RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2016, **6**, 14763

Received 2nd December 2015
Accepted 26th January 2016

DOI: 10.1039/c5ra25627e

www.rsc.org/advances

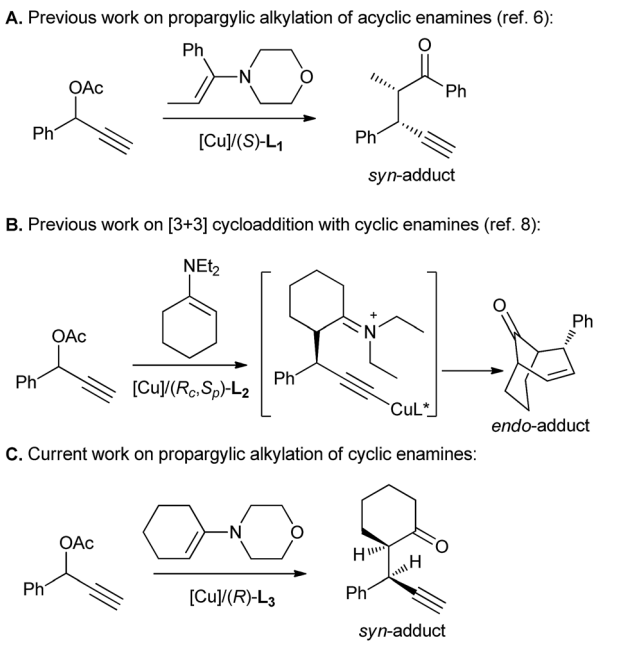
Highly diastereo-/enantioselective Cu-catalyzed propargylic alkylations of propargyl acetates with cyclic enamines†

Cheng Zhang,[ab] Yun-Ze Hui,[c] De-Yang Zhang[b] and Xiang-Ping Hu*[b]

Highly diastereo- and enantioselective copper-catalyzed propargylic alkylations of propargylic acetates with morpholine-derived cyclic enamines for the construction of vicinal tertiary stereocenters have been developed. By the employment of a less sterically hindered chiral tridentate P,N,N-ligand, good to excellent diastereo- (up to >98 : 2 dr) and enantioselectivity (up to 99% ee) could be achieved for a wide range of substrates.

Transition-metal-catalyzed propargylic substitutions represent an important class of reactions due to their ability to introduce an electron-rich triple bond that is a versatile entity for further chemical transformations.[1] In 2008, van Maarseveen[2] and Nishibayashi[3] independently reported the first copper-catalyzed asymmetric propargylic amination. Since then, a variety of nitrogen, oxygen, and carbon nucleophiles have proved to be suitable reagents for the copper-catalyzed asymmetric propargylic substitution.[4] However, the methods for Cu-catalyzed propargylic substitution that employ prochiral nucleophiles to build two vicinal stereocenters and display high diastereo- and enantioselectivity remain elusive.[5]

Recently, our group have demonstrated the power of copper catalysis in accessing vicinal tertiary stereocenters with our report on the diastereo- and enantioselective asymmetric propargylic alkylation of acyclic enamines (Scheme 1A).[6] However, the use of cyclic enamines was less successful, leading to poor chemoselectivity. The success of this protocol combined with the virtual absence of successful reports describing the application of this transformation to cyclic enamines[7] encouraged our further exploration of copper catalysts in the domain of this substrate class. In fact, our previous studies have disclosed that a highly diastereo- and enantioselective [3 + 3] cycloaddition instead of propargylic alkylation preferentially took place for the reaction between propargylic esters and cyclic enamines although this cycloaddition is believed to proceed *via* the propargylic alkylation as the key step (Scheme 1B).[8] It's therefore anticipated that an enantioselective propargylic alkylation of propargylic esters with cyclic enamines could be realized if the last cyclization step can be efficiently inhibited. Herein we report a highly diastereo- and enantioselective



