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Gold-Catalyzed Cross-Coupling

Gold-Catalyzed Allylation of Aryl Boronic Acids: Accessing Cross-Coupling Reactivity with Gold**

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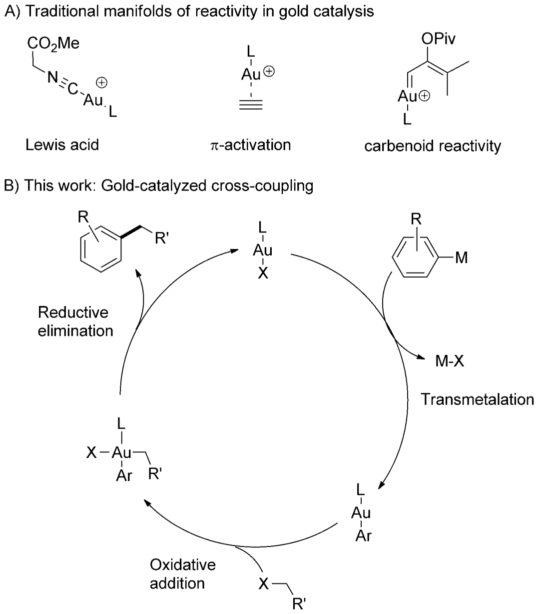
Abstract: *A sp^3–sp^2 C–C cross-coupling reaction catalyzed by gold in the absence of a sacrificial oxidant is described. Vital to the success of this method is the implementation of a bimetallic catalyst bearing a bis(phosphino)amine ligand. A mechanistic hypothesis is presented, and observable transmetalation, C–Br oxidative addition, and C–C reductive elimination in a model gold complex are shown. We expect that this method will serve as a platform for the development of novel transformations involving redox-active gold catalysts.*

The air- and water-stability of gold catalysts, coupled with their ability to promote complex transformations under mild conditions has attracted considerable interest from the academic community.[1] Despite the rapid pace of recent developments, the majority of gold-catalyzed processes rely on a select few reaction manifolds: 1) Lewis acid catalysis, 2) π-activation, and 3) the generation of carbenoid intermediates (Scheme 1 A).[2] While these modes of reactivity have yielded important catalytic methodologies of broad scope and synthetic utility,[3] they are typified by catalytic cycles wherein gold maintains a +1 oxidation state, in stark contrast to the 2-electron redox cycles characteristic of late transition metal catalysis.[4] Indeed, access to Au^{III} intermediates under catalytic conditions typically requires strong F^+ or I^{3+} oxidants.[5,6]

Despite this limitation, seminal work by Kochi and Schmidbaur has shown that Au^I complexes oxidatively add alkyl halides, and are further competent to undergo C–C reductive elimination, furnishing formally cross-coupled products.[7] However, this mode of reactivity has not previously been realized in a catalytic fashion.

A possible barrier to the implementation of such a redox cycle is the slow rate at which alkyl–alkyl reductive elimination occurs.[8] Nevertheless, we were encouraged by our own recent observations that in contrast, aryl–aryl reductive elimination from Au^{III} is remarkably fast.[9] As such, we hypothesized that a process involving oxidative addition to a gold aryl species followed by sp^2–sp^3 reductive elimination might prove achievable under the influence of a gold catalyst (Scheme 1 B).



Scheme 1. Reactivity in gold catalysis.

After examining several classes of aryl nucleophiles and alkyl electrophiles, we found that allyl bromide and phenylboronic acid produced allylbenzene and biphenyl as products when Ph_3PAuCl was used as a catalyst (Table 1, entry 1). However, we were unable to substantially improve the yield by implementing other traditional gold catalysts or by increasing catalyst loading (entries 2–6, 11).

In seeking to improve the reaction, we were drawn to the observation that closely linked bimetallic gold complexes undergo accelerated oxidative addition, due to the formation of Au^{II}–Au^{II} species (rather than discrete Au^{III}) upon oxidation (Scheme 2).[10] While [dppm(AuCl)$_2$] (dppm = bis(diphenylphosphino)methane) showed considerable instability under the reaction conditions, the bimetallic complex **1** produced the desired product in an improved 66 % yield.[11]

Intriguingly, the analogous monometallic aminophosphine complex **2** afforded substantially lower yield (even at 10 % loading), suggesting that the bimetallic catalyst architecture is responsible for the activity of **1**, rather than the electronic character of the aminophosphine ligand.[12] However, because monometallic complexes are capable of catalyzing this transformation (albeit with lower efficiency), the

