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Highly Diastereo- and Enantioselective Cu-Catalyzed [3 + 3] Cycloaddition of Propargyl Esters with Cyclic Enamines toward Chiral Bicyclo[*n*.3.1] Frameworks

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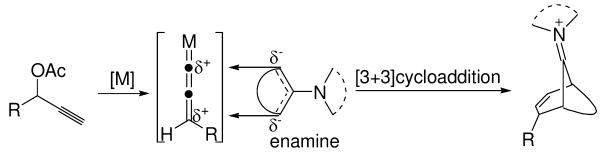
Supporting Information

ABSTRACT: A new Cu-catalyzed asymmetric [3 + 3] cycloaddition of propargyl esters with cyclic enamines is reported. With a combination of $Cu(OAc)_2·H_2O$ and a chiral tridentate ferrocenyl-P,N,N ligand as the catalyst, perfect endo selectivities (endo/exo > 98/2) and excellent enantioselectivities (up to 98% ee) for endo cycloadducts were achieved under mild conditions. This method provides a simple and efficient approach for the synthesis of optically active bicyclo[*n*.3.1] frameworks.

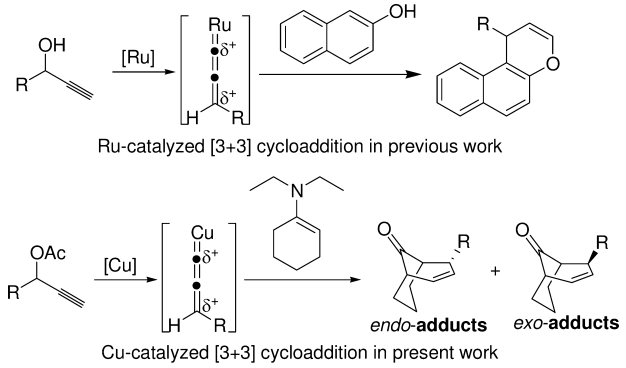
Bicyclo[*n*.3.1]alkane frameworks are quite common in nature as a constituent of many natural and biologically active products and their metabolites.[1] Cycloaddition of appropriate C_3 synthons with cyclic ketones via α,α'-annulation or with their enamine derivatives via β,β'-annulation would offer straightforward access to such frameworks. Since cyclic ketones or enamines provide two nucleophilic C atoms, C_3 synthons possessing two electrophilic centers are required. With this strategy, many approaches have been developed, including asymmetric versions.[2] However, only a few catalytic asymmetric methods have been achieved to date.[3] The development of catalytic enantioselective access to stereochemically defined bicyclo[*n*.3.1] molecules remains challenging.

Recently, catalytic transformations featuring metal−allenylidene intermediates generated from propargyl alcohols or their derivatives have attracted a great deal of attention.[4] Theoretical and experimental studies have indicated that the C_α and C_γ atoms of the metal−allenylidene complexes are the electrophilic centers.[5] We therefore envisioned that a cycloaddition of cyclic enamines with propargyl esters as C_3 synthons would be possible if the metal−allenylidene could be catalytically generated in the presence of a suitable metal catalyst (Scheme 1). In fact, some Au-[6] and Ru-catalyzed[7] cycloadditions using propargyl alcohol derivatives as C_3 synthons have recently been reported, and the Ru-catalyzed cycloadditions of propargyl alcohols with 2-naphthols reported by Uemura and Nishibayashi have demonstrated that propargyl alcohols can be used as dielectrophilic C_3 synthons via Ru−allenylidene intermediates (Scheme 2). In this work, we report the first example of highly diastereo- and enantioeslective Cu-catalyzed [3 + 3] cycloaddition of cyclic enamines with propargyl esters as C_3 synthons employing a chiral ferrocenyl-P,N,N ligand, leading to optically active bicyclo[*n*.3.1] skeletons.

