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Copper-Mediated Aryloxylation and Vinyloxylation of β-C(sp^3)−H Bond of Propionamides with Organosilanes

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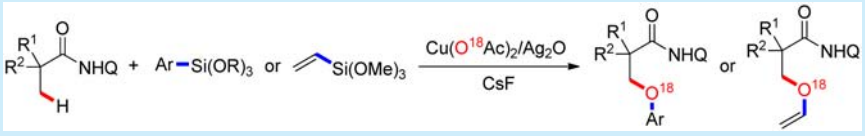
Supporting Information

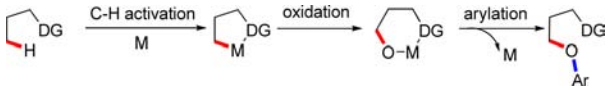


ABSTRACT: A novel copper-mediated method for the aryloxylation and vinyloxylation of β-C(sp^3)−H bonds of propioamides with organosilanes is described. The reaction proceeds with the assistance of an 8-aminoquinolyl auxiliary in a tandem way by the first oxidation of β-C(sp^3)−H bonds and subsequent arylation/vinylation to give the aryloxylation/vinyloxylation products. This unusual aryloxy/vinyloxy forming reaction offers a new avenue for the functionalization of unactivated sp^3 C−H bonds in organic synthesis.

The metal-mediated functionalization of C−H bonds has exerted a huge impact on the bond-disconnection strategies for complex molecules through a direct and step-economical manner.[1] Over the past decades, significant progress has been attained for the chelation-assisted direct functionalization of C−H bonds of arenes, olefins, and alkanes.[2−5] A common requirement for these transformations is the activation of the C−H bond by the formation of five- or six-membered metallacycles, which facilitates the subsequent diverse couplings. While a large number of transformations can be achieved with various coupling partners, the catalyst and directing group serve a single reaction in most cases. The sequential multistep reaction via C−H activation by exploiting an identical directing group would be valuable, expanding the range of C−H functionalities.

The development of site-selective activation of sp^3 C−H bonds constitutes important transformations in synthetic chemistry which allows the conversion of the least expensive alkanes to valuable products.[6] However, compared with the functionalization of C(sp^2)−H bonds, the development of catalytic methods for activating sp^3 C−H bonds is still in its early stage.[7] Few methods are available for selective conversion of alkanes into more valuable products due to the inertness of the C(sp^3)−H bond and the challenge of selectivity. It is highly desirable to design a new concept based on C(sp^3)−H activation for the assembly of diverse complex organic structures. Aryl-alkyl ethers serve as useful intermediates in organic synthesis and are found in an impressive number of biologically relevant molecules and natural products.[8,9] Although the Ullmann aryl-alkyl ether synthesis has been widely used, the method requires preactivation of substrates and often suffers from harsh reaction conditions.[10] A powerful alternative to the synthesis of aryl-alkyl ethers is the use of metal to promote sequential transformations of oxidation and arylation via C−H activation with the assistance of an identical directing group (Scheme 1). In this approach, the initial metal

Scheme 1. Strategy of Multistep Reaction Using Identical Directing Group



mediated oxidation of the sp^3 C−H bond followed by the arylation in a position-selective mode generates the expected aryl-alkyl ether derivatives in a tandem way. The challenges for successful implementation of this strategy include (1) the requirement of a metal center that is not only reactive for the oxidation of unactivated sp^3 C−H bonds but also effective for the following arylation; (2) the achievement of reactivity through both the five-membered metallacycles and relatively remote coordination; (3) the definite sequence of first oxidation and subsequent arylation. Recently, a number of elegant chelation-directing strategies have been successfully developed for the oxidation of inactive C(sp^3)−H bonds.[11,12] Herein, we disclose a novel method for the synthesis of β-aryloxylated propionic amides through the copper-mediated aryloxylation of unactivated sp^3 C−H bonds at the β-position of propionic amides with a range of organosilanes. Unprecedentedly, the two different intermolecular couplings execute serially through the promotion of copper at different steps with the assistance of an 8-aminoquinolyl auxiliary.

