ORGANIC
LETTERS

2010
Vol. 12, No. 21
4728−4731

Gold-Catalyzed Oxidative Coupling Reactions with Aryltrimethylsilanes

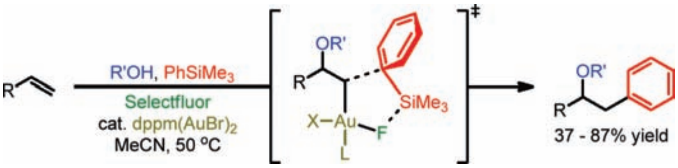
William E. Brenzovich, Jr., Jean-François Brazeau, and F. Dean Toste*

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

fdtoste@berkeley.edu

Received September 13, 2010

ABSTRACT



During continuing studies with a novel oxidative gold oxyarylation reaction, arylsilanes were found to be competent coupling partners, providing further evidence for an intramolecular electrophilic aromatic substitution mechanism. While providing yields complementary to those of the previously described boronic acid methods, the use of trimethylsilanes reduces the observation of homocoupling byproducts and allows for facile intramolecular coupling reactions.

With the development of transition metal-catalyzed cross-coupling reactions, significant effort has been expended in the development of inexpensive and reliable organometallic reagents as coupling partners.[1] In this context, organosilanes present an attractive solution; however, there have been relatively few reports of transition-metal-catalyzed reactions with the readily accessible aryltrimethylsilanes. Moreover, a stoichiometric additive such as fluoride or hydroxide is typically employed to activate the relatively unreactive silicon center for transmetalation.[2] Alternatively, a variety of reactive silicon reagents have been designed and utilized in transition metal-catalyzed cross-coupling reactions on milder conditions.[3] During our recent examination of the Selectfluor-mediated gold-catalyzed amino- and oxyarylation of terminal olefins with boronic acids,[4] mechanistic experimentation and computational analysis provided evidence against transmetalation to the gold center. Instead, studies suggested a bimolecular reductive elimination reminiscent of an electrophilic aromatic substitution. While unactivated trimethylarylsilanes do not typically directly engage in cross-couplings,[5] they can readily react as nucleophiles in aromatic

---

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vols. *1* and *2*. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002.

(2) For recent reviews on cross-coupling with silicon reagents, see ref 1 and. (a) Denmark, S. E.; Butler, C. R. *Chem. Commun.* **2009**, 20. (b) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486. (bb) Denmark, S. E.; Baird, J. D. *Chem.—Eur. J.* **2006**, *12*, 4954. (c) Nakoa, Y.; Sahoo, A. K.; Imanaka, H.; Yada, A.; Hiyama, T. *Pure Appl. Chem.* **2006**, *78*, 435. (d) Handy, C. J.; Manoso, A. S.; McElroy, W. T.; Seganish, W. M.; DeShong, P. *Tetrahedron* **2005**, *61*, 12201. (e) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *1*, 211.

(3) Selected silicon-based cross-coupling reactions: (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 920. (b) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, 1711. (c) Mowery, M. E.; DeShong, P. *J. Am. Chem. Soc.* **1999**, *64*, 1684. (d) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, 2137. (e) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (f) Murata, M.; Shimazaki, R.; Watanabe, S.; Masuda, Y. *Synthesis* **2001**, 2231. (g) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439. (h) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616. (i) Nakao, Y.; Takeda, M.; Matsumoto, T.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4447.

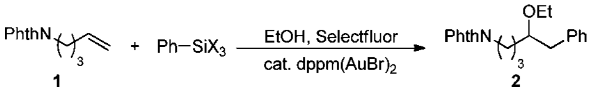
(4) For Au-catalyzed amino- and oxyarylation of alkenes: (a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. (b) Brenzovich, W. E., Jr.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5519. (c) Melhado, A. D.; Brenzovich, W. E., Jr.; Lackner, A. D.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8885. For other oxidative gold-catalyzed reactions, see: (d) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, *3*, 386. (e) Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F. *J. Organomet. Chem.* **2009**, *694*, 592. (f) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3112. (i) Iglesias, A.; Muñiz, K. *Chem.—Eur. J.* **2009**, *15*, 10563. (j) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (k) Hopkinson, M. N.; Tessier, A.; Salisbury, A.; Giuffredi, G. T.; Combettes, L. E.; Gee, A. D.; Gouverneur, V. *Chem.—Eur. J.* **2010**, *16*, 4739.

