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Gold-Catalyzed 1,2-Aminoarylation of Alkenes with External Amines

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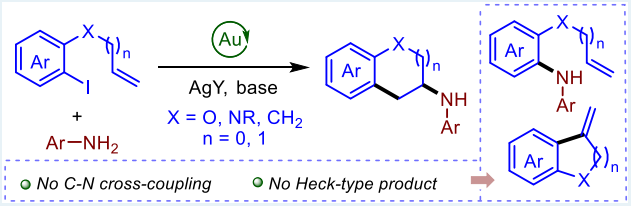
ABSTRACT: Reported herein is the gold-catalyzed 1,2-aminoarylation of alkenes that engages external amine as a coupling partner. Careful optimization studies revealed a significant role of the concentration of base to achieve highly chemoselective access to the aminoarylation products over potential C−N cross-coupled products. Overcoming all the limitations, the current strategy provided straightforward access to the medicinally relevant 3-aminochroman, 2-aminotetrahydronaphthalene, and 2-aminoindane derivatives.



KEYWORDS: *gold catalysis, π-activation, oxidative addition, aminoarylation, cross-coupling*

The compounds containing 3-aminochroman, 2-aminotetrahydronaphthalene, and 2-aminoindane moieties are biologically active and numerously found in many drug molecules. For instance, alnespirone (+) S 20499[1] and robalzotan (NAD-299)[2] which contain 3-aminochroman cores show very high affinity and selectivity toward the 5-HT_{1A} serotonin receptor and are commonly used in the treatment of anxiety and depression (Figure 1). Rotigotin (neupro)

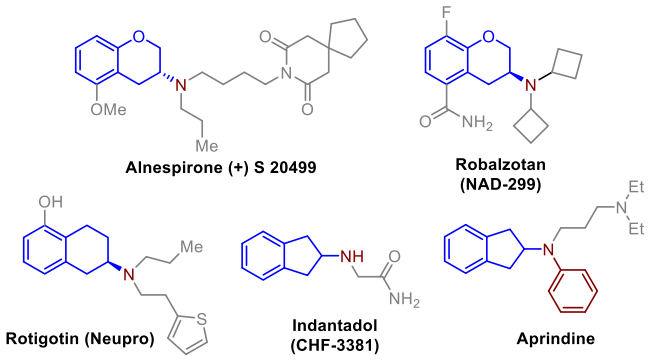


Figure 1. Biologically significant compounds.

consisting of a 2-aminotetrahydronaphthalene core is used in the treatment of Parkinson's disease and restless leg syndrome.[3] Similarly, 2-aminoindane is also recognized as a biologically important class of compound and often referred to as a designer drug.[4] For example, indantadol (CHF-3381)[5] is an anticonvulsant agent and used in the treatment of neuropathic pain, and aprindine[6] displays anesthetic and antiarrhythmic properties. Thus, the design and synthesis of these functionalized carbo(hetero)cycles is of prime importance in medicinal chemistry.

Alkene difunctionalization, the addition of two functional groups across a C−C double bond, typifies a class of reactions with outstanding synthetic potential.[7] Notably, gold complexes have emerged as a catalyst of choice for selective functionalization of C−C multiple bonds because of their excellent π-Lewis acidity.[8] However, owing to the innate reluctance of gold to oscillate between Au(I)/Au(III) redox cycle,[9] realizing the alkene difunctionalization reactions under the gold catalysis portfolio remained highly elusive. As a solution to tackle this challenge, the use of strong external oxidants[10] and photocatalysts[11] came into the practice which subsequently triggered the development of an array of gold-catalyzed difunctionalization reactions by facilitating the Au(I)/Au(III) redox cycle. However, the need for a superstoichiometric amount of sacrificial oxidants and highly reactive aryl diazonium salts hindered the attractiveness of these strategies. Though few other strategies appeared recently to facilitate the gold redox catalysis, they mostly remain confined to specific coupling partners.[12] Barring all these limitations, our laboratory has recently developed a suite of redox-neutral interplay mode of gold catalysis which integrate the cross-coupling reactivity and π-activation ability of gold complexes to facilitate the selective difunctionalization of C−C multiple bonds.[13] The newly developed strategy mainly relies on the ligand-enabled Au(I)/Au(III) catalysis which utilizes the hemilabile P,N-bidentate ligand (i.e., MeDalPhos)[14] to achieve the key oxidative addition of aryl halides on the cationic gold(I) species.[15] We demonstrated the synthetic potential of our strategy by

