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Copper-Catalyzed Enantioselective Propargylic Amination of Nonaromatic Propargylic Esters with Amines

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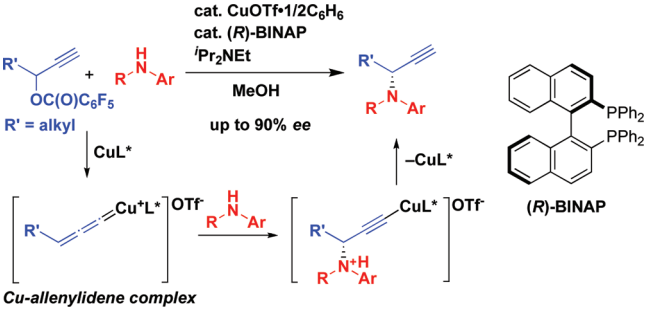
ABSTRACT



The enantioselective propargylic amination of propargylic pentafluorobenzoates bearing an alkyl group at the propargylic position with amines in the presence of catalytic amounts of a copper complex and an optically active diphosphine such as BINAP has been found to give the corresponding propargylic amines in good yields with high enantioselectivity.

Quite recently we have found copper-catalyzed enantioselective propargylic substitution reactions of propargylic acetates with amines to give the corresponding propargylic amines with up to 98% *ee*.[1,2] The result of the density functional theory calculation on a model reaction indicates that the propargylic amination proceeded via copper−allenylidene[3] complexes as key intermediates.[1,2] We believe that the methods developed by our group and Maarseveen's group[4] opened up a new field for transition-metal-catalyzed enantioselective propargylic substitution reactions.[5−7] However, unfortunately, only propargylic acetates bearing an aryl group at the propargylic position

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(2) 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; see: Fang, P.; Hou, X.-L. *Org. Lett.* **2009**, *11*, 4612.

(3) 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.

(4) (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).

(5) For recent reviews, see: (a) Nishibayashi, Y.; Uemura, S. *Curr. Org. Chem.* **2006**, *10*, 135. (b) Nishibayashi, Y.; Uemura, S. *Comprehensive Organometallic Chemistry III*, Vol. 11; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Amsterdam, 2007; 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. (g) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; Vincentiis, F. D.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647.

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(7) Motoyama, K.; Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Eur. J. Org. Chem.* **2011**, 2239.

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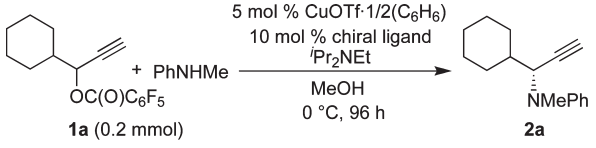
were available as substrates for copper-catalyzed enantioselective amination.

We have now envisaged that the introduction of other leaving groups, in place of the acetate group, into the propargylic ester may promote the propargylic amination of propargylic esters even bearing an alkyl group at the propargylic position. In fact, the propargylic amination of propargylic pentafluorobenzoates with amines proceeded in the presence of catalytic amounts of a copper complex and a chiral diphosphine such as BINAP to give the corresponding propargylic amines in good yields with high enantioselectivity. This is the first successful example of the enantioselective propargylic substitution reactions of propargylic alcohol derivatives bearing an alkyl group at the propargylic position with nucleophiles catalyzed by transition metal catalysts.[8,9] Preliminary results are described here.

Scheme 1

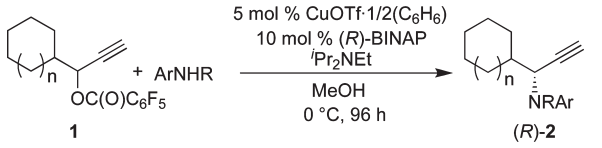


chiral ligand	yield (%)[a]	*ee* (%)
(*R*)-BINAP	50%	82% *ee* (*R*)
(*R*)-Cl-MeO-BIPHEP	51%	76% *ee* (*R*)
(*R*)-DTBM-MeO-BIPHEP	44%	26% *ee* (*R*)

[a] Isolated yield of **2a**.

