Chiral Diamine-Copper(I) Complexes as Asymmetric Catalysts in the Enantioselective Addition of Phenylacetylene to Imines

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Received 24 March 2005

Abstract: The stereoselective addition of phenyl acetylene to imines, catalysed by chiral bis-amine-Cu(I) complexes was studied. The chiral ligands are either commercially available or easily prepared in one or two steps. This very convenient and extremely simple experimental procedure at room temperature allowed optically active propargyl amines to be obtained in good yields with enantioselectivities up to 70%.

Key words: chiral bis-amines, copper complexes, propargylamines, enantioselective catalysis, acetylene addition

Optically active propargylamines are synthetically versatile intermediates for the construction of many biologically active nitrogen compounds[1] and key intermediates for the synthesis of polyfunctional amino derivatives.[2]

Among the several synthetic methodologies available for the preparation of these useful structures,[3] the addition of an organometallic reagent to chiral imine derivatives still represents an important method.[4] However, the development of efficient catalytic enantioselective methods for the preparation of enantiomerically enriched propargylamines is a very appealing synthetic alternative.[5]

While several catalytic methods are known to promote the reaction of acetylenes with aldehydes in very high yields and enantioselectivities,[6] only very recently a few different organometallic systems were reported to catalyse the formation of enantiomerically enriched propargyl amines by employing acetylenic derivatives. Hoveyda and Snapper[7] used a Zr(IV) complex in the presence of a chiral amino acid-based ligand. Li developed a Cu(I) complex of pyridyl-bisoxazoline[8] able to promote direct alkyne-imine addition in toluene and in water. Knochel[9] described the addition of functionalised alkynes to enamines catalysed by Cu(I) salts complexed to quinap, a mixed P,N-chiral ligand. Lately Carreira developed a new atropisomeric P,N ligand (pinap), structurally related to quinap, that showed a similar reactivity and stereochemical efficiency in promoting the CuBr-catalysed three-component reaction[10] among dibenzylamine, an aldehyde and various acetylenes.[11] Finally, Jiang reported zinc acetylides addition to reactive ketoimines in the presence of a chiral amino alcohol under mild reaction conditions.[12]

We have recently demonstrated that enantiomerically pure bis-imines copper(I) complexes are efficient catalysts in the direct addition of phenyl and alkyl acetylene to imines.[13] Copper(I) triflate complexes of enantiomerically pure bis-imines derived from (*R*)-binaphthyl diamine have been shown to catalyse the formation of optically active propargyl amines at room temperature often in very good yields and ee values of up to 81%.

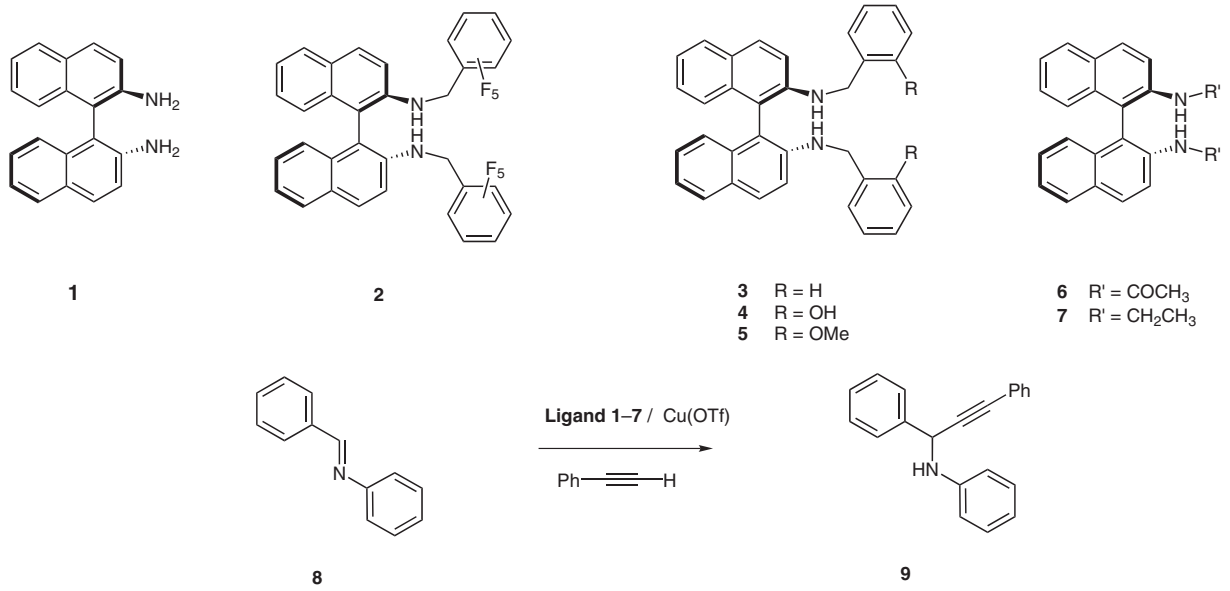
Following our interest in developing new chiral Cu(I) complexes in asymmetric catalysis,[14] we decided to investigate the use of enantiomerically pure diamines as ligands for the copper(I)-promoted addition of phenyl acetylene to imines.[15] We wish to report here the preliminary results of our study.

