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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 reactions between the chalcones and diethylmalonate under mild reaction conditions such as lower concentration of base, catalyst and ultrasonic conditions with very good chemical yields (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 of conducting reactions on a large scale.[1,2] The role of chiral phase transfer catalysts (CPTC) is to transfer reagents from the aqueous phase into the organic phase, thus providing 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 a number of organic reactions (Fig. 1), due to their poor diffusion and inseparability their usage is often limited.[3,4]

In order to increase the chemical yield and ee's, most of the researchers concentrated their effort on the 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 carried out by the Merck group, a new class of cinchona based catalysts was 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 has been reported by Park *et al.*, and Shibasaki *et al.*, respectively, in which they used CPTCs for different organic transformations to get very good chemical yields and ee's compared with the corresponding mono-quaternary ammonium salts.[7]

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 formation reactions, the most powerful Michael addition reaction is able to access a variety of optically active adducts, affording useful synthetic building blocks for 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 used single site quaternary ammonium chiral catalysts wherein moderate yields and ee's were obtained.[17] Recently, we reported the enantioselective Michael addition reaction with very good yields and ee's under CMPTC conditions (Fig. 2).[18] We have enhanced the effectiveness of asymmetric Michael addition reactions of malonate **4** and chalcone **3**[18,19] under ultrasonic irradiation conditions (Scheme 1). In this work, we report that the multi-site containing chiral quaternary ammonium catalysts derived from mesitylene **9a** and **9b** (Scheme 2) can offer very good chemical yields and ee's compared with the previously reported PTCs (Fig. 1 and 2) for performing the Michael addition reaction under mild base as well as ultrasonic irradiation conditions.

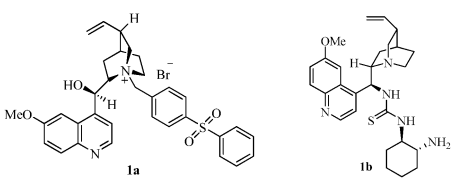

Fig. 1 Cinchona based chiral phase transfer catalyst.

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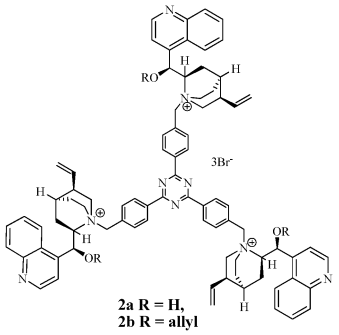


Fig. 2 Our group previously reported cinchona based chiral phase transfer catalyst.

Experimental section

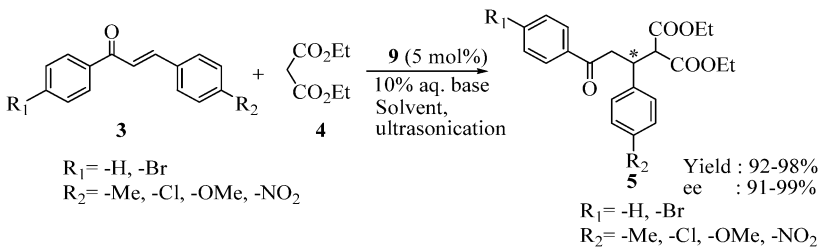
Materials and methods

All the chemicals and reagents used in this work were of 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 obtained were of laboratory grade.

