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Letter

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Decarboxylative Hydroalkylation of Alkynes *via* Dual Copper-Photoredox Catalysis

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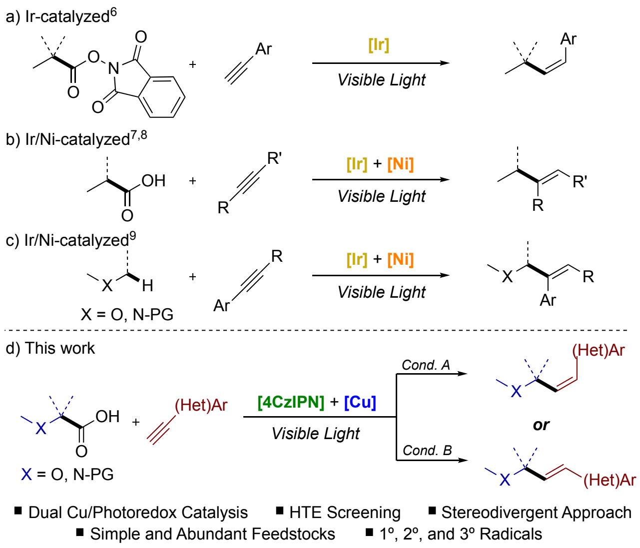
KEYWORDS: High-Throughput Experimentation • Photoredox catalysis • Hydroalkylation • Stereodivergent • Copper catalysis.

ABSTRACT: A photoredox strategy for the synthesis of a wide range of allylic amines and ethers from carboxylic acids and alkynes has been developed. This approach relies on the perturbation of the ground-state electronical properties of terminal alkynes through the formation and photoexcitation of copper acetylide intermediates. This process takes place through cooperative copper and organic photoredox catalysis and can be carried out in stereodivergent manner. Thus, a systematic multivariate HTE screening spotlighted that a switch in the stereochemical outcome can be provoked by choosing an appropriate combination of ligand and base. The developed methodology has been applied to the stereoselective coupling of primary, secondary and tertiary alkyl radicals with (hetero)aromatic terminal alkynes. As an additional practicality, similar reaction conditions allowed for the use of aromatic amines as radical precursors in a cross dehydrogenative coupling for the direct vinylation of inactivated C–H bonds.

Over the last decade, the resurgence of visible-light photoredox catalysis has disclosed unprecedented opportunities in the generation of radical intermediates by selective activation of small organic molecules under mild reaction conditions. These open-shell intermediates are often formed by a photocatalyst mediated single-electron or by energy transfer and engaged in peculiar reaction pathways which are complementary to thermal two-electron processes.[1]

In this context, the radical additions to simple alkenes, styrenes, and α,β-unsaturated carbonyl compounds have been widely explored.[2] In contrast and despite its attractiveness, the reaction of radicals with alkynes has been less exploited.[3] In fact, alkynes are ubiquitous structural motifs and the ability of a photocatalyst to perform selective energy transfer to them may lay the foundations for unprecedented stereoselective processes.[4] From a mechanistic perspective, the reasons for the limited development of radical addition to alkynes can be probably assigned to the slow rate of C–C bond formation, this being in turn related to the larger singlet-triplet gap of triple bonds with respect to the corresponding double bonds.[5] Nevertheless, Tang and co-workers have proposed an Ir-catalyzed *Z*-selective synthesis of alkenes employing NHPI esters as radical sources, terminal arylalkynes and a superstoichiometric amount of DIPEA under visible light irradiation (Scheme 1a).[6] MacMillan,[7] Rueping[8] and Wu[9] circumvented the aforementioned lack of reactivity adopting multicatalytic approaches. Thus, MacMillan and Rueping independently developed an Ir/Ni photocatalytic decarboxylative hydroalkylation of alkynes that takes advantage of a migratory insertion step to afford terminal and internal alkenes (Scheme 1b), while Wu proposed a Ni–H catalyzed hydroalkylation of phenylacetylenes and enynes with photocatalytically generated α-heteroatom radicals (Scheme 1c).