Treatment of 1-cyclohexyl-2-propynyl pentafluorobenzoate (**1a**) with *N*-methylaniline (3 equiv) and *N*,*N*-diisopropylethylamine (1.2 equiv) in the presence of catalytic amounts of copper trifluoromethanesulfonate–benzene complex CuOTf·$^1/_2(C_6H_6)$ (5 mol %) and (*R*)-BINAP[10] (10 mol %) in methanol at 0 °C for 96 h gave *N*-(1-cyclohexyl-2-propynyl)-*N*-methylaniline (**2a**) in 50% yield with 82% *ee* (Scheme 1). No propargylic amination occurred at all when 1-cyclohexyl-2-propynyl acetate was used in place of **1a**. This result indicates that the nature of the ester group in propargylic esters plays a critical role in promoting the catalytic amination. This result is in sharp contrast to the previous result that only a lower enantioselectivity was observed when 1-phenyl 2-propynyl pentafluorobenzoate was used in place of 1-phenyl 2-propynyl acetate.[1a,b] The use of (*R*)-Cl-MeO-BIPHEP[11] as a chiral ligand slightly decreased the enantioselectivity of **2a** (76% *ee*). Other diphosphines such as (*R*)-DTBM-MeO-BIPHEP[12] as chiral ligands did not work as effective ligands toward the propargylic amination.

Table 1. Copper-Catalyzed Enantioselective Propargylic Amination of Propargylic Pentafluorobenzoates (**1**) with Anilines[a]



	1	aniline			
run	*n*	Ar	R	yield of **2** (%)[b]	ee of **2** (%)[c]
1	1 (**1a**)	Ph	Me	50 (**2a**)	82
2	1 (**1a**)	4-ClC_6H_4	Me	50 (**2b**)	83
3	1 (**1a**)	4-MeC_6H_4	Me	57 (**2c**)	81
4	1 (**1a**)	indoline		56 (**2d**)	77
5	1 (**1a**)	Ph	H	53 (**2e**)	54
6	2 (**1b**)	Ph	Me	47 (**2f**)	83
7	3 (**1c**)	Ph	Me	52 (**2g**)	78

[a] All reactions of **1** (0.20 mmol) with anilines (0.60 mmol) were carried out in the presence of CuOTf·1/2C_6H_6 (0.01 mmol), (*R*)-BINAP (0.02 mmol), and ^{i}Pr$_2$NEt (0.24 mmol) in MeOH (2 mL) at 0 °C. [b] Isolated yield of **2**. [c] Determined by HPLC (see the Supporting Information for experimental details).

Propargylic amination with various anilines proceeded smoothly to afford the corresponding propargylic amines with high enantioselectivity. Typical results are shown in Table 1. Reactions of **1a** with 4-chloro-*N*-methylaniline and *N*,4-dimethylaniline under the same reaction conditions gave the corresponding propargylic amines (**2b** and **2c**) with similarly high enantioselectivity (Table 1, runs 2 and 3). Interestingly, indoline was also available as aniline derivatives to give the *N*-propargylic indoline (**2d**) (Table 1, run 4). Unfortunately, only low enantioselectivity was observed when aniline was used in place of *N*-methylaniline (Table 1, run 5). On the other hand, propargylic amination of propargylic pentafluorobenzoates bearing a cyclic alkyl group such as cycloheptyl and cyclooctyl moieties at the propargylic position (**1b** and **1c**) with *N*-methylaniline under the same reaction conditions gave the corresponding propargylic amines (**2f** and **2g**) (Table 1, runs 6 and 7). These results indicate that a variety of propargylic pentafluorobenzoates bearing a cyclic alkyl moiety at the propargylic position are available as substrates toward the propargylic amination.

(8) (a) Prof. van Maarseveen and co-workers have already found the copper-catalyzed enantioselective propargylic amination of propargylic acetates bearing an alkyl group at the propargylic position by using pybox derivatives as a chiral ligands. However, the detailed result has been reported only in a Ph.D. thesis; see: Detz, R. J. Ph.D. thesis, University of Amsterdam (2009). (b) Prof. van Maarseveen and co-workers described a comment on the preliminary result in ref 5f.

(9) Prof. Fu and co-worker found the nickel-catalyzed cross-coupling reactions between propargylic halides and organozinc reagents, but we do not include this type of cross-coupling reactions as nucleophilic substitution reactions of propargylic alcohol derivatives; Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645.

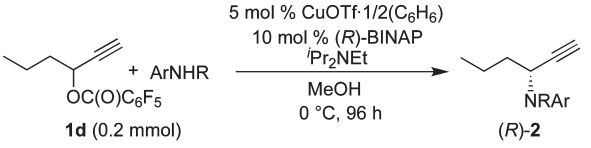
(10) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl: Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(11) (*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.

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

Next, we investigated the reaction of propargylic pentafluorobenzoates bearing an acyclic alkyl group at the propargylic position. The reaction of 1-hexyn-3-yl pentafluorobenzoate (**1d**) with *N*-methylaniline (3 equiv) under the same reaction conditions gave the *N*-(1-hexyn-3-yl)-*N*-methylaniline (**2h**) in 50% yield with 89% *ee* (Scheme 2). Similar results were observed when substituted *N*-methylanilines such as 4-chloro-*N*-methylaniline and *N*,4-dimethylaniline were used in place of *N*-methylaniline to give the corresponding propargylic amines with 90% and 86% *ee* (**2i** and **2j**), respectively. Indoline was also available as aniline derivatives to give the *N*-propargylic indoline with 82% *ee* (**2k**). It is noteworthy that the presence of a simple linear alkyl moiety at the propargylic position of propargylic pentafluorobenzoates affords the high enantioselectivity of the produced propargylic amines.

