OL | Organic Letters

pubs.acs.org/OrgLett Letter

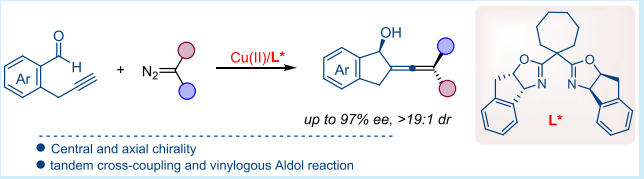
Copper-Catalyzed Tandem Cross-Coupling and Alkynylogous Aldol Reaction: Access to Chiral Exocyclic α-Allenols

Guangyang Xu, Zhen Wang, Ying Shao, and Jiangtao Sun*

Cite This: *Org. Lett.* 2021, 23, 5175–5179 Read Online

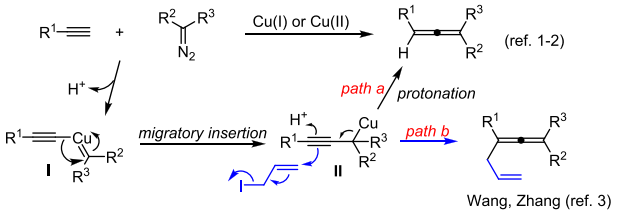
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An enantioselective copper-catalyzed tandem cross-coupling/alkynylogous aldol reaction has been developed. The tetrasubstituted allenoates containing both central and axial chirality have been obtained in moderate to good yields and excellent enantio- and diastereoselectivity. Distinct from the previous use of Cu(I) salts, this protocol features the use of copper(II) salts as a catalytic precursor in this asymmetric cross-coupling reaction.



Copper-catalyzed cross-coupling reactions of terminal alkynes with diazo compounds represent one important protocol to synthesize polysubstituted allenes and allenoates.[1,2] A common accepted mechanism for the allene formation involves the formation of copper species **I** which undergoes migratory insertion to generate a propargyl copper species **II** (Scheme 1). Subsequent protonation produces the final di- or

Scheme 1. Common Mechanism



trisubstituted allene (path a). Pioneered by the Wang group, this copper species **II** can be trapped through the addition of a strong electrophile-allyl halide and directly converted to tetrasubstituted allene (path b).[3]

By using a chiral copper catalytic system, the axially chiral allenes could be obtained via this protocol.[4−6] In 2015, Liu and co-workers reported the first highly enantioselective diazo-alkyne coupling reaction for synthesizing chiral allenoates via a copper(I)-chiral cationic guanidinium salt system (Scheme 2a).[4] Later, Wang and co-workers developed a Cu(I)-chiral bisoxazoline-catalyzed coupling of diazoalkanes with terminal alkynes for the enantioselective synthesis of trisubstituted allenes.[5] In 2017, the Ley group established a Cu(I)-chiral pyridinebis(imidazoline) system to prepare chiral disubstituted allenes by the coupling of diazo compounds and propargylated amines.[6] Recently, Liu and co-workers discovered an asymmetric three-component reaction to reach chiral tetrasubstituted allenoates, in which the isatin was used as an electrophile to trap the in situ generated allenoate-Cu(I) intermediate (Scheme 2b).[7] As part of our research on carbene transformations, we previously reported a series of tandem reactions for synthesizing heterocycles and functionalized molecules through the tandem reactions of terminal alkynes and diazoacetates.[8] Inspired by Wang's seminal work,[3] and by introducing a Machael-acceptor into the alkyne skeleton, we also reported a tandem coupling of alkynes with diazo compounds and subsequent cyclization to synthesize tetrasubstituted allenoates.[8b] Also encouraged by Liu's protocol,[6] we envisioned that, by introducing a strong electrophile such as the aldehyde moiety into the alkyne molecule, the chiral exocyclic allenols bearing axially chiral allenes would be obtained through an effective catalytic system. As depicted in Scheme 2c, the reaction might start with the formation of copper species **Int-2** via the preferential formation of copper acetylide **Int-1**[1] or copper-carbene **Int-1′**,[2,9] which would undergo alkynyl migratory insertion to form propargyl copper species **Int-3**. Then, the alkynylogous Aldol reaction[10] would occur to yield the allenoate copper species **Int-4**. Alternatively, the 1,3-copper migration of **Int-3** forms allenoate-copper intermediate **Int-3′**, which can be trapped by the aldehyde moiety to generate **Int-4**, too. Finally, protonation of **Int-4** delivers the final chiral exocyclic α-allenol and regenerates the copper catalyst. It should be noted that nominal catalysis by Cu(II) complexes involves prior reduction to Cu(I) by either diazo compounds[11] or terminal alkynes.[12]