At the outset of our study, we focused our investigation by employing propionamide **1a** as a model substrate, which

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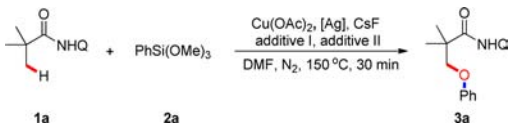
contains a well-behaved aminoquinoline auxiliary discovered by Daugulis (Table 1; see the Supporting Information).[13] We were

Table 1. Optimization of Reaction Conditions[a]



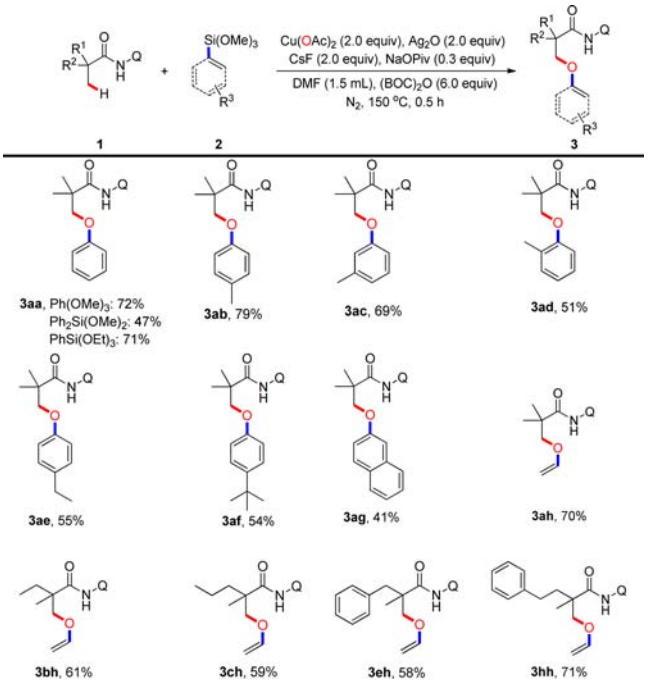
entry	[Ag]	additive I	additive II	yield (%)[b]
1				trace
2	Ag_2CO_3			19
3	AgOAc			28
4	Ag_2O			47
5	Ag_2O	NaOPiv		56
6	Ag_2O	NaOPiv	PC	62
7	Ag_2O	NaOPiv	GBL	50
8	Ag_2O	NaOPiv	$(BOC)_2O$	72

[a]Reactions conditions: **1a** (0.1 mmol), **2a** (0.5 mmol), $Cu(OAc)_2$ (0.2 mmol), [Ag] (2.0 equiv), CsF (2.0 equiv), additive I (0.3 equiv), additive II (6.0 equiv), DMF (1.5 mL), N_2, 150 °C, 0.5 h. [b]Isolated yield by flash column chromatography. PC = Propylene carbonate, GBL = γ-Butyrolactone, $(BOC)_2O$ = di-*tert*-Butyl dicanonate, Q = Quinolin-8-yl.

pleased to observe the formation of a trace of desired product **3a** by the treatment of propioamide **1a** and arysiloxane **2a** in the presence of 2.0 equiv of $Cu(OAc)_2$ at 150 °C for 0.5 h (Table 1, entry 1). The reaction was significantly improved by the addition of 2.0 equiv of silver salt as the oxidant, and a superior outcome was provided by Ag_2O to give a 47% yield (Table 1, entries 2−4). Despite the low yield, this reaction revealed that two different couplings could indeed proceed in sequence with the copper to promote different product-forming steps under the assistance of an identical directing group. In order to increase the yield, we surveyed carboxylate additives that were reported to be promoters of proton abstraction by Echavarren[14] and Fagnou.[15] It was found that a catalytic amount (30 mol %) of sodium pivalate hydrate did accelerate the C−H aryloxylation to give the desired **3a** in 56% yield (Table 1, entry 5). This result implicated that a concerted metalation−deprotonation pathway might be involved in the C−H oxidation step. Interestingly, esters and carbonic anhydride dramatically improved the efficiency of the reaction (Table 1, entries 6−8), and di-*tert*-butyl dicanonate ($(BOC)_2O$) gave the best yield (72%) (Table 1, entry 8). No reaction was observed in the absence of a copper promoter.

