Tetrahedron Letters 55 (2014) 2033–2036

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantioselective Cu-catalyzed decarboxylative propargylic amination of propargyl carbamates

Yuan Zou [a,b], Fu-Lin Zhu [b], Zheng-Chao Duan [c], Ya-Hui Wang [b], De-Yang Zhang [b], Zhong Cao [a], Zhuo Zheng [b], Xiang-Ping Hu [b,*]

[a] School of Chemistry and Biological Engineering, Changsha University of Science and Technology, Changsha 410004, China
[b] Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China
[c] School of Chemical and Environmental Engineering, Hubei University for Nationalities, Enshi 445000, Hubei, China

ARTICLE INFO

Article history:
Received 13 December 2013
Revised 7 February 2014
Accepted 13 February 2014
Available online 20 February 2014

Keywords:
Copper
Asymmetric catalysis
Decarboxylation
Propargylic amination
Propargyl carbamate

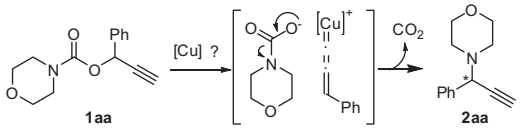
ABSTRACT

A copper-catalyzed asymmetric propargylic amination with a chiral ketimine P,N,N-ligand that proceeds via decarboxylation of propargyl carbamates has been developed. The reaction can be performed under the mild condition for a broad range of substrates, providing the corresponding propargylic amines in high yields and with up to 97% ee. This reaction represents a new and facile access to optically active propargylic amines.

Chiral propargylic amines are widely used as intermediate products in the preparation of biologically active compounds and polyfunctional amino derivatives.[1] Among various methods for the synthesis of these compounds,[2] catalytic asymmetric propargylic amination should be one of the most attractive strategies.[3] Although great progress has been made in the transition-metal catalyzed propargylic substitution in the past decades,[4] the synthesis of chiral propargylic amines via the catalytic asymmetric propargylic amination is still highly limited. In 1994, Murahashi and co-workers[5] found that propargylic amines could be obtained via the copper-catalyzed propargylic amination of propargylic esters with various amines, which sets the stage for the development of an asymmetric version. In 2008, van Maarseveen and co-workers[6] and Nishibayashi and co-workers[7] independently reported the first copper-catalyzed asymmetric propargylic amination of propargylic acetates with primary amines and secondary amines, respectively. Following them, some copper-catalyzed asymmetric propargylic aminations have been reported.[8] Despite these advances, the development of a new strategy for the catalytic asymmetric synthesis of optically active propargylic amines remains a highly desirable and challenging task.

Very recently, we have reported the first copper-catalyzed asymmetric decarboxylative propargylic alkylation of propargyl β-ketoesters.[9] In this method, the loss of CO_2 replaces the need to selectively prepare preformed enolate equivalents, and both the nucleophile and the electrophile are formed in situ in catalytic concentration. The reaction could be performed under the mild condition, and proceeded in highly enatioselective form. We envisaged that this strategy should also provide an ideal solution for the synthesis of optically active propargylic amines if a propargyl carbamate is employed as the substrate instead of propargyl β-ketoester (Scheme 1). As a result, herein we described the first enantioselective copper-catalyzed decarboxylative propargylic amination of propargyl carbamates with a tridentate ketimine P,N,N-ligand, in which excellent performance could be achieved (Fig. 1).

The corresponding propargyl carbamates can be easily prepared by the reaction of carbamic chlorides with various substituted



Scheme 1. General reaction scheme for Cu-catalyzed asymmetric decarboxylative propargylic amination.

* Corresponding author. Tel.: +86 411 84379276; fax: +86 411 84684746.
E-mail address: xiangping@dicp.ac.cn (X.-P. Hu).

http://dx.doi.org/10.1016/j.tetlet.2014.02.030
0040-4039/

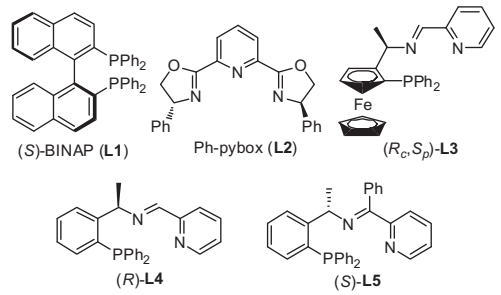
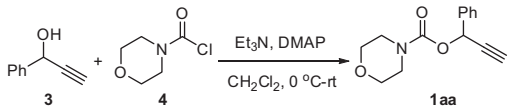


Figure 1. Ligands for Cu-catalyzed decarboxylative propargylic amination.

