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Unexpected solvent/substitution-dependent inversion of the enantioselectivity in Michael addition reaction using chiral phase transfer catalysts

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ABSTRACT

New cinchonium salts bearing 5,5′-bis(methyl)-2,2′-bipyridine **1** group show solvent/substitution-dependent reversal of enantioselectivity. When used as chiral phase transfer catalyst in the asymmetric Michael addition of chalcones with diethylmalonate within two hours these catalysts result in high chemical yield (up to 98%) and enantiomeric excess (up to 99%) under lower concentrations of base and cold conditions.

Introduction

Michael addition is one of the most useful methods for the formation of C–C bonds in organic synthesis.[1] Hence, the catalytic asymmetric version has been extensively studied.[2] Enantioselective Michael addition of various malonates and chalcones has been reported in the presence of many kinds of catalysts, such as chiral phase transfer catalysts,[3] chiral ionic liquids,[4] chiral N,N′-dioxide–Sc complexes,[5] chiral bis-sulfonamide–Sr complexes,[6] chiral bisphosphazide–Li complexes,[7] chiral SIPAD–Co complexes,[8] DPEN/NAP-MgO,[9] and organocatalysts.[10] Even though some of these catalysts could not give reasonable enantioselectivity, chalcones are still demanding substrates in Michael addition reactions with malonates. However, reports on asymmetric Michael addition reactions involving chalcones are limited. Previously, we reported a series of tri-functional triazine based cinchona alkaloids as a chiral phase transfer catalysts (CPTC) for highly enantioselective Michael addition reactions of chalcones with very good yield and ee's.[11] In all the previously reported cases, the cinchonine and cinchonidine based chiral catalysts give their respective *R*- and *S*-enantiomers of the Michael adduct, though both the compounds act as pseudoenantiomers.

Dehmlow et al. have reported base dependent inversion of stereochemistry in Michael addition using chiral crown ethers as PTC catalysts at high concentration (50%) of potassium/sodium *tert*-butoxide as bases.[12] Najera and co-workers reported the unexpected metal base-dependent inversion of the enantioselectivity in the asymmetric synthesis of α-amino acids using cinchonidine based CPTC.[13] Consecutively, Keiji Maruoka[14] reported the unusual anti-selective asymmetric conjugate addition of aldehydes to nitroalkenes catalyzed by a biphenyl-based chiral secondary amine as a catalyst. Recently, Blackmond[15] and co-workers, Chinchilla and co-workers[16] reported the solvent dependent formation of *S*- or *R*- enantioenriched succinimides from a single enantiomer of the organocatalysts. In this work, first time we report the unexpected solvent/substitution-dependent enantioselectivity in the Michael addition reaction using new types of CPTCs derived from cinchonine under mild reaction conditions with very good chemical yield up to 98% and ee's up to 99%.

New type of CPTCs **4** (**4a**/**4b**) were synthesized from commercially available starting material 5,5′-dimethyl-2,2′-bipyridine **1** (Scheme 1)[17] and their catalytic efficiencies were studied by the enantioselective Michael addition reaction between diethyl malonate **6** and enone derivatives **5** (Scheme 2).

Results and discussion

The reaction conditions were optimized by using 5 mol % of catalysts, diethylmalonate **6** (as the Michael donor) and enone **5** (as the Michael acceptor), and various bases as well as solvents at different temperatures (Table 1). From the obtained results (Table 1),

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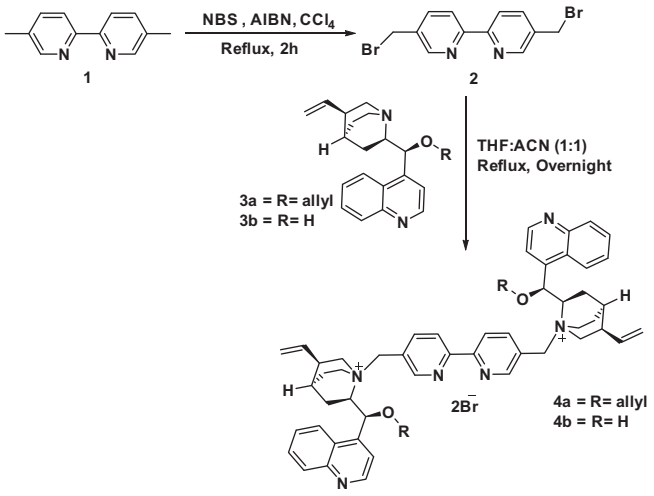


