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ARTICLE TYPE

Highly Enantioselective Michael Addition Reactions with New Trimeric Chiral Phase Transfer Catalysts

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New types of mesitylene based tri-site containing asymmetric quaternary ammonium salts 9a and 9b have been prepared and used as efficient chiral phase transfer catalysts for enantioselective Michael addition reaction between the chalcones and diethylmalonate under mild reaction conditions such as lower concentration of base, catalyst and ultrasonic conditions with very good chemical yield (up to 98%) and ee's (up to 99%).

Introduction

Phase transfer catalysis (PTC) is one of the most important and efficient techniques for various organic transformations due to its operational simplicity, mild reaction conditions, use of safe and inexpensive reagents and solvents, and possibility to conduct reactions on large scale.[1, 2] The role of chiral phase transfer catalysts (CPTC) is to transfer reagent from the aqueous phase into the organic phase, thus provides the organic substrate and the required anion to form the corresponding product in the organic phase. In the past decade, though single-site CPTC have been extensively used for the number of organic reactions (Figure 1), due to its poor diffusion and inseparability usage is often limited.[3, 4]

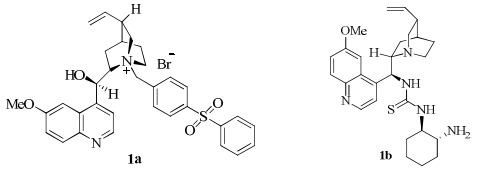

Fig. 1 Cinchona based chiral phase transfer catalyst.

In order to increase the chemical yield and ee's, the most of the researchers concentrated their effort to development of chiral multi-site phase transfer catalysts (CMPTCs) [5] to improve the catalytic actions. The first pioneer of the achiral MPTCs was introduced by Idoux *et al*.,[6] and they have synthesized phosphonium and quaternary onium ions containing more than one active site per molecule. After the ground breaking work by Merck group, a new class of cinchona based catalyst has been developed in 1990s.[7] Most of the chiral-PTCs derived from natural alkaloids such as cinchonidine, cinchonine, and quinine have induced extremely high enantioselectivity. The development of bis[8] and tris-ammonium[9, 10] CPTCs have been reported by Park et.al., and Shibasaki et. al., respectively, they have used CPTCs for different organic transformations to get very good chemical yield and ee's than the corresponding mono-quaternary ammonium salts.[7]

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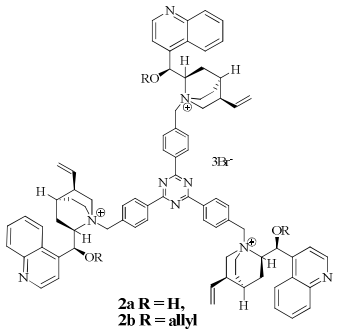

Fig. 2 Our group previously reported cinchona based chiral phase transfer catalyst.

Recently, Maruoka and co-workers[11] have reported the synthesis of non-natural chiral-PTCs, and demonstrated their application to versatile enantioselective reactions. Among the various C-C bond formations, the most powerful Michael addition reaction is enable to access a variety of optically active adducts affording synthetic useful building blocks in organic synthesis.[12] Many types of catalysts such as proline salts[13], chiral metal complexes,[14] chiral ionic liquids,[4] phase-transfer catalysts,[15] and organocatalysts have been developed for the Michael addition of malonates to enones.[16] All the previously reported Michael addition reactions are using single site quaternary ammonium chiral catalysts wherein moderate yield's and ee's were obtained.[17] Recently, we reported the enantioselective Michael addition reaction with very good yield and ee's under CMPTC conditions (Figure 2).[18] We have enhanced the effectiveness of asymmetric Michael addition reaction of malonate **4** and chalcone **3**[18, 19] under ultrasonic irradiation conditions (Scheme 1). In this work, we report the multi-site containing chiral quaternary ammonium catalysts derived from mesitylene **9a** and **9b** (Scheme 2) can offer very good chemical yield and ee's than the previously reported PTCs (Figure 1 and 2) for Michael addition reaction under mild base as well as ultrasonic irradiation condition.

