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Direct β-Selective Cross-Coupling of Alkenyl Gold Complexes with Alkyl Electrophiles

Julia Nguyen, Nicole Duncan, and Gojko Lalic*[a]

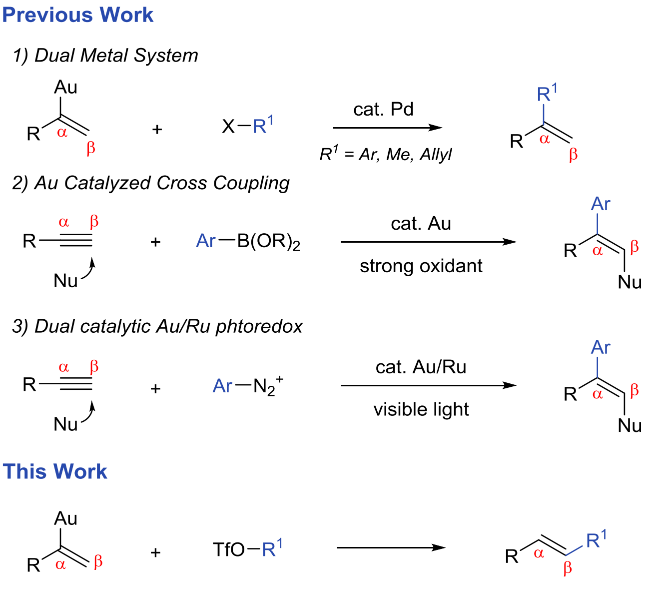
Abstract: Alkenyl gold complexes are common intermediates in gold-catalyzed transformations of allenes and alkynes, and numerous methods for their functionalization have been explored. Particularly valuable are cross-coupling reactions, which result in the formation of a new C-C bond. Several strategies are known that allow α-selective cross-coupling of alkenyl gold complexes with aryl, allyl, or acyl coupling partners. We describe a direct β-selective cross-coupling of alkenyl gold complexes with simple alkyl electrophiles. We also describe effects that the steric and electronic properties of alkenyl gold complexes have on the selectivity of the cross-coupling reaction.

One of the most common themes in gold catalysis is the use of gold's exceptional carbophilic π acidity to activate alkynes and allenes towards nucleophilic attack.[1] Belying the wide variety of products accessible through this reactivity is the fact that most of these reactions preceed through an alkenyl gold intermediate.[2] In a vast majority of reactions, the alkenyl gold complex either undergoes protodeauration or is intercepted by an electrophile in an intramolecular reaction.[3] More recently, several examples of intermolecular interception of alkenyl gold intermediates have been reported, further expanding the scope and utility of gold catalysis. Particularly valuable are methods that enable direct cross-coupling of alkenyl gold intermediates and lead to the formation of a new carbon-carbon bond.[4]

So far, three strategies have been developed to achieve cross-coupling reactions of alkenyl gold complexes. One approach is to use a second metal, such as palladium or nickel, to catalyze cross-coupling between alkenyl gold complexes and an organohalide, such as aryl iodide, acyl chloride, and methyl iodide.[5] Another method is to access Au(I)/Au(III) redox cycles using Selectfluor as an oxidant. This strategy has been successfully applied to homocoupling[6] and to cross-coupling with aryl boronic acids.[7] The third approach also involves Au(I)/Au(III) redox cycles, but instead of a stoichiometric oxidant, a ruthenium photoredox catalyst is used to generate a Au(III) species. This dual gold-ruthenium catalytic system has been used to accomplish coupling of alkenyl gold intermediates with aryl diazonium salts.[8]

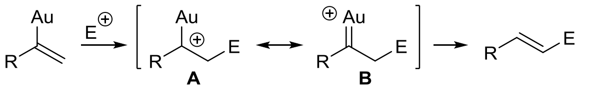
All three strategies for cross-coupling of alkenyl gold complexes have been mostly focused on aryl and acyl coupling partners, generating $C(sp^2)$-$C(sp^2)$ bonds. Exceptions are methyl and allyl electrophiles, which have been used palladium-catalyzed cross-coupling of alkenyl gold complexes.[9] Another common feature of these three strategies is that the new C-C bond is formed at the α-carbon of the alkenyl gold complex.

