Enantioselective Asymmetric Michael Addition of ~| -Unsaturated Ketones using New Chiral Trisite Phase Transfer Catalysts

Jayaraman Sivamani, Ponmuthu Kottalavijaya, Veeramanoharan Ashokkumar, Sepperumal Murugesan, Ayyanar Siva*

Department of Inorganic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai-625 021, Tamilnadu, India.
E. mail:drasiva@gmail.com

***Abstract*-Highly enantioselective Michael addition of diethyl malonate to various chalcones have been achieved under mild chiral multisite phase-transfer catalytic conditions by the successful utilization of 2,4,6-(triscinchoniummethyl)phenyl-1,3,5-triazine 1 (1a & 1b) and 2,4,6-(triscinchonium)mesitylene 2 (2a & 2b) as new chiral quaternary ammonium catalysts. This simple asymmetric Michael addition process was found to be quite effective Michael adducts with very good yield (70-98%) and ee's (74-99%).**

***Keywords*-Phase Transfer Catalysts, Michael Reaction, Enantioselective reaction, Quaternary ammonium salt, Cinchona alkaloid.**

I. INTRODUCTION

Phase transfer catalysis (PTC) is the most important and efficient technique for various organic field [1-6] and this was one of the most interesting and fascinating topics of research during the last few years being successful for a multitude of organic transformations. [7] In addition, when a chiral phase-transfer catalyst (CPTC) is employed in reactions, producing a new stereogenic centers, reactions may proceed stereo selectively to give optically active products. The role of phase transfer catalyst is to transfer reagent from the aqueous phase into the organic phase, thus provides the organic substrate to react with the transferred anion and form the product in the organic phase reactions. Single-site PTCs have extensively used for number of reactions because of its inseparability and usage is often limited. [8] However, it has a lower activity and diffusion limitation the applicability of single-site phase transfer catalyst has always received poor attention. [9] In order to develop the catalytic efficiency, the most of the researchers were concentrate their effort to development of phase-transfer catalysts. Researchers have developed a multi-site phase transfer catalyst (MPTCs) [10, 11] to improve the catalytic actions. Most of the chiral-PTCs derived from natural alkaloids such as cinchonidine, cinchonine, and quinine have induced extremely high enantioselectivity. The development of bis [12, 13] and tris-ammonium [14, 15] chiral phase-transfer catalysts represented by Park, Jew and co-workers and Shibasaki and co-workers [16, 17] are especially significant and they have used for different organic transformations. The past two decades, a large amount progress has been made in the development of asymmetric reaction, allowing to the embellishment of Michael adducts of high enantioselective product with very good yield and high purity. In recent years most of the researchers have been concentrated to the catalysis of asymmetric Michael reaction using chiral metal complexes and cinchona alkaloid based chiral catalysts, they have been developed as an efficient method for the enantioselective construction of carbon-carbon bonds. [18] Recently, Corey et al. and Kim et al. [19, 20] have been reported the enantioselective Michael addition of nitromethane and nitroalkane to α, β-enone using chiral quarternary ammonium salt as chiral catalyst respectively. All the previously reported Michael addition reactions are using single site quaternary ammonium chiral catalysts also they have achived moderate yield and ee's. In our study for the first time we reported the multi-site containing chiral quaternary ammonium catalysts for Michael addition reaction under mild basic conditions with very good yield and ee's . As part of our research program related to the development of effective cinchona alkaloid derived chiral multisite phase-transfer catalysts (CMPTC),[21, 22] We reported the catalytic enantioselective Michael reaction promoted by quaternary ammonium salts from cinchonine as phase-transfer catalysts 1 (1a/1b) [23] and 2 (2a/2b).

II. EXPERIMENTAL

A. Materials and methods

All the chemicals and reagents used in this work were of analytical grade. Mesitylene, allylbromide, (+)-Cinchonine were obtained from Alfa Aesar, *p*-toluonitrile, N-bromosuccinimide, *p*-tolualdehyde, 4-

chlorobenzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, trifluoromethane sulphonic acid, acetophenone and 4-bromo acetophenone were obtained from Sigma Aldrich. Benzyl chloride, sodium hydroxide and potassium hydroxide were obtained from Merck and all the solvents were obtained from laboratory grade.

