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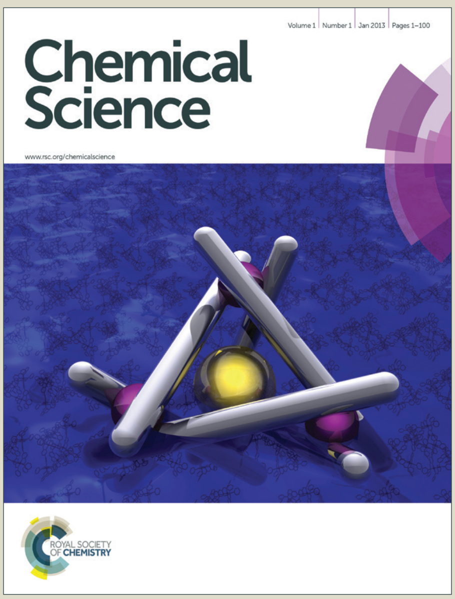

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EDGE ARTICLE

Stoichiometric to catalytic reactivity of the aryl cycloaurated species with arylboronic acids: insight into the mechanism of gold-catalyzed oxidative C(sp^2)–H arylation

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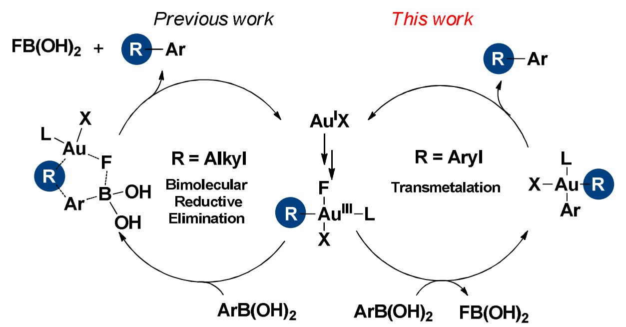
Based on the well-defined five-membered aryl gold(III) complexes [Au(tpy)X_2] (**3a** and **3b**) and [AuBr(Ph)(tpy)] (**7**) as well as the aryl gold(III) complex [AuCl_2(Ph)(tpy)] (**8**) (tpy = 2-(*o*-tolyl)pyridine) as reliable models, we present a detailed study of mechanism for gold(III)-catalyzed oxidative cross-coupling reactions between cycloaurable arenes and arylboronic acids. Here is reported the direct evidence for a mechanistic proposal including arene C–H activation, transmetallation and biaryl reductive elimination. The chelation-assisted C–H activation strategy has been used for the development of the gold(III)-catalyzed C–H bond arylation of arenes with aryl reagents to forge extended π-conjugated systems.

Introduction

Gold-catalyzed organic transformations have turned the spotlight of the chemistry stage over the past decade. Gold salts and complexes are most commonly used as a redox-neutral, carbophilic π acid for the activation of carbon–carbon multiple bonds such as alkynes, alkenes, and allenes towards nucleophilic attack.[1] In contrast, the gold-catalyzed oxidative coupling reactions proposed to involve Au(I)/Au(III) cycles are still underrepresented.[2] In particular, the gold-catalyzed C–H bond arylation of simple arenes to forge the biaryl scaffolds is still in its infancy. In addition to a few examples of catalytic homo-coupling of simple arenes,[3] stoichiometric homo- and hetero-coupling processes have nearly exclusively dominated the previous literature.[4-6] It has proven to be a challenge to evolve a stoichiometric hetero-coupling between an unactivated arene and an aromatic nucleophile to a catalytic version. The only known catalytic scenario is the oxidative cross-coupling reaction between arylsilanes and simple arenes recently illuminated by Lloyd-Jones and Russell.[7,8] The development of such transformations may encounter two major obstacles: (1) The relatively high redox potential of the Au(I)/Au(III) couple (E^0 = +1.41 V) traditionally precludes the catalytic cycles;[9] and (2) there are considerable uncertainties about the reaction mechanism in part due to the difficulties to access appropriate aryl Au(III) models and the use of a strong external oxidant that complicates the catalytic system.

