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Enol Silyl Ethers via Copper(II)-Catalyzed C–O Bond Formation

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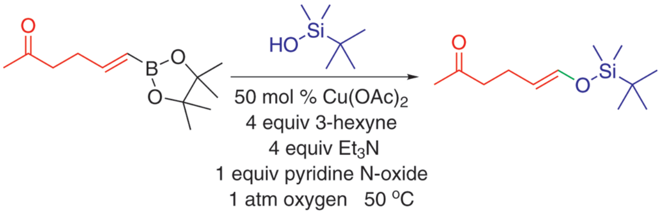
ABSTRACT



Copper(II) acetate catalyzes the coupling of pinacol vinylboronates with silanols producing enol silyl ethers. This represents a novel enol silyl ether synthesis via formation of the C–O bond instead of the conventional Si–O bond. This also constitutes the first transition-metal-catalyzed oxidative cross-coupling with silanols.

Enol silyl ethers are exceptionally important intermediates in organic synthesis functioning as latent enolates or reactive electron rich alkenes. Enol silyl ethers are utilized in many prominent organic transformations such as Mukaiyama aldol reactions,[1] Michael reactions,[2] Diels–Alder reactions,[3] Rubottom oxidations,[4] and Saegusa oxidations.[5] The vast majority of enol silyl ethers are generated via O-silylation of carbonyl derivatives using an electrophilic silicon source (Figure 1).[6] Typically, this involves silylation of preformed enolates or addition of potent silylating agents to neutral carbonyl derivatives in the presence of a weak base. These approaches can be problematic in controlling chemoselectivity and the regio- and stereochemistry of the resultant enol silyl ether. We envisioned a novel synthesis of enol silyl ethers wherein the C–O bond is formed instead of the Si–O bond by employing cross coupling of a vinyl derivative with a silanol (Figure 1). We reported a stereospecific copper(II)-promoted coupling of aliphatic and allylic alcohols with vinylboronates as a facile method by which to synthesize vinyl ethers.[7] This advanced the work originally published

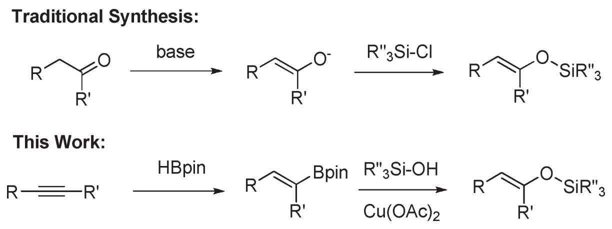


Figure 1. Approaches to enol silyl ether synthesis.

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(1) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *2*, 1011. (b) Mukaiyama, T. *Org. React*. **1982**, *28*, 203. For examples, see: (c) Panek, J. S.; Jain, N. F. *J. Org. Chem*. **2001**, *66*, 2747. (d) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc*. **1998**, *120*, 908.

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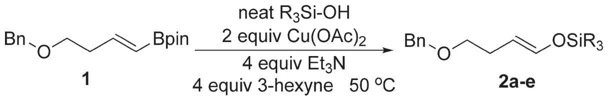
10.1021/ol2009297

by Chan, Lam, and Evans[8] now known as Chan–Lam couplings wherein two nucleophiles are oxidatively coupled (modern Ullmann).[9] Herein, we report a copper-catalyzed coupling with silanols to synthesize enol silyl ethers. This is, to the best of our knowledge, the first report of transition-metal-catalyzed oxidative couplings using silanols.

