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Enantioselective Ring-Opening Reactions of Racemic Ethynyl Epoxides via Copper−Allenylidene Intermediates: Efficient Approach to Chiral β-Amino Alcohols

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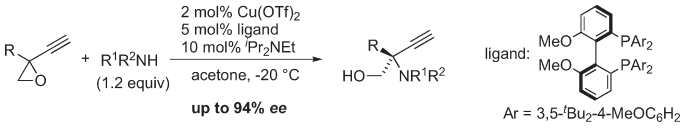

Enantioselective copper-catalyzed ring-opening reactions of racemic ethynyl epoxides with amines using (*R*)-DTBM-MeO-BIPHEP as a chiral ligand have been found to give the corresponding amino alcohols in high yields with up to 94% ee. The reaction is considered to proceed via copper−allenylidene complexes as key intermediates. This methodology may provide a novel synthetic approach to optically active amino alcohols, the structures of which are widely found in many natural products, biologically active compounds, and chiral ligands.

Introduction

Since the first discovery of enantioselective ruthenium-catalyzed propargylic substitution reactions of propargylic alcohols with acetone as a carbon-centered nucleophile,[1] much attention has been paid to develop transition-metal-catalyzed propargylic substitution reactions with nucleophiles because enantioselective bond-forming reactions at the propargylic position provide a highly useful synthetic method for constructing a chiral carbon center with an alkyne moiety.[2,3] Quite recently, copper-catalyzed propargylic substitution reactions of propargylic acetates with amines were reported to give the corresponding propargylic amines with up to 89% enantiomeric excess (ee).[4] It is noteworthy that these reactions are considered to proceed via copper−allenylidene[5] complexes as key intermediates (Scheme 1).[4] Although the copper−allenylidene complexes have not yet been isolated, the possibility of the presence of these reactive intermediates prompted us to develop other novel catalytic reactions. We have now envisaged that ethynyl epoxides may also be used as precursors to generate similar complexes, leading to chiral β-ethynyl-β-amino alcohols as products (Scheme 2). Optically active β-amino alcohols have been found in a large number of natural products and biologically active compounds and often used as chiral ligands.[6] Results are described here.

Results and Discussion

Treatment of 2-ethynyl-2-phenyloxirane (**1a**) with aniline (1.2 equiv) in the presence of a catalytic amount of $Cu(OTf)_2$ (2 mol %), (*R*)-DTBM-MeO-BIPHEP[7] (5 mol %), and $^iPr_2NEt$ (10 mol %) in acetone at −20 °C for 1 h gave β-ethynyl-β-amino alcohol (**2a**) in 95% yield with 79% ee

(1) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715.

(2) (a) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488. (b) Matsuzawa, H.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2007**, *9*, 5561. (c) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 10498. (d) Kanao, K.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Synthesis* **2008**, 3869. (e) Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2009**, *28*, 2920.

(3) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645.

(4) (a) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777. (b) Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781.

(5) For recent reviews, see: (a) *Metal Vinylidenes and Allenylidenes in Catalysis: From Reactivity to Applications in Synthesis*; Bruneau, C., Dixneuf, P. H., Eds.; Wiley-VCH: Weinheim, Germany, 2008. (b) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176.

(6) For reviews, see: (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Fache, F.; Schulz, E.; Tommasino, M. L.; Lamaire, M. *Chem. Rev.* **2000**, *100*, 2159. (c) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151. (d) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.

(7) BIPHEP = 2,2′-Bis(diphenylphosphino)-1,1′-biphenyl.

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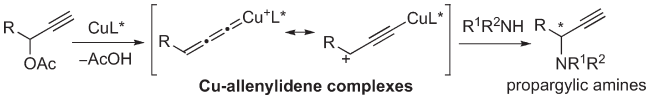
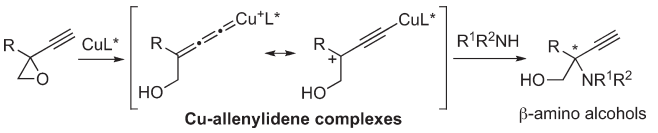
SCHEME 1. Enantioselective Copper-Catalyzed Propargylic Amination from Propargylic Acetate



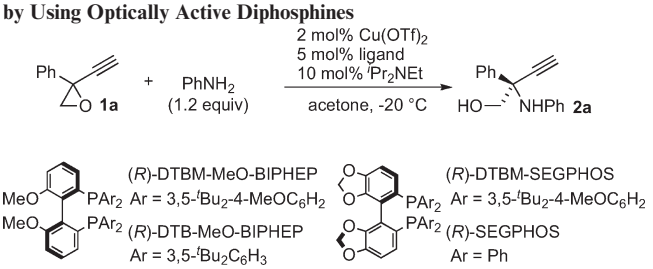
SCHEME 2. This Work



(Table 1, run 1).[8] When other diphosphine ligands such as (*R*)-DTB-MeO-BIPHEP and (*R*)-DTBM-SEGPHOS[9] were used in place of (*R*)-DTBM-MeO-BIPHEP, almost the same enantioselectivity was observed in both cases (Table 1, runs 2 and 3), while no reaction occurred at all when (*R*)-SEGPHOS[9] was used as a chiral ligand (Table 1, run 4).

