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Enantioselective Copper-Catalyzed Formal [4 + 2] Cycloaddition of *o*-Aminophenol Derivatives with Propargylic Esters for Synthesis of Optically Active 3,4-Dihydro-2*H*-1,4-benzoxazines

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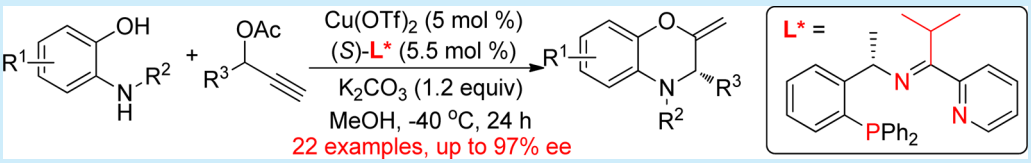
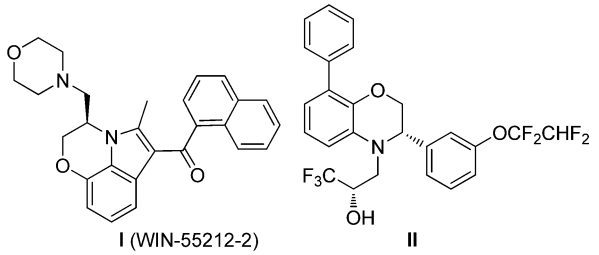
Supporting Information



ABSTRACT: The first copper-catalyzed asymmetric formal [4 + 2] cycloaddition of *o*-aminophenol derivatives with propargylic esters as the bis-electrophilic C2 synthons for the stereoselective construction of chiral 2,3,4-trisubstituted 2*H*-1,4-benzoxazines bearing an exocyclic double bond has been developed. By using a structurally modified chiral ketimine P,N,N-ligand, a wide range of optically active 2*H*-1,4-benzoxazines were prepared in high yields and with excellent enantioselectivities (up to 97% ee).

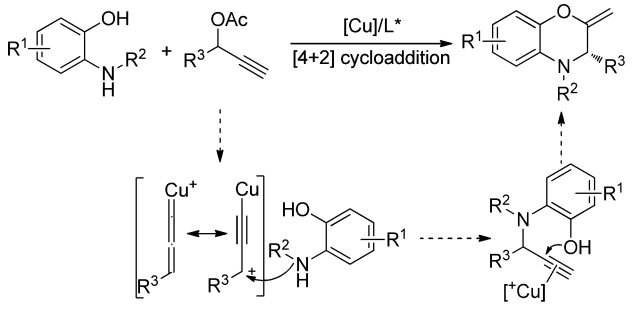
Optically active 3,4-dihydro-2*H*-1,4-benzoxazines are core structures found in a wide array of bioactive compounds such as naturally occurring alkaloids and pharmaceuticals;[1] e.g., compound **I**[1e,f] is a cannabinoid receptor agonist and **II**[1g] is a cholesteryl ester transfer protein inhibitor. The development of efficient methodologies for enantioselective synthesis of these chiral compounds therefore becomes an important issue.[2] In the past few decades, some catalytic asymmetric approaches, mostly relying on the catalytic asymmetric hydrogenation and reduction of benzoxazines, have been successfully developed, which traditionally give rise to optically active 3-substituted 2*H*-1,4-benzoxazines.[3] To our knowledge, however, no catalytic asymmetric method has been reported for the stereoselective construction of chiral 2,3,4-multisubstituted 2*H*-1,4-benzoxazines. The development of novel strategies for the enantioselective synthesis of optically active 2*H*-1,4-benzoxazines with functional diversity remains a highly desirable and challenging task.