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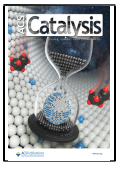

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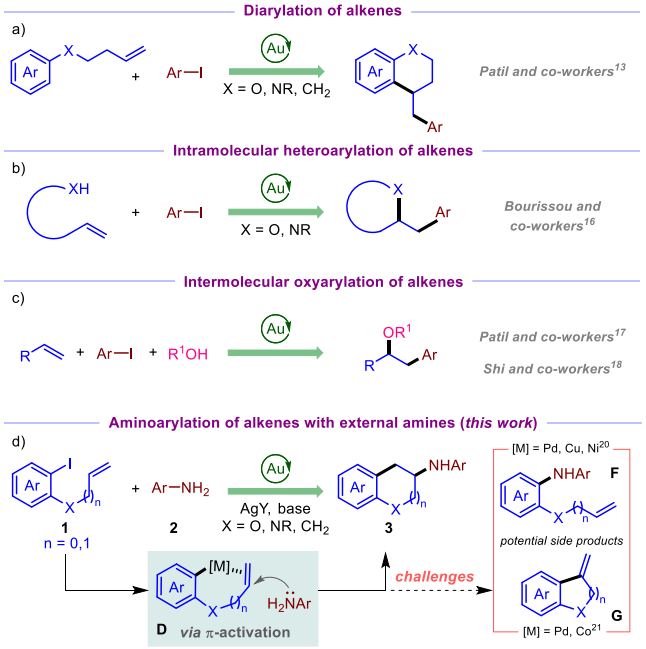
presenting the first example of 1,2-diarylation of alkenes under gold catalysis by utilizing aryl alkenes and aryl iodides as reacting partners (Scheme 1a).[13] In an ensuing work, the

Scheme 1. Gold-Catalyzed Difunctionalization of Alkenes: Known and Present Work

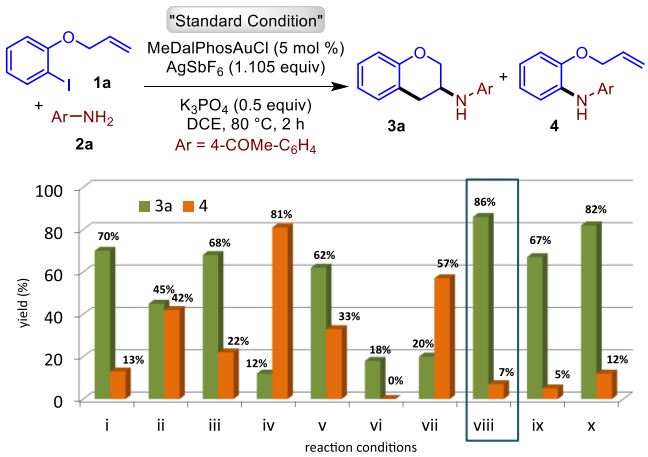


group of Bourissou reported the two-component 1,2-heteroarylation of alkenes, in which alkenes with tethered nucleophiles were used as reacting partners along with external aryl halides (Scheme 1b).[16] Soon after, our group[17] and Shi's group[18] reported the more challenging three-component 1,2-oxyarylation of alkenes based on the same concept (Scheme 1c).

