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Thioether-based copper(I) Schiff base complex as a catalyst for a direct and asymmetric A^3-coupling reaction

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ABSTRACT

A novel thiosalen ligand based on a thioether has been prepared and readily coordinated with copper(I) salts (CuCl, CuBr, CuI, and CuCN). The new organometallic catalyst was used for the direct and enantioselective alkynylations of imines in an A^3-coupling reaction. In this reaction, the corresponding propargylamines were obtained as single products in excellent yields and with good enantioselectivities.

1. Introduction

The development of new enantiopure ligands that provide a chiral environment around metals so that they perform efficient asymmetric syntheses, is one of the most straightforward challenges for organic chemists.[1] In addition, due to the high coordination ability of the sulfur atom to most transition metals,[2,3] asymmetric sulfur ligands have been developed for enantioselective catalysis over the last 20 years.[4–6] The sulfur atom is considered to be a soft atom and forms strong bonds with soft metals. Moreover, sulfur-containing compounds are easily available and highly stable, especially when compared to phosphine derivatives. They also allow easy storage and handling.

There have been some reports of transition metal complexes containing thiosalen and other ligands with two sulfur and two nitrogen donor atoms;[7–13] the first report on the preparation of copper(I) and copper(II) complexes containing related ligands was published in 1992.[14]

The C—C bond forming reactions, such as the preparation of propargylamines catalyzed by transition-metal complexes, are amongst the most fundamental transformations in synthetic chemistry.[15–18] Propargylamines are significant intermediates for the synthesis of various nitrogen compounds as pharmaceutically active compounds[19] and natural products.[19,20] Also several noteworthy modifications of the A^3-coupling have been developed towards the synthesis of new heterocycles and new compounds.[16] Although the first example of an enantioselective A^3-coupling reaction was developed by using bis(oxazolinyl) ligands in combination with CuOTf,[21] the asymmetric A^3-coupling (AA^3-coupling) with secondary amines required the use of another type of chiral ligand to participate in the asymmetric synthesis of tertiary propargylamines.

Knochel et al. reported on the use of Quinap in the presence of CuBr as a chiral bidentate P,N-ligand.[22–24] Furthermore the use of Quinap/CuBr as a powerful catalytic system was expanded to the some related three component reactions in the synthesis of chiral tertiary propargylamines.[25–30]

Since commercially available Quinap is expensive and the preparation of the enantiomerically pure ligand is very difficult,[31] a new family of P,N ligands were developed by Knöpfel et al. who used Pinap for AA^3-coupling reactions with secondary amines.[32,33]

Until now, Quinap and Pinap are two chiral auxiliary ligands that have been used for AA^3-coupling reactions specifically for secondary amines in the synthesis of chiral tertiary propargylamines. In addition to economic considerations and the difficulty in preparing these ligands, it is almost impossible to recycle these ligands from the reaction media due to the low stability and oxidation of the phosphorus atoms.[34–36]

2. Results and discussion

Herein we report the development of a copper(I) phenylthioether-based N_2S_2-donor complex (CuTS) as a rate accelerator for A^3-coupling reactions (Fig. 1). To the best of our knowledge, this is a novel thiosalen complex based on N_2S_2 donor atoms in asymmetric form. This new catalytic system is highly stable and the copper(I) complexes are soluble in common organic solvents that

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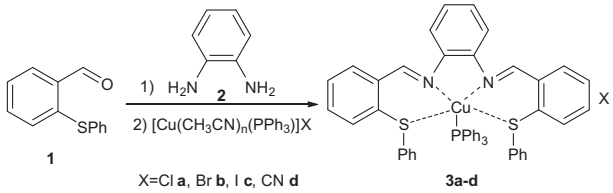


Figure 1. Synthesis of N_2S_2 Schiff base complexes.

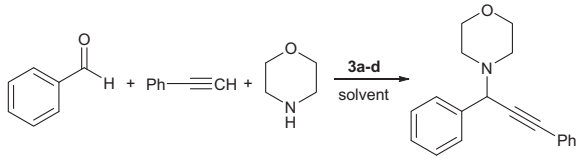
can be used for the preparation of propargylamines from the three component coupling reactions of aldehydes, secondary amines, and phenylacetylene.

The Cu[(TS)PPh_3]X complexes **3a–d** were prepared via the addition of thiosalen **3** [prepared by the reaction of 2-(phenylthio)-benzaldehyde[37] and *ortho*-phenylenediamine **2** in EtOH] to a solution of Cu[($H_3CCN)_n$(PPh_3)]X (X = Cl, Br, I, CN) in acetonitrile at room temperature. These complexes are soluble in organic solvents such as $CHCl_3$, CH_2Cl_2, hot toluene, DMF, and DMSO. However, they are insoluble in diethyl ether, acetonitrile, and *n*-hexane and are stable in air and moisture. Initially, the properties of the prepared complexes as catalysts were tested in the formation of a C—C bond between benzaldehyde, morpholine, and phenyl acetylene towards the related propargylamine. We found that the reaction was completed using 10 mol % Cu[TS(PPh_3)]Br **3b** as a catalyst in toluene at 80 °C within 5.3 h (Table 1, entry 2). We were able to successfully perform the A^3-coupling under atmospheric conditions and at moderate temperatures using this method (Table 1).

