Alkynylation Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 16926–16932
International Edition: doi.org/10.1002/anie.202006317
German Edition: doi.org/10.1002/ange.202006317

Photoinduced Copper-Catalyzed Asymmetric Decarboxylative Alkynylation with Terminal Alkynes

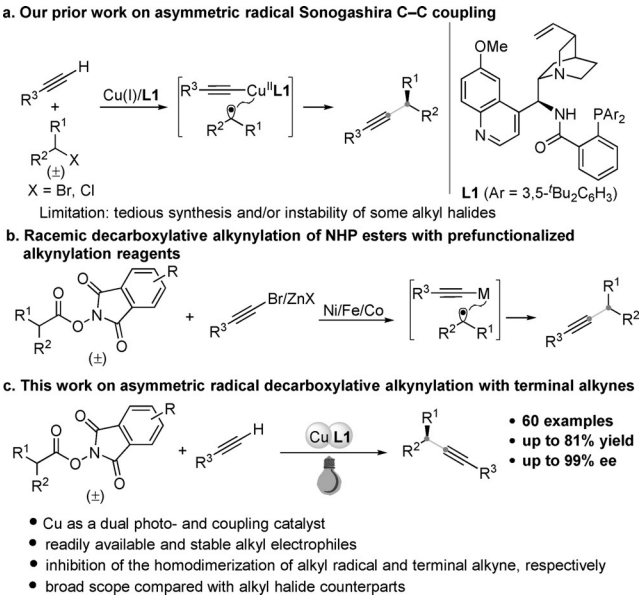
*Hai-Dong Xia[+], Zhong-Liang Li[+], Qiang-Shuai Gu[+], Xiao-Yang Dong[+], Jia-Heng Fang, Xuan-Yi Du, Li-Lei Wang, and Xin-Yuan Liu**

Dedicated to Prof. Henry N. C. Wong on the occasion of his 70th birthday

Abstract: *We describe a photoinduced copper-catalyzed asymmetric radical decarboxylative alkynylation of bench-stable N-hydroxyphthalimide(NHP)-type esters of racemic alkyl carboxylic acids with terminal alkynes, which provides a flexible platform for the construction of chiral C(sp^3)–C(sp) bonds. Critical to the success of this process are not only the use of the copper catalyst as a dual photo- and cross-coupling catalyst but also tuning of the NHP-type esters to inhibit the facile homodimerization of the alkyl radical and terminal alkyne, respectively. Owing to the use of stable and easily available NHP-type esters, the reaction features a broader substrate scope compared with reactions using the alkyl halide counterparts, covering (hetero)benzyl-, allyl-, and aminocarbonyl-substituted carboxylic acid derivatives, and (hetero)aryl and alkyl as well as silyl alkynes, thus providing a vital complementary approach to the previously reported method.*

Introduction

Transition-metal-catalyzed cross-coupling reactions have evolved into a powerful tool to forge carbon–carbon bonds and have revolutionized every aspect of chemistry.[1] While tremendous progress has been made in the cross-coupling of aryl or vinyl (pseudo)halides, the cross-coupling of alkyl (pseudo)halides has remained unexplored for a long time due to the difficult oxidative addition and the facile β-H elimination of alkyl metal complexes.[2] Such transformations would potentially open up new vistas in organic synthesis, especially when the stereochemistry of the sp^3-hybridized carbon centers can be controlled. In this scenario, transition-metal-catalyzed enantioconvergent C(sp^3)–C cross-coupling of racemic alkyl halides has received much attention over the past two decades.[3,4] In particular, Fu and others have pioneered this field by utilizing chiral first-row transition-metal catalysts for the construction of stereogenic carbon centers via prochiral alkyl radical intermediates.[3,4] Recently, our group has discovered a copper-catalyzed enantioconvergent radical C(sp^3)–C(sp) cross-coupling of racemic secondary alkyl halides and terminal alkynes (Scheme 1a).[5] During this course, a chiral alkaloid-derived multidentate N,N,P-ligand is used for enhancing the reducing capability of copper catalyst, thus converting alkyl halides to prochiral alkyl radical species via a single electron transfer (SET) process. However, the reaction has suffered from two major restrictions: 1) Many alkyl halides require tedious synthesis; 2) some of the alkyl halides are instable and do not provide the corresponding chiral alkynes. These apparent limitations would thwart the wide application of this method in organic synthesis. Given the importance of chiral alkynes as versatile synthetic intermediates and medicinally relevant molecules, the development of easily available and stable alkyl electrophiles as alkyl halide surrogates to enrich the synthetic toolbox for enantioconvergent C(sp^3)–C(sp) cross-coupling of terminal alkynes is highly desirable.



Scheme 1. Asymmetric radical decarboxylative alkynylation.

[*] Dr. H.-D. Xia,[+] X.-Y. Dong,[+] J.-H. Fang, X.-Y. Du, L.-L. Wang, Prof. Dr. X.-Y. Liu
Shenzhen Grubbs Institute and Department of Chemistry
Guangdong Provincial Key Laboratory of Catalysis
Southern University of Science and Technology
Shenzhen 518055 (China)
E-mail: liuxy3@sustech.edu.cn
Homepage: https://liuxy.chem.sustech.edu.cn
Dr. Z.-L. Li,[+] Dr. Q.-S. Gu[+]
Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology
Shenzhen 518055 (China)
[+] These authors contributed equally to this work.
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202006317.

