JACS ARTICLES

Published on Web 07/09/2010

Copper-Catalyzed Enantioselective Propargylic Amination of Propargylic Esters with Amines: Copper−Allenylidene Complexes as Key Intermediates

Gaku Hattori,[†] Ken Sakata,*[,‡] Hiroshi Matsuzawa,[†] Yoshiaki Tanabe,[†] Yoshihiro Miyake,[†] and Yoshiaki Nishibayashi*[,†]

Institute of Engineering Innovation, School of Engineering, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-8656, Japan, and Faculty of Pharmaceutical Sciences, Hoshi University, Ebara, Shinagawa-ku, Tokyo 142-8501, Japan

Received June 1, 2010; E-mail: ynishiba@sogo.t.u-tokyo.ac.jp; sakata@hoshi.ac.jp

Abstract: The scope and limitations of the copper-catalyzed propargylic amination of various propargylic esters with amines are presented, where optically active diphosphines such as Cl-MeO-BIPHEP and BINAP work as good chiral ligands. A variety of secondary amines are available as nucleophiles for this catalytic reaction to give the corresponding propargylic amines with a high enantioselectivity. The results of some stoichiometric and catalytic reactions indicate that the catalytic amination proceeds via copper−allenylidene complexes formed in situ, where the attack of amines to the electrophilic γ-carbon atom in the allenylidene complex is an important step for the stereoselection. Investigation of the relative rate constants for the reaction of several *para*-substituted propargylic acetates with *N*-methylanilines reveals that the formation of the copper−allenylidene complexes is involved in the rate-determining step. The result of the density functional theory calculation on a model reaction also supports the proposed reaction pathway involving copper−allenylidene complexes as key intermediates. The catalytic procedure presented here provides a versatile and direct method for the preparation of a variety of chiral propargylic amines.

Introduction

Transition-metal-catalyzed allylic substitution reactions of allylic alcohol derivatives with nucleophiles are among the most reliable methods in organic synthesis. The process is catalyzed by various transition-metal complexes, and a wide variety of nucleophiles are available for this reaction to afford the corresponding allylated products with high chemo- and regioselectivities. An enantioselective version of this process has also been extensively studied, providing useful methods for the synthesis of various optically active compounds, including natural products.[1]

In sharp contrast, much less attention has been paid to transition-metal-catalyzed propargylic substitution reactions of propargylic alcohol derivatives with nucleophiles, although an acetylenic carbon−carbon triple bond has a high potential for a wide variety of transformations.[2,3] The Nicholas reaction has been used as an effective tool for propargylic substitution reactions of propargylic alcohols and their derivatives with a variety of nucleophiles to give the corresponding propargylic-substituted products.[4] In fact, various kinds of natural products have already been prepared by the use of the Nicholas reaction.[4] However, in this reaction, a stoichiometric amount of $Co_2(CO)_8$ is required, and several steps are necessary to obtain the propargylic-substituted products from propargylic alcohols via cationic dicobalt hexacarbonyl complexes such as $[(propargyl)Co_2(CO)_6]^+$.[4,5]

Since the ruthenium-catalyzed propargylic substitution reactions of propargylic alcohols with heteroatom-centered nucleophiles as well as carbon-centered ones have been reported by us,[6,7] where ruthenium−allenylidene complexes worked as key intermediates,[8–10] a number of catalytic propargylic substitution reactions have appeared.[11] Thus, several Lewis acids as well as transition-metal complexes were disclosed to work as

[†] The University of Tokyo.
[‡] Hoshi University.

(1) For selected reviews, see: (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995; p 290. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Lee, C. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 593. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (e) Nishibayashi, Y.; Uemura, S. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Amsterdam, 2007; Vol. 11, p 75. (f) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(2) (a) Brandsma, L. *Preparative Acetylene Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988. (b) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995. (c) *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; VCH: Weinheim, 2005. (d) Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques*; Elsevier: Amsterdam, 2004.

(3) For recent reviews, see: (a) Tejedor, D.; López-Tosco, S.; Cruz-Acosta, F.; Méndez-Abt, G.; García-Tellado, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 2090. (b) Anaya de Parrodi, C.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4679.

(4) For recent reviews, see: (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. (b) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 685. (c) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809. (d) Müller, T. J. J. *Eur. J. Org. Chem.* **2001**, 2021. (e) Díaz, D. D.; Betancort, J. M.; Martín, V. S. *Synlett* **2007**, 343.

(5) Asymmetric versions of the Nicholas reaction have already been reported: (a) Nicholas, K. M.; Mulvaney, M.; Bayer, M. *J. Am. Chem. Soc.* **1980**, *102*, 2508. (b) Ljungdahl, N.; Pera, N. P.; Andersson, K. H. O.; Kann, N. *Synlett* **2008**, 394.

 10.1021/ja1047494

effective catalysts to give the corresponding propargylic compounds from propargylic alcohols or their derivatives.[11] These catalytic processes are now becoming a powerful synthetic method as an alternative to the Nicholas reaction. As an extension of these studies, their asymmetric versions have also been disclosed, such as the ruthenium-catalyzed asymmetric propargylic alkylation of propargylic alcohols with acetone (up to 82% ee)[12] and similar propargylation of aromatic compounds (up to 95% ee).[13,14] Further, we have also disclosed that ruthenium-catalyzed intramolecular carbon−carbon bond-forming reactions between propargylic alcohols and alkenes gave the corresponding 1,5-enynes in good to high yields with a high to excellent enantioselectivity (up to 99% ee),[15] while Fu and Smith have reported nickel-catalyzed enantioselective carbon−carbon bond-forming reactions at the propargylic position of propargylic halides.[16] These results prompted us to investigate other transition-metal-catalyzed enantioselective propargylic substitution reactions with a variety of nucleophiles.

We focused on the copper-catalyzed propargylic amination of propargylic esters with a variety of amines, where the corresponding propargylic amines have been produced in good to high yields.[17] In this reaction system, we envisioned that this propargylic amination may proceed via copper−allenylidene complexes as key intermediates because only propargylic esters bearing a terminal acetylene moiety were available as substrates. In fact, the first successful example of the copper-catalyzed enantioselective propargylic amination of propargylic acetates with primary amines was reported by van Maarseveen and co-workers, where optically active 2,6-bis(oxazolinyl)pyridines (pybox) worked as good chiral ligands (up to 88% ee).[18] Independently, we have found a similar copper-catalyzed enantioselective reaction,[19] and, in the present article, the scope and limitations of our catalytic enantioselective propargylic substitution reactions of propargylic esters with various secondary amines by using optically active diphosphines such as BINAP[20] and BIPHEP[21] as chiral ligands are described in detail, together with the density functional theory calculation of the proposed reaction pathway which involves copper−allenylidene complexes as key intermediates.

Optically active propargylic amines are synthetically versatile intermediates for the construction of various biologically active compounds and polyfunctional amino derivatives.[22] Recently, the transition-metal-catalyzed enantioselective addition of terminal alkynes to imines has been developed to produce the corresponding chiral propargylic amines with a high enantiose-

(6) (a) Nishibayashi, Y.; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019. (b) Nishibayashi, Y.; Wakiji, I.; Ishii, Y.; Uemura, S.; Hidai, M. *J. Am. Chem. Soc.* **2001**, *123*, 3393. (c) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 7900. (d) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846. (e) Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172. (f) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1495. (g) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 6060. (h) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 3408. (i) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem.—Eur. J.* **2005**, *11*, 1433. (j) Inada, Y.; Yoshikawa, M.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Eur. J. Org. Chem.* **2006**, 881. (k) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4835. (l) Daini, M.; Yoshikawa, M.; Inada, Y.; Uemura, S.; Sakata, K.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2008**, *27*, 2046. (m) Yamauchi, Y.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2009**, *28*, 48. (n) Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2010**, *29*, 2126.

(7) (a) Nishibayashi, Y.; Imajima, H.; Onodera, G.; Hidai, M.; Uemura, S. *Organometallics* **2004**, *23*, 26. (b) Nishibayashi, Y.; Imajima, H.; Onodera, G.; Inada, Y.; Hidai, M.; Uemura, S. *Organometallics* **2004**, *23*, 5100. (c) Miyake, Y.; Endo, S.; Nomaguchi, Y.; Yuki, M.; Nishibayashi, Y. *Organometallics* **2008**, *27*, 4017. (d) Miyake, Y.; Endo, S.; Yuki, M.; Tanabe, Y.; Nishibayashi, Y. *Organometallics* **2008**, *27*, 6039. (e) Tanabe, Y.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2009**, *28*, 1138.

(8) The result of the density functional theory calculation on the model reaction also supports the proposed reaction pathway of the ruthenium-catalyzed propargylic substitution reactions of propargylic alcohols with nucleophiles, where ruthenium−allenylidene complexes work as key intermediates: (a) Ammal, S. C.; Yoshikai, N.; Inada, Y.; Nishibayashi, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 9428. (b) Sakata, K.; Miyake, Y.; Nishibayashi, Y. *Chem. Asian J.* **2009**, *4*, 81.

(9) For recent reviews of transition metal−allenylidene complexes, see: (a) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. (b) *Metal Vinylidenes and Allenylidenes in Catalysis: From Reactivity to Applications in Synthesis*; Bruneau, C., Dixneuf, P. H., Eds.; Wiley-VCH: Weinheim, 2008. (c) Cadierno, V.; Gimeno, J. *Chem. Rev.* **2009**, *109*, 3512.

(10) (a) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (b) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712. (c) Milton, M. D.; Onodera, G.; Nishibayashi, Y.; Uemura, S. *Org. Lett.* **2004**, *6*, 3993. (d) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2004**, *126*, 16066. (e) Onodera, G.; Matsumoto, H.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Org. Lett.* **2005**, *7*, 4029. (f) Onodera, G.; Matsumoto, H.; Nishibayashi, Y.; Uemura, S. *Organometallics* **2005**, *24*, 5799. (g) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Organometallics* **2006**, *25*, 35. (h) Yamauchi, Y.; Onodera, G.; Sakata, K.; Yuki, M.; Miyake, Y.; Uemura, S.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 5175. (i) Yamauchi, Y.; Yuki, M.; Tanabe, Y.; Miyake, Y.; Inada, Y.; Uemura, S.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 2908. (j) Yada, Y.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2008**, *27*, 3614.

(11) For reviews on catalytic propargylic substitution reactions, see: (a) Nishibayashi, Y.; Uemura, S. *Curr. Org. Chem.* **2006**, *10*, 135. (b) Nishibayashi, Y.; Uemura, S. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Amsterdam, 2007; Vol. 11, p 123. (c) Kabalka, G. W.; Yao, M.-L. *Curr. Org. Synth.* **2008**, *5*, 28. (d) Ljungdahl, N.; Kann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 642. (e) Miyake, Y.; Uemura, S.; Nishibayashi, Y. *ChemCatChem* **2009**, *1*, 342. (f) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, 6263.

(12) (a) Nishibayashi, Y.; Onodera, G.; Inada, Y.; Hidai, M.; Uemura, S. *Organometallics* **2003**, *22*, 873. (b) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715.

(13) (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) Kanao, K.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Synthesis* **2008**, 3869. (d) Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2009**, *28*, 2920.

(14) For a recent review, see: *Catalytic Asymmetric Friedel−Crafts Alkylations*; Bandini, M., Umani-Ronchi, A., Eds.; VCH: Weinheim, 2009.

(15) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 10498.

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

(17) (a) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282. (b) Geri, R.; Polizzi, C.; Lardicci, L.; Caporusso, A. M. *Gazz. Chim. Ital.* **1994**, *124*, 241. (c) Godfrey, J. D., Jr.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405.

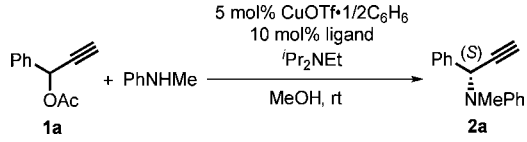
(18) (a) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777. (b) Prof. van Maarseveen and co-workers achieved the first enantioselective propargylic amination and presented a part of their result at the PAC Symposium 2007 (March 1, 2007, Utrecht).

(19) A preliminary result of the copper-catalyzed enantioselective propargylic amination has already been reported by our group: Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781.

(20) (*R*)-BINAP = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl: Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(21) BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl: Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.

Table 1. Investigation of the Effect of Optically Active Phosphine Ligands on Copper-Catalyzed Propargylic Amination of Propargylic Acetate (**1a**) with *N*-Methylaniline[a]



1a **2a**

run	ligand	time (h)	yield of **2a** (%)[b]	ee of **2a** (%)[c]
1	**L1**	1.5	69	78
2	**L2**	3	78	3
3	**L3**	18	71	3
4	**L4**	24	46	4
5	**L5**	24	0[d]	
6	**L6**	18	0[d]	
7	**L7**	24	86	10
8	**L8**	9	67	2
9	**L9**	24	44	15

[a] All the reactions of **1a** (0.20 mmol) with *N*-methylaniline (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper trifluoromethanesulfonate−benzene complex (0.010 mmol) and ligand (0.020 mmol) in MeOH (2.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details). [d] 1-Phenyl--2-propyn-1-ol was obtained quantitatively.

