SYNTHESIS OF BIPHENYL-BASED LIGAND: APPLICATION IN COPPER-MEDIATED CHEMOSELECTIVE MICHAEL REACTION

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GRAPHICAL ABSTRACT

Abstract A biphenyl-based ligand attached was synthesized and screened in copper-mediated Michael reaction. The catalyst system works well with carbon or sulfur nucleophiles as Michael donors and cyclohexenone or chalcones as the acceptors under mild and neutral reaction conditions in a chemoselective manner.

Keywords Copper catalyst; homogeneous catalysis; Michael reaction; thia-Michael

INTRODUCTION

Michael reaction of active methylene compounds with \(\alpha,\beta\)-unsaturated ketones is one of the most powerful and well-studied carbon–carbon bond-forming reactions of modern chemistry.\(^1\) Similarly the Michael reaction with other heteroatom nucleophiles with activated \(\pi\)-system is extensively utilized for making carbon–heteroatom bonds.\(^2\) This reaction is extensively studied under various conditions such as presence of ionic liquids,\(^3\) aqueous,\(^4\) micellar,\(^5\) presence of base\(^6\) and DNA,\(^7\) Lewis acids,\(^8\) other acidic reagents,\(^9\) etc., with considerable success. The Michael reaction of conjugated systems with amines as nucleophiles, aza-Michael reaction, is a quite common method to synthesize important derivatives of \(\beta\)-amino ketones, esters, and acids. Similarly, the reaction with sulfur nucleophile, thia-Michael reaction, is widely employed in biosynthesis and for the synthesis of bioactive compounds\(^10\) and protection of a double bond.\(^11\)

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Many homogeneous catalyst systems are developed for promoting the Michael reaction. The homogeneous complexes of different ligands with metal salts of vanadium, copper, nickel, cobalt, iron, boron, zinc, ruthenium, palladium, etc. have been investigated for variants of the Michael reaction. Some of these catalysts work equally well with different types of nucleophiles toward reactive conjugated substrates. The crucial aspect for a useful catalyst system is the possibility of achieving a certain degree of selectivity in favor of one type of reaction or reactivity. For Michael reaction the addition of amine nucleophile to $\alpha,\beta$-unsaturated ketones is favored in most of the homogeneous catalysts. The heterogeneous catalyst of Li-X-type zeolite was found to be selective for sulfur nucleophile compared to the oxygen nucleophile for the Michael reaction. The thia-Michael reaction is also frequently studied and several efficient catalysts are developed. However, the availability of catalyst systems for chemoselective Michael reaction is not widespread.

In this paper we present a synthesis of a new biphenyl-based bis-Schiff ligand and the preliminary applications in copper-catalyzed Michael reaction of $\alpha,\beta$-unsaturated ketones. There are two literature references available for the structurally similar ligands in the literature. In one of the references its cobalt complex is explored as a catalyst for the addition of diethyl zinc to aldehydes, whereas in another the crystal structure of its bromo derivative has been solved.

RESULTS AND DISCUSSION

The design of new ligands is a crucial aspect of the process of developing homogeneous catalyst systems. The structure of new biphenyl-based ligand 1 is given in Fig. 1. The present biphenyl-based bis-Schiff base ligand is made with an aim to offer two symmetrical binding sites for complexation with metal ions and to study its catalytic activity for important chemical transformations.

The synthesis of ligand 1 is outlined in Scheme 1. The dicarboxylic acid 2 is prepared by oxidation of phenanthrene and converted to the diol 3 by known reduction with NaBH$_4$–iodine. We required to convert the diol 3 to the dibromo 4; the conditions screened are presented in supporting information. In acidic conditions the cyclization of 4 was observed, whereas in neutral conditions the dibromo 4 was the only product. The dibromo 4 thus obtained was converted to the diamine 6 via diazide 5 and further converted to desired bis-Schiff base 1 in reasonably good yields.

The role of copper catalysts for promoting the Michael reaction has been previously established and hence in the present study we chose this catalyst.