Scheme 1. Photoredox-catalyzed hydroalkylation of alkynes.[6-9]



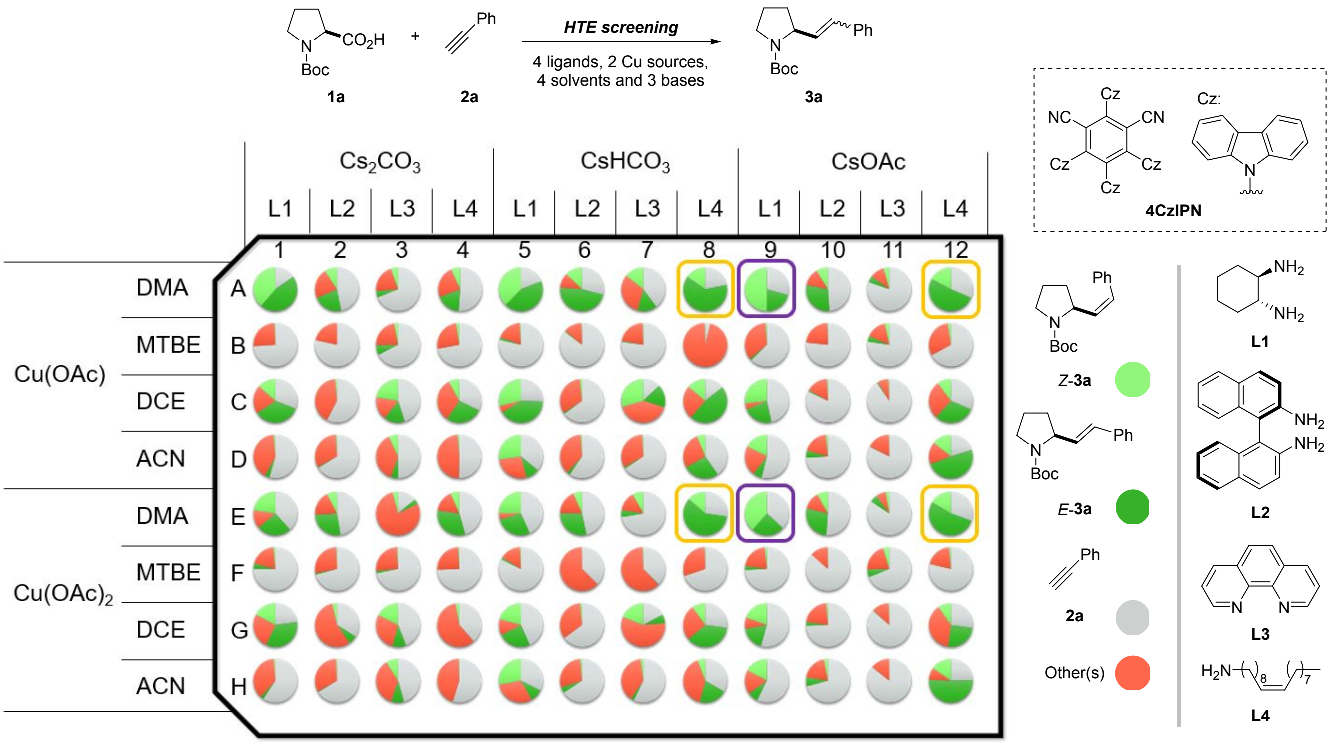


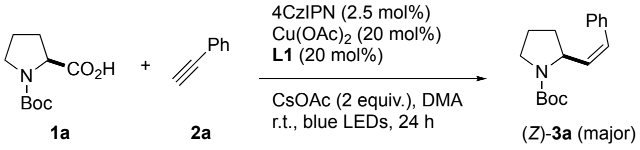
Figure 1. Multivariate-HTE screening of solvents, bases, ligands and copper sources for the hydroalkylation of **2a** under standard conditions [**1a** (15 µmol), **2a** (10 µmol), Base (20 µmol), Copper Source (2 µmol), Ligand (4 µmol if monodentate, 2 µmol if bidentate), 4CzIPN (0.25 µmol), solvent (0.1 mL), blue LEDs irradiation, room temperature, 18 hours]. Yields (%) and (*Z:E*) ratios [GC-FID analysis on the reaction crude using 1,1'-biphenyl as internal standard] for selected entries: **A8**: 79% (20:80), **A9**: 71% (71:29), **A12**: 69% (25:75), **E8**: 73% (19:81), **E9**: 71% (63:39), **E12**: 71% (23:77).

