RSC Advances

PAPER

Check for updates

Cite this: *RSC Adv.*, 2020, **10**, 38478

Highly enantioselective copper-catalyzed propargylic amination to access *N*-tethered 1,6-enynes†

Si-Jia Li,‡ Jian Huang,‡ Jin-Yu He, Rui-Jin Zhang, Hao-Dong Qian, Xue-Lin Dai, Han-Han Kong and Hao Xu *

Received 8th September 2020
Accepted 12th October 2020

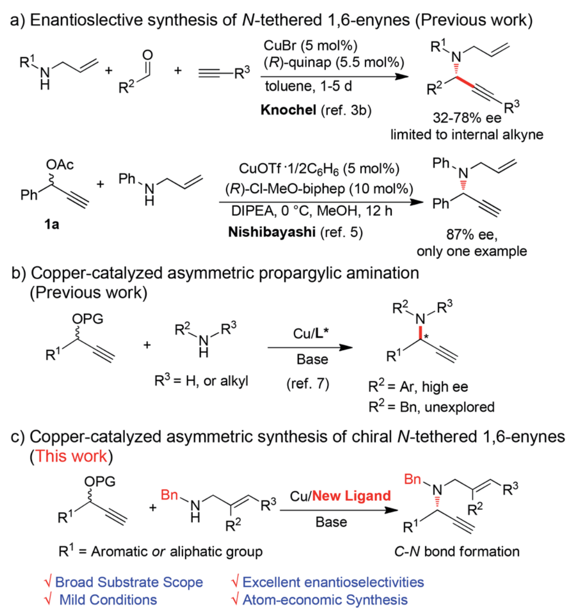
DOI: 10.1039/d0ra07698h

rsc.li/rsc-advances

A highly enantioselective copper-catalyzed propargylic amination starting from benzylic allylic amines has been developed with a new chiral N,N,P ligand. A series of *N*-tethered 1,6-enynes were synthesized in good to excellent yields with excellent enantioselectivities. Utilization of transition metal-catalyzed cycloisomerization of 1,6-enynes provides several enantioselectively enriched chiral five-membered N-heterocycles efficiently.

The *N*-tethered 1,6-enyne skeleton is a highly versatile motif which plays a key role in organic synthesis.[1] In particular, *N*-tethered 1,6-enynes are key synthetic precursors of transition metal catalyzed cycloisomerizations, providing diversity of nitrogen-containing heterocycles (N-heterocycles) efficiently.[2] In the last decades, lots of effort has been dedicated to developing enantioselective methods to synthesize *N*-tethered 1,6-enynes.[3,4] Among those methods, through C–N bond formation of allylic amines and alkynes was regarded as a promising approach. For examples, addition of alkynylides to *N*-allyliminium intermediates generated *in situ* could yield *N*-tethered 1,6-enynes.[3b,c] Using this strategy, Knochel and coworkers disclosed a copper-catalyzed three component reaction for the preparation of *N*-tethered 1,6-enynes with moderate ees (Scheme 1a).[3b] However, this reaction is limited to the synthesis of internal alkynes. In 2010, the Nishibayashi group reported a high enantioselective copper-catalyzed asymmetric propargylic amination, giving the desired product in 87% ee, but only one example was studied (Scheme 1b).[5] Thus, a general and practical method to synthesize *N*-tethered 1,6-enynes in high enantioselectivities is highly desirable.

Copper-catalyzed asymmetric propargylic amination of propargylic esters and amines is a powerful method to construct C–N bond for the preparation of propargylic amines.[6] Nishibayashi, van Maarseveen and Hu *et al.* achieved several pioneering works by their asymmetric catalytic systems.[7] However, those systems are still suffering from low efficiency and limited substrates scope. For instance, both primary and second amines bearing aryl substituted groups were suitable substrates for obtaining excellent ees. However, aryl groups are difficult to remove, thus obstacling its application in organic synthesis. Copper-catalyzed asymmetric propargylic amination of propargylic esters with benzylic amines has not been investigated, probably attributing to their stronger basicity and flexible configuration. It has been well known that benzylic amines not only play important roles in organic synthesis but



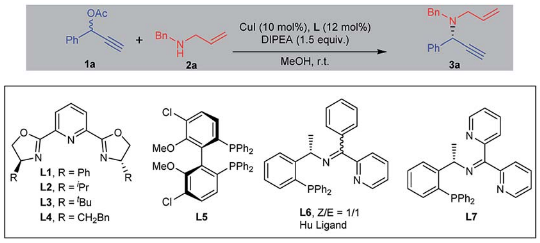
Scheme 1 Enantioselective synthesis of *N*-tethered 1,6-enynes.

