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$TiCl_3(OTf)$ AND $TiO(TFA)_2$ EFFICIENT CATALYSTS FOR RING OPENING OF EPOXIDES WITH ALCOHOLS, ACETIC ACID AND WATER

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Abstract: *$TiCl_3(OTf)$ and $TiO(TFA)_2$ can efficiently catalyze nucleophilic ring opening of epoxides in primary, secondary and tertiary alcohols, acetic acid and water to give the corresponding β-alkoxy alcohols, β-acetoxy alcohols and vicinal diols with high stereo- and regioselectivity in excellent yields. The reaction of optically active styrene oxide in MeOH with two titanium reagents was found to be highly stereospecific and afforded the corresponding S-(+)-2-methoxy-2-phenyl ethanol in 89-95% ee.*

Ring opening of epoxides in the presence of different nucleophiles is important in organic synthesis.[1-8] The use of $TiCl_4$ and $Ti(O\text{-}iPr)_4$ for methanolysis of styrene oxide has also been reported in 88% and 0% yields respectively.[9] In the course of our studies on applications of $TiCl_3(OTf)$[10] and $TiO(TFA)_2$[11] which are both solid and stable compounds of Ti(IV) in organic synthesis,[12] it was observed that they are efficient catalysts for stereo- and regioselective ring opening of styrene oxide in methanol.

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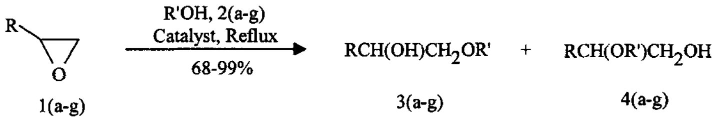
Due to the more reactivity and higher stability of these Ti(IV) compounds than $TiCl_4$ and $Ti(O\text{-}iPr)_4$, it was decided to investigate the possibility of using them for ring opening reaction of epoxides in different alcohols, water and acetic acid. Reaction of different classes of epoxides carrying activated and deactivated groups were performed in different alcohols, acetic acid and water in the presence of these two catalysts. The reactions took place at room temperature or under reflux conditions and catalytic amounts of $TiCl_3(OTf)$ and $TiO(TFA)_2$ were required to produce the corresponding β-alkoxyalcohols, β-acetoxyalcohols and vicinal diols in high yields. (Scheme 1, Table)

(Scheme 1)



Cat: $TiCl_3(OTf)$, $TiO(O_2CCF_3)_2$

R or Epoxide: (a) Ph- (b) Cyclohexen oxide (c) $(CH_3)_2CHOCH_2$- (d) $PhOCH_2$-

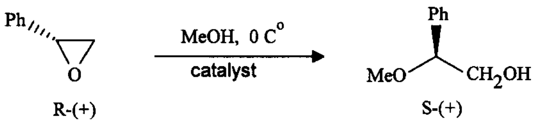
(e) $CH_2{=}CH\text{-}CH_2OCH_2$- (f) $ClCH_2$-

R'OH: (a) MeOH (b) EtOH (c) n-PrOH (d) i-PrOH (e) t-BuOH (f) CH_3CO_2H (g) H_2O

The results obtained in the reaction of epoxides with catalytic amounts of $TiCl_3(OTf)$ and $TiO(TFA)_2$ are shown in Table. The reactions of cyclic compounds were found to be completely stereoselective and the trans products were obtained in 91-98%. In the case of unsymmetrical epoxides, the regiochemistry is strongly dependent on the electronic nature of the substituting on the epoxide. The catalytic effect of $TiCl_3(OTf)$ and $TiO(TFA)_2$ in the present reactions is played by the Ti(IV) ion through its ability to coordinate with oxygen atom of the epoxide ring.[13]

The reaction of R-(+)-styrene oxide with 0.02 molar equivalents of $TiCl_3(OTf)$ and $TiO(TFA)_2$ in methanol were also studied at 0°C. The reactions were found to be highly regioselective and stereospecific. The corresponding S-(+)-2-methoxy-2-phenyl ethanol was obtained in 95-96% yield and 89-95% optical purity which was identified according to the literature data.[9] The comparison of our results on the methanolysis of optically active styrene oxide with those reported for other Ti(IV) catalysts are shown in Scheme 2.

(Scheme 2)



Catalyst	Mole % of Cat.	Time(min)	Yield(%)	(ee%)
$TiCl_3(OTf)$	2	5	95	89
$TiO(O_2CCF_3)_2$	2	10	96	95
$TiCl_4$[9]	1.25	30	88	95
$Ti(O\text{-}iPr)_4$[9]	1.25	23 h	0	-

In conclusion, the catalytic method described here appears to be an efficient and mild method for alcoholysis, acetolysis and hydrolysis of epoxides. In addition, the advantages such as high stereo- and regioselective, non-toxicity and stability of the reagents, easy work-up, high yields and short reaction times make these methods a useful addition to the present methodologies in organic synthesis.

Experimental: Products were characterized by comparison of their physical data with those of authentic samples. All yields refer to isolated products. IR spectra were recorded on a Perkin Elmer 781 and Pye Unicam 8725 spectrometers. NMR

Table. Catalytic ring opening of epoxides with $TiO(TFA)_2$ and $TiCl_3(OTf)$ under reflux condition.