Here we report a dual copper and photoredox catalyzed decarboxylative hydroalkylation of alkynes leading to *Z*- or *E*-enriched alkenes in a diastereodivergent manner from simple carboxylic acids as radical sources[10] and an organic photocatalyst (Scheme 1d).

Our approach to address this synthetic challenge is based on the perturbation of the ground-state electronic properties of terminal alkynes through the formation and photoexcitation of the corresponding copper acetylides. The irradiation of copper acetylides with visible light results in a ligand-to-metal charge transfer (LMCT) increasing the electrophilicity on the alkyne moiety.[11] Hwang and coworkers, instead, exploited the ability of such copper complexes to act as excited-state single-electron reductants, and then be engaged in cross-coupling reactions and functional group transformations.[12]

Considering all the variables involved in the designed process, we considered a multivariate high-throughput experimentation (HTE) approach to screen the ligand, base, copper source and solvent in a rapid and cost-effective manner (Figure 1). We chose *N*-Boc Proline (**1a**) and phenylacetylene (**2a**) as model substrates, and 4CzIPN[13] as a photocatalyst. It emerged that the best results in terms of yield and *Z*:*E* ratio were achieved employing either CuOAc or $Cu(OAc)_2$, (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane (**L1**) as ligand[14] and CsOAc as base under blue LEDs irradiation for 18 hours (wells A9 and E9, Figure 1). Translation of the optimal conditions to synthetically relevant scale allowed us to isolate the desired product (**3a**) in 82% yield with a *Z*:*E* ratio of 78:22. Moreover, the HTE screening also revealed that the reaction can be performed in a diastereodivergent manner just by switching the ligand and the base to oleylamine (**L4**) and $CsHCO_3$ (wells A8 and E8, Figure 1), the *E* isomer being preferentially obtained under these conditions with minimal erosion of the yield (entry 2, Table 1).

Table 1. Control experiments for the hydroalkylation of **2a**.[a]



Entry	Deviation from standard[a]	Yield (%)[b]	*Z*:*E*[c]
1	None	82	78:22
2	**L4** (40 mol%) instead of **L1**. $CsHCO_3$ instead of CsOAc[d]	72	23:77
3	No $Cu(OAc)_2$	19	78:22
4	CuCl instead of $Cu(OAc)_2$	78	77:23
5	No **L1**	58	69:31
6	No photocatalyst	0	n.d.
7	Dark	0	n.d.
8	3 mmol scale	76	67:33

[a] Standard conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), CsOAc (0.4 mmol), DMA (2.0 mL), blue LEDs (4.5 W, Irradiation Setup 1). [b] Isolated yield. [c] Determined by GC-FID analysis on the reaction crude. [d] 36 hours, Irradiation Setup 2 (see SI for further details).

The choice of the ligand turned out to be key for the stereoselectivity switch, since the combination of **L4** and CsOAc also provided **3a** as an *E*-enriched product (wells A12 and E12, Figure 1). Control experiments showed that copper, photocatalyst and light are fundamental for the reaction efficiency (entries 3, 4, 6 and 7, Table 1) and the nature of the ligand is important for the selectivity of the transformation (entries 2 and 5, Table 1). Interestingly, work at 3 mmol scale (entry 8) is well tolerated.

The scope of this transformation was next investigated under the optimal reaction conditions (Figure 2). Sources of primary, secondary, tertiary α-amino radicals as well as secondary α-oxy radicals were tested in the *Z*-selective coupling. In all cases the desired products were isolated in synthetically useful yields ranging from moderate to good. It is worth mentioning that the standard purification procedure by flash chromatography affords in some instances completely separated *Z*:*E* stereoisomers. These results have been highlighted in green in Figure 2. For comparison purposes, the combined yield is also given in these cases. As a general trend, a clear selectivity towards the *Z* isomer is recorded except for the reactions in which a quaternary carbon is formed: in these circumstances (with the notable exception of **3j**) the selectivity is reversed in favor of the *E* isomer likely because of steric factors. In the two cases where stereocenters with defined configuration were already present in the carboxylic acids, the corresponding products (**3n** and **3o**) were isolated with very high diastereoselectivity (**3n** >20:1; **3o** >12:1). In the exploration of the scope of the alkyne partner we first examined terminal phenylacetylenes bearing electron withdrawing and electron donating groups in *ortho* or *para* position. In the case of electron-rich aromatic rings, a reverse stoichiometry of both coupling partners was needed in order to achieve good yields. Besides this, all products were obtained in good yields regardless of the nature and position of the substituents (Figure 2). Also, more challenging heteroaromatic alkynes could be employed in the reaction (**4j-l**) as well as an enyne (**4m**), albeit the reaction took place in this case with moderate yield and *E*-selectivity. Other non-conjugated alkynes (1-hexyne and *tert*-butyldimethylsilylacetylene) turned out to be unsuitable substrates for this transformation and failed to afford the corresponding decarboxylative hydroalkylation products. We then tested on selected substrates (**3a**, **3c**, **4b** and **4i**) the applicability of the stereo-complementary approach. Notably, all of them were obtained in good yields and *E*-selectivities.