I (WIN-55212-2) II

In the past few years, copper-catalyzed asymmetric propargylic transformation has made significant progress, featuring Cu–allenylidene complexes as the key intermediates.[4] In particular, we have very recently disclosed that propargylic esters could be used as the C2 synthons for the copper-catalyzed asymmetric formal [3 + 2] cycloaddition with bis-nucleophilic *β*-ketoesters via the sequential propargylic alkylation/intramolecular hydroalkoxylation process, leading to highly functionalized chiral 2,3-dihydrofurans.[5] Considering the high potential of this cycloaddition strategy in the construction of optically active heterocyclic frameworks with structural diversity, further exploration of a new type of bis-nucleophiles to enrich the scope and utility of this category of synthetic transformations is therefore in high demand. In this context, we envisioned that an N,O-bis-nucleophile may be a suitable reaction partner for the cycloaddition with propargylic esters due to recent progress in the copper-catalyzed asymmetric propargylic amination,[6] a key step proposed in the realization of the cycloaddition using this type of bis-nucleophile (Scheme 1).

Scheme 1. Proposed Copper-Catalyzed Asymmetric Formal [4 + 2] Cycloaddition of Propargylic Esters with *o*-Aminophenol Derivatives



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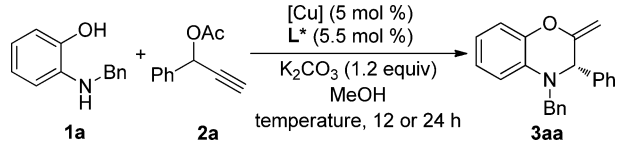
As a result, herein we describe the first copper-catalyzed enantioselective formal [4 + 2] cycloaddition of *o*-aminophenol derivatives with propargylic esters via the sequential propargylic amination/hydrophenoxylation process, giving rise to highly functionalized chiral 2*H*-1,4-benzoxazines. By employing a structurally modified ketimine tridentate P,N,N-ligand, a variety of optically active 2*H*-1,4-benzoxazines bearing an exocyclic double bond at the 2-position can be achieved in high yields and good to excellent enantioselectivities. The present methodology represents a new synthetic strategy for the stereoselective construction of chiral 2,3,4-trisubstituted-2*H*-1,4-benzoxazines that remain unavailable with the reported methods.

At the beginning of this study, 2-(benzylamino)phenol **1a** and 1-phenylprop-2-yn-1-yl acetate **2a** were selected as model substrates to evaluate the title reaction, and representative results are summarized in Table 1. Inspired by recent success in the copper-catalyzed asymmetric propargylic transformation,[4] we focused our initial experiments on the copper-catalyst system by screening a variety of chiral ligands. The reaction was performed in MeOH at 0 °C for 12 h in the presence of a catalyst prepared in situ from $Cu(OTf)_2$ and chiral ligand. To our disappointment, initial screening with BINAP (**L1**) and diPh-pybox (**L2**) did not lead to the envisioned cycloadduct but instead gave propargylic amination product (entries 1 and 2). Fortunately, subsequent ligand screening revealed that the use of tridentate P,N,N-ligands enabled the anticipated [4 + 2] cycloaddition (entries 3−6). In particular, the bulky and structurally rigid ketimine-type P,N,N-ligands (*S*)-**L4b** and (*S*)-**L4c** displayed good performance, with (*S*)-**L4b** identified as the optimal ligand, affording the desired cycloadduct 4-benzyl-2-methylene-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine **3aa** in high yield (97%) and with good enantioselectivity (84% ee) (entry 5). Copper salts showed less effect in the enantioselectivity, and in all cases, good enantioselectivities have been achieved (entries 7−10). The reaction proved to be highly sensitive to the solvent, and the protic solvent MeOH showed superiority over aprotic solvents such as CH_2Cl_2, toluene, and THF (entries 11−13). The base additive proved to be crucial to the reaction since no reaction was observed in its absence (entry 14). The use of organic bases such as $^iPr_2NEt$ and Et_3N led to reduced yields (entries 15 and 16). Stronger basicity of K_2CO_3 in comparison with these organic bases should be responsible to the increased reactivity. With K_2CO_3, phenoxide can be more readily generated, which is crucial to the last hydrophenoxylation step. Lowering the reaction temperature to −40 °C significantly improved the reaction outcome, delivering the [4 + 2] cycloadduct **3aa** in 97% yield and with enantioselectivity of 93% ee (entry 17). The modification of the ligand structure disclosed that (*S*)-**L4e** bearing an isopropyl group on the imino moiety could further increase the enantioselectivity to 94% ee (entry 19).