The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (Avance) 300 & 400 MHz NMR instrument using TMS as an internal standard, $CDCl_3$ and DMSO as a solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of n-hexane and ethylacetate as an eluent. Column chromatography was carried out in silica gel (60-120 mesh) using n-hexane, DCM, Methanol and ethylacetate as an eluent. Electrospray Ionization Mass Spectrometry (ESI-MS) analyses were recorded in LCQ Fleet, Thermo Fisher Instruments Limited, US. ESI-MS was performed in positive ion mode. The collision voltage and ionization voltage were −70 V and −4.5 kV, respectively, using nitrogen as atomization and desolvation gas. The desolvation temperature was set at 300°C. The relative amount of each component was determined from the LC-MS chromatogram, using the area normalization method. The HPLC was recorded in SHIMADZU LC-6AD with chiral column (Phenomenex Chiralpack), using HPLC grade n-hexane and isopropanol as solvents.

B. Synthesis of masitylene based CMPTCs (2)

A mixture of 1, 3, 5-tribromomesitylene [24] (0.1g, 10 mmol), alkylated cinchonine (30 mmol) [12] was dissolved in 5 ml of THF and heated to reflux for overnight, the white solid was filtered, washed with diethylether and dried it to get pure three site chiral PTC. (86% yield).

C. Mesitylene based benzylcinchonine (2a)

^{1}H NMR (400 MHz, DMSO) δ_H 9.04 (d, *J* = 4.4 Hz, 1H), 8.45 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.4 Hz, 1H), 6.61 (s, 1H), 5.96 (ddd, *J* = 17.3, 10.3, 6.9 Hz, 1H), 5.20 (d, *J* = 12.8 Hz, 1H), 5.09 (d, *J* = 10.6 Hz, 1H), 4.94 (t, *J* = 14.4 Hz, 2H), 4.79 (d, *J* = 12.5 Hz, 1H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.02 (s, 2H), 3.91 (d, *J* = 9.0 Hz, 1H), 3.81 (s, 1H), 3.69 (s, 1H), 3.10 (d, *J* = 7.7 Hz, 1H), 1.97 (s, 1H), 1.74 (dd, *J* = 20.6, 9.1 Hz, 2H), 1.35 (s, 1H). ^{13}C NMR (75 MHz, DMSO) δ_C 145.52, 143.37, 135.87, 133.03, 132.59, 132.20, 125.12, 123.88, 123.72, 123.60, 123.36, 123.21, 123.08, 120.55, 111.56, 66.30, 65.70, 62.28, 58.10, 54.39, 51.29, 45.85, 44.02, 43.72, 42.97, 42.77, 31.75, 21.16, 20.35, 19.15, 16.47. ESI-MS $(M)^{3+}$; 1510.67.

D. Mesitylene based allylcinchonine (2b)

^{1}H NMR (400 MHz, DMSO) δ 9.05 (d, *J* = 4.2 Hz, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 8.17 (d, *J* = 7.9 Hz, 1H), 7.94 – 7.89 (m, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 4.3 Hz, 1H), 6.53 (s, 1H), 6.35 – 6.26 (m, 1H), 6.02 – 5.95 (m, 1H), 5.55 – 5.45 (m, 2H), 5.34 (d, *J* = 9.8 Hz, 2H), 5.16 (d, *J* = 10.6 Hz, 2H), 4.86 (d, *J* = 12.2 Hz, 1H), 4.43 (dd, *J* = 12.8, 5.3 Hz, 1H), 4.02 (s, 4H), 3.76 (s, 1H), 3.21 (s, 1H), 1.96 (s, 1H), 1.76 (s, 4H), 1.24 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_C 150.21, 149.39, 148.04, 145.99, 140.73, 137.06, 135.74, 134.29, 131.93, 129.92, 129.66, 125.20, 119.64, 117.97, 90.55, 85.62, 69.35, 67.55, 60.81, 36.15, 30.28, 26.16, 22.23, 21.04. ESI-MS $(M)^{3+}$; 1359.75.

