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

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Supporting Information Placeholder

ABSTRACT: The first copper-catalyzed asymmetric decarboxylative [4+1] cycloaddition of propargylic carbamates and sulfur ylides has been 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 stereo-induction 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 an 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).

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, an 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

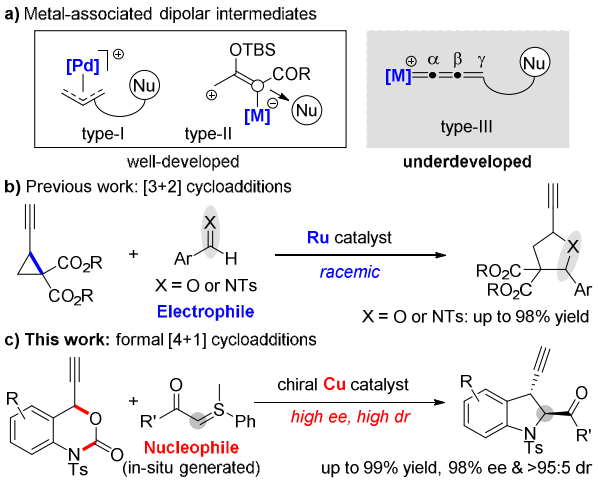
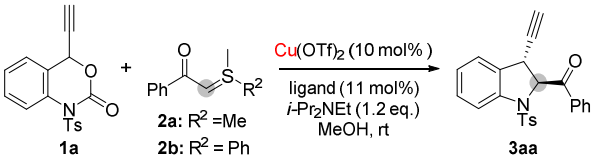


Figure 1. Cycloaddition reactions via metal-associated dipolar intermediates.

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]

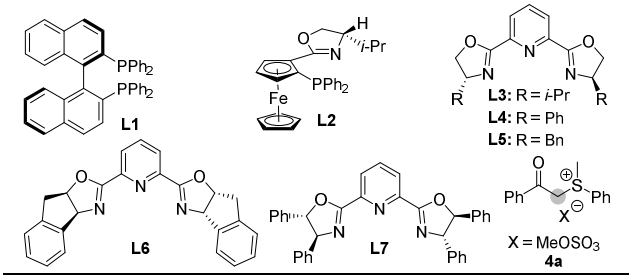
Initially, we performed the cycloaddition reaction of ethynyl benzoxazinanone **1a** and benzoyl sulfur ylide **2a** at room temperature (rt) in the presence of *i*-Pr_2NEt, $Cu(OTf)_2$ and chiral ligand *R*-BINAP (**L1**) in MeOH (Table 1, entry 1). To our delight, the reaction did indeed occur and 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). The investigation of the solvent effect revealed that THF provided the best reaction efficiency despite similar enantiocontrol (entry 8: 97% yield, 53% ee;

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	91
11[d,f,g]	**L4**	**24 h**	**95(94)**[h]	**95**

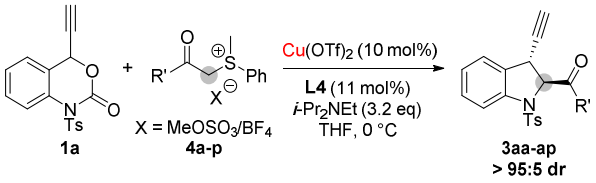
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), **L** (11 mol%) and *i*-Pr_2NEt (1.2 eq.) in MeOH at rt. [b]Determined by ^1H NMR of the reaction mixture containing 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by chiral HPLC analysis. [d]Using THF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



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). Delightfully, when applying a simplified operation 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). The 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

Table 2. Scope of Sulfonium Salts[a]



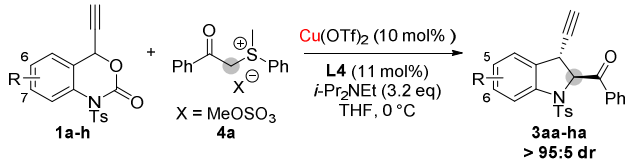
entry	**4**: R'	**3**	yield (%)[b]	ee (%)[c]
1	**4a**: C_6H_5	**3aa**	94	95
2	**4b**: 4-NO_2-C_6H_4	**3ab**	98	96
3	**4c**: 4-CN-C_6H_4	**3ac**	99	94
4	**4d**: 4-F-C_6H_4	**3ad**	99(99)[d]	94(92)[d]
5	**4e**: 4-Cl-C_6H_4	**3ae**	92	98
6	**4f**: 4-Br-C_6H_4	**3af**	93	96
7[e]	**4g**: 4-Me-C_6H_4	**3ag**	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, the reactions were performed at 0.2 mmol scale as entry 11 in Table 1. [b]Isolated yield. [c]Determined by a chiral HPLC analysis. [d]A gram-scale reaction was performed with 1.0 g of **1a** and 2.3 g of **4d** in 28 h and 1.26g of 3ad was obtained (some results are given in parentheses.). [e]Corresponding sulfur ylide was used. [f]Tetrafluoroborate sulfonium salt was used.