CCNU-uOttawa Joint Research Centre, Key Laboratory of Pesticides & Chemical Biology Ministry of Education, International Joint Research Center for Intelligent Biosensing Technology and Health, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China. E-mail: hao.xu@ccnu.edu.cn

† Electronic supplementary information (ESI) available: General information, experimental procedures, NMR spectra, and HPLC spectra (PDF) crystallographic structure of complexes of CuCl and **L7** (CIF). CCDC 1975893. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra07698h

‡ S. L. and J. H. contributed equally.

Table 1 Optimization of the reaction condition[a]



Entry	L	t (h)	Yield[b] (%)	ee[c] (%)
1	**L1**	2	81	50
2	**L2**	2	82	25
3	**L3**	2	15	19
4	**L4**	2	82	21
5	**L5**	2	<5	—
6	**L6**	2	78	82
7	**L7**	2	83	86
8[d]	**L7**	2	87	93
9[e]	**L7**	3	90	97

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), MeOH (0.1 M), DIPEA (1.5 equiv.), CuI (10 mol%), **L** (12 mol%). [b] Isolated yield after flash chromatography. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] $Cu(OAc)_2 \cdot H_2O$ was used instead of CuI. [e] $Cu(OAc)_2 \cdot H_2O$ (5 mol%), **L7** (6 mol%), −20 °C. DIPEA = diisopropylethylamine.

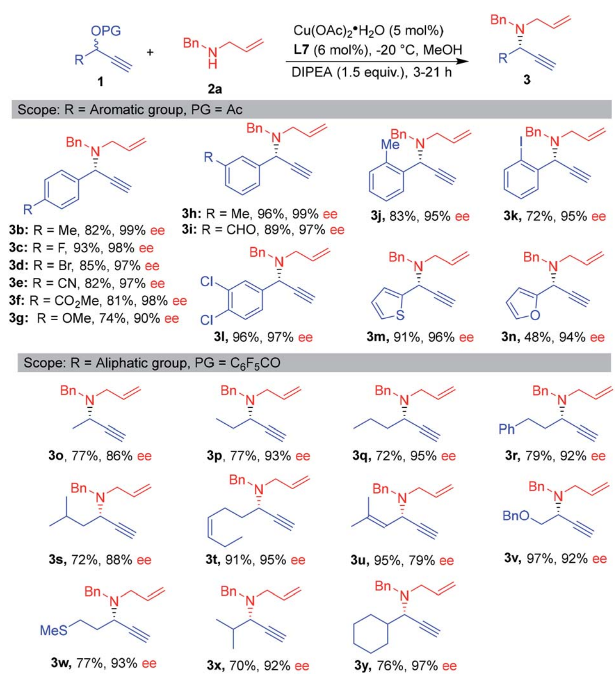
also are core structures of many pharmaceuticals and bioactive compounds.[8] Therefore, devising for the asymmetric propargylic amination from benzylic amines are very important, and remains a challenging task.

Considering the important role of *N*-tethered 1,6-enynes in organic synthesis and our continuing effort in propargylic substitutions,[9] we developed a new catalyst system to realize copper-catalyzed asymmetric propargylic aminations efficiently and mildly. Diverse *N*-tethered 1,6-enynes could be obtained in excellent enantioselectivities. Furthermore, several N-heterocycles could be synthesized by the transition metal promoted cycloisomerization of thus obtained 1,6-enynes.