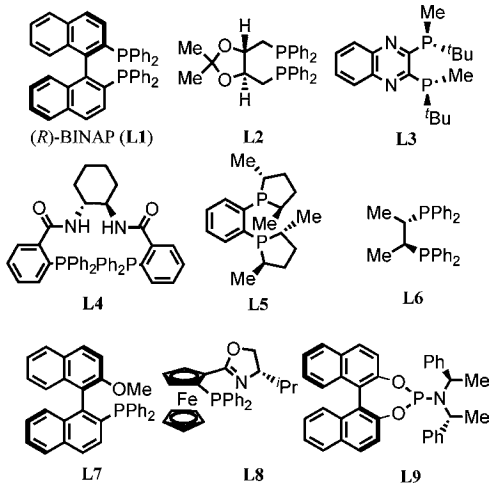
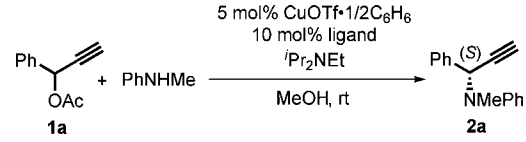


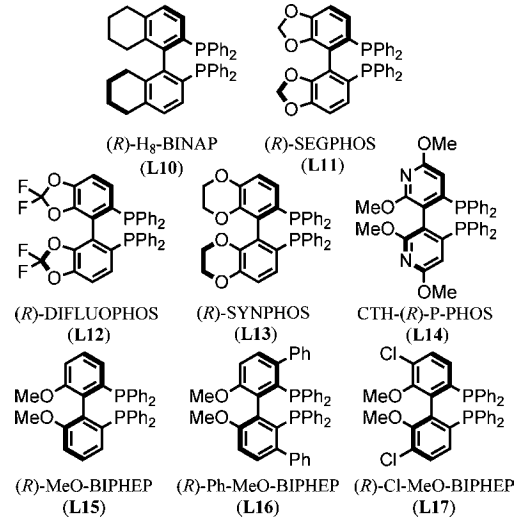
Table 2. Investigation of the Effect of Optically Active Biaryl Diphosphine Ligands on Copper-Catalyzed Propargylic Amination of Propargylic Acetate (**1a**) with *N*-Methylaniline[a]



1a **2a**

run	ligand	time (h)	yield of **2a** (%)[b]	ee of **2a** (%)[c]
1	**L1**	1.5 (12)[d]	69 (80)[d]	78 (85)[d]
2	**L10**	18	62	18
3	**L11**	1.5	58	59
4	**L12**	12	75	71
5	**L13**	1.5	67	75
6	**L14**	1.5	61	71
7	**L15**	12	75	68
8	**L16**	24	61	1
9	**L17**	1.5 (12)[d]	91 (88)[d]	79 (86)[d]

[a] All the reactions of **1a** (0.20 mmol) with *N*-methylaniline (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper trifluoromethanesulfonate−benzene complex (0.010 mmol) and ligand (0.020 mmol) in MeOH (2.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details). [d] At 0 °C.

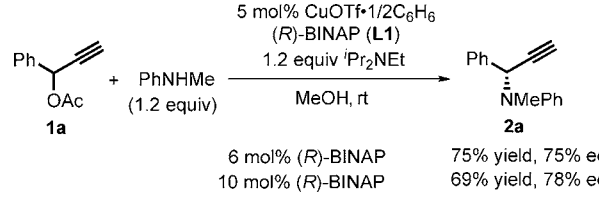


lectivity.[23] Especially the copper-catalyzed reactions are used as the most reliable method to obtain chiral propargylic amines.[24] The procedure described in the present article provides another versatile and direct method for the preparation of chiral propargylic amines.[25]

Results and Discussion

Catalytic Propargylic Amination. Treatment of 1-phenyl-2-propynyl acetate (**1a**) with *N*-methylaniline (1.2 equiv) and *N*,*N*-diisopropylethylamine (1.2 equiv) in the presence of catalytic amounts of copper trifluoromethanesulfonate−benzene complex, $CuOTf\cdot{}^{1}/_{2}C_6H_6$ (5 mol %), and (*R*)-BINAP (**L1**; 6 mol %) in methanol at room temperature for 1.5 h gave *N*-methyl-*N*-(1-phenyl-2-propynyl)aniline (**2a**) in 75% yield with 75% ee (*S*) (Scheme 1). No formation of other byproducts such as allenylic isomers was observed by ^{1}H NMR. Use of an excess amount of (*R*)-BINAP (10 mol %) slightly increased the enantioselectivity of **2a** (78% ee). The excess amount of (*R*)-BINAP is considered to inhibit the dissociation of (*R*)-BINAP from the copper atom of the catalyst. This catalytic reaction proceeded smoothly even when triethylamine was used in place of *N*,*N*-diisopropylethylamine, but no reaction occurred at all in the

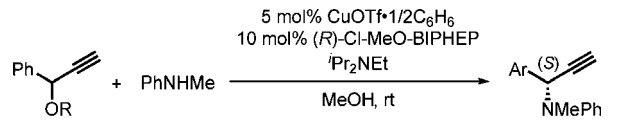
Scheme 1. Enantioselective Propargylic Amination of **1a** with PhNHMe Catalyzed by $CuOTf\cdot{}^{1}/_{2}C_6H_6$ and (*R*)-BINAP (**L1**)



(22) (a) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (b) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. (c) Yu, P. H.; Davis, B. A.; Boulton, A. A. *J. Med. Chem.* **1992**, *35*, 3705. (d) Jiang, B.; Xu, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2543. (e) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804. (f) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926.

(23) For a recent review, see Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.

Table 3. Investigation of the Effect of Leaving Groups in Propargylic Alcohol Derivatives on Copper-Catalyzed Propargylic Amination of Propargylic Alcohol Derivatives (**1a**) with *N*-Methylaniline[a]



1 **2a**

run	propargylic esters **1** (R)	time (h)	yield of **2a** (%)[b]	ee of **2a** (%)[c]
1	COMe (**1a**)	1.5	91	79
2	COPh (**1b**)	1.5	91	76
3	COC_6F_5 (**1c**)	0.5	87	25
4	CO_2Me (**1d**)	0.5	88	54
5[d]	CO_2Me (**1d**)	1.5	71	13
6	H (**1e**)	48	0[e]	
7	$COCF_3$ (**1f**)	0.5	0[f]	

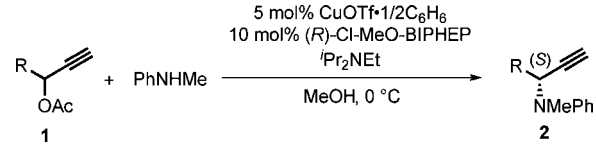
[a] All the reactions of **1** (0.20 mmol) with *N*-methylaniline (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper trifluoromethanesulfonate−benzene complex (0.010 mmol) and (*R*)-Cl-MeO-BIPHEP (0.020 mmol) in MeOH (2.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details). [d] In the absence of *N*,*N*-diisopropylethylamine. [e] **1e** was recovered in quantitative yield. [f] **1e** was obtained in 97% ^{1}H NMR yield.

absence of such base, showing that use of a stoichiometric amount of tertiary amine is necessary to promote the catalytic reaction.

We examined this catalytic amination in the presence of a variety of chiral ligands. Typical results are shown in Table 1. When optically active diphosphines such as (*S*,*S*)-DIOP[26] (**L2**), (*R*,*R*)-QuinoxP*[27] (**L3**), and Trost ligand[28] (**L4**) were used in place of **L1**, low enantioselectivities were observed in all cases (Table 1, runs 2−4). Use of other diphosphines such as (*R*,*R*)-Me-DUPHOS[29] (**L5**) and (*S*,*S*)-CHIRAPHOS[30] (**L6**) as chiral ligands resulted in the formation of the corresponding propargylic alcohol in quantitative yields (Table 1, runs 5 and 6). In the case of other optically active compounds such as (*R*)-MeO-MOP[31] (**L7**), (*S*)-(*S*)-ip-FOXAP[32] (**L8**), and (*S*)-(*R*,*R*)-phosphoramidite[33] (**L9**), the enantioselectivities were also low (Table 1, runs 7−9). These results clearly show that (*R*)-BINAP is the best ligand for the present enantioselective propargylic amination.

Next, we investigated the propargylic amination in the presence of a variety of atropisomeric diphosphines based on a

Table 4. Copper-Catalyzed Enantioselective Propargylic Amination of Propargylic Acetates (**1**) with *N*-Methylaniline[a]

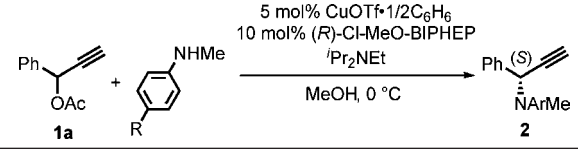


1 **2**

run	propargylic acetate **1** (R)	time (h)	yield of **2** (%)[b]	ee of **2** (%)[c]
1	Ph (**1a**)	12	88 (**2a**)	86
2	*p*-MeC_6H_4 (**1g**)	12	92 (**2b**)	81
3	*m*-MeC_6H_4 (**1h**)	12	91 (**2c**)	83
4	*o*-MeC_6H_4 (**1i**)	12	92 (**2d**)	82
5	*p*-PhC_6H_4 (**1j**)	12	95 (**2e**)	82
6	*p*-ClC_6H_4 (**1k**)	48	91 (**2f**)	85
7	*p*-BrC_6H_4 (**1l**)	48	88 (**2g**)	85
8	*p*-$MeOC_6H_4$ (**1m**)	12	91 (**2h**)	77
9	3,5-$Me_2C_6H_3$ (**1n**)	12	83 (**2i**)	83
10	2,6-$Me_2C_6H_3$ (**1o**)	12	72 (**2j**)	7
11	1-naphthyl (**1p**)	12	95 (**2k**)	86
12	2-naphthyl (**1q**)	12	90 (**2l**)	82
13	2-furyl (**1r**)	12	94 (**2m**)	85
14	3-furyl (**1s**)	12	92 (**2n**)	85
15	2-thienyl (**1t**)	12	94 (**2o**)	80
16	3-thienyl (**1u**)	12	95 (**2p**)	85
17	Ph_2C=CH (**1v**)	12	92 (**2q**)	30
18	cyclohexyl (**1w**)	48	0	

[a] All the reactions of **1** (0.20 mmol) with *N*-methylaniline (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper trifluoromethanesulfonate−benzene complex (0.010 mmol) and (*R*)-Cl-MeO-BIPHEP (0.020 mmol) in MeOH (2.0 mL) at 0 °C. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details).

Table 5. Copper-Catalyzed Enantioselective Propargylic Amination of Propargylic Acetate (**1a**) with *para*-Substituted *N*-Methylanilines[a]



1a **2**

run	R	time (h)	yield of **2** (%)[b]	ee of **2** (%)[c]
1	CF_3	12	72 (**2r**)	93
2	Cl	12	87 (**2s**)	89
3	H	12	88 (**2a**)	86
4	Me	12	94 (**2t**)	82
5	MeO	12	82 (**2u**)	80

[a] All the reactions of **1a** (0.20 mmol) with *N*-methylanilines (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper trifluoromethanesulfonate−benzene complex (0.010 mmol) and (*R*)-Cl-MeO-BIPHEP(0.020 mmol) in MeOH (2.0 mL) at 0 °C. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details).

(24) For examples, see: (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (c) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (d) Dube, H.; Gommermann, N.; Knochel, P. *Synthesis* **2004**, 2015. (e) Sakai, N.; Uchida, N.; Konakahara, T. *Synlett* **2008**, 1515.

(25) In related work, we have found the copper-catalyzed diastereo- and enantioselective sequential reactions of propargylic acetates with (*E*)-2,4-pentadienylaniline to give the corresponding 1,2-disubstituted tetrahydroisoindoles in high yields with high diastereo- and enantioselectivities, where only a single copper salt works as a catalyst to promote both propargylic amination and intramolecular [4+2] cycloaddition reaction: Hattori, G.; Miyake, Y.; Nishibayashi, Y. *ChemCatChem* **2010**, *2*, 155.

(26) (*S*,*S*)-DIOP = (4*S*,5*S*)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane: Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

(27) (*R*,*R*)-QuinoxP* = (*R*,*R*)-2,3-bis(*tert*-butylmethylphosphino)quinoxaline: Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934.

(28) Trost ligand = (1*R*,2*R*)-1,2-diaminocyclohexane-*N*,*N*-μ-bis-2′-(diphenylphosphinobenzoyl): Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747, and references therein.

(29) (*R*,*R*)-Me-DUPHOS = 1,2-bis-((2*R*,5*R*)-2,5-dimethylphospholano)benzene: Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363, and references therein.

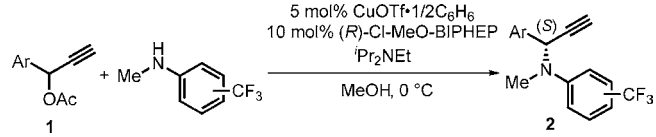
(30) (*S*,*S*)-CHIRAPHOS = (2*S*,3*S*)-bis(diphenylphosphino)butane: Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.

(31) (*R*)-MeO-MOP = (*R*)-2-(diphenylphophino)-2′-methoxy-1,1′-biphenyl: Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354, and references therein.

(32) (*S*)-(*S*)-ip-FOXAP = (*S*,*S*)-[2-(4′-isopropyloxazolin-2′-yl)ferrocenyl-]diphenylphosphine: Miyake, Y.; Nishibayashi, Y.; Uemura, S. *Synlett* **2008**, 1747, and references therein.

(33) (*S*)-(*R*,*R*)-Phosphoramidite = (*S*)-(+)-(3,5-dioxa-4-phospha-cyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl)bis[(1*R*)-1-phenylethyl]amine: (a) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374–2376. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623.