In a series of explorative experiments, we found that among the commercially available enantiomerically pure C_2-symmetric primary diamines, in our reaction conditions, only (*R*)-binaphthyl diamine gave a complex with copper(I) triflate showing interesting catalytic properties.[16] With only 10 mol% of catalyst, generated simply by mixing an equimolar amount of copper triflate and (*R*)-binaphthyl diamine, it was possible to promote the phenyl acetylene addition to *N*-phenyl benzaldehyde imine (**8**), in dichloromethane, to give the propargyl amine **9** in quantitative yield and 45% ee. Among different solvents examined, the catalytic system performed better in toluene (Table 1, entry 3), where the product was obtained in quantitative yield and 67% ee.

The temperature seems to influence the reaction rate, but not the enantioselectivity of the process. Running the reaction at 0 °C lowered the yields (87% vs 99% in CH_2Cl_2, and 47% vs 99% in toluene), but the enantioselectivities remained virtually unchanged (Table 1, entry 1 vs 5, entry 3 vs 6).

Among the different copper(I) salts tested, copper trifluoromethanesulfonate out-performed any other, affording the product always with the highest enantioselectivity. The use of chiral diamines as ligands in asymmetric catalysis opens the attractive possibility to ultilise aqueous solvents.[17] Interestingly the binaphthyl diamine/copper(I) complex was able to promote the reaction also in a toluene–water (9:1) mixture, affording the product **9** in very good yield (91%) but diminished ee (Tables 1, 36% vs 67%, entry 4 vs 3).[18]

SYNTHESIS 2005, No. 10, pp 1689–1692
Advanced online publication: 18.05.2005
DOI: 10.1055/s-2005-869896; Art ID: C03405SS



Scheme 1 Chiral bis-amines employed in the Cu(I)-promoted addition of phenylacetylene to *N*-phenylbenzaldehyde imine (**8**).

Secondary amines were also tested as chiral ligands with copper trifluoromethanesulfonate in the phenyl acetylene addition to imines. Ligands **2–5** were easily prepared by reduction[19] of the corresponding imines;[13] ligand **6**[20] was obtained by reaction of diamine **1** with acetyl chloride; finally, reduction of **6** with $LiAlH_4$ afforded diamine **7** in very high yield.

Table 1 Phenylacetylene Addition to Imine **8** Catalysed by Chiral Bis-Diamine/Cu(I) Complexes

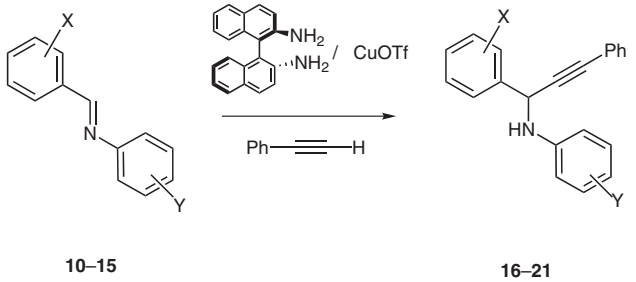
Entry	Solvent	Catalyst (10 mol%)	Yield (%)[a]	ee (%)[b]
1	CH_2Cl_2	**1**/Cu(OTf)	>99	45
2	CH_3CN	**1**/Cu(OTf)	25	14
	Toluene	**1**/Cu(OTf)	>99	67
4	Toluene–H_2O (9:1)	**1**/Cu(OTf)	91	36
5[c]	CH_2Cl_2	**1**/Cu(OTf)	87	41
6[c]	Toluene	**1**/Cu(OTf)	47	67
7	Toluene	**2**/Cu(OTf)	43	<5
8	Toluene	**4**/Cu(OTf)	17	n.d.
9	Toluene	**5**/Cu(OTf)	51	15
10	Toluene	**6**/Cu(OTf)	43	<5
11	Toluene	**7**/Cu(OTf)	55	23

[a] Determined by ^1H NMR on the crude reaction mixture and confirmed by silica gel flash column chromatography.
[b] Determined by HPLC on a chiral stationary phase, DAICEL Chiralcel OD, hexane–*i*-PrOH, 95:5.
[c] The reaction was run at 0 °C for 72 h.