Then, we tested the developed methodology in the direct vinylation of inactivated C–H bonds. Upon single-electron oxidation and deprotonation, aromatic amines generate the corresponding α-amino radicals[15] that could be trapped by the excited copper acetylide complex thus forging a new C–C bond. However, when we tested the feasibility of the transformation using the optimized conditions to the cross dehydrogenative coupling between **1r** and **2a**, we were unable to achieve satisfactory results. Fortunately, a second HTE screening of photocatalysts and bases (See SI for further details) revealed that switching from 4CzIPN to $[Ir(ppy)_2(4,4'\text{-dtbbpy})]PF_6$, the formation of **3r** could be achieved in good yield (75%) and high *Z*-selectivity (82:18) (Scheme 2).

From a synthetic perspective, it is important to note that simple stereoconvergent transformations of **3-4**, such as the selective hydrogenation of the double bond would result in products formally arising from a very general decarboxylative hydroxyalkylation of alkenes, a process being actively developed these days.[16]

Next, we performed a series of experiments aimed at shedding light on key mechanistic aspects of this transformation. First, we questioned whether Cu(I) phenylacetylide (**2a'**) is an active intermediate in the reaction. To examine this hypothesis, we conducted the reaction under the standard conditions replacing $Cu(OAc)_2$ with 0.2 equiv. of **2a'** and reducing the amount of phenylacetylene to 0.8 equiv. (Scheme 3a).

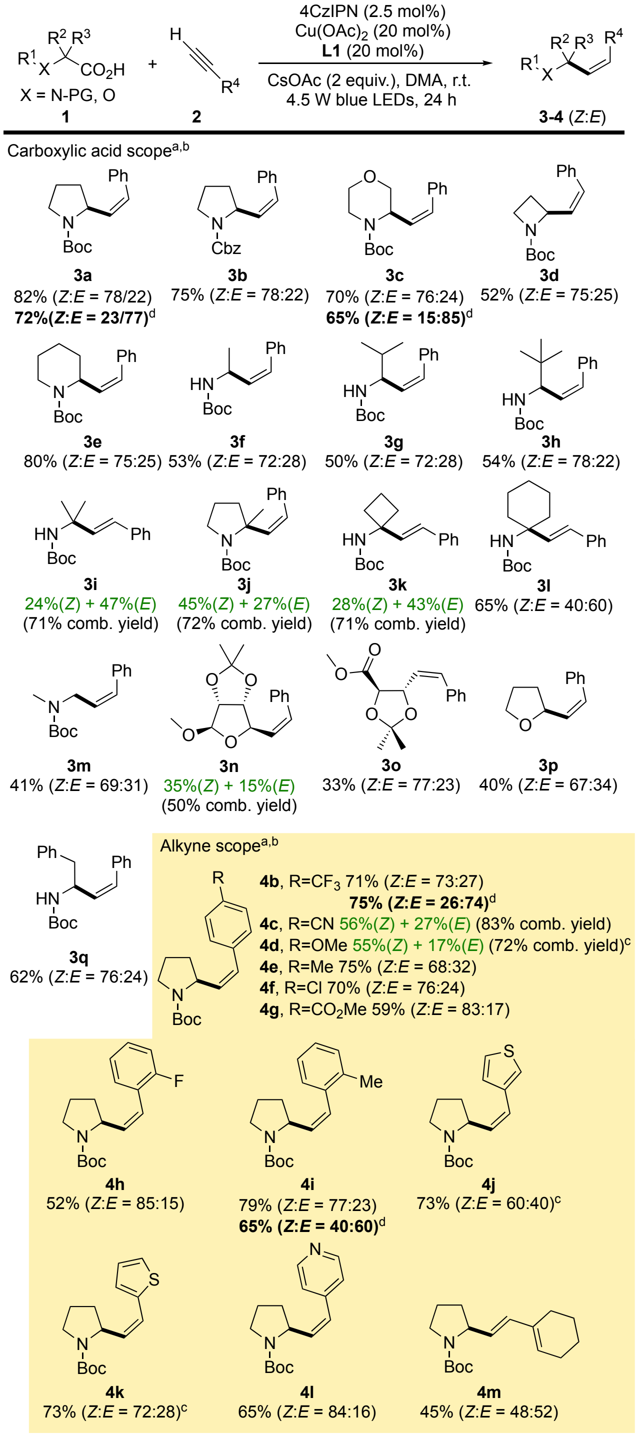
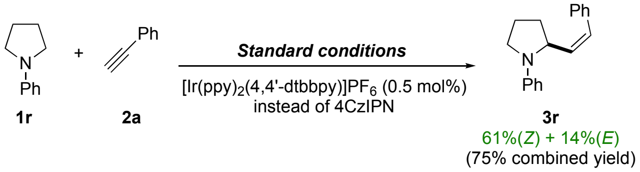