Table 6. Copper-Catalyzed Enantioselective Propargylic Amination of Propargylic Acetates (**1**) with Trifluoromethyl-*N*-methylanilines[a]



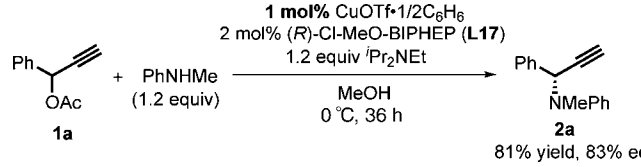
1 2

run	propargylic acetate **1** (Ar)	position of CF_3 group	time (h)	yield of **2** (%)[b]	ee of **2** (%)[c]
1	Ph (**1a**)	*p*-CF_3	12	72 (**2r**)	93
2	*p*-ClC_6H_4 (**1k**)	*p*-CF_3	48	72 (**2v**)	92
3	*p*-BrC_6H_4 (**1l**)	*p*-CF_3	48	78 (**2w**)	93
4	3-furyl (**1s**)	*p*-CF_3	12	85 (**2x**)	90
5	3-thienyl (**1u**)	*p*-CF_3	12	87 (**2y**)	92
6	1-naphthyl (**1p**)	*p*-CF_3	12	93 (**2z**)	98
7	2-naphthyl (**1q**)	*p*-CF_3	12	91 (**2aa**)	91
8	1-(4-methyl)naphthyl (**1x**)	*p*-CF_3	12	90 (**2ab**)	90
9	Ph (**1a**)	*m*-CF_3	12	81 (**2ac**)	89
10	1-naphthyl (**1p**)	*m*-CF_3	12	91 (**2ad**)	88

[a] All the reactions of **1** (0.20 mmol) with trifluoromethyl-*N*-methylanilines (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper trifluoromethanesulfonate−benzene complex (0.010 mmol) and (*R*)-Cl-MeO-BIPHEP (0.020 mmol) in MeOH (2.0 mL) at 0 °C. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details).

biaryl skeleton similar to **L1** as chiral ligands (Table 2). In contrast to **L1**, (*R*)-H_8-BINAP[34] (**L10**) was not a suitable ligand (Table 2, run 2). Use of (*R*)-SEGPHOS[35] (**L11**), which is known to be a more effective chiral ligand than **L1** in several catalytic reactions, resulted in only a moderate enantioselectivity (Table 2, run 3). In the case of other atropisomeric diphosphines such as (*R*)-DIFLUOPHOS[36] (**L12**), (*R*)-SYNPHOS[37] (**L13**), CTH-(*R*)-P-PHOS[38] (**L14**), and (*R*)-MeO-BIPHEP[39] (**L15**), the amine **2a** was produced in a similar yield with a slightly lower enantioselectivity (Table 2, runs 4−7). Unfortunately, no enantioselectivity was observed at all when (*R*)-Ph-MeO-BIPHEP[40] (**L16**) was used as a chiral ligand (Table 2, run 8). In contrast to the case of **L15**, the presence of a chloro group in the benzene ring dramatically increased the catalytic activity. Thus, the propargylic amination in the presence of (*R*)-Cl-MeO-BIPHEP[41] (**L17**) proceeded quite smoothly to give **2a** in 91% yield with 79% ee (Table 2, run 9) and even at a lower reaction temperature such as 0 °C provided **2a** in 88% yield with 86% ee (Table 2, runs 1 and 9). Interestingly, the reaction proceeded effectively even in the presence of a lower concentration of the catalyst such as 1 mol % of CuOTf•$^1/_2C_6H_6$ and 2 mol % of **L17** to give **2a** in 81% yield (turnover number (TON) = 81) with 83% ee (*S*), although a longer reaction time was necessary to complete the conversion (Scheme 2). It is noteworthy that only 1 mol % of the catalyst promoted the propargylic amination quite smoothly.

Scheme 2. Enantioselective Propargylic Amination of **1a** Catalyzed by a Lower Concentration of CuOTf•$^1/_2C_6H_6$ and (*R*)-Cl-MeO-BIPHEP (**L17**)



The nature of a leaving group in the propargylic ester affected the enantioselectivity of the propargylic amination (Table 3). A similar enantioselectivity was observed when propargylic benzoate (**1b**) was used as a substrate (Table 3, run 2). Reactions of other propargylic esters such as pentafluorobenzoate (**1c**) and methyl carbonate (**1d**) proceeded rapidly, but substantially lower enantioselectivities were achieved in both cases (Table 3, runs 3 and 4). Even in the absence of *N*,*N*-diisopropylethylamine, the reaction of propargylic carbonate (**1d**) proceeded, but with a low enantioselectivity (Table 3, run 5). No reaction occurred at all when propargylic alcohol (**1e**) was used as a substrate (Table 3, run 6). Merely the hydrolyzed product, propargylic alcohol **1e**, was obtained (97%) when the reaction of propargylic trifluoroacetate (**1f**) was carried out under the same reaction conditions (Table 3, run 7).

Next, the catalytic amination of various propargylic acetates (**1**) with *N*-methylaniline (1.2 equiv) and *N*,*N*-diisopropylethylamine (1.2 equiv) was carried out in the presence of catalytic amounts of CuOTf•$^1/_2C_6H_6$ (5 mol %) and (*R*)-Cl-MeO-BIPHEP (10 mol %) in methanol at 0 °C (Table 4). The introduction of a substituent such as a methyl, chloro, bromo, or phenyl group at the *para*-, *meta*-, or *ortho*-position in the benzene ring of **1** did not much affect the enantioselectivity (Table 4, runs 1−7). A substantially lower enantioselectivity was observed when a methoxy group was introduced at the *para*-position of the

(34) (*R*)-H_8-BINAP = (*R*)-2,2′-bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl: Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283.

(35) (*R*)-SEGPHOS = (*R*)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole: Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385, and references therein.

(36) (*R*)-DIFLUOROPHOS = (*R*)-5,5′-bis(diphenylphosphino)-2,2′,2,2′-tetrafluoro-5,5′-bi-1,3-benzodioxole: Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320.

(37) (*R*)-SYNPHOS = (*R*)-6,6′-bis(diphenylphosphino)-2,2′,3,3′-tetrahydro-5,5′-bi-1,4-benzodioxin: Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Tetrahedron Lett.* **2003**, *44*, 823.

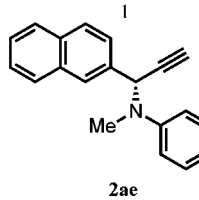
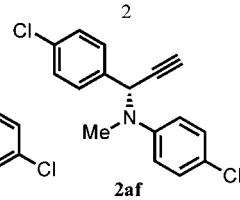
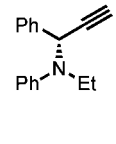
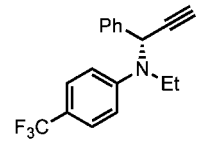
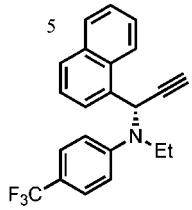
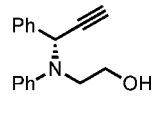
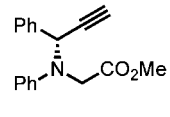
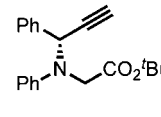
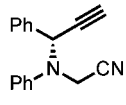
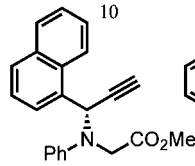
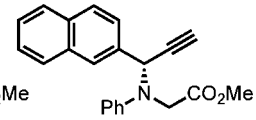
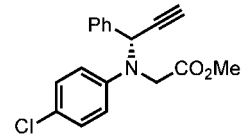
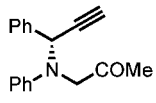
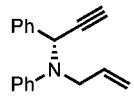
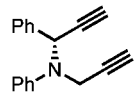
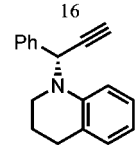
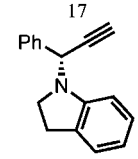
(38) CTH-(*R*)-P-PHOS = (*R*)-2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine: Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 11513.

(39) (*R*)-MeO-BIPHEP = (*R*)-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl: see ref 21.

(40) (*R*)-Ph-MeO-BIPHEP = (*R*)-3,3′-diphenyl-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl: Wu, S.; He, M.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2177.

(41) (*R*)-Cl-MeO-BIPHEP = (*R*)-5,5′-dichloro-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl: (a) Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488. (b) Jang, H.-Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 6174. (c) Rhee, J. U.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 10674. (d) Skucas, E.; Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242.

Table 7. Copper-Catalyzed Enantioselective Propargylic Amination of Propargylic Acetates (**1**) with Amines[a]

run				
	1	2	3	4
				
	2ae	**2af**	**2ag**	**2ah**
	36 h	36 h	12 h	12 h
	91%[b], 85% ee[c]	94%[b], 89% ee[c]	92%[b], 85% ee[c]	85%[b], 94% ee[c]
	5	6	7	8
				
	2ai	**2aj**	**2ak**	**2al**
	12 h	12 h	18 h	18 h
	88%[b], 92% ee[c]	92%[b], 87% ee[c]	93%[b], 90% ee[c]	86%[b], 86% ee[c]
	9	10	11	12
				
	2am	**2an**	**2ao**	**2ap**
	48 h	18 h	18 h	12 h
	61%[b], 90% ee[c]	85%[b], 87% ee[c]	84%[b], 88% ee[c]	63%[b], 90% ee[c]
	13	14	15	16	17
					
	2aq	**2ar**	**2as**	**2at**	**2au**
	24 h	12 h	12 h	12 h	12 h
	81%[b], 79% ee[c]	85%[b], 87% ee[c]	61%[b], 90% ee[c]	93%[b], 81% ee[c]	95%[b], 76% ee[c]

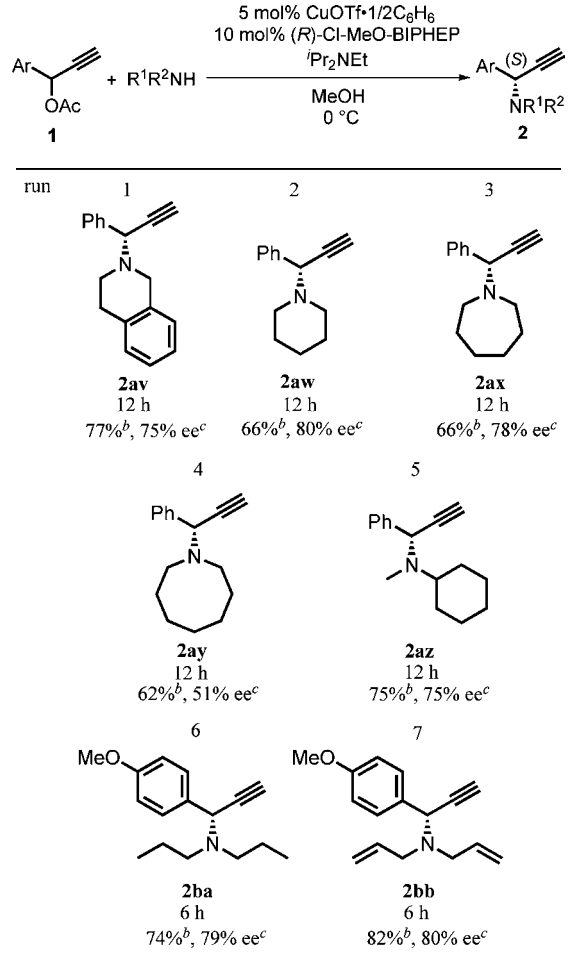
[a] All the reactions of **1** (0.20 mmol) with amines (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper trifluoromethanesulfonate−benzene complex (0.010 mmol) and (*R*)-Cl-MeO-BIPHEP (0.020 mmol) in MeOH (2.0 mL) at 0 °C. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details).

benzene ring of **1** (Table 4, run 8). In sharp contrast to propargylic acetate bearing a 3,5-dimethylphenyl moiety, the reaction of propargylic acetate bearing a 2,6-dimethylphenyl moiety afforded the corresponding propargylic amine in a similar yield but with quite low enantioselectivity (Table 4, runs 9 and 10). The propargylic amination of propargylic acetates bearing a naphthyl, furyl, or thienyl moiety proceeded with a high enantioselectivity (Table 4, runs 11−16). On the other hand, the reaction of propargylic acetate bearing an alkenyl group at the propargylic position gave the corresponding propargylic amine without any formation of byproduct, but only a low enantioselectivity was observed in the produced amine (Table 4, run 17). No reaction occurred at all under the same reaction conditions when 1-cyclohexyl-2-propynyl acetate was used as a substrate (Table 4, run 18). These results indicate that the presence of an aryl moiety at the propargylic position of **1** is necessary to promote the catalytic amination with a high enantioselectivity. The reason for a quite low enantioselectivity in the reaction of **1o** is mentioned in the later section.

The substituent in the benzene ring of *N*-methylaniline affects the enantioselectivity of the propargylic amination of **1a** (Table 5). Reactions with *N*-methyl-4-trifluoromethylaniline and *N*-methyl-4-chloroaniline gave the corresponding propargylic amines with 93 and 89% ee, respectively (Table 5, runs 1 and 2). In contrast, reactions with *N*-methyl-4-methylaniline and *N*-methyl-4-methoxyaniline proceeded with a slightly lower enantioselectivity (82 and 80% ee, respectively) (Table 5, runs 4 and 5). These results show that the presence of an electron-withdrawing group such as trifluoromethyl in the benzene ring of aniline increases the enantioselectivity.

The propargylic amination of various propargylic acetates with *N*-methyl-trifluoromethylanilines was then carried out

Table 8. Copper-Catalyzed Enantioselective Propargylic Amination of Propargylic Acetate (**1**) with Dialkylamines[a]

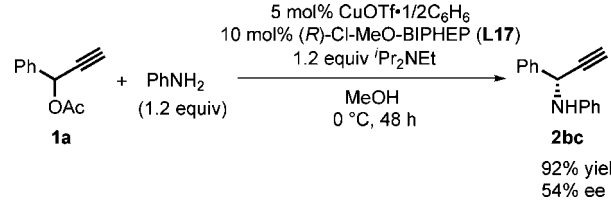


[a] All the reactions of **1** (0.20 mmol) with dialkylamines (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper trifluoromethanesulfonate−benzene complex (0.010 mmol) and (*R*)-Cl-MeO-BIPHEP (0.020 mmol) in MeOH (2.0 mL) at 0 °C. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details).

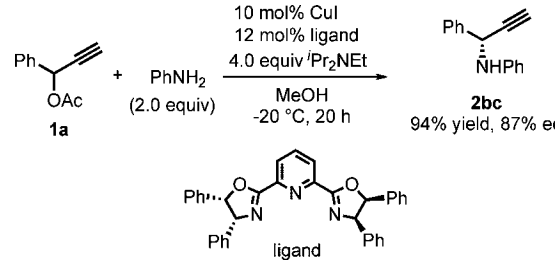
(Table 6). Reactions of propargylic acetates bearing a *p*-chlorophenyl, *p*-bromophenyl, furyl, or thienyl moiety with *N*-methyl-4-trifluoromethylaniline gave the corresponding aminated products with high enantioselectivities (90−93% ee) (Table 6, runs 2−5). The enantioselectivity was substantially increased when 1-(1-naphthyl)-2-propynyl acetate was used as a substrate (Table 6, run 6). In contrast, catalytic reactions with *N*-methyl-3-trifluoromethylaniline gave the corresponding amines with a slightly lower enantioselectivity (Table 6, runs 9 and 10).

