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## Homogeneous Catalysis

Ligand-Enabled Cu-Catalyzed Deoxyalkynylation of  $\alpha$ -Unfunctionalized Alcohols with Terminal Alkynes

Xiao-Yang Dong,\* Zi-Jian Zhou, Zhong-Liang Li, Peng-Fei Wang, Jun (Joelle) Wang, and Xin-Yuan Liu\*

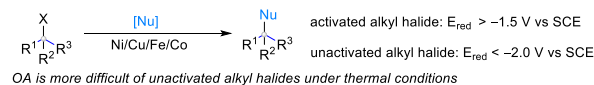
**Abstract:** Despite the widespread utility of transition metal-catalyzed cross-couplings in organic synthesis, the coupling of unactivated alkyl electrophiles remains challenging due to sluggish oxidative addition and competing side reactions. Here, we describe a general and practical copper-catalyzed radical deoxyalkynylation of  $\alpha$ -unfunctionalized alcohols through a synergistic combination of Barton-McCombie deoxygenation and copper-catalyzed radical cross-coupling. Key to the success of this method lies in not only the development of rigid anionic multiple *N,N,N*-ligand to exert remarkable selectivity of highly reactive unactivated alkyl radicals, but also the selection of one suitable oxidant to suppress Glaser homocoupling and other side products. This method provides a complementary approach for the cross-coupling of unactivated alkyl halides, which face notable difficulties in reaction initiation and bond formation under mild thermal conditions, especially the tertiary variants. This protocol not only exhibits a broad scope with respect to both coupling partners, covering alkyl- and (hetero)aryl alkynes, as well as  $\alpha$ -unfunctionalized primary-, secondary-, and tertiary- alcohols with good functional group compatibility, but also facilitates the late-stage functionalization of a series of important natural and bioactive complex molecules.

## Introduction

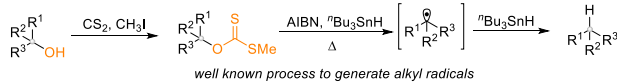
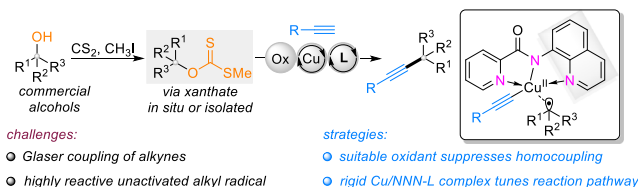
Transition metal-catalyzed cross-coupling reactions have emerged as a robust strategy for synthesizing a wide range of organic compounds, serving as pivotal tools in organic synthesis, drug discovery, and materials science.<sup>[1–4]</sup> In this area, 3d-transition metal-catalyzed radical cross-coupling of alkyl electrophiles provided a practical platform for the C(sp<sup>3</sup>)-C/X cross-coupling to build sp<sup>3</sup>-hybridized carbon frameworks.<sup>[5,6]</sup> Nevertheless, while the cross-coupling of activated alkyl halides has been well-established, the corresponding reactions involving unactivated alkyl halides have been scarce due to the substantially lower reduction potentials

of unactivated alkyl halides ( $E_{\text{red}} < -2.0$  V versus SCE) compared to activated analogs ( $E_{\text{red}} > -1.5$  V versus SCE), which impedes their reduction to alkyl radicals and limits their synthetic utility (Scheme 1a).<sup>[7,8]</sup> Thus, the development of a general and practical cross-coupling reaction with the use of the challenging unactivated alkyl electrophiles is highly desirable and is in great demand.

## a) 3d-transition metal-catalyzed cross-coupling reactions of alkyl halides



## b) Barton-McCombie deoxygenative reaction

c) Deoxyalkynylation of  $\alpha$ -unfunctionalized alcohols under thermal conditions (This Work)

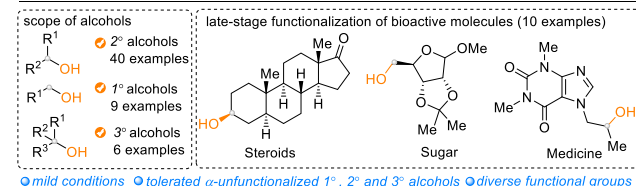
[\*] Dr. X.-Y. Dong, Z.-J. Zhou, Dr. Z.-L. Li  
Dongguan Key Laboratory of Interdisciplinary Science for Advanced Materials and Large-Scale Scientific Facilities, School of Physical Science, Great Bay University, Dongguan 523000, China  
E-mail: [dongxy@gbu.edu.cn](mailto:dongxy@gbu.edu.cn)