Enantioselective ring-opening reactions of **1a** with other amines were investigated using (*R*)-DTBM-MeO-BIPHEP as a chiral ligand. Typical results are shown in Table 2. The presence of methyl, methoxy, chloro, bromo, trifluoromethyl, and methoxycarbonyl groups at *para, meta*, and *ortho* positions of the benzene ring of aniline did not much affect the reactivity (Table 2, runs 2−9), while in the case of 4-cyanoaniline and 4-nitroaniline, a longer reaction time was necessary to complete the reaction (Table 2, runs 10 and 11). On the other hand, the enantioselectivity of **2** depended on the nature of functional groups. The introduction of substituents in the benzene ring of aniline substantially affected the enantioselectivity. The highest enantioselectivity (93−94% ee) was observed when 4-trifluoromethylaniline and 4-methoxycarbonylaniline were used (Table 2, runs 6 and 8). Unfortunately, only the moderate enantioselectivity was observed when alkylamines such as *tert*-butylamine and 1-adamantylamine were used as amines (Table 2, runs 12 and 13). The use of secondary amines such as *N*-methylaniline and piperidine resulted with only moderate enantioselectivities, although the reaction proceeded smoothly (Table 2, runs 14 and 15). It is considered that classical S_N2-type ring-opening reaction in the copper−acetylide complex (complex **B** in Scheme 3, vide infra) may partly occur to give the racemic ring-opening products when monoalkyl- and diakylamines were used as nucleophiles. As a result, only amines bearing an electron-withdrawing group are available to achieve the high enantioselectivity.

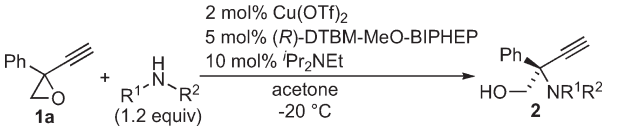
TABLE 1. Enantioselective Ring-Opening Reactions of 1a with Aniline by Using Optically Active Diphosphines



run	ligand	time (h)	yield of **2a** (%)	ee of **2a** (%)
1	(*R*)-DTBM-MeO-BIPHEP	1	95	79
2	(*R*)-DTB-MeO-BIPHEP	1	95	78
3	(*R*)-DTBM-SEGPHOS	1	95	76
4	(*R*)-SEGPHOS	20	0[a]	

[a] **1a** was recovered in 83%.

TABLE 2. Enantioselective Copper-Catalyzed Ring-Opening Reactions of 1a with Amines[a]



run	R^1	R^2	time (h)	yield of **2** (%)	ee of **2** (%)[b]
1	Ph	H	1	95 (**2a**)	79
2	4-MeC_6H_4	H	3	96 (**2b**)	75
3	4-$MeOC_6H_4$	H	2	85 (**2c**)	57
4	4-ClC_6H_4	H	3	94 (**2d**)	87
5	4-BrC_6H_4	H	2	95 (**2e**)	89
6	4-$CF_3C_6H_4$	H	3	93 (**2f**)	94
7	3-$CF_3C_6H_4$	H	2	94 (**2g**)	86
8	4-$MeOC(O)C_6H_4$	H	2	95 (**2h**)	93
9	2-$MeOC(O)C_6H_4$	H	2	97 (**2i**)	79
10	4-CNC_6H_4	H	46	96 (**2j**)	88
11	4-$NO_2C_6H_4$	H	18	94 (**2k**)	85
12[c]	^{t}Bu	H	18[d]	87 (**2l**)	55
13[c]	1-adamantyl	H	24	83 (**2m**)	55
14	Ph	Me	1	91 (**2n**)	52
15	$-(CH_2)_5-$[e]		4	93 (**2o**)	26

[a] All reactions of **1a** (0.20 mmol) with amines (0.24 mmol) were carried out in the presence of $Cu(OTf)_2$ (0.004 mmol), (*R*)-DTBM-MeO-BIPHEP (0.01 mmol), and $^i Pr_2NEt$ (0.02 mmol) in acetone (2.0 mL) at −20 °C. [b] Determined by HPLC. [c] $^i Pr_2NEt$ (0.24 mmol) was used. [d] At −40 °C. [e] Piperidine was used.