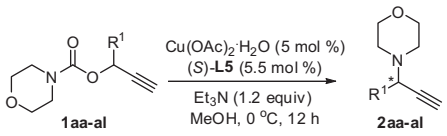


Scheme 2. Synthesis of propargyl carbamate **1aa**.

prop-2-yn-1-ols, as exemplified by the synthesis of 1-phenylprop-2-yn-1-yl morpholine-4-carboxylate (**1aa**) in Scheme 2.

At the outset of our studies on the copper-catalyzed asymmetric decarboxylative propargylic amination, 1-phenylprop-2-yn-1-yl morpholine-4-carboxylate (**1aa**) was selected as the model substrate for the optimization of reaction conditions, and the results are summarized in Table 1. Initially, ligand effect was investigated, and ligands including BINAP (**L1**),[10] Ph-pybox (**L2**),[11] and P,N,N-ligand (**L3**–**L5**),[9,12] that have proved to be efficient in the Cu-catalyzed asymmetric propargylic substitution, were examined. The reaction was conducted with 0.5 mmol of **1aa**, 5 mol % of the copper catalyst prepared in situ from $Cu(CH_3CN)_4BF_4$ and chiral ligand, and 1.2 equiv of Et_3N in 2 mL of MeOH at room temperature for 12 h. The result disclosed that the structure of ligand had a significant influence on the reactivity and enantioselectivity, although the desired propargylic amine **2aa** could be obtained in all cases (entries 1–5). Thus, with BINAP (**L1**) and ferrocenyl P,N,N-ligand **L3**, the reaction provided **2aa** in moderate yield and with very low enantioselectivity (entries 1 and 3). By use of tridentate N-ligand, Ph-pybox (**L2**), good yield but with low enantioselectivity was achieved (entry 2). The result indicated that 1-phenylethylamine-derived tridentate P,N,N-ligands **L4** and **L5** were highly efficient to this reaction with the ketimine ligand **L5** being optimal in terms of the yield and the enantioselectivity (entries 4 and 5). The following investigation on copper salt showed a dramatic effect on the reactivity and enantioselectivity (entries 5–10), and

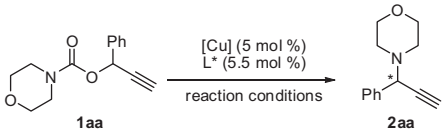
Table 2
Cu-catalyzed decarboxylative propargylic amination of carbamates: scope of propargyl moieties[a]



Entry	Substrate	Product	Yield[b] (%)	ee[c] (%)
1	**1aa**: R^1 = Ph	**2aa**	96	94
2	**1ab**: R^1 = 2-ClC_6H_4	**2ab**	91	95
3	**1ac**: R^1 = 3-ClC_6H_4	**2ac**	90	96
4	**1ad**: R^1 = 4-ClC_6H_4	**2ad**	93	94
5	**1ae**: R^1 = 4-FC_6H_4	**2ae**	95	92
6	**1af**: R^1 = 4-BrC_6H_4	**2af**	92	94
7	**1ag**: R^1 = 4-$CF_3C_6H_4$	**2ag**	94	94
8	**1ah**: R^1 = 4-$CH_3C_6H_4$	**2ah**	93	96
9	**1ai**: R^1 = 4-$CH_3OC_6H_4$	**2ai**	92	83
10	**1aj**: R^1 = 2-naphthyl	**2aj**	95	92
11	**1ak**: R^1 = thienyl	**2ak**	90	89
12	**1al**: R^1 = Me	**2al**	—	—[d]

[a] Reaction conditions: **1** (0.5 mmol), $Cu(OAc)_2·H_2O$ (0.025 mmol, 5 mol %), (*S*)-**L5** (0.0275 mmol, 5.5 mol %), Et_3N (0.6 mmol, 1.2 equiv), 2 mL of MeOH, 0 °C, 12 h.
[b] Yield of isolated product.
[c] The ee values were determined by HPLC analysis (for **2aa**–**ah**: chiralcel OJ-H, *n*-hexane/*i*-PrOH = 95:5, 0.8 mL/min, 254 nm, 40 °C; for **2ai** and **2ak**: chiralpak AD-H, *n*-hexane/*i*-PrOH = 98:2, 0.8 mL/min, 254 nm, 40 °C; for **2aj**: chiralpak AD-H, *n*-hexane/*i*-PrOH = 95:5, 0.8 mL/min, 254 nm, 40 °C).
[d] Not determined because of low conversion.

