

# Hydroalkylation of Alkynes: Functionalization of the Alkenyl Copper Intermediate through Single Electron Transfer Chemistry

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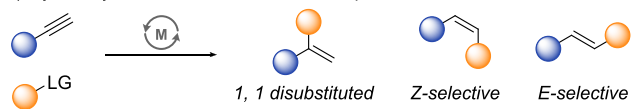
Supporting Information

**ABSTRACT:** We have developed a method for the stereoselective coupling of terminal alkynes and  $\alpha$ -bromo carbonyls to generate functionalized *E*-alkenes. The coupling is accomplished by merging the closed-shell hydrocupration of alkynes with the open-shell single electron transfer (SET) chemistry of the resulting alkenyl copper intermediate. We demonstrate that the reaction is compatible with various functional groups and can be performed in the presence of aryl bromides, alkyl chlorides, alkyl bromides, esters, nitriles, amides, and a wide range of nitrogen-containing heterocyclic compounds. Mechanistic studies provide evidence for SET oxidation of the alkenyl copper intermediate by an  $\alpha$ -bromo ester as the key step that enables the cross coupling.

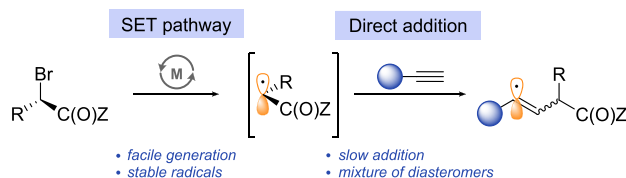
Selective and efficient synthesis of isomerically pure alkenes is challenging and has continuously inspired the development of new synthetic strategies. One recent approach is hydroalkylation of alkynes,<sup>1–9</sup> which involves the direct coupling of unactivated alkyl electrophiles with alkynes. In the last several years, numerous hydroalkylation methods have been developed and now provide access to all three forms of disubstituted alkenes: 1,1-disubstituted alkenes, *Z*- and *E*-alkenes (Scheme 1a). Furthermore, the high selectivity of these

## Scheme 1

### a) Hydroalkylation with unactivated electrophiles



### b) Reactivity paradigm with activated electrophiles



processes often enables the formation of a single regio- and stereoisomer of alkene products. Together, these methods have established hydroalkylation of alkynes as one of the most versatile and efficient strategies for selective alkene synthesis.

Despite these advancements, selective hydroalkylation remains difficult to accomplish with certain functionalized coupling partners. Particularly notable are  $\alpha$ -halo carbonyls. These *activated* electrophiles have high redox potentials and readily generate alkyl radicals in the presence of first-row transition-metals through a single electron transfer (SET) process.<sup>10,11</sup> However, leveraging this feature in selective hydroalkylation has proved to be challenging. So far, efforts have focused on the direct addition of these SET-generated

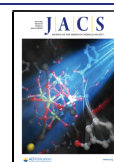
alkyl radicals to the alkyne (Scheme 1b). Unfortunately, the addition step is slow<sup>12,13</sup> and typically generates a mixture of *E* and *Z* isomers.<sup>12,14–16</sup> As a result, the direct radical addition approach has found success only with activated aryl-substituted alkynes providing the alkene products with varying degrees of *Z*-diastereoselectivity.<sup>17,18</sup>

Recent developments in copper hydride chemistry have enabled a new approach to the hydrofunctionalization of alkynes based on the *hydrocupration* of the alkyne and subsequent functionalization of the reactive *E*-alkenyl copper intermediate.<sup>1,3,19–28</sup> We propose to merge the hydrocupration of alkynes with the SET chemistry of  $\alpha$ -halo carbonyls in order to achieve a selective hydroalkylation reaction (Scheme 2). The highly regio- and diastereoselective hydrocupration step would ensure selective formation of the anti-Markovnikov addition product with excellent *E* selectivity. Subsequent halogen atom transfer via inner-sphere SET (ISET)<sup>10</sup> would provide a facile alternative to the high barrier two-electron oxidative addition pathway<sup>29,30</sup> and would lead to the alkylation of the alkenyl copper intermediate. Overall, the proposed combination of closed-shell copper-hydride addition to alkynes with open-shell SET chemistry provides a new strategy for hydroalkylation of alkynes.<sup>31</sup>

