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REGULAR ARTICLE

Enantioselective Michael addition of malonic esters to benzalacetophenone by using chiral phase transfer catalysts derived from proline-mandelic acid/tartaric acid

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Abstract. Herein, we have explored the enantioselective Michael addition of various malonate esters to benzalacetophenone by successful utilization of chiral phase transfer catalysts derived from proline, mandelic acid and tartaric acid under mild phase transfer conditions. The obtained results signify that these chiral phase transfer catalysts are efficacious towards enantioselective Michael addition as the use of it resulted in good enantioselectivity and appreciable chemical yields.

Keywords. Chiral phase transfer catalysts; enantioselective Michael addition; benzalacetophenone; proline; mandelic acid and tartaric acid.

1. Introduction

The formation of a carbon-carbon bond by using catalytical methodology is an attractive and demanding process in the chemical synthesis. Among all well-established catalytical carbon-carbon bond formation reactions, the Michael addition is one of the most effective carbon-carbon bond forming reaction.[1] The asymmetric Michael addition reaction can provide several enantiomerically pure Michael adducts from respective Michal acceptors and donors.[2] Amidst all these Michael additions, the enantioselective addition of malonic esters to α, β- unsaturated carbonyls provides an atom-economical chemical transformation to produce an optically active tricarbonyl Michael adducts.[3] Asymmetric Michael addition furnishes a useful tool for the asymmetric synthesis of various valuable enantiomerically pure or enantio-enriched chemical compounds through the combination of different electrophiles and nucleophiles. Asymmetric Michael addition reaction of malonate esters to enones by using catalysts is a foremost transformation in organic chemistry as it involves asymmetric induction at the β-position to the enone. Asymmetric Michael addition reaction is useful in the synthesis of various drugs molecules and some natural products.[1] There are a number of catalytic methodologies reported in the literature for the asymmetric conjugate addition of malonate esters to benzalacetophenones, such as organocatalysts,[4] chiral ionic liquids,[5] chiral metal complexes,[6] and chiral phase-transfer catalysts.[7] However, among all these methodologies, asymmetric phase-transfer catalysis has been found to be a simple, ecologically innocuous and most effective methodology for the enantioselective Michael addition of malonate esters to benzalacetophenone. High enantioselectivity is reported by Maruoka group by using *N*-spiro quaternary ammonium salt as a phase-transfer catalyst.[7a] Chiral phase-transfer catalysis (PTC) demonstrates in the way weak interactions arising from ion pairing can be applied to the enantioselectivity in conjugate addition reactions. The formation of chiral ion pair can be due to deprotonation with a chiral base, or by employing a chiral phase-transfer catalyst, and this chiral ion pair is responsible for the induction of asymmetry during the product formation. The phase transfer reactions are mostly carried out in

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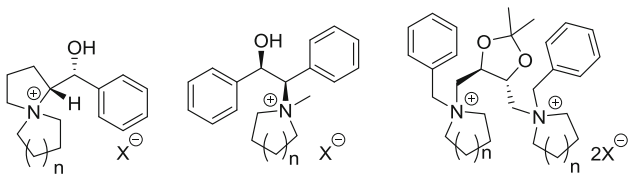

Figure 1. Chiral cyclic phase transfer catalysts **(I–VI)**.

two or three-phase systems in which generally aqueous and nonpolar solvent mixtures are used. Initially, the PTC reactions were carried out by using Cinchona alkaloids derivatives. However, recently better results for enantioselectivities have been reported in conjugate addition reaction by modifying the structures of phase transfer catalysts. The design and development of chiral phase-transfer catalysts are based on the use of chiral moiety. These PTCs are structurally well-defined by various effective substitutions on quaternary nitrogen. Enantiomerically pure catalysts have provided notable achievements in various bond formation reactions under mild phase-transfer-catalyzed conditions.[8]

1.1 *Chiral phase transfer catalysts*

By referring to this rational molecular design of chiral phase-transfer catalysts reported in literature,[7,8] we have recently reported the designing and synthesis of the chiral cyclic phase transfer catalysts derived from proline**,** mandelic acid and tartaric acid (**I–VI**, Figure 1) along with their successful evaluation for the effectiveness in enantioselective epoxidation and Darzens condensation.[9] To explore the further scope in enantioselective synthesis, we have utilized these PTCs for enantioselective Michael addition.

