Organic LETTERS

Letter

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Highly Enantioselective Copper-Catalyzed Propargylic Substitution of Propargylic Acetates with 1,3-Dicarbonyl Compounds

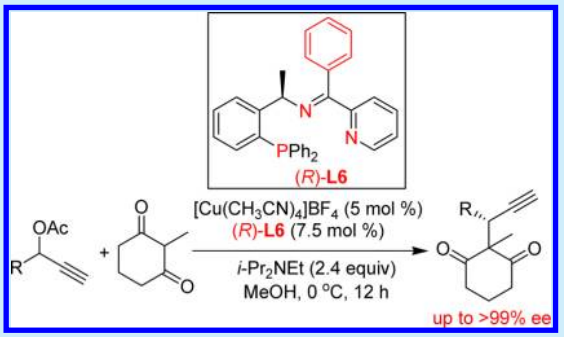
Fu-Zhong Han,[†,‡] Fu-Lin Zhu,[‡] Ya-Hui Wang,[‡] Yuan Zou,[‡] Xin-Hu Hu,[‡] Song Chen,[‡] and Xiang-Ping Hu*[,‡]

[†]College of Chemistry and Chemical Engineering, Qiqihar University, Qiqihar 161006, China

[‡]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China

Supporting Information

ABSTRACT: A chiral tridentate ketimine *P,N,N*-ligand has been successfully applied in the copper-catalyzed enantioselective propargylic substitution of propargylic acetates with a variety of *β*-dicarbonyl compounds, in which excellent enantioselectivities (up to >99% ee) and high yields have been obtained.



Catalytic allylic alkylation of allylic alcohol derivatives with the stabilized "soft" carbanions, such as *β*-diketones and *β*-ketoesters, represents one of the most reliable methods in organic synthesis.[1] In sharp contrast, few examples have been realized for the catalytic propargylic alkylation of propargylic alcohol derivatives with *β*-dicarbonyl compounds, although the transition-metal-catalyzed propargylic substitution has made considerable progress in the past decades.[2] The development of catalytic propargylic substitution with *β*-dicarbonyl compounds as nucleophiles, especially in an asymmetric catalytic version, remains a great challenge.

In 2011, van Maarseveen[3] attempted the first copper-catalyzed asymmetric propargylic substitution of 1-phenyl-2-propynyl acetate with 2,2,5-trimethyl-1,3-dioxane-4,6-dione, a cyclic derivative of malonate. However, only low enantioselectivity (6% ee) was obtained. Quite recently, Nishibayashi and co-workers[4] have reported a cooperative ruthenium- and copper-catalyzed propargylic alkylation of propargylic alcohols with *β*-ketoesters, in which up to 95% ee was achieved by the enantioselective attack of an enolate generated in situ from a chiral copper complex and a *β*-ketoester at the electrophilic C_γ atom in an achiral ruthenium allenylidene intermediate. Although the reaction scope was limited to acyclic *β*-ketoesters, this "indirect" strategy represents the first successful application of *β*-dicarbonyl compounds to asymmetric propargylic substitutions. In addition to these two examples, however, the use of other *β*-dicarbonyl compounds, in particular *β*-diketones as nucleophiles, has not been explored. The development of a catalytic system that could catalyze the asymmetric propargylic substitution in broad substrate spectrum with regard to *β*-dicarbonyl compounds is therefore highly desirable.