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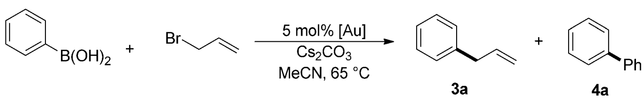
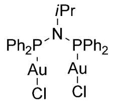
Table 1: Catalyst optimization.[a]



Entry	Catalyst	Yield **3a** [%]	Yield **4a** [%]
1	[Ph$_3$PAuCl]	36	10
2	[IPrAuCl]	1	0
3	[*t*Bu$_3$PAuCl]	5	6
4	[(Johnphos)AuCl]	11	3
5	[(PhO)$_3$PAuCl]	1	0
6	[(pOMePh)$_3$PAuCl]	31	6
7	[dppm(AuCl)$_2$]	24	14
8	**1**	**66**	**9**
9	**2**	16	7
10[b]	**2**	17	9
11[b]	[Ph$_3$PAuCl]	41	15
12	[IPrAuOH]	5	0
13	none	0	0
14[c]	**1**	0	0

[a] Conditions: 4 equiv halide, 3 equiv base, 0.2 M, 18 h; calibrated GC yields vs. PhCO$_2$Et as an internal standard. [b] 10 mol% catalyst. [c] No allyl bromide added; IPr = 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-2(3*H*)-ylidene, Johnphos = 2-dicyclohexylphosphinobiphenyl.

1:



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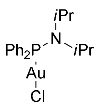
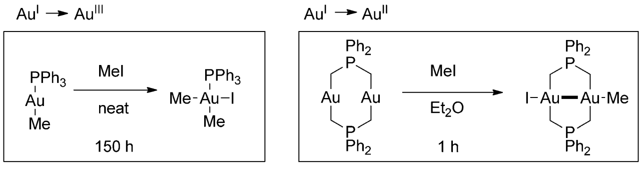


influence of the bimetallic catalyst remains to be fully elucidated.

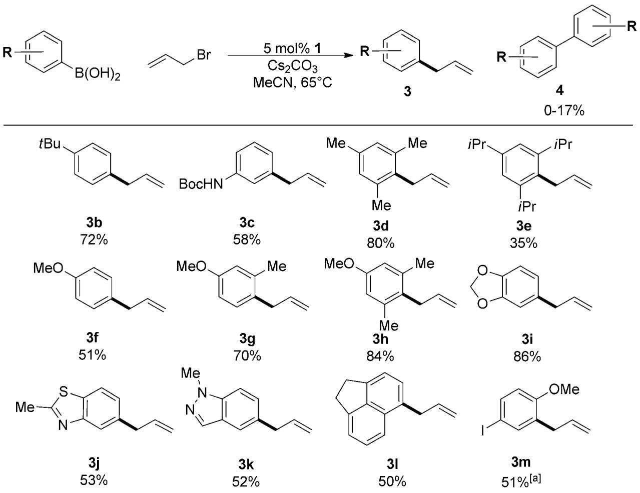
In the absence of allyl bromide (entry 14), neither product was observed, signifying that allyl bromide serves as the oxidant in the homocoupling process. Notably, the reaction proceeded with identical efficiency in the presence of air and water.

Scheme 3 illustrates the scope of the boronic acid component. While highly basic or nucleophilic functionality was not tolerated, heteroaromatic boronic acids (**3j**, **3k**) were coupled smoothly. Of note, substrates bearing aryl halide moieties reacted with complete chemoselectivity for the external allylic halide (**3m**), showcasing the discrimination inherent in the S$_N$2-type oxidative addition typically observed with Au^I.[7] Interestingly, sterically encumbering substituents were found to facilitate the reaction (compare **3f**, **3g**, **3h**). This effect ostensibly arises because the *ortho* substituents block the formation of homocoupling side-products.

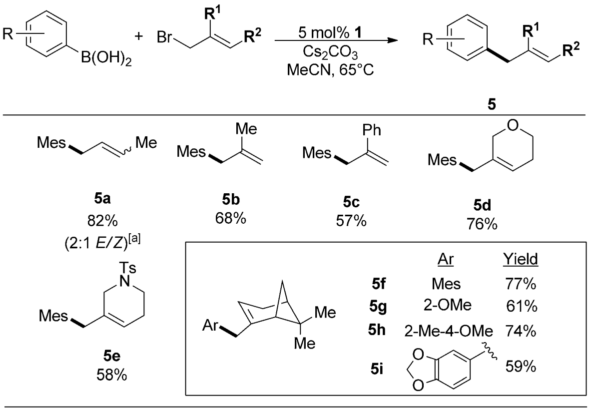
The beneficial effect of sterics led us to examine the scope of the allylic electrophile with mesityl boronic acid, an otherwise challenging cross-coupling substrate (Scheme 4).