Due to the high solubility of the catalyst in the solvents used, the yields of the reactions were similar; however, toluene was selected as the desired solvent for this protocol because in addition to its performance as a solvent, the catalyst could be separated from the solvent after completion of the reaction.

We also found that the oxidation state of Cu(I) was preserved by using a cyclic voltammetry technique. In order to examine the scope of this Cu(I) complex-catalyzed A^3-coupling, the reaction was carried out using the optimized protocol in the presence of substituted aldehydes (Table 2). As shown in Table 2, we were able to successfully couple a wide-range of aldehydes containing both electron donating and electron withdrawing groups with morpholine and phenylacetylene in excellent yields. The reaction also worked well for aliphatic aldehydes (Table 2, entries 13 and 14).

Table 1
A^3-coupling reaction conditions[a]

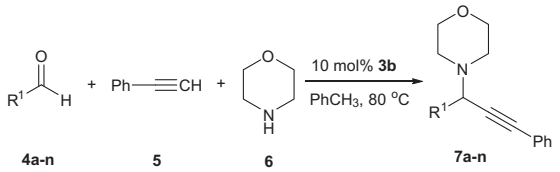


Entry	Cat (*x* mol %)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	**3a** (10 mol %)	$PhCH_3$	80	7.0	86
2	**3b** (10 mol %)	$PhCH_3$	80	5.3	93
3	**3c** (10 mol %)	$PhCH_3$	80	7.0	84
4	**3d** (10 mol %)	$PhCH_3$	80	6.2	78
5	**3b** (20 mol %)	$PhCH_3$	80	5.0	93
6	**3b** (15 mol %)	$PhCH_3$	80	5.3	93
7	**3b** (5 mol %)	$PhCH_3$	80	8.5	77
8	**3b** (10 mol %)	CH_2Cl_2	Reflux	15	63
9	**3b** (10 mol %)	THF	Reflux	10	68
10	**3b** (10 mol %)	EtOAc	Reflux	7.0	86

[a] Solution of benzaldehyde (1 mmol), morpholine (1.1 mmol), and phenylacetylene (1.2 mmol) in the selected solvent (10 ml) was heated, after the given time, the reaction was cooled to 0 °C, and the precipitate catalyst was filtered off. The product was purified from the filtrate by using silica TLC plate.

[b] Isolated yields based on benzaldehyde conversion.

Table 2
Substrate scope of the catalyst **3b** in the A^3-coupling[a]



Entry	R^1	Product	Time (h)	Isolated yield (%)
1	C_6H_5	**7a**	5.3	93
2	*p*-$CH_3C_6H_4$	**7b**	6.0	92
3	*p*-$NO_2C_6H_4$	**7c**	4.5	93
4	*p*-$CH_3OC_6H_4$	**7d**	7.2	84
5	*p*-$N(CH_3)_2C_6H_4$	**7e**	7.7	82
6	*m*-$CH_3OC_6H_4$	**7f**	6.2	86
7	*p*-$CH(Me_2)C_6H_4$	**7g**	6.2	89
8	*o*-ClC_6H_4	**7h**	5.8	90
9	*p*-ClC_6H_4	**7i**	5.0	93
10	*m*-$NO_2C_6H_4$	**7j**	5.3	91
11	2-Furan	**7k**	8.2	85
12	2-Thiophene	**7l**	9.4	83
13	*n*-C_4H_9	**7m**	7.5	89
14	*n*-C_6H_{13}	**7n**	7.8	91

[a] A solution of aldehydes (1 mmol), morpholine (1 mmol), phenylacetylene (1 mmol), and **3b** (0.1 mmol) in $PhCH_3$ (10 ml) was stirred at 80 °C. After the given time, the reaction was cooled to 0 °C and the catalyst was filtered off. The filtrate was concentrated and the desired product was purified from the filtrate by using a silica TLC plate.

The catalytic enantioselective formation of new C—C bonds via multicomponent reactions which allows for the formation of several bonds in a one-pot procedure, is an important class of reactions.[38,39] We examined the efficacy of the chiral (*R*,*R*)-thiosalen copper(I) complex **3e** as a chiral catalyst in the AA^3-coupling reaction, especially with secondary amines, towards asymmetric tertiary propargylamines. Chiral complex **3e** was prepared via the condensation of 2-(phenylthio)benzaldehyde[37] and (*R*,*R*)-1,2-diaminocyclohexane (+)-tartrate[40,41] in EtOH followed by coordination with Cu[($H_3CCN)_n$(PPh_3)]Br in acetonitrile.

