JOC*Article*

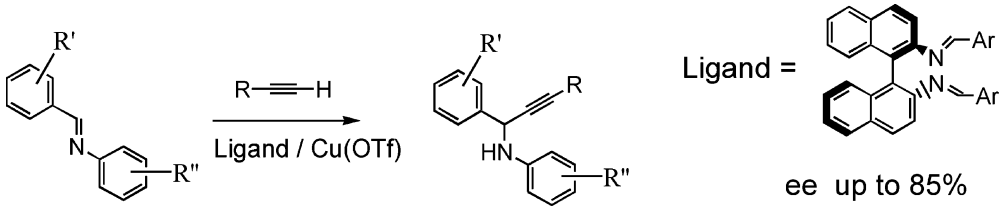
Very Mild, Enantioselective Synthesis of Propargylamines Catalyzed by Copper(I)−Bisimine Complexes

Federica Colombo,[†] Maurizio Benaglia,*[,†] Simonetta Orlandi,[†] Fabio Usuelli,[†] and Giuseppe Celentano[‡]

Centro di Eccellenza CISI and Dipartimento di Chimica Organica e Industriale, and Istituto di Chimica Organica della Facoltá di Farmacia, Università degli Studi di Milano, via Golgi 19 -20133- Milano, Italy

maurizio.benaglia@unimi.it

Received December 1, 2005



The stereoselective addition of aryl- and alkylacetylene derivatives to imines was studied. The reaction is catalyzed by copper complexes of enantiomerically pure bisimines, readily prepared in very high yields from the commercially available binaphthyl diamine. A very simple experimental procedure allowed to obtain at room temperature optically active propargylamines in high yields and enantioselectivity. Interestingly, bisimine/copper(I) complexes were able to promote the direct, enantioselective, catalytic addition to imines of alkylacetylenes. The effects of catalyst loading and other reaction parameters on the stereochemical outcome of the transformation were investigated. The extremely convenient methodology, the mild reaction conditions, and the possibility of a modular approach for developing new and more efficient bisimine-based chiral ligands make the present methodology very attractive.

Introduction

The enantioselective addition of acetylenic reagents to imines or other related aza-carbonyl derivatives to give optically active propargylamines is a valuable tool in the construction of highly functionalized structures.[1] Optically active propargylamines are synthetically versatile intermediates for the construction of many biologically active nitrogen compounds[2] and key intermediates for the synthesis of polyfunctional amino derivatives.[3]

Among the several synthetic methodologies available for the preparation of these useful structures, the addition of an organometallic reagent to chiral imine derivatives still represents an important method.[4] In this context, the development of an efficient catalytic enantioselective version of this reaction is a very appealing synthetic alternative.[5]

While several catalytic methods are known to promote the addition of acetylenes to aldehydes in very high yields and enantioselectivities,[6] only very recently a limited number of different organometallic systems have been reported to catalyze the addition of acetylenes to imines to afford enantiomerically enriched propargylamines. Hoveyda and co-workers used a Zr-(IV) complex in the presence of a chiral amino acid-based

* Corresponding Author. Tel.: +39.02.50314171. Fax: +39.02.50314159.
[†] Centro di Eccellenza CISI and Dipartimento di Chimica Organica e Industriale.
[‡] Instituto di Chimica Organica della Facoltá di Farmacia.

(1) Review: Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757. For a review of the asymmetric synthesis of propargylamines, see: Blanchet, J.; Bonin, M.; Micouin, L. *Org. Prep. Proced. Int.* **2002**, *34*, 459.

(2) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. *J. Org. Chem.* **1995**, *60*, 1590.

(3) Nilsson, B.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1992**, *35*, 285. Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

(4) For the addition of organometallic reagents to chiral imines, see: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. See also: Frantz, D. E.; Fassler, R.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054. Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245 and references cited therein.

(5) For a few selected examples of interesting methodologies affording racemic compounds, see also: Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319. Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497. Wei, C.; Li, Z.; Li, C. J. *Org. Lett.* **2003**, *5*, 4473. Sakaguchi, S.; Mizuta, T.; Furuwan, M.; Kubo, T.; Ishii, Y. *Chem. Commun.* **2004**, 1638−1639.

(6) Reviews: Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095. Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757. Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373.

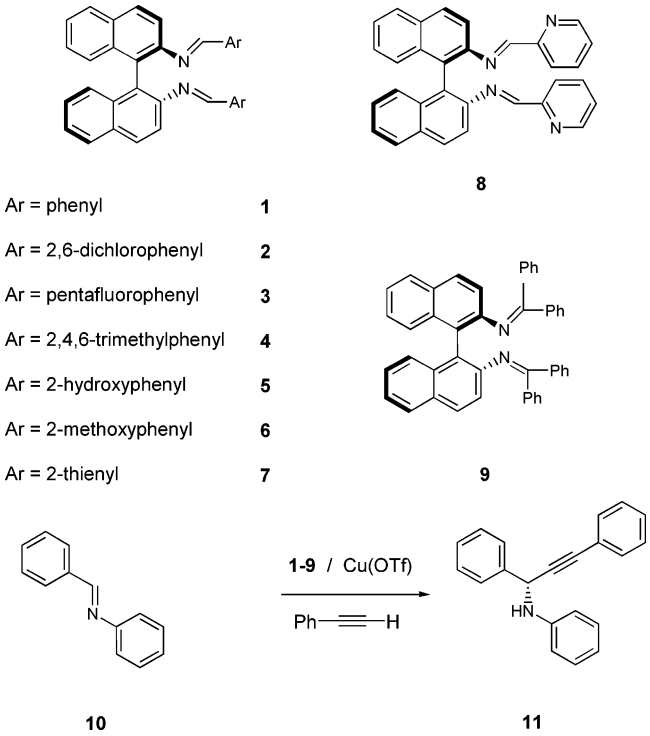
10.1021/jo052481g CCC: $33.50
Published on Web 02/09/2006

ligand.[7] Li developed a Cu(I) complex of pyridyl−bisoxazoline[8] that was able to promote the direct alkyne-imine addition in toluene and in water. Knochel and co-workers[9] described the addition of functionalized alkynes to enamines catalyzed by Cu(I)−Quinap complexes. More recently, Carreira and co-workers developed a new atropisomeric P,N ligand (Pinap), structurally related to Quinap, that showed a similar reactivity and stereochemical efficiency in promoting the CuBr-catalyzed three-component reaction[10] among dibenzylamine, an aldehyde, and various acetylenes.[11] Finally, Jiang and Si[12] reported the zinc acetylide addition to reactive ketoimines in the presence of a chiral amino alcohol under mild reaction conditions.[13]