Next, we investigated the scope and limitations of amines in the catalytic amination as shown in Table 7. In addition to *N*-methylaniline derivatives, the amination proceeded smoothly with a high enantioselectivity (up to 94% ee) when *N*-ethylaniline derivatives were used as nucleophiles (Table 7, runs 1−5). The introduction of a functional group such as a hydroxymethyl, alkoxycarbonyl, or cyano group at the methyl moiety in *N*-methylaniline did not greatly affect the enantioselectivity of the produced amines (Table 7, runs 6−9). Thus, reactions of various propargylic acetates with *N*-methylaniline bearing an alkoxycarbonyl group gave the corresponding propargylic amines with a high enantioselectivity (Table 7, runs

Scheme 3. Copper-Catalyzed Enantioselective Propargylic Amination of **1a** with Aniline



Scheme 4. Propargylic Substitution Reaction of **1a** with Aniline Catalyzed by CuI and Optically Active Pyridine-2,6-bisoxazoline Derivative Reported by van Maarseveen's Group[18]



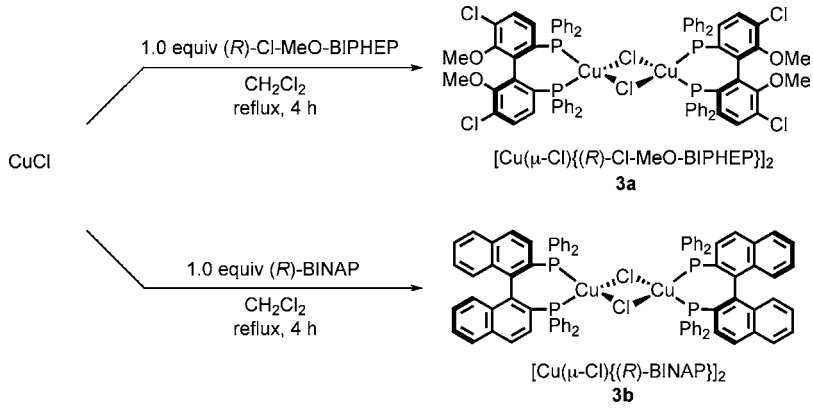
10−12), while a slightly lower enantioselectivity was observed in the reaction with *N*-methylaniline bearing a carbonyl moiety at the methyl part (Table 7, run 13). Use of other acyclic amines such as *N*-allylaniline and *N*-propargylaniline gave the corresponding amines with a high enantioselectivity (Table 7, runs 14 and 15). Cyclic amines such as 1,2,3,4-tetrahydroquinoline and indoline were also available as nitrogen-centered nucleophiles, where a high enantioselectivity was achieved in both cases (Table 7, runs 16 and 17).

Furthermore, the catalytic amination with secondary dialkylamines was investigated under the same reaction conditions (Table 8). Good enantioselectivity was observed in the reaction with cyclic dialkylamines such as 1,2,3,4-tetrahydroisoquinoline, piperidine, and azepane (hexamethyleneimine) (Table 8, runs 1−3), although azocane (heptamethyleneimine) did not work as an effective nucleophile (Table 8, run 4). This result indicates that the enantioselectivity of the produced amines depends much on the ring size of the cyclic dialkylamines. Reactions with acyclic dialkylamines such as *N*-cyclohexyl-*N*-methylamine, dipropylamine, and diallylamine proceeded smoothly to give the corresponding amines with high enantioselectivities (Table 8, runs 5−7). It is noteworthy that simple dialkylamines work as effective nucleophiles for our reaction system.

It is also noteworthy that the reaction with a primary amine such as aniline proceeded smoothly, but only a moderate enantioselectivity (54% ee) was achieved under the same reaction conditions (Scheme 3).[42] This result is in sharp contrast to the result reported by van Maarseveen and co-workers, where only aniline derivatives worked as suitable nucleophiles (Scheme 4).[18] Interestingly, van Maarseveen and co-workers did not achieve a high enantioselectivity when secondary amines were used as nitrogen-centered nucleophiles.[18] Thus, our system described in the present paper using secondary amines complements van Maarseveen's system[18] for the copper-catalyzed propargylic amination.

(42) (a) Reactions of **1a** with other anilines such as 4-methylaniline, 4-chloroaniline, and 4-trifluoromethylaniline were investigated under the same reaction conditions to give the corresponding propargylic amines in good yields with only a moderate enantioselectivity (45−55% ee). (b) Unfortunately, no propargylic amination occurred at all when primary alkylamines such as *tert*-butylamine and 1-adamantylamine were used as nucleophiles.

Scheme 5. Preparation of [Cu(μ-Cl)diphosphine]$_2$ by Reaction of CuCl with Diphosphines



Copper Complexes. In order to obtain some information on the reaction pathway, the following stoichiometric and catalytic reactions were investigated. Treatment of CuCl with a stoichiometric amount of (*R*)-Cl-MeO-BIPHEP in dichloromethane at reflux temperature for 4 h gave the corresponding chloride-bridged dicopper complex [Cu(μ-Cl){(*R*)-Cl-MeO-BIPHEP}]$_2$ (**3a**) in quantitative yield (Scheme 5). The molecular structure of **3a** was unambiguously characterized by X-ray crystallography, and an ORTEP drawing of **3a** is shown in Figure 1. The X-ray study has revealed that **3a** is a diamagnetic copper(I) centrosymmetrical dimer where two copper atoms bridged by two chlorine atoms are located at a nonbonding distance of 3.1580(5) Å apart. Each copper(I) atom chelated by (*R*)-Cl-MeO-BIPHEP exhibits four-coordination with a slightly distorted tetrahedral geometry. The P−Cu−P bite angles (102.6°, mean) and Cu−P distances (2.25 Å, mean) are quite close to the reported values found in other dicopper complexes [Cu(μ-Cl)(diphosphine)]$_2$.[43] Similarly, chloride-bridged dicopper complex [Cu(μ-Cl){(*R*)-BINAP}]$_2$ (**3b**) was obtained in quantitative yield from the reaction of CuCl with a stoichiometric amount of (*R*)-BINAP under the same reaction conditions (Scheme 5).[44] The molecular structure of **3b** was also unambiguously characterized by X-ray crystallography, and an ORTEP drawing of **3b** is shown in Figure 2.

We then carried out the propargylic amination using the above isolated chloride-bridged dicopper complexes as catalysts. Typical results are shown in Table 9. Treatment of **1a** with *N*-methylaniline (1.2 equiv) and *N*,*N*-diisopropylethylamine (1.2 equiv) in the presence of a catalytic amount of **3a** (2.5 mol %) in methanol at 0 °C for 12 h gave **2a** in 84% yield with 85% ee (*S*) (Table 9, run 1). The catalytic activity of **3a** was almost the same as that of the complex which might be formed in situ under the present catalytic reaction conditions using (*R*)-Cl-MeO-BIPHEP (Table 9, run 2). This result indicates that the copper complex bearing one chiral diphosphine ligand works as a reactive species in the catalytic propargylic amination, even though twice the amount of (*R*)-Cl-MeO-BIPHEP was used relative to the copper complex in many cases. Separately, we also confirmed that the catalytic activity of **3b** was similar to that of the complex formed in situ using (*R*)-BINAP (Table 9, runs 4 and 5).

As described above, we confirmed that the reaction of propargylic acetates bearing an internal alkyne moiety such as 1,3-diphenyl-2-propynyl acetate under similar conditions did not proceed at all.[19] In addition, we have previously reported many ruthenium-catalyzed propargylic substitution reactions with a variety of nucleophiles, where ruthenium−allenylidene complexes from reactions of ruthenium complexes with propargylic alcohols bearing a terminal alkyne moiety were clarified to work as key intermediates experimentally and theoretically.[6–8] These results lead us to envisage that copper-catalyzed propargylic amination may proceed via copper−allenylidene complexes as key intermediates. At first, we attempted to isolate some reactive intermediates of the catalytic amination. The reaction of **3b** with a stoichiometric amount of **1a** in the presence of *N*,*N*-diisopropylethylamine in methanol gave only a complex mixture,

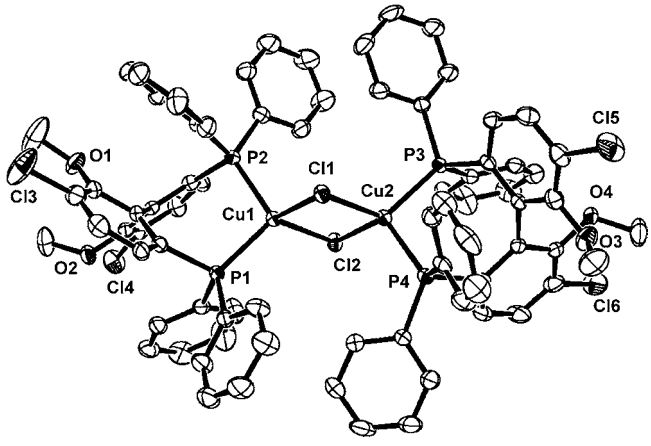


Figure 1. ORTEP drawing of [Cu(μ-Cl){(*R*)-Cl-MeO-BIPHEP}]$_2$ (**3a**). Selected bond distances (Å) and angles (deg) for **3a**: Cu−Cl, 2.366; Cu−P, 2.248; Cl−Cu−Cl, 96.3; Cl−Cu−P, 114.6; P−Cu−P, 102.6; Cu−Cl−Cu, 83.7 (mean values).

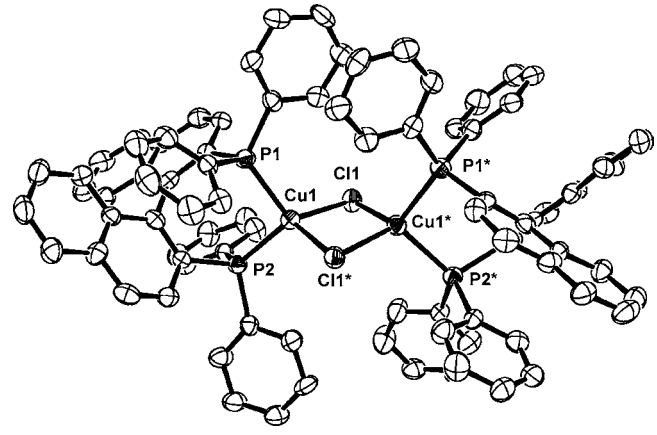
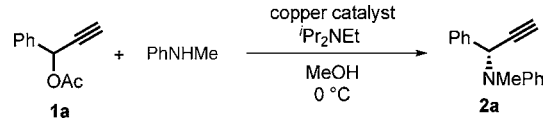


Figure 2. ORTEP drawing of [Cu(μ-Cl){(*R*)-BINAP}]$_2$ (**3b**). Selected bond distances (Å) and angles (deg) for **3b** (values without standard errors in parentheses are averaged): Cu−Cl, 2.378; Cu−P, 2.260; Cl−Cu−Cl, 98.01(5); Cl−Cu−P, 114.9; P−Cu−P, 100.15(5); Cu−Cl−Cu, 81.26(4).

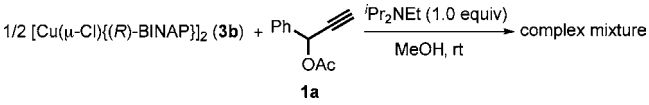
Table 9. Catalytic Reactivities of [Cu(μ-Cl)diphosphine]$_2$ and [Cu(μ-C≡Ctol)diphosphine]$_2$[a]



run	copper catalyst	time (h)	yield of **2a** (%)[b]	ee of **2a** (%)[c]
1	2.5 mol % [Cu(μ-Cl){(*R*)-Cl-MeO-BIPHEP}]$_2$ (**3a**)	12	84	85
2	5 mol % CuOTf·$^1/_2$C$_6$H$_6$ + 10 mol % (*R*)-Cl-MeO-BIPHEP	12	88	86
3	2.5 mol % [Cu(μ-C≡Ctol){(*R*)-Cl-MeO-BIPHEP}]$_2$ (**4a**)	12	85	85
4	2.5 mol % [Cu(μ-Cl){(*R*)-BINAP}]$_2$ (**3b**)	36	81	80
5	5 mol % CuOTf·$^1/_2$C$_6$H$_6$ + 10 mol % (*R*)-BINAP	12	80	85
6	2.5 mol % [Cu(μ-C≡Ctol){(*R*)-BINAP}]$_2$ (**4b**)	36	82	80

[a] All the reactions of **1a** (0.20 mmol) with *N*-methylaniline (0.24 mmol) and *N*,*N*-diisopropylethylamine (0.24 mmol) were carried out in the presence of copper catalyst in MeOH (2.0 mL) at 0 °C. [b] Isolated yield of **2a**. [c] Determined by HPLC (see Supporting Information for experimental details).

Scheme 6. Attempts for Preparation of Copper−Allenylidene Complex



where the corresponding copper−allenylidene complex was not isolated in a pure form (Scheme 6). In the absence of *N*,*N*-diisopropylethylamine or methanol, no reaction occurred at all. At present, we have been unsuccessful in isolating any reactive intermediates, including copper−allenylidene complexes.

