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Homogeneous Gold-Catalyzed Oxidative Carboheterofunctionalization of Alkenes

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Although alkynes and allenes are selectively activated in the presence of alkenes in homogeneous gold catalysis,[1] reactions of alkenes with nucleophiles such as amides/carbamates,[2] activated methylene groups/furans,[3] and oxygen nucleophiles[4] in the presence of gold catalysts have been amply reported. While transformations of in situ-generated alkenylgold intermediates using alkynes as substrates are diverse and rich, the corresponding alkylgold intermediate (e.g., **A**, Scheme 1) generated from alkene substrates,[5] however, mostly underwent protonation or elimination. The only exception is an intramolecular oxidative C−N bond formation recently reported by Muñiz.[6] This deficiency in engaging the C(sp^3)−Au bond in bond-forming processes, especially in *intermolecular* manners, hampers further development of gold alkene chemistry.

We have previously reported gold-catalyzed homogeneous oxidative transformations of Au−C(sp^2) bonds including homodimerization,[7a] cross-coupling,[7b] and C−O bond formations.[7c] These studies provided strong evidence for the existence of Au(I)/Au(III) catalytic cycles and unveiled a new area of gold catalysis where in situ-generated Au−C(sp^2) bonds can be oxidatively transformed in the presence of external oxidants.[6,8]

To further explore the synthetic potential of Au(I)/Au(III) catalysis, we speculated that alkylgold **A** may behave similarly to alkenylgold intermediates in gold redox chemistry and participate in oxidative C−C bond-forming processes with external organometallic reagents (Scheme 1). Herein we disclose the first example of catalytically converting C(sp^3)−Au bonds into C(sp^3)−C(sp^2) bonds in an intermolecular oxidative cross-coupling manner; moreover, our deuterium-labeling studies support the *anti* nature[2b,6] of the auroheterofunctionalization of alkenes and confirm the existence of Au(I)/Au(III) catalysis.

We started by subjecting pent-4-en-1-ol to the conditions previously optimized in our oxidative cross-coupling reaction[7b] using phenylboronic acid as the organometallic reagent. To our delight, 2-benzyltetrahydrofuran (i.e., **2**) was indeed formed, and moreover, the yield was good (Table 1, entry 1).[9] Inspection of the crude ^{1}H NMR spectrum revealed that significant amounts of phenylboronic acid remained unreacted and homodimerization and protonated products were minimal. Consequently, 2 equiv of the boronic acid was found sufficient, and a similar yield was achieved using anhydrous MeCN at 60 °C (entry 3). Decreasing Selectfluor loading or using other gold catalysts led to inferior results (entries 4−7). $PtCl_2$ did not catalyze this reaction at all (entry 8), and other oxidants such as *N*-fluorobenzenesulfonimide and $PhI(OAc)_2$[6,8a] did not afford any product either. Under the optimal reaction conditions (Table 1, entry 3), this oxidative carboalkoxylation can be readily applied to substituted pent-4-en-1-ols, including secondary and tertiary alcohols, yielding various tetrahydrofurans in mostly acceptable yields albeit without much diastereoselectivity (Table 2, **5a**−**5d**). However, hex-5-en-1-ol led to a low yield of tetrahydropyran **5e**, and substrates with an internal or a 1,1-disubstituted C−C double bond did not afford any desired product. We were pleased to find out that tosylamides were better substrates for this oxidative gold catalysis, and various pyrrolidine products (**5f**−**5k**) were isolated in good to excellent yields; similarly, piperidine **5l** was obtained in a much better yield than **5e**. This chemistry also provided rather straightforward access to γ-lactones (**5m**−**5n**). Beside phenylboronic acid, other arylboronic acids with weakly activated or deactivated benzene rings participated in the reaction readily, yielding pyrrolidines **5o**−**5t** in mostly good yields. The low efficiency with 3-cyanophenylboronic acid was surprising. In contrast to our previous cross-coupling chemistry,[7b] the 2-tolyl group was tolerated, suggesting that this chemistry is more tolerant of sterics. For electron-rich boronic acids, the reaction did not proceed well, likely due to their incompatibility with Selectfluor. Of note, all the reaction mixtures were homogeneous, and no gold precipitate was observed during the reactions.

