Highly Enantioselective Asymmetric Michael Addition Reactions with New Chiral Multisite Phase-Transfer Catalysts

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Abstract: Highly enantioselective Michael addition reactions of diethyl malonate to various chalcones have been achieved under mild chiral multisite phase-transfer reaction conditions by the successful utilization of 2,4,6-(triscinchoniummethyl)phenyl-1,3,5-triazines as new chiral quaternary ammonium catalysts. This simple asymmetric Michael addition process was found to be quite effective and to obtain Michael adducts with very good yields and enantiomeric excesses.

Key words: phase-transfer catalysts, Michael reaction, enantioselective reaction, quaternary ammonium salt, cinchona alkaloid

Phase-transfer catalysis is a versatile, well-established synthetic technique applicable to a number of organic biphase reactions.[1] This technique has become one of the most interesting and fascinating topics of research during the last few years being successful for a multitude of organic transformations.[2] One of the most general, efficient, and environmental benign methodologies that can successfully be employed to solve the predicament of insolubility of aqueous phase with organic phase is phase-transfer catalysis.[3] As the chemical reactants reside in immiscible phases, phase-transfer catalysts have the ability to carry one of the reactants as a highly active species for penetrating the interface, into the other phase where the reaction takes place, and to give a high conversion and selectivity for the desired product under mild reaction conditions. Since the mid 1880's the Michael addition reaction has been extensively investigated and applied in organic chemistry.[4] During the past two decades, a large progress has been made in the development of asymmetric catalyzed Michael addition reactions in the presence of cinchona-based chiral catalysts with very good yield and high enantiomeric excesses.

In recent years most of the researchers concentrated on 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.[5] Recently, Corey et al.[6a] and Kim et. al.[6b] have reported the enantioselective Michael addition of nitromethane and nitroalkane to α,β-enone using a chiral quaternary ammonium salt as chiral catalyst, respectively. Shishido et al. has reported on the synthesis of (+)-triptoquinone using the chiral cinchonidine-based quaternary ammonium bromide as catalyst.[7] All the previously reported Michael addition reactions are using single-site quaternary ammonium chiral catalysts also they have achieved moderate yield and enantiomeric excesses. In our study for the first time we reported the multisite-containing chiral quaternary ammonium catalysts for the Michael addition reaction under mild basic conditions with very good yield and enantiomeric excesses (Figure 1, 1–3). As part of our research program related to the development of effective cinchona alkaloid derived chiral multisite phase-transfer catalysts (CMPTC),[8] we reported the catalytic enantioselective Michael reaction promoted by quaternary ammonium salts from cinchonine as phase-transfer catalysts **11a** and **11b**.[9]

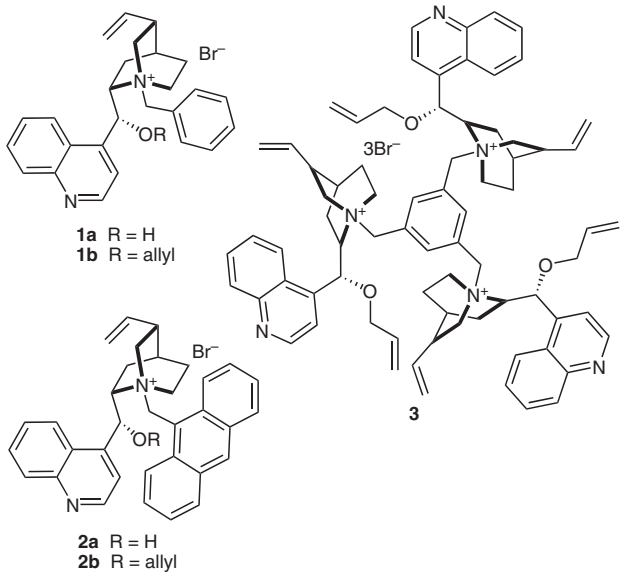

Figure 1 Cinchona-derived chiral phase-transfer catalysts

In this paper, we wish to report the catalytic enantioselective Michael reaction of diethyl malonate **5** to chalcone derivative **4** using the cinchona alkaloid derived quaternary ammonium salts **11a** and **11b** (Scheme 1). In order to determine suitable reaction conditions, we initially investigated the reaction system using 5 mol% of catalyst with diethyl malonate **5** as the Michael donor and chalcone **4** as the Michael acceptor with various solvents as well as bases. Catalysts **11a** and **11b** (Scheme 2) having an *O*-ben-