Figure 2. Carboxylic acid and alkyne scope in the Copper/Photoredox catalyzed hydroalkylation of alkynes. All yields shown refer to isolated products. [a]Reactions performed with carboxylic acid (0.3 mmol), alkyne (0.2 mmol), CsOAc (0.4 mmol), DMA (2.0 mL), blue LEDs (4.5 W). [b]*Z*:*E* ratios determined by GC-FID on the reaction crude. Compounds isolated as pure stereoisomers contained <1% of the alternative geometrical isomer. [c]Reactions performed with carboxylic acid (0.2 mmol), alkyne (0.7

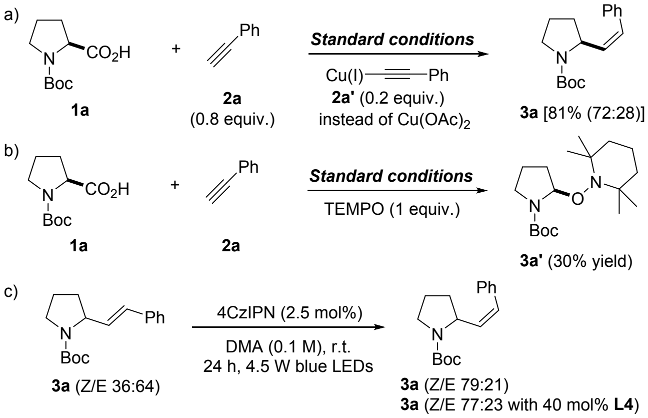
mmol). ^{d}Results in boldface refer to reaction conditions favoring *E* selectivity: **L4** (40 mol%) instead of **L1**, $CsHCO_3$ instead of CsOAc.

Scheme 2. Cross dehydrogenative coupling between **1q** and **2a** allowing the vinylation of inactivated C-H bonds.