Dr. P.-F. Wang, Dr. Prof. X.-Y. Liu  
Shenzhen Grubbs Institute, Department of Chemistry, Guangming Advanced Research Institute, and Shenzhen Key Laboratory of Cross-Coupling Reactions, Southern University of Science and Technology, Shenzhen 518055, China  
E-mail: [liuxy3@sustech.edu.cn](mailto:liuxy3@sustech.edu.cn)

Z.-J. Zhou  
Department of Materials Science and Engineering, Southern University of Science and Technology, Shenzhen 518055, China

Dr. X.-Y. Dong, Dr. Prof. J. (Joelle) Wang  
Department of Chemistry, Hong Kong Baptist University, Kowloon, Hong Kong 999077, China

Additional supporting information can be found online in the Supporting Information section



• mild conditions • tolerated  $\alpha$ -unfunctionalized 1°, 2° and 3° alcohols • diverse functional groups

**Scheme 1.** Motivation and design of deoxyalkynylation cross-coupling of  $\alpha$ -unfunctionalized alcohols with terminal alkynes.

Given that alcohols are far more abundant, cost-effective, and readily accessible than alkyl halides in nature, the deoxyfunctionalization of alcohols to build target molecules has been recognized as a long-standing prominent objective in modern chemical research. Recently, radical deoxyfunctionalization has opened new doors in this area, paving the way for substantial progress in radical deoxygenative cross-coupling methodologies.<sup>[9–12]</sup> A series of alcohol derivatives—including oxalates, carboxylic esters, and phosphates—has been successfully utilized as versatile electrophilic partners under photocatalytic, electrocatalytic, and transition metal-catalyzed conditions pioneered by Overman,<sup>[13,14]</sup> MacMillan,<sup>[15–22]</sup> Gong,<sup>[23,24]</sup> Shu,<sup>[25–27]</sup> Diao,<sup>[28]</sup> and others.<sup>[29–35]</sup> This methodology establishes a versatile platform for forging C(sp<sup>3</sup>)-C/X bonds under mild and environmentally benign conditions. Its capacity to deliver high site-selectivity while maintaining broad functional group tolerance positions it as a robust strategy in many disciplines. Notably, this approach circumvents the inherent limitations of traditional alkyl halide-based cross-coupling methods, thereby emerging as an efficient complementary paradigm for constructing C(sp<sup>3</sup>)-hybridized architectures. Despite these impressive advances, the development of a new catalytic system to achieve the deoxygenative cross-coupling of more radical precursors derived from diverse alcohols—particularly under mild thermal conditions—remains highly desirable, given the significance of alcohol transformations in organic synthesis.

The Barton–McCombie reaction<sup>[36–38]</sup> converts alcohol-derived xanthates into alkyl radicals under thermal initiation, effectively reducing C(sp<sup>3</sup>)-OH to C(sp<sup>3</sup>)-H (Scheme 1b). Renowned for its mild conditions, broad functional group tolerance, and applicability across primary, secondary, and tertiary alcohols, this reaction exemplifies a powerful strategy for generating alkyl radicals under thermal conditions.<sup>[39–42]</sup> On the other hand, copper is an earth-abundant first-row transition metal,<sup>[43–46]</sup> and the metalloradical Cu<sup>II</sup> complex could easily interact with alkyl radicals to forge new chemical bonds.<sup>[47]</sup> The distinct advantages of copper catalysis in radical cross-coupling reactions have been well-documented.<sup>[48–50]</sup> Integrating Barton–McCombie deoxygenation with copper-catalyzed radical cross-coupling could therefore unlock unprecedented opportunities for deoxygenative cross-coupling of alcohols. Liu and colleagues pioneered this strategy<sup>[51]</sup> by developing a copper-catalyzed deoxygenative difluoromethylation of alcohols bearing activated  $\alpha$ -functional groups, such as benzylic, propargylic, amide, and ester moieties. As part of our ongoing interest in radical reactions, we have recently developed a copper/multidentate anionic ligand system for radical cross-coupling. Key to success of the protocol is that ligand enhances the reducing capacity of copper, enabling efficient radical generation from activated alkyl halides and stereocontrolled bond formation.<sup>[52,53]</sup> However, this current system only tolerated activated alkyl halides under thermal conditions. Inspired by the above-mentioned works, we hypothesized that merging Barton–McCombie deoxygenation with our developed copper catalysis could enable a deoxygenative cross-coupling of  $\alpha$ -unfunctionalized alcohols with