Ligands **2–7** all showed a modest catalytic efficiency in promoting the reaction, affording the product in the best case with 55% yield (Table 1, entry 11, ligand **7**). A free OH group on the ligand affects detrimentally its catalytic ability (Table 1, entry 8); a methoxy group is tolerated, but it has a negative influence on the stereoselectivity of the process (Table 1, entry 9, 51% yield, 15% ee vs 67% ee for entry 3). In any case the enantioselectivities were very modest and clearly lower than those obtained with the primary chiral diamine **1**.

To further study the general applicability of this new catalytic system, the methodology was then extended to differently substituted imines (Scheme 2). The catalytic system worked with imines modified both at the N-residue or at the C-residue, affording products **16–21** in yields from modest to excellent, and enantioselectivities up to 70% (Table 2).

Substituents at the *N*-phenyl residue seem to have a negative effect on the enantioselectivity and sometimes on the chemical efficiency as well of the process (Table 2, entries 2 and 3). However, substituents are well-tolerated on



Scheme 2 Cu(I)-promoted addition of phenylacetylene to differently substituted imines.

the *C*-phenyl residue, with ee values constantly higher than 53% obtained (Table 2, entries 4–6).[21]

It is worth mentioning that the diamine **1**/Cu(I) complex was also able to promote the addition of 4-bromophenyl acetylene to imine **8** to give the corresponding propargyl amine in 33% yield and 51% ee.

Table 2 Phenylacetylene Addition to Imines **10**–**15** Catalysed by **1**/Cu(I)-Complex

Entry	X	Y	Product	Isolated yield (%)[a]	ee (%)[b]
1	H	H	**9**	>99	67
2	H	4-OMe	**16**	>99	27
3	H	2-OMe	**17**	<10	n.d.
4	2-OMe	H	**18**	>99	53
5	4-OMe	H	**19**	31	70
6	4-Me	H	**20**	27	55
7	2-Cl	H	**21**	11	n.d.

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture and confirmed by silica gel flash column chromatography.
[b] Determined by HPLC on a chiral stationary phase, DAICEL Chiralcel OD and Chiralpak AD, hexane–*i*-PrOH mixtures.

Although some results are quite puzzling, any attempt at rationalisation would be highly speculative at this time; we believe that this new catalytic system shows some interesting features and it deserves further studies.

In summary, we have developed a new asymmetric catalyst, easily prepared in situ by mixing commercially available chiral diamines and copper trifluoromethanesulfonate, to promote phenyl acetylene addition to imines. An extremely simple experimental procedure, the mild reaction conditions, the use of all commercially available reagents, and the possibility of running the reaction in aqueous solvents, are all positive features that make the present methodology very attractive.

Synthesis of Lignads 2–5; General Procedure
To a mixture of THF–AcOH (2:1, 6 mL) was added chiral bis-imine (0.5 mmol); to the cooled solution at 0 °C, $NaBH_4$ (1 mmol) was slowly added. The reaction mixture was stirred at r.t. for 30 min. After checking the complete consumption of the starting material by TLC, the mixture was quenched with H_2O. Extraction with CH_2Cl_2, followed by drying and solvent evaporation under reduced pressure afforded the corresponding chiral diamine that does not require chromatographic purification. For example, for ligand **4**:

^{1}H NMR: δ = 7.33–7.00 (m, 8 H), 7.00–6.80 (m, 6 H), 6.70–6.50 (m, 6 H), 6.55 (br s, 2 H), 6.50 (br s, 2 H), 4.05 (s, 2 H), 3.90 (A proton of AB system, *J* = 14 Hz, 2 H), 3.60 (B proton of AB system, *J* = 14 Hz, 2 H).

Phenylacetylene Addition to Imines; Typical Procedure
In a typical experimental procedure, Cu(OTf) (0.02 mmol) was added to a toluene solution (2 mL) of the chiral ligand (0.02 mmol) at r.t. under a nitrogen atmosphere. After stirring for 10 min, imine **8** (0.2 mmol) and phenylacetylene (0.3 mmol) were added. The reaction mixture was allowed to stir for 72 h at r.t., then it was filtered through celite and purified by flash chromatography, if necessary. For example, for compound **9**:

^{1}H NMR: δ = 7.77 (d, *J* = 8 Hz, 2 H), 7.40–7.30 (m, 5 H), 7.30–7.20 (m, 5 H), 6.80 (m, 3 H), 5.55 (s, 1 H), 4.05 (br s, 1 H).

Acknowledgment

This work was supported by MIUR (Progetto Nazionale Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni) and C.I.N.M.P.I.S. (Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi).

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