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Asymmetric copper-catalyzed propargylic amination with amine hydrochloride salts†

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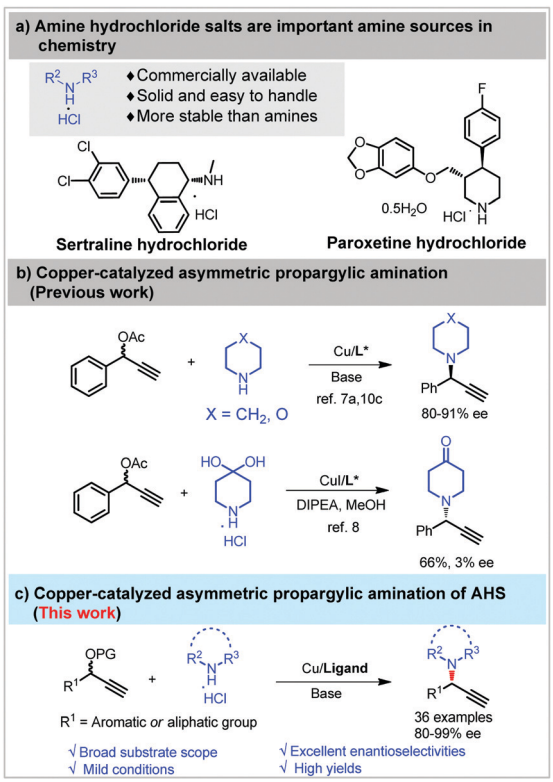
The highly enantioselective copper-catalyzed propargylic amination of propargylic esters with amine hydrochloride salts has been realized for the first time using copper salts with chiral *N,N,P*-ligands. This method features a broad substrate scope and wide functional group tolerance, generating propargylic amines in good to excellent yields with high enantioselectivities (up to 99% ee). The utility of the approach was demonstrated by late-stage functionalization of marketed pharmaceuticals.

Nitrogen-containing compounds are widely applied in organic synthesis and biological studies and transition-metal-catalyzed C–N bond formation reactions are powerful tools for preparing such compounds.[1,2] Compared with aliphatic and aromatic amines, which are frequently used as nitrogen sources, amine hydrochloride salts (AHS) are more attractive because they are often commercially available, inexpensive, and quite stable in air.[3] Furthermore, many N-containing pharmaceuticals and biologically active compounds are stored in the form of AHS (Scheme 1a), providing alternative sources for C–N bond formation reactions.[4] The resistance toward oxidation of AHS has enabled both copper- and iron-catalyzed oxidative amidation of AHS with aldehydes to be successfully developed during the last decade.[5] Although there have been a few reports regarding transition-metal-catalyzed C–N bond formation reactions, enantioselective syntheses involving AHS are limited and need further development. To our knowledge, there has only been one successful example, developed by Carreira *et al.*[6] In their work, 4-piperidone hydrate hydrochloride was used as the masked primary amine, which was applied in a copper-catalyzed asymmetric three-component reaction, delivering the propargylic amines in high to excellent enantioselectivities. The limited number of successful reactions of AHS were reported maybe attributed to their harmful to transition-metal catalyst. Therefore, the development of transition-metal-catalyzed asymmetric reactions from AHS is not only very challenging, but also highly desirable.

Copper-catalyzed asymmetric propargylic amination represents a powerful C–N bond formation reaction that offers a



Scheme 1 Introduction of Amine Hydrochloride Salts (AHS).

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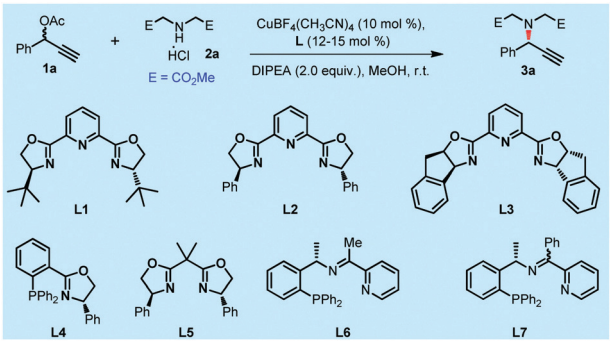
direct and practical approach to the synthesis of propargylic amines. As has been reported, aryl amines as well as cyclic and acyclic amines are suitable substrates.[7] In 2011, van Maarseveen reported a systemic study of copper-catalyzed asymmetric propargylic amination.[8] However, in that study, when cyclohexylamine and morpholine were changed to 4-piperidone hydrate hydrochloride, almost racemic products were obtained (Scheme 1b). We also found that AHS and chloride ions decrease both the efficiency and enantioselectivities of copper-catalyzed asymmetric propargylic amination (see the ESI†). Therefore, employing AHS in copper-catalyzed asymmetric propargylic amination remains a challenging task. Over the last decades, considerable efforts have been devoted to copper-catalyzed asymmetric propargylic substitution.[9] Several catalytic systems have been successfully developed, including by Nishibayashi,[10] van Maarseveen,[7d,8] Hu,[11] Wu,[12] and Niu.[13] Considering the basicity of these systems, we envisioned that adjusting the number of equivalents of base and selecting appropriate chiral ligands could help to achieve copper-catalyzed asymmetric amination from AHS. Herein, we report our recent efforts toward copper-catalyzed asymmetric propargylic amination reaction from AHS (Scheme 1c).

