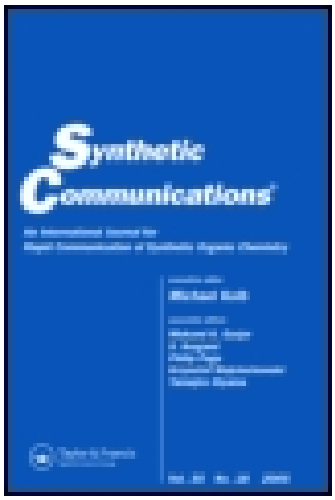

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Synthesis of Biphenyl Based Ligand: Application in Copper Mediated Chemoselective Michael Reaction

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Synthesis of biphenyl based ligand: Application in copper mediated chemoselective Michael reaction

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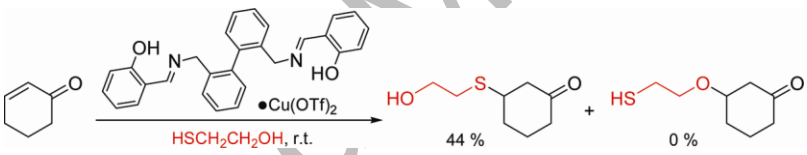
Abstract

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 chemoselective manner.



KEYWORDS: Homogeneous catalysis, Michael reaction, Thia-Michael, Copper catalyst

INTRODUCTION

Michael reaction of active methylene compounds with α,β-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 π-system is extensively utilized for making carbon-heteroatom bonds.[2] This reaction is extensively studied under various conditions such as in 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 quite common method to synthesize important derivatives of β-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 for the protection of a double bond.[11]

Many homogeneous catalyst systems are developed for promoting the Michael reaction.[12] The homogeneous complexes of different ligands with metal salts of vanadium,[13] copper,[14] nickel,[15] cobalt,[16] iron,[17] boron,[18] zinc,[19] ruthenium,[20] palladium[21] etc. have been investigated for variants of Michael reaction. Some of these catalysts works equally well with different types of nucleophiles towards 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 α,β-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.[22] The thia-Michael reaction is also frequently studied and several efficient catalysts are developed.[23] However, the availability of catalyst systems for chemoselective Michael reaction is not widespread.

In this paper we present synthesis of a new biphenyl based bis-Schiff ligand and the preliminary applications in copper catalyzed Michael reaction of α,β-unsaturated ketones. There are two literature references available for the structurally similar ligands in the literature.[24] In one of the references its cobalt complex is explored as a catalyst for the addition of diethyl zinc to aldehydes,[24b] while in another crystal structure of its bromo derivative has been solved.[24c]

RESULT 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 Figure 1. The present biphenyl based bis-Schiff base ligand is made with an aim to offer two symmetrical binding cites for the 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[25] and converted to the diol **3** by known reduction with $NaBH_4$-iodine.[26] We required to convert the diol **3**[27] to the dibromo **4**,[28] the conditions screened are presented in supporting information. In acidic condition the cyclization of **4** was observed,[29] while in the neutral condition 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 Michael reaction has been previously established[14f] hence in the present study we chose this catalyst system. Reaction of chalcone **7** as the π-conjugated substrate, 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 best result was obtained when two equivalent metal salt was 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 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** (Figure 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 crystal of the catalytic species were not successful. The mixture of ligand and $Cu(OTf)_2$ in 1,2-dichloroethane gave a light greenings color 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 condition for Michael reaction a number of other α,β-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_3COCH_2COOEt (43 % Y, d.r. 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 β-naphthol did not furnish oxo-Michael product but gave BINOL (36 % Y) by copper catalyzed oxidation reaction.[30] Similarly reaction with amino nucleophiles as Michael donors such as piperidine, aniline, 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 while the thia-Michael product **21** was isolated, though in lesser yield (Scheme 2). This observation of chemoselectivity in favor of thia-Michael over aza-Michael is noted previously.[2a]

In the next experiment the comparison between aromatic and aliphatic thiols was examined (Scheme 3). Reaction of the benzyl mercaptan **23** was slightly favored because

of more nucleophilic sulfhydryl sulfur atom and the corresponding product **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 **20** and **23** with cyclohexenone.[3d] In the study weaker nucleophilic but stronger acidic **20** gave faster product **21** in the thia-Michael reaction. Reaction of **17** with only aryl alkyl thiol **23** (1.5 eq.) gave product **24** in good yield (84 %), not shown in the scheme.