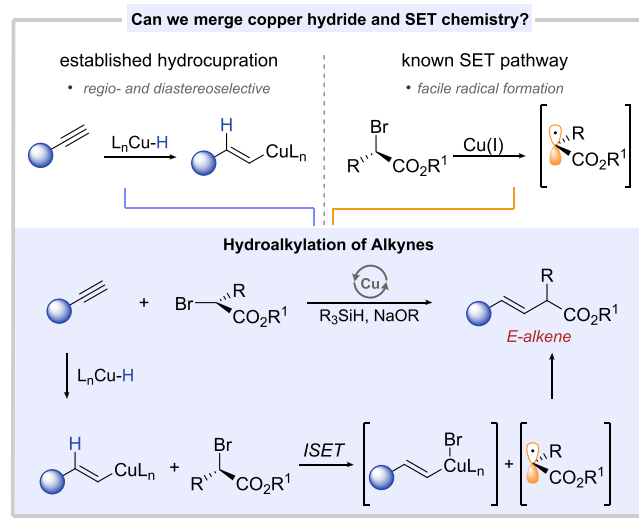
We envision the mechanism of hydroalkylation reaction as shown in Scheme 3. The alkenyl copper intermediate is formed according to the well-established mechanism (I–III).<sup>32</sup> In a key step, the ISET involving alkenyl copper intermediate and an alkyl bromide (VI) would generate an alkenyl copper(II) species and a carbon-centered radical (VII).<sup>33</sup> Finally, the reaction of the alkenyl copper(II) intermediate with the free

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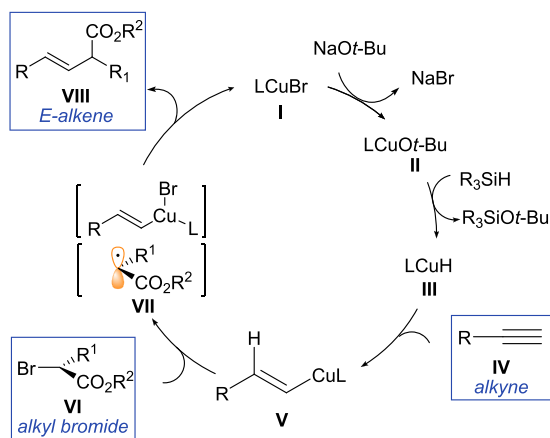
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## Scheme 2. Overcoming the SET/Direct Addition Paradigm



## Scheme 3



radical delivers the product (VIII),<sup>34–36</sup> possibly through radical capture followed by reductive elimination.

From the outset, we recognized that a generally facile SET oxidation of copper(I) complexes by  $\alpha$ -halo carbonyls could prevent the desired two-electron hydrocupration pathway. In effect, we had to suppress SET oxidation of all copper(I) complexes involved in forming the alkenyl copper intermediate (intermediates I–III).

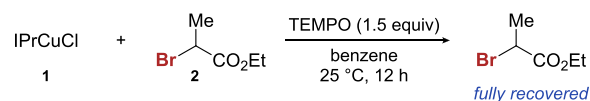
We reasoned that a catalyst supported by an NHC ligand would allow us to achieve this goal by modulating the oxidation potential of these copper(I) intermediates. NHC ligands, such as IPr, favor the formation of linear two coordinate copper(I) complexes that are unusually resistant to oxidation.<sup>37–41</sup> Hence, we expected that despite the  $\sigma$ -donating ability of NHC ligands, they would yield catalytic copper(I) intermediates with high reduction potentials ( $E_{1/2}^{\text{red}}[\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}]$ ) and therefore relatively low rates in reaction with  $\alpha$ -halo carbonyls. This correlation between the redox potentials of copper(I) complexes and rates of their reactions with  $\alpha$ -halo carbonyls through ISET has been established in mechanistic studies of atom transfer radical polymerization (ATRP).<sup>33,42,43</sup> We were also aware that the IPr ligand promotes the rapid formation of the alkenyl copper intermediate through hydrocupration. Overall, we hoped that these features of IPr ligand will allow us to merge the two-