Table 1
Optimization of asymmetric Cu-catalyzed decarboxylative propargylic amination of 1-phenylprop-2-yn-1-yl morpholine-4-carboxylate (**1aa**)[a]



Entry	[Cu]	Ligand	Base	Solvent	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	$Cu(CH_3CN)_4BF_4$	**L1**	Et_3N	MeOH	25	51	<5
2	$Cu(CH_3CN)_4BF_4$	**L2**	Et_3N	MeOH	25	92	35
3	$Cu(CH_3CN)_4BF_4$	**L3**	Et_3N	MeOH	25	50	10
4	$Cu(CH_3CN)_4BF_4$	**L4**	Et_3N	MeOH	25	91	84
5	$Cu(CH_3CN)_4BF_4$	**L5**	Et_3N	MeOH	25	90	88
6	$Cu(CH_3CN)_4ClO_4$	**L5**	Et_3N	MeOH	25	86	82
7	CuCl	**L5**	Et_3N	MeOH	25	60	45
8	CuI	**L5**	Et_3N	MeOH	25	65	73
9	$Cu(OTf)_2$	**L5**	Et_3N	MeOH	25	87	90
10	$Cu(OAc)_2·H_2O$	**L5**	Et_3N	MeOH	25	96	92
11	$Cu(OAc)_2·H_2O$	**L5**	—	MeOH	25	56	59
12	$Cu(OAc)_2·H_2O$	**L5**	DBU	MeOH	25	73	15
13	$Cu(OAc)_2·H_2O$	**L5**	$^iPr_2NEt$	MeOH	25	91	88
14	$Cu(OAc)_2·H_2O$	**L5**	Et_3N	CH_2Cl_2	25	85	31
15	$Cu(OAc)_2·H_2O$	**L5**	Et_3N	THF	25	83	10
16	$Cu(OAc)_2·H_2O$	**L5**	Et_3N	toluene	25	80	15
17	$Cu(OAc)_2·H_2O$	**L5**	Et_3N	MeOH	0	96	94

[a] Reaction conditions: **1aa** (0.5 mmol), [Cu] (0.025 mmol, 5 mol %), **L*** (0.0275 mmol, 5.5 mol %), base (0.6 mmol, 1.2 equiv), 2 mL of solvent, indicated temperature, 12 h.
[b] Isolated yields.
[c] The ee values were determined by HPLC analysis (chiralcel OJ-H, *n*-hexane/*i*-PrOH = 95:5, 0.8 mL/min, 254 nm, 40 °C).

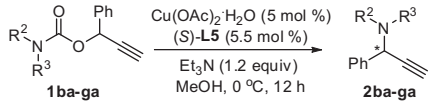
$Cu(OAc)_2{\cdot}H_2O$ was found to be the best choice (entry 10). The addition of a base was crucial for this reaction, and poor performance was observed in its absence (entry 11). With other base additives such as DBU and $^{i}Pr_2NEt$, lower reactivity and enantioselectivity were achieved in comparison with Et_3N (entries 12 and 13). The effect of the solvent was also investigated, and an obvious solvent dependency was observed. Except in MeOH, all reactions in other solvents such as CH_2Cl_2, THF, and toluene furnished the desired propargylic amine **2aa** in low enantioselectivity albeit good yield (entries 14–16). This is different with those observed on the corresponding decarboxylative propargylic alkylation of propargyl β-ketoesters, in which no obvious solvent influence was observed.[9] By lowering the reaction temperature to 0 °C, the enantioselectivity could be further increased to 94% ee without loss of the yield (entry 17).