Scheme 2. Oxidative addition to Au^I.[6a, 9g]



Scheme 3. Arylboronic acid scope. Conditions: 4 equiv halide, 3 equiv base, 0.2 M, 18 h. Yields of isolated products. [a] 10 mol% catalyst. Boc = *tert*-butoxycarbonyl.

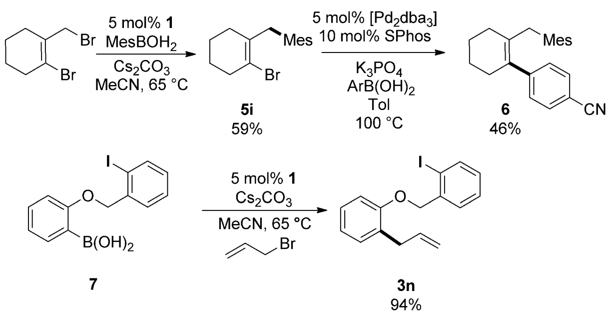


Scheme 4. Allylic bromide scope. Conditions: 4 equiv halide, 3 equiv base, 0.2 M, 18 h. Yields of isolated products. Mes = 2,4,6-trimethylphenyl. No biaryl detected. [a] Starting from 5:1 *E*:*Z* crotyl bromide.

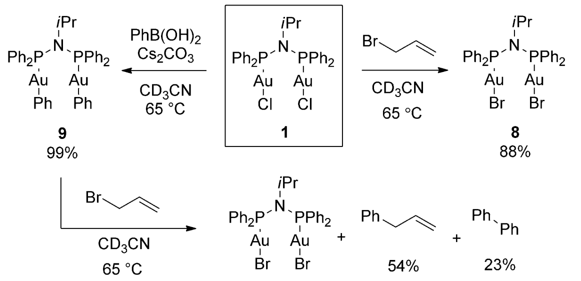
This effect is further exhibited in products **5f**–**5i**. In all cases, linear products were observed.[13]

The orthogonality of this method to traditional cross-coupling reactions allows the chemoselective preparation of polyfunctionalized products (Scheme 5). While gold and palladium catalysts are both capable of producing **5j**, our gold-catalyzed protocol provided higher efficiency and chemoselectivity, allowing access to bifunctionalized products such as **6**.[14] Furthermore, **3n** can be prepared without competitive cyclization or oligomerization.[15]

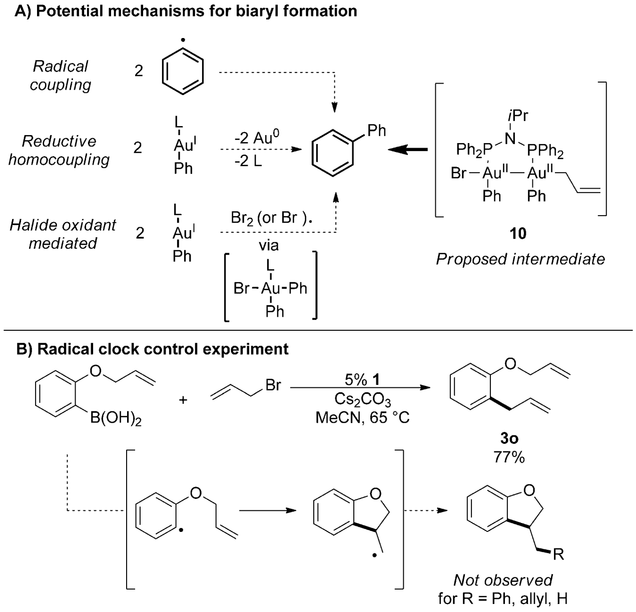
Having developed this method, we sought to better understand the mechanism of the overall transformation. In initial stoichiometric experiments (Scheme 6) we found that while **1** underwent halide metathesis upon reaction with allyl bromide, no oxidized species were detected.[10f] However, the gold aryl complex **9** was formed cleanly by transmetalation from the boronic acid under the reaction conditions.[16] Futhermore, **9** underwent facile conversion in reaction with allyl bromide to give the dibromide **8**, affording allylbenzene



Scheme 5. Orthogonal reactivity of [Au] and [Pd].



Scheme 6. Stoichiometric reactivity of **1**.