Our group has recently started a program devoted to the development of new catalytic systems, readily prepared from commercially available and cheap chiral reagents, easy to handle, in very simple experimental procedures. Following our interest in developing new copper(I)-catalyzed reactions,[14] we were attracted by the copper complexes of bisimines derived from enantiopure biaryl diamine, recently employed with success by Suga et al.[15] and by Scott et al.[16] in the synthesis of aziridines and cyclopropanes.[17] We thought that Cu(I), chiral, bisimine-based catalysts could represent readily available candidates as catalytic systems to actively promote the direct addition of acetylene derivatives to imines, without the need of any addictive or further reagent transformation. The fact that the catalyst would be less expensive than Quinap or Pybox added further appeal to the new catalytic system.

Here we report that the stereoselective addition of phenylacetylene and alkylacetylenes to imines may be catalyzed by copper(I) complexes of enantiomerically pure bisimines, readily prepared in one step in very high yields from commercially available enantiomerically pure binaphthyl diamine,[18] to afford propargylamines often in quantitative yields and enantioselectivities up to 85%.[19]

SCHEME 1. Chiral Bisimine/Cu(I) Complex-Promoted Enantioselective Addition of Phenylacetylene to *N*-Phenylbenzaldehyde Imine 10



Results and Discussion

Synthesis of the Ligands. The synthesis of all the ligands followed the same general strategy, starting from the commercially available (*R*)-binaphthyl diamine that was reacted with different aromatic and heteroaromatic aldehydes to afford the corresponding enantiomerically pure bisimines **1**−**8** in good yields (Scheme 1). In a typical procedure, a 0.5 M solution of the chiral diamine (1 mol/equiv) and the aromatic aldehyde (2.2 mol/equiv) was refluxed in dry toluene for 24−72 h in the presence of molecular sieves. The reaction mixture, cooled to room temperature, was filtered, and the solvent was evaporated under reduced pressure to give the expected bisimine in more than 90% yield, that was shown to be pure enough by ^{1}H NMR to be used as such.

Analytically pure samples could be obtained by crystallization, typically in ethanol (see Experimental Section). The ligand **9** was prepared according to the literature procedure.[20]

Cu(I)-Catalyzed Asymmetric Phenylacetylene Addition to Imines. The ligands were tested in the copper(I)-trifluoromethanesulfonate-catalyzed reaction between *N*-phenylbenzaldehyde imine **10** and phenylacetylene to afford the optically

(7) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273. See also: Akullian, L. C.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244.

(8) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749.

(9) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

(10) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472.

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

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

(13) For other recent reports on the asymmetric catalyzed addition of acetylenic reagents to imines, see: Rosa, J. N.; Santos, A. G.; Alfonso, C. A. M. *J. Mol. Catal. A: Chem.* **2004**, *214*, 161. Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175. See also: Park, S. B.; Alper, H. *Chem. Commun.* **2005**, 1315.

(14) Puglisi, A.; Benaglia, M.; Annunziata, R.; Bologna, A. *Tetrahedron Lett.* **2003**, *44*, 2947.

(15) Suga, H.; Kakehi, A.; Ito, S.; Ibata, T.; Fudo, T.; Watanabe, Y.; Kinoshita, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 189.

(16) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132. Sanders, C. J.; Gillespie, K. M.; Scott, P. *Tetrahedron: Asymmetry* **2001**, *12*, 1055. Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P. *J. Org. Chem.* **2002**, *67*, 3450−3458. O'Shaughnessy, P.; Scott, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1979. O'Shaughnessy, P.; Knight, P. D.; Morton, C.; Gillespie, K. M.; Scott, P. *Chem. Commun.* **2003**, 1770. O'Shaughnessy, P.; Gillespie, K. M.; Knight, P. D.; Munslow, I. J.; Scott, P. *Dalton Trans.* **2004**, 2251.

(17) For other recent uses of binaphthyl diamine-based imines as ligands in asymmetric catalysis, see also: Zhou, X.; Huang, J.; Ko, P.; Cheung, K.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1999**, 3303. Suga, H.; Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 327. Suga, H.; Kakehi, A.; Mitsuda, M. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 561. Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2004**, 1414 and references cited therein. Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431 and references cited therein.

(18) Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* **2004**, *45*, 8705−8708.

(19) We have recently found that the arylacetylene addition to imines is promoted also by chiral diamine/Cu(I) complexes. See: Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005**, 1689−1691. The bisimine/Cu(I) catalysts usually performed better than diamine/Cu(I) complexes in terms of yields and stereoselectivities.

(20) Reetz, M. T.; Haderlein, G.; Angermund, K. *J. Am. Chem. Soc.* **2000**, *122*, 996. Following the reported procedure, in our hands, product **9** was obtained in 51% yield after chromatographic purification.

TABLE 1. Cu(I)-Catalyzed Asymmetric Phenylacetylene Addition to Imine 10[a]

entry	ligand	yield[b] (%)	ee[c] (%)
1	**1**	98	77
2	**2**	97	63
3	**3**	98	81
4	**4**	98	77
5	**5**	77	73
6	**6**	67	23
7	**7**	98	65
8	**8**	–	–
9	**9**	81	7

[a] Reaction conditions: 72 h, 25 °C, toluene, 10 mol % of catalyst. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC on chiral stationary phase.

active propargylamine **11**. In a typical experimental procedure, to a 2 mL toluene solution of the chiral ligand (0.02 mmol), kept at room temperature under nitrogen, copper(I)-trifluoromethanesulfonate (0.02 mmol) was added. After stirring for 10 min, imine **10** (0.2 mmol) and phenylacetylene (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. It is noteworthy that at the end of reaction, after filtration onto a Celite cake, the recovered crude reaction mixture did not show any trace of phenylacetylene addition to the bisimine ligand, but only product **11** and, in some cases, nonreacted starting material **10**. The results are reported in Table 1.