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

[a]*Department of Drug Discovery and Biomedical Sciences, South Carolina College of Pharmacy, Medical University of South Carolina, 280 Calhoun Street MSC140 QF307, Charleston, South Carolina 29425, USA*

[b]*Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China. E-mail: xiangping@dicp.ac.cn; xiangping1974@163.com*

[c]*Faculty of Engineering and Built Environment, University of Newcastle, Callaghan, NSW 2308, Australia*

† Electronic supplementary information (ESI) available: Experimental details, characterization data and copies of NMR spectra for all products, and Crystallographic Information Framework (CIF) file of compound (*S*,*R*)-**3r**. CCDC 1439964. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra25627e

copper-catalyzed propargylic alkylation of propargylic acetates with morpholine-derived cyclic enamines by the employment of a less sterically hindered chiral tridentate P,N,N-ligand to build up two vicinal tertiary stereocenters, in which >98 : 2 dr and up to 99% ee for *syn*-diastereoisomers have been achieved (Scheme 1C).

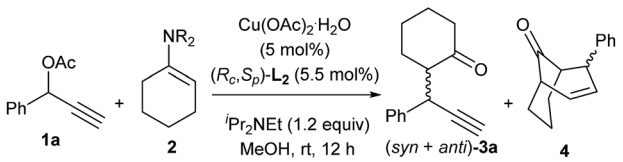
Considering the significant influence of the amino moiety of enamine substrates on the outcomes in the copper-catalyzed [3 + 3] cycloaddition,[8] our initial attempt focused on probing the effect of enamines on the reaction. As shown in Table 1, the amino moiety of enamines displayed the crucial role in the chemoselectivity of the reaction. When *N*,*N*-diethylamino substituted enamine **2a** was used as the reaction partner, only [3 + 3] cycloadduct was obtained and no alkylation product was detected (entry 1). By the introduction of cyclic amino group into enamines, the formation of the alkylation product **3a** was observed (entries 2–4). In particular, the use of enamine **2d** bearing a morpholine structure as the nucleophile predominantly gave rise to the alkylation product **3a** in 80% yield (entry 4).

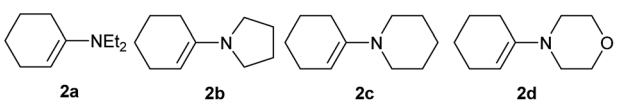
Having established an efficient copper-catalyzed propargylic alkylation of cyclic enamine **2d**, we next investigated the effects of different ligands, copper salts, reaction temperature on the efficiency and selectivity of the reaction. 1-Phenyl-2-propynyl acetate **1a** and 4-(cyclohex-1-en-1-yl)morpholine **2d** were chosen as standard reaction partners, and some selected results of these experiments are summarized in Table 2. Initially, the effect of the ligand was investigated (Fig. 1). As we have disclosed, the use of chiral ferrocenyl P,N,N-ligand $\mathbf{L_2}$ led to the predominant formation of the alkylation products **3a** with *syn*-**3a** as the major diastereoisomer in 91% ee (entry 2). An attempt to improve the reaction outcome by the use of structurally rigid and bulky ketimine P,N,N-ligand $\mathbf{L_1}$, which displayed excellent diastereo-/enantioselectivity in the Cu-catalyzed asymmetric propargylic alkylation of acyclic enamines,[6] however, was disappointed. Only poor chemoselectivity (**3a** : **4** = 61 : 39) was obtained although the enantioselectivity for *syn*-**3a** was high (entry 1). This should be high reactivity of copper/$\mathbf{L_1}$ complex that couldn't efficiently suppress the last cyclization step. We therefore envisioned that ligand having lower reactivity should be more suitable to this reaction. A less sterically hindered P,N,N-ligand $\mathbf{L_3}$ was therefore employed in the reaction, and as expected, gave the similar result to that with $\mathbf{L_2}$ (entry 3). Excellent chemo- and diasteroselectivity was observed with (*S*,*S*)-Ph-pybox $\mathbf{L_4}$ as ligand, however, enantioselectivity for *syn*-**3a** was low (entry 4). With (*S*)-SegPhos $\mathbf{L_5}$, high chemoselectivity but low diasteteo- and enantioselectivity was achieved (entry 5). Following investigation of copper salts didn't improve the reaction outcome (entries 6–8). Lowering the reaction temperature to 0 °C could significantly improve the chemoselectivity, exclusively giving the alkylation product **3a** in good diastereoselectivity, regardless of the use of $\mathbf{L_2}$ or $\mathbf{L_3}$ (entries 9–10). Especially, ligand $\mathbf{L_3}$ led to the alkylation product **3a** in 82% yield, and with 94/6 dr and an ee-value of up to 94% for the major *syn*-diastereoisomer (entry 10).