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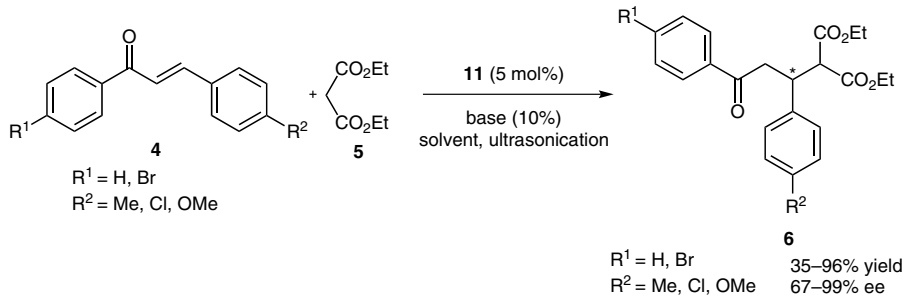
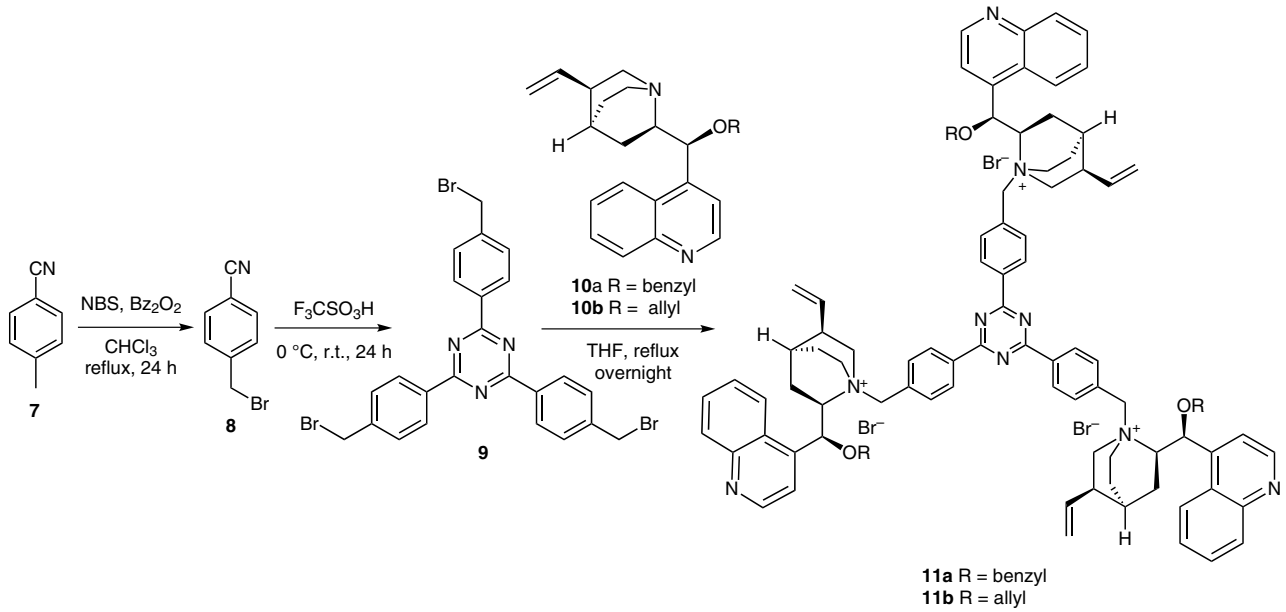


Scheme 1 Enantioselective Michael addition of diethylmalonate **5** to chalcone derivative **4** using CMPTC **11** in aqueous media



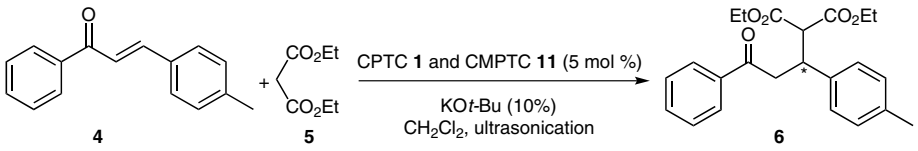
Scheme 2 Synthesis of enantioselective chiral catalysts **11**

zyl/allyl group showed higher catalytic efficiencies than other catalysts such as single-site CPTC **1a** and **1b** in terms of yields and enantioselectivity due to the multiactive center (tri-site) present in the catalysts **11a** and **11b** which can influence the formation of an ion-pair interaction between the α-carbon of the diethylmalonate with tri-site catalysts (Table 1, entries 1–4). Compound **6** was formed using cinchonine-derived catalysts (**1** and **11**) as the excessive enantiomer, which should be the case because all of these catalysts posses the same chirality.