Benzaldehyde-derived bisimine **1** afforded the propargylamine with 77% ee, the same enantioselectivity being obtained with the more sterically crowded mesityl derivative **4** (Table 1, entries 1 and 4). However, by employing a ligand more sterically demanding at the 2,6-phenyl positions as bisimine **2**, the enantiomeric excess drops to 63% (Table 1, entry 2). The best results were obtained with the pentafluorobenzaldehyde-derived binaphthyl bisimine **3**, which promoted the addition of phenylacetylene to imine **10**, in quantitative yield and 81% ee (Table 1, entry 3).

The presence of a hydroxy group does not seem to have any appreciable influence on the stereoselectivity (Table 1, entry 5, 73% ee).[21] However, surprisingly enough, ligand **6** bearing a methoxy group promoted the reaction in a very low ee (23%, Table 1, entry 6). The use of bisimines derived from heteroaromatic aldehydes strongly depended on the presence of the latter of a coordinating atom. Indeed, a possible weak coordinating element like a thiophene ring does not show any appreciable effect (ligand **7**, 65 vs 77% ee, Table 1, entry 7 vs entry 1).[22] However, as expected, the stronger coordinating pyridine rings inactivated the catalyst, and the reaction did not occur (Table 1, entry 8). Finally, for this copper(I)-promoted transformation, the benzophenone-derived bisimine **9** showed a good catalytic activity but a poor stereocontrol ability.

The results of this initial screening are very interesting in light of the extremely simple experimental procedure, the very mild reaction conditions, and the easy synthesis in one step of the chiral ligands. The chiral-copper complex guarantees high chemical efficiency as well as good enantioselectivity (up to 81%). It is important to note that a single crystallization of the product **11** allows the increase of the enantiomeric excess of the propargylamine from 81% to more than 99%[23] (see Experimental Section).

TABLE 2. Optimization of the Cu(I)-Catalyzed Phenylacetylene Addition to Imine 10[a]

entry	ligand	temp (°C)	solvent	yield[b] (%)	ee[c] (%)
1	**3**	25	toluene	98	81
2	**3**	25	DCM	91	41
3	**3**	25	THF	11	n.d.
4	**3**	25	*n*-hexane	7	n.d.
5	**1**	25	*n*-hexane	71	21
6	**1**	25	NO_2CH_3	83	5
7	**3**	25	MeOH	7	n.d.
8[d]	**3**	25	toluene	83	82
9[e]	**3**	25	toluene	98	82
10	**3**	0	toluene	37	83
11	**1**	0	toluene	21	75

[a] Reaction conditions: 72 h, 10 mol % of catalyst. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC on chiral stationary phase. [d] Reaction conditions: 24 h, 10 mol % of catalyst. [e] Reaction conditions: 48 h, 10 mol % of catalyst.

Having identified bisimine **3** as the ligand of choice, the dependence of the catalyst behavior on solvent and temperature was investigated (Table 2).

Toluene proved to be the best performing solvent; other solvents were tested, like dichloromethane or hexane, but they proved to be less effective for the enantioselectivity of the reaction (Table 2, entries 2, 4, and 5 vs entry 1). Polar solvents, like tetrahydrofuran, acetonitrile, methanol, or *N*,*N*-dimethylformamide, were not good reaction solvents both for enantioselectivity and chemical efficiency.

In toluene, ligand **3** worked well and, after 12 h, afforded the product **11** in 83% yield and in quantitative yield after 40 h, always maintaining a comparable level of stereoselectivity (Table 2, entries 8 and 9).[24] Also, the temperature played a crucial role, because the phenylacetylene addition did not proceed for temperatures lower than room temperature. For instance, at 0 °C the reaction rate was slowed and no change in the enantioselectivity was observed.[25]

The dependence of the results on the nature of the copper salt was then studied (Table 3).

The phenylacetylene addition seems to be a ligand-accelerated reaction, because copper(I)-trifluoromethanesulfonate as such promoted the reaction in toluene after 72 h at 25 °C in only 15% yield (Table 3, entry 2 vs entry 1). However, in dichloromethane (DCM), a catalytic amount, 10 mol %, of CuOTf was able to catalyze the formation of **11** in 90% yield; the lower enantioselectivity of the reaction promoted by the ligand **3**/Cu(I) complex in DCM compared to that of the reaction in toluene (41 vs 81% ee, Table 2, entries 1 and 2) may be explained in terms of different solubility profiles. Other salts were completely

(21) The use of other, even more hindered, ligands like a chiral bisimine derived from 2-hydroxy-3-*t*-butyl-benzaldehyde did not allow the improvement of the enantioselectivity, which was always in a 70−80% ee range. See also ref 29.

(22) On the contrary, in a chiral bisimine/metal catalyzed allylation of imines, we have recently discovered a positive effect of the thiophene ring on the stereoselectivity of the process. See: Colombo, F.; Benaglia, M.; Cozzi, F.; Cinquini, M. manuscript in preparation.

(23) In the case of product **11**, it was possible to obtain a basically enantiomerically pure compound after a single crystallization step even starting from a sample with 65% ee.

(24) Other ligands were less efficient; for example, with ligand **1**, after 48 h, less than 60% conversion was observed. Furthermore, because with other substrates and different acetylenic reagents different reaction rates were observed, for the sake of comparison, a 72 h reaction time was kept in all the experiments.

(25) At 0 °C, other ligands, like **2**, **5**, and **6**, did not promote the reaction at all.

