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Catalytic Asymmetric [4 + 3] Annulation of *C,N*-Cyclic Azomethine Imines with Copper Allenylidenes

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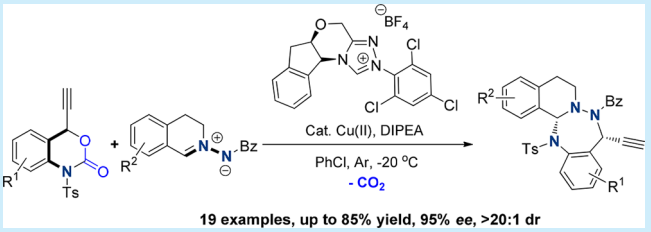
Supporting Information

ABSTRACT: The first asymmetric decarboxylative [4 + 3] annulation of propargylic carbamates with *C,N*-cyclic azomethine imines has been developed successfully by a copper−*N*-heterocyclic carbine system. This strategy led to a series of optically active isoquinoline-fused triazepine derivatives in good yields and with excellent enantio- and diastereoselectivities. Remarkably, Cu−allenylidene intermediates play a crucial role in this transformation.



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Seven-membered dinitrogen-fused *N*-heterocycles are important structural motifs in organic synthesis[1] and have been found as key structural elements commonly appearing in a series of bioactive natural alkaloids and clinically useful pharmaceuticals, including acetyl-CoA carboxylase inhibitors, acaricides, and herbicides.[2] Therefore, the development of highly efficient asymmetric synthetic methods to access these compounds is particularly appealing. Notably, among the wide variety of synthetic approaches,[3] the 1,3-dipolar cycloaddition reaction of cyclic azomethine imines has emerged as one of the most efficient strategies. However, the [4 + 3] cycloaddition reaction of cyclic azomethine imines, especially of catalytic asymmetric variants, still remains elusive and much less developed than their [3 + 2][4] and [3 + 3][5] cycloaddition reactions. To our knowledge, only a few reports of asymmetric catalytic [4 + 3] cycloadditions of *N,N*-cyclic azomethine imines have been described by Chi's group[6a] and Wang's group,[6b] respectively. Furthermore, the more versatile *C,N*-cyclic azomethine imine involved enantioselective [4 + 3] reaction has not yet been achieved to date (Scheme 1a).

Enantioselective decarboxylation of allylic benzoxazinanones has been attracting considerable interest[7] since the development of the palladium-catalyzed [4 + 2] asymmetric decarboxylative cycloaddition (ADC) through in situ generation of an allylpalladium intermediate by Tunge and co-workers in 2008.[8] In 2016, Glorius and co-workers[9] reported the first Pd/NHC-catalyzed ADC [4 + 3] reaction between vinyl benzoxazinanones and *α,β*-unsaturated aldehydes to synthesize seven-membered dinitrogen-fused *N*-heterocycles (Scheme 1b). Alternatively, Xiao and co-workers[10] reported the first copper-catalyzed ADC [4 + 1] reaction employing ethynyl benzoxazinanones by a different copper−allenylidene intermediate activation. In the wake of the emergence of this elegant work, several remarkable asymmetric variants of copper−allenylidene intermediate mediated [4 + 2] annulations have been achieved from the groups of Gong,[11a] You,[11b]

