Advanced Synthesis & Catalysis

## Accepted Article

**Title:** Copper-Catalyzed Enantioselective Synthesis of β-Amino Alcohols Featuring Tetrasubstituted Tertiary Carbons

**Authors:** Lan Tian, Liang Gong, and Xia Zhang



**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.201701613

**Link to VoR:** http://dx.doi.org/10.1002/adsc.201701613

10.1002/adsc.201701613

UPDATE

**DOI: 10.1002/adsc.201**((will be filled in by the editorial staff))

# Copper-Catalyzed Enantioselective Synthesis of β-Amino Alcohols Featuring Tetrasubstituted Tertiary Carbons

Lan Tian,[a,†] Liang Gong,[a,†] and Xia Zhang[a,*]

[a] State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center for Biotherapy, Chengdu, PR China
[†] These authors contribute equally.
Email: zhang-xia@scu.edu.cn

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

**Abstract.** Here we report a copper-catalyzed asymmetric propargylic substitution reaction to prepare tetrasubstituted β-amino-β-ethynyl alcohols in high yields and with enantiomeric ratio (*er*) up to 94:6. This transformation generates tetrasubstituted tertiary carbons by utilizing stable cyclic carbonates and amines as substrates, economical copper catalysts, and easily accessible ligands.

**Keywords:** copper; catalysis; propargylation; tetrasubstituted β-amino-β-ethynyl alcohols

The enantioselective construction of tetrasubstituted tertiary carbons remains one of the most challenging tasks in synthetic chemistry. One difficulty lies in the steric congestion imposed by four attached substituents.[1] In addition, the stereoselective construction of tetrasubstituted tertiary carbons requires bond-forming reactions that yield the correct absolute configuration.[2] It is even more challenging if the product molecules are acyclic because of the rotational freedom associated with the acyclic structures.[3] Tetrasubstituted chiral amino alcohols contain such carbon centers and are important scaffolds present in many natural products and bioactive molecules (Figure 1). For example, myriocin is a potent immunosuppressant ($IC_{50}$ value of 15 nM) and a widely used chemical probe in the sphingolipid research.[4] Natural products salinosporamide A ($IC_{50}$ = 11 ng/mL against HCT116 colon cancer cells)[5], omuralide[6], and lactacystin[7] are potent proteasome inhibitors. Lycodoline shows inhibitory activities against butyrylcholinesterase.[8] Thus, the construction of tetrasubstituted chiral amino alcohols is of high interest in the fields of organic chemistry and medicinal chemistry. However, to build such motifs from simple and readily available starting materials remains daunting in synthetic chemistry probably because of the difficulties mentioned above, and only a limited number of synthetic methodologies were reported.[9]

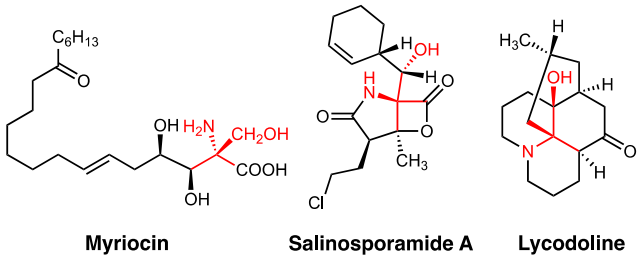
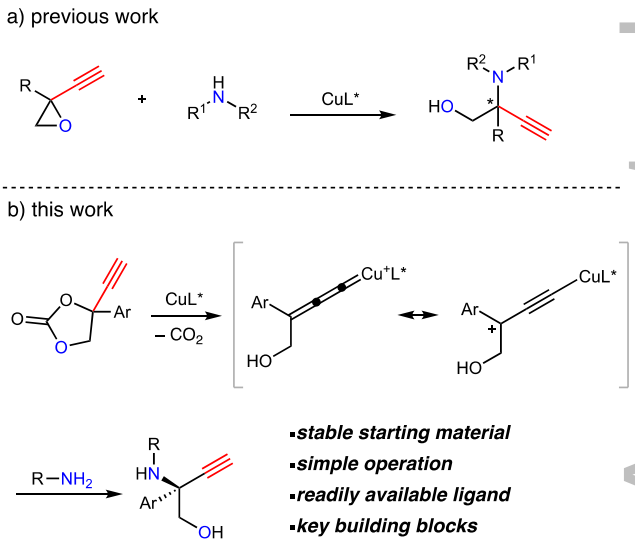