TABLE 3. Different Copper Salts Employed in the Cu(I)-Catalyzed Asymmetric Synthesis of 11[a]

entry	ligand	copper salt	yield[b] (%)	ee[c] (%)
1	**3**	CuOTf	98	81
2		CuOTf	15	
3[d]		CuOTf	90	
4	**3**	CuCl	<5	<5
5		CuCl	<5	
6	**3**	$CuPF_6$	47	27
7		$CuPF_6$	39	

[a] Reaction conditions: toluene, 25 °C, 72 h, 10 mol % of catalyst. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC on chiral stationary phase. [d] Reaction in DCM.

TABLE 4. Effect of Catalyst Loading in the Cu(I)-Catalyzed Phenylacetylene Addition to Imine 10[a]

entry	mol % cat.	cat. concn	yield[b] (%)	ee[c] (%)
1	10	1.5×10^{-2} M	98	81
2	5	1.5×10^{-2} M	87	77
3	1	1.5×10^{-2} M	77	71
4	5	1.5×10^{-3} M	98	75
5	1	1.5×10^{-3} M	71	85
6[d]	10	1.5×10^{-2} M	98	77
7[d]	5	1.5×10^{-3} M	75	71
8[e]	10	1.5×10^{-2} M	77	63
9[e]	5	1.5×10^{-3} M	51	69

[a] Reaction conditions: toluene, ligand **3**, 25 °C, 72 h. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC on chiral stationary phase. [d] Ligand **1** was used. [e] Ligand **2** was used.

ineffective, as CuCl (Table 3, entries 4 and 5),[26] or less efficient both in terms of chemical yield and stereoselectivity ($CuPF_6$, Table 3, entries 6 and 7).

To better understand the nature of the catalytic system and to propose a possible mechanism for the reaction, a few experiments were performed. Scott et al. have already demonstrated how the copper complexes of bisimines derived from C_2-symmetric biaryl diamine may exist both as either a "monomeric" or a "dimeric" form, depending on the steric requirements of the substituents in 2,6 positions of the aldehyde aromatic ring.[16] To understand if different catalytic species were present in the reaction medium, the phenylacetylene addition was performed with a different catalyst loading and in different dilution conditions (Table 4).

By employing the pentafluorobenzaldehyde derivative, ligand **3**, the reaction was promoted by 10, 5, and 1 mol % of catalyst. It is noteworthy that the chiral bisimine−copper(I) complex catalyzed the phenylacetylene addition also at a lower catalyst loading, with marginal loss of enantioselectivity. By running the reaction at 10^{-3} M catalyst concentration, similar results were observed, with the product being obtained with 75% ee for the 5 mol % catalyst-promoted reaction and even with 85% ee for the reaction performed with only 1 mol % of the chiral catalyst (Table 4, entries 2−5).

A similar trend was observed with other ligands, characterized by different steric requirements. The use of a copper complex of ligand **1** at a 10^{-3} M concentration afforded the product in 75% yield and 71% ee, while ligand **2** allowed to obtain the product in 51% yield and 69% ee. The comparison with the

(26) CuBr was reported to be a poor catalyst for the reaction also by Li et al.,[8] who showed that the Pybox/CuBr complex worked as active chiral catalyst but with less efficiency than Cu(OTf). Knochel et al.[9] and Carreira et al.[11] do use CuBr as the Cu(I) source, but it is complexed with Quinap or other related biaryl P,N ligands, and the reaction is believed to proceed through a different mechanism that involves an enamine formation.

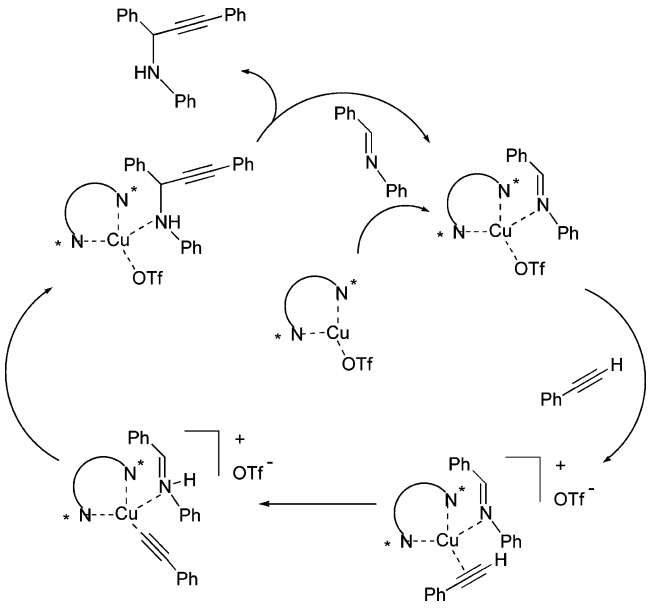


FIGURE 1. Catalytic cycle for the phenylacetylene addition to imines.

performance of the same catalysts, employed at 10 mol % of catalyst and at 10^{-2} M concentration, indicate there is not a clear difference in the results obtained by two ligands with different steric environments and at variable concentrations. These data seem to indicate that the catalyst is not sensitive to the reaction concentration parameters, suggesting that chiral bisimine behavior is not dependent on a possible equilibrium between monomeric and dimeric species.

To get further insight into the structure of the catalytic species, the isolation and characterization of the chiral bisimine/copper complex was attempted. The ^{1}H NMR spectrum of a mixture of an equimolar amount of copper-trifluoromethanesulfonate and chiral ligand **3** in toluene-d_8 accounts for the formation of a single species (see Experimental Section). Although, as already pointed out by Scott et al.,[16] the NMR spectra in solution of the free ligand and the complex are very similar; nevertheless, the ^{1}H NMR of the complex presented clear differences from that of the free ligand. Also, the complexation of the more hindered ligand **5** afforded a catalyst whose NMR both in $CDCl_3$ and in $CD(CN)_3$ clearly illustrated the formation of a new species, even if in this case the shift of the imine signal is less evident.

On the basis of the collected results, a tentative mechanism is suggested in Figure 1.

