Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 379–382

Enantioselective alkynylation to aldimines catalyzed by chiral 2,2′-di(2-aminoaryloxy)-1,1′-binaphthyl-copper(I) complexes

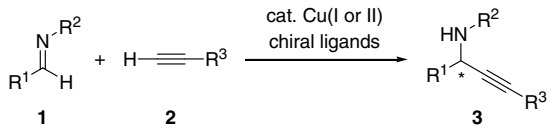
Manabu Hatano, Takafumi Asai and Kazuaki Ishihara*

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-6603, Japan

Received 19 September 2007; revised 25 October 2007; accepted 6 November 2007
Available online 26 November 2007

Abstract—The enantioselective alkynylation of aldimines with terminal acetylenes catalyzed by chiral Cu(I) complexes with (*R*)-2,2′-di(2-aminoaryloxy)-1,1′-binaphthyl ligands (**7**) was examined. Chiral C_2-symmetric N,N-ligands **7**, which have primary aniline moieties, were readily prepared from inexpensive (*R*)-1,1′-binaphthol (BINOL) as a chiral source. In particular, the reaction of *N*-benzylidenebenzeneamine **1a** with phenylacetylene **2a** proceeded smoothly in the presence of 5 mol % of $(CuOTf)_2{\cdot}C_6H_5CH_3$ and 10 mol % of (*R*)-**7d** at room temperature for 24 h, and the corresponding propargylamine **3a** was obtained with up to 82% ee.

Catalytic enantioselective addition to C=N bonds provides a versatile method for synthesizing chiral nitrogen-containing scaffolds in biologically active compounds and natural products.[1] In particular, propargylamines (**3**) are some of the most important nitrogen-containing compounds,[2] and can be obtained by the alkynylation of aldimines (**1**) with terminal acetylenes (**2**) via C–H bond activation and C–C bond formation (Scheme 1).[3,4] To date, a variety of chiral Cu(I or II) complexes have been developed in these catalyses, and chiral P,N-ligands such as QUINAP[5] and PINAP[6] and chiral N,O-ligands such as amino acids[7] and amino alcohols[8] have been found to be effective. Chiral N,N-ligands or N,N,N-ligands such as binaphthyldiimines[9] and PYBOXes[10] have also been established. Although chiral aniline derivatives as C_2-symmetric N,N-ligands are promising ligands for activating Cu(I or II) in general,[11] examples have been limited to the pioneering work by Benaglia et al.[12] who used chiral binaphthyldiamine. We report here the Cu(I)-catalyzed enantioselective alkynylation of aldimines with terminal acetylenes by using chiral 2,2′-di(2-aminoaryloxy)-1,1′-binaphthyl ligands (**7**), particularly with primary aniline moieties, which are readily prepared from inexpensive 1,1′-binaphthol (BINOL) as a chiral source.



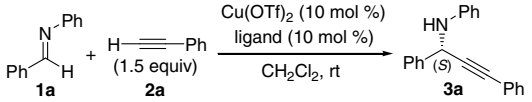
Scheme 1. Cu(I or II)-catalyzed enantioselective alkynylations of aldimines with terminal alkynes.

In our preliminary study, we first examined the catalytic enantioselective alkynylation of *N*-benzylidenebenzeneamine (**1a**) with phenylacetylene (**2a**) (1.5 equiv) in the presence of 10 mol % each of $Cu(OTf)_2$ and the commercially available chiral primary N,N-ligands (**4**, **5**, and **6a**) in CH_2Cl_2 at room temperature (Table 1). (*R*,*R*)-1,2-Diphenylethanediamine (**4**) and (*R*,*R*)-1,2-cyclohexanediamine (**5**) gave the corresponding product (**3a**) in low yield in an almost racemic manner (entries 1 and 2). In sharp contrast to **4** and **5**, binaphthyldiamine (**6a**) showed a significant improvement in both yield and enantioselectivity as reported by Benaglia et al.[9,12] using CuOTf (entry 3). Binaphthyldiamine-derivatives with no *N*-substitutions (**6b** and **6c**) also promoted the reactions, although the enantioselectivities were moderate (36–48% ee) (entries 4 and 5). However, *N*,*N*′-disubstituted binaphthyldiamine derivatives such as **6d** and **6e** did not work well even though they had the same axially chiral binaphthyl backbone as **6a**. Therefore, in this catalysis, primary aniline derivatives ($ArNH_2$) should work effectively as chiral N,N-ligands, compared to other more basic primary alkylamines (RNH_2) or less basic secondary anilines ($ArNHR'$) and acidic sulfonamides ($ArNHSO_2R'$).[13]

