J|A|C|S COMMUNICATIONS

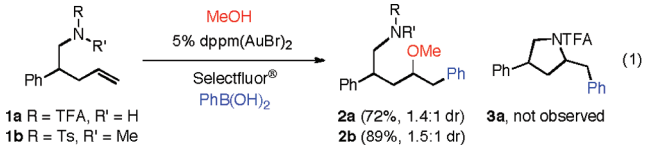
Gold-Catalyzed Three-Component Coupling: Oxidative Oxyarylation of Alkenes

Asa D. Melhado, William E. Brenzovich, Jr., Aaron D. Lackner, and F. Dean Toste*

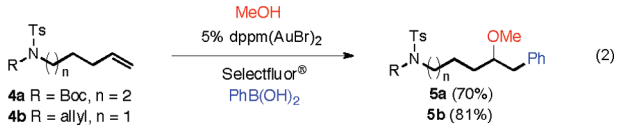
Department of Chemistry, University of California, Berkeley, California 94720

Received April 21, 2010; E-mail: fdtoste@berkeley.edu

The past decade has seen rapid expansion in the area of homogeneous gold catalysis. The majority of reported methods rely on the π-acidic nature of cationic gold species to activate π-bonds toward nucleophilic attack.[1] On the other hand, the two electron oxidation/reduction cycles typical of other late transition metal catalysts are not commonly encountered in gold catalysis.[1e,2] Recently, a few reports of transformations best explained by Au(I)/(III) redox cycles, including Au-catalyzed oxidative intramolecular heteroarylation reactions, have appeared.[3] Different modes of such heteroarylation reactions are accessible by combining two or all three reactant functional groups into a single substrate.[4] Notably, examples of the fully intermolecular, three-component coupling variant have not previously been reported.[5,6] Herein we disclose a protocol for the three-component gold-catalyzed oxidative oxyarylation of alkenes; alcohols, carboxylic acids, and even water are viable nucleophiles in this context.



(1)

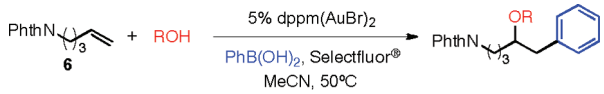


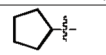
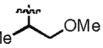
(2)

We initially observed this mode of reactivity while studying the related intramolecular aminoarylation.[3b] In an attempt to improve the solubility of the arylboronic acid, methanol was used as a co-solvent; however, the expected pyrrolidine **3a** was not observed. Instead, the alkoxyarylation product **2a** was isolated in 38% yield (eq 1). The yield of **2a** could be improved to 72% by increasing the temperature and employing 2 equiv of phenylboronic acid.[7] While previously reported gold-catalyzed additions of oxygen nucleophiles to alkenes have required temperatures greater than 85 °C,[8] the oxidative alkoxyarylation proceeds efficiently at 50 °C. Under these conditions, various alkenylamines (**1b** and **4a**,**b**) participated in the methoxyarylation reaction to afford the adducts of a three-component coupling in good yields (eq 2). Moreover, gold-catalyzed reaction of **4b** shows excellent chemoselectivity, leaving the more electron-deficient allylic amine unreacted.

In order to probe the scope of the reaction, 5-phthalimidopentene (**6**) was subjected to the optimized conditions for coupling with various alcohols and phenylboronic acid (Table 1). The expected ethers were obtained in high yield when using several primary alcohols (entries 1, 2, 4, and 6) and secondary alcohols (entries 3, 7, and 8). While neopentyl ether **10** was formed in 91% yield (entry 4), gold-catalyzed reaction with the more sterically encumbered *tert*-butyl alcohol gave only 33% of *tert*-butyl ether **11** (entry 5).[9] Substituting carboxylic acids in place of alcohols afforded the corresponding esters, albeit in slightly lower yield (entries 9−12).