As far as the gold-catalyzed 1,2-aminoarylation of alkenes is concerned only intramolecular versions[19] are known, and to date there are no reports where external amines are used as coupling partners. This could be mainly attributed to the fact that amines, especially anilines, are highly prone to undergo direct coupling with aryl iodides under Pd, Cu, or Ni catalysis.[20] Even, our group and soon after Bourissou's group reported that such C−N cross-coupling reactions are feasible under gold catalysis utilizing MeDalPhosAuCl as a catalyst.[15d,e] Bypassing this highly facile C−N cross-coupling reaction would be a major hurdle in this type of scenario. Moreover, the Heck-type reaction which is obvious under transition metal catalysis would be another challenge that needs to be considered.[21] Clearly, overcoming these potential side reactions and achieving the desired aminoarylation products demands a special catalytic system capable of possessing an optimally balanced reactivity and selectivity. Based on the prior knowledge in the field of ligand-enabled Au(I)/Au(III) catalysis,[13,17] we wondered that whether it is possible to utilize our newly developed "redox-neutral interplay mode" of gold catalysis to facilitate such highly arduous transformation in a chemo- and regioselective fashion by circumventing all the undesired pathways (Scheme 1d). For instance, it was hypothesized that the MeDalPhosAuCl catalyst should oxidatively insert into the C(sp^2)−I bond of iodoaryl alkenes **1** in the presence of a silver-based halide scavenger to generate the Au(III) species. As Au(III) complexes are highly prone to coordinate with C−C multiple bonds,[22,13,16−18] the cationic Au(III) complex, instead of undergoing ligand-exchange with aniline **2** that leads to direct C−N cross-coupled product **F**, should selectively intercept with tethered alkene to generate Au(III)−π complex **D**. Since, the gold complexes are reluctant to follow migratory insertion and β-hydride elimination pathways[23] which leads to the Heck-type side-product **G**, the so-formed intermediate **D** should trigger the nucleophilic attack from aniline **2** onto the activated alkene. The subsequent reductive elimination should selectively deliver the desired 1,2-aminoarylation product **3**. Herein, we unveil the successful implementation of our hypothesis that provided a straightforward access to biologically significant 3-amino-chroman, 2-aminotetrahydronaphthalene, and 2-aminoindane derivatives.

Our initial investigation into this proposed aminoarylation reaction began with the use of iodoaryl alkene **1a** (1.1 equiv), 4-aminoacetophenone **2a** (1 equiv), MeDalPhosAuCl (5 mol %), $AgSbF_6$ (1.105 equiv), and K_3PO_4 (0.5 equiv) in DCE (0.1 M) at 80 °C (Table 1). To our delight, the desired product **3a**

Table 1. Optimization of Reaction Conditions[a,b]



[a]Deviation from standard conditions: (i) none, (ii) 1.105 equiv of AgOTf was used instead of $AgSbF_6$, (iii) 1.105 equiv of $AgNTf_2$ was used instead of $AgSbF_6$, (iv) 1.105 equiv AgOTs was used instead of $AgSbF_6$, (v) 0.5 equiv of Cs_2CO_3 was used instead of K_3PO_4, (vi) without K_3PO_4, (vii) 1 equiv K_3PO_4 was used, (viii) 0.3 equiv K_3PO_4 was used, (ix) 0.1 equiv K_3PO_4 was used, (x) 1.05 equiv $AgNTf_2$ instead of $AgSbF_6$ along with 0.3 equiv K_3PO_4 was used. Reaction conditions: 0.22 mmol **1a**, 0.20 mmol **2a**, 5 mol % MeDalPhosAuCl, x equiv base, 1.105 equiv AgX, DCE (0.1 M), 80 °C, 2 h. [b]Isolated yields.

was formed in 70% yield along with 13% C−N cross-coupled product **4**. In an attempt to improve the yield of **3a**, we screened various other silver salts such as AgOTf, $AgNTf_2$, and AgOTs; however, all of them were found to be inferior as compared to $AgSbF_6$, favoring the undesired C−N cross-coupled product (condition ii, iii, and iv).[24] Given that the base holds a significant influence on the 1,2-difunctionalization reactions,[13,17] a series of bases were evaluated in lieu of K_3PO_4, but none was found to be beneficial (see the Supporting Information (SI)).[24] Most strikingly, we found that varying the concentration of K_3PO_4 significantly affected the reaction outcome. For instance, the use of 1 equiv of K_3PO_4 in otherwise identical reaction conditions afforded **3a** in poor