We chose *N*-alkyl cinchonium salts **11a** and **11b**, which are well-known as chiral MPTCs to give valuable Michael adducts under mild biphasic conditions. The results are shown in Table 1. Enantioselective Michael addition reaction was carried out in different nonaqueous solvents using test CMPTC **11** under biphasic conditions keeping the other variables as constant. From the obtained results (Table 2), it is seen that the change of solvent is found to be an important influential factor in the Michael addition reaction owing to solvent polarity. The chemical yield and enantiomeric excesses have been found to increase gradually, when we are using polar solvents (Table 2, entries 1–16). The results obtained with various solvents have been related to their dielectric constants. The decreased product yield/enantiomeric excesses in high polar solvents like DMF (Table 2, entries 11 and 12) is due to the higher degree of solvation of CMPTC, which in turn decreases the efficiency of the catalyst. That is, most probably, the high polar solvents should reduce the ionic interaction between the catalyst and the anionic agents (diethylmalonate) reducing the yield and enantiomeric excess. In the case of toluene and cyclohexane, which is a low polar solvent, the degree of solvation of CMPTC is considerably less. Hence, the degree of decay due to solvation of CMPTC of the catalyst is almost minimized/ignored. Otherwise, the interaction between R_4N^+ of the catalyst and anion of the diethylmalonate is more. This in turn improves the potential of the catalyst as well as effective attraction of the substrate and catalyst, and hence the reaction yield and enantiomeric excesses were found to be higher in toluene and cyclohexane medium (Table 2, entries 7–10).

Catalyst **11b** having an O-allyl group showed higher catalytic efficiencies than the *O*-benzyl-protected catalyst **11a** in terms of yields and enantioselectivity (Table 3, en-

Table 1 Catalytic Asymmetric Michael Addition of Diethyl Malonate **5** to Chalcone **4** with Different CPTC **1** and CMPTC **11** under Ultrasonic Conditions

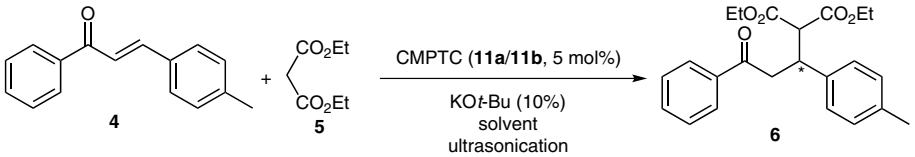


Entry	Catalyst	Time (h)[a]	Yield (%)[b]	ee (%)[c]	Abs. config.[d]
1	**1a**	7	46	51	*R*
2	**1b**	7	60	65	*R*
3	**11a**	7	96	98	*R*
4	**11b**	7	97	99	*R*

[a] The Michael reaction of chalcone **4** (0.1 mmol), diethyl malonate **5** (0.12 mmol), and CPTC **1** and CMPTC **11** (5 mol%) with solvent (1 mL) and base (10%, 0.5 mL) base under ultrasonic conditions.
[b] Isolated yield of purified material.
[c] Enantiopurity was determined by HPLC analysis of the Michael adduct **6** using a chiral column (Phenomenex Chiralpack) with hexane–2-PrOH as solvent.
[d] Absolute configuration was determined by comparison of the HPLC retention time.