E. Preparation of chalcones (3a-h)

Acetophenone (5 mmol) and aromatic aldehyde (5 mmol) were dissolved in 2 ml of ethanol and 10% sodium hydroxide was added, the mixture was stirred for 5 min. After completion of the reaction, the mixture was poured into ice; the precipitate was filtered and recrystallized with ethanol, to get pure chalcone.[23,25,26].

F. Typical method for synthesis of enantioselective catalytic Michael addition of α, β-unsaturated compounds with diethylmalonate under CMPTCs conditions.

To a mixture of chalcone 3 (a-f, 0.1 mmol), diethylmalonate 4 (0.12 mmol) and CMPTCs (5 mol%) 1/2 was dissolved in 1 ml of solvent and added 0.5 ml of 10% base. Then the reaction mixture was ultra sonicated. The reaction mixture was extracted with ethylacetate, washed with water (3× 2 ml), then washed with brine (5ml), dried over sodiumsulphate and concentrated it. The crude material was purified by column

chromatography on silica gel (ethylacetae and n-hexane as an eluent), to afford the corresponding Michael adduct 5. An enantiomeric excess of 5 was determined by chiral stationary-phase HPLC analysis.

G. Characterization of Michael adduct (5)

Characterization of 5a, 5b, 5e are compared to previously reported data's [23].

GI. diethyl 2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)malonate (5c)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 7.82 (dd, *J* = 17.9, 11.1 Hz, 3H), 7.66 (dd, *J* = 11.4, 7.6 Hz, 2H), 7.60 – 7.51 (m, 2H), 4.19 – 4.08 (m, 4H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.72 (d, *J* = 9.7 Hz, 1H), 3.36 (dt, *J* = 16.6, 8.2 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 197.69, 168.44, 167.81, 148.56, 141.05, 137.53, 133.38, 128.94, 128.83, 128.60, 124.22, 61.62, 61.33, 57.70, 42.72, 40.46, 14.04, 13.79. The enantiomeric excess was determined by HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50:2, 1 mL/min]: 17.70 min (minor), 101.52 min (major).

GII. diethyl 2-(3-(4-bromophenyl)-3-oxo-1-p-tolylpropylpropyl)malonate (5d)

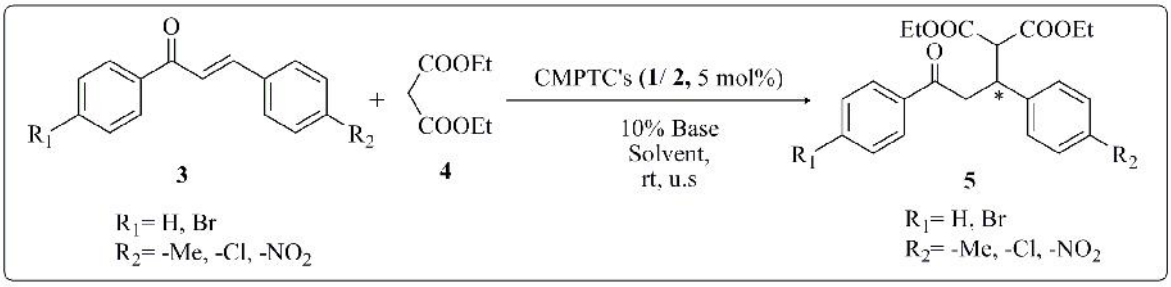
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.67 – 7.57 (m, 4H), 6.94 (d, *J* = 8.6 Hz, 2H), 4.19 – 4.08 (m, 4H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.72 (d, *J* = 9.7 Hz, 1H), 3.36 (dt, *J* = 16.6, 8.2 Hz, 1H), 2.18 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 197.69, 168.44, 167.81, 161.87, 137.23, 131.85, 130.36, 129.96, 127.42, 118.98, 114.38, 61.62, 61.33, 57.70, 42.72, 40.46, 21.03, 14.04, 13.79. The enantiomeric excess was determined by HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50:2, 1 mL/min]: 4.14 min (minor), 20.41 min (major).