Scheme 1. Catalytic Asymmetric [4 + 3] Annulation with Different Strategies

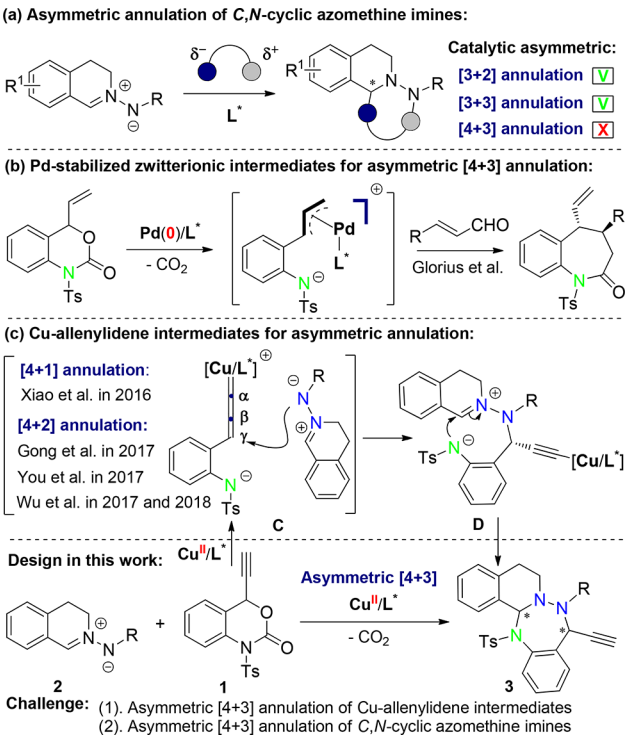

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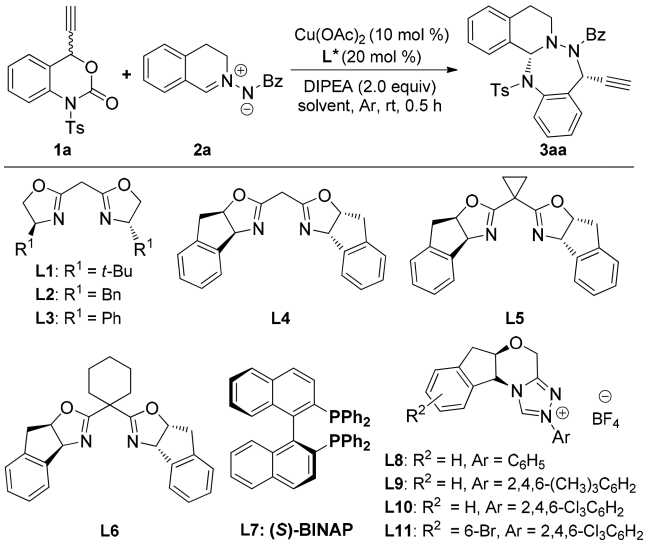
Table 1. Condition Optimization[a]