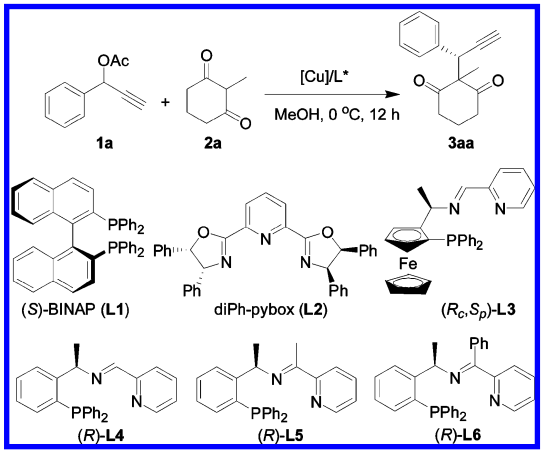
Recent progress on the catalytic asymmetric propargylic substitution has demonstrated that high enantioselectivity could be obtained by the direct attack of a nucleophile at the C_γ atom of the metal−allenylidene complex bearing a chiral ligand.[5−9] We therefore believe that *β*-dicarbonyl compounds should be also a suitable nucleophile kind for the "direct" catalytic asymmetric propargylic substitution. As a result, herein we describe the first highly enantioselective copper-catalyzed propargylic alkylation of propargylic acetates with various *β*-diketones using a tridentate ketimine *P,N,N*-ligand, in which excellent enantioselectivities (up to >99% ee) were achieved. Importantly, the present catalytic system showed broad generality with regard to *β*-dicarbonyl nucleophiles, in which cyclic *β*-ketoesters and malonate derivatives also proved to be suitable nucleophiles.

We started our investigation by looking at the catalytic asymmetric propargylic alkylation of 1-phenyl-2-propynyl acetate (**1a**) with 2-methyl-1,3-cyclohexanedione (**2a**), and the results are summarized in Table 1. Initially, ligands such as BINAP (**L1**), diPh-pybox (**L2**), and ferrocenyl *P,N,N*-ligand (R_c,S_p)-**L3**, which have proved to be efficient in the Cu-catalyzed asymmetric propargylic substitution, were investigated. However, all of these ligands led to disappointingly low conversion and/or enantioselectivity (entries 1−3). Interestingly, ligand (*R*)-**L4**, a phenyl analogue of (R_c,S_p)-**L3** developed in our group,[9b] showed a promising enantiomeric excess of 53% ee and a yield of 85% (entry 4). We therefore evaluated the effect that modifications to the ligand structure of (*R*)-**L4** had on the reaction outcome. The results in Table 1

Received: November 29, 2013
Published: December 27, 2013

dx.doi.org/10.1021/ol403469m | *Org. Lett.* 2014, 16, 588−591

Table 1. Optimization of Cu-Catalyzed Asymmetric Propargylic Alkylation of 1-Phenyl-2-propynyl Acetate (1a) with 2-Methyl-1,3-cyclohexanedione (2a)[a]



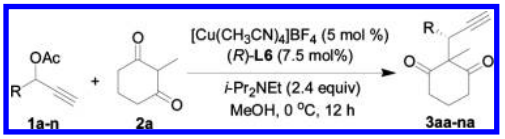
entry	[Cu]	L*	base	yield[b] (%)	ee[c] (%)
1	CuI	**L1**	Et_3N		–[d]
2	CuI	**L2**	Et_3N	90	10
3	CuI	**L3**	Et_3N		–[d]
4	CuI	**L4**	Et_3N	85	53
5	CuI	**L5**	Et_3N	82	92
6	CuI	**L6**	Et_3N	85	94
7	CuI	**L6**	DBU		–[d]
8	CuI	**L6**	*i*-Pr_2NEt	89	95
9	$Cu(OTf)_2$	**L6**	*i*-Pr_2NEt	87	97
10	$Cu(OAc)_2.H_2O$	**L6**	*i*-Pr_2NEt	95	96
11	$[Cu(CH_3CN)_4]BF_4$	**L6**	*i*-Pr_2NEt	95	98
12	$[Cu(CH_3CN)_4]ClO_4$	**L6**	*i*-Pr_2NEt	92	91

[a]The reaction was carried out with **2a** (0.5 mmol), **1a** (0.6 mmol), [Cu] (5 mol %), **L*** (7.5 mol %), and base (1.2 mmol) in 4 mL of MeOH at 0 °C for 12 h. [b]Yield of isolated product. [c]ee values were determined by HPLC analysis using a chiral stationary phase. [d]Not determined due to low conversions.