electron hydrocupration pathway with the SET-based alkylation of the alkenyl copper intermediate.

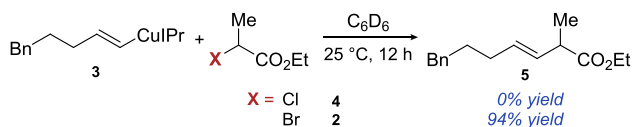
We began our study by measuring the redox potential of IPrCuCl, a common catalyst in the hydrofunctionalization of alkynes. The anticipated effect of the IPr ligand was evident in the measured anodic peak potential ( $E_{\text{pa}} = 1.68$  V vs SCE in MeCN; 1.58 V vs SCE in DCM),<sup>44</sup> which is high relative to the redox potentials for various copper(I) catalysts ( $E_{1/2}^{\text{red}} = 0.1$  V to  $-0.3$  V vs SCE in MeCN depending on the ligand) readily oxidized by  $\alpha$ -halo carbonyls and used to promote ATRP<sup>33</sup> or related ATR alkylation reactions.<sup>45</sup>

As expected, IPrCuCl did not readily react with  $\alpha$ -halo carbonyls. The exposure of secondary  $\alpha$ -bromo ester 2 ( $E_{1/2}^{\text{red}} = -0.43$  V vs SCE in DMF)<sup>10</sup> to IPrCuCl and TEMPO at 25 °C, resulted in full recovery of the  $\alpha$ -bromo ester, indicating that SET did not occur (Scheme 4a). On the other hand, alkenyl

## Scheme 4

a) Reaction of IPrCuCl with  $\alpha$ -bromo ester

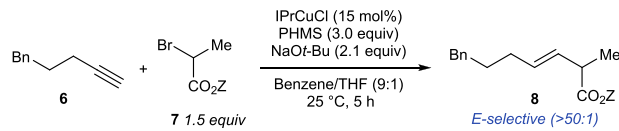
## b) Alkylation of NHC-supported alkenyl copper complex



copper complex 3 was significantly more easily oxidized ( $E_{\text{pa}} = 0.90$  V vs SCE in DCM) and, under similar reaction conditions, readily afforded cross-coupling product 5 (Scheme 4b). Less reactive electrophiles, such as  $\alpha$ -chloro ester 4, did not provide the desired coupling product.

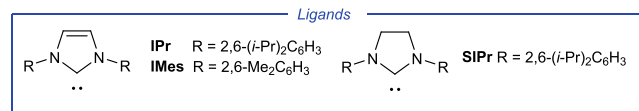
Encouraged by the results of our preliminary experiments and using them as a starting point, we developed the catalytic hydroalkylation of terminal alkynes with secondary  $\alpha$ -bromo esters shown in Table 1. The best results were obtained using IPrCuCl as the catalyst, polymethylhydrosiloxane (PMHS) as the hydride source, and NaOt-Bu as the turnover reagent. The reaction is performed in a benzene/THF solvent combination and is complete in 5 h at room temperature. During our efforts to identify the best conditions, we made several observations summarized in Table 1. In accordance with the results of the stoichiometric experiments shown in Scheme 4b, an  $\alpha$ -chloro ester failed to provide any desired product in the catalytic reaction, while the corresponding  $\alpha$ -iodo ester gave only 11% yield of the desired product. Copper complexes supported by IPr and SIPr ligand were the best catalysts. Even the closely related IMesCuCl catalyst provided less than 5% yield of the desired product. A catalyst prepared in situ from Cu(OAc)<sub>2</sub> and (*R*)-DTBM-Segphos gave similarly low yield of the product.<sup>24</sup> The choice of silane proved crucial to the success of the reaction. PMHS and structurally related tetrameric silicone hydride performed well. More reactive triethoxysilane or less reactive diphenylmethyl silane were ineffective. Sodium alkoxides were particularly successful in this transformation. Changing the alkoxide counterion from sodium to lithium or potassium led to significantly lower yields. While both sodium *tert*-butoxide and sodium *tert*-siloxy were effective turnover reagents, sodium isopropoxide was inferior and sodium methoxide failed to turn over the catalyst, presumably due to

