

Synthesis of Allylic Alcohols via Cu-Catalyzed Hydrocarbonylative Coupling of Alkynes with Alkyl Halides

Li-Jie Cheng, Shahidul M. Islam, and Neal P. Mankad*

Department of Chemistry, University of Illinois at Chicago, 845 W. Taylor St., Chicago, IL 60607

ABSTRACT: We have developed a modular procedure to synthesize allylic alcohols from tertiary, secondary, primary alkyl halides and alkynes via a Cu-catalyzed hydrocarbonylative coupling and 1,2-reduction tandem sequence. The use of tertiary alkyl halides as electrophiles was found to enable synthesis of various allylic alcohols bearing α -quaternary carbon centers in good yield with high 1,2-reduction selectivity. Mechanistic studies suggested a different pathway was operative with tertiary alkyl halides compared to primary and secondary alkyl halides for generating the key copper(III) oxidative adduct. For tertiary electrophiles, an acyl halide likely forms via radical atom transfer carbonylation (ATC). The preference for 1,2-reduction over 1,4-reduction of α,β -unsaturated ketones bearing tertiary substituents was rationalized using DFT transition state analysis. Based on this computational model, the coupling method was extended to primary and secondary alkyl iodide electrophiles by using internal alkynes with aryl substituents, providing tri-substituted allylic alcohols in high yield with good regioselectivity.

INTRODUCTION

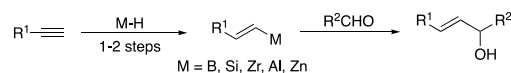
Allylic alcohols are common structural motifs in many complex organic molecules and, moreover, are versatile synthetic building blocks due to their dual alkene/alcohol functionalities. In the past decades, numerous approaches have been developed for the preparation of allylic alcohols.¹ Among them, the use of alkynes as substrates has received significant interest due to their wide availability. The conventional method for synthesis of allylic alcohols involves the preparation of stoichiometric metal-alkyne complexes² or metal-alkenyl reagents³ from alkynes, followed by nucleophilic addition to carbonyl compounds (Scheme 1a). However, the use of stoichiometric organometallic reagents can be undesirable due to their possible sensitivity toward air/water, poor functional group tolerance, and necessity to be purified before use. Therefore, much effort has been devoted to the transient generation of the alkenyl metal reagent in catalytic quantities.⁴ For example, the Ni-catalyzed reductive coupling of aldehydes and alkynes has been well developed for the synthesis of allylic alcohols (Scheme 1b).⁵ In addition, the electrophiles can be extended from aldehyde to alcohols via a redox coupling process.⁶ Furthermore, Rh-catalyzed coupling of terminal alkynes with carboxylic acids to synthesize branched allylic esters via a redox-neutral propargylic C-H activation was also reported (Scheme 1c).⁷

However, despite these impressive successes, several challenges still remain. These established coupling methods rely on electrophilic partners where the carbonyl group is pre-installed, while the use of electrophiles such as alkyl halides has not been reported for the synthesis of allylic alcohols. Moreover, these current methods are normally applied to prepare allylic alcohols bearing primary or secondary carbon centers at the α position. There is no general approach to synthesize the allylic alcohols bearing α -quaternary carbon centers,⁸ even though these structures not only exist in many pharmaceuticals and natural products⁹ but also are ideal precursors to access a variety of

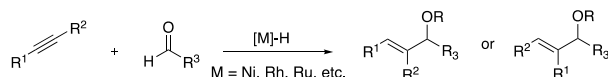
other motifs with quaternary carbon centers¹⁰ due to versatile transformations of both alkene and hydroxyl functional groups.

Scheme 1. Synthesis of allylic alcohols from alkynes

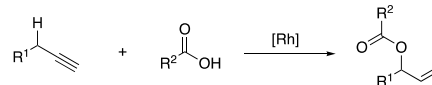
(a) Stoichiometric use of alkenyl organometallic reagents



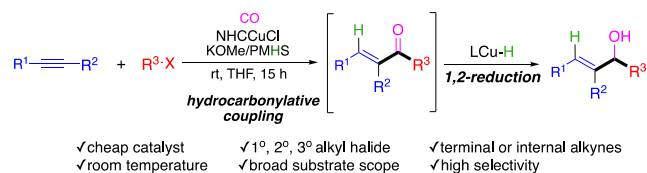
(b) Transition metal-catalyzed reductive coupling of alkynes and aldehydes