Table 1. Silanol Cross-Coupling Screening



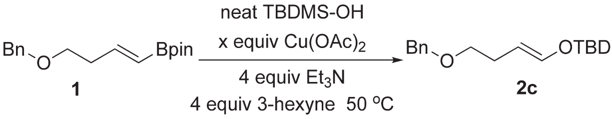
(1)

entry	R$_3$Si	yield (%)
1	TMS	0
2	TES	47
3	TBDMS	52
4	TIPS	26
5	DMPS	0

To explore a cross-coupling synthesis of enol silyl ethers, vinylboronate **1** was coupled with several silanols using stoichiometric copper conditions that employ 3-hexyne as a ligand for copper (Table 1).[10] No desired product could be isolated when using trimethylsilanol (entry 1). However, a 20% yield of 4-benzoxybutanal was obtained indicating that the product was synthesized, but desilylation of the product occurred during purification. Triethylsilanol and *tert*-butyldimethylsilanol coupled to give silyl enol ethers with similar efficiencies (47% and 52%, respectively; entries 2 and 3). The more sterically inhibited triisopropylsilanol coupled in a mere 26% yield and dimethylphenylsilanol failed to provide any coupled product (entries 4 and 5).

With *tert*-butyldimethylsilanol chosen as the best coupling partner, a variety of conditions were screened in order to find the optimal protocol (Table 2). In accord with our report on dienyl ether synthesis,[10] we found that added 3-hexyne ligand was critical (entries 1 vs 2) for obtaining the best yield. Neat silanol was preferred (entry 3), and attempts to make the silanol more nucleophilic via generation of the silyloxide with sodium hydride decreased yields (entry 4). Using 3 equiv of Cu(OAc)$_2$ improved the yield to 63% (entry 5), and using an oxygen atmosphere was disadvantageous with excess copper (entry 6). Much to our delight, catalytic conditions fared as well as using excess Cu(OAc)$_2$ (entries 7 vs 5).

Table 2. Silanol Coupling Optimization



(2)

entry	Cu(OAc)$_2$ (equiv)	change	yield (%)
1	2		52
2	2	without 3-hexyne	40
3	2	12 equiv of TBS-OH, DCM	36
4	2	2 equiv of NaH	32
5	3	N/A	63
6	3	1 atm of O$_2$	32
7	0.5	2 equiv of PNO, 1 atm of O$_2$	62
8	0.5	2 equiv of PNO, 1 atm of O$_2$, mol sieves	45
9	0.5	2 equiv of PNO, 1 atm of O$_2$, 14 d	57
10	0.5	2 equiv of PNO, 1 atm of O$_2$, 8 equiv of Et$_3$N	42
11	1.0	1 equiv of PNO, 1 atm of O$_2$	62
12	0.25	1 equiv of PNO, 1 atm of O$_2$	31
13	0.5	1 equiv of PNO, 1 atm of O$_2$	72

After our initial report on couplings with alcohols,[7] we optimized a catalytic protocol for vinyl, but not dienyl, ethers. Systematic examination of the reaction components by running parallel reactions with changes of single components revealed that both triethylamine and 3-hexyne ligand were essential for operation of this catalytic protocol (Table 3, entries 2 and 3). Additionally, both pyridine *N*-oxide (PNO) and oxygen were required oxidants in order to achieve catalysis (entries 4 and 5). Pyridine *N*-oxide was chosen as the oxidant based on observations made by the Lam group.[11] Lastly, using 20 mol % of Cu(OAc)$_2$ resulted in a drastic decrease in yield (entry 6), indicating that 50 mol % was the necessary catalyst loading.

Returning to entry 7 employing catalytic conditions in the silanol couplings of Table 2, ^{1}H NMR analysis of a sample of **2** prior to purification on silica gel found 20% aldehyde derived from product hydrolysis and 10% alkene derived from protodeboration present. That suggested that hydrolysis was occurring in the reaction mixture. Speculating that water might be responsible, molecular sieves were added, but without improvement (entry 8). Testing product stability under the reaction conditions by leaving a reaction run for 14 days did not lower the yield significantly (entry 9). Attempting to reduce protodeboration by adding more triethylamine was not beneficial either (entry 10). Using stoichiometric copper acetate did not improve the yield (entry 11), and lowering to only 25 mol % reduced the yield (entry 12) in accordance with the alcohol screening results (Table 3, entry 6). Finally, reducing the amount of pyridine *N*-oxide (PNO) to 1 equiv gave the best yield (entry 13).