With the optimized reaction conditions in hand, the substrate scope of *o*-aminophenol derivatives for the catalytic asymmetric [4 + 2] cycloaddition with **2a** was first examined by varying the substituents on both the phenyl ring and amino moiety, and the results are summarized in Table 2. The results indicated that the reaction well tolerated the substituent on the phenyl ring, irrespective of its electronic properties and the substitution pattern (entries 1−10). The best enantioselectivity was achieved with the substrate **1e** bearing a 6-Me group, providing an ee value of up to 97% (entry 5). However, the substitution pattern on the amino group significantly affected the reactivity and enantioselectivity. Thus, the simplest substrate *o*-aminophenol **1k** did not

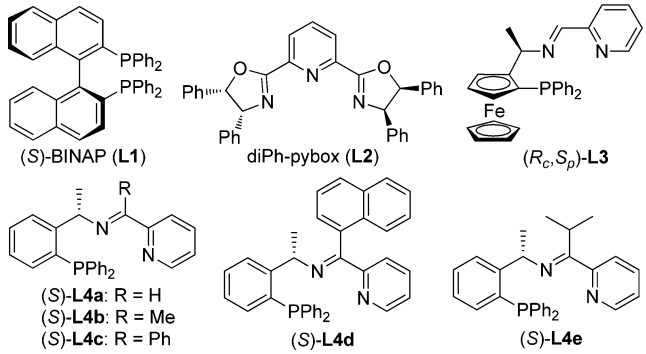
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	[Cu]	t (°C)	L*	yield[b] (%)	ee[c] (%)
1	$Cu(OTf)_2$	0	**L1**		
2	$Cu(OTf)_2$	0	**L2**		
3	$Cu(OTf)_2$	0	**L3**	96	68
4	$Cu(OTf)_2$	0	**L4a**	89	67
5	$Cu(OTf)_2$	0	**L4b**	97	84
6	$Cu(OTf)_2$	0	**L4c**	95	82
7	$Cu(OAc)_2.H_2O$	0	**L4b**	89	80
8	$Cu(MeCN)_4BF_4$	0	**L4b**	95	84
9	CuI	0	**L4b**	83	82
10	CuCl	0	**L4b**	88	84
11[d]	$Cu(OTf)_2$	0	**L4b**	50	35
12[e]	$Cu(OTf)_2$	0	**L4b**	28	48
13[f]	$Cu(OTf)_2$	0	**L4b**	22	0
14[g]	$Cu(OTf)_2$	0	**L4b**		
15[h]	$Cu(OTf)_2$	0	**L4b**	85	83
16[i]	$Cu(OTf)_2$	0	**L4b**	67	89
17	$Cu(OTf)_2$	−40	**L4b**	97	93
18	$Cu(OTf)_2$	−40	**L4d**	89	87
19	$Cu(OTf)_2$	−40	**L4e**	97	94

[a]The reaction was carried out using **1a** (0.3 mmol), **2a** (0.3 mmol), [Cu] (0.015 mmol, 5 mol %), **L*** (0.0165 mmol, 5.5 mol %), base (0.36 mmol, 1.2 equiv) in 3 mL of MeOH at 0 °C for 12 h or −40 °C for 24 h unless otherwise noted. [b]Yield of isolated product. [c]Determined by chiral HPLC. [d]CH_2Cl_2 as the solvent. [e]Toluene as the solvent. [f]THF as the solvent. [g]No base additive. [h]$^iPr_2NEt$ as the base additive. [i]Et_3N as the base additive.



serve as an efficient reaction partner under the optimized conditions for the cycloaddition, with which no cycloadduct was observed (entry 11), while *o*-(methylamino)phenol **1l** gave the desired cycloadduct in good yield and with high enantioselectivity (entry 12). The presence of an acetyl group on the amino moiety substantially reduced the nucleophility of the *N*-atom, which inhibited the initial propargylic amination step. As a result, 2-acetaminophenol **1m** did not serve as the reaction partner for this cycloaddition (entry 13). These results suggested that the presence of an electron-donating group on the amino moiety is crucial to this cycloaddition. The reaction also did not tolerate aliphatic aminoethanols, such as 2-(benzylamino)ethanol.