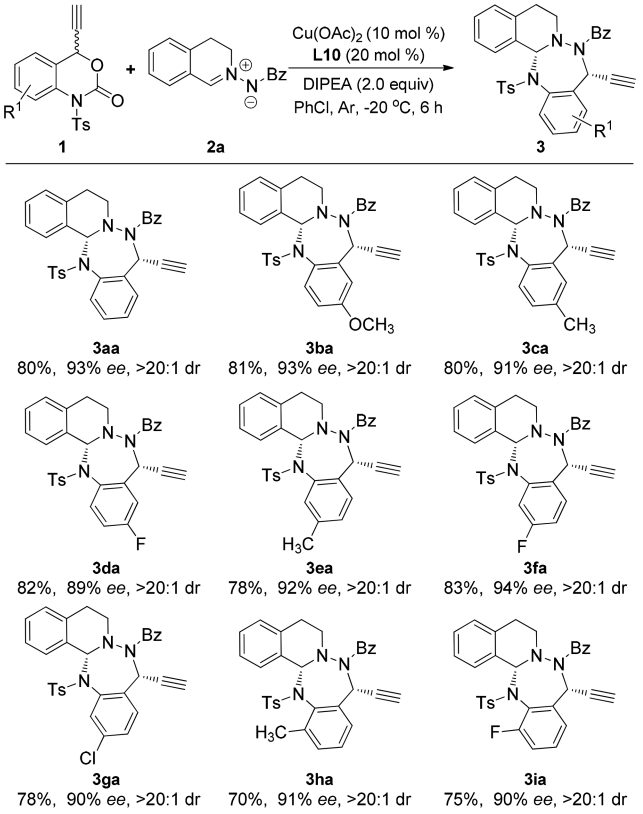


entry	L*	solvent	yield[b] (%)	ee[c] (%)
1	**L1**	MeOH	68	<5
2	**L2**	MeOH	63	<5
3	**L3**	MeOH	65	16
4	**L4**	MeOH	64	16
5	**L5**	MeOH	61	22
6	**L6**	MeOH	57	17
7	**L7**	MeOH	72	<5
8	**L8**	MeOH	70	20
9	**L9**	MeOH	74	30
10	**L10**	MeOH	80	53
11	**L11**	MeOH	78	−20
12	**L10**	CH_2Cl_2	75	32
13	**L10**	THF	64	<5
14	**L10**	$CHCl_3$	74	10
15	**L10**	CH_3CN	35	<5
16[d]	**L10**	Tol	58	55
17	**L10**	PhCl	85	82
18[e]	**L10**	PhCl	82	90
19[f]	**L10**	PhCl	80	93
20[g]	**L10**	PhCl	74	93

[a]Unless noted, reactions were conducted with **1a** (0.20 mmol), **2a** (0.24 mmol), DIPEA (0.40 mmol), $Cu(OAc)_2$ (10 mol %), **L*** (20 mol %), and 2.0 mL of solvent under argon and stirred at room temperature for 0.5 h. [b]Isolated yields. [c]The ee values were determined by HPLC. The dr (>20:1) values were determined by ^{1}H NMR spectroscopy. [d]Stirred for 12 h. [e]Stirred at 0 °C for 1 h. [f]Stirred at −20 °C for 6 h. [g]Stirred at −30 °C for 10 h.

and Wu,[11c,d] respectively. However, although these efficient catalytic asymmetric reactions have been well-established,[12] to date, a catalytic asymmetric higher order annulation reaction such as [4 + 3] ADC has not yet been established, and we believe this represents a considerable challenge (Scheme 1c). Herein, we introduce a copper−NHC catalytic system for a strategy of in situ generating copper−NHC−allenylidene as a new platform for the design of catalytic intermolecular [4 + 3] ADC processes, and we also hope to expand our studies beyond model compounds to develop an efficient protocol for accessing potentially bioactive seven-membered chiral dinitrogen-fused *N*-heterocycles. In this context, we document decarboxylative [4 + 3] annulation of propargylic carbamates with *C*,*N*-cyclic azomethine imines.

Scheme 2. Scope of Substituents of 1 for Enantioselective [4 + 3] Annulation[a]



[a]Unless noted, all of the reactionsfollowed the conditions of entry 19 in Table 1. Yields are of isolated of **3**. The ee values were determined by HPLC. The dr values were determined by ^{1}H NMR spectroscopy. The configuration was assigned by comparison of HPLC data and X-ray crystal data of **3da**.

To explore the possibility of the proposed [4 + 3] annulation process, a model reaction of ethynyl benzoxazinanone (**1a**) with benzoyl (3,4-dihydroisoquinolin-2-ium-2-yl)amide (**2a**) in the presence of $Cu(OAc)_2$ (10 mol %), chiral ligand **L** (20 mol %), and DIPEA (2.0 equiv) was performed at room temperature in methanol (Table 1, entries 1−11). These results indicate that the NHC ligand **L10** provided the highest chemical yield and enantioselectivity of the ligands tested, furnishing the desired product **3aa** in 80% yield and 53% ee (entry 10). Subsequently, a survey of solvents was carried out (entries 12−17). We found that the solvent had a significant effect on the enantioselective outcome. Among the solvents tested, chlorobenzene was optimal, giving the product with 85% yield in high stereoselectivity (82% ee and a >20:1 diastereomeric ratio (dr), entry 17). Gratifyingly, the more favorable outcome of 93% ee was observed without a significant decrease in yield when the reaction was performed at −20 °C (entry 19).