Scheme 1. General Reaction Scheme for [3 + 3] Cycloaddition of Propargyl Esters with Cyclic Enamines



Scheme 2. Propargyl Alcohol Derivatives as C_3 Synthons for Cycloaddition via Metal−Allenylidene Intermediates



We started our investigation by screening different metal catalysts for the cycloaddition of 1-phenyl-2-propynyl acetate (**1a**) with *N*,*N*-diethyl-1-cyclohexen-1-amine (**2a**), and some representative results are summarized in Table 1. Whereas most of the tested metal catalysts were inefficient in the attempted catalytic cycloaddition, $Cu(OAc)_2·H_2O$ was found to be a probable catalyst [see the Supporting Information (SI)]. The use of $Cu(OAc)_2·H_2O$ afforded the propargyl alkylation product **4**,[8] accompanied by the formation of the expected cycloadduct **3a** to a small extent as detected by ^{1}H NMR analysis (entry 1). This result prompted us to modify $Cu(OAc)_2·H_2O$ with a chiral ligand in an attempt to improve the cyclization outcome and achieve enantioinduction in **3a**. Gratifyingly, the addition of (*S*)-BINAP (**L1**) significantly facilitated cycloaddition over competitive propargyl substitution

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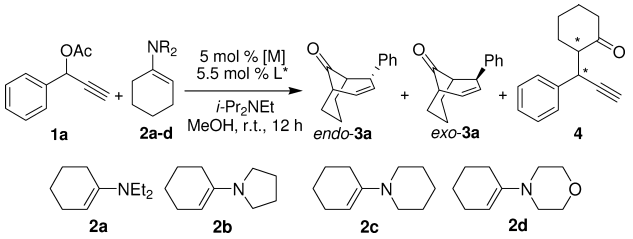
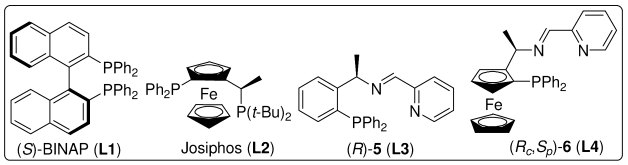
Table 1. Optimization of [3 + 3] Cycloaddition of Propargyl Acetate 1a with Cyclic Enamines 2a–d[a]



entry	[M]	2	L*	yield of 3a (%)[b]	*endo*-3a (% ee[c]):*exo*-3a:4[d]
1	$Cu(OAc)_2·H_2O$	2a	–	trace	7:0:93
2	$Cu(OAc)_2·H_2O$	2a	L1	58	61 (60):12:27
3	$Cu(OAc)_2·H_2O$	2a	L2	62	78 (42):6:16
4	$Cu(OAc)_2·H_2O$	2a	L3	82	97 (90):3:0
5	$Cu(OAc)_2·H_2O$	2a	L4	86	>98 (95):<2:0
6	$Cu(OTf)_2$	2a	L4	87	97 (94):3:0
7	CuCl	2a	L4	25	34 (93):1:65
8	CuOAc	2a	L4	82	97 (96):3:0
9	$Cu(OAc)_2·H_2O$	2b	L4	52	49 (80):29:22
10	$Cu(OAc)_2·H_2O$	2c	L4	49	48 (82):16:36
11	$Cu(OAc)_2·H_2O$	2d	L4	–	6:0:94

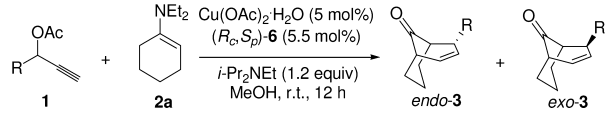
[a]Conditions: **1a** (0.3 mmol, 1.0 equiv), **2a–d** (0.36 mmol, 1.2 equiv), [M] (0.015 mmol, 5 mol %), L* (0.0165 mmol, 5.5 mol %), *i*-Pr_2NEt (0.36 mmol, 1.2 equiv), 2 mL of MeOH, rt, 12 h. [b]Isolated yields. [c]The %ee was determined by chiral HPLC analysis. [d]The *endo*-**3a**:*exo*-**3b**:**4** ratios were determined by ^{1}H NMR analysis.