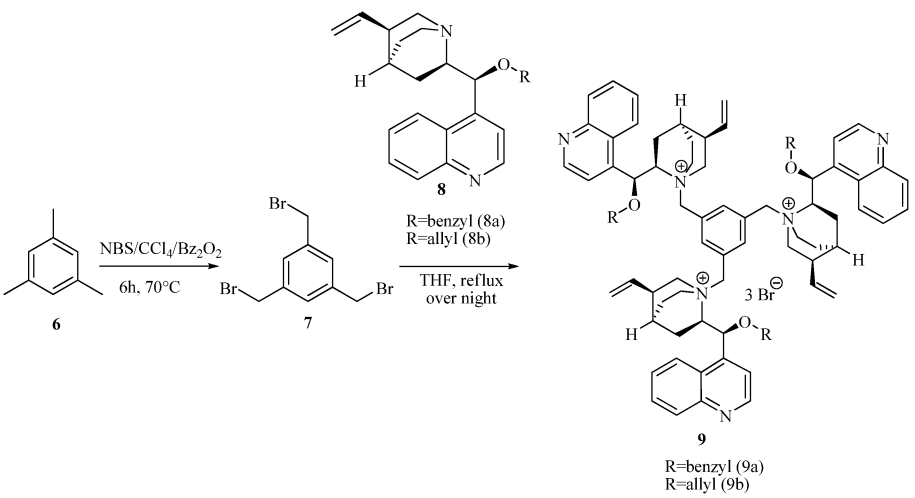
The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker (Avance) 300 and 400 MHz NMR instruments using TMS as an internal standard, $CDCl_3$ and DMSO as solvents. Standard Bruker software was used throughout. Chemical shifts 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 eluents. Electrospray Ionization Mass Spectrometry (ESI-MS) analyses were recorded on a LCQ Fleet, Thermo Fisher Instruments Limited, US. ESI-MS was performed in the positive ion mode. The collision voltage and ionization voltage were −70 V and −4.5 kV, respectively, using nitrogen as an 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 was carried out in an ULTRASONIC STERICLEANER. HPLC was recorded on a SHIMADZU LC-6AD using a chiral column (Phenomenex Chiralpack), and HPLC grade *n*-hexane and isopropanol as solvents.

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

Mesitylene **6** (10 ml, 72.0 mmol), NBS (44.8 g, 252 mmol), a 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 h at 70 °C. After the completion of reaction time, the formed solid was removed by filtration at room temperature



Scheme 1 Enantioselective Michael addition of chalcones.



Scheme 2 Synthesis of CMPTCs **9**.

and the required filtrate was washed with water and extracted with DCM; the combined organic layer was washed with brine, dried over sodium sulphate and concentrated. The crude product was purified using 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 (0.1 g, 10 mmol), and cinchona derivatives **8**[18] (**8a**/**8b**, 30 mmol) was dissolved in 5 ml of THF and heated to reflux overnight; the white solid was filtered, washed with diethylether and dried to get pure tri-site chiral PTC (86% yield of **9a** and 88% yield of **9b**).

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 CMPTC conditions

A mixture of chalcone **3**[18,19] (**a–h**, 0.1 mmol), diethylmalonate **4** (0.12 mmol) and CMPTCs (5 mol%) **9** (**9a**/**9b**) was dissolved in 1 ml toluene and 0.5 ml of 10% K_2CO_3 was added. Then the reaction mixture was ultrasonicated for 1 h. The reaction mixture was extracted with ethylacetate, washed with water (3 × 2 ml), then washed with brine (5 ml), dried over sodium sulphate and concentrated. The crude material was purified using column chromatography on silica gel (ethylacetate and *n*-hexane as eluents), to afford the corresponding Michael adduct **5**. An enantiomeric excess of **5** was determined using chiral stationary-phase HPLC analysis.

Characterization of the 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 using HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50 : 2, 1 mL min^{-1}]: 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 using HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50 : 2, 1 mL min^{-1}]: 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 using HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50 : 2, 1 mL min^{-1}]: 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 using HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50 : 2, 1 mL min^{-1}]: 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 using HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50 : 2, 1 mL min^{-1}]: 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 using HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50 : 2, 1 mL min^{-1}]: 4.6 min (minor), 12.9 min (major).

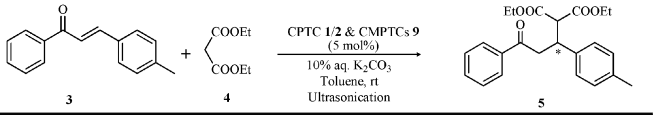
Diethyl 2-(3-(4-bromophenyl)-1-(4-methoxyphenyl)-3-oxopropyl)-malonate (5g). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.88 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 4.19–4.08 (m, 4H), 3.89 (q, J = 7.1 Hz, 2H), 3.72 (d, J = 9.7 Hz, 1H), 3.36 (dt, J = 16.6, 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 using HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50 : 2, 1 mL min^{-1}]: 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 using HPLC. [Phenomenex Chiralpack, 254 nm, hexane: IPA = 50 : 2, 1 mL min^{-1}]: 7.02 min (minor), 45.18 min (major).

