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Practical Stereoselective Synthesis of an α-Trifluoromethyl-α-alkyl Epoxide via a Diastereoselective Trifluoromethylation Reaction

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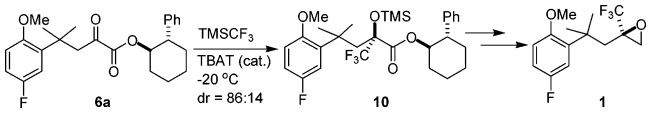
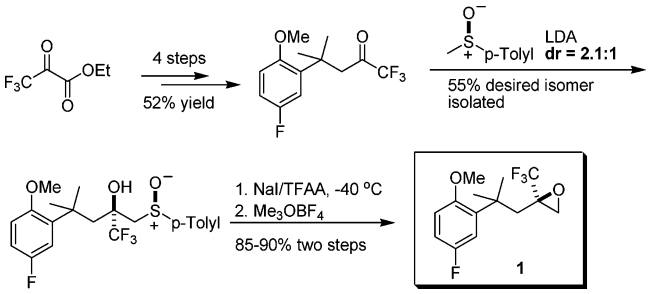


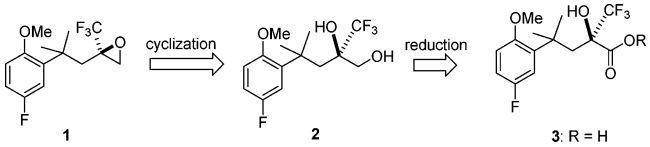
A practical stereoselective synthesis is reported for an α-trifluoromethyl-α-alkyl epoxide (**1**), which is an important pharmaceutical intermediate. The key step involves a chiral auxiliary-controlled asymmetric trifluoromethylation reaction for the introduction of the unique trifluoromethyl-substituted tertiary alcohol stereogenic center in the target molecule. The fluoride-initiated CF_3 addition to chiral keto ester **6a** proceeded with a diastereoselectivity up to 86:14. The major diastereomer was readily obtained with a >99.5:0.5 dr through a simple crystallization of the crude product mixture.

Trifluoromethyl-containing molecules have found wide applications in the discovery and development of novel therapeutic agents.[1] For example, α-trifluoromethyl-α-alkyl epoxides were recently utilized as key intermediates for the synthesis of biologically active compounds such as nonsteroidal gestagens and antiinflammatory agents.[2] The greatest challenge we had to overcome for the synthesis of this family of molecules was the construction of the trifluoromethyl-substituted tertiary alcohol stereogenic center. These compounds were initially prepared in racemic forms, and the enantiomers were separated by preparative chiral HPLC or chemical resolution. Recently, an asymmetric route to compound **1** and its analogues was established in which the configuration of the CF_3-substituted tertiary alcohol was introduced through a chiral sulfoxide-mediated asymmetric addition to a trifluoromethyl ketone intermediate (Scheme 1).[2a] However, the diastereoselectivity of the addition step was only 2.1:1. Separation of two diastereomers required chromatography, which is not suitable for multikilogram-scale synthesis.

SCHEME 1



SCHEME 2



To further support our drug discovery programs, we needed to develop a more efficient route to chiral epoxide **1**. During this study, we have discovered a diastereoselective, auxiliary-controlled CF_3 addition reaction to chiral keto esters. On the basis of this discovery, a scalable, cost-effective asymmetric route to compound **1** was achieved. In this paper, we describe this work in a full account.[3]

In our new retrosynthetic analysis (Scheme 2), the target molecule (**1**) would be derived from the chiral diol intermediate **2**, which in turn could be synthesized by reduction of chiral α-trifluoromethyl-α-hydroxy acid derivatives (**3**, R = H).