**Figure 1.** Natural products and bioactive molecules containing tetrasubstituted β-amino alcohols.




**Scheme 1.** The copper-catalyzed propargylic substitution reactions to make tetrasubstituted chiral amino alcohols.

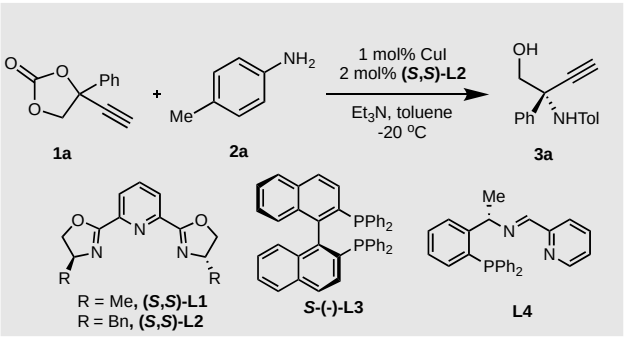
Nishibayashi and co-workers reported a copper-catalyzed asymmetric synthesis of propargyl β-amino alcohols using ethynyl epoxides as starting materials (Scheme 1a).[9b] The Kleij group reported an asymmetric approach of generating α,α-disubstituted

10.1002/adsc.201701613

allylic β-amino alcohols based on a palladium-catalyzed allylic amination.[9c] Our group decided to construct tetrasubstituted chiral amino alcohols that contain a linear shaped propargyl group. When compared with other bulkier groups, the linear shaped propargyl group may lead to less steric hindrance on a tetrasubstituted tertiary carbon center. Moreover, the terminal propargyl group is a versatile functional group, allowing for a plethora of further chemical transformations.[10] In this work, we developed an asymmetric approach using stable cyclic carbonates as substrates, economical copper catalysts, and easily accessible ligands to enable practical synthesis of tetrasubstituted β-amino-β-ethynyl alcohols. This method provides access to complex tetrasubstituted β-amino-β-ethynyl alcohols in high yields with enantiomeric ratio (*er*) up to 94:6.

Inspired by the previously reported copper-catalyzed propargylic substitution reactions, [11] we investigated a model reaction between propargyl carbonate **1a** and 4-toluidine **2a** (Table 1). We identified conditions that yielded the target molecule **3a** in excellent yield and good enantioselectivity (Table 1, entry 12). The reaction conditions are mild, involving $Et_3N$ as the base, the reaction temperature at -20 °C, 1 mol% of CuI, and 2 mol% of ligand **L2**. The key factors that affected the yield and enantioselectivity of this transformation are listed in Table 1. The identity of copper salt is critical, because the use of CuCl or $Cu(OTf)_2$ dramatically reduced the *er* of the products and slightly reduced the reaction yield (entries 1-2). In the absence of a ligand, (±)**3a** was produced in lower yield (entry 4). If the base was omitted, the reaction did not proceed (entry 13). Among the four ligands screened, **L2** yielded the best results in terms of reaction yield and enantioselectivity. Further screening of the reaction

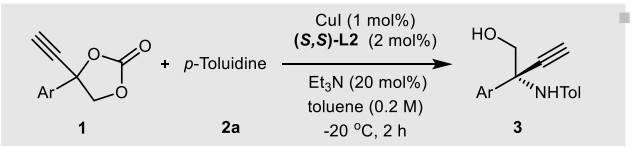
**Table 1.** Optimization of reaction conditions.[a)]

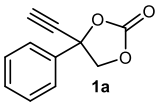
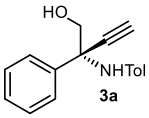
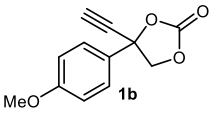
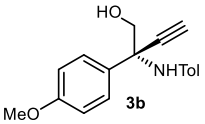
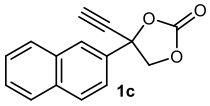
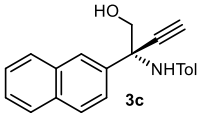
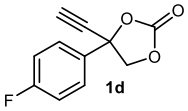
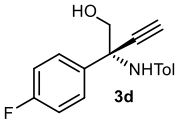
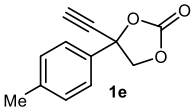
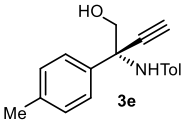
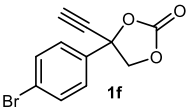
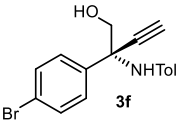
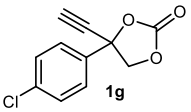
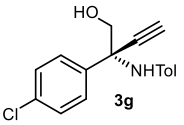
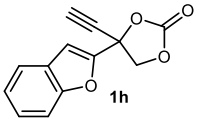
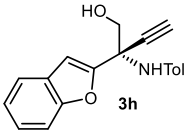