1.2 *Enantioselective Michael addition of dialkyl malonates to benzalacetophenone by using chiral phase transfer catalysts*

It is reported that for enantioselective Michael additions, chiral quaternary ammonium salts (PTCs) have excellent results.[7] So, to check the effectiveness of these chiral PTCs (**I–VI**), these catalysts have been applied for the enantioselective Michael additions of malonate esters (**2a–2e**) to benzalacetophenone (**1**) (Figure 2). In this chiral phase transfer catalyzed enantioselective addition reaction, the conjugate addition of malonic esters (**2a–2e**) to benzalacetophenone (**1**) were carried out in a solid-liquid bi-phasic system to get the chiral Michael adducts (**3a–3e**). The artless and amiable conditions have been used for these Michael addition reactions by loading 5 mol% as well as 10 mol% of the catalysts (**I–VI**). The nonpolar aprotic toluene was used as a solvent (the liquid phase), powdered potassium carbonate (solid phase) was used as a base and the reaction temperature was 20–30 °C.

2. Experimental

2.1 *Materials and physical measurements*

Benzalacetophenone was purchased from Sisco research laboratories Pvt. Ltd. (SRL) India. Dimethyl malonate, diisopropyl malonate and dibenzyl malonate were purchased from Sigma Aldrich. Diethyl malonate and di-tertiary butyl malonate were purchased from Spectrochem (India). All these raw materials were used directly without additional treatment. Commercial grade solvents were used for reaction and purification. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were obtained as solutions in deuterium substituted reagent on Bruker 500 MHz AVANCE III HD, Software- Topspin 3.5. Chemical shifts were reported in parts per million (ppm, δ). Melting points were recorded on Mettler Toledo MP-03 melting point apparatus. IR spectra (FTIR) were recorded on a Perkin spectrum 400 FTIR spectrometer using the ATR method. The C, H and N elemental analyses were performed on a Yanaco CHN FOER MT-3 element analyzer. The HPLC analysis were carried out by using Chiralpak AS-H Column and HPLC grade solvents (n-Hexane-Isopropanol).

2.2 *General procedure for the synthesis of enantioselective Michael adduct (**3a-3e**)*

In a round bottom flask, to a solution of benzalacetophenone (**1**) (25 g, 120 mmol, 1.0 eq) in toluene (150 mL), dialkyl malonate (**2a–2e**) (360 mmol, 3.0 eq), potassium carbonate (47.58 g, 360 mmol, 3.0 eq) and chiral PTC (5 mol% or 10 mol%) (**I–VI**) was charged and stirred. After the completion of reaction, the reaction mixture was filtered. Filtrate was concentrated under vacuum to get crude product as a residue, which was purified by recrystallization from methanol to get pure respective Michael adducts.

2.2a *dimethyl (S)-2-(3-oxo-1,3-diphenylpropyl)malonate (**3a**) (Table 1)*: The title compound (**3a**) was prepared according to the general procedure described for the synthesis of enantioselective Michael adduct by using dimethyl malonate (**2a**) (47.58 g, 360 mmol, 3.0 eq).

(**3a**) -White solid, Yield 39.7 g (97.0%), Melting range 83–85 °C. (Lit. Melting range 82–83 °C).[10] $[\alpha]_D^{26.9}$ 18.50° (*c* 1.0 in $CHCl_3$). (Lit. $[\alpha]_D^{26.9} = +21.0°$ for 99% ee (*c* 1.0 in $CHCl_3$).[11] Optical purity (% ee) 87.2%[12] (Entry 8, Table 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47–3.59 (m, 2H), 3.52 (s, 3H), 3.75 (s, 3H), 3.87 (d, J = 9.5 Hz, 1H), 4.19–4.24 (m, 1H), 7.18–7.21 (m, 1H), 7.25–7.29 (m, 4H), 7.43–7.46 (m, 2H), 7.53–7.57 (m, 1H), 7.90–7.93 (m, 2H); ^{13}C NMR (125