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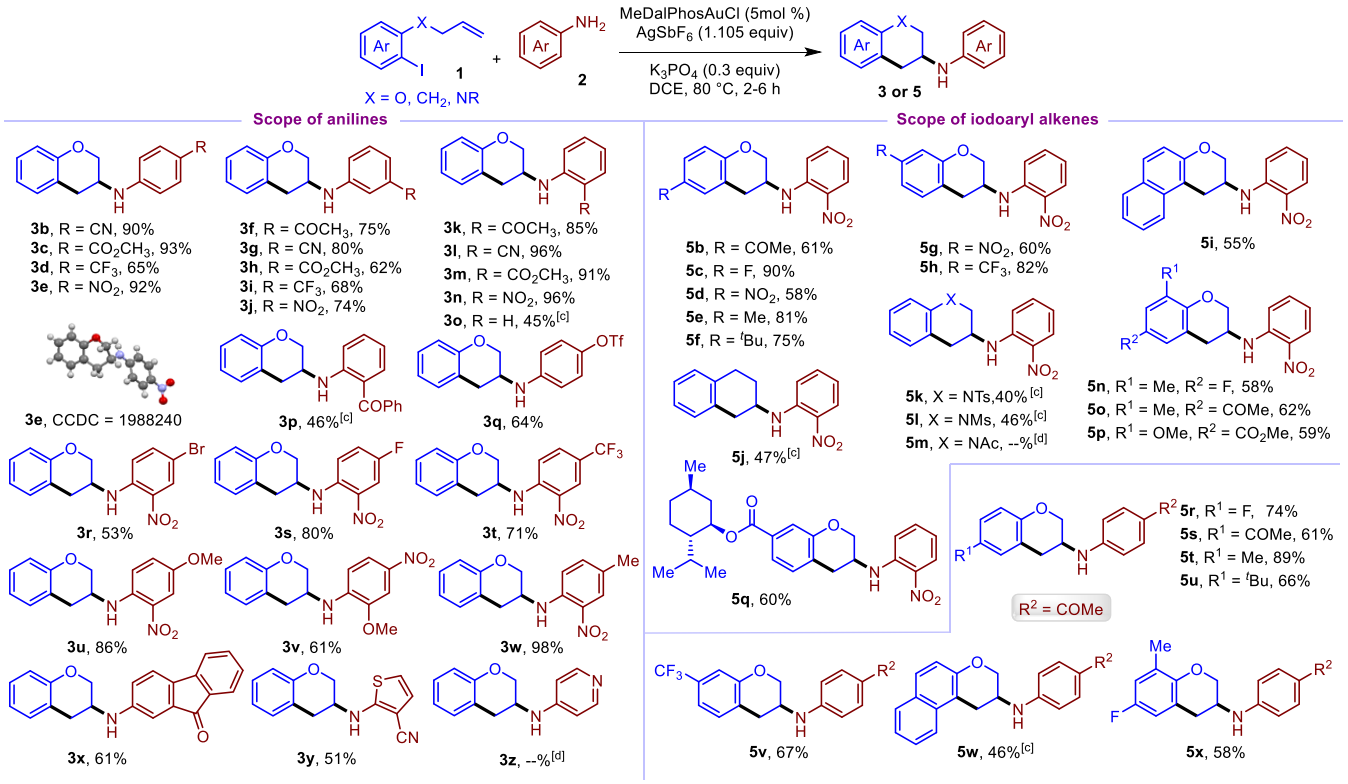
Table 2. Scope of Gold-Catalyzed 1,2-Aminoarylation of Alkenes[a,b]



[a]Reaction conditions: 0.22 mmol **1**, 0.20 mmol **2**, 5 mol % MeDalPhosAuCl, 1.105 equiv $AgSbF_6$, 0.3 equiv K_3PO_4, DCE (0.1 M), 80 °C, 2−6 h. [b]Isolated yields. [c]Unreacted starting material was recovered. [d]No reaction.

yield (20%) along with 57% C−N cross-coupled product **4** (condition vii). In contrast, by lowering the base loading to 0.3 equiv, the yield of **3a** was improved to 86% with minimal formation of **4** (7% yield) (condition viii). This observation is in line with our previous studies,[15d] suggesting that the more concentration of base favors the formation of C−N cross-coupled product by facilitating the strong coordination of amine with the *in situ* generated Au(III) species. Further, lowering the base loading to 0.1 equiv had detrimental effect on the reaction outcome.

