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Asymmetric multicomponent copper catalyzed synthesis of chiral propargylamines

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Abstract

A three-component stereoselective reaction between an aldehyde, an amine and phenylacetylene to afford optically active propargyl amines in good yields was developed. The reaction is catalysed by copper complexes of enantiomerically pure bis-imines. The best results were obtained with imines readily prepared in very high yields from the commercially available binaphtyl diamine.

A very simple experimental procedure at room temperature allowed to obtain optically active propargyl amines in very good yields and enantioselectivity up to 75%. 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.

Keywords: Multicomponent reactions; Chiral copper(I) complexes; Asymmetric catalysis; Phenylacetylene addition; Chiral propargylamines

1. Introduction

The discovery and development of multicomponent reactions is receiving a growing attention from industrial research groups in view of the high chemical productivity and product structural diversity that such methodology may offer [1]. A multicomponent condensation has been defined as a process where three or more reactants are combined in a single reaction vessel to form a new product which contains portions of all the components [2]. "Ideally" the starting materials should be different and all or most of the atoms of those reactants should be incorporated into the final product. Superior atom economy, selectivity, low level of by-products, simple procedures and equipment are all features that make the multicomponent reactions specially attractive in the field of combinatorial chemistry [3].

The development of new asymmetric catalysed multicomponent reactions is even more desirable, since, in Prof. Seebach's words, "chemists' attention has shifted to areas such as combinatorial synthesis (driven by robot, computer and miniaturization), material sciences, supramolecular chemistry, the origin of life, the biological and even medical sciences. Yet, in all these fields chirality plays a central role" [4].

Among several asymmetric reactions, the addition of organometallic reagents to imines or imine-derivatives is an important method to produce nitrogen containing building blocks. The condensation of acetylenic reagents to C=N bonds allows to synthesize propargyl amines [5], useful starting point for further synthetic manipulations. Enantiomerically enriched propargylamines are synthetically versatile intermediates for the construction of many biologically active nitrogen compounds [6] and key intermediates for the synthesis of polyfunctional amino derivatives [7].

While several catalytic methods are known to promote the reaction of acetylenes with aldehydes in very high yields and enantioselectivities [8], only over the last few years a limited number of different organometallic systems were reported to catalyze the formation of enantiomerically enriched propargyl amines by employing acetylenic derivatives. Decisive progresses to the development of an asymmetric catalyzed addition of acetylens to C=N bonds were made by Hoveyda and co-workers [9], Wei and Li [10], Knochel and co-workers [11], Carreira and co-workers [12], and Jiang and Si [13] (Figs. 1 and 2).

Recently we have also reported the direct enantioselective aryl and alkylacetylenes addition to imines, promoted by cop-

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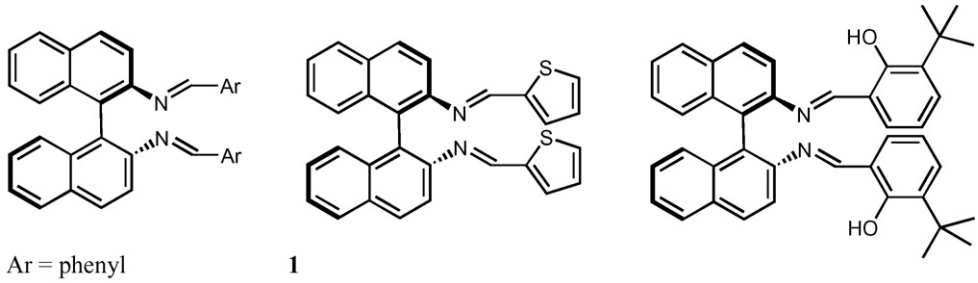


Fig. 1. Chiral bis-imines ligands **1–7**.

per(I) complexes of chiral bis-imines [14] and bis-amines [15]. A very simple experimental procedure at room temperature allowed to obtain optically active propargyl amines in very good yields and enantioselectivity up to 81%.

With the aim of developing new multicomponents reactions [16], we decided to investigate the possibility of performing an asymmetric catalysed three-component synthesis of optically propargyl amines [17]. Here we wish to report the results of this study.