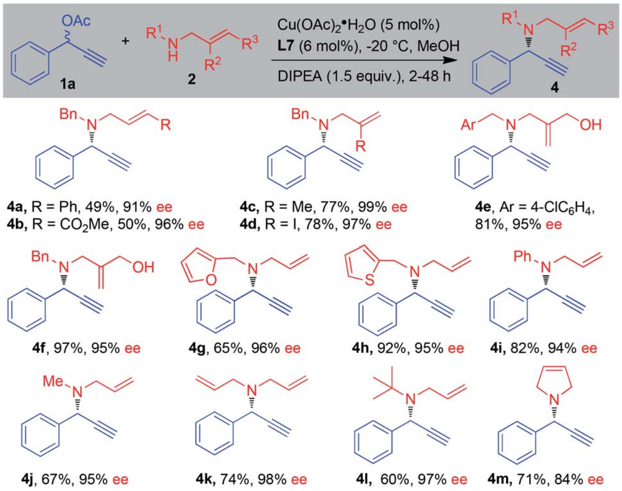
We began our investigation by using the phenyl-2-propynyl acetate **1a** in combination with *N*-allylbenzylamine **2a** as model substrates (Table 1). Examination of the influence of chiral ligands showed that Ph-PyBOX (**L1**) could catalyze the reaction smoothly at room temperature, giving the target product **3a** in 81% yield with 50% ee (entry 1). To improve the enantioselectivity of this transformation, we checked different analogs of the PyBOX, but all the ligands gave poor results (entries 2–4). When using chiral diphosphine ligands such as Cl–MeO-BIHPEP (**L5**), no product was obtained (entry 5). To our delight, improved ee of 82% was obtained by using tridentate ligand **L6** developed by Hu *et al.* (entry 6).[10] We then prepared a novel ligand **L7** bearing two pyridyl group. This ligand gave an even higher ee (86%) (entry 7). When using $Cu(OAc)_2 \cdot H_2O$ as the catalyst instead of CuI, we obtained the product in 87% yield with 93% ee (entry 8). Optimized conditions were finally established by lowering the temperature to −20 °C, the reaction was completed in three hours even with 5 mol% of catalyst loading (entry 9).

The scope of the reaction with respect to the propargylic esters was then investigated under the optimal conditions. By introducing electron-withdrawing or -donating groups at the *para*-position of the phenyl group, the reaction delivered the products **3b–3g** with 90–99% ee values. Different substitutions on the *meta*- and *ortho*-position were also proved compatible for this reaction, again, the corresponding products **3h–3l** were obtained with 95–99% ee. Notably, hetero-aromatic esters served as suitable substrates (**3m–3n**). To our delight, aliphatic-substituted propargylic substrates reacted smoothly with allylic amine **2a** by using perfluorobenzoyl instead of acetate as the protecting group of propargylic alcohols.[11] Several secondary propargylic esters worked well, providing the desired products **3o–3s** in excellent ees. The chain length (from one to three) did not have much influence on the enantioselectivities. This work is different from Zhang's work reported recently, which at least two carbons aliphatic chain is necessary to obtain high enantioselectivities.[11b] Pleasingly, the reaction exhibited high functional-group tolerance. The propargylic esters bearing alkene, ether and thioether moieties underwent the reaction smoothly (**3t–3w**). Furthermore, the reaction also worked well with steric hindrance propargylic esters, giving the products **3x** and **3y** in good yield with 92–97% ee (Scheme 2).

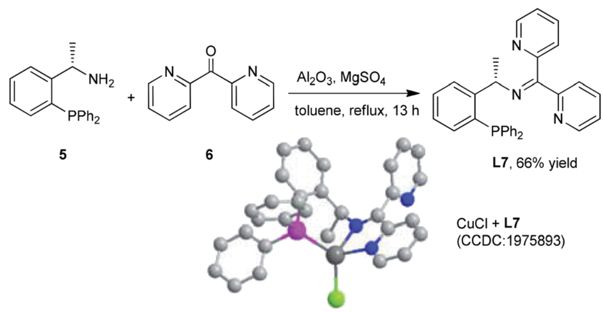
The scope of benzylic allylic amines was examined next (Scheme 3). Diversity of functional groups on the allylic amines such as methyl, iodine, hydroxyl, phenyl and ester groups were well tolerated, delivering the corresponding products **4a–4f** in



Scheme 2 Scope of propargylic esters. [a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), MeOH (0.1 M), DIPEA (1.5 equiv.), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), **L7** (6 mol%), −20 °C.



Scheme 3 Scope of benzylic allylic amines. [a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), MeOH (0.1 M), DIPEA (1.5 equiv.), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), **L7** (6 mol%), −20 °C.

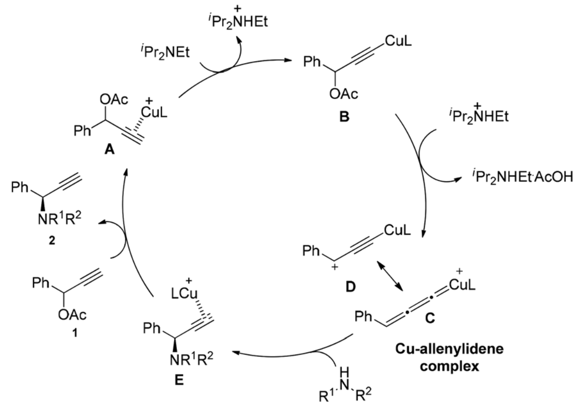


Scheme 4 Synthesis of N,N,P ligand and the complexes of CuCl and **L7**.

