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Influence of ionic liquids on the phase transfer-catalysed enantioselective Michael reaction

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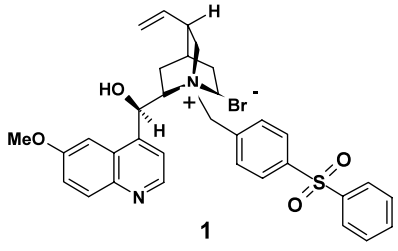
Abstract—The enantioselective Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one promoted by a quaternary derived ammonium salt from quinine as a phase transfer catalyst in different ionic liquids, 1-butyl-3-methyl imidazolium hexafluorophosphate, [bmim]PF_6, 1-butyl-3-methyl pyridinium tetrafluoroborate, [bpy]BF_4, 1-butyl-3-methyl imidazolium tetrafluoroborate [bmim]BF_4 as well as in conventional organic solvents was studied.

The development of catalytic asymmetric carbon–carbon bond forming reactions is one of the most challenging aspects of organic synthesis.[1] Over the past two decades many successes involving molecular catalysts in which well-designed chiral ligands and transition metals have played an important role have been reported.[1,2] Phase transfer catalysts (PTC) possessing many advantages such as mild reaction conditions, safety, operational simplicity, and selectivity, have been widely accepted as one of the most powerful reagents in industry. Efforts towards achieving asymmetric conjugate addition of malonates to chalcones in the presence of chiral catalysts have been the subject of several reports. Recently, the field of chemistry in ionic liquids has been escalating at an overwhelming rate. These liquids have captivated us for quite some time owing to their remarkable properties. In continuation of our quest to explore different reactions in ionic liquids,[3] we thought it would be worthwhile to employ these liquids as solvents in the asymmetric conjugate addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one using quinine, as a chiral catalyst. The reaction of dimethyl malonate with 1,3-diphenylprop-2-en-1-one **2** using K_2CO_3 in the presence of catalytic quinine, in an ionic liquid, at room temperature, afforded the Michael adduct **3** in good yield but with low enantioselectivity.

There have been many successful applications of catalytic asymmetric synthesis using cinchona-alkaloid derived quaternary ammonium salts.[4] Hence, we decided to use a quaternary ammonium salt of quinine as a phase transfer catalyst. The introduction of a bulky subunit at the bridge head nitrogen leads to a quaternary ammonium salt, which enhances the stereoselectivity in catalytic phase transfer reactions.[5] Also, the introduction of an electron withdrawing group at the 4-position on the phenyl ring of the *N*-benzyl unit is quite effective.[6] PTCs including electron withdrawing groups on the phenyl ring afforded the desired product with higher enantiomeric excess. During our research work in order to develop a more effective cinchona-alkaloid derived phase transfer catalyst, we quaternised the bridgehead nitrogen of quinine with a bulky group in order to give quininium bromide **1**.[10]



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We have carried out the asymmetric conjugate addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one using quininium bromide **1** in ionic liquids and organic solvents.

In this communication, we report for the first time, the enantioselective Michael reaction in an ionic liquid as the reaction media employing a novel chiral phase transfer catalyst. The ionic liquids employed for the current study are 1-butyl-3-pyridinium tetrafluoroborate, [bpy]BF_4, 1-butyl-3-methylimidazolium

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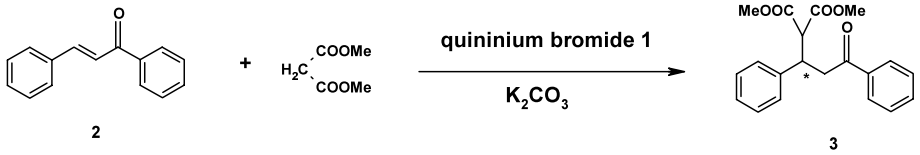
Table 1. Catalytic enantioselective Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one in ionic liquids and organic solvents



2 3

Entry	Solvents	Temp. (°C)	Time (h)	Yield (%)[a]	ee (%)[b]	$[\alpha]_D^{26}$
1	DMSO	28	6	96	61	+20.31
2	Toluene	28	8	92	56	+18.64
3	DCM	0	6	94	46	+15.31
4	[bmim]PF_6	28	3	99	50	−16.64
5	[bmim]BF_4	28	4	97	44	−14.65
6	[bpy]BF_4	28	4	97	42	+13.98

[a] Isolated yields are shown.
[b] Enantiomeric excesses were determined from optical rotations.

hexafluorophosphate [bmim]PF_6 and 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim]BF_4. These liquids are distinctly different in their properties in two senses: the [bmim]BF_4 and [bpy]BF_4 are hydrophilic and [bmim]PF_6 is highly hydrophobic in nature. To study the influence of this novel reaction media on the rate as well as on the enantioselectivity of the reaction, we investigated the asymmetric Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one in the presence of K_2CO_3 in ionic liquids [bmim]PF_6, [bmim]BF_4 and [bpy]BF_4 at room temperature. As expected the reactions worked well in these liquids and the results are shown in Table 1. The reactions in ionic liquids afforded excellent yields of the product in relatively short periods of time but interestingly and to our surprise, the enantioselectivity was reversed in the reactions in [bmim]BF_4 and [bmim]PF_6, whereas it remained the same in [bpy]BF_4 as was the case for the conventional organic solvents under investigation. In order to ascertain the factor responsible for the reversal of enantioselectivity, we carried out the Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one in the presence of K_2CO_3 by employing quinine (yield 97%, 21% ee), (*c* 2, $CHCl_3$) ($[\alpha]_D^{26}$ −7.062) and a chiral quaternary ammonium salt, *N*-(4-nitrobenzyl) quininium bromide (yield 95%, 32% ee), (*c* 2, $CHCl_3$), ($[\alpha]_D^{26}$ −10.64) in ionic liquids. However, results indicated that the reversal of enantioselectivity was not due to the PTC but can be attributed to the cation associated with the anion of the ionic liquid. Recently, several groups have investigated lipase-catalysed transesterification of chiral substrates in ionic liquids and have reported that rates and enantioselectivity were dependent on both the anion and the alkyl group in the 1-methyl-3-alkyl imidazolium cation.[7]