(c) Rhodium-catalyzed coupling of terminal alkynes with carboxylic acids



(d) This work



- ✓ cheap catalyst
- ✓ room temperature
- ✓ 1°, 2°, 3° alkyl halide
- ✓ broad substrate scope
- ✓ terminal or internal alkynes
- ✓ high selectivity

On the other hand, transition-metal-catalyzed carbonylative C-C coupling of organic electrophiles with organometallic reagents represent one of most efficient methods to construct carbonyl compounds due to its modularity and use of cheap and abundant CO as a C₁ feedstock.¹¹ Although carbonylative coupling reactions have long been established for C(sp²)-hybridized electrophiles, use of unactivated C(sp³)-hybridized electrophiles is far less developed¹²⁻¹³ due to their slow rate of oxidative addition¹⁴ as well as competitive β -hydride elimination under carbonylative conditions.¹⁵ In particular, while carbonylative C-C coupling with tertiary alkyl halide electrophiles is known to enable the synthesis of ketones with quaternary carbon centers, reported examples invariably suffer from requiring induction

by photoirradiation, use of precious-metal Pd catalysts, and limited scope.^{12a, 12c}

In this context, our group recently developed a Cu-catalyzed hydrocarbonylative C-C coupling of terminal alkynes with unactivated primary or secondary alkyl iodides¹⁶ based on established Cu-catalyzed hydrofunctionalization of alkynes.¹⁷⁻¹⁸ Dialkyl ketone products were formed via 1,4-reduction of α,β -unsaturated ketone intermediates generated by hydrocarbonylative C-C coupling. We wondered whether 1,2-reduction could be preferred over 1,4-reduction under controlled conditions,¹⁹ providing allylic alcohols instead of ketones as products. Herein, we reported a general method for highly regioselective synthesis of allylic alcohols from tertiary, secondary, primary alkyl halides and alkynes via a Cu-catalyzed hydrocarbonylative coupling and 1,2-reduction tandem sequence (Scheme 1d). Notably, the use of tertiary alkyl halides enables the synthesis of various allylic alcohols bearing α -quaternary carbon centers. It is noteworthy that despite great achievements in the coupling of primary and secondary alkyl electrophiles,²⁰ the construction of all carbon quaternary centers via catalytic C-C coupling with tertiary alkyl electrophiles remains a challenge.²¹

RESULTS AND DISCUSSION

Using our previously established conditions,¹⁶ we did not observe formation of either allylic alcohol or ketone products when *tert*-butyl iodide was used as the electrophilic partner. However, after intensive investigation, we found that the desired allylic alcohol **3a** could be obtained in 94% yield when ^{Cl}IPrCuCl was used as the catalyst and *tert*-butyl bromide as the electrophile in the presence of KOMe as the base and polymethylhydrosiloxane (PMHS) as the reducing reagent at room temperature (Table 1, entry 1). The saturated alcohol **4a** was also obtained as a minor product. Control experiments established that **4a** arose from the competitive 1,4-reduction of the relevant enone intermediate followed by reduction of the resulting saturated ketone, not from reduction of **3a**.²² We also investigated different NHC ligands, and ^{Cl}IPr was found to be superior to other ligands (Table 1, entry 2-4). The use of more reactive *tert*-butyl iodide could also give the product in slightly lower yield with moderate selectivity, whereas the less reactive *tert*-butyl chloride did not react at all (Table 1, entry 5-6). Use of NaOMe as the base gave significantly decreased yield, and other bases such as LiOMe and K^tOBu did not afford the desired product (Table 1, entry 7-9). We also evaluated different silanes as reducing reagents. While (EtO)₃SiH and (Me₂HSi)₂O gave no product or trace product, the use of (EtO)₂MeSiH could afford the product in comparable yield and slightly higher selectivity (Table 1, entry 10-12). Considering that PMHS is a cheap, easy-to-handle, and environmentally friendly as a reducing agent, we decided to continue using PMHS in all the reactions. Reducing the amount of PMHS to 3.0 equivalents led to a decreased yield and lower selectivity (Table 1, entry 13). Changing the solvent to either 1,4-dioxane or toluene resulted in no product formation (Table 1, entry 14-15). Finally, we found that keeping the CO pressure at 6 atm is necessary to obtain high yield and excellent selectivity (Table 1, entry 16).

