JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Catalytic Asymmetric [4 + 1] Annulation of Sulfur Ylides with Copper−Allenylidene Intermediates

Qiang Wang,[†] Tian-Ren Li,[†] Liang-Qiu Lu,*[,†] Miao-Miao Li,[†] Kai Zhang,[†] and Wen-Jing Xiao*[,†,‡]

[†]College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China
[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, China

Supporting Information

ABSTRACT: The first copper-catalyzed asymmetric decarboxylative [4 + 1] cycloaddition of propargylic carbamates and sulfur ylides was successfully developed. This strategy led to a series of chiral indolines with synthetically flexible alkyne groups in good yields and with high enantio- and diastereoselectivities (up to 99% yield, 98% ee, and >95:5 dr). A possible mechanism and stereoinduction mode with copper−allenylidenes were proposed as the possible dipolar intermediate.

Transition-metal-catalyzed cycloaddition reactions have been the focus of extensive study because of their fundamental importance in organic, medicinal, and materials chemistry.[1] Many reactions proceed via metal-associated dipolar intermediates, which involve two independent reaction centers: one acts as an electrophile, and the other acts as a nucleophile. For example, various nucleophile-containing π-allyl−Pd complexes[2] (Figure 1a, type-I) and metallo-enolcarbenes[1c,3] (type-II: M = Rh and Au) have been widely applied in transition-metal-catalyzed cycloadditions. To expand this cycloaddition chemistry, we applied asymmetric catalysis by earth-abundant metals to achieve the first example of formal [4 + 1] cycloaddition of copper−allenylidene dipolar intermediates with high reaction yields and enantio- and diastereoselectivities (Figure 1c).

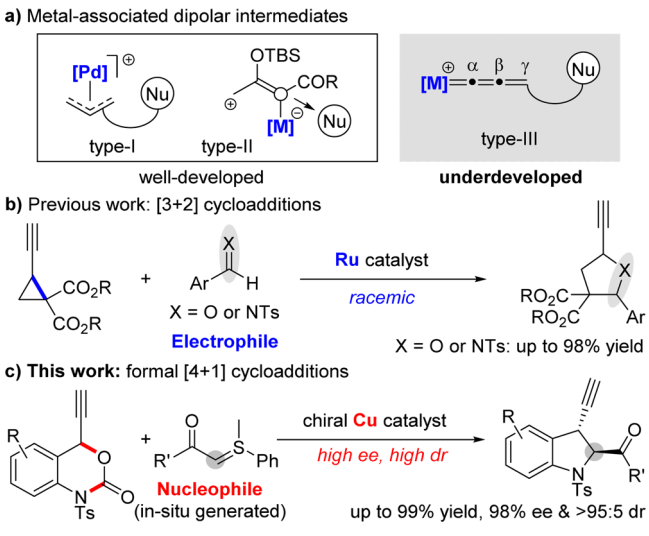


Figure 1. Cycloaddition reactions via metal-associated dipolar intermediates.

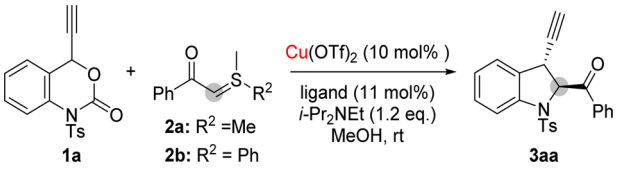
The metal−allenylidene species is a promising synthetic intermediate for organic chemists; it enables the integration of a synthetically flexible alkyne functional group.[4] Over the past decade, Ru- or Cu-catalyzed asymmetric transformations of terminal propargylic alcohols and their derivatives have been extensively developed, particularly transformations involving asymmetric processes with excellent enantiocontrols.[5,6] However, the cycloaddition reaction with metal−allenylidene dipolar intermediates has remained underdeveloped. The only such transformation which produced cycloaddition products in racemic form was disclosed in 2013 (Figure 1b).[7] In that work, a Ru-catalyzed [3 + 2] cycloaddition of ethynyl cyclopropanes with aldehydes/aldimines was elegantly designed and well-implemented using stoichiometric Lewis acids, which efficiently produced 2-ethynyltetrahydrofurans/pyrrolidines. Over the past few years, we have devoted our efforts to developing new methodologies using sulfur ylides, and we efficiently constructed various carbo- and heterocyclic systems beyond three-membered rings.[8,9] In this work, we disclose the first example of catalytic asymmetric formal [4 + 1] cycloaddition of sulfur ylides with copper−allenylidene dipolar intermediates (Figure 1c). Using this protocol, we have produced a vast range of chiral indolines[10] with synthetically flexible alkyne groups in high reaction efficiencies and selectivities, which is a complement to previous achievements.[9c,d] Notably, this study represents one of the limited reports on the transition-metal-catalyzed asymmetric cycloadditions of sulfur ylides.[11]