Next, we carried out enantioselective ring-opening reactions of other 2-aryl-2-ethynyloxiranes (**1**) with 4-methoxycarbonylaniline and 4-trifluoromethylaniline (Table 3, runs 1−12). On the other hand, the reaction of 2-alkyl-2-ethynyloxiranes (**1**) such as 2-ethynyl-2-methyloxirane (**1h**) and 2-*tert*-butyl-2-ethynyloxirane (**1i**) proceeded well with a slightly lower enantioselectivity (Table 3, runs 13−16).

As shown in Tables 2 and 3, the ring-opening products were obtained in more than 90% yield based on the starting racemic ethynyl epoxides with up to 94% ee. In addition, we separately confirmed that no reaction occurred at all when ethynyl epoxides bearing an internal alkyne moiety such as 2-phenyl-2-(2-phenylethynyl)oxirane and 2-phenyl-2-(1-propynyl)oxirane were used as substrates. These results indicate

(8) (a) An excess amount of diphosphine to the copper complex to $Cu(OTf)_2$ was added in the catalytic ring-opening reaction. We consider that an equivalent amount of diphosphine is used to reduce Cu(II) complex to the active species Cu(I) complex: Nieto, S.; Metola, P.; Lynch, V. M.; Anslyn, E. V. *Organometallics* **2008**, *27*, 3608. (b) Cu(II)-catalyzed reactions of epoxides with carbonyl compounds such as acetone gave the corresponding 1,3-dioxolanes: Krasik, P.; Bohemier-Bernard, M.; Yu, Q. *Synlett* **2005**, 854. (c) Separately, we confirmed that the ring-opening reaction proceeded smoothly in the presence of a catalytic amount of Cu(OTf), but the catalytic use of $Cu(OTf)_2$ promoted the ring-opening reaction more smoothly under the same reaction conditions.

(9) For a recent review, see: Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385.

SCHEME 3. Proposed Reaction Pathway for Ring-Opening Reaction of Ethynyl Epoxide

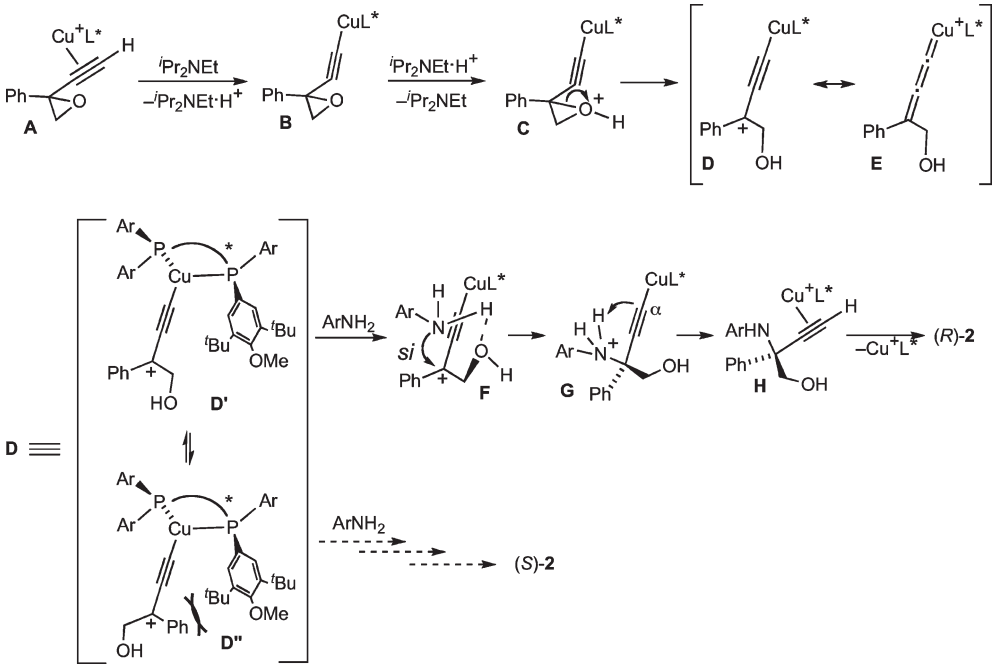
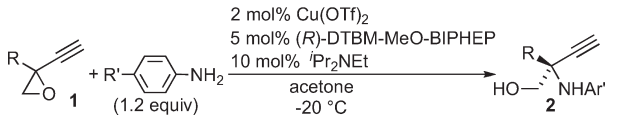