With the optimized conditions in hand, we explored the scope of organosiloxanes with the substrate **1** as summarized in Scheme 2. Initially, the ability of different arysilane precursors to participate in the reaction was probed. Several commercially available arylsilanes, such as dimethoxydiphenylsilane, trimethoxy(phenyl)silane, and triethoxyl(phenyl)silane, were examined. Trimethoxy(phenyl)silane and triethoxyl(phenyl)-silane were identified to be the superior arylation reagents that provided the desired aryloxylation product in high efficiency, albeit dimethoxydiphenylsilane was much less reactive (Scheme 2, **3aa**). The electronic properties of aryl group in the arylsilanes exerted a dramatic effect on the reaction. The electron-rich arylsilanes showed very good reactivity to afford the β-aryloxylated products in good yields (Scheme 2, **3ab**−**3af**). However, the aryloxylation of electron-deficient arylsilanes took place sluggishly to give a trace of the product (data not

Scheme 2. Substrate Scope of Organosiloxanes[a,b]



[a]Reactions conditions: **1** (0.1 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (0.2 mmol), Ag_2O (2.0 equiv), CsF (2.0 equiv), NaOPiv (0.3 equiv), $(BOC)_2O$ (6.0 equiv), DMF (1.5 mL), N_2, 150 °C, 0.5 h. [b]Isolated yield by flash column chromatography. $(BOC)_2O$ = di-*tert*-Butyl dicanonate, Q = Quinolin-8-yl.

shown). Sterically hindered arylsilanes delivered a lower yield even after the modification of the reaction time (Scheme 2, **3ad**). 2-Naphthylsilane could participate in the reaction, providing the aryloxylation product in 41% yield (Scheme 2, **3ag**). In all cases studied, diaryloxylated products were not observed.

Vinyl ethers are highly valuable organic molecules considering their numerous applications in polymer formulations, surfactants, drug delivery systems, and general organic synthesis.[16] The important utility of the vinyl ether structure motif has prompted intense research directed at discovering efficient and high-yielding methods for its preparation.[17] It would be extremely valuable from the synthetic point of view if vinylsilanes could perform the oxidation/vinylation sequential transformation via direct C−H cleavage to synthesize vinyl ethers. To our great delight, we found that trimethoxyvinylsilane indeed was a good substrate for this aryloxylation reaction and diverse vinyl ethers could be prepared from the corresponding propionamides readily (Scheme 2, **3ah**−**3hh**).

Next, we investigated the compatibility of the reaction with amide derivatives as summarized in Scheme 3. Pivalamide was an excellent substrate to give the aryloxylation product in 72% yield (**3aa**). Replacement of one methyl group in the α-carbon of pivalamide with other alkyl groups, such as ethyl, propyl and butyl, afforded the corresponding products in good yields (**3ba**−**3da**). The reaction showed high selectivity to give only the monoaryloxylation product, and the diaryloxylation product was not detected. The substrate bearing one methyl group such as 2-ethyl-2-methyl-*N*-(quinolin-8-yl)pentanamide could participate in the reaction smoothly to deliver the desired product in good yield (**3ea**). It should be noted that a variety of aryl containing carboxamides selectively gave the sole aryloxylation

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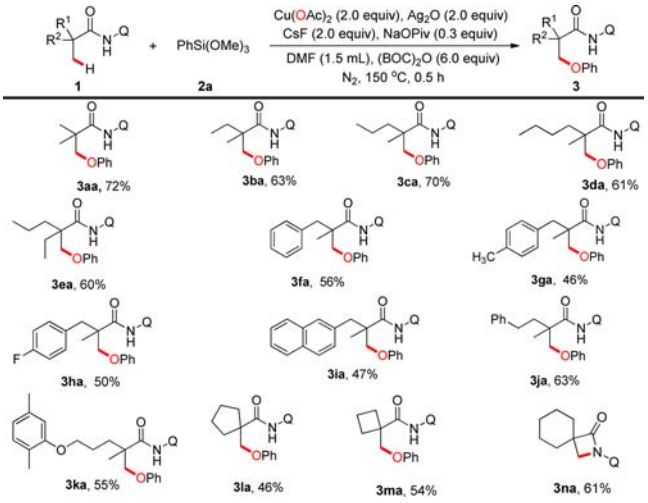
Scheme 3. Substrate Scope of Amides[a,b]