Initially, we performed the cycloaddition reaction of ethynyl benzoxazinanone **1a** and benzoyl sulfur ylide **2a** at room temperature (rt) in the presence of *i*-Pr_2NEt, $Cu(OTf)_2$ and chiral ligand *R*-BINAP (**L1**) in MeOH (Table 1, entry 1). The reaction did occur and produced the desired indoline product **3aa** in *trans* configuration in good yield, albeit with low enantioselectivity (entry 1, 88% yield and 8% ee). Encouraged by this result, we evaluated chiral ligands widely used in Cu-catalyzed asymmetric propargylic alkylation of propargyl esters for the present cycloaddition reaction (entries 2−7). Accordingly, the commercially available phenyl-substituted Pybox ligand **L4** stood out as the superior choice, producing chiral indoline **3aa** in 66% yield and 50% ee (entry 4). Investigation of the solvent effect revealed that THF provided the best reaction efficiency despite similar enantiocontrol (entry 8, 97% yield, 53%

Received: April 29, 2016
Published: June 29, 2016

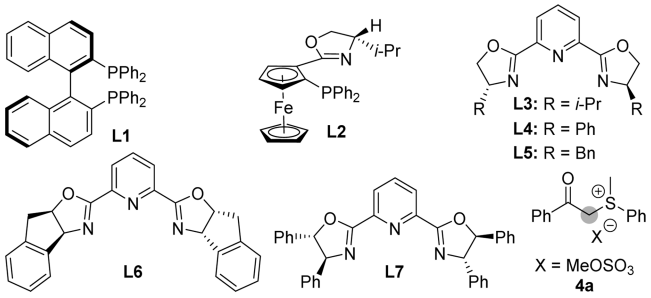
DOI: 10.1021/jacs.6b04414
J. Am. Chem. Soc. 2016, 138, 8360−8363

Table 1. Selected Condition Optimization[a]



entry	ligand	time	yield (%)[b]	ee (%)[c]
1	**L1**	30 min	88	8
2	**L2**	30 min	36	36
3	**L3**	30 min	53	50
4	**L4**	30 min	66	50
5	**L5**	30 min	56	44
6	**L6**	30 min	32	−6
7	**L7**	30 min	35	−38
8[d]	**L4**	40 min	97	53
9[d,e]	**L4**	40 min	99	88
10[e,d,f]	**L4**	16 h	99	92
11[d,f,g]	**L4**	**24 h**	**95(94)**[h]	**95**

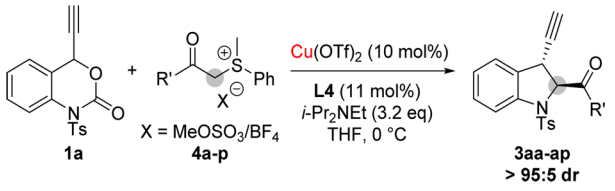
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Cu(OTf)_2$ (10 mol %), **L** (11 mol %), and *i*-Pr_2NEt (1.2 equiv) in MeOH at rt. [b]Determined by ^1H NMR of the reaction mixture containing 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by chiral HPLC analysis. [d]Using THF as the solvent. [e]Using sulfur ylide **2b**. [f]0 °C. [g]Using sulfonium salt **4a** (0.2 mmol) and *i*-Pr_2NEt (3.2 equiv). [h]Isolated yields in parentheses. THF: tetrahydrofuran.