GIII. diethyl 2-(3-(4-bromophenyl)-1-(4-nitrophenyl)-3-oxopropyl)malonate (5f)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.30 (d, *J* = 8.7 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 4.19 – 4.08 (m, 4H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.72 (d, *J* = 9.7 Hz, 1H), 3.36 (dt, *J* = 16.6, 8.2 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 197.69, 168.44, 167.81, 148.56, 141.05, 137.53, 133.38, 128.94, 128.83, 128.60, 124.22, 61.62, 61.33, 57.70, 42.72, 40.46, 14.04, 13.79. The enantiomeric excess was determined by HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50:2, 1 mL/min]: 7.02 min (minor), 45.18 min (major).

III. RESULTS AND DISCUSSION

The Chiral Multisite Phase Transfer Catalyst (CMPTCs, 1/2) were synthesised from cinchona alkaloids as per previously reported procedures [23] and 2, 4, 6-Tris-(4-bromomethyl-phenyl)-[1, 3, 5]triazine or 1,3,5-tribromomesitylene [24]. In order to examine the catalytic efficiency of these four different CMPTCs, they were studied individually to effect the Michael addition reaction of chalcone 3 (Michael acceptor) with dietylmalonate 4 (Michael donor) in a biphasic system using various solvents in the presence of 10% aqueous base. All the compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR and mass spectra.



Scheme 1. Enantioselective Michael addition of chalcone 3 in the presence of CMPTC's.

We have conducted the Michael addition reaction using different inorganic bases viz., K_2CO_3, NaOH and K^{t}OBu, individually and keeping the other parameters kept as constant.The obtained results reveal that the change of the solvent, bases and their corresponding concentration had been remarkably influenced chemical yield and ee's in the Michael addition reactions (Table 1, entries 1-24). From the observed results, O-allyl group protected catalysts 1b/2b showed higher catalytic efficiencies than the O-benzyl protected catalyst 1a/2a (Table

1, entries 1-24). This may be due to the steric hindrance of the benzyl group with neighbouring group of the cinchonine. Under the optimized reaction conditions described above (5 mol% of catalyst 1a/2a and 1b/2b, 10% bases, solvent, ultrasonic conditions), we investigated catalytic asymmetric Michael reaction of diethyl malonate to chalcone 3, the catalytic efficiencies is irrespective of the solvents as well as the base. In the case of K^tOBu and DCM containing Michael reaction has higher chemical yield and ee's than the other bases under CMPTC 1. Similarly, K_2CO_3 and toluene mediated reaction yield and ee's is higher than the other solvent and bases under CMPTC 2 (Table 1, entries 3, 4 & 21, 22). Further, the ee's were also found to improve based on their chiral action and position of the chiral center. It was observed that the "R" enantiomers were more predominant than the "S" ones with cinchonine as a catalyst (Table 1). Similar studies are also reported in literature [27, 28] with a view to visualize a mechanism; a two-dimensional diagram of the molecular is presented (Fig. 1).

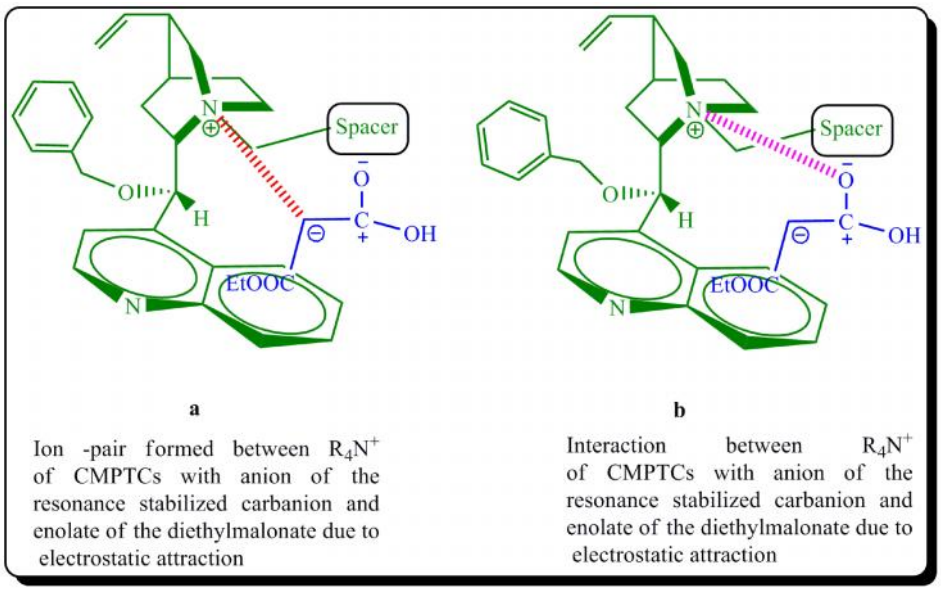


Figure 1. Formation of various intermediates/molecular assemblies during enantioselective Michal addition of diethylmalonate with chalcone using C_9 (O) protected CMPTCs.