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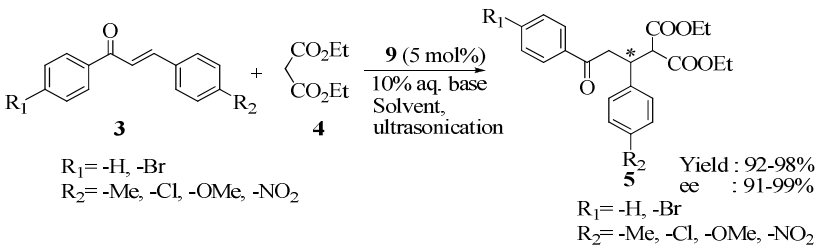
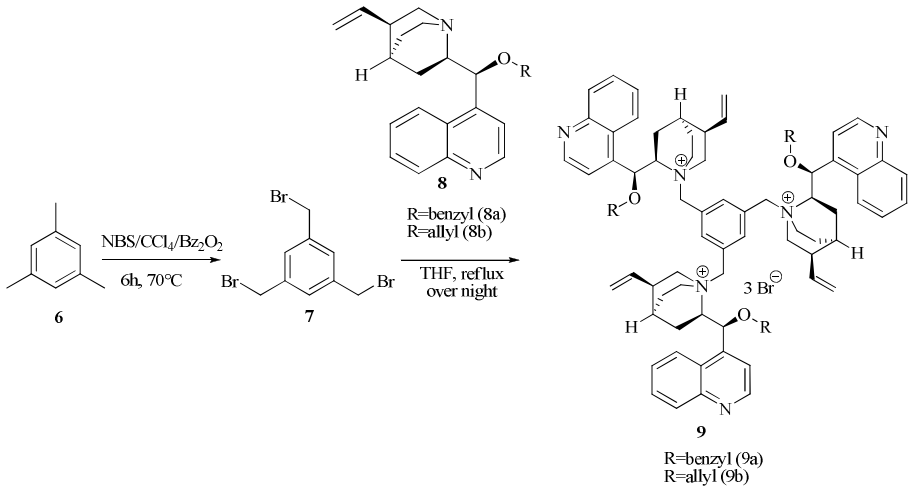


Scheme 1 Enantioselective Michael addition of chalcones.



Scheme 2 Synthesis of CMPTCs **9**.

Experimental Section

Materials and Methods

All the chemicals and reagents were used in this work as an analytical grade. Mesitylene, allylbromide, (+)-Cinchonine were obtained from Alfa Aesar. N-bromosuccinimide, *p*-tolualdehyde, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, 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. Ultrasonication were carried out in ULTRASONIC STERI-CLEANER. The HPLC was recorded in SHIMADZU LC-6AD with chiral column (Phenomenex Chiralpack), using HPLC grade n-hexane and isopropanol as solvents.

Preparationof 1, 3, 5-tribromomesitylene (7)[17]

Mesitylene **6** (10 ml, 72.0 mmol), NBS (44.8 g, 252 mmol), catalytic amount of benzoyl peroxide and CCl_4 (100 ml) were taken in a 150 ml RB flask. The reaction mixture was refluxed for about 6 hrs at 70°C. After completion of reaction time, the formed solid was removed by filtration at room temperature and the required filtrate was washed with water and extracted with DCM, combined organic layer was washed with brain, dried over sodium sulphate and concentrated it. The crude product was purified by column chromatography using 5% ethylacetate and n-hexane as an eluent. Pale yellow solid, Yield is 96%, m.p. 86-87°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 (s, 3H), 4.45 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ_C 139.00, 129.55, 32.19.

Synthesis of mesitylene based CMPTCs (9)

A mixture of 1, 3, 5-tribromomesitylene 6 (0.1g, 10 mmol), cinchona derivatives 8[18] (8a/ 8b, 30 mmol) 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 of 9a and 88% yield of 9b).