Having identified the optimal set of reaction conditions, we then investigated the scope of this reaction with respect to propargylic acetates, and the results are shown in Table 3. We found that the reaction proceeded smoothly for all 1-aryl-2-propynyl acetates. In all cases, only alkylation products, predominately *syn*-diastereoisomers, were obtained and no [3 + 3] cycloadduct was detected. The position of the substituent on the phenyl ring had less influence on the reaction. Thus, all three substrates bearing a Cl-group at the different position on the phenyl ring gave the similarly good results (entries 2–4). The electronic properties of the substituent at the *para*-position showed little effect on the diastereo-/enantioselectivity. Propargylic acetates bearing either electron-donating or electron-withdrawing substituents on the phenyl ring fared very well in the reaction, delivering the alkylation products in high yield, diastereo-, and enantioselectivity (entries 5–8). 2-Naphthyl substrate **1i** also worked well, gave the alkylation product **3i** in 88% yield, 94 : 6 dr and 92% ee for *syn*-diastereoisomer (entry 9). We were pleased to discover that the use of heteroaryl-substituted propargylic acetates (substrates **1j** and **1k**) resulted in smooth reactions and delivered the alkylation products **3j** and **3k** with high yield and diastereoselectivity and with good to excellent enantioselectivity (entries 10–11).

To further evaluate this asymmetric protocol, we next examined the diversity of cyclic enamines permitted in the reaction, and the results are listed in Table 4. In all cases, the reaction proceeded smoothly to afford the alkylation products as the only outcome with *syn*-diastereoisomers as the major products. In comparison to 4-(cyclohex-1-en-1-yl)morpholine **2d**, five-membered cyclic enamines gave the similar yield and diastereoselectivity, but a slightly decreased enantioselectivity. The substituents in cyclohexenyl ring were well tolerated, delivering the corresponding alkylation products in high yield and with excellent diastereo- and enantioselectivity. Importantly, aliphatic acyclic ketone enamine also served well as the

Table 1 Screening the reaction between propargylic acetate **1a** and enamines **2**[a]

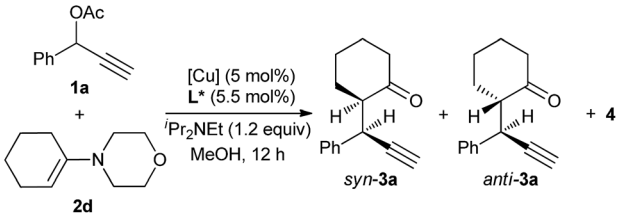




Entry	Enamine (2)	**3a** (*syn*/*anti*) : **4**[b]	Yield of **3a**[c] (%)
1	**2a**	<2 (—) : >98	—
2	**2b**	22 (71/29) : 78	16
3	**2c**	36 (78/22) : 64	27
4	**2d**	94 (91/9) : 6	80

[a] Reaction conditions: $Cu(OAc)_2 \cdot H_2O$ (0.015 mmol), (R_c,S_p)-$\mathbf{L_2}$ (0.0165 mmol), **1a** (0.3 mmol), **2** (0.36 mmol), $^iPr_2NEt$ (0.36 mmol) were stirred in 2 mL of MeOH at rt for 12 h. [b] Determined by ^1H NMR. [c] Isolated yield after column chromatography.