Scheme 1. Synthesis of chiral phase transfer catalysts **4**.

it is found that NaOH is the more effective base in this reaction (entries 1–10, Table 1). The yields at 0 °C are always higher than those at room temperature while the enantiomeric excesses were more or less same at both the temperatures (entries 1–5 compared to 6–10, Table 1). It can be noted that upon increasing the polarity of the solvent, the stereo induction is reduced in the Michael addition reactions and hence very poor ee's are observed. While (*R*)-configuration has been obtained as major product in non-polar solvents (entries 1–14, Table 1), (*S*)-configuration has been obtained as major product in more polar solvents (entries 15–17, Table 1). The polar solvents like DCM, acetone, methanol gave lower chemical yield and ee's than non-polar solvents. This may be attributed to the fact that the high polar solvents reduce the ion-pair interaction between the catalyst (N^+) and the enolate anion, due to the high degree of solvation of catalyst, thereby reduce the efficiency of the catalysts and consequently the product yield and ee's are decreased.

Among the non polar solvents toluene gave higher chemical yield and ee's than others like xylene, benzene (entries 10–13, Table 1). This may be explained as follows: the high electron density in the aromatic ring makes them behave as a base to form charge-transfer π-complexes with quaternary ammonium ion which facilitate easy transfer of CPTC to organic phase. Toluene has lower polarity than xylene and benzene thus strongly interact with the N^+ ion of the catalysts as discussed above. This strong interaction would have taken place in the *Si face*, which helps easy interaction with the enolate anion of the substrate on *Re face* to direct the *R*-configuration of Michael adduct (Fig. 1). Hence, we have chosen toluene as a solvent for further investigations.

With the best reaction conditions in hand (5 mol % of catalyst **4a** and **4b**, 10% aq NaOH, toluene, 0 °C), we next considered the scope of the Michael reaction by employing different chalcones **5** with diethylmalonate **6** (Table 2). Consistently high

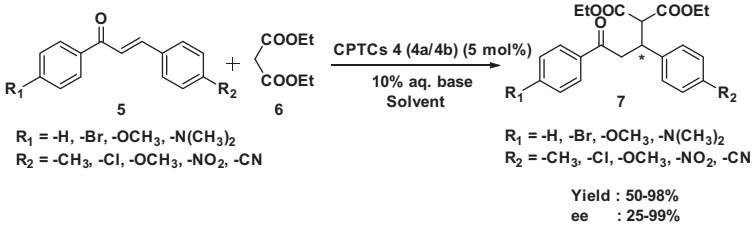
Table 1
Optimization of asymmetric Michael addition reaction between enone **5** and diethylmalonate **6** with CPTC **4a** in various conditions

Entry	Base	Solvent	Temp[a] (°C)	Yield[b] (%)	% of ee[c]	Abs. config.[d]
1	K_2CO_3	Toluene	RT	50	99	*R*
2	Cs_2CO_3	Toluene	RT	65	99	*R*
3	K^{t}OBu	Toluene	RT	62	96	*R*
4	KOH	Toluene	RT	68	98	*R*
5	NaOH	Toluene	RT	70	99	*R*
6	K_2CO_3	Toluene	0	70	98	*R*
7	Cs_2CO_3	Toluene	0	80	96	*R*
8	K^{t}OBu	Toluene	0	75	98	*R*
9	KOH	Toluene	0	82	99	*R*
10	NaOH	Toluene	0	95	99	*R*
11	NaOH	Xylene	0	80	96	*R*
12	NaOH	Benzene	0	64	50	*R*
13	NaOH	THF	0	84	69	*R*
14	NaOH	Cyclohexane	0	80	68	*R*
15	NaOH	DCM	0	53	35	*S*
16	NaOH	Acetone	0	55	38	*S*
17	NaOH	Methanol	0	60	45	*S*