TABLE 3. Enantioselective Copper-Catalyzed Ring-Opening Reactions of 1 with Anilines[a]



run	R	R′	time (h)	yield of **2** (%)	ee of **2** (%)[b]
1	4-ClC_6H_4 (**1b**)	MeOC(O)	3	98 (**2p**)	91
2	4-ClC_6H_4 (**1b**)	CF_3	3	95 (**2q**)	91
3	4-BrC_6H_4 (**1c**)	MeOC(O)	3	96 (**2r**)	92
4	4-BrC_6H_4 (**1c**)	CF_3	3	93 (**2s**)	91
5	4-MeC_6H_4 (**1d**)	MeOC(O)	6	96 (**2t**)	94
6	4-MeC_6H_4 (**1d**)	CF_3	6	97 (**2u**)	93
7	4-PhC_6H_4 (**1e**)	MeOC(O)	3	97 (**2v**)	91
8	4-PhC_6H_4 (**1e**)	CF_3	3	95 (**2w**)	91
9	4-FC_6H_4 (**1f**)	MeOC(O)	3	95 (**2x**)	92
10	4-FC_6H_4 (**1f**)	CF_3	3	97 (**2y**)	93
11	2-naphthyl (**1g**)	MeOC(O)	2	95 (**2z**)	90
12	2-naphthyl (**1g**)	CF_3	2	92 (**2aa**)	87
13	Me (**1h**)	MeOC(O)	12	87 (**2ab**)	77
14	Me (**1h**)	CF_3	12	84 (**2ac**)	54
15	^{t}Bu (**1i**)	MeOC(O)	48	81 (**2ad**)	65
16	^{t}Bu (**1i**)	CF_3	48	80 (**2ae**)	69

[a]All reactions of **1** (0.20 mmol) with anilines (0.24 mmol) were carried out in the presence of $Cu(OTf)_2$ (0.004 mmol), (*R*)-DTBM-MeO-BIPHEP (0.01 mmol), and $^i Pr_2NEt$ (0.02 mmol) in acetone (2.0 mL) at −20 °C. [b]Determined by HPLC.

that this catalytic reaction proceeds not via classical S_N2-type ring-opening reaction at the oxirane moiety[10] but via the formation of copper−allenylidene complexes.[4]

Preliminary results of a theoretical study on the copper-catalyzed propargylic amination[4] of propargylic acetates with amines indicate that copper−allenylidene complexes may be formed as key intermediates.[11] Similarly, we consider that the copper−allenylidene complex (**E**) might be formed by the ring-opening reaction in the copper−acetylide complex (**C**), which is formed from the copper−π-alkyne complex (**A**) between **1a** and copper complex bearing (*R*)-DTBM-MeO-BIPHEP, via the copper−acetylide complex (**B**) (Scheme 3). $^i Pr_2NEt$ promotes this deprotonation and protonation processes from **A** to the copper−acetylide complex bearing a carbocation at the γ-carbon (**D**: a resonance structure of **E**) smoothly. The interaction between a phenyl group in acetylide and a bulky aryl group in BIPHEP favors the formation of the copper−acetylide complex (**D′**). Then, aniline attacks the γ-carbon of **D′** from *si* face,[12] where the hydrogen bonding between the oxygen of the hydroxyl group and hydrogen of aniline is considered to play an important role to achieve the high enantioselectivity (**F**). Finally, the higher acidity of the proton of conjugate aniline in **G** promotes a hydrogen atom shift to the α-carbon on the ligand to give another copper−π-alkyne complex (**H**).

This proposed reaction pathway is supported by the deuterium incorporation at the C-1 position in the ring-opening product (**2a-d_1**), which is due to the proton transfer in the proposed reaction pathway, when **1a** was treated with aniline-d_7 (Scheme 4). At present, we cannot exclude other reaction pathways,[13] where

(10) For reviews of the classical S_N2 type of ring-opening reactions of racemic epoxides with nucleophiles, see: (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Schneider, C. *Synthesis* **2006**, 3919. For recent examples of the classical S_N2 type of ring-opening reactions of optically active epoxides with nucleophiles, see: (c) Taber, D. F.; He, Y.; Xu, M. *J. Am. Chem. Soc.* **2004**, *126*, 13900. (d) Lim, S. M.; Hill, N.; Myers, A. G. *J. Am. Chem. Soc.* **2009**, *131*, 5763.