with a **3a**/**4** selectivity of 73/27 (entry 2). Subsequent ligand screening identified chiral P,N,N-tridentate ligands developed within our group as promising ligands (entries 3–5). Among them, the ferrocenyl ligand (R_c,S_p)-**6** (**L4**) showed the best performance, affording the cycloadduct **3a** as the only product in good yield (86%) with excellent endo selectivity (endo/exo > 98/2) and high enantioselectivity (95% ee) for *endo*-**3a** (entry 5). Investigation of Cu salts modified with (R_c,S_p)-**6** showed that except for CuCl,[9] all of the Cu salts, including $Cu(OTf)_2$ and CuOAc, displayed excellent performance, exclusively providing the cycloadduct **3a** in good yields with high diastereo- and enantioselectivities (entries 5, 6, and 8).[10] In addition, we investigated the influence of the amino group of the cyclic enamine substrate on the selectivity between cycloaddition and competitive propargyl alkylation. The results disclosed that the presence of cyclic amino groups dramatically decreases the selectivity for cycloaddition. Thus, the use of morpholine-derived enamine **2d** greatly suppressed the cycloaddition, predominantly forming the alkylation product **4** (entry 11).

Under the optimized conditions (see Table 1, entry 5), the scope of the cycloaddition with respect to the propargyl acetate substrate was investigated (Table 2). We were pleased to find that the reaction worked efficiently for all of the phenyl-substituted substrates tested, which gave the desired endo adducts in good yields with excellent enantioselectivities (92–98% ee). In all cases, the cycloadduct was the only product

Table 2. Enantioselective Cu-Catalyzed [3 + 3] Cycloaddition: Propargyl Acetate Scope[a]



entry	R	1	3	yield (%)[b]	endo/exo[c]	ee of *endo*-3 (%)[d]
1	C_6H_5	1a	3a	86	>98/2	95
2	4-ClC_6H_4	1b	3b	85	>98/2	97
3	3-ClC_6H_4	1c	3c	88	>98/2	98
4	2-ClC_6H_4	1d	3d	86	>98/2	96
5	4-FC_6H_4	1e	3e	86	>98/2	97
6	4-BrC_6H_4	1f	3f	88	>98/2	97
7	4-$CF_3C_6H_4$	1g	3g	80	>98/2	97
8	4-MeC_6H_4	1h	3h	84	>98/2	94
9	4-$MeOC_6H_4$	1i	3i	87	>98/2	92
10	2-naphthyl	1j	3j	86	>98/2	97
11	2-furyl	1k	3k	86	>98/2	95
12[e]	3-pyridyl	1l	3l	71	>98/2	89
13	*n*-Pr	1m	3m	68	>98/2	91
14	Me	1n	3n	58	>98/2	97
15[f]	H	1o	3o	74	–	67

[a]Conditions: **1** (0.3 mmol, 1.0 equiv), **2a** (0.36 mmol, 1.2 equiv), $Cu(OAc)_2·H_2O$ (0.015 mmol, 5 mol %), (R_c,S_p)-**6** (0.0165 mmol, 5.5 mol %), *i*-Pr_2NEt (0.36 mmol, 1.2 equiv), 2 mL of MeOH, rt, 12 h. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis. [e]A catalyst loading of 10 mol % was used. [f]Instead of propargyl acetate **1o**, the corresponding ethyl carbonate was used, and (*R*)-**5** was used as the catalyst ligand.

observed, with an endo/exo ratio as high as >98/2. It appeared that the position of the substituent on the phenyl ring had little effect on this process. Thus, the three substrates with a Cl group at the different positions of the phenyl ring gave similar results (entries 2–4). However, the electronic properties of the substituent at the para position showed some influence on the enantioselectivity, with substrates having an electron-withdrawing group tending to give higher enantioselectivities than those having an electron-donating group (entries 5–9). Thus, a *p*-methoxy substituent led to slightly decreased enantioselectivity (92% ee) (entry 9). 2-Naphthyl-substituted substrate **1j** was also a suitable reaction partner, giving endo cycloadduct **3j** with 97% ee (entry 10). O-Heteroaromatic substrate **1k** turned out to serve well as the substrate for this process, providing endo cycloadduct **3k** with 95% ee (entry 11). However, 3-pyridyl substrate **1l** was less efficient in this reaction, as a 71% yield with 89% ee was achieved under a catalyst loading of 10 mol % (entry 12). It is noteworthy that the propargyl acetates **1m** and **1n** with a nonaromatic substituent were also suitable substrates, providing the corresponding endo cycloadducts **3m** and **3n** with good enantioselectivities (entries 13 and 14). However, using the most simple propargyl acetate, **1o** (R = H), as the substrate for this cycloaddition was less successful. With a combination of $Cu(OAc)_2·H_2O$ and (*R*)-**5** as the catalyst, the ethyl carbonate corresponding to **1o** (i.e., the ethyl carbonate of prop-2-yn-1-ol) smoothly gave cycloadduct **3o** in 74% yield with 67% ee (entry 15).