broad substrate scopes and easily available and transformable terminal alkynes under mild thermal conditions (Scheme 1c), which, if achieved, would complement previously reported methods. However, the realization of this transformation presents several critical challenges: i) Identifying suitable oxidants to initiate the reaction while suppressing Glaser homocoupling of terminal alkynes. ii) Development of ligands to selectively trap thus-generated highly reactive unactivated alkyl radicals by Cu<sup>II</sup> species while inhibiting other side reactions. We herein present a general copper-catalyzed deoxygenative alkynylation of  $\alpha$ -unfunctionalized alcohols with terminal alkynes. Key to the success of this method lies in not only the development of rigid anionic multiple *N,N,N*-ligand to exert remarkable selectivity of highly reactive unactivated alkyl radicals, but also the selection of one suitable oxidant to suppress Glaser homocoupling and other side products. Moreover, this protocol demonstrates broad applicability toward both coupling partners, accommodating  $\alpha$ -unfunctionalized primary, secondary, and tertiary alcohols alongside alkyl- and (hetero)aryl alkynes—all with excellent functional group tolerance. Notably, it enables late-stage functionalization of complex natural products and bioactive molecules, highlighting its broad synthetic utility.

## Results and Discussion

### Reaction Development

To validate this hypothesis, we selected *S*-methyl *O*-(4-phenylbutan-2-yl) carbonodithioate (**XE1**) derived from easily available 4-phenylbutan-2-ol and phenylacetylene (**N1**) as the model substrates. Given the pivotal role of reaction initiation, we first screened a series of oxidants. Under standard conditions employing CuI and 1,10-phenanthroline (**L1**) as catalysts, Cs<sub>2</sub>CO<sub>3</sub> as base, and benzene (PhH) as solvent, the use of phenyldiazonium tetrafluoroborate (**Ox1**) or mesityldiazonium tetrafluoroborate (**Ox2**) predominantly afforded the Glaser coupling product **1'** (Table 1, entries 1 and 2). Switching to diphenyliodonium trifluoromethanesulfonate (**Ox3**) yielded the desired product **1** in only 5%, alongside significant amounts of **1'** (entry 3). Further evaluation of dimesityliodonium trifluoromethanesulfonate (**Ox4**) improved the yield of **1** to 16% while reducing **1'** to 30% (entry 4). These results suggest that arylidonium salts, being milder oxidants than aryl diazonium salts, could partially inhibit Glaser coupling. Additionally, increasing steric hindrance on the aromatic ring of oxidant further reduced Glaser coupling product. To further enhance chemoselectivity, different types of ligands were screened. Screening the neutral bipyridine ligand (**L2**) still favored **1'**, whereas the bidentate anionic amide *N,N*-ligand (**L3**), marginally improved product formation (entries 5 and 6). However, substantial amounts of **1'** and the side product **1''** persisted, indicating that electron-rich anionic ligands modestly enhanced reaction selectivity. More interestingly, employing the tridentate anionic amide *N,N,N*-ligand (**L4**) dramatically increased the yield of **1** to 63%, while reducing **1'** and **1''** to 24% and 15%, respectively (entry

Table 1: Optimization of reaction conditions<sup>a)</sup>

Reaction scheme showing the synthesis of compound 1 from XE1 and N1, catalyzed by Ox (10 mol%), L (15 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) in PhH at room temperature.