Figure 1. New biphenyl-based ligand for the present study.
system. Reaction of chalcone 7 as the $\pi$-conjugated substrate with acetyl acetone as the active methylene compound was investigated with the ligand 1 and Cu(OTf)$_2$ as the metal source. It was interesting to note that the best result was obtained when 2 equivalents of metal salt were employed with respect to the bidentate ligand 1. Neither the reverse ratio nor equal ratio of copper and ligand was effective. Absence of copper and ligand did not provide any product under the present condition of carbon–carbon-bond forming Michael reaction (Table 1). Efforts to hasten the

Scheme 1. Synthesis of ligand 1. Reaction conditions: (a) NaBH$_4$, I$_2$, THF, reflux, 18 h, 99%; (b) PPh$_3$, Br$_2$, MeCN, rt, 15 h, 88%; (c) NaN$_3$, MeCN, reflux, 24 h, 98%; (d) H$_2$, Pd-C (10%), EtOH, 1 atm., rt, 15 h; and (e) salicylaldehyde, EtOH, rt, 15 h, 65% from 5.

Table 1. Optimization of reaction parameters for Michael reaction

| No. | Acetyl acetone (eq.) | Cu(OTf)$_2$ (mol %) | Ligand 1 (mol %) | Conditions | Isolated yield (%) |
|-----|---------------------|---------------------|------------------|------------|-------------------|
| 1   | 1.0                 | 10                  | 5.5              | rt, 6 d    | 35                |
| 2   | 1.5                 | 10                  | 5.5              | rt, 6 d    | 67.6              |
| 3   | 1.5                 | 10                  | 10               | rt, 6 d    | Trace             |
| 4   | 1.5                 | 5.5                 | 10               | rt, 6 d    | Trace             |
| 5   | 1.5                 | 0                   | 0                | rt, 6 d    | NR$^b$            |
| 6   | 1.5                 | 10                  | 0                | rt, 6 d    | Trace             |
| 7   | 1.5                 | 10                  | 5.5              | 75 $^\circ$C, 30 h | 21                |
| 8   | 2.0                 | 10                  | 5.5              | rt, 6 d    | 37                |
| 9   | 1.5                 | 10$^c$              | 5.5              | rt, 6 d    | Trace             |
| 10  | 1.5                 | 10$^d$              | 5.5              | rt, 6 d    | Trace             |

$^a$For PhCOCH=CHPh 7 (1.0 eq.), 1,2-dichloroethane.

$^b$No reaction.

$^c$With Cu(OAc)$_2$.

$^d$With CuCl$_2$. 
reaction by elevating temperature also did not see any dramatic results. The other copper metal salts such as copper acetate and copper chloride were ineffective under the optimized reaction conditions.

The structure of the active catalyst of the complex of ligand 1 and Cu(OTf)$_2$ can have the possible structure I (Fig. 2). Based on our observation of best conversion, the possible structure may be complex I formed by ratio of ligand to Cu(OTf)$_2$ of 1:2 (entry 2, Table 1). Our initial efforts to grow crystals of the catalytic species were not successful. The mixture of ligand and Cu(OTf)$_2$ in 1,2-dichloroethane gave a light green powder, which showed a mass peak of 1236 (TOF MS ES$^+$), indicating to the structure I along with four sodium ions.

Having established mild and neutral conditions for the Michael reaction a number of other $\alpha,\beta$-unsaturated ketones were subjected to the same to test the generality (Table 2). The reaction with other active methylene compounds with 7 under identical conditions was not as effective: CH$_2$(CN)$_2$ (trace), CH$_2$(COOCH$_3$)$_2$ (trace), and CH$_3$COCH$_2$COOEt (43% yield, dr 80:20 by NMR).

The results of the present neutral and mild Michael reaction are encouraging and hence were further studied from the chemoselectivity angle. It was interesting to observe negligible conversions in oxo- and aza-Michael reaction with phenol and amines. Reaction of cyclohexenone 17 with $\beta$-naphthol did not furnish oxo-Michael product but gave BINOL (36% yield) by copper-catalyzed oxidation reaction.$^{[30]}$ Similarly reaction with amino nucleophiles as Michael donors such as piperidine, aniline, and imidazole did not furnish 1,4-addition products. On the other hand reaction with soft nucleophile such as thiols gave the desired thia-Michael reaction products in good yields.

