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Diastereoselective and Regioselective Epoxidations of Allylic Alcohols by the in situ-generated Dioxirane of 2,2,2-Trifluoroacetophenone

Estella L. Grocock, Brian A. Marples* and Richard C. Toon

Department of Chemistry, Loughborough University, Leicestershire LE11 3TU, UK

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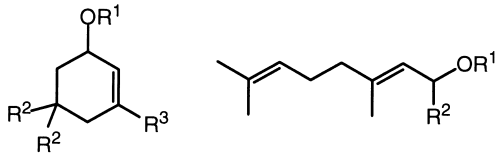
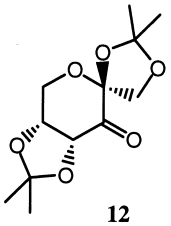
Abstract—The diastereoselective epoxidations of cyclohex-2-en-1-ols and the regioselective epoxidations of geraniol and their acetates using the in situ-generated dioxirane from 2,2,2-trifluoroacetophenone are reported along with comparable epoxidations with Oxone®.

Epoxidation of allylic alcohols with isolated dimethyldioxirane (DMDO) has been extensively studied and shown to depend markedly on solvent, substrate and temperature.[1–6] Intramolecular hydrogen bonding between the OH group and DMDO in a spiro transition state is shown to be important in determining regio- and diastereoselectivity. Reactions of allylic alcohols with in situ-generated dioxiranes are relatively few and are complicated by concomitant reaction with Oxone® directly.[6–9] Although such direct reactions are dependent on the pH of the reaction medium,[7] little detailed preparative or mechanistic evaluation has been reported. Recent work[6,8,9] suggests that diastereoselectivity and regioselectivity in the direct Oxone®-mediated epoxidations are determined by intramolecular hydrogen bonding in cyclohexenols (**1**) and (**2**) and 1-methylgeraniol (**7**), although in all of these reactions low conversions were observed.

We recently reported[10,11] the use of 2,2,2-trifluoroacetophenone (TFAP)/Oxone® as a useful reagent for epoxidation of alkenes. In order to explore further the scope of this reagent and of Oxone® itself, we have examined their reactions with isophorol (**3**), 3-phenylcyclohex-2-en-1-ol (**4**), geraniol (**8**) and their respective acetates (**5**), (**6**) and (**9**). The results of the epoxidation reactions are shown in Tables 1 and 2.

Cyclohexene epoxidations: The greater conversions for the partial reactions of 3-phenylcyclohex-2-en-1-ol (**4**) versus





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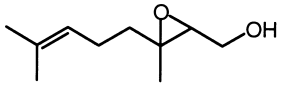

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1, $R^1=R^2=R^3=H$
2, $R^1=R^2=H, R^3=Me$
3, $R^1=H, R^2=R^3=Me$
4, $R^1=R^2=H, R^3=Ph$
5, $R^1=Ac, R^2=R^3=Me$
6, $R^1=Ac, R^2=H, R^3=Ph$
7, $R^1=H, R^2=Me$
8, $R^1=R^2=H$
9, $R^1=Ac, R^2=H$
10, $R^1=TBS, R^2=H$
11, $R^1=Me, R^2=H$

Figure 1.

Keywords: diastereoselection; regioselection; epoxidation; dioxiranes.
* Corresponding author. Tel.: +01509-222554; fax: +01509-223925; e-mail: b.a.marples@lboro.ac.uk

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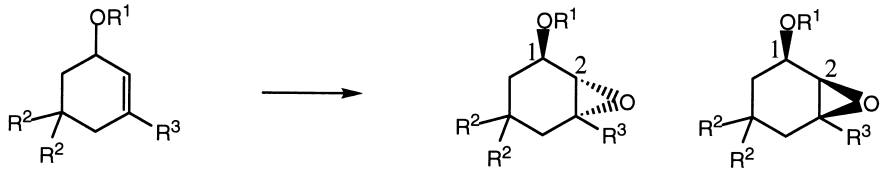
Table 1. Epoxidation of cyclohexenols