ee; see Table S2 in the Supporting Information for more details). To further improve the result, other sulfur ylides were tested (Table S3). As a result, sulfur ylide **2b**, in which one methyl group was replaced with a phenyl group, was converted into the same product **3aa** in 99% yield and 88% ee (entry 9). Decreasing the reaction temperature gave a slightly improved enantioselectivity with 99% yield at a prolonged reaction time (entry 10). When a simplified operation was applied using easily available sulfonium salt **4a** and excess of *i*-Pr_2NEt to in situ generate sulfur ylide **2b**, the enantioselectivity increased to 95% ee with 94% isolated yield.

With the optimal conditions in hand, we examined the scope of sulfonium salts for this cycloaddition reaction. As summarized in Table 2, excellent levels of yield, diastereo-, and enantioselectivity were obtained using sulfonium salts with various substituents on the benzene ring (entries 1−10). Substrates with electron-withdrawing groups (e.g., NO_2, CN) and those with fluoro, chloro, bromo, and methyl at the 4-position were transformed into chiral indoline products with high efficiency and selectivity (**3aa**−**3ag**: 92−99% yields, 90−98% ee, and >95:5 dr). Precursors with various substituent positions on the sulfonium salts, such as 3-bromo (**4h**), 2-fluoro (**4i**), and 2,4-difluoro (**4j**), tolerated this cycloaddition and were converted into the corresponding products with good results (**3ah**−**3aj**: 97−99% yields, 90−94% ee, and >95:5 dr). In

Table 2. Scope of Sulfonium Salts[a]



entry	**4**: R′	**3**	yield (%)[b]	ee (%)[c]
1	**4a**: C_6H_5	**3aa**	94	95
2	**4b**: 4-NO_2-C_6H_4	**3ab**	98	96
3	**4c**: 4-CN-C_6H_4	**3ac**	99	94
4	**4d**: 4-F-C_6H_4	**3ad**	99(99)[d]	94(92)[d]
5	**4e**: 4-Cl-C_6H_4	**3ae**	92	98
6	**4f**: 4-Br-C_6H_4	**3af**	93	96
7[e]	**4g**: 4-Me-C_6H_4	**3ag**	96	90
8	**4h**: 3-Br-C_6H_4	**3ah**	97	94
9	**4i**: 2-F-C_6H_4	**3ai**	99	90
10	**4j**: 2,4-$F_2C_6H_4$	**3aj**	97	93
11	**4k**: 2-thienyl	**3ak**	95	84
12[f]	**4l**: 2-benzofuryl	**3al**	90	94
13[f]	**4m**: methyl	**3am**	95	91
14	**4n**: cyclopropyl	**3an**	99	92
15	**4o**: cyclohexyl	**3ao**	90	95
16	**4p**: *i*-Bu	**3ap**	95	93

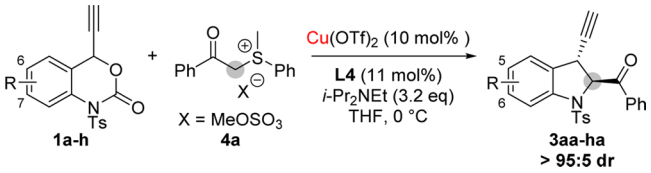
[a]Unless otherwise noted, reactions were performed at 0.2 mmol scale as in Table 1, entry 11. [b]Isolated yield. [c]Determined by a chiral HPLC analysis. [d]Gram-scale reaction was performed with 1.0 g of **1a** and 2.3 g of **4d** in 28 h, and 1.26 g of **3ad** was obtained (some results are given in parentheses). [e]Corresponding sulfur ylide was used. [f]Tetrafluoroborate sulfonium salt was used.