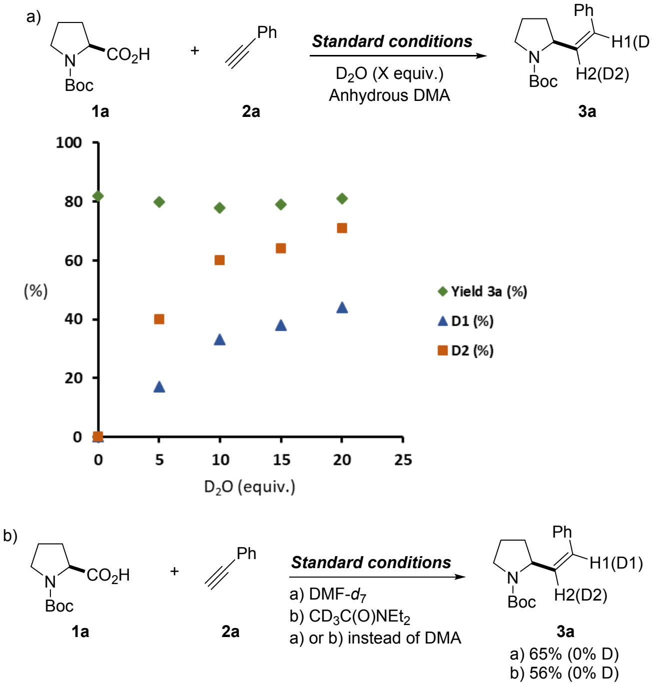
The corresponding product **3a** was obtained in similar yield and *Z*-selectivity, supporting the intermediacy of Cu(I)-phenylacetylide. On the other hand, the addition of TEMPO (1 equiv.) completely quenches the reaction (Scheme 3b) and yields **3a'** indicating the involvement of α-amino/oxy radical intermediates in the transformation. Then, an *E*-enriched mixture of **3a** (0.1 M in DMA) was irradiated for 24 hours in the presence of 4CzIPN (2.5 mol%) being isomerized to the same *Z*:*E* value of the model reaction. This experiment suggests that the *E*/*Z* selectivity of the reaction arises from an energy transfer process mediated by the photocatalyst (Scheme 3c). The same result was obtained adding **L4** (40 mol%) to the mixture, excluding that the *E* selectivity arises from quenching of the triplet state of 4CzIPN exerted by the double bond present in the ligand.

Scheme 3. Mechanistic experiments.

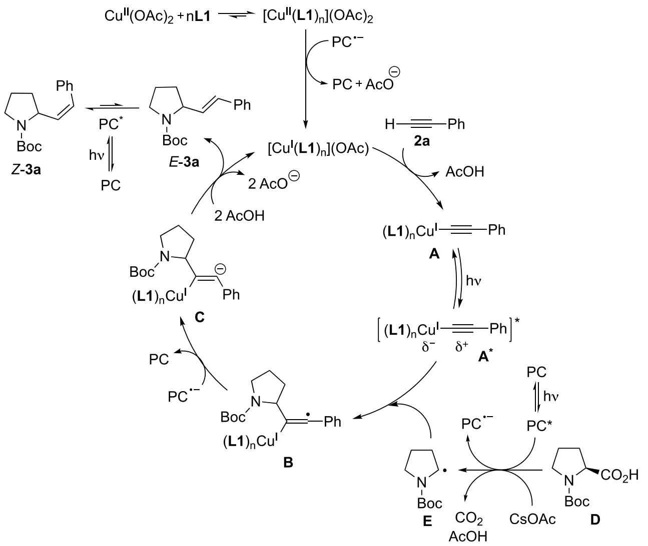


Finally, we investigated the source of vinylic hydrogens in the final product and consequently the process involved in their incorporation. To do so, we designed experiments choosing deuterated compounds able to exchange deuterium *via* a polar or a radical process (deuterium atom abstraction). We selected deuterium oxide as deuterons exchanger and performed the model reaction adding increasing amounts of D_2O. These experiments show that there is a correlation between the amount of D_2O and the incorporation of deuterium in both positions of the double bond (Scheme 4, a). On the other hand, experiments using other deuterated solvents such as DMF-d_7 and *N*,*N*-diethylacetamide-d_3 (chosen as deuterium atoms donors) furnished the desired product with no significant deuterium incorporation (Scheme 4, b).

Scheme 4. Deuterium labelling experiments.



Scheme 5. Proposed reaction mechanism.