Table 2 Optimization of reaction parameters[a]



Entry	[Cu]	L*	*syn*-3a : *anti*-3a : 4[b]	Yield of 3a[c] (%)	ee of *syn*-3a[d] (%)
1	$Cu(OAc)_2 \cdot H_2O$	**L1**	55 : 6 : 39	51	94
2	$Cu(OAc)_2 \cdot H_2O$	**L2**	86 : 8 : 6	80	91
3	$Cu(OAc)_2 \cdot H_2O$	**L3**	84 : 8 : 8	76	92
4	$Cu(OAc)_2 \cdot H_2O$	**L4**	97 : 3 : 0	88	42
5	$Cu(OAc)_2 \cdot H_2O$	**L5**	55 : 45 : 0	63	52 (51)[f]
6	CuI	**L3**	80 : 20 : 0	74	76 (56)[f]
7	$CuOTf \cdot (C_6H_6)_{1/2}$	**L3**	89 : 7 : 4	72	92
8	$Cu(OTf)_2$	**L3**	88 : 7 : 5	72	90
9[e]	$Cu(OAc)_2 \cdot H_2O$	**L2**	90 : 10 : 0	67	92
10[e]	$Cu(OAc)_2 \cdot H_2O$	**L3**	94 : 6 : 0	82	94

[a] Reaction conditions: copper salt (0.015 mmol), **L*** (0.0165 mmol), **1a** (0.3 mmol), **2d** (0.36 mmol), $^iPr_2NEt$ (0.36 mmol) were stirred in 2 mL of MeOH at rt for 12 h unless otherwise specified. [b] Determined by GC or ^1H NMR. [c] Isolated yield of *syn*-**3a** and *anti*-**3a** in total. [d] Determined by HPLC on chiral column. [e] The reaction was performed at 0 °C for 10 h. [f] The ee-values of *anti*-**3a** in parentheses.

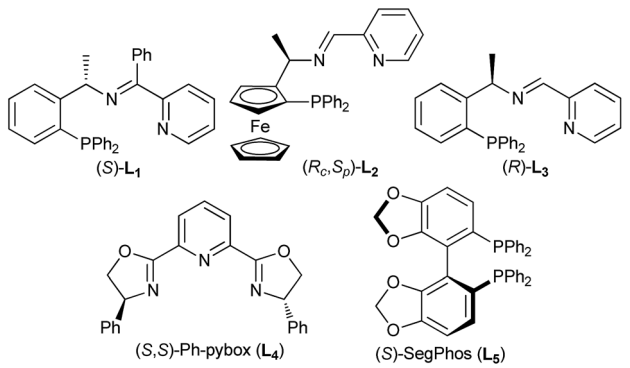


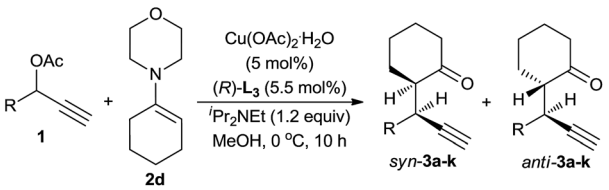
Fig. 1 Ligand evaluated in the Cu-catalyzed asymmetric propargylic alkylation.

reaction partner although the use of (*S*)-$\mathbf{L_1}$ instead of (*R*)-$\mathbf{L_3}$ was required. In this case, (*S*)-$\mathbf{L_1}$ showed better performance than (*R*)-$\mathbf{L_3}$ presumably due to the steric effect, giving the alkylation product **3q** in moderate yield and diastereoselectivity but with perfect ee of 99%.

The absolute configuration of the propargylic alkylation product was unambiguously determined by X-ray structure analysis of **3r**,[9] which was prepared by the reaction of 1-(4-bromophenyl)prop-2-yn-1-yl acetate **1f** with 4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)morpholine in the catalysis of $Cu(OAc)_2 \cdot H_2O$ and (*S*)-$\mathbf{L_3}$. A (*S*,*R*)-absolute configuration was assigned as shown in Scheme 2, which is corresponding to *syn*-diastereoisomer.