				Oxidant: TFAP/Oxone®[a]		Oxidant: Oxone®[a]	
Entry	Substrate	Time (h)	Temp	% Conversion	*cis*: *trans* epoxides	% Conversion	*cis*: *trans* epoxides
1	**4**[16]	24	RT	100	14:86[19]	80	74:26
2	**4**	4.5	0°C	91	21:79	38	69:31
3	**4**	1.5	0°C	82	22:78	25	71:29
4	**6**[17]	24	RT	100	19:81	10	21:79
5	**6**	1.5	0°C	50[b]	25:75	0	–
6	**3**	24	RT	100	53:47[3]	100	97:3
7	**5**[18]	24	RT	100	43:57[18]	10	50:50

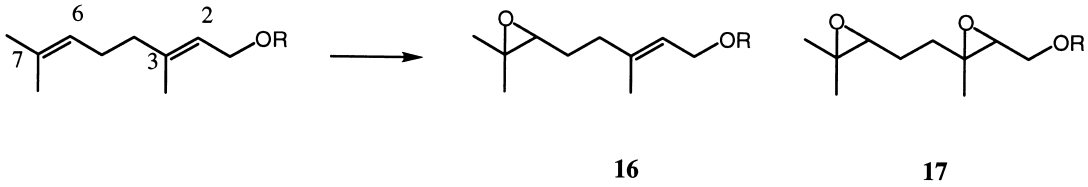
[a] Conversions and ratios determined by analysis of ^{1}H NMR spectra of the crude mixtures.
[b] Somewhat variable but consistently < that for alcohol.

its acetate (**6**) (Table 1, entries 3 and 5) presumably arises from the lower nucleophilicity of the double bond which is due to the greater electron withdrawing properties of OAc versus OH. The high *trans*-selectivity for (**4**) and the much lower selectivity for (**3**) confirms the controlling importance of steric effects rather than intramolecular hydrogen bonding for in situ dioxirane epoxidations.[8] The *trans*-selectivity might be expected to be greater than that observed were it not for the background *cis*-selective and intramolecular hydrogen bond-mediated direct reactions with Oxone® (Table 1, entries 1 and 6). However, this looks to be only significant for (**3**) and may be a reflection of the greater rate of the catalysed reaction for (**4**) versus (**3**), the latter being subject to much more steric hindrance to approach on the *trans*-face (Fig. 1).

In general the direct Oxone® reactions with (**3**) and (**4**) are relatively slow and the reactions with the acetates (**5**) and (**6**) even slower. Both of the acetates show similar *trans*-selectivity in the TFAP-mediated and direct Oxone® reactions (Table 1, entries 4 and 7) in contrast to the parent alcohols (**3**) and (**4**) where intramolecular hydrogen bonding facilitates the *cis*-selectivity for the direct reaction (see above).

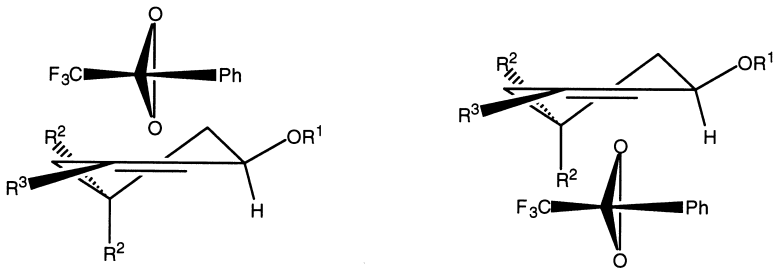
The presence of the bulky phenyl group in the dioxirane generated from TFAP seems to have a minor effect on diastereoselectivity since with isophorol (**3**) this [53:47, *cis*:*trans*] is not markedly different from that observed [62:38] with isolated DMDO in acetone: methanol (1:9) in which the effects of intramolecular hydrogen bonding are minimised.[3] Furthermore, the high *trans*-selectivity for the reactions of (**4**) [86:14] and (**6**) [81:19] in TFAP-mediated reactions are similar to that observed [82:18] for the reaction of DMDO in the same solvent with 3-methylcyclohex-2-en-1-ol (**2**).[4] In situ reactions for (**2**) with a variety of ketones excluding acetone and cyclohexanone gave *trans*-selectivities >74% and that closest to the TFAP value with (**4**) was with 1,3-dichloropropanone.[8] Interestingly, 1,1,1-trifluoropropanone (TFP) gave[8] *trans*-selectivities in the range 86–95%