The relativistically expanded 5d orbitals of gold suggest another possible mode of reactivity and an opportunity to change the regioselectivity and expand the scope of cross-coupling reactions with alkenyl gold-complexes.[10] It is known that gold can facilitate trapping of an electrophile at the β-carbon of alkenyl gold complexes through backbonding (eq 1). After a hydride shift, the resulting gold carbenoid provides the desired alkene product.[11] The formation of gold carbenoid intermediates has been postulated in several examples of *intramolecular* reactions of alkenyl gold complexes with electrophiles.[12] Inspired by these examples, we hypothesised that the same reactivity can be used to accomplish β-selective cross-coupling of alkenyl gold complexes with simple alkyl electrophiles. Here, we demonstrate a direct β-selecitve cross-coupling of alkenyl gold complex with alkyl triflates. We also show that the mode of reactivity of the alkenyl gold complexes with alkyl triflates varies dramatically as we change the electronic and steric properties of the gold complexes.



Scheme 1. Intermolecular Cross-Coupling of Alkenyl Gold Complexes

In our initial attempts to intercept alkenyl gold complexes with alkyl triflate, we used triphenylphosphine as the ligand on gold. Unfortunately, with such complexes, we saw significant formation of the products of protodeauration and negligible formation of desired products. Hypothesizing that a better σ donor ligand was needed to increase the electron density on the gold center, we switched to *N,N'*-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene (IPr) supported complexes.[13] This change proved to be constructive, and treatment of alkenyl gold complex **1** with alkyl triflate **2** in C_6D_6 at room temperature generated the



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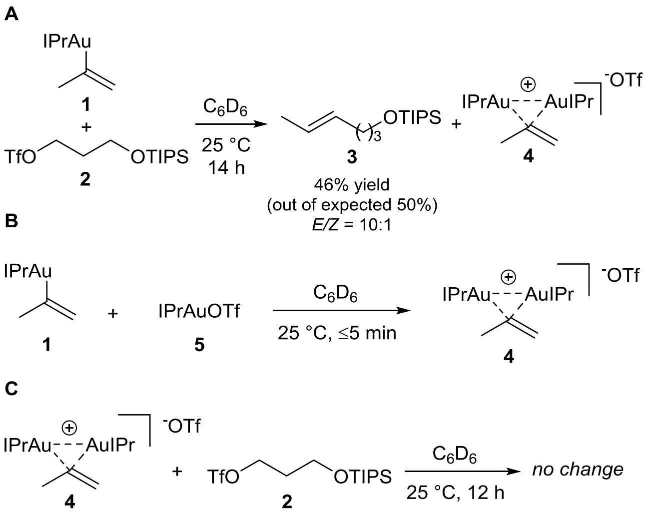
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) expected alkene product **3**, with the *E* isomer being the major product (Scheme 2A). Though initially product formation occurs relatively rapidly, upon approaching 50% yield, the rate of product formation dramatically decreases and the final yield generally does not rise above 50%. Curiously, ^{1}H NMR showed complete consumption of the alkenyl gold **1** and there was no evidence of the protodeauration product, propylene. We made several efforts to increase the yield, including conducting a solvent screen, increasing the temperature, increasing the equivalents of alkyl triflate, and adding 2,6-lutidine as a proton scavenger. None of these changes significantly increased yield of the desired product.

