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Catalytic Enantioselective Fluorination of *β*-Keto Esters by Phase-Transfer Catalysis Using Chiral Quaternary Ammonium Salts

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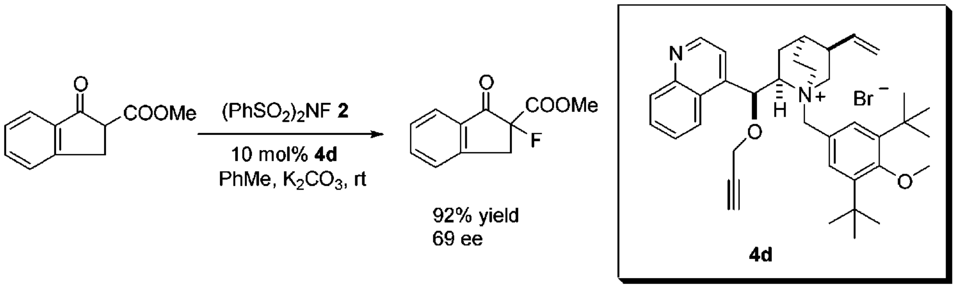
ABSTRACT



The catalytic enantioselective electrophilic fluorination promoted by quaternary ammonium salt from cinchonine as a phase-transfer catalyst is described. Treatment of *β*-keto esters with *N*-fluorobenzenesulfonimide as the fluorine source under mild reaction conditions afforded the corresponding α-fluoro *β*-keto esters in exellent yields with good to moderate enantiomeric excesses

Organic fluorine compounds are of importance in organic synthesis because of their use as medicinals and agrochemicals and in fundamental studies of biochemical and metabolic processes.[1] Chiral organofluorine compounds are interesting and important materials with uses in analytical, biological, and medicinal chemistry and also in the chemistry of polymers and materials.[2] In particular, chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center have been utilized in studies of enzyme mechanisms and as intermediates in asymmetric syntheses.[3] The development of effective methodologies for the preparation of new selectively fluorinated, stereochemically defined compounds is critical to further advances of fluorine chemistry.[4] The reagent-controlled enantioselective fluorination is an efficient method for the asymmetric introduction of a fluorine atom in organic molecules.[5] Initial work on reagent control by Differding and Lang, who introduced chiral *N*-fluorocamphorsultam as the first enantioselective electrophilic fluorinating agent,[6] was followed by the introduction of modified *N*-fluorosultam structures[7] and the development of the saccharin-based agents,[8] as well as acyclic *N*-fluoro compounds.[9] The disadvantage of these reagents is their multistep synthesis with the use of toxic molecular fluorine or explosive gaseous perchloryl fluoride.

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(1) (a) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II*; American Chemical Society: Washington, DC, 1995. (b) Filler, R.; Kobayashi, Y. *Biomedicinal Aspect of Fluorine Chemistry*; Kodansha Ltd., Elsevier Biochemical Press: Tokyo, New York, 1982.

(2) (a) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Applications*; Springer-Verlag: Berlin, 2000. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (c) *Fusso & Yakugaku*; Kobayashi, Y., Kumadaki, I., Taguchi, T., Eds.; Hirokawa Publishing Co.: Tokyo, 1992.

(3) (a) *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1999. (b) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661−692.

(4) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737−1755.

(5) Davis, F. A.; Kasu, P. V. N. *Org. Prep. Proced. Int.* **1999**, *31*(2), 125−143.

(6) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *19*, 6087−6090.

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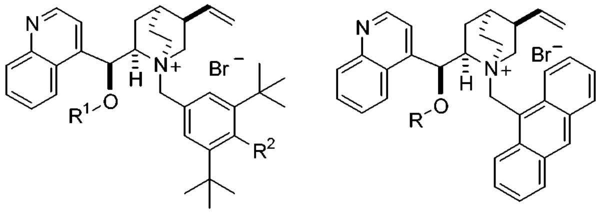
Recently, two reports have described the preparation and application of enantiopure *N*-fluoroammonium salts from cinchona alkaloids. In an elegant contribution, Takeuchi used an in situ protocol to generate the active fluorinating species from each of dihydroquinine and dihydroquinidine, with Selectfluor.[10] Independently, Cahard described the synthesis of preformed cinchona alkaloid *N*-fluoroammonium salts.[12,13] The commercial availability of both Selectfluor and cinchona alkaloids also ensures easy accessibility of the chiral reagents. Hintermann and Togni have recently achieved the first real breakthrough in catalytic enantioselective fluorination using a TADDOL-modified titanium complex and nonchiral Selectfluor. This new catalytic fluorination can readily compete with the results from stoichiometric reactions with chiral *N*-fluoro compounds.[14] From an economic point of view a new catalytic enantioselective fluorination process is desirable.