49–97% yield with 91–99% ee. Heterocycle substituents such as 2-furyl and 2-thienyl have no significant effect on the reaction course, and the amination products **4g–4h** were obtained in good yields and excellent enantioselectivities. Aromatic secondary amine was compatible for the reaction, giving propargylic amination product **4i** in 82% yield with 94% ee.[12] It seemed that the size of the substitutions on allylic amines did not affect the efficiency of this reaction. Different size groups such as methyl, allyl and *tert*-butyl were compatible for the reaction, providing the desired products **4j–4l** in 60–74% yield with 95–98% ee. Interestingly, 3-pyrrodine also proved as a suitable substrate and 1,6-enyne **4m** was obtained in 71% yield with 84% ee.

The chiral N,N,P ligand **L7** could be prepared by condensation of commercial available chiral amine **5** and di-2-pyridyl ketone **6** in 66% yield in one step.[10] The tridentate coordination mode of **L7** with Cu(I) was unambiguously confirmed by X-ray analysis of CuCl/**L7** complexes (Scheme 4).[13]

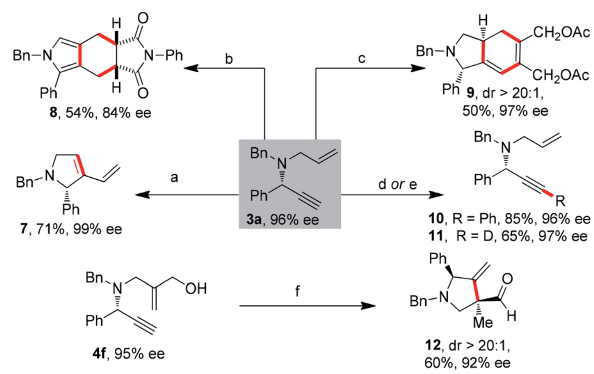
Based on the previous literatures,[5,7c,i] we proposed the possible mechanism of the reaction (Scheme 5). In the first step, the copper complex forms π complex **A** with substrate **1a**.



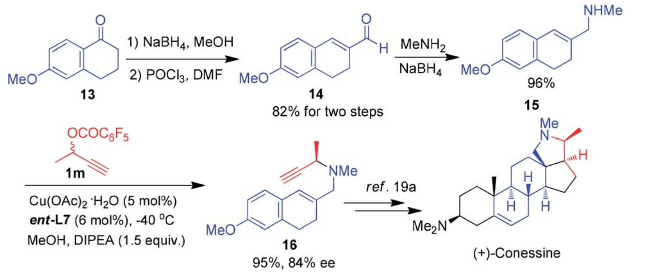
Scheme 5 Proposed reaction mechanism.

Deprotonation with DIPEA gives the copper acetylide **B.** This intermediate loses the acetate group forms Cu–allenylidene complex **C**, where the intermediate **D** bearing a cationic γ-carbon exists as a resonance structure of **C.** Subsequently, the amine attacks the copper–allenylidene complex **C**, followed by a hydrogen atom shift, gives a Cu–π-alkyne complex **E.** After the ligand exchange, the product is released, completing the catalytic cycle.

The significant interest in chiral 1,6-enynes is based on their ability to be readily converted into enantiomerically enriched cyclic compounds. To illustrate the utility of our products, we prepared four different highly substituted scaffolds (Scheme 6). Importantly, bicyclic and polycyclic products were obtained efficiently. By means of enyne metathesis of **3a** by Grubbs 1st generation catalyst afforded 2,5-dihydro-1*H*-pyrrole 7 in 71% yield.[14] A novel polycyclic pyrrole **8** was synthesized by Ir-catalyzed cycloisomerization/Diels–Alder reaction/dehydrogenative aromatization of the 1,6-enyne **3a.**[3a,15] To the best of our knowledge, it is the best result among the literature for synthesizing this scaffold. Moreover, bicyclohexadiene **9** was synthesized by the intermolecular Ru-catalyzed [2 + 2



Scheme 6 Derivatization of the enantiomerically enriched 1,6-enynes. [a]Grubbs catalyst 1st generation (10 mol%), 40 °C, CH_2Cl_2; [b]$[Ir(cod)Cl]_2$ (10 mol%), AcOH (6 equiv.), *N*-phenylmaleimide (1.5 equiv.), toluene, reflux; [c][RuCl(cod)(Cp*)] (10 mol%), but-2-yne-1,4-diyl diacetate (3 equiv.), THF, 60 °C; [d]$Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (7.5 mol%), PhI (1.1 equiv.), 50 °C; [e]K_2CO_3 (3 equiv.), MeCN, D_2O; [f]$Rh(cod)_2Cl$ (10 mol%), *rac*-BINAP, 40 °C.



