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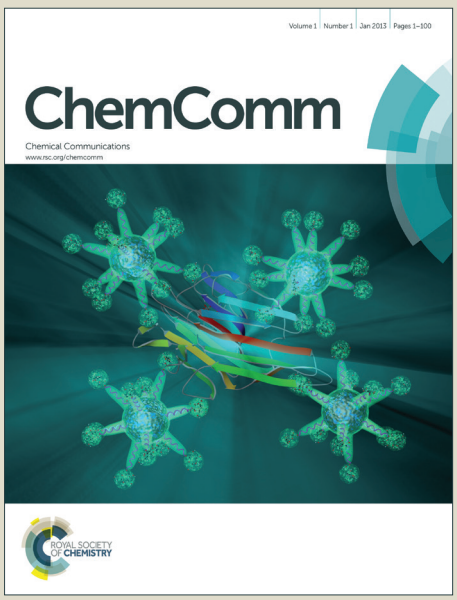

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Highly diastereo- and enantioselective copper-catalyzed propargylic alkylation of acyclic ketone enamines for the construction of two vicinal stereocenters

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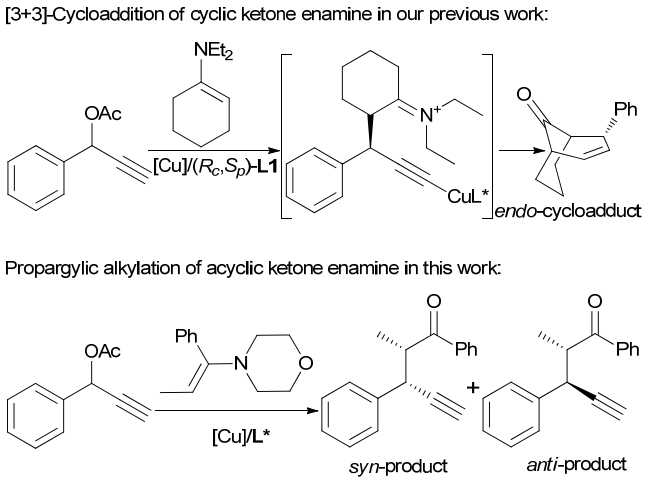
The first highly diastereo- and enantioselective propargylic alkylation of acyclic ketone enamines to form vicinal tertiary stereocenters has been reported by the employment of copper catalysis in combination with a bulky and structurally rigid tridentate ketimine *P,N,N*-ligand.

The stereoselective construction of contiguous multiple stereocenters from simple achiral starting materials is an enduring challenge and a longstanding goal in organic chemistry. In this context, the catalytic asymmetric propargylic alkylation of unstabilized ketone enolates or their equivalents for establishing vicinal stereocenters should be an ideal way toward this end since the corresponding allylic alkylation has recently emerged as one of the most successful strategies in the control of regio-, diastereo- and enantioselectivities.[1] However, the lack of a successful example in terms of diastereo- and enantioselectivities on this domain highlights the challenging nature of this method[2] although the transition metal-catalyzed asymmetric propargylic substitutions have made considerable progress in the past decade.[3-6] Hence, the ability to facilitate the highly diastereo- and enantioselective propargylic alkylation of unstabilized ketone enolates or their equivalents with propargylic esters to directly and selectively generate two adjacent chiral centers would represent a significant advance in the catalytic propargylic substitution.

Recently, we have developed a Cu-catalyzed [3+3] cycloaddition of propargylic acetates with cyclic *N,N*-diethyl-1-enamines for facile access to optically active bicyclo[n.3.1] frameworks bearing three stereocenters in a highly diastereo-/enantioselective form, which proceeds via an asymmetric propargylic alkylation as the key step (Scheme 1).[7] The research also indicated that the use of morpholine-derived cyclic enamine could greatly suppress the last cyclization step, mainly leading to the propargylic alkylation products, presumably since the increased stability of the resulting morpholinium ion prevents the shift of H-atom to C_β of the Cu-acetylide complex. This observation combined with the availability of ketone enamines as surrogates of unstabilized ketone enolates encouraged our further exploration of the application of this transformation to acyclic ketone enamines. To our knowledge, no example of the propargylic alkylation of acyclic ketone enamines for the formation of two adjacent stereogenic centers has been developed. Herein, we report the first highly diastereo-/enantioselective copper-catalyzed propargylic alkylation of morpholine-derived acyclic ketone enamines with propargylic esters in the presence of a bulky and structurally rigid tridentate ketimine *P,N,N*-ligand to forge two vicinal tertiary stereocenters, in which the perfect performance (up to >95/5 dr and >99% ee) has been achieved.