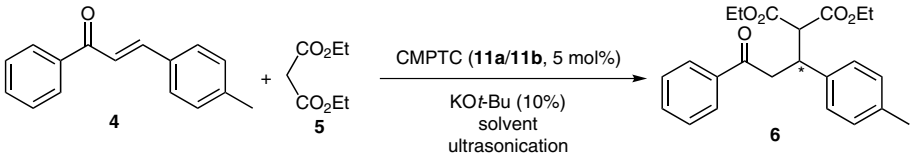
tries 1–12,). It has been also found that KO*t*-Bu, K_2CO_3, and Cs_2CO_3 were the more effective bases in this reaction than others such as NaOH, KOH, and Et_3N (Table 3, entries 1–12). Under the optimized reaction conditions described above (5 mol% of catalyst **11a** and **11b**, 10% base, CH_2Cl_2, ultrasonic conditions), we investigated the catalytic asymmetric Michael addition of diethyl malonate to chalcone **4**. The reaction smoothly proceeded to afford the corresponding adduct **6** with good enantioselectivities. Reaction of 1.2 equivalents of diethyl malonate **5** with 1.0 equivalent of chalcone **4**, cinchonium salts **11a** and **11b** (5 mol%) and KO*t*-Bu in CH_2Cl_2 at room temperature with stirring for 1–8 hours afforded the Michael adducts **6** in good yields with very good enantioselectivities (67–99% ee, Table 3). In all cases the enantiomeric excesses were determined by HPLC analysis.

Table 2 Catalytic Asymmetric Michael Addition of Diethyl Malonate **5** to Chalcone **4** with Different Solvents and CMPTC **11a** and **11b** under Ultrasonic Conditions



Entry	Solvent	Catalyst	Time (h)[a]	Yield (%)[b]	ee (%)[c]	Abs. config.[d]
1	CH_2Cl_2	**11a**	4	90	93	*R*
2	CH_2Cl_2	**11b**	4	90	99	*R*
3	THF	**11a**	4	90	93	*R*
4	THF	**11b**	4	90	95	*R*
5	MeOH	**11a**	8	35	75	*R*
6	MeOH	**11b**	8	55	72	*R*
7	toluene	**11a**	8	82	88	*R*
8	toluene	**11b**	8	89	96	*R*
9	cyclohexane	**11a**	8	90	92	*R*
10	cyclohexane	**11b**	8	88	98	*R*
11	DMF	**11a**	8	90	68	*R*
12	DMF	**11b**	8	51	73	*R*

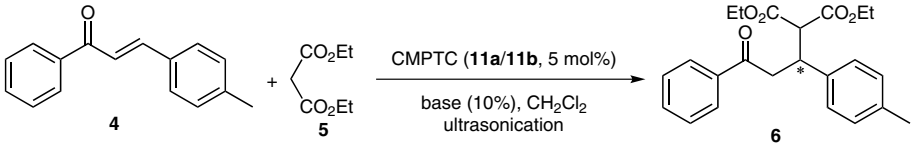
Table 2 Catalytic Asymmetric Michael Addition of Diethyl Malonate **5** to Chalcone **4** with Different Solvents and CMPTC **11a** and **11b** under Ultrasonic Conditions (continued)



Entry	Solvent	Catalyst	Time (h)[a]	Yield (%)[b]	ee (%)[c]	Abs. config.[d]
13	$CHCl_3$	**11a**	5	93	71	*R*
14	$CHCl_3$	**8b**	6	70	76	*R*
15	acetone	**8a**	8	79	83	*R*
16	acetone	**8b**	6	80	89	*R*

[a] The Michael reaction of chalcone **4** (0.1 mmol), diethyl malonate **5** (0.12 mmol), and CMPTC **11** (**11a**/**11b**, 5 mol%) with solvent (1 mL) and KO*t*-Bu (10%, 0.5 mL) under ultrasonic conditions.
[b] Isolated yield of purified material.
[c] Enantiopurity was determined by HPLC analysis of the Michael adduct **6** using a chiral column (Phenomenex Chiralpack) with hexane–2-PrOH as solvent.
[d] Absolute configuration was determined by comparison of the HPLC retention time.

Table 3 Catalytic Asymmetric Michael Addition of Diethyl Malonate **5** to Chalcones **4** with Different Bases and CMPTC **11a** and **11b**



Entry	Base	Catalyst	Time (h)[a]	Yield (%)[b]	ee (%)[c]	Abs. config.[d]
1	K_2CO_3	**11a**	6	86	91	*R*
2	K_2CO_3	**11b**	7	86	97	*R*
3	Cs_2CO_3	**11a**	7	80	85	*R*
4	Cs_2CO_3	**11b**	8	80	96	*R*
5	NaOH	**11a**	1	68	74	*R*
6	NaOH	**11b**	1	68	89	*R*
7	KOH	**11a**	1	65	69	*R*
8	KOH	**11b**	1	63	84	*R*
9	KO*t*-Bu	**11a**	4	90	93	*R*
10	KO*t*-Bu	**11b**	4	90	99	*R*
11	Et_3N	**11a**	8	–	–	–
12	Et_3N	**11b**	8	30	67	*R*

