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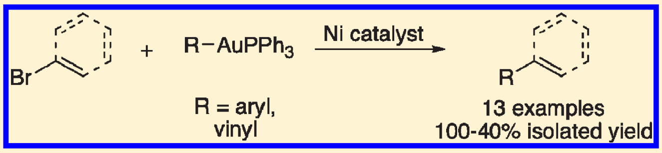
Nickel-Catalyzed Cross-Coupling of Organogold Reagents

Joshua J. Hirner and Suzanne A. Blum*

Department of Chemistry, University of California, Irvine, California 92697-2025, United States

S *Supporting Information*

ABSTRACT: Organogold compounds undergo nickel-catalyzed cross-coupling reactions with aryl and vinyl bromides in high yield under mild conditions. The reaction tolerates both electron-rich and electron-poor organogold complexes, and olefinic bromides undergo cross-coupling with high stereoselectivity. This novel transformation links well-established nickel catalysis with more recent developments in organogold transformations.



The field of homogeneous gold catalysis has experienced a rapid growth over the past decade.[1−4] Despite the versatility of these reactions, the catalyst-regenerating step often relies upon carbene insertion[5−7] or the trapping of the gold−carbon bond with an electrophile, such as a proton,[1−3,8] carbocation,[9,10] or silicon[11] or sulfonyl[12] cation equivalent. The interception of organogold compounds by a second transition metal, however, would allow for more synthetically diverse transformations. Our group has demonstrated the palladium-catalyzed addition of organogold reagents across alkynes and the palladium-catalyzed cross-coupling of organogold reagents,[13] as well as a palladium/gold dual-catalyzed rearrangement and cross-coupling reaction.[14] Palladium-catalyzed coupling reactions stoichiometric in gold have since been studied more generally,[15−20] highlighting the potentially broad applicability of reactions involving gold and another transition metal. The compatibility of organogold(I) complexes with single-electron-reducing transition metals under catalytic conditions is not well-established.[21,22]

We herein report a transmetalation between homogeneous organogold and nickel complexes[21] and its application to an efficient nickel-catalyzed cross-coupling reaction of organogold reagents. This cross-coupling reaction outcompetes the potential reduction of gold(I)[23,24] by nickel(I).[25] The reaction proceeds at mild temperatures and is effective with organogold compounds with a variety of electronic properties, establishing a breadth of coupling reactions available to organogold compounds by opening the door to nickel catalysis, which can offer reactivity both parallel to[26] and unique from that of palladium.[27]

During initial experiments to establish standard reaction conditions, $NiCl_2(PCy_3)_2$ (**1**) was identified as an optimal nickel precatalyst. When treated with 5 mol % **1** and an aryl bromide, electron-rich and electron-poor organogold reagents afforded cross-coupled products in quantitative conversion[28] (Table 1, entries **4a**−**d**). Heterocycles such as bromopyridine, bromopyrazine, and bromofurfural are equally effective coupling partners (**4f**−**h**). The scope of the transformation is not limited to arylgold reagents; isopropenyl- and alkynylgold reagents proved to be suitable cross-coupling partners (**4i**−**j** and **4m**). The isopropenylgold couplings demonstrate the tolerance of the reaction for branching at the α carbon, while the comparatively slow formation of **4j** versus **4a**−**d** suggests that the organogold hybridization plays a role in the transmetalation rate. Consistent with this hybridization dependence, Ph_3PAuMe failed to afford a cross-coupling product with **3a** under standard reaction conditions. A similar dependence has been reported in the protodeauration of organogold compounds, the rate of which also decreases in the order of $sp^2 > sp > sp^3$.[29] The involvement of the π system has been postulated as the cause of this rate dependence in protodeauration[29] and in the transmetalation of other organometallic reagents to nickel;[30] therefore, the diminished reaction rate of **2j** may be due to a reduced kinetic accessibility of the alkynylgold π system resulting from a lower HOMO versus arylgold reagents **2a**−**d**.[29,31] This similarity to protodeauration in hybridization dependence suggests that nickel may display electrophilic character in transmetalation reactions with organogold compounds.