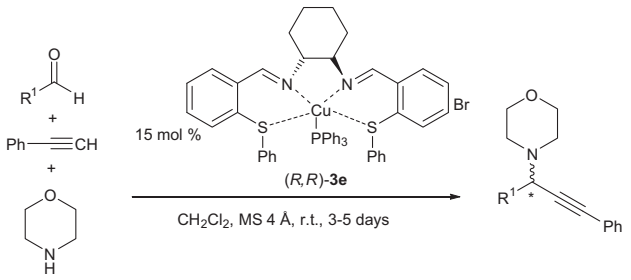
We found that (*R*,*R*)-**3e** {$[\alpha]_D^{20} = +284$ (*c* 4 $CHCl_3$)} can catalyze the asymmetric addition of phenylacetylene to aldimines to form related propargylamines with moderate to good enantiomeric excess using 15 mol % of catalyst **3e** (Table 3).

The reaction of various aldehydes **4a–4c**, **4e**, **4f**, and **4h–4k** with morpholine and phenylacetylene in the presence of **3e** (15 mol %) provided the related propargylamines in 80–94% isolated yields and with 43–69% enantiomeric excess.

All of the electron-donating and electron-withdrawing aldehydes in this procedure gave the desired propargylamines in excellent yields and with good ee (Table 3). Due to the low steric hindrance of the catalyst around the copper atom, the enantiomeric excesses of the products are relatively poor but increased with the steric demand of the aldehydes. Thus, the introduction of a functional group at the *para*-position of the aldehyde **4b**, **4c**, **4e,** and **4i** led to related products with lower enantiomeric excesses versus aldehydes with a branch at the *ortho*- or *meta*-positions (Table 3, entries 5, 6, and 8). The furan-2-carboxaldehyde-derived propargylamine **7k** was obtained in 51% ee and 81% yield (Table 3, entry 9), whereas other aldehydes showed higher enantiomeric excesses. This result is due to the ring size of the aldehyde.

A proposed mechanism for the three-component coupling reaction of aldehydes, amines, and alkynes toward propargylamine is

Table 3
Enantioselective synthesis of propargylamines[a]



Entry	R^1	Product	Time (h)	Isolated yield (%)	% ee[b]
1	C_6H_5	**7a**	85	91	44
2	*p*-$CH_3C_6H_4$	**7b**	85	90	43
3	*p*-$NO_2C_6H_4$	**7c**	75	94	58
4	*p*-$N(CH_3)_2C_6H_4$	**7e**	120	80	54
5	*m*-$CH_3OC_6H_4$	**7f**	95	85	57
6	*o*-ClC_6H_4	**7h**	90	91	69
7	*p*-ClC_6H_4	**7i**	78	93	43
8	*m*-$NO_2C_6H_4$	**7j**	85	90	62
9	*2*-Furan	**7k**	110	81	51

[a] A solution of selected aldehyde (0.5 mmol), morpholine (0.55 mmol), and phenylacetylene (0.60 mmol) in CH_2Cl_2 as solvent (10 ml) was stirred at room temperature. After the given time, the reaction mixture was filtered to remove the molecular sieves. The filtrate was concentrated and the solvent replaced with $PhCH_3$. The precipitated catalyst was filtered and the product was purified from the filtrate by using a silica TLC plate.

[b] Enantiomeric excess (ee) was determined by using HPLC with a chiral OD β-cyclodextrin-based column and 2:98 *n*-hexane/*n*-propanol as the eluent.

illustrated in Scheme 1. At first, the aldehyde is condensed with the secondary amine to give an iminium ion in situ, so that the copper(I)–thiosalen complex activates the C—H bond of the terminal alkyne to generate a copper acetylide intermediate. The copper acetylide intermediate then undergoes nucleophilic attack onto the iminium ion to give a propargylamine, along with the release of the initial catalyst for further cycles.

Notwithstanding the positive results, our knowledge in this field and about the complex-catalyzed reaction is still limited and further work is still required to make this worthwhile procedure a comprehensive and well-established method. Further applications of this method towards the preparation of more sterically hindered ligands to obtain propargylamines with high enantiomeric excess are currently underway in our laboratories.

3. Conclusion

Herein we have reported on a novel asymmetric thiosalen copper(I) complex based on N_2S_2 donor atoms as the catalyst in direct and asymmetric additions of phenylacetylenes to imines. The preparation of these complexes is very simple and due to the electron-rich character of sulfur atoms, the thiosalen ligand increases the stability of the complex and improves the catalytic activity of copper(I), especially in the AA^3-coupling reaction towards propargylamines. The reaction does not required any co-catalyst and after completion of the reaction, the catalyst was recovered by filtration and reused with only a slight decrease of activity under the same reaction conditions.