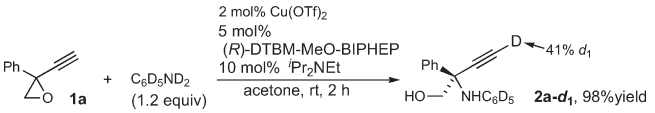
(11) We will report more detailed results in due course. Hattori, G.; Matsuzawa, H.; Sakata, K.; Miyake, Y.; Nishibayashi, Y. Unpublished results.

(12) The X-ray analysis of a major enantiomer of the tosylated compound of **2f** indicates that the absolute configuration of **2f** is *R*. The molecular structure of the tosylated compound of **2f** was confirmed by X-ray analysis. See the Supporting Information for experimental details.

(13) Murahashi and his co-workers proposed a free copper allenylidene as an intermediate in the copper-catalyzed propargylic amination of propargylic esters with amines. However, no experimental evidence of this intermediate appeared: Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282.

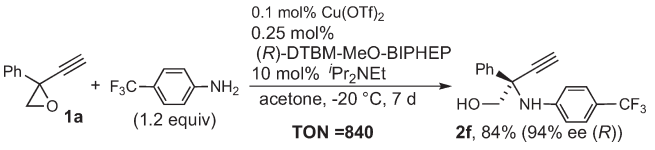
copper−allenylidene complexes may be formed via copper−vinylidene complexes.[14] Separately, we carried out the reaction of **1a** in the absence of aniline under the same reaction conditions, where only a complex mixture was formed. This result is in sharp contrast to the result of the molybdenum-catalyzed intramolecular cyclization of 2-ethynyloxiranes to afford the corresponding furans via molybdenum−vinylidene intermediates.[15]

SCHEME 4. Ring-Opening Reaction with Aniline-d_7



Finally, we carried out the ring-opening reaction of **1a** with 4-trifluoromethylaniline in the presence of 0.1 mol % of $Cu(OTf)_2$ and 0.25 mol % of (*R*)-DTBM-MeO-BIPHEP (Scheme 5). Interestingly, the reaction proceeded effectively to give **2f** in 84% yield (TON = 840) with 94% ee (*R*).

SCHEME 5. Ring-Opening Reaction in the Presence of 0.1 mol % of Copper Catalyst



Conclusion

We have found enantioselective copper-catalyzed ring-opening reactions of racemic ethynyl epoxides with amines to give the corresponding amino alcohols in high yields with up to 94% ee. The reaction is considered to proceed via copper−allenylidene complexes as key intermediates. This methodology may provide a novel synthetic approach to optically active amino alcohols, the structures of which are widely found in many natural products, biologically active compounds, and chiral ligands. Further work is currently in progress to broaden its synthetic applicability to natural products and pharmaceuticals.

Experimental Section

Preparation of Ethynyl Epoxides. A typical experimental procedure for the preparation of 2-ethynyl-2-phenyloxirane (**1a**) is described below. In a 100 mL round-bottomed flask were placed phenacyl chloride (1.54 g, 10.0 mmol) and anhydrous tetrahydrofuran (10 mL). Ethynylmagnesium bromide (0.5 M in tetrahydrofuran; 22.0 mL, 11.0 mmol) was added to the solution, and the mixture was stirred at room temperature for 2 h. The reaction was quenched by saturated NH_4Cl aqueous solution (20 mL), and organic materials were extracted with diethyl ether (20 mL × 2). The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was concentrated under reduced pressure by an aspirator to give crude chlorohydrin. The resulting crude material was used for the next step without further purification. In a 100 mL round-bottomed flask were placed the crude chlorohydrin and anhydrous diethyl ether (10 mL). Powdered NaOH (2.0 g, 50.0 mmol) was added to the solution slowly, and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered, and the solvent was concentrated under reduced pressure by an aspirator, and the residue was purified by column chromatography (SiO_2 supported by amino group) with hexane and ethyl acetate (9:1) as an eluent to give 2-ethynyl-2-phenyloxirane (**1a**)[16] as a colorless oil (634 mg, 4.4 mmol; 44% yield).

Preparation of other ethynyl epoxides (**1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**,[17] **1i**, 2-phenyl-2-(2-phenylethynyl)oxirane, and 2-phenyl-2-(1-propynyl)oxirane) was carried out according to this method. In the case of 2-phenyl-2-(2-phenylethynyl)oxirane or 2-phenyl-2-(1-propynyl)oxirane, lithium phenylactylide or lithium 1-propynyllithium[18] was used instead of ethynylmagnesium bromide. Spectroscopic data of some ethynyl epoxides are as follows.