Phase-transfer catalysis is a clean and efficient processes involving high yields, operational simplicity, mild conditions, low cost, safety, and environmental profit.[15] Recently, there have been successful applications to catalytic asymmetric synthesis using cinchona alkaloid-derived quaternary ammonium salts.[16] The introduction of the bulky subunit at the bridgehead nitrogen of cinchona alkaloids leads to enhancement of the stereoselectivity in catalytic phase-transfer reactions.[17] As part of our research program toward the development of a more effective cinchona alkaloid derived phase-transfer catalyst, we introduced a bulky environment at the bridgehead nitrogen using the (3,5-di-*tert*-butyl-4-methoxy)benzyl group.[18] In this paper, we wish to report the catalytic enantioselective electrophilic fluorination of β-keto esters using the cinchona alkaloid derived quaternary ammonium salts **4** and **5** (Figure 1).



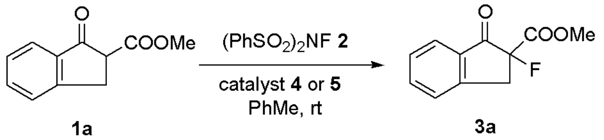
4a, R^1 = H, R^2 = OMe
4b, R^1 = allyl, R^2 = OMe
4c, R^1 = benzyl, R^2 = OMe
4d, R^1 = propargyl, R^2 = OMe
4e, R^1 = allyl, R^2 = H
4f, R^1 = benzyl, R^2 = H

5a, R = H
5b, R = allyl
5c, R = benzyl
5d, R = propargyl

Figure 1.

To determine suitable reaction conditions for the catalytic enantioselective electrophilic fluorination of β-keto esters, we initially investigated the reaction system using 10 mol % of catalyst, with indanone carboxylate **1** and *N*-fluorobenzenesulfonimide (NFSi, **2**) as the electrophilic fluorinating agent (Table 1).

Table 1. Catalytic Enantioselective Fluorination of **1a** with NFSi **2** in the Presence of Phase-Transfer Catalysts



entry	catalyts	base	yields (%)	ee[a] (%)
1	**4a**	K_2CO_3	87	20
2	**4b**	K_2CO_3	91	55
3	**4b**	KOH	84	58
4	**4b**	Cs_2CO_3	82	21
5	**4b**	RbOH	80	20
6	**4b**	Rb_2CO_3	81	41
7	**4c**	K_2CO_3	81	28
8	**4d**	K_2CO_3	92	69
9	**4d**	KOH	89	37
10	**4d**	$KHCO_3$	82	15
11	**4d**	Cs_2CO_3	94	60
12	**4d**	RbOH	82	27
13	**4d**	Rb_2CO_3	83	36
14[b]	**4d**	K_2CO_3	81	36
15[c]	**4d**	K_2CO_3	87	68
16[d]	**4d**	K_2CO_3	88	6
17[e]	**4d**	K_2CO_3	82	13
18	**4e**	K_2CO_3	84	56
19	**4e**	KOH	83	65
20	**4e**	RbOH	85	60
21	**4f**	K_2CO_3	88	20
22	**5a**	K_2CO_3	82	6
23	**5b**	K_2CO_3	90	66
24	**5b**	KOH	85	60
25	**5b**	Cs_2CO_3	87	61
26	**5b**	RbOH	83	38
27	**5b**	Rb_2CO_3	86	31
28	**5c**	K_2CO_3	83	7

[a] Enantiopurity of **3a** was determined by HPLC analysis with a Chiralcel OD-H column, 2-propanol−hexane (1:9), 1.0 mL/min, λ_{max} = 254 nm, retention times 10.4 min (minor) and 12.1 min (major). It was established by analysis of racemic **3a** that the enantiomers were fully resolved. [b] This reaction was carried out at −78 °C for 40 min. [c] 30 mol % of catalyst was used. [d] Carried out in CH_2Cl_2 solvent. [e] Carried out in THF solvent.

We first examined electrophilic fluorination of indanone carboxylate **1a** with *N*-fluorobenzenesulfonimide (**2**) in the presence of phase-transfer catalyst (10 mol %) in toluene at room temperature. Catalyst **4d** and **4e** were more effective than other catalysts in the presence of the base (entries 8−17 and 18−20). Known cinchona-type phase-transfer catalyst **5b**[17] was an effective catalyst also in this reaction (entries 19−24). Compound (+)-**3a** was always formed under the various reaction conditions listed in the Table 1 as the excessive enantiomer, which should be the case because all of the catalysts used possess the same chirality. The reaction

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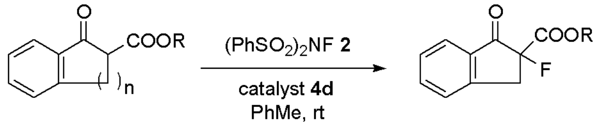
(7) (a) Davis, F. A.; Zhou, R.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34*, 3971−3974. (b) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi. H.; Przeslawski, R. M.; Chen, B−C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273−2280. (c) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135−6138.

(8) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708−5711.

using catalyst **4d** (30 mol %) gave **3a** with similar selectivity as in the case of using 10 mol % (entries 8 and 15). K_2CO_3 and Cs_2CO_3 were the effective bases in this reaction. As we expected, the reaction proceeded but the enantioselectivity was 0% ee in the case without base or chiral phase-transfer catalyst. Concerning the solvent, the use of toluene gave the best results, whereas the fluorination in methylene chloride or THF led to lower enantioselectivity (entries 16 and 17). Compared with known reagent-controlled[6−12] and catalytic[14] enantioselective fluorination procedures needing a polar solvent such as acetonitrile, this reaction was complete within 10 min in nonpolar solvent at room temperature. Lowering the temperature to −78 °C with catalyst **4d** decreased the entioselectivity (entry 14).