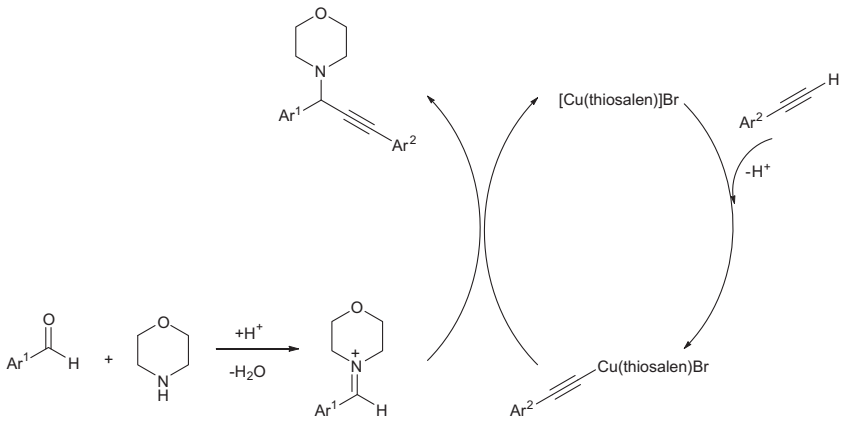
4. Experimental

4.1. General

All of the solvents were purchased from Merck Company (reagent grades) and all commercial reagents were used without further purification. IR spectra were recorded as KBr pellets on a Nicolet FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer. XRD patterns were recorded by an X'PertPro (Philips) instrument with 1.54 Å wavelengths of X-ray beam and Cu anode material. A Unicam 929 model flame atomic absorption spectrophotometer was used during the copper determination. The atomic absorption spectrometer was equipped with a copper hollow cathode lamp.

4.2. Synthesis of 2-phenylthiobenzaldehyde

2-(Phenylthio)benzaldehyde[37] was prepared according to the previously published procedure. Freshly prepared magnesium methoxide (0.90 g, 10 mmol) was placed in a 50 ml reaction flask. *N*,*N*-Dimethylformamide (30 ml), 2-nitrobenzaldehyde (1.50 g, 10 mmol) and thiophenol (1.10 g, 10 mmol) were added and stirred at 80 °C for 4 h. The progress of the reaction was monitored by TLC; after completion of the reaction, water (50 ml) was added, and the aqueous solution was extracted twice with ethyl acetate (2 × 10 ml). The combined organic layers were then dried over magnesium sulfate. The solvent was evaporated at a reduced pressure to give a yellow oil, which was purified by column chromatography using *n*-hexane/ethyl acetate (8:2) as the eluent to afford 2-phenylthiobenzaldehyde (1.85 g 87% yield). IR (thin film): 3060 (H-Ar), 2846, 2738 (HCO), 1686 (C=O), 1584, 1445 (C=C, Ar), 1392, 1299, 1195, 751, 694. ^1H NMR ($CDCl_3$): 10.38 (s, 1H,



Scheme 1. A proposed mechanism for the three component coupling reaction toward propargylamines catalyzed by copper(I)–thiosalen.

HC=O), 7.88 (s, 1H, Ar), 7.26–7.43 (m, 7H, Ar), 7.10 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$): 126.3, 128.4, 129.7, 130.3, 131.9, 133.1, 133.2, 133.7, 134.1, 141.5, 191.4. MS: 215 ([M+1]+, 1.5), 215 (M+, 12), 185 (45), 109 (74), 105 (23), 76 (100). Anal. Calcd for $C_{13}H_{10}OS$ (214.28): C 72.8, H 4.7; Found: C 72.7, H 4.6.

4.3. Synthesis of *N*,*N*-bis[2-(phenylthio)benzylidene]1,2-phenyl enediamine 3

To prepare *N*,*N*-bis[2-(phenylthio)benzylidene]1,2-phenylene diamine **3**, a solution of 2-(phenylthio)benzaldehyde (0.856 g, 4 mmol) in ethanol (50 ml) was added slowly over a solution of 1,2-diaminobenzene (0.216 g, 2 mmol) in the same solvent (20 ml). The mixture was stirred at 50 °C for 5 h and the precipitated product was obtained as a yellowish orange solid. The crude solid was filtered off and washed with ethanol twice (2 × 20 ml) and recrystallized from a dichloromethane/methanol mixed solvent to give pure crystals, conversion 98%, isolated yield 90.5% (1.80 g), mp 110–113 °C.

4.4. General procedure for the synthesis of Cu[(TS)PPh_3]X (X = Cl, Br, I, CN) complexes 3a–d

Two consecutive processes were carried out for the preparation of Cu[(TS)(PPh_3)]X (X = Cl, Br, I, CN). At first, 1.0 mmol of each one of the CuCl, CuBr, CuI, and CuCN salts of copper(I) and 1.0 mmol triphenylphosphine (PPh_3) were added to 25 ml of acetonitrile at room temperature with continuous stirring for approximately 2 h to give white solid complexes of [Cu(CH_3CN)$_n$(PPh_3)]X (X = Cl, Br, I, CN) suspended in acetonitrile. These four complexes were used during the preparation of the target catalyst in subsequent processes. To each one of these suspension complexes, 1.0 mmol (0.50 g) of ligand **3**, which had been dried in a vacuum desiccator in 30 °C for 10 h, was added, and the mixture was stirred for 5 h at room temperature. With further stirring at 50 °C for 2 h, the Cu[(TS)(PPh_3)]X (X = Cl, Br, I, CN) complexes **3a–d** were prepared as a yellow solid. The reaction mixture was filtered off and the solid was collected and washed with acetonitrile (3 × 5 ml). The complexes were dried at 30 °C under vacuum overnight.

