1a** can be readily replaced with Bn, alkyl, or Ph groups (**2b**–**2d**) without much affecting the efficiency of the reaction. A methyl group was introduced into different positions of the aniline benzene ring to probe the reactivity and regioselectivity (**2e**–**2g**). Even though a *para*-methyl group (**2e**) was readily tolerated, this reaction was apparently sensitive to sterics because **2f**, which contains an *ortho*-methyl group, was formed in a low yield. In the case of a *meta*-methyl group, the *para* C–H bond was preferably functionalized with a good overall efficiency (**2g**). Electron-withdrawing substituents were generally tolerated (**2h**–**2l**), and better yields were realized with ethoxycarbonyl or acetyl substituents (**2k** and **2l**). On the contrary, the electron-donating methoxy group led to a complex mixture of products. These results can be explained by considering the stability of the benzene ring in the presence of Selectfluor; that is electron-rich aromatic rings such as anisole can be oxidized under these reaction conditions. Surprisingly, Br and Cl substituents were not tolerated, however, a tosyl group could be incorporated (**2i**), and this group provides access to other substitution patterns through cross-coupling reactions[21]. Substitution on the allylic position did not affect the reaction, albeit the product was obtained with a low diastereoselectivity (**2m**), and substitution on the C–C double bond proved to be detrimental.

Since gold-catalyzed hydroaminations of allenes by ureas produce *N*-allylureas,[22] we wondered whether [**L1**$AuNTf_2$] could catalyze the conversion of allenylurea **3** directly into tetracyclic indoline **2n** in a 'zipper' process. Unfortunately, [**L1**$AuNTf_2$] was not effective for the initial hydroamination. Hence, the transformation was realized by two consecutive gold-catalyzed reactions [Eq. (1)].

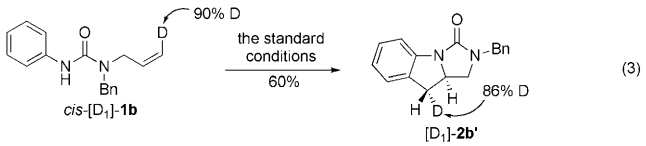


(1)

To gain an insight into the reaction mechanism and therefore lay the foundation for further studies, the vinyl group in **1b** was labeled with a deuterium atom. Similar to our previous work,[9] the reactions were highly diastereoselective with less than 5% deuterium scrambling and no deuterium loss [Eq. (2) and (3); Bn = benzyl]. Scheme 3 outlines a



(2)



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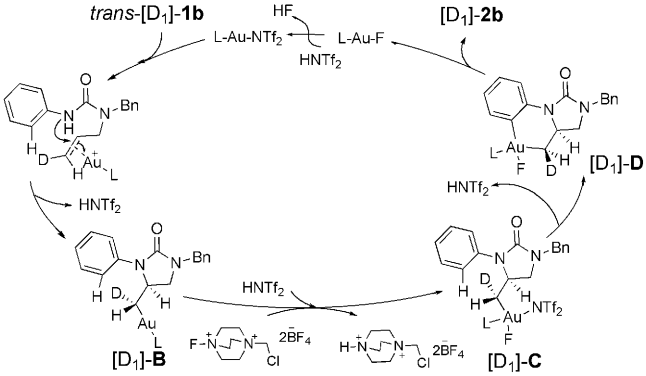
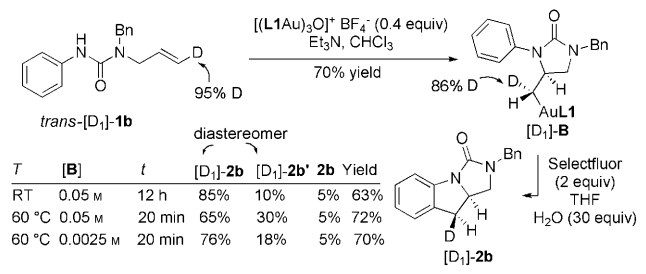


Scheme 3. A plausible reaction mechanism.

plausible mechanism that can rationalize these results: the cationic gold(I) initially promotes a 5-*exo-trig* cyclization involving the aniline nitrogen atom, thus forming the gold(I) intermediate [D_1]-**B** by *anti* addition; subsequent Selectfluor oxidation of [D_1]-**B** into the gold(III) [D_1]-**C** and subsequent electrophilic aromatic auration[4c] leads to the tricyclic intermediate [D_1]-**D**, which then undergoes reductive elimination with retention of the stereochemistry to afford the indoline product [D_1]-**2b**.