10.1021/ol102194c

substitution reactions.[6] We therefore hypothesized that arylsilanes might be utilized as the terminating nucleophile in oxidative gold-catalyzed coupling with alkenes.

On the basis of this hypothesis, we were delighted to find that when olefin **1** was reacted with phenyltrimethylsilane under the previously described reaction conditions, the desired intermolecular oxyarylation product (**2**) was observed in 50% yield (Table 1, entry 1). No exogenous base or fluoride is required for silicon activation, and a wide variety of readily available silanes, silanols, and siloxanes are capable oxyarylation coupling partners. In attempting to identify the optimal silicon coupling reagent, we found that silanediols and -triols provided excellent yields (entries 5, 8), though rapid oligomerization led to concerns regarding reproducibility. The more bench-stable trisiloxane derivatives[7] unfortunately resulted in significantly lower conversions (entry 7). Given their ease of synthesis, general stability, and orthogonality to a wide variety of conditions, trimethylsilanes provide the greatest potential benefits in terms of further reaction development. Moreover, the formation of biphenyl, a major byproduct formed from the reaction with boronic acids, is severely reduced by the use of aryltrimethylsilanes.[8] Further optimization of the reaction conditions demonstrated that the yield can be increased by the use of 2 equiv of Selectfluor (entry 2).[9]

Table 1. Ethoxyarylation of **1** with Arylsilicon Reagents[a]

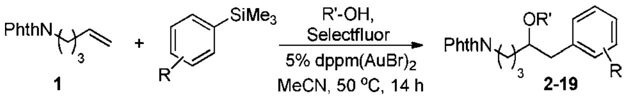


entry	Ph-SiX$_3$	equiv	yield (%)[b]
1	$PhSiMe_3$	1.5	50
2	**$PhSiMe_3$**	**1.5**	**77**[c]
3	$PhMe_2SiOH$	2.0	41
4	Ph_3SiOH	1.0	33
5	$Ph_2Si(OH)_2$	2.0	65
6	$PhMeSi(OH)_2$	2.0	22
7	$[(Ph_2SiO)_3]$	1.0	28
8	$PhSi(OH)_3$	2.0	83
9	$PhSi(OEt)_3$	2.0	74

[a] Conditions: **1** (30 μmol), EtOH (300 μmol), Selectfluor (45 μmol), 5 mol % dppm(AuBr)$_2$, 0.05 M in CD_3CN, 50 °C for 14 h. [b] Yield determined by ^{1}H NMR with nitrobenzene as internal standard. [c] 2.0 equiv (60 μmol) of Selectfluor used.

One limitation of the oxyarylation reaction with boronic acids is the incompatibility of nitrogen- and oxygen-containing coupling partners, due in part to competing reactions with Selectfluor.[10,11] In contrast, we found that the scope of the gold-catalyzed methoxyarylation using arylsilanes was significantly expanded using aryltrimethylsilanes to afford the acetoxy-, trifloxy-, and sulfonamide-substituted adducts in good to excellent yields. (Table 2, entries 1−3).[12] In addition, the reaction remains functional for a wide variety of electron-neutral and electron-poor coupling partners, readily tolerating substitution in the *para* (entries 1−7), *meta* (entry 8), and *ortho* positions (entries 9, 18).

Table 2. Oxyarylation of **1** with Trimethylsilanes[a,b]



entry	R	R′	product	yield (%)[c]
1	4-OAc	Me	**3**	83
2	4-OTf	Me	**4**	53
3	4-N(Me)Ts	Me	**5**	66
4	4-Me	Me	**6**	73
5	4-Br	Me	**7**	82
6	4-CHO	Me	**8**	77
7	4-CO_2Me	Me	**9**	68
8	3-CO_2Me	Me	**10**	83
9	2-CH_2CH_2OH	Me	**11**	69
10	H	Me	**12**	87
11	H	Et	**2**	83
12	H	*i*-Pr	**13**	81
13	H	*t*-Bu	**14**	37
14	H	neopentyl	**15**	64
15	H	cyclopentyl	**16**	68
16	H	2-methoxyethyl	**17**	86
17	H	H	**18**	77
18	2-CH_2CH_2OH	H	**19**	55

[a] Conditions: **1** (100 μmol), R′OH (1.0 mmol), Selectfluor (200 μmol), $ArSiMe_3$ (150 μmol), 5 mol % dppm(AuBr)$_2$, 0.1 M in CH_3CN, 50 °C for 14 h. [b] Catalyst addition in two portions over 2 h. [c] Isolated yields.

