Gold Catalysis

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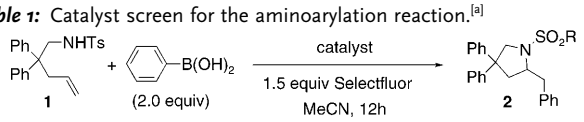
Gold-Catalyzed Intramolecular Aminoarylation of Alkenes: C–C Bond Formation through Bimolecular Reductive Elimination**

*William E. Brenzovich, Jr., Diego Benitez, Aaron D. Lackner, Hunter P. Shunatona, Ekaterina Tkatchouk, William A. Goddard, III, and F. Dean Toste**

The utility of homogeneous gold complexes as carbophilic π-acids has been well-established, with numerous reports of gold-catalyzed reactions that were initiated by addition of nucleophiles into unsaturated carbon–carbon bonds.[1] Although 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 that were 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. Although the electrophile is often a proton, gold(I)-catalyzed carboheterofunctionalization 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 that are derived from addition of an amine to a π bond might react with nucleophilic boronic acids in an intramolecular aminoarylation reaction.[7] Whilst our initial studies using allenyl tosylamides were unsuccessful, we were encouraged to find that the Ph_3PAuCl-catalyzed reaction of alkenyl tosylamide **1** with 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 $Ph_3PAuOTf$ (Table 1, 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 the counterion on the aminoarylation reaction. Whilst the use of $Ph_3PAuOBz$ as a catalyst resulted in decreased conversion (Table 1, entry 3), Ph_3PAuBr led to a significant increase in the yield of **2** (Table 1, entry 4). The corresponding gold(I) iodide (Table 1, entry 5) provided **2** in only trace amounts, as the iodide itself is likely susceptible to oxidation by Selectfluor.

Table 1: Catalyst screen for the aminoarylation reaction.[a]



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

[a] Reactions run in a sealed vial at 0.05 M in **1**. [b] Yields determined by ^{1}H NMR with diethyl phthalate as an internal standard. [c] Yield of isolated product. dppm = bis(diphenylphosphanyl)methane, dppb = bis(diphenylphosphanyl)butane, Ts = 4-toluenemethanesulfonyl.

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 $PhB(OH)_2$ led to the formation of a major signal in the ^{31}P NMR spectrum at $\delta =$ 44.28 ppm, which we identified as $[(Ph_3P)_2Au]^+$. Moreover, in situ monitoring of the reaction mixture by ^{31}P NMR spectroscopy showed this cationic complex to be the dominant gold species in solution during the catalytic reaction; however, independently prepared $[(Ph_3P)_2Au]BF_4$ was found to produce **2** in inferior yield (Table 1, 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 the use of bimetallic[9] gold complexes as catalysts might minimize the formation of this type of bisphosphinogold(I) species. We were delighted to find that [dppm(AuBr)$_2$] was an excellent catalyst at room temperature (Table 1, entry 7).[10,11]

The optimized conditions appear to tolerate a wide variety of sulfonamides and to be independent of substitution pattern (Table 2); in addition, trifluoroacetamides are reasonable substrates for the reaction (Table 2, entry 1). The cyclization provides N-protected pyrrolidines at room temperature, even for substrates that do not have the benefit of the Thorpe–Ingold effect (Table 2, entry 2). The ability to form six-membered rings (Table 2, entry 3) is notable, with

[*] Dr. W. E. Brenzovich, Jr., A. D. Lackner, H. P. Shunatona, Prof. F. D. Toste
Department of Chemistry, University of California, Berkeley
Berkeley, CA 94720 (USA)
Fax: (+1) 510-643-9480
E-mail: fdtoste@berkeley.edu
Dr. D. Benitez, Dr. E. Tkatchouk, Prof. W. A. Goddard, III
Materials and Process Simulation Center, California Institute of Technology
Pasadena, CA 02215 (USA)