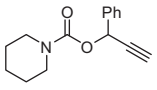
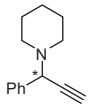
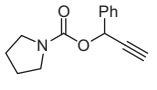
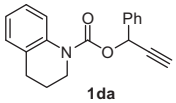
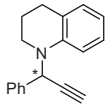
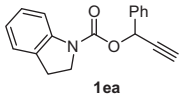
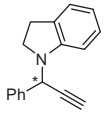
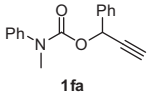
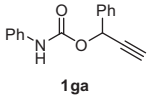
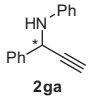
Under the optimized reaction conditions (Table 1, entry 17),[13] we next investigated the effect of the propargyl moiety of propargyl carbamates on the copper-catalyzed asymmetric decarboxylative propargylic amination, and typical results are shown in Table 2. To our delight, the reaction worked efficiently for all of phenyl-substituted substrates (entries 1–9). The results indicated that the position of the substituent on the phenyl ring had little effect in the reaction. Thus, all three substrates with a Cl group at the different positions of the phenyl ring gave similar outcomes (entries 2–4). It appeared that the electronic properties of the substituent at the *para* position of the phenyl ring also showed little influence on the reactivity and enantioselectivity (entries 4–8). An exception was the substrate **1ai** with a methoxy group at the *para* position of the phenyl ring, which led to somewhat decreased enantioselectivity of 83% ee (entry 9). 2-Naphthyl substrate **1aj** served well for this reaction, giving the corresponding chiral amine **2aj** in 95% yield and with 92% ee (entry 10). 2-Thienyl substrate **1ak** also proved to be a suitable reaction partner, providing **2ak** in 90% yield and with 89% ee (entry 11). However, the present catalytic system showed less efficiency to aliphatic substrate (**1al**) (entry 12), which is consistent with the observation in the Cu-catalyzed asymmetric propargylic substitution.[8]

We also investigated the reaction of propargyl carbamates bearing various amino moieties. The results in Table 3 indicated that a variety of tertiary carbamates including those derived from cyclic and acyclic amines undergo the decarboxylative coupling under the optimized reaction condition, providing the corresponding tertiary propargylic amines in good yields and with high enantioselectivities (entries 1–5). The reaction also tolerated a secondary carbamate. Thus, 1-phenylprop-2-yn-1-yl phenylcarbamate **1ga** led to *N*-(1-phenylprop-2-yn-1-yl)aniline **2ga** in 93% yield and with 82% ee (entry 6).

In conclusion, we have developed the first Cu-catalyzed asymmetric decarboxylative propargylic amination of propargyl carbamates, furnishing a variety of chiral propargylic amines in good yields and with high enantioselectivities. The reaction can be performed under the mild conditions with a broad substrate spectrum, which represents a new and complementary strategy for the catalytic asymmetric synthesis of optically active propargylic amines. The further development and application of this reaction, as well as study of the mechanism, is underway in our laboratory.

Table 3
Cu-catalyzed decarboxylative propargylic amination of carbamates: scope of amino moieties[a]



Entry	Substrate	Product	Yield[b] (%)	ee[c] (%)
1	 1ba	 2ba	95	93
2	 1ca	 2ca	94	91
3	 1da	 2da	92	97
4	 1ea	 2ea	93	84
5	 1fa	 2fa	94	95
6	 1ga	 2ga	93	82

[a] Reaction conditions: **1** (0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.025 mmol, 5 mol %), (*S*)-**L5** (0.0275 mmol, 5.5 mol %), Et_3N (0.6 mmol, 1.2 equiv), 2 mL of MeOH, 0 °C, 12 h.
[b] Yield of isolated product.
[c] The ee values were determined by HPLC analysis (for **2ba**: chiralcel OJ-H, *n*-hexane/*i*-PrOH = 95:5, 0.8 mL/min, 254 nm, 40 °C; for **2ca**: chiralcel OJ-H, *n*-hexane/*i*-PrOH = 90:10, 0.8 mL/min, 254 nm, 40 °C; for **2da**–**fa**: chiralcel OD-H, *n*-hexane/*i*-PrOH = 95:5, 0.8 mL/min, 254 nm, 40 °C; for **2ga**: chiralcel OD-H, *n*-hexane/*i*-PrOH = 98:2, 0.6 mL/min, 254 nm, 40 °C).