| Entry | [Cu] | Ligand | Base | Solvent | Yield[%] (*er*)[b)] |
|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | L1 | $^iPr_2NEt$ | toluene | 84(60:40) |
| 2 | CuCl | L1 | $^iPr_2NEt$ | toluene | 88(71:29) |
| 3 | CuI | L1 | $^iPr_2NEt$ | toluene | 92(85:15) |
| 4 | CuI | none | $^iPr_2NEt$ | toluene | 56(50:50) |
| 5 | CuI | L2 | $^iPr_2NEt$ | toluene | 96(92:08) |
| 6 | CuI | L3 | $^iPr_2NEt$ | toluene | 68(67:33) |
| 7 | CuI | L4 | $^iPr_2NEt$ | toluene | 82(66:34) |
| 8 | CuI | L2 | DBU | toluene | 88(85:15) |
| 9 | CuI | L2 | $K_2CO_3$ | toluene | 66(57:43) |
| 10 | CuI | L2 | $Et_3N$ | toluene | 95(92:08) |
| 11[c)] | CuI | L2 | $Et_3N$ | toluene | 92(90:10) |
| 12[d)] | CuI | L2 | $Et_3N$ | toluene | 98(94:06) |
| 13 | none | L2 | $Et_3N$ | toluene | N.R.[e)] |
| 14 | CuI | L2 | $Et_3N$ | THF | 80(61:39) |
| 15 | CuI | L2 | $Et_3N$ | MeOH | 78(56:44) |
| 16 | CuI | L2 | $Et_3N$ | DCM | 85(73:27) |
| 17 | CuI | L2 | $Et_3N$ | DMF | 75(60:40) |
| 18 | CuI | L2 | $Et_3N$ | MeCN | 65(53:47) |
| 19[f)] | CuI | L2 | $Et_3N$ | toluene | 70(90:10) |
| 20[g)] | CuI | L2 | $Et_3N$ | toluene | 95(93:07) |

[a)] Reaction conditions: All reactions were run at 0.2 mmol scale, under nitrogen, 1 mL solvent, and -20 °C for 2 h. [b)] Yields were determined by $^1$H-NMR and *er* were determined by HPLC. [c)] 5 mol% of base. [d)] 20 mol% of base. [e)] No reaction. [h)] -78 °C for 10 h. [g)] One pot.

**Table 2.** Scope of the propargyl carbonate substrates.[a)].




| Entry | 1 | 3 | Yield [%][b)] | *er*[c)] |
|---|---|---|---|---|
| 1 |  1a |  3a | 98 | 94:6 |
| 2 |  1b |  3b | 99 | 86:14 |
| 3 |  1c |  3c | 93 | 89:11 |
| 4 |  1d |  3d | 90 | 89:11 |
| 5 |  1e |  3e | 90 | 91:9 |
| 6 |  1f |  3f | 88 | 94:6 |
| 7 |  1g |  3g | 80 | 93:7 |
| 8 |  1h |  3h | 98 | 77:23 |

[a)] Reaction conditions: All reactions of 1 (0.20 mmol) with 2a (0.24 mmol) were carried out in the presence of CuI (0.002 mmol), *(S,S)*-**L2** (0.004 mmol), and $Et_3N$ (0.04