The inefficiency of [**L1**AuCl] and the expected difficulty in oxidizing highly electron-deficient [**L1**AuNTf$_2$] into a gold(III) intermediate by Selectfluor suggested that the initial cyclization is promoted by [**L1**AuNTf$_2$] instead of a gold(III) species.[10] Pleasingly, we were able to prepare both the deuterated and nondeuterated gold(I) intermediate **B** using a recently reported procedure,[23] and NMR studies confirmed that the 5-*exo-trig* cyclization was diastereoselective, thus following an expected *anti* addition, and again no deuterium loss was detected (Scheme 4). Surprisingly, some deuterium scrambling (9%, not shown in Scheme 4 for clarity) occurred, albeit in the presence of Et_3N; this scrambling might be due to ligand exchange between the gold complexes[24] instead of acid-promoted double bond

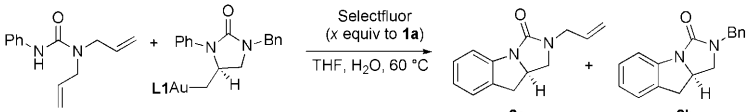


T	[B]	t	[D_1]-**2b**	[D_1]-**2b'**	**2b**	Yield
RT	0.05 M	12 h	85%	10%	5%	63%
60 °C	0.05 M	20 min	65%	30%	5%	72%
60 °C	0.0025 M	20 min	76%	18%	5%	70%

Scheme 4. Mechanistic studies.

isomerization. Pleasingly, treatment of the gold complex [D_1]-**B** with Selectfluor gave the cyclized products in 63% yield, even at room temperature; importantly, a little deuterium scrambling (approximately 1%) was observed. As expected, when the reaction was run at 60 °C, significant deuterium scrambling (21%) was observed; the extent of scrambling was decreased substantially to 10% when the concentration of gold was lowered to the catalytic level (from 0.05 M to 0.0025 M). These deuterium scramblings can be explained by invoking ligand exchanges[24] that could be facilitated by higher gold concentrations and reaction temperatures. Notably, the reaction proceeded to completion in 20 minutes at 60 °C, indicating that the oxidative coupling between the alkyl gold moiety and the phenyl C–H bond is facile.

While the above labeling studies are consistent with the proposed mechanism, one could argue that [D_1]-**B** may not be a reaction intermediate even though it can be converted into the product [D_1]-**2b**. Although this is unlikely, we performed further studies using **B** as the source of gold (Scheme 5). A 1:1 mixture of **B** and **1a** was treated with Selectfluor (4 equiv relative to **1a**) at 60 °C. Somewhat surprisingly, there was

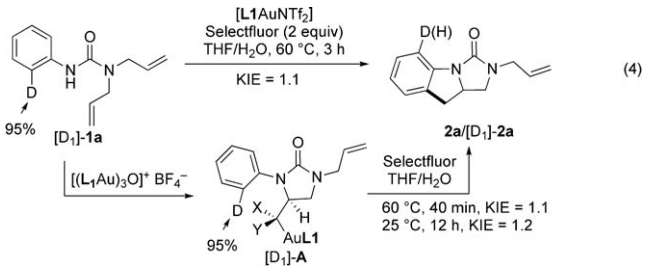


1a		**B**		**2a**	**2b**
1	:	1	*x* = 4; 20 min	80%	81%
1		5%	*x* = 2; 5 h	70%	4%
1	:	1	*x* = 0.9; 20 min	14%[a]	50%[b]

Scheme 5. Mechanistic studies. [a] 28% of **1a** unreacted and the other 40% converted into **A**. [b] 30% of **B** unreacted.