Having established the optimal reaction conditions, we explored a new method for the asymmetric [4 + 3] annulation with a variety of substituted ethynyl benzoxazinanones **1**. As summarized in Scheme 2, various substituted ethynyl benzoxazinanones including those bearing electron-withdrawing and electron-donating substituents at different positions on the aromatic ring could be tolerated and gave the corresponding compounds **3ba**−**ga** in high yields (78%−

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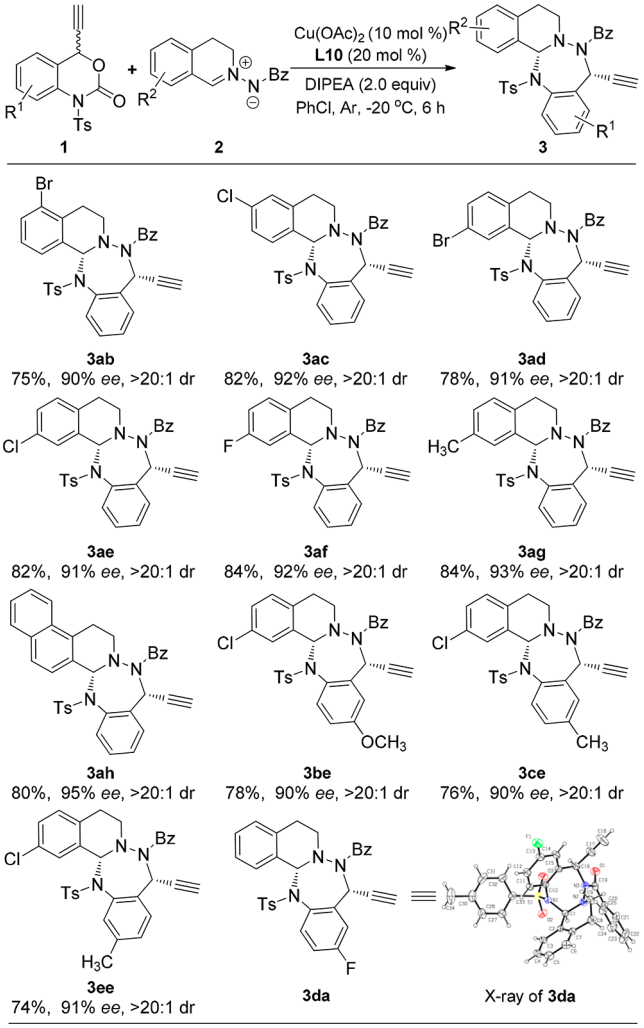
Scheme 3. Scope of Substituents of 2 for Enantioselective [4 + 3] Annulation[a]



[a]Unless noted, all the reactions followed the conditions of entry 19 in Table 1. Yields are of isolated of **3**. The ee values were determined by HPLC. The dr values were determined by ^{1}H NMR spectroscopy. The configuration was assigned by comparison of HPLC data and X-ray crystal data of **3da**.

Scheme 4. Synthetic Transformations of 3aa

83%), diastereoselectivities (>20:1 dr), and high to excellent enantioselectivities (89%−94% ee). Additionally, **1h** and **1i** bearing electron-donating and electron-withdrawing substituents at the C8 position also gave the desired products in good yields and excellent enantioselectivities (**3ha**: 70% yield, 91% ee; **3ia**: 75% yield, 90% ee).