Having optimized reaction conditions in hand, we set out to explore the scope of various anilines **2** in the present 1,2-aminoarylation reaction using iodoaryl alkene **1a** as a model substrate. As summarized in Table 2, we were delighted to find that our methodology served as a broadly applicable platform for coupling a wide array of anilines. For instance, various substituents at ortho, meta, or para positions of aniline were well tolerated to afford the 2-aminochroman derivatives **3b**−**3p** in up to 45−96% yield. Notably, the aniline **2q** bearing pseudohalide (−OTf) substituent reacted chemoselectively with iodoaryl alkene **1a** to furnish the desired product **3q** in 64% yield. Next, various disubstituted anilines with electron-donating and withdrawing substituents at ortho and para position were also found to be compatible, giving products **3r**−**3w** in 53−98% yield. Moreover, the reactions of fused aniline **2x** and heterocyclic aniline **2y** afforded products **3x** and **3y** in 61% and 51% yields, respectively. However, 4-aminopyridine **2z** did not produce the desired product **3z**, probably due to the quenching of active Au(I) or Au(III) catalyst by the strong coordination of pyridine nitrogen. Besides this, direct C−N cross-coupled products were observed when $PhCONH_2$ and $TsNH_2$ were used. Further, the electron-rich anilines are not suitable under current reaction conditions as a complex reaction mixture was obtained when 4-OMe-$C_6H_4NH_2$ and 4-NMe_2-$C_6H_4NH_2$ were used as substrates.

Next, we turned our attention to interrogate the scope of iodoaryl alkene **1** (Table 2). At first, differently substituted 2-iodoallyloxybenzene derivatives **1b**−**1h** were tested against 2-nitroaniline **2n** under the optimized reaction conditions, and all of them were well-reacted to afford the respective 2-aminochromans **5b**−**5h** in 58−90% yield. The 2-aminotetrahydronaphthalene derivative **5j** could also be obtained in decent yield (47%) from **1j**. Moreover, iodoaryl alkenes linked through −NTs and −NMs groups provided corresponding tetrahydroquinoline derivatives **5k** and **5l**; albeit, in slightly lower yields (40 and 46%). However, iodoaryl alkene with an −NAc group **1m** remained inert under the present reaction conditions. Of note, the suitability of present methodology for the late-stage functionalization was assessed by successfully evaluating the L-menthol derived iodoaryl alkene **1q**, which afforded the product **5q** in 60% yield (dr 1:1). The current method does not really demand 2-nitroaniline, as can be judged from the examples **5r**−**5x** where 4-aminoacetophenone **2a** also reacted well with various iodoaryl alkenes.

To further expand the horizon of current aminoarylation reaction, we considered 1-allyl-2-iodobenzenes **6** as potential substrates to access 2-aminoindane derivatives **7** (Table 3). Gratifyingly, a series of anilines having different substituents at ortho and para positions worked well to deliver 2-amino-indanes **7a**−**7g** up to 96% yield. A heterocyclic amine **2y** also reacted well to furnish the corresponding indane derivative **7h**