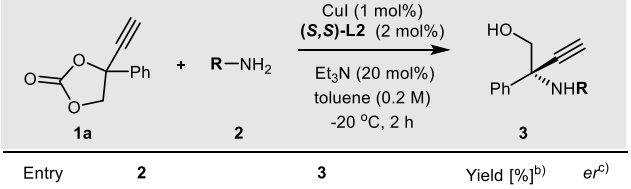
10.1002/adsc.201701613

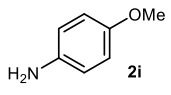
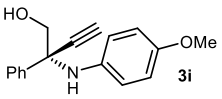
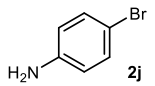
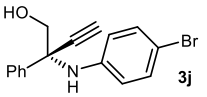
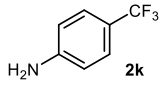
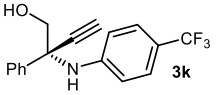
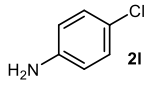
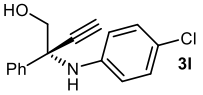
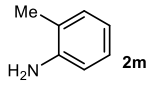
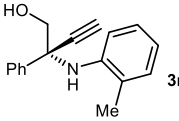
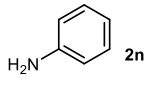
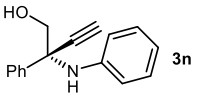
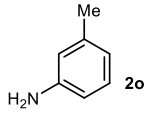
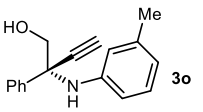
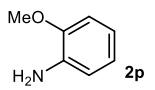
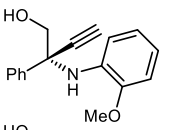
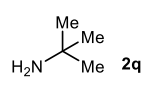
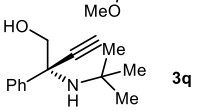
mmol) in toluene (1.0 mL) at -20 °C. [b] Isolated yield. [c] Determined by HPLC.

conditions revealed that toluene served as the best solvent compared with THF, MeOH, dichloromethane, DMF, or MeCN (entries 14-18). Lowering the reaction temperature significantly reduced the product yield (entry 19).

With the optimized conditions in hand, we proceeded to explore the scope of this transformation. As shown in Table 2, a variety of aryl propargyl carbonates could be converted to the corresponding product in excellent isolated yields and with moderate enantioselectivities (**3a-h**). For example, propargyl carbonates with both electron-rich (**3b**) and electron-deficient (**3d** and **3g**) aromatic rings were effective reaction partners. Those containing halogenated aromatic rings (**3d**, **3f**, and **3g**) were tolerated.

**Table 3.** Scope of the amines.[a]

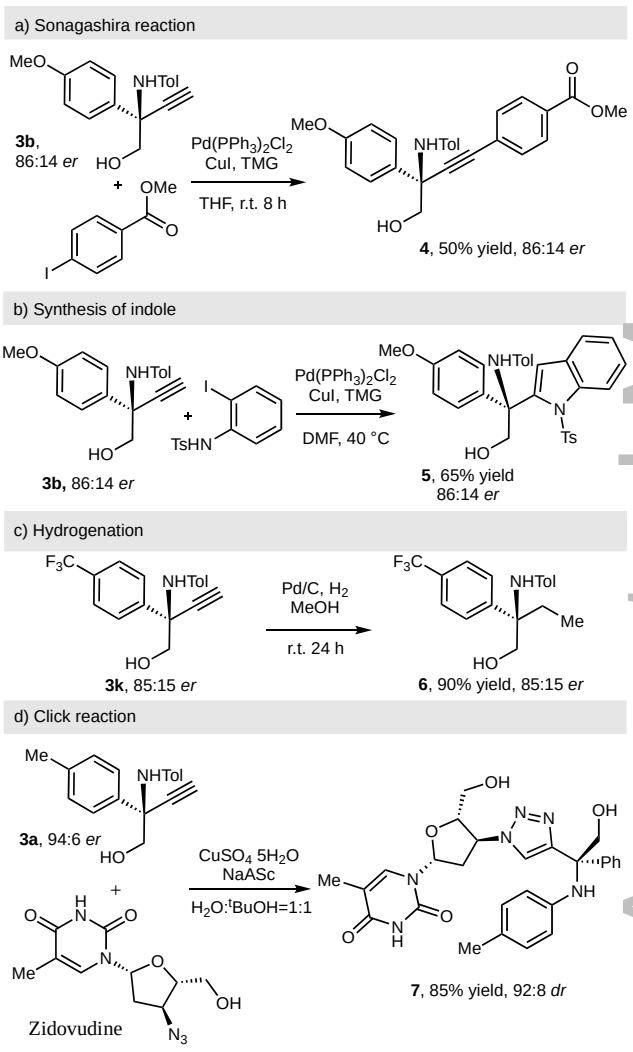



| Entry | 2 | 3 | Yield [%][b] | *er*[c] |
|---|---|---|---|---|
| 1[a] |  **2i** |  **3i** | 96 | 89:11 |
| 2 |  **2j** |  **3j** | 91 | 88:12 |
| 3 |  **2k** |  **3k** | 65 | 85:15 |
| 4 |  **2l** |  **3l** | 99 | 92:8 |
| 5 |  **2m** |  **3m** | 99 | 86:14 |
| 6 |  **2n** |  **3n** | 99 | 94:6 |
| 7 |  **2o** |  **3o** | 98 | 90:10 |
| 8 |  **2p** |  **3p** | 96 | 90:10 |
| 9[d] |  **2q** |  **3q** | 75 | 82:18 |