Acknowledgments

Support for this research was from the Dalian Institute of Chemical Physics (CAS). The authors also thank Professor Hongchao Guo for providing several chiral ligands (synthesized in the National Key Technologies R&D Program of China, 2012BAK25B03, CAU). Dr. Duan Z.-C. acknowledges the National Natural Science Foundation of China (No. 21262011) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02. 030.

References and notes

1. Aschwanden, P.; Carreira, E. M. In *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005; pp 101–138.
2. For reviews, see: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095–4105; (b) Wei, C.-M.; Li, Z.-G.; Li, C.-J. *Synlett* **2004**, 1472–1483; (c) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263–4275; (d) Blay, G.; Monleon, A.; Pedro, J. R. *Curr. Org. Chem.* **2009**, *13*, 1498–1539; (e) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983; (f) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581–590.
3. For reviews, see: (a) Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914–1937; (b) Nishibayashi, Y. *Synthesis* **2012**, 489–503.
4. For reviews on the propargylic substitution, see: (a) Ljungdahl, N.; Kann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 642–644; (b) Miyake, Y.; Uemura, S.; Nishibayashi, Y. *ChemCatChem* **2009**, *1*, 342–356; (c) Debleds, O.; Gayon, E.; Vrancken, E.; Campagne, J.-M. Beilstein. *J. Org. Chem.* **2011**, *7*, 866–877; (d) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, 6263–6276; (e) Bauer, E. B. *Synthesis* **2012**, *44*, 1131–1151.
5. Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282–2284.

6. Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777–3780.
7. Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781–3783.
8. (a) Hattori, G.; Yoshida, A.; Miyake, Y.; Nishibayashi, Y. *J. Org. Chem.* **2009**, *74*, 7603–7607; (b) Hattori, G.; Miyake, Y.; Nishibayashi, Y. *ChemCatChem* **2010**, *2*, 155–158; (c) Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 10592–10608; (d) Detz, R. J.; Abiri, Z.; le Griel, R.; Hiemstra, H.; van Maarseveen, J. H. *Chem. Eur. J.* **2011**, *17*, 5921–5930; (e) Yoshida, A.; Hattori, G.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2011**, *13*, 2460–2463; (f) Zhang, C.; Wang, Y.-H.; Hu, X.-H.; Zheng, Z.; Xu, J.; Hu, X.-P. *Adv. Synth. Catal.* **2012**, *354*, 2854–2858; (g) Mino, T.; Taguchi, H.; Hashimoto, M.; Sakamoto, M. *Tetrahedron: Asymmetry* **2013**, *24*, 1520–1523.
9. Zhu, F.-L.; Zou, Y.; Zhang, D.-Y.; Wang, Y.-H.; Hu, X.-H.; Chen, S.; Xu, J.; Hu, X.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 1410–1414.
10. Noyori, R. *Acc. Chem. Res.* **1990**, *23*, 345–350.
11. Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119–3154.
12. (a) Dai, H.; Hu, X.; Chen, H.; Bai, C.; Zheng, Z. *J. Mol. Catal. A: Chem.* **2004**, *211*, 17–21; (b) Zhang, C.; Hu, X.-H.; Wang, Y.-H.; Zheng, Z.; Xu, J.; Hu, X.-P. *J. Am. Chem. Soc.* **2012**, *134*, 9585–9588; (c) Han, F.-Z.; Zhu, F.-L.; Wang, Y.-H.; Zou, Y.; Hu, X.-H.; Chen, S.; Hu, X.-P. *Org. Lett.* **2014**, *16*, 588–591.
13. *General procedure for Cu-catalyzed asymmetric decarboxylative propargylic amination*: $Cu(AcO)_2{\cdot}H_2O$ (7.9 mg, 0.025 mmol) and (*S*)-**L5** (12.9 mg, 0.0275 mmol) were stirred at room temperature in 1 mL of anhydrous MeOH under nitrogen atmosphere for 1 h. The solution was then cooled to 0 °C, and a solution of propargyl carbamate (0.5 mmol) and Et_3N (84 μL, 0.6 mmol) in 1 mL of anhydrous MeOH was added. The mixture was stirred at 0 °C for 12 h. The reaction was quenched by 1 mL of a buffer of NaOAc/AcOH, and extracted with EtOAc (5 mL × 2). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was then purified by silica gel chromatography, and was submitted to ee analysis by HPLC with a chiral column.