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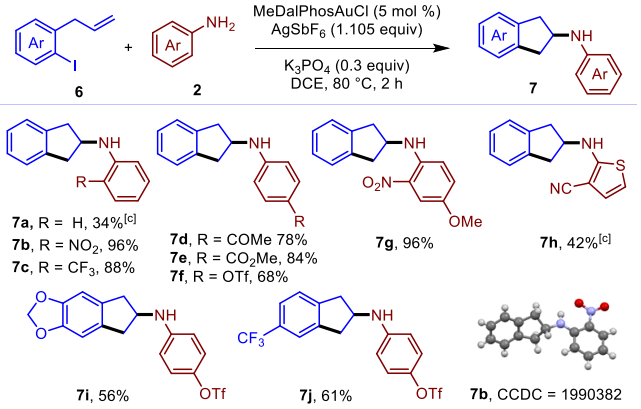
Table 3. Synthesis of 2-Aminoindane Derivatives[a,b]



[a]Reaction conditions: 0.22 mmol **6**, 0.20 mmol **2**, 5 mol % MeDalPhosAuCl, 1.105 equiv $AgSbF_6$, 0.3 equiv K_3PO_4, DCE (0.1 M), 80 °C, 2 h. [b]Isolated yields. [c]Unreacted starting material was recovered.

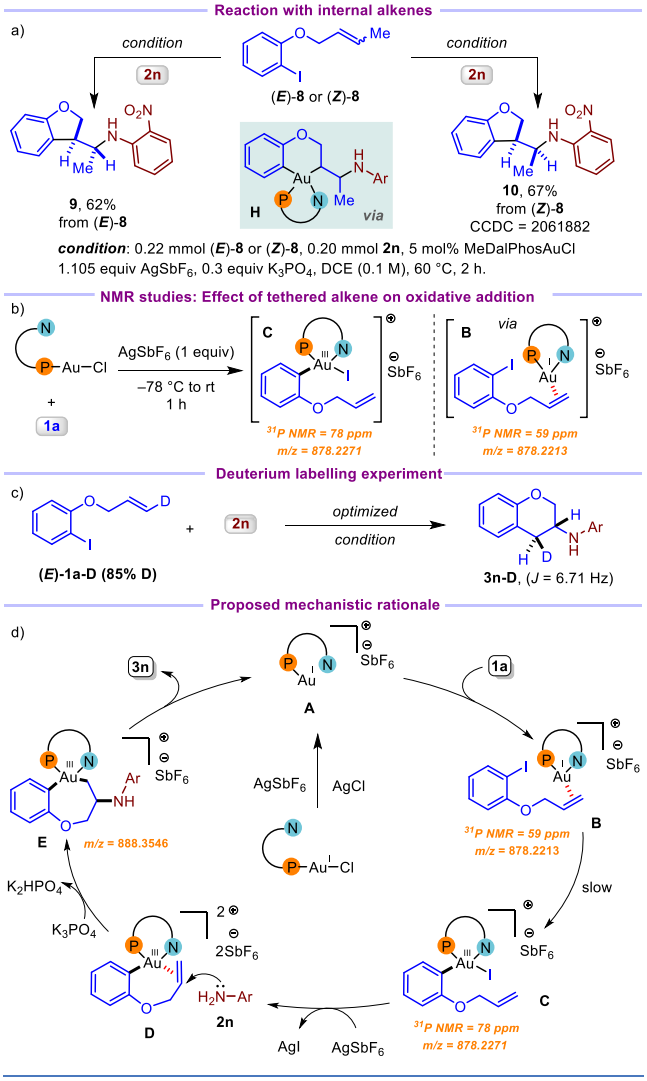
in 42% yield. Moreover, the substituted 2-iodoallyl benzenes were also tolerated to furnish **7i** and **7j** in moderate yields (56% and 61%).