[a] Reaction conditions: All reactions of **1a** (0.20 mmol) with **2** (0.24 mmol) were carried out in the presence of CuI (0.002 mmol), *(S,S)*-**L2** (0.004 mmol), and $Et_3N$ (0.04 mmol) in toluene (1.0 mL) at -20 °C. [b] Isolated yield. [c] Determined by HPLC. [d] 0 °C, 4 h.

Propargyl carbonates bearing naphthyl group (**3c**) and heterocyclic moieties (**3h**) underwent this reaction smoothly and generated products in excellent yields.[12] The absolute configuration of **3c** was determined by X-ray crystallography.[13]

The scope with respect to the amine reaction partner was summarized in Table 3. Aryl amines containing electron-donating (**3i**, and **3n-p**) or electron-withdrawing groups (**3j-l**) could engage in this reaction. Those with *para*- (**3i-l**), *meta*- (**3o**) and *ortho*- (**3n-p**) substitutions were tolerated. The use of an alkyl amine yielded product **3q** in moderate yield and *er*.




**Scheme 2.** Product Derivatization.

To further demonstrate the utility of this method, we performed some derivatization reactions on our products. For example, Sonagashira coupling installed an aryl group onto compound **3b**, yielding

compound **4**.[14] The reaction of **3b** with an *ortho*-iodo aniline derivative resulted in the formation of indole **5**. The terminal alkyne group in **3h** could also be reduced to an ethyl (**6**) group smoothly. We then made a Zidovudine derivative **7** (Scheme 2).[15] Zidovudine is an FDA approved drug for preventing and treating AIDS, which is also on the World Health Organization's List of Essential Medicines.[16] Taking advantage of the click reaction,[10a] we obtained compound **7** from **3a** and Zidovudine in 85% yield. Not surprisingly, the enantiopurity of the alkyne starting materials was translated to the corresponding products in all cases.

In summary, we report an efficient copper-catalyzed asymmetric approach to form tetrasubstituted β-amino-β-ethynyl alcohols in high yields and with *er* up to 94:6. This procedure utilizes stable cyclic carbonates and amines as substrates, economical copper catalysts, and easily accessible ligands. This method is amenable for the preparation of various tetrasubstituted β-amino-β-ethynyl alcohols, including those with *ortho*-substitutions and heterocycles. The utility of these products was further demonstrated by their straightforward derivatization reactions.

## Experimental Section

Synthesis of (*R*)-2-phenyl-2-(*p*-tolylamino)but-3-yn-1-ol (**3a**): in a nitrogen-filled glove-box, CuI (0.002 mmol, 1 mol%) and (*S*,*S*)-**L2** (0.004 mmol, 2 mol%) were dissolved in anhydrous toluene (0.5 mL). The resulting solution was capped with a septum, taken out of the glove-box, and heated at 60 °C for 1 h. The reaction flask was then cooled to -20 °C. To this flask was sequentially added a solution of 4-acetenyl-4-phenyl-1,3-dioxolan-2-one (**1a**, 0.2 mmol, 1.0 equiv.) in toluene, and a solution of *p*-toluidine (0.24 mmol, 1.2 equiv.) and triethylamine (0.04 mmol) in toluene by a gas-tight syringe. The reaction flask was kept at -20 °C for 2 h. The solvent was concentrated under reduce pressure and the residue was purified by column chromatography ($SiO_2$) using petroleum ether and ethyl acetate (30:1 to 10:1) as eluents to give **3a** as a white solid (50 mg, 0.199 mmol, 98%).

## Acknowledgements

*We acknowledge gratefully the funding from State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University.*

## References

[1] K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181-191.

[2] I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik, J. P. Das, *J. Am. Chem. Soc.* **2014**, *136*, 2682-2694.

[3] J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593-4623.