To examine the generality of the enantioselective fluorination using chiral phase-transfer catalyst **4d**, we studied the fluorination of cyclic β-keto ester **1b−d** (Table 2). The fluorination reaction was carried out at room temperature. As can be seen by the results summarized in Table 2, the corresponding α-fluoro β-keto esters **3b−d** all were obtained in high yields and moderate selectivities. In some case, Cs_2CO_3 was better than K_2CO_3 as the base.

Table 2. Catalytic Enantioselective Fluorination of **1** with Phase-Transfer Catalyst **4d**



1

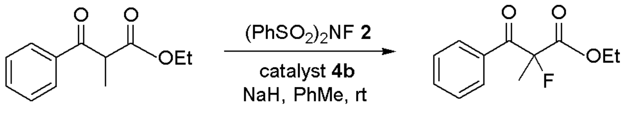
3a, n =1, R = Me
3b, n =1, R = Et
3c, n =2, R = Me
3d, n =2, R = Et

entry	n	R	base	yields (%)	ee[a](%)
1	1, **1a**	Me	K_2CO_3	**3a**, 92	69
2	1, **1a**	Me	Cs_2CO_3	**3a**, 94	60
3	1, **1b**	Et	K_2CO_3	**3b**, 92	50
4	1, **1b**	Et	Cs_2CO_3	**3b**, 91	63
5	2, **1c**	Me	RbOH	**3c**, 87	40
6	2, **1c**	Me	Cs_2CO_3	**3c**, 88	48
7	2, **1d**	Et	K_2CO_3	**3d**, 74	41
8	2, **1d**	Et	CsOH	**3d**, 78	52

[a] Enantiopurity of **3** were determined by HPLC analysis with a Chiralcel OD-H column, 2-propanol−hexane (1:9), 1.0 mL/min, $\lambda_{max} = 254$ nm. It was established by analysis of racemic **3** that the enantiomers were fully resolved. The excessive enantiomer was (+)-**3**.

The present catalytic asymmetric fluorination can be applied to acyclic β-keto esters, the fluorination of ethyl benzoylpropanoate **6** catalyzed by catalyst **4b** giving fluorinated product **7** with 40% ee. We have developed a mild and practical catalytic enantioselective fluorination using a chiral phase-transfer catalyst with *N*-fluorobenzenesulfonimide. β-Keto ester derivatives were fluorinated enantioselectively to give the corresponding α-fluoro compounds in excellent yields with good to moderate enantioselective excess under phase-transfer conditions. We are currently involved in the extension of this convenient fluorination process to other enolizable substrates and are investigating the applicability of phase-transfer catalysts to other asymmetric phase-transfer processes.

Scheme 1



6

7
89% yield, 40% ee

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Supporting Information Available: Experimental procedures for the preparation of catalyst **4d**, general electrophilic fluorination procedure, and spectral data of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Takeuchi, Y.; Satoh, A.; Suzuki, T.; Kameda, A.; Dohrin, M.; Satoh, T.; Koizumi, T.; Kirk, K. K. *Chem. Pharm. Bull.* **1997**, *45*, 1085−1088.

(10) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728−10729.

(11) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1−17.

(12) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699−3701.

(13) Isolation of the chiral ammonium salts, see: (a) Abdul-Ghani, M.; Banks, R. E.; Besheesh, M. K.; Sharif, I.; Syvret, R. G. *J. Fluorine Chem.* **1995**, *73*, 255−257. (b) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42*, 1867−1869.

(14) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359−4362.

(15) (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993. (b) Goldberg, Y. *Phase Transfer Catalysis: Selected Problems and Application*; Gordon & Breach Science Publ.: Reading, 1992. (c) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994. (d) Shioiri, T. Chiral Phase Transfer Catalysis. In *Handbook of Phase Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997; Chapter 14. (e) Nelson, A. *Angew. Chem., Intl. Ed.* **1999**, *38*, 1583−1585.

(16) (a) Perrard, T.; Plaquevent, J.-C.; Desmurs, J-R.; Hebrault, D. *Org. Lett.* **2000**, *2*, 2956−2962. (b) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778. (c) Arai, S.; Oku, M.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 6785−6769. (d) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375−6386. (e) Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 4215−4218. (f) Gasparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367−5378. (g) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710−4711. (h) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446−447.

(17) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (b) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000−13001. (c) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347−5350. (d) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *39*, 3843−3846. (e) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287−1290. (f) Zhang, F.-Y; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097−1100. (g) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Intl. Ed.* **1999**, *38*, 1931−1934. (h) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598. (i) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599−1602. (j) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671−8674. (k) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289−6300.

(18) (a) Kim, D. Y.; Huh, S. C.; Kim, S. M.*Tetrahedron Lett.* **2001**, *42*, 6299−6301. (b) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933−8938.