2. Experimental

2.1. General

^{1}H NMR spectra were recorded at 300 MHz on $CDCl_3$ solutions and were referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to 77.0 ppm in $CDCl_3$. IR spectra were recorded on thin film or as solution in CH_2Cl_2. Optical rotations were measured at the Na-D line in a 1 dm cell at 22 °C. IR spectra were recorded on thin film or as solution in CH_2Cl_2.

Products **7** [18], **8** [10], **10** [9a], **13** [10] are known compounds.

2.2. General procedure for the synthesis of ligands *1–6*

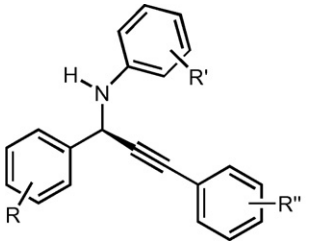
To a solution of chiral diammine (10 mmol) in dry toluene (20 mL) aromatic aldehyde (20.2 mmol) was added. The mixture was stirred in presence of molecular sieves and $MgSO_4$ for 40–72 h at 110 °C. The reaction mixture was cooled to room temperature, filtered and the solvent was evaporated under vacuum to give the corresponding imines in yields >90%. Eventually the bis-imines may be cristallized from ethanol.

2.2.1. Ligand *1*

It had m.p. 119–124 °C; $[\alpha]_D^{23}$ 112.9 ($c = 0.23$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.24 (s, 2H, CH=N), 7.98 (d, ^3J(H, H) = 5.1 Hz, 2H, H^4 e H$^{4'}$ binaphtyl ring), 7.93 (d, ^3J(H, H) = 4.8 Hz, 2H, H^5 e H$^{5'}$ binaphtyl ring), 7.44 (m, 2H, H^6 e H$^{6'}$ binaphtyl ring), 7.42 (m, 2H, proton ortho of Ar), 7.37 (m, 1H, proton para of Ar), 7.36 (d, m, 2H, H^8 e H$^{8'}$ binaphtyl ring), 7.34 (d, ^3J(H, H) = 5.1 Hz, 2H, H^3 e H$^{3'}$ binaphtyl ring), 7.30 (m, 2H, H^7 e H$^{7'}$ binaphtyl ring), 7.28 (m, 2H; proton meta of Ar); ^{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; elemental analysis calculated 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 6.15.

2.2.2. Ligand *2*

It had m.p. >200 °C; $[\alpha]_D^{23}$ −404.1 ($c = 0.29$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.69 (s, 2H, CH=N), 8.13 (d, ^3J(H, H) = 8.82 Hz, 2H, H^4 e H$^{4'}$ binaphtyl ring), 8.00 (d, ^3J(H, H) = 8.16 Hz, 2H, H^5 e H$^{5'}$ binaphtyl ring), 7.67 (d, ^3J(H, H) = 8.82 Hz, 2H, H^3 e H$^{3'}$ binaphtyl ring), 7.49 (m, 2H, H^6 e H$^{6'}$ binaphtyl ring), 7.32 (m, 2H, H^7 e H$^{7'}$ binaphtyl ring), 7.31 (m, 2H, H^8 e H$^{8'}$ binaphtyl ring), 7.22 (m, 1H, H6 Ar ring), 7.20 (m, 1H, H4 Ar ring), 6.80 (t, ^3J(H, H) = 7.47 Hz 1H; H5 Ar ring), 6.75 (d, ^3J(H, H) = 8.46 Hz 1H, H3 Ar ring); ^{13}C NMR: δ 161.9,



R = H; R' = H; R" = H **8**

R = H; R' = 2-OMe; R" = H **10**

R = H; R' = H; R" = 4-Br **14**

Fig. 2. Chiral propargylamines obtained with the two- and three-component methodologies.

160.8, 143.8, 133.3, 132.7, 132.5, 130.0, 129.5, 128.3, 127.0, 125.9, 119.3, 118.6, 117.1, 116.9; elemental analysis calculated for $C_{34}H_{24}N_2O_2$ (492.57): C 82.91, H 4.91, N 5.69; found: C 83.03, H 5.00, N 6.95.