Reaction of 2-mercaptoethanol **25** with cyclohexene selectively gave thia-Michael product **26** (Scheme 4), while **27** was not detected. Such observations of selectivity are in accordance with other reported catalytic systems.[23,24j] The isolated 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 underway 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, Qualigens Limited etc. Thin Layer Chromatography was performed on Merck 60 F_{254} Aluminium coated plates. The spots were visualized under UV light or with iodine vapour. All the

compounds were purified by column chromatography using silica gel (60-120 mesh). All the products were characterized by H-NMR, IR, Mass spectroscopy and by comparison of m.p. 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)

To a one litter two neck round bottom flask, fitted with magnetic stir bar and a reflux condenser was added sodium borohydride (7.404 g, 0.198 mol), dry THF (200 mL), diacid **2** (10.0 g, 0.041 mol) in one portion. 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 in 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), cooled to room temperature and 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 % aq. 200 mL). The resultant solution was stirred (4 h) and extracted with ethyl acetate (3 x 250 mL). The organic layer was dried over sodium sulfate and concentrated in vacuum, affording a white solid (8.77 g, 99 %).

M. p. = 110 - 112 ^{o}C (Lit.[29] 110.5 - 111.5 ^{o}C)

IR (KBr): □ 3355, 3064, 2918, 1479, 1448, 1428, 1423, 1339, 1250, 1194, 1104, 1034, 998, 774, 755, 654 cm.$^{-1}$

^{1}H NMR (400 MHz, $CDCl_3$): 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 1.6 Hz, 2H), 7.18-7.16 (dd, *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):

To an oven dried two neck round bottom flask triphenyl phoshine (25.76 g, 0.098 mol) and acetonitrile (100 mL) was added 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, 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 wash with water (2 × 250 mL) and extracted with ethyl acetate (2 × 250 mL). The organic layer were 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.

M. p. = 86-88 ^{o}C (Lit.[31] 87-89 ^{o}C)

IR (KBr): υ 3064, 3025, 1972, 1558, 1479, 1434, 1272, 1219, 1158, 1135, 1006, 953, 805, 772, 606, 537cm.$^{-1}$

^{1}H NMR (400 MHz, $CDCl_3$): 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), 7.42-7.38 (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 (10), 308 (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), sodium azide (3.35 g, 0.044 mol) in acetonitrile (30 mL) was refluxed for 24 h. The mixture was cooled to room temperature and solvent was removed at high vacuum, 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.

Colorless oil.[32]

IR (Neat): □ 3063, 3023, 2941, 2877, 2097, 1598, 1477, 1446, 1344, 1256, 1193, 1007, 886, 759 $cm.^{-1}$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.41 (m, 6H), 7.26-7.24 (m, 2H), 4.18-4.14 (d, *J* = 13.6 Hz, 2H), 4.11-4.08 (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), 167 (11), 166 (18), 165 (36), 164 (8), 153 (12), 52 (38), 151 (17), 77 (9), 76 (8), 63 (8), 51 (7).

2,2'-{(1*E*,1'*E*)-(([1,1'-Biphenyl]-2,2'diylbis(Methylene))Bis(Azanylylidene))Bis(Methanylylid- Ene)}Diphenol (1):

A solution of diazide **5** (2.0 g, 0.007 mol) in ethanol (20 mL) was hydrogenated (H_2 balloon) in presence of palladium/carbon (10 % Pd, 0.2 g) for 15 h with stirring at room temperature. After the reaction was complete (tlc), the catalyst was removed by filtration through Celite and wash with ethanol (2 X 5 mL). The filtered solution was concentrated to its half volume on rotary evaporator.

To this salicylaldehyde (2.02 mL, 0.018 mol) was added and the mixture stirred at room temperature. After about 1h, slowly yellow slurry was formed and the reaction was continue (15 h). The yellow precipitates were filtered through sintered funnel and wash with cold ethanol (2 x 5 mL), further purified by recrystallization from methanol to get yellow crystals of **1** (2.08 g, 65%).