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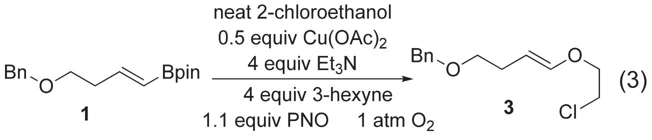
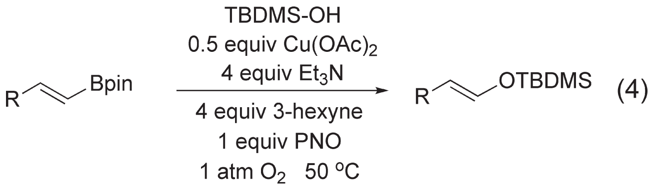
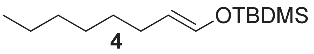
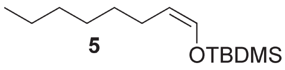
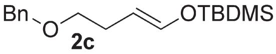
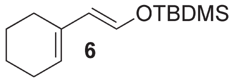
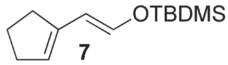
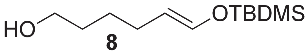
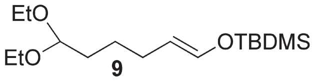
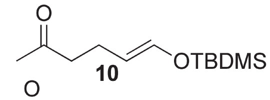
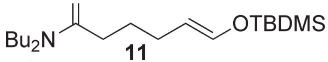
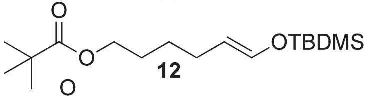
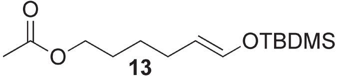
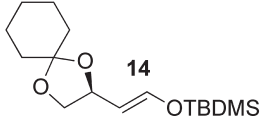
Table 3. Probing Catalytic Conditions for Alcohol Couplings by Deleting Components



entry	change	yield (%)
1	none	95
2	delete Et_3N	66
3	delete 3-hexyne	29
4	delete O_2	18
5	delete PNO	14
6	0.3 equiv of $Cu(OAc)_2$	19

Table 4. Silyl Enol Ether Synthesis



entry	product	yield (%)
1	 **4**	62
2	 **5**	28
3	 **2c**	72
4	 **6**	57
5	 **7**	55
6	 **8**	43
7	 **9**	53
8	 **10**	44
9	 **11**	57
10	 **12**	60
11	 **13**	59
12	 **14**	41

The optimized coupling conditions were then applied to cross couplings of vinylboronates with *tert*-butyldimethylsilanol to make enol silyl ethers (Table 4). A number of these examples are quite remarkable as the products would not be accessible via direct silylation of carbonyl substrates. While no aldehyde silylation protocol is available that is completely stereoselective for an *E* or *Z* product, entries 1 and 2 prove that the cross coupling reaction is stereospecific. The modest yield in entry 2 is in line with a low yield obtained in coupling an alcohol with a pinacol *Z*-vinylboronate.[7] Entries 4 and 5 prepare very acid-labile dienyl silyl ether targets. Entry 6 is formally the enol silyl ether of an aldehyde−alcohol. Entry 8 is the mono enol silyl ether of a ketoaldehyde, while entry 9 is the mono enol silyl ether of an aldehyde−amide. Entries 10 and 11 illustrate access to base-sensitive targets. Finally, entry 12 presents another exceptionally acid-labile enol silyl ether. Most of these examples would be quite challenging to prepare by direct silylation using either preformed enolates or highly electrophilic silylating agents in the presence of weak bases.

As a final capstone example, we tested the coupling of vinylboronate **15** containing both alcohol and ketone functional groups (Scheme 1). Direct silylation of a hydroxy ketoaldehyde would not be feasible using conventional methods, but silanol coupling with hydroxy ketoboronate ester **15** provided the target **16** in a reasonable yield. As with entry 6 in Table 4, no evidence for coupling with the alcohol was detected.