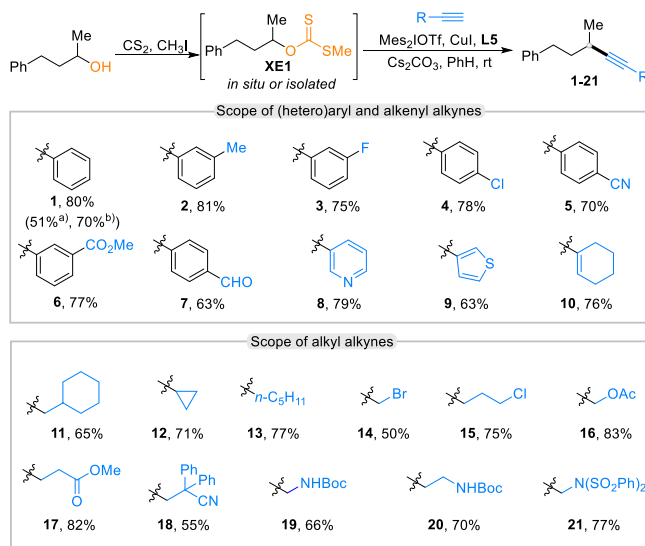
Chemical structures of Ox1, Ox2, Ox3, and Ox4 are shown in the dashed box.

Chemical structures of L1, L2, L3, L4, L5, and L6 are shown in the dashed box.

Entry	Ox	L	Conv.(%)	Yield (%)		
				1	1'	1''
1	Ox1	L1	83	0	88	0
2	Ox2	L1	82	0	39	0
3	Ox3	L1	86	5	66	0
4	Ox4	L1	90	16	30	0
5	Ox4	L2	88	10	35	0
6	Ox4	L3	66	17	39	26
7	Ox4	L4	90	63	24	15
8	Ox4	L5	95	85	8	6
9	Ox4	L6	57	41	31	22
10 <sup>b)</sup>	Ox4	L5	94	83	7	5
11 <sup>c)</sup>	Ox4	L5	92	81	8	6

<sup>a)</sup> Reaction conditions: **XE1** (1.0 equiv., 0.10 mmol), **N1** (1.2 equiv., 0.12 mmol), **Ox** (1.5 equiv., 0.15 mmol), **CuI** (10 mol%), **L** (15 mol%), **Cs<sub>2</sub>CO<sub>3</sub>** (2.0 equiv., 0.20 mmol) in **PhH** (1.0 mL) under argon at room temperature for 48 h; Yield was determined by <sup>1</sup>H NMR with 1,3,5-trimethoxybenzene as an internal standard based on **XE1**. <sup>b)</sup> **CuI** (5.0 mol%), **L5** (7.5 mol%). <sup>c)</sup> **CuI** (5.0 mol%), **L5** (6.0 mol%).

7). This underscores the importance of an anionic tridentate *N,N,N*-ligand-coordinated Cu<sup>II</sup> intermediate in selectively trapping highly reactive alkyl radicals. Notably, in the initial results, we observed a trend where the more rigid ligand **L1** was more advantageous than **L2** in increasing the product yields of **1** and suppressing the homocoupling product **1'**. This observation led us to question whether a more rigid ligand scaffold, building upon **L4**, might enhance chemoselectivity. To enhance structural rigidity, the pyridin-2-ylmethanamine moiety in ligand **L4** was replaced with quinolin-8-amine—a group previously demonstrated by Shi and coworkers<sup>[54]</sup> to exhibit excellent directing effects in alkynylation cross-coupling reactions. This modification yielded the novel, more rigid tridentate *N,N,N*-ligand **L5**. Surprisingly, this modification resulted in a dramatic improvement in reaction performance, elevating the yield of the desired product **1** to 85% while simultaneously suppressing the formation of by-products **1'** and **1''** to just 8% and 6%, respectively (entry 8). These results provide compelling support for our initial hypothesis regarding the beneficial effects of ligand rigidity on reaction selectivity. Notably, when **L5** was modified with a methyl group at the  $\alpha$ -position of the pyridine to form **L6** (entry 9), the yields decreased significantly. This highlights the crucial role of unhindered N-coordination in maintaining the stability of the copper complex. Screening of solvents

