Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2901–2904

Chiral Cu(II) complex catalyzed enantioselective addition of phenylacetylene to *N*-aryl arylimines

Bao Liu,[a] Ling Huang,[a] Juntao Liu,[a] Yao Zhong,[a] Xingshu Li[a,*] and Albert S. C. Chan[a,b,*]

[a]*School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou 510006, China*
[b]*Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China*

Received 14 October 2007; accepted 27 November 2007

Abstract—Chiral tridentate *N*-tosylated aminoimine ligands were used in the Cu(II)-catalyzed enantioselective addition of phenylacetylene to *N*-aryl arylimines, affording products up to 92% ee.

1. Introduction

The catalytic enantioselective addition of alkynyl reagents to imines or imine derivatives is an important and challenging field in organic synthesis. Due to the strong coordination of the amine products to the metal center, which deactivates the catalyst, stoichiometric amounts of catalyst are frequently used in such reactions. In recent years, some effective methods have been developed for the metal-catalyzed addition of acetylenes to imines or their derivatives.[1] For example, Li et al.[2] reported the use of a mixed Ru/Cu catalyst system for the addition of terminal acetylenes to imines. Knochel et al. employed Cu(I) or Cu(II) bromide as a catalyst for the addition of terminal alkynes to enamines, which were derived from enolisable aldehydes.[3] Black et al. reported the alkynylation of acyliminium ions with a catalytic amount of copper(I) iodide as the promoter. Under the optimized conditions, 10 mol % of CuI was enough to obtain *N*-acyl-propargylamines with satisfactory yields (76–99%).[4] Yadav et al. studied the alkyne addition reaction of acyliminium ions, which were prepared from aromatic heterocycles, such as pyridines and quinolines, with a catalyst system containing CuI and Hünig's base.[5]

The asymmetric metal-catalyzed addition of alkynyl reagents to the C=N bonds of imines has also been developed in the past few years. Several chiral catalysts, such as Cu(I)–pyridyl-bisoxazoline,[6] Zr–amino acid derivatives,[7] Cu(I)–Quinap,[8] Cu(I)–Pinap,[9] copper(I)–bisimine[10] and norephedrine derivatives[11] have been used for the synthesis of propargylamines with good to excellent enantioselectivity. In our study of the asymmetric alkynylation of imines and their derivatives, we have developed the synthesis of β,γ-alkynyl-α-amino acid derivatives[12] and a recyclable copper(I)–bis(oxazoline) catalyst system for the enantioselective addition of alkyne to imines in water with stearic acid as an additive.[13] Recently, we have devised a new class of chiral tridentate *N*-tosylated aminoimine ligands, which were effective in the preparation of propargylamines with good enantioselectivities and yields.[14]

However, the Cu(II)-catalyzed asymmetric addition of alkynyl reagents to carbonyl compounds and imine derivatives has remained less studied. We have reported a highly enantioselective catalytic addition of alkynylzinc reagents to aromatic ketones catalyzed by chiral Cu(II)–camphorsulfonamide ligands with good yields and excellent ee values.[15] Wang et al described a bis(hydroxycamphorsulfonamide)–Cu(II) complex[16] for the same reaction. Recently, O'Learya et al reported their study of electrostatic immobilization of copper(I) and copper(II) bis(oxazolinyl)pyridine catalysts on silica: application in the synthesis of propargylamines via direct addition of terminal alkynes to imines.[17] In contrast to Cu(I) complexes, Cu(II) complexes are not sensitive to air or moisture and are commercially available at low cost. From a practical standpoint, it is highly desirable to develop methods for the Cu(II)-catalyzed asymmetric addition of alkynyl