addition, identical transformation with heteroaryl-substituted sulfonium salts **4k** and **4l** also proceeded notably well and produced **3ak** and **3al** in 95 and 90% yields with 84 and 94% ee, respectively (entries 10 and 11). Significantly, success of this transformation was further extended to aliphatic sulfonium salts (entries 13−16). For example, substrates with methyl (**4m**), cyclopropyl (**4n**), cyclohexyl (**4o**), and *i*-butyl (**4p**) reacted well with ethynyl benzoxazinanone **1a** in the chiral copper catalyst system and produced chiral indoline products **3am**−**3ap** in 90−99% yield, 91−95% ee, and >95:5 dr.

We next explored the cycloaddition reaction of sulfonium salt **4a** with various ethynyl benzoxazinanones (Table 3). Use of substrates with a bromo (**1b**), methyl (**1c**), or methoxyl (**1d**) group at the 6-position gave the corresponding products in high yields and with great enantioselectivities (**3ba**−**3da**: 95−99% yields, 81−91% ee, and >95:5 dr). Introducing a chlorine atom (**1e**) to the 7-position of ethynyl benzoxazinanone yields the corresponding product **3ea** in excellent stereocontrol (entry 5, 99% yield, 95% ee, and >95:5 dr). Similarly, addition of a trifluoro group to the 7-position of the ethynyl benzoxazinanone was compatible with the present catalyst system, converting into desired product **3fa** in an excellent reaction efficiency and selectivity (entry 6, 96% yield, 94% ee, and >95:5 dr). Substrates with a fluoro atom at the 5- and 8-positions were tested under the optimal conditions. Fluoro-incorporated chiral indolines **3ga** and **3ha** were obtained in good yields and with high enantiocontrol (entry 7, 93% yield, 80% ee, and >95:5 dr; entry 8, 82% yield, 88% ee, and >95:5 dr). Relatively low enantiomeric excess of **3ga** was probably attributed to the steric effects of the F-substituent at the 5-position. Moreover, we have successfully used this Cu-catalyzed asymmetric cycloaddition to prepare chiral pyrroli-

DOI: 10.1021/jacs.6b04414
J. Am. Chem. Soc. 2016, 138, 8360−8363

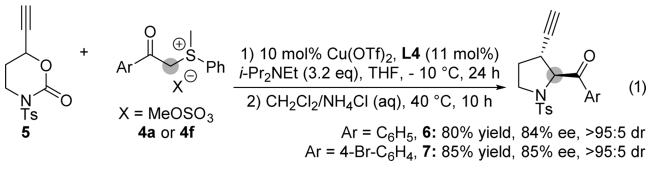
Table 3. Scope of Ethynyl Benzoxazinanones[a]



entry	1: R^1	3	yield (%)[b]	ee (%)[c]
1	**1a**: H	**3aa**	94	95
2	**1b**: 6-Br	**3ba**	97	90
3	**1c**: 6-Me	**3ca**	99	91
4[d]	**1d**: 6-MeO	**3da**	95	81
5	**1e**: 7-Cl	**3ea**	99	95
6	**1f**: 7-CF_3	**3fa**	96	94
7	**1g**: 5-F	**3ga**	93	80
8	**1h**: 8-F	**3ha**	82	88