The chiral ligand/copper complex coordinates the imine **10** and the phenylcetylene.[9] After the intramolecular addition of the alkyne to the imine has occurred, the propargylamine, a product of the reaction, is released, regenerating by decomplexation the catalytic species, which is then ready to coordinate with new molecules of imine and alkyne to start again the catalytic cycle.[27]

Cu(I)-Catalyzed Asymmetric Aryl- and Alkylacetylene Additions to Various Imines. The methodology was then

(27) Any attempt to obtain crystals of the chiral bisimine/copper(I) complex was unsuccessful. For the proposed reaction mechanism, we do have NMR evidence of Cu(I)−imine coordination. Then the formation of a Cu−alkynide, as suggested by one of the referees, is a possibility. However, on the basis of our own investigation, at the moment we are not in the position to indicate the structure of the real active catalytic species and to assign the geometry at the copper ion.

SCHEME 2. Cu(I)-Promoted Addition of Phenylcetylene to Differently Substituted Imines

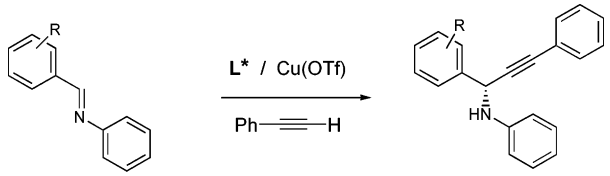


TABLE 5. Cu(I)-Catalyzed Phenylacetylene Addition to Imines 12−20[a]

entry	ligand	imine	R group	product	yield[b] (%)	ee[c] (%)
1	**1**	**12**	4-OMe	**21**	55	73
2	**3**	**12**	4-OMe	**21**	77	45
3	**5**	**12**	4-OMe	**21**	75	55
4	**1**	**13**	2-OMe	**22**	97	77
5	**3**	**13**	2-OMe	**22**	73	51
6	**5**	**13**	2-OMe	**22**	21	n.d.
7	**3**	**14**	2-Cl	**23**	91	80
8	**3**	**15**	2,6-diCl	**24**	<10	n.d.
9	**3**	**16**	4-F	**25**	98	71
10	**3**	**17**	4-Cl	**26**	91	73
11	**3**	**18**	4-Br	**27**	98	75
12	**3**	**19**	4-NO_2	**28**	98	15
13	**3**	**20**	4-Me	**29**	71	73

[a] Reaction conditions: toluene, 25 °C, 72 h, 10 mol % of catalyst. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC on chiral stationary phase.

extended to differently substituted imines (Scheme 2). The catalytic system worked with imines **12**−**20**, obtained by the reaction of aniline with several aromatic aldehydes, affording products **21**−**29** in fair to excellent yields and with enantioselectivities up to 80% (Table 5).

For imine **12**, derived from 4-methoxybenzaldehyde, ligand **1** performed better than the usual ligand of choice, ligand **3**, affording the product **21** with 73% ee (Table 5, entries 1 and 2). This behavior was confirmed also in the case of phenylacetylene addition to imine **13**, a derivative of 2-methoxybenzaldehyde, which in the presence of ligand **1** produced the propargylamine **22** in basically quantitative yield and 77% ee (Table 5, entry 4).

With other derivatives, ligand **3** performed constantly better; for example, it promoted the addition to imine **14** to give the corresponding *o*-chloro-substituted product **23** in 80% ee (Table 5, entry 7).[28] While the sterically hindered imine **15** did not react, the 4-halogen derivatives, **16**−**18**, reacted very well and afforded the corresponding products, **25**−**27**, in yields always higher than 90% and with enantioselectivities between 70 and 75%. While the presence of a methyl group does not seem to have an effect on the outcome of the reaction (73% ee, Table 5, entry 13), a nitro group heavily interferes, depressing the enantioselectivity of the process (15% ee) but not the chemical efficiency of the catalyst (Table 5, entry 12).

The phenylacetylene addition to different benzaldimines derived from variously substituted anilines was also studied (Scheme 3).

The *N*-4-methoxyphenyl imine **30** is a substrate of great interest, because it is possible to remove the aryl group by

SCHEME 3. Cu(I)-Promoted Addition of Phenylcetylene to Differently Substituted Imines

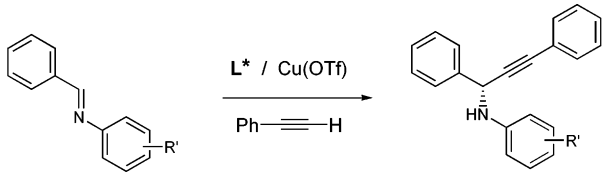


TABLE 6. Cu(I)-Catalyzed Phenylacetylene Addition to Imines 30−34[a]

entry	ligand	imine	R′ group	product	yield[b] (%)	ee[c] (%)
1	**1**	**30**	4-OMe	**35**	91	31
2	**3**	**30**	4-OMe	**35**	55	41
3	**5**	**30**	4-OMe	**35**	53	27
4	**1**	**31**	2-OMe	**36**	25	51
5	**3**	**31**	2-OMe	**36**	81	71
6	**3**	**32**	4-Cl	**37**	98	25
7	**1**	**33**	4-F	**38**	71	41
8	**3**	**33**	4-F	**38**	75	61
9	**3**	**34**	3,5-diCl	**39**	98	27

[a] Reaction conditions: toluene, 25 °C, 72 h, 10 mol % of catalyst. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC on chiral stationary phase.

oxidative degradation and thus obtain the *N*-unprotected propargylamine. Unfortunately, none of the chiral ligands tested in the usual conditions showed a good ability to stereocontrol the phenylacetylene addition to **30**, affording the product **35** in the best case with 41% ee (Table 6, entries 1−3). It must be noted also that, in the work of Li et al., by using a Pybox/copper(I) catalytic system, the enantioselective addition of phenylacetylene to imine **30** was not reported.[8] However, better results were obtained with the *N*-2-methoxyphenyl derivative **31**; by employing ligand **3**, the phenylacetylene addition was promoted in 81% yield and 71% ee (Table 6, entry 5). The result is extremely interesting from a synthetic point of view, because also the 2-methoxyphenyl group is removable[29] and product **36** represents a direct precursor of an enantiomerically enriched propargylamine with a free NH_2 group. By comparison of the analytical data of **36** with those reported by Hoveyda et al.,[29] it was possible to assign the (*R*) absolute configuration to the chiral propargylamines obtained with our methodology by employing chiral ligands derived from (*R*)-binaphthyl diamine.[30]

Also in the case of *N*-4-fluorophenylimine **33**, ligand **3**, derived from pentafluorobenzaldehyde, performed better than ligand **1**, obtained from benzaldehyde, affording the propargylamine **38** in 75% yield and 61% ee (Table 6, entries 7 and 8).