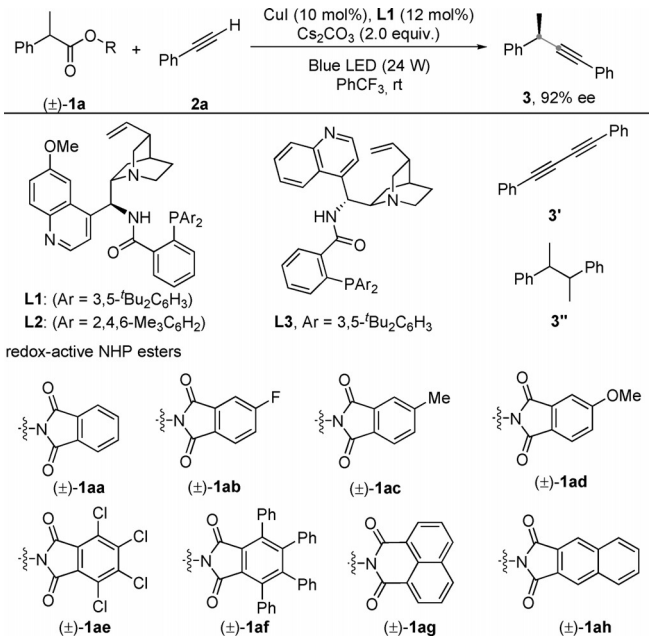
Alkyl carboxylic acids are cheap, highly stable, and easily available building blocks, and are among the most ubiquitous organic molecules found in nature.[6] Great progress has been recently made in the utility of carboxylic acids or their redox-active esters (e.g., *N*-hydroxyphthalimide (NHP) ester) as radical precursors in transition-metal-catalyzed radical decarboxylative cross-coupling reactions.[6,7] Despite these advances, the exploration of the asymmetric variants for expedite access to chiral C–C/X bonds has been few and far between.[8] In 2016, Fu and MacMillan jointly disclosed the first asymmetric decarboxylative arylation by a cooperative photo- and nickel catalysis.[8a] Subsequently, Reisman and Liu independently developed an asymmetric decarboxylative vinylation and cyanation of NHP esters utilizing either a nickel catalysis[8b] or a cooperative photo- and copper catalysis,[8c] respectively. In light of the urgent demand for new catalysis for asymmetric decarboxylation, we wondered whether our developed copper/N,N,P-ligand catalyst[5] could be used for realizing an asymmetric decarboxylative alkynylation of racemic carboxylic NHP esters. Although Baran and others[9] have elegantly achieved the racemic variants with prefunctionalized alkynylation partners, the asymmetric transformation with easily available terminal alkynes has never been reported, probably due to the challenging stereocontrol over the highly reactive prochiral alkyl radical intermediates (Scheme 1b). Another problem associated terminal alkynes is the facile Glaser homocoupling of terminal alkynes.[10] The success of this approach would provide a new platform for the enantioconvergent radical decarboxylative alkynylation reactions.

At the beginning, we speculated that the chiral copper(I) acetylide complex generated in situ from copper(I), terminal alkyne and chiral ligand might directly reduce NHP esters to afford alkyl radicals. Unfortunately, the initial attempts indicated very low reaction efficiency, possibly due to the weak reducing capacity of copper(I) acetylide. Notably, recent studies have demonstrated that the copper(I) acetylide complex can be excited under visible-light irradiation, thereby transforming it into a long-lived and strong reductant.[11–13] We wondered whether the chiral copper(I) acetylide complex could act as both the photocatalyst and the cross-coupling catalyst to realize the asymmetric transformation. As part of our continuous interest in Cu^{I}-catalyzed asymmetric reactions involving radicals,[5,14] we herein describe a photoinduced copper-catalyzed asymmetric radical decarboxylative C(sp^3)–C(sp) cross-coupling of racemic NHP esters with terminal alkynes (Scheme 1c). Notably, this strategy exhibits unique features in terms of tolerating substrates that are challenging or even inapplicable to our previous Sonogashira coupling of alkyl halides,[5] thus rendering it a valuable alternative to the previous approach.

Results and Discussion

Based on the above-mentioned proposal, we began to investigate the cross-coupling of racemic ester **1aa**, prepared in one step from commercially available 2-phenylpropanoic acid, with phenylacetylene **2a** (Table 1). However, screening of different solvents and bases under blue-LED irradiation in the presence of CuI and **L1** delivered the desired product **3** in poor yield, albeit with excellent enantioselectivity, along with the starting carboxylic acid resulting from the hydrolysis of **1aa**, the Glaser homocoupling product **3′**, and radical dimerization product[15] **3″** (Tables S1 and S2 in Supporting

Table 1: Screening of reaction conditions.[a]



Entry	(±)-**1a**	Conversion [%]	Yield of **3** [%]	Yield of **3′** [%]	Yield of **3″** [%]
1	(±)-**1aa**	89	21	ca. 30	12
2	(±)-**1ab**	83	12	ca. 30	19
3	(±)-**1ac**	85	14	ca. 30	5
4	(±)-**1ad**	80	21	ca. 30	17
5	(±)-**1ae**	90	12	ca. 30	11
6	(±)-**1af**	47	20	ca. 10	5
7	(±)-**1ag**	49	30	trace	trace
8	(±)-**1ah**	53	37	trace	trace
9[b]	(±)-**1ah**	50	21	trace	trace
10[c]	(±)-**1ah**	55	30	trace	trace
11[d]	(±)-**1ah**	65	37	trace	trace
12[e]	(±)-**1ah**	87	58	trace	trace
13[f]	**(±)-1ah**	**95**	**70**	**trace**	**trace**
14[g]	(±)-**1ah**	92	64	trace	trace