disclosed that both of (*R*)-**L5** and (*R*)-**L6** bearing a ketimine moiety were suitable ligands for the model reaction, with (*R*)-**L6** derived from 2-benzopyridine being optimal in terms of the yield and enantioselectivity (entries 5 and 6). Subsequent optimization of reaction conditions with ligand (*R*)-**L6** was then carried out. The results disclosed that the base showed a significant effect on the reaction. Thus, no desired product was separated in the presence of DBU as the base (entry 7), while the use of *i*-Pr_2NEt provided better results than that of Et_3N (entry 8). Investigation of copper precursors showed that all of the copper salts tested displayed excellent to perfect performance, although some influence on the reaction was observed. Among these copper salts, $[Cu(MeCN)_4]BF_4$ proved to be the best choice, which gave the corresponding alkylation product in 95% yield with an ee value of 98% (entry 11).

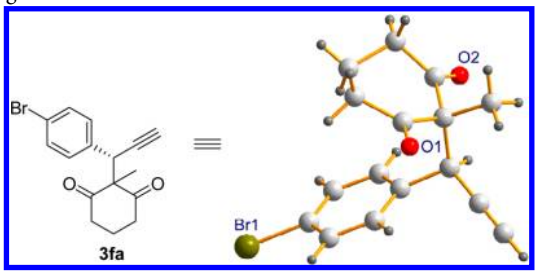
Utilizing the optimized conditions, we investigated the scope of propargylic acetates, and the results are summarized in Table 2. The reaction worked efficiently for all 1-aryl-substituted substrates tested, with the desired products being obtained in high yields and with excellent to perfect enantioselectivities (up to >99% ee). It appeared that the position of the substituent on the phenyl ring had little effect on the reactivity and enantioselectivity. Thus, all of 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

Table 2. Cu-Catalyzed Asymmetric Propargylic Alkylation with 2-Methyl-1,3-cyclohexanedione (2a) as Nucleophile: Scope of Propargylic Acetates[a]



entry	1: R	3	yield[b] (%)	ee[c] (%)
1	**1a**: R = Ph	**3aa**	95	98
2	**1b**: R = 2-ClC_6H_4	**3ba**	87	99
3	**1c**: R = 3-ClC_6H_4	**3ca**	90	99
4	**1d**: R = 4-ClC_6H_4	**3da**	90	99
5	**1e**: R = 4-FC_6H_4	**3ea**	88	98
6	**1f**: R = 4-BrC_6H_4	**3fa**	93	99
7	**1g**: R = 4-$CF_3C_6H_4$	**3ga**	85	>99
8	**1h**: R = 4-MeC_6H_4	**3ha**	95	98
9	**1i**: R = 4-$MeOC_6H_4$	**3ia**	92	94
10	**1j**: R = 3-$MeOC_6H_4$	**3ja**	91	98
11	**1k**: R = 2-naphthyl	**3ka**	94	98
12	**1l**: R = 2-thienyl	**3la**	90	96
13[d]	**1m**: R = Me	**3ma**	65	97
14[d]	**1n**: R = Bn	**3na**	63	98

[a]The reaction was carried out with **1a–n** (0.6 mmol), **2a** (0.5 mmol), $[Cu(MeCN)_4]BF_4$ (5 mol %), (*R*)-**L6** (7.5 mol %), and *i*-Pr_2NEt (1.2 mmol) in 4 mL of MeOH at 0 °C for 12 h. [b]Yield of isolated product. [c]The ee values were determined by HPLC analysis using a chiral stationary phase. [d]The reaction was performed at rt under a catalyst loading of 10 mol %.