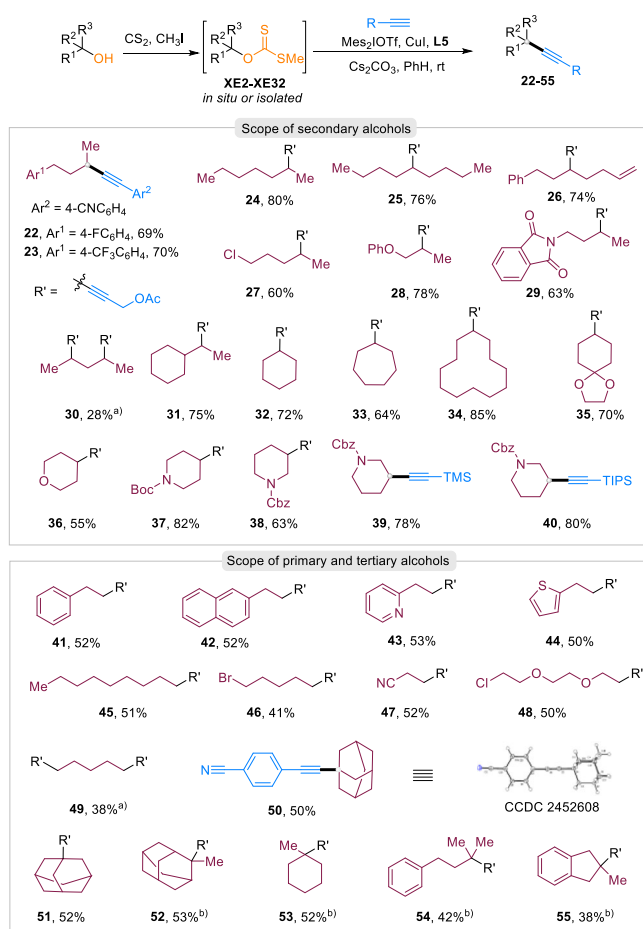


**Scheme 2.** Substrate scope of alkynes. Reaction conditions: xanthate ester (**1.2** equiv., 0.24 mmol), alkyne (1.0 equiv., 0.20 mmol), Mes<sub>2</sub>lOTf (1.5 equiv., 0.30 mmol), CuI (5.0 mol%), **L5** (6.0 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv., 0.40 mmol) in benzene (2.0 mL) under argon at room temperature for 24–48 h; isolated yield. <sup>a)</sup> Toluene as solvent. <sup>b)</sup> One-pot process on 6.0 mmol scale starting from 4-phenylbutan-2-ol.

revealed that moderate yields can also be obtained in toluene and isopropyl ether, with the yield in isopropyl ether reaching 61% (Table S1). Further optimization of copper salts (Table S2), and bases (Table S3), confirmed that CuI, benzene, and Cs<sub>2</sub>CO<sub>3</sub> at room temperature remained optimal. Remarkably, reducing the catalyst loading did not significantly compromise yields (entries 10 and 11). Ultimately, the optimized protocol—combining **XE1**, **N1**, and **Ox4** in a 1.0:1.2:1.5 molar ratio with 5.0 mol% CuI and 6.0 mol% **L5** in benzene at room temperature—delivered product **1** in 81% yield with minimal by-product formation.

### Substrates Scope

After optimizing the reaction conditions, we first explored the substrate scope of alkynes (Scheme 2). Under standard conditions, the reaction demonstrated broad compatibility with various aryl alkynes (**1–7**) bearing diverse substituents at different positions, including methyl, fluoride, chloride, cyanide, methoxycarbonyl, and formyl group. Heteroaromatic and alkenyl alkynes (**8–10**) were also successfully transformed under standard condition. All could afford the corresponding products in moderate to good yields. Even using toluene as the solvent, **1** was still obtained in a respectable 51% isolated yield, despite a moderate reduction. Notably, the developed protocol showed remarkable versatility with alkyl alkynes, enabling the efficient synthesis of products **11–21** in good yields. The reaction exhibited excellent functional group tolerance, accommodating various structural motifs such as cyclohexyl (**11**), cyclopropyl (**12**), *n*-pentyl groups (**13**), bromide (**14**), chloride (**15**), acetal (**16**), ester (**17**), cyano (**18**), amide (**19–20**), and even sulfonamide (**21**).



**Scheme 3.** Substrate scope of alcohols. Reaction conditions: alkyne (1.0 equiv., 0.20 mmol), xanthate ester (1.2 equiv., 0.24 mmol), Mes<sub>2</sub>IOtF (1.5 equiv., 0.30 mmol), CuI (5.0 mol%), L5 (6.0 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv., 0.40 mmol) in benzene (2.0 mL) under argon at room temperature for 24–48 h; isolated yield. <sup>a)</sup>Alkyne (2.2 equiv., 0.44 mmol), xanthate ester (1.0 equiv., 0.20 mmol), and Mes<sub>2</sub>IOtF (3.0 equiv., 0.60 mmol). <sup>b)</sup>One-pot process.