Received: May 21, 2021
Published: June 17, 2021

https://doi.org/10.1021/acs.orglett.1c01712
Org. Lett. 2021, 23, 5175–5179

Scheme 2. Previous Reports and Our Design

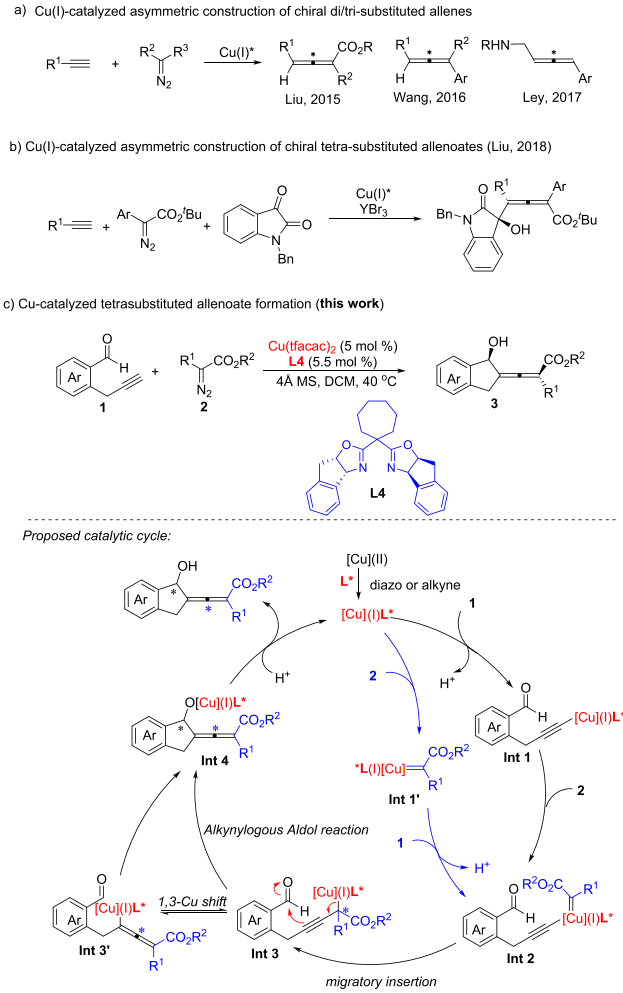
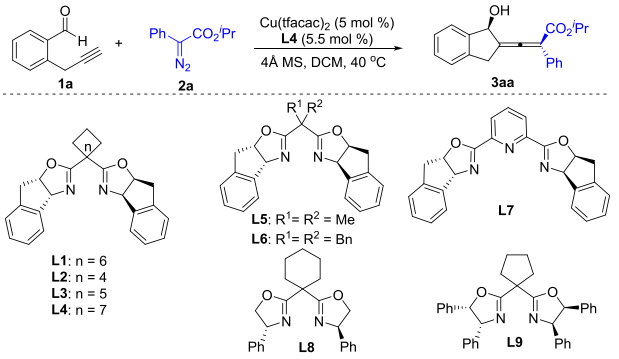