We then sought to expand the reaction to various *C,N*-cyclic azomethine imines (Scheme 3). Variation of the electronic properties of the substituents at different positions on the aromatic ring of *C,N*-cyclic azomethine imines was tolerated,

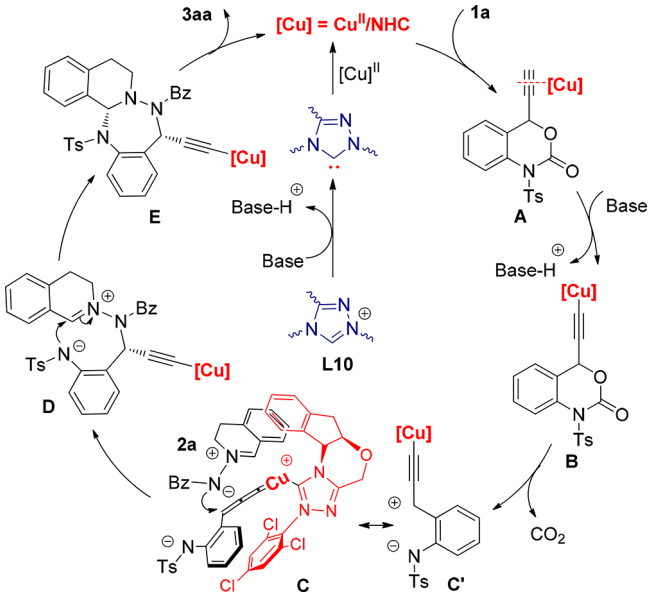


Figure 1. Proposed mechanism for Cu-catalyzed asymmertric [4 + 3] annulation.

and **3ab**−**ag** were obtained with excellent enantioselectivities (90%−93% ee) and diastereoselectivities (>20:1 dr) in yields ranging from 75% to 84%. The catalytic system also proved to be efficient with **2h** bearing a naphthyl substituent, furnishing the distinct pentacyclic compound **3ah** in a higher enantioselectivity (95% ee). In addition, the reactions of 7-chlorine-substituted **2e** with differently substituted **1** (**1b**, **1c**, and **1e**) were successful and provided the optically pure products (**3be**, **3ce**, and **3ee**) with high enantioselectivities (90%−91% ee), albeit in reduced yields (74%−78% yields). The absolute configurations of the products were determined to be (9*R*,14*aR*) by X-ray crystal structure analysis of **3da** (Scheme 3; see the Supporting Information for details).

As an illustration in Scheme 4, the ethynyl moiety of the optically active benzazepine **3aa** could be converted smoothly into the triazole **4** via Huisgen cycloaddition with tosyl azide in the presence of the copper(I) thiophene-2-carboxylate (CuTc). As expected, **4** was formed in 89% yield and without a significant loss in enantiopurity (89% ee).

On the basis of our experimental results and recent studies,[11] a plausible catalytic cycle has been proposed in Figure 1. Initially, the alkyne of substrate **1a** could be activated by a Cu^{II}−NHC complex, which was formed from $Cu(OAc)_2$ and **L10**, generating a π-complex **A**, and a subsequent deprotonation to deliver intermediate **B**. Then the decarboxylation reaction of **B** could successfully afford the copper π-alkyne complex **C**′ or its resonance structure **C**. Next, a thermal [4 + 3] cycloaddition between the copper−allenylidene intermediate **C** as a 1,3-dipolarophile and *N*-cyclic azomethine imine **2a** enables intermediates **D** and **E**. Finally, the intermediate **E** with the top face blocked by the substituents on NHC undergoes a protonation to yield the chiral tetracyclic product **3aa** and releases the active copper catalyst. As a result of the main stereochemical control from π−π stacking and steric hindrance from the substituents on NHC, high *Re* face and endo diastereoselectivity would be enforced to give the desired chiral product, which is consistent with the experimental results.

In summary, we have disclosed a highly efficient asymmetric [4 + 3] annulation of ethynyl benzoxazinanones with *C,N*-

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cyclic azomethine imines using a copper catalyst combined with chiral NHC ligand. This process provides a direct method for the enantioselective construction of isoquinoline-fused triazepine derivatives with excellent stereoselectivities (up to 85% yield, 95% ee, >20:1 dr). Additional studies and applications of this type of copper−allenylidene intermediate to other asymmetric cycloaddition reactions are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02828.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 1836545 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.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to the memory of Professor Carlos F. Barbas III.

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