Results and discussion

The mesitylene based chiral PTCs **9** (**9a** and **9b**) were synthesized *via* 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 bromides as the 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 Table 1, we observed that the results of Michael addition using different catalysts such as **1**, **2**, **9a** and **9b**, and the newly synthesized cinchona catalysts **9a** and **9b** have more efficient yields as well as ee's compared to the previously reported catalysts such as **1** and **2** under identical conditions but different reaction times, mild base and non-polar solvents (Table 1, entries 1–6). This may be due to the presence of multiactive sites in the catalysts,

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[a] (h)	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]

the strong ion pair interaction between the enolate anion of the chalcone and the catalysts containing electron deficient sites *i.e.* R_4N^+, and also the cooperative influence of neighbouring groups of the R_4N^+ ion with the substrate.[20] Although the CPTCs derived from triazine (**2a**, **2b**) in both cases possess two R_4N^+ cationic sites, the relative positions of these two cationic sites are far away from each other. As a result, the enolate anions of chalcone and diethylmalonate are not favourably fixed between the two R_4N^+ catalytic sites as in mesitylene derived CMPTCs (**9a** and **9b**). That is, there are no co-operative influences/attractions between R_4N^+ sites and the enolate anions (Fig. 3).

The initial step of the optimization of the Michael addition reaction of chalcone **3** with diethylmalonate **4** was carried out in the presence of different temperature under ultrasonication

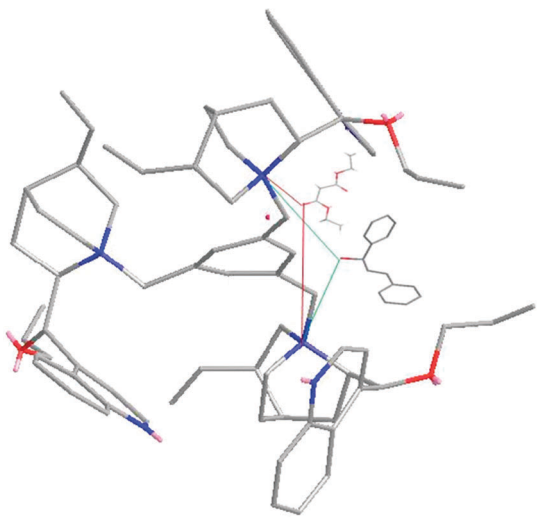
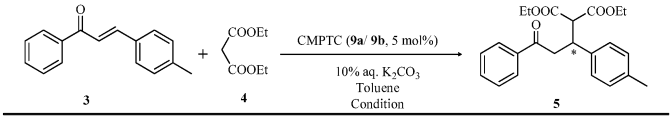


Fig. 3 A schematic representation for the two cationic moieties of CMPTC **9a** is simultaneously activated and co-operatively influenced the reaction due to dipole–dipole interaction (ion-pair).

Table 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

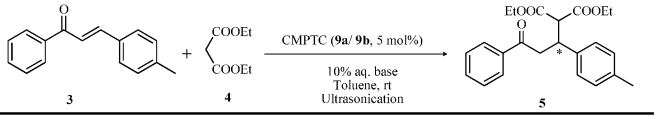


Entry	Catalyst	Condition	Time[a] (h)	Yield[b] (%)	% of ee[c]	Abs. conf.[d]
1	**9a**	RT	24	No reaction	—	—
2	**9b**	RT	24	15	29	R
3	**2a**	RT	24	No reaction	—	—
4	**2a**	RT	24	No reaction	—	—
5	**9a**	50 °C	24	No reaction	—	—
6	**9b**	50 °C	24	No reaction	—	—
7	**2a**	50 °C	24	No reaction	—	—
8	**2b**	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]

conditions. From the observed results, the ultrasonic mediated reaction conditions led to higher chemical yields and enantiomeric excess than the other temperature conditions (*i.e.* −20 °C, RT and 50 °C) (entries 1–16, Table 2). We also obtained higher chemical yields and enantiomeric excess than the previously reported tri-site 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 keeping the other parameters constant. The results showed that the *O*-allyl protected catalyst (**9b**) showed greater chemical yields and ee's than the *O*-benzylated catalyst (**9a**) (entries 1–10, Table 3). It has also been found that K_2CO_3, KOH and Cs_2CO_3 are more effective bases (higher yields above 90% and 95% ee's) in this reaction compared to other 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 conditions, with the other parameters kept constant. The results obtained (Table 4) show that the change of the solvent is found to be an important crucial factor in the Michael addition reaction due to the polarity of the solvents. The product yields and ee's were found to decrease gradually, upon moving from non-polar to polar solvents (entries 1–16, Table 4), which may be due to the increasing dielectric constant of the solvents. The decreased product yields/ee's in highly polar solvents like chloroform, acetone, acetonitrile and methanol (entries 7–16, Table 4), are