Table 1. Optimization of the Reaction Conditions[a]



entry	[Cu]	ligand	solvent	yield[b] (%)	ee[c] (%)	dr[d]
1	CuI	**L1**	DCM	33	57	>19:1
2	$Cu(MeCN)_4BF_4$	**L1**	DCM	24	94	>19:1
3	$Cu(tfacac)_2$	**L1**	DCM	79	95	>19:1
4	$Cu(OTf)_2$	**L1**	DCM	0		
5	$CuBr_2$	**L1**	DCM	15	50	>19:1
6	$Cu(tfacac)_2$	**L2**	DCM	0		
7	$Cu(tfacac)_2$	**L3**	DCM	78	78	9:1
8	$Cu(tfacac)_2$	**L4**	DCM	87	97	>19:1
9	$Cu(tfacac)_2$	**L5**	DCM	68	86	>19:1
10	$Cu(tfacac)_2$	**L6**	DCM	<5		
11	$Cu(tfacac)_2$	**L7**	DCM	41	96	19:1
12	$Cu(tfacac)_2$	**L8**	DCM	62	80	5:1
13	$Cu(tfacac)_2$	**L9**	DCM	44	63	3:1
14	$Cu(tfacac)_2$	**L4**	DCE	0		
15	$Cu(tfacac)_2$	**L4**	toluene	59	76	>19:1
16	$Cu(tfacac)_2$	**L4**	MeCN	31	19	1:1
17[e]	$Cu(tfacac)_2$	**L4**	DCM	79	93	13:1
18	Cu(cod)(tfacac)	**L4**	DCM	56	92	>19:1

[a]Reaction conditions: A mixture of copper catalyst (0.005 mmol), chiral ligand (0.0055 mmol), 4 Å MS (60 mg), **1a** (0.1 mmol), and solvent (4 mL) was stirred for 1 h at 25 °C under argon; then, **2** (0.15 mmol) was added and stirred at 40 °C. [b]Isolated yield. [c]ee was determined by chiral HPLC analysis. [d]dr was determined by crude ^1H NMR. [e]Without 4 Å MS. $Cu(tfacac)_2$ = copper(II) trifluoroacetylacetonate.

We commenced our studies by examining the copper-catalyzed cross-coupling reaction between alkyne **1a** and α-phenyl diazoacetate **2a** (Table 1). As it was demonstrated that chiral bisoxazoline (Box) was a privileged chiral ligand in the copper-catalyzed cross-coupling of terminal alkynes with diazoacetates, we tested Box **L1** as the chiral ligand to combine with a series of copper salts (5 mol %) in this reaction. The initial experiment with CuI and **L1** in dichloromethane at 40 °C delivered the desired product **3aa** in 33% yield and 57% ee (entry 1), and the use of $Cu(MeCN)_4BF_4$ gave **3aa** in 94% ee, but only in 24% yield, albeit in excellent diastereoselectivity (>19:1) (entry 2).