Scheme 7. Mechanisms for biaryl formation.

and biphenyl. These experiments suggest a mechanism for the catalytic process in which transmetalation to gold precedes oxidative addition.[17,18]

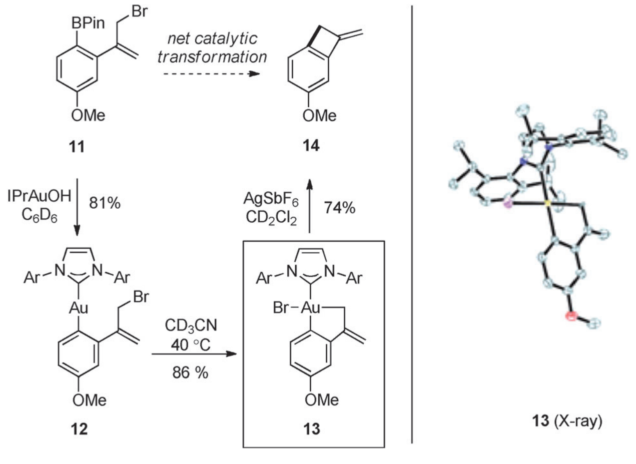
While a number of mechanisms can be proposed for the formation of the desired allylbenzene product from the gold aryl **9**, fewer mechanisms can account for the formation of biaryl. Because alternatives to the oxidative addition/reductive elimination process almost invariably necessitate distinct pathways to cross- and homocoupled products, examination of potential homocoupling processes can be used to discern between possible mechanistic scenarios (Scheme 7 A).[19]

Of the likely mechanisms, radical clock experiments (Scheme 7 B) argue against the implication of radicals, while the stability of **9** to high temperatures argues against reductive homocoupling processes (cf. Table 1, entry 12).[14] Finally, halide scavenger experiments argue against trace bromine (or bromine atom) oxidants as agents for the production of biaryl.[14,20,21]

Combined, these experiments ultimately lead us to implicate the Au^{II}–Au^{II} intermediate **10** as the most likely source of biaryl. Reductive elimination from **10** can presumably also lead to alkyl–aryl bond formation, immediately suggesting a parsimonious mechanism for the overall transformation. Despite this evidence, attempts to isolate or detect the Au^{II}–Au^{II} intermediate directly have so far proven fruitless, likely due to the rapid rate of reductive elimination.[9]

In light of these difficulties, we turned to the tethered substrate **11** as a mechanistic probe, expecting that the resulting aurocyclic product (e.g. **13**) would exhibit hampered reductive elimination, allowing direct observation of reaction intermediates.[22] Although transmetalation of **11** to phosphine supported gold complexes such as **1** was accompanied by hydrolysis of the allylic bromide moiety, it was found that clean transmetalation could be accomplished by employing IPrAuOH.[23] Although **12** does not react further in benzene, oxidative addition could be initiated upon gentle heating in acetonitrile to yield the isolable Au^{III} species **13** (Scheme 8).[24] Finally, halide abstraction results in reductive elimination to give the exomethylene cyclobutene **14**.

With the viability of allylic halide oxidative addition to gold aryl complexes demonstrated, we propose the following overall mechanism for this process, following the general outline of Scheme 1 B: 1) base-assisted transmetalation of the arylboronic acid to a gold bromide complex, 2) bimetallic oxidative addition of an allylic halide to the gold aryl species, and 3) fast C–C reductive elimination to give either allylbenzene or biaryl as product.[25,26]



Scheme 8. Model catalytic cycle and isolable product of oxidative addition. Ar = 2,6-diisopropylphenyl. Asymmetric unit contains two molecules of **13**, only one shown; hydrogen atoms omitted for clarity. O red, N blue, Au yellow, purple Br.

In conclusion, we have developed the first example of a net redox-neutral cross-coupling catalyzed by gold.[27] The method provides access to sp^2–sp^3 coupled products under mild conditions with complete tolerance for air and water. The reaction exhibits unique scope and chemoselectivity, allowing entry to a variety of allylbenzene products. Furthermore, initial experiments suggest an unprecedented mechanism involving oxidative addition to a gold aryl species as a key step. This reaction manifold promises to serve as a powerful strategy for the development of novel gold-catalyzed reactions.

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[18] The difference in product ratio between the catalytic and stoichiometric experiments is likely due to the higher concentration of $[Au^I]$-Ar species, which transmetalate rapidly with Au^{III} (see Ref. [9]). Monoaryl species have been detected by ^{31}P NMR spectroscopy in the stoichiometric reaction of **9** with allyl bromide and are clearly likewise competent to produce allylbenzene products.

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[26] Based on the analogous aryl–aryl reductive elimination, we expect that isomerization from **10** (or its monoaryl analogue) to a mixed-valent Au^{III}–Au^{I} species precedes reductive elimination. (see Ref. [9]).

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