Mp. = 128-130 $^{\circ}$C.

IR (KBr): υ 3649, 3060, 3017, 2884, 1670, 1636, 1582, 1500, 1472, 1462, 1441, 1375, 1333, 1279, 1210, 1159, 1119, 1058, 1030, 995, 959, 943, 895, 876, 847, 757, 722, 655 $cm.^{-1}$

^{1}H NMR (400 MHz, $CDCl_3$) : 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.68; H, 5.67; N, 6.77.

4-Acetyl-1,3-Diphenylhexane-1,5-Dione (8) [Table 2, Entry 1]:

In an oven dried round bottom flask (10 mL capacity) placed copper(II)trifluomethanesulfonate (17 mg, 0.048 mmol, 10.0 mol %) and the Ligand **1** (11 mg, 0.026 mmol, 5.5 mol%) in 1,2–dichloroethane (2 mL) stirred (15 min). to this mixture the appropriate chalcone (0.10 g, 0.48 mmol, 1.0 eq.), acety acetone (0.07 g ,0.72 mmol, 1.5 eq.) was added and resulting mixture was stirred at room temperature (6 d). After the completion of reaction (as monitored by TLC) the material was loaded on silica gel column for chromatographic separation using light petroleum ether:ethyl acetate (100:0 to 70:30) as eluent to obtain a white solid (**8**) (0.10 g, 67%).

M. p. = 144-146 ^{o}C (Lit.[8g] 146-147 ^{o}C)

IR (KBr): □ 3085, 3060, 3028, 2938, 2916, 1693, 1595, 1496, 1449, 1411, 1262, 1242, 1209, 1187, 1154, 1074, 1004, 982, 948, 919, 746, 700, 688 $cm.^{-1}$

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.81 (m, 2H), 7.55-7.50 (m, 1H), 7.43-7.39 (m, 2H), 7.26-7.21 (m, 4H), 7.19-7.17 (m, 1H), 4.34-4.31 (d, *J* = 11.2 Hz, 1H), 4.26-4.19 (m, 1H), 3.36-3.29 (dd, *J* = 16.4 and 9.2 Hz, 1H), 3.22-3.17 (dd, *J* = 16.4 and 4 Hz, 1H), 2.29 (s, 3H), 1.89 (s, 3H).

Mass (EI^{+}) m/z (%) 266 (4), 264 (47), 248 (5), 247 (27), 246 (13), 209 (5), 208 (5), 147 (5), 146 (11), 130 (6), 119 (6), 114 (5), 106 (5), 104 (100), 102 (8), 90 (4), 78 (4), 76 (43), 68 (5).

For detail procedure and characterization for other examples, see supporting Information.

CONCLUSION

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

SUPPORTING INFORMATION

Full experimental procedures and analytical data of all the catalytic applications.

Supplemental data for this article can be accessed on the publisher's website.