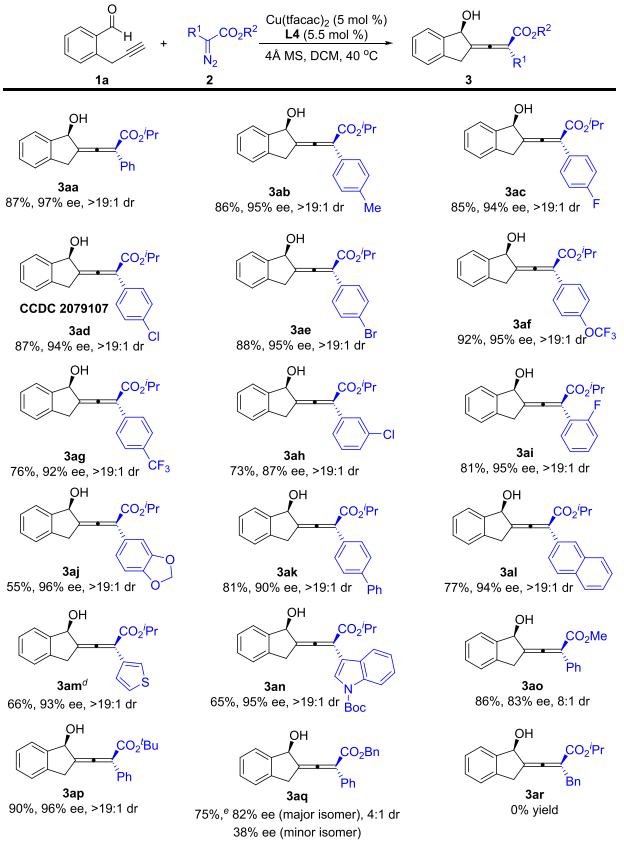
Considering the poor catalytic reactivity for Cu(I) salts, we then attempted to screen Cu(II) salts in this reaction. Gratifyingly, $Cu(tfacac)_2$ exhibited a good catalytic reactivity and selectivity, affording **3aa** in 79% yield and 95% ee (entry 3). However, other Cu(II) salts gave poor results. For example, $Cu(OTf)_2$ was ineffective (the self-coupling reaction of diazo was observed as the major reaction, entry 4), and $CuBr_2$ showed both poor catalytic reactivity and selectivity (entry 5). Next, using $Cu(tfacac)_2$ as the copper catalyst, a series of Box ligands were evaluated. It was found that decreasing the ring size of Box ligands gave poor results. No catalytic reactivity was observed for Box **L2** (n = 4) (entry 6). The use of **L3** (n = 5) provided **3aa** in 78% yield and 78% ee (entry 7). Typically, using Liu's Box ligand **L4** (n = 7) delivered **3aa** in 87% yield and 97% ee (entry 8).[13] These results indicated that the Box ligands with a small bite-angle are beneficial to both reactivity and enantioselectivity. Further ligand screening was then performed. Box ligand **L5** containing a gem-dimethyl linkage showed moderate catalytic reactivity and decreased enantioselectivity (entry 9); however, **L6** bearing a gem-dibenzyl linkage gave only a trace amount of **3aa** (entry 10). The PyBox ligand **L7** exhibited moderate catalytic reactivity and good enantioselectivity (entry 11). Further modifications to the ligand scaffold gave inferior results. For instance, **L8** and **L9** exhibited moderate reactivity and enantioselectivity but poor diastereoselectivity (entries 12 and 13). Subsequent solvent screening failed to improve the reaction. No reaction occurred when 1,2-dichloroethane (DCE) was used (entry 14). Toluene gave **3aa** in moderate yield and enantioselectivity (entry 15), and acetonitrile gave both poor enantio- and diastereoselectivity (entry 16). It should be noted that both the yield and enantioselectivity of **3aa** slightly dropped without the addition of a molecular sieve (entry 17). Finally, to verify whether the Cu(II) complexes might be reduced to Cu(I) in the reaction

https://doi.org/10.1021/acs.orglett.1c01712
Org. Lett. 2021, 23, 5175−5179

system, Cu(cod)(tfacac) was examined, and **3aa** was obtained in 56% yield with 92% ee (entry 18).

Under the optimal reaction conditions, the scope of diazo compounds was then evaluated (Scheme 3). A range of α-aryl

Scheme 3. Scope of Diazo Compounds[a,b]