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Mesitylene based benzylcinchonine (9a)

^{1}H NMR (400 MHz, DMSO) δ_H 9.04 (d, J = 4.4 Hz, 3H), 8.45 (d, J = 8.5 Hz, 3H), 8.20 (d, J = 8.4 Hz, 3H), 8.01 (d, J = 8.8 Hz, 3H), 7.92 (t, J = 7.6 Hz, 3H), 7.87 – 7.78 (m, 6H), 7.62 (d, J = 7.5 Hz, 6H), 7.51 (t, J = 7.5 Hz, 6H), 7.41 (d, J = 7.4 Hz, 3H), 6.61 (s, 3H), 5.96 (ddd, J = 17.3, 10.3, 6.9 Hz, 6H), 5.20 (d, J = 12.8 Hz, 3H), 5.09 (d, J = 10.6 Hz, 3H), 4.94 (t, J = 14.4 Hz, 6H), 4.79 (d, J = 12.5 Hz, 3H), 4.65 (d, J = 11.8 Hz, 3H), 4.02 (s, 6H), 3.91 (d, J = 9.0 Hz, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 3.10 (d, J = 7.7 Hz, 3H), 1.97 (s, 3H), 1.74 (dd, J = 20.6, 9.1 Hz, 6H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ_C 150.31, 148.05, 147.99, 141.43, 140.52, 137.80, 137.26, 137.02, 129.85, 129.75, 128.62, 128.44, 128.38, 128.11, 127.87, 125.16, 123.74, 119.79, 116.28, 79.28, 78.98, 70.91, 70.23, 58.94, 36.55, 30.80, 26.51, 25.78. ESI-MS (M) $^{3+}$; 1510.67.

Mesitylene based allylcinchonine (9b)

^{1}H NMR (400 MHz, DMSO) δ 9.05 (d, J = 4.2 Hz, 3H), 8.49 (d, J = 8.5 Hz, 3H), 8.17 (d, J = 7.9 Hz, 3H), 7.94 – 7.89 (m, 3H), 7.86 (d, J = 7.9 Hz, 3H), 7.73 (d, J = 4.3 Hz, 3H), 6.53 (s, 3H), 6.35 – 6.26 (m, 3H), 6.02 – 5.95 (m, 3H), 5.55 – 5.45 (m, 6H), 5.34 (d, J = 9.8 Hz, 6H), 5.16 (d, J = 10.6 Hz, 6H), 4.86 (d, J = 12.2 Hz, 3H), 4.43 (dd, J = 12.8, 5.3 Hz, 3H), 4.02 (s, 12H), 3.76 (s, 3H), 3.21 (s, 3H), 1.96 (s, 3H), 1.76 (s, 12H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ_C 150.41, 150.16, 147.93, 136.99, 134.25, 129.68, 129.12, 128.10, 127.61, 125.13, 124.08, 119.68, 118.15, 116.56, 79.00, 78.64, 72.91, 69.06, 55.83, 53.77, 35.87, 26.15, 22.22, 21.01. ESI-MS (M^{3+}); 1359.75.

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

To a mixture of chalcone **3**[18, 19] **(a-h,** 0.1 mmol), diethylmalonate **4** (0.12 mmol) and CMPTCs (5 mol%) **9 (9a/9b)** were dissolved in 1 ml toluene and added 0.5 ml of 10% K_2CO_3. Then the reaction mixture was ultra sonicated for 1 h, after that the reaction mixture was extracted with ethylacetate, washed with water (3 × 2 ml), then washed with brine (5 ml), dried over sodiumsulphate and concentrated it. The crude material was purified by column chromatography on silica gel (ethylacetate 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.