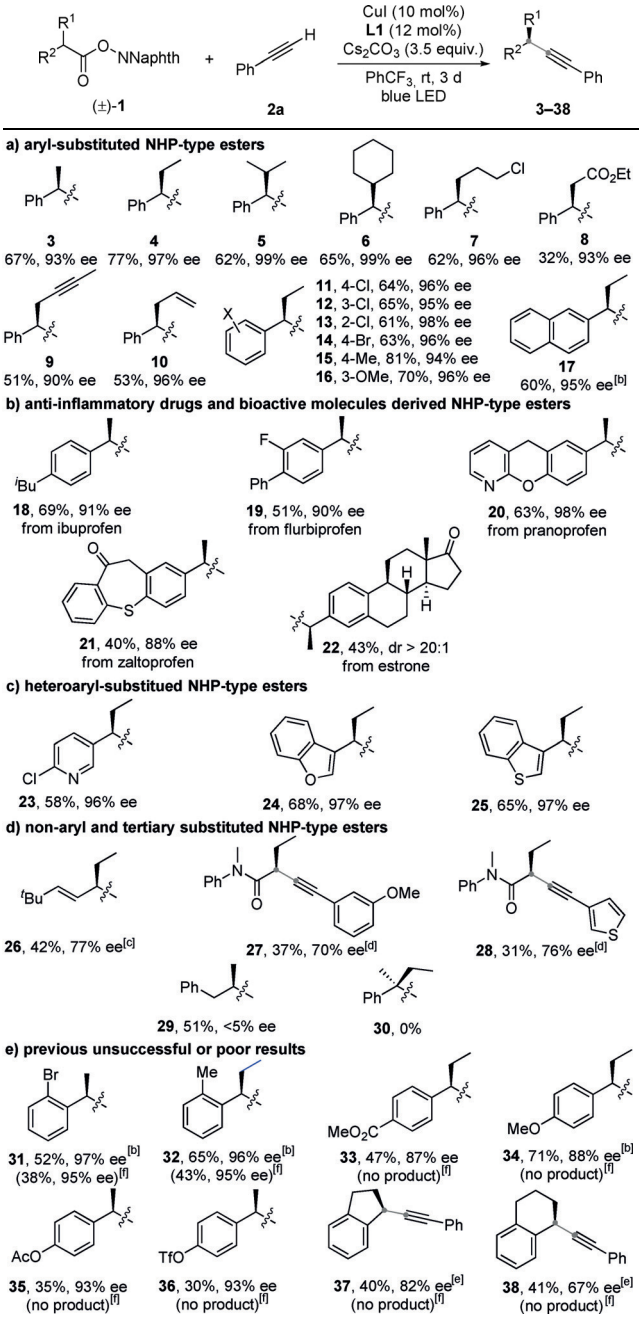
[a] Reaction conditions: (±)-**1a** (0.050 mmol), **2a** (0.075 mmol), CuI (10 mol%), **L1** (12 mol%), and Cs_2CO_3 (0.10 mmol, 2.0 equiv) in $PhCF_3$ (0.50 mL) at room temperature under irradiation of blue LED (24 W) for 72 h under argon. Yields of **3** and **3″** were based on ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard. Isolated yield of **3′** is shown. Ee value was determined by HPLC analysis. [b] CuI (15 mol%) and **L1** (18 mol%) were used. [c] **2a** (0.10 mmol) with 1.0 mL of $PhCF_3$ was used. [d] 2.5 equiv of Cs_2CO_3 was used. [e] 3.0 equiv of Cs_2CO_3 was used. [f] 3.5 equiv of Cs_2CO_3 was used. [g] 4.0 equiv of Cs_2CO_3 was used.

Information). We then screened various copper salts and cinchona alkaloid-derived N,N,P-ligands, but the hydrolysis of **1aa** and the dimerization process cannot be inhibited (Table S3 and S4 in the Supporting Information). We speculated that the low reaction efficiency and occurrence of the dimerization reactions might be attributed to the reactivity of NHP ester **1aa**. We then coupled different type of N-hydroxy imides with the carboxylic acid to achieve a good reaction efficiency. After screening diverse esters **1aa**–**1ah** (Table 1, entries 2–8), we were pleased to find that with *N*-hydroxy 2,3-naphthalimide (R = NNaphth)-derived ester **1ah** as the substrate, the reaction efficiency was enhanced, and the dimerization products were also inhibited (Table 1, entry 8). Further increasing either catalytic loading of CuI and **L1** or the amount of **2a** could not improve the reaction efficiency (entries 9 and 10). It is worth noting that increasing the amount of Cs_2CO_3 to 3.5 equiv could efficiently improve the reaction efficiency and give **3** in 70% yield and 92% *ee* (entry 13). No reaction occurred in the absence of copper or Cs_2CO_3 and only trace amounts of desired products were detected in the absence of light or ligand, thus suggesting that all the parameters are essential to the success of the asymmetric alkynylation (Table S5 in the Supporting Information).