[a] The Michael reaction of chalcone **4** (0.1 mmol), diethyl malonate **5** (0.12 mmol), and CMPTC **11** (**11a**/**11b**, 5 mol%) with solvent (1 mL) and base (10%, 0.5 mL) under ultrasonic conditions.
[b] Isolated yield of purified material.
[c] Enantiopurity was determined by HPLC analysis of the Michael adduct **6** using a chiral column (Phenomenex Chiralpack) with hexane–2-PrOH as solvent.
[d] Absolute configuration was determined by comparison of the HPLC retention time.

The enantioselective Michael addition of chalcone at higher concentration of base irrespective of CMPTC gave disparate results, which can be explained by invoking a catalyst-degradation mechanism (Figure 2). Initially, the deprotonation of the catalysts **11** occurred at high concentrations of base leading to Hofmann elimination and giv-

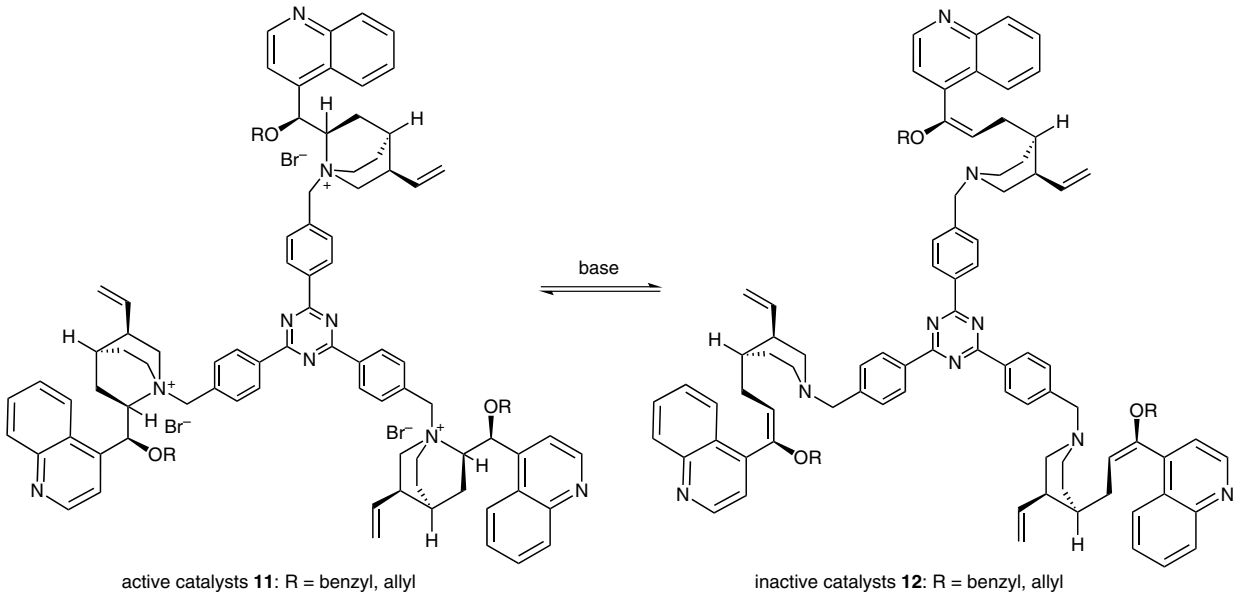


Figure 2 Catalysts decomposition mechanism at higher concentrations of base

ing compound of **12**, viz. olefinic compound (inactive catalysts). Based on these observations, the base concentration was fixed at 10% and the structural stability of CMPTC was maintained without decomposition. Similar studies have been reported by Paramzitsinghet al.,[10] Siva et al.,[11] Maruoka et al.,[12] and O'Donnell et al.[13] for cinchona alkaloid derived CPTC in the alkylation of glycine imine at higher concentration of base.

