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Gold-Catalyzed Intramolecular Aminoarylation of Alkenes: C-C bond Formation *via* a Bimolecular Reductive Elimination**

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The utility of homogeneous gold complexes as carbophilic π–acids has been heretofore well established, with numerous reports of gold-catalyzed reactions initiated by addition of nucleophiles into unsaturated carbon-carbon bonds.[1] While protodeauration is common, several reactions have been developed in which the resulting organogold intermediate was intercepted. For example, nucleophilic reagents have been employed to intercept cationic organogold intermediates derived from reactions with π-bonds.[2] In contrast, reactions involving neutral organogold intermediates are terminated by reaction of the resulting carbon-gold bond with an electrophile. While the electrophile is often a proton, gold(I)-catalyzed carbohetero-functionalization reactions using carbon-based electrophiles have been reported.[3] On the basis of recent reports of gold-catalyzed oxidative transformations,[4] we envisioned that the oxidized analogues of these gold(I) intermediates might also be susceptible to reactive nucleophilic reagents.

In line with our efforts in the area of gold-catalyzed hydroamination reactions,[5,6] we hypothesized that oxidized organogold intermediates derived from addition of an amine to a π-bond might react with nucleophilic boronic acids in an intramolecular aminoarylation reaction.[7] While our initial studies using allenyl tosylamides were unsuccessful, we were encouraged to find that the Ph_3PAuCl-catalyzed reaction of alkenyl tosylamide **1** with

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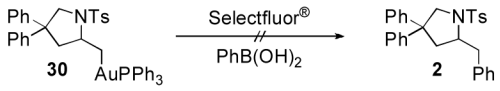
excess phenylboronic acid and Selectfluor® provided a modest yield of the desired aminoarylation product, **2** (Table 1, entry 1). Using a more cationic gold species, such as $Ph_3PAuOTf$ (entry 2) led to diminished reactivity. On the basis of our previous observation of counterion effects in gold-catalyzed reactions,[5] we examined the impact of counterion on the aminoarylation reaction. While the use of $Ph_3PAuOBz$ as a catalyst resulted in decreased conversion (entry 3), use of Ph_3PAuBr led to a significant increase in the amount of **2** produced (entry 4). The corresponding gold(I) iodide (entry 5) provided **2** in only trace amounts, as the iodide itself is likely susceptible to oxidation by Selectfluor®.

In order to optimize the reaction further, we sought to identify the active gold species. The combination of either Ph_3PAuCl or Ph_3PAuBr with Selectfluor® and $PhB(OH)_2$ lead to the formation of a major signal in the ^{31}P NMR at 44.28 ppm, which we identified as $[(Ph_3P_2)]^+$. Moreover, *in situ* monitoring of the reaction mixture by ^{31}P NMR showed this cationic complex as the dominant gold species in solution in the catalytic reaction; however, independently prepared $[(Ph_3P)_2Au]BF_4$ was found to produce **2** in inferior yields (entry 6**)** to those obtained when Ph_3PAuBr was employed as a catalyst. As strong aurophilic interactions are maintained for Au^I-Au^{III} species,[8] we reasoned that use of bimetallic[9] gold complexes as catalysts might minimize formation of this type of bisphosphinogold(I) species. We were delighted to find that $dppm(AuBr)_2$ (entry 7) was an excellent catalyst at room temperature.[10,11]

The optimized conditions appear general to a wide variety of sulfonamides and independent of substitution pattern (Table 2); additionally, trifluoroacetamides are reasonable substrates for the reaction (entry 1). The cyclization provides N-protected pyrrolidines, at room temperature, even for substrates without the benefit of the Thorpe–Ingold effect (entry 2). The ability to form six-membered rings (entry 3) is notable with only a slight increase in temperature required. We also have achieved mild access to functionalized 2,3-dihydroindole and 1,2,3,4-tetrahydroisoquinoline products (entries 7, 8). The reaction tolerated a variety of sulfonamide protecting groups and boronic acids (Table 3), including both electron poor and rich. More hindered and more electron poor boronic acids reacted sluggishly under the standard room temperature conditions, but functional yields are obtained by heating the reaction mixture to 40 °C. Sensitive moieties, such as aldehydes, readily withstood the mild reaction conditions. Reduced yields were observed with highly electron rich coupling partners, such as *p*-methoxyphenylboronic acid, due to competing oxidation of the boronic acid by Selectfluor®.