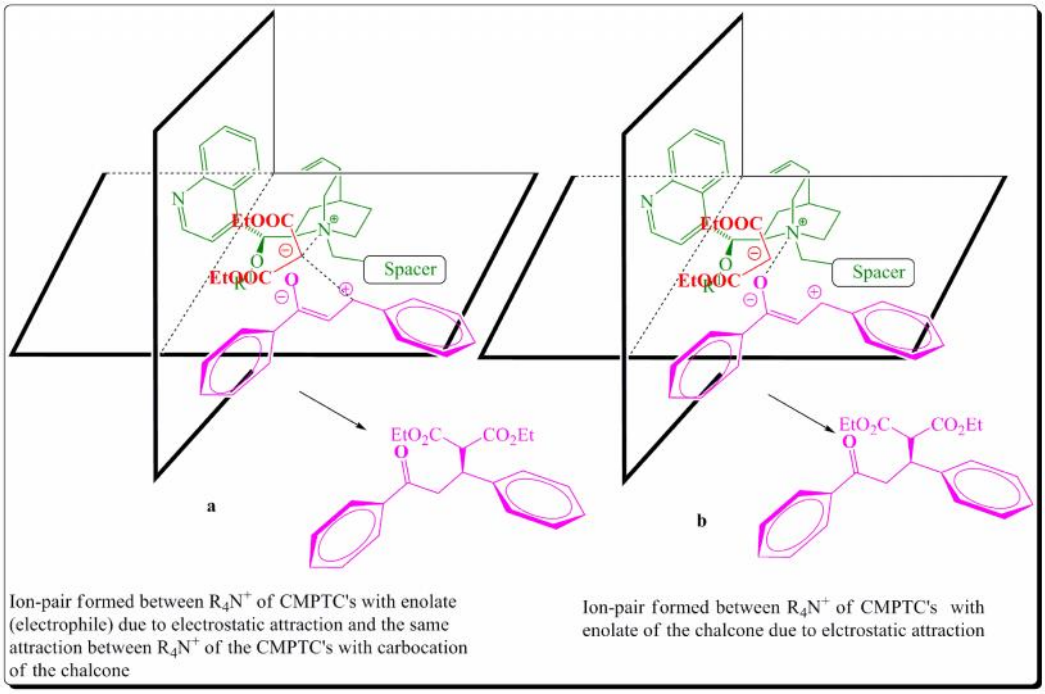


Figure 2. Formation higher enantioselective and chemical yield of various intermediates/molecular assemblies during enantioselective Michael addition reaction using CMPTCs.

Further, we investigate the Michael addition reaction of chalcones 3 under the optimized reaction conditions described above (5 mol% of catalyst 1, K^tOBu, DCM and 5 mol% of catalyst 2, K_2CO_3, Toluene,

u.s.), as listed in Table 2. From the observed results both electron withdrawing and electron donating groups on the aryl groups are influenced the chemical yield as well as ee's (Table 2, entries 1-24). The obtained results indicated that the stereochemical course of the Michael addition reaction mainly depends on the stereochemistry/molecular assembly between the substrates such as electrophile 4 and different chalcones 3 with CMPTC's.

C_9 (O) protected CMPTCs would be mainly attributed to an effective contact of ion-pair formed between the positive quaternary onium ions (R_4N^+) of the respective CMPTC's with electrophile (Fig. 2a), at the same time the interaction between the electrophile with carbocation of the chalcone due to electrostatic attraction [29, 30] and also the same attraction between the R_4N^+ of the respective CMPTC's with enolate of the chalcone (Fig. 2b).The formation of higher Michael adduct yield (Table 2, entries 1-24) and its ee's of each reaction catalyzed by different CMPTCs. The results also suggested that apart from the ionic interaction between the catalyst and substrates, there is also a π-π stacking interaction [31, 32] between the benzyl group of the respective C_9 (O) protected CMPTC with aryl group of the chalcone which would further facilitate the binding of the two species. This in turn shows to facilitate effective ion-pair interaction and thus effect for parallel increasing of chemical yield and ee's.