Characterization of Michael adduct (5)

diethyl 2-(3-oxo-3-phenyl-1-*p*-tolylpropyl) malonate (5a)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.82 (d, J = 7.5 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.06 (d, J = 7.9 Hz, 2H), 6.96 (d, J= 7.9 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, 137.37, 136.85, 136.63, 133.00, 129.09, 128.13, 128.06, 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]: 7.58 min (minor), 35.46 min (major).

diethyl 2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)malonate (5b)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.03 (d, J = 7.0 Hz, 2H), 7.62 – 7.56 (m, 3H),), 7.55 – 7.51 (m, 2H), 7.40 (d, J = 8.5 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, 137.93, 133.30, 132.85, 129.51, 129.15, 128.59, 128.42, 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]: 4.52 min (minor), 23.68 min (major).

diethyl 2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (5c)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 7.0 Hz, 2H), 7.75 – 7.66 (m, 3H), 7.61 (d, J = 7.5 Hz, 2H), 7.04 (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), 2.39 (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, 161.52, 144.51, 132.38, 130.06, 128.39, 128.24, 119.59, 114.26, 61.62, 61.33, 57.70, 55.22, 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]: 13.17 min (minor), 49.49 min (major).

diethyl 2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)malonate (5d)

^{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).

diethyl 2-(3-(4-bromophenyl)-3-oxo-1-*p*-tolylpropylpropyl)malonate (5e)

^{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).

diethyl 2-(3-(4-bromophenyl)-1-(4-chlorophenyl)-3-oxopropyl)malonate (5f)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.88 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 6.9 Hz, 2H), 7.57 (d, J = 6.9 Hz, 2H), 7.40 (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, 136.57, 133.07, 131.89, 129.92, 129.58, 129.20, 128.00, 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]: 4.6 min (minor), 12.9 min (major).

diethyl 2-(3-(4-bromophenyl)-1-(4-methoxyphenyl)-3-oxopropyl)malonate (5g)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.88 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.23 (d,

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J = 7.9 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), 2.39 (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, 145.41, 137.06, 131.84, 129.97, 129.72, 128.51, 127.66, 61.62, 61.33, 57.70, 42.72, 40.46, 21.24, 14.04, 13.79.The enantiomeric excess was determined by HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50:2, 1 mL/min]: 4.5 min (minor), 31.12 min (major).

Diethyl 2-(3-(4-bromophenyl)-1-(4-nitrophenyl)-3-oxopropyl)malonate (5h)

^{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).

Results and Discussion

The mesitylene based chiral PTCs **9** (**9a** and **9b**) were synthesized from the reaction of 1,3,5-tribromomesitylene **7** with 9-(O)-benzyl cinchonine **8a**[18] and 9-(O)-allyl cinchonine **8b**[18] respectively as depicted in scheme 2. Further, the newly synthesized trimeric quaternary ammonium salts bearing bromide as counter-anions were employed as chiral MPTCs (5 mol%) in the Michael addition reaction of chalcone **3**[18, 19] with diethylmalonate (Scheme 1, Table 1). From the table 1, we observed that the results of Michael addition with different catalysts such as **1**, **2**, **9a** and **9b**, newly synthesized cinchona catalysts **9a** and **9b** have more efficient (yield as well as ee's) than the previously reported catalysts such as **1** and **2** under identical conditions but different in reaction time, mild base and non polar solvent (Table 1, entries 1-6). This may be due to the multiactive sites are present in the catalysts, the strong ion pair interaction between the enolate anion of the chalcone and the electron deficient containing catalysts ie. R_4N^+, and also cooperative influence of neighbouring group of the R_4N^+ ion with substrate.[20] The CPTC derived from triazine (**2a**, **2b**) in both cases, although they possess two R_4N^+ cationic site, but the relative special position of these two cationic sites are just positioned away with each other. As a result, enolate anion of chalcone and diethylmalonate are not appropriately fixed between the two R_4N^+ catalytic sites favourably as in mesitylene derived CMPTC's (**9a** and **9b**). That is, instead of co-operative influences/attraction of R_4N^+ site on the anions of the enolate anions (Figure 3).