Based on the experimental results and previous reports,[4b,7b] a reaction pathway is proposed as shown in Scheme 3. In the first step, a copper complex forms the π-complex **A** with propargylic acetate **1a**. Deprotonation of **A** with a base then gives a Cu–acetylide complex **B**, which would explain why

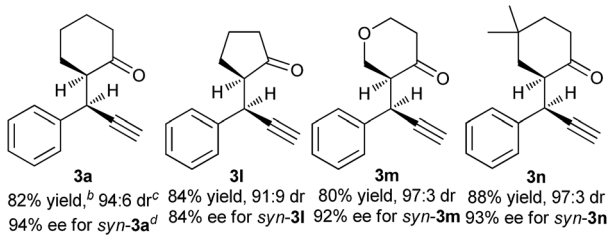
Table 3 Scope of propargylic esters 1[a]

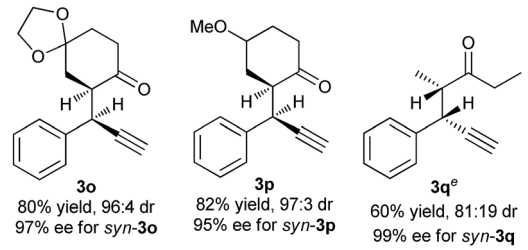


Entry	1 (R)	3	Yield of 3[b] (%)	dr[c]	ee of *syn*-3[d] (%)
1	**1a:** R = Ph	**3a**	82	94 : 6	94
2	**1b:** R = 4-ClC_6H_4	**3b**	80	93 : 7	95
3	**1c:** R = 3-ClC_6H_4	**3c**	85	>98 : 2	97
4	**1d:** R = 2-ClC_6H_4	**3d**	88	>98 : 2	95
5	**1e:** R = 4-FC_6H_4	**3e**	88	97 : 3	92
6	**1f:** R = 4-BrC_6H_4	**3f**	90	94 : 6	95
7	**1g:** R = 4-$CF_3C_6H_4$	**3g**	84	94 : 6	95
8	**1h:** R = 4-MeC_6H_4	**3h**	92	92 : 8	91
9	**1i:** R = 2-naphthyl	**3i**	88	94 : 6	92
10	**1j:** R = 2-furyl	**3j**	90	94 : 6	80
11	**1k:** R = 3-pyridyl	**3k**	86	91 : 9	95

[a] Reaction conditions: $Cu(OAc)_2 \cdot H_2O$ (0.015 mmol), $\mathbf{L_3}$ (0.0165 mmol), **1** (0.3 mmol), **2d** (0.36 mmol), $^iPr_2NEt$ (0.36 mmol) were stirred in 2 mL of MeOH at 0 °C for 10 h. [b] Isolated yield of *syn*-**3a** and *anti*-**3a** in total. [c] Determined by GC or ^1H NMR. [d] Determined by HPLC on chiral column.

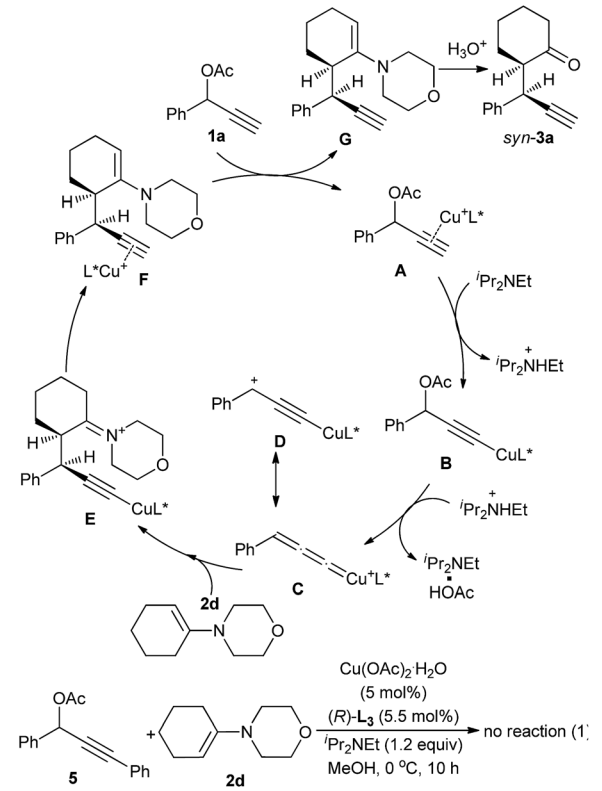
Table 4 Scope of morpholine-derived cyclic enamines[a]