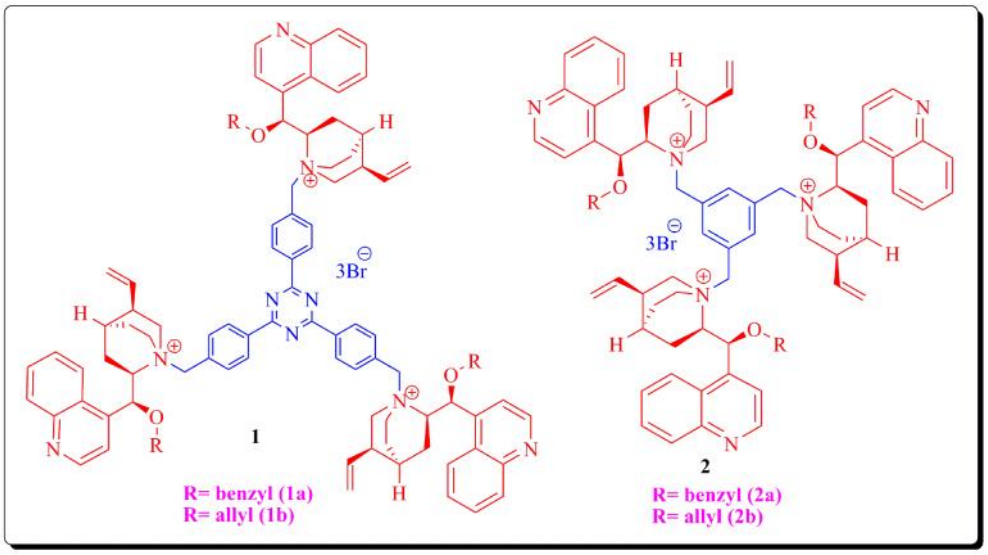


Figure 3. Structure of CMPTCs (1 & 2).

TABLE I. OPTIMIZATION REACTION OF THE MICHAEL ADDUCT WITH CMPTCS (1/2, 5 MOL %).

Entry	Solvent	Base	Catalyst	Time (min) [a]	Yield (%)[b]	% of ee[c]	Absolute Configuration[d]
1	Toluene	K_2CO_3	1a	6	86	92	R
2	Toluene	K_2CO_3	1b	8	70	96	R
3	Toluene	K_2CO_3	2a	1	98	97	R
4	Toluene	K_2CO_3	2b	1	98	99	R
5	Toluene	NaOH	1a	6	85	87	R
6	Toluene	NaOH	1b	5	90	91	R
7	Toluene	NaOH	2a	1	85	92	R
8	Toluene	NaOH	2b	1	85	95	R
9	Toluene	K^{t}OBu	1a	8	70	74	R
10	Toluene	K^{t}OBu	1b	8	70	87	R
11	Toluene	K^{t}OBu	2a	1	88	87	R

12	Toluene	K^tOBu	2b	1	88	90	R
13	DCM	K_2CO_3	1a	6	86	91	R
14	DCM	K_2CO_3	1b	7	86	97	R
15	DCM	K_2CO_3	2a	6	86	92	R
16	DCM	K_2CO_3	2b	8	72	95	R
17	DCM	NaOH	1a	1	75	74	R
18	DCM	NaOH	1b	1	80	89	R
19	DCM	NaOH	2a	1	98	91	R
20	DCM	NaOH	2b	1	98	95	R
21	DCM	K^tOBu	1a	4	90	93	R
22	DCM	K^tOBu	1b	4	90	99	R
23	DCM	K^tOBu	2a	4	86	92	R
24	DCM	K^tOBu	2b	4	90	95	R

a. The Michael reaction of chalcone 3 (0.1 mmol), diethyl malonate 4 (0.12 mmol), CMPTCs (1/2, 5 mol%), with 1 ml solvent and 0.5 ml of 10% base in ultrasonic condition.
b. Isolated yield of purified material.
c. Enantiopurity was determined by HPLC analysis of the Michael adduct 5 using a chiral column (Phenomenex Chiralpack) with hexane-IPA as a solvent.
d. Absolute configuration was determined by comparison of the HPLC retention time.