This methodology is also applicable to aryl substrates as demonstrated by the coupling of phenylboronic acid and pinacol phenylboronate with *tert*-butyldimethylsilanol to generate the aryl silyl ether **18** (Scheme 2). These couplings were considerably slower than the vinyl couplings and required several days for complete consumption of the substrates. This is the first synthesis of an aryl silyl ether via C−O bond formation in an oxidative cross coupling. In contrast, alkyl aryl ethers have been synthesized via cross couplings using both copper[12] and palladium.[13]

While the yields in these couplings are not spectacular, three aspects are especially noteworthy. First, many of the products are acid sensitive, yet all were isolated by silica gel chromatography. Second, yields herein are based on boronate ester, whereas many other reports on copper-based couplings with heteroatom nucleophiles use an excess of the boron substrates.[8,9] Third, coordination of the byproduct acetoxypinacolborate to the enol silyl ether could lead to desilylation and the boron enolate via a six-center transition state.

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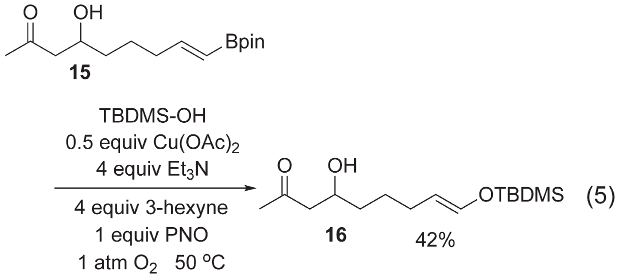
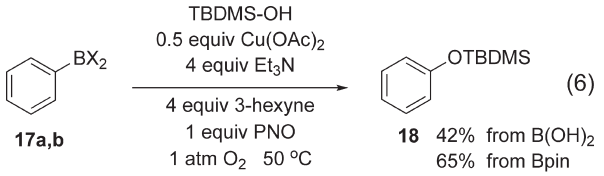
Scheme 1. Capstone Coupling Example



Scheme 2. Phenyl Couplings



C−O bond formation via cross coupling with silanols is not an obvious choice since aryl,[14] alkenyl,[15] and alkynyl[16] silanols have been demonstrated to deliver the *carbon* substituent in cross couplings and that reactivity is used beneficially in complex molecule total synthesis.[17] Indeed, in the reaction employing dimethylphenylsilanol (Table 1, entry 5), no silyl enol ether or aldehyde was detected, but a small amount (< 10%) of phenyl coupling was detected by mass spectrometry. *tert*-Butyldimethylsilanol has been utilized in a typical metal(0)-catalyzed cross coupling with aryl bromides,[18] but the analogous reaction with alkenyl halides has not been reported. Furthermore, aryl or vinyl oxidative cross couplings using silanols has not been reported.

Related to direct silylation of carbonyl compounds, oxidation of vinyl metal compounds to enolates with molecular oxygen or peroxides *followed* by silylation of the resultant enolates with electrophilic silicon reagents has been reported.[19] There are a few reports on oxidation of vinyllithium anions with silyl peroxide to provide enol silyl ethers directly,[20] but that method clearly suffers from chemoselectivity issues.

Our working hypothesis for the reaction mechanism is that it is analogous to the copper-based couplings with alcohols[7−9] and that a silyloxy vinyl copper(III) intermediate is key for reductive elimination forming the C−O bond and copper(I). Copper(0) is not observed in the reactions, and a mechanistic rationale for the importance of both oxygen and pyridine *N*-oxide is not clear.

In conclusion, we found that silanols can be coupled with vinylboronate esters using catalytic $Cu(OAc)_2$ as a facile, chemoselective, and stereospecific method to synthesize enol silyl ethers. This represents a novel synthesis of silyl ethers as it involves C−O instead of Si−O bond formation. Use of 0.5 equiv of $Cu(OAc)_2$ with both pyridine *N*-oxide and oxygen as oxidants was found to be optimal for these couplings. These catalytic conditions were effective for synthesis of a variety of enol silyl ethers containing functional groups that would be problematic or impossible using typical carbonyl silylation conditions for Si−O bond formation.

Acknowledgment. We are grateful to the National Science Foundation and the Research Corporation for Science Advancement for financial support.

Supporting Information Available. Experimental procedures and spectral data for all new compounds, including scanned images of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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