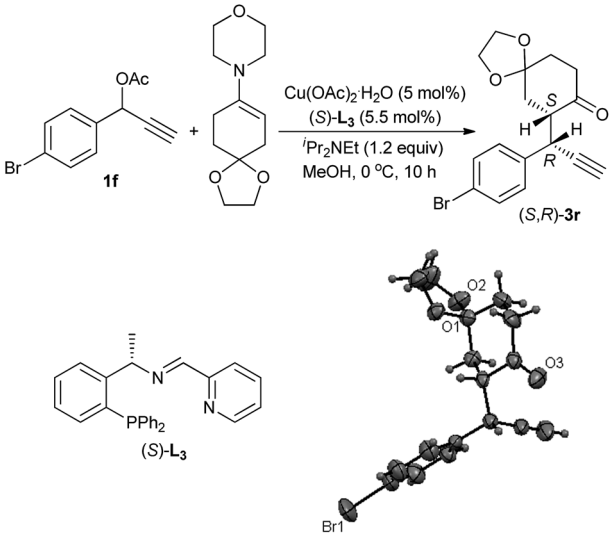
[a] Reaction conditions: $Cu(OAc)_2 \cdot H_2O$ (0.015 mmol), $\mathbf{L_3}$ (0.0165 mmol), **1a** (0.3 mmol), **2d–j** (0.36 mmol), $^iPr_2NEt$ (0.36 mmol) were stirred in 2 mL of MeOH at 0 °C for 10 h. [b] Isolated yield of *syn*-**3a** and *anti*-**3a** in total. [c] Determined by GC or ^1H NMR. [d] Determined by HPLC on chiral column. [e] (*S*)-$\mathbf{L_1}$ was used instead of (*R*)-$\mathbf{L_3}$.

a propargylic acetate bearing an internal alkyne moiety such as 1,3-diphenyl-2-propynyl acetate **5** did not react at all. Elimination of an acetoxyl moiety from **B** affords the copper–allenylidene complex **C** or its resonance structure, the copper–acetylide complex **D** bearing a cationic γ-carbon. The nucleophilic attack of β-carbon atom of enamine **2d** to the C_γ-atom of the copper–allenylidene complex (**C**) gives the corresponding copper–acetylide complex (**E**), which should be the key step for the stereoselection. The intramolecular shift of H atom generates the copper π-alkyne complex **F**. The starting complex **A** is then regenerated from **F** by liberating the propargylic alkylation product **G** by the ligand exchange with another propargylic acetate **1a**.

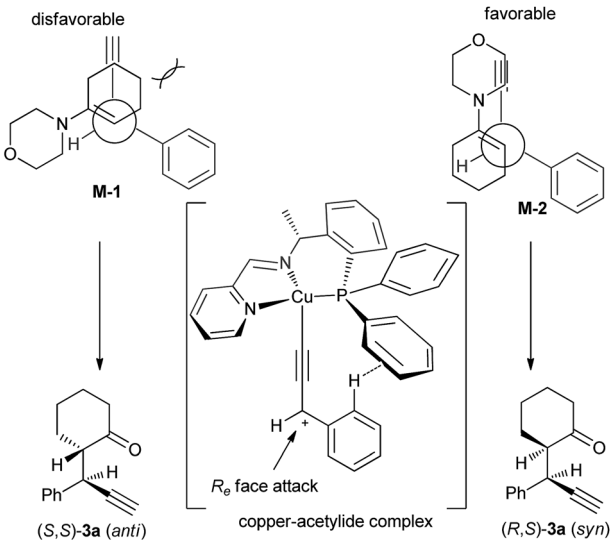


Scheme 3 Proposed mechanism.