Scheme 2



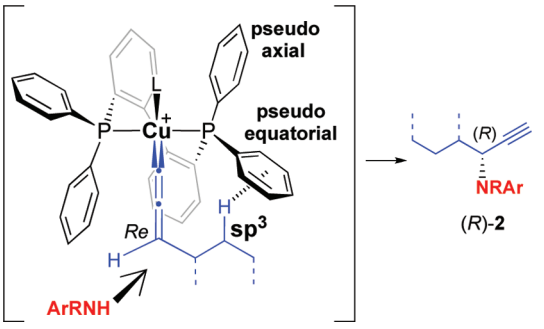
aniline	yield of **2** (%)[a]	*ee* of **2** (%)
N-methylaniline	50% (**2h**)	89% *ee* (*R*)
4-chloro-*N*-methylaniline	60% (**2i**)	90% *ee* (*R*)
N,4-dimethylaniline	40% (**2j**)	86% *ee* (*R*)
indoline	57% (**2k**)	82% *ee* (*R*)

[a] Isolated yield of **2**.

After one recrystallization of the protonated products of **2a** and **2h** with trifluoromethanesulfonic acid and HCl, respectively, enantiomerically pure ammonium salts **3a** and **3h** were obtained and their absolute configurations (*R*) were determined by X-ray analysis.[13] ORTEP drawings of (*R*)-**3a** and (*R*)-**3h** are shown in Figures S1 and S2, respectively.[13]

The information on the stereochemistry of the propargylic amines indicates that the asymmetric induction of the propargylic amination catalyzed by the copper complex was achieved in a similar way with that by the edge-to-face aromatic interaction between the two phenyl groups, which was proposed in the previous paper.[1a,b] Thus, an edge-to-face interaction[14−17] between a C−H bond of the substrate and a phenyl group at the pseudoequatorial position of BINAP is considered to play an important role in achieving high enantioselectivity (Scheme 3). In this reaction system, for the formation of major products (*R*)-**2**, anilines attack the *Re*-face of copper−allenylidene complexes leading to the carbon−nitrogen bond formation of (*R*)-**2** at the propargylic position.[18,19]

Scheme 3[a]



[a] For clarity, biphenyl group was used in place of binaphthyl moiety in BINAP.

It is well-known that optically active propargylic amines are synthetically versatile intermediates for the construction of various biologically active compounds and polyfunctional amino derivatives. In sharp contrast to the enantioselective preparation of propargylic amines bearing an aryl group at the propargylic position, the preparation of optically active propargylic amines bearing an alkyl group at the propargylic position is quite limited to only a few examples.[20] We believe that the procedure described in the present article provides a versatile method for the preparation of chiral propargylic amines bearing a simple cyclic or acyclic alkyl moiety at the propargylic position.

In summary, we have found the copper-catalyzed enantioselective propargylic amination of propargylic esters bearing an alkyl group at the propargylic position with aniline derivatives to give the corresponding propargylic amines in good yields with high enantioselectivity (up to 90% *ee*). The introduction of pentafluorobenzoate as an ester group results in the propargylic amination of propargylic esters even bearing an alkyl group at the propargylic position. We believe that the method described in this paper may provide a novel synthetic approach to the preparation of optically active propargylic amines bearing an alkyl moiety at the propargylic position. Further work is currently in progress to apply this strategy to other reaction systems and to clarify the scope and limitations of the present propargylic amination.

(13) See Supporting Information for experimental details.

(14) 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.

(15) For a recent review, see: Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.

(16) Ribas, J.; Cubero, E.; Luque, F. J.; Orozco, M. *J. Org. Chem.* **2002**, *67*, 7057.

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

(18) Separately, we confirmed that no effective kinetic resolution occurred effectively under these reaction conditions. In fact, the catalytic reaction of **1a** with *N*-methylaniline was carried out only for 24 h; **1a** was recovered in 16% recovery with 32% *ee* together with **2a** in 31% yield with 84% *ee*.

(19) The reaction of 1-cyclohexyl-3-phenyl-1-propynyl pentafluorobenzoate with *N*-methylaniline under the same reaction conditions gave the corresponding propargylic alcohol in 92% NMR yield. This result indicates that only the use of propargylic esters bearing a terminal alkyne moiety were available as substrates.

(20) Gommermann, N.; Knochel, P. *Tetrahedron* **2005**, *61*, 11418.

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Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.