The cyclic enamine scope was also surveyed (Table 3). The reaction demonstrated a broad generality with respect to the cyclic enamine. In all cases, the cycloadducts were obtained as the only product, with endo selectivities of >98/2. Enamine **2e**

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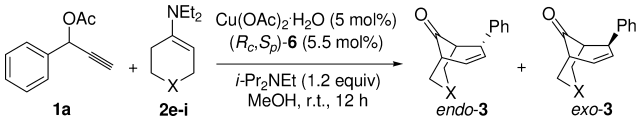
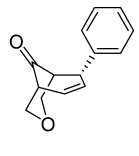
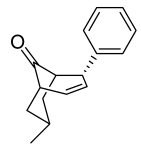
Table 3. Enantioselective Cu-Catalyzed [3 + 3] Cycloaddition: Cyclic Enamine Scope[a]

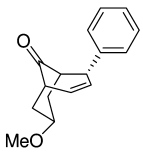




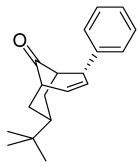
endo-**3p**
78% yield, 93% ee
endo/*exo* > 98/2



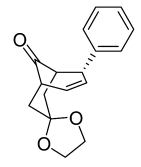
endo-**3q**
84% yield[b], 89% ee
endo/*exo* > 98/2
trans/*cis* = 95/5



endo-**3r**
60% yield[b], 95% ee
endo/*exo* > 98/2
trans/*cis* = 87/13



endo-**3s**
74% yield[b], 81% ee
endo/*exo* > 98/2
trans/*cis* > 98/2



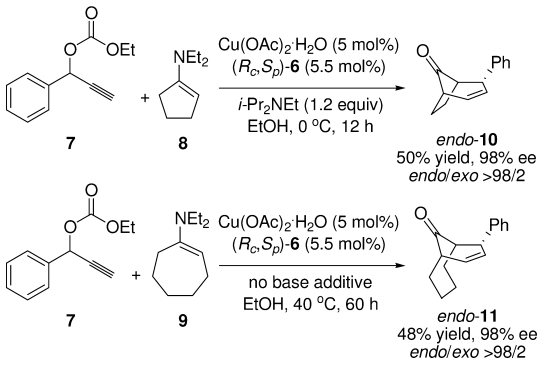
endo-**3t**[c]
76% yield, 89% ee
endo/*exo* > 98/2

[a]Conditions: **1** (0.3 mmol, 1.0 equiv), **2a** (0.36 mmol, 1.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (0.015 mmol, 5 mol %), (R_c,S_p)-**6** (0.0165 mmol, 5.5 mol %), *i*-Pr_2NEt (0.36 mmol, 1.2 equiv), 2 mL of MeOH, rt, 12 h. All yields are isolated yields, and ee values were determined by chiral HPLC analysis. The endo/exo and trans/cis ratios were determined by ^1H NMR analysis. [b]Isolated yield of a cis/trans mixture. [c]The reaction was performed at 40 °C.

derived from 4-oxacyclohexanone worked as efficiently as its cyclohexenyl analogue **2a**. The presence of a para group on the cyclohexenamine had some effect on the reactivity and enantioselectivity, and a bulky *tert*-butyl group led to diminished enantioselectivity (81% ee). When a 4,4-disubstituted cyclohexenamine was probed as the substrate, an elevated reaction temperature (40 °C) was necessary for complete conversion.

In contrast to **2a**, its five- and seven-membered analogues **8** and **9** proved to be more difficult substrates for this process (Scheme 3). Under the optimized conditions, the reactions of propargyl acetate **1a** with **8** and **9** proceeded very sluggishly. When **1a** was replaced with the corresponding ethyl carbonate **7** and the reaction was performed in EtOH at 0 °C, the

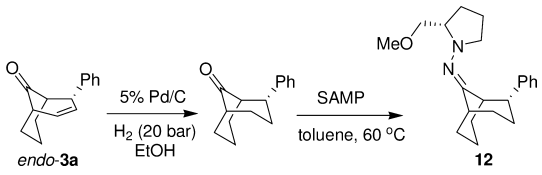
Scheme 3. Cycloaddition of Propargyl Carbonate 7 with Five- and Seven-Membered Cyclic Enamines



cycloaddition with five-membered substrate **8** resulted in efficient formation of endo cycloadduct **10** as the only product in 50% yield with 98% ee. For **9**, however, a higher reaction temperature (40 °C) and a longer reaction time (60 h) were required in order to obtain a reasonable conversion.