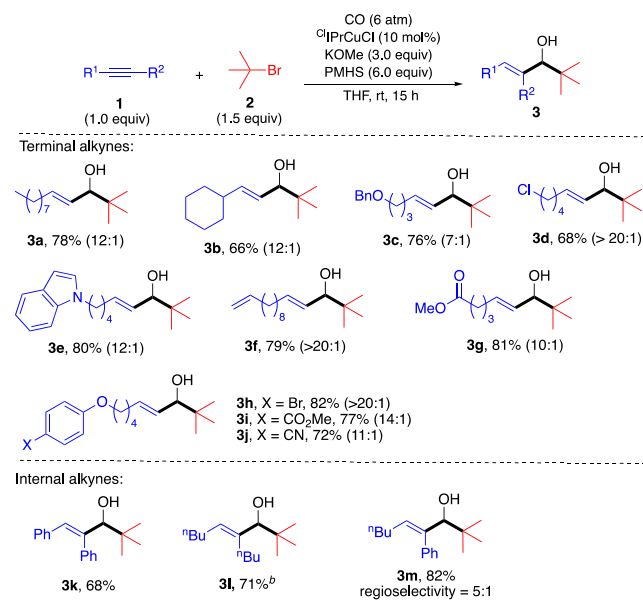
Table 1. Hydrocarbonylative Coupling of an Unactivated Tertiary Alkyl Bromide: Selected optimization studies^a

“standard” conditions CO (6 atm) ^{Cl}IPrCuCl (10 mol%) KOMe (3.0 equiv) PMHS (6.0 equiv) THF, rt, 15 h				
Legend: ^{Cl}IPr R' = H, R = 2,6-(diisopropyl)phenyl ^{Cl}IPr, R' = Cl, R = 2,6-(diisopropyl)phenyl Me^{Cl}IPr, R' = Me, R = 2,6-(diisopropyl)phenyl IMes R' = H, R = 2,4,6-(trimethyl)phenyl				
entry	variations from “standard” conditions	3a yield (%) ^b	3a/4a ^b	
1	None	94	12:1	
2	IPrCuCl instead of ^{Cl} IPrCuCl	72	4:1	

3	Me ^{Cl} IPrCuCl instead of ^{Cl} IPrCuCl	72	4:1
4	IMesCuCl instead of ^{Cl} IPrCuCl	28	1:1
5	^t Butyl-I instead of ^t Butyl-Br	74	6:1
6	^t Butyl-Cl instead of ^t Butyl-Br	0	--
7	NaOMe instead of KOMe	36	3:1
8	LiOMe instead of KOMe	0	--
9	K ^t OBu instead of KOMe	0	--
10	(EtO) ₃ SiH instead of PMHS	0	--
11	(Me ₂ HSi) ₂ O instead of PMHS	10	1:2
12	(EtO) ₂ MeSiH instead of PMHS	90	14:1
13	3.0 equiv PMHS instead of 6.0	78	5:1
14	1,4-dioxane instead of THF	0	--
15	Toluene instead of THF	0	--
16	3 atm CO instead of 6 atm	58	5:1

^a The reaction was performed on 0.1 mmol scale. ^b Yield and the ratio of **3a/4a** were determined by ¹H NMR integration against an internal standard.

Table 2. Hydrocarbonylative Coupling of Unactivated Tertiary Alkyl Bromides: Scope with Respect to Alkynes^a

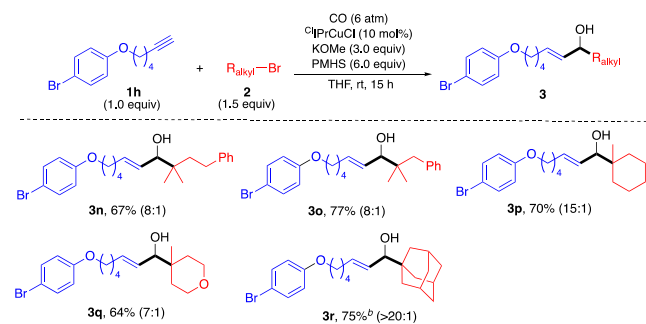


^a The reaction was performed on 0.2 mmol scale. All yields are combined isolated yields of product **3** and saturated alcohols **4**. The ratios of **3/4** (in parentheses) were determined by ¹H NMR analysis after purification. ^b IPrCuCl was used as catalyst and the reaction was conducted at 45°C.