In 2008, the seminal work of Gouverneur and co-workers demonstrated the potential of electrophilic fluorinating reagents in oxidizing Au(I) to Au(III) species.[10] Subsequently, substantial progress has been made in the gold-catalyzed oxidative heteroarylations (e.g., oxyarylation and aminoarylation) of alkenes with various arylating reagents by using electrophilic fluorinating reagents as the oxidants,[11] which have been proposed to embrace alkylgold(III) fluorides as the intermediates. These gold(III) species undergo a bimolecular reductive elimination with arylboronic acid (*devoid of transmetallation*) by a concerted process wherein B–F and C–C bonds are formed simultaneously (Scheme 1, left).[11a,11c,11e,12] In this work, we wish to establish the well-defined aryl gold(III) models to comprehensively understand their elementary reactivities with arylboronic acids and further get insight into the mechanism of gold-catalyzed oxidative C(sp^2)–H arylation, which will benefit the maturation of catalytic biaryl couplings involving a gold(I)/gold(III) redox cycle.



Scheme 1 Reactivities of alkylgold(III) (left) and arylgold(III) (right) species with arylboronic acid.

Gold actually has a rich histotry in organometallic chemistry. As early as in 1931, a seminal work by Kharasch and Isbell illustrated the C–H bond activation of arenes with gold(III) chloride to form aryl gold(III) complexes.[13] Hereafter, a variety of aryl gold(III) complexes have been prepared by C–H bond activation[14,15] and transmetallation reactions with Au(III)

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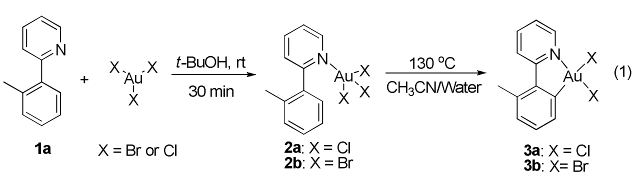
species.[16] Inspired by chelation-assisted transition-metal catalyzed C–H bond arylation of arenes,[17,18] we envisaged that the installation of a coordinating group on the aromatic ring would help us further understand the fundamental chemistry of aryl gold(III) reactivity, particularly involving a redox cycling. The introduction of a coordinating unit would have the following advantages: (1) The extra chelation could help activate C(sp^2)–H bond to form a cyclometalated Au(III) complex and synchronously stabilize the resulting Au(III) species; and (2) more importantly, the fixed coordinating group may partially avoid associative ligand/anion exchange, facilitating discrimination of the active Au(III) species. Thus, the well-defined aryl cycloaurated complexes would allow us to gain more insigts into the mechanism of transformations.

Results and discussion

The gold-catalyzed aryl C–H bond functionalization via chelation-assisted stratergy has never been reported. Given that the 2-phenylpyridine derivatives are the most commonly used scaffolds for investigating transition metal-catalyzed directed C–H activation of arenes,[17a-c,17e-f] we herein took 2-(*o*-tolyl)pyridine **1a** as a molecular modeling to illuminate both stoichiometric and catalytic reactivities[19] of aryl gold(III) species. Dihaloauracycles like [Au(py)X_2] can be easily prepared by the cycloauration of the corresponding arenes with $HAuCl_4$ or $NaAuCl_4$ by Constable[20] and later other researchers.[21] By a modification of the above methods, stoichiometric AuX_3 (X = Cl, Br) was first chosen to react with **1a** in *t*-BuOH at ambient temperature. The resulting coordination compounds **2a** and **2b** were heated in a mixture of acetonitrile and water at 130 °C, affording the five-membered *cis*-aryl gold(III) complexes [Au(tpy)X_2] **3a** and **3b**, respectively (eqn (1)). The cyclometalated Au(III) structure of **3b** was demonstrated by X-ray crystallographic analysis (Fig. 1).[22] Similar to other cycloaurated [Au(C^N)Cl_2] species,[16a,23] complexes **3a** and **3b** are exceedingly stable towards water and air.



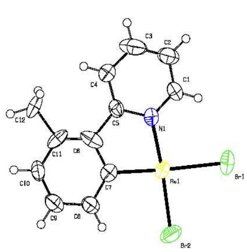
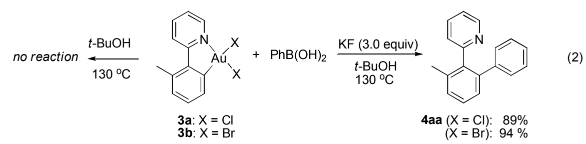
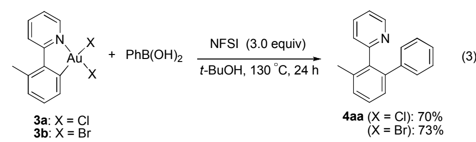
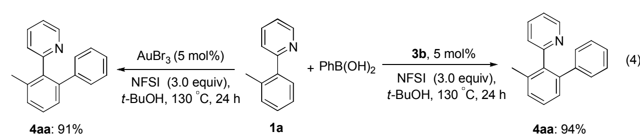


Fig. 1 ORTEP diagram of **3b**. Thermal ellipsoids are shown at the 50% probability level.