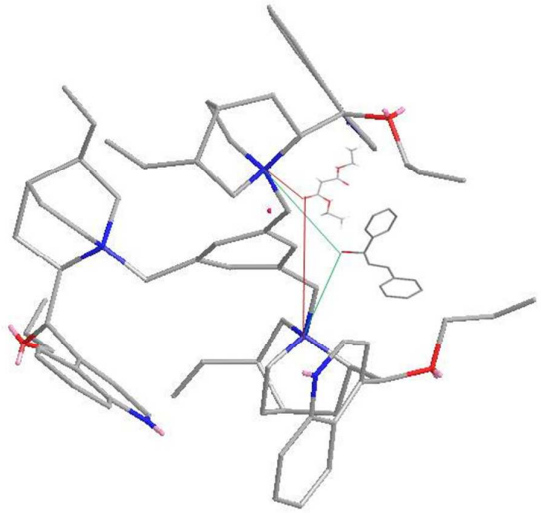
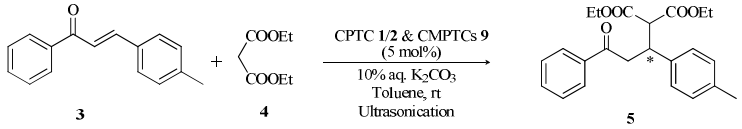


Fig. 3 A schematic representation for the two cationic moieties of CMPTC **9a** is simultaneously activated and co-operatively influenced the reaction due to dipole-dipole interaction (ion-pair).

Table 1 Catalytic asymmetric Michael addition reaction of diethyl malonate **4** to chalcone **3** with different CPTCs **1**, **2** and CMPTCs **9 (9a/ 9b)** in ultrasonic conditions.



3 4 5

Entry	Catalyst	Time (h)[a]	Yield (%)[b]	ee[c] %	Abs.Conf.[d]
1	**1a**	10	70	56	R
2	**1b**	10	75	65	R
3	**2a**	6	84	89	R
4	**2b**	6	91	92	R
5	**9a**	1	98	97	R
6	**9b**	1	98	99	R

[a] The Michael reaction of chalcone **3** (0.1 mmol), diethyl malonate **4** (0.12 mmol), **CMPTCs 9** (**9a/9b**, 5 mol%), with 1 ml toluene and 0.5 ml of 10% aq. K_2CO_3 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 solvents.
[d] Absolute configuration was determined by comparison of the HPLC retention time.[18]

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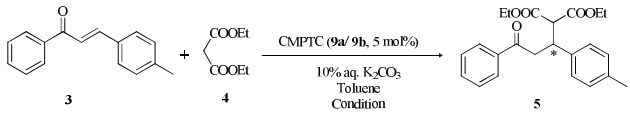
The initial step of the optimization of the Michael addition reaction of chalcone **3** with diethylmalonate **4** is carried out in the presence of different temperature and ultrasonication conditions. From the observed results, the ultrasonic mediated reaction condition having higher chemical yield and enantiomeric excess than the other temperature conditions (i.e. -20 °C, RT and 50 °C) (entries 1-16, Table 2), and also we got higher chemical yield and enantiomeric excess than the previously reported trisite catalysts (**2a** and **2b**) under similar reaction conditions. Hence, all the Michael addition reactions were carried out under ultrasonic reaction conditions. Further, we carried out the Michael addition of chalcone **3** with diethylmalonate **4** in the presence of different bases and other parameters are kept constant. From the results, *O*-allyl protected catalyst (**9b**) having more chemical yield and ee's than the *O*-benzylated catalyst (**9a**) (entries 1-10, Table 3). It has been also found that K_2CO_3, KOH and Cs_2CO_3 are the more effective bases (higher yield above 90% and 95% ee's) in this reaction than others bases such as NaOH, K^{t}OBu (entries 1-10 Table 3). Then the asymmetric Michael addition reaction was carried out in different organic solvents using tri-site catalysts **9a** and **9b** under biphasic condition, the other parameters are kept as constant. The obtained results (Table 4) show that, the change of solvent is found to be an important crucial factor in the Michael addition reaction due to their polarity of the solvents. The product yield and ee's have been found to decrease gradually, when we are using non polar to polar solvents (entries 1-16, Table 4), this may be due to the increasing the dielectric constant of the solvents. The decreased product yield/ee's in high polar solvents like chloroform, acetone, acetonitrile and methanol (entries 7-16, Table4), because the higher degree of solvation of chiral catalysts and also protect the ion pair interaction between the R_4N^+ of the catalyst and enolate anion of the substrates (diethylmalonate and chalcones). Hence, it can be reduced the chemical yield and ee's. In the case of non polar solvents such as toluene and cyclohexane, the degree of solvation of CMPTC's are considerably less and hence it can be influenced the ion pair interaction between the catalysts and enolate ions. (entries 1-4, Table 4).