*2.2.3. Ligand **3***

It had m.p. 203–206 °C; $[\alpha]_D^{23}$ −60.8 ($c = 0.21$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.74 (s, 2H, CH=N), 8.05 (d, ^3J(H, H) = 8.66 Hz, 2H, H^4 e $H^{4'}$ binaphtyl ring), 7.96 (d, ^3J(H, H) = 8.09 Hz, 2H, H^5 e $H^{5'}$ binaphtyl ring), 7.48 (d, ^3J(H, H) = 8.66 Hz, 2H, H^3 e $H^{3'}$ binaphtyl ring), 7.45 (m, 4H, H^6 e $H^{6'}$, H8 e H8′ binaphtyl ring), 7.34 (m, 2H, H^7 e $H^{7'}$ binaphtyl ring), 7.11 (d, 2H, proton *meta* of Ar), 7.00 (m, 1H; proton *para of Ar*), 6.7; ^{13}C NMR: δ 157.0, 148.6, 135.1, 133.8, 132.5, 132.2, 130.3, 129.2, 128.8, 128.6, 127.9, 126.8, 126.4, 125.1, 119.3; elemental analysis calculated for $C_{34}H_{22}Cl_2N_2$ (529.46): C 77.13, H 4.19, N 5.29; found: C 78.11, H 4.64, N 5.95.

*2.2.4. Ligand **4***

It had m.p. 124–127 °C; $[\alpha]_D^{23}$ −169.3 ($c = 0.22$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.55 (s, 2H, CH=N), 8.03 (d, ^3J(H, H) = 8.7 Hz, 2H, H^4 e $H^{4'}$ binaphtyl ring), 7.93 (d, ^3J(H, H) = 8.1 Hz, 2H, H^5 e $H^{5'}$ binaphtyl ring), 7.45 (m, 2H, H^6 e $H^{6'}$ binaphtyl ring), 7.39 (d, ^3J(H, H) = 8.7 Hz, 2H, H^3 e $H^{3'}$ binaphtyl ring), 7.30 (m, 2H, H^7 e $H^{7'}$ binaphtyl ring), 7.26 (d, ^3J(H, H) = 8.4 Hz, 2H, H^8 e $H^{8'}$ binaphtyl ring); ^{13}C NMR: δ 148.9, 147.9, 145.8, 142.2, 137.5, 133.4, 132.2, 129.5, 128.1, 126.9, 126.5, 125.8, 125.5, 118.0, 115.5; ^{19}F NMR ($CDCl_3$): δ −131.5, −139.9, −151.3; elemental analysis calculated for $C_{34}H_{14}F_{10}N_2$ (640.47): C 63.76, H 2.20, N 4.37; found: C 63.48, H 2.32, N 4.51.

*2.2.5. Ligand **5***

It had m.p. 119–121 °C; $[\alpha]_D^{23}$ −78.715 ($c = 0.29$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.71 (s, 2H, CH=N), 7.95 (d, ^3J(H, H) = 8.65 Hz, 2H, H^4 e $H^{4'}$ binaphtyl ring), 7.90 (d, ^3J(H, H) = 8.15 Hz, 2H, H^5 e $H^{5'}$ binaphtyl ring), 7.39 (m, 2H, H^6 e $H^{6'}$ binaphtyl ring), 7.38 (m, 2H, H^3 e $H^{3'}$ binaphtyl ring), 7.28 (m, 2H, H^7 e $H^{7'}$ binaphtyl ring), 7.33 (m, 2H, H^8 e $H^{8'}$ binaphtyl ring), 7.54 (d, 1H, ^3J(H, H) = 7.72 Hz, H6 *Ar ring*), 7.26 (m, 1H, H4 *Ar ring*), 6.79 (m, 1H; H5 *Ar ring*), 6.77 (m, 1H; H3 *Ar ring*), 3.63 (s, 3H; OCH_3); ^{13}C NMR: δ 159.5, 156.7, 149.0, 133.8, 131.5, 128.7, 128.1, 127.8, 126.8, 126.2, 125.1, 124.4, 120.6, 119.7, 110.7, 55.3; elemental analysis calculated for $C_{36}H_{28}N_2O_2$ (520.62): C 83.05, H 5.42, N 53.80; found: C 83.48, H 5.62, N 54.95.