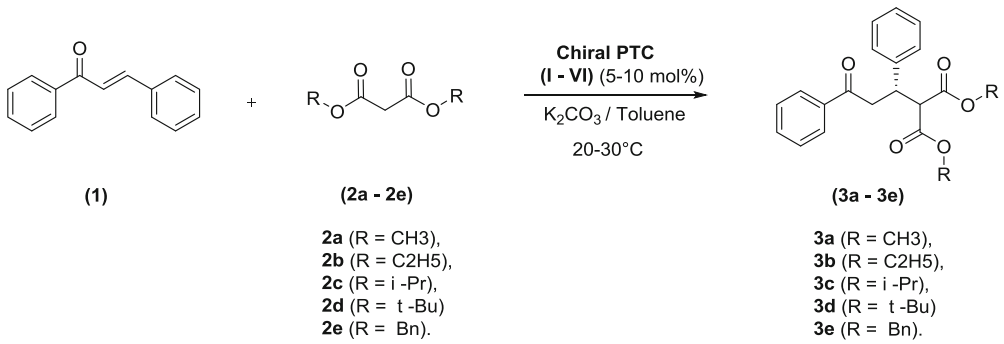

Figure 2. Michael addition of malonates (**2a–2e**) to benzalacetophenone (**1**) to get Michael adduct (**3a**–**3e**).

Table 1. Michael addition of dimethyl malonate (**2a**) to benzalacetophenone by using chiral cyclic PTCs to get the Michael adduct, dimethyl (S)-2-(3-oxo-1,3-diphenylpropyl) malonate (**3a**).

Entry	Chiral PTC	Chiral PTC (mol %)	Time (h)	Yield[a] (%)	SOR[α][b] (°)	Cal. Opt. Purity[c] (% ee)
1	**I**	5	3	96	18.12	85.4%
2	**I**	10	2	94	18.18	85.7%
3	**II**	5	3	95	18.26	86.0%
4	**II**	10	2	95	18.29	86.2%
5	**III**	5	3	96	18.39	86.7%
6	**III**	10	2	95	18.41	86.8%
7	**IV**	5	3	96	18.49	87.1%
8	**IV**	10	2	97	18.50	87.2%
9	**V**	5	3	95	17.72	83.5%
10	**V**	10	2	94	17.71	83.4%
11	**VI**	5	3	95	17.82	84.0%
12	**VI**	10	2	95	17.88	84.3%

[a]Isolated yield after purification. [b]SOR- (*c* 1.0 in $CHCl_3$ at 26.9 °C).[11] [c]Optical purity (% ee) has been calculated based on reported data in literature.[12]

MHz, $CDCl_3$) δ 197.5, 168.7, 168.1, 140.4, 136.7, 133.0, 128.5, 128.4, 128.0, 127.2, 57.3, 52.6, 52.4, 42.3, 40.7; IR (neat), ν/cm^{-1} 1727, 1698, 1680, 1595, 1579, 1498, 1449, 1433, 1414, 1370, 1343, 1307, 1233, 1210, 1198, 1184, 1159, 1117, 1095, 1080, 1064, 1024, 1001, 981,960, 929, 911, 872, 850, 793, 767, 746, 699, 686, 660. Anal. calculated for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found; C, 70.63; H, 5.93. Chiral HPLC analysis: n-Hexane-Isopropanol (90:10), 1 mL/min, Chiralpak AS-H Column, major enantiomer (*S*) t*r* = 12.13 min, minor enantiomer (*R*) t*r* = 15.52 min. ee 87% (Table 6, entry 1).

2.2b *diethyl (S)-2-(3-oxo-1,3-diphenylpropyl) malonate (3b) (Table 2)*: The title compound (**3b**) was prepared according to the general procedure described for the synthesis of enantioselective Michael adduct by using diethyl malonate (**2b**) (57.6 g, 360 mmol, 3.0 eq).