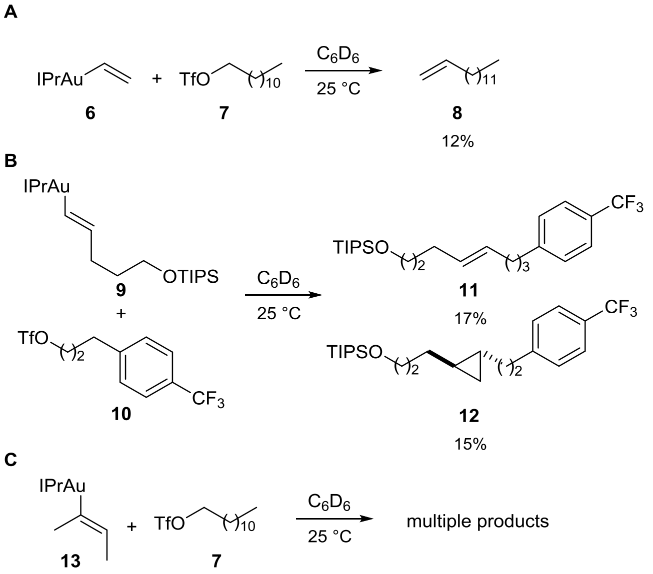
While monitoring the reaction by ^{1}H NMR, we had observed the appearance of two doublets between 4.3 to 4.6 ppm, which grew during the start of the reaction and disappeared towards the end. This development was accompanied by the formation of a white solid in the NMR tube. We suspected that those peaks corresponded to alkenyl bis(gold) complex **4** and disappeared as **4** crystallized out of solution. Alkenyl bis(gold) complex **4** could be generated by a reaction between IPrAuOTf **5**, a presumed product of the reaction between alkenyl gold and alkyl triflate, and alkenyl gold **1**. To test this idea, alkenyl gold **1** and excess **5** were combined in C_6D_6, and based on ^{1}H NMR, **1** was completely consumed within 5 minutes (Scheme 2B). ^{1}H NMR spectrum of the newly formed complex featured the characteristic doublets (see above) we had previously observed in a reaction shown in Scheme 2A. X-ray crystallography confirmed the structure of complex **4**.



Scheme 2. Cross-Coupling of Alkenyl Gold Complex with Alkyl Triflate

Hypothesizing that the low yield of the cross-coupling product in reaction shown in Scheme 2A is due to the lower nucleophilicity of the alkenyl (bis)gold species **4**, we treated **4** with alkyl triflate and did not observe significant product formation after 4 days. These results suggest that IPrAuOTf **5**, which is formed as a side product of the alkenyl gold and alkyl triflate reaction, can sequester any remaining alkenyl gold species **1** through the generation of (bis)gold species **4**, thus limiting yields of the final alkene product to 50%.

Formation of unreactive alkenyl (bis)metal species have several precedents in the literature. Previous work in our lab had found that in stoichiometric reactions between alkenyl Cu complex and alkyl triflate, formation of a dinuclear alkenyl copper complex also limited the yield of the desired product to approximately 50%.[14] Additionally, Widenhoefer et al. found an alkenyl bis(gold) species to be an off cycle catalyst resevoir in their gold catalyzed allene hydroalkoxylation reaction.[15] Notably, in catalytic variants of these reactions, the formation of an alkenyl bis(metal) species did not prevent complete conversion of the starting material to the desired products and excellent yields (>90%) were achieved. In catalytic reactions, the presence of a turnover reagent (CsF) or the presence of an additional substrate facilitate further transformation of the alkenyl bis(metal) complex. Thus, the reactivity revealed in this stoichiometric study of alkenyl gold and alkyl triflate offers insight for the development of a catalytic reaction that does not need to be limited by the formation of bis(gold) complexes.



Scheme 3. Reactivity of Alkenyl Gold Complexes

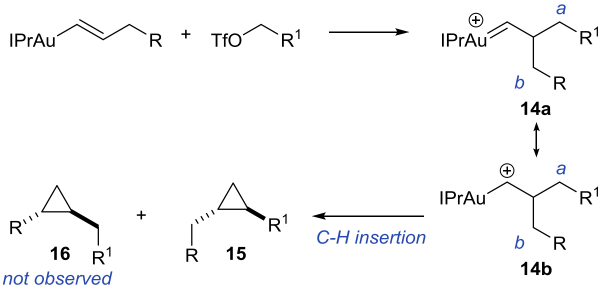
Having confirmed that alkyl triflate can intercept 2-propenyl gold, we next explored the scope of alkenyl gold species that can undergo this electrophilic interception. Treatment of ethenyl gold **6** with dodecyl triflate **7** afforded expected alkene product **8** (Scheme 3A). Interestingly, both the yield and rate of the reaction were significantly reduced as compared to those of the 2-propenyl gold complex reaction (eq 1). It seems that the additional methyl on the 2-propenyl gold complex plays an important role in facilitating electrophilic interception, possibly by stabilizing the cationic intermediate generated upon trapping of the alkenyl gold species (eq. 1).