*2.2.6. Ligand **6***

It had m.p. 87–89 °C; $[\alpha]_D^{23}$ −88.76 ($c = 0.39$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 2H, CH=N), 7.95 (d, ^3J(H, H) = 8.68 Hz, 2H, H^4 e $H^{4'}$ binaphtyl ring), 7.91 (d, ^3J(H, H) = 8.15 Hz, 2H, H^5 e $H^{5'}$ binaphtyl ring), 7.40 (m, 2H, H^6 e $H^{6'}$ binaphtyl ring), 7.33 (m, 2H, H^3 e $H^{3'}$ binaphtyl ring), 7.30 (m, 2H, H^7 e $H^{7'}$ binaphtyl ring), 7.29 (m, 2H, H^8 e $H^{8'}$ binaphtyl ring), 6.97 (d, 1H, H4 *tiophene ring*), 7.31 (m, 1H, H5 *tiophene ring*), 7.15 (m, 1H; H3 *tiophene ring*); ^{13}C NMR: δ 153.21, 148.3, 143.3, 133.6, 131.6, 131.1, 129.8, 129.0, 128.1, 127.9, 127.3, 126.9, 126.3, 124.7, 119.2; elemental analysis calculated for $C_{30}H_{20}N_2S_2$ (472.62): C 76.24, H 4.27, N 5.93; found: C 77.08, H 4.92, N 6.05.

2.3. General procedure for the enantioselective multicomponent reaction of arylacetylenes with an aldehyde and an amine

To a 2 mL toluene solution of the chiral ligand (0.03 mmol), at room temperature, under nitrogen atmosphere, copper(I) trifluoromethane sufonate (0.03 mmol) was added. After stirring for 15 min, acetylene (0.48 mmol) was added first, followed by the addition of aldehyde (0.03 mmol) and amine (0.03). 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 if necessary (hexanes/ethylacetate 95/5 mixture as eluant).

*2.3.1. Compound **9***

^{1}H NMR ($CDCl_3$): δ 7.70 (m, 1H), 7.15–7.40 (m, 8H), 6.90–7.05 (m, 2H), 6.75–6.80 (m, 3H), 5.85 (s, 1H), 3.9 (s, 3H); ^{13}C NMR: δ 157.1, 147.3, 132.2, 129.6, 129.9, 128.5, 128.6, 128.8, 127.9, 123.5, 121.4, 118.8, 114.7, 111.5, 89.5, 84.2, 56.2, 45.9; elemental analysis calculated for $C_{22}H_{19}NO$ (313.39): C 84.31, H 6.11, N 4.47; found: C 85.01, H 6.45, N 4.41. HPLC analysis (Chiralcel AD, flow rate 0.8 mL/min, $\lambda = 230$; hexane/iPrOH = 98:2; t_R: 18.8 min (minor) and 22.1 min (major)).

*2.3.2. Compound **11***

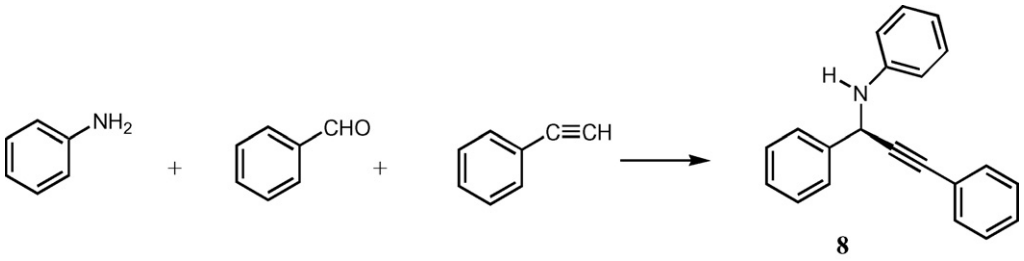
^{1}H NMR (CDCl3): δ 7.70 (m, 2H), 7.45–7.60 (m, 8H), 6.85 (m, 4H), 6.75, 5.50 (s, 1H), 3.8 (s, 3H); ^{13}C NMR: δ 153.1, 142.6, 131.7, 128.6, 128.2, 127.6, 127.3, 126.8, 122.9, 114.7, 114.3, 109.5, 88.9, 85.2, 55.6, 51.8; elemental analysis calculated for $C_{22}H_{19}NO$ (313.39): C 84.31, H 6.11, N 4.47; found: C 84.01, H 6.15, N 4.61. HPLC analysis (Chiralcel OD, flow rate 0.8 mL/min, $\lambda = 230$; hexane/iPrOH = 95:5; t_R: 14.2 min (major) and 15.5 min (minor)).