Reaction of cyclohexenone 17 with 2-naphthalenethiol 20 (1.5 eq.) furnished the thia-Michael product 21 in good yield (81%) under the standard condition. The chemoselectivity of the system was then investigated with different combinations. In the first reaction cyclohexenone was exposed to the established conditions with piperidine and 2-naphthalenethiol and the products were analyzed. The aza-Michael product 22 was not detected whereas the thia-Michael product 21
Table 2. Examples of Michael reaction with the present catalyst system$^a$

| No. | $\alpha,\beta$-Unsaturated ketone | Product | Yield$^b$ (%) |
|-----|----------------------------------|---------|--------------|
| 1   | ![Image](image1.png)  | ![Image](image2.png)  | 67           |
| 2   | ![Image](image3.png)  | ![Image](image4.png)  | 54           |
| 3   | ![Image](image5.png)  | ![Image](image6.png)  | 89           |
| 4   | ![Image](image7.png)  | ![Image](image8.png)  | 65           |
| 5   | ![Image](image9.png)  | ![Image](image10.png) | 40           |
| 6   | ![Image](image11.png) | ![Image](image12.png) | 81           |
| 7   | ![Image](image13.png) | ![Image](image14.png) | 82           |
| 8   | ![Image](image15.png) | ![Image](image16.png) | 83$^c$       |

$^a$With acetyl acetone (1.5 eq.), 1,2-dichloroethane, Cu(OTf)$_2$ (10.0 mol %), 1 (5.5 mol %), rt, 6 d.

$^b$Isolated.

$^c$$dr = 50:50$. 

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was isolated, though in lesser yield (Scheme 2). This observation of chemoselectivity in favor of thia-Michael over aza-Michael was noted previously.\cite{2a}

In the next experiment the comparison between aromatic and aliphatic thiols was examined (Scheme 3). Reaction of the benzyl mercaptan \textbf{23} was slightly favored because of more nucleophilic sulfhydryl sulfur atoms, and the corresponding product \textbf{24} was formed in excess compared to the product of weaker nucleophilic aromatic thiol. This observation is slightly different than the recently reported example for ionic-liquid-mediated Michael reaction for \textbf{20} and \textbf{23} with cyclohexenone.\cite{3d}

In the study weaker nucleophilic but stronger acidic \textbf{20} gave faster product \textbf{21} in the thia-Michael reaction. Reaction of \textbf{17} with only aryl alkyl thiol \textbf{23} (1.5 eq.) gave product \textbf{24} in good yield (84%), not shown in the scheme.

Reaction of 2-mercaptoethanol \textbf{25} with cyclohexene selectively gave thia-Michael product \textbf{26} (Scheme 4), while \textbf{27} was not detected. Such observations of selectivity are in accordance with other reported catalytic systems.\cite{23,24} The isolated

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\text{Scheme 2. Selective thia-Michael reaction of 17.}
\]

\[
\text{Scheme 3. Selectivity toward R-SH compared to Ar-SH.}
\]
yields of the experiments run to test chemoselectivity were lower because only 1.0 or 1.2 equivalent reagents were utilized to assess the selectivity and no attempts were made to optimize conditions.

The new ligand 1 was prepared as a part of our ongoing project on atropisomeric compounds and efforts are under way to prepare its derivatives and separate their isomers to study the applications in asymmetric version of these reactions.

**EXPERIMENTAL**

Reagents were purchased from Sigma-Aldrich Chemicals Limited, SD Fine, and Qualigens Limited. Thin-layer chromatography was performed on Merck 60 F254 aluminium-coated plates. The spots were visualized under ultraviolet light or with iodine vapor. All the compounds were purified by column chromatography using silica gel (60–120 mesh). All the products were characterized by $^1$H NMR, infrared (IR), and mass spectroscopy and by comparison of melting points with the reported values. $^1$H NMR spectra were recorded on Bruker Avance 400 spectrometer and were run in CDCl$_3$. Mass spectra were recorded on Thermo-Fischer DSQ II GCMS instrument. IR spectra were recorded on a Perkin-Elmer FTIR RXI spectrometer as KBr pallets. Melting points were recorded in Thiele’s tube using paraffin oil and are uncorrected.