Building upon these findings, we subsequently investigated the reaction scope of  $\alpha$ -unfunctionalized alcohols (Scheme 3). The optimized conditions demonstrated excellent compatibility with various  $\alpha$ -unfunctionalized secondary alcohols, accommodating structurally diverse substrates including fluoro-substituted phenyl groups (22–23), acyclic alkyl chain (24–29) with diverse functional groups, such as chloride, phenoxide, and phthalimide derivatives. Notably, a 2,4-diol substrate unexpectedly yielded the target product (30), albeit with diminished efficiency. The protocol proved particularly effective for cyclic  $\alpha$ -unfunctionalized secondary alcohols (31–40), successfully incorporating cyclohexyl, cycloheptyl, and 12-membered ring systems. Remarkably, the reaction tolerated multiple ring-substituted motifs (35–40), including 4-oxacyclohexane, *N*-Boc-protected (4-position), and *N*-Cbz-substituted (3-position) derivatives. Of significant interest, silyl-protected alkynes (TMS and TIPS) were incorporated with exceptional efficiency. The methodology extended effectively to  $\alpha$ -unfunctionalized primary alcohols, demonstrating versatility across aromatic systems (41–48) including naph-

thyl, thienyl, and pyridyl groups, as well as acyclic alkyl chains bearing bromo and cyano functionalities, all proceeding in moderate yields. Besides, a 1,5-diol substrate could also afford dialkynylation product (49), albeit with reduced yield. The system exhibited unprecedented capacity for  $\alpha$ -unfunctionalized tertiary alcohols (50–55), achieving successful transformation under standard conditions. The deoxyalkynylation of tertiary adamantanol afforded the corresponding crystalline product (50), as confirmed by X-ray crystallographic analysis (Figure S1).<sup>[55]</sup> Rigid tertiary adamantanol substituted at distinct positions afforded the desired products (51–52) in moderate yields. Furthermore, methyl- and cyclohexyl-substituted tertiary alcohols underwent successful transformation to yield the target product 53. Acyclic alkyl chain tertiary alcohols were also compatible with the standard deoxyalkynylation cross-coupling conditions, furnishing product 54. Notably, the tertiary alcohol derived from 2,3-dihydro-1*H*-indene formed the coupling product 55, albeit with diminished yield. These results collectively demonstrate the broad functional group tolerance of tertiary alcohols within this reaction system.