4.5. General procedure for the synthesis of (*R*,*R*)-Cu[(TS) (PPh_3)] Br complex 3e

Two consecutive processes were carried out for the preparation of Cu[(TS)(PPh_3)]Br. At first, 1.0 mmol of CuBr as a halide of copper(I) and 1.0 mmol triphenylphosphine (PPh_3) were added to 25 ml of acetonitrile at room temperature with continuous stirring for approximately 2 h to give a white solid of [Cu(CH_3CN)$_n$(-PPh_3)]Br complex suspended in acetonitrile. This complex was used during the preparation of target catalyst **3e** in subsequent processes. To the suspension complex, 1.0 mmol (0.5 g) of ligand **3** [that previously prepared by using (*R*,*R*)-1,2-diaminocyclohexane (+)-tartrate as the diamine source in the procedure for the preparation of **3**] was added, and the mixture was stirred for 5 h at room temperature. With further stirring at 50 °C for 2 h, the Cu[(TS)(PPh_3)]Br complex **3e** wasere prepared as a yellowish brown solid. The reaction mixture was filtered off and the solid was collected and washed with acetonitrile (3 × 5 ml). The complexes were dried at 30 °C under vacuum overnight; mp 116–119 °C, $[\alpha]_D^{20} = +284$ (*c* 4, $CHCl_3$).

4.6. General procedure for the Cu[(TS)(PPh_3)]X complex-catalyzed three component coupling reaction 7a–n

All of the reactions were carried out at 80 °C in a 25 ml flask equipped with a magnetic stirrer bar and reflux condenser. In a typical procedure, to a mixture of the selected aldehyde (1.0 mmol), morpholine (1.1 mmol) and phenyl acetylene (1.2 mmol) in toluene as the solvent, the desired catalyst 0.045 g (5 mol %) was added. The final mixture was then stirred at 80 °C. After completion of the reaction (monitored by TLC), the reaction was cooled to 0 °C and the catalyst was filtered off. The filtrate was concentrated under reduced pressure to give a crude product as a viscous oil and the desired product was purified from the filtrate by using silica TLC plate with 10% EtOAc in hexane as the eluent to give the desired propargylamine. Most of the compounds thus formed are known compounds: propargylamines **7a**,[42] **7b**,[42] **7d**,[43] **7g**,[44] **7h**,[42] **7i**,[45,46] **7j**,[44] have been previously reported.

4.7. General procedure for the asymmetric synthesis of propar gylamines

All of the reactions were carried out at room temperature in a 10 ml flask equipped with a magnetic stirrer bar. A solution of the selected aldehyde (0.5 mmol), morpholine (0.55 mmol), phenylacetylene (0.60 mmol), the desired catalyst **3e** (0.06 g, 15 mol %) and 1.0 g of MS 4 Å in CH_2Cl_2 as the solvent (5 ml) was stirred at room temperature. After a given time, the reaction mixture was filtered to remove the molecular sieves. The filtrate was concentrated and the solvent replaced with $PhCH_3$. The precipitated catalyst was filtered and the product was purified from the filtrate by using a silica TLC plate with 10% EtOAc in hexane as the eluent to give the desired propargylamine. The enantiomeric excess (ee) was determined by using HPLC with a Chiral OD β-cyclodextrin-based column and *n*-hexane/*n*-propanol (2:98) as the eluent with a 254 nm UV detector.

4.8. Characterization data of thioether complexes 3a–3e

4.8.1. *N*,*N*-Bis[2-(phenylthio)benzylidene]1,2-phenylene-diamine 3

Mp 123–127 °C; IR (neat, thin film): 3043 (m), 2911 (m), 1609 (s), 1578 (m), 1490 (w), 1468 (m), 1433 (m), 1350 1265 (m), 1191 (m), 832 (m), 744 (s) and 688 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.03 (2H, s), 8.24 (2H, d, J = 6.8 Hz), 7.41–7.45 (6H, m), 7.22–7.33 (10H, m), 7.13 (4H, s); ^{13}C ($CDCl_3$, 100 MHz): δ 158.1, 150.0, 136.6, 136.5, 136.2, 133.7, 131.6, 130.0, 129.4, 128.6, 128.2, 126.9, 122.0; MS (EI) *m*/*z* (%): 500 (M^+, 12.42), 109 (100); Anal. Calcd for $C_{32}H_{24}N_2S_2$: C, 76.76; H, 4.83; N, 5.60; S, 12.81. Found: C, 76.70, H, 4.88; N, 5.54; S, 12.84.

