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Asymmetric alkylation reaction of α-fluorotetralone under phase-transfer catalyzed conditions

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Abstract

The catalytic asymmetric alkylation reaction of α-fluorotetralones promoted by a chiral quaternary ammonium salt derived from cinchonine under phase-transfer catalyzed conditions was described. The reaction proceeded smoothly to give the desired products with up to 91% ee. This methodology provides a practical protocol for the preparation of optically active fluoro compounds on a large scale.

Keywords: alkylation; asymmetric synthesis; catalysts; phase transfer.

Numerous compounds involving the fluorine atom have been recognized as useful molecules because of their bioactivities. Because the potential electronegativity of the fluorine atom causes an effective increase in bioactivity, the drugs including a fluorine atom have been promising. Also the efficient synthesis of such molecules in optically active form is a significant problem in modern synthetic organic chemistry.[1] To provide the biologically important compound and its precursor by way of a practical protocol requires mild reaction conditions, operational simplicity, low cost, and environmental consciousness. The reactions promoted by a PTC (phase-transfer catalyst) enable the above-mentioned advantages to be established and phase-transfer catalysis has been recognized as one of the best potential methodologies for the development of a practical strategy. Recently, we have succeeded in the development of some PTC-catalyzed asymmetric reactions. According to our successful results, the optically active products are obtained by way of a Darzens reaction[2] and epoxidation of enones[3] with a catalytic amount of chiral quaternary ammonium salts derived from cinchona alkaloids under quite mild conditions. Herein, we report the catalytic asymmetric alkylation[4] of α-fluoroketones under PTC conditions.

At the outset, we examined the reaction of the easily prepared α-fluoroketone **1**[5] with benzyl bromide **2a** in the presence of KOH and a catalytic amount of commercially available PTC **A**. The alkylation reaction proceeded smoothly to give the desired product **3a** in good yield under quite mild reaction conditions. Toluene and THF were found to be efficient solvents to give **3a** with 33 and 39% ee,

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respectively (entries 1 and 4), as shown in Table 1. After screening of the base (2 equiv.) under similar conditions, the reaction was found to proceed slowly with other kinds of metal hydroxides in toluene though rubidium carbonate and LiOH were quite ineffective. On the other hand, in a THF system, RbOH monohydrate was found to be the most effective base (Table 2). As shown in Tables 1 and 2, both the KOH/PhMe and RbOH monohydrate/THF systems gave better results.

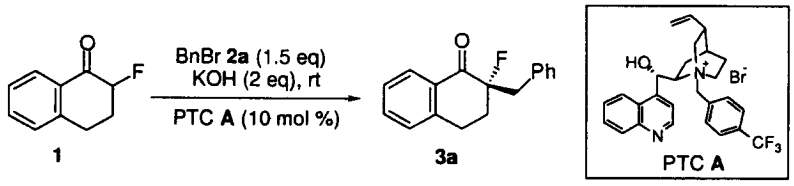


Table 1
Solvent effect[a]

entry	solvent	time (h)	yield (%)	ee (%)[b]
1	PhMe	2.5	74	**35**
2	hexane	72	66	15
3	CH_2Cl_2	72	73	29
4	THF	8	76	**39**
5	Et_2O	2.5	83	29

a) Reaction was carried out in 0.3 M. b) Enantiomeric excess was determined by chiral HPLC analysis using DAICEL CHIRALPAK AS (hexane:*i*-PrOH = 50:1; 8.1 min (minor) and 11.6 min (major); flow rate, 1.0 mL/min).

Table 2
Base effect[a]

entry	base	solvent	time (h)	yield (%)	ee (%)
1	NaOH	PhMe	20	45	25
2	$RbOH{\cdot}H_2O$	PhMe	8	72	32
3	Rb_2CO_3	PhMe	48	11	26
4	LiOH	THF	48	0	-
5	NaOH	THF	6	66	38
6	$RbOH{\cdot}H_2O$	THF	3	81	**38**
7	Rb_2CO_3	THF	72	29	42

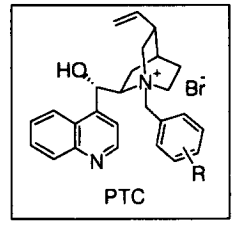
a) Reaction was carried out in the presence of 10 mol % of PTC **A** with 2 equiv. of base at rt (0.3 M).