A transition state of Cu–allenylidene complex with chiral P,N,N-ligand is also proposed to explain the observed stereochemistry as shown in Scheme 4. The edge-to-face aromatic interaction[4b] and the steric hinderance make the attack of



Scheme 2 Synthesis of (*S*,*R*)-**3r** and its absolute configuration determined by X-ray analysis.



Scheme 4 Proposed model for the diastereo-/enantioselectivities.

enamine C_β-nucleophile at the propargylic cation favourably from the R_e face *via* **M-2** mode to generate (*R*,*S*)-**3a**.

Conclusions

In conclusion, we have developed a highly diastereo- and enantioselective copper-catalyzed propargylic alkylation of propargylic acetates with morpholine-derived cyclic enamines for the construction of two vicinal tertiary stereocenters. The reaction was preferential to the formation of *syn*-diastereoisomers of the propargylic alkylation products in the complete chemoselectivity. By the employment of a chiral 1-phenylethylamine-derived tridentate P,N,N-ligand, good to excellent diastereoselectivity (>98 : 2) and enantioselectivity (up to 99% ee) have been achieved for a wide range of substrates. In comparison with the reaction of acyclic enamines, less sterically hindered P,N,N-ligand showed better performance in the propargylic alkylation of cyclic enamines in term of chemoselectivity, suggesting that its lower reactivity efficiently supressed the last cyclization step. Further development and application of this reaction are underway.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (21572226, 21262011) and the Dalian Institute of Chemical Physics.

Notes and references

1 For reviews, see: (*a*) Y. Nishibayashi and S. Uemura, *Curr. Org. Chem.*, 2006, **10**, 135; (*b*) N. Ljungdahl and N. Kann, *Angew. Chem., Int. Ed.*, 2009, **48**, 642; (*c*) Y. Miyake, S. Uemura and Y. Nishibayashi, *ChemCatChem*, 2009, **1**, 342; (*d*) R. J. Detz, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2009, 6263; (*e*) O. Debleds, E. Gayon, E. Vrancken and J.-M. Campagne, *Beilstein J. Org. Chem.*, 2011, **7**, 866; (*f*) C.-H. Ding and X.-L. Hou, *Chem. Rev.*, 2011, **111**, 1914; (*g*) E. B. Bauer, *Synthesis*, 2012, **44**, 1131; (*h*) Y. Nishibayashi, *Synthesis*, 2012, **44**, 489; (*i*) D.-Y. Zhang and X.-P. Hu, *Tetrahedron Lett.*, 2015, **56**, 283; (*j*) X.-H. Hu, Z.-T. Liu, L. Shao and X.-P. Hu, *Synthesis*, 2015, **47**, 913.

2 R. J. Detz, M. M. E. Delville, H. Hiemstra and J. H. van Maarseveen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3777.