Table 1. Reaction Development



entry	change from standard conditions	yield <sup>a</sup> (%)
1	none	81
2	chloro ester <i>instead of</i> bromo ester	0
3	iodo ester <i>instead of</i> bromo ester	11
4	SIPrCuCl <i>instead of</i> IPrCuCl	72
5	IMesCuCl <i>instead of</i> IPrCuCl	1
6	( <i>R</i> )-DTBM-Segphos/Cu(OAc) <sub>2</sub> <i>instead of</i> IPrCuCl	<5
7	Ph <sub>2</sub> MeSiH <i>instead of</i> PMHS	3
8	Me(OEt) <sub>2</sub> SiH <i>instead of</i> PMHS	0
9	(MeOSiH) <sub>4</sub> <i>instead of</i> PMHS	46
10	LiOt-Bu <i>instead of</i> NaOt-Bu	37
11	NaOi-Pr <i>instead of</i> NaOt-Bu	22
12	NaOSiMe <sub>3</sub> <i>instead of</i> NaOt-Bu	74
13	KOt-Bu <i>instead of</i> NaOt-Bu	0
14	benzene <i>instead of</i> benzene/THF (9:1)	58
15	benzene/THF (1:1) <i>instead of</i> benzene/THF (9:1)	66
16	toluene <i>instead of</i> benzene/THF (9:1)	52
17	THF <i>instead of</i> benzene/THF (9:1)	27
18	ethyl ester <i>instead of</i> pinacolyl ester	61

<sup>a</sup>Determined by GC using standard. Z stands for pinacolyl.



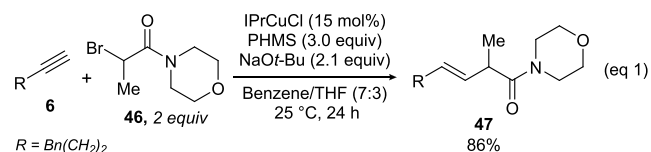
lower solubility. The highest yields of the desired product were obtained using a 9:1 benzene/THF solvent mix. Other ratios of these solvents and other aryl/etherial solvent mixtures resulted in depressed yields (see the Supporting Information, Table S6) Benzene or toluene alone provided less of the desired product and a significant amount of the reduced alkyne.

Using the standard conditions from Table 1, we found that a wide range of *E*-alkenes could be synthesized (Table 2) with *E*-selectivity greater than 50:1 (see the Supporting Information). We also found that the reaction is compatible with many functional groups and can be accomplished in the presence of esters (11), epoxides (10), nitriles (17), alkyl chlorides (13), aryl bromides (24) and fluorides (9), acetals (20), and amides (22). Sterically demanding alkynes such as 15 and 25 also performed well under the reaction conditions. The reaction also tolerates several nitrogen-containing heteroarenes, such as halo pyridines (12, 26), indoles (21), quinoxalines (16), phenoxazines (19), and phenothiazines (14).

