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Asymmetric Cyclopropanation Reaction Under Phase-Transfer Catalyzed Conditions

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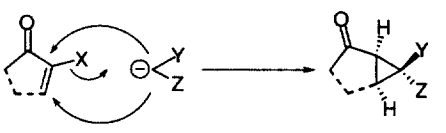
Abstract: An asymmetric cyclopropanation reaction was developed using chiral quaternary ammonium salts as the phase-transfer catalyst (PTC). The reaction smoothly proceeded to give the desired bicyclic compounds with complete stereocontrol in the presence of a catalytic amount of chiral quaternary salts as the PTC, which are derived from readily available chiral amines, with up to 83% ee under mild reaction conditions.

Keywords: Asymmetric reactions, Catalysts, Cyclopropanes, Phase transfer

Phase-transfer catalysts (PTC) that possess many advantages such as mild reaction conditions, safety, operational simplicity, and environmental consciousness have been widely accepted as one of the most powerful reagents for the establishment of the practical protocols from its discovery.[1] Recently, we have reported some efficient asymmetric reactions which are promoted by chiral quaternary ammonium salts derived from readily available amines such as cinchona alkaloids as chiral PTCs.[2] Moreover, the efficient stereoselective cyclization reactions such as cyclopropanation and dihydrofuran formation promoted by PTC under mild reaction conditions have been achieved.[3] In this communication, we report the first example of the PTC-catalyzed asymmetric cyclopropanation reaction via the successive Michael addition, proton transfer, and intermolecular alkylation processes (Scheme 1).

Scheme 1



At the outset, we began to examine the reaction of nitromethane with easily prepared α-bromocyclopentenone **1a**[4] that seems to act as both a Michael acceptor and carbon electrophile in the presence of reactive nucleophiles under PTC conditions (Table 1). The reaction proceeded with a stoichiometric amount of K_2CO_3 and 10 mol % of PTC derived from quinidine to afford the desired product **2a**. Although the chemical yields were low, a PTC having an electron donating group was found to be effective (entries 3 and 4). In order to increase the chemical yield, we attempted to use achiral co-PTC to accelerate the reaction and avoid the decomposition of **1a** under basic media. Although the racemic products could be obtained when the cyclopropanation promoted by achiral PTC is fast, the cation exchange between chiral and achiral ammonium salts would be expected as an effective process to afford the desired products as an *optically active* form in such a reaction system. Surprisingly, the addition of a catalytic amount (1 mol %) of tetrahexylammonium bromide (THAB) as an achiral co-PTC with chiral PTC (10 mol %) was found to be quite effective to give the desired product **2a** (entry 5) and also the reaction time is remarkably

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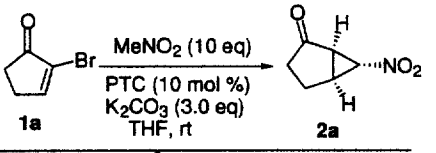
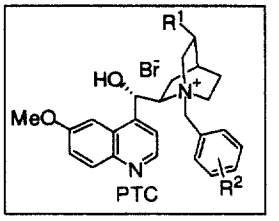
shortened. Moreover, the chemical yield was successfully increased to 50% yield (62% ee) by use of Rb_2CO_3 instead of K_2CO_3 (entry 6). The relative configuration of the product **2a** was determined by ^1H NMR through comparison to the literature data.[3a] The absolute configurations of **2a** was determined by its transformation to the corresponding methylene cyclopropane **3a** by treatment with *n*-Bu_3SnH[5] and the comparison of the optical rotation with the literature data[6] (Scheme 2).

Table 1. Catalytic Asymmetric Cyclopropanation of 2-Bromo-2-cyclopentenone with Nitromethane

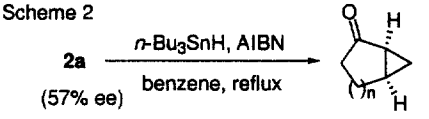


entry	R^1	R^2	time (h)	y (%)	ee (%)[a]
1	vinyl	H_5	21	25	6
2	vinyl	4-OMe	13	29	4
3	vinyl	F_5	17	19	59
4	ethyl	F_5	130	14	76
5	ethyl	F_5	11	34[b]	64
6	ethyl	F_5	22	**50**[b]	**62**[c,d]

a) Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OD. b) The reaction was carried out in the presense of 1 mol % of $(n\text{-Hex})_4NBr$. c) Three equivalents of Rb_2CO_3 was used. d) $[\alpha]_D$ +9.4 (*c*, 0.75, $CHCl_3$)