We commenced our study by testing the performance of a set of chiral ligands in the reaction of model substrate phenyl-2-propynyl acetate (**1a**) and dimethyl iminodiacetate hydrochloride (**2a**) in the presence of 2.0 equivalent base (DIPEA). As shown in Table 1, ^{t}Bu-PyBOX (**L1**) catalyzed the reaction smoothly at room temperature, giving the target product **3a** in 54% yield with 5% ee (entry 1). Different analogues of the PyBOX were further screened, and the use of indane-PyBOX (**L3**) provided better enantioselective control (entry 3), delivering **3a** in 77% yield with 73% ee. Disappointingly, bidentate ligands such as PHOX (**L4**) and BOX (**L5**) both led to poor results; however, to our delight, improved ee was obtained by using tridentate ligand **L6** (75% ee) and **L7** (80% ee) developed by Hu ***et al.*** (entries 6 and 7).[7a,11] Thus, the result obtained with **L7** proved to be promising; in particular, the ee of the target molecule was entirely retained even when the catalyst loading was reduced from 10 to 5 mol% (entry 8). Based on the superior chiral induction of **L7** noted above, switching from $CuBF_4(CH_3CN)_4$ to $CuPF_6(CH_3CN)_4$ provided even higher ee (85%, entry 9). Decreasing the reaction temperature from room temperature to −20 °C was also found to be beneficial, with the reaction affording the desired product with excellent isolated yield (97%) and excellent ee (95%, entry 10). Other protic or aprotic solvents instead of methanol did not give superior results.

With the optimal conditions in hand, we then explored the scope of the reaction with respect to the propargylic esters (Scheme 2). A variety of aryl propargylic esters were tolerated and participated in the reaction smoothly. For example, a range of substituents on the *meta*- and *ortho*-positions proved to be compatible with this reaction, producing the corresponding products **3b–d** with 94–97% ee. Similarly, the introduction of either electron-withdrawing or electron-donating groups at the *para*-position of the phenyl group delivered the products **3e–k** with 90–95% ee values. Chlorine on both the *meta*- and *para*-positions of the phenyl served as a suitable substrate; in this case, the corresponding product **3l** was obtained in 89% yield

Table 1 Optimization of the reaction conditions[a]