In the oxyarylation reaction reported by Bourissou and co-workers, the reversal of regioselectivity was observed in case of internal alkenes.[16] We wondered that what would be the fate in our case when internal alkene **8** was utilized as a substrate (Scheme 2a). Interestingly, upon treatment of 2-nitroaniline **2n**, with (*E*)-**8** as well as (*Z*)-**8** provided dihydrobenzofuran derivatives **9** and **10** instead of regular chromans. In the current case, the partial positive charge, generated during the formation of Au(III)−π complex, could be equally stabilized at both the position of alkene. However, the formation of more stable 6-membered auracycle **H** after nucleophilic attack of aniline onto the Au(III)−π complex leads the reversal of regioselectivity. The structure of compound **10** was unambiguously confirmed by SC-XRD analysis.[24]

It is known that alkenes can greatly affect the rate of oxidative addition of cationic gold(I) species[13] by generating the Au(I)−π complex[25] as a catalyst resting state. In the current scenario, we thought that as alkene is tethered with aryl iodide, the Au(I)−π complex (*cf.* **B**) should in fact bring the Au(I) species in close proximity with C(sp^2)−I bond and thus accelerate the oxidative addition process (Scheme 2b). To shed light on this phenomenon, a stoichiometric experiment was performed by using equimolar amounts of MeDalPhosAuCl and **1a** in the presence of $AgSbF_6$. Monitoring the reaction with ^{31}P NMR confirmed the instantaneous formation of a putative Au(I)−π complex **B** (59 ppm). However, the complete conversion of **B** to Au(III) complex **C** (78 ppm) was observed only after 1 h.[24] Such a slow rate of oxidative addition could be attributed to the lack of vacant coordination sites at the putative Au(I)−π complex **B**. As a result, the Au(I) catalyst has no option rather to dissociate from the alkene for inserting into the C(sp^2)−I bond, which ultimately causes the decrease in the rate of oxidative addition process. Next, the deuterium labeling experiments revealed the anti-addition of aniline and aryl group across alkene which is in agreement with the anticipated π-activation pathway for the current transformation (Scheme 2c).

Based on the gathered experimental evidence and our previous reports,[13,17] the catalytic cycle for gold-catalyzed 1,2-

Scheme 2. Reaction with Internal Alkenes, Mechanistic Investigations, and Proposed Catalytic Cycle



aminoarylation of alkenes is given in Scheme 2d. As suggested by our ^{31}P NMR studies, the cationic Au(I) species generated from the reaction of MeDalPhosAuCl and $AgSbF_6$ should intercept with the iodoaryl alkene **1a** to form the Au(I)−π complex **B**[25] as a catalyst resting state. The slow dissociation of active cationic Au(I) species from π-complex **B**, in the presence of tethered aryl iodide should facilitate the oxidative addition with C(sp^2)−I bond leading to the formation of Au(III) species **C**. The subsequent iodide abstraction by silver salt would furnish the coordinatively unsaturated Au(III) species capable of activating internal alkene (*cf.* **D**) toward nucleophilic attack of aniline **2n**. Stereochemically, this step should follow the anti-addition across alkene as suggested by our deuterium labeling experiment. The so-formed Au(III) intermediate **E** should rapidly undergo concerted inner sphere reductive elimination to forge a key C(sp^2)−C(sp^3) bond leading to product **3n**.

In summary, we have developed the first gold-catalyzed 1,2-aminoarylation of alkenes that engages external amine as a nucleophile. The current reactivity was harnessed by exploiting the potential of our redox-neutral interplay mode of gold catalysis, which integrates the cross-coupling reactivity and π-activation ability of gold complexes. Careful optimization

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studies, involving judicious choice of base and halide scavenger, were found to be the key to achieve highly chemoselective aminoarylation of alkenes. Barring the formation of undesired C−N cross-coupling and Heck-type side-products that are facile under Pd, Cu, or Ni catalysis, the current methodology offers straightforward access to highly valuable 3-aminochroman, 2-aminotetrahydronaphthalene, and 2-aminoindane derivatives. The mechanistic paradigm was corroborated with several control experiments involving ^{31}P NMR, mass spectrometry, and deuterium labeling studies. The future research work will be directed toward accessing the library of these valuable compounds for evaluating their medicinal potential.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00789.

Experimental procedures, analytical data, and copies of ^{1}H, ^{13}C NMR spectra of all newly synthesized compounds (PDF)

X-ray crystallographic data of **3e** (CIF)

X-ray crystallographic data of **7b** (CIF)

X-ray crystallographic data of **10** (CIF)

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Notes

The authors declare no competing financial interest.

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