We next investigated the scope of this catalytic asymmetric [4 + 2] cycloaddition with regard to propargylic esters, and the results are summarized in Table 3. A series of aromatic propargylic esters could be utilized to generate the [4 + 2]

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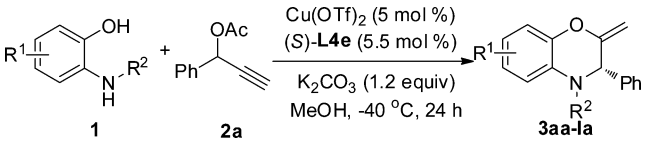
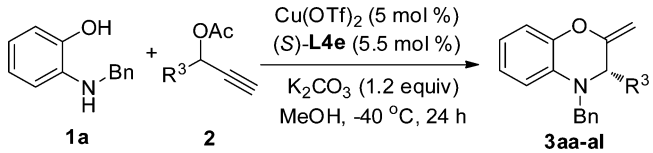
Table 2. Substrate Scope of *o*-Aminophenols[a]



entry	1 (R^1, R^2)	3	yield[b] (%)	ee[c] (%)
1	**1a**: R^1 = H, R^2 = Bn	**3aa**	97	94
2	**1b**: R^1 = 3-Me, R^2 = Bn	**3ba**	97	90
3	**1c**: R^1 = 4-Me, R^2 = Bn	**3ca**	84	92
4	**1d**: R^1 = 5-Me, R^2 = Bn	**3da**	90	94
5	**1e**: R^1 = 6-Me, R^2 = Bn	**3ea**	79	97
6	**1f**: R^1 = 4-NO_2, R^2 = Bn	**3fa**	98	85
7	**1g**: R^1 = 4-SO_2NH_2, R^2 = Bn	**3ga**	97	91
8	**1h**: R^1 = 4-Br, R^2 = Bn	**3ha**	97	96
9	**1i**: R^1 = 4-Cl, R^2 = Bn	**3ia**	98	96
10	**1j**: R^1 = 5-Cl, R^2 = Bn	**3ja**	97	95
11	**1k**: R^1 = H, R^2 = H	**3ka**		
12	**1l**: R^1 = H, R^2 = Me	**3la**	95	90
13	**1m**: R^1 = H, R^2 = Ac	**3ma**		

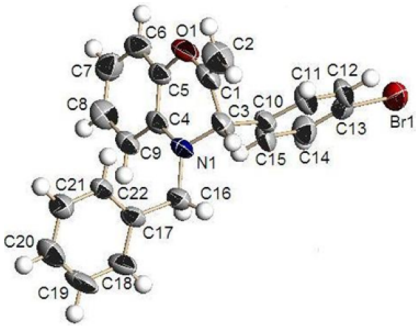
[a]The reaction was carried out using **1** (0.3 mmol), **2a** (0.3 mmol), $Cu(OTf)_2$ (0.015 mmol, 5 mol %), (*S*)-**L4e** (0.0165 mmol, 5.5 mol %), and K_2CO_3 (0.36 mmol, 1.2 equiv) in 3 mL of MeOH in a Schlenk tube at −40 °C for 24 h. [b]Yield of isolated product. [c]Determined by chiral HPLC.