2-(4-Chlorophenyl)-2-ethynyloxirane (1b): A pale yellow oil; TLC (SiO_2 supported by amino group) R_f (hexane/EtOAc 9:1) 0.45; ^{1}H NMR δ 2.54 (s, 1H), 2.97 (d, J = 5.9 Hz, 1H), 3.44 (d, J = 5.9 Hz, 1H), 7.33 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H); ^{13}C NMR δ 50.3 (C), 58.9 (CH_2), 73.0 (CH), 80.8 (C), 126.9 (CH), 128.6 (CH), 134.5 (C), 135.1 (C); HRMS calcd for $C_{10}H_7ClO$ [M] 178.0185, found 178.0178.

2-(4-Bromophenyl)-2-ethynyloxirane (1c): A colorless solid, 41.4−43.4 °C; TLC (SiO_2 supported by amino group) R_f (hexane/EtOAc 9:1) 0.45; ^{1}H NMR δ 2.54 (s, 1H), 2.97 (d, J = 5.9 Hz, 1H), 3.44 (d, J = 5.9 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H); ^{13}C NMR δ 50.3 (C), 58.9 (CH_2), 73.0 (CH), 80.7 (C), 122.6 (C), 127.2 (CH), 131.6 (CH), 135.7 (C). Anal. Calcd for $C_{10}H_7BrO$: C, 53.84; H, 3.16. Found: C, 54.20; H, 3.18.

Copper-Catalyzed Asymmetric Ring-Opening Reactions of Racemic Ethynyl Epoxides with Amines. A typical experimental procedure for the reaction of 2-ethynyl-2-phenyloxirane (**1a**) with aniline is described below. In a 20 mL round-bottomed flask were placed $Cu(OTf)_2$ (1.5 mg, 0.004 mmol) and (*R*)-DTBM-MeO-BIPHEP (12.1 mg, 0.010 mmol) under N_2. Anhydrous acetone (1.0 mL) was added, and then the mixture was magnetically stirred at 60 °C for 1 h. Then, **1a** (29.8 mg, 0.20 mmol), aniline (23.5 mg, 0.24 mmol), and diisopropylethylamine (2.6 mg, 0.020 mmol) in anhydrous acetone (1.0 mL) were added under N_2, and the reaction flask was kept at −20 °C for 1 h. The solvent was concentrated under reduced pressure by an aspirator, and the residue was purified by column chromatography (SiO_2) with hexane and ethyl acetate (90:10 to 70:30) as eluents to give 2-phenyl-2-(phenylamino)-3-butyn-1-ol (**2a**) as a pale yellow oil (46.7 mg, 0.19 mmol; 95% yield).

2-Phenyl-2-(phenylamino)-3-butyn-1-ol (2a): Yield 95%; a pale yellow oil; TLC (SiO_2) R_f (hexane/EtOAc 7:3) 0.33; ^{1}H NMR δ 2.24 (br, 1H), 2.54 (s, 1H), 3.64 (br d, 1H), 3.77 (d, J = 11.0 Hz, 1H), 5.01 (br, 1H), 6.56 (d, J = 7.6 Hz, 2H), 6.73 (t, J = 7.6 Hz, 1H), 7.07 (dd, J = 7.6, 7.6 Hz, 2H), 7.32−7.41 (m, 3H), 7.69 (d, J = 7.6 Hz, 2H); ^{13}C NMR δ 61.5 (CH_3), 72.9 (C), 74.6 (CH), 83.3 (CH_2), 116.1 (CH), 118.8 (CH), 126.5 (CH), 128.1 (CH), 128.6 (CH), 128.8 (CH), 139.0 (C), 144.9 (C); HRMS calcd for $C_{16}H_{15}NO$ [M] 237.1154, found 237.1147; $[\alpha]^{25}_D$ = +144 (c = 1.21, $CHCl_3$); the optical purity was determined by HPLC analysis; Daicel Chiralcel AD, hexane/^{i}PrOH = 90/10, flow rate = 1.0 mL/min, λ = 254 nm, retention time = 8.5 min (minor) and 13.3 min (major), 79% ee.

Spectroscopic data of some products are as follows.