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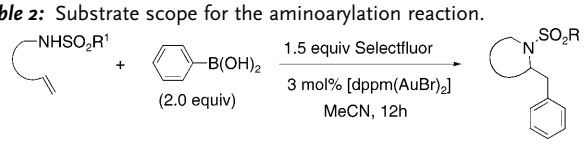
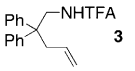
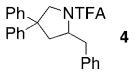
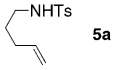
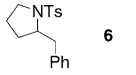
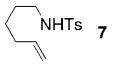
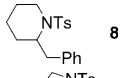
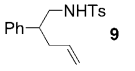
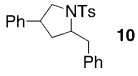
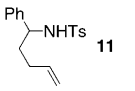
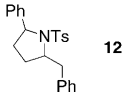
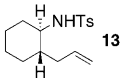
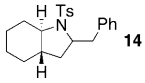
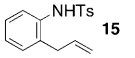
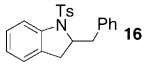
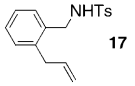
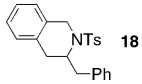
Table 2: Substrate scope for the aminoarylation reaction.

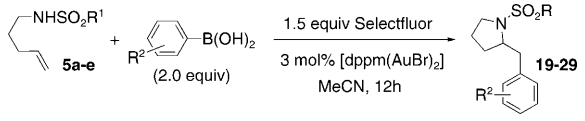


Entry	Substrate	Product	*T* [°C]	Yield [%]
1	 **3**	 **4**	60	51
2	 **5a**	 **6**	RT	70
3	 **7**	 **8**	40	82
4	 **9**	 **10**	RT	72[b]
5	 **11**	 **12**	RT	72[c]
6	 **13**	 **14**	RT	92[d]
7	 **15**	 **16**	40	64
8	 **17**	 **18**	40	63

[a] Yield of isolated product. [b] d.r. = 1.5:1. [c] d.r. = 1.1:1. [d] d.r. = 1.8:1. TFA = trifluoroacetic acid.

only a slight increase in temperature required. We have also achieved mild access to functionalized 2,3-dihydroindole and 1,2,3,4-tetrahydroisoquinoline products (Table 2, entries 7 and 8). The reaction tolerated a variety of sulfonamide protecting groups and boronic acids (Table 3), both electron poor and electron rich. More-hindered and more-electron-poor boronic acids reacted sluggishly under the standard room temperature conditions, but functional yields were 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 *para*-methoxyphenylboronic acid, owing to competing oxidation of the boronic acid by Selectfluor.

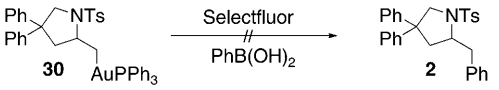
Table 3: Sulfonyl and boronic acid scope for the aminoarylation reaction.[a]



Entry	R^1	R^2	Product	*T* [°C]	Yield [%]
1	4-$MeOC_6H_4$ (**5b**)	H	**19**	RT	57
2	4-BrC_6H_4 (**5c**)	H	**20**	RT	79
3	2-$O_2NC_6H_4$ (**5d**)	H	**21**	RT	75
4	4-$O_2NC_6H_4$] (**5e**)	H	**22**	40	75
5	4-Me-C_6H_4 (**5a**)	3-F	**23**	40	75
6	4-MeC_6H_4 (**5a**)	2-Cl	**24**	40	56
7	4-MeC_6H_4 (**5a**)	4-CO_2Me	**25**	40	83
8	4-MeC_6H_4 (**5a**)	2-CO_2Me	**26**	40	77
9	4-MeC_6H_4 (**5a**)	4-CHO	**27**	40	68
10	4-MeC_6H_4 (**5a**)	4-Me	**28**	RT	81
11	4-MeC_6H_4 (**5a**)	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%.

Several possibilities exist for the mechanism of this transformation. First, we 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 failed to catalyze the reaction (Table 1, entry 2). Moreover, treatment of alkylgold(I) complex **30**[12] with phenylboronic acid and Selectfluor failed to produce pyrrolidine **2** [Eq. (1)]. Therefore, we surmised that oxidation of Au^I into Au^{III} must precede the aminoauration step.