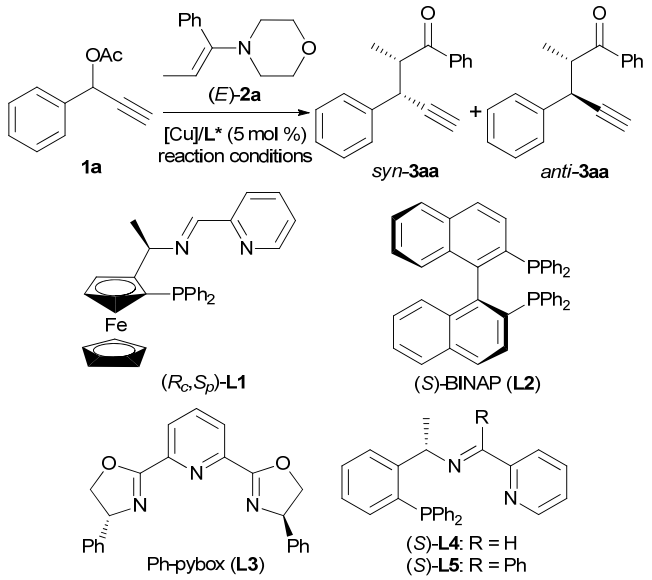


Scheme 1. Copper-catalyzed asymmetric reaction between propargylic esters and enamines.

Initially, we focused our research on looking at the propargylic alkylation of (*E*)-4-(1-phenylprop-1-en-1-yl)morpholine (**2a**) with 1-phenyl-2-propynyl acetate (**1a**) and screening different reaction conditions. Some selected results are summarized in Table 1. Morpholine-derived acyclic enamine **2a** can be readily prepared from propiophenone with morpholine in a nearly pure *E*-configuration (*E*/*Z* > 95/5),[8] which would certainly simplify the reaction screening process. The effect of the ligand was investigated at the outset of our studies, and the reaction was conducted in the presence of 5 mol % of the catalyst prepared in situ from $Cu(OAc)_2 \cdot H_2O$ and chiral ligand. To our disappointment, chiral ferrocenyl P,N,N-ligand (**L1**), which exhibited excellent performance in our previous studies on the Cu-catalyzed asymmetric [3+3] cycloaddition of propargylic esters with cyclic enamines,[7]

provided the propargylic alkylation product **3aa** with low levels of conversion, diastereo-, and enantioselectivities (entry 1). (*S*)-BINAP (**L2**) was also an inferior ligand, leading to very low conversions (entry 2). The use of Ph-pybox (**L3**) afforded **3aa** with good conversion and diastereoselectivity but moderate enantioselectivity (entry 3). We were pleased to find that (*S*)-1-phenylethylamine derived tridentate P,N,N-ligands **L4** and **L5**, developed within our group,[2b,7] furnished the promising yield, dr, and ee (entries 4 and 5). Especially, the sterically bulky **L5** led to the alkylation product **3aa** in 87% yield, and with 89/11 dr and an ee value of up to 98% ee for the major diastereoisomer (entry 5).