TABLE II. CATALYTIC ASYMMETRIC MICHAEL REACTION OF DIETHYL MALONATE 4 TO CHALCONE DERIVATIVES 3 UNDER CMPTCS CONDITIONS.

Entry	**Enone (9)**	**R_1**	**R_2**	**Solvent**	**Base**	**Catalyst**	**Product[a]**	**Time (min) [a]**	**Yield (%)[b]**	**% of ee[c]**	**Abs. Conf.[d]**
1	9a	-H	-Me	DCM	K^tOBu	7a	11a	4	90	93	R
2	9a	-H	-Me	DCM	K^tOBu	7b	11a	4	90	99	R
3	9a	-H	-Me	Toluene	K_2CO_3	8a	11a	1	98	97	R
4	9a	-H	-Me	Toluene	K_2CO_3	8b	11a	1	98	99	R
5	9b	-H	-Cl	DCM	K^tOBu	7a	11b	4	92	92	R
6	9b	-H	-Cl	DCM	K^tOBu	7b	11b	4	92	99	R
7	9b	-H	-Cl	Toluene	K_2CO_3	8a	11b	1	94	92	R
8	9b	-H	-Cl	Toluene	K_2CO_3	8b	11b	1	94	99	R
9	9c	-H	$-NO_2$	DCM	K^tOBu	7a	11c	4	96	98	R
10	9c	-H	$-NO_2$	DCM	K^tOBu	7b	11c	4	96	98	R
11	9c	-H	$-NO_2$	Toluene	K_2CO_3	8a	11c	1	97	98	R
12	9c	-H	$-NO_2$	Toluene	K_2CO_3	8b	11c	1	97	98	R
13	9d	-Br	-Me	DCM	K^tOBu	7a	11d	4	95	94	R
14	9d	-Br	-Me	DCM	K^tOBu	7b	11d	4	95	94	R
15	9d	-Br	-Me	Toluene	K_2CO_3	8a	11d	1	93	94	R
16	9d	-Br	-Me	Toluene	K_2CO_3	8b	11d	1	93	94	R

17	9e	-Br	-Cl	DCM	K^{t}OBu	7a	11e	4	90	91	R
18	9e	-Br	-Cl	DCM	K^{t}OBu	7b	11e	4	90	97	R
19	9e	-Br	-Cl	Toluene	K_2CO_3	8a	11e	1	92	91	R
20	9e	-Br	-Cl	Toluene	K_2CO_3	8b	11e	1	92	97	R
21	9f	-Br	-NO_2	DCM	K^{t}OBu	7a	11f	4	96	99	R
22	9f	-Br	-NO_2	DCM	K^{t}OBu	7b	11f	4	96	99	R
23	9f	-Br	-NO_2	Toluene	K_2CO_3	8a	11f	1	97	99	R
24	9f	-Br	-NO_2	Toluene	K_2CO_3	8b	11f	1	97	99	R

a. The Michael reaction of chalcone 3 (0.1 mmol), diethyl malonate 4 (0.12 mmol), CMPTCs (1/2, 5 mol%), with 1 ml solvent and 0.5 ml of 10% base in ultrasonic condition.
b. Isolated yield of purified material.
c. Enantiopurity was determined by HPLC analysis of the Michael adduct 5 using a chiral column (Phenomenex Chiralpack) with hexane-IPA as a solvent.
d. Absolute configuration was determined by comparison of the HPLC retention time.

IV. CONCLUSIONS

In conclusion, we have developed a new class of asymmetric phase-transfer catalyst, which shows good yield and enantioselectivity in the Michael reaction of diethyl malonate to chalcones. We are currently involved in the further development of these catalyst systems and investigating their applicability to other asymmetric phase-transfer processes.

V. ACKNOWLEDGMENT

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