[a] The Michael reaction of enone **5** (0.1 mmol), diethyl malonate **6** (0.12 mmol), catalysts **4a** (5 mol %), with 1 ml of solvent and 0.5 ml of 10% aq base.
[b] Isolated yield of purified material.
[c] Enantiopurity was determined by HPLC analysis of the Michael adduct **7** using a chiral column (Phenomenex Chiralpack) with hexane–IPA as an eluent.
[d] Absolute configuration was determined by the comparison of the HPLC retention time.[11]

enantioselectivities, excellent chemical yields, and unexpected substitution dependent inversion were observed for a wide range of aryl substituted chalcones (entries 1–24). From the Table 2, it is clear that the substitution on the aryl group of the enones strongly affects the product yield and ee's. When Ar^1 was a phenyl group (entries 1–6, Table 2), the property of the substituent's on Ar^2 in chalcones either electron donating (4-Me, 4-MeO–) or electron with drawing groups (–Cl) did not affect the chemical yields as well as enantioselectivities (*R*-enantiomers). But the electron-withdrawing group $–NO_2$ and –CN on Ar^2 is obviously not favorable for the ee's. Therefore, chalcones with 4-nitro substituted Ar^2 gave moderate yields (70%) and 32–36% ee's (entries 13 and 14; Table 2). On the other hand, a higher yield was achieved for the chalcones with electron donating/withdrawing substituents on Ar^1 (entries 7–12 and 15–24, Table 2), but, affect the ee's and inversion of configuration (*S*-enantiomers) was achieved on the electron withdrawing groups present on the Ar^2 in chalcones (entries 13–24, Table 2).

We believe that the π–π interaction of the aromatic rings of the chalcone and the quinoline moiety of the catalyst keep the carbonyl of the chalcone with the ammonium in close proximity and favor the strong ion pair interaction of the substrates and catalysts which in turn would give high chemical yield and ee's (Fig. 2). Similar reversal of enantioselectivity has been observed by tuning the conformational flexibility of chiral catalysts in various reactions, such as asymmetric Michael addition reaction of chalcones with 2-nitropropane,[18] and enantioselective



Scheme 2. Enantioselective Michael addition of enone derivatives **5** with diethylmalonate **6** using CPTCs **4** (**4a**/**4b**) in aqueous/organic solvent media.

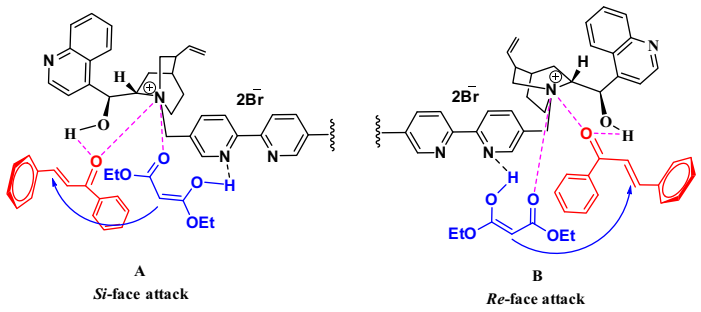
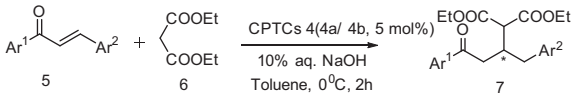


Figure 1. Possible transition state for the enantioselective Michael addition reaction.