(**3b**) - White solid, Yield 42.0 g (95.0%), Melting range 64–66 °C. (Lit. Melting range 65–68 °C).[11] $[\alpha]_D^{28}$ 16.65° (*c* 1.0 in $CHCl_3$). (Lit. $[\alpha]_D^{28} = 18.5°$ for 99% ee (*c* 1.0 in $CHCl_3$).[11] Optical purity (% ee) 89.1%[13] (Entry 8, Table 2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.0, 7.5 Hz, 3H), 1.26 (t, *J* = 7.0, 7.5 Hz, 3H), 3.48–3.57 (m, 2H), 3.83 (dd, *J* = 4.0, 6.0 Hz, 1H), 3.95 (q, *J* = 14.5, 7.5 Hz, 2H), 4.18–4.23 (m, 3H), 7.16–7.20 (m, 1H), 7.24–7.29 (m, 4H), 7.42–7.45 (m, 2H), 7.52–7.56(m, 1H), 7.90–7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 168.3, 167.7, 140.4, 136.8, 133.0, 128.5, 128.4, 128.2, 128.1, 127.1, 61.6, 61.3, 57.5, 42.6, 40.8, 14.0, 13.7; IR (neat), ν/cm^{-1} 1745, 1721, 1680, 1598, 1581, 1496, 1476, 1449, 1416, 1392, 1367, 1354, 1332, 1293, 1237, 1211, 1192, 1182, 1166, 1117, 1090, 1062, 1031, 1004, 973, 952, 915, 860, 830, 815, 764, 745, 701, 686, 659. Anal. calculated for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found; C, 71.66; H, 6.56. Chiral HPLC analysis: n-Hexane-Isopropanol (90:10), 1 mL/min, Chiralpak AS-H Column, major enantiomer (*S*) t*r* = 20.35 min, minor enantiomer (*R*) t*r* = 24.59 min. ee 90% (Table 6, entry 2).

2.2c *diisopropyl (S)-2-(3-oxo-1,3-diphenylpropyl) malonate (3c) (Table 3)*: The title compound (**3c**) was prepared according to the general procedure described for the synthesis of enantioselective Michael adduct by using diisopropyl malonate (**2c**) (67.75 g, 360 mmol, 3.0 eq).

(**3c**) - White solid, Yield 45.3 g (95.0%), Melting range 67–68 °C. (Lit. Melting range 69–71 °C).[14] $[\alpha]_D^{28}$19.32° (*c* 0.925 in $CHCl_3$). (Lit. $[\alpha]_D^{28} = +18.9°$ for 90% ee (*c* 0.925 in

Table 2. Michael addition of diethyl malonate (**2b**) to benzalacetophenone by using chiral cyclic PTCs to get the Michael adduct, diethyl (S)-2-(3-oxo-1,3-diphenylpropyl) malonate (**3b**).

Entry	Chiral PTC	Chiral PTC (mol %)	Time (h)	Yield[d] (%)	SOR[α][e] (°)	Cal. Opt. Purity[f] (% ee)
1	**I**	5	5	92	16.17	86.5%
2	**I**	10	3	92	16.15	86.4%
3	**II**	5	5	93	16.20	86.7%
4	**II**	10	3	92	16.22	86.8%
5	**III**	5	5	94	16.32	87.3%
6	**III**	10	3	95	16.36	87.5%
7	**IV**	5	5	95	16.56	88.6%
8	**IV**	10	3	95	16.65	89.1%
9	**V**	5	5	93	15.84	84.7%
10	**V**	10	3	93	15.82	84.6%
11	**VI**	5	5	94	15.93	85.2%
12	**VI**	10	3	93	15.94	85.3%

[d]Isolated yield after purification. [e]SOR- (*c* 1.0 in $CHCl_3$ at 28 °C).[11] [f]Optical purity (% ee) has been calculated based on reported data in literature.[13]

Table 3. Michael addition of disopropyl malonate (**2c**) to benzalacetophenone by using chiral cyclic PTCs to get the Michael adduct, disopropyl (S)-2-(3-oxo-1,3-diphenylpropyl) malonate (**3c**).

Entry	Chiral PTC	Chiral PTC (mol %)	Time (h)	Yield[g] (%)	SOR[α][h] (°)	Cal. Opt. Purity[i] (% ee)
1	**I**	5	11	91	18.82	89.6%
2	**I**	10	8	91	18.80	89.5%
3	**II**	5	11	92	18.86	89.8%
4	**II**	10	8	91	18.89	89.9%
5	**III**	5	11	93	19.13	91.1%
6	**III**	10	8	93	19.11	91.0%
7	**IV**	5	11	94	19.30	91.9%
8	**IV**	10	8	95	19.32	92.0%
9	**V**	5	11	89	18.01	85.7%
10	**V**	10	8	90	18.04	85.9%
11	**VI**	5	11	90	18.12	86.2%
12	**VI**	10	8	89	18.16	86.4%

[g]Isolated yield after purification. [h]SOR-(*c* 0.925 in $CHCl_3$ at 28 °C).[15] [i]Optical purity (% ee) has been calculated based on reported data in literature.[16]