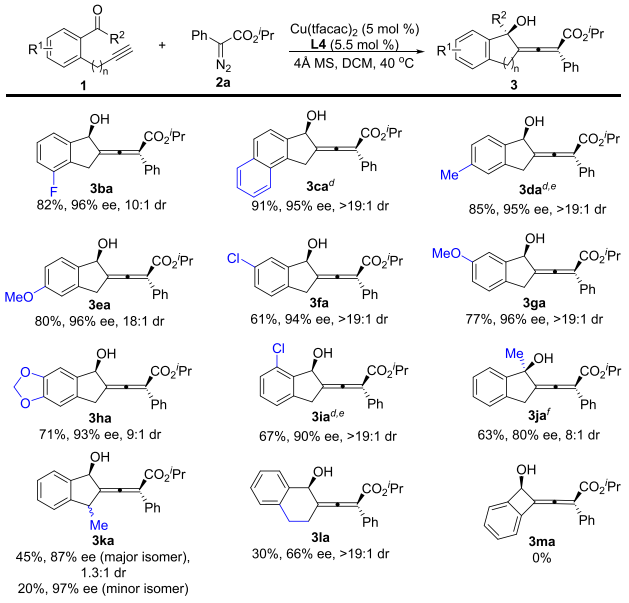


[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), $Cu(tfacac)_2$ (0.005 mmol), **L4** (0.0055 mmol), 4 Å MS (60 mg), DCM (4 mL), 40 °C. [b]Yields of isolated products. [c]ee was determined by chiral HPLC analysis. [d]$Cu(tfacac)_2$ (0.01 mmol) and **L4** (0.011 mmol) were used. [e]Combined yield.

diazoacetates containing either electron-donating or electron-withdrawing substituents on the phenyl ring reacted smoothly with **1a** to give the corresponding exocyclic α-allenols (**3ab**–**3al**) in 55–92% yield, 87–96% ee, and an excellent dr value (>19:1). Typically, the strong electron-withdrawing substituents, such as OCF_3 (**3af**) and CF_3 (**3ag**), were tolerated. The absolute configuration of **3ad** was assigned as (R, S_a) by X-ray diffraction analysis. α-Heteroaryl diazoacetates, such as α-thienyl diazoacetate and α-indole diazoacetate, reacted well with **1a**, providing the corresponding products **3am** and **3an** in moderate yields and excellent enantioselectivities. The ester moiety of phenyl diazoacetate was also examined. The methyl ester gave the product **3ao** in almost the same yield but with a diminished enantioselectivity (83% ee) and relatively poor diastereoselectivity (8:1). The *tert*-butyl ester afforded **3ap** in a slightly higher yield (90%) and 96% ee. However, the benzyl ester led to both lower yield and enantioselectivity, and also a poor dr value (**3aq**). Unfortunately, for α-alkyl diazoacetate, the reaction was messy, and the corresponding product **3ar** was not obtained.

Subsequently, the scope of the reaction with respect to alkynes **1** was investigated (Scheme 4). Various alkynes

Scheme 4. Scope of Alkyne[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), $Cu(tfacac)_2$ (0.005 mmol), **L4** (0.0055 mmol), 4 Å MS (60 mg), DCM (4 mL), 40 °C. [b]Yields of isolated products. [c]ee was determined by chiral HPLC analysis. [d]Performed at 50 °C. [e]$Cu(tfacac)_2$ (0.01 mmol) and **L4** (0.011 mmol) were used. [f]Performed at 60 °C.

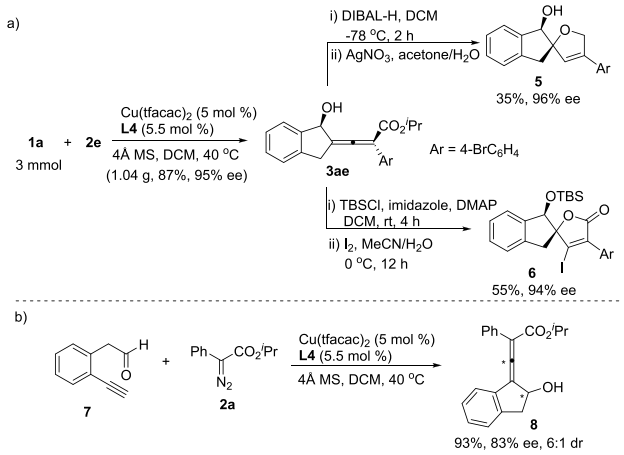
bearing either electron-donating or electron-withdrawing groups at different positions of the aromatic ring were smoothly reacted with diazoacetate **2a**, providing the corresponding exocyclic α-allenols (**3ba**–**3ia**) in 61–91% yield, 90–96% ee, and 9:1 to >19:1 dr. Replacing the aldehyde moiety with ketone in the alkyne substrate, the product **3ja** containing a tetrasubstituted stereocenter was obtained in 63% yield, 80% ee, and 8:1 dr. However, the reaction of 2-(but-3-yn-2-yl)benzaldehyde with **2a** led to poor diastereoselectivity (1.3:1), of which the major isomer **3ka** was isolated in 45% yield and 87% ee. The minor isomer was isolated in 20% yield and 97% ee. The comparatively lower yield for **3fa**, **3ia**, and **3la** is attributed to the self-coupling of diazoacetates. For 2-(but-3-yn-1-yl)benzaldehyde, the desired product was obtained in 30% yield and 66% ee. With respect to 2-ethynylbenzaldehyde, the desired product **3ma** was not observed, but the diazo self-coupling product was detected.

