ORGANIC LETTERS

2006
Vol. 8, No. 11
2405−2408

Enantioselective One-Pot Three-Component Synthesis of Propargylamines

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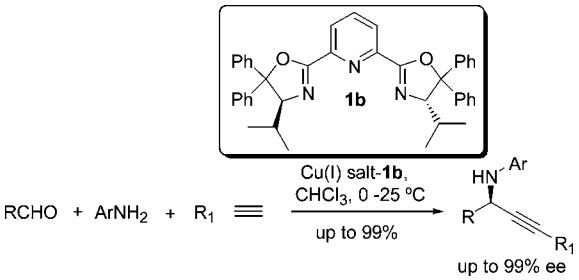
Received April 3, 2006

ABSTRACT



A copper(I) complex of *i*-Pr-pybox-diPh has been found to be an efficient catalyst for an enantioselective one-pot three-component synthesis of propargylamines from aldehydes, amines, and alkynes. The reaction has been applied to a wide variety of aromatic aldehydes with excellent yields (up to 99%) and enantiomeric excesses (up to 99% ee). A transition-state model has been proposed to explain the stereochemical outcome of the reaction.

The enantioselective addition of terminal alkynes to imines provides direct access to optically active propargylamines, which are important for the synthesis of many biologically active nitrogen compounds.[1] This is an important C−C bond formation reaction that proceeds via C−H bond activation by a metal complex.[2] A variety of chiral ligands have been used in this reaction. High asymmetric induction has been reported using quinap ligands.[3,4] A metal complex of chiral amino acids,[5] chiral alcohols,[6] and chiral binaphthylamines[7] has also been used in this reaction. Although reasonable progress has been made in this area, tunable and easily procured ligands are often desired because of their strong substrate dependence in most cases. Even small changes in conformational, steric, and/or electronic properties of the chiral ligands can often lead to dramatic variation in the enantioselectivity. The pybox ligand of the type **1a** (Figure 1) has marked a place in the area of enantioselective reactions.[8,9]

During our pursuit in this area, we used *i*-Pr-pybox-diPh **1b** for enantioselective cyclopropanation[10] and enantiose-

(1) (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. 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.

(2) (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

(3) (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (c) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem.−Eur. J.* **2003**, *9*, 2997. (d) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324. (e) Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175.

(4) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.

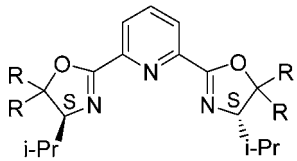
(5) (a) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273. (b) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5971.

(6) Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216.

(7) (a) Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* **2004**, *45*, 8705. (b) Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005**, 1689. (c) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064.

(8) The pybox ligand **1a** was first introduced by Professor Nishiyama. For reference, see: Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846.

10.1021/ol060793f CCC: $33.50
Published on Web 05/06/2006



1a: R = H; **1b**: R = Ph; **1c**: R = Et

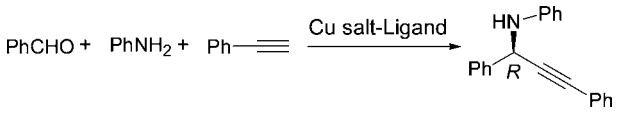
Figure 1. C_2 symmetric pyridine bis(oxazoline) ligands.

lective allylic oxidation of olefins.[11] We observed that the diphenyl group at the 5-carbon of the oxazoline rings played a crucial role in enhancing the ee in the enantioselective allylic oxidation of olefins. Looking at the lower enantioselectivity (<45% ee) with the pybox ligand **1a**,[12] one would not think of using ligand **1b** for the addition of an alkyne to an imine. Nevertheless, on the basis of our intuition, we used it in this reaction, and to our delight, the enantioselectivity was excellent. It was further observed that there was no need to use preformed imine, and the reaction worked in one-pot fashion as well. Above all, N-protected amines such as *p*-methoxyphenylamine also gave high ee. In this paper, we wish to report the preliminary results of this reaction.

At the outset, the three-component coupling reaction was examined by taking a 1:1:1.5 mixture of benzaldehyde, aniline, and phenylacetylene at 0−25 °C in chloroform for 12 h using 10 mol % of a complex of **1b** with Cu(MeCN)$_4$PF$_6$. The product was obtained in 98% yield and 96% ee (Table 1, entry 9). This result was highly promising in contrast to the results obtained from the ligands **1a** and **1c**, which required 4 days for completion of the reaction with much lower enantioselectivities of less than 45% and 56% ee, respectively. This clearly indicated that diphenyl groups have a drastic effect in enhancing the ee and reducing the reaction time. The reaction was carried out in different solvents (Table 1), but chloroform gave the best results. The enantioselectivity was similar (96% ee) if (CuOTf)$_2$·PhMe (Table 1, entry 13) was used as a salt. The reaction was equally catalyzed with an almost similar enantioselectivity (94% ee) by using Cu(II) triflate as a salt.