With the isolated monometallic *cis*-aryl gold(III) complexes **3a** and **3b** in hand, we wish to explore both stoichiometric and catalytic reactivities with arylboronic acids. A series of stoichiometric experiments were first conducted. The *cis*-aryl gold(III) complexes **3a** and **3b** proved unreactive upon treatment with phenylbronic acid in *t*-BuOH at 130 ºC. Encouraged by the role of fluoride in the gold-catalyzed oxidative heteroarylations of alkenes,[11] potassium fluoride was added to the reaction mixture. Fortunately, the desired product **4aa** was obtained in excellent yields (for **3a**, 89%; for **3b**, 94%) (eqn (2)). To clarify the role of the fluoride anion, we subsequently investigated the reaction of **3a** with phenylboronic acid in the presence of either *t*-BuOK or KOH instead of KF. The coupled product **4aa** was obtained in 84% and 87% yields, respectively. The ^{19}F NMR spectra of a mixture of **3a** and KF either in the presence or absence of phenylbronic acid in DMSO-d_6 solution did not exhibit the presence of Au(III)-F bond, which indicated that the anion exchange between Cl^- or Br^- and F^- did not occur (Fig. 2a). On the basis of the above observations, we rationalized that the fluoride anion might perform as a Lewis base to cooperatively activate the C–B bond and further promote the cleavage of C–B bond in the transmetallation, which was similar to that of the transition metal-catalyzed oxidative coupling reactions involving arylboronic acids.[24]







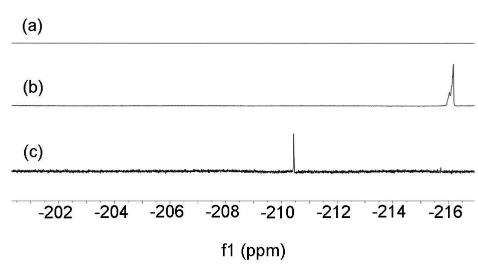


Fig. 2 The ^{19}F NMR spectra of (a) a mixture of **3a** and KF in DMSO-d_6 in the presence or absence of phenylbronic acid, (b) a mixture of AuCl and NSFI in DMSO-d_6, and (c) the catalytic reaction system in DMSO-d_6.

Next, we attempted to develop a catalytic version by using an external oxidant to access a gold(I)/gold(III) catalytic cycle. It is known that electrophilic fluorinating reagents and iodine(III) oxidants could efficiently accomplish the oxidation of Au(I) to Au(III). In combination with the role of the fluoride anion as a Lewis base mentioned above, we herein concentrated on the fluorine-containing oxidants. The stoichiometric gold (III) complexes **3a** and **3b** could react with phenylbronic acid (3.0 equiv) to form the biaryl **4aa** in 70% (X = Cl) and 73% (X = Br) yields in the presence of *N*-fluorobenzenesulfonimide (NFSI) (eqn

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(3)), whereas $PhI(OAc)_2$ failed to promote the coupling reaction (Table S1, entry 11). Treatment of **3b** with phenylboronic acid and Selectfluor also produced **4aa** in 72% yield. Importantly, both the cyclometalated gold (III) complex **3b** (5 mol%) and $AuBr_3$ (5 mol%) could catalyze the reaction between **1a** and phenylbronic acid to form the cross-coupled **4aa** in 94% and 91% yields, respectively, which hinted that the five-membered aryl gold(III) species might be a plausible intermediate in the catalytic cycle (eqn (4)). In addition, the yield of **4aa** was reduced to 58% in the presence of $AuBr_3$ (5 mol%) when the amounts of phenylboronic acid were decreased from 3.0 equiv to 1.0 equiv. GC-MS analysis of the stoichiometric reaction of **3a** with $PhB(OH)_2$ in the presence of NFSI showed the formation of biphenyl. Further ^{19}F NMR spectrum analysis of a mixture of NFSI and *t*-BuOH demonstrated a new signal at -39.3 ppm (^{19}F NMR of NSFI: -169.2 ppm). These observations implied the fluoride equivalents might be produced from the reduction of NFSI by phenylbronic acid and/or *t*-BuOH in the reaction system.