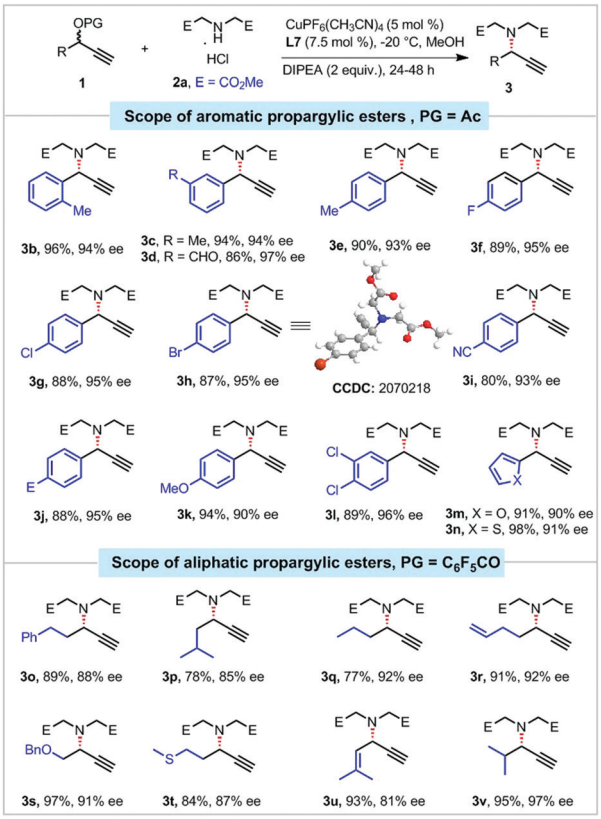


Entry	L	t (h)	Yield[b] (%)	ee[c] (%)
1	**L1**	14	54	5
2	**L2**	3	91	23
3	**L3**	4	77	73
4	**L4**	48	9	3
5	**L5**	6	32	10
6	**L6**	8	50	75
7	**L7**	7	74	80
8[d]	**L7**	3	71	80
9[e]	**L7**	5	61	85
10[f]	**L7**	24	97	95
11[g]	**L7**	48	21	90
12[h]	**L7**	48	NR	—

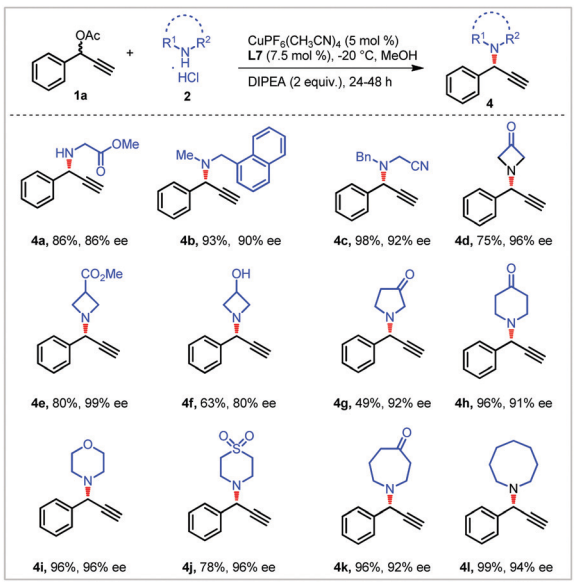
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), MeOH (0.1 M), DIPEA (2 equiv.), $CuBF_4(CH_3CN)_4$ (10 mol%), **L** (12–15 mol%). [b] Isolated yield after flash chromatography. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] $CuBF_4(CH_3CN)_4$ (5 mol%), **L7** (7.5 mol%) was used. [e] $CuPF_6(CH_3CN)_4$ (5 mol%), **L7** (7.5 mol%) was used. [f] −20 °C. [g] EtOH as solvent. [h] Aprotic solvents DIPEA = diisopropylethylamine. NR = no reaction.

with 96% ee. Notably, hetero-aromatic esters also proved to be compatible with this reaction, providing the desired products **3m–n** in 91–98% yield with 90–91% ee. Aliphatic-substituted propargylic substrates are generally less active, which may present a challenge to realizing effective propargylic substitutions, especially with single-catalyst systems.[7b] Nevertheless, pleasingly, aliphatic propargylic alcohols protected by perfluorobenzoyl also reacted smoothly with dimethyl iminodiacetate hydrochloride (**2a**) under our optimal catalytic conditions. Moreover, a variety of secondary propargylic esters also reacted well, and excellent enantioselectivities of the products **3o–s** were observed. The propargylic esters bearing alkene, ether, and thioether moieties proved to be suitable substrates, demonstrating the high functional-group compatibility of this transformation. Furthermore, use of the sterically bulky isopropyl substituent did not decrease the reactivity or efficiency of the reaction, giving the product **3v** in 95% yield with 97% ee. The structure as well as absolute configuration of the propargylic amine was unambiguously determined by single-crystal X-ray analysis of **3h**.

Propargylic amination with various AHS proceeded smoothly to afford the corresponding products with high enantioselectivities (Scheme 3). Not only the secondary AHS, but also primary AHS such as glycine methyl ester hydrochloride was found to be suitable substrates for this transformation. Linear AHS such as *N*-methyl 1-naphthalenemethylamine and *N*-benzyl



Scheme 2 Scope of the reaction with propargylic esters.