Scheme 7 Asymmetric formal total synthesis of (+)-conessine.

+ 2] carbocyclization reaction with more than 20 : 1 dr.[16] Additionally, Sonogashira coupling proceeded smoothly to afford **10** in 85% yield.[17] Terminal deuteration of alkyne was achieved in very mild conditions, providing the deuterated alkyne **11** in 65% yield.[18] Of particular importance, Rh-catalyzed intramolecular cyclization of enyne **4f** afforded functionalized cyclic compound **12** with a chiral quaternary carbon center and a ketone moiety in 60% yield.[2a]

Remarkably, this reaction can be further applied to the formal total synthesis of (+)-conessine, which was isolated from the bark of *Holarrhena antidysenterica* and had been used in the treatment of dysentery.[19] As shown in Scheme 7, carbaldehyde **14** was easily available from inexpensive 6-methoxy-1-tetralone **13** by $NaBH_4$ reduction, elimination-vinylogous Vilsmeier reaction in multigram quantities with excellent overall yield (82%).[19e] Subsequently the reductive amination of **14** provided allylic amine **15** in 96% yield. The asymmetric propargylic… amination of **15** with aliphatic propargylic ester **1m** gave the corresponding 1,6-enyne **16** in 95% yield with 84% ee, which is the key synthetic intermediate to the target natural product (+)-conessine.[19a,20] It is worth noting that purification by column chromatography was required only in the last step among the four-step synthetic route.

Conclusions

In summary, we have developed a highly enantioselective propargylic amination of propargylic esters with benzylic allylic amines, which is a practical and general method for the synthesis of chiral *N*-tethered 1,6-enynes. The reaction shows a very broad substrate scope regarding the propargylic esters and allylic amines. Subsequently, transition metal-catalyzed cycloisomerization reaction affords the functionalized cyclic and polycyclic pyrolines derivatives, which could not be easily synthesized by traditional methods. Furthermore, the formal total synthesis of (+)-conessine is achieved.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

Generous financial support from the National Natural Science Foundation of China (21801087) and Fundamental Research Funds for the Central Universities CCNU (CCNU19QN064) is gratefully acknowledged. We thank Prof. Houhua Li (Perking University) for helpful discussion.

Notes and references

1 (*a*) J. Xuan and A. Studer, Radical Cascade Cyclization of 1,*n*-Enynes and Diynes for the Synthesis of Carbocycles and Heterocycles, *Chem. Soc. Rev.*, 2017, **46**, 4329–4346; (*b*) J. D. Ricker and L. M. Geary, Recent Advances in the Pauson–Khand Reaction, *Top. Catal.*, 2017, **60**, 609–619; (*c*) Y. Hu, M. Bai, Y. Yang and Q. Zhou, Metal-Catalyzed Enyne Cycloisomerization in Natural Product Total Synthesis, *Org. Chem. Front.*, 2017, **4**, 2256–2275; (*d*) V. Michelet, P. Y. Toullec and J.-P. Genêt, Cycloisomerization of 1,*n*-Enynes: Challenging Metal-Catalyzed Rearrangements and Mechanistic Insights, *Angew. Chem., Int. Ed.*, 2008, **47**, 4268–4315; (*e*) L. Zhang, J. Sun and S. A. Kozmin, Gold and Platinum Catalysis of Enyne Cycloisomerization, *Adv. Synth. Catal.*, 2006, **348**, 2271–2296.