$CHCl_3$).[14] Optical purity (% ee) 92.0%[16] (Entry 8, Table 3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, J = 6.0 Hz, 3H), 1.05 (d, J = 6.5 Hz, 3H), 1.25 (d, J = 6.0 Hz, 6H), 3.44 (q, J = 7.0 Hz, 1H), 3.53 (dd, J = 16.5, 4.0 Hz, 1H), 3.78 (d, J = 10.0 Hz, 1H), 4.17–4.19 (m, 1H), 4.79–4.82 (m, 1H), 5.06–5.11 (m, 1H), 7.15–7.92 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.6, 167.9, 167.2, 140.4, 136.8, 132.9, 128.5, 128.4, 128.3 128.1, 127.0, 69.2, 68.8, 57.8, 42.9, 40.7, 21.6, 21.5, 21.3, 21.2; IR (neat), ν/cm^{-1} 1727, 1698, 1680, 1595, 1579, 1498, 1449, 1433, 1414, 1370, 1343, 1307, 1233, 1210, 1198, 1184, 1159, 1117, 1095, 1080, 1064, 1024, 1001, 981, 960, 929, 911, 872, 850, 793, 767, 746, 699, 686, 660. Anal. calculated for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found; C, 72.75; H, 7.11. Chiral HPLC analysis: n-Hexane-Isopropanol (90:10), 1 mL/min, Chiralpak AS-H Column, major enantiomer (*S*) t*r* = 24.24 min, minor enantiomer (*R*) t*r* = 32.03 min. ee 91% (Table 6, entry 3).

2.2d *di-tert-butyl (S)-2-(3-oxo-1,3-diphenylpropyl) malonate (**3d**) (Table 4)*: The title compound (**3d**) was prepared according to the general procedure described for the synthesis of enantioselective Michael adduct by using di-tert-butyl malonate (**2d**) (77.86 g, 360 mmol, 3.0 eq).

(**3d**) - White solid, Yield 46.0 g (90.0%), Melting range 97–99 °C (Lit. Melting point 102 °C).[17] $[\alpha]_D^{20}$ 22.52° (*c* 0.24 in $CHCl_3$). (Lit. $[\alpha]_D^{20}$ = 23.4° for 98% ee (*c* 0.24 in $CHCl_3$).[17] Optical purity (% ee) 94.3%[18] (Entry 8, Table 4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.48 (s, 9H), 3.39–3.44 (m, 1H), 3.51 (dd, J = 16.0, 3.5 Hz, 1H), 3.64 (d, J = 10.5 Hz, 1H), 4.06–4.11 (m, 1H), 7.15–7.92 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 167.7, 167.0, 140.7, 136.9, 132.9, 128.6, 128.5, 128.2, 128.1, 126.9, 82.0, 81.4, 59.3, 59.1, 43.3, 40.8, 27.9, 27.5; IR (neat), ν/cm^{-1}1732, 1720, 1681, 1596, 1580, 1539, 1495, 1477, 1449, 1402, 1394, 1367, 1337, 1300, 1272, 1224, 1204, 1189, 1152, 1136, 1098, 1070, 1062, 1029,

Table 4. Michael addition of di-tert-butyl malonate (**2d**) to benzalacetophenone by using chiral cyclic PTCs to get the Michael adduct, di-tert-butyl (S)-2-(3-oxo-1,3-diphenylpropyl) malonate (**3d**).

Entry	Chiral PTC	Chiral PTC (mol %)	Time (h)	Yield[j] (%)	SOR[α][k] (°)	Cal. Opt. Purity[l] (% ee)
1	**I**	5	36	87	21.80	91.3%
2	**I**	10	28	85	21.84	91.4%
3	**II**	5	32	85	21.92	91.8%
4	**II**	10	25	85	21.89	91.7%
5	**III**	5	30	86	22.00	92.2%
6	**III**	10	23	85	22.08	92.4%
7	**IV**	5	30	89	22.48	94.2%
8	**IV**	10	24	90	22.52	94.3%
9	**V**	5	38	85	20.92	87.6%
10	**V**	10	31	84	20.98	87.8%
11	**VI**	5	38	85	21.30	89.2%
12	**VI**	10	30	85	21.26	89.0%

[j]Isolated yield after purification. [k]SOR- (*c* 0.24 in $CHCl_3$ at 20 °C).[17] [l]Optical purity (% ee) has been calculated based on reported data in literature.[18]

Table 5. Michael addition of dibenzyl malonate (**2d**) to benzalacetophenone by using chiral cyclic PTCs to get the Michael adduct, dibenzyl (S)-2-(3-oxo-1,3-diphenylpropyl)malonate (**3e**).