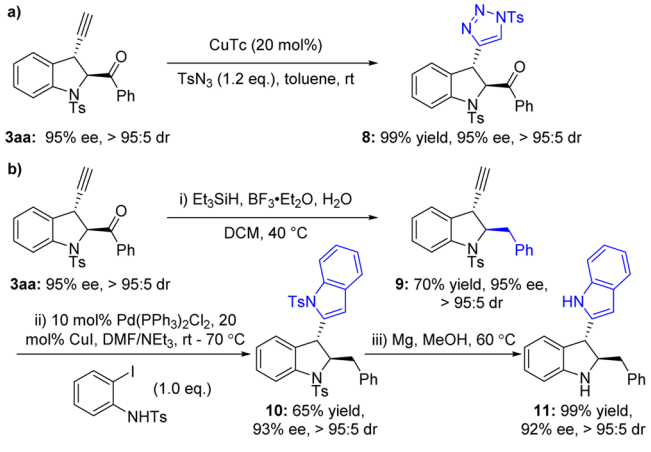
[a]Unless otherwise noted, reactions were performed at 0.2 mmol scale as in Table 1, entry 11. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Sulfur ylide **2b** was used.

dines. For example, reactions of ethynyl carbamate **5** with sulfonium salts **4a** and **4f** could afford the corresponding pyrrolidine **6** and **7**, which were produced in high enantio- and diastereoselectivity, respectively (eq 1).



Synthetic transformations were performed to demonstrate the utility of this method. For example, a copper-catalyzed 1,3-dipolar cycloaddition of **3aa** with TsN_3 produced 1,2,3-triazole-substituted chiral indoline **8** in 99% yield with retained enantiopurity (Scheme 1a). Although the active sulfur ylides

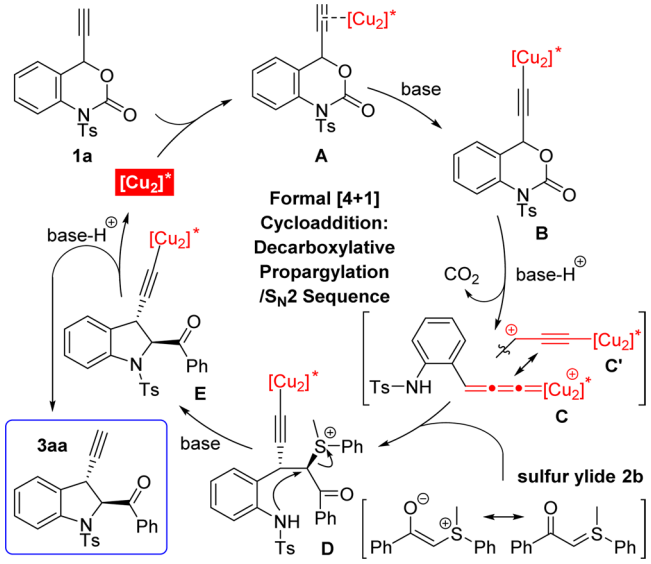
Scheme 1. Synthetic Transformation



were not suitable for this cycloaddition,[12] the deoxygenation operation of the products with triethyl silane and boron trifluoride (e.g., **3aa**) produced the indoline with an alkyl group at the 2-position in good results (Scheme 1b, **9**: 70% yield, 95% ee, and >95:5 dr). A Pd/Cu-catalyzed sequence reaction can easily convert **9** into a 2-indole-substituted chiral indoline **10** in 65% yield without significant loss in enantiopurity (Scheme 1b, **10**).[13] Treatment of **10** with magnesium powder afforded the N-free 2-indole-substituted indoline **11** with high yield (Scheme 1b, **11**).

A nonlinear relationship between the enantiopurity of product **3aa** and ligand **L4** was clearly observed in the copper-catalyzed asymmetric cycloaddition of **1a** with **4a** (Figure S1). This result indicates that a dinuclear complex of copper salts and chiral ligand may function as an active catalytic species to promote this transformation according to previous works.[14] A plausible mechanism is proposed in Scheme 2. First, the copper complex

Scheme 2. Proposed Mechanism



likely activates the alkyne part of substrate **1a** by forming a π-complex **A**, which generates the copper–acetylide species **B** upon deprotonation with *i*-Pr_2NEt. Then, a copper–allenylidene intermediate **C**, which is stabilized by its resonance form **C′**, is generated through a CO_2 extrusion process. Subsequently, the selective capture of sulfur ylide **2b** by intermediate **C** forms the transient species **D**, which converts into copper-containing cycloadduct **E** via an intramolecular S_N2 reaction. Finally, the chiral indoline is produced through a proton transfer process, and the dinuclear copper catalyst is simultaneously regenerated.