With the optimal reaction conditions established, the substrate scope with respect to racemic carboxylic acid derived NHP-type esters was then investigated (Table 2). We found that various substituents in the alkyl branch of the NHP-type esters was compatible with the reaction conditions, and the alkynylation products **3**–**10** were obtained in good yields and 90–99% *ee* (Table 2a). Many potentially reactive groups, such as chloride (**7**), ester (**8**), alkyne (**9**), and terminal alkene (**10**), were left untouched. As for the aryl ring, a range of NHP-type esters, including those bearing halides (**11**–**14**), methyl (**15**), or methoxyl (**16**) groups at different positions (*ortho*, *meta*, or *para*) of phenyl rings and a naphthalene ring (**17**), reacted smoothly to afford chiral alkynes in good yields and excellent *ee*. Furthermore, for carboxylic acids commonly used as anti-inflammatory drugs, such as ibuprofen, flurbiprofen, pranoprofen, and zaltoprofen, the NHP-type esters underwent the reaction smoothly as well to generate the coupling products **18**–**21** in good yields and 88–98% *ee* (Table 2b). The late-stage modification of the natural product estrone was also feasible to give the alkylation product **22** in 43% yield. Furthermore, NHP-type esters containing heterocycles, such as pyridine, benzo[*b*]furan, and benzo[*b*]thiophene, also worked well to deliver **23**–**25** in excellent *ee* (Table 2c). Interestingly, the allylic and α-aminocarbonyl substrates were also found to be suitable for the reaction to afford the expected products **26**–**28** in good *ee*, albeit with low yield (Table 2d). Unfortunately, the homobenzylic substrate delivered a racemic coupling product **29**, while the tertiary substrate did no provide the desired product **30** (Table 2d). These reactions are currently under further optimization in our lab.

Direct comparisons were also made between the NHP-type esters and alkyl halides.[5] As such, the reaction of *ortho*-substituted benzylic substrates provided the desired products **31** and **32** in good yields. In contrast, the *ortho*-substituted benzyl halides always reacted in much lower efficiency in our previous work[5] (Table 2e). Further, benzyl halides with strong electron-withdrawing or -donating functional groups at the *para* positions of phenyl rings and cyclic benzylic halides are generally unstable, rendering them inapplicable to our previous conditions.[5] To our delight, the desired enantioen-

Table 2: Substrate scope of NHP-type esters.[a]



[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), CuI (10 mol%), **L1** (12 mol%), and Cs_2CO_3 (0.70 mmol) in $PhCF_3$ (4.0 mL). Yield was determined after isolation; Ee value was determined using HPLC analysis. [b] Reaction time is 4 d. [c] CuI (20 mol%) and **L1** (24 mol%) in Et_2O. [d] CuI (15 mol%) and **L1** (18 mol%). [e] With **L2** as the ligand and Et_2O as the solvent. [f] Our recent reported results of asymmetric alkynylation reaction in parenthesis.[5]

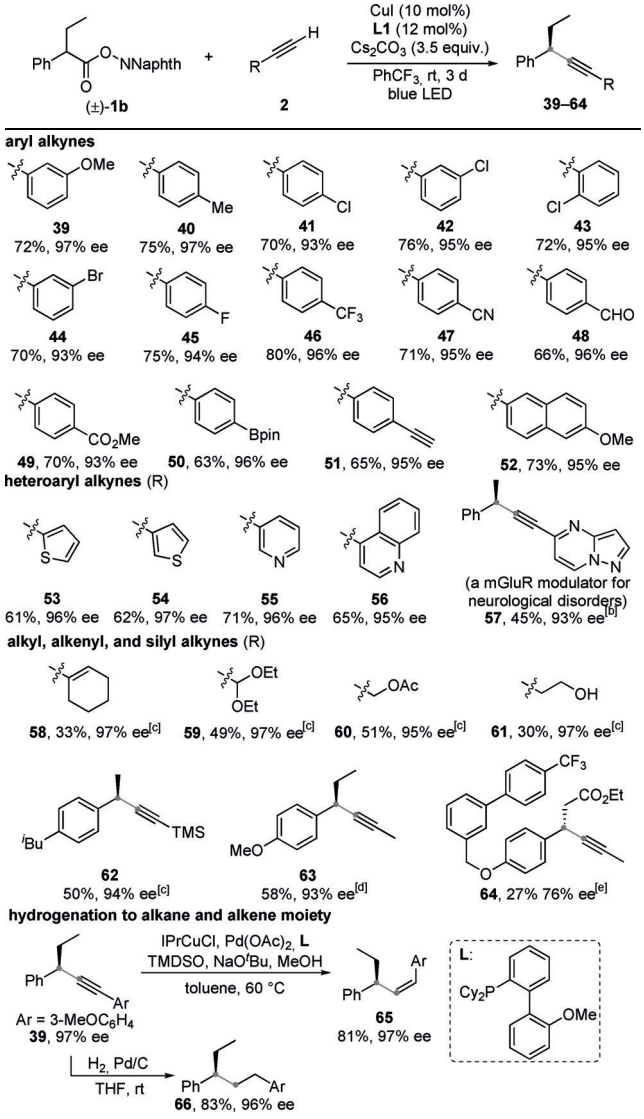
riched alkynes **33**–**38** were successfully generated from the decarboxylative alkynylation of the stable NHP-type esters in 67–93 % *ee*, but the yields are low for substrates with electron-withdrawing groups.