Table 2
Catalytic asymmetric Michael addition reaction of diethylmalonate 6 to enone derivatives 5 under the optimized conditions



Entry	Enone (**1**)	Ar^1	Ar^2	Catalyst	Product[a]	Yield[b] (%)	% of ee[c]	Abs. Config.[d]
1	**5a**	Ph	4-Me-C_6H_4	**4a**	**7a**	98	99	*R*
2	**5a**	Ph	4-Me-C_6H_4	**4b**	**7a**	98	90	*R*
3	**5b**	Ph	4-Cl-C_6H_4	**4a**	**7b**	94	98	*R*
4	**5b**	Ph	4-Cl-C_6H_4	**4b**	**7b**	94	92	*R*
5	**5c**	Ph	4-MeO-C_6H_4	**4a**	**7c**	96	90	*R*
6	**5c**	Ph	4-MeO-C_6H_4	**4b**	**7c**	96	91	*R*
7	**5d**	4-Br-C_6H_4	4-Me-C_6H_4	**4a**	**7d**	93	95	*R*
8	**5d**	4-Br-C_6H_4	4-Me-C_6H_4	**4b**	**7d**	93	98	*R*
9	**5e**	4-Br-C_6H_4	4-Cl-C_6H_4	**4a**	**7e**	92	99	*R*
10	**5e**	4-Br-C_6H_4	4-Cl-C_6H_4	**4b**	**7e**	92	91	*R*
11	**5f**	4-Br-C_6H_4	4-MeO-C_6H_4	**4a**	**7f**	95	99	*R*
12	**5f**	4-Br-C_6H_4	4-MeO-C_6H_4	**4b**	**7f**	95	99	*R*
13	**5g**	Ph	4-NO_2-C_6H_4	**4a**	**7g**	70	32	*S*
14	**5g**	Ph	4-NO_2-C_6H_4	**4b**	**7g**	70	36	*S*
15	**5h**	4-Br-C_6H_4	4-NO_2-C_6H_4	**4a**	**7h**	97	86	*S*
16	**5h**	4-Br-C_6H_4	4-NO_2-C_6H_4	**4b**	**7h**	97	83	*S*
17	**5i**	4-MeO-C_6H_4	4-NO_2-C_6H_4	**4a**	**7i**	92	85	*S*
18	**5i**	4-MeO-C_6H_4	4-NO_2-C_6H_4	**4b**	**7i**	92	81	*S*
19	**5j**	4-MeO-C_6H_4	4-CN-C_6H_4	**4a**	**7j**	83	41	*S*
20	**5j**	4-MeO-C_6H_4	4-CN-C_6H_4	**4b**	**7j**	83	25	*S*
21	**5k**	4-$(Me)_2N$-C_6H_4	4-NO_2-C_6H_4	**4a**	**7k**	95	98	*S*
22	**5k**	4-$(Me)_2N$-C_6H_4	4-NO_2-C_6H_4	**4b**	**7k**	95	97	*S*
23	**5l**	4-$(Me)_2N$-C_6H_4	4-CN-C_6H_4	**4a**	**7l**	90	84	*S*
24	**5l**	4-$(Me)_2N$-C_6H_4	4-CN-C_6H_4	**4b**	**7l**	90	86	*S*

[a] The Michael reaction of enone **5** (0.1 mmol), diethylmalonate **6** (0.12 mmol), catalysts (**4a**/**4b**, 5 mol %), with 1 ml solvent and 0.5 ml of 10% aq base.
[b] Isolated yield of purified material.
[c] Enantiopurity was determined by HPLC analysis of the Michael adduct **7** using a chiral column (Phenomenex Chiralpack) with hexane–IPA as an eluent.
[d] Absolute configuration was determined by comparison of the HPLC retention time.[11]

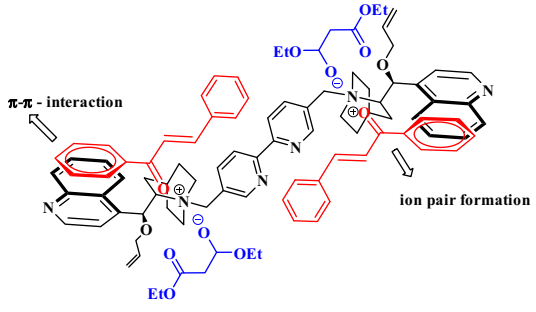


Figure 2. Possible formation of π–π stacking and ion pair interaction between the quinoline moieties of the catalyst, chalcone, and ammonium (R_4N^+).

hydrosilylation reduction of ketones in the presence of (*S*,*S*)-BOPA/$FeCl_2$ complexes as chiral catalysts.[19] However, to the best of our knowledge, till date no such solvent (polar/non-polar) and substitution dependent inversion of configuration has been demonstrated in Michael addition reaction under phase transfer catalysts.