Taking all these results into account, the tentative mechanistic proposal shown in Scheme 5 was formulated. Upon irradiation, the photocatalyst 4CzIPN can reach its excited state **PC*** ($E_{1/2}$ $\mathbf{PC^{\cdot+}/PC^{*}}$ = -1.04 V vs SCE and $E_{1/2}$ $\mathbf{PC^{*}/PC^{\cdot-}}$ = +1.35 V vs SCE)[11] and it is able to reduce the Cu(II) complexes present in solution (e.g., $E_{1/2}$ Cu(II)/Cu(I) = -0.363 V vs SCE for $[Cu(\mathbf{L1})_2](ClO_4)_2$)[15,17,18] as well as to oxidize α-amino and α-oxy carboxylates (e.g., Boc-Pro-OCs, $E_{1/2}^{ox}$ = +0.95 V vs SCE).[19] Stern-Volmer studies indicates that the reductive quenching of the catalyst exerted by the Boc-Pro-OCs is faster ($K_{SV} = 2.9 \cdot 10^{-2}$ M^{-1}) than the one exerted by $[Cu(\mathbf{L1})_2](OAc)_2$ ($K_{SV} = 1.4 \cdot 10^{-2}$ M^{-1}).[20] The Cu(I) complex generated either by disproportionation of the Cu(II) source or SET by **PC*** (or $\mathbf{PC^{\cdot-}}$ [$\mathbf{PC/PC^{\cdot-}}$ = -1.21 V vs SCE]) can form complex **A** (the structure of **A** might be either a monomeric or a polymeric form or both) with the assistance of a base (CsOAc).[21] Direct photoexcitation of **A** (λ_{abs} = 476 nm for Cu(I) phenylacetylide)[12f] to **A*** could determine a depletion of charge on the alkyne moiety through ligand-to-metal charge transfer (LMCT), accelerating the attack of the radical **E** (formed upon deprotonation and single electron oxidation of **D** either by **PC*** or $\mathbf{PC}^{\cdot+}$ [$\mathbf{PC}^{\cdot+}$/**PC** = +1.52 V vs SCE]). This addition results in the formation of the vinyl radical **B** which forms the corresponding vinyl anion **C** oxidizing $\mathbf{PC}^{\cdot-}$. Anion protonation and proto-demetallation of the Cu–C bond afford the desired product **3a**, regenerating the Cu(I) species. Taking into account the outcome of the *E*-selective methodology, and the control experiment previously shown, it is reasonable to assume that the product is formed as an *E*-enriched mixture and then is isomerized *via* energy transfer (ET (4CzIPN) = 60 kcal·mol^{-1})[22] mediated by the photocatalyst.

In summary, we have developed a catalytic method for intermolecular hydroalkylation of terminal alkynes with carboxylic acids. The use of a widely available and stable copper-based catalyst allows the overcoming of the intrinsic kinetic barrier associated with the addition of radicals to triple bonds. At the same time, this transformation exploits the ability of an organic photocatalyst to generate alkyl radicals from *in situ* generated carboxylates and isomerize the formed alkene to the less stable *Z* isomer. In this work, HTE screening of reaction conditions revealed that the proper choice of copper ligand and base makes possible the selective shutdown of the latter process without compromising the efficiency of the former thereby paving the way to the stereodivergency of the reaction. These aspects, along with the low cost and abundance of the starting materials as well as catalysts, suggest that this synthetic methodology can complement other photoredox hydroalkylation reactions of alkynes relying upon the use of iridium catalysts and PR functionalized substrates.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Experimental procedures and spectral data (PDF)

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(14) The reaction works identically with racemic *trans*-1,2-diaminocyclohexane. The reaction product (**3a**) is obtained in racemic form, as it is the case for all products in Figure 2 derived from carboxylic acids containing a single stereocenter α to the carboxy group. Wedge bonds are used in this manuscript to indicate a defined stereochemistry.

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(18) Excited Cu(I)-acetylides, albeit present in low concentration, could also play a role as reductants in the catalytic cycle due to its long lifetime and high reducing potential ($E_{1/2} = -1.77$ V vs SCE). See refs. 11b and 11c.

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(20) See SI, Section 2e.

(21) **A** can also be formed in presence of Cu(I) species under visible light irradiation without the assistance of a base, see reference 7f.

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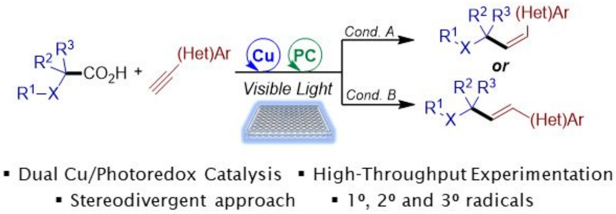

Synopsis TOC (if needed)

A dual copper and organic photoredox catalysis approach for the synthesis of allylic amines and ethers from carboxylic acids and alkynes has been developed. This approach relies on the perturbation of the ground-state electronical properties of terminal alkynes *via* visible-light excitation of copper acetylide intermediates. HTE spotlighted the stereodivergency of this reaction by choosing an appropriate combination of ligand and base.