*2.3.3. Compound **12***

^{1}H NMR ($CDCl_3$): δ 7.75 (m, 2H), 7.45–7.51 (m, 2H), 7.40–7.25 (m, 6H), 7.15 (m, 2H), 6.85 (m, 3H), 5.55 (s, 1H), 4.1 (bs, NH); ^{13}C NMR: δ 153.2, 142.8, 131.9, 129.5, 128.2, 127.9, 127.1, 127.0, 126.3, 125.3, 122.1, 115.7, 89.9, 85.5, 55.8; elemental analysis calculated for $C_{21}H_{16}FN$ (301.13): C 83.70, H 5.35, N 4.65; found: C 84.01, H 5.45, N 4.65. HPLC analysis (Chiralcel OJ-H flow rate 0.8 mL/min, $\lambda = 230$; hexane/iPrOH = 90:10; t_R: 40.4 min (major) and 42.5 min (minor)).

*2.3.4. Compound **14***

^{1}H NMR ($CDCl_3$): δ 8.00 (m, 2H), 7.65 (m, 2H), 7.35–7.50 (m, 5H), 7.2–7.3 (m, 4H), 6.8 (m, 3H), 5.5 (s, 1H), 4.1 (br s, 1H); ^{13}C NMR: δ 147.08, 140.10, 133.78, 132.08, 129.81, 129.43, 128.76, 127.88, 123.16, 122.25, 119.31, 114.76, 90.49, 84.67, 51.27 elemental analysis calculated for $C_{21}H_{16}BrN$ (361.05): C 69.62, H 4.45, N 3.87; found: C 69.75, H 4.85, N 3.90. HPLC analysis (Chiralcel OD flow rate 0.8 mL/min, $\lambda = 230$; hexane/iPrOH = 95:5; t_R: 13.7 min (major) and 15.3 min (minor)).



Scheme 1. Catalytic stereoselective synthesis of propargyl amine **8**.

*2.3.5. Compound **15***

^{1}H NMR ($CDCl_3$): δ 7.65 (m, 2H), 7.35–7.50 (m, 5H), 7.35–7.50 (m, 5H), 7.25 (m, 2H), 6.85 (m, 3H), 5.5 (s, 1H), 4.2 (br s, 1H), 3.8 (s, 3H); ^{13}C NMR: δ 167.1, 149.5, 146.5, 146.0, 132.1, 129.8, 129.6, 129.4, 129.3, 128.5, 127.7, 119.1, 114.6, 92.1, 80.5, 52.9, 51.2; elemental analysis calculated for $C_{23}H_{19}NO_2$ (341.14): C 80.92, H 5.61, N 4.10; found: C 81.01, H 5.60, N 4.19. HPLC analysis (Chiralcel OJ-H flow rate 0.8 mL/min, λ = 230; hexane/iPrOH = 90:10; t_R: 13.9 min (major) and 18.4 min (minor)).

3. Results and discussion

3.1. Synthesis of the chiral bis-imine ligands

First we synthesised a series of bis-imines by reaction of commercially available (R)-binaphtyl diamine with different aromatic aldehydes in toluene to give the corresponding bis-imines **1**–**7** in good yields (Scheme 1). In a typical procedure a 0.5 M dry toluene solution of the chiral diamine (1 mol/equiv.) and the aromatic aldehyde (2.2 mol/equiv.) was refluxed for 40–72 h in the presence of molecular sieves. The reaction mixture, cooled to room temperature, was filtered and the solvent evaporated under reduced pressure to give the expected bis-imine in more than 90% yield. The crude products, that may be purified by cristallization (see Section 2), usually showed to be analytically pure by NMR and were used as chiral ligands in the copper catalysed reaction.

3.2. Copper(I) catalysed phenylacetylene addition

Then we studied the behaviour of such ligands in the copper(I) trifluoro-methanesulfonate catalysed test reaction between aniline, benzaldehyde and phenylacetylene in toluene at room temperature for 72 h, to afford the optically active propargyl amine **8** [19] (Scheme 1).

In a typical experimental procedure, to a 2 mL toluene solution of the chiral ligand (0.03 mmol), at room temperature, under nitrogen atmosphere, copper(I) trifluoromethane sulfonate (0.03 mmol) was added. After stirring for 10 min, phenylacetylene (0.48 mmol) was added and, after a few minutes, benzaldehyde (0.3 mmol) and aniline (0.3 mmol) were added to the solution too. The reaction mixture was allowed to stir for 72 h at room temperature, then it was filtered onto a celite cake and, if necessary, purified by flash chromatography. The results are collected in Table 1.