The reaction was extended to different aldehydes, and most of them gave high enantioselectivity (Table 2). Both electron-rich and -poor aldehydes gave 94−95% ee in this one-pot reaction (Table 2, entries 1 and 2). A maximum of 98% ee was obtained in the case of 2-chlorobenzaldehyde (Table 2, entry 9) using aniline as an aromatic amine. The chemical yield was excellent in most of the cases.

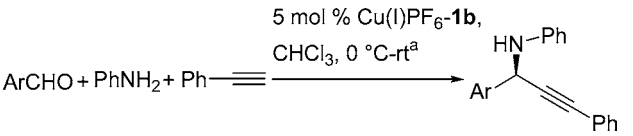
Table 1. Solvent Study on Enantioselectivity



entry	Cu salt−ligand[a]	solvent	temp	time	% yield	ee (%)[b,c]
1	Cu^{I}PF$_6$−**1b**	toluene	rt	5 h	95	85
2	Cu^{I}PF$_6$−**1c**	toluene	rt	4 days	43	56
3	Cu^{I}PF$_6$−**1b**	hexane	rt	36 h	72	63
4	Cu^{I}PF$_6$−**1b**	DCE	rt	8 h	99	90
5	Cu^{I}PF$_6$−**1b**	EtOAc	rt	19 h	92	62
6	Cu^{I}PF$_6$−**1b**	CH_2Cl_2	rt	6 h	99	93
7	Cu^{I}PF$_6$−**1b**	$CHCl_3$	rt	5 h	99	95
8[d]	Cu^{I}PF$_6$−**1b**	$CHCl_3$	rt	16 h	92	95
9	Cu^{I}PF$_6$−**1b**	$CHCl_3$	0−rt	12 h	98	96
10	Cu^{I}PF$_6$−**1b**	$CHCl_3$	10 °C	43 h	80	96
11	Cu^{I}PF$_6$−**1b**[e]	$CHCl_3$	0−rt	12 h	98	96
12	Cu^{I}OTf−**1b**	$CHCl_3$	0−rt	12 h	95	95
13	Cu^{I}OTf−**1b**[e]	$CHCl_3$	0−rt	18 h	94	96
14	Cu(OTf)$_2$−**1b**	$CHCl_3$	0−rt	24 h	95	94
15	Cu(OTf)$_2$−**1b**[e]	$CHCl_3$	0−rt	72 h	85	94

[a] 10 mol % of the complex was used unless stated otherwise. [b] ee's were determined by a Chiralcel OD-H column using 2-propanol and hexane as eluent. [c] The absolute configuration was made by analogy according to the literature data. [d] 4 Å MSs were also used. [e] 5 mol % of the complex was used.

Table 2. Effect of Different Aldehydes on Enantioselectivity[a]



entry	Ar	time (h)	% yield[b,c]	ee (%)[d]
1	4-*i*-Pr-Ph	20	89	95 (*R*)
2	4-NO$_2$-Ph	28	82	94 (*R*)
3	3-Me-Ph	12	91	96 (*R*)
4	4-Cl-Ph	24	94	96 (*R*)
5	3-F-Ph	28	85	93 (*R*)
6	3-Br-Ph	26	92	91 (*R*)
7	3,5-diMe-Ph	12	98	95 (*R*)
8	3-Cl-4-F-Ph	26	97	91 (*R*)
9	2-Cl-Ph	12	93	98 (*S*)

[a] All the reactions were done under an argon atmosphere. [b] Ratio of Cu^{I}PF$_6$, *i*-Pr-pybox-diPh, aldehyde, aniline, and phenylacetylene was 0.05: 0.06:1:1:1.5. [c] Isolated yield after column chromatography over silica gel using 5−10% of EtOAc in hexane. [d] Enantiomeric excess was determined by HPLC using Chiralcel OD-H and Chiralpak AD-H columns (see Supporting Information).

We, then, extended the three-component coupling reaction by using different aromatic amines. Halogen-substituted aromatic amines were found to be equally efficient. For

(9) For some applications of the pybox ligand **1a** in enantioselective reactions, see: (a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res*. **2000**, *33*, 325. (c) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 9928. (d) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 4594. (e) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 10482.

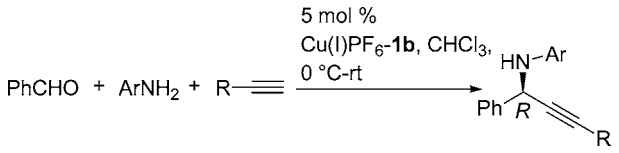
(10) DattaGupta, A.; Bhuniya, D.; Singh, V. K. *Tetrahedron* **1994**, *50*, 13725.