Furthermore, the formation of lower yield and lower enantiomeric excess (Table 3, entries 5–8) may be explained as follows: The CMPTC, containing lone-pairs of electrons on the nitrogen atoms (present in triazine), shift the electron density to the electron-deficient terminal R_4N^+ site of the CMPTC via an aromatic ring spacer chain, and, as a result, no bond resonance is formed (Figure 3). This leads to detachment/deactivation of the catalytic sites, thus losing their attracting power (i.e., electrophile-attracting power) towards the anions of the α-carbon of the diethylmalonate. As a result, the degree of ion pair formation between R_4N^+ of CMPTC (**11b** and **12b**) with anions of the α-carbon of the diethylmalonate is relatively lower, hence it has produced a lower yield and enantiomeric excesses (Table 3, entries 5–8).

Further, we investigate the Michael addition reaction of 1,4-diarylenone **4** under the optimized reaction conditions described above (5 mol% of catalyst **11**, KO*t*-Bu, CH_2Cl_2, ultrasonic conditions), as listed in Table 4. From the observed results both electron-withdrawing and electron-do-

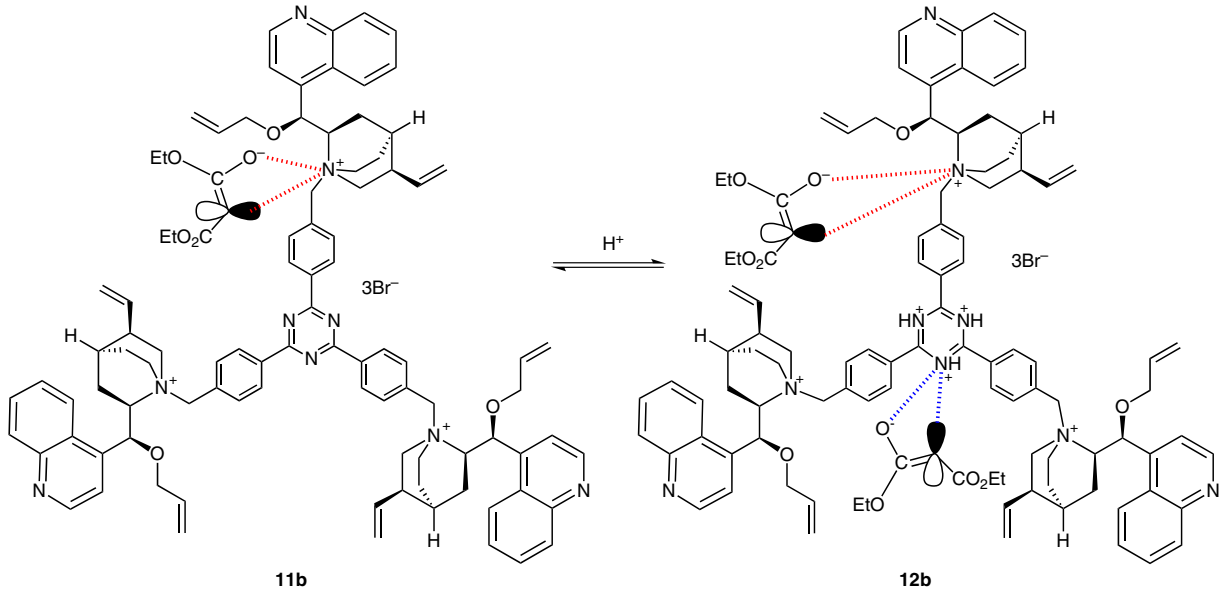
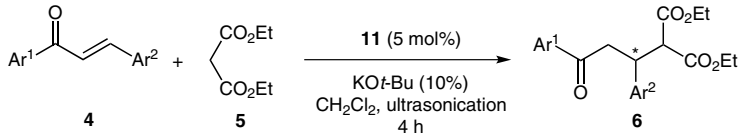


Figure 3 Detachment/deactivation of CMPTC due to ion-pair formation between the quaternary ammonium of triazine with anions of α-carbon of the diethylmalonate

Table 4 Catalytic Asymmetric Michael Addition of Diethyl Malonate **5** to Chalcone Derivatives **4** under CPTC Conditions[a]