**2,2'-bis(Hydroxymethyl)biphenyl (3)**

Sodium borohydride (7.404 g, 0.198 mol), dry THF (200 mL), and diacid 2 (10.0 g, 0.041 mol) were added in one portion to a 1-L, two-necked, round-bottomed flask fitted with magnetic stir bar and a reflux condenser. The flask was cooled in an ice bath. To this a solution of iodine (21.95 g, 0.087 mol) in dry THF (100 mL) was poured via an addition funnel slowly over 45 min, resulting in vigorous evolution of hydrogen. After the addition of iodine was complete, the flask was heated to reflux (18 h) and cooled to room temperature. Methanol (30 mL) was added cautiously until the mixture become clear. After stirring (30 min), the solvent was removed, leaving a white paste, which was dissolved in KOH solution (20% aqueous 200 mL). The resultant solution was stirred (4 h) and extracted with ethyl acetate.
The organic layer was dried over sodium sulfate and concentrated in vacuum, affording a white solid (8.77 g, 99%). Mp = 110–112 °C (lit. 110.5–111.5 °C). IR (KBr): ν 3355, 3064, 2918, 1479, 1448, 1428, 1423, 1339, 1250, 1194, 1104, 1034, 998, 774, 755, 654 cm⁻¹. ¹H NMR (400 MHz, CDCl₃); δ 7.51–7.49 (dd, J = 6.4 and 1.2 Hz, 2H), 7.44–7.39 (td, J = 6.0 and 1.6 Hz, 2H), 7.38–7.34 (td, J = 6.0 and J = 1.2 Hz, 2H), 4.35 (broad s, 4H), 3.07 (s, 2H). Mass (EI⁺) m/z (%): 198 (6), 197 (40), 196 (9), 195 (10), 181 (2), 180 (2), 179 (11), 168 (14), 167 (100), 165 (1).

2,2'-bis(Bromomethyl)biphenyl (4)

Triphenyl phoshine (25.76 g, 0.098 mol) and acetonitrile (100 mL) were added to an oven-dried, two-necked, round-bottomed flask and cooled in an ice bath. To this stirred mixture bromine (5.29 mL, 0.103 mol) was slowly added (30 min). After addition, the yellow slurry was formed, to which the diol 3 (10.0 g, 0.047 mol) was added in one portion. The yellow slurry changed to a clear solution, but after 10 min again the yellow slurry was formed. The whole reaction mixture was stirred (15 h) at room temperature. Then solvent was removed at reduced pressure, and the resulting product was washed with water (2 × 250 mL) and extracted with ethyl acetate (2 × 250 mL). The organic layer was dried over sodium sulfate and concentrated in vacuum. The crude product was purified by column chromatography on silica gel using petroleum ether as eluent to give 2,2'-bis(bromomethyl)biphenyl 4 (13.98 g, 88%) as colorless prisms. Mp = 86–88 °C (lit. 87–89 °C). IR (KBr): ν 3064, 3025, 2941, 2877, 2097, 1558, 1479, 1434, 1272, 1219, 1158, 1135, 1006, 953, 805, 772, 537 cm⁻¹. ¹H NMR (400 MHz, CDCl₃); δ 7.59–7.56 (dd, J = 7.6 and 1.6 Hz), 7.47–7.43 (td, J = 7.6 and 1.6 Hz, 2H), 7.31–7.28 (dd, J = 7.6 and 1.6 Hz, 2H), 4.39–4.36 (d, J = 10 Hz, 2H), 4.23–4.21 (d, J = 10 Hz, 2H). Mass (EI⁺) m/z (%): 348 (20), 346 (36), 344 (48), 342 (23), 314 (20), 312 (60), 311 (12), 310 (100), 310 (79), 306 (22), 279 (19), 274 (76), 272 (51), 241 (24), 239 (34), 236 (18), 61 (12), 57 (9).