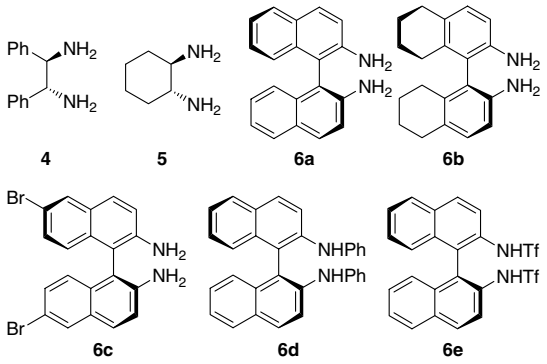
* Corresponding author. Tel.: +81 52 789 3331; fax: +81 52 789 3222; e-mail: ishihara@cc.nagoya-u.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.032

Table 1. Enantioselective phenylacetynylation to **1a** catalyzed by chiral primary diamine-Cu(II) complexes

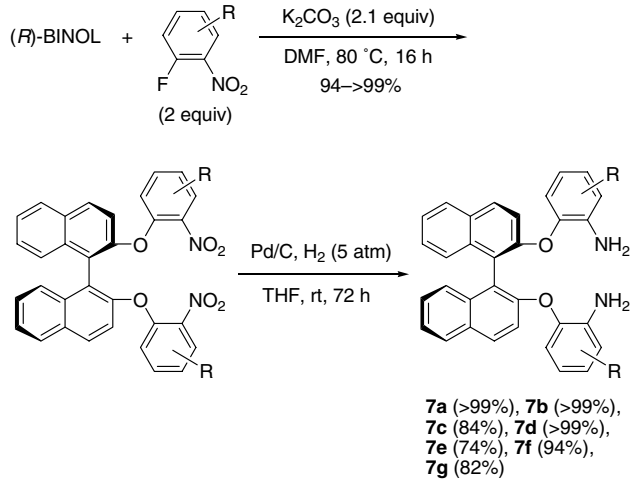


Entry	Ligand	Time (h)	Yield (%)	ee (%)
1	**4**	24	26	5
2	**5**	24	12	0
3	**6a**	24	99	61
4	**6b**	24	31	36
5	**6c**	7	100	48
6	**6d**	48	24	0
7	**6e**	48	5	3



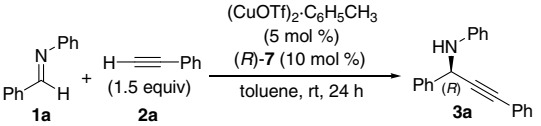
Based on our preliminary hypothesis, we prepared chiral primary aniline **7** with a binaphthyl backbone as C_2-symmetric chiral N,N-ligands according to the reported procedure (Scheme 2 and Table 2).[14] From commercially available (*R*)-BINOL or (*R*)-H_8-BINOL, **7a**–**g** were readily obtained in 74–>99% yields in two steps.