With the optimal conditions in hand, we next investigated the substrate scope with respect to alkynes (Table 2). In most cases, the allylic alcohols were obtained in good yield with excellent selectivity (>10:1). The mild reaction conditions allow the use of a variety of alkynes containing different functional groups, such as benzyl ether (**3c**), chloroalkyl (**3d**), indolyl (**3e**), terminal alkene (**3f**) and ester (**3g**). Aryl bromide, ester, and cyanide groups also survived the reaction (**3h-3j**). Moreover, we were delighted to find that internal alkynes are also applicable, providing tri-substituted allylic alcohols with α -quaternary carbons as single products in good yields (**3k-3m**). Use of IPrCuCl as a catalyst at 45°C was required for the reaction of less reactive 5-decyne (**3l**). Satisfactory regioselectivity was obtained when an unsymmetrical internal alkyne was used as substrate (**3m**).

We also evaluated the scope with respect to different tertiary alkyl bromides (Table 3). A tertiary bromide with a benzyl group was also applicable in the coupling reaction (**3o**). Cyclic tertiary alkyl iodides are also suitable substrates (**3p-3q**). Ether functional groups within the cyclic electrophile are tolerated (**3q**). Although the steric bulky 1-bromoadamantane only gave the product in poor yield (36%), the more reactive 1-iodoadamantane afforded the product (**3r**) in good yield with excellent selectivity.

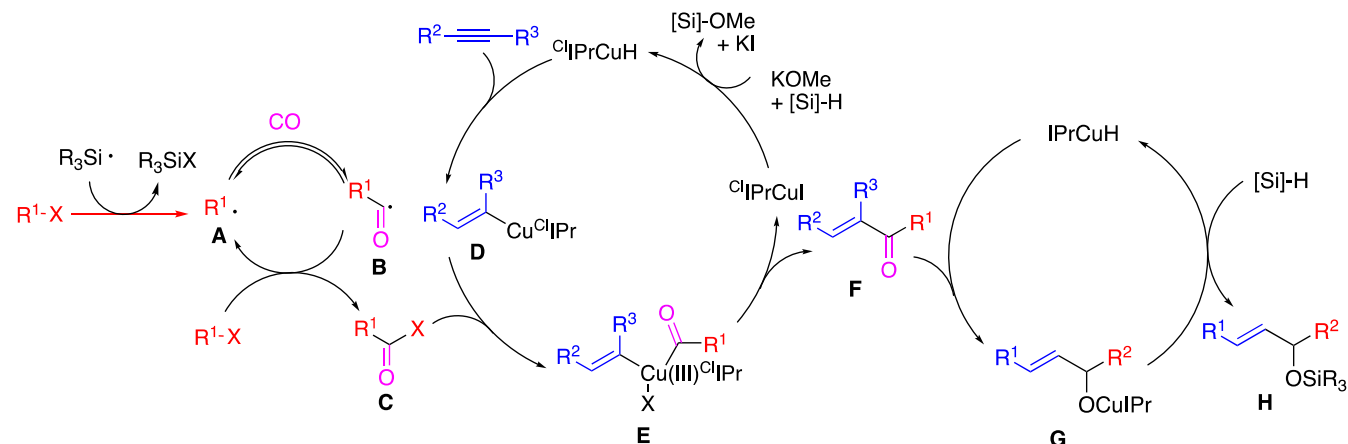
Table 3. Hydrocarbonylative Coupling of Unactivated Tertiary Alkyl Bromides: Scope with Respect to Electrophiles^a



^a The reaction was performed on 0.2 mmol scale. All yields are combined isolated yields of product and saturated alcohols **4**. The ratios of **3/4** (in parentheses) were determined by ¹H NMR analysis after purification. ^b 1-iodoadamantane was used as the electrophile.