Entry	Chiral PTC	Chiral PTC (mol %)	Time (h)	Yield[m] (%)	SOR[α][n] (°)	Cal. Opt. Purity[o] (% ee)
1	**I**	3	4	93	11.36	90.0%
2	**I**	10	3	93	11.38	90.1%
3	**II**	5	4	94	11.43	90.5%
4	**II**	10	3	93	11.41	90.4%
5	**III**	5	4	95	11.48	90.9%
6	**III**	10	3	96	11.50	91.1%
7	**IV**	5	4	96	11.74	93.0%
8	**IV**	10	3	96	11.81	93.5%
9	**V**	5	4	94	10.90	86.3%
10	**V**	10	3	93	10.92	86.5%
11	**VI**	5	4	93	11.11	88.0%
12	**VI**	10	3	94	11.10	87.9%

[m]Isolated yield after purification.[n]SOR- (*c* 0.97 in $CHCl_3$ at 27.9 °C).[11] [o]Optical purity (% ee) has been calculated based on reported data in literature.[19]

1003, 970, 956, 920, 912, 851, 838, 801, 780, 763, 740, 701, 687, 658. Anal. calculated for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found; C, 73.51; H, 7.62. Chiral HPLC analysis: n-Hexane-Isopropanol (90:10), 1 mL/min, Chiralpak AS-H Column, major enantiomer (*S*) t*r* = 25.94 min, minor enantiomer (*R*) t*r* = 30.30 min. ee 95% (Table 6, entry 4).

2.2e *dibenzyl (S)-2-(3-oxo-1,3-diphenylpropyl)malonate (**3e**) (Table 5)*: The title compound (**3e**) was prepared according to the general procedure described for the synthesis of enantioselective Michael adduct by using dibenzyl malonate (**2e**) (102.35g, 360 mmol, 3.0 eq).

(**3e**)**-** White solid, Yield 55.0 g (93.0%), Melting range 88.1–89.9 °C (Lit. M.p. 90 °C).[11] $[\alpha]_D^{27.9}$ 12.02° (*c* 0.97 in $CHCl_3$). (Lit. $[\alpha]_D^{27.9} = 12.5°$ for 99% ee (*c* 0.97 in $CHCl_3$).[11] Optical purity (% ee) 93.50%[19] (Entry 8, Table 5); ^{1}H NMR (500 MHz, $CDCl_3 + D_2O$) δ 3.47 (d, J = 6.5 Hz, 2H), 3.98 (d, J = 9.5 Hz, 1H), 4.24–4.27 (m, 1H), 4.94 (s, 2H), 5.14 (d, J = 12.5 Hz, 1H), 5.19 (d, J = 12.5 Hz, 1H), 7.83 (d, J = 7.0 Hz, 2H), 7.53–7.56 (m, 1H), 7.40–7.43 (m, 2H), 7.19–7.33 (m, 13H), 7.09–7.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 168.0, 167.5, 140.3, 136.7, 135.1, 135.0, 133.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.2, 67.3, 67.1, 57.5, 42.2, 40.7; IR (neat), ν/cm^{-1} 1750, 1723, 1688, 1596, 1580, 1496, 1455, 1408, 1373, 1312, 1264,1248, 1222, 1203, 1165, 1134, 1093, 1067, 1022, 1008, 990, 954, 912, 825, 811, 747, 696. Anal. calculated for $C_{32}H_{28}O_5$: C, 78.03; H, 5.73. Found; C, 78.09; H, 5.72. Chiral HPLC analysis: n-Hexane-Isopropanol (90:10), 1 mL/min, Chiralpak AS-H Column, major enantiomer (*S*) t*r* = 13.98 min, minor enantiomer (*R*) t*r* = 17.08 min. ee 93% (Table 6, entry 5).

Table 6. Michael addition of malonate esters (**2a–2e**) to benzalacetophenone by using 10 mol% of chiral PTC (**IV**) to get the Michael adduct (**3a–3e**).