3 G. Hattori, H. Matsuzawa, Y. Miyake and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2008, **47**, 3781.

4 (*a*) G. Hattori, A. Yoshida, Y. Miyake and Y. Nishibayashi, *J. Org. Chem.*, 2009, **74**, 7603; (*b*) G. Hattori, K. Sakata, H. Matsuzawa, Y. Tanabe, Y. Miyake and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2010, **132**, 10592; (*c*) G. Hattori, Y. Miyake and Y. Nishibayashi, *ChemCatChem*, 2010, **2**, 155; (*d*) R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra and J. H. van Maarseveen, *Chem.–Eur. J.*, 2011, **17**, 5921; (*e*) A. Yoshida, G. Hattori, Y. Miyake and Y. Nishibayashi, *Org. Lett.*, 2011, **13**, 2460; (*f*) C. Zhang, Y.-H. Wang, X.-H. Hu, Z. Zheng, J. Xu and X.-P. Hu, *Adv. Synth. Catal.*, 2012, **354**, 2854; (*g*) T. Mino, H. Taguchi, M. Hashimoto and M. Sakamoto, *Tetrahedron: Asymmetry*, 2013, **24**, 1520; (*h*) F.-Z. Han, F.-L. Zhu, Y.-H. Wang, Y. Zou, X.-H. Hu, S. Chen and X.-P. Hu, *Org. Lett.*, 2014, **16**, 588; (*i*) F.-L. Zhu, Y.-H. Wang, D.-Y. Zhang, J. Xu and X.-P. Hu, *Angew. Chem., Int. Ed.*, 2014, **53**, 10223; (*j*) Y. Zou, F.-L. Zhu, Z.-C. Duan, Y.-H. Wang, D.-Y. Zhang, Z. Cao, Z. Zheng and X.-P. Hu, *Tetrahedron Lett.*, 2014, **55**, 2033; (*k*) M. Shibata, K. Nakajima and Y. Nishibayashi, *Chem. Commun.*, 2014, **50**, 7874; (*l*) F.-L. Zhu, Y.-H. Wang, D.-Y. Zhang, X.-H. Hu, S. Chen, C.-J. Hou, J. Xu and X.-P. Hu, *Adv. Synth. Catal.*, 2014, **356**, 3231; (*m*) B. Wang, C. Liu and H. Guo, *RSC Adv.*, 2014, **4**, 53216; (*n*) F. Zhu and X. Hu, *Chin. J. Catal.*, 2015, **36**, 86; (*o*) K. Nakajima, M. Shibata and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2015, **137**, 2472; (*p*) D.-Y. Zhang, L. Shao, J. Xu and X.-P. Hu, *ACS Catal.*, 2015, **5**, 5026; (*q*) G. Huang, C. Cheng, L. Ge, B. Guo, L. Zhao and X. Wu, *Org. Lett.*, 2015, **17**, 4894.

5 For successful examples in the construction of vicinal stereocenters in terms of diastereo- and enantioselectivity, see: (*a*) L. Zhao, G.-X. Huang, B.-B. Guo, L.-J. Xu, J. Chen, W.-G. Cao, G. Zhao and X.-Y. Wu, *Org. Lett.*, 2014, **16**, 5584; (*b*) W. Shao, H. Li, C. Liu, C.-J. Liu and S.-L. You, *Angew. Chem., Int. Ed.*, 2015, **54**, 7684.

6 D.-Y. Zhang, F.-L. Zhu, Y.-H. Wang, X.-H. Hu, S. Chen, C.-J. Hou and X.-P. Hu, *Chem. Commun.*, 2014, **50**, 14459.

7 For a singular example of a copper-catalyzed propargylic alkylation of *N*,*N*-diethyl-1-cyclohexen-1-amine with 1-phenyl-2-propynyl benzoate in 33% yield and with 10/1 dr and 72% ee, see: (*a*) P. Fang and X.-L. Hou, *Org. Lett.*, 2009, **11**, 4612; for a singular example of a copper-catalyzed decarboxylative propargylic alkylation of 1-phenylprop-2-yn-1-yl 2-oxocyclohexanecarboxylate in 88% yield with 7/1 dr and 86% ee, see: (*b*) F.-L. Zhu, Y. Zou, D.-Y. Zhang, Y.-H. Wang, X.-H. Hu, S. Chen, J. Xu and X.-P. Hu, *Angew. Chem., Int. Ed.*, 2014, **53**, 1410.

8 C. Zhang, X.-H. Hu, Y.-H. Wang, Z. Zheng, J. Xu and X.-P. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 9585.

9 CCDC 1439964 for (*S*,*R*)-**3r** †.