Notes

Epoxidation of Olefins Using Methyl(trifluoromethyl)dioxirane Generated *in Situ*

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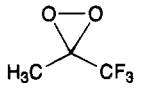
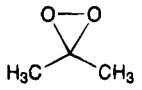
Dioxiranes are powerful epoxidation reagents with high reactivity toward both electron-rich and electron-deficient olefins, under neutral reaction conditions.[1] Despite the fact that dioxiranes (*e.g.*, **1** and **2**) can be generated from potassium peroxomonosulfate and ketones, the procedures for the isolation of dioxiranes are rather cumbersome,[2] which limits their practical use.



1



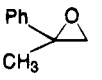
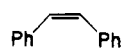
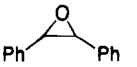
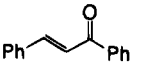
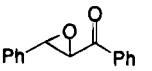
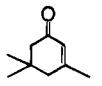
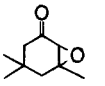
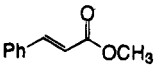
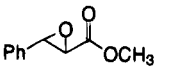
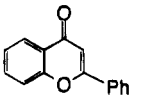
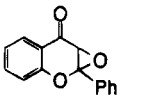
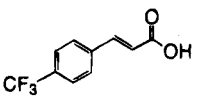
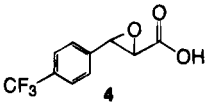
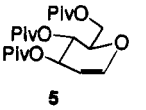
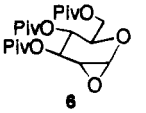
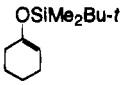
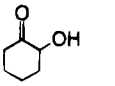
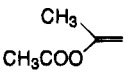
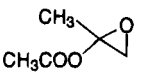
2

Epoxidation using dioxiranes generated *in situ* is more convenient but suffers from low epoxidation rates when acetone,[3a] 2-butanone,[3b] and cyclohexanones[3c] are used as the catalysts. Here, we report on an efficient and general epoxidation protocol that uses methyl(trifluoromethyl)dioxirane (**1**) generated *in situ*.[4]

Since methyl(trifluoromethyl)dioxirane (**1**) has the highest reactivity among dioxiranes reported so far,[1] we reasoned that trifluoroacetone might be an ideal catalyst for the *in situ* dioxirane epoxidation. In addition, we find that trifluoroacetone catalyzes epoxidation much faster when a homogeneous acetonitrile–water mixture is used as the solvent.[5] As summarized in Table 1, unfunctionalized olefins with various substitution patterns (entries 1 and 2), strongly electron-deficient olefins (such as α,β-unsaturated ketones, acids, and esters; entries 3–7), and electron-rich olefins (such as enol ethers and enol esters; entries 8–10) are epoxidized in excellent yields, at 0–1 °C and neutral pH.[6]

It is interesting to note that epoxidation reactions under the *in situ* conditions proceed much faster than those that use distilled dimethyldioxirane (**2**). For example, chalcone epoxidation by distilled anhydrous **2**

Table 1. Epoxidation[a] of Olefins Using Methyl(trifluoromethyl)dioxirane Generated *in Situ*

Entry	Substrate	Time	Epoxide	Yield (%)[b]
1		15 min		96 (Ref. 14)
2		30 min		99 (Ref. 2e)
3		1.3 h	 **3**	99 (Ref. 7)
4		1.5 h		90[c] (Ref. 2e)
5		2 h		97 (Ref. 15)
6		1.25 h		99 (Ref. 16)
7		2 h	 **4**	96
8	 **5**	15 min	 **6**	84[c,d,e]
9	 **7**	30 min	 **8**	97[c,f]
10		20 min	 **9**	97

[a] In CH_3CN and aqueous Na_2·EDTA solution (4×10^{-4} M), 0.2 mL of CF_3COCH_3, 0–1 °C (unless otherwise indicated). [b] Isolated yield. [c] Isolated yield after flash column chromatography. [d] 8 °C. [e] Overall yield after epoxidation and methanolysis; ratio of epoxides α:β = 3:1. [f] Upon completion of epoxidation in 30 min, sodium bisulfite was added to quench the reaction and the mixture was stirred at rt for 2 h to give 2-hydroxycyclohexanone before the workup.