(11) (a) Ginotra, S.; Singh, V. K. *Tetrahedron* **2006**, *62*, 3573. (b) Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961. (c) DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 2633.

(12) (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Wei, C.; Mague, J. T.; Li, C.-J. *PNAS* **2004**, *101*, 5749. (c) For a review, see: Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472.

instance, 4-bromoaniline gave 96% ee in the above reaction (Table 3, entry 3). To our delight, we could get more than

Table 3. Effect of Different Aromatic Amines on Enantioselectivity

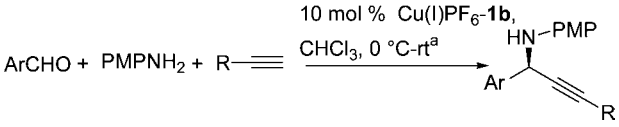


entry	Ar	R	time (h)	% yield[a]	ee (%)
1	Ph	Ph	12	98	96
2	3-F-Ph	Ph	24	93	95
3	4-Br-Ph	Ph	24	98	96
4	3-Cl-Ph	Ph	24	93	95
5	PMP	Ph	48	56	77
6	PMP	Ph	16	98	90[b]

[a] Isolated yield after column chromatography. [b] 10 mol % of the complex was used.

90% ee in this reaction using *p*-methoxyphenyl (PMP) amines, which could be oxidatively removed (Table 3, entry 6).[13] Using PMP amines, we carried out the reaction with different aldehydes and alkynes (Table 4). It is very clear

Table 4. Reactions with *p*-Methoxyaniline[a]



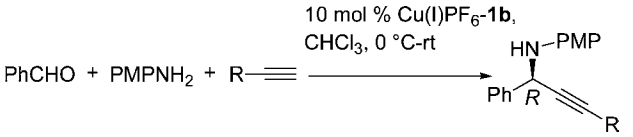
entry	Ar	R	time (h)	% yield	ee (%)[b]
1	3-Me-Ph	Ph	22	99	92 (*R*)
2	4-*i*-Pr-Ph	Ph	22	87	83 (*R*)
3	4-Cl-Ph	Ph	28	91	90 (*R*)
4	3-F-Ph	Ph	26	90	85 (*R*)
5	4-F-Ph	Ph	24	95	91 (*R*)
6	3-Br-Ph	Ph	26	96	80 (*R*)
7	3-Cl-Ph	Ph	16	92	82 (*R*)
8	3-Cl-4-F-Ph	Ph	16	90	86 (*R*)
9	2-Cl-Ph	Ph	16	94	97 (*S*)
10	2-Cl-Ph	$PhCH_2CH_2$	48	61	85 (*S*)
11	2-Cl-Ph	*n*-Bu	48	67	87 (*S*)
12	3,5-diMe-Ph	Ph	16	98	93 (*R*)
13	4-NO_2-Ph	Ph	16	90	90 (*R*)
14	2,4-diMe-Ph	Ph	18	97	99 (*S*)

[a] Ratio of $Cu^{I}PF_6$, *i*-Pr-pybox-diPh, aldehyde, *p*-methoxyaniline, and phenylacetylene was 0.10:0.12:1.0:1.0:1.5. [b] Enantiomeric excess was determined by a Chiralpak AD-H column.

from the table that the synthesis of propargylamine by this one-pot protocol catalyzed by a Cu(I) complex of **1b** is efficient as 99% ee was obtained in the case of 2,4-dimethylbenzaldehyde (Table 4, entry 14). The reaction worked very well in the case of aliphatic alkynes (Table 4, entries 10 and 11).

Further, we examined the effect of a variety of terminal alkynes on the asymmetric induction in the reaction. It is noteworthy that the enantioselectivity was excellent in all the substituted aromatic alkynes (Table 5, entries 2−4).

Table 5. Effect of Different Terminal Alkynes on Enantioselectivity



entry	R	time (h)	% yield[a]	ee (%)[b]
1	Ph	16	98	90
2	4-Me-Ph	18	98	93
3	4-MeO-Ph	20	96	93
4	4-Br-Ph	20	93	90
5	$PhCH_2CH_2$	42	86	84
6	*n*-Bu	28	67	87

[a] Isolated yield after column chromatography. [b] Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column.

However, aliphatic alkynes afforded propargylamines with slightly lower ee's and the reaction was also sluggish in comparison with aromatic alkynes (Table 5, entries 5 and 6).