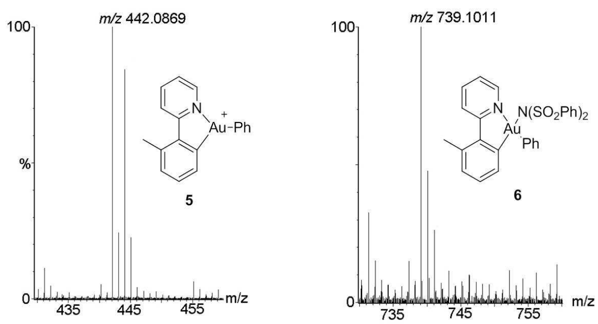
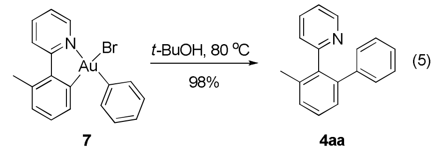


Fig. 3 The ESI-HRMS analysis of the $AuBr_3$-catalyzed reaction of **1a** with phenylbronic acid.

To further clarify the biaryl gold (III) intermediates, the ESI-HRMS analysis of the reactions of **3b** or **1a**/$AuBr_3$ with phenylboronic acid was performed in the presence of NSFI. Fortunately, the peaks at m/z 442.0869 and 739.1011 respectively corresponding to the characteristic patterns of the five-membered biaryl gold (III) species **5** ($[M]^+$, MW 442.0870) and **6** ($[M+H]^+$, MW 739.1000) were observed,[25] which suggested a transmetallation process from boronic acid to gold(III) (Fig. 3). Despite this evidence, attempts to separate the intermediacy from the reaction system failed probably due to the rapid reductive elimination at 130 °C. Alternatively, we turned to synthesize the cyclometalated biaryl gold(III) species [AuBr(Ph)(tpy)] (**7**), allowing direct observation of the reaction intermediacy. By a modified method of Tilset,[26] the sequential reaction of **1a** with $Au(OAc)_3$ and PhMgBr afforded complex **7**, which was determined by single crystal X-ray diffraction (Fig. 4).[22] [AuBr(Ph)(tpy)] could give the hetero-coupled product **4aa** in 98% yield in *t*-BuOH at 80 °C (eqn (5)), elucidating that the biaryl reductive elimination step was similar to those of traditional palladium and rhodium-catalyzed biaryl coupling reactions. This observation also clearly disclosed that the presence of Au(III)-F bond was not indispensable in the reductive elimination step and was distinguished from the reactivity of alkylgold(III) species with arylboronic acid (Scheme 1, left). Considering that the catalytic reaction required a high reaction temperature of 130 °C (eqn (4)) and failed to give the arylated product **4aa** at 80 °C, it was suggested that reductive elimination might not be rate-determining step.



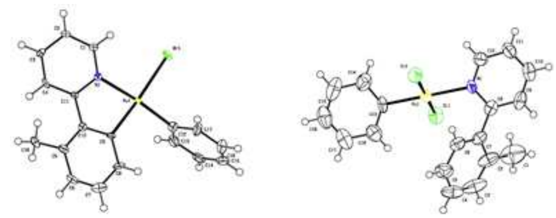
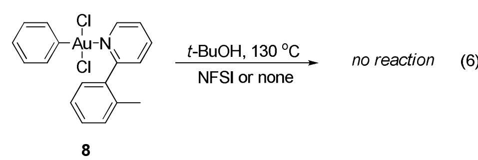


Fig. 4 ORTEP diagrams of **7** (left) and **8** (right). Thermal ellipsoids are shown at the 50% probability level.

As the gold-catalyzed cross-coupling reaction between an arene and an arylboronic acid was demonstrated, this raised a question of whether the arene C–H auration forerun the C–B auration or vice versa. The discrimination between these two scripts could be realized by the reaction of $[AuCl_2(Ph)(tpy)]$ (**8**). The gold(III) complex **8** could be preapared by the modified method of Fuchita[15d] and Limbach[27] involving the auration of benzene with $AuCl_3$ and subsequent coordination with **1a**. The structure of complex **8** was demonstrated by X-ray crystallographic analysis (Fig. 4).[22] As a result, the stoichiometric reaction of **8** in *t*-BuOH did not afford the cross-coupled product either in the presence or absence of NFSI (eqn (6)). These results not only indicated that the C–B auration occurred after cyclometallation, but also precluded the possibility of the C–B activation before the Au(I) was oxidized to Au(III).



