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Enantioselective addition of phenyl and alkyl acetylenes to imines catalyzed by chiral Cu(I) complexes

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Abstract—The stereoselective addition of phenyl acetylene and alkyl acetylenes to imines, catalyzed by chiral bis-imines-Cu(I) complexes was studied. A very simple experimental procedure allowed to obtain at room temperature optically active propargyl amines in very good yields and enantioselectivity up to 81%.

The stereoselective carbon–carbon bond formation promoted by a chiral catalyst is an area of major interest in asymmetric catalysis.[1] In this field, the enantioselective addition of acetylenic reagents to carbonyl compounds or imines to give respectively optically active propargyl alcohols or amines is a viable tool in the construction of highly functionalized structures.[2]

While several catalytic methods are known to promote the reaction of acetylenes with aldehydes in very high yields and enantioselectivities,[3] the stereoselective addition of acetylenic reagents to imines is more difficult.[4] Only very recently three different organometallic systems were reported to catalyze the formation of enantiomerically enriched propargyl amines by employing acetylenic derivatives.[5] Knochel and co-workers[6] described the addition of functionalized alkynes to enamines catalyzed by Cu(I) salts complexed to Quinap, a mixed P, N chiral ligand. Hoveyda and co-workers[7] used a (O*i*-Pr)$_4$Zr···OH*i*-Pr complex in the presence of a chiral amino acid-based ligand. Li developed a Cu(I) complex of pyridyl-bis-oxazoline[8] able to promote the direct alkyne–imine addition in toluene and in water.

Following our interest in developing new chiral Cu(I) complexes in asymmetric catalysis,[9] we decided to investigate the use of enantiomerically pure bis-imines copper(I) complexes as catalysts in the addition of phenyl and alkyl acetylene to imines. We wish to report here the preliminary results of our study.

Our idea was to develop a simple experimental procedure, with a catalytic system easy to handle, less expensive than Quinap or Pybox and active enough to promote the direct addition of acetylene derivatives to imines without need of any addictive or further transformation. The copper complexes of bis-imines derived from binaphthyl diamine recently employed with success by Suga et al.[10] in cyclopropanations and by Scott and co-workers[11] in the synthesis of aziridines and cyclopropanes attracted our attention.

First we synthesized a series of bis-imines by reaction of (*S*)-binaphthyl diamine[12] with different aromatic aldehydes in toluene to give the corresponding bis-imines **1**–**5** in good yields (Fig. 1). Reaction with 2-pyridylcarboxyaldehyde afforded easily bis-imine **6**,[13] while the benzophenone-derived bis-imine **7** was obtained after prolonged reaction times in presence of activated molecular sieves.[14]

The catalytic activity of Cu(I) complexes of the enantiomerically pure ligands **1**–**7** was investigated in a test reaction, the addition of phenyl acetylene to *N*-phenyl benzaldehyde imine **8** to give the propargyl amine **9**. Selected results of this preliminary study are collected in Table 1.

In a typical experimental procedure, to a 2 mL toluene solution of the chiral ligand (0.02 mmol), at room temperature, under nitrogen atmosphere, copper(I)

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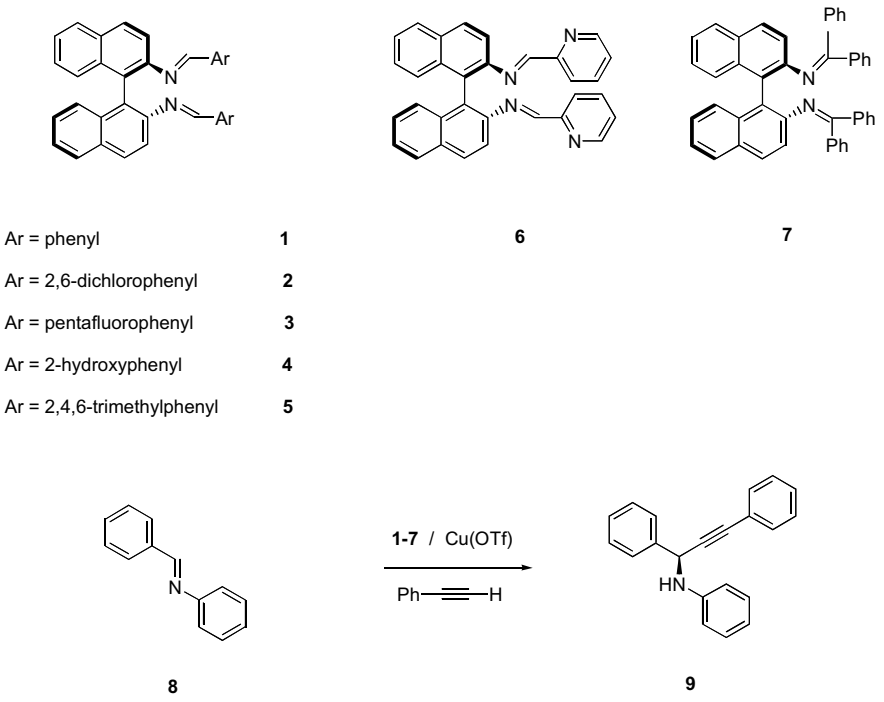