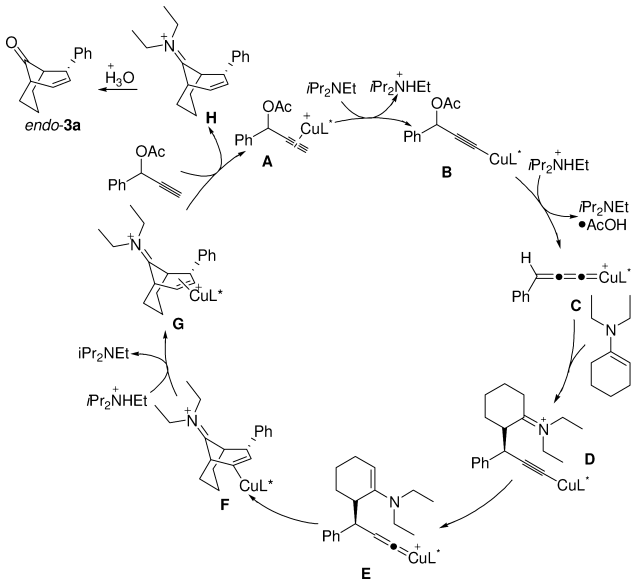
The absolute configuration of *endo*-**3a** was determined by X-ray analysis of compound **12**, which was obtained by derivatization of *endo*-**3a** with (*S*)-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP) (Scheme 4).[11]

Scheme 4. Derivatization of *endo*-3a for Determination of the Absolute Configuration



We propose the plausible mechanism shown in Scheme 5. In the first step, the Cu complex probably forms a π complex with

Scheme 5. Proposed Mechanism for [3 + 3] Cycloaddition of Propargyl Acetate with Cyclic Enamine



the propargyl acetate (**A**). Deprotonation of **A** with a base would then give Cu−acetylide complex **B**, which would explain why a propargyl acetate bearing an internal alkyne moiety such as 1,3-diphenyl-2-propynyl acetate did not react at all (see the SI). Loss of an acetyl group from **B** would form Cu−allenylidene complex **C**.[12] Recent studies of Cu-catalyzed propargyl substitution have supported the formation of a Cu−allenylidene complex as a key intermediate.[13] Nucleophilic attack of the enamine C_β at the C_γ atom of **C** would give the corresponding Cu−acetylide complex **D**, which should be the key step for the stereoselection. The H atom could then shift to C_β of the Cu−acetylide complex to give Cu−vinylidene complex **E**. Intramolecular nucleophilic attack of the enamine C_β at the C_α atom of **E** would afford alkenyl complex **F**. Further investigations to elucidate the reaction mechanism are underway and will be reported in due course. In addition,

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unambiguous structural characterization of a CuCl−(R_c,S_p)-**6** complex by X-ray analysis has been achieved.[14]

In summary, we have developed the first example of Cu-catalyzed asymmetric [3 + 3] cycloaddition of propargyl esters with cyclic enamines. A combination of $Cu(OAc)_2 \cdot H_2O$ and a chiral tridentate ferrocenyl-P,N,N ligand has been identified as an efficient catalyst that afforded excellent endo selectivity (endo/exo > 98/2) and normally excellent enantioselectivity for a wide range of substrates. The mild conditions, broad substrate scope, good yield, and high diastereo- and enantioselectivity make the present process highly useful in the synthesis of optically active bicyclo[*n*.3.1] frameworks. Efforts to expand the scope of this cycloaddition and to determine the reaction mechanism are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; characterization data, ^{1}H NMR and ^{13}C NMR spectra, and HPLC data for ee analysis for *endo*-**3a**−**t**, *exo*-**3a**, **4**, and **10**−**12**; and X-ray data (CIF) for **12** and the CuCl/(R_c,S_p)-**6** complex. 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 interest.

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