Table 3. Substrate Scope of Propargylic Esters[a]



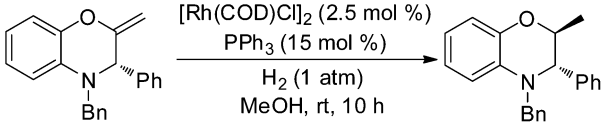
entry	2 (R^3)	3	yield[b] (%)	ee[c] (%)
1	**2a**: R^3 = Ph	**3aa**	97	94
2	**2b**: R^3 = 2-ClC_6H_4	**3ab**	95	80
3	**2c**: R^3 = 3-ClC_6H_4	**3ac**	90	96
4	**2d**: R^3 = 4-ClC_6H_4	**3ad**	96	91
5	**2e**: R^3 = 4-FC_6H_4	**3ae**	97	90
6	**2f**: R^3 = 4-BrC_6H_4	**3af**	97	91
7	**2g**: R^3 = 4-$CF_3C_6H_4$	**3ag**	76	84
8	**2h**: R^3 = 4-MeC_6H_4	**3ah**	97	93
9	**2i**: R^3 = 2-naphthyl	**3ai**	70	93
10	**2j**: R^3 = 2-thienyl	**3aj**	97	78
11[d]	**2k**: R^3 = Me	**3ak**	96	80
12[d]	**2l**: R^3 = Bn	**3al**	84	94

[a]The reaction was carried out using **1a** (0.3 mmol), **2** (0.3 mmol), $Cu(OTf)_2$ (0.015 mmol, 5 mol %), (*S*)-**L4e** (0.0165 mmol, 5.5 mol %), and K_2CO_3 (0.36 mmol, 1.2 equiv) in 3 mL of MeOH in a Schlenk tube at −40 °C for 24 h. [b]Yield of isolated product. [c]Determined by chiral HPLC. [d]The corresponding ethyl carbonates were used instead of acetates.



(*S*)-**3af**

Scheme 2. Synthetic Application



cycloadducts in high yields and enantioselectivities. The substitution pattern of the functionality on the phenyl ring showed some influence on the enantioselectivity (entries 1−8). Thus, the reaction with the substrate **2b** bearing a 2-Cl group led to significantly reduced enantioselectivity in comparison with its 3-Cl or 4-Cl analogues (entries 2−4). The electronic property of the substituent at the para-position of the phenyl ring also affected the reactivity and enantioselectivity (entries 4−8). Decreases in the reactivity and enantioselectivity were observed when 4-CF_3-substituted substrate **2g** was used in the reaction (entry 7). 2-Naphthyl-substituted substrate **2i** also worked well for the reaction (entry 9). However, the use of heteroaromatic propargylic ester **2j** led to a decrease in the enantioselectivity (entry 10). As for the aliphatic substrates, very low conversions were observed. To our delight, good performance was observed by using ethyl carbonates instead of the corresponding acetates since the ethoxycarbonyl group is a much better leaving group for the Cu-catalyzed propargylic amination of aliphatic substrates than the acetoxyl group (entries 11 and 12).[4k] The absolute configuration of the cycloadduct was unambiguously determined by X-ray structure analysis of **3af**, to which an *S*-configuration was assigned.

To demonstrate the utility of 2,3,4-trisubstituted 2*H*-1,4-benzoxazines, we conducted the hydrogenation to generate an additional stereocenter as shown in Scheme 2. The hydrogenation was favorable to give *trans*-distereoisomer (*R*,*S*)-**4** on the basis of the NOE experiments without the deterioration of enantiomeric purity.

In summary, we have disclosed the first copper-catalyzed asymmetric formal [4 + 2] cycloaddition of *o*-aminophenol derivatives with propargylic esters as the C2 synthons. By employing a structurally rigid and finely modified ketimine P,N,N-ligand, a wide array of *o*-aminophenol derivatives and propargylic esters could be efficiently coupled to generate the chiral 2,3,4-trisubstituted 2*H*-1,4-benzoxazines in high yields and good to excellent enantioselectivities (up to 97% ee). The present synthetic protocol represents a novel strategy for the stereoselective construction of optically active 2,3,4-trisubstituted 2*H*-1,4-benzoxazines that remain unavailable via other catalytic asymmetric methods. Further development and application of this reaction are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00322.

Experimental procedures and characterization data for all new compounds (PDF)

X-ray crystallographic data for (*S*)-**3af** (CIF)

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Notes

The authors declare no competing financial interest.

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