Very few methods exist in the literature for the asymmetric synthesis of chiral tertiary α-CF_3-substituted α-hydroxy acids. Recently, asymmetric Friedel−Crafts[4] and ene reactions[5] between electron-rich arenes/alkenes and trifluoropyruvates have been used to synthesize a number of chiral tertiary α-CF_3-substituted α-hydroxy acid derivatives. Certain chiral tertiary α-CF_3-substituted α-hydroxy acids were obtained from racemic starting materials via enzymatic reactions or chemical resolutions.[6]

An unexplored approach to this class of compounds is the direct addition of a CF_3 group to keto esters in an asymmetric

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(4) (a) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901. (b) Toeroek, B.; Abid, M.; London, G.; Esquibel, J.; Toeroek, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086.

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(6) Recent examples: (a) Kuko, Y.; Yamada, K.; Nishizaki, K.; Hidaka, T. (Mitsubishi Gas Chemical Co., Ltd., Japan), Jpn. Kokai Tokkyo Koho, CODEN: JKXXAF JP 2005023055 A2 20050127 Application: JP 2003-27098.3 20030704, 2005. Priority: CAN 142:155646 AN 2005:72783. (b) Shaw, N. M.; Naughton, A.; Robins, K.; Tinschert, A.; Schmid, E.; Hischier, M.-L.; Venetz, V.; Werlen, J.; Zimmermann, T.; Brieden, W.; de Riedmatten, P.; Roduit, J.-P.; Zimmermann, B.; Neumueller, R. *Org. Process Res. Dev.* **2002**, *6*, 497.

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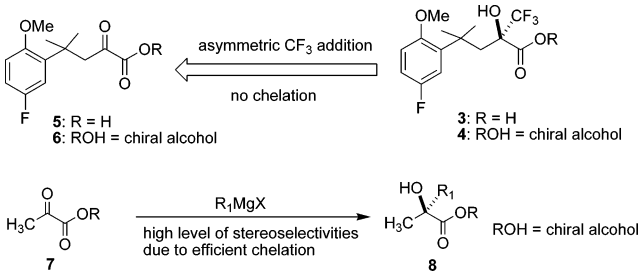
SCHEME 3

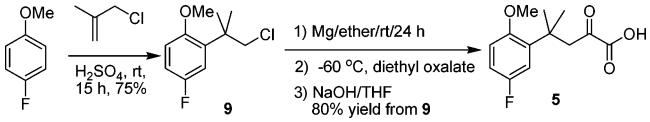


fashion. It has been known for many years that CF_3 addition to carbonyl groups can be efficiently initiated by fluorides such as TBAF.[7] However, the development of a generally applicable asymmetric version of trifluoromethyl addition reactions has met with very limited success.[8] Chiral cinchonine-based ammonium fluoride was first reported by the Iseki group, and it gave moderate enantioselectivities (15−51% ee).[9] Later, Caron et al. further optimized the structure of cinchonine-derived ammonium fluoride and achieved up to a 92% enantiomeric excess for one single aryl ketone substrate.[10] However, much lower enantioselectivities were observed for other generic substrates. Therefore, despite the aforementioned efforts, the stereoselective addition of a trifluoromethide anion to *carbonyl groups* still presents a major synthetic challenge.

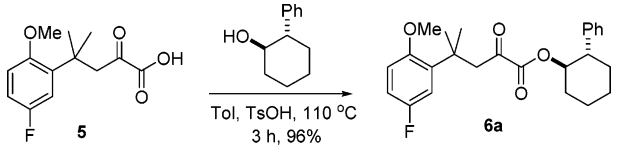
Our strategy is to investigate the direct CF_3 addition reactions to chiral keto esters as a new method to prepare chiral tertiary α-CF_3-substituted α-hydroxy acid derivatives as shown in Scheme 3. It is well-known that the addition of an organometallic reagent to α-keto esters bearing a chiral auxiliary, such as in the conversion of keto ester **7** to chiral α-hydroxy ester **8**, usually proceeds with high levels of stereoselectivities thanks to the tight *chelation control* (Scheme 3).[11] However, it was not obvious at the outset of our study what stereochemical outcome we would observe in the proposed asymmetric trifluoromethide addition to chiral α-keto esters because *no chelation* is possible for the fluoride-mediated trifluoromethylation reactions. In this paper, we would like to report that this proposed approach was indeed effective, leading to the discovery of a diastereoselective trifluoromethylation reaction. Our preliminary account on this work has previously been documented in a patent application filed in 2003.[3] During the course of the preparation of this manuscript, two interesting papers dealing with this topic appeared in the literature in early 2006. Pedrosa and co-workers reported an asymmetric CF_3 addition reaction to glyoxalate-based substrates.[12] Mukaiyama group reported a synthesis of Mosher's acid derivatives using a chiral auxiliary-controlled asymmetric trifluoromethylation reaction of aryl-substituted α-keto esters.[13] These reports prompted us to disclose our own findings in this area immediately.