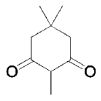
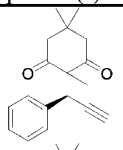
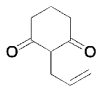
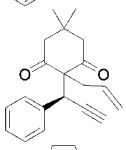
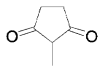
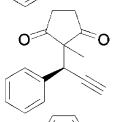
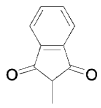
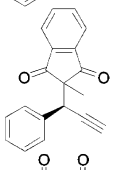
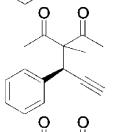
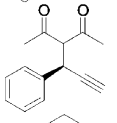
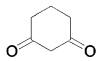
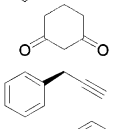
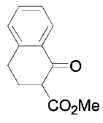
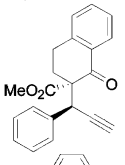
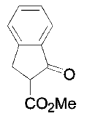
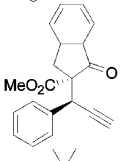
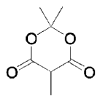
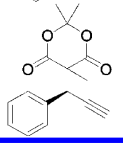


substituent at the *para*-position of the phenyl ring showed some influence on the enantioselectivity. Thus, a *p*-methoxy substituent led to slightly decreased enantioselectivity (94% ee) (entry 9). In addition, 2-naphthyl-substituted substrate presented a suitable substrate for the reaction (entry 11). Heteroaromatic propargylic acetate **1l** turned out to serve well as the substrate for our methodology (entry 12). Furthermore, aliphatic substrates **1m,n** worked well, leading to the desired propargylic products in excellent enantioselectivity. However, an elevated catalyst loading (10 mol %) and higher reaction temperature were required for achieving a reasonable conversion in these cases (entries 13 and 14). The absolute configuration of chiral propargylic products was unambiguously determined by X-ray crystal structure analysis of **3fa**, which is assigned as (*S*).[10]

Furthermore, the scope of *β*-dicarbonyl nucleophiles was investigated (Table 3). The reaction demonstrated a broad generality for *β*-dicarbonyl compounds, in which various cyclic and acyclic diketones, *β*-ketoesters, and malonate derivatives were found to be suitable substrates. For both 1,3-cyclohexanediones (**2b,c**) with a tertiary carbon as the nucleophilic atom, the reaction proceeded with excellent performance (entries 1 and 2). In comparison with its six-membered analogues, 2-methyl-1,3-cyclopetanedione **2d** showed slightly

dx.doi.org/10.1021/ol403469m | Org. Lett. 2014, 16, 588–591

Table 3. Cu-Catalyzed Asymmetric Propargylic Alkylation of 1-Phenyl-2-propynyl Acetate (1a): Scope of β-Dicarbonyl Compounds[a]

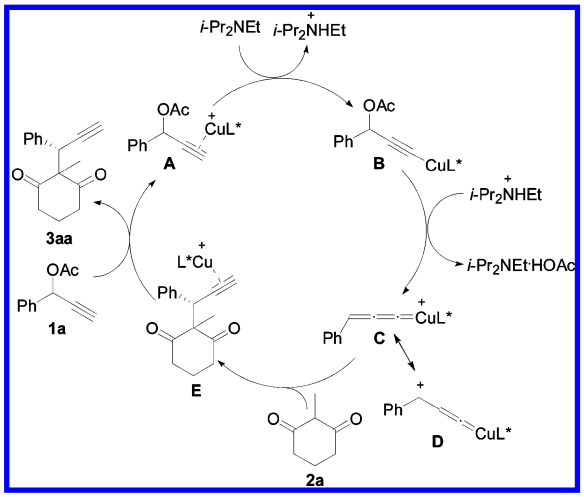
entry	nucleophile (2)		product (3)[b]	
1		**2b**		**3ab** 92% yield 98% ee
2		**2c**		**3ac** 90% yield 96% ee
3		**2d**		**3ad** 88% yield 91% ee
4		**2e**		**3ae** 94% yield 98% ee
5		**2f**		**3af** 83% yield >99% ee
6		**2g**		**3ag** 80% yield 95% ee
7		**2h**		**3ah** 90% yield 86% ee
8[c]		**2i**		**3ai** 95% yield *anti*/*syn*: 2.8/1 98% ee for *anti*-**3ai**
9[c]		**2j**		**3aj** 94% yield *anti*/*syn*: 3.5/1 99% ee for *anti*-**3aj**
10[d]		**2k**		**3ak** 65% yield 97% ee