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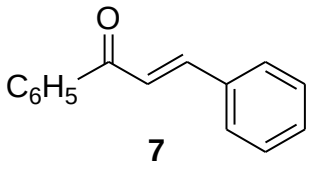
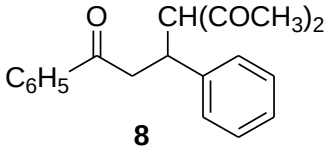
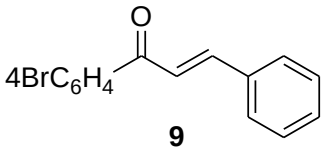
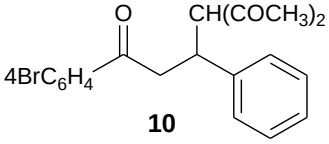
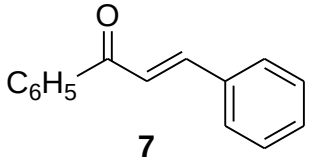
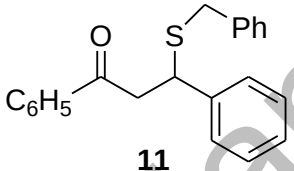
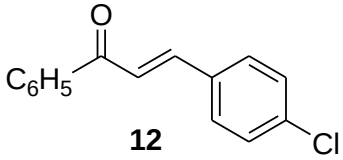
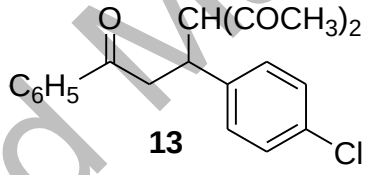
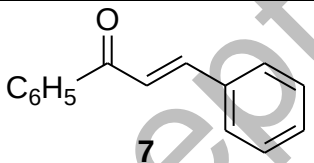
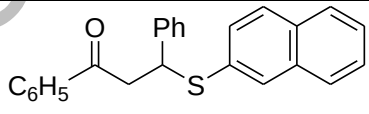
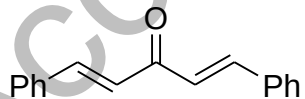
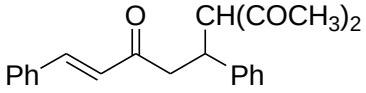
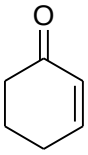
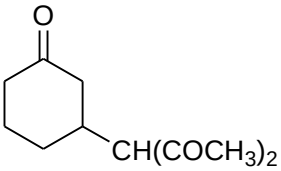
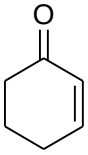
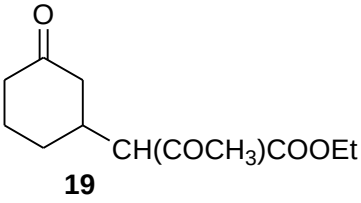
Table 1 Optimization of reaction parameters for Michael reaction.

No	Ratio[a]			Conditions	Isolated yield/%
	Acetyl acetone (eq.)	$Cu(OTf)_2$ (mol %)	Ligand **1** (mol %)		
1	1.0	10	5.5	r.t., 6 d	35
2	1.5	10	5.5	r.t., 6 d	67.6
3	1.5	10	10	r.t., 6 d	*trace*
4	1.5	5.5	10	r.t., 6 d	*trace*
5	1.5	0	0	r.t., 6 d	NR[b]
6	1.5	10	0	r.t., 6 d	*trace*
7	1.5	10	5.5	75 ^oC, 30 h	21
8	2.0	10	5.5	r.t., 6 d	37
9	1.5	10[c]	5.5	r.t., 6 d	*trace*
10	1.5	10[d]	5.5	r.t., 6 d	*trace*

[a]For PhCOCH=CHPh **7** (1.0 eq.), 1,2-dichloroethane; [b]No reaction. [c]With $Cu(OAc)_2$, [d]With $CuCl_2$

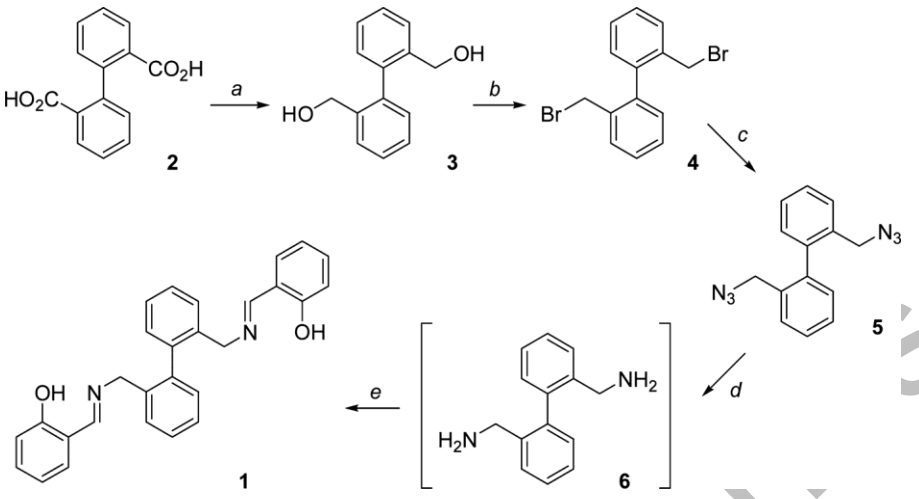
Table 2 Examples of Michael reaction with the present catalysts system.[a]