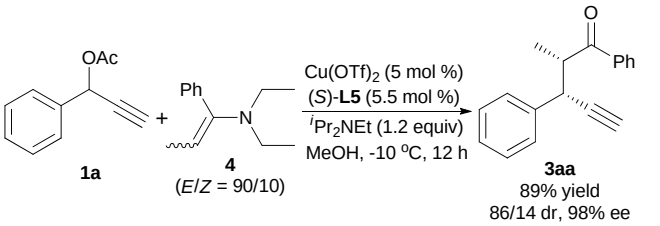
Table 1 Optimization of reaction conditions [a]



Entry	[Cu]	L*	Base	Yield (%)[b]	*syn*/*anti*[c]	ee of *syn*-**3aa** (%)[d]
1	$Cu(OAc)_2{\cdot}H_2O$	**L1**	^{i}Pr$_2$NEt	37	72/28	33
2	$Cu(OAc)_2{\cdot}H_2O$	**L2**	^{i}Pr$_2$NEt	10	77/23	60
3	$Cu(OAc)_2{\cdot}H_2O$	**L3**	^{i}Pr$_2$NEt	87	92/8	55
4	$Cu(OAc)_2{\cdot}H_2O$	**L4**	^{i}Pr$_2$NEt	81	87/13	83
5	$Cu(OAc)_2{\cdot}H_2O$	**L5**	^{i}Pr$_2$NEt	87	89/11	98
6	$Cu(OTf)_2$	**L5**	^{i}Pr$_2$NEt	89	91/9	99
7	CuI	**L5**	^{i}Pr$_2$NEt	71	90/10	91
8	$Cu(MeCN)_4BF_4$	**L5**	^{i}Pr$_2$NEt	88	90/10	96
9	$Cu(OTf)_2$	**L5**	-	63	75/25	99
10	$Cu(OTf)_2$	**L5**	Et_3N	86	88/12	99
11	$Cu(OTf)_2$	**L5**	DBU	25	73/27	61
12	$Cu(OTf)_2$	**L5**	^{t}BuOK	27	65/35	45
13[e]	$Cu(OTf)_2$	**L5**	^{i}Pr$_2$NEt	14	69/31	90
14[f]	$Cu(OTf)_2$	**L5**	^{i}Pr$_2$NEt	-	-	-
15[g]	$Cu(OTf)_2$	**L5**	^{i}Pr$_2$NEt	94	>95/5	>99

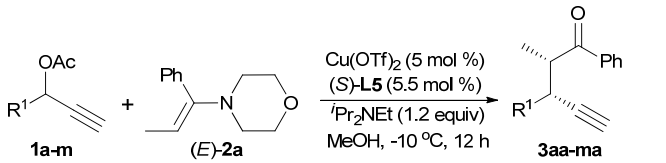
[a] Reaction conditions: [Cu] (0.015 mmol, 5 mol %), **L*** (0.0165 mmol, 5.5 mol %), **1a** (0.3 mmol), **2a** (0.36 mmol), base (0.36 mmol) were stirred in 3 mL of MeOH at 0 °C for 12 h, unless otherwise specified. [b] Isolated yields. [c] Determined by ^{1}H NMR or GC. [d] Determined by chiral HPLC analysis. [e] The reaction was performed in CH_2Cl_2. [f] The reaction was performed in toluene. [g] The reaction was performed at -10 °C.

Investigation of the Cu salt showed $Cu(OTf)_2$ gave the best result in terms of yield, diastereo-, and enantioselectivities (entries 5-8). The base additives showed an important effect on the reaction. The absence of a base didn't affect the enantioselectivity but led to the decreased yield and diastereoselectivity (entry 9). The use of Et_3N gave the similar result (entry 10). However, the dramatically diminished yield, diastereo-, and enantioselectivities were observed with DBU or ^{t}BuOK (entries 11 and 12). MeOH is the only suitable solvent tested, and a very sluggish reaction was observed when the reaction was carried out in CH_2Cl_2 or toluene (entries 13 and 14). Lowering the reaction temperature to -10 °C could significantly improve the reaction outcome, delivering the alkylation product **3aa** in 94% yield and with perfect diastereoselectivity (>95/5 dr) and enantioselectivity (>99% ee) (entry 15). A stringent requirement on the enamine geometry for this transformation was observed, and the presence of the geometrical isomer of the enamine damaged the diastereoselectivity presumably due to the formation of different diastereoisomers. Thus, *N*,*N*-diethyl-1-phenylprop-1-en-1-amine **4**, which was prepared from propiophenone with diethylamine in a 90% (*E*)-geometrical purity, led to **3aa** in 86/14 dr but keeping an excellent enantioselectivity of 98% ee (Scheme 2). However, the attempt to synthesize a pure (*Z*)-enamine for examining the effect of the geometrical isomer on the diastereoselectivity failed, since the (*E*)-isomer was predominantly formed as the preferred configuration in all reported methods.[8]



Scheme 2 Copper-catalyzed asymmetric propargylic alkylation of *N*,*N*-diethyl-1-phenylprop-1-en-1-amine (**4**) with 1-phenyl-2-propynyl acetate (**1a**).

Table 2 Scope of propargylic esters **1**[a]



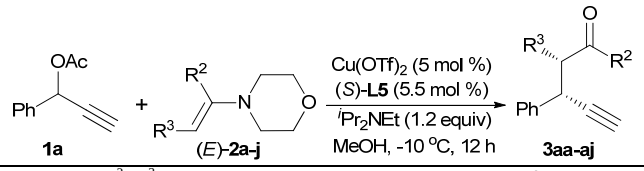
Entry	**1** (R^1)	Product (**3**)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**1a** (Ph)	**3aa**	94	>95/5	>99
2	**1b** (2-ClC_6H_4)	**3ba**	86	>95/5	99
3	**1c** (3-ClC_6H_4)	**3ca**	94	94/6	99
4	**1d** (4-ClC_6H_4)	**3da**	93	>95/5	99
5	**1e** (4-FC_6H_4)	**3ea**	95	>95/5	>99
6	**1f** (4-BrC_6H_4)	**3fa**	92	95/5	>99
7	**1g** (4-$CF_3C_6H_4$)	**3ga**	93	94/6	99
8	**1h** (4-MeC_6H_4)	**3ha**	93	>95/5	99
9	**1i** (4-MeOC_6H_4)	**3ia**	87	>95/5	98
10	**1j** (2-naphthyl)	**3ja**	90	94/6	99
11[e]	**1k** (3-pyridinyl)	**3ka**	74	92/8	97
12	**1l** (2-thienyl)	**3la**	96	>95/5	97
13	**1m** (Me)	**3ma**	27	89/11	98

[a] Reaction conditions: $Cu(OTf)_2$ (0.015 mmol, 5 mol%), (*S*)-**L5** (0.0165 mmol, 5.5 mol%), **1** (0.3 mmol), **2a** (0.36 mmol), ^{i}Pr$_2$NEt (0.36 mmol) were stirred in 3 mL of MeOH at -10 °C for 12 h, unless otherwise specified. [b] Isolated yields. [c] Determined by ^{1}H NMR or GC. [d] Determined by chiral HPLC analysis. [e] A catalyst loading of 10 mol % for 24 h was employed.

Having identified the optimal set of reaction conditions, we then investigated the scope of this process with respect to propargylic esters, and the results are shown in Table 2. We were delighted to discover that the reaction proceeded smoothly with all of phenyl and substituted-phenyl substrates **1a-i**, providing the corresponding propargylic alkylation products **3aa-ia** in up to 95% yield with

remarkably high diastereoselectivities (94/6->95/5 dr) as well as perfect enantioselectivities (98->99% ee), regardless of the electronic properties and the position of the substituent on the phenyl ring (entries 1-9). 2-Naphthyl-substituted propargylic ester **1j** also worked well in the reaction, delivering the alkylation product **3ja** in high yield (90%) and with high diastereoselectivity (94/6 dr) and outstanding enantioselectivity (99% ee) (entry 10). The reaction is remarkably tolerant to various functional groups including 3-pyridinyl and 2-thienyl groups, providing good catalytic performance (entries 11 and 12). However, aliphatic substrates proved to be less efficient to this transformation. Thus, the reaction of but-3-yn-2-yl acetate (**1m**) with enamine **2a** led to the desired alkylation product **3ma** in only 27% yield and with 89/11 dr and excellent enantioselectivity of 98% ee (entry 13).

Table 3 Scope of acyclic ketone enamines **2** [a]



Entry	**2** (R^2, R^3)	Product (**3**)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**2a** (Ph, Me)	**3aa**	94	>95/5	>99
2	**2b** (2-FC_6H_4, Me)	**3ab**	92	>95/5	>99
3	**2c** (3-FC_6H_4, Me)	**3ac**	94	95/5	>99
4	**2d** (4-FC_6H_4, Me)	**3ad**	95	>95/5	>99
5	**2e** (4-ClC_6H_4, Me)	**3ae**	94	>95/5	>99
6	**2f** (4-BrC_6H_4, Me)	**3af**	89	94/6	98
7	**2g** (4-MeC_6H_4, Me)	**3ag**	93	93/7	>99
8	**2h** (4-$MeOC_6H_4$, Me)	**3ah**	91	93/7	98
9	**2i** (Ph, Et)	**3ai**	92	>95/5	>99
10	**2j** (Et, Me)	**3aj**	60	81/19	99

[a] Reaction conditions: $Cu(OTf)_2$ (0.015 mmol, 5 mol %), (*S*)-**L5** (0.0165 mmol, 5.5 mol %), **1a** (0.3 mmol), **2** (0.36 mmol), $^iPr_2NEt$ (0.36 mmol) were stirred in 3 mL of MeOH at -10 °C for 12 h. [b] Isolated yields. [c] Determined by ^1H NMR or GC. [d] Determined by chiral HPLC analysis.

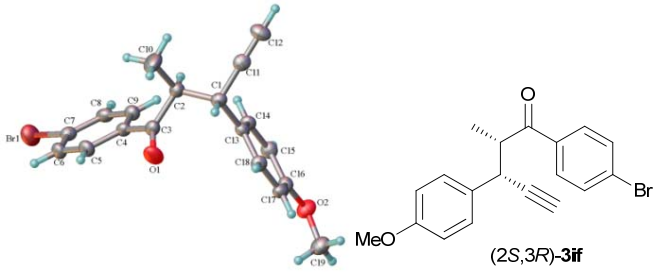
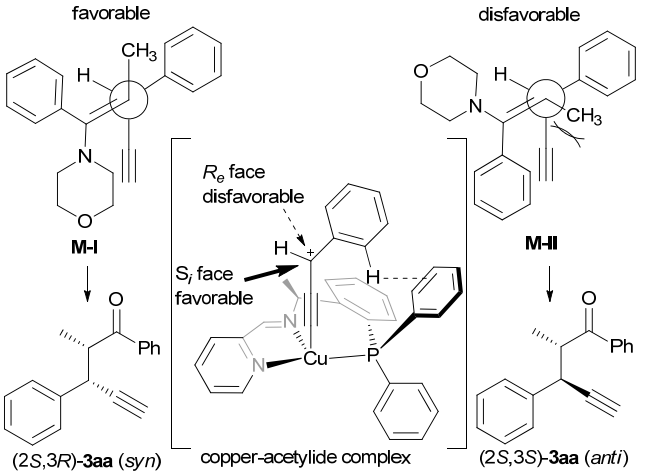


Figure 1 X-ray crystal structure of (2*S*,3*R*)-**3if**.