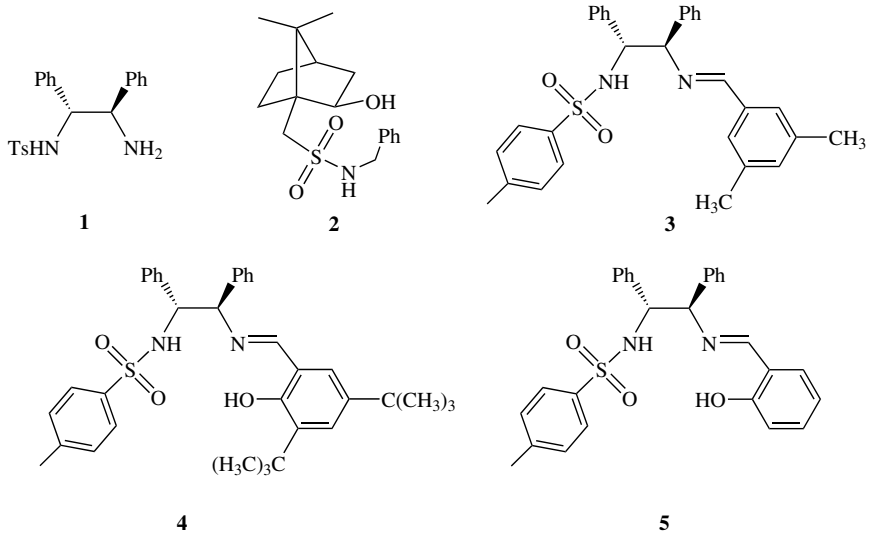
* Corresponding authors. Tel.: +86 2035693517 (X.L.); e-mail addresses: xsli219@yahoo.com; bcachan@polyu.edu.hk

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.11.033

reagents to imines or imine derivatives with good stereocontrol, so that the related chemical application can be easily amplified on a larger scale. Herein we report the utilization of chiral *N*-tosylated amine–imine ligands in Cu(II)-catalyzed enantioselective addition of alkynes to imines. The catalyst system is easy to prepare and handle, which can be conveniently applied to asymmetric synthesis.

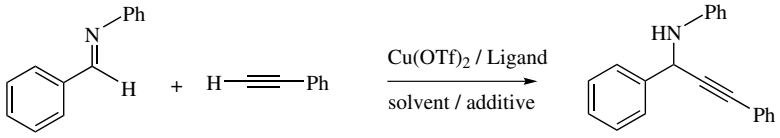
2. Results and discussion

Chiral *N*-tosylated aminoimine **4** (Scheme 1) was proven to be effective in the Cu(I)-catalyzed enantioselective additions of alkynes to imines in our previous study.[14] In a preliminary screen study to develop a chiral Cu(II) catalyst, we first chose ligand **4** as the chiral ligand. When *N*-benzylideneaniline was used as the model substrate and toluene as the



Scheme 1. Chiral ligands.

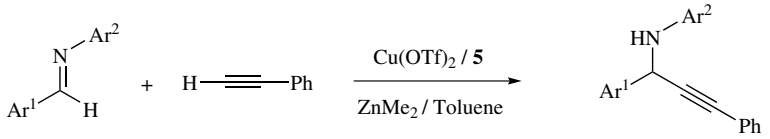
Table 1. Enantioselective addition of phenyl acetylene to *N*-benzylindeneaniline under various reaction conditions[a]



Entry	Ligands	Solvents	Metal	Additives	Yield[b] (%)	ee[c] (%)
1	4	Toluene	Cu(II)	—	65	63
2	5	Toluene	Cu(II)	—	51	73
3	1	Toluene	Cu(II)	—	70	0
4	2	Toluene	Cu(II)	—	56	2
5	3	Toluene	Cu(II)	—	36	11
6	5	THF	Cu(II)	—	43	47
7	5	CH_2Cl_2	Cu(II)	—	55	12
8	5	Et_2O	Cu(II)	—	51	4
9	5	Hex	Cu(II)	—	65	52
10[e]	5	Toluene	Cu(II)	—	18	58
11	5	Toluene	Cu(II)	$(CH_3)_3CONa$	82	63
12	**5**	**Toluene**	**Cu(II)**	**$Zn(Me)_2$**	**83**	**75**
13	5	Toluene	Cu(II)	CH_3OK	43	55
14	5	Toluene	Cu(II)	*n*-BuLi	61	47
15[d]	5	Toluene	Cu(II)	—	45	58
16	4	Toluene	Cu(I)	—	51	65
17	5	Toluene	Cu(I)	—	65	55

[a] All reactions were carried out with 20 mol % Cu $(OTf)_2$ and the same amount of ligands at room temperature for 24 h.
[b] Isolated yields after purification by flash column chromatography.
[c] Enantiomeric excess was determined by HPLC with a Chiralcel OD column.
[d] 10 mol % of catalyst was used.
[e] The reaction was carried out at 0 °C.