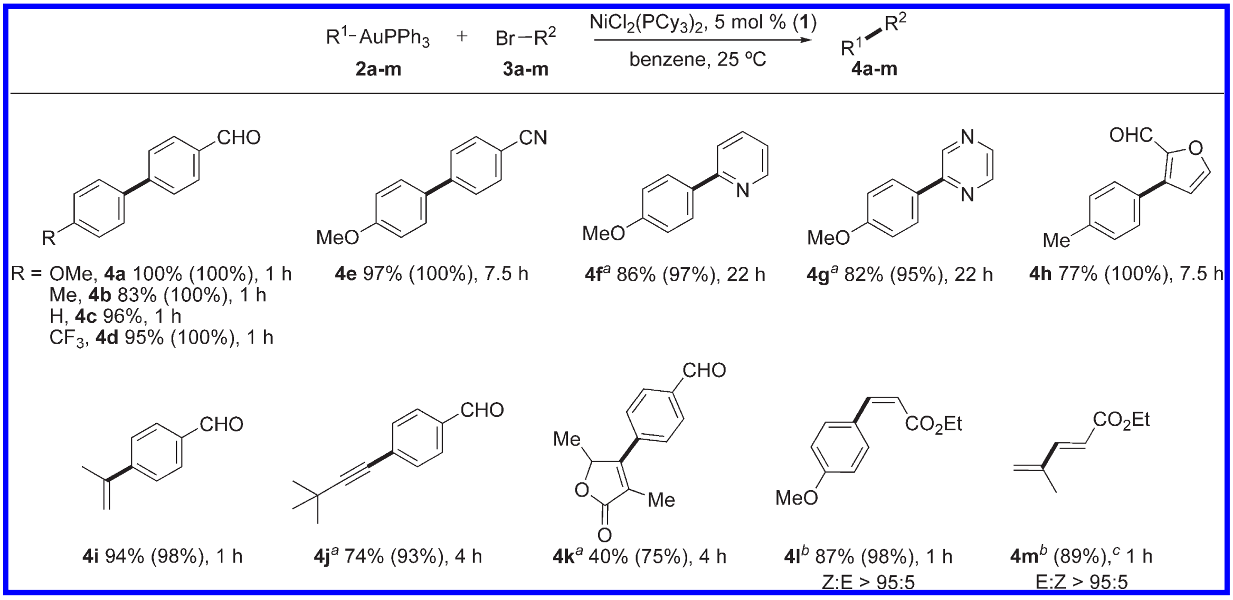
Organogold butenolide rearrangement substrate **2k** was isolated by Hammond,[32] and derivatives have been implicated as intermediates in gold-catalyzed rearrangements.[14,33,34] When introduced to our nickel catalyst system, **2k** afforded cross-coupled product **4k** in 75% yield by ^1H NMR spectroscopy, demonstrating the ability to functionalize catalytic organogold intermediates with this nickel-catalyzed cross-coupling reaction.

A stereocontrol study was conducted using 1-bromo-1-propene (**5**) as a model vinyl bromide. The reaction of organogold compound **2a** with (*E*)-**5** yielded exclusively the *E* cross-coupled product **6** (eq 1), while (*Z*)-**5** was converted predominately to (*Z*)-**6** (*Z*:*E* = 81:19, eq 2). Control experiments to probe the origin of the incomplete stereospecificity observed with (*Z*)-**5** revealed that neither the product nor the starting material was subject to a nickel-catalyzed isomerization. Partial loss of stereochemical integrity could have occurred through the formation of a vinyl radical through bromine atom abstraction by Ni.[35] The predominance of a stereospecific cross-couping confirms that the primary pathway for oxidative addition by nickel into **5** does not

Received: January 21, 2011
Published: February 23, 2011

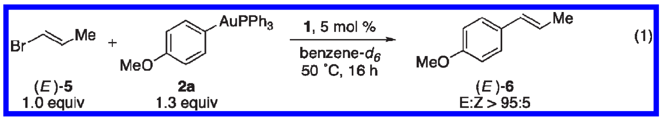
dx.doi.org/10.1021/om200060x | *Organometallics* 2011, 30, 1299–1302