To test the proposed asymmetric CF_3 addition reaction, we synthesized the requisite keto acid **5** from 4-fluoroanisole in three steps (Scheme 4). Sulfuric acid catalyzed Friedel−Crafts alkylation of 4-fluoroanisole with methallyl chloride gave compound **9** in 75% yield after purification by vacuum distillation. The reaction was quite clean with 95% conversion and less than 5% dialkylated byproduct. Chloride **9** was then converted into its corresponding Grignard reagent. The Grignard reagent was then allowed to react with diethyl oxalate to give the monoester, which was hydrolyzed immediately to afford keto acid **5** (80% overall yield from **9**). At this point, all impurities that were generated in preceding steps could be easily removed through an acid−base extraction. Compound **5** is typically isolated with greater than 99% purity by HPLC.

SCHEME 4



SCHEME 5



Two commonly used chiral auxiliaries, 8-phenyl menthol and *trans*-2-phenylcyclohexanol, were initially selected to test the proposed CF_3 addition reactions. It was found that esterification of keto acid **5** with 8-phenyl menthol was unsuccessful under a variety of reaction conditions, presumably due to steric reasons.[14] On the other hand, the (1*R*,2*S*)-*trans*-2-phenylcyclohexanol can be readily attached to keto acid **5** in refluxing toluene in the presence of a catalytic amount of TsOH, furnishing ester **6a** in excellent yield (Scheme 5).

The *trans*-2-phenylcyclohexanol is commercially available in small quantities. For larger amounts, it can be readily prepared through enantioselective opening of cyclohexene oxide by phenyllithium under the catalysis of a chiral Schiff base, following a literature procedure.[15] This compound was synthesized in our pilot plant in multikilogram quantities using this one-step protocol. The *trans*-2-phenylcyclohexanol is a highly crystalline compound and has a relatively small molecular weight. These properties indeed make this molecule a much more desirable chiral auxiliary for large-scale synthesis than 8-phenyl menthol which is an oil, is very expensive, and requires three steps to make.

Results from the investigation of the key asymmetric CF_3 addition reaction are summarized in Table 1. When keto ester **6a** was subjected to a standard TBAF-initiated trifluoromethylation reaction in THF, a diastereoselectivity of 73:27 was achieved with compound **10** as the major isomer (entry 1).[16] When the reaction was carried out in toluene with 5 mol % TBAF or TBAT ($Bu_4NPh_3SiF_2$) at −20 °C to room temperature, a diastereoselectivity of up to 86:14 was obtained for our substrate (entries 6 and 7). Other solvents that were tested, for example, DMF, methylene chloride, MTBE, and hexane, gave

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(8) For recent reviews, see: (a) Ma, J.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (c) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1.

(9) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137.

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(11) (a) Whitesell, J. K.; Allen, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 3585. (b) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

(12) Pedrosa, R.; Sayalero, S.; Vicente, M.; Maestro, A. *J. Org. Chem.* **2006**, *71*, 2177.

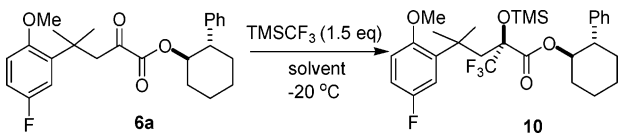
(13) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 304.