By employing chiral ligand **1**, the product **8** was obtained in quantitative yield, with a 61% enantiomeric excess, determined by HPLC on chiral stationary phase. The fact that no molecular sieves were necessary in the performing the reaction [20], where a mol/equiv. of water is produced by the equimolar condensation of aniline and benzaldehyde, prompted us to investigate the possibility to run the reaction in aqueous solvents. Unfortunately already in a 99/1 toluene/water mixture a dramatic drop both for the chemical yield and enantioselectivity was observed (entry 2 versus 1) [21]. It must be noted that a clear decomposition of the chiral catalyst in presence of water had been already observed [14].

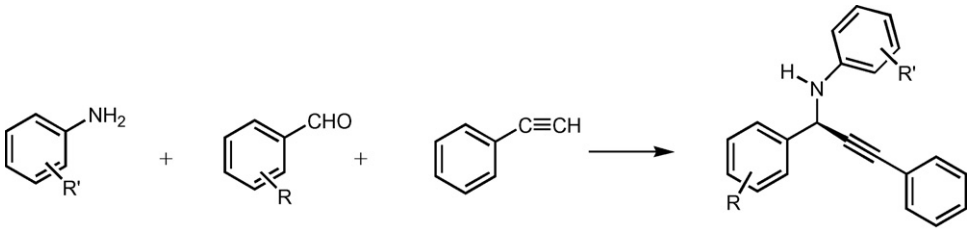
The order of the addition of the reagents was also studied; by adding the phenylacetylene as last reagent, the propargyl amine **8** was produced in lower yield and much lower enantioselectivity (65% yield and 16% ee versus >98% yield and 61% ee, entry 3 versus 1). A competitive coordination of aromatic amines to copper(I) before phenylacetylene complexation to the chiral catalyst, with generation of alternative, not selective catalytic cycles, may account for this phenomenon [22].

In the same experimental conditions of entry 1 other chiral ligands were tested in the same reaction. Best results were given by ligand **2**, derivative of the 2-hydroxybenzaldehyde, that afforded the product in quantitative yield and 75% ee (entry 4). The chiral

Table 1
Catalytic stereoselective synthesis of propargyl amine **8**

Entry	Ligand	Yield (%)[a]	ee (%)[b]
1	**1**	>98	61
2[c]	**1**	21	31
3[d]	**1**	65	16
4	**2**	>98	75
5[e]	**2**	89	71
6[f]	**2**	35	68
7	**3**	>98	59
8	**4**	>98	63
9	**5**	43	35
10	**6**	31	43
11	**7**	73	67

[a] Yields determined by 300 MHz ^{1}H NMR spectroscopy on the crude products and confirmed on the isolated products.
[b] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.
[c] Reaction run in 99/1 toluene/water solution.
[d] The phenylacetylene was added as last reagent to the catalyst, aniline, benzaldehyde toluene mixture.
[e] Reaction run with 5%mol/equiv. of chiral catalyst.
[f] Reaction time, 24 h.



R = H; R' = H; **8**
R = 2-OMe; R' = H; **9**
R = H; R' = 2-OMe; **10**
R = H; R' = 4-OMe; **11**
R = 4-F; R' = H; **12**
R = 4-Cl; R' = H; **13**

Scheme 2. Phenylacetylene reaction with differently substituted amines and aldehydes.

bis-imine **2**/Cu(I) trifluoromethanesulfonate complex worked as catalyst for this reaction also at 5%mol/equiv., affording the product with comparable enantioselectivity and only slightly lower yield (89% yield and 71 ee% versus 98% yield and 75 ee%, entry 5 versus 1). Preliminary experiments showed that shorter reaction times did not assure complete disappearance of the starting material (after 24 h only 35% conversion, entry 6).