Scheme 1. Trapping Alkylgold via Oxidative Cross-Coupling?

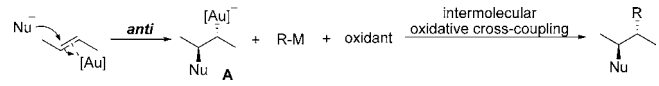
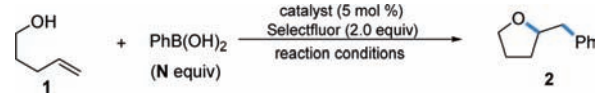
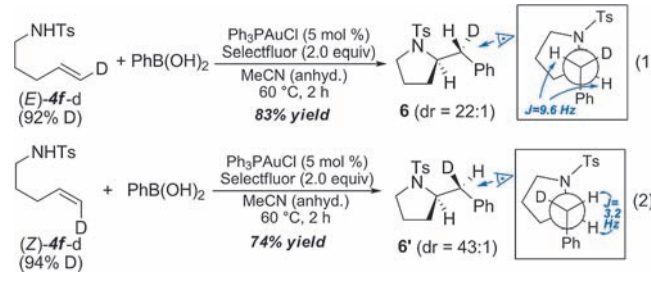


Table 1. Au-Catalyzed Oxidative Carboalkoxylation of Alkene: Reaction Conditions Optimization[a]



entry	catalyst	*N*	reaction conditions	yield (%)[b]
1	Ph_3PAuCl	4	MeCN:H_2O = 20:1, 80 °C	77
2	Ph_3PAuCl	3	MeCN:H_2O = 20:1, 60 °C	66
3	**Ph_3PAuCl**	2	**MeCN, 60 °C**	**75 (73[c])**
4	Ph_3PAuCl	2[d]	MeCN, 60 °C	66
5	$Ph_3PAuNTf_2$	2	MeCN, 60 °C	61
6	**3**[e]	2	MeCN, 60 °C	36
7	$AuCl_3$	2	MeCN, 60 °C	11
8	$PtCl_2$	2	MeCN, 60 °C	−

[a] Flask reactions with anhydr. MeCN; [**1**] = 0.1 M; reaction time: 2 h. The substrate concentration was 0.1 M. [b] ^{1}H NMR estimation using diethyl phthalate as internal reference. [c] Isolated yield. [d] 1.5 equiv of Selectfluor. [e] (2-Biphenyl)$Cy_2PAuNTf_2$.



This efficient gold-catalyzed oxidative functionalization of alkenes, although without much diastereoselectivity, offers a rare opportunity to probe the mechanisms of gold-catalyzed reactions of alkenes and Au(I)/Au(III) catalysis. To this end, tosylamide **4f** stereoselectively