Next, we attempted to find the most effective PTCs which could be easily prepared from cinchonine by alkylation with the corresponding benzyl halide derivatives which are commercially available to optimize the reaction conditions. As represented in Table 3, PTCs which have electron-withdrawing groups such as PTC **B** and **C** gave **3a** with lower ee (entries 1 and 2). On the other hand, the electron-donating groups such as MeO or methyl groups were found to afford better results in comparison with the benzyl group (entries 3–5). In screening of the methylated PTCs, the pentamethyl derivative (PTC **H**) was found to be the most efficient catalyst to give **3a** with 72% ee (entry 7). Moreover, the reaction carried out at −10°C (0.1 M) afforded **3a** with 80% ee (entry 9). In spite of our efforts, no results superior to the KOH–PhMe system were obtained when PTC **H** was used (entries 7–13).

Although the correct mechanism in the enantioselection is unclear at present, it seems that the introduction of the sterically hindered groups into the benzyl moiety of PTC is apparently essential to achieve high ee (Table 3). We believe that the π–π interaction[6] between the quinoline moiety and the aromatic unit of **1** occurs to provide effective enantioselection of the enolate anion. According to

Table 3
PTC effect on asymmetric alkylation of **1** with **2a**[a,b]

entry	base/solvent	PTC	conditions	yield of **3a** (%)	ee of **3a** (%)
1	KOH/PhMe	**B** : R = 2,3,4,5,6-F_5	rt, 48 h	72	29
2	KOH/PhMe	**C** : R = 4-NO_2	rt, 24 h	72	29
3	KOH/PhMe	**D** : R = 4-H	rt, 24 h	75	32
4	KOH/PhMe	**E** : R = 4-MeO[c]	rt, 24 h	80	40
5	KOH/PhMe	**F** : R = 4-Me	rt, 12 h	89	41
6	KOH/PhMe	**G** : R = 3,5-Me_2	rt,12 h	78	**46**
7	KOH/PhMe	**H** : R = 2,3,4,5,6-Me_5	rt, 8 h	89	72
8	KOH/PhMe	**H** : R = 2,3,4,5,6-Me_5	rt, 24 h	71	**76**[d]
9	KOH/PhMe	**H** : R = 2,3,4,5,6-Me_5	-10°C, 24 h	71	**80**[d,e]
10	KOH/THF	**H** : R = 2,3,4,5,6-Me_5	rt, 4 h	86	60
11	RbOH·H_2O/THF	**H** : R = 2,3,4,5,6-Me_5	rt, 3 h	82	63
12	RbOH·H_2O/THF	**H** : R = 2,3,4,5,6-Me_5	-10°C, 24 h	78	70
13	RbOH·H_2O/THF	**H** : R = 2,3,4,5,6-Me_5	-10°C, 24 h	54	74[d]

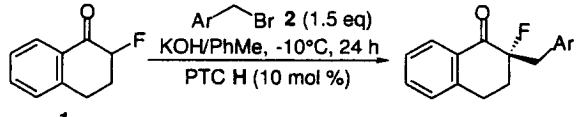


a) Reaction was carried out in the presence of 10 mol % of PTC in the presense of 2 equiv. of base at rt in 0.3 M. b) PTC **I** (R = 2,4-Me_2): 81% (36% ee), PTC **J** (R = 2-Me): 73% (39% ee), PTC **K** (R = 3-Me): 84% (46% ee) with KOH/PhMe (0.3 M) at rt. c) Ammonium chloride was used. d)Reaction was carried out in 0.1 M. e) $[\alpha]_D^{22}$ +28.3 (*c* 1.0, $CHCl_3$)

the observed tendency using PTC **H**–**K** (Table 3), steric effects caused by pentamethyl groups would be significant factors in this reaction system.

Next, we further investigated the effect of other electrophiles under optimized conditions to confirm the scope and limitation of this asymmetric alkylation in the presence of PTC **H**. As shown in Table 4, other arylmethyl bromides were also effective in affording the desired product **3** with moderate to high enantiomeric excess. In particular, the reaction of **1** with 2,3,4,5,6-pentamethylbenzyl bromide **2f** proceeded smoothly to give the corresponding product **3f** with 91% ee (entry 5).

Table 4
Effect of various electrophiles



1 **3**

entry	Ar	time (h)	yield of **3** (%)	ee of **3** (%)	$[\alpha]_D$[a] (temp)
1	**2b** : 2-Me-C_6H_4	24	**3b** : 60	84	-2.7 (22°C)
2	**2c** : 3-Me-C_6H_4	24	**3c** : 45	84	+30.1 (23°C)
3	**2d** : 4-Me-C_6H_4	24	**3d** : 58	82	+34.3 (23°C)
4	**2e** : 4-Br-C_6H_4	24	**3e** : 83	78	+24.2 (23°C)
5	**2f** : 2,3,4,5,6-Me_5-C_6	24	**3f** : 44	**91**	-38.9 (23°C)
6	**2g** : β-Naphthyl	24	**3g** : 60	79	+31.7 (23°C)
7	**2h** : (*E*)-PhCH=CH	24	**3h** : 33	70	+53.3 (24°C)

a) Optical rotation was measured in $CHCl_3$ (*c* 1.0).