Instead of copper−allenylidene complexes, we separately attempted to isolate copper−acetylide complexes because copper−allenylidene complexes are expected to be formed via copper−acetylide complexes from propargylic acetates. Thus, the reaction of **3a** with an excess amount of lithium acetylide in THF at room temperature for 2 h gave the corresponding acetylide-bridged dicopper complex [Cu(μ-C≡Ctol){(*R*)-Cl-MeO-BIPHEP}]$_2$ (**4a**) in 21% isolated yield (Scheme 7). The molecular structure of **4a** was unambiguously characterized by X-ray crystallography, and an ORTEP drawing of **4a** is shown in Figure 3. An X-ray analysis of **4a** has demonstrated that **4a** contains two copper(I) atoms bridged by two acetylide groups in a $\mu-\eta^1$ bonding mode. Each copper atom chelated by (*R*)-Cl-MeO-BIPHEP displays a slightly distorted tetrahedral geometry. The two copper atoms are separated from one another at a distance of 2.4199(4) Å, which is close to the reported values found among the acetylide-bridged complexes [Cu(μ-C≡CR)(diphosphine)]$_2$, the short copper−copper separation of which having been suggested to be derived from the σ-donor

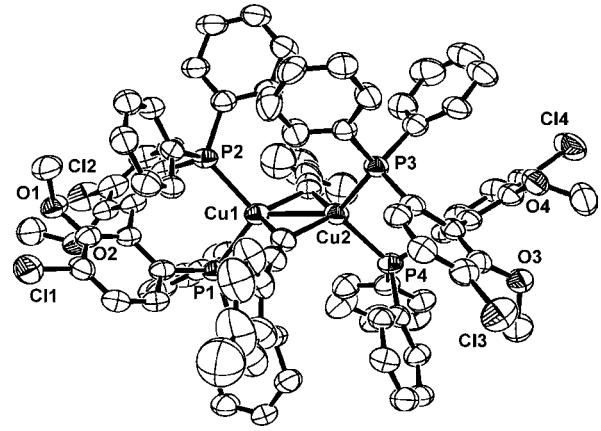
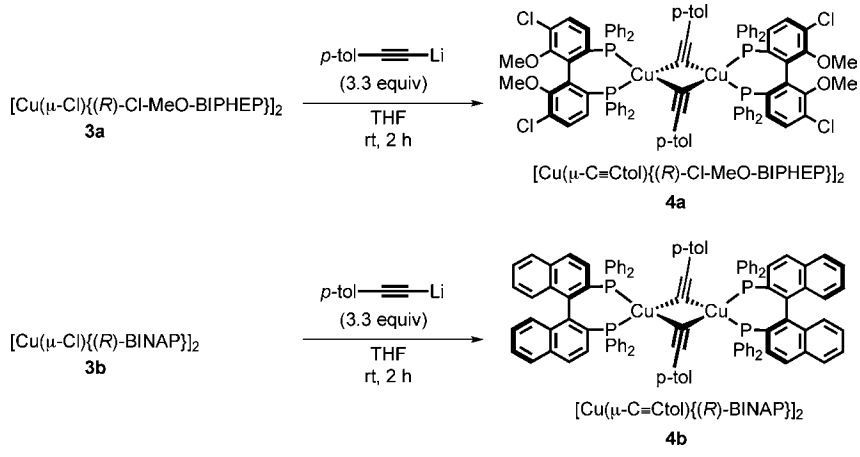


Figure 3. ORTEP drawing of [Cu(μ-C≡Ctol){(*R*)-Cl-MeO-BIPHEP}]$_2$ (**4a**). Selected bond distances (Å) and angles (deg) for **4a** (values without standard errors in parentheses are averaged): Cu−C, 2.095; Cu−P, 2.271; C−Cu−C, 109.44(10); C−Cu−P, 111.6; P−Cu−P, 101.16(3); Cu−C−Cu, 70.6.

capabilities of the acetylides.[45] A similar acetylide-bridged dicopper complex, [Cu(μ-C≡Ctol){(*R*)-BINAP}]$_2$ (**4b**), was also obtained in 25% isolated yield from the reaction of **3b** with lithium acetylide under the same reaction conditions (Scheme 7). The molecular structure of **4b** was also confirmed by a preliminary X-ray crystallographic study.[46]

Interestingly, the produced acetylide-bridged dicopper complexes also have a catalytic activity to promote the amination. In fact, the reaction of **1a** with *N*-methylaniline (1.2 equiv) and *N*,*N*-diisopropylethylamine (1.2 equiv) in the presence of a

Scheme 7. Preparation of [Cu(μ-C≡Ctol)diphospine]$_2$



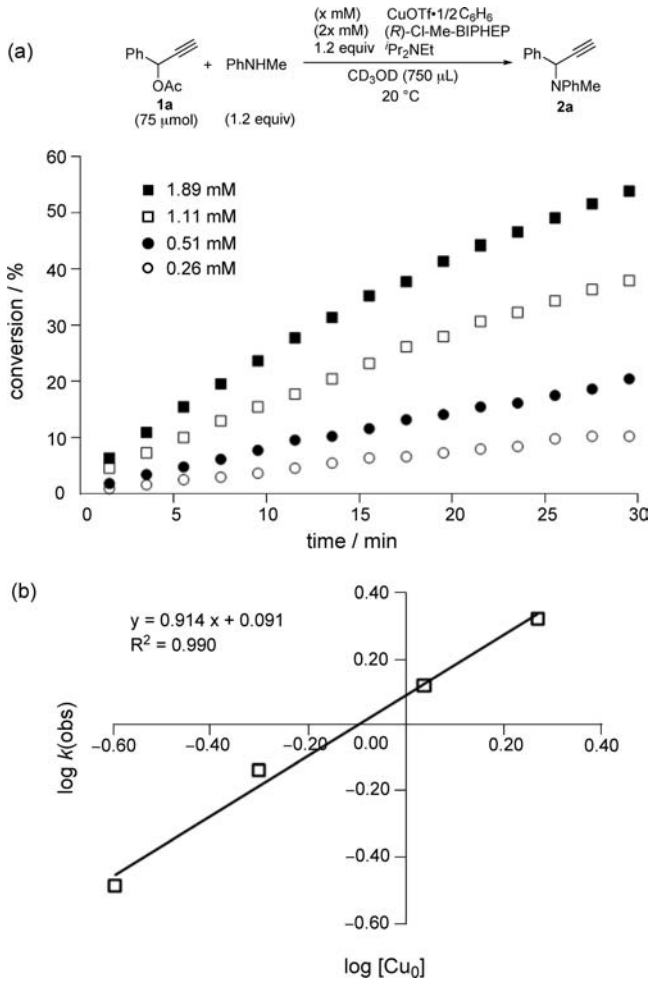


Figure 4. Rate measurement for the propargylic amination of **1a** with *N*-methylaniline catalyzed by CuOTf•$^1/_2C_6H_6$ and (*R*)-Cl-MeO-BIPHEP in CD_3OD at 20 °C: (a) kinetic data obtained for different catalyst concentrations; (b) reaction order with respect to CuOTf•$^1/_2C_6H_6$ and (*R*)-Cl-MeO-BIPHEP.

catalytic amount of **4a** (2.5 mol %) in methanol at 0 °C for 12 h gave **2a** in 85% yield with 85% ee (*S*) (Table 9, run 3). The catalytic activity of **4a** is almost the same as that of the complex prepared in situ from the reaction of CuOTf•$^1/_2C_6H_6$ with 2 equiv of (*R*)-Cl-MeO-BIPHEP. Separately, we confirmed that the catalytic activity of **4b** is also similar to that of the complex prepared in situ from the reaction of CuOTf•$^1/_2C_6H_6$ with 2 equiv of (*R*)-BINAP (Table 9, run 6). These results show that the copper−acetylide complexes bearing a chiral diphosphine might work as precursors of the reactive species in the catalytic propargylic amination.

In order to obtain more information on the reactive intermediates in the propargylic amination, the rate constants at different initial concentrations of the catalyst were estimated, and the reaction order with respect to the catalyst, 0.91 for the copper complex (an almost first order to copper salt), was obtained by plotting the log *k* against log [Cu_0] of the catalyst as shown in Figure 4. As described in the previous paragraph, copper−

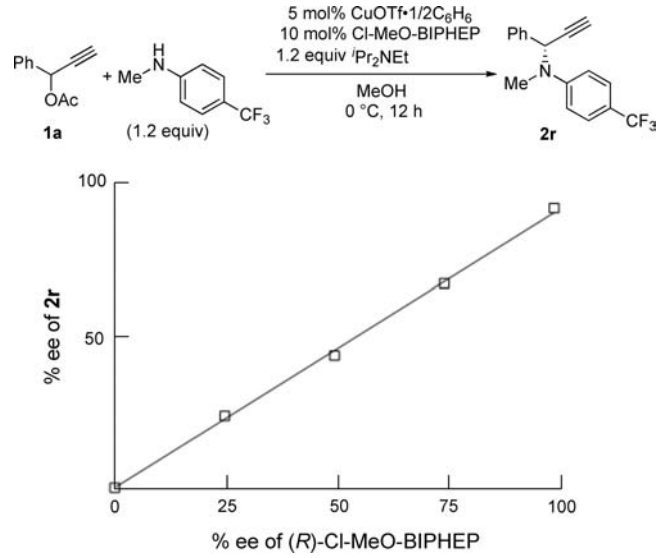


Figure 5. Linear relationship between the ee value of (*R*)-Cl-MeO-BIPHEP and the ee value of **2r** obtained for the reaction of **1a** with *N*-methyl-4-trifluoromethylaniline catalyzed by CuOTf•$^1/_2C_6H_6$ in MeOH at 0 °C.

acetylide complexes generally have a tendency to aggregate into the corresponding polynuclear complexes.[47,48] However, we consider that a monomeric copper−acetylide complex generated from polynuclear copper−acetylide complexes works as one (or more) species to promote the catalytic reaction. In addition, we plotted the ee value of (*R*)-Cl-MeO-BIPHEP against the ee value of the produced propargylic amine **2a** in the catalytic reaction of **1a** with *N*-methylaniline (Figure 5). The result clearly showed the linear relationship[49,50] between the ee value of (*R*)-Cl-MeO-BIPHEP and the ee value of the produced propargylic amine, supporting our proposal that a monomeric complex may work as one (or more) species to promote the catalytic reaction.

Proposed Reaction Pathway. By considering all the experimental evidence, a reaction pathway for the catalytic amination is proposed in Scheme 8, where copper−allenylidene[51] complex may be formed as a key intermediate.[52] The copper−allenylidene

(43) (a) Baker, R. T.; Calabrese, J. C.; Westcott, S. A. *J. Organomet. Chem.* **1995**, *498*, 109. (b) Pinto, P.; Calhorda, M. J.; Félix, V.; Avilés, T.; Drew, M. G. B. *Monatsh. Chem.* **2000**, *131*, 1253.

(44) The complex **3b** has already been prepared by the Lipshutz group, but the crystallographic structure of **3b** has not yet been mentioned: Lipshutz, B. H.; Frieman, B.; Birkedal, H. *Org. Lett.* **2004**, *6*, 2305.

(45) (a) Díez, J.; Gamasa, M. P.; Gimeno, J.; Aguirre, A.; García-Granda, S.; Holubova, J.; Falvello, L. R. *Organometallics* **1999**, *18*, 662. (b) Mealli, C.; Godinho, S. S. M. C.; Calhorda, M. J. *Organometallics* **2001**, *20*, 1734.

(46) Preliminary crystallographic data for **4b**•CH_2Cl_2: $C_{107}H_{80}Cl_2Cu_2P_4$, FW = 1687.70, monoclinic, space group $P2_1$, a = 13.4997(5), b = 20.7940(6), and c = 15.3709(5) Å, β = 94.0290(10)°, V = 4304.1(2) Å^3, Z = 2, d_{calcd} = 1.302 g cm^{-3}, μ = 6.800 cm^{-1}, $R1$ ($wR2$) = 0.0762 (0.1419) for 18 587 unique reflections and 1032 parameters. Heavy disorder among acetylides and dichloromethane prohibited sufficient refinement of the structure.

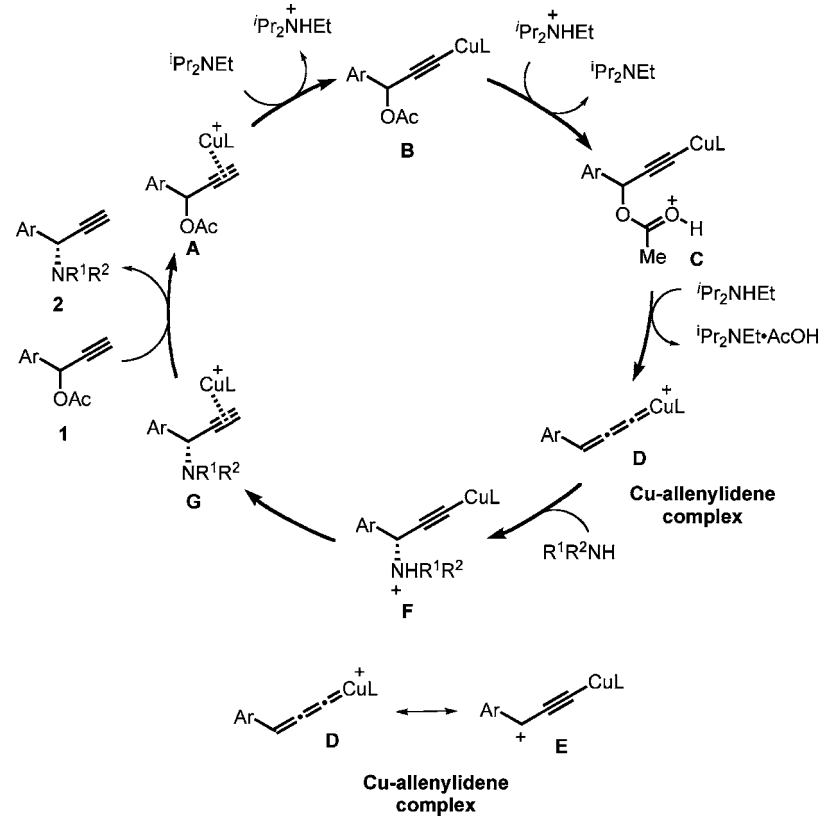
(47) (a) Knotter, D. M.; Spek, A. L.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1989**, 1738. (b) Díez, J.; Gamasa, M. P.; Gimeno, J.; Aguirre, A.; García-Granda, S. *Organometallics* **1991**, *10*, 380. (c) Baxter, C. W.; Higgs, T. C.; Bailey, P. J.; Parsons, S.; McLachlan, F.; McPartlin, M.; Tasker, P. A. *Chem.—Eur. J.* **2006**, *12*, 6166. (d) Bruce, M. I.; Zaitseva, N. N.; Skelton, B. W.; Somers, N.; White, A. H. *Inorg. Chim. Acta* **2007**, *360*, 681. (e) Asano, Y.; Ito, H.; Hara, K.; Sawamura, M. *Organometallics* **2008**, *27*, 5984.