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 addition, the 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, the 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). The 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 chlo-

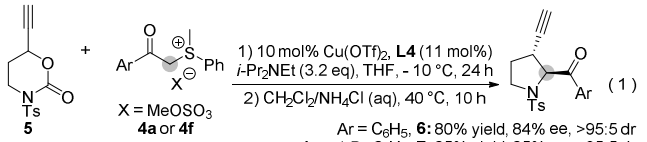
Table 3. Scope of Ethynyl Benzoxazinanones[a]



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

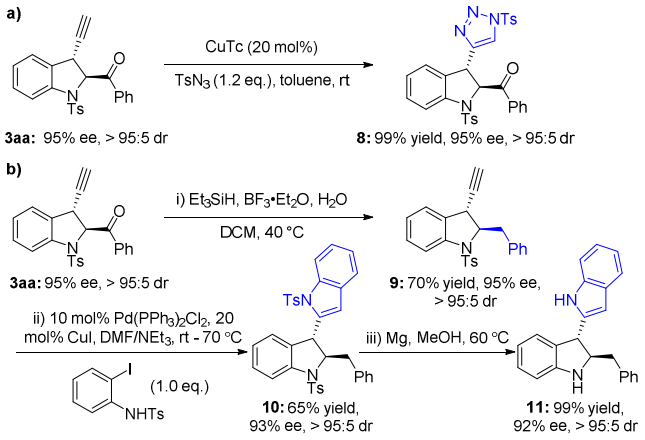
rine atom (**1e**) to the 7-position of ethynyl benzoxazinanone yields the corresponding product **3ea** in an excellent stereocontrol (entry 5: 99% yield, 95% ee and >95:5 dr). Similarly, addition of a trifluoro group to the 7-position of the ethynyl benzoxazinanone was compatible with the present catalyst system, converting into desired product **3fa** in an excellent reaction efficiency and selectivity (entry 6: 96% yield, 94% ee and >95:5 dr). The 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: 80% yield, 88% ee and >95:5 dr). Relatively low enantiomeric excess of chiral indoline **3ga** was probably attributed to the steric effects of the F-substituent at 5 position. Moreover, we have successfully used this Cu-catalyzed asymmetric cycloaddition to prepare chiral pyrrolidines. For example, the reactions of ethynyl carbamate **5** with sulfonium salt **4a** and **4f** could afford the corresponding pyrrolidine **6** and **7** were produced in high enantio- and diastereoselectivity, respectively (eq 1).



(1)

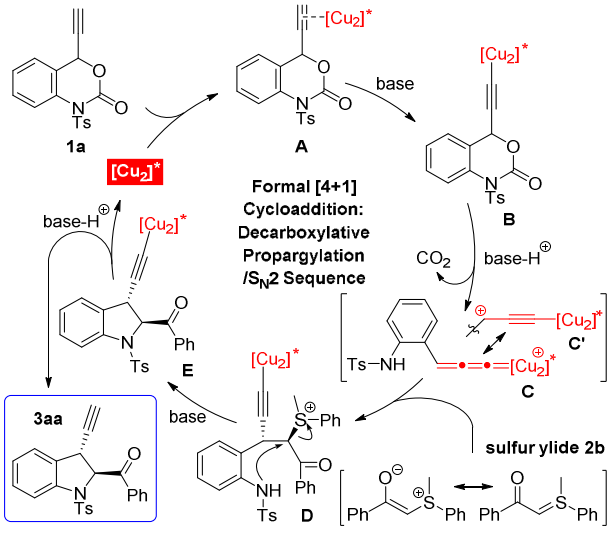
Synthetic transformations were performed to demonstrate the utility of this method. For example, a copper-catalyzed 1,3-dipolar cycloaddition of **3aa** with TsN_3 produced 1,2,3-triazole-substituted chiral indoline **8** in 99% yield with retained enantiopurity (Scheme 1a). Although the active sulfur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

Scheme 1. Synthetic Transformation



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 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.

Scheme 2. Proposed Mechanism



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

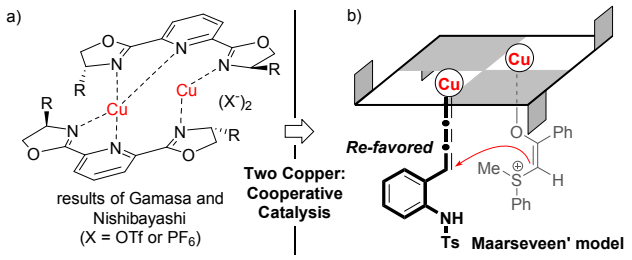


Figure 2. Possible asymmetric induction mode.

In conclusion, we developed a copper-catalyzed asymmetric formal [4+1] cycloaddition for the first time through trapping copper-allenylidene dipolar intermediates by sulfur ylides. Thus, a new approach to chiral indoline products and related cycloadducts was explored in high reaction yields and stereoselectivities (up to 99% yield, 98% ee and >95:5 dr). 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 intermediates are currently in progress.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

*The authors declare no competing financial interests.

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(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.

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Graphic Abstract: