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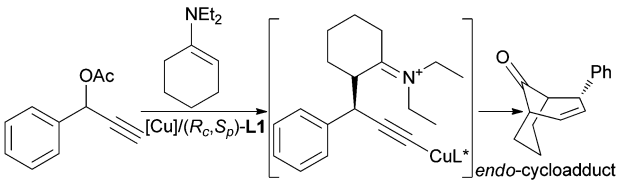
**The first highly diastereo- and enantioselective propargylic alkylation of acyclic ketone enamines to form vicinal tertiary stereocenters has been reported by employing copper catalysis in combination with a bulky and structurally rigid tridentate ketimine *P,N,N*-ligand.**

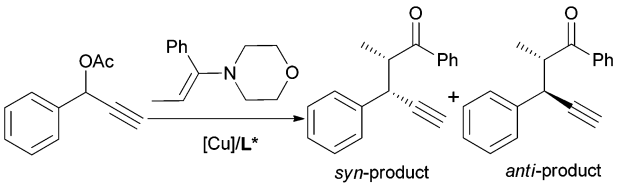
The stereoselective construction of contiguous multiple stereocenters from simple achiral starting materials is an enduring challenge and a longstanding goal in organic chemistry. In this context, the catalytic asymmetric propargylic alkylation of unstabilized ketone enolates or their equivalents for 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 controlling regio-, diastereo- and enantioselectivities.[1] However, the lack of successful examples in terms of diastereo- and enantioselectivities in 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 enamines could greatly suppress the last cyclization step, mainly leading to the propargylic alkylation products, presumably since the increased stability of the resulting

[3+3]-Cycloaddition of cyclic ketone enamine in our previous work:




Propargylic alkylation of acyclic ketone enamine in this work:




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

morpholinium ions prevents the shift of the H-atom to $C_\beta$ 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.

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

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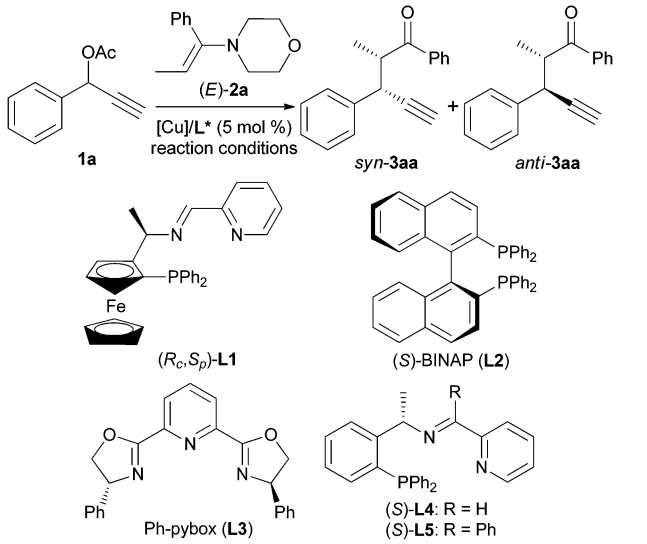
† Electronic supplementary information (ESI) available: Experimental details. CCDC 1004896. For the ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc06863g

Table 1 Optimization of reaction conditions[a]



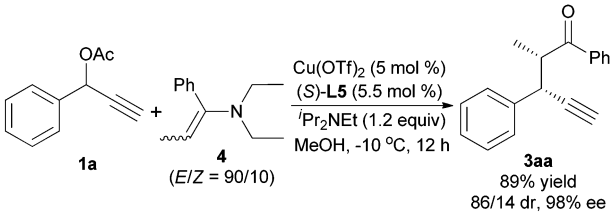

| Entry | [Cu] | L* | Base | Yield[b] (%) | *syn*/*anti*[c] | ee of *syn*-3aa[d] (%) |
|---|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2{\cdot}H_2O$ | **L1** | $^iPr_2NEt$ | 37 | 72/28 | 33 |
| 2 | $Cu(OAc)_2{\cdot}H_2O$ | **L2** | $^iPr_2NEt$ | 10 | 77/23 | 60 |
| 3 | $Cu(OAc)_2{\cdot}H_2O$ | **L3** | $^iPr_2NEt$ | 87 | 92/8 | 55 |
| 4 | $Cu(OAc)_2{\cdot}H_2O$ | **L4** | $^iPr_2NEt$ | 81 | 87/13 | 83 |
| 5 | $Cu(OAc)_2{\cdot}H_2O$ | **L5** | $^iPr_2NEt$ | 87 | 89/11 | 98 |
| 6 | $Cu(OTf)_2$ | **L5** | $^iPr_2NEt$ | 89 | 91/9 | 99 |
| 7 | CuI | **L5** | $^iPr_2NEt$ | 71 | 90/10 | 91 |
| 8 | $Cu(MeCN)_4BF_4$ | **L5** | $^iPr_2NEt$ | 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** | $^iPr_2NEt$ | 14 | 69/31 | 90 |
| 14[f] | $Cu(OTf)_2$ | **L5** | $^iPr_2NEt$ | — | — | — |
| 15[g] | $Cu(OTf)_2$ | **L5** | $^iPr_2NEt$ | 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.

(*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 the 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 and 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 promising yield, dr, and ee (entries 4 and 5). Especially, 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% for the major diastereoisomer (entry 5).

Investigation of the Cu salt showed that $Cu(OTf)_2$ gave the best results in terms of yields and 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 a decreased yield and diastereoselectivity (entry 9). The use of $Et_3N$ gave similar results (entry 10). However, the dramatically diminished yield and 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 of 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% (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]

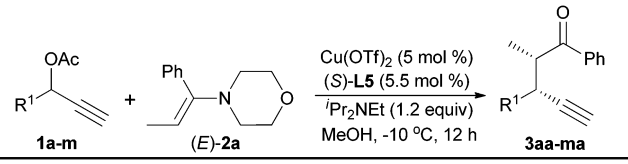
Having identified the optimal set of reaction conditions, we then investigated the scope of this process with respect to propargylic esters, and the results are shown in Table 2. We were delighted to discover that the reaction proceeded smoothly with all phenyl and substituted-phenyl substrates **1a–i**, 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).




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]

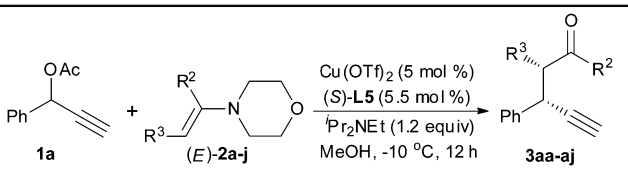



| Entry | **1** ($R^1$) | Product (**3**) | Yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | **1a** (Ph) | **3aa** | 94 | >95/5 | >99 |
| 2 | **1b** (2-$ClC_6H_4$) | **3ba** | 86 | >95/5 | 99 |
| 3 | **1c** (3-$ClC_6H_4$) | **3ca** | 94 | 94/6 | 99 |
| 4 | **1d** (4-$ClC_6H_4$) | **3da** | 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), $^iPr_2NEt$ (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 $^1H$ NMR or GC. [d] Determined by chiral HPLC analysis. [e] A catalyst loading of 10 mol% for 24 h was employed.

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*-forms (*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 different positions 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 and 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 outstanding results (92% yield, >95/5 dr, and >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).

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.

The absolute configuration of the propargylic alkylation product was unambiguously determined by X-ray structure analysis of **3if**, which was assigned a (2*S*,3*R*)-configuration (Fig. 1).[9] A transition state of the Cu–allenylidene complex with the 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[5f] and the steric hindrance make the attack of the enamine $C_\beta$-nucleophile at the propargylic cation favourably from the *Si* face *via* the M-I mode to generate 2*S*,3*R*-stereogenic centers.

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 is a privileged structure for a large number of natural products and biologically active molecules.[11]

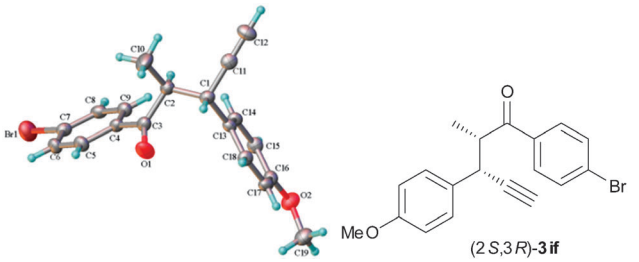
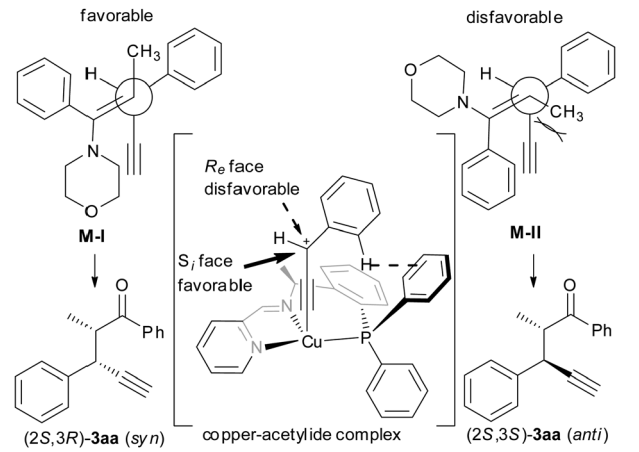
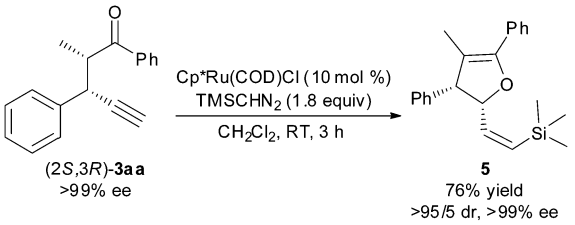



Fig. 1 X-ray crystal structure of (2*S*,3*R*)-**3if**.




Scheme 3 Proposed model for the diastereo- and enantioselectivities.




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

In conclusion, we have developed a highly diastereo-/enantioselective installment of two vicinal chiral centers *via* the copper-catalyzed propargylic alkylation of acyclic ketone enamines with propargylic esters by using 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) have been obtained for a wide range of substrates. Further development and application of this reaction are underway.

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