4.8.2. *N*,*N*-Bis[2-(phenylthio)benzylidene]-1,2-diamino-benzene triphenylphosphine copper(I) bromide 3b

IR (neat, thin film): 3065 (m), 2922 (m), 1601 (s), 1585 (m), 1520 (w), 1473 (m), 1430 (m), 1345 (m) 1255 (m), 1201 (m), 845 (m), 745 (s), 693 (m), 501 (m) and 446 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.02 (2H, s), 8.25 (2H, d, J = 6.5 Hz), 7.41–7.40 (16H, m), 7.33–7.36 (6H, m), 7.25–7.33 (13H, m); MS (EI) *m*/*z* (%): 904 (M^+, 3.18), 262 (100).

4.8.3. (1*R*,2*R*)-*N*,*N*-Bis[2-(phenylthio)benzylidene]-1,2-diamino cyclohexane 3′

IR (neat, thin film): 3049 (m), 2923 (m), 1612 (s), 1581 (m), 1480 (w), 1434 (m), 1354 (m), 1266 (m) 1191 (m), 1096 (m), 745 (m), 693 (s), 511 (m), 454 (m) and 440 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.11 (2H, s), 8.07 (2H, d, J = 6.3 Hz), 7.36–7.51 (6H, m), 7.11–7.23 (10H, m), 3.17–3.23 (2H, m); 1.65–1.82 (8H, m); ^{13}C ($CDCl_3$, 100 MHz): 159.3, 148.2, 131.1, 130.3, 130.0, 129.4, 127.2, 127.1, 126.1, 126.0, 123.7, 123.3, 33.0, 32.9, 32.9, 32.8, 25.9, 25.9, 25.9 MS (EI) *m*/*z* (%): 506 (M^+, 8.24), 109 (100);

Anal. Calcd for $C_{32}H_{30}N_2S_2$: C, 75.85; H, 5.97; N, 5.53; S, 12.66. Found: C, 75.92, H, 5.90; N, 5.48; S, 12.55.

4.8.4. (1*R*,2*R*)-*N*,*N*-Bis[2-(phenylthio)benzylidene]-1,2-diamin ocyclohexane triphenyl phosphine copper(I) bromide 3e

IR (neat, thin film): 3062 (m), 2941 (w), 1608 (m), 1504 (s), 1454 (m), 1442 (m), 1247 (s), 1240 (m) 1124 (m), 1038 (m), 843 (s), 739 (m), 682 (s), 502 (m), 462 (m) and 431 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.28 (2H, s), 8.17 (2H, d, J = 6.6 Hz), 7.24–7.38 (15H, m), 7.16–7.24 (16H, m), 3.14–3.19 (2H, m); 1.84–1.97 (8H, m); MS (EI) m/z (%): 910 (M^+, 3.54), 262 (100).

4.9. Characterization data of propargylamines 7a–n

4.9.1. 4-(1,3-Diphenylprop-2-yn-1-yl)morpholine 7a

red oil; IR (thin film): 3059, 3029, 2957, 2853, 2820, 2221, 1598, 1489, 1449, 1318, 1280, 1114, 1001, 865, 758, 694, 562, 526 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 2.68 (m, 4H), 3.78 (m, 4H), 4.84 (s, 1H), 7.33–7.44 (m, 6H), 7.56–7.58 (m, 2H), 7.69 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 54.3, 55.2, 68.7, 86.2, 88.4, 115.1, 116.3, 121.9, 123.0, 124.2, 126.6, 130.4, 135.8, 137.0, 140.5, 160.7 ppm; $[\alpha]_D^{20} = +50.3$ (c 1.35, $CDCl_3$); 44% ee as a light yellow oil; R_f = 0.60 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/*n*-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 13.27 min and TR (major) = 15.65 min.

4.9.2. 4-(3-Phenyl-1-(*p*-tolyl)prop-2-yn-1-yl)morpholine 7b

red oil; IR (thin film): 3024, 2964, 2925, 2862, 2820, 1486, 1446, 1314, 1109, 999, 854, 757, 687, 562, 525, 473 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 2.39 (s, 3H), 2.65 (s, 4H), 3.75 (s, 4H), 4.78 (s, 1H), 7.20–7.22 (m, 2H), 7.34–7.36 (m, 3H), 7.53–7.55 (m, 2H); $[\alpha]_D^{20} = +37.2$ (c 1.10, $CDCl_3$); 43% ee as a light yellow oil; R_f = 0.60 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/*n*-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 10.34 min and TR (major) = 12.32 min.

4.9.3. 4-(1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-yl)morpholine 7c

IR (thin film): 3067, 2958, 2854, 2216, 1690, 1600, 1522, 1450, 1347, 1275, 1113, 1006, 864, 819, 757, 695, 539. ^1H NMR ($CDCl_3$, 400 MHz): 2.63–2.66 (m, 4H), 3.76 (m, 4H), 4.89 (s, 1H), 7.38 (s, 3H), 7.53 (m, 2H), 7.88 (m, 2H), 8.24 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 49.90, 61.45, 67.04, 83.16, 89.78, 122.31, 123.48, 128.45, 128.72, 129.33, 131.85, 145.45 ppm; $[\alpha]_D^{20} = -28.3$ (c 0.85, $CDCl_3$); 58% ee as a light yellow oil; R_f = 0.60 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/*n*-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 12.47 min and TR (major) = 14.65 min.