Table 2. Epoxidation of geraniol and geranyl acetate



				Oxidant: TFAP/Oxone®[a]			Oxidant: Oxone®[a]		
Entry	Substrate	Time (h)	Temp	% Conversion	% 6,7-epoxide	% *bis*-epoxide	% Conversion	% 6,7-epoxide	% *bis*-epoxide
1	**8**	1	0°C	89	46	43	84	40	45
2	**8**	2	0°C	100	Trace	>97	93	34	59
3	**8**	24	RT	100	0	>99	100	0	>99
4	**9**	2	0°C	76	76	–	15	15	–
5	**9**	24	RT	100	41	59	100	98	2

[a] Conversions and ratios determined by ^{1}H NMR spectra of the crude mixtures.



Scheme 1.

for (**2**) and other 1-substituted 3-methylcyclohex-2-enes. The results with TFAP are probably best explained through the spiro transition states depicted in Scheme 1 in which the phenyl group is remote from the ring substituent (R^3), and it can be concluded that TFAP is a reasonable and more easily recoverable alternative to TFP for in situ dioxirane-mediated epoxidations.[10,11] Polar effects appear to make only minor contributions to diastereoselectivity (compare Ref. [8]).

Geraniol and geranyl acetate epoxidations: Shi reported[7] that background epoxidation of geraniol (**8**) by Oxone® reduced the enantioselectivity in using the catalyst (**12**). Our results (Table 2) confirm that Oxone® readily oxidises both double bonds of geraniol (**8**) and suggest that the 6,7-double bond oxidises first. We have used considerably more Oxone® than Shi in accordance with our previously published procedure with TFAP[10] and did not detect the 2,3-epoxide (**13**). As expected from observations with geranyl TBS ether (**10**), the acetate (**9**) was much less reactive with Oxone® than geraniol (Table 2, entries 1, 2 and 4) but it can be used to selectively oxidise the 6,7-double to give (**16**, R=Ac) (Table 2, entry 5) as can TFAP/Oxone® (Table 2, entry 4). Similar selectivity has been observed in the reactions of (**9**) with *m*CPBA, $RuTMP(O)_2$ and UHP-maleic anhydride.[13–15] The use of TFAP allows complete oxidation of geraniol (**8**) to the *bis*-epoxide (**17**, R=H) at 0°C in 2 h (Table 2, entry 2) and Oxone® alone may be used to effect the same transformation under somewhat more vigorous conditions (Table 2, entry 3). The greater nucleophilicity of the 6,7-double bond seems to be the controlling feature in all of these reactions, in common with those observed in the reactions of geraniol (**8**) and its methyl ether (**11**) with DMDO in acetone: methanol (1:9).[1,5]

The work reported here demonstrates that TFAP/Oxone® and Oxone® itself are useful for epoxidation of allylic alcohols and complements recent reports on similar systems[6–9] and on the use of Oxone® as a useful general oxidant in its own right.[12,20]

Experimental

A mixture of Oxone® (0.85 g, 1.38 mmol) and sodium bicarbonate (0.39 g, 4.5 mmol) was added to a mixture of the alcohol or its acetate (0.27 mmol), 2,2,2-trifluoroacetophenone (0.185 ml, 1.32 mmol) and EDTA (5 ml of a 4×10^{-4} M solution) in acetonitrile (7.5 ml). The solution was stirred rapidly overnight excluding light and at room temperature except where indicated otherwise. The reactions with Oxone® alone were performed in the same manner but TFAP was omitted. After the stated time (see Tables 1 and 2) water (100 ml) was added and the solution was extracted with DCM (3×20 ml), the combined extracts then being dried over magnesium sulfate and evaporated to dryness. (In the case of volatile compounds the solutions were evaporated to just dryness at room temperature.) Product ratios were determined from ^{1}H NMR spectra of the crude products.