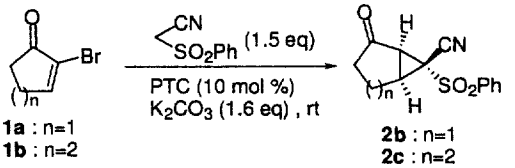
Scheme 2



3a : 26% yield,
$[\alpha]_D^{26}$ -11.1
(*c* 0.5, $CHCl_3$)

Next, we investigated another carbon nucleophile such as cyanomethylsulfone or cyanoacetate in order to construct chiral quaternary carbons on the cyclopropane rings. In these reaction systems, it is needless to add the achiral PTC to accelerate the reaction because of their higher acidity. The cyanomethylsulfone (p*K*a = 12.0, in DMSO) and the cyanoacetate (p*K*a = 13.1, in DMSO) possess the more acidic protons than nitromethane (p*K*a = 17.2, in DMSO) and they would smoothly generate the corresponding carbanion. Therefore, the reaction is expected to afford the corresponding products before the decomposition of the enone **1** under basic conditions with good to high chemical yields.

Table 2. Catalytic Asymmetric Cyclopropanation of 1 with Cyanosulfone[a]



1a : n=1
1b : n=2

2b : n=1
2c : n=2

entry	enone	R	solvent	time (h)	y (%)	ee (%)[a]
1	**1a**	Me_5	PhMe	42	**2a** : 77	**49**[c]
2	**1a**	Me_5	THF	11	**2a** : 64	11
3	**1a**	Me_5	$ClCH_2CH_2Cl$	7	**2a** : 93	11
4	**1a**	Me_5	PhCl	38	**2a** : 78	21
5	**1a**	2,4-Me_2	PhMe	34	**2a** : 72	22
6	**1a**	F_5	PhMe	61	**2a** : 64	22
7	**1a**	2,4-$(CF_3)_2$	PhMe	110	**2a** : 60	10
8	**1b**	Me_5	PhMe	62	**2b** : 63	15
9	**1b**	2,4-Me_2	PhMe	69	**2b** : 55[d]	58
10	**1b**	2,4-Me_2	PhMe	96	**2b** : 60[d]	**60**[e]

a) All reactions were performed with 0.17 M except enrty 10 (0.33 M). b) Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OD and AD. c) $[\alpha]_D$ +48.9 (*c*, 1.0, $CHCl_3$) d) Reaction was carried out at 4°C. e)$[\alpha]_D$ +75.6 (*c*, 1.0, $CHCl_3$)

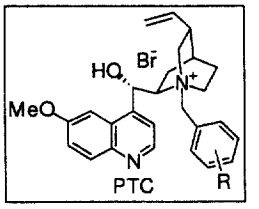
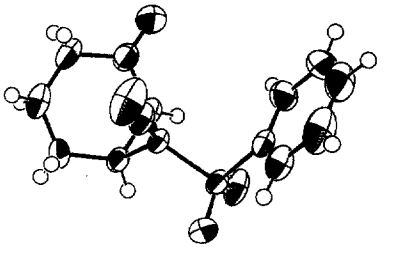
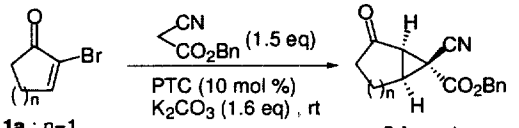