To elucidate whether a Au(III)-F bond was formed in the catalytic cycle, the ^{19}F NMR spectra were investigated. The ^{19}F NMR spectrum of a mixture of AuCl and NSFI in *t*-BuOH at 130 °C exhibited a signal of -216.2 ppm (Fig. 2b). Indeed, AuCl (5.0 mol%) as the pre-catalyst could promote the reaction of **1a** with phenylboronic acid to produce **4aa** albeit in a lower yield of 38%. The catalytic system of **1a** and $PhB(OH)_2$ showed a ^{19}F NMR peak at 210.4 ppm (Fig. 2c). These results suggested that the Au(III)-F bond might be generated in the catalytic reaction.[28]

Subsequently, the H/D exchange experiments were performed. Exposure of 2-(*o*-tolyl)pyridine **1a** to *t*-BuOD did not lead to the deuterated product either in the presence or absence of phenylboronic acid, which indicated that the directed cleavage of *ortho* C–H bond was actually an irreversible process (eqn (7)). A small H/D kinetic isotope effect (KIE) of 0.96 for two separate reactions with **1a** and [D]-**1a** revealed that the $C(sp^2)$–H bond cleavage was not involved in the rate-determining step (eqn (8)).[29] The observed k_H/k_D value implied that the formation of a C–H(D) sigma-agostic complex might be rate limiting.[30]

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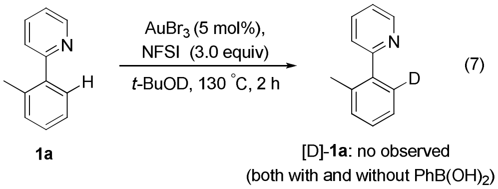

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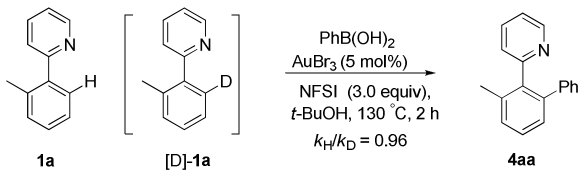
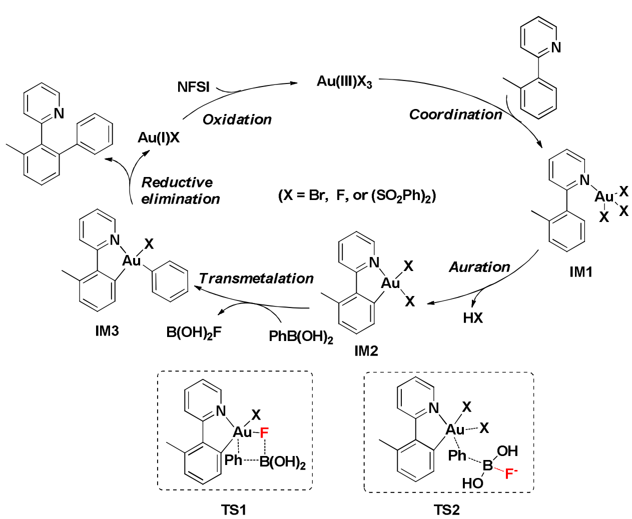


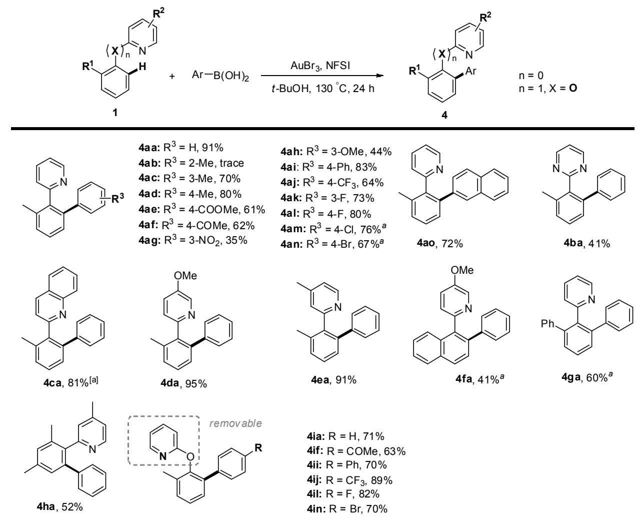
(8)