2 (*a*) Y. Oonishi, S. Masusaki, S. Sakamoto and Y. Sato, Rhodium(I)-Catalyzed Enantioselective Cyclization of Enynes by Intramolecular Cleavage of the Rh-C Bond by a Tethered Hydroxy Group, *Angew. Chem., Int. Ed.*, 2019, **58**, 8736–8739; (*b*) H. Zheng, Y. Wang, C. Xu, Q. Xiong, L. Lin and X. Feng, Diversified Cycloisomerization/Diels–Alder Reactions of 1,6-Enynes through Bimetallic Relay Asymmetric Catalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 5327–5331; (*c*) S. Yoshizaki, Y. Nakamura, K. Masutomi, T. Yoshida, K. Noguchi, Y. Shibata and K. Tanaka, Rhodium-Catalyzed Asymmetric [2 + 2 + 2] Cycloaddition of 1,6-Enynes with Cyclopropylideneacetamides, *Org. Lett.*, 2016, **18**, 388–391; (*d*) T. Shibata, Y. Tahara, K. Tamura and K. Endo, Enantioselective Syntheses of Various Chiral Multicyclic Compounds with Quaternary Carbon Stereocenters by Catalytic Intramolecular Cycloaddition, *J. Am. Chem. Soc.*, 2008, **130**, 3451–3457; (*e*) T. Shibata and Y. Tahara, Enantioselective Intramolecular [2 + 2 + 2] Cycloaddition of 1,4-Diene-ynes: A New Approach to the Construction of Quaternary Carbon Stereocenters, *J. Am. Chem. Soc.*, 2006, **128**, 11766–11767; (*f*) P. A. Evans, K. W. Lai and J. R. Sawyer, Regio- and Enantioselective Intermolecular Rhodium-Catalyzed [2 + 2 + 2] Carbocyclization Reactions of 1,6-Enynes with Methyl Arylpropiolates, *J. Am. Chem. Soc.*, 2005, **127**, 12466–12467; (*g*) T. Shibata, Y. Arai and Y. Tahara, Enantioselective Construction of Quaternary Carbon Centers by Catalytic [2 + 2 + 2] Cycloaddition of 1,6-Enynes and Alkynes, *Org. Lett.*, 2005, **7**, 4955–4957.

3 (*a*) Y. Yamamoto and H. Hayashi, Multi-component Coupling Synthesis of Polycyclic Pyrrole Derivatives via Ir- and Rh-Catalyzed Cycloisomerizations with Microwave Heating, *Tetrahedron*, 2007, **63**, 10149–10160; (*b*) N. Gommermann, C. Koradin, K. Polborn and P. Knochel, Enantioselective Copper(I)-Catalyzed Three-Component Reaction for the Preparation of Propargylamines, *Angew. Chem., Int. Ed.*, 2003, **42**, 5763–5766; (*c*) C. Koradin,

K. Polborn and P. Knochel, Enantioselective Synthesis of Propargylamines by Copper-Catalyzed Addition of Alkynes to Enamines, *Angew. Chem., Int. Ed.*, 2002, **41**, 2535–2538; (*d*) B. Jiang and M. Xu, Catalytic Diastereoselective Pauson−Khand Reaction: An Efficient Route to Enantiopure Cyclopenta[c]proline Derivatives, *Org. Lett.*, 2002, **4**, 4077–4080.

4 T. Sugiishi and H. Nakamura, Zinc(II)-Catalyzed Redox Cross-Dehydrogenative Coupling of Propargylic Amines and Terminal Alkynes for Synthesis of N-Tethered 1,6-Enynes, *J. Am. Chem. Soc.*, 2012, **134**, 2504–2507.

5 G. Hattori, K. Sakata, H. Matsuzawa, Y. Tanabe, Y. Miyake and Y. Nishibayashi, Copper-Catalyzed Enantioselective Propargylic Amination of Propargylic Esters with Amines: Copper-Allenylidene Complexes as Key Intermediates, *J. Am. Chem. Soc.*, 2010, **132**, 10592–10608.

6 For selected reviews on the Cu-catalyzed asymmetric propargylic substitution: (*a*) X.-H. Hu, Z.-T. Liu, L. Shao and X.-P. Hu, Recent Advances in Catalytic Stereocontrolled Cycloaddition with Terminal Propargylic Compounds, *Synthesis*, 2015, **47**, 913–923; (*b*) D.-Y. Zhang and X.-P. Hu, Recent Advances in Copper-Catalyzed Propargylic Substitution, *Tetrahedron Lett.*, 2015, **56**, 283–295; (*c*) E. B. Bauer, Transition-Metal-Catalyzed Functionalization of Propargylic Alcohols and Their Derivatives, *Synthesis*, 2012, **44**, 1131–1151; (*d*) Y. Nishibayashi, Transition-Metal-Catalyzed Enantioselective Propargylic Substitution Reactions of Propargylic Alcohol Derivatives with Nucleophiles, *Synthesis*, 2012, **44**, 489–503; (*e*) C.-H. Ding and X.-L. Hou, Catalytic Asymmetric Propargylation, *Chem. Rev.*, 2011, **111**, 1914–1937; (*f*) Y. Miyake, S. Uemura and Y. Nishibayashi, Catalytic Propargylic Substitution Reactions, *ChemCatChem*, 2009, **1**, 342–356; (*g*) R. J. Detz, H. Hiemstra and J. H. van Maarseveen, Catalyzed Propargylic Substitution, *Eur. J. Org. Chem.*, 2009, 6263–6276; (*h*) N. Ljungdahl and N. Kann, Transition-Metal-Catalyzed Propargylic Substitution, *Angew. Chem., Int. Ed.*, 2009, **48**, 642–644.