As with the coupling of boronic acids, the reaction was general to a variety of alcohol nucleophiles, providing homobenzylic ethers in functional yields (Table 2). The reaction readily proceeded with secondary and bulky primary alcohols (entries 12, 14, and 15), although the reaction with a tertiary alcohol did not reach completion (entry 13). Additionally, the reluctance of gold(III) to undergo β-hydride elimination allowed for hydroxyarylation with water as the

---

(5) For examples of trimethylsilyl cross-coupling reactions involving an intermediate metal species, see: (a) Farinola, G. M.; Fiandanese, V.; Mazzone, L.; Naso, F. *J. Chem. Soc., Chem. Commun.* **1995**, 2523. (b) Smith, A. B., III; Kim, W.-S.; Tong, R. *Org. Lett.* **2010**, *12*, 588.

(6) For silicon reagents in electrophilic aromatic substitution reactions, see: Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761, and references therein.

(7) Endo, M.; Sakurai, T.; Ojima, S.; Katayama, T.; Unno, M.; Matsumoto, H.; Kowase, S.; Sano, H.; Kosugi, M.; Fugami, K. *Synlett* **2006**, 749.

(8) The reaction of $PhB(OH)_2$ with dppm(AuBr)$_2$ and Selectfluor provides biphenyl in about 80% yield, whereas $PhSiMe_3$ yields <10%.

(9) For full details on reaction optimization and catalyst screening, see Supporting Information.

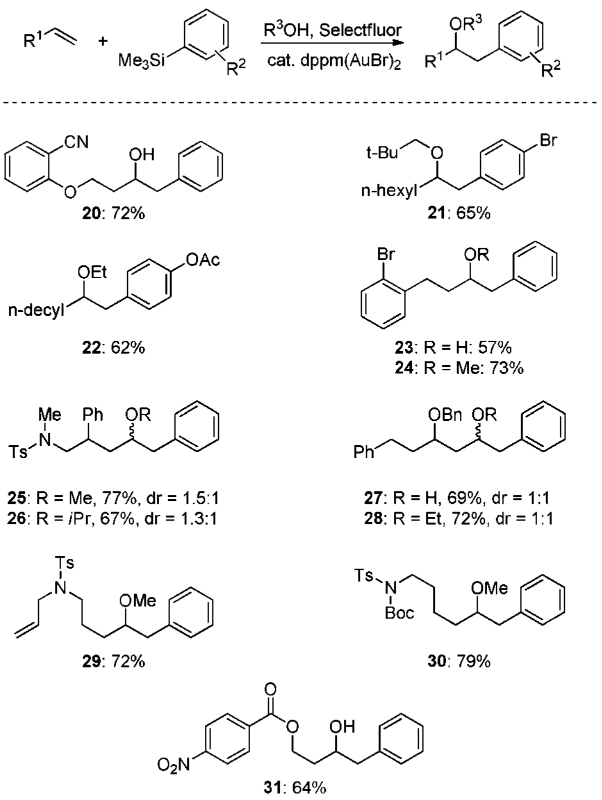
(10) For metal-mediated reactions of Selectfluor with arylboronic acids, see: (a) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993. (b) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860. (c) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150.

(11) For Selectfluor-induced oxidations of electron-rich arenes, see: (a) Zupan, M.; Iskra, J.; Stavber, S. *J. Fluor. Chem.* **1995**, *70*, 7. (b) Stavber, G.; Zupan, M.; Jereb, M.; Stavber, S. *Org. Lett.* **2004**, *6*, 4973. (c) Stavber, G.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2007**, *48*, 2671.

(12) Use of the more electron-rich silanes, such as 4-(methoxyphenyl)-trimethylsilane, yielded no product.

nucleophile (entries 17, 18) in contrast to the Wacker oxidation that is typically observed under palladium catalysis.[13]

As demonstrated in Figure 1, the olefin substrate scope remained broad, and the reaction tolerated a variety of functional groups, including esters, sulfonamides, carbamates, and halides. The addition was sensitive to the electronic environment, allowing for selective reaction at the less electron-deficient olefin (**29**). When pendent esters were employed in the reaction, either on the olefin (**32** or **33**) or the incoming silane (**38**), use of an alcohol nucleophile provided ether products, while water addition provided cyclized products following *in situ* lactonization (Scheme 1).