(48) (a) Straub, B. F. *Chem. Commun.* **2007**, 3868. (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952, and references therein.

(49) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922, and references therein.

(50) (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779. (c) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103.

Scheme 8. Proposed Reaction Pathway



complex (**D**) might be formed by the elimination of an acetyl moiety from the copper−acetylide complex (**C**), the protonated species of **B**, while **B** is formed from the copper−π-alkyne complex (**A**) between **1** and copper complex bearing (*R*)-Cl-MeO-BIPHEP. *N*,*N*-Diisopropylethylamine promotes these deprotonation and protonation processes from **A** to the copper−allenylidene complex **D**, where the copper−acetylide complex bearing a cationic γ-carbon (**E**) exists as a resonance structure of **D**. An amine then attacks the copper−allenylidene complex **D** to afford the corresponding copper−acetylide complex (**F**). Finally, the higher acidity of the proton of conjugated amine in **F** promotes a hydrogen atom shift to the α-carbon on the ligand to give a copper−π-alkyne complex (**G**). This proposed reaction pathway is supported by the following kinetic study on the catalytic reactions. The relative reactivity (the Hammett linear free-energy relationship)[53] of substituted propargylic acetates ($XC_6H_4CH(OAc)C{\equiv}CH$, X = *p*-Me, H, *p*-Cl) with *N*-methylaniline in the presence of a catalytic amount of the chiral copper complex was determined from the relative rates of the conversion of propargylic acetates when conversions were low (<10%) (Figure 6 and Table 10). The rate data correlated well with the Hammett linear free energy relationship by use of σ and σ^+ values. Better correlation ($\rho = -2.50$) was obtained with a σ^+ (Figure 7),[53] showing that the formation of the propargylic cation

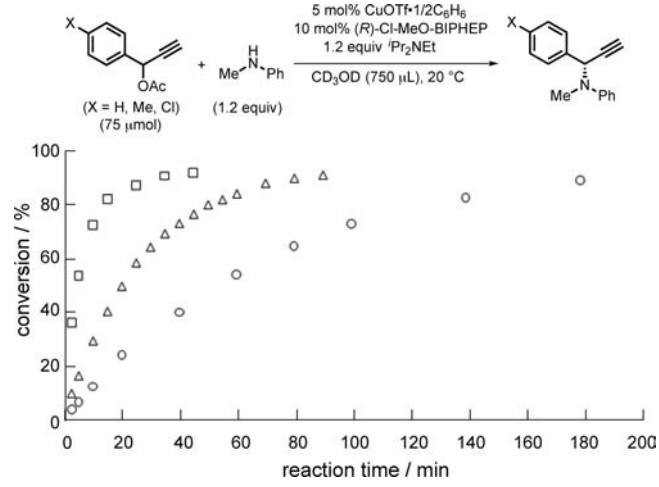


Figure 6. Relative reactivity of substituted propargylic acetates (X = Me, □; X = H, △; X = Cl, ○) in the reaction with *N*-methylaniline in the presence of catalytic amounts of $CuOTf\cdot{}^1/_2C_6H_6$ and (*R*)-Cl-MeO-BIPHEP.

Table 10. Relative Rate Constants for the Copper-Catalyzed Propargylic Amination of Propargylic Acetate (**1**) with *N*-Methylaniline

X in propagylic acetate (**1**)	σ^+	(σ)	k_X/k_H	$\log(k_X/k_H)$
p-Me	−0.31	(−0.17)	4.90	0.69
H	0	(0)	0	0
p-Cl	0.11	(0.23)	0.41	−0.39

(51) No copper−allenylidene complex has yet been isolated until now, but the first example of a silver−allenylidene complex has recently been reported: (a) Asay, M.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4796. Recently, the first example of a palladium−allenylidene complex has been reported: (b) Kessler, F.; Szesni, N.; Põhako, K.; Weibert, B.; Fischer, H. *Organometallics* **2009**, *28*, 348.

(52) Quite recently, we reported the copper-catalyzed enantioselective ring-opening reactions of ethynyl epoxides with amines, where copper−allenylidene complexes were proposed to work as key intermediates: Hattori, G.; Yoshida, A.; Miyake, Y.; Nishibayashi, Y. *J. Org. Chem.* **2009**, *74*, 7603.

(53) For reviews, see: (a) Exner, O. In *Correlation Analysis in Chemisty*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; Chapter 10. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

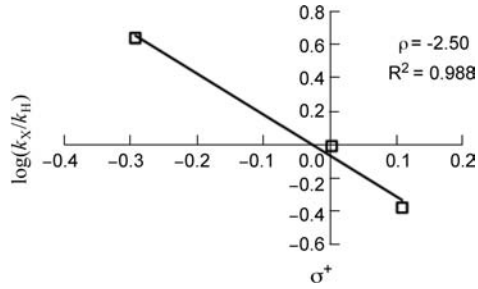
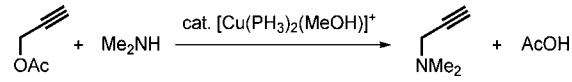


Figure 7. Hammett linear free-energy relationship between σ^+ and $\log(k_X/k_H)$.

as reactive intermediate may be involved in the rate-determining step. On the other hand, no correlation was observed with a σ value when the relative reactivity of propargylic acetate with substituted *N*-methylanilines (XC_6H_4NMe, X = *p*-Me, H, *p*-Cl) was determined in the presence of a catalytic amount of the chiral copper complex.

Scheme 9. Model Reaction between Propargyl Acetate and *N*,*N*-Dimethylamine Catalyzed by Copper Complex $[Cu(PH_3)_2(MeOH)]^+$



Theoretical Calculations for Reaction Pathway. To get further insight into the reaction pathway of the copper-catalyzed propargylic amination, density functional theory (DFT) calculations using the B3LYP hybrid functional[54] with Gaussian03 program[55] (SDD[56] for Cu atom and 6-311G**[57] for other atoms) were carried out for the following model reaction between propargyl acetate and *N*,*N*-dimethylamine in the presence of a cationic copper complex $[Cu(PH_3)_2(MeOH)]^+$ (Scheme 9). For simplicity, we adopted the model where the aryl group at the propargylic position of propargylic acetates is replaced with a hydrogen atom, ignoring the π-conjugation effect by the aryl group in intermediate structures.

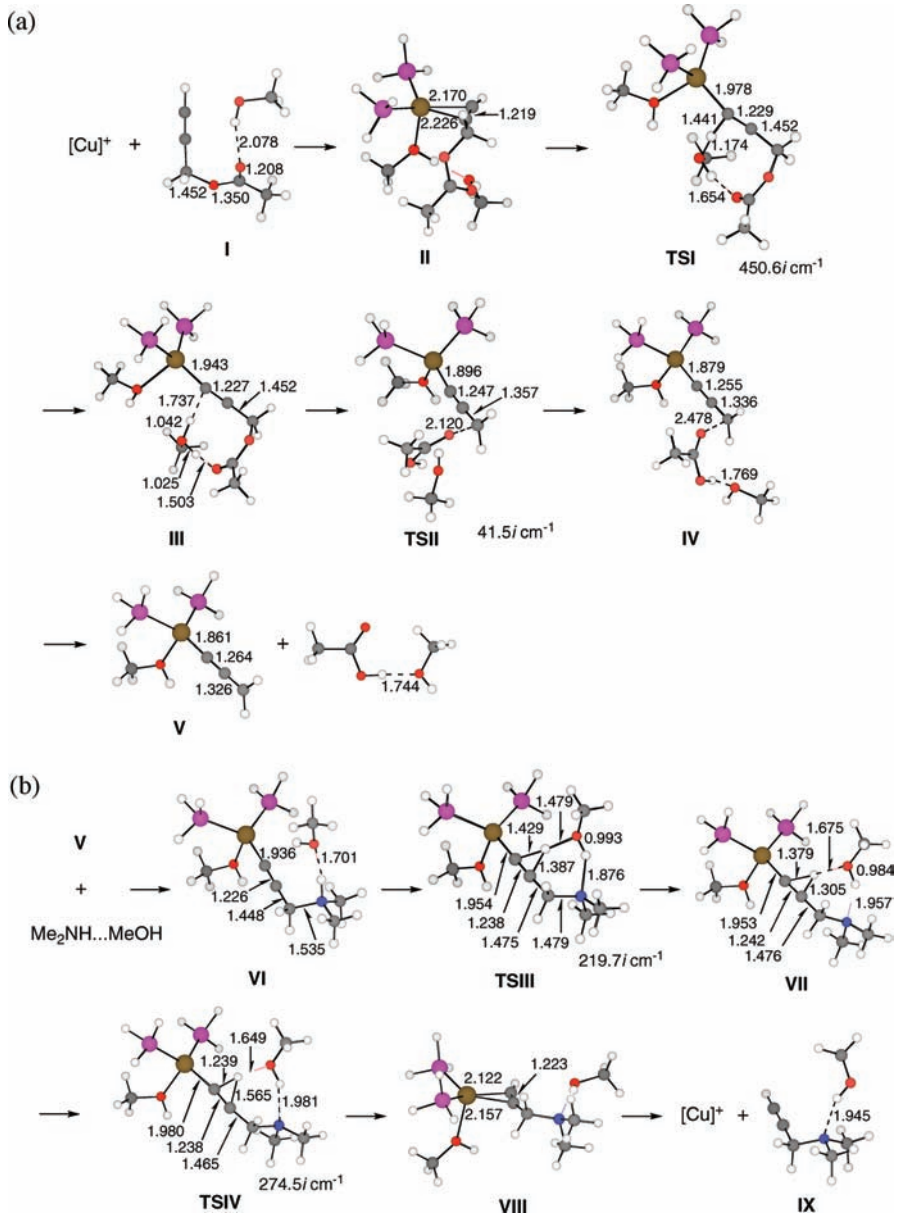


Figure 8. Optimized structures of stationary points for (a) the reaction between $[Cu(MeOH)(PH_3)_2]^+$ and propargyl acetate bearing methanol **I** and (b) the reaction between the copper−allenylidene complex **V** and *N*,*N*-dimethylamine bearing methanol. Bond lengths are in Å.

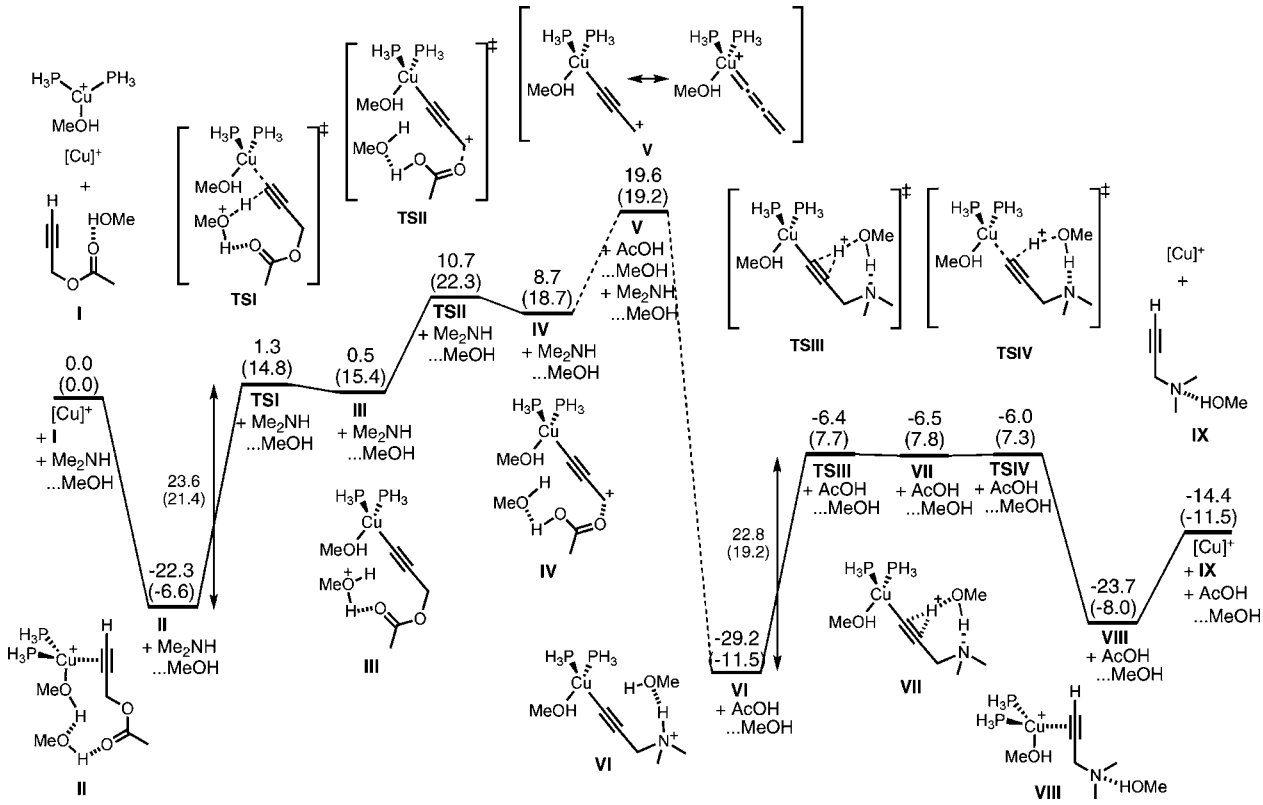
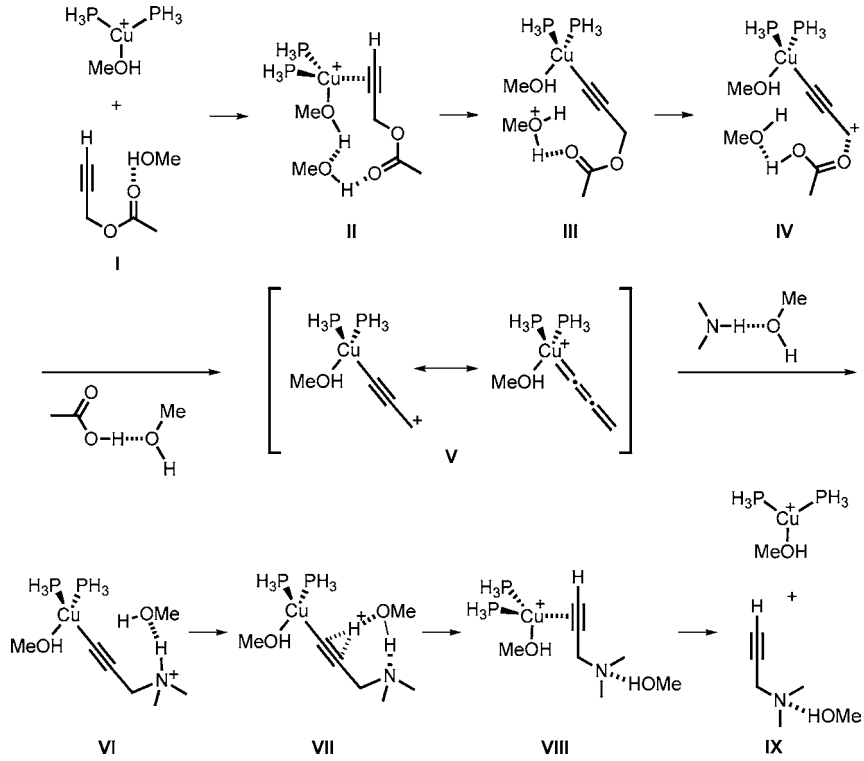


Figure 9. Relative energy diagram (kcal/mol) for the model reaction. Values in parentheses are relative Gibbs free energies at 298.15 K in the gas phase.