Finally, the addition of different acetylenic reagents was studied (Scheme 4).

As can be seen from the reported data, the methodology seems to work with differently substituted arylacetylenes. For example, ligand **1** promoted the 4-bromo-phenylacetylene addition to

(28) Imines derived from heteroaromatic aldehydes reacted sluggishly and with low enantioselectivity; imines derived from cinnamic aldehyde and aliphatic aldehydes did not react at all, as well as *N*-alkyl imines. *N*-phenyl imine of ethylglyoxalate was completely consumed after only 12 h of reaction, but any attempt to isolate a well-defined product was unsuccessful.

(29) For the degradation of *N*-2-methoxyphenyl anilines, see ref 7.

(30) The assigned absolute configuration has been confirmed also by the comparison of the analytical data of compound **11** with those reported by Li et al.[8] Product **11** was isolated as a white solid: mp 56−57 °C; $[\alpha]^{23}_D$ +71.3° (*c* 1.03, CH_2Cl_2) for a sample of 77% ee, determined by HPLC analysis on a Chiracel OD column with a hexane/2-propanol, 95:5, mixture as eluent (flow rate, 1 mL/min); t_R of the major enantiomer, 12.79 min; t_R of the minor enantiomer, 16.1 min. After crystallization, the product, with 95% ee (determined by HPLC), is a white solid: mp 91−92 °C; $[\alpha]^{23}_D$ +124° (*c* 0.32, CH_2Cl_2). These results match with those reported in the recent paper by Li et al. (ref 8), where the absolute configuration of *N*-[1-(3-bromophenyl)-3-phenyl-2-propynyl]-aniline was determined by X-ray crystallography.

SCHEME 4. Cu(I)-Promoted Addition of Aryl- and Alkylacetylene Derivatives to Substituted Imines

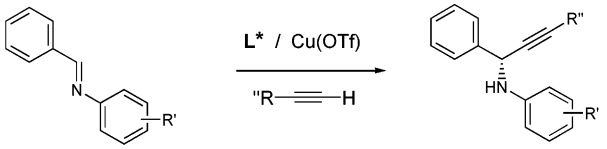


TABLE 7. Cu(I)-Catalyzed Aryl- and Alkylacetylene Additions to Imines[a]

entry	ligand	R′ group	R″ group	product	yield[b] (%)	ee[c] (%)
1	**3**	4-H	Ph	**11**	98	81
2	**1**	4-H	Ph	**11**	98	77
3	**1**	4-H	4-BrPh	**40**	98	75
4	**1**	4-H	3,5-diNO_2Ph	**41**	77	33
5	**1**	2-OMe	4-BrPh	**42**	97	57
6	**3**	4-H	C_4H_9	**43**	73	71
7	**3**	4-H	C_8H_{17}	**44**	91	73
8[d]	**3**	4-H	C_8H_{17}	**44**	81	71
9[e]	**3**	4-H	C_8H_{17}	**44**	37	65
10	**1**	4-H	C_8H_{17}	**44**	63	61
11	**3**	4-H	COOMe	**45**	51	21
12	**3**	2-OMe	COOMe	**46**	25	31
13	**3**	4-H	TMS	**47**	35	27

[a] Reaction conditions: toluene, 25 °C, 72 h, 10 mol % of catalyst. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC on chiral stationary phase. [d] A 5 mol % of catalyst was employed. [e] A 1 mol % of catalyst was employed.

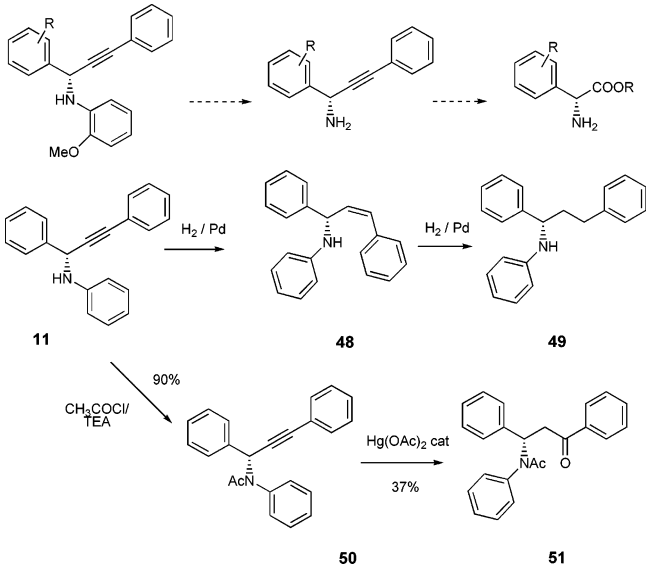
imine **10** in quantitative yield and 75% enantioselectivity, comparable to that obtained in the phenylacetylene addition to imine **10** (Table 7, entries 2 and 3). The addition of 4-bromophenylacetylene to *N*-2-methoxyphenyl-benzaldehyde imine **31** occurred in good yield and 57% ee. Once again, the presence of the nitro group on one of the reagents determined a marked drop in the stereoselectivity of the process, as demonstrated by the reaction of the 3,5-dinitro-phenylacetylene with imine **10** (33% ee, Table 7, entry 4).