To our delight, the catalytic enantioselective alkynylation of **1a** with **2a** (1.5 equiv) in the presence of 5 mol % of $(CuOTf)_2{\cdot}C_6H_5CH_3$ and 10 mol % of **7a** in toluene at room temperature for 24 h gave **3a** in 72% yield with 73% ee (Table 2, entry 1). Compound **7b** with an (*R*)-H_8-binaphthyl backbone was also effective, and **3a** was obtained with 75% ee (entry 2). The effects of

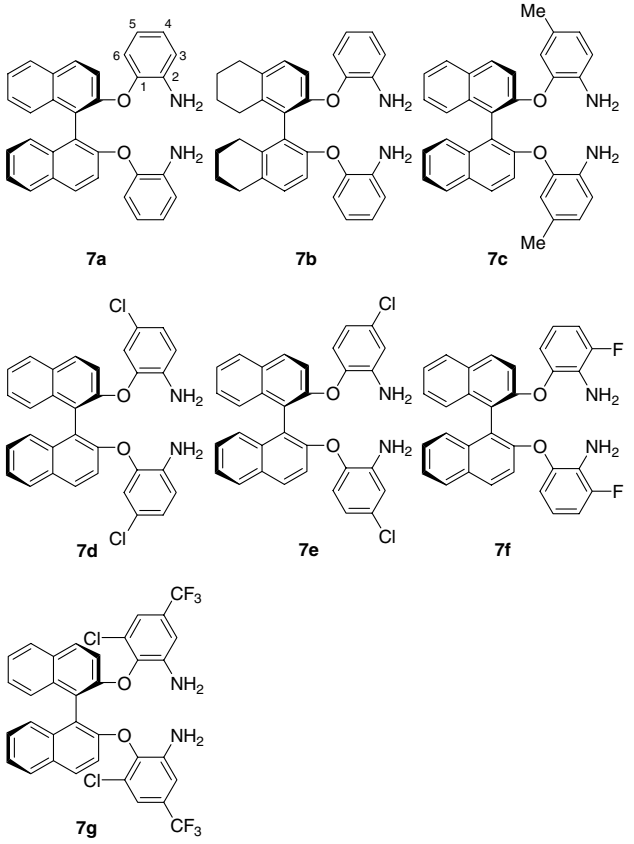


Scheme 2. Preparation of chiral 2,2′-di(2-aminoaryloxy)-1,1′-binaphthyl ligand (**7**) with primary aniline moieties.

Table 2. Enantioselective phenylacetynylation to **1a** catalyzed by (*R*)-**7**·Cu(I) complexes



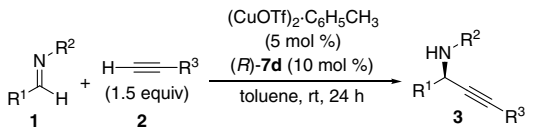
Entry	Ligand	Yield (%)	ee (%)
1	**7a**	72	73
2	**7b**	89	75
3	**7c**	75	71
4	**7d**	73	82
5	**7e**	12	37
6	**7f**	34	9
7	**7g**	12	12



substitution in the aniline moiety were examined. We found that substitution at the 5-position with an electron-withdrawing group such as Cl in **7d** was better than an electron-donating group such as Me in **7c**, and we finally obtained **3a** in 73% yield with up to 82% ee (entry 4).[15] Other substitutions with electron-withdrawing groups at the 3-, 4-, or 6-position as in **7e**–**g** did not work well (entries 5–7).

With the optimized conditions with $(CuOTf)_2{\cdot}C_6H_5CH_3$ and **7d**, we next examined the generality of the alkynylation to aldimines (**1**) (Table 3). Other terminal acetylenes such as 1-bromo-4-ethynylbenzene (**2b**) and trimethylsilylacetylene (**2c**) had low reactivities (0–16% yield), although **3b** was obtained with 71% ee (entries 2 and 3). Next, other aldimines (**1b**–**e**) with substitutions at the *p*-position of R^1 and/or R^2 moieties in **1a** were

Table 3. Enantioselective acetynylation to aldimines **1** catalyzed by (*R*)-**7d**·Cu(I)