Conclusion

In conclusion we have successfully synthesized new asymmetric CPTCs **4** (**4a**/**4b**) and thoroughly characterized them by various spectral techniques. Their catalytic efficiency was measured by Michael addition reaction between diethylmalonate **6** and enone **5**. Within 2 h high chemical yield (up to 98%) and enantiomeric excess (up to 99%) under lower concentration of base and cold conditions are obtained. The formation of *R* and *S* Michael adducts strongly depends upon the substitution pattern of the chalcone.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.074.

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17. *General procedure for synthesis of CPTCs* (**4**). A mixture of 5,5′-bis(bromomethyl)-2,2′-bipyridine **2** (0.1 g, 10 mmol), cinchona derivatives **3** (**3a**/**3b**, 20 mmol) was dissolved in 5 ml of THF and heated to reflux for overnight, the brown solid was filtered, washed with diethylether and dried it to get pure di site chiral PTC (96% yield of **4a** and 98% yield of **4b**). *Synthesis of allylated cinchonine based CPTC* (**4a**). ^{1}H NMR (400 MHz, DMSO) δ 9.10 (s, 2H), 9.02 (d, J = 4 Hz, 2H), 8.65 (d, J = 8 Hz, 2H), 8.43–8.37 (m, 4H), 8.14 (d, J = 8 Hz, 2H), 7.89–7.78 (m, 6H), 6.87 (d, J = 4 Hz, 2H), 6.56 (s, 2H), 6.08–6.01 (m, 4H), 5.26 (t, J = 10 Hz, 6H), 5.14–5.04 (m, 4H), 4.31 (t, J = 10 Hz, 2H), 4.02–3.94 (m, 6H), 3.14–3.07 (m, 2H), 2.65 (t, J = 8 Hz, 2H), 2.34 (t, J = 10 Hz, 4H), 1.92 (s, 2H), 1.83–1.74 (m, 4H), 1.11 (t, J = 12 Hz, 2H), 0.88 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 155.60, 153.70, 150.14, 147.56, 144.92, 142.76, 137.04, 129.72, 129.41, 128.85, 127.34, 125.03, 124.32, 123.91, 120.74, 120.07, 118.92, 117.02, 67.36, 64.64, 60.32, 59.28, 55.92, 54.06, 36.67, 30.66, 26.35, 22.97. ESI-MS (M^+); 1010.09. *Synthesis of cinchonine (contains free –OH) based CPTC* (**4b**). ^{1}H NMR (400 MHz, DMSO) δ 9.12 (s, 2H), 9.00 (d, J = 4 Hz, 2H), 8.64 (d, J = 8 Hz, 2H), 8.41 (t, J = 8 Hz, 4H), 8.12 (d, J = 8 Hz, 2H), 7.88–7.71 (m, 6H), 6.86 (t, J = 6 Hz, 2H), 6.55 (s, 2H), 6.09–5.98 (m, 2H), 5.33–5.22 (m, 6H), 5.11 (d, J = 16 Hz, 2H), 4.00 (t, J = 16 Hz, 4H), 3.58–3.50 (m, 2H), 3.11 (d, J = 8 Hz, 2H), 2.67 (d, J = 8 Hz, 2H), 2.33 (t, J = 12 Hz, 2H), 1.91 (s, 2H), 1.79 (d, J = 8 Hz, 2H), 1.08 (t, J = 8 Hz, 2H), 0.87 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 155.60, 153.60, 150.14, 147.99, 144.89, 142.76, 137.05, 129.42, 128.79, 127.29, 125.02, 124.33, 120.75, 120.08, 118.94, 117.03, 67.38, 64.68, 59.37, 55.92, 54.08, 36.69, 27.51, 26.34, 22.98. ESI-MS (M^+); 931.28.
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