2,2'-bis(Azidomethyl)biphenyl (5)

A solution of dibromo (4) (7.0 g, 0.177 mol) and sodium azide (3.35 g, 0.044 mol) in acetonitrile (30 mL) was refluxed for 24 h. The mixture was cooled to room temperature, solvent was removed at high vacuum, and the crude product was quenched with water. The aqueous layer was extracted with ethyl acetate (3 × 250 mL) and then dried with anhydrous sodium sulfate. The organic solvent was evaporated under reduced pressure to give a pale yellow liquid as crude product, which was purified by column chromatography on silica gel using petroleum ether as eluent to give diazide 5 (5.35 g, 98%) as a colorless oil. IR (neat): ν 3063, 3023, 2941, 2877, 2097, 1598, 1477, 1446, 1344, 1256, 1193, 1007, 886, 759 cm⁻¹. ¹H NMR (400 MHz, CDCl₃); δ 7.52–7.41 (m, 6H), 7.26–7.24 (m, 2H), 4.18–4.14 (d, J = 13.6 Hz, 2H). Mass (EI⁺) m/z (%): 207 (7), 195 (10), 194 (12), 193 (20), 192 (17), 181 (15), 180 (100), 179 (20), 178 (15), 176 (11), 166 (18), 165 (36), 164 (8), 153 (12), 52 (38), 151 (17), 77 (9), 76 (8), 63 (8), 51 (7).
2,2’-{(1E,1’E)-[[1,1’-Biphenyl]-2,2’diylbis(methylene)]
  bis(Azanylylidene)bis(methanylylidene)}diphenol (1)

A solution of diazide 5 (2.0 g, 0.007 mol) in ethanol (20 mL) was hydrogenated
(H2 balloon) in the presence of palladium/carbon (10% Pd, 0.2 g) for 15 h with
stirring at room temperature. After the reaction was complete, as monitored by
thin-layer chromatography (TLC), the catalyst was removed by filtration through
Celite and washed with ethanol (2 x 5 mL). The filtered solution was concentrated
to its half volume on a rotary evaporator.

Salicylaldehyde (2.02 mL, 0.018 mol) was added and the mixture was stirred at
room temperature. After about 1 h, yellow slurry was slowly formed and the reaction
continued (15 h). The yellow precipitates were filtered through sintered funnel,
washed with cold ethanol (2 x 5 mL), and further purified by recrystallization
from methanol to get yellow crystals of 1 (2.08 g, 65%). Mp = 128–130 °C. IR
(KBr): δ 3649, 3060, 3017, 2884, 1670, 1636, 1582, 1505, 1472, 1462, 1441, 1375,
1333, 1279, 1210, 1159, 1058, 1030, 995, 959, 943, 895, 876, 847, 757, 722,
655 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 13.33 (s, 2H), 7.78 (s, 2H), 7.44–7.36
(m, 6H), 7.31–7.26 (m, 2H), 7.24–7.22 (d, J = 6.8 Hz, 2H), 7.06–7.04 (dd, J = 7.6
and 1.2 Hz, 2H), 6.95–6.93 (d, J = 8.4 Hz, 2H), 6.85–6.82 (m, 2H), 4.59–4.56
(d, J = 14.0 Hz, 2H), 4.36–4.33 (d, J = 14.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃):
δ 165.76, 160.95, 139.79, 135.87, 132.30, 131.48, 129.88, 128.99, 128.18, 127.43,
118.67, 118.58, 116.89, 61.61. Mass (EI⁺) m/z (%) 301 (4), 300 (21), 299 (92), 298
(6), 286 (3), 180 (16), 179 (90), 178 (100), 177 (7), 175 (7), 166 (9), 165 (30), 152
(5), 134 (3), 122 (6), 121 (35), 119 (4), 106 (10), 77 (5). Anal. calcd. for
C₂₈H₂₄N₂O₂: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.68; H, 5.67; N, 6.77.

CONCLUSION
The new ligand 1 is easy to make and is effective in copper-catalyzed Michael
reaction. Furthermore, the homogeneous catalysts system is capable of assisting the
Michael reaction in chemoselective manner for the useful carbon–carbon and carbon–sulfur bond-forming Michael reaction.

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SUPPORTING INFORMATION

Full experimental procedures and analytical data of all the catalytic applications can be accessed on the publisher’s website.

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