The absolute configuration was determined by X-ray diffraction, CD spectrum, and chemical transformation. The configuration of the alkylated adduct **3e** was determined to be *R* by the unusual dispersion of the bromine atom observed in configuration of the X-ray crystallographical analysis, as shown in Fig. 1, and **3e** was converted to **3a** using a palladium(II) catalyst[7] (Scheme 1). Compared with the optical rotation of **3a** derived from **3e** with that of **3a** obtained by asymmetric alkylation, **3a** was assigned to

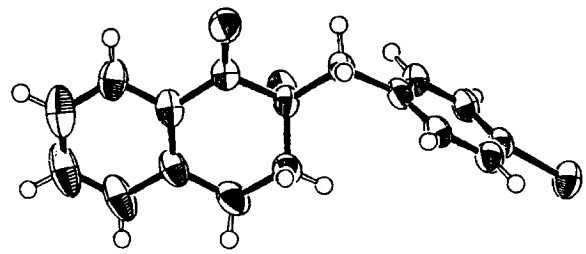
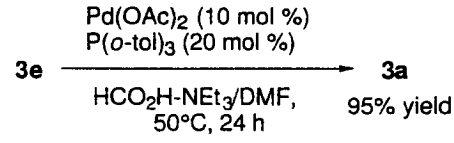
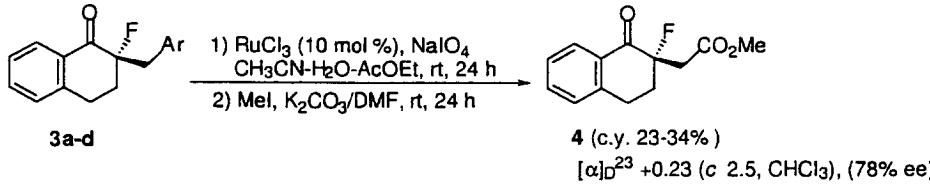


Figure 1. The ORTEP diagram of **3e**

possess *R* configuration. Because other derivatives **3f–h** shown in Table 4 also show CD spectra similar to those of **3a**, their absolute configurations were assigned to be *R*. Other products such as **3a–d** were also revealed to possess the same absolute configuration by the transformation of the aryl groups to carboxyl ones by ruthenium-catalyzed oxidation,[8] as shown in Scheme 2.

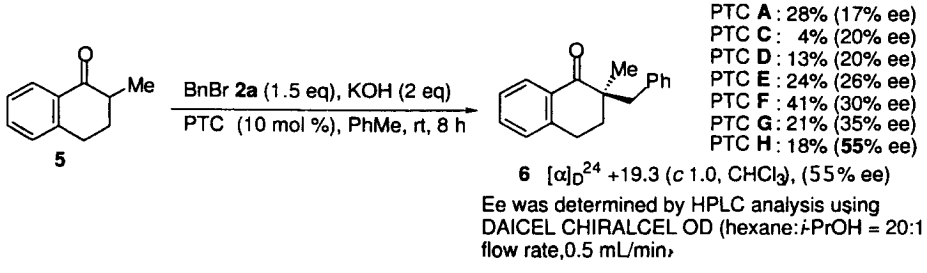


Scheme 1.



Scheme 2.

On the other hand, α-methyltetralone **5** was revealed to be quite an ineffective substrate to afford the corresponding alkylated product **6** with 55% ee ($[\alpha]_D^{20}$ +19.3 (*c* 1.0, $CHCl_3$)) using PTC **H** under similar conditions, and also their chemical yields were much lower using any PTCs, as outlined in Scheme 3. The ammonium enolate generated from **5** is slightly bulky and its planarity was lower relative to that of the corresponding fluoroenolate anion. In order to achieve high ee in this alkylation reaction promoted by chiral PTC-derived cinchona alkaloids, higher planarity of the active species would be required to attach to the chiral quaternary ammonium cation via ionic bonding. Although the reason why PTC **H** is more effective in this reaction system is presently unclear, we think that the bulkier substituents such as a methyl group induced into the benzene ring in the PTC would prevent the rotation of the CH_2–N^+ bond and enable the planar enolate to assume the favored orientation in asymmetric sites.



Scheme 3.

In conclusion, we have realized the catalytic asymmetric alkylation of α-fluorotetralone using phase-transfer catalysts and demonstrated that PTC **H** is the most effective catalyst to give the desired alkylated product with up to 91% ee. This protocol can be one of the most efficient methodologies to provide the optically active fluoro compounds by way of a practical protocol. Although the enantioselectivities described above should be improved, the investigation along this line will lead to further progress.

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