We also explored the reaction with different secondary  $\alpha$ -bromo esters. In general, esters of sterically bulky alcohols afforded the desired product in good yield, presumably because of the increased stability of these esters under catalytic conditions. The presence of heteroatomic substituents, such as bromide (37) or thioether (38), at the  $\gamma$  position of the ester

was well tolerated. Sterically demanding secondary bromides (36) also gave the product in good yield.

Our initial attempts to couple secondary  $\alpha$ -bromo amides were unsuccessful. Under the reaction conditions used for coupling  $\alpha$ -bromo esters, product 47 was formed in only 47% yield. The primary side reactions were the reductions of both the  $\alpha$ -bromo amide and the alkyne. Eventually, we found that by subtly changing the reaction conditions, we could obtain product 47 in 86% yield.



To achieve these results, we lowered the solvent ratio of benzene/THF from 9:1 to 7:3, adjusted the stoichiometry of the reactants, and increased the reaction time to 24 h.

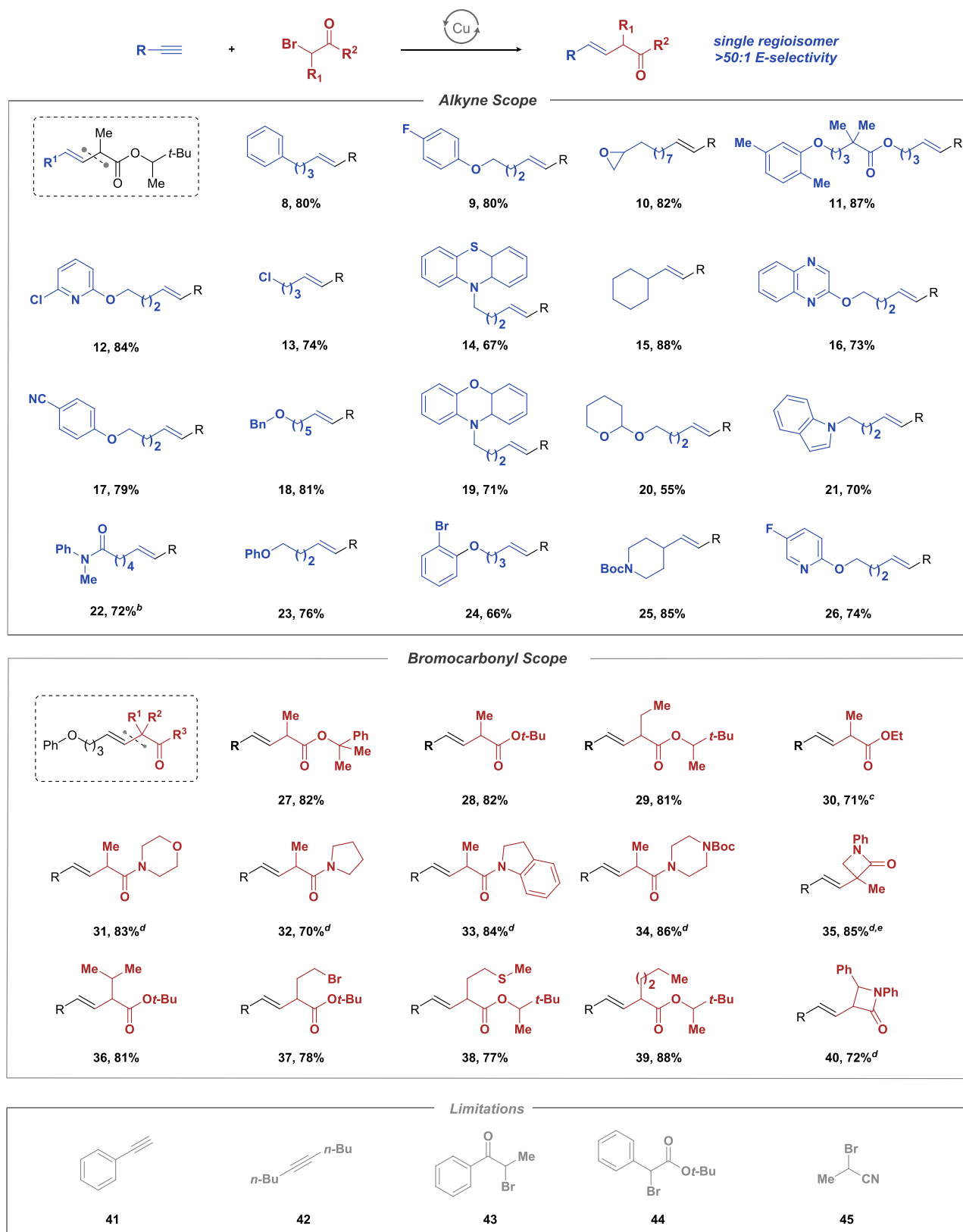
These modified conditions could be applied to the coupling of a variety of secondary  $\alpha$ -bromo amides. These included amide derivatives of numerous biologically important amines, such as piperazine (34), pyrrolidine (32), indolone (33), and morpholine (31). This adaptation could also be used to couple cyclic tertiary  $\alpha$ -bromo amides. Tertiary  $\alpha$ -bromo- $\beta$ -lactams (35) as well as secondary  $\alpha$ -bromo- $\beta$ -lactams (40) were found to provide the desired products in useful yields. Acyclic tertiary amides or esters failed to provide any product.