Next, we conducted several experiments to investigate the mechanism. No product was observed when TEMPO was added to the reaction (Scheme 2a), which is indicative of radical activation of the alkyl halide. A radical mechanism also was found to be operative in our previous hydrocarbonylative C-C coupling reaction with primary and secondary alkyl iodides.¹⁶ We also attempted the stoichiometric coupling of alkenylcopper **5** with *tert*-butyl bromide under the CO atmosphere (Scheme 2b). To our surprise, the α,β -unsaturated ketone **6** was not observed, indicating that tertiary alkyl halides have a different radical initiation pathway than what was discovered for primary and secondary alkyl halides previously.¹⁶ Further studies revealed the allylic alcohol product was obtained only in the presence of PMHS, which suggests that the silane plays a vital role to initiate alkyl radical generation. We also synthesized α,β -unsaturated ketone **6** and subjected it to the same conditions in the absence of CO. Results mirroring the catalytic experiments were obtained, with the allylic alcohol resulting from 1,2-reduction being observed as a major product (Scheme 2c). This observation is consistent with the α,β -unsaturated ketone being an intermediate in a tandem coupling/reduction process.

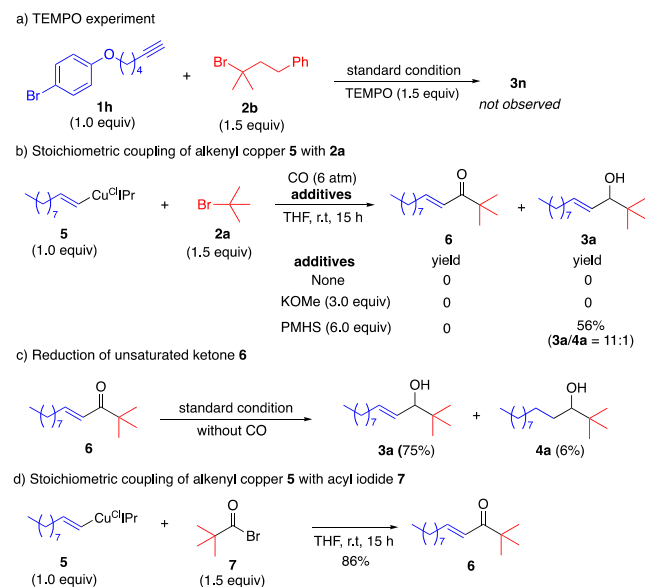
Scheme 3. Hypothetical mechanism



Inspired by Ryu's work,²³ we next sought to probe whether the α,β -unsaturated ketone was formed via coupling of an alkenyl copper intermediate with an acyl halide generated through an atom transfer carbonylation (ATC) pathway. We conducted the stoichiometric coupling of alkenyl copper **5** with pivaloyl bromide **7**, and the α,β -unsaturated ketone **6** was obtained in 86% isolated yield (Scheme 2d). This is distinct from hydrocarbonylative coupling with primary alkyl electrophiles,¹⁶ where an ATC pathway can be ruled out because no product could be generated from stoichiometric coupling of an alkenyl copper complex with a primary acyl iodide.

Based on the above results, we hypothesize a mechanism for hydrocarbonylative coupling with tertiary alkyl electrophiles that diverges from the previous work with primary and secondary alkyl electrophiles (Scheme 3). First, an alkyl radical **A** is likely generated from the reaction between a silyl radical²⁴ and the alkyl halide. The alkyl radical **A** then undergoes carbonylation with CO to give an acyl radical **B**, which reacts with alkyl halide to afford acyl halide **C** and propagate the radical chain. Then, the oxidative addition of acyl halide **C** to the alkenyl copper **D** forms the copper(III) complex **E**. Finally, the desired α,β -unsaturated ketone **F** is obtained via reductive elimination of **E**. In the next part of the tandem sequence, intermediate **F** undergoes Cu-catalyzed 1,2-reduction to provide the ultimate allylic alcohol product upon workup of **G**.

Scheme 2. Mechanistic studies



Because the relative preferences for enones **F** to undergo 1,2-reduction when R^1 is tertiary and to undergo 1,4-reduction when R^1 is primary/secondary was initially counterintuitive to us based on sterics, we decided to conduct a DFT analysis. Using a model Cu-H complex supported by the small N,N' -dimethylimidazol-2-ylidene carbene, reactions with a methyl enone and a *tert*-butyl enone were examined. Transition states for 1,2-reduction and 1,4-reduction were located for both substrates (Figure 1). For reduction of the methyl enone, the 1,4-reduction pathway was calculated to have a lower barrier than the 1,2-reduction pathway by 4.9 kcal/mol, which is consistent with previous calculations on phosphine-ligated Cu-H systems.^{19c} For the *tert*-butyl enone, the activation barrier for 1,2-reduction was lower than that for 1,4-reduction by 13.7 kcal/mol, consistent with our experimental observations. In examining the two transition states for the *tert*-butyl enone substrate, we can rationalize that the 1,2-reduction transition state is actually less crowded due to the approach trajectory of the Cu-H reductant. In the 1,4-reduction pathway, the Cu-H species approaches the enone with a trajectory that places the carbene substituents over the *tert*-butyl group. In contrast, in the 1,2-reduction pathway the Cu-H species approaches the enone with a trajectory for which the carbene substituents are rotate away into a plane that is orthogonal to the C(O)-*t*-Bu plane.