Noteworthy, ligand **5** obtained by reaction of binaphtylamine with 2-methoxy-benzaldehyde, promoted the reaction in lower yield (43%) and decreased enantioselectivity (35% ee) compared to ligand **2** (entry 9 versus 4). The use of ligand **7**, with a sterically hindering group in ortho to the hydroxy group, did not improve the stereoselectivity of the reaction (67% ee, entry 11). Finally, the addition catalyzed by copper(I) complex of **6**, a ligand bearing supplementary weak coordinating elements like the sulfur atoms of the thiophene rings, produced **8** in only 31% yield and 43% of enantiomeric excess.

Next the general applicability of this new asymmetric catalytic multicomponent methodology was studied by investigating the behaviour of differently substituted imines (Scheme 2). The catalytic system worked with imines modified both at the N-residue or at the C-residue, affording products **8**–**13** in yields from modest to excellent, and enantioselectivities up to 75% (Table 2). *Ortho*-methoxy benzaldehyde reacts with aniline and phenylacetylene in the presence of catalytic amounts of Cu(OTf) and a chiral ligand to afford product **9** but with decreased enantioselectivites (30 and 37% enantiomeric excess with ligand **1** and **4** respectively, entries 2 and 3 of Table 2). Better results were obtained in the reaction of benzaldehyde with 2-methoxyaniline; by employing ligand **1** the chiral propargyl amine **10** was isolated in 67% yield and 65% ee (entry 4) [23]. It is worth mentioning that **10** is a valuable compound, since it is the direct precursor of the by free NH_2 group containing product, obtained by degradation of the orthomethoxyphenyl group [9a].

Unfortunately the analogous reaction of 4-methoxyaniline afforded the propargyl amine **11** in almost quantitative yield but only 27% ee (entry 7), showing the same behaviour already observed in the two-component reaction, where enantioselectivities up to 41% were obtained [14].

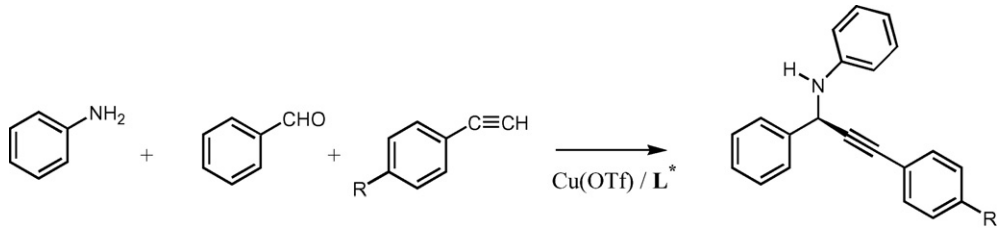
The use of 4-fluoro and 4-chloro benzaldehydes afforded interesting results; the compounds **12** and **13** were produced in good yields and enantioselectivities (61 and 61% ee, respectively, entries 8 and 9). The derivative **13** is quite attractive in view of possible further synthetic transformations that might take advantage of the chlorophenyl group, for example by using palladium catalysed C–C couplings.

It is worth mentioning the chiral bis-imine/Cu(I) complex was able to promote also the addition of differently substituted

Table 2
Reaction of phenylacetylene with differently substituted amines and aldehydes

Entry	Ligand	R	R′	Product	Yield (%)[a]	ee (%)[b]
1	**2**	H	H	**8**	>98	75
2	**1**	2-OMe	H	**9**	61	30
3	**4**	2-OMe	H	**9**	51	37
4	**1**	H	2-OMe	**10**	67	65
5	**2**	H	2-OMe	**10**	90	45
6	**4**	H	2-OMe	**10**	47	43
7	**2**	H	4-OMe	**11**	95	27
8	**1**	4-F	H	**12**	98	61
9	**1**	4-Cl	H	**13**	61	63

[a] Yields determined by 300 MHz ^{1}H NMR spectroscopy on the crude products and confirmed on the isolated products.
[b] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.



R = H;	$L^* = 2$	Y = 95%	ee 75%	**8**
R = Br;	$L^* = 1$	Y = 75%	ee 70%	**14**
R = CO_2Me;	$L^* = 1$	Y = 35%	ee 10%	**15**

Scheme 3. Reaction of functionalized arylacetylenes with aniline and benzaldehyde.