Figure 1. Chiral bis-imines employed in the Cu(I) promoted addition of phenyl acetylene to *N*-phenyl benzaldehyde imine **8**.

Table 1. Enantioselective addition of phenyl acetylene to imine **8**

Entry	Solvent	Ligand	Yield[a] (%)	Ee[b] (%)
1	Toluene	**1**	98	77
2	Toluene	**2**	97	63
3	Toluene	**3**	98	81
4	Toluene	**4**	77	73
5	Toluene	**5**	98	77
6	Toluene	**6**	—	—
7	Toluene	**7**	80	7
8	DCM	**3**	91	41
9	THF	**3**	11	n.d.
10[c]	Toluene	**3**	87	77
11[d]	Toluene	**3**	77	61

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Chiracel OD).
[c] Reaction run with 5%mol of catalyst.
[d] Reaction run with 1%mol of catalyst.

trifluoromethane sulfonate (0.02 mmol) was added. After stirring for 10 min, imine **8** (0.2 mmol) and phenyl acetylene (0.3 mmol) were added. The reaction mixture was allowed to stir for 72 h at room temperature, then it was filtered onto a Celite cake and purified by flash chromatography.

The copper(I) triflate complexes of all ligands were able to promote the reaction at room temperature, except in the case of ligand **6**, when no reaction occurred. Probably the presence of the pyridyl nitrogen atoms, two binding sites for copper ion, in addition to the two imine groups, makes the Cu(I) complex catalytically inactive. The benzophenone-derived bis-imine **7** seems less active than aldehydes derived bis-imines **1**–**5**, and it promotes the reaction with basically no enantioselectivity.

With ligands **1**–**5**, product **9** was isolated in yields often higher than 90%, with enantioselectivities ranging from 41% to 81%.[15]

Benzaldehyde derived bis-imine **1** afforded the propargyl amine with 77% ee, the same enantioselectivity being obtained with the more sterically crowded mesityl derivative **5** (entries 1 and 5). However by employing a ligand more sterically demanding at 2,6-phenyl positions as bis-imine **2** the enantiomeric excess drops to 63% (entry 2). The presence of a hydroxy functional group does not seem to have any appreciable influence on the stereoselectivity (entry 4, 73% ee).

Best results were obtained with the pentafluorobenzaldehyde-derived binaphthyl bis-imine **3**, which promoted the addition of phenyl acetylene to imine **8**, in quantitative yield and 81% ee (72 h, room temperature, toluene, entry 3).[16]

Other solvents proved to be less effective, either for the enantioselectivity of the reaction (entry 8) or even for the chemical efficiency of the addition (entry 9).[17] Also the temperature played a crucial role, since the reaction did not proceed below 0 °C. Among different copper(I) salts tested, copper trifluoromethanesulfonate performed better than any other, affording the product always with the highest enantioselectivity. Interestingly in absence of the ligand and under the reaction conditions of entry 1, the use of CuOTf led to the product only in 15% yield.[18] Noteworthy the chiral bis-imine-copper(I) complex promoted the phenyl acetylene addition also at lower catalyst loading. For example, with 5%mol of ligand **3** the product was isolated in 87% yield and 77% ee, while with a catalyst loading as low as

1%mol, **9** was obtained after purification in 77% yield and 61% ee (entries 10 and 11).

In other experiments the methodology was then extended to differently substituted imines (Fig. 2).