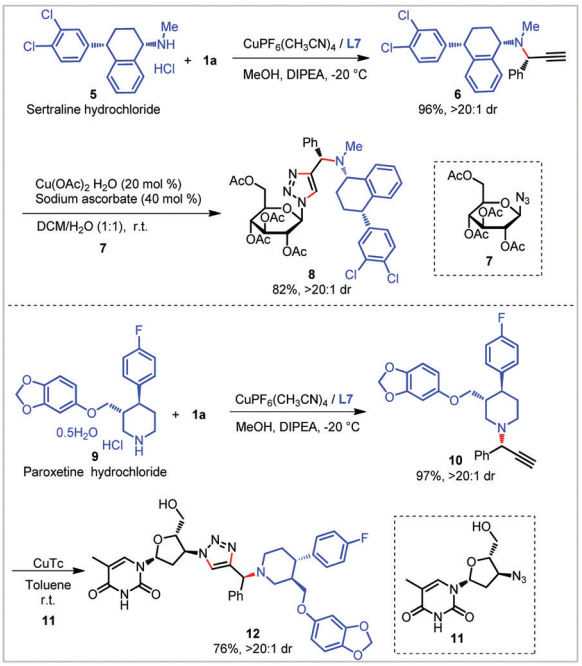


Scheme 3 Scope of the reaction with amine hydrochloride salts.

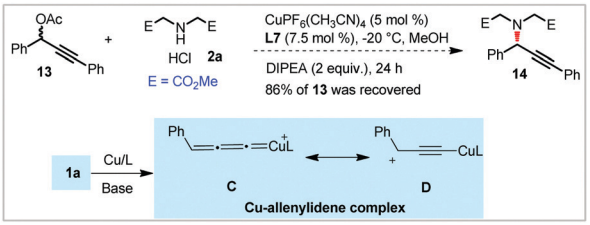
aminoacetonitrile hydrochloride reacted with 1a smoothly, providing the products in 93–98% yield with 90–92% ee. Interestingly, cyclic AHS were also well-tolerated substrates. Changing the ring size of cyclic AHS from four- to seven-membered had no significant effect on the efficiency of the reactions. Reaction of **1a** with 3-pyrrolidinone hydrochloride gave the corresponding derivative **4g** in high ee up to 92% ee with a slightly diminished yield, indicating that this transformation has superior functional-group tolerance with respect to AHS. AHS bearing cyano (**4c**), ketone (**4d**, **4h**, **4k**), ester (**4e**), hydroxyl (**4f**), ether (**4i**), or sulfonyl groups (**4j**) are well tolerated in this synthesis, providing a diverse range of propargylic amines in generally high yields with excellent ee values. The reaction worked very well by using secondary amines instead of AHS, indicating the powerful catalytic abilities (**4l**).[14]

The potential utility of the copper–catalyzed propargylic amination was further demonstrated in the late-stage modification of pharmaceuticals. Sertraline and paroxetine are antidepressants of the selective serotonin reuptake inhibitor class, and are both secondary AHS.[15] As shown in Scheme 4, both of the compounds reacted with **1a** smoothly under the standard conditions, providing the modified drugs with excellent reactivity and diastereoselectivities. It is worth mentioning that only moderate diastereoselectivities could be achieved without **L7**, indicating that the combination of copper salt and chiral *N*,*N*,*P*-ligand plays an important role in controlling the diastereoselectivities. Moreover, the sertraline-derived product 6 and paroxetine-derived product 10 could be connected with zidovudine and 1-azido-1-deoxy-β-D-flucopyranoside tetraacetate, respectively, through a Cu-catalyzed azide–alkyne cycloaddition, allowing the efficient connection of two pharmaceutical fragments.

To explore the mechanism of this reaction, internal alkyl acetate 13 was applied in the reaction of AHS under the standard reaction conditions. As might have been expected, no target product was observed and compound 13 was recovered in 86% yield, showing that the terminal propargylic ester is a key structural element in the reaction. Based on our experiments and



Scheme 4 Late-stage functionalization of pharmaceuticals.



Scheme 5 Mechanistic studies.

on previous reports,[7a,10c] we proposed that a Cu-allenylidene complex is the core intermediate. (Plausible mechanism was also proposed and see the ESI† for details) (Scheme 5).

In summary, we have developed the first highly enantioselective propargylic amination of propargylic esters with AHS under mild conditions. The reaction shows broad substrate scope with respect to both the propargylic esters and AHS. The chiral *N*,*N*,*P*-ligand plays an important role in this transformation. The utility of this method has been demonstrated by the late-stage functionalization of pharmaceuticals and by the connection of two drug fragments. This approach is expected to be beneficial for drug discovery and developing biologically active compounds.

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Conflicts of interest

The authors declare no competing financial interest.

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