Scheme 10. Reaction Pathway for the Reaction via Copper−Allenylidene Complex Assisted by One Methanol Molecule (Path A)



The optimized structures and energy diagram for the reaction pathway are shown in Figures 8 and 9, respectively (Scheme 10). The complexation between the copper complex $[Cu]^+$ ($[Cu(PH_3)_2(MeOH)]^+$) and propargyl acetate with a methanol molecule (**I**) gives the π-alkyne complex **II** with a stabilization

(54) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

(55) Frisch, M. J.; et al. *Gaussian 03*, revision D.02; Gaussian, Inc.: Wallingford, CT, 2004.

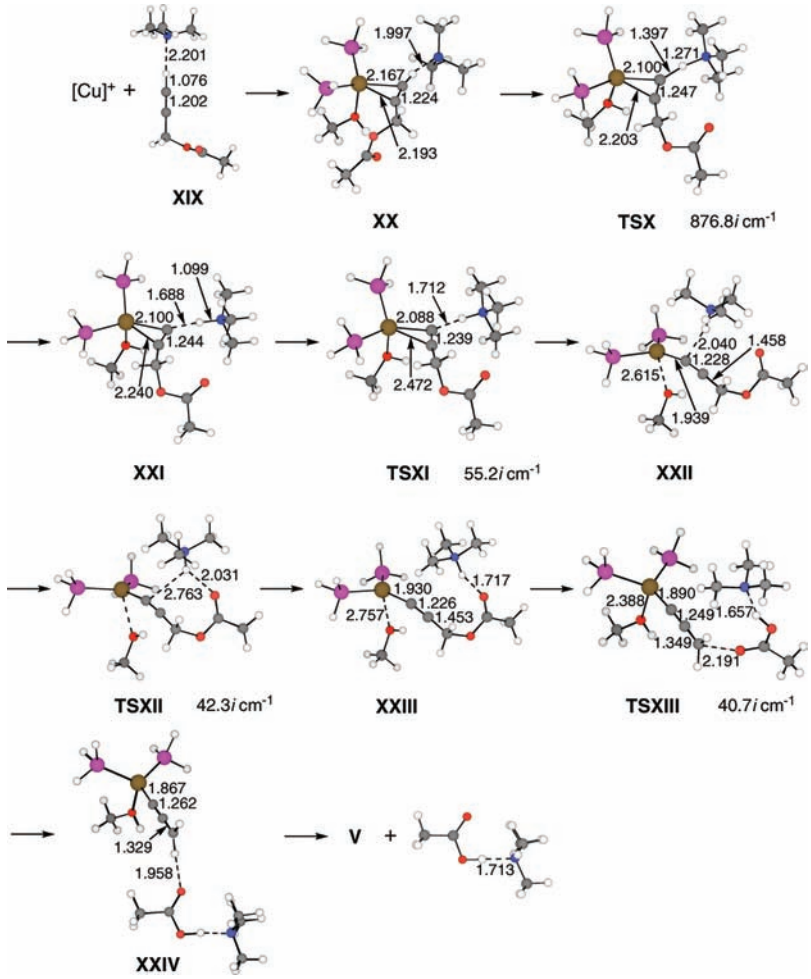


Figure 10. Optimized structures of stationary points for the reaction between $[Cu(MeOH)(PH_3)_2]^+$ and propargyl acetate bearing trimethylamine **XIX**. Bond lengths are in Å.

energy of 22.3 kcal/mol. The deprotonation of acetylenic hydrogen in the propargyl acetate with methanol molecule via **TSI** then gives the copper−acetylide complex **III**. In the complex **III**, the protonated methanol interacts with both the acetate group and the α-carbon. The reaction barrier of **TSI** from the complex **II** to **III** is +23.6 kcal/mol, and the relative energy ΔE of **TSI** is +1.3 kcal/mol. The dissociation of acetic acid from **III** gives the complex **IV** via **TSII**. The acetic acid in **IV** still interacts weakly with the γ-carbon. The energy required for the complete dissociation of **IV** into acetic acid and the copper−allenylidene complex **V** is 10.9 kcal/mol, and the ΔE of the state **V** is +19.6 kcal/mol. Nucleophilic attack of *N,N*-dimethylamine at the γ-carbon atom in **V** then gives the complex **VI** without a barrier height. This attack of dimethylamine provides the large stabilization energy (48.8 kcal/mol). In the following step, the activation barrier from **VI** to give the copper−acetylide complex **VII** via **TSIII** is 22.8 kcal/mol. Hydrogen transfer from an acidic proton on the methanol molecule to the α-carbon in the acetylide ligand via **TSIV** affords the π-alkyne complex **VIII**. Finally, the dissociation of propargyl amine (**IX**) from **VIII** occurs to give the starting copper complex $[Cu]^+$. The relative Gibbs free energy of the state ($[Cu]^+$ + **IX**) at 298 K is lower than that of **VIII** by 3.5 kcal/mol, so the dissociation into the product **IX** is considered to occur smoothly. The relative energy ΔE and the relative free energy ΔG of the product state ($[Cu]^+$ + **IX**) are −14.4 and −11.5 kcal/mol, respectively. Thus, the calculated reaction system as shown in Schemes 9 and 10 is exothermic as a whole.

As described in Figures 8 and 9, the catalytic reaction proceeds smoothly via the copper−allenylidene complex **V** as a key intermediate (Scheme 10, Path A). In this reaction pathway, one methanol molecule assists the formation of the copper−acetylide complexes **III** and **VII**, where the reaction barriers are 23.6 kcal/mol in **TSI** from **II** and 22.8 kcal/mol in **TSIII** from **VI**, respectively. Separately, we confirmed that the formation of the copper−acetylide complexes hardly occurred in the absence of one assisting methanol molecule,[58] indicating that the assistance of one methanol molecule is one of the most important factors to promote the propargylic amination. The result of the present theoretical study is consistent with the experimental result, because no propargylic amination occurred when dichloromethane was used as a solvent in place of methanol.

Another important factor to be considered is the role of base, $^i Pr_2NEt$ or triethylamine, in the present reaction system. We investigated further the reaction pathway between the copper complex $[Cu]^+$ and propargyl acetate with trimethylamine (**XIX**). The optimized structures and energy diagram for the reaction are shown in Figures 10 and 11, respectively (Scheme 11, Path C). From the reactant species, $[Cu]^+$ and **XIX**, the π-

(56) Dolg, M.; Wedig, U.; Stoll, H.; Preuss, H. *J. Chem. Phys.* **1987**, *86*, 866.
(57) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

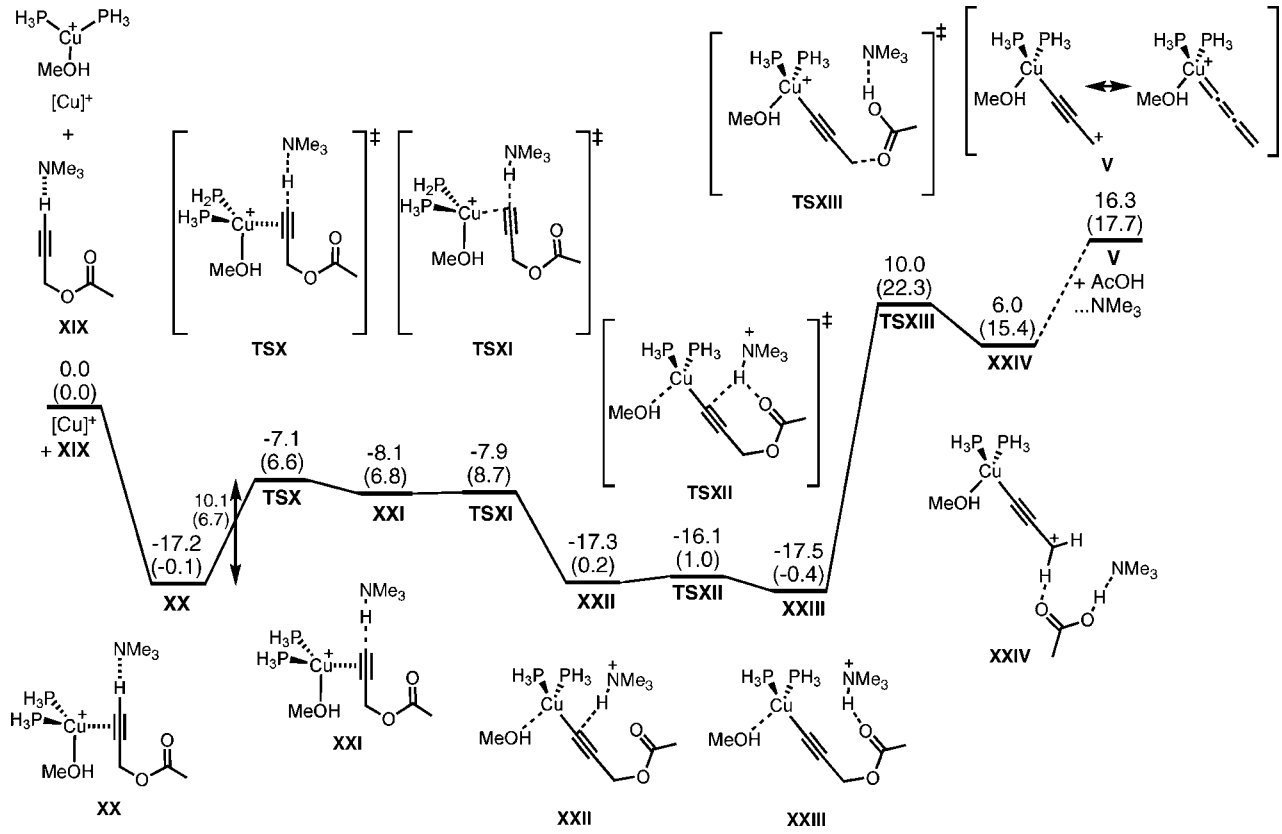
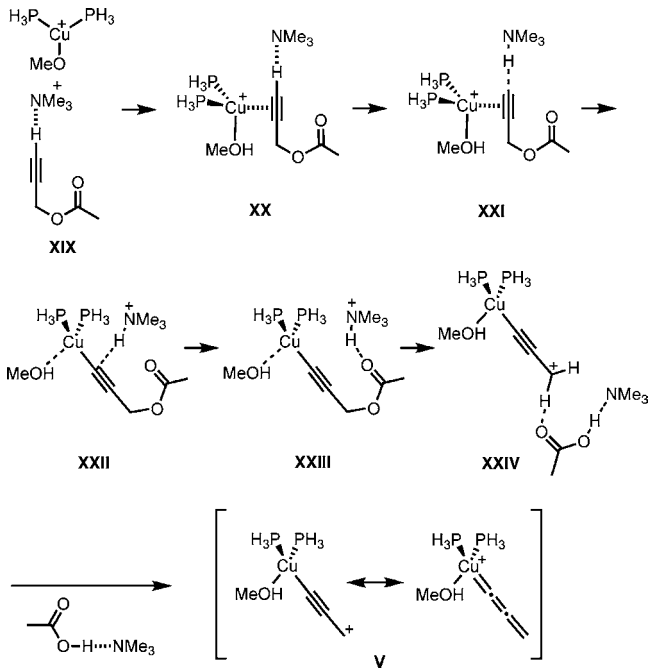


Figure 11. Relative energy diagram (kcal/mol) for the model reaction (Path C). Values in parentheses are relative Gibbs free energies at 298.15 K in the gas phase.

Scheme 11. Reaction Pathway for the Reaction Assisted by Trimethylamine (Path C)



alkyne complex **XX** is formed. The abstraction of the acetylenic hydrogen by trimethylamine gives the complex **XXI** via **TSX**, and then **XXI** is easily transformed into the copper−acetylide complex **XXII**, in which the protonated trimethylamine interacts weakly with the α-carbon, via **TSXI**. The protonated trimethylamine in **XXII** transfers from the α-carbon to the oxygen atom of acetyl group via **TSXII**. Bond dissociation between the α-carbon and the oxygen atom then occurs, together with hydrogen transfer from trimethylamine to an acetyl group, affording the complex **XXIV** via **TSXIII**. Finally, the complete dissociation of acetic acid with trimethylamine from **XXIV** gives the copper−allenylidene complex **V**.