Entry	**1** (R^1, R^2)	**2** (R^3)	**3**	Yield (%)	ee (%)
1	**1a** (Ph, Ph)	**2a** (Ph)	**3a**	73	82 (*R*)
2	**1a** (Ph, Ph)	**2b** (*p*-BrC_6H_4)	**3b**	16	71
3	**1a** (Ph, Ph)	**2c** (TMS)	**3c**	0	—
4	**1b** (Ph, *p*-FC_6H_4)	**2a** (Ph)	**3d**	28	48
5	**1c** (Ph, *p*-MeC_6H_4)	**2a** (Ph)	**3e**	27 [58][a]	75 [78][a]
6	**1d** (*p*-$MeOC_6H_4$, *p*-$ClOC_6H_4$)	**2a** (Ph)	**3f**	11	50
7	**1e** (*p*-ClC_6H_4, *p*-$MeOC_6H_4$)	**2a** (Ph)	**3g**	19 [57][a]	74 (*R*) [71][a]
8	**1f** (2-Naph, Ph)	**2a** (Ph)	**3h**	48	74
9	**1g** (2-Furyl, Ph)	**2a** (Ph)	**3i**	56	33
10	**1h** (Ph, Boc)	**2a** (Ph)	**3j**	16	29

[a] Reactions were examined in the presence of $(CuOTf)_2{\cdot}C_6H_5CH_3$ (10 mol %) and (*R*)-**7d** (20 mol %) for 48 h.

examined. The enantioselectivities were decreased to 48–50% ee when aldimines **1b** and **1d** with *N*-R^2 bearing an electron-withdrawing group were used (entries 4 and 6). However, good enantioselectivities (74–75% ee) were observed for **1c** and **1e** when an electron-donating group was introduced to *N*-R^2 (entries 5 and 7). Compound **1f**, which was derived from 2-naphthaldehyde, also gave the corresponding adduct **3h** in moderate yield with good enantioselectivity (74% ee) (entry 8), while **1g**, which was derived from 2-furaldehyde, gave the corresponding adduct **3i** with 33% ee (entry 9). *N*-Boc aldimine **1h** gave adduct **3j** in 16% yield with 29% ee. Running the reaction for longer times (48 h) with a higher catalyst loading (20 mol %) improved the yield and the enantioselectivities (see the brackets in Table 3). Products **3e** and **3g** were obtained in 58% yield with 78% ee and 57% yield with 71% ee, respectively (entries 5 and 7).

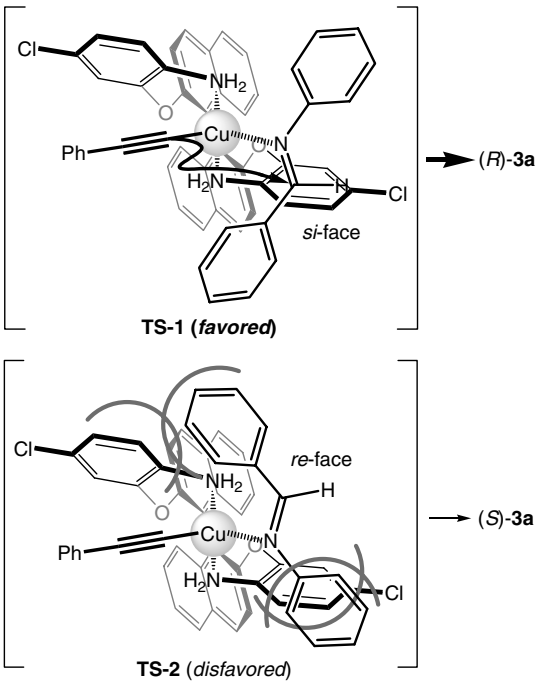


Figure 1. Proposed transition states.

Finally, we considered mechanistic aspects including transition states in the reaction between **1a** and **2a** with a (*R*)-**7d**·Cu(I) complex as a working model. In the transition states, four-coordinated Cu(I) intermediates are postulated, and *si*-face attack (**TS-1**) should be favored to avoid steric repulsion between aldimine **1a** and the aniline moieties of **7d** (**TS-2**) (Fig. 1). Probably, 5-Cl in **7d** would partially have a steric and/or electronic effect to control the aniline and naphthyl rings in a face-to-edge relationship.[16] Moreover, we cannot completely deny the possibility that 5-Cl *para* to the NH_2 group effectively enhanced the Lewis acidity of the Cu(I) center, and thus other possible transition states that could provide the corresponding propargylamine **3a** with low enantioselectivities are effectively prevented. Eventually, (*R*)-**3a**[10e] could be obtained with release from the catalyst, and coordinatively unsaturated active Cu(I) intermediates towards the C–H activation of **2a** would be regenerated.