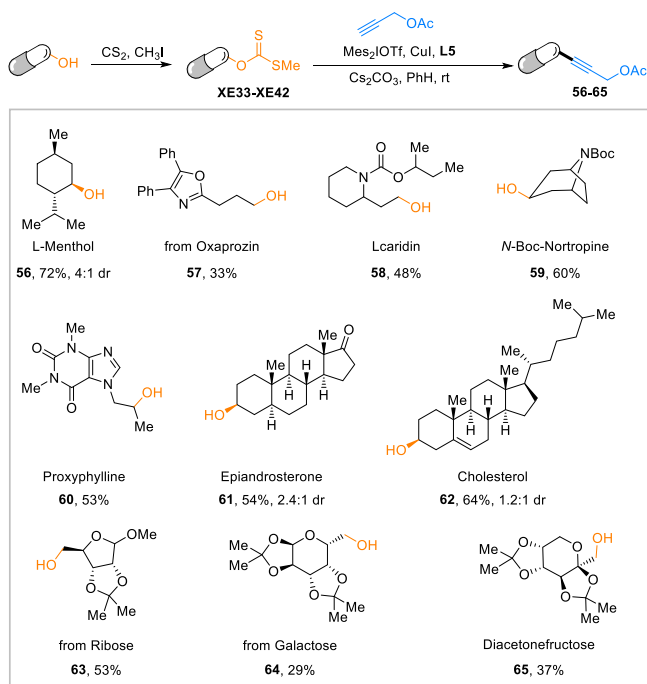
### One-pot Deoxyalkynylation

An ideal deoxyalkynylation reaction would bypass the isolation of xanthate intermediates entirely, allowing alcohols to serve as direct starting materials. To improve the practicality of this transformation, we developed a concise one-pot protocol that converts alcohols directly into alkynylated products. As a demonstration, 4-phenylbutan-2-ol (6.0 mmol) was smoothly converted in situ to the crude XE1, which, without purification, underwent efficient one-pot deoxyalkynylation to furnish product 1 in 70% isolated yield (Scheme 2). Remarkably, this strategy also proved effective for several  $\alpha$ -unfunctionalized tertiary alcohols (52–55) directly from its corresponding crude xanthate, thereby significantly improving synthetic efficiency and step economy (Scheme 3).

### Late-Stage Cross-Coupling of Bioactive Molecules

To establish the synthetic utility of this methodology, we further explored its application in late-stage functionalization of pharmaceuticals and bioactive molecules (Scheme 4). A series of xanthate ester derivatives from relevant precursors of bioactive molecules underwent successful transformation under standard conditions (56–65). The synthetic protocol demonstrated remarkable functional group tolerance, enabling efficient modification of diverse bioactive molecules bearing primary and secondary hydroxyl moieties. The methodology proved particularly effective for pharmacologically relevant compounds, such as menthol (56), a monoterpene alcohol exhibiting dual anti-inflammatory and antimicrobial activities; oxaprozin (57), a non-steroidal anti-inflammatory drug (NSAID) widely prescribed for rheumatoid and osteoarthritis therapy; lcaridin (58), a broad spectrum arthropod repellent; nortriptyline (59), a second-generation tricyclic antidepressant that maintained excellent



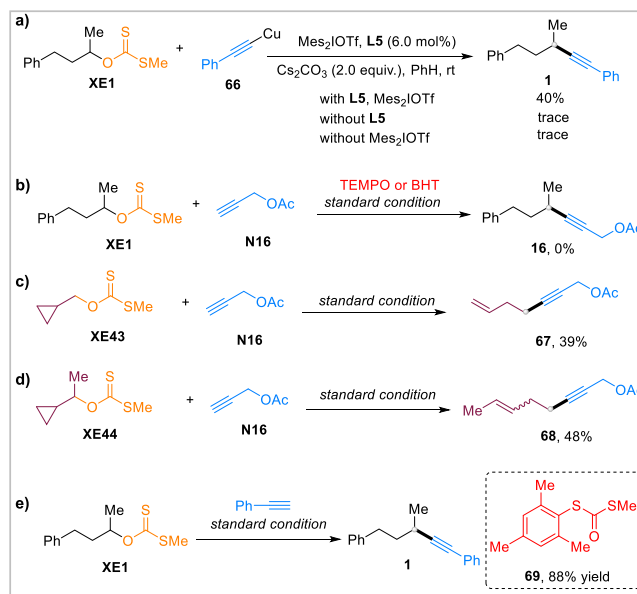


**Scheme 4.** Late-stage cross-coupling of bioactive molecules. Reaction conditions: xanthate ester (1.0 equiv., 0.20 mmol), alkyne (1.2 equiv., 0.24 mmol), Mes<sub>2</sub>IOTf (1.5 equiv., 0.30 mmol), CuI (5.0 mol%), **L5** (6.0 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv., 0.40 mmol) in benzene (2.0 mL) under argon at room temperature for 24–48 h; isolated yield.

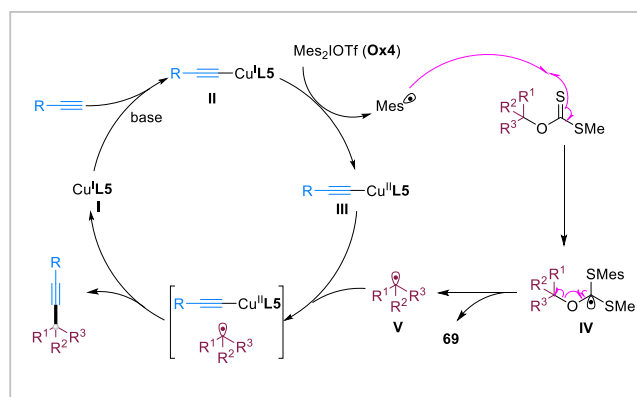
pharmacophore integrity postmodification; and proxiphylline (**60**), a xanthine-based bronchodilator indicated for obstructive pulmonary disorders. Notably, complex steroid frameworks (**61** and **62**) and carbohydrate derivatives (**63**–**65**) were successfully engaged in deoxyalkynylation, albeit with reduced yields. This transformation effectively installs alkynyl handles onto bioactive scaffolds, creating valuable chemical anchors for subsequent modifications or structure–activity relationship studies. The demonstrated capacity to directly functionalize pharmaceutically relevant architectures highlights the potential of this method for drug discovery applications.