Several possibilities exist for the mechanism of this transformation. We first considered the initial cyclization event. Treatment of **1** with neutral phosphinegold(I) halide complexes in the absence of Selectfluor® produced no detectable reaction. Cationic Au^I species are typically required for addition to **π**-bonds; however, in this case cationic triphenylphosphinegold(I) complexes fail to catalyze the reaction (Table 1, entry 2). Moreover, treatment of alkylgold(I) complex **30**[12] with phenylboronic acid and Selectfluor® failed to produce pyrolidine **2** [Eq. (1)]. We therefore surmised that oxidation of Au^I to Au^{III} must precede the aminoauration step.



(1)

We next considered the potential of a transmetallation of the phosphinegold(I) halide with the boronic acid as the initial step in the catalytic cycle. However, the combination of

Ph_3PAuCl and phenylboronic acid in acetonitrile, even after several hours both at RT and 60 °C gave no Ph_3PAuPh as judged by ^{31}P NMR.[13] This observation suggests that any transmetallation likely follows oxidation and subsequent formation of a Au^{III}–F intermediate, thereby allowing for the favorable formation of a B–F bond.

In examining the mechanism of C–C bond formation, we assessed the possibility of a traditional reductive elimination from a gold(III)-phenyl intermediate in analogy to related transition metal-catalyzed oxidative cyclization reactions.[7] Reductive elimination from gold(III) alkyl and aryl complexes have been examined, but typically require elevated temperatures to proceed[14], while our reaction occurs readily even at room temperature. Additionally, we found that while Ph_3PAuPh was a competent catalyst for the reaction,[15] treatment of **5a** with stoichiometric Ph PAuPh and Selectfluor® 3 in the absence of boronic acid lead to only trace product formation (Table 4, entry 1). Addition of a boronic acid recovers the reaction, and provides **6** in reasonable yields (entry 2). Moreover, the reaction of **5a** with alternate boronic acids and Ph_3PAuPh produced adducts **25** and **28** derived from transfer from the arylboronic acid almost exclusively, and not from the phenylgold species, regardless of the electronic properties of the boronic acid (entries 3,4).

These observations suggest that formation of the C–C bond by a reductive elimination from phenylgold(III) intermediate **32** is unlikely, and that in the case of Ph_3PAuPh, the phenyl acts as a spectator ligand. Therefore, we propose that interaction of the boronic acid with alkylgold(III) fluoride intermediate **31** does not result in transmetalation to **32**, but instead induces a bimolecular reductive elimination. In this hypothesis, the B–F interaction is key for the reductive elimination, as it increases the nucleophilicity of the boronic acid and the electrophilicity of the carbon-gold(III) moiety. While the formation of the boronate and the subsequent nucleophilic displacement of the gold moiety can occur as separate steps, we envision that these events occur simultaneously *via* five-centered transition state **33** (Scheme 1).[16]

The stereochemical course of the gold-catalyzed aminoarylation reaction was probed with deuterium-labeled alkene **34** (Scheme 2). The deuterium labeled products **35** and **37** are consistent with either *anti*-aminoauration[12] followed by C-C bond formation proceeding with stereochemical retention, or initial *syn*-aminoauration[17] and inversion of the stereochemistry during the reductive elimination. We envision that the latter is operative, given the S_N2-like reaction of the arylboronic acid at the carbon-gold center in transition state **33**.

In conclusion, we have reported a gold-catalyzed aminoarylation reaction of alkenes and arylboronic acids. The reaction is proposed to proceed *via* a redox cycle involving the initial oxidation of gold(I) to gold(III) with Selectfluor®. Ligand and halide effects played a dramatic role in the development of an exceptionally mild catalyst system for addition to alkenes. Finally, while it is tempting to invoke a mechanism for reductive elimination similar to that proposed for other transition metal complexes, our experimental studies suggest that the C–C bond forming reaction occurs *via* a bimolecular reductive elimination. Studies directed towards the application of this catalyst system and reactivity paradigm towards the development of further transformations are ongoing in our laboratory and shall be reported in time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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[10]. The effect of the halide on catalytic activity is maintained, as the dppm$(AuCl)_2$-catalyzed reaction produced 2 in only 37% yield. For full details of catalysts examined, see Supporting Information.