The synthetic utility of this protocol was then demonstrated (Scheme 5). A gram-scale synthesis of **3ae** was performed (Scheme 5a). Under the optimal reaction conditions, the reaction with 3 mmol of **1a** and 4.5 mmol of **2e** afforded 1.04 g of **3ae** (87% yield) with 95% ee. With the reduction of **3ae** with DIBAL-H followed by $AgNO_3$-promoted cyclization, chiral spiro compound **5** was isolated in 35% yield and 96% ee.[14] Moreover, iodolactonization of **3ae** with I_2 led to the corresponding spiro-iodobutenolide **6** in 55% yield and 94% ee.[15] Finally, the reaction of 2-acetaldehyde phenylacetylene **7** with **2a** gave the corresponding product **8** in 93% yield, 83% ee, and 6:1 dr (Scheme 5b).

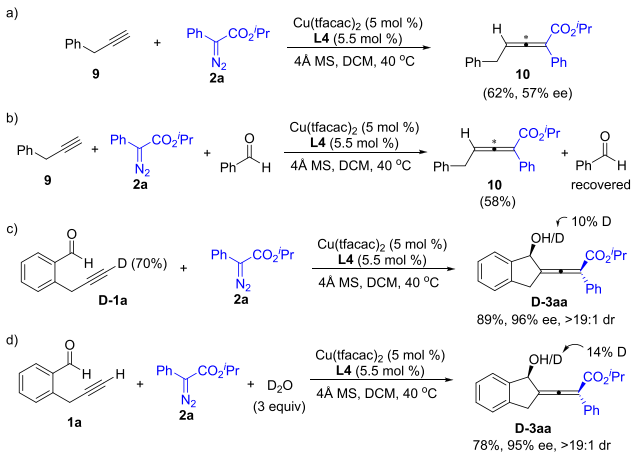
Control experiments were conducted to understand the reaction mechanism (Scheme 6). Under the optimal reaction conditions, the reaction of terminal alkyne **9** with **2a** produced

https://doi.org/10.1021/acs.orglett.1c01712
Org. Lett. 2021, 23, 5175–5179

Scheme 5. Further Elaboration



Scheme 6. Control Experiments



allenoate **10** in 62% yield and 58% ee (Scheme 6a). The three-component reaction of **9**, **2a**, and benzaldehyde gave a 58% yield of **10**, and the benzaldehyde was recovered (Scheme 6b). These two experiments indicated the preferential reaction of the alkyne moiety with diazo in alkyne substrate **1**; subsequent addition to the aldehyde moiety then gave the final product in Scheme 1c. Moreover, Scheme 6b also indicates that this copper catalytic system did not support an intermolecular three-component reaction, because the protonation is preferred over the subsequent addition to aldehyde. The deuterium-labeling experiments were also conducted. The reaction of **D-1a** with **2a** generated **D-3aa** in 89% yield and 96% ee, with 10% deuterium labeling (Scheme 6c). The addition of 3 equiv of D_2O resulted in 14% deuterium labeling of **D-3aa** (Scheme 6d). These two experiments indicated that the deprotonation and protonation did occur in the whole reaction process.