Table 1. Alkoxy- and Acyloxyarylation with Various Nucleophiles[a]

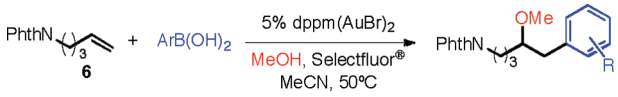


entry	R	product	yield (%)	entry	R	product	yield (%)
1	Me	**7**	79	7		**13**	85
2	Et	**8**	85	8		**14**	88 1:1 d.r.
3	^{i}Pr	**9**	90	9	Me(CO)-	**15**	62
4	$(Me)_3CCH_2$	**10**	91[c]	10	Et(CO)-	**16**	69
5	^{t}Bu	**11**	33[b]	11	^{i}Pr(CO)-	**17**	50
6		**12**	85	12	Ph(CO)-	**18**	48[c]

[a] 100 μmol of alkene, 0.1 M in 9:1 MeCN:ROH at 50 °C for 14 h; 2 equiv of $PhB(OH)_2$, 2 equiv of Selectfluor reagent (Air Products and Chemicals Inc.). The catalyst and $PhB(OH)_2$ were added in two portions at $t = 0$ and 2 h. [b] Yield determined by ^{1}H NMR versus an internal standard (nitrobenzene). [c] 10 equiv of ROH used.

The arylboronic acid component of the reaction was also varied with similar success. The gold-catalyzed coupling of alkene **6**, methanol, and various arylboronic acids gave the expected methyl ethers in good yields (Table 2). The reaction performed well with alkyl-, halo-, carboxymethyl-, and formyl-substituted arylboronic acids. Moreover, *ortho*- (eq 3), *meta*- (entries 3 and 6), and *para*-substituted (entries 1, 2, 4, and 5) arylboronic acids were tolerated in the methoxyarylation reaction.

Table 2. Methoxyarylation with Various $ArB(OH)_2$[a]



entry	R	product	yield (%)	entry	R	product	yield (%)
1	4-Me	**19**	88	4	4-MeO_2C	**22**	83
2	4-Br	**20**	90	5	4-H(CO)	**23**	82
3	3-F	**21**	79	6	3,5-bis-CF_3	**24**	77

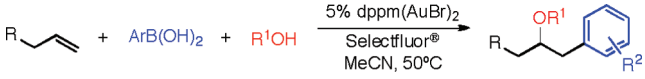
[a] 100 μmol of alkene, 0.1 M in 9:1 MeCN:MeOH at 50 °C for 14 h; 2 equiv of $ArB(OH_2)$, 2 equiv of Selectfluor reagent. The catalyst and $ArB(OH)_2$ were added in two portions at $t = 0$ and 2 h.

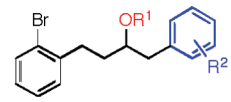
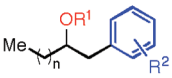
The nitrogen-containing functional groups in **1a**,**b**, **4a**,**b**, and **6** are not required for successful oxyarylation. Simple alkenes lacking these functionalities proved to be suitable substrates for alkoxy- and acyloxyarylation under our optimized conditions. The expected ethers were obtained in good yields when alkenes such as 1-octene and 1-bromo-2-(3-buten-1-yl)benzene were reacted with several combinations of alcohols and arylboronic acids (Table 3). Acetate

10.1021/ja1034123

esters were isolated in attenuated but synthetically useful yields from simple alkenes when using acetic acid as the nucleophile (entries 2 and 7).

Table 3. Alkoxy- and Acyloxyarylation of Simple Alkenes[a]

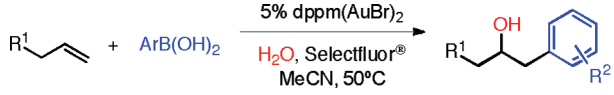


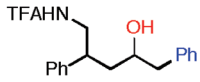
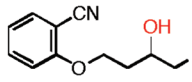
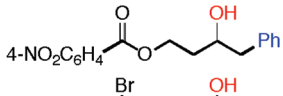
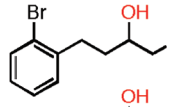
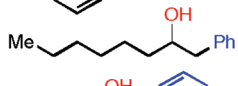
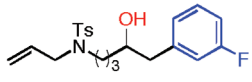
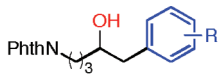
entry			R1	R2	product	yield (%)
1				4-Br	**25**	69
2			Me	2-CO_2Me	**26**	78
3			Me(CO)	4-Br	**27**	51[b]
4		n = 5		4-Br	**28**	76
5		n = 5	$(Me)_3CCH_2$	4-Br	**29**	73
6		n = 9	$(Me)_3CCH_2$	H	**30**	66
7		n = 5	Me(CO)	4-Br	**31**	53[b]

[a] 100 μmol of alkene, 0.1 M in 9:1 MeCN:R^1OH at 50 °C for 14 h; 2 equiv of $ArB(OH)_2$, 2 equiv of Selectfluor reagent. The catalyst and $ArB(OH)_2$ were added in two portions at $t = 0$ and 2 h. [b] Only 5 equiv of R^1OH used, 0.1 M in MeCN.