In a previous communication we reported the direct, enantioselective, alkylacetylene-derivatives addition to imines.[18] Indeed, the reaction between imine **10** and 1-hexyne afforded the corresponding propargylamine **43** in 73% yield and 71% ee. Analogously, the addition of 1-decyne to imine **10** gave **44** in 91% yield and 73% ee. Also, for alkylacetylene addition, the reaction promoted by only 5 mol % of catalyst afforded product **44** in very good yield (81%) and without appreciable loss of enantioselectivity (71%, Table 7, entry 8 vs entry 7), while in the presence of 1 mol % catalyst, a clear decrease of chemical yield was observed (Table 7, entry 9). Also, in the case of alkylacetylenes, ligand **3** seems to perform better than ligand **1** both in chemical efficiency and stereoselectivity. It is worth mentioning that, to our knowledge, only one other example of direct, enantioselective, catalytic addition to imines of alkylacetylenes is known.[31]

Unfortunately, the methodology did not work well with propargylic ester or trimethylsilyl acetylene, which reacted with imine **10** to give the corresponding propargylamines **45** and **47** in 51 and 35% yields, respectively and, in both cases, with low enantioselectivity (Table 7, entries 11 and 13).

The propargylamines easily prepared by this methodology represent useful starting materials for further synthetic transformations. For example, as already mentioned, the *N*-2-methoxyphenyl group undergoes an oxidative cleavage to afford enantiomerically enriched propargylamines,[7] direct precursors for the preparation of amino acids. Propargylamine **11** may be reduced selectively to the corresponding highly functionalized allylic amine **48** or may be completely hydrogenated to the saturated compound **49**, without loss of stereochemical integrity (Scheme 5).

SCHEME 5. Synthetic Transformations of Chiral Propargyl Amines



The nitrogen atom of amine **11** may be protected as the *N*-acetyl compound **50**, which was converted to the *β*-amino ketone **51** in a not-optimized 35% yield, after chromatographic purification.[32] Also, the adduct **51** is a very attractive building block for the preparation of enantiomerically enriched, functionalized molecules, among which chiral 1,3-hydroxy-amino derivatives occupy a pre-eminent role.

Conclusions

A highly stereoselective addition of aryl- and alkylacetylene derivatives to imines was developed. The reaction is catalyzed by copper complexes of enantiomerically pure bisimines, readily prepared in one step and in very high yields from binaphthyl diamine, commercially available in both enantiomeric forms. A very simple experimental procedure allowed to obtain at room temperature optically active propargylamines in up to >98% yields and up to 85% ee. Interestingly, bisimines/copper(I) complexes were also able to promote the direct, enantioselective, catalytic addition of alkylacetylenes to imines.

It is worth mentioning that a multicomponent, stereoselective reaction between an aldehyde, an amine, and arylacetylenes to afford optically active propargylamines at room temperature has been also developed.[33] The extremely convenient methodology, which involves the use of commercially available reagents, mild reaction conditions, and the possibility of a modular approach for developing new and more efficient bisimine-based chiral ligands, make the present catalytic system very attractive.

(31) Only very recently have alkylacetylenes been employed in a direct addition to imines (see ref 8). For other examples of the use of alkylacetylenes in other methodologies, see refs 9 and 7.

(32) Meyer, A.; Flammang, M.; Wermuth, C.-G. *Synthesis* **1976**, 832.

(33) An asymmetric, multicomponent, copper-catalyzed synthesis of chiral propargylamines was developed. See: Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F. *J. Mol. Catal. A: Chem.* **2005**, submitted.

Experimental Section

General Procedure for the Synthesis of Ligands 1−8. To a solution of chiral diamine (10 mmol) in dry toluene (20 mL) was added aromatic aldehyde (20.2 mmol). The mixture was stirred in the presence of molecular sieves for 40−72 h at 110 °C. The reaction mixture was cooled to room temperature and filtered, and the solvent was evaporated under vacuum to give the corresponding imines in yields >90%. Eventually the bisimines may be crystallized from ethanol.

Ligand 1. Mp 119−124 °C; $[\alpha]^{23}_D$ +112.9 (*c* 0.23, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.24 (s, 2H), 7.98 (d, $^3J_{H,H}$ = 5.1 Hz, 2H), 7.93 (d, $^3J_{H,H}$ = 4.8 Hz, 2H), 7.44 (m, 2H), 7.42 (m, 2H), 7.37 (m, 1H), 7.36 (d, m, 2H), 7.34 (d, $^3J_{H,H}$ = 5.1 Hz, 2H), 7.30 (m, 2H), 7.28 (m, 2H). ^{13}C NMR: δ 160.7, 148.8, 136.3, 133.6, 131.6, 131.0, 129.1, 128.5, 128.4, 128.2, 127.9, 126.8, 126.4, 124.7, 119.3. Elem anal. Calcd for $C_{34}H_{24}N_2$ (460.57): C, 88.67; H, 5.25; N, 6.08. Found: C, 89.01; H, 5.44; N, 6.01.

Complexation Experiments of Chiral Bisimines with Copper-Trifluoromethanesulfonate. Cu(OTf) (0.01 mmol) was added to a toluene-d_8 solution (1 mL) of the chiral ligand (0.01 mmol) at rt, under a nitrogen atmosphere. After stirring for 15 min, ^{1}H NMR spectra were obtained. After 12 h, the copper complexes showed the same NMR spectra, with no appreciable differences.

Ligand 3. ^{1}H NMR (C_7D_8): δ 8.50 (s, 2H), 7.78 (d, $^3J_{H,H}$ = 9.0 Hz, 2H), 7.67 (d, $^3J_{H,H}$ = 8.5 Hz, 2H), 7.35 (d, $^3J_{H,H}$ = 8.3 Hz, 2H), 7.27 (d, $^3J_{H,H}$ = 8.8 Hz, 2H), 7.19 (m, 2H), 7.09 (m, 2H).

Cu(OTf)/ligand 3 complex. ^{1}H NMR (C_7D_8): δ 8.05 (s, 2H), 7.75 (d, $^3J_{H,H}$ = 8.7 Hz, 2H), 7.68 (d, $^3J_{H,H}$ = 8.5 Hz, 2H), 7.16−7.00 (m, 8H).