complete consumption of **1a** aswell as **B** after 20 minutes, and both **2a** and **2b** were formed in good yields. Intermediate **B** can also be used as a catalyst to afford **2a** in a 70% yield, as determined by NMR analysis. When a 1:1 mixture of **1a** and **B** was treated with 0.9 equivalents of Selectfluor, **2a** was formed in a 14% yield and 28% of **1a** was recovered. **2b** was formed in a 50% yield and 30% of **B** remained unreacted. Importantly, 40% of the gold intermediate **A** (Table 1) was detected in the reaction mixture. These results strongly suggest that gold complexes such as **A** and [D_1]-**B** are indeed reaction intermediates.

The formation of the cyclic gold(III) intermediate [D_1]-**D** from [D_1]-**C** (Scheme 3) is most likely to occur through a Friedel–Crafts-type electrophilic aromatic substitution. An alternative C–H oxidative cleavage would be impossible because the gold(III) center in [D_1]-**C** is highly electron deficient, and a σ-bond-metathesis mechanism is inconsistent with the following kinetic isotope effect (KIE) studies because a much higher KIE would be expected for this mechanism [Eq. (4)].[25] Urea **1a** was labeled with deuterium (95%) at the *ortho* position on the aniline, and a small KIE (1.1) was observed. A practically identical KIE was detected when the alkyl gold intermediate [D_1]-**A** was treated with



(4)

Selectfluor at the same temperature (60 °C). Notably, the reaction time for the reaction of [D_1]-**1a** was much longer than that of [D_1]-**A** (3 h versus 40 min), and this result suggests that there is no deuterium lost during the reactions. The identical KIEs are also consistent with the proposal that the reactions proceed via an intermediate such as **A** and **B**. As expected, a lower reaction temperature led to an increase of the KIE to 1.2 [Eq. (4)]. The normal KIE suggests that the loss of proton/deuteron from the σ complex is at least partially rate determining during the electrophilic aromatic substitution, similar to known Friedel–Crafts acylation reactions,[26] and the small value might also be due to an early transition state. These results are consistent with the proposed Friedel–Crafts-type C–H functionalization.

The last step must be an inner-sphere reductive elimination of [D_1]-**D**. This lends support for the proposed mechanism in our previous gold-catalyzed oxidative carboheterofunctionalization reactions.[9]

In summary, we have developed the first oxidative cross-coupling reaction between an aryl C–H and an in situ generated alkyl gold compound, combining gold(I)/gold(III) catalysis with C–H functionalization. Coupled with an initial aminoauration, this chemistry constitutes an intramolecular [3+2] annulation approach to tricyclic indolines. Deuterium labeling and kinetic isotope effect studies along with the isolation of alkyl gold intermediates strongly support an electrophilic aromatic substitution for the C–H functionalization and a subsequent inner-sphere concerted reductive elimination for the C_{sp^2}–C_{sp^3} bond formation in the reaction mechanism. These mechanistic insights should help spur further development in gold(I)/gold(III) catalysis.

Experimental Section

General procedure for the gold-catalyzed synthesis of tricyclic indolines: An oven-dried reaction tube was charged with *N*-allylurea **1** (0.1 mmol), Selectfluor (2 equiv), THF (2 mL, 0.05 M), deionized water (54 μL, 30 equiv), and [(4-CF_3Ph)$_3$PAuNTf_2] (4.6 mg, 5 mol%). The resulting mixture was stirred at 60 °C until the urea was completely consumed. The reaction mixture was concentrated under vacuum. The residue was partitioned between Et_2O (30 mL) and H_2O (10 mL). After phase separation, the aqueous layer was washed with Et_2O (20 mL). The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (eluent: hexanes/ethyl acetate).

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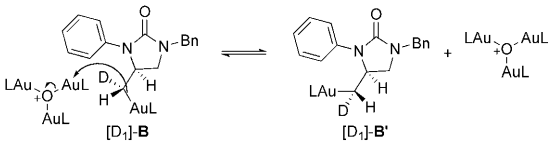
[24] A likely mechanism for the ligand exchange is outlined below:



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