Encouraged by the above results, we next examined the scope with respect to alkynes (Table 3). A number of aryl alkynes proceeded smoothly to give **39**–**52** in good yields with excellent *ee* under the standard conditions. Diverse functional groups such as methoxyl (**39**), chloro (**41**–**43**), bromo (**44**), fluoro (**45**), trifluoromethyl (**46**), nitrile (**47**), formyl (**48**), methoxycarbonyl (**49**), pinacolborato (**50**), and terminal alkyne (**51**) were well tolerated. The absolution configuration of **39** was determined to be *R* by comparing its HPLC spectrum and optical rotation with those reported[5] and the configurations were inferred accordingly. The decarboxylative alkynylation was also applicable to heteroaryl alkynes that contain medicinally relevant heterocycles, such as thiophene (**53** and **54**), pyridine (**55**), and quinoline (**56**), affording the desired chiral alkynes in excellent *ee*. Furthermore, the direct decarboxylative alkynylation enabled single-step access to a patented mGluR modulator **57** in 93 % *ee*. More significantly, many aliphatic alkynes with different functional groups, such as conjugated alkene (**58**), acetal (**59**), acetate (**60**), and even a free alcohol (**61**) group reacted smoothly in this process. Trimethylsilyl acetylene also worked well to provide **62** in 50 % yield and 94 % *ee*. The direct incorporation of industrial feedstocks into organic molecules for synthesis of complex synthetic intermediates or medicinally relevant compounds is an important goal of chemical research. As such, we were delighted to find that the industrially relevant propyne[16] was also suitable to provide **63** in 58 % yield and 93 % *ee*. Furthermore, direct decarboxylative alkynylation with propyne provided **64** in 76 % *ee*, which is a key intermediate in the synthesis of a drug lead (AMG 837, a G-protein coupled receptor GPR40 agonist)[5,17] under slightly modified conditions. Furthermore, the enantioenriched alkyne **39** could undergo either a stereoselective partial or complete hydrogenation to afford chiral *Z*-alkene **65** or alkane **66**, respectively, without any loss of *ee*. Thus, the asymmetric decarboxylative alkynylation, when combined with simple transformations, provides an excellent complementary strategy for the construction of chiral $C(sp^3)$–$C(sp^2)$ and $C(sp^3)$–$C(sp^3)$ bonds from cheap and stable carboxylic acids.

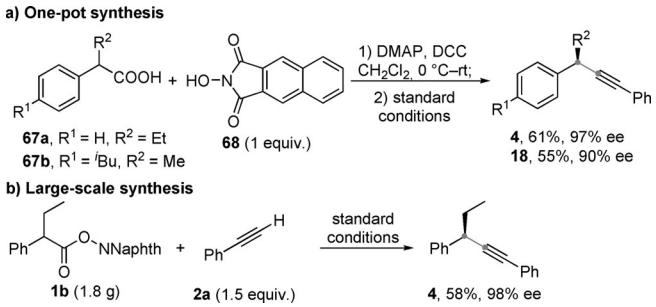
To demonstrate the practicality of this method, we next developed a tandem one-pot procedure for the direct use of readily available racemic carboxylic acids in the reaction. Thus, the crude esters obtained by coupling of carboxylic acids **67a** and **67b** with **68** were applied directly to the standard conditions without further purification, delivering the chiral alkynes **4** and **18** with good results, respectively (Scheme 2a). In addition, a large-scale reaction of **1b** and phenyl acetylene **2a** was also performed to deliver the desired product **4** in 58 % yield with 97 % *ee* (Scheme 2b).

To gain some insight into the reaction mechanism, we carried out a series of control experiments. When TEMPO was added under the otherwise standard conditions, the reaction was completely inhibited and only the Glaser reaction occurred to provide **3′** (Scheme 3a). The reaction

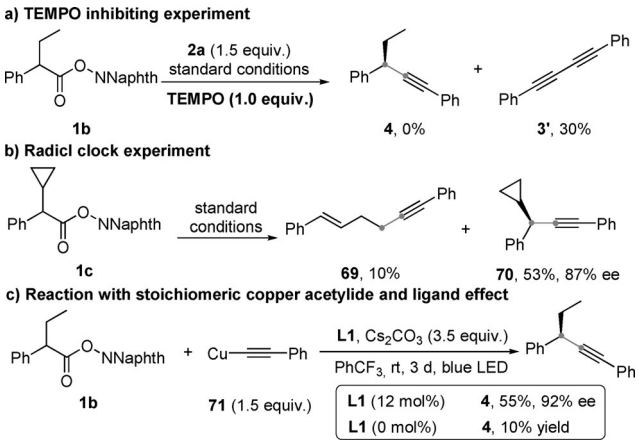
Table 3: Substrate scope of alkynes.[a]



[a] Reaction conditions: **1** (0.30 mmol), **2** (0.20 mmol), CuI (10 mol%), **L1** (12 mol%), and Cs_2CO_3 (0.70 mmol) in $PhCF_3$ (4.0 mL). The yield was isolated and the *ee* value was determined by HPLC. [b] CuI (15 mol%), **L1** (18 mol%). [c] **1** (0.20 mmol), **2** (0.24 mmol), CuI (15 mol%), **L1** (12 mol%), for 4 d. [d] CuI (15 mol%), **L1** (12 mol%), and propyne (5.0 equiv). [e] CuI (20 mol%), **L3** (24 mol%), and propyne (5.0 equiv).



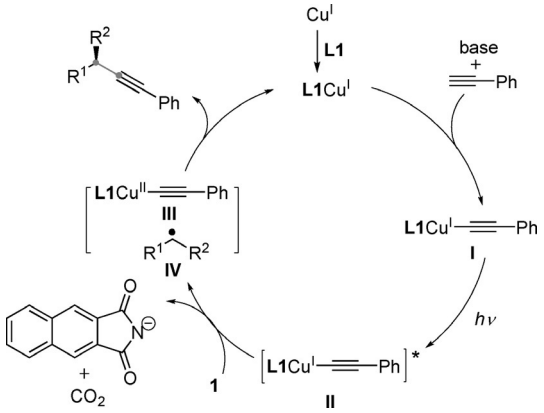
Scheme 2. Synthetic applications.



Scheme 3. Control experiment for mechanistic investigation.

of radical clock substrate **1c** delivered the ring-opening/alkynylation product **69** in 10% yield along with the alkynylation product **70** (Scheme 3b). These experiments demonstrated that a radical process might be involved in this reaction. The replacement of CuI and phenylacetylene **2a** with stoichiometric copper acetylide **71** under otherwise identical conditions provided the desired product **4** in 55% yield and 92% *ee*, showing that **71** might be involved in the process. Only 10% yield of **4** was observed in the absence of ligand, thus indicating that the ligand significantly promoted the transformation (Scheme 3c).