(14) 8-Phenyl menthol ester formation through the acid chloride of compound **5** was attempted, and a low conversion was observed (20−25%).

(15) Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 9023.

(16) The absolute stereochemistry of the major diastereomer (**10**) was confirmed by converting **10** to epoxide **1** and comparison with an authentic sample by chiral HPLC and optical rotation.

TABLE 1. Asymmetric Trifluoromethylation of Keto Ester 6a



entry	solvent	initiator (loading)	time (min)	dr
1	THF	TBAF (5 mol %)	20	73:27
2	DMF	TBAF (5 mol %)	20	47:53
3	CH_2Cl_2	TBAF (5 mol %)	20	58:42
4	MTBE	TBAF (5 mol %)	20	79:21
5	hexane	TBAF (5 mol %)	20	75:25
6	toluene	TBAF (5 mol %)	20	84:16
7	toluene	TBAT (5 mol %)	30	86:14
8	toluene	TBAF (0.5 mol %)	20	77:23

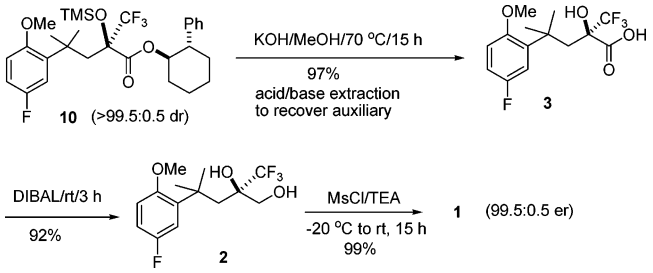
lower selectivities (entries 2−5). Attempts were made to reduce the amount of TBAF to minimize the amount of desilylated product. However, this resulted in a slight drop in diastereoselectivity (entry 8). Therefore, 5 mol % of TBAF was used for scale-up. It is interesting to note that reaction temperature does not have a major influence on the stereoselectivity. The reaction can be run at as high as −20 °C. In fact, this is a very attractive feature for industrial applications because, unlike in regular laboratories, it is usually difficult to achieve temperatures below −20 °C in a production plant.

The two diastereoisomers could be separated by silica gel column chromatography. However, for large-scale synthesis, a direct crystallization method must be developed. A number of solvents (THF, toluene, hexane, dichloromethane, MeOH) were screened in the crystallization study, and it turned out that the desired isomer **10** could be easily crystallized from the MeOH solution of the crude product mixture. This procedure was successfully executed to produce 3 kg of compound **10** (>99.5:0.5 dr, >99% purity by HPLC, 50% isolated yield).

Optically pure ester **10** can be reduced directly to diol **2**. However, the separation of diol **2** and the cleaved chiral auxiliary necessitates silica gel chromatography. To avoid this issue, ester **10** was first saponified to give hydroxy acid **3**. The chiral auxiliary was separated and recovered in nearly quantitative yield through simple acid−base extractions (Scheme 6). The recovered *trans*-2-phenylcyclohexanol can be reused without any additional purification. For reduction of hydroxy acid **3** to diol **2**, a number of different reagents (BH_3-THF, BH_3-DMS, Red-Al, $NaBH_4$-H_2SO_4, $NaBH_4$-I_2, DIBAL) were evaluated. It was found that treatment of hydroxy acid **3** with DIBAL at room temperature led to a complete and clean conversion to diol **2** within 3 h. Other methods gave either incomplete reaction or large amounts of byproducts. Ring closure of diol **2** was achieved by means of MsCl/TEA to furnish chiral epoxide **1** in 99% yield with excellent purity (99.5:0.5 er, 98% by HPLC). A batch of 2.5 kg of chiral epoxide **1** was synthesized using this new sequence, and it proved to be identical to an authentic sample by HPLC, ^{1}H NMR, ^{13}C NMR, chiral HPLC, and optical rotation.