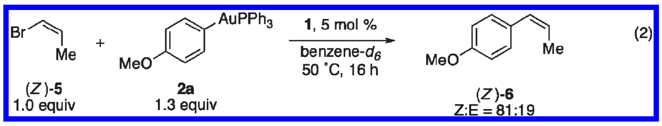
Table 1. Cross-Coupling Substrate Scope[d]



[a] Reaction conducted at 45 °C. [b] Starting from the Z bromide. [c] Not isolated due to product volatility. [d] Conditions: 1.30 equiv of organogold, 1.00 equiv of aryl bromide (30.0 mM), and 5 mol % $NiCl_2(PCy_3)_2$. Isolated yield (^1H NMR yield of small-scale reaction in C_6D_6 with mesitylene internal standard).

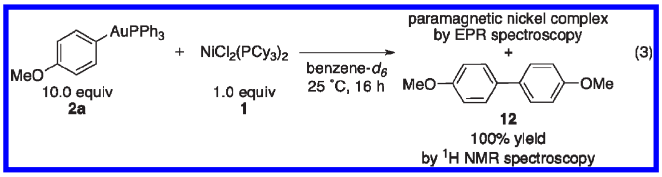
generate a free organic radical,[36] which would result in a thermodynamic mixture of isomers of **6** regardless of the starting olefin geometry. In contrast, the reactions of ethyl (*Z*)-3-bromopropenoate yielded the cross-coupled products (*Z*)-**4l** and (*E*)-**4m** in both high yield and stereochemical purity, but with inversion of configuration for **4m**. An alternative mechanism, such as Michael addition−elimination of a nucleophilic nickel intermediate,[37] may explain the stereochemical scrambling observed with **4m**.





A proposed catalytic cycle for this reaction is shown in Scheme 1. Two successive transmetalation reactions between organogold **2** and nickel precatalyst **1** yield the diorganonickel(II) intermediate **7** (step 1), reductive elimination from which is kinetically disfavored;[38] therefore, single-electron oxidation by gold(I)[39] or the organobromide[38] could provide a nickel(III) species, **8**, which gives nickel(I) intermediate **9** upon reductive elimination (steps 2, 3).[40] In analogy to nickel-catalyzed cross-couplings with metals other than gold, transmetalation of organogold **2** to nickel(I) is expected to precede oxidative addition into bromide **3**.[36,41] The resulting nickel(III) intermediate **11** then affords the observed cross-coupled product **4** via a rapid reductive elimination.[40] Notably, once the active nickel catalyst has been generated (steps 1−3), the absence of further homocoupling reactivity suggests that the organogold coupling partner is not reduced[23] under these cross-coupling conditions despite the potential thermodynamic favorability of a Au(I)/Ni(I) redox reaction to form Au(0) and Ni(II).[24,25,42]

Steps 1 and 4 in this mechanism involve a transmetalation from a homogeneous organogold complex to nickel.[21] The transmetalation step was investigated through a stoichiometric transfer from an arylgold compound to $NiCl_2(PCy_3)_2$. Treatment of 1.0 equiv of **1** under the pseudocatalytic conditions of excess **2a** (10.0 equiv) afforded quantitative conversion to homocoupled product **12** (eq 3).[43] Detection of a paramagnetic coproduct in this reaction by EPR spectroscopy is consistent with the generation of a nickel(I) complex as proposed in the catalyst-generating steps 1−3 in Scheme 1.