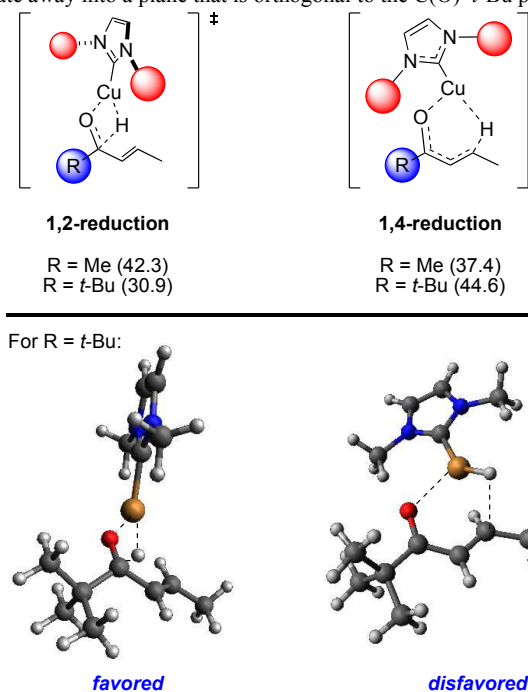


Figure 1. Transition states (DFT, B3LYP/6-311G(d,p), THF PCM model) for 1,2- and 1,4-reduction of enones by a model Cu-H species. Transition state barriers (in parentheses) are given as Gibbs free energies in units of kcal/mol.

Next, we questioned whether 1,2-reduction of the enone intermediate could be amenable to primary and secondary alkyl electrophiles, thus providing a general method to synthesize allylic alcohols. The computational studies indicated that the steric effect adjacent to the carbonyl group of the enone intermediate plays a vital role in controlling the regioselectivity between 1,2-reduction and 1,4-reduction. We reasoned the introduction of a substitute at the α position of the enone intermediate would substantially increase the steric hindrance near the carbonyl group, making the 1,2-reduction more favorable regardless of the alkyl halide electrophile's identity. This would require the use of internal alkynes as substrates. While in our previous work we observed that dialkyl-substituted alkynes such as 5-decyne did not react at all,¹⁶ we are delighted to find that replacing one of the alkyl substitutes with an aryl group enhanced

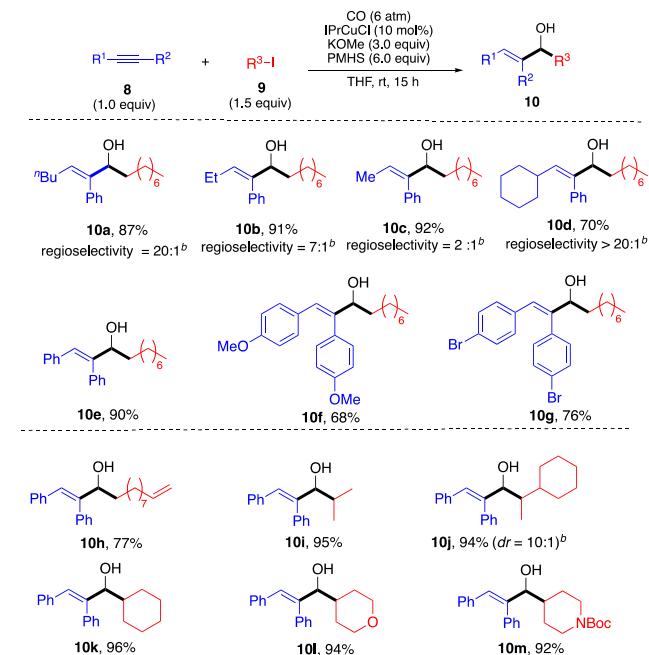
reactivity. The hydrocarbonylative coupling of 1-phenyl-1-hexyne **8a** with 1-iodooctane **9a** could afford the tri-substituted alcohol **10a** in high yield with excellent regioselectivity when the IPrCuCl was used as catalyst (Table 4, entry 1). Briefly screening the NHC ligands showed the commercial available IPr is superior to other NHC ligands (Table 4, entry 2-5).