Table 2. Enantioselective addition of phenylacetylene to *N*-aryl arylimines using ligand **5** in the presence of $ZnMe_2$



Entry	Ar^1	Ar^2	Yield[a] (%)	ee[b] (%)
1	Ph	Ph	83	75
2	4-$MeOC_6H_4$	Ph	67	78
3	4-ClC_6H_4	Ph	89	77
4	4-$NO_2C_6H_4$	Ph	56	73
5	2-$MeOC_6H_4$	Ph	51	73
6	2-ClC_6H_4	Ph	80	81
7	Ph	4-MeC_6H_4	77	81
8	Ph	4-$MeOC_6H_4$	60	85
9	2-$MeOC_6H_4$	4-$MeOC_6H_4$	42	83
10	4-MeC_6H_4	4-MeC_6H_4	70	92
11	4-$MeOC_6H_4$	4-$MeOC_6H_4$	63	87

[a] Isolated yields after purification by flash column chromatography.
[b] Enantiomeric excesses were determined by HPLC with a Chiralcel OD column.

solvent, 65% yield and 63% ee were obtained (Table 1, entry 1), compared with the Cu(I) complex with the same chiral ligand (Table 1, entry 16: 51% yield with 65% ee). This result indicated that the oxidation state of the metal did not have much effect on the enantioselectivity of the reaction with **4** as the chiral ligand. In contrast, the utilization of *N*-tosylated aminoimine ligand **5** gave relatively poorer enantioselectivity (Table 1, entry 17: 65% yield with 55% ee) in Cu(I)-catalyzed enantioselective addition of phenylacetylene to *N*-benzylideneaniline, while better results (Table 1, entry 2: 51% yield and 73% ee) were obtained with the use of Cu(II)-catalyzed system under the same reaction conditions. Other bidentate ligands, such as TsDPEN **1**, camphorsulfonamide **2** and *N*-tosylated aminoimine ligand **3** were also tested. However, either poor enantioselectivities or low yields were obtained (Table 1, entry 3: TsDPEN: 70% yield, 0% ee; entry 4: camphorsulfonamide: 56% yield, 2% ee; entry 5: bidentate *N*-tosylated aminoimine ligand: 36% yield, 11% ee). Detailed studies of the Cu(II) complex of ligand **5** were carried out to optimize the reaction conditions including the choice of solvent and reaction temperature, which might influence the enantioselectivities of the reaction. The results shown in Table 1 clearly revealed that toluene was the best solvent and room temperature was a good choice for this reaction. Strong bases, such as CH_3OK, $(CH_3)_3CONa$ and butyllithium, were tested on the terminal acetylenic C–H bond to form alkynyl-metal reagents. $(CH_3)_3CONa$ gave good results in yield improvement but poor results with regard to the enantioselectivity [Table 1, entry 11, $(CH_3)_3CONa$: 82% yield with 63% ee]. CH_3OK and butyllithium gave neither high yield nor good enantioselectivity (Table 1, entry 13: 43% yield with 55% ee; entry 14: 61% yield with 47% ee). When dimethylzinc was added to form the alkynylzinc reagent, the yield was distinctly improved and also the enantioselectivity was slightly increased (Table 1, entry 12: 83% yield with 75% ee). This result was consistent with our previous study of Cu(I) complexes, which proved that organozinc reagents were favorable for both Cu(I) and Cu(II) complexes.

Various *N*-aryl arylimines derived from aromatic aldehydes and amines reacted with phenylacetylene in the presence of dimethylzinc, catalyzed by Cu(II)–tridentate *N*-tosylated amine–imine ligand **5** under optimal reaction conditions and the results are listed in Table 2. All the *N*-aryl arylimines derived from aniline and substituted aldehydes in the reaction gave moderate to good ee values (Table 2, entries 1–6: 51–89% yields with 73–81% ees). *N*-Aryl arylimines derived from substituted anilines and benzaldehyde also provided good results (Table 2, entries 7–9: 42–77% yields with 81–85% ees). The results revealed that electron donor groups on the phenyl ring of the substrates were favorable for enantioselectivity (Table 2, entries 10 and 11). The highest ee value was obtained with the substrate derived from *p*-methyl aniline and *p*-methyl benzaldehyde (Table 2, entry 10: 70% yield with 92% ee).

3. Conclusion

In conclusion, we have demonstrated that a new catalyst system consisting of Cu(II) and chiral tridentate *N*-tosylated aminoimine ligands was effective in the enantioselective addition of phenylacetylene to *N*-aryl arylimines. Further studies on the scope and mechanism of this reaction are currently underway.