The ionic liquid [bmim]PF_6 being polar due to its ionic nature, is hydrophobic and it is unlike common polar organic solvents. This feature of [bmim]PF_6 made us inquisitive about the behaviour of PTC in such a medium. We observed that the rate of the reaction is much better in [bmim]PF_6 than in [bpy]BF_4, [bmim]BF_4 and other organic solvents.[8] The reaction time is also reduced drastically even under ambient conditions, in contrast to reported procedures[9] with an excellent yield of product **3**. Phase transfer catalysts are a commercially viable option for asymmetric synthesis, however, if the phase transfer catalyst-containing medium were recyclable then it would be an added advantage. We carried out several experiments where quininium bromide **1** was taken in [bmim]PF_6 and charged with substrate **2** and dimethyl malonate. Similarly, the recyclability of the medium containing the quininium bromide **1** was studied for three consecutive runs. Thus, ionic liquids can act as a medium for phase transfer catalysed asymmetric synthesis. There are four advantages of the use of ionic liquids as the reaction medium rather than the corresponding organic solvents: (1) the reaction is fast, (2) good enantioselectivity and yields, (3) easy work up of the reaction and (4) recyclability of the ionic liquid (Table 2).

Table 2. Recyclability of the Michael reaction in [bmim]PF_6

Cycle	Time (h)	Yield (%)
1	3	97
2	3	95
3	3	94

In conclusion, we have developed a new class of asymmetric phase transfer catalyst, which shows good enantioselectivity in the Michael reaction of dimethyl malonate to 1,3-diphenylprop-2-en-1-one in both organic solvents and ionic liquids.[11] Work on further development of these catalyst systems and investigating their applicability to other asymmetric phase transfer processes is underway.

Acknowledgements

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8. Catalysed by **1** (10 mol%), dimethyl malonate reacted with 1,3-diphenylprop-2-en-1-one in the presence of K_2CO_3, at room temperature, to afford the Michael adduct **3** in 96% yield and 61% ee (Table 1, entry 1). Among the organic solvents tried, DMSO proved to be most effective in this reaction.
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10. A mixture of quinine (1.47 g, 5.0 mmol) and 4-bromomethylphenyl phenyl sulfone (1.43 g, 5.0 mmol) in THF (20 ml) was refluxed for 24 h. The precipitated solid was filtered and washed with benzene. Purification of the residue by flash chromatography (90:10 dichloromethane:methanol) afforded the desired product *N*-(4-phenyl sulfonyl)benzyl quininium bromide **1** (93%, 2.72 g) as a white solid. ($C_{33}H_{35}O_4N_2SBr$), ESI-MS: (M^+−Br) 555, $[\alpha]_D^{26}$ −57.74 (*c* 2, $CHCl_3$); mp: 210–211°C; IR (KBr. cm^{-1}) 3834, 3742, 2948, 1620, 1511, 1460, 1399, 1309, 1245, 1156, 1105, 1069, 1025, 928; ^{1}H NMR (MeOH, 500 MHz); 1.5–1.6 (d, J=10 Hz, 1H), 1.8–1.9 (m, 1H), 2.1 (m, 1H), 2.2–2.4 (m, 3H), 2.7 (s, 1H), 3.4–3.6 (m, 3H), 3.8–3.9 (t, J=8 Hz, 1H), 4.0 (s, 3H), 4.4 (m, 1H), 5.0–5.15 (m, 3H), 5.4 (m, 1H), 5.7 (m, 1H), 6.6 (s, 1H), 7.4 (d, J=2.5 Hz, 1H), 7.5–7.7 (m, 4H), 7.9 (m, 3H), 8.05 (m, 3H), 8.15 (d, J=8 Hz, 2H), 8.80 (d, J=4.5 Hz, 1H); ^{13}C NMR (MeOH) δ 22.65, 26.29, 28.49, 39.57, 53.58, 57.12, 62.57, 64.98, 66.51, 71.06, 103.22, 118.18, 122.14, 123.64, 127.85, 129.50, 129.95,131.35, 132.37, 134.78, 135.61, 136.66, 138.99, 142.68, 145.22, 145.59, 146.39, 148.75, 160.55.
11. *General procedure for the Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one*: A mixture of dimethyl malonate (0.132 ml, 1.15 mmol), K_2CO_3 (0.829 g, 6.0 mmol), chiral quininium salt **1** (0.063 g, 0.1 mmol), and 1,3-diphenylprop-2-en-1-one (0.208 g, 1 mmol) in DMSO (3 ml) was stirred at room temperature for 6–8 h. The mixture was diluted with water (10 ml) and extracted with ethyl acetate (2×10 ml). The organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (silica gel, dichloromethane) to afford the Michael adduct.