(1) (a) Adam, W.; Curci, R.; Edward, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Cuici, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 1. (d) Adam, W.; Hadjiarapoglou, L. P.; Cuici, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; J. Wiley & Sons: New York, 1992; Chapter 4. (e) Adam, W.; Hadjiarapoglou, L. P. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1993; Vol. 164, p 45.

(2) For distillation from a solution of ketone and oxone (using a special apparatus), see: (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890. (c) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. (d) Reference 1e. For the salting out protocol, see: (e) Murray, R. W.; Singh, M.; Jeyaraman, R. *J. Am. Chem. Soc.* **1992**, *114*, 1346.

(3) (a) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. (b) Adam, W.; Hadjiarapoglou, L. P.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227. (c) Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*, 1577.

(4) For enantioselective oxidation of sulfides to sulfoxides using methyl(trifluoromethyl)dioxirane (**1**) generated *in situ*, see: Colonna, S.; Gaggero, N. *Tetrahedron Lett.* **1989**, *30*, 6233.

(5) The homogeneous CH_3CN–H_2O solvent system gave the best rate for the epoxidation of chalcone (less than 2 h at 0 °C) using our *in situ* protocol. Other solvent systems (such as CH_2Cl_2–H_2O, Et_2O–H_2O, THF–H_2O, and dioxane–H_2O) were found to be less effective.

(6) In principle, trifluoroacetone functions as a catalyst in the *in situ* epoxidation; yet an excess amount of trifluoroacetone does speed up the epoxidation, and its low boiling point (22 °C) assures complete removal during the workup.

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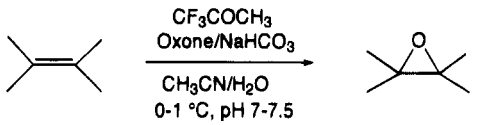
was carried out at room temperature for 18 h,[7] whereas it was completed in 1.3 h at 0 °C under the *in situ* conditions. Considering the higher reactivity (at least 1000-fold) of methyl(trifluoromethyl)dioxirane (**1**) compared with dimethyldioxirane (**2**),[1] the actual oxidant under the *in situ* conditions is certainly methyl(trifluoromethyl)dioxirane (**1**). This is further supported by the observation that, under the same neutral conditions, noepoxidation of chalcone can be detected in the absence of trifluoroacetone.

The pH of the reaction is maintained at 7−7.5 by sodium bicarbonate[8] (obviating the need for a pH-stat), and the virtually neutral condition allows various acid- or base-labile epoxides (such as those of flavone and enol esters) to be isolated in excellent yields.



In addition, the epoxides of 3,4,6-tri-*O*-pivaloyl-D-glucal (**5**)[9a] (entry 8) were obtained in good yield from aqueous solution by controlling the solvent composition and reaction temperature.[9b] Subsequent methanolysis of the epoxides gave a mixture of two methyl glycosides, *i.e.*, methyl 3,4,6-tri-*O*-pivaloyl-β-D-glucopyranoside (**6a**) and methyl 3,4,6-tri-*O*-pivaloyl-α-D-mannopyranoside (**6b**), which suggests that the α- and β-epoxides of glucal **3** are formed in a *ca.* 3:1 ratio. In fact, this protocol is suitable for the epoxidation of glycals with electron-withdrawing substituents.[10] As epoxides of glycals are important and versatile intermediates in carbohydrate synthesis,[11] our method offers a simple approach to this class of compounds.

On the other hand, the epoxide of silyl enol ether **7** was not stable and was further hydrolyzed under the reaction conditions to give the α-hydroxy ketone **8** in high yield (entry 9). Since silyl enol ethers of ketones can be easily synthesized and purified, our *in situ* epoxidation method provides a mild and efficient way of synthesizing α-hydroxy ketones.[12]

In summary, we have developed an efficient epoxidation protocol that should significantly extend the synthetic utility of methyl(trifluoromethyl)dioxirane. More importantly, our homogeneous solvent system should have potential for asymmetric epoxidation of olefins when chiral ketones are used as catalysts.[13] Work in that direction is in progress.