It is known that the copper acetylide complex can be photoexcited with photons of relatively low energy.[12] Fluorescence quenching experiments revealed that the excited copper acetylide was quenched by the NHP-type ester **1b** rather than **2a**, thus indicating a possible SET process between the NHP-type esters and the excited copper acetylide (Figure 1a and b). This process was also supported by a cyclic voltammetry study, which showed that the reported redox potential (−2.048 V vs. SCE in CH_3CN)[12d] of the excited copper acetylide **71** is strong enough to reduce the ester **1b** (−1.174 V vs. SCE in CH_3CN, Figure S1 in the Supporting Information). Further fluorescence quenching experiments demonstrated that the NHP-type esters **1aa**–**1ae** quenched the excited copper acetylide more efficiently than **1af**–**1ah**, which might cause higher concentration of Cu^{II} acetylide and benzylic radical **IV** (Scheme 4, Figure 1c). Accordingly, fast radical–radical homocoupling might be favored to provide **3″**, and the left Cu^{II} acetylide might have to undergo Glaser coupling to deliver product **3′** as observed during the condition optimization (Table 1).[10,15] However,



Scheme 4. Mechanistic proposal.

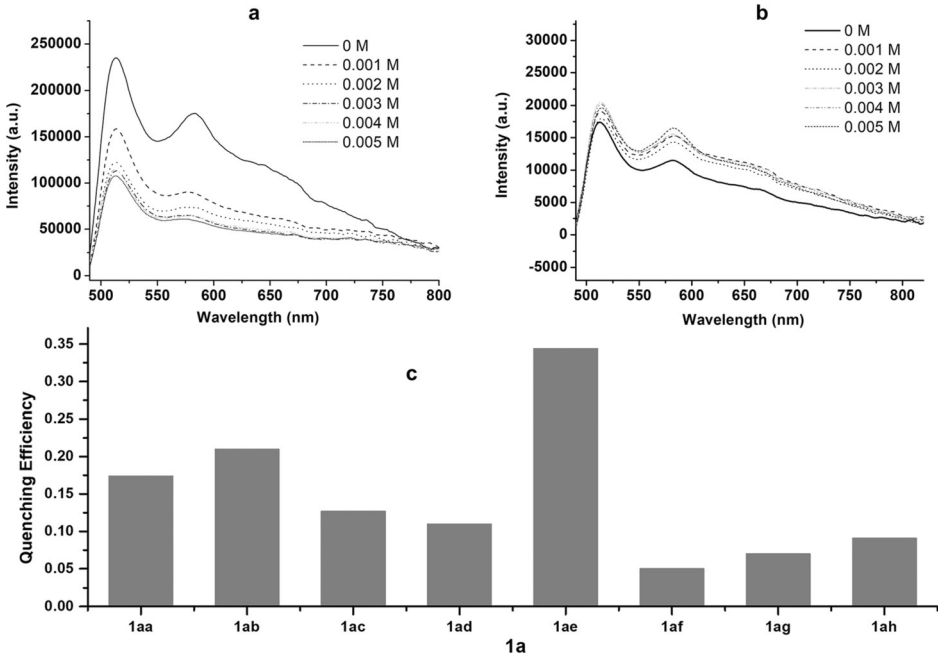


Figure 1. Fluorescence quenching experiments. a) Copper acetylide emission quenching by **1b**. b) Copper acetylide emission quenching by **2a**. c) Quenching efficiency with **1aa**–**1ah**.

too-low quenching efficiency may cause a low reaction efficiency and **1ah** is the most suitable NHP-type ester for the reaction.

Based on these results and previous reports,[5,12] we propose a possible mechanism as shown in Scheme 4. Cu^{I} catalyst, acetylene, and the ligand **L1** reacted in the presence of Cs_2CO_3 to generate the intermediate **I**,[14h] which was directly excited to give the complex **II**. Subsequently, the excited copper acetylide **II** can transfer an electron to NHP-type ester **1** to deliver the Cu^{II} complex **III**. Meanwhile, the formed anionic radical of NHP-type ester undergoes a radical decarboxylation process to generate the radical intermediate **IV**. This intermediate would undergo a $C(sp^3)$–C(sp) bond formation with **III**, providing chiral alkynes and releasing the **L1**Cu^{I} complex for the next catalytic cycle (See Scheme S1 in the Supporting Information for a proposed model for asymmetric induction).

Conclusion

In summary, we have developed a strategy for direct asymmetric radical decarboxylative alkynylation of NHP-type esters with terminal alkynes utilizing photoinduced copper catalysis. One striking feature of this strategy is the dual role of the copper catalyst as both the photo- and the cross-coupling catalyst. The NHP-type esters are tuned to inhibit the facile Glaser reaction, thus achieving good reaction efficiency. Owing to the ready availability of carboxylic acids and the high stability of NHP-type esters, this strategy largely expands the substrate scope compared with that using the corresponding alkyl halide counterparts. Therefore, it provides an efficient and general synthetic tool for not only chiral $C(sp^3)$–C(sp) but also chiral $C(sp^3)$–$C(sp^2/sp^3)$ bond formations when allied with follow-up transformations. Further studies toward the development of direct asymmetric radical decarboxylative reactions with other nucleophiles are ongoing in our laboratory.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 21722203, 21831002, and 21801116), Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), Guangdong Innovative Program (No. 2019BT02Y335), Shenzhen Nobel Prize Scientists Laboratory Project (No. C17783101) and SUSTech Special Fund for the Construction of High-Level Universities (No. G02216303) are gratefully acknowledged. The authors acknowledge the assistance of SUSTech Core Research Facilities.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynylation · asymmetric radical reactions · copper · decarboxylation · photocatalysis

[1] Selected reviews: a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062; *Angew. Chem.* **2012**, *124*, 5150; b) A. de Meijere, S. Bräse, M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH, Weinheim, **2014**; c) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74; *Angew. Chem.* **2014**, *126*, 76; d) T. J. Colacot, S. Nolan, C. Hardacre, M. Stradiotto, Z. Ismagilov, U. Ozkan, M. Lautens, J. Spivey, G. Lloyd-Jones, X. F. Wu, *New Trends in Cross-Coupling: Theory and Applications*, Royal Society of Chemistry, London, **2014**.