20: 72%

21: 65%

22: 62%

23: R = H: 57%
24: R = Me: 73%

25: R = Me, 77%, dr = 1.5:1
26: R = *i*Pr, 67%, dr = 1.3:1

27: R = H, 69%, dr = 1:1
28: R = Et, 72%, dr = 1:1

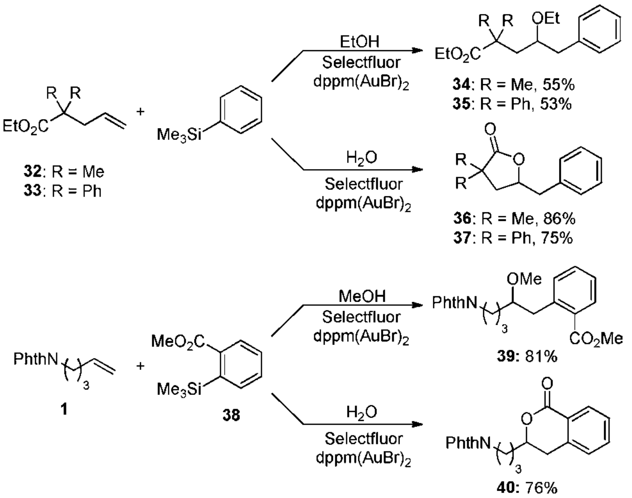
29: 72%

30: 79%

31: 64%

Figure 1. Products of the oxyarylation of terminal olefins.

Scheme 1. *In Situ* Lactonizations with Pendant Esters



32: R = Me
33: R = Ph

34: R = Me, 55%
35: R = Ph, 53%

36: R = Me, 86%
37: R = Ph, 75%

1

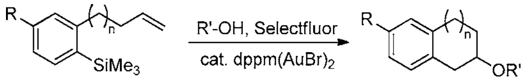
38

39: 81%

40: 76%

We were interested in performing the coupling reaction in an intramolecular fashion to provide bicyclic systems. Initial attempts utilizing boronic acids yielded only moderate success, likely due to dimerization during the reaction and problems with isolation and purification of the requisite boronic acids, which are prone to oligomerization. We hypothesized that the trimethylsilanes, which are readily synthesized and purified, would circumvent these issues. We were pleased to find that the use of silanes as intramolecular coupling partners in the gold-catalyzed oxidative process provided tetrahydronaphthalenes in excellent yields (Table 3). The intramolecular coupling has a similar scope to the three-component reaction, tolerating a variety of ring substitutions. The formation of indanes (entry 4), however, provides significantly lower yields, possibly due to the geometric constraints imposed by the mechanism.

Table 3. Intramolecular Coupling Reactions[a,b]



entry	R	R′	*n*	product	yield (%)
1	H	H	1	**41**	66
2		Me	1	**42**	73
3		Et	1	**43**	70
4		H	0	**44**	15[c]
5	4-F	H	1	**45**	47
6		Et	1	**46**	68
7	4-Cl	H	1	**47**	62
8		Me	1	**48**	65
9	4-CF$_3$	H	1	**49**	51
10		Me	1	**50**	59
11	4-Ph	Me	1	**51**	74

[a] Conditions: aryltrimethylsilane (100 μmol), Selectfluor (200 μmol), 5 mol % dppm(AuBr)$_2$, 0.1 M in CH$_3$CN/R′OH (10/1), 50 °C for 14 h. [b] Catalyst addition in two portions over 2 h. [c] Yield based on ^{1}H NMR versus nitrobenzene as internal standard.

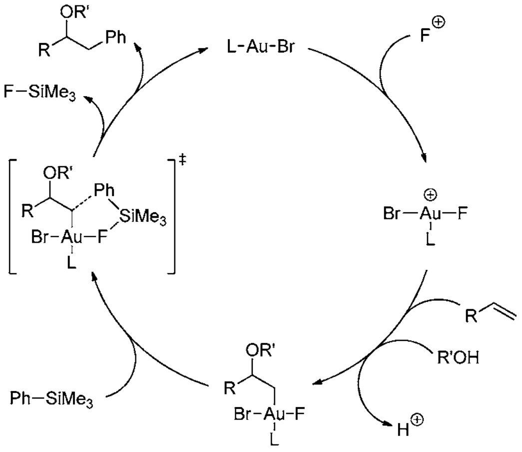
Given the scarcity of cross-couplings with aryltrimethylsilanes, we performed several experiments to investigate the reaction mechanism. In our hands, trimethylsilanes proved inert to all attempts at transmetalation under relevant reaction conditions.[14,15] In addition, the use of an external fluoride source generally had a negative impact on the reaction,[16] suggesting that the gold fluoride itself is essential for the requisite activation of the silicon.[17] We therefore propose a