We also noted a few limitations of the present hydroalkylation reaction. Aryl acetylenes (41) and disubstituted internal alkynes (42) did not participate in the hydroalkylation reaction. Similarly,  $\alpha$ -bromo ketones (43),  $\alpha$ -bromo nitriles (45), aryl substituted  $\alpha$ -bromo esters (44), and primary  $\alpha$ -halo carbonyls were not viable substrates. Finally, protic functional groups, such as hydroxyl groups and unprotected amines, and reducible functional groups, like aldehydes and ketones, were not tolerated.

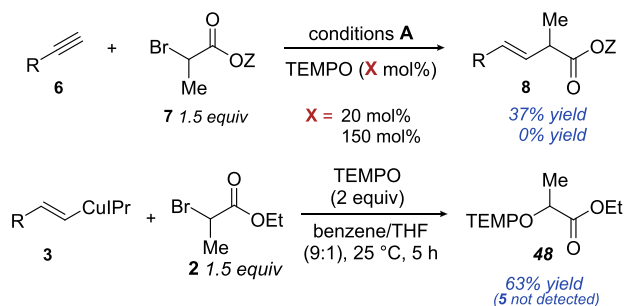
The key feature of the mechanism proposed in Scheme 3 is the cross coupling of the alkenyl copper intermediate with the  $\alpha$ -bromo carbonyl. Although stoichiometric experiments shown in Scheme 4b established the feasibility of this elementary step, the exact mechanism of this process was unclear. While we initially postulated a pathway initiated by SET, a two-electron oxidative addition/reductive elimination sequence is also plausible.

Support for a SET pathway came from radical trap experiments (Scheme 5). Our previous work has shown that the electrophilic functionalization of the alkenyl copper intermediate is not affected by the addition of TEMPO.<sup>20</sup> On the other hand, the SET pathway is expected to show sensitivity to TEMPO.<sup>43,46,47</sup> We observed that as little as 20 mol % of TEMPO impacts the catalytic reaction and 1.5 equiv of TEMPO completely prevents the formation of the alkene product (Scheme 5). Stoichiometric experiment with alkenyl copper revealed that TEMPO inhibits the cross-coupling step of the reaction, producing TEMPO adduct 48 as the major product of the reaction (63% yield).