[2] I. D. Hills, M. R. Netherton, G. C. Fu, *Angew. Chem. Int. Ed.* **2003**, *42*, 5749; *Angew. Chem.* **2003**, *115*, 5927.

[3] Selected reviews: a) J. Choi, G. C. Fu, *Science* **2017**, *356*, eaaf7230; b) G. C. Fu, *ACS Cent. Sci.* **2017**, *3*, 692; c) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587.

[4] Representative examples: a) H. Huo, B. J. Gorsline, G. C. Fu, *Science* **2020**, *367*, 559; b) H. Yin, G. C. Fu, *J. Am. Chem. Soc.* **2019**, *141*, 15433; c) B. Li, T. Li, M. A. Aliyu, Z. H. Li, W. Tang, *Angew. Chem. Int. Ed.* **2019**, *58*, 11355; *Angew. Chem.* **2019**, *131*, 11477; d) Z. Wang, H. Yin, G. C. Fu, *Nature* **2018**, *563*, 379; e) K. E. Poremba, N. T. Kadunce, N. Suzuki, A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2017**, *139*, 5684; f) J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, *Science* **2016**, *354*, 1265; g) M. Sidera, S. P. Fletcher, *Nat. Chem.* **2015**, *7*, 935; h) M. Jin, L. Adak, M. Nakamura, *J. Am. Chem. Soc.* **2015**, *137*, 7128; i) J. Mao, F. Liu, M. Wang, L. Wu, B. Zheng, S. Liu, J. Zhong, Q. Bian, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 17662; j) F. O. Arp, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 10482.

[5] X.-Y. Dong, Y.-F. Zhang, C.-L. Ma, Q.-S. Gu, F.-L. Wang, Z.-L. Li, S.-P. Jiang, X.-Y. Liu, *Nat. Chem.* **2019**, *11*, 1158.

[6] Selected reviews: a) J. Xuan, Z.-G. Zhang, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 15632; *Angew. Chem.* **2015**, *127*, 15854; b) S. Murarka, *Adv. Synth. Catal.* **2018**, *360*, 1735.

[7] Representative examples: a) H.-P. Bi, L. Zhao, Y.-M. Liang, C.-J. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 792; *Angew. Chem.* **2009**, *121*, 806; b) X. Liu, Z. Wang, X. Cheng, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 14330; c) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437; d) C. P. Johnston, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature* **2016**, *536*, 322; e) T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, P. S. Baran, *Science* **2016**, *352*, 801; f) X. Tan, Z. Liu, H. Shen, P. Zhang, Z. Zhang, C. Li, *J. Am. Chem. Soc.* **2017**, *139*, 12430; g) C. Li, J. Wang, L. M. Barton, S. Yu, M. Q. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, eaam7355; h) E. R. Welin, C. Le, D. M. Arias-Rotondo, J. K. McCusker, D. W. C. MacMillan, *Science* **2017**, *355*, 380; i) J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate, P. S. Baran, *Nature* **2017**, *545*, 213; j) W. Xue, M. Oestreich, *Angew. Chem. Int. Ed.* **2017**, *56*, 11649; *Angew. Chem.* **2017**, *129*, 11808; k) L. Candish, M. Teders, F. Glorius, *J. Am. Chem. Soc.* **2017**, *139*, 7440; l) M. Koy, F. Sandfort, A. Tlahuext-Aca, L. Quach, C. G. Daniliuc, F. Glorius, *Chem. Eur. J.* **2018**, *24*, 4552; m) R. Mao, A. Frey, J. Balon, X. Hu, *Nat. Catal.* **2018**, *1*, 120; n) R. Mao, J. Balon, X. Hu, *Angew. Chem. Int. Ed.* **2018**, *57*, 9501; *Angew. Chem.* **2018**, *130*, 9645; o) H. Cao, H. Jiang, H. Feng, J. M. C. Kwan, X. Liu, J. Wu, *J. Am. Chem. Soc.* **2018**, *140*, 16360; p) I. Scheipers, C. Mück-Lichtenfeld, A. Studer, *Angew. Chem. Int. Ed.* **2019**, *58*, 6545; *Angew. Chem.* **2019**, *131*, 6616; q) Z. Li, R. O. Torres-Ochoa, Q. Wang, J. Zhu, *Nat. Commun.*

2020, *11*, 403; r) J. He, G. Chen, B. Zhang, Y. Li, J.-R. Chen, W.-J. Xiao, F. Liu, C. Li, *Chem* **2020**, *6*, 1149.