[a]Reaction conditions: **1a** (0.6 mmol), **2b**–**k** (0.5 mmol), [Cu(MeCN)$_4$]BF$_4$ (5 mol %), (*R*)-**L6** (7.5 mol %), and *i*-Pr$_2$NEt (1.2 mmol) in 4 mL of MeOH at 0 °C for 12 h. [b]Yield of isolated product was provided, and ee values were determined by HPLC analysis using a chiral stationary phase. [c]Reactions were performed at room temperature. The ratio of *anti*/*syn* was determined by ^{1}H NMR. [d]The reaction was performed at −20 °C.

lower enantioselectivity in 91% ee (entry 3). For 2*H*-indene-1,3-dione substrate **2e**, excellent performance (94% yield, and 98% ee) was achieved (entry 4). Acyclic diketone, 3-methyl-2,4-pentanedione (**2f**), also worked well, leading to the desired product in good yield and with perfect enantioselectivity (>99% ee) (entry 5). Interestingly, 1,3-diketones without an additional substituent on the nucleophilic atom were also suitable reaction partners, giving the corresponding substitution products with good results (entries 6 and 7). Cyclic β-ketoesters were also investigated, and the reaction was performed at room temperature. In all cases, the reaction resulted in the alkylation product in high yield as a mixture of two diastereoisomers with perfect enantioselectivities for major diastereomer (entries 8 and 9). 2,2,5-Trimethyl-1,3-dioxane-4,6-dione, an inefficient nucleophile in van Maarseveen's catalytic system, also proved to be a suitable nucleophile, with the corresponding propargylic alkylation product being obtained in excellent enantioselectivity (97% ee) (entry 10).

Based upon our experimental results and other data, we proposed the plausible mechanism for the formation of **3aa** as shown in Scheme 1. Initially, the Cu complex forms a π-

Scheme 1. Proposed Reaction Pathway



complex **A** with the propargylic acetate.[11] Deprotonation with *N*,*N*-diisopropylethylamine gives Cu–acetylide complex **B**, which explains why 1,3-diphenyl-2-propynyl acetate, an internal alkyne, did not react at all in this reaction. Loss of an acetyl group from **B** forms Cu–allenylidene complex **C**, where the copper–acetylide complex **D** bearing a cationic γ-carbon exists as a resonance structure.[7f,12] Nucleophilic attack of 2-methyl-1,3-cyclohexanedione **2a** at the C$_\gamma$ atom of **C**, followed by a hydrogen atom shift, gives a Cu–π-alkyne complex **E**. Further investigations to elucidate the reaction mechanism are underway and will be reported in due course.

In conclusion, we have documented the first copper-catalyzed propargylic alkylation of propargylic acetates with β-diketones as nucleophiles by employing a chiral tridentate ketimine *P*,*N*,*N*-ligand derived from 2-benzopyridine, in which excellent enantioselectivities (up to >99% ee) were achieved. The result disclosed that the ligand structure has a great impact on the efficiency and selectivity of the reaction, and the presence of a ketimine moiety in *P*,*N*,*N*-ligand structure appears to be necessary for achieving good performance. The present catalytic system was also efficient for cyclic β-ketoesters and cyclic malonate derivatives. Studies on mechanistic investigations as well as the extension of the protocol to other carbon nucleophiles are in progress.

dx.doi.org/10.1021/ol403469m | *Org. Lett.* 2014, 16, 588–591

■ ASSOCIATED CONTENT

Supporting Information

Procedures, characterization, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xiangping@dicp.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Dalian Institute of Chemical Physics (CAS) is gratefully acknowledged. We also thank Prof. Hongchao Guo for providing several chiral ligands (synthesized in the National Key Technologies R&D Program of China, 2012BAK25B03, CAU) for screening reaction conditions.

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