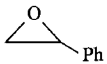
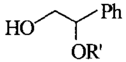
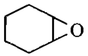
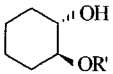
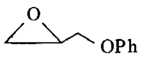
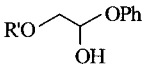
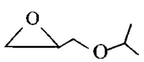
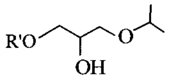
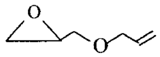
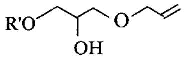
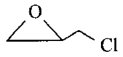
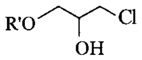
Entry	Substrate	R'OH	Product	$TiCl_3(OTf)$			$TiO(TFA)_2$		
				Molar Ratio Cat./Sub.	Time(h)	Yield(%)I	Molar Ratio Cat./Subs.	Time(h)	Yield(%)I
1		MeOH		0.01II	0.05	99	0.02	0.08	98
2		EtOH		0.01	0.17	97	0.02	0.25	96
3		n-PrOH		0.01	0.17	98	0.02	0.75	99
4		i-PrOH		0.01	0.17	96	0.09	0.33	95
5		t-BuOH		0.01	0.17	95	0.17	0.67	97
6		CH_3CO_2H		0.01	0.17	92	0.02	0.17	96
7		H_2O		0.01	0.08	89	0.02	0.08	90
8		MeOH		0.01	0.17	99	0.02	0.75	98
9		EtOH		0.01	0.17	95	0.09	0.34	96
10		n-PrOH		0.02	0.12	93	0.15	0.75	98
11		i-PrOH		0.03	0.34	97	0.17	0.5	95
12		t-BuOH		0.04	0.25	98	0.2	1.5	96
13		CH_3CO_2H		0.01	0.17	90	0.02	0.08	89
14		H_2O		0.01	0.67	83	0.02II	0.05	85

Table. (Continued)

13		MeOH		0.1	1.75	99	0.43	5.5	98
14		CH_3CO_2H		0.06	0.5	93	0.17	1	91
15		H_2O		0.1	1.5	88	0.07	1.5	90
16		MeOH		0.05	2.25	99	0.26	3.5	99
17		CH_3CO_2H		0.06	0.67	90	0.14	1.25	88
18		H_2O		0.03	1	80	0.04	1	82
19		MeOH		0.05	1.75	96	0.26	3.5	97
20		CH_3CO_2H		0.06	0.67	87	0.14	0.75	85
21		H_2O		0.04	1	72	0.04	1.25	70
22		MeOH		0.2	1.5	86	0.68	2.75	85
23		CH_3CO_2H		0.06	1	79	0.09	0.67	80
24		H_2O		0.07	1.5	70	0.06	1.67	68

I Yield referes to isolated product. II These reactions were performed at room temperature.

spectra were recorded on a Bruker DPX 250. Mass spectra were recorded on a Shimadzu GCMS-QP 1000EX. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-14A instrument

Typical Procedure for Methanolysis of Styrene Oxide with $TiCl_3(OTf)$: A solution of styrene oxide (1 mmol, 0.12 g) and $TiCl_3(OTf)$ (0.01 mmol, 3 mg) in methanol (8 ml) was stirred at room temperature for 5 min. The completion of the reaction was monitored by GLC or TLC. The solvent was then evaporated and water (10 ml) was added and the mixture was stirred for 20 min. The mixture was extracted with CH_2Cl_2 (3×15 ml) and was dried with anhydrous sodium sulfate. Evaporation of the solvent followed by a short column chromatography of silica gel afforded the pure colorless 2-methoxy-2-phenyl ethanol in 99% yield. (0.15 g)

Typical Procedure for Acetolysis of Styrene Oxide with $TiO(TFA)_2$: A solution of styrene oxide (1 mmol, 0.12 g) and $TiO(TFA)_2$ (0.017 mmol, 5 mg) in acetic acid (8 ml) was stirred under reflux condition for 10 min. The completion of the reaction was monitored by GLC or TLC. The solvent was evaporated and water (10 ml) was added and the mixture was stirred for 20 min. The mixture was extracted with CH_2Cl_2 (3×20 ml). The organic solvent was washed with 2% aqueous solution of sodium bicarbonate and was then dried with anhydrous sodium sulfate. Evaporation of the solvent followed by a short column chromatography of silica gel afforded the pure colorless 2-acetoxy-2-phenyl ethanol in 96% yield. (0.172 g)

Typical Procedure for Hydrolysis of Styrene Oxide with $TiO(TFA)_2$: A solution of styrene oxide (1 mmol, 0.12 g) and $TiO(TFA)_2$ (0.017 mmol, 5 mg) in a mixture of CH_3CN-H_2O (1:1, 8 ml) was stirred under reflux condition for 5 min. The completion of the reaction was monitored by GLC or TLC. The organic solvent was evaporated and aqueous solution was saturated with sodium chloride and the product was extracted with CH_2Cl_2 by continuos extraction. The organic solvent was dried with anhydrous sodium sulfate. Evaporation of the solvent followed by a short column chromatography of silica gel afforded the white crystals of 1-phenyl-1,2-ethanediol in 90% yield. (0.124 g)

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13. The possibility of releasing of trifluoroacetic acid from $TiO(TFA)_2$ in protic solvents was ruled out since when $TiO(O_2CCF_3)_2$ was refluxed in methanol for 2 h, the quantitative yield of unchanged $TiO(O_2CCF_3)_2$ was obtained. In the case of $TiCl_3(OTf)$ with assumption of releasing of three molar equivalents of HCl through its reaction with methanol, methanolysis of styrene oxide with 0.03 molar equivalents of hydrochloric acid was studied. In comparison with the reaction of styrene oxide with 0.01 molar equivalent of $TiCl_3(OTf)$, the reaction with hydrochloric acid was found to be five times slower.

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