Based on the above observations, a plausible mechanistic pathway of the gold(III)-catalyzed directed C–H bond arylation of an arene with an arylbronic acid was proposed. First, the intermediate **IM1** was formed by the rapid coordination of a gold(III) species with **1a**, followed by an irreversible C–H bond auration to give the five-membered cycloaurated species **IM2**. The transmetalation from boronic acid to gold(III) center might involve both scenarios **TS1** and **TS2**.[16d,16e,31] In **TS1**, the Au(III)–F bond formed via an oxidation of Au(I)X by NFSI[11a-c,12] activated the C–B bond through a four-membered transition state (Fig. 2, right). In **TS2**, the non-coordinated fluoride anion promoted the cleavage of C–B bond. In the coupling reaction, NFSI not only served as a strong oxidant, but also offered a fluoride source to promote the transmetallation process. The biaryl gold(III) intermediate **IM3** underwent a reductive elimination to generate the desired biaryl product. Finally, the released gold(I) species was reoxidized by NFSI to complete the catalytic cycle.



Scheme 2 Proposed mechanism of gold(III)-catalyzed C(sp^2)–H bond arylation with arylboronic acid via chelation-assisted strategy.

Finally, we sought to examine the scope of this protocol with respect to both arylboronic acids and arenes (Scheme 3).[32] We were pleased to observe that a series of *meta*- or *para*-substituted phenylboronic acids smoothly reacted with 2-(*o*-tolyl)pyridine **1a** to deliver the heterocoupled products in mediate to excellent yields. However, the *ortho*-substituted phenylboronic acid gave a trace amount of product presumably due to steric effect (**4ab**). Furthermore, arylboronic acids bearing either electron-rich (**4ac-ad** and **4ah**) or electron-deficient (**4ae-ag** and **4aj-al**) substituents proceeded smoothly. Other biaryls containing *N*-heteroarenes such as pyridine, quinoline and pyrimidine also underwent the cross-coupling reactions with phenylboronic acid. The gold(III)-catalyzed oxidative reaction was well tolerance of halogen groups such as Cl and Br (**4am**, **4an** and **4in**). In addition to heteroaryl-aryls proposed to form a five-membered auracycle, 2-(*o*-tolyloxy)pyridine also went through the arene C–H arylation with a variety of arylbronic acids (**4ia-4in**), which might involve a six-membered auracycle. The pyridyl group of the resulting biaryls could be removed to afford the 1,1'-biphenyl-2-ol derivatives.[33]



Scheme 3 $AuBr_3$-catalyzed directed C–H arylation of arenes with arylboronic acids. Reaction conditions: biaryl or biaryl ether (0.2 mmol), arylboronic acid (3.0 equiv), gold(III) bromide (5 mol%), and NFSI (3.0 equiv) in *t*-BuOH (2 mL) at 130 °C under N_2 for 24 h. [a] At 140 °C .

Conclusions

In summary, taking advantage of chelation-assisted C–H bond activation strategy, we have established the well-defined five-membered aryl gold(III) complexes [Au(tpy)X_2] (**3a** and **3b**) and [AuBr(Ph)(tpy)] (**7**) as well as the aryl gold(III) complex [$AuCl_2$(Ph)(tpy)] (**8**) as proper models for a comprehensive insight into the mechanism of gold-catalyzed oxidative C–H arylation of arenes. The stoichiometric behaviors of the complexes with arylboronic acids provide straightforward access to propel our nascent understanding of the immature redox chemistry of gold catalysts. Observable arene C–H activation, transmetallation and biaryl reductive elimination have provided direct evidence for a mechanistic hypothesis. In this work, the chelation-assisted C–H activation strategy has been used for the development of the gold(III)-catalyzed oxidative cross-coupling reactions between arenes and arylating reagents. Compared with the works of Lloyd-Jones and Russell,[7,8] the present work discloses that it is possible a different catalytic cycle in which 1) the auration reaction step could be replaced by a cycloauration reaction if the arene has an appropiate *ortho*-substituent, 2) the aryl boronic acids can be used instead of aryl silanes as transmetallating agents, and 3) the oxidant can be NFSI instead of iodine(III) oxidant.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Detailed experimental procedures, analytical data. See DOI: 10.1039/b000000x/

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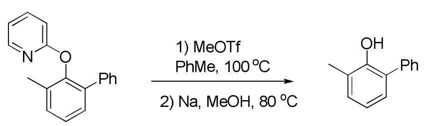

4ia **9**, 77% yield