4. Experimental

4.1. General methods

All reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. All solvents were distilled and dried before use. Reagents were purchased from either Acros or Aldrich. The aldehydes were redistilled before use. NMR spectra were recorded on a Varian-300 spectrometer. Optical rotations were measured with a Perkin Elmer 341 polarimeter. Chiral HPLC analysis was

performed on a Waters 600 instrument with Chiralcel OD column (4.6 mm × 250 mm).

4.2. Preparation of chiral ligands

Chiral ligands **4** and **5** were prepared according to the procedure, which we previously reported.[14]

Chiral ligand **3**: To a solution of 2.00 g (5.46 mmol) of (*R*,*R*)-TsDPEN in 40 ml of methanol were added 0.73 g (5.5 mmol) of 3,5-dimethylbenzaldehyde and 3.57 g of anhydrous Na_2SO_4 (30 mmol). The reaction mixture was stirred and refluxed for 8 h until the reaction was completed (monitored by TLC). After cooling to room temperature, the mixture was filtrated and the solvent was removed in vacuo to afford chiral (*R*,*R*)-**3** as a white solid (2.47 g, 94%). Mp = 174–176 °C. $[\alpha]_D^{20} = +56.5$ (*c* 0.1, CH_2Cl_2). Anal. Calcd for $C_{30}H_{30}N_2O_2S$: C, 74.66; H, 6.27; N, 5.80. Found: C, 74.37; H, 6.52; N, 5.52. IR *v*: 3030(w), 2954(m), 1650(s), 1451(m), 1161(s), 1088(w), 911(w), 855(w), 771(w), 701(w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.68 (d, $J = 6.0$ Hz, 1H), 7.35–7.05 (m, 14H), 6.97 (d, $J = 9.0$ Hz, 2H), 6.91 (s, 1H), 2.36–2.45 (m, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), δ: 144.1, 140.1, 139.5, 138.4, 138.2, 135.0, 133.3, 129.9, 128.9, 128.2, 126.9, 126.5, 125.2, 72.3, 70.8, 64.2, 21.9 ppm.

4.2.1. General procedure for the enantioselective alkynylation of *N*-aryl arylimines. To a solution of 2.0 M dimethylzinc in toluene (0.15 ml, 0.3 mmol) was added phenylacetylene (0.033 ml, 0.3 mmol) under nitrogen at room temperature. The mixture was stirred for 15 min to produce the alkynylzinc reagent. Copper(II) triflate (14.4 mg, 0.04 mmol) was added to a solution of the chiral ligand (0.04 mmol) and *N*-aryl arylimines substrate (0.2 mmol) in 0.5 ml of toluene. The preformed alkynylzinc reagent was added to the mixture of the catalyst and substrate via a syringe. After a certain period of time, the reaction was quenched by the addition of 2 ml of water. The mixture was extracted twice with 2 ml of dichloromethane, and then the combined organic phase was concentrated in vacuo. The residue was purified by flash chromatography (2% ethyl acetate in petroleum ether as eluents) to give the desired product. The enantiomeric excess was determined by chiral HPLC using a Chiralcel OD column (5% isopropanol in hexane as eluents).

Acknowledgments

We thank the National Science Foundation of China (20472116), the Guangdong Province Natural Science Foundation (04009804), the Hong Kong Research Grants Commercial (Project Polyu 5002/05P) and the University Grants Committee of Hong Kong (Areas of Excellence Scheme, AOE P/10-01) for the financial support of this study.

References

1. Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.
2. Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268.
3. (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535; (b) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797.
4. Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.
5. Yadav, J. S.; Reddy, B. V. S.; Sreenivas, M.; Sathaiah, K. *Tetrahedron* **2005**, *46*, 8905.
6. (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.
7. (a) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273; (b) Akullian, L. C.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244.
8. (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.
9. Knopfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.
10. Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064.
11. Zani, L.; Eichhorn, T.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 2587.
12. Ji, J.-X.; Wu, J.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11196.
13. Liu, J.; Liu, B.; Jia, X.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 396.
14. Liu, B.; Liu, J.; Jia, X.; Huang, L.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 1124.
15. Lu, G.; Li, X. S.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057.
16. Liu, L.; Wang, R.; Kang, Y.-F.; Cai, H.-Q.; Chen, C. *Synlett* **2006**, 1245.
17. McDonagh, C.; O'Conghaile, P.; Klein Gebbinkb, R. J. M.; O'Learya, P. *Tetrahedron Lett.* **2007**, *48*, 4387.