General Procedure for the Enantioselective Addition of Aryl- and Alkylacetylenes to Imines. 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 rt, 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 rt and was then filtered through Celite and purified by silica gel flash chromatography, if necessary (hexanes/ethyl acetate mixtures as eluent).[34]

***N*-[1-(4-Methoxyphenyl)-3-phenyl-2-propynyl]aniline 21.** ^{1}H NMR ($CDCl_3$): δ 7.55 (d, $^3J_{H,H}$ = 7.5 Hz, 2H), 7.40 (m, 2H), 7.20−7.30 (m, 5H), 6.90 (d, $^3J_{H,H}$ = 6.5 Hz, 2H), 6.75 (m, 3H), 5.45 (s, 1H,), 3.8 (s, 3H). ^{13}C NMR: δ 147.5, 130.2, 129.6, 129.1, 127.5, 127.0, 126.9, 123.9, 122.4, 119.8, 116.7, 111.1, 90.5, 87.1, 56.9, 46.4. Elem anal. Calcd for $C_{22}H_{19}NO$ (313.39): C, 84.31; H, 6.11; N, 4.47. Found: C, 84.01; H, 6.15; N, 4.55. HPLC analysis (Chiralcel OD; flow rate, 0.8 mL/min; λ = 230; hexane/*i*-PrOH, 95:5; t_R, 17.0 min (minor) and 19.4 min (major)).

Hydrogenation of Chiral Propargylamines. 50 mg of *N*-[1,3-diphenyl-2-propynyl]aniline **11** was dissolved in 10 mL of absolute ethanol and hydrogenated in the presence of 5 mg of Pd(C)/$CaCO_3$. After 15 min at room temperature, the propenylamine **48**[35] was isolated, while prolonged reaction times (1 h) afforded in quantitative yield the saturated compound **49**.

***N*-(1,3-Diphenyl-2-propenyl)aniline 48.** ^{1}H NMR ($CDCl_3$): δ 7.10−7.50 (m, 13H), 6.6−6.8 (m, 2H), 6.50 (d, $^3J_{H,H}$ = 6.1 Hz, 1H), 5.80 (dd, $^3J_{H,H}$ = 5.1, 6.1 Hz, 1H), 5.30 (d, $^3J_{H,H}$ = 5.1 Hz, 1H), 4.1 (br s, 1H). $[\alpha]^{23}_D$ +87.1 (*c* 0.33, CH_2Cl_2).

***N*-(1,3-Diphenyl-2-propyl)aniline 49.** ^{1}H NMR ($CDCl_3$): δ 7.15−7.40 (m, 12H), 6.7 (m, 1H), 6.60 (m, 2H), 4.40 (t, $^3J_{H,H}$ = 5.5 Hz, 1H), 2.70 (m, 2H), 2.10 (m, 2H). ^{13}C NMR: δ 147.1, 143.7, 141.2, 129.0, 128.5, 128.4, 127.0, 126.4, 126.2, 126.0, 176.7, 113.1, 57.7, 40.1, 32.6. Elem anal. Calcd for $C_{21}H_{21}N$ (287.40): C, 87.36; H, 7.36; N, 4.87. Found: C, 87.05; H, 7.55; N, 4.91. $[\alpha]^{23}_D$ +15.3 (*c* 0.33, CH_2Cl_2).

Synthesis of *β*-Amino Ketone 51. To a solution of 130 mg of amine **11** (0.46 mmol) in 5 mL of dry dichloromethane was added at 0 °C triethylamine (0.77 mL, 0.55 mmol), followed by acetyl chloride (0.4 mL, 0.56 mmol). The reaction mixture was allowed to stir at 0 °C for 30 min, then it was quenched with water and the organic phase was separated, dried over magnesium sulfate, and evaporated under reduced pressure to give the *N*-acetyl derivative **50** in 90% yield (135 mg).

A solution of 253 mg of **50** (0.78 mmol) in 1 mL of acetic acid was poured into a solution of 0.5 mL of formic acid in 0.05 mL of water. To the reaction mixture was added dropwise a 5% catalytic amount of a 15% $Hg(OAc)_2$ aqueous solution. The mixture was stirred for 2 h, hydrolyzed with water, and extracted with diethyl ether. The organic phase was separated, dried over magnesium sulfate, and evaporated under reduced pressure to give a crude reaction mixture that was purified by flash chromatography (eluent: hexanes/ethyl acetate 6/4) to afford the ketone **51**[36] in 37% yield (103 mg), $[\alpha]^{23}_D$ −25.3 (*c* 0.43, CH_2Cl_2).

***N*-Acetyl-*N*′-(1,3-diphenyl-2-propynyl)aniline 50.** ^{1}H NMR ($CDCl_3$): δ 7.25−7.40 (m, 6H), 7.15−7.25 (m, 9H), 6.90 (br s, 1H), 1.80 (s, 3H). ^{13}C NMR: δ 170.0, 139.9, 133.7, 131.6, 130.4, 129.1, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 127.2, 122.6, 89.3, 86.0, 50.5. Elem anal. Calcd for $C_{23}H_{19}NO$ (325.40): C, 84.89; H, 5.89; N, 4.30. Found: C, 85.11; H, 5.85; N, 4.10. $[\alpha]^{23}_D$ −65.3 (*c* 0.53, CH_2Cl_2).

Acknowledgment. This work was supported by MIUR (Progetto Nazionale Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni).

Supporting Information Available: Synthesis and characterization of ligands **2**−**9**, synthesis and HPLC analysis details for products **22**, **23**, **25**, **38**−**44**, and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052481G

(34) The enantiomerically enriched propargylamines **11**, **21**−**29**, **35**−**39**, and **41**−**44** all showed positive optical rotation values.

(35) Kodama, H.; Taji, T.; Ohta, T.; Furukawa, I. *Tetrahedron: Asymmetry* **2000**, *11*, 4009.

(36) Blatt, A. H.; Gross, N. *J. Org. Chem.* **1964**, *29*, 3306.