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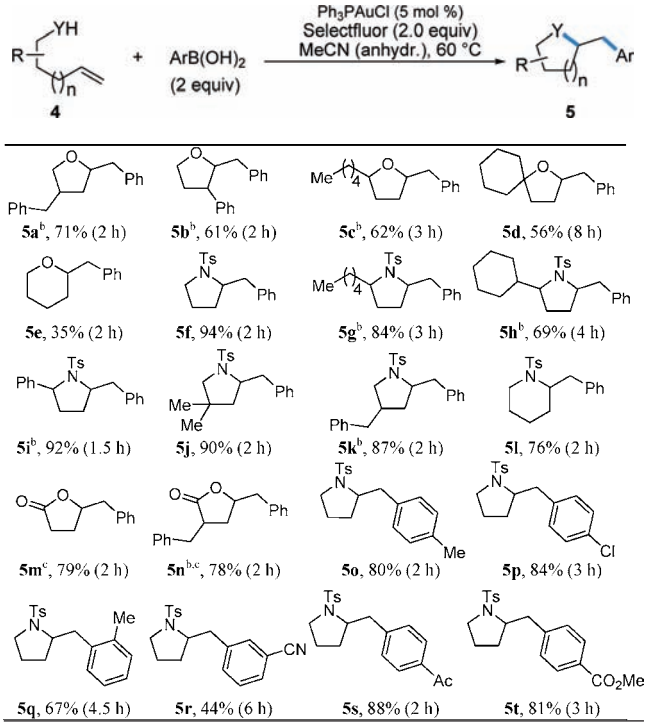
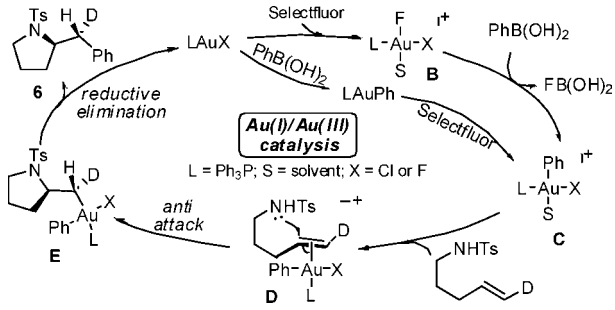
Table 2. Scope of the Gold-Catalyzed Homogeneous Oxidative Carboheterofunctionalization of Alkenes[a]



[a] The concentration of **4** was 0.1 M, and isolated yields were shown. [b] ~1:1 diastereomeric ratio. [c] Reaction temperature: 80 °C.

Scheme 2. Proposed Reaction Mechanism



labeled with deuterium at the unsubstituted end of the C−C double bond was subjected to the reaction. As shown in eq 1, from sulfonamide (*E*)-**4f**-d, no deuterium loss was detected, and moreover, excellent diastereoselectivity was observed; similarly, with (*Z*)-**4f**-d, there was no deuterium loss and the other diastereomer (i.e., **6′**, eq 2) was formed highly selectively. The relative stereochemistries were established on the basis of conformation analysis and $^1H-^1H$ coupling constants. These results revealed an *anti* addition of the sulfonamide and the phenyl group to the C−C double bond.

The above deuterium-labeling studies offered important insights for the proposed reaction mechanism (Scheme 2 using eq 1 as an example): (a) the initial attack by the sulfonamide to the gold-activated alkene should be *anti*, consistent with literature precedents,[2b,6] and a *syn* attack followed by a configuration inversion of the gold-bound carbon center via an S_N2 process is highly unlikely; (b) the formation of the C(sp^3)−Ph bond (i.e., from **E** to **6**) must involve a concerted reductive elimination; a radical mechanism is unlikely. This concerted process demands a central role of gold in mediating the C−C bond formation and necessitates oxidation of Au(I) to Au(III) by an external oxidant in the catalytic cycle. Although Ph_3PAuCl is unlikely to be the metal complex promoting the amide *anti* attack, it could be oxidized by Selectfluor to Au(III) **B**, which might undergo transmetalation with phenylboronic acid facilitated by the formation of a strong B−F bond. Alternatively, Ph_3PAuPh[10] could be initially formed via transmetalation[11] and then oxidized, which may help explain the result shown in Table 1, entry 5. The thus-generated cationic complex **C** would then activate the alkene toward tosylamide attack. The lack of total stereoselectivity (stereospecificity) is likely due to some double bond isomerization during the reaction.

In conclusion, we have developed carboamination, carboalkoxylation and carbolactonization of terminal alkenes via oxidative gold catalysis, providing expedient access to various substituted *N*- or *O*-heterocycles. Deuterium-labeling studies established the *anti* nature of the alkene functionalization and the indispensable role of Au(I)/Au(III) catalysis. This study constitutes the first example of catalytically converting C(sp^3)−Au bonds into C(sp^3)−C(sp^2) bonds in a cross-coupling manner and opens new opportunities to study gold alkene catalysis where alkylgold intermediates can be readily functionalized.

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Note Added after ASAP Publication. Reference 6 was changed on January 12, 2010.

Supporting Information Available: Experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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