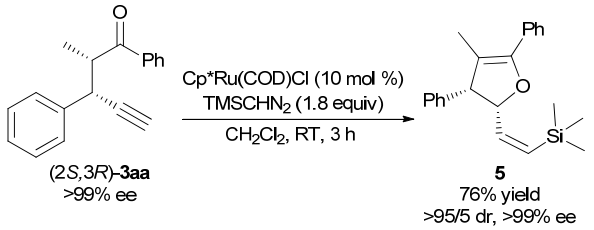
After investigating the substrate scope with respect to the propargylic esters, we next examined the diversity of acyclic enamines permitted in this reaction, and the results are summarized in Table 3. All acyclic aromatic enamines were prepared from the corresponding ketones and morpholine in nearly pure *E*-form (*E*/*Z* >95/5). The results indicated that the position of the substituent on the phenyl ring had little effect on the reaction. Thus, all three substrates having an F at the different position on the phenyl ring gave similarly high yields (92-95%), excellent diastereoselectivities (95/5->95/5 dr), and perfect enantioselectivities (>99% ee) (entries 2-4). The electronic nature of the substituent at the para position showed a slight influence on the diastereoselectivity, but less effect on the yield and enantioselectivity (entries 4-8). The substrate bearing an electron-donating group (Me, OMe) gave high but slightly diminished diastereoselectivity (93/7 dr) (entries 7 and 8). Besides those derived from 1-arylpropan-1-ones, other acyclic ketone enamines were also examined and found to be well suited for our reaction. Thus, enamine **2i** (R^2 = Ph, R^3 = Et) derived from 1-phenylbutan-1-one gave the outstanding result (92% yield, >95/5 dr, >99% ee) (entry 9). Importantly, aliphatic acyclic ketone enamine **2j** also served as the reaction partner, giving the alkylation product **3aj** in moderate yield and diastereoselectivity but with 99% ee (entry 10).

The absolute configuration of the propargylic alkylation product was unambiguously determined by X-ray structure analysis of **3if**, which is assigned as having a (2*S*,3*R*)-configuration (Figure 1).[9] A transition state of the Cu-allenylidene complex with chiral P,N,N-ligand is proposed to account for high diastereo- and enantioselectivities as shown in Scheme 3. The edge-to-face aromatic interaction[7f] and the steric hindrance make the attack of enamine C_β-nucleophile at the propargylic cation favourably from the *Si* face via the **M-I** mode to generate 2*S*,3*R*-stereogenic centers.



Scheme 3 Proposed model for the diastereo- and enantioselectivities.

The synthetic utility of the alkylation products was illustrated by the conversion of (2*S*,3*R*)-**3aa** via a Ru-catalyzed heterocyclization[10] into optically active 2,3-dihydrofuran **5** (Scheme 4), which are privileged structures for a large number of natural products and biologically active molecules.[11]



Scheme 4 Transformation of the alkylation product (2*S*,3*R*)-**3aa** to optically active 2,3-dihydrofuran **5**.

Conclusions

In conclusion, we have developed a highly diastereo-/enantio-selective installment of two vicinal chiral centers via the copper-catalyzed propargylic alkylation of acyclic ketone enamines with propargylic esters by use of a bulky and structurally rigid tridentate

ketimine P,N,N-ligand, in which excellent diastereoselectivities (up to >95/5 dr) and perfect enantioselectivities (up to >99% ee) has been obtained for a wide range of substrates. The further development and application of this reaction are underway.

Notes and references

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[b] University of Chinese Academy of Sciences, Beijing 100049, China.
[c] Dalian Polytechnic University, 1 Qinggongyuan, Dalian 116034, China.

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Graphical Abstract

Highly diastereo- and enantioselective copper-catalyzed propargylic alkylation of acyclic ketone enamines for the construction of two vicinal stereocenters

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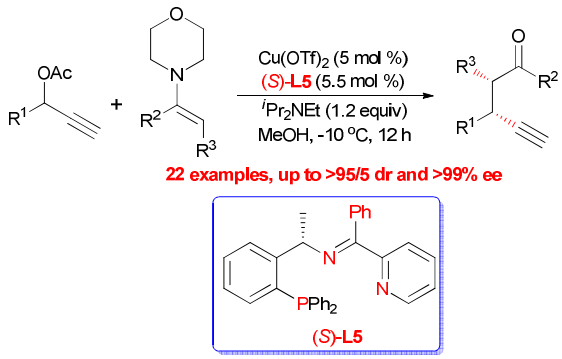

With a chiral tridentate ketimine P,N,N-ligand, the highly diastereo-/enantioselective Cu-catalyzed propargylic alkylation of acyclic ketone enamines to form vicinal tertiary stereocenters was developed.