Using water as a nucleophile would allow for the formation of alcohols directly via hydroxyarylation, circumventing the requirement for protective groups for installation of the alcohol functionality.[10] We were pleased to find that simply replacing the alcohol in our protocol with water cleanly effected the formation of the desired hydroxyarylation products. A variety of terminal alkenes and arylboronic acids were subjected to these conditions, furnishing the expected products in good yield (Table 4). Various functional

Table 4. Scope of Hydroxyarylation Reaction[a]

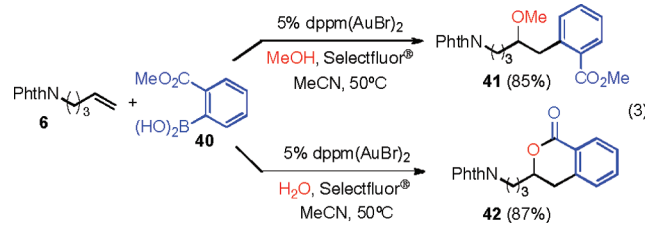


entry	product		yield (%)
1		**32**	88[b]
2		**33**	85[c]
3		**34**	67[d]
4		**35**	76
5		**36**	73
6		**37**	72
7		R = 3-F, **38**	83
8		R = 4-Me, **39**	71

[a] At 0.1 M alkene in MeCN, 10 equiv of H_2O, catalyst (2.5 mol %/addition), and $ArB(OH)_2$ (1 equiv/addition) were added in two portions each, at $t = 0$ and 1 h. [b] Isolated as a 1.2:1 mixture of diastereomers. [c] Three portions of catalyst (2.5 mol %/addition) and $ArB(OH)_2$ (1 equiv/addition). [d] Using $(4\text{-}CF_3C_6H_4)_3PAuBr$ as catalyst, two portions of 5 mol % each.

groups, including ether (entry 2), ester (entry 3), amide (entry 1), cyano (entry 2), nitro (entry 3), and aryl halide (entries 5−7), were well-tolerated.

The ability to use either alcohols or water as nucleophiles in the gold-catalyzed three-component coupling provides access to a greater diversity of products. Moreover, the hydroxyarylation reaction offers the opportunity to form an additional C−O bond to the resulting alcohol. For example, methoxyarylation of **6** with boronic acid **40** furnished methyl ether **41** in 85% yield. Using water as a nucleophile, **42** was formed in 87% yield from gold-catalyzed hydroxyarylation, followed by *in situ* lactone formation of the resulting alcohol (eq 3).



At present, we proffer a catalytic cycle for the gold-catalyzed oxyarylation of alkenes that is analogous to the mechanism proposed for the related intramolecular aminoarylation reaction.[3b] Initial oxidation of the gold(I) bromide is thought to provide a cationic gold(III) species capable of activating the alkene toward nucleophilic attack. Oxyauration of the π-bond is then followed by C−C bond formation, without prior transmetalation of the aryl group from boron to gold (Figure 1).

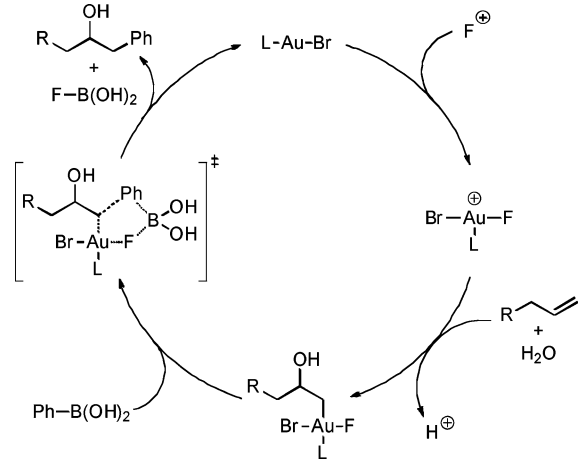
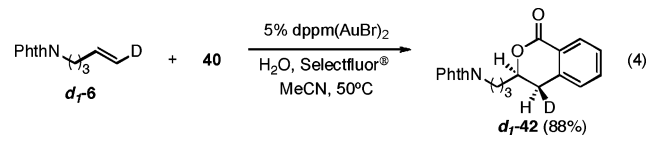


Figure 1. Proposed catalytic cycle for alkene hydroxyarylation.