[11]. Addition of Selectfluor® followed by phenylboronic acid to a solution of dppm$(AuBr)_2$ lead to no appreciable change in the ^{31}P NMR.

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[15]. Under the standard reaction conditions, 5 mol % Ph3PAuPh provides 2 from substrate 1 in 31% yield. See Supporting Information for more details.

[16]. Ongoing theoretical (DFT) investigations support this type of a nucleophilic reductive elimination pathway. Relaxed coordinate scans found a concerted reductive elimination, in which the B–F bond is formed prior to the C–C bond, effectively achieving regeneration of the catalyst and product demetallation. In contrast, we could not find a pathway for transmetallation, where the phenyl group is transferred to gold leading to the formation of alkylphenylgold(III) intermediate 32.

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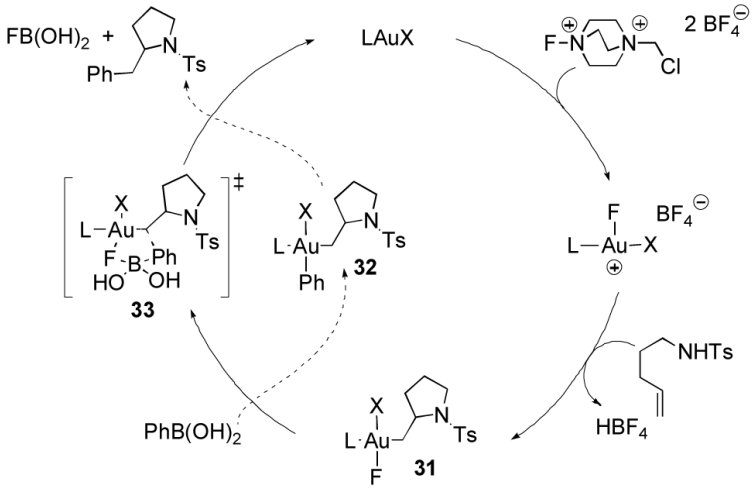
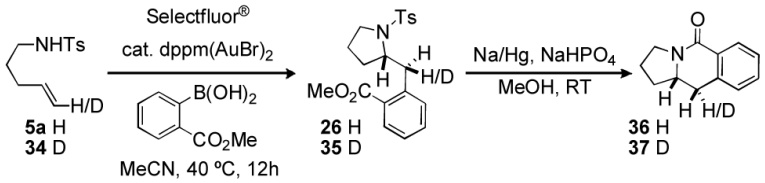
[18]. For full details and analysis, see Supporting Information.



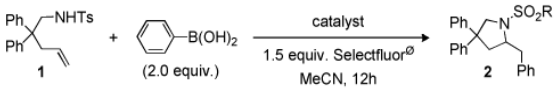
Scheme 1.
Proposed Mechanism for gold-catalyzed aminoarylation.



Scheme 2.
Examination of reaction stereochemistry by deuterium labelling.[18]

Table 1

Catalysts for the aminoarylation reaction.[[a]]



entry	Catalyst	% yield[[b]]
1	5 mol % Ph_3PAuCl	24%
2	5 mol % $Ph_3PAuOTf$	< 5%
3	5 mol % $Ph_3PAuOBz$	18%
4	5 mol % Ph_3PAuBr	47%
5	5 mol % Ph_3PAuI	< 5%
6	5 mol % $[(Ph_3P)_2Au]BF_4$	22%
7	**3 mol % dppm$(AuBr)_2$**	**81% (72%)[[c]]**
8	3 mol % dppb$(AuBr)_2$	26%[[c]]

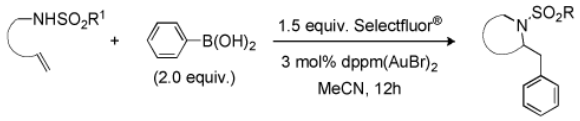
[a] Reactions run in a sealed vial at 0.05 M in **1**.