Entry	Malonate ester	Time (h)	Michael adduct	Yield [p] (%)	Opt. Purity of reaction mass [q](ee)	Opt. Purity of isolated product [r](ee)
1	**2a**	2	**3a**	97	87.6%	87.5%
2	**2b**	3	**3b**	95	90.6%	90.2%
3	**2c**	8	**3c**	95	90.9%	91.3%
4	**2d**	24	**3d**	90	95.3%	95.0%
5	**2e**	3	**3e**	96	93.3%	93.2%

[p]Isolated yield after purification. [q]Enantiomeric excess (% ee) of reaction mass for absolute configuration (*S*) was determined by HPLC analysis. [r]Enantiomeric excess (% ee) of Isolated products for absolute configuration (*S*) was determined by HPLC analysis. (HPLC analysis carried out by using: Chiralpak AS-H Column, n-Hexane-Isopropanol (90:10) mobile phase, the flow rate of 1 mL/min. and by comparison with the HPLC retention time using known standard).

3. Results and Discussion

Quaternary ammonium salts of Proline, Mandelic acid and tartaric acid (**I–VI**) are ideal because one of the tetrahedra faces about the charged quaternary nitrogen is blocked by the cyclic ring system itself. The second tetrahedral face about quaternary nitrogen is blocked by the aromatic ring, whose position is fixed for steric reasons. Further, it is noticeable that a third tetrahedral face of charged quaternary nitrogen is attached to an alkyl or benzyl or another cyclic group. So, only one side of charged quaternary nitrogen is available to form ion pairing with the anion of the reactant. These PTCs have -OH or -OR group at β position to the quaternary nitrogen which can help to form hydrogen bonding or attractive van der Waals interaction to get an advantage for enhancing the enantioselectivity.

It is reported that for enantioselective Michael additions, chiral quaternary ammonium salts (PTCs) have excellent results.[7a] So, to check the effectiveness of these chiral PTCs (**I–VI**), these catalysts have been applied for the enantioselective Michael additions of malonate esters (**2a–2e**) to benzalacetophenone (**1**) (Figure 2) to get enantioselective Michael adduct (**3a–3e**). In this application, it has been observed that all the PTCs are producing good enantioselectivity. Mandelic acid derivatives (**III** and **IV**) (ee 87–95%) are producing more enantioselectivity as compared to proline (**I** and **II**) (ee 85–90%) and tartaric acid derivatives (**V** and **VI**) (ee 83–89%). Whereas, the proline derivatives (**I** and **II**) (ee 85–90%) are producing better enantioselectivity than the tartaric acid derivatives (**V** and **VI**) (ee 83–89%). In addition to this, among the same category of catalysts, the catalysts which have larger cyclic rings (**II**, **IV** and **VI**) are producing more enantioselectivity than the smaller cyclic rings (**I**, **III** and **V**) due to bulkiness or steric hindrance generated on quaternary nitrogen by the larger cyclic groups (Tables 1–5). The obtained enantioselectivity may be due to more steric hindrance at the quaternary nitrogen of mandelic acid derivatives as compared to the steric hindrance at quaternary nitrogen of proline and tartaric acid derivatives. Along with this, there was a huge difference observed in the rate of reaction. The observed sequence of the rate of reaction for the addition of malonic esters with benzalacetophenone was Di tert. Butyl malonate < Di isopropyl malonate < Diethyl malonate < Dibenzyl malonate < Dimethyl malonate (Tables 1–6). This may be also due to steric hindrance and electron realizing (positive) Inductive effect provided by the alkoxy group of respective malonic esters.

Moreover, in all applications of chiral PTCs, the Michael adducts having tertiary butyl ester (Table 4),

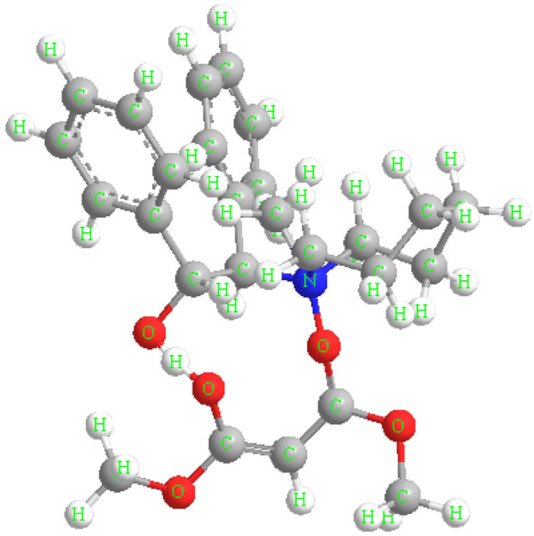

Figure 3. Plausible ion pair formation of PTC with the nucleophiles (malonic esters).