No	α,β-Unsaturated ketone	Product	Yield[b] (%)
1	 **7**	 **8**	67
2	 **9**	 **10**	54
3	 **7**	 **11**	89
4	 **12**	 **13**	65
5	 **7**	 **14**	40
6	 **15**	 **16**	81

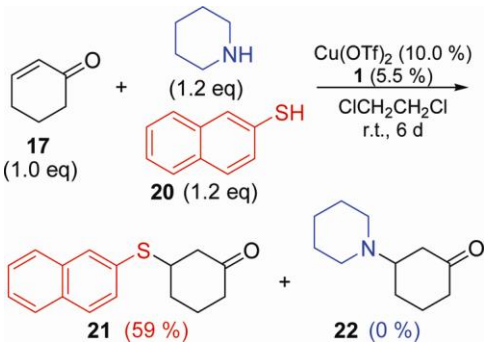
7	 **17**	 **18**	82
8	 **17**	 **19**	83[c]

[a]With acetyl acetone (1.5 eq.), 1,2-dichoroethane, $Cu(OTf)_2$ (10.0 mol %), **1** (5.5 mol %), r.t., 6 d; [b]Isolated, [c]d.r. = 50:50.

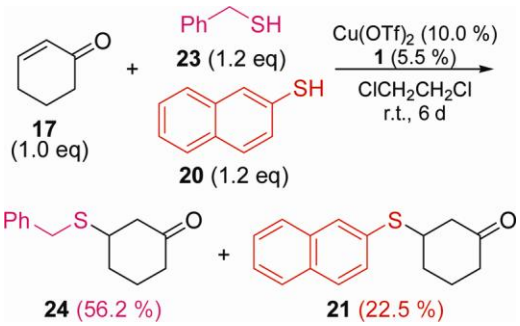
Scheme 1 Synthesis of ligand **1**. *Reaction conditions*: *a*. $NaBH_4$, I_2, THF, reflux, 18 h, 99%; *b*. PPh_3, Br_2, MeCN, r.t., 15 h, 88%; *c*. NaN_3, MeCN, reflux, 24 h, 98%. *d*. H_2, Pd-C (10%), EtOH, 1atm., r.t., 15 h; *e*. salicylaldehyde, EtOH, r.t., 15 h, 65% from **5**.



Scheme 2 Selective thia-Michael reaction of **17**.



Scheme 3 Selectivity towards R-SH compared to Ar-SH.



Scheme 4 Selectivity between thiol and alcohol.

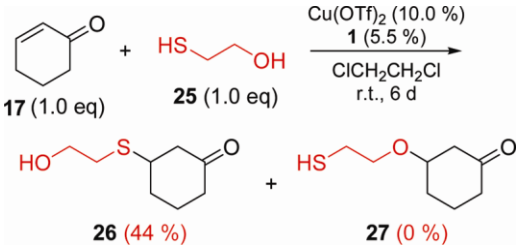
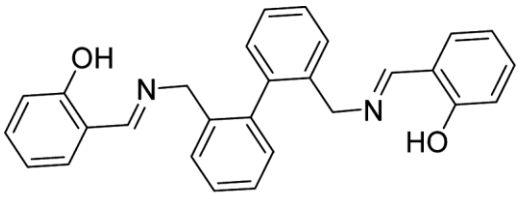
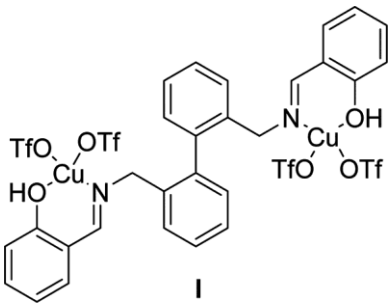


Figure 1 The new biphenyl based ligand for the present study.



1

Figure 2 Possible compositions of complex of ligand **1** and $Cu(OTf)_2$.



I

Ligand - Cu ratio = 1 : 2