In summary, we have developed an eight-step asymmetric synthesis of the chiral α-trifluoromethyl-α-alkyl epoxide **1**, which is an important intermediate for the synthesis of pharmaceutically active compounds. The new synthesis features a newly discovered chiral auxiliary-controlled asymmetric trifluoromethylation reaction. The key asymmetric step uses the readily available *trans*-2-phenylcyclohexanol as the chiral

SCHEME 6



auxiliary and provides up to a 6.3:1 (86:14) diastereoselectivity. The major diastereomer was readily isolated with 99.5:0.5 dr via simple crystallization. The chiral auxiliary was quantitatively recovered and reused. Overall, this new synthesis is practical, chromatography free, robust, and cost effective. It has been successfully implemented on kilogram scales.

Experimental Section

Diastereoselective Trifluoromethylation Reaction. (α*R*)-5-Fluoro-2-methoxy-γ,γ-dimethyl-α-(trifluoromethyl)-α-[(trimethylsilyl)oxy]-benzenebutanoic Acid [(1*R*,2*S*)-2-Phenylcyclohexyl] Ester (10). Keto ester **6a** (10 g, 24.2 mmol) was placed in a dry 250 mL three-neck flask equipped with a mechanical stirrer and under a constant nitrogen flush. Anhydrous toluene (100 mL) was added to form a slightly yellow clear solution. $TMSCF_3$ (5.2 g, 36.4 mmol) was added, and the solution was cooled to −20 °C. TBAF (1.2 mL, 1.2 mmol of a 1 M solution in THF) was added slowly while the internal temperature was kept below −15 °C. The resulting solution was stirred at −20 °C for 5 min before it was allowed to warm to room temperature. After 30 min, HPLC indicated that there was no ester left and that the desired CF_3 adducts were formed in an 84:16 diastereomeric ratio. Water (20 mL) was added to the flask, and the mixture was then stirred for 15 min. The layers were separated, and the organic layer was washed with 20 mL of brine. Solvent was removed under vacuum, and the oil was chased with 40 mL of heptane to yield 14.2 g of crude product as an orange oil. Under vigorous agitation, 30 mL of MeOH was added. After about 5 min, white crystals appeared. After 15 min, the solids were filtered and washed with MeOH (5 mL twice) and dried. The desired isomer **10** (6.75 g, 50%) was obtained as a white crystalline compound. The diastereomeric ratio was >99.5:0.5, and the chemical purity was >99% (HPLC peak area at 220 nm). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.20 (m, 5H), 6.77 (m, 1H), 6.66 (m, 1H), 4.92 (ddd, J = 4.4, 10.8, 10.8 Hz, 1H), 3.73 (s, 3H), 3.28 (d, J = 14.6 Hz, 1H), 2.75 (ddd, J = 3.7, 11.0, 12.4 Hz, 1H), 1.62 (dq, J = 3.6, 12.8 Hz, 1H), 1.55−1.27 (m, 4H), 0.85 (s, 3H), 0.43 (s, 3H), −0.22 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 166.7, 154.4, 152.6, 141.8, 137.8, 137.7, 127.3, 126.3, 125.5, 124.1, 113.2, 113.0, 110.7, 110.6, 110.5, 110.2, 79.0, 78.8, 78.5, 54.1, 48.0, 38.8, 35.0, 32.2, 29.8, 28.6, 24.2, 23.5, 23.1, 0.0. IR (cm^{-1}) 3377, 2941, 1748, 1494, 1243, 1268, 1173, 1081, 1031, 1007, 868, 845, 741. HRMS: Sodium adduct was observed. $[M + Na]^+$: obsd, 577.2371; calcd, 577.2367. Mp: 89.0 °C. $[\alpha]^{25}_{365}$ +4.34 (*c* 1.2, MeOH).

Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**3**, **5**, **6a**, and **9** as well as copies of ^{1}H NMR spectra for compounds **1**−**3**, **5**, **6a**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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