### Mechanistic Studies

To elucidate the reaction mechanism of  $\alpha$ -unfunctionalized alcohol deoxyalkynylation, systematic mechanistic investigations were conducted (Scheme 5). Initial control experiments revealed that the reaction between copper phenylacetylide (**66**), xanthate ester **XE1**, and **Ox4** in the presence of ligand **L5** afforded product **1** in 40% yield, whereas no product was obtained when either oxidant **Ox4** or ligand **L5** was omitted (Scheme 5a). These observations strongly suggest that the ligand-stabilized copper acetylide complex serves as the catalytically active species, and both oxidant and specific ligand coordination are essential for reaction initiation and product generation. The proposed radical-mediated pathway



**Scheme 5.** Control experiments.



**Scheme 6.** Proposed mechanism.

trapping studies using TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) and BHT (butylated hydroxytoluene) completely suppressed product formation (Scheme 5b). Radical clock substrates **XE43** and **XE44** underwent characteristic ring-opening transformations under standard conditions, yielding products **67** and **68** with moderate yield, respectively (Scheme 5c and Scheme 5d). Moreover, the *S*-aryl dithiocarbonate side product **69** was isolated in all deoxyalkynylation reactions (Scheme 5e). Its structure was confirmed by NMR and HRMS analyses. The isolation of **69**, along with the absence of deoxyalkynylation products in reactions lacking Mes<sub>2</sub>IOTf, supports the proposal that aryl radicals are key to activating xanthate esters.

Based on these experimental outcomes and earlier observations,<sup>[51–53]</sup> we proposed a plausible mechanistic pathway (Scheme 6). In the presence of base, the Cu<sup>I</sup>, **L5** reacts with the alkyne substrate to generate intermediate **II**. This Cu<sup>I</sup> intermediate then activates **Ox4** to form a Cu<sup>III</sup> complex **III** and an aryl radical species. The aryl radical subsequently adds to the xanthate moiety, forming radical intermediate

IV. Subsequent homolysis of **IV** generates alkyl radical **V** and by-product **69**. Finally, radical **V** couples with Cu<sup>II</sup> complex **III** to form the C(sp<sup>3</sup>)–C(sp) bond in the target product, regenerating the Cu<sup>I</sup>**L5** catalyst **I** for subsequent turnover.

## Conclusion

In summary, we have successfully developed a copper-catalyzed deoxyalkynylation protocol for  $\alpha$ -unfunctionalized alcohols. This methodology demonstrates broad substrate compatibility, accommodating diverse primary, secondary, and tertiary alcohols, as well as various terminal alkynes. Key to the success of the reaction was the identification of an optimal oxidant system to suppress Glaser coupling side reactions. Furthermore, the implementation of a rigid anionic *N,N,N*-ligand proved critical for stabilizing highly reactive alkyl radical intermediates and minimizing undesired pathways, thereby ensuring efficient formation of the target products. Notably, this method provides an alternative approach to the cross-coupling of unactivated alkyl halides, which present substantial challenges in terms of reaction initiation and bond formation under mild thermal conditions, especially tertiary variants. Notably, this strategy enables late-stage functionalization of drug molecules and bioactive compounds, highlighting its potential for practical applications. We anticipate that this strategy will spur the development of more cross-coupling reactions of unactivated alkyl electrophiles with distinct types of nucleophiles, particularly enabling advances in enantioconvergent cross-coupling transformations. Current efforts in our laboratory are focused on systematically exploring the broader applicability of this catalytic system across diverse reaction platforms.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

**Keywords:** Copper catalysis • Deoxyalkynylation • Ligand •  $\alpha$ -Unfunctionalized alcohols

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