Figure 1: An ORTEP diagram of **2c**



As shown in Table 2, the reaction of **1a** and **1b** with cyanomethylsulfone proceeded smoothly to give **2** in good yield. When the pentamethyl derivative was used as a PTC, toluene was found to be best (entries 1-4). PTCs having elecron withdrawing groups were revealed to be ineffective (entries 6-7). On the other hand, the 2,4-dimethyl derivative was quite an effective PTC in the reaction of **1b** and gave **2b** with 60% ee (entry 10). The X-ray crystallographical analysis using abnormal dispersion of sulfur atom revealed the absolute configuration of **2c** (Figure 1). Similar to the results of the cyanomethylsulfone, the cyanoacetate was also found to be quite an effective carbon nucleophile, as shown in Table 3. Chlorobenzene was the solevent of choice (entries 1-3) while lower ee was obtained by use of other solvents such as THF and *n*-Bu_2O or other PTCs. The PTC which is subtituted at 2 position in benzene ring was found to be effective in this reaction system. Especially, the reaction of **1b** in the presence of a catalytic amount of *N*-(2,4-ditrifluoromethylbenzyl)quinidinium bromide afforded the product in 60% yield with 83% ee[7,8] (entry 8). In the cyanoacetate case, electron withdrawing group such as CF_3 induced at 2-position seems to be essential to obtain **3** with good to moderate ee.

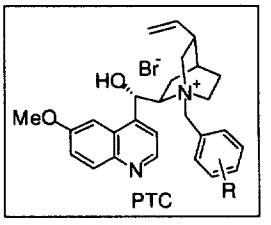
Table 3. Catalytic Asymmetric Cyclopropanation of **1** with Cyanoacetate



1a : n=1
1b : n=2

2d : n=1
2e : n=2

entry	enone	R	solvent	time (h)	y (%)	ee (%)[a]
1	**1a**	2,4-$(CF_3)_2$	PhMe	34	**2d**: 76	31
2	**1a**	2,4-$(CF_3)_2$	$ClCH_2CH_2Cl$	34	**2d**: 74	44
3	**1a**	2,4-$(CF_3)_2$	PhCl	13	**2d**: 74	**45**[b]
4	**1a**	4-CF_3	PhCl	26	**2d**: 82	25
5	**1a**	2,4-Me_2	PhCl	48	**2d**: 96	15
6	**1a**	F_5	PhCl	31	**2d**: 62	24
7	**1b**	2,4-Me_2	PhCl	112	**2e**: 51	6
8	**1b**	2,4-$(CF_3)_2$	PhCl	43	**2e**: 60	**83**[c]



a) Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OD. b) $[\alpha]_D$ +7.7 (*c*, 0.5, $CHCl_3$) c) $[\alpha]_D$ +51.4 (*c*, 0.5, $CHCl_3$)

In conclusion, we have realized the catalytic asymmetric cyclopropanation reaction via the Michael addition, proton transfer, and intramolecular alkylation processes using chiral PTC under mild reaction conditions. To the best of our knowledge, this is the first successful results of PTC-catalyzed asymmetric cyclopropanation reaction. Although the mechanism of the enantioselection of the initial Michael addition is unclear at present, a general tendency was suggested from the above-mentioned results that the effective PTC in each reaction system possesses the substituent at the *ortho* position on the benzene ring. We anticipate that the substituents at the 2-position of the arylmethyl moiety in PTC prevent the free rotation of C-N^+ bond due to its steric hindrance and arrange the nucleophile in the favored direction. According to our procedure, all stereocenters on the cyclopropane rings could be controlled in a diastereo and enantioselective fashion. Although the enantioselectivities observed in the desired products should be further improved, the results described here do promise further progress.

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7. A typical procedure for the catalytic asymmetric cyclopropanation reaction under phase-transfer catalyzed conditions is as follows. To a stirred solution of 2-bromo-2-cyclohexenone **1b** (87.5 mg, 0.5 mmol), benzyl cyanoacetate (131.3 mg, 0.75 mmol), and *N*-(2,4-ditrifluromethylbenzyl) quinidinium bromide (31.6 mg, 0.05 mmol) in chlorobenzene (3.0 mL) was added K_2CO_3 (110.4 mg, 0.8 mmol) at room temperature. After stirring for 43 h, the reaction mixture was quenched with water and extracted with diethyl ether. The combined organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvents followed by flash column chromatography on silica gel (hexane:diethyl ether = 3:2) gave the desired product **2e** (80.1 mg, 60%) as a colorless oil; $[\alpha]_D^{24}$ +51.4 (*c*, 0.5, $CHCl_3$) (83% ee); Enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane:*i*-PrOH = 9:1, flow rate =1.0 mL/min). The retention times were 21.6 min (major) and 24.9 min (minor), respectively.
8. The absolute configurations of **2b**, **2d**, and **2e** were tentatively assigned as described in Tables 2 and 3 due to both their sign of optical rotation and the behavior observed in HPLC analysis.