---

(13) For a recent review on the mechanism of the Wacker oxidation, see: (a) Keith, J. A.; Henry, P. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038.

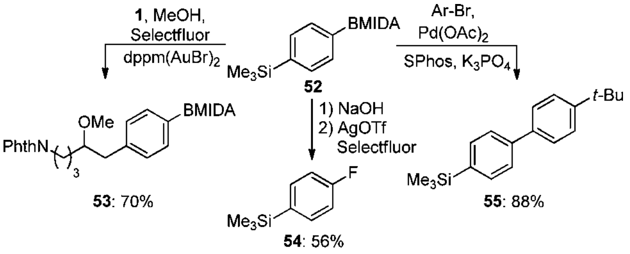
mechanism involving nucleophilic attack by ROH on the alkene promoted by a cationic gold(III) fluoride,[18] followed by reductive aryl transfer from a pentavalent silicon species (Scheme 2). This mechanism is consistent with the observations from the gold-catalyzed oxidative alkene functionalization reactions with boronic acids.

Scheme 2. Proposed Mechanism for Oxyarylation with Arylsilanes



As the gold-catalyzed alkoxyarylation does not proceed through a direct transmetalation, the reaction can be used to differentiate between two reactive metal species (Scheme 3). When the arylsilane **52** containing a MIDA boronate[19] was reacted with **1** under the standard gold conditions, homobenzylic ether **53** was the sole product. However, when treated under standard palladium Suzuki–Miyaura cross-coupling conditions, the 4-trimethylsilylbiphenyl **55** was formed exclusively. More notable is the orthogonal reactivity observed in group 11 metal-catalyzed reaction with Selectfluor; **52** underwent silver-catalyzed fluorination of the boronate to provide **54**,[10] while the aryltrimethylsilyl selectively participated in the gold-catalyzed coupling.

Scheme 3. Selective Coupling of Bifunctional Arylsilane MIDA Boronates



In conclusion, we report the first examples of gold-catalyzed oxidative coupling reactions using organosilicon reagents. The reaction employs generally unreactive aryltrimethylsilanes as coupling partners, allows for the extension to phenol and aniline derived aryl groups, produces significantly less biphenyl byproducts, and provides a means to better access intramolecular couplings. Additionally, the reluctance of trimethylsilanes to undergo transmetalation with gold provides further evidence against a standard reductive elimination pathway and support for our previously proposed bimolecular reductive couplings from gold(III) fluorides.

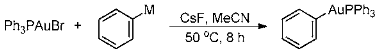
Acknowledgment. We gratefully acknowledge NIHGMS (RO1 GM073932), Amgen, and Novartis for financial support and thank Johnson Matthey for a gift of AuCl$_3$. J.-F. B. thanks the FQRNT for a postdoctoral research fellowship.

Supporting Information Available: Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102194C

---

(14) Under the action of CsF in MeCN, Ph$_3$PAuBr readily transmetallates with boronic acids and silanols but not trimethylsilanes:



Ph-M	yield
PhB(OH)$_2$	78%
PhSiMe$_3$	0%

See: David, V.; Partyka, D. V.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 8188. (b) Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F. *J. Organomet. Chem.* **2009**, *694*, 592.

(15) In investigations with the sila-Cope rearrangement, no transmetalation to gold(I) was observed; see: Horino, Y.; Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 11364.

(16) Addition of fluoride sources, such as CsF and KF, significantly retarded the reaction. See Supporting Information for more details.

(17) Mankad, N.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 12859.

(18) LaLonde, R. L.; Brenzovich, W. E., Jr.; Benitez, D.; Tkatchouk, E.; Kelley, K.; Goddard, W. A., III; Toste, F. D. *Chem. Sci.* **2010**, *1*, 226.

(19) For synthetic applications of MIDA boronates, see: (a) Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17. (b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961. (c) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084.