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2-Phenyl-2-[4-(trifluoromethyl)phenylamino]-3-butyn-1-ol (2f): Yield 93%; a colorless solid, 88.1−89.0 °C; TLC (SiO_2) R_f (hexane/EtOAc 7:3) 0.35; ^{1}H NMR δ 2.25 (br, 1H), 2.57 (s, 1H), 3.64 (d, J = 11.3 Hz, 1H), 3.80 (d, J = 11.3 Hz, 1H), 5.24 (br, 1H), 6.58 (d, J = 8.6 Hz, 2H), 7.29−7.39 (m, 5H), 7.65 (d, J = 7.6 Hz, 2H); ^{13}C NMR δ 61.1 (C), 72.8 (CH), 74.8 (CH_2), 82.6 (C), 115.3 (CH), 120.3 (C, q, J = 32 Hz), 124.8 (C, q, J = 270 Hz), 125.9 (CH, q, J = 3.9 Hz), 126.3 (CH), 128.4 (CH), 129.0 (CH), 138.2 (C), 147.7 (C); $[\alpha]^{25}_D$ = +250 (c = 0.61, $CHCl_3$). Anal. Calcd for $C_{17}H_{14}F_3NO$: C, 66.88; H, 4.62; N, 4.59. Found: C, 66.99; H, 4.80; N, 4.35. The optical purity was determined by HPLC analysis; Daicel Chiralcel AD, hexane/^{i}PrOH = 90/10, flow rate = 1.0 mL/min, λ = 254 nm, retention time = 8.3 min (minor) and 10.8 min (major), 94% ee.

Methyl 4-[*N*-(1-hydroxymethyl-1-phenyl-2-propynyl)amino]-benzoate (2h): Yield 95%; a white solid, 132.2−134.8 °C; TLC (SiO_2) R_f (hexane/EtOAc 7:3) 0.21; ^{1}H NMR δ 2.57 (s, 1H), 3.64 (d, J = 11.3 Hz, 1H), 3.81 (d, J = 11.3 Hz, 1H), 3.81 (s, 3H), 6.54 (d, J = 8.9 Hz, 2H), 7.33−7.42 (m, 3H), 7.65 (d, J = 8.9 Hz, 2H), 7.76 (d, J = 8.9 Hz, 2H); ^{13}C NMR δ 51.5 (CH_3), 61.0 (C), 72.8 (CH), 74.2 (CH_2), 82.6 (C), 115.0 (CH), 120.0 (C), 126.3 (CH), 128.4 (CH), 128.9 (CH), 130.7 (CH), 138.2 (C), 149.0 (C), 167.2 (C); $[\alpha]^{24}_D$ = +269 (c = 0.82, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.10; H, 6.01; N, 4.58. The optical purity was determined by HPLC analysis; Daicel Chiralcel AD, hexane/^{i}PrOH = 90/10, flow rate = 1.0 mL/min, λ = 254 nm, retention time = 21.5 min (minor) and 26.3 min (major), 93% ee.

Methyl 4-[*N*-[1-hydroxymethyl-1-(*p*-tolyl)-2-propynyl]amino]-benzoate (2t): Yield 96%; a white solid, mp decompose; TLC (SiO_2) R_f (hexane/EtOAc 7:3) 0.26; ^{1}H NMR δ 2.33 (s, 3H), 2.53 (s, 1H), 3.61 (d, J = 11.2 Hz, 1H), 3.77 (d, J = 11.2 Hz, 1H), 3.79 (s, 3H), 6.52 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 8.9 Hz, 2H), 7.74 (d, J = 8.9 Hz, 2H); ^{13}C NMR δ 21.0 (CH_3), 51.5 (CH_3), 60.8 (C), 72.8 (CH), 74.5 (CH_2), 82.7 (C), 114.9 (CH), 119.8 (C), 126.2 (CH), 129.6 (CH), 130.7 (CH), 135.2 (C), 138.2 (C), 149.1 (C), 167.2 (C); HRMS calcd for $C_{19}H_{19}NO_3$ [M] 309.1365, found 309.1355; $[\alpha]^{25}_D$ = +192 (c = 0.88, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.31; H, 6.30; N, 4.55. The optical purity was determined by HPLC analysis; Daicel Chiralcel AD, hexane/^{i}PrOH = 90/10, flow rate = 1.0 mL/min, λ = 254 nm, retention time = 20.8 min (minor) and 28.0 min (major), 94% ee.