Having confirmed the viability of the key nickel−gold transmetalation step, we sought to gain a deeper understanding of the electronic effects involved. A series of competition experiments was performed in order to determine the relative rate of formation of cross-coupling products **4a**, **4c**, and **4d**. Relative rates were calculated using the relative abundance of each product as determined by ^1H NMR spectroscopy after completion of the reaction (Table 2). An excess of both organogold competition reagents, **2a** and **2c** or **2a** and **2d** (3.0 equiv), was employed in order to minimize variations in concentration throughout the course of the experiments. The competitive coupling for R = OMe versus R = H yielded an equimolar mixture of products (entry 2), and only slight selectivity was observed for the more electron-rich product with R = OMe versus R = CF_3 (entry 3). This minimal selectivity contrasts with nickel/boron and nickel/zinc cross-coupling reactions, which depend more significantly and linearly on σ_p ($\rho = 0.84$[44] and $\rho = -1.74$,[45] respectively).

Scheme 1. Proposed Catalytic Cycle

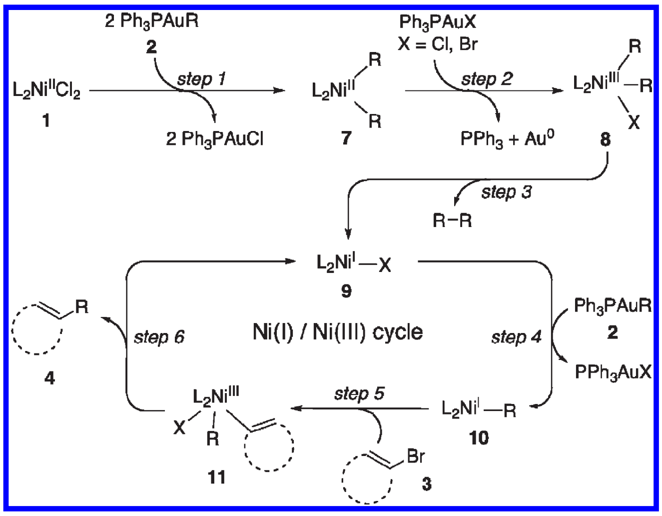
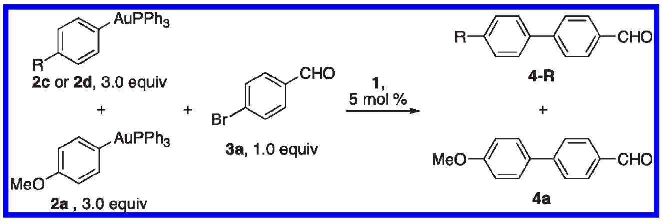


Table 2. Competition Experiments between Organogold Reagents[a]



entry	organogold	R	k_{rel} = 4-R/4a
1	**2a**	OMe	1.0
2	**2c**	H	1.0
3	**2d**	CF_3	0.6

[a] Conditions: benzene (0.010 M in **3a**), 25 °C, 2.0 h.

The modest selectivity suggests a different dependence on the electronic properties in the nickel/gold cross-coupling reaction than in nickel/boron and nickel/zinc coupling reactions.

In summary, we have demonstrated a transmetalation reaction between homogeneous nickel and organogold compounds.[46] The demonstration of this key step permitted the development of the first nickel-catalyzed cross-coupling reaction of organogold reagents at ambient temperatures in high, often quantitative yield. This cross-coupling reaction outcompetes potential single-electron reduction of gold(I) by nickel. This new reactivity bridges the long-standing synthetic and mechanistic research regarding nickel catalysis and the organogold reactivity that has more recently gained notoriety by probing the compatibility of the two metals. The ability of this reaction to functionalize known catalytic organogold intermediates provides access to unconventional cross-coupling bond disconnections, allowing for the rapid installation of molecular complexity. Studies that exploit the unique reactivity of both nickel and gold catalytically are underway in our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: blums@uci.edu.

■ ACKNOWLEDGMENT

We thank the National Science Foundation for funding through a CAREER Award for S.A.B. (CHE-0748312) and a Graduate Research Fellowship for J.J.H. (NSF-2010105893). We also thank the University of California−Irvine for funding, Dr. John Greaves and Ms. Shirin Sorooshian for mass spectrometry analysis, Mr. David C. Lacy for assistance with EPR spectroscopy, and Mr. Yili Shi and Ms. Katrina E. Roth for helpful conversations.

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