The catalytic system worked with imines modified both at the N-residue or at the C-residue, affording products **10–13** in yields from fair to excellent, and enantioselectivities up to 55% (Table 2).

It is worth mentioning that the copper(I) complex of ligand **3** was able to catalyze also the addition of alkyl acetylenes derivatives to imines. Indeed, the reaction between imine **8** and 1-hexyne afforded the corresponding propargyl amine **14** with 73% yield and 71% ee. Analogously the addition of 1-decyne to imine **8** gave **15** in 91% yield and 73% ee.[19] Also for alkyl acetylene addition the reaction promoted by only 5%mol of catalyst afforded product **15** in very good yield (81%) and without appreciable loss of enantioselectivity (71%, entry 8 vs entry 9).

In summary, we have developed a new, asymmetric catalyst to promote phenyl and alkyl acetylene derivatives addition to imines. A very simple experimental procedure at room temperature allowed to obtain optically active propargyl amines in very good yields and enantioselectivity up to 81%. The chiral bis-imine ligands are readily prepared in very high yields from commercially available materials.

We believe that the extremely simple methodology and the mild reaction conditions, as well as the possibility of a modular approach for developing new and more efficient bis-imine-based chiral ligands make the present methodology very attractive.

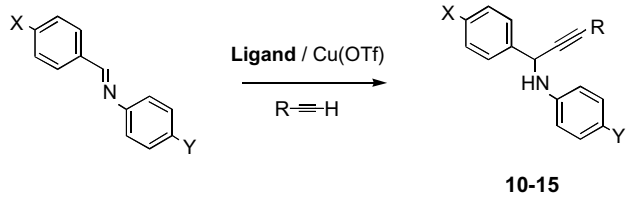

Figure 2. Cu(I) promoted addition of phenyl and alkyl acetylene of differently substituted imines.

Table 2. Enantioselective addition of phenyl and alkyl acetylene to differently substituted imines

Entry	Ligand	R	X	Y	Product	Yield[a] (%)	Ee[b] (%)
1	**3**	Ph	OMe	H	**10**	77	45
2	**3**	Ph	H	OMe	**11**	55	41
3	**3**	Ph	H	Cl	**12**	98	25
4	**4**	Ph	OMe	H	**10**	75	55
5	**4**	Ph	H	OMe	**11**	53	27
6	**3**	Ph	H	Tos	**13**	37	n.d.
7	**3**	C_4H_9	H	H	**14**	73	71
8	**3**	C_8H_{17}	H	H	**15**	91	73
9[c]	**3**	C_8H_{17}	H	H	**15**	81	71

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Chiracel OD).
[c] Reaction run with 5%mol of catalyst.

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12. Binaphthyl diamine is available in both enantiomeric forms and it costs about three times less than pyridyl-bis-oxazolines employed by Li and 20 times less than Quinap used by Knochel. Products **1**, **2**, **3**, **4**, **5** were obtained in 98%, 85% 91%, 98%, 77% yields, respectively.
13. Vogtle, F.; Thomessen, R.; Steckhan, E.; Schumacher, K. *Tetrahedron Lett.* **1985**, *26*, 2077. Product **6** was obtained in 97% yield.
14. Reetz, M. T.; Haderlein, G.; Angermund, K. *J. Am. Chem. Soc.* **2000**, *122*, 996. Following the reported procedure, in our hands, product **7** was obtained in 51% yield after chromatographic purification.

15. At the end of reaction, after filtration onto a Celite cake, the recovered crude reaction mixture did not show any trace of phenyl acetylene addition to the chiral bis-imine ligand, but only product **9** and eventually non reacted starting material **8**.
16. Product **9** was isolated as white solid, mp 56–57 °C, $[\alpha]_D$ +71.3, *c* 1.03 in CH_2Cl_2 for a sample of 77% ee, determined by HPLC analysis on a Chiracel OD column with a hexane/isopropanol 95:5 mixture as eluant (flow rate 1 mL/min); T_R of the major enantiomer: 12.79 min; T_R of the minor enantiomer: 16.1 min.
17. Addition did not occur in methanol, *N*,*N*-dimethylformammide and 9/1 mixture of toluene/water.
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19. To our knowledge this is the first example of direct, enantioselective catalytic addition to imines of alkyl acetylenes; for other examples of use of alkyl acetylenes in other methodologies see Refs. 6 and 7.