[4] a) Y. Miyake, Y. Kozutsumi, S. Nakamura, T. Fujita, T. Kawasaki, *Biochem. Biophys. Res. Commun.* **1995**, *211*, 396-403; b) J. M. Wadsworth, D. J. Clarke, S. A. McMahon, J. P. Lowther, A. E. Beattie, P. R. R. Langridge-Smith, H. B. Broughton, T. M. Dunn, J. H. Naismith, D. J. Campopiano, *J. Am. Chem. Soc.* **2013**, *135*, 14276-14285.

[5] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355-357.

[6] H. Tomoda, S. Omura, *Yakugaku Zasshi* **2000**, *120*, 935-949.

[7] G. Fenteany, R. F. Standaert, W. S. Lane, S. Choi, E. J. Corey, S. L. Schreiber, *Science* **1995**, *268*, 726-731.

[8] E. S. Halldorsdottir, J. W. Jaroszewski, E. S. Olafsdottir, *Phytochemistry* **2010**, *71*, 149-157.

[9] a) W. S. Guo, A. J. Cai, J. N. Xie, A. W. Kleij, *Angew. Chem. Int. Ed.* **2017**, *56*, 11797-11801; b) G. Hattori, A. Yoshida, Y. Miyake, Y. Nishibayashi, *J. Org. Chem.* **2009**, *74*, 7603-7607; c) A. J. Cai, W. S. Guo, L. Martinez-Rodriguez, A. W. Kleij, *J. Am. Chem. Soc.* **2016**, *138*, 14194-14197.

[10] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021; b) X. W. Wu, B. Wang, Y. Zhou, H. Liu, *Org. Lett.* **2017**, *19*, 1294-1297; c) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467-4470; d) R. Z. Li, H. Tang, K. R. Yang, L. Q. Wan, X. Zhang, J. Liu, Z. Y. Fu, D. W. Niu, *Angew. Chem. Int. Ed.* **2017**, *56*, 7213-7217; e) R. Z. Li, H. Tang, L. Q. Wan, X. Zhang, Z. Y. Fu, J. Liu, S. Y. Yang, D. Jia, D. W. Niu, *Chem* **2017**, *3*, 834-845.

[11] a) R. J. Detz, M. M. E. Delville, H. Hiemstra, J. H. van Maarseveen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3777-3780; b) G. Hattori, H. Matsuzawa, Y. Miyake, Y. Nishibayashi, *Angew. Chem. Int. Ed.* **2008**, *47*, 3781-3783; c) G. Hattori, K. Sakata, H. Matsuzawa, Y. Tanabe, Y. Miyake, Y. Nishibayashi, *J. Am. Chem. Soc.* **2010**, *132*, 10592-10608; d) A. Yoshida, G. Hattori, Y. Miyake, Y. Nishibayashi, *Org. Lett.* **2011**, *13*, 2460-2463; e) R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra, J. H. van Maarseveen, *Chem. Eur. J.* **2011**, *17*, 5921-5930; f) C. Zhang, Y. H. Wang, X. H. Hu, Z. Zheng, J. Xu, X. P. Hu, *Adv. Synth. Catal.* **2012**, *354*, 2854-2858; g) M. Shibata, K. Nakajima, Y. Nishibayashi, *Chem. Commun.* **2014**, *50*, 7874-7877; h) K. Tsuchida, Y. Senda, K. Nakajima, Y. Nishibayashi, *Angew. Chem. Int. Ed.* **2016**, *55*, 9728-9732.

[12] We tried a propargyl carbonate with a cyclohexyl group. However, no reaction occured under standard conditions.

[13] CCDC-1584495 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. We used Cu Kα (λ = 1.54184 Å) radiation for the diffraction experiments.

[14] K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46-49.

[15] E. M. Connor, R. S. Sperling, R. Gelber, P. Kiselev, G. Scott, M. J. Osullivan, R. Vandyke, M. Bey, W. Shearer, R. L. Jacobson, E. Jimenez, E. Oneill, B. Bazin, J. F. Delfraissy, M. Culnane, R. Coombs, M.

10.1002/adsc.201701613

Elkins, J. Moye, P. Stratton, J. Balsley, *New Engl. J. Med.* **1994**, *331*, 1173-1180.

[16] M. S. Kinch, E. Patridge, *Drug Discov. Today* **2014**, *19*, 1510-1513.

10.1002/adsc.201701613

**UPDATE**

# Copper-Catalyzed Enantioselective Synthesis of β-Amino Alcohols Featuring Tetrasubstituted Tertiary Carbons

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

Lan Tian, Liang Gong, and Xia Zhang*