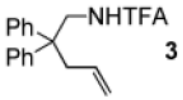
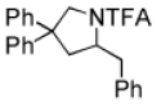
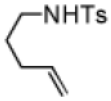
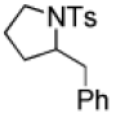
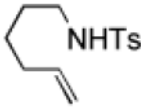
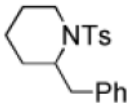
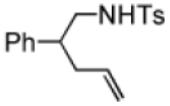
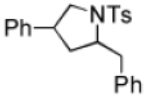
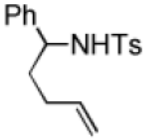
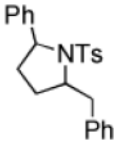
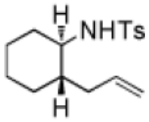
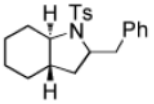
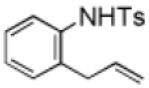
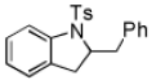
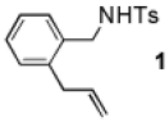
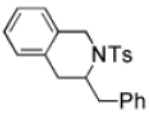
[b] Yields determined by ^1H NMR with diethyl phthalate as an internal standard.

[c] Isolated yield.

Table 2

Substrate scope for the aminoarylation reaction.



entry	substrate	product	Temp. (°C)	yield
1	 **3**	 **4**	60	51%
2	 **5a**	 **6**	RT	70%
3	 **7**	 **8**	40	82%
4	 **9**	 **10**	RT	72%[b]
5	 **11**	 **12**	RT	72%[c]
6	 **13**	 **14**	RT	92%[d]
7	 **15**	 **16**	40	64%
8	 **17**	 **18**	40	63%

[a] Isolated yield.

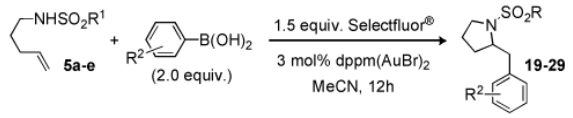
[b] d.r. = 1.5:1.

[c] d.r. = 1.1:1

[d] d.r. = 1.8:1.

Table 3

Sulfonyl and boronic acid scope for the aminoarylation reaction.[a]



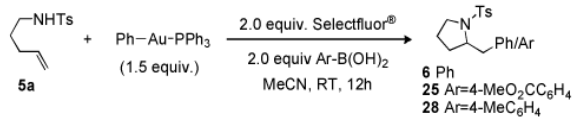
	R[1]	R[2]	product	T (°C)	yield
1	**5b** [4-MeO-C_6H_4]	H	**19**	RT	57%
2	**5c** [4-Br-C_6H_4]	H	**20**	RT	79%
3	**5d** [2-O_2N-C_6H_4]	H	**21**	RT	75%
4	**5e** [4-O_2N-C_6H_4]	H	**22**	40	75%
5	**5a** [4-Me-C_6H_4]	3-F	**23**	40	75%
6	**5a** [4-Me-C_6H_4]	2-Cl	**24**	40	56%
7	**5a** [4-Me-C_6H_4]	4-CO_2Me	**25**	40	83%
8	**5a** [4-Me-C_6H_4]	2-CO_2Me	**26**	40	77%
9	**5a** [4-Me-C_6H_4]	4-CHO	**27**	40	68%
10	**5a** [4-Me-C_6H_4]	4-Me	**28**	RT	81%
11	**5a** [4-Me-C_6H_4]	4-MeO	**29**	RT	17%[b]

[a]Reactions conditions: **5** (100 μmol), boronic acid (200 μmol), Selectfluor® (150 μmol), and dppm(AuBr)$_2$ (3 μmol) in MeCN (1.0 mL) for 12 h.

[b]Recovered **5a** = 74%.

Table 4

C-C Bond formation with Ph_3PAuPh



entry	R-B(OH)$_2$	Yield[*[a]*]	Ar/Ph
1	None	< 5%	---
2	Ph-B(OH)$_2$	52%	---
3	4-Me-C$_6$H$_4$-B(OH)$_2$	58%	94:6
4	4-MeO$_2$C-C$_6$H$_4$-B(OH)$_2$[*[b]*]	37%	93:7

*[a]*Yield determined by ^{1}H NMR with diethyl phthalate as an internal standard.

*[b]*Reaction carried out at 40 °C.