Table 4. Hydrocarbonylative Coupling of an Unactivated primary Alkyl iodide: Effect of Catalysts^a

entry	catalyst	10a yield (%) ^b	10a/11a ^b
1	IPrCuCl	98	20:1
2	SIPrCuCl	85	4:1
3	ⁱ PrCuCl	69	15:1
4	MeIPrCuCl	69	3:1
5	IMesCuCl	0	--

^a The reaction was performed on 0.1 mmol scale. ^b Yield and the ratio of **10a/11a** were determined by ¹H NMR integration against an internal standard.

Table 5. Hydrocarbonylative Coupling of Unactivated Primary and Secondary Alkyl iodides^a

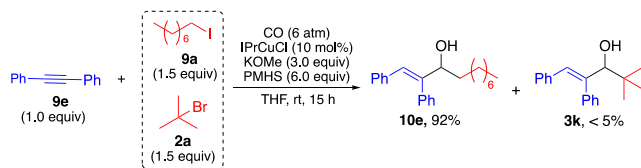


^a The reaction was performed on 0.2 mmol scale. All yields are isolated yields. ^b Determined by ¹H NMR analysis after purification.

Under the optimized reaction conditions, the substrate scope was tested. While low regioselectivity was found when replacing the butyl group with sterically less demanding methyl group (**10c**), good and excellent regioselectivities were obtained with the ethyl (**10b**) and cyclohexyl groups (**10d**), respectively. Diphenylacetylenes are also suitable substrate (**10e**). Diaryl acetylenes bearing either electron-donating or electron-withdrawing groups gave the corresponding products (**10f-10g**) in good yields. We also investigated the substrate scope with alkyl iodides. A terminal alkene moi-

ety (**10h**) remained intact under the present conditions. The alkyl electrophile scope can also be extended from primary alkyl iodides to secondary alkyl iodides (**10i**). Increasing the steric hindrance of secondary alkyl iodide has no effect on the yield and good diastereoselectivity was successfully achieved during the 1,2-reduction process (**10j**). Cyclic alkyl iodides are also suitable substrates (**10k-10m**). Both of ether (**10l**) and *N*-Boc functional groups (**10m**) within the electrophile are well tolerated. It is noteworthy that neither saturated ketone nor alcohol side products were detected under these conditions, indicating that the 1,4-reduction pathway was fully suppressed.

Scheme 4. Competition experiment between primary and tertiary alkyl halides



A competition experiment was conducted to compare the relative reaction rate of primary iodide and tertiary alkyl bromide (Scheme 4). Interestingly, the product **10e** derived from the primary alkyl halide was formed as the major product, which contrasts with previous studies in which tertiary alkyl halide are more reactive due to the generation of more thermodynamically stable tertiary alkyl radicals.²⁵ Our observation clearly supports the two distinct mechanisms we proposed for the primary and tertiary alkyl halides, respectively. We attributed our results to generation of the tertiary alkyl radical by atom transfer carbonylation (ATC) being slow relative to primary alkyl radical generation by a Cu-mediated pathway.

SUMMARY

In summary, we have developed a modular procedure to synthesize allylic alcohols from tertiary, secondary, and primary alkyl halides and alkynes via a Cu-catalyzed hydrocarbonylative coupling and 1,2-reduction tandem sequence. The reaction tolerates a variety of functional groups under mild reaction conditions, affording corresponding allylic alcohol in good yield with excellent selectivity. The use of tertiary alkyl halide enables the synthesis of various allylic alcohols bearing α -quaternary carbon centers, which are still challenging using the previous catalytic methods. Mechanistic studies suggest a different pathway was involved with the tertiary alkyl halide and a tertiary acyl halide was formed via radical atom transfer carbonylation (ATC) pathway. The preference for 1,2-reduction over 1,4-reduction of this intermediate was supported by DFT analysis. By employing internal alkynes with one aryl substituent, primary and secondary alkyl electrophiles are also applicable under the similar reaction conditions, providing tri-substituted allylic alcohols in high yield with good

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures & spectral data (PDF)

AUTHOR INFORMATION

Corresponding Author

* npm@uic.edu

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