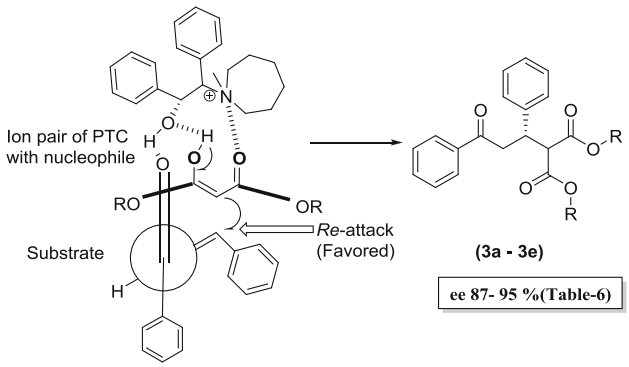

Figure 4. Plausible mechanism for the enantioselective Michael by using PTC (**IV**).

benzyl ester (Table 5) and isopropyl ester (Table 3) have slightly high enantiomeric excess than the Michael adducts having ethyl ester (Table 1) and methyl esters (Table 2). The enantioselectivity trend was also confirmed by the chiral HPLC data of different Michael adduct synthesized by using chiral PTC (**IV**) (Table 6). The trend of getting enantioselectivity was Di tert. Butyl malonate > Di benzyl malonate > Di isopropyl malonate > Di ethyl malonate > Di methyl malonate. This may be also due to steric hindrance provided by the respective alkoxy group of Malonic esters.

The reason for obtaining good enantioselectivity in all the cases may be due to effective ion pairing formation of PTC with the Michael donor/nucleophile (Figure 3 and 4) followed by the interaction of this ion paired Michael donor with the β carbon of the substrate from the unique direction (*Re*-face attack) to produce S configuration of addition product (Figure 3).

The scope of the reaction by variation in enone substrate was not studied because as reported in the literature, the nature of electronic properties of substituents in both the aromatic systems as well as a substitution at β carbon has very little or insignificant effect on the enantioselectivity of Michael adduct.[20,21]

4. Conclusions

After the successful evaluation of these catalysts in enantioselective epoxidation and Darzen reactions, these catalysts have been examined for enantioselective Michael additions of malonate esters to benzalacetophenone. It has been observed that all the PTCs are producing good enantioselectivity. Among all these three derivatives, mandelic acid derivatives are producing more enantioselectivity as compared to proline and tartaric acid derivatives. In addition to this, among the same category of catalysts, the catalysts which have large cyclic ring has more enantioselectivity than the small cyclic ring PTCs. This may be because the quaternary nitrogen of mandelic acid derivatives has more steric hindrance as compared to the quaternary nitrogen of proline derivatives and tartaric acid derivatives. Along with this, the ring size of cyclic substituents among the same class of derivatives is also helpful to enhance the enantioselectivity.

So, based on these results, we can conclude that the designed derivatives of proline, mandelic acid and tartaric acid are effectual as chiral phase transfer catalysts for enantioselective Michael additions. Moreover, it can be concluded that the bulkier malonic ester has less reactivity and slightly more selectivity during Michael addition. Further applications for enantioselective synthesis by using these chiral PTCs are in progress.

Supplementary Information (SI)

^{1}H, ^{13}C NMR spectra and chiral HPLC Chromatograms for chiral Michael adducts (Figures S1–S20) are available in Supplementary Information. Supplementary Information is available at www.ias.ac.in/chemsci.

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19. The reported specific optical rotation for dibenzyl (S)-2-(3-oxo-1,3-diphenylpropyl)malonat (**3e**) is 12.5° for 99% ee, $[\alpha]_D^{27.9}$ (*c* 0.97 in $CHCl_3$)[11]. So, the known SOR $[\alpha]_\lambda$ for 100% ee would be, [12.5 ÷ 99x100] = 12.626°. Optical purity (% ee) has been calculated by using formula. [12b]
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