4.9.4. 4-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)morpholine 7d

IR (thin film): 3034, 2987, 2888, 1976, 1584, 1469, 1453, 1329, 1243, 1128, 1105, 1061, 1008, 854, 738, 664, 593. ^1H NMR ($CDCl_3$, 400 MHz): 2.59 (m, 4H), 3.45 (m, 4H), 3.70 (s, 3H), 4.83 (s, 1H), 6.79 (d, 8.3 Hz, 1H), 7.18–7.27 (m, 6H), 7.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 51.04, 53.68, 62.24, 68.61, 84.26, 87.08, 111.42, 112.66, 118.26, 121.07, 126.18, 127.25, 128.19, 130.48, 132.70, 140.04, 162.69.

4.9.5. *N*,*N*-Dimethyl-4-(1-morpholino-3-phenylprop-2-yn-1-yl) aniline 7e

IR (thin film): 2955, 2892, 2854, 2815, 1965, 1611, 1521, 115, 757, 692, 556. ^1H NMR ($CDCl_3$, 400 MHz): 2.65 (m, 4H, H_2C-17, H_2C-21), 2.97 (s, 6H), 3.73 (m, 4H), 4.70 (s, 1H), 6.72 (d, J = 8.4 Hz, 2H), 7.32 (m, 3H), 7.45 (m, 2H), 7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 44.11, 49.25, 61.48, 68.03, 85.15, 88.54, 113.85, 120.41, 123.74, 128.19, 130.04, 131.21, 134.30, 152.71. MS: 320 ($[M+1]^+$, 2.7), 215 (M+, 11), 276 (38), 234 (22), 219 (38), 101 (10), 86 (100), 76 (100); $[\alpha]_D^{20} = +30.7$ (c 0.85, $CDCl_3$); 54% ee as a light red oil; R_f = 0.80 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/*n*-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 13.27 - min and TR (major) = 14.98 min.

4.9.6. 4-(1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-yl) morpholine 7f

IR (thin film): 3057, 2995, 2851, 1965, 1599, 1486, 1449, 1314, 1256, 1314, 1256, 1150, 1115, 1044, 1001, 867, 758, 692, 564. ^1H NMR ($CDCl_3$, 400 MHz): 2.66 (m, 4H), 3.77 (m, 4H), 3.85 (s, 3H), 4.79 (s, 1H), 6.87 (d, 8.3 Hz, 1H), 7.25–7.36 (m, 6H), 7.53 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 49.99, 55.24, 62.01, 67.20, 85.15, 88.54, 113.10, 114.39, 120.99, 123.03, 128.36, 128.42, 129.28, 131.88, 132.17, 139.57, 159.71 ppm; $[\alpha]_D^{20} = +58.0$ (c 1.5, $CDCl_3$); 57% ee as a light orange oil; R_f = 0.50 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/*n*-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 12.07 min and TR (major) = 14.41 min.

4.9.7. 4-(1-(4-Isopropylphenyl)-3-phenylprop-2-yn-1-yl) mor pholine 7g

colorless oil; IR (thin film): 3069, 2971, 2936, 2873, 1980, 1430, 1326, 1128, 1011, 859, 783, 690, 606, 568, 472 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 1.32 (m, 6H), 2.60 (m, 4H), 2.86 (m, 1H), 3.80 (m, 4H), 4.92 (s, 1H), 7.16–7.24 (m, 2H), 7.38–7.51 (m, 3H), 7.70–7.83 (m, 2H).

4.9.8. 4-(1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-yl)morpholine 7h

IR (thin film): 3047, 2997, 2897, 2750, 1562, 1472, 1452, 1324, 1274, 1321, 1232, 1145, 1117, 1055, 1008, 888, 765, 627, 520. ^1H NMR ($CDCl_3$, 400 MHz): 2.69 (m, 4H), 3.71 (m, 4H), 5.14 (s, 1H), 7.25–7.30 (m, 2H), 7.33–7.36 (m, 3H), 7.41–7.43 (m, 1H), 7.50–7.52 (m, 2H), 7.75–7.77 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 49.87, 58.96, 67.14, 84.70, 88.40, 122.82, 125.58, 126.39, 128.38, 128.41, 129.18, 129.94, 130.58, 130.93, 131.85, 134.69, 135.56, 135.82 ppm; $[\alpha]_D^{20} = +54.8$ (c 2.0, $CDCl_3$); 69% ee as an orange oil; R_f = 0.70 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/*n*-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 10.77 min and TR (major) = 12.91 min.