Entry	Enone **4** Ar^1	Enone **4** Ar^2	Catalyst	Product[a]	Yield (%)[b]	ee (%)[c]	Abs. config.[d]
1	Ph	4-MeC_6H_4	**11a**	**6a**	90	93	*R*
2	Ph	4-MeC_6H_4	**11b**	**6a**	90	99	*R*
3	Ph	4-ClC_6H_4	**11a**	**6b**	92	92	*R*
4	Ph	4-ClC_6H_4	**11b**	**6b**	92	99	*R*
5	4-BrC_6H_4	4-ClC_6H_4	**11a**	**6c**	90	91	*R*
6	4-BrC_6H_4	4-ClC_6H_4	**11b**	**6c**	90	97	*R*
7	4-BrC_6H_4	4-$MeOC_6H_4$	**11a**	**6d**	91	95	*R*
8	4-BrC_6H_4	4-$MeOC_6H_4$	**11b**	**6d**	91	97	*R*

[a] The Michael reaction of chalcone **4** (0.1 mmol), diethyl malonate **5** (0.12 mmol), and CMPTC **11** (**11a**/**11b**, 5 mol%) with CH_2Cl_2 (1 mL) and KO*t*-Bu (10%, 0.5 mL) under ultrasonic conditions.
[b] Isolated yield of purified material.
[c] Enantiopurity was determined by HPLC analysis of the Michael adducts **6** using a chiral column (Phenomenex Chiralpack) with hexane-2-PrOH as solvent.
[d] Absolute configuration was determined by comparison of the HPLC retention time.

nating groups on the aryl groups and hence the corresponding Michael adducts **6** were obtained in excellent product yield and higher enantiomeric excess (Table 4, entries 1–8).

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 **5** and different chalcones **4** with CMPTC. The formation of higher Michael adduct yield (Table 4, entries 1–8,) and its enantiomeric excesses of each reaction catalyzed by C_9(O)-protected CMPTC would be mainly attributed to an effective contact of ion pair formed between the positive quaternary ammonium ions (R_4N^+) of the respective CMPTC with an electrophile (Figure 4, a), at the same time the interaction between the

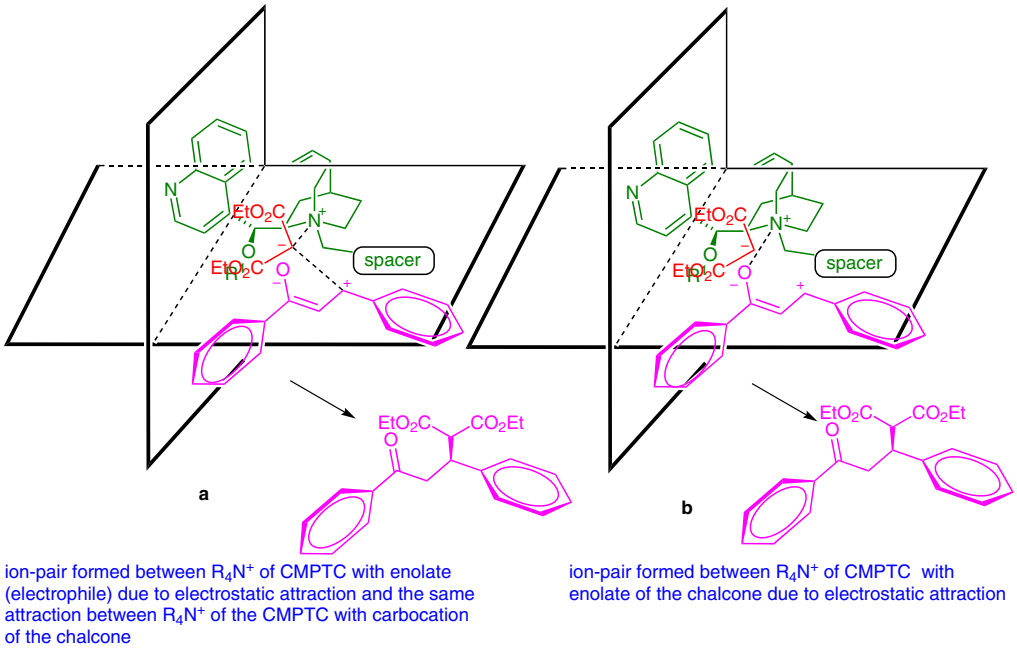


Figure 4 Formation of higher enantioselectivity and chemical yield of various intermediates/molecular assemblies during the enantioselective

electrophile with a carbocation of the chalcone due to electrostatic attraction[14] and also the same attraction between the R_4N^+ of the respective CMPTC with enolate of the chalcone (Figure 4, b). The results also suggested that apart from the ionic interaction between the catalyst and substrates, there is also a π–π-stacking interaction[15] between the benzyl group of the respective C_9(O)-protected CMPTC with the aryl group of the chalcone which would further facilitate the binding of the two species. This in turn shows to facilitate an effective ion-pair interaction and thus effect for parallel increasing of chemical yield and enantiomeric excesses.