[8] a) Z. Zuo, H. Cong, W. Li, J. Choi, G. C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832; b) N. Suzuki, J. L. Hofstra, K. E. Poremba, S. E. Reisman, *Org. Lett.* **2017**, *19*, 2150; c) D. Wang, N. Zhu, P. Chen, Z. Lin, G. Liu, *J. Am. Chem. Soc.* **2017**, *139*, 15632; d) F.-D. Lu, D. Liu, L. Zhu, L.-Q. Lu, Q. Yang, Q.-Q. Zhou, Y. Wei, Y. Lan, W.-J. Xiao, *J. Am. Chem. Soc.* **2019**, *141*, 6167; e) R. S. J. Proctor, H. J. Davis, R. J. Phipps, *Science* **2018**, *360*, 419; f) J. Ma, J. Lin, L. Zhao, K. Harms, M. Marsch, X. Xie, E. Meggers, *Angew. Chem. Int. Ed.* **2018**, *57*, 11193; *Angew. Chem.* **2018**, *130*, 11363.

[9] One leading review on C(sp^3)–C(sp) formation: a) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; related works: b) X.-G. Liu, C.-J. Zhou, E. Lin, X.-L. Han, S.-S. Zhang, Q. Li, H. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 13096; *Angew. Chem.* **2018**, *130*, 13280; c) J. M. Smith, T. Qin, R. R. Merchant, J. T. Edwards, L. R. Malins, Z. Liu, G. Che, Z. Shen, S. A. Shaw, M. D. Eastgate, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 11906; *Angew. Chem.* **2017**, *129*, 12068; d) L. Huang, A. M. Olivares, D. J. Weix, *Angew. Chem. Int. Ed.* **2017**, *56*, 11901; *Angew. Chem.* **2017**, *129*, 12063.

[10] P. Leophairatana, S. Samanta, C. C. De Silva, J. T. Koberstein, *J. Am. Chem. Soc.* **2017**, *139*, 3756.

[11] Selected reviews: a) A. Hossain, A. Bhattacharyya, O. Reiser, *Science* **2019**, *364*, eaav9713; b) O. Reiser, *Acc. Chem. Res.* **2016**, *49*, 1990.

[12] Representative examples: a) A. Sagadevan, V. K. K. Pampana, K. C. Hwang, *Angew. Chem. Int. Ed.* **2019**, *58*, 3838; *Angew. Chem.* **2019**, *131*, 3878; b) A. Hazra, M. T. Lee, J. F. Chiu, G. Lalic, *Angew. Chem. Int. Ed.* **2018**, *57*, 5492; *Angew. Chem.* **2018**, *130*, 5590; c) A. Sagadevan, V. P. Charpe, A. Ragupathi, K. C. Hwang, *J. Am. Chem. Soc.* **2017**, *139*, 2896; d) A. Sagadevan, A. Ragupathi, K. C. Hwang, *Angew. Chem. Int. Ed.* **2015**, *54*, 13896; *Angew. Chem.* **2015**, *127*, 14102; e) A. Sagadevan, A. Ragupathi, C.-C. Lin, J. R. Hwu, K. C. Hwang, *Green Chem.* **2015**, *17*, 1113; f) A. Sagadevan, K. C. Hwang, *Adv. Synth. Catal.* **2012**, *354*, 3421.

[13] Visible-light-induced copper-catalyzed C–N bond formation: a) S. E. Creutz, K. J. Lotito, G. C. Fu, J. C. Peters, *Science* **2012**, *338*, 647; b) Q. M. Kainz, C. D. Matier, A. Bartoszewicz, S. L. Zultanski, J. C. Peters, G. C. Fu, *Science* **2016**, *351*, 681.

[14] Selected reviews on our work: a) Q.-S. Gu, Z.-L. Li, X.-Y. Liu, *Acc. Chem. Res.* **2020**, *53*, 170; b) Z.-L. Li, G.-C. Fang, Q.-S. Gu, X.-Y. Liu, *Chem. Soc. Rev.* **2020**, *49*, 32; our other representative works: c) Y.-F. Cheng, J.-R. Liu, Q.-S. Gu, Z.-L. Yu, J. Wang, Z.-L. Li, J.-Q. Bian, H.-T. Wen, X.-J. Wang, X. Hong, X.-Y. Liu, *Nat. Catal.* **2020**, *3*, 401; d) C.-J. Yang, C. Zhang, Q.-S. Gu, J.-H. Fang, X.-L. Su, L. Ye, Y. Sun, Y. Tian, Z.-L. Li, X.-Y. Liu, *Nat. Catal.* **2020**, *3*, 539; e) L. Ye, Y. Tian, X. Meng, Q.-S. Gu, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2020**, *59*, 1129; *Angew. Chem.* **2020**, *132*, 1145; f) X.-T. Li, L. Lv, T. Wang, Q.-S. Gu, G.-X. Xu, Z.-L. Li, L. Ye, X. Zhang, G.-J. Cheng, X.-Y. Liu, *Chem* **2020**, *6*, 1692; g) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 9357; h) X.-Y. Dong, J.-T. Cheng, Y.-F. Zhang, Z.-L. Li, T.-Y. Zhan, J.-J. Chen, F.-L. Wang, N.-Y. Yang, L. Ye, Q.-S. Gu, X.-Y. Liu, *J. Am. Chem. Soc.* **2020**, *142*, 9501.

[15] A. C. P. F. de Sá, G. M. A. Pontes, J. A. L. dos Anjos, S. R. Santana, L. W. Bieber, I. Malvestiti, *J. Braz. Chem. Soc.* **2003**, *14*, 429.

[16] M. A. Berliner, E. M. Cordi, J. R. Dunetz, K. E. Price, *Org. Process Res. Dev.* **2010**, *14*, 180.

[17] R. Yazaki, N. Kumagai, M. Shibasaki, *Org. Lett.* **2011**, *13*, 952.

Manuscript received: May 1, 2020
Revised manuscript received: June 24, 2020
Accepted manuscript online: June 25, 2020
Version of record online: August 20, 2020