The absolute configuration of the indoline products was unambiguously determined to be *S,S* on the basis of the X-ray crystallographic analysis of **3af** (Figure S2).[13] The stereocontrol that led to this isomer might be rationalized with Maarseveen's model of cooperative catalysis (Figure 2b),[14] which was established according to crystallographic results (Figure 2a).[14b,15] The propargylation step possibly favors the *re*-face

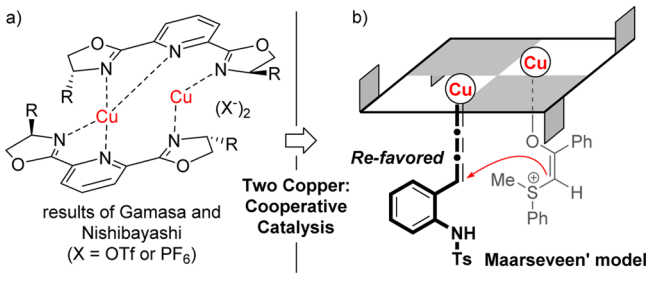


Figure 2. Possible asymmetric induction mode.

DOI: 10.1021/jacs.6b04414
J. Am. Chem. Soc. 2016, 138, 8360–8363

attack of the copper−allenylidene complex by sulfur ylides, where the sulfur ylide reacts with its *re*-face.

In conclusion, we developed a copper-catalyzed asymmetric formal [4 + 1] cycloaddition for the first time by trapping copper−allenylidene dipolar intermediates with sulfur ylides. Thus, a new approach to chiral indoline products and related cycloadducts with high reaction yields and stereoselectivities (up to 99% yield, 98% ee and >95:5 dr) was explored. Mechanistic studies suggest that this reaction is a sequence process that involves decarboxylative propargylation/S_N2 reactions promoted by dinuclear copper complexes. Further studies with this type of metal-associated dipolar intermediate are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04414.

X-ray data for **3af** (CIF)
X-ray data for **10** (CIF)
Experimental procedures; spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*luliangqiu@mail.ccnu.edu.cn
*wxiao@mail.ccnu.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Nos. 21232003, 21472057, and 21572074) and other financial support (Nos. 201422, CCNU15A02007, and 2015CFA033) for this research.

■ REFERENCES

(1) (a) Kobayashi, S.; Jorgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (c) Xu, X.; Doyle, M. P. *Acc. Chem. Res.* **2014**, *47*, 1396. (d) Chen, J.-R.; Hu, X.-Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4038.

(2) (a) Trost, B. M.; Morris, P. J.; Sprague, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 17823. (b) Khan, A.; Zheng, R.; Kan, Y.; Ye, J.; Xing, J.; Zhang, Y.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6439. (c) Ohmatsu, K.; Imagawa, N.; Ooi, T. *Nat. Chem.* **2014**, *6*, 47. (d) Xu, C.-F.; Zheng, B.-H.; Suo, J.-J.; Ding, C.-H.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 1604.

(3) (a) Guzmán, P. E.; Lian, Y.; Davies, H. M. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13083. (b) Cheng, Q.-Q.; Yedoyan, J.; Arman, H.; Doyle, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 44 and refs therein.

(4) (a) Ljungdahl, N.; Kann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 642. (b) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, *2009*, 6263. (c) Miyake, Y.; Uemura, S.; Nishibayashi, Y. *ChemCatChem* **2009**, *1*, 342. (d) Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914. (e) Nishibayashi, Y. *Synthesis* **2012**, *44*, 489. (f) Bauer, E. *Synthesis* **2012**, *44*, 1131. (g) Hu, X.-H.; Liu, Z.-T.; Shao, H.; Hu, X.-P. *Synthesis* **2015**, *47*, 913. (h) Zhang, D.-Y.; Hu, X.-P. *Tetrahedron Lett.* **2015**, *56*, 283.