The results of these experiments allow us to exclude the alkylation mechanism involving two electron processes. Distinguishing between different SET mechanisms is much harder. Extensive mechanistic investigations of similar processes involved in ATRP suggest ISET as the most likely SET mechanism for the reaction of alkenyl copper with an  $\alpha$ -

Table 2. Substrate Scope<sup>a</sup>

<sup>a</sup>Yields of isolated products are reported. Reactions performed on the 0.5 mmol scale. Condition A: IPrCuCl (15 mol %), NaOt-Bu (2.1 equiv), bromoester (1.5 equiv), PMHS (3 equiv), benzene/THF (9:1) 5 mL, 5–24 h. <sup>b</sup>NaOTMS was used as based instead of NaOt-Bu. <sup>c</sup>2 equiv of bromoester were used. <sup>d</sup>Condition B: IPrCuCl (15 mol %), NaOt-Bu (2.1 equiv), bromoamide (2.0 equiv), PMHS (3 equiv), benzene/THF (7:3) 5 mL, 24 h. <sup>e</sup>R = PhCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, 1:1 benzene/THF was used as a solvent.

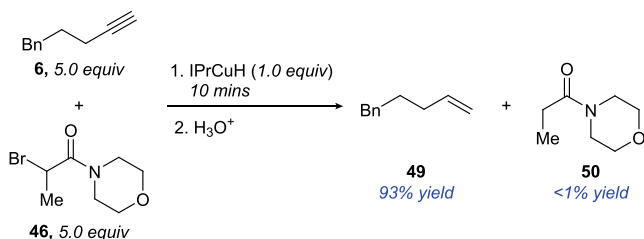
Scheme 5. Radical Trap Probe<sup>a</sup>

<sup>a</sup>Z = pinacolyl, R = Ph(CH<sub>2</sub>)<sub>3</sub>. Condition A: IPrCuCl (15 mol %), NaOt-Bu (2.1 equiv), bromoester (1.5 equiv), PMHS (3 equiv), benzene/THF (9:1), 5–24 h.

bromo carbonyl.<sup>10,33,48</sup> Furthermore, the relatively high redox potential of alkenyl copper intermediate makes the mechanisms involving outer-sphere SET processes unlikely, although we cannot completely exclude them.

We finished our preliminary investigation of the reaction mechanism by measuring redox potentials of other copper complexes involved in the proposed catalytic cycle. We found that IPrCuBr ( $E_{p,a} = 1.51$  V vs SCE in DCM) and IPrCuOt-Bu ( $E_{p,a} = 1.13$  V vs SCE in DCM) are both less reducing than the alkenyl copper intermediate 3. IPrCuH ( $E_{p,a} = -0.39$  V vs SCE in THF), on the other hand, is significantly more reducing than alkenyl copper intermediate 3, suggesting a potential for rapid SET with  $\alpha$ -bromo carbonyls. Despite the highly reducing nature of IPrCuH, in a competition experiment, IPrCuH reacts significantly faster with a terminal alkyne than with  $\alpha$ -bromo amide 46 (Scheme 6). Alkene 49, the nearly

## Scheme 6



exclusive product of the competition experiment, is obtained through hydrocupration and protonation of the alkenyl copper intermediate (3) upon aqueous workup. Furthermore, a stoichiometric reaction of IPrCuH with  $\alpha$ -bromo amide 46 is slow and not inhibited by TEMPO, suggesting that the mechanism of the reaction does not involve SET or radical intermediates (see the Supporting Information, Table S13). These results indicate surprising resistance of IPrCuH toward SET, despite its highly reducing nature.

In conclusion, we have developed a hydroalkylation of alkynes using  $\alpha$ -bromo carbonyls as alkylating reagents. The hydroalkylation reaction affords the *E*-alkene product with high selectivity and is compatible with several classes of alkynes and  $\alpha$ -bromo carbonyls. Furthermore, the reaction can be accomplished in the presence of acetals, epoxides, aryl halides, and heteroaromatics. Mechanistic experiments reveal that the direct alkylation of the alkenyl copper intermediate obtained by hydrocupration of an alkyne is accomplished through a SET pathway.

## ■ ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c03396>.

Experimental procedure and product characterization (PDF)

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## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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