Reaction of monodeuterated alkene $\mathbf{d_1}$-**6** stereospecifically produced $\mathbf{d_1}$-**42** with stereochemistry consistent with initial *syn*-hydroxyauration followed by invertive C−C bond formation. The stereochemical course of the hydroxyarylation is consistent with our earlier observations from the gold-catalyzed intramolecular aminoarylation (eq 4).[3b]



In conclusion, we have demonstrated the gold-catalyzed three-component coupling reaction of alkenes, arylboronic acids, and several types of oxygen nucleophiles, including alcohols, carboxylic

acids, and water. It is notable that the latter effectively participates as a nucleophile in these reactions, especially given difficulties associated with transition metal-catalyzed hydration of alkenes.[11] This method represents the first fully intermolecular alkene heteroarylation reaction and stands as one of the few examples of gold-catalyzed multicomponent couplings.[12]

Acknowledgment. We gratefully acknowledge NIHGMS (RO1 GM073932), Amgen, and Novartis for financial support and thank Johnson Matthey for a gift of $AuCl_3$.

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

References

(1) For recent reviews on gold-catalyzed reactions, see: (a) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675. (b) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (c) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239.

(2) Garcia, P.; Malacria, M.; Aubert, C.; Gandon, V.; Fensterback, L. *ChemCatChem* **2010**, *2*, 493.

(3) For Au-catalyzed amino- and oxyarylation of alkenes, see: (a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. (b) Brenzovich, W. E., Jr.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, doi: 10.1002/anie.201002739. For other oxidative Au-catalyzed reactions, see: (c) Hopkinson, M. N.; Tessier, A.; Salisbury, A.; Giuffredi, G. T.; Combettes, L. E.; Gee, A. D.; Gouverneur, V. *Chem. Eur. J.* **2010**, *16*, 4739. (d) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (e) Iglesias, A.; Muñiz, K. *Chem. Eur. J.* **2009**, *15*, 10563. (f) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3112. (g) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, *3*, 386. (h) Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F. *J. Organomet. Chem.* **2009**, *694*, 592.

(4) For selected reports of Pd-catalyzed amino- and oxyarylation, see: (a) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1028. (b) Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 2533. (c) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893. (d) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575. (e) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468. (f) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906. (g) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620. (h) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945. (i) Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *131*, 9488. (j) Hayashi, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7224. For Cu catalysis, see: (k) Sherman, E. S.; Chemler, S. R. *Adv. Synth. Catal.* **2009**, *351*, 467. (l) Fuller, P. H.; Kim, J. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638.

(5) For a Pd-catalyzed intermolecular aminofluorination of styrenes, see: Qui, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2956.

(6) For reviews on multicomponent coupling, see: (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (b) Domling, A. *Chem. Rev.* **2006**, *106*, 17.

(7) The arylboronic acids are known to dimerize under similar conditions, see ref 3f and Carrettin, S.; Guzman, J.; Corma, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2242.

(8) (a) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. (b) Zhang, X.; Corma, A. *Chem. Commun.* **2007**, 3080. (c) Hirai, T.; Hamasaki, A.; Nakamura, A.; Tokunaga, M. *Org. Lett.* **2009**, *11*, 5510. For gold-catalyzed hydroamination of simple alkenes, see: (d) Giner, X.; Nájera, C. *Org. Lett.* **2008**, *10*, 2929. (e) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (f) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (g) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707. (h) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (i) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744.

(9) Readily oxidized (benzyl, allyl) alcohols do not participate in the reaction.

(10) For gold-catalyzed hydration of allenes, see: Zhang, Z.; Lee, S. D.; Fisher, A. S.; Widenhoefer, R. A. *Tetrahedron* **2009**, *65*, 1794.

(11) For relevant discussion, see: Koch, H. F.; Girard, L. A.; Roundhill, D. M. *Polyhedron* **1999**, *18*, 2275.

(12) For examples of gold-catalyzed three-component (alkyne, aldehyde, amine) coupling, see: (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (b) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. (c) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (d) Zhang, X.; Corma, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4358. (e) Zhang, Q.; Cheng, M.; Hu, X.; Li, B.-G.; Ji, J.-X. *J. Am. Chem. Soc.* **2010**, *132*, 725. For gold/Brønsted acid co-catalysis, see: (f) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 2269. For a related reaction (alkyne, alkyne, amine), see: (g) Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2009**, *131*, 8690. For alcohol nucleophiles, see: (h) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 4917.

JA1034123