Table 3
Comparison of two- and three-component methodologies

Entry	Ligand	Product	Two component		Three component	
			Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	**2**	**8**	77	73	>98	75
2	**4**	**8**	>98	81	>98	63
3	**4**	**10**	81	75	61	30
4	**1**	**10**	21	51	67	65
5	**1**	**14**	90	75	75	65

[a] Yields determined by 300 MHz ^{1}H NMR spectroscopy on the crude products and confirmed on the isolated products.
[b] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.

aryl acetylens. 4-Bromophenyl acetylene reacted with aniline and benzaldehyde to give the corresponding propargyl amine **14** in 75% yield and 70% ee (Scheme 3). In this case the best ligand was shown to be the chiral bis-imine **1**. Also the addition of 4-carbomethoxyphenyl acetylene was performed in the presence of a catalytically amount of chiral ligand **1**/Cu(I) complex, to afford the product **15** in 35% yield but with 10% only of enantiomeric excess [24].

It is interesting to compare the results obtained for a few compounds with the two methodologies, the two-component method, where the arylacetylene is added to a preformed imine, and the three-component methodology, where the acetylenic compound, the aldeyhde and the amine are mixed all together to afford the expected enantiomerically enriched propargyl amine (Table 3).

By observing the few selected data reported about the preparation of product **8** and the methoxy substituted derivative **10** it is clear that it is not possible to indicate a ligand of choice, that performs constantly better than the other ones. For example, for the synthesis of **8** the pentafluorophenyl derivative, ligand **4**, which gave the best result in the two-component version (81% ee), performed in the multicomponent methodology worse than ligand **2** (63% ee versus 75% ee, entries 1 and 2). Also in the synthesis of **10**, the best ligand for the two-component methodology, ligand **4**, is not the best one for the three-component version, where ligand **1** offered the highest enantioselectivity (65% ee, entries 3 and 4).

The addition of 4-bromophenylacetylene, reported in entry 5, is better catalysed by the same ligand, the chiral bis-imine **1**, that allows to synthesize the product **14** in 75% ee by the two-component and 65% ee by the three-component methodologies. These numbers seem to confirm another general trend: in the multicomponent methodology the products are usually obtained in comparable or little less yields and stereoselectivities.

Finally, the results seem to confirm what already appeared in the two-component reaction [14], the relatively scarce importance in these chiral bis-imine ligands derived from the binaphtyl diamine of the steric and electronic effects of the aldehydic component, capable to affect the stereoselectivity of the process only marginally [25].

4. Conclusions

In conclusion a multicomponent stereoselective reaction between an aldehyde, an amine and arylacetylenes to afford optically active propargyl amines in good yields and up to 75% ee at room temperature was developed. The reaction is catalysed by copper(I) complexes of enantiomerically pure bis-imines readily prepared in very high yields from commercially available enantiomerically pure binaphtyl diamine.

An extremely simple experimental procedure, the mild reaction conditions, the use of all commercially available reagents, 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.

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[19] In ancillaries experiments it was demonstrated that in these conditions copper(I)-bis-imine complexes were not able to promote the phenylacetylene addition to aldehydes.
[20] Noteworthy the reaction did not afford any product in the presence of molecular sieves. A preliminary investigation by NMR tecniques have shown a marked decomposition of the copper(I)/bis-imine complex in the presence of molecular sieves. Further studies are currently underway in our group.
[21] In a 95/5 toluene/water solution no product was obtained.
[22] As expected, the (R)-binaphtyl amine/copper trifluoromethanesulfonate complex was not able to promote the multicomponent reaction, while it catalyzed the phenylacetylene addition to *N*-phenyl benzaldeyde imine in quantitative yield and 67% ee (see Ref. [15]).
[23] The good level of enantioselectivity reached in the reaction is even more interesting considering that preliminary experiments have shown that it is possible to enrich the optical purity of the propargyl amines simply by recristallization. For example, for product **8**, starting from a sample of 69% ee, one recristallization only afforded an enantiomerically pure compound (ee > 99%, by HPLC analysis; see: F. Colombo, M. Benaglia, S. Orlandi, F. Usuelli, G. Celentano, in preparation).
[24] Also the reaction of 3,5-dinitrophenylacetylene with benzaldehyde and aniline was efficiently performed to give the corresponding chiral propargyl amine in 95% yield but 5% only enantiomeric excess. Further experiments on the topic are ongoing in our laboratories.
[25] At the moment the results are quite puzzling; for example, it is not clear the role, if any, of the OH group of the chiral ligand and any attempt of rationalization would be highly speculative at this time.