In summary, we have developed a copper-catalyzed asymmetric construction of chiral exocyclic α-allenols from the reaction of diazoacetates and terminal alkynes, featuring the concurrent construction of both central and axial chirality. Key to realize this high enantio- and diastereoselective reaction is the use of $Cu(tfacac)_2$ as the catalyst precursor, which is distinct with the use of Cu(I)-salts in previous allene formation through coupling of diazo compounds and terminal alkynes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01712.

Experimental procedures along with characterizing data and copies of NMR spectra (PDF)

Accession Codes

CCDC 2079107 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Jiangtao Sun − *Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, P. R. China;* orcid.org/0000-0003-2516-3466; Email: jtsun@cczu.edu.cn

Authors

Guangyang Xu − *Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, P. R. China*

Zhen Wang − *Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, P. R. China*

Ying Shao − *Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, P. R. China;* orcid.org/0000-0002-7379-8266

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01712

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21971026) and the Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology (BM2012110) for their financial support.

■ REFERENCES

(1) (a) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. Coupling of N-Tosylhydrazones with Terminal Alkynes Catalyzed by Copper(I): Synthesis of Trisubstituted Allenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114−1117. (b) Hossain, M. L.; Ye, F.; Zhang, Y.; Wang, J. CuI-Catalyzed Cross-Coupling of N-Tosylhydrazones with Terminal Alkynes: Synthesis of 1,3-Disubstituted Allenes. *J. Org. Chem.* **2013**, *78*, 1236−1241. (c) Ye, F.; Wang, C.; Ma, X.; Hossain, M. L.; Xia, Y.; Zhang, Y.; Wang, J. Synthesis of Terminal Allenes through Copper-Mediated Cross-Coupling of Ethyne with N-Tosylhydrazones or α-Diazoesters. *J. Org. Chem.* **2015**, *80*, 647−652. (d) Poh, J. S.; Tran, D. N.; Battilocchio, C.; Hawkins, J. M.; Ley, S. V. A Versatile Room-Temperature Route to Di- and Trisubstituted Allenes Using Flow-Generated Diazo Compounds. *Angew. Chem., Int. Ed.* **2015**, *54*,