In summary, the Cu(I)-catalyzed enantioselective alkynylations of aldimines with terminal acetylenes were achieved by using chiral 2,2′-di(2-aminoaryloxy)-1,1′-binaphthyl ligands **7**. The chiral N,N-ligands **7**, which have primary aniline moieties, were readily prepared from inexpensive BINOL as a chiral source. In particular, the reaction of aldimine **1a** with phenylacetylene **2a** proceeded smoothly in the presence of 10 mol % each of Cu(I) precursor and (*R*)-**7d** at room temperature for 24 h, and the corresponding propargylamine **3a** was obtained with up to 82% ee in 73% yield. Further studies towards other catalytic enantioselective reactions including the process of C–H bond activation/C–C bond formation are in progress.

Acknowledgments

Financial support for this project was provided by Grant-in-Aid for Young Scientists B (19750072) of MEXT, Toray Science Foundation, and Toyoaki Scholarship Foundation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.032.

References and notes

1. For reviews: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388; (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407; (c) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541; (d) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873.
2. (a) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715; (b) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590; (c) Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L., Jr.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119.
3. For reviews: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879; (b) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472; (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095; (d) Zhu, H. J.; Jiang, J. X.; Ren, J.; Yan, Y. M.; Pittman, C. U., Jr. *Curr. Org. Synth.* **2005**, *2*, 547; (e) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127.
4. Recent progress of Cu(I or II) catalyzed alkynylation with C–H bond activation/C–C bond formation: (a) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682; (b) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964; (c) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997; (d) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901.
5. (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535; (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763; (c) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324; (d) Gommermann, N.; Gehrig, A.; Knochel, P. *Synlett* **2005**, 2796; (e) Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175; (f) Gommermann, N.; Knochel, P. *Chem. Eur. J.* **2006**, *12*, 4380.
6. Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.
7. Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273.
8. Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216.
9. (a) Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* **2004**, *45*, 8705; (b) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064.
10. (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638; (b) Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749; (c) Rosa, J. N.; Santos, A. G.; Afonso, C. A. M. *J. Mol. Catal. A: Chem.* **2004**, *214*, 161; (d) Ji, J.-X.; Wu, J.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11196; (e) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405.
11. Enantioselective conjugate addition of dialkylzinc to cyclic enones catalyzed by chiral binaphthyldiamine-copper(I) complexes Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2007**, *48*, 8590.
12. Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005**, 1689.
13. (a) Bordwell, F. G.; Algrim, D.; Vanier, N. R. *J. Org. Chem.* **1977**, *42*, 1817; (b) Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964.
14. Grill, J. M.; Reibenspies, J. H.; Miller, S. A. *J. Organometal. Chem.* **2005**, *690*, 3009.
15. *Representative reaction procedure* (Table 2, entry 4): $(CuOTf)_2{\cdot}C_6H_5CH_3$ (25.8 mg, 0.05 mmol) and (*R*)-2,2′-di(2-amino-5-chlorophenoxy)-1,1′-binaphthyl (**7d**) (53.7 mg, 0.10 mmol) were mixed in a pyrex Schlenk tube at room temperature under nitrogen atmosphere. To the mixture was added freshly distilled and well-degassed toluene (10 mL), and this solution was stirred for 30 min at that temperature. Then, phenylacetylene (**2a**) (153.2 mg, 1.5 mmol) and *N*-benzylidenebenzeneamine (**1a**) (181.2 mg, 1.0 mmol) were added, and the mixture was stirred at room temperature for 24 h. The resulting mixture was then filtered through a pad of Celite and purified by neutral silica gel column chromatography (eluent: hexane/EtOAc), to give the desired propargylamine (**3a**) in 73% yield (206.9 mg). The enantiomeric purity was determined by HPLC on chiral column (OD-H) (82% ee, *R*).
16. (a) Pirkle, W. H.; Welch, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 777; (b) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.