7 (*a*) Z.-T. Liu, Y.-H. Wang, F.-L. Zhu and X.-P. Hu, 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, *Org. Lett.*, 2016, **18**, 1190–1193; (*b*) D.-Y. Zhang, L. Shao, J. Xu and X.-P. Hu, Copper-Catalyzed Asymmetric Formal [3 + 2] Cycloaddition of Propargylic Acetates with Hydrazines: Enantioselective Synthesis of Optically Active 2-Pyrazolines, *ACS Catal.*, 2015, **5**, 5026–5030; (*c*) F.-Z. Han, F.-L. Zhu, Y.-H. Wang, Y. Zou, X.-H. Hu, S. Chen and X.-P. Hu, Highly Enantioselective Copper-Catalyzed Propargylic Substitution of Propargylic Acetates with 1,3-Dicarbonyl Compounds, *Org. Lett.*, 2014, **16**, 588–591; (*d*) C. Zhang, Y.-H. Wang, X.-H. Hu, Z. Zheng, J. Xu and X.-P. Hu, Chiral Tridentate P,N,N Ligands for Highly Enantioselective Copper-Catalyzed Propargylic Amination with both Primary and Secondary Amines as Nucleophiles, *Adv. Synth. Catal.*, 2012, **354**, 2854–2858; (*e*) A. Yoshida, G. Hattori, Y. Miyake and Y. Nishibayashi, Copper-Catalyzed Enantioselective Propargylic Amination of Nonaromatic Propargylic Esters with Amines, *Org. Lett.*, 2011, **13**, 2460–2463; (*f*) R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra and J. H. van Maarseveen, Enantioselective Copper-Catalysed Propargylic Substitution: Synthetic Scope Study and Application in Formal Total Syntheses of (+)-Anisomycin and (-)-Cytoxazone, *Chem.–Eur. J.*, 2011, **17**, 5921–5930; (*g*) G. Hattori, Y. Miyake and Y. Nishibayashi, Copper-Catalyzed Diastereo- and Enantioselective Sequential Reactions of Propargylic Acetates with (*E*)-2,4-Pentadienylamine, *ChemCatChem*, 2010, **2**, 155–158; (*h*) G. Hattori, H. Matsuzawa, Y. Miyake and Y. Nishibayashi, Copper-Catalyzed Asymmetric Propargylic Substitution Reactions of Propargylic Acetates with Amines, *Angew. Chem., Int. Ed.*, 2008, **47**, 3781–3783; (*i*) R. J. Detz, M. M. E. Delville, H. Hiemstra and J. H. van Maarseveen, Enantioselective Copper-Catalyzed Propargylic Amination, *Angew. Chem., Int. Ed.*, 2008, **47**, 3777–3780.

8 (*a*) Y. Liu, A. Afanasenko, S. Elangovan, Z. Sun and K. Barta, Primary Benzylamines by Efficient *N*-Alkylation of Benzyl Alcohols Using Commercial Ni Catalysts and Easy-to-Handle Ammonia Sources, *ACS Sustainable Chem. Eng.*, 2019, **7**, 11267–11274; (*b*) J.-B. Peng, F.-P. Wu, C. Xu, X. Qi, J. Ying and X.-F. Wu, Direct Synthesis of Benzylic Amines by Palladium-Catalyzed Carbonylative Aminohomologation of Aryl Halides, *Commun. Chem.*, 2018, **1**, 29; (*c*) T. Ide, J. P. Barham, M. Fujita, Y. Kawato, H. Egami and Y. Hamashima, Regio- and Chemoselective Csp^3-H Arylation of Benzylamines by Single Electron Transfer/Hydrogen Atom Transfer Synergistic Catalysis, *Chem. Sci.*, 2018, **9**, 8453–8460.

9 H. Xu, L. Laraia, L. Schneider, K. Louven, C. Strohmann, A. P. Antonchick and H. Waldmann, Highly Enantioselective Catalytic Vinylogous Propargylation of Coumarins Yields a Class of Autophagy Inhibitors, *Angew. Chem., Int. Ed.*, 2017, **56**, 11232–11236.