(7) Adam, W.; Hadjiarapoglou, L.; Nestler, B. *Tetrahedron Lett.* **1990**, *31*, 331.
(8) Corey, P. F.; Ward, F. E. *J. Org. Chem.* **1986**, *51*, 1925.
(9) (a) 3,4,6-Tri-*O*-pivaloyl-D-glucal was prepared in two steps from 3,4,6-tri-*O*-acetyl-D-glucal in 70% overall yield: (i) MeOH, NaOMe catalyst; (ii) pivaloyl chloride, DMAP, pyridine. (b) A 3:1 ratio of acetonitrile to water and higher reaction temperature (8 °C) were chosen to shorten the reaction time.
(10) Yang, D.; Wong, M. K. Unpublished results.
(11) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science* **1993**, *260*, 1307.
(12) For the literature procedure of using organic peracids to synthesize α-hydroxy ketones from silyl enol ethers, see: Shono, T.; Matsumura, Y.; Ogaki, M.; Onomura, O. *Chem. Lett.* **1987**, 1447.
(13) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155.
(14) Camps, F.; Coll, J.; Messeguer, A.; Pujol, F. *J. Org. Chem.* **1982**, *47*, 5402.
(15) Conan, A.; Sibille, S.; Perichon, J. *J. Org. Chem.* **1991**, *56*, 2018.
(16) Adam, W.; Golsch, D.; Hadjiarapoglou, L. *Tetrahedron Lett.* **1991**, *32*, 1041.

Experimental Section

The alkenes, Oxone, and 1,1,1-trifluoroacetone were purchased from Aldrich Chemical Co. and used without further purification. The known epoxides were identified by comparison of their spectral and physical data with those reported. All epoxidation reactions were carried out at 0.1−0.3 mmol scale, and chalcone epoxidation at 1 mmol scale gave essentially the same result.

General *in Situ* Epoxidation Procedure. Preparation of Chalcone Epoxide 3. To an acetonitrile solution (1.5 mL) of chalcone (0.2 mmol) was added an aqueous Na_2·EDTA solution (1 mL, 4×10^{-4} M). The resulting homogeneous solution was cooled to 0−1 °C, followed by addition of trifluoroacetone (0.2 mL) *via* a precooled syringe. To this homogeneous solution was added in portions a mixture of sodium bicarbonate (1.55 mmol) and Oxone (1 mmol) over a period of 1 h (pH ~7). The reaction was complete in 1.3 h as shown by TLC. The reaction mixture was then poured into water (20 mL), extracted with methylene chloride (3 × 20 mL), and dried with anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was shown to be pure chalcone epoxide **3** by ^{1}H NMR (99% yield).

***trans*-4-(Trifluoromethyl)-α,β-dihydro-α,β-epoxycinnamic acid (4)**: mp 128−130 °C; IR (Nujol) 3400, 1707 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 4.21 (d, J = 1.2 Hz, 1H), 4.09 (br, 1H), 3.53 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.19, 138.48, 131.46 (q, $^2J_{C,F}$ = 33.2 Hz), 126.18, 125.81 (q, $J_{C,F}$ = 4.2 Hz), 125.79 (q, $^1J_{C,F}$ = 272 Hz), 57.49, 56.29; EI-MS (20 eV) m/z 232 (M^+), 213, 186, 175, 159; HRMS m/z calcd for $C_{10}H_7O_3F_3$ (M^+) 232.0347, found 232.0341. Anal. Calcd for $C_{10}H_7O_3F_3$: C, 51.74; H, 3.04. Found: C, 51.65; H, 2.80.

Glycal Epoxidation. Two methods were used in preparation of 1,2-anhydro-3,4,6-tri-O-pivaloyl-D-glucopyranose (**6**).

Method A. To an acetonitrile solution (1 mL) of 3,4,6-tri-*O*-pivaloyl-D-glucal (**5**) (40 mg, 0.1 mmol) was added an aqueous Na_2·EDTA solution (0.4 mL, 4×10^{-4} M). The resulting homogeneous solution was cooled to 8 °C, followed by addition of trifluoroacetone (0.2 mL) *via* a precooled syringe. To this solution was added a mixture of sodium bicarbonate (0.130 g, 1.55 mmol) and Oxone (0.307 g, 1 mmol) all at once. The reaction was complete in 15 min as shown by TLC. Anhydrous sodium sulfate (*ca.* 3 g) was added, followed by anhydrous methylene chloride (20 mL). The solid was filtered out, and the filtrate was concentrated under high vacuum to dryness to yield the 1,2-anhydro sugar **6** as a white solid. To this white solid under nitrogen was added anhydrous methanol, and the resulting solution was stirred at room temperature. Methanolysis was finished within 1 h as shown by TLC. Methanol was removed *in vacuo*, and the residue was purified by flash column chromatography to provide the methyl glycosides **6a** and **6b** in an overall yield of 70%.