Based on the formation of product **8**, it is unclear whether the new C-C bond is formed at the α or the β carbon. In an effort to probe the regioselectivity of the reaction, we synthesized (*E*)-alkenyl gold species **9** and found that after treatment with alkyl triflate **10**, only trace amounts of the 1,1 disubstituted alkene (the expected product based on the mechanism detailed in eq 1) were formed. Instead, the major products were trans cyclopropane product **12** and alkene **11**, together with a dinuclear alkenyl gold complex analogous to **4**.

A plausible mechanism for the formation of alkene **11** is an oxidative addition/reductive elimination sequence. In a classic paper by Kochi et al., methyl Au(I) was found to cross-couple with MeI in a sequence that involves oxidative addition and reductive elimination.[16] Formation of compound **11** through an oxidative addition/reductive elimination mechanism is consistent with the generation of a C-C bond at the α-carbon and the conservation of the double bond geometry seen in product **11**.

A plausible mechanism for the formation of **12** is shown in Scheme 4 and involves the formation of a gold carbenoid intermediate, followed by C-H insertion reaction. While the insertion is possible at both postions *a* and *b* (products **15** and **16**, respectively), only the product from the insertion at position *a* has been observed in reaction shown in Scheme 3C. We have prepared the autentic sample of the product analogous to **16** and confirmed that this product is not present in the crude reaction mixture. This selectivity of the proposed C-H insertion step is difficult to explain.

The divergent reactivity of the α- and β-substituted alkenyl gold complexes is interesting in the context of the recent investigation of gold carbenoids and the contribution the carbene form (represented by structure **14a**) makes to their structure and reactivity.[17] The reactivity of the disubstituted carbenoid derived from α-substituted alkenyl gold complex is consistent with the idea that the dominant form of the carbenoid is the gold stabilized carocation represented by resonance structure **A** in eq 1. However, the C-H insertion observed with monosubstituted carbenoids derived from complex **9** suggests significant contribution of the carbene form.[18]



Scheme 4. Mechanism of formation of **12**

Finally, we synthesized α, β-disubstituted alkenyl gold complex **13** (Scheme 3C). Combining **13** with alkyl triflate generated at least seven different products. These results suggests that sterics play an important role in modulating the reactivity of alkenyl gold complexes.

In summary, we described the reactions of various alkenyl gold complexes with alkyl triflates. We demonstrated that the efficiency and product distribution of the reaction strongly depend on the structure of the gold complexes. With α-subsitutied alkenyl gold complexes, an efficient and highly β-selecitve cross-coupling is observed, together with the formation of the dinuclear alkenyl gold complex. The substitution at the α position facilitates the cross-coupling reaction, presumably by stabilizing the cationic intermediate. The substitution at the β position, on the other hand, hinders the β-selective cross-coupling, presumably by steric hindrance. Finally, in the absence of an α substituent, we observe a reactivity consistent with the formation of the gold carbene intermediates. Overall, reactions with alkyl triflates broaden the synthetic potential of alkenyl gold intermediates, which are ubiquitous in the field of homogeneous gold catalysis, and provide an opportunity for the development of new catalytic processes.

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Keywords: catalysis 1 • gold 2 • alkenes 3 • alkylation 4 • cross-coupling 5

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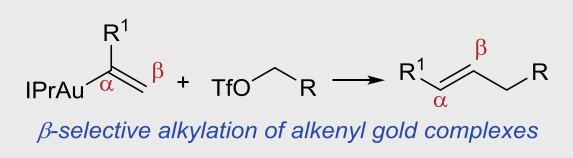

β-selective alkylation of alkenyl gold complexes

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Page No. – Page No.

Title

Direct β-selective alkylation of alkenyl gold complexes is achieved using alkyl triflates as electrophiles. Steric and electronic properties of the alkenyl gold complexes are shown to effect both the selectivity and the reactivity of the alkylation. The observed selectivity to the alkylation reaction, and the formation of cyclopropane-containing by-products suggest the formation of a gold carbene intermediates.

Key topic: gold catalysis