In conclusion, we have developed a new class of asymmetric phase-transfer catalyst, which shows good enantioselectivity in the Michael addition 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.

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(9) A mixture of 2,4,6-tris-(4-bromomethylphenyl)-[1,3,5]triazine (**9**, 0.1 g, 10 mmol), cinchona derivatives **10a** or **10b** (30 mmol) was dissolved in THF (5 mL) and heated to reflux overnight, the white solid was filtered, washed with Et_2O, and dried to get pure three-site chiral phase-transfer catalyst (86% yield).

Triazine-Based Benzylcinchonine (11a)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.08 (s, 1 H), 8.97 (d, *J* = 7.5 Hz, 2 H), 8.48–8.37 (m, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.04–7.98 (m, 1 H), 7.97–7.91 (m, 1 H), 7.86 (d, *J* = 9.6 Hz, 2 H), 7.62 (d, *J* = 7.3 Hz, 2 H), 7.51 (dd, *J* = 20.1, 12.4 Hz, 2 H), 7.42 (dd, *J* = 12.7, 5.5 Hz, 1 H), 6.67–6.51 (m, 1 H), 6.07–5.83 (m, 1 H), 5.80 (dd, *J* = 22.9, 13.5 Hz, 1 H), 5.29 (d, *J* = 11.4 Hz, 1 H), 5.20–5.13 (m, 1 H), 5.10–4.91 (m, 2 H), 4.85–4.69 (m, 1 H), 4.66–4.53 (m, 1 H), 4.51–4.29 (m, 1 H), 4.10 (s, 2 H), 2.68 (s, 2 H), 2.11–1.90 (m, 2 H), 1.82 (d, *J* = 12.0 Hz, 2 H), 1.27 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.49, 150.8, 148.58, 141.57, 140.86, 138.26, 137.58, 137.36, 137.23, 135.08, 130.35, 130.21, 130.08, 129.6, 129.23, 128.97, 128.93, 128.85, 128.72, 128.58, 128.42, 128.33, 128.07, 117.16, 116.85, 116.12, 71.22, 70.97, 70.86, 68.48, 59.46, 37.32, 27.04, 26.38, 24.69. ESI-MS: m/z = 1765.00 $[M]^{3+}$.

Triazine-Based Allylcinchonine (11b)

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.06 (d, *J* = 3.9 Hz, 1 H), 8.96 (d, *J* = 6.7 Hz, 2 H), 8.44 (d, *J* = 7.5 Hz, 1 H), 8.17 (d, *J* = 8.2 Hz, 1 H), 8.15–8.08 (d, *J* = 6.7 Hz, 2 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 7.85–7.81 (m, 1 H), 7.74 (s, 1 H), 6.46 (s, 1 H), 6.29–6.19 (m, 1 H), 6.04 (dd, *J* = 17.2, 6.7 Hz, 1 H), 5.50 (d, *J* = 17.4 Hz, 1 H), 5.37 (d, *J* = 10.0 Hz, 1 H), 5.27 (t, *J* = 13.5 Hz, 2 H), 4.82 (s, 1 H), 4.35 (d, *J* = 7.1 Hz, 1 H), 4.17 (d, *J* = 22.3 Hz, 2 H), 4.05 (s, 2 H), 3.66 (d, *J* = 9.9 Hz, 1 H), 3.06 (s, 2 H), 2.70 (s, 1 H), 1.95 (s, 1 H), 1.81 (s, 3 H), 1.25 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.53, 150.65, 148.45, 141.16, 137.43, 137.26, 135.17, 134.66, 133.24, 130.21, 129.64, 128.0, 125.66, 124.58, 120.27, 118.49, 117.58, 73.55, 69.95, 67.55, 62.94, 56.71, 54.98, 37.0, 26.77, 23.28, 21.61. ESI-MS: *m/z* = 1599.9200 $[M]^{3+}$.

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