2-(*p*-Tolyl)-2-[4-(trifluoromethyl)phenylamino]-3-butyn-1-ol (2u): Yield 97%; a white solid, 142.1−144.7 °C; TLC (SiO_2) R_f (hexane/EtOAc 7:3) 0.35; ^{1}H NMR δ 2.17 (br, 1H), 2.36 (s, 3H), 2.56 (s, 1H), 3.62 (d, J = 11.1 Hz, 1H), 3.77 (d, J = 11.1 Hz, 1H), 6.59 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 8.9 Hz, 2H), 7.52 (d, J = 8.9 Hz, 2H); ^{13}C NMR δ 21.0 (CH_3), 60.8 (C), 72.9 (CH), 74.6 (CH_2), 82.8 (C), 115.2 (CH), 120.2 (C, q, J = 32 Hz), 124.8 (C, q, J = 270 Hz), 125.9 (CH, q, J = 3.9 Hz), 126.2 (CH), 129.7 (CH), 135.2 (C), 138.2 (C), 147.8 (C); $[\alpha]^{24}_D$ = +210 (c = 1.12, $CHCl_3$). Anal. Calcd for $C_{18}H_{16}F_3NO$: C, 67.70; H, 5.05; N, 4.39. Found: C, 67.93; H, 5.10; N, 4.44. The optical purity was determined by HPLC analysis; Daicel Chiralcel AD, hexane/^{i}PrOH = 90/10, flow rate = 1.0 mL/min, λ = 254 nm, retention time = 9.3 min (minor) and 16.6 min (major), 93% ee.

2-(4-Fluorophenyl)-2-[4-(trifluoromethyl)phenylamino]-3-butyn-1-ol (2y): Yield 97%; a colorless amorphous; TLC (SiO_2) R_f (hexane/EtOAc 7:3) 0.30; ^{1}H NMR δ 2.27 (br, 1H), 2.58 (s, 1H), 3.60 (d, J = 11.1 Hz, 1H), 3.77 (d, J = 11.1 Hz, 1H), 5.20 (br, 1H), 6.57 (d, J = 8.4 Hz, 2H), 7.07 (dd, J = 8.4, 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 8.4, 5.4 Hz, 2H); ^{13}C NMR δ 60.6 (C), 72.8 (CH), 75.0 (CH_2), 82.4 (C), 115.3 (CH), 115.9 (CH, d, J = 21 Hz), 120.5 (C, q, J = 32 Hz), 124.7 (C, q, J = 270 Hz), 126.0 (CH, q, J = 3.9 Hz), 128.1 (CH, d, J = 8.3 Hz), 134.0 (C, d, J = 2.8 Hz), 147.6 (C), 162.7 (C, d, J = 247 Hz); HRMS calcd for $C_{17}H_{13}F_4NO$ [M] 323.0933, found 323.0926; $[\alpha]^{24}_D$ = +215 (c = 0.80, $CHCl_3$). The optical purity was determined by HPLC analysis; Daicel Chiralcel AD, hexane/^{i}PrOH = 90/10, flow rate = 1.0 mL/min, λ = 254 nm, retention time = 9.4 min (minor) and 13.6 min (major), 93% ee.

Tosylation of 2f. In a 20 mL round-bottomed flask were placed **2f** (85.0 mg, 0.28 mmol) and anhydrous dichloroethane (1.0 mL). *p*-Toluenesulfonyl chloride (58.3 mg, 0.31 mmol) and triethylamine (34.0 mg, 0.34 mmol) were added to the solution, and the mixture was stirred at room temperature for 6 h. The reaction was quenched by water, and organic materials were extracted with dichloroethane (20 mL × 2). The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was concentrated under reduced pressure by an aspirator, and the residue was purified by column chromatography (SiO_2) with hexane and ethyl acetate (85:15) as an eluent to give tosylated **2f** as a white solid (97.8 mg, 0.21 mmol; 76% yield).

2-Phenyl-2-[4-(trifluoromethyl)phenylamino]-3-butynyl *p*-toluenesulfonate: A white solid, mp decompose; TLC (SiO_2) R_f (hexane/EtOAc 7:3) 0.50; ^{1}H NMR δ 2.46 (s, 3H), 2.49 (s, 1H), 4.12 (s, 2H), 6.54 (d, J = 8.4 Hz, 2H), 7.23−7.36 (m, 7H), 7.60−7.63 (m, 2H), 7.77 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.6 (CH_3), 58.5 (C), 75.2 (CH), 75.8 (CH_2), 80.5 (C), 115.5 (CH), 120.6 (C, q, J = 32 Hz), 124.7 (C, q, J = 270 Hz), 125.8 (CH, q, J = 3.9 Hz), 126.7 (CH), 128.0 (CH), 128.9 (CH), 129.0 (CH), 130.0 (CH), 132.2 (C), 136.7 (C), 145.4 (C), 146.8 (C); $[\alpha]^{25}_D$ = +176 (c = 0.84, $CHCl_3$). Anal. Calcd for $C_{24}H_{20}F_3NO_3S$: C, 62.74; H, 4.39; N, 3.05. Found: C, 62.64; H, 4.60; N, 2.80.

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Supporting Information Available: Spectroscopic data and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.