The mechanism of this type of reaction has been proposed previously.[3,7c] There is enough evidence in the literature that Cu(I) salt can form a pentacoordinated (distorted trigonal bipyramid) complex through a Cu(III) intermediate, which has been detected spectroscopically.[11b,14] Our results inferred the superiority of the *i*-Pr-pybox-diPh ligand over *i*-Pr-pybox-diEt and *i*-Pr-pybox. On the basis of our earlier experience on the enantioselective allylic oxidation of olefins using the same kind of ligands,[11] we propose that the 'N' of an imine prefers to chelate the Cu complex in a manner where there are three stabilizing π-interactions; two C−H$\cdots\pi$ and one $\pi\cdots\pi$ as indicated in Figure 2. In this favored model, the aryl group on the sp^2 carbon of the imine could orient itself in a manner so that it is orthogonal to the pyridine ring. Thus, one of the phenyl rings on each oxazoline unit can attain a conformation to provide a suitable distance (~3.5 Å) from the aryl ring so as to provide stabilizing interactions.[15] This is possible when the right-side phenyl is parallel and the left-side phenyl is orthogonal to the aryl ring. Thus, the transition state becomes highly organized because of the above three stabilizing interactions, and the copper acetylide attacks the

(13) (a) Córdova, A.; Notz, W.; Zhong, G.; Betancort, M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (b) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079.

(14) Beckwith, A. L. J.; Zavitas, A. A. *J. Am. Chem. Soc.* **1986**, *108*, 8230 and references therein.

(15) For a review on the π-stacking effect in asymmetric synthesis, see: (a) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475. (b) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.

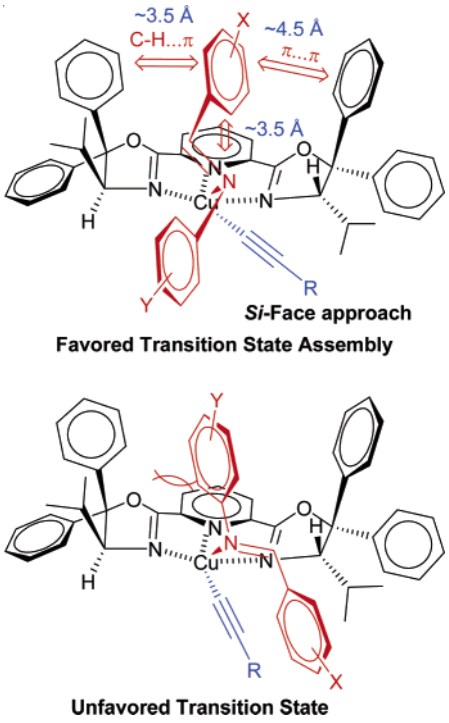


Figure 2. Proposed transition-state model.

imine from the *si* face to provide propargylamine. The *re* face attack is retarded because of the β-alkyl group on the chiral carbon atom of the left oxazoline ring. In an unfavored model, the 'N' of the imine can chelate with the copper complex in a manner where the aryl of the 'N' is orthogonal to the pyridine ring causing severe nonbonding repulsion.

In conclusion, the chiral Cu(I)−**1b** complex prepared from $Cu^{I}PF_6$ and the C_2-symmetric *i*-Pr-pybox-diPh ligand **1b** was found to be an effective catalyst for the enantioselective three-component synthesis of aromatic alkynylamines from aldehydes, amines, and alkynes. The reaction is complete in a few hours. The procedure is operationally very simple and can furnish a wide variety of propargylamines in good to excellent yields with excellent enantioselectivities (up to 99% ee). We have also explained the stereochemical outcome of these type of reactions by invoking a transition-state model. These results open a novel way to design and synthesize new chiral ligands for enantioselective reactions.[16,17]

Acknowledgment. V.K.S. thanks the Department of Science and Technology, India, for a research grant. A.B. thanks the Council of Scientific and Industrial Research, New Delhi, for a Senior Research Fellowship.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The chiral ligand **1b** has also been used for other enantioselective reactions. For references, see: (a) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (b) Lu, J.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, 2345. (c) Lu, J.; Hong, M. L.; Ji, S.-J.; Teo, Y. C.; Loh, T. P. *Chem. Commun.* **2005**, 4217. (d) Lu, J.; Ji, S. J.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 7435.

(17) General Procedure for the enantioselective three-component synthesis of propargylamines catalyzed by the Cu(I)−(*S*,*S*)-**1b** complex: A solution of ligand **1b** (0.012 mmol, 6 mol %) and $Cu^{I}(MeCN)_4PF_6$ (0.010 mmol, 5 mol %) in dry chloroform (2 mL) was stirred at room temperature for 30 min. An aldehyde (0.20 mmol) and an aromatic amine (0.20 mmol) were added, and the whole mixture was stirred for an additional 15 min at the same temperature. The reaction mixture was cooled to 0 °C, and an alkyne (0.30 mmol) was added. The reaction mixture was allowed to warm to 20−25 °C. After completion of the reaction (monitoring by TLC), the mixture was concentrated in vacuo and purified over silica gel by column chromatography (2−10% EtOAc in hexane) yielding pure propargylamine.