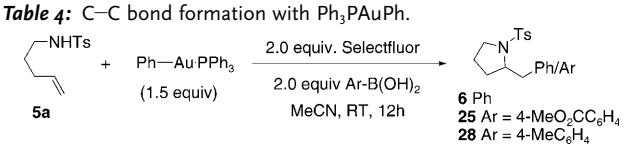
(1)

Next, we considered the potential transmetalation 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 room temperature and 60 °C, gave no Ph_3PAuPh as judged by ^{31}P NMR spectroscopy.[13] This observation suggests that any transmetalation likely follows oxidation and the or 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 pathway from a gold(III)–phenyl intermediate, analogous to the related transition-metal-catalyzed oxidative cyclization reactions.[7] Reductive eliminations from gold(III)–alkyl and gold(III)–aryl complexes have been reported, but typically require elevated temperatures,[14] whereas our reaction occurs readily even at room temperature. Furthermore, we found that whilst Ph_3PAuPh was a competent catalyst for the reaction,[15] treatment of **5a** with stoichiometric Ph_3PAuPh and Selectfluor in the absence of boronic acid led to only trace product formation (Table 4, entry 1). Addition of a phenylborate recovers the reaction, and provides **6** in reasonable yields (Table 4, entry 2). Moreover, the reaction of **5a** with different boronic acids and Ph_3PAuPh produced adducts **25** and **28** derived from transfer from the arylboronic acid and not from the phenylgold species, almost exclusively, regardless of the electronic properties of the boronic acid (Table 4, entries 3 and 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

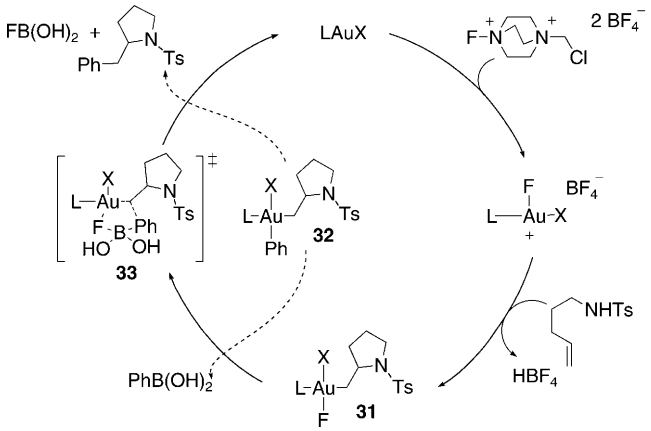
Table 4: C–C bond formation with Ph_3PAuPh.



Entry	Ar-B(OH)$_2$	Yield [%][a]	Ar/Ph
1	–	< 5	–
2	Ph-B(OH)$_2$	52	–
3	4-MeC$_6$H$_4$-B(OH)$_2$	58	94:6
4	4-MeO$_2$CC$_6$H$_4$-B(OH)$_2$[b]	37	93:7

[a] Yield determined by ^{1}H NMR spectroscopy with diethyl phthalate as an internal standard. [b] Reaction carried out at 40 °C.

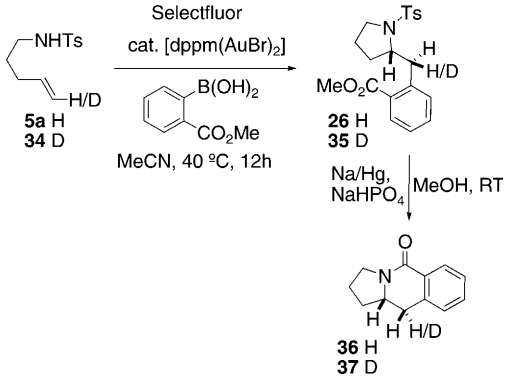
phenyl group acts as a spectator ligand. Therefore, we propose that interaction of the boronic acid with alkylgold(III) fluoride intermediate **31** does not result in transmetalation to **32**, but instead induces a bimolecular reductive elimination. In this hypothesis, the B–F interaction is key for the reductive elimination step, as it increases the nucleophilicity of the boronic acid and the electrophilicity of the carbon–gold(III) moiety. Although 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]



Scheme 1. Proposed mechanism for the gold-catalyzed aminoarylation reaction.

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 with stereochemical retention, or initial *syn*-aminoauration[17] with 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 through a redox cycle involving the initial oxidation of gold(I) into gold(III) with



Scheme 2. Examination of the reaction stereochemistry using deuterium labeling.[18]

Selectfluor. Ligand and halide effects played a dramatic role in the development of an exceptionally mild catalyst system for the addition to alkenes. Finally, although 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 through a bimolecular reductive elimination. Studies directed towards the application of this catalyst system and reactivity paradigm towards the development of further transformations are underway in our laboratory.

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Keywords: alkenes · C–C bond formation · cyclization · gold · homogeneous catalysis

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

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