10 (*a*) F.-L. Zhu, Y. Zou, D.-Y. Zhang, Y.-H. Wang, X.-H. Hu, S. Chen, J. Xu and X.-P. Hu, Enantioselective Copper-Catalyzed Decarboxylative Propargylic Alkylation of Propargyl β-Ketoesters with a Chiral Ketimine P,N,N-Ligand, *Angew. Chem., Int. Ed.*, 2014, **53**, 1410–1414; (*b*) C. Zhang, X.-H. Hu, Y.-H. Wang, Z. Zheng, J. Xu and X.-P. Hu, Highly Diastereo- and Enantioselective Cu-Catalyzed [3 + 3] Cycloaddition of Propargyl Esters with Cyclic Enamines toward Chiral Bicyclo[*n*.3.1] Frameworks, *J. Am. Chem. Soc.*, 2012, **134**, 9585–9588.

11 Aliphatic propargylic esters were less investigated in asymmetric propargylic substitution(*a*) Q. Zhu, B. Meng, C. Gu, Y. Xu, J. Chen, C. Lei and X. Wu, Diastereo- and Enantioselective Synthesis of Quaternary α-Amino Acid Precursors by Copper-Catalyzed Propargylation, *Org. Lett.*, 2019, **21**, 9985–9989; (*b*) X. Gao, R. Cheng, Y.-L. Xiao, X.-L. Wan and X. Zhang, Copper-Catalyzed Highly Enantioselective Difluoroalkylation of Secondary Propargyl Sulfonates with Difluoroenoxysilanes, *Chem*, 2019, **5**, 2987–2999; (*c*) K. Nakajima, M. Shibata and Y. Nishibayashi,

Copper-Catalyzed Enantioselective Propargylic Etherification of Propargylic Esters with Alcohols, *J. Am. Chem. Soc.*, 2015, **137**, 2472–2475. Also see ref. 7*d* and *e*.

12 The absolute configuration of **4a** was assigned by comparison with the literature (see the ESI†). All other compounds was assigned by analogy.

13 CCDC 1975893 (CuCl + **L7**) contain the supplementary crystallographic data for this paper.

14 Q. Yang, H. Alper and W.-J. Xiao, Efficient Method for the Synthesis of Chiral Pyrrolidine Derivatives via Ring-Closing Enyne Metathesis Reaction, *Org. Lett.*, 2007, **9**, 769–771.

15 Y. Yamamoto, H. Hayashi, T. Saigoku and H. Nishiyama, Domino Coupling Relay Approach to Polycyclic Pyrrole-2-carboxylates, *J. Am. Chem. Soc.*, 2005, **127**, 10804–10805. The absolute configuration of **8** was not assigned in this paper.

16 R. Liu, L. Giordano and A. Tenaglia, Ruthenium-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Enynes and Unactivated Alkynes: Acess to Ring-Fused Cyclohexadienes, *Chem.–Asian J.*, 2017, **12**, 2245–2257.

17 K. Sonogashira, Development of Pd–Cu Catalyzed Cross-coupling of Terminal Acetylenes with sp^2-Carbon Halides, *J. Organomet. Chem.*, 2002, **653**, 46–49.

18 S. P. Bew, G. D. Hiatt-Gipson, J. A. Lovell and C. Poullain, Mild Reaction Conditions for the Terminal Deuteration of Alkynes, *Org. Lett.*, 2012, **14**, 456–459.

19 (*a*) B. Jiang and M. Xu, Highly Enantioselective Construction of Fused Pyrrolidine Systems that Contain a Quaternary Stereocenter: Concise Formal Synthesis of (+)-Conessine, *Angew. Chem., Int. Ed.*, 2004, **43**, 2543–2546; (*b*) A. M. Lannang, S. Anjum, J. G. Tangmouo, K. Krohn and M. I. Choudhary, Conessine Isolated from Holarrhena Floribunda, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2007, **63**, 4398–4399; (*c*) M. E. Kopach, A. H. Fray and A. I. Meyers, An Asymmetric Route to the Conanine BCDE Ring System. A Formal Total Synthesis of (+)-Conessine, *J. Am. Chem. Soc.*, 1996, **118**, 9876–9883; (*d*) K. K. Bhutani, M. Ali, S. R. Sharma, R. M. Vaid and D. K. Gupta, Three New Steroidal Alkaloids from the Bark of Holarrhena antidysenterica, *Phytochemistry*, 1988, **27**, 925–928; (*e*) K. Tiefenbacher, L. Tröndlin, J. Mulzer and A. Pfaltz, An Expeditious Asymmetric Formal Synthesis of the Antibiotic Platensimycin, *Tetrahedron*, 2010, **66**, 6508–6513.

20 The *R*-configuration of Ligand (*ent*-**L7**) was used. The data of compound **15** consistent with data reported in the literature. (see the ESI†).