(5) For selected examples of Ru catalysis, see: (a) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715. (b) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7289. (c) Senda, Y.; Nakajima, K.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 4060.

(6) For selected examples of Cu catalysis, see: (a) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777. (b) Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781. (c) Fang, P.; Hou, X.-L. *Org. Lett.* **2009**, *11*, 4612. (d) Yoshida, A.; Ikeda, M.; Hattori, G.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2011**, *13*, 592. (e) Zhang, C.; Hu, X.-H.; Wang, Y.-H.; Zheng, Z.; Xu, J.; Hu, X.-P. *J. Am. Chem. Soc.* **2012**, *134*, 9585. (f) Zhu, F.-L.; Zou, Y.; Zhang, D.-Y.; Wang, Y.-H.; Hu, X.-H.; Chen, S.; Xu, J.; Hu, X.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 1410. (g) Zhu, F.-L.; Wang, Y.-H.; Zhang, D.-Y.; Xu, J.; Hu, X.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 10223. (h) Shao, W.; Li, H.; Liu, C.; Liu, C. J.; You, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 7684.

(7) Miyake, Y.; Endo, S.; Moriyama, T.; Sakata, K.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1758.

(8) (a) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841. (b) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (c) Li, G.-C.; Wang, L.-Y.; Huang, Y. *Chin. J. Org. Chem.* **2013**, *33*, 1900.

(9) For recent work on sulfur ylides from our group, see: (a) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278. (b) Yang, Q.-Q.; Xiao, C.; Lu, L.-Q.; An, J.; Tan, F.; Li, B.-J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9137. (c) Li, T.-R.; Tan, F.; Lu, L.-Q.; Wei, Y.; Wang, Y.-N.; Liu, Y.-Y.; Yang, Q.-Q.; Chen, J.-R.; Shi, D.-Q.; Xiao, W.-J. *Nat. Commun.* **2014**, *5*, 5500. (d) Wang, Q.; Qi, X.; Lu, L.-Q.; Li, T.-R.; Yuan, Z.-G.; Zhang, K.; Li, B.-J.; Lan, Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2016**, *55*, 2840.

(10) For select examples on the biological significance and synthesis of chiral indolines, see: (a) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661. (b) Duan, Y.; Li, L.; Chen, M.-W.; Yu, C.-B.; Fan, H.-J.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2014**, *136*, 7688. (c) Romano, C.; Jia, M.; Monari, M.; Manoni, E.; Bandini, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13854.

(11) (a) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924. (b) Huang, X.; Klimczyk, S.; Veiros, L. F.; Maulide, N. *Chem. Sci.* **2013**, *4*, 1105. (c) Klimczyk, S.; Misale, A.; Huang, X.; Maulide, N. *Angew. Chem., Int. Ed.* **2015**, *54*, 10365 and ref 9c..

(12) Phenyl-substituted sulfur ylide and Corey ylide were tested, but only the fast decomposition of substrate **1a** was observed.

(13) CCDC 1471938 and CCDC 1450138 contain the crystallographic data of **10** and **3af**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) (a) Detz, R. J. Triazole-based P,N ligands: discovery of an enantioselective copper catalyzed propargylic amination reaction. Ph.D. thesis, 2009. (b) Nakajima, K.; Shibata, M.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2015**, *137*, 2472.

(15) (a) Díez, J.; Gamasa, M. P.; Panera, M. *Inorg. Chem.* **2006**, *45*, 10043. (b) Panera, M.; Díez, J.; Merino, I.; Rubio, E.; Gamasa, M. P. *Inorg. Chem.* **2009**, *48*, 11147.

DOI: 10.1021/jacs.6b04414
J. Am. Chem. Soc. 2016, 138, 8360−8363