The allylic alcohols and their acetates are all literature compounds as are all of the isolated epoxides (see Table 1 and text) except the *trans*-epoxide (**14**, R^1=R^2=H, R^3=Ph) and the epoxides from (**6**). Simple acetylation of *cis*-epoxide (**15**, R^1=R^2=H, R^3=Ph) with acetic anhydride in pyridine gave the acetate, an oil, (**15**, R^1=Ac, R^2=H, R^3=Ph), ν_{max} (neat) 1733 (C=O) cm^{-1}, δ_H (250 MHz; $CDCl_3$) 7.35 (5H, m, Ph), 5.23 (1H, dt, *J*=6.5 and 2.5 Hz, 1-CH), 3.27 (1H, d, *J*=2.5 Hz, 2-CH) 2.13 (3H, s, Me), δ_c (62.9 MHz; $CDCl_3$) 170.8 (CO), 140.9 (Ar-C), 128.3 (Ar-CH), 127.6 (Ar-CH), 125.3 (Ar-CH), 69.9 (1-CH), 62.8 (3-C), 61.6 (2-CH), 27.7 (CH_2), 24.9 (CH_2), 21.1 (Me), 19.1 (CH_2). Found: M^+ 232.1079, $C_{14}H_{16}O_3$ requires M^+ 232.1099.

In a slightly modified procedure, oxidation of (**4**) (500 mg, 2.87 mmol) was carried out at room temperature and excluding light in a rapidly stirred reaction mixture containing 2,2,2-trifluoroacetophenone (0.805 ml, 5.74 mmol), EDTA (20 ml of a 4×10^{-4} M solution) in acetonitrile (30 ml), Oxone® (8.81 g, 14.3 mmol) and sodium bicarbonate (3.69 g, 44.4 mmol). After ca. 18 h, water (100 ml) was added and the solution was extracted with DCM (3×30 ml); the combined extracts were dried over sodium sulfate and evaporated to dryness. Careful chromatography of the reaction mixture, using diethyl ether: hexane mixtures as eluent, afforded the *trans*-epoxide (**14**, R^1=R^2=H, R^3=Ph) (23%), mp 75–76°C (white crystalline solid, from diethyl ether: hexane), ν_{max} ($CDCl_3$ film) 3406 (OH) cm^{-1}, δ_H (250 MHz; $CDCl_3$) 7.3 (5H, m, Ph), 4.1 (1H, dt, *J*=8.8 Hz, 5.6 Hz, 1-CH), 3.07 (1H, s, 2-CH), 2.2 (3H, m, CH_2), 1.77 (1H, d, *J*=5.2 Hz, OH), 1.4 (3H, m, CH_2), δ_c (62.9 MHz; $CDCl_3$) 141.1 (Ar-C), 128.3 (Ar-CH), 127.5 (Ar-CH), 125.4 (Ar-CH), 66.8 (1-CH), 65.5 (2-CH), 61.4 (3-C), 30.2 (CH_2), 28.4 (CH_2), 15.8 (CH_2). Found: M^+ 190.0993, $C_{12}H_{14}O_2$ requires M^+ 190.0994.

Acetylation of (**14**, R^1=R^2=H, R^3=Ph) in the usual way afforded a quantitative yield of the *trans*-epoxide, an oil, (**14**, R^1=Ac, R^2=H, R^3=Ph), ν_{max} ($CDCl_3$ film) 1738 (C=O) cm^{-1}, δ_H (400 MHz; $CDCl_3$) 7.3 (5H, m, Ph), 5.1 (1H, dd, *J*=8.8 Hz, 6.4 Hz, 1-CH), 3.04 (1H, br s, 2-CH),

2.3 (1H, m, CH_2), 2.2 (1H, m, CH_2), 2.06 (3H, s, Me), 2.0 (1H, m, CH_2), 1.6 (1H, m, CH_2), 1.5 (1H, m, CH_2), 1.3 (1H, m, CH_2), δ_c (100 MHz; $CDCl_3$) 170.1 (CO), 140.7 (Ar-C), 128.3 (Ar-CH), 127.6 (Ar-CH), 125.3 (Ar-CH), 68.7 (1-CH), 62.9 (2-CH), 60.9 (3-C), 28.0 (CH_2), 26.4 (CH_2), 21.1 (Me), 15.7 (CH_2). Found: M^+ 233.1177, $C_{14}H_{16}O_3$ requires M^+ 233.1178.

Acknowledgements

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