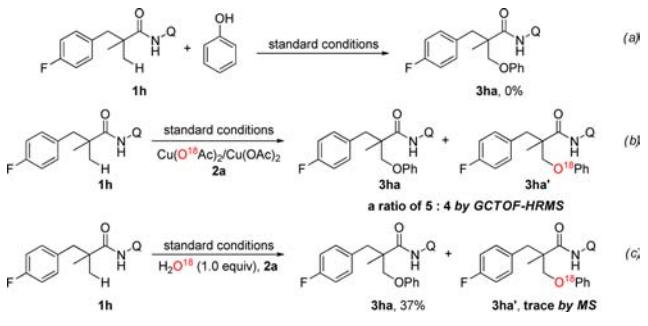


[a]Reactions conditions: **1** (0.1 mmol), **2a** (0.5 mmol), $Cu(OAc)_2$ (0.2 mmol), Ag_2O (2.0 equiv), CsF (2.0 equiv), NaOPiv (0.3 equiv), $(BOC)_2O$ (6.0 equiv), DMF (1.5 mL), N_2, 150 °C, 0.5 h. [b]Isolated yield by flash column chromatography. $(BOC)_2O$ = di-*tert*-Butyl dicanonate, Q = Quinolin-8-yl.

products at the methyl group without the formation of any byproduct at the active benzyl position (**3fa**−**3ja**).[18] Furthermore, the ether group, which contains the active C−H bond adjacent to oxygen,[19] tolerated the reaction conditions to give the target product **3ka** in 63% yield. Gratifyingly, the five- and four-membered cyclic carboxamides showed good reactivity to give the corresponding aryloaylation products that are not easy to synthesize by known methods. Interestingly, the corresponding cyclohexanecarboxamide failed to give the aryloxylation product but underwent the intramolecular $C(sp^3)$−H bond amidation to afford the spiro compound **3na** in 61% yield.

To gain some insights into this copper-promoted novel process in terms of generality and mechanism, we performed a series of preliminary studies (Scheme 4). No desired product

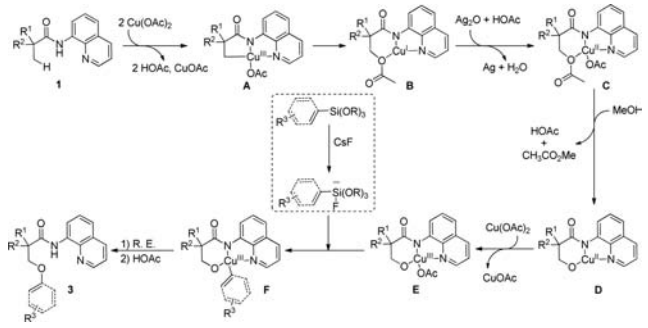
Scheme 4. Control Experiments



was observed when phenol was employed in the standard conditions (Scheme 4, eq a). This result excluded the C−O coupling of the $C(sp^3)$−H bond with phenol which might generate from trimethoxy(phenyl)silane. Furthermore, the O^{18}-labeling experiment using a mixture of $Cu(O^{18}Ac)_2$ and $Cu(OAc)_2$ resulted in a sharp increase in the scale of O^{18}-labeling product **3ha′** (Scheme 4, eq b; see the Supporting Information). In contrast, only a trace of O^{18}-labeling product **3ha′** was observed in the presence of H_2O^{18} (Scheme 4, eq c; see the Supporting Information). These results revealed that $Cu(OAc)_2$ served as the source of the oxygen in the aryloxylation product.

Based on an earlier precedent[5i−k] and our own preliminary studies above, a plausible reaction pathway was proposed as shown in Scheme 5. Coordination of a substrate to a copper(II)

Scheme 5. Mechanistic Hypothesis



species and the subsequent C−H activation and disproportionation generate an organocopper(III) intermediate **A**, which undergoes reductive elimination to generate the acetoxylated product and form the copper(I) species **B**. The oxidation of **B** by Ag_2O produces the copper(II) species **C**, which reacts with methanol liberated from organosiloxanes under the reaction conditions to give rise to intermediate **D**. The disproportionation and subsequent transmetalation of intermediate **E** with aryl or alkenyl silicate generate the organocopper(III) intermediate **F**, which undergoes the reductive elimination and protonation to give the final aryloxylation product.

In conclusion, a new copper-mediated aryloxylation/vinyloxylation of the $C(sp^3)$−H bond with organosiloxane reagents was developed through a sequential oxidation and arylation/vinylation process with the assistance of an 8-aminoquinolyl auxiliary. This reaction pattern allows the efficient synthesis of aryl-alkyl ethers from readily available starting materials and provides a new avenue for direct C−H bond functionalizations. The preliminary studies on the reaction mechanism indicate that $Cu(OAc)_2$ performs as both the promoter and the source of oxygen. Efforts to further understand the reaction parameters and to extend this approach to other synthesis of valuable compounds are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral and analytical data, copies of ^1H and ^{13}C NMR spectra for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01192.

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Notes

The authors declare no competing financial interest.

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