Table 2. Optimization of asymmetric Michael addition between the chalcone **3** and diethyl malonate **4** with CMPTCs **9 (9a/ 9b)** and **2 (2a/2b)** in various conditions.



3 4 5

Entry	Catalyst	Condition	Time (h)[a]	Yield(%)[b]	% of ee[c]	Abs.Conf.[d]
1	**9a**	RT	24	No Reaction	-	-
2	**9b**	RT	24	15	29	R
3	**2a**	RT	24	No Reaction	-	-
4	**2a**	RT	24	No Reaction	-	-
5	**9a**	50°C	24	No Reaction	-	-
6	**9b**	50°C	24	No Reaction	-	-
7	**2a**	50°C	24	No Reaction	-	-
8	**2b**	50°C	24	No Reaction	-	-
9	**9a**	-20°C	24	17	32	R
10	**9b**	-20°C	24	21	37	R
11	**2a**	-20°C	24	No Reaction	-	-
12	**2b**	-20°C	24	No Reaction	-	-
13	**9a**	Ultrasonication	1	98	97	R
14	**9b**	Ultrasonication	1	98	99	R
15	**2a**	Ultrasonication	6	84	89	R
16	**2b**	Ultrasonication	6	91	92	R

[a] The Michael reaction of chalcone **3** (0.1 mmol), diethyl malonate **4** (0.12 mmol), CMPTCs **9** (**9a/9b**, 5 mol%), with 1 ml toluene and 0.5 ml of 10% aq. K_2CO_3 in various conditions.

[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 solvents.

[d] Absolute configuration was determined by comparison of the HPLC retention time.[18]

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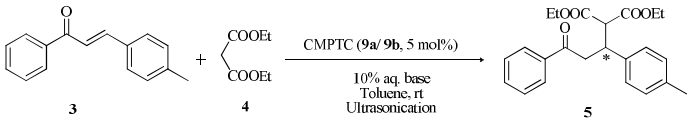
Table 3 Effect of 10% aq. base in the Michael addition reaction in presence of the chalcone **3** and diethyl malonate **4** with CMPTCs **9** (**9a/9b**), under ultrasonic conditions.

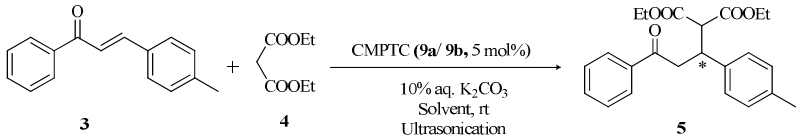


3 4 5

Entry	10% Base	Catalyst	Time (min) [a]	Yield(%) [b]	% ee [c]	Abs. Conf. [d]
1	K_2CO_3	**9a**	60	98	97	R
2	K_2CO_3	**9b**	60	98	99	R
3	Cs_2CO_3	**9a**	60	95	93	R
4	Cs_2CO_3	**9b**	60	95	95	R
5	NaOH	**9a**	55	85	92	R
6	NaOH	**9b**	55	85	95	R
7	KOH	**9a**	60	95	95	R
8	KOH	**9b**	60	95	97	R
9	K^{t}OBu	**9a**	50	88	87	R
10	K^{t}OBu	**9b**	50	88	90	R