Method B. To an acetonitrile solution (1 mL) of 3,4,6-tri-*O*-pivaloyl-D-glucal (**5**) (40 mg, 0.1 mmol) was added an aqueous Na_2·EDTA solution (0.4 mL, 4×10^{-4} M). The resulting homogeneous solution was cooled to 8 °C, followed by addition of trifluoroacetone (0.2 mL) *via* a precooled syringe. To this solution was added a mixture of sodium bicarbonate (0.130 g, 1.55 mmol) and Oxone (0.307 g, 1 mmol) all at once. The reaction was complete in 15 min as shown by TLC. Anhydrous sodium sulfate (*ca.* 3 g) was added, followed by anhydrous methanol (10 mL). Methanolysis was finished in less than 1 h as shown by TLC. To this reaction mixture was added water (20 mL), and extraction with methylene chloride was carried out (20 mL × 3). The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (23% ethyl acetate in hexane as eluent) to provide 28.2 mg of methyl 3,4,6-tri-*O*-pivaloyl-β-D-glucopyranoside (**6a**) as a white crystalline solid (63% yield) and 9.5 mg of methyl 3,4,6-tri-*O*-pivaloyl-α-D-mannopyranoside (**6b**) as a colorless oil (21% yield). Methyl 3,4,6-tri-*O*-pivaloyl-β-D-glucopyranoside (**6a**): R_f (50% EtOAc in hexane) 0.52; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.16 (t, J = 9.7 Hz, 1H), 5.05 (t, J = 9.7 Hz, 1H), 4.28 (d, J = 7.8 Hz, 1H), 4.21 (dd, J = 12.2, 2.2 Hz, 1H), 4.07 (dd, J = 12.2, 6.3 Hz, 1H), 3.72 (ddd, J = 9.7, 6.3, 2.2 Hz, 1H), 3.56 (s, 3H), 3.54 (br t, 1H), 2.41 (br s, 1H), 1.22 (s, 9H), 1.18 (s, 9H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.2, 178.1, 176.7, 103.8, 74.1, 72.8, 72.4, 67.8, 62.2, 57.3, 38.9,

38.8, 27.1; LRMS (20 ev) m/z 415 (M^+ − OMe), 381, 331, 284, 199, 182; HRMS m/z calcd for $C_{22}H_{38}O_9$ 446.2516, found 446.2502. Anal. Calcd for $C_{22}H_{38}O_9$: C, 59.18; H, 8.58. Found: C, 58.89; H, 8.27. Methyl 3,4,6-tri-*O*-pivaloyl-α-D-mannopyranoside (**6b**): R_f (50% EtOAc in hexane) 0.59; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.37 (t, J = 10.0 Hz, 1H), 5.23 (dd, J = 10.0, 3.3 Hz, 1H), 4.76 (d, J = 1.7 Hz, 1H), 4.20 (dd, J = 12.0, 2.0 Hz, 1H), 4.11 (dd, J = 12.0, 5.7 Hz, 1H), 4.03 (br s, 1H), 3.98 (ddd, J = 10.0, 5.7, 2.0 Hz, 1H), 3.42 (s, 3H), 2.03 (br s, 1H), 1.23 (s, 9H), 1.19 (s, 9H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.1, 177.2, 176.9, 100.4, 71.4, 69.3, 68.7, 65.4, 62.3, 55.2, 38.9, 38.8, 27.2, 27.1; LRMS (EI) m/z 415 (M^+ − OMe), 381, 331, 284, 199, 182; HRMS m/z calcd for $C_{22}H_{38}O_9$ (M^+) 446.2516, found 446.2517. Anal. Calcd for $C_{22}H_{38}O_9$: C, 59.18; H, 8.58. Found: C, 58.86; H, 8.28.

2-Acetoxy-1,2-epoxipropane (9): ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.96 (d, J = 4.4 Hz, 1H), 2.82 (d, J = 4.4 Hz, 1H), 2.07 (s, 3H), 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.70, 80.66, 53.10, 21.09, 19.30; HRMS (EI, 20 eV) m/z calcd for $C_5H_8O_3$ (M^+) 116.0473, found 116.0468.

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