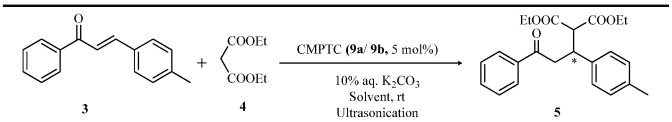
Table 3 Effect of 10% aq. base in the Michael addition reaction in presence of the chalcone **3** and diethyl malonate **4** with CMPTCs **9** (**9a**/**9b**), under ultrasonic conditions



Entry	10% base	Catalyst	Time[a] (min)	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

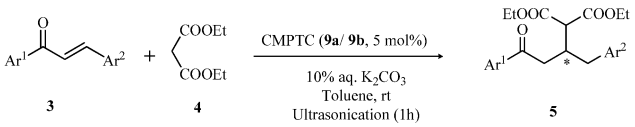


Entry	Solvent	Catalyst	Time[a] (min)	Yield[b] (%)	% of ee[c]	Abs. conf.[d]
1	Toluene	**9a**	60	98	97	R
2	Toluene	**9b**	60	98	99	R
3	Cyclohexane	**9a**	75	95	92	R
4	Cyclohexane	**9b**	75	95	93	R
5	THF	**9a**	60	93	95	R
6	THF	**9b**	60	93	96	R
7	Methanol	**9a**	90	80	75	R
8	Methanol	**9b**	90	80	72	R
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 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]

due to the higher degrees of solvation of chiral catalysts and also protection of the ion pair interaction between the R_4N^+ of the catalyst and the enolate anion of the substrates (diethylmalonate and chalcones). Hence, the chemical yield and ee's can be reduced. In the case of non-polar solvents such as

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



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]

toluene and cyclohexane, the degrees of solvation of CMPTC's are considerably less and hence the ion pair interaction between the catalysts and enolate ions can be influenced (entries 1–4, Table 4).

Further, the catalytic efficiencies, studied *via* 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), are listed in Table 5. The observed results suggested that independent of the substitution on the aryl group of the chalcones, both the electron withdrawing and electron donating groups were present on the aryl groups which could not affect the product yields and ee's. We found an excellent product yield and higher enantiomeric excess (entries 1–16, Table 5). This may be due to the fact 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 the aryl group of the chalcone which further influenced the interaction between the enolated ions of the chalcone and the electron deficient sites of the R_4N^+ of the respective catalysts (Fig. 4).

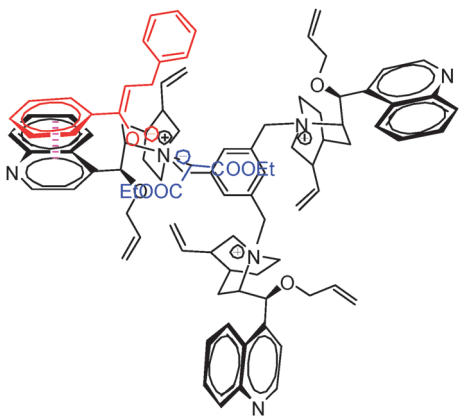


Fig. 4 Possible formation of ion pair between the R_4N^+ of the CMPTC with enolate anion of the chalcone as well as the π–π stacking interaction with the quinoline moiety of the catalyst and aryl group of the chalcone.

Conclusion

We have successfully synthesized mesitylene based tris-quaternary ammonium bromides as chiral phase transfer catalysts and characterized them well using various spectral techniques. The catalytic efficiencies were studied *via* the Michael addition of chalcones and diethylmalonate with very good chemical yields (up to 98%) and enantiomeric excess (up to 99%) at lower concentrations of base and catalysts under ultrasonic irradiation conditions.

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