[a] The Michael reaction of chalcone **3** (0.1 mmol), diethyl malonate **4** (0.12 mmol), CMPTCs **9** (**9a/9b**, 5 mol%), with 1 ml toluene and 0.5 ml of 10% aq. base in ultrasonic conditions.
[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 solvents.
[d] Absolute configuration was determined by comparison of the HPLC retention time.[18]

Table 4 Effect of solvent in the Michael addition reaction of chalcone **3**, diethyl malonate **4**, CMPTCs **9** (**9a/9b**), under ultrasonic conditions.



3 4 5

Entry	Solvent	Catalyst	Time (min) [a]	Yield(%) [b]	% of ee [c]	Abs. Conf. [d]
1	Toluene	**9a**	60	98	97	R
2	Toluene	**9b**	60	98	99	R
3	Cyclohexane	**9a**	75	95	92	R
4	Cyclohexane	**9b**	75	95	93	R
5	THF	**9a**	60	93	95	R
6	THF	**9b**	60	93	96	R
7	Methanol	**9a**	90	80	75	R
8	Methanol	**9b**	90	80	72	R
9	Acetonitrile	**9a**	60	90	93	R
10	Acetonitrile	**9b**	60	90	96	R
11	DCM	**9a**	120	73	68	R
12	DCM	**9b**	120	73	73	R
13	Chloroform	**9a**	150	78	71	R
14	Chloroform	**9b**	150	80	76	R
15	Acetone	**9a**	125	75	83	R
16	Acetone	**9b**	125	75	89	R

[a] The Michael reaction of chalcone **3** (0.1 mmol), diethyl malonate **4** (0.12 mmol), **CMPTCs 9** (**9a/9b**, 5 mol%), with 1 ml solvent and 0.5 ml of 10% aq. K_2CO_3 in ultrasonic condition; [b] Isolated yield of purified material; [c] Enantiopurity was determined by HPLC analysis of the

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Michael adduct **5** using a chiral column (Phenomenex Chiralpack) with hexane-IPA as solvents; [d] Absolute configuration was determined by comparison of the HPLC retention time.[18]

Further, the catalytic efficiencies were studied by the Michael addition reaction of 1, 4-diarylenones **3** under the optimized reaction conditions described above (5 mol% of the catalyst **9a** and **9b**, 10% aq. K_2CO_3, toluene, ultrasonic irradiation), were listed in Table 5. From the observed results, independent of the substitution on the aryl group of the chalcones, both the electron withdrawing and electron donating groups are present on the aryl groups which could not affect the product yield and ee's. We found an excellent product yield and higher enantiomeric excess (entries 1-16, Table 5). This may be due to that apart from the ionic interaction between the catalyst and substrates, there is also a π-π stacking interaction between the benzyl group of the respective C_9 (O) protected tris-ammonium catalysts with aryl group of the chalcone which would further influenced the interaction between the enolated ions of the chalcone and electron deficient site of the R_4N^+ of the respective catalysts (Figure 4).

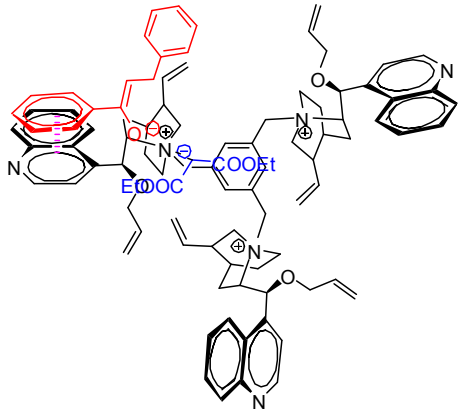
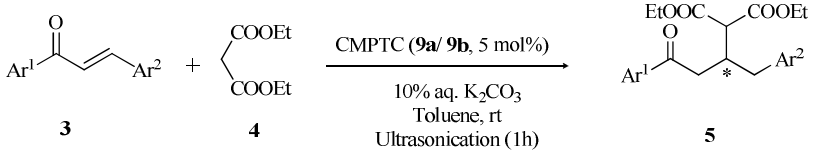


Fig. 4 Possible formation of ion pair between the R_4N^+ of the CMPTC with enolate anion of the chalcone as well as the π-π stacking interaction with the quinoline moiety of the catalyst and aryl group of the chalcone.