4.9.9. 4-(1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl)morpholine 7i

IR (thin film): 3063, 3028, 2956, 2932, 1494, 1454, 1028, 746, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 2.62 (m, 4H), 3.73 (m, 4H), 4.77 (s, 1H), 7.36–7.45 (m, 5H), 7.52 (m, 2H), 7.58–7.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 49.85, 61.40, 67.15, 84.43, 88.98, 122.77, 125.59, 128.08, 128.43, 128.48, 129.70, 129.94, 131.57, 131.88, 132.16, 133.61, 135.86, 136.53 ppm; $[\alpha]_D^{20} = +74.6$ (c 2.0, $CDCl_3$); 43% ee as a yellow oil; R_f = 0.60 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/*n*-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 13.62 min and TR (major) = 15.84 min.

4.9.10. 4-(1-(3-Nitrophenyl)-3-phenylprop-2-yn-1-yl)morpholine 7j

IR (thin film): 3070, 3029, 2957, 2859, 1494, 1454, 1428, 1113, 1075, 739, 711, 703, 672, 534 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 2.67 (m, 4H), 3.76 (m, 4H), 4.90 (s, 1H), 7.38–7.41 (m, 3H), 7.56–

7.58 (m, 3H), 8.02–8.04 (d, J = 7.6 Hz, 1H), 8.17–8.19 (d, J = 7.6 Hz, 1H), 8.55 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 49.78, 61.31, 66.95, 83.17, 89.76, 122.29, 122.85, 123.41, 125.53, 128.47, 128.71, 129.15, 131.91, 134.55, 140.44, 148.39 ppm; $[\alpha]_D^{20} = +41.0$ (c 1.2, $CDCl_3$); 62% ee as a light red oil; R_f = 0.70 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/n-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 12.39 min and TR (major) = 15.60 min.

4.9.11. 4-(1-(Furan-2-yl)-3-phenylprop-2-yn-1-yl)morpholine 7k

IR (thin film): 3063, 3028, 2932, 1604, 1494, 1454, 1261, 1028, 802, 746, 698; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.71 (m, 4H), 3.79 (m, 4H), 4.89 (s, 1H), 6.36 (m, 1H), 6.52 (d, J = 2.8 Hz, 1H), 7.31–7.35 (m, 3H), 7.45 (m, 1H), 7.49–7.52 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 49.61, 56.12, 66.95, 82.85, 87.02, 109.76, 110.13, 122.57, 125.53, 128.35, 128.50, 131.87, 142.87, 150.76 ppm; $[\alpha]_D^{20} = +22.7$ (c 0.7, $CDCl_3$); 51% ee as an orange oil; R_f = 0.70 (EtOAc/petroleum ether = 2:8); HPLC conditions: Diacel chiralcel OD-H (4.6 cm I.D. × 25 cm), 98:2 hexane/n-PrOH, 500 μL/min flow rate, λ = 254 nm, TR (minor) = 10.77 min and TR (major) = 12.91 min.

4.9.12. 4-(3-Phenyl-1-(thiophen-2-yl)prop-2-yn-1-yl)morpholine 7l

IR (thin film): 3062, 3028, 2955, 2934, 2248, 1603, 1494, 1454, 1122, 747, 699. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.71 (m, 4H), 3.79 (m, 4H), 5.03 (s, 1H), 6.98 (m, 1H), 7.30 (m, 1H), 7.34–7.36 (m, 3H), 7.51–7.54 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 49.69, 57.83, 67.15, 84.29, 87.63, 122.69, 125.57, 125.87, 126.36, 126.44, 128.39, 128.48, 128.84, 131.89, 142.80 ppm.

4.9.13. 4-(1-Phenylhept-1-yn-3-yl)morpholine 7m

Colourless oil; IR (thin film): 3102, 3054, 2980, 2963, 2941, 1529, 1460, 1423, 1171, 765, 607. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.03 (t, J = 6.8 Hz, 3H), 1.25–1.48 (m, 4H), 1.67 (m, 2H), 2.73–2.79 (m, 4H), 3.85–3.96 (m, 4H), 4.88 (s, 1H), 7.30–7.38 (m, 3H), 7.44–7.42 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 14.58, 21.75, 26.10, 35.08, 52.42, 56.70, 66.90, 77.51, 86.48, 122.04, 123.08, 128.71, 128.97 ppm.

4.9.14. 4-(1-Phenylnon-1-yn-3-yl)morpholine 7n

Colourless oil; IR (thin film): 3094, 3029, 2937, 2903, 1984, 1608, 1473, 1462, 1120, 772, 681. ^{1}H NMR ($CDCl_3$, 400 MHz): 0.92 (t, J = 5.7 Hz, 3H), 1.19–1.37 (m, 8H), 1.55 (m, 2H), 2.60–2.72 (m, 4H), 3.82–3.90 (m, 4H), 5.04 (s, 1H), 7.22–7.29 (m, 3H), 7.50–7.57 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 15.18, 20.11, 22.56, 27.64, 32.84, 33.30, 50.41, 55.74, 68.07, 84.79, 89.08, 121.90, 123.47, 127.08, 128.12 ppm.

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