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

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

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. 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. In the last decades, lots of effort has been dedicated to developing enantioselective methods to synthesize N-tethered 1,6-enynes. 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. 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). 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). 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.

Nishibayashi, van Maarseveen and Hu et al. achieved several pioneering works by their asymmetric catalytic systems. 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 obstructing its application in organic synthesis. Copper-catalyzed asymmetric propargylic amination of propargylic esters with benzyl amines has not been investigated, probably attributing to their stronger basicity and flexible configuration. It has been well known that benzyl amines not only play important roles in organic synthesis but also are crucial substrates for asymmetric catalysis.

Scheme 1  Enantioselective synthesis of N-tethered 1,6-enynes.
also are core structures of many pharmaceuticals and bioactive compounds. Therefore, devising for the asymmetric propargylic amination from benzyl 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 propargyl substitution, 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). Then we prepared a novel ligand L7 bearing two pyridyl group. This ligand gave an even higher ee (86%) (entry 7). When using Cu(OAc)$_2$·H$_2$O 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 propargyl substrates reacted smoothly with allylic amine 2a by using perfluorobenzoyl instead of acetate as the protecting group of propargylic alcohols. 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. 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 benzyl 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 excellent ees. The meta-substituted 5a and 5p were also obtained with 95% ee values. The entry 11 is a special case, in which the phenyl group was replaced with a 1,2,4-trisubstituted benzene, delivering product 5r with 99% ee. The reaction worked well with electron-withdrawing or -donating groups at the ortho-position of the phenyl group, the reaction delivered the products 5s–5w with 95–99% ee values. The function groups on the aliphatic chain such as methyl, iodine, hydroxyl, ester, and alkene were all well-tolerated, delivering the corresponding products 5x–5z in excellent ees.

**Table 1** Optimization of the reaction condition

| Entry | L   | t (h) | Yield (%) | ee (%) |
|-------|-----|------|-----------|--------|
| 1     | L1  | 2    | 81        | 50     |
| 2     | L2  | 2    | 82        | 25     |
| 3     | L3  | 2    | 15        | 19     |
| 4     | L4  | 2    | 82        | 21     |
| 5     | L5  |      | <5        |        |
| 6     | L6  | 2    | 78        | 85     |
| 7     | L7  | 2    | 83        | 86     |
| 8     | L7  |      | 87        | 93     |
| 9     | L7  | 3    | 90        | 97     |

* Reaction conditions: 1a (0.2 mmol), 2a (0.3 mmol), MeOH (0.1 M), DIPEA (1.5 equiv.), CuI (10 mol%), L (12 mol%). * Isolated yield after flash chromatography. * The ee value was determined by HPLC analysis on a chiral stationary phase. * Cu(OAc)$_2$·H$_2$O (5 mol%), L7 (6 mol%), −20 °C. DIPEA = diisopropylethylamine.
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.

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-pyrridine 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. 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, we proposed the possible mechanism of the reaction (Scheme 5). In the first step, the copper complex forms a complex A with substrate 1a. 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-1H-pyrrole 7 in 71% yield. A novel polycyclic pyrrole 8 was synthesized by Ir-catalyzed cycloisomerization/Diels–Alder reaction/dehydrogenative aromatization of the 1,6-enyne 3a. 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
(+)-conessine. Additionally, Sonogashira coupling proceeded smoothly to afford 10 in 85% yield. 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.

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. As shown in Scheme 7, carboxaldehyde 14 was easily available from inexpensive 6-methoxy-1-tetralone 13 by NaBH₄ reduction, elimination-vinlogous Vilsmeier reaction in multigram quantities with excellent overall yield (82%). 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-ename 16 in 95% yield with 84% ee, which is the key synthetic intermediate to the target natural product (+)-conessine. 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 allicy amines, which is a practical and general method for the synthesis of chiral N-tethered 1,6-ynes. 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 pyrroles 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 (Perkin University) for helpful discussion.

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