Table 5 Catalytic asymmetric Michael addition reaction of diethyl malonate **4** to chalcone derivatives **3** under CMPTCs conditions[a]



3 **4** **5**

Entry	Enone (**3**)	Ar^1	Ar^2	Catalyst	Product[a]	Yield (%)[b]	% of ee[c]	Abs.Conf.[d]
1	3a	Ph	4-Me-C_6H_4	**9a**	5a	98	97	R
2	3a	Ph	4-Me-C_6H_4	**9b**	5a	98	99	R
3	3b	Ph	4-Cl-C_6H_4	**9a**	5b	94	92	R
4	3b	Ph	4-Cl-C_6H_4	**9b**	5b	94	99	R
5	3c	Ph	4-OMe-C_6H_4	**9a**	5c	96	98	R
6	3c	Ph	4-OMe-C_6H_4	**9b**	5c	96	98	R
7	3d	Ph	4-NO_2-C_6H_4	**9a**	5d	97	98	R
8	3d	Ph	4-NO_2-C_6H_4	**9b**	5d	97	98	R
9	3e	4-Br- C_6H_4	4-Me-C_6H_4	**9a**	5e	93	94	R
10	3e	4-Br- C_6H_4	4-Me-C_6H_4	**9b**	5e	93	94	R
11	3f	4-Br- C_6H_4	4-Cl-C_6H_4	**9a**	5f	92	91	R
12	3f	4-Br- C_6H_4	4-Cl-C_6H_4	**9b**	5f	92	97	R
13	3g	4-Br- C_6H_4	4-OMe-C_6H_4	**9a**	5g	95	95	R
14	3g	4-Br- C_6H_4	4-OMe-C_6H_4	**9b**	5g	95	97	R
15	3h	4-Br- C_6H_4	4-NO_2-C_6H_4	**9a**	5h	97	99	R
16	3h	4-Br- C_6H_4	4-NO_2-C_6H_4	**9b**	5h	97	99	R

[a] The Michael reaction of chalcone **3** (0.1 mmol), diethyl malonate **4** (0.12 mmol), **CMPTCs 9** (**9a/9b**, 5 mol%), with 1 ml toluene and 0.5 ml of 10% aq. K_2CO_3 in ultrasonic conditions; [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 solvents; [d] Absolute configuration was determined by comparison of the HPLC retention time.[18]

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Conclusion

We successfully synthesized mesitylene based tris-quaternary ammonium bromide as chiral phase transfer catalysts and well characterized by various spectral techniques. The catalytic efficiencies were studied by the Michael addition of chalcones and diethylmalonate with very good chemical yield (up to 98%) and enantiomeric excess (up to 99%) under lower concentration of base and catalysts under ultrasonic irradiation conditions.

Acknowledgment

We acknowledge the financial support of the Department of Science and Technology, New Delhi, India (Grant No. SR/F/1584/2012-13), University Grants Commission, New Delhi, India (Grant No. UGC No.41-215/2012 (SR) and Council of Scientific and Industrial Research, New Delhi, India (Grant No. 01(2540)/11/EMR-II).

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Graphical Abstract

Highly Enantioselective Michael Addition Reactions with New Trimeric Chiral Phase Transfer Catalysts

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New types of mesitylene based tri-site containing asymmetric quaternary ammonium salts **9** (**9a** and **9b**) were synthesized and the catalytic activities were studied by the Michael addition reactions with various chalcones and diethylmalonate under mild basic conditions with very good yield and ee's.