In the Path C reaction pathway, trimethylamine instead of methanol in Path A assists the formation of the copper−acetylide complex. The reaction barrier in **TSX** from **XX** to **XXI** is 10.1 kcal/mol, which is smaller than that in **TSI** from **II** to **III** at Path A. Therefore, trimethylamine, which is more basic than methanol, makes the formation of the copper−acetylide complex easier. Furthermore, dissociation of acetic acid leads to the formation of the copper−allenylidene complex **V** in Path C, where the acetic acid is neutralized with trimethylamine. Thus, the relative energy of **V** in Path C (16.3 kcal/mol) is smaller than that in Path A (19.6 kcal/mol). These results are consistent with the experimental results and support the proposed reaction pathway shown in Scheme 8.

(58) (a) Separately, we carried out theoretical calculations of the propargylic amination in the absence of one methanol molecule. In this case, the propargylic amination is considered to proceed via copper−vinylidene complexes as key intermediates (Path B; see Supporting Information for experimental details). However, the energy barriers of the propargylic amination via copper−vinylidene complexes (Path B) are relatively higher than those via copper−acetylide complexes (Path A). Thus, Path A is more preferred than Path B. (b) Some copper-catalyzed transformations of terminal alkynes are considered to proceed via copper−vinylidene complexes as key intermediates. For example, see: Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

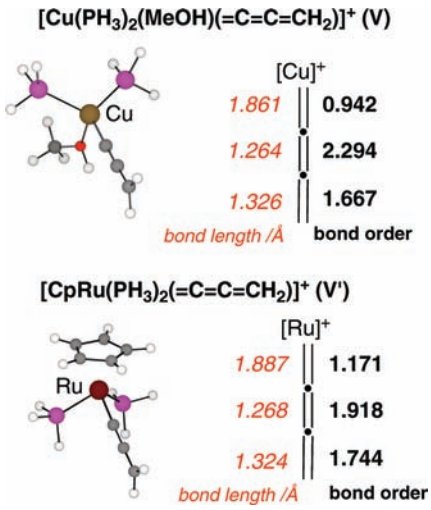
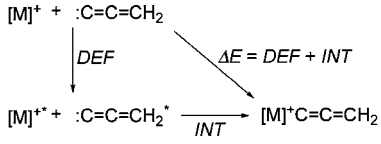


Figure 12. Optimized molecular structures of $[Cu(PH_3)_2(MeOH)(=C=C=CH_2)]^+$ (**V**) and $[CpRu(PH_3)_2(=C=C=CH_2)]^+$ (**V′**). Bond lengths (Å) are in italics, and bond orders are in bold.

Scheme 12. Fragment Analysis of the Copper−Allenylidene Complex (**V**) and Ruthenium−Allenylidene Complex (**V′**)



(kcal/mol)

$[M]^+$	*DEF*	*INT*	*ΔE*
$[Cu(PH_3)_2(MeOH)]^+$	+16.4	-55.3	-38.9
$[CpRu(PH_3)_2]^+$	+8.0 (+6.7)[a]	-91.4 (-88.4)[a]	-83.4 (-81.4)[a]

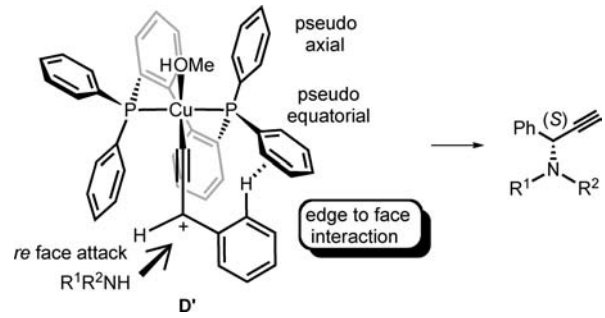
[a] B3LYP/631LAN level by Nakamura and co-workers.[8a]

As described in the proposed reaction pathway, the copper−allenylidene complex **V** is considered to be a key reactive intermediate. Next, we compared the molecular structure and reactivity of **V** with those of the ruthenium−allenylidene complex[8a] $[CpRu(PH_3)_2(=C=C=CH_2)]^+$ (**V′**; Cp = η^5-C_5H_5) because the chemistry of allenylidene complexes is dominated by a series of ruthenium−allenylidene complexes which are prepared by simple activation of propargylic alcohols.[9] As shown in Figure 12, the bond distance between the α- and β-carbons in **V** (1.264 Å) is slightly shorter than that in **V′** (1.268 Å), while the bond distance between the β- and γ-carbons in **V** (1.326 Å) is slightly longer than that in **V′** (1.324 Å). In response to these bond lengths, the Mayer bond order[59] between the α- and β-carbons in **V** (2.294) is larger than that in **V′** (1.918), while the bond order between the β- and γ-carbons in **V** (1.667) is smaller than that in **V′** (1.744). These results indicate that, in **V**, the weight of the copper−acetylide complex bearing a cationic γ-carbon (**E** in Scheme 8) is larger than that of its resonance structure, the copper−allenylidene complex (**D** in Scheme 8).

In order to examine the bond strength between the metal and the α-carbon, fragment analysis of **V** and **V′** was carried out (Scheme 12). The complexes were separated into two fragments, and the complexation energies between two fragments Δ*E* were divided into the deformation energy associated with the structural changes (DEF) and the interaction energy between two fragments (INT). As a result, the stabilization by the INT term in **V** is much smaller than that in **V′**, and the bond strength between the copper and the α-carbon in **V** is relatively weak. This result indicates that the copper−allenylidene complex **V** should be less stable than the ruthenium−allenylidene complex **V′**.

(59) Mayer, I. *Chem. Phys. Lett.* **1983**, *97*, 270.

Scheme 13. Model of the Transition State of the Copper−Allenylidene Complex Bearing (*R*)-BIPHEP



Origin of Enantioselectivity. As described in the previous section, we have not yet isolated any copper−allenylidene complexes, but we proposed a transition state consisting of copper−allenylidene complex bearing a chiral ligand BIPHEP to account for the high enantioselective formation of (*S*)-propargylic amine (**2a**) as shown in Scheme 13 and Figure 13. *N*-Methylaniline attacks the γ-carbon of the ligand in the copper−allenylidene complex **D′** from the *re* face,[21,60] where edge-to-face aromatic interaction between the two phenyl groups is considered to play an important role in achieving the high enantioselectivity.[61,62] Thus, the presence of a CH moiety at the *ortho*-position in the benzene ring of propargylic acetate is necessary to achieve the high enantioselectivity. In fact, no enantioselectivity was observed at all in the catalytic amination of propargylic acetate bearing a 2,6-dimethylphenyl moiety (**1o**) at the propargylic position, in sharp contrast to the high enantioselectivity in the catalytic amination of propargylic acetate bearing a 2-methylphenyl moiety (**1i**) (Table 4, runs 4 and 10). A similar edge-to-face aromatic interaction between a phenyl group of the substrate and a phenyl group of the ligand has been observed in the ruthenium-catalyzed transfer hydrogenation of carbonyl compounds reported by Noyori and co-workers.[63,64]

As described in the previous section, a good enantioselectivity was observed in the catalytic amination only when atropisomeric

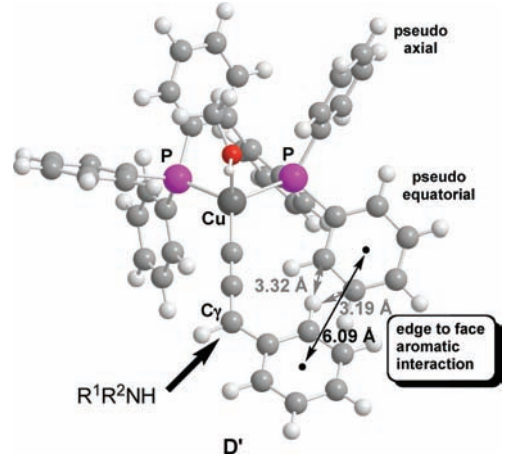


Figure 13. Model for the transition state of the copper−allenylidene complex bearing (*R*)-BIPHEP.

Table 11. Dihedral Angles of the Biaryl Backbone in the Optimized Structure of [Cu(diphosphine)]$^{+}$ [a]

diphosphines	dihedral angle in [Cu(diphosphine)]$^{+}$ (°)	ee of propargylic amine **2a** (%)[b]
Cl-MeO-BIPHEP	92.9	79
BINAP	92.3	78
MeO-BIPHEP	94.0	68
SEGPHOS	95.1	59
H_8-BINAP	97.0	18

[a] B3LYP-6-31G*(C, H, O, N, P, Cl)/LANL2DZ(Cu). [b] Detailed conditions are shown in Table 2.

Table 12. $^{31}P-^{77}Se$ Coupling Constants in Optically Active Diphosphine−Diselenides

diphosphine	$^{1}J_{P,Se}$ in diselenide (Hz)	ee of propargylic amine **2a** (%)[a]
Cl-MeO-BIPHEP	739	79
BINAP	738[b]	78
SYNPHOS	740[b]	75
MeO-BIPHEP	742[b]	68
SEGPHOS	738[b]	59

[a] Detailed conditions are shown in Table 2. [b] Reported constant.[36]

diphosphines were used as chiral ligands. Finally, we estimated the relationship between the ee value of the produced propargylic amine and the dihedral angle[36] of the biaryl backbone in the copper−diphosphine complex. Due to the lack of information about the copper−diphosphine complexes, the dihedral angles of the biaryl backbone in [Cu(diphosphine)]$^{+}$ were determined by geometry optimization using B3LYP hybrid density functional theory.[65] Typical results are shown in Table 11. The dihedral angles of SEGPHOS and H_8-BINAP are larger than those of Cl-MeO-BIPHEP and BINAP, indicating that use of a chiral diphosphine bearing a smaller dihedral angle of the biaryl backbone has a tendency to give a higher enantioselectivity in the propargylic amination.

On the other hand, we compared the σ-donor ability of Cl-MeO-BIPHEP with that of other diphosphines by measuring the magnitude of J_{P-Se} in the ^{77}Se isotopomer of the corresponding phosphine−selenide (Table 12).[36,66] The result shows that Cl-MeO-BIPHEP displays an equivalent σ-basicity with BINAP and SEGPHOS, although MeO-BIPHEP has a slightly lower σ-basicity. At present, we believe that only the steric property of Cl-MeO-BIPHEP may control the enantioselectivity in the propargylic amination.

Conclusion

We have found that copper-catalyzed enantioselective propargylic amination of propargylic acetates with a variety of secondary amines gives the corresponding propargylic amines in high yields with a high to excellent enantioselectivity. The high enantioselectivity in the catalytic substitution reaction has been realized by use of atropisomeric diphosphines such as Cl-MeO-BIPHEP and BINAP as chiral ligands.[67] The result of the density functional theory calculation on the model reaction supports that the catalytic amination proceeds via a copper−allenylidene complex, where the attack of amines to the γ-carbon atom of the allenylidene ligand is a key step, although the isolation of copper−allenylidene complexes has not been successful until now. The procedure described in the present article provides a versatile method for the preparation of optically active propargylic amines, which are synthetically versatile intermediates for the construction of various biologically active compounds and polyfunctional amino derivatives.[22]

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research for Young Scientists (S) (No. 19675002) and for Scientific Research on Priority Areas (No. 18066003) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. Some of the calculations were performed at Research Center for Computational Science, Okazaki, Japan. K.S. is grateful to the Research Center for Computational Science for generous permission to use its computing facilities. G.H. is a recipient of the JSPS Predoctoral Fellowships for Young Scientists and acknowledges the Global COE Program for Chemistry Innovation. Y.N. thanks the Asahi Glass Foundation.

Supporting Information Available: Experimental and computational details, characterization data, X-ray data, and complete ref 55 (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA1047494

(60) The X-ray analysis of a major enantioisomer of **2ae** indicates that the absolute configuration of **2ae** is *S*. The molecular structure of **2ae** was confirmed by X-ray analysis. See Supporting Information for experimental details.

(61) The result of the calculated model structure of the copper−allenylidene complex **D′** with the collinearity of the Cu−C(α)−C(β)−C(γ) bond and the dihedral angle (C(1)(phenyl)−C(γ)−Cu−O(methanol)) of −90° supports the edge-to-face interaction between the two phenyl groups, where one of the *ortho* C−H bonds of the phenyl group in the allenylidene ligand is tilting toward one of the phenyl groups at the phosphorous atom in BIPHEP. The phenyl ring centroid−centroid separation (6.09 Å) of these neighboring two phenyl groups is within the range of phenyl ring centroid separations observed for the existence of aromatic−aromatic interactions (3.4−6.5 Å). To obtain more exact information, we are investigating isolation of the copper−allenylidene complex.

(62) For the edge-to-face aromatic interaction, see: (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. (b) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995. (c) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210. (d) Nishio, M. *Tetrahedron* **2005**, *61*, 6923.

(63) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931.

(64) Quite recently, we found that edge-to-face aromatic interaction between two the phenyl groups in the ruthenium−allenylidene complex plays a critical role for the ruthenium-catalyzed enantioselective propargylic substitution reactions: Kanao, K.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2010**, *29*, 2381.

(65) Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. *J. Am. Chem. Soc.* **2009**, *131*, 14317.

(66) (a) Allen, D. W.; Taylor, B. F. *J. Chem. Soc., Dalton Trans.* **1982**, 51. (b) Socol, S. M.; Verkade, J. G. *Inorg. Chem.* **1984**, *23*, 3487. (c) Andersen, N. G.; Parvez, M.; Keay, B. A. *Org. Lett.* **2000**, *2*, 2817. (d) Suárez, A.; Mendez-Rojas, M. A.; Pizzano, A. *Organometallics* **2002**, *21*, 4611.

(67) During the preparation of this manuscript, the copper-catalyzed enantioselective propargylic alkylation of propargylic acetates with enamines was reported by using our reaction system, where Cl-MeO-BIPHEP and BINAP worked as good chiral ligands: Fang, P.; Hou, X.-L. *Org. Lett.* **2009**, *11*, 4612.