7920−7923. (e) Hossain, M. L.; Wang, J. Cu(I)-Catalyzed Cross-Coupling of Diazo Compounds with Terminal Alkynes: An Efficient Access to Allenes. *Chem. Rec.* **2018**, *18*, 1548−1559.
(2) Hassink, M.; Liu, X.; Fox, J. M. Copper-Catalyzed Synthesis of 2,4-Disubstituted Allenoates from α-Diazoesters. *Org. Lett.* **2011**, *13*, 2388−2391.
(3) Ye, F.; Hossain, M. L.; Xu, Y.; Ma, X.; Xiao, Q.; Zhang, Y.; Wang, J. Synthesis of Allyl Allenes through Three-Component Cross-Coupling Reaction of N-Tosylhydrazones, Terminal Alkynes, and Allyl Halides. *Chem. - Asian J.* **2013**, *8*, 1404−1407.
(4) Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X. Direct Synthesis of Chiral Allenoates from the Asymmetric C-H Insertion of α-Diazoesters into Terminal Alkynes. *Angew. Chem., Int. Ed.* **2015**, *54*, 9512−9516.
(5) Chu, W. D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J. Enantioselective Synthesis of Trisubstituted Allenes via Cu(I)-Catalyzed Coupling of Diazoalkanes with Terminal Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 14558−14561.
(6) Poh, J. S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V. Rapid Asymmetric Synthesis of Disubstituted Allenes by Coupling of Flow-Generated Diazo Compounds and Propargylated Amines. *Angew. Chem., Int. Ed.* **2017**, *56*, 1864−1868.
(7) Tang, Y.; Xu, J.; Yang, J.; Lin, L.; Feng, X.; Liu, X. Asymmetric Three-Component Reaction for the Synthesis of Tetrasubstituted Allenoates via Allenoate-Copper Intermediates. *Chem.* **2018**, *4*, 1658−1672.
(8) (a) Liu, K.; Zhu, C.; Min, J.; Peng, S.; Xu, G.; Sun, J. Stereodivergent Synthesis of N-Heterocycles by Catalyst-Controlled, Activity-Directed Tandem Annulation of Diazo Compounds with Amino Alkynes. *Angew. Chem., Int. Ed.* **2015**, *54*, 12962−12967. (b) Xu, G.; Liu, K.; Sun, J. Divergent Synthesis of Fused Tricyclic Compounds via a Tandem Reaction from Alkynyl-Cyclohexadienones and Diazoesters. *Org. Lett.* **2017**, *19*, 6440−6443. (c) Ji, D.; Liu, K.; Sun, J. Tandem Reaction of Allenoate Formation and Cyclization: Divergent Synthesis of Four- to Six-Membered Heterocycles. *Org. Lett.* **2018**, *20*, 7708−7711. (d) Li, Z.; Sun, J. Copper-Catalyzed 1,1-Boroalkylation of Terminal Alkynes: Access to Alkenylboronates via a Three-Component Reaction. *Org. Lett.* **2021**, *23*, 3706−3711.
(9) Lv, X.; Kang, Z.; Xing, D.; Hu, W. Cu(I)-Catalyzed Three-Component Reaction of Diazo Compound with Terminal Alkyne and Nitrosobenzene for the Synthesis of Trifluoromethyl Dihydroisoxazoles. *Org. Lett.* **2018**, *20*, 4843−4847.
(10) (a) Zhong, F.; Xue, Q. Y.; Yin, L. Construction of Chiral 2,3-Allenols through a Copper(I)-Catalyzed Asymmetric Direct Alkynylogous Aldol Reaction. *Angew. Chem., Int. Ed.* **2020**, *59*, 1562−1566. (b) Wang, G.; Liu, X.; Chen, Y.; Yang, J.; Li, J.; Lin, L.; Feng, X. Diastereoselective and Enantioselective Alleno-Aldol Reaction of Allenoates with Isatins to Synthesis of Carbinol Allenoates Catalyzed by Gold. *ACS Catal.* **2016**, *6*, 2482−2486.
(11) Salomon, R. G.; Kochi, J. K. Copper(I) Catalysis in Cyclopropanations with Diazo Compounds. The Role of Olefin Coordination. *J. Am. Chem. Soc.* **1973**, *95*, 3300−3310.
(12) Zhang, G.; Yi, H.; Zhang, G.; Deng, Y.; Bai, R.; Zhang, H.; Miller, J. T.; Kropf, A. J.; Bunel, E. E.; Lei, A. Direct Observation of Reduction of Cu(II) to Cu(I) by Terminal Alkynes. *J. Am. Chem. Soc.* **2014**, *136*, 924−926.
(13) Wu, L.; Wang, F.; Wan, X.; Wang, D.; Chen, P.; Liu, G. Asymmetric Cu-Catalyzed Intermolecular Trifluoromethylarylation of Styrenes: Enantioselective Arylation of Benzylic Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2904−2907.
(14) Li, Z.; Boyarskikh, V.; Hansen, J. H.; Autschbach, J.; Musaev, D. G.; Davies, H. M. L. Scope and Mechanistic Analysis of the Enantioselective Synthesis of Allenes by Rhodium-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement between Donor/Acceptor Carbenoids and Propargylic Alcohols. *J. Am. Chem. Soc.* **2012**, *134*, 15497−15504.
(15) Wang, Y.; Ma, S. Optically Active 2,3-Allenoates via Palladium-Catalyzed Carbonylation of Enantioenriched Propargylic Mesylates. *Adv. Synth. Catal.* **2013**, *355*, 741−750.

https://doi.org/10.1021/acs.orglett.1c01712
Org. Lett. 2021, 23, 5175−5179