A Powerful New Stereo-controlled Method for Epoxidation of Electrophilic Alkenes

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t-Butyl hydroperoxide and an alkyl-lithium in dry tetrahydrofuran are shown to epoxidise α,β-unsaturated esters and sulphones efficiently in a stereo- and regio-specific manner, while esters of chiral alcohols undergo diastereofacially selective epoxidation.

α,β-Unsaturated aldehydes, ketones, esters, nitriles, sulphones, and related species are difficult to epoxidise by peracid or metal-catalysed methods and the alternative use of alkaline hydrogen peroxide (the Weitz–Scheffer reaction) is generally non-stereospecific[†] and of limited application.[1] Thus α,β-unsaturated esters are not epoxidised this way,[1] though many such compounds are available by the Darzens glycidic ester condensation.[3] The pioneering work of Payne on tungstate-catalysed, buffered, aqueous hydrogen peroxide-mediated epoxidations allows some α,β-unsaturated acids to be epoxidised stereospecifically[4] and this reaction has recently been considerably improved by Sharpless.[5] However, it is not a regiospecific process. We herein describe a versatile alkaline epoxidation procedure that is totally stereospecific and regiospecific, and especially suited to α,β-unsaturated esters. Furthermore, initial attempts to induce chirospecificity are most encouraging.

Anhydrous solutions of t-butyl hydroperoxide in benzene are easily and safely generated by azeotroping commercial material.[6] When such solutions are treated with an organolithium in tetrahydrofuran (THF) at −78 °C the lithium t-butyl peroxide is formed [reaction (1)], accompanied by a small amount of peroxide cleavage [reaction (2)] (Scheme 1). Addition of an α,β-unsaturated ester (or sulphone) and warming to the reaction temperature indicated by t.l.c. (see Table 1) results in smooth epoxidation with complete regio- and stereo-chemical control, probably as shown in Scheme 1.

Several features highlighted in Table 1 deserve comment.

(i) The reactions of the α,β-unsaturated esters are totally stereospecific, unlike the Weitz–Scheffer reaction (expt. 16; *cf.* expts. 7—10, 12—15, 17). We explain this remarkable stereocontrol by the mechanism outlined in Scheme 1, involving chelate-locking of the stereochemistry. Similarly

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[†] Using poly-*S*-amino acids as catalyst, asymmetric epoxidation of certain chalcones has been accomplished in a three-phase system,[2a] while use of bovine serum albumin as catalyst gives low enantiomeric excesses of epoxyquinones.[2b]

Table 1. Epoxidation of α,β-unsaturated-esters and -sulphones with t-butyl hydroperoxide (1.5 mol. equiv.)–RLi (1.1 mol. equiv.) in THF.

Expt.	Alkene	R in RLi	Temp./ °C	Time/ h	Product[a] (A) [or (B)[b]]	% Yield	% D.e.
	Acrylates: $CH_2{=}CHCO_2X$						
1	X = Bu^n	Bu^n	20	1	(R^g—R^t = H)	59	—
2	(*R*)-Menthyl	,,	20	1	,,	76	19[c]
3	Cholesteryl	,,	−20	18	,,	80	0
4	Lanosteryl	,,	−20	3.5	,,	51	10
5	8-PM	,,	−20	18	,,	95	40
6	COSA	,,	−20	18	,,	95	65
	Crotonates: *trans*-$MeCH{=}CHCO_2X$						
7	X = Me	Me	20	16	R^t = Me	54[d]	—
8	Bu^n	Me	20	22	,,	41	—
9	Bu^i	Bu^n	20	22	,,	69	—
10	(*R*)-Menthyl	Bu^n	−20	70	,,	65	35
	Methacrylate: $CH_2{=}CMeCO_2X$						
11	X = (*R*)-Menthyl	Bu^n	−20	70	R^g = Me	51[e]	23
	Fumarates: *trans*-$XO_2CCH{=}CHCO_2X$						
12	X = Me	Me	20	1	R^t = CO_2X	50[f]	—
13	Bu^t	Me	20	3	,,	52	—
14	(*R*)-Menthyl	Me	20	18	,,	63	15
15	8-PM	Bu^n	20	18	,,	56	55
	Maleate: *cis*-$XO_2CCH{=}CHCO_2X$						
16	X = Me	Me	20	5	R^c = CO_2Me	50[f]	—
	Cinnamate: *trans*-$PhCH{=}CHCO_2X$						
17	X = (*R*)-Menthyl	Bu^n	−20	60	R^t = Ph	64	41
	Substituted acrylates						
18	**(3)**	Me	−70	18	R^g = $PhCH_2$	72	—
19	**(3)**	Bu^t	0	18	R^g = $PhCH_2$	57[g]	—
20	**(4)**	Bu^n	20	48	R^c = R^t = Me	51	34
21	**(5)**	Bu^n	−20	288	R^t = Pr^i	49	30
22	**(6)**	Bu^n	−20	144	R^t = Pr^i	48	28
	Sulphones: $XCH{=}CHSO_2Ph$						
23	X = H	Bu^n	−20	1	(R^g—R^t = H)	85	—
24	X = Ph	Bu^n	−20	1.5	R^c = Ph	90	—

[a] R^g = R^c = R^t = H unless otherwise noted. [b] From sulphones. [c] At −20 °C d.e. = 25%; at −70 °C d.e. = 25%. [d] +9% of compound with X = Bu^t. [e] 63% starting material recovered; yield based on consumed methacrylate. [f] Yield after transesterification of mixed epoxy esters with MeOH, toluene-*p*-sulphonic acid, heat for 2 days. [g] 19% starting material recovered; yield based on consumed acrylate.

cis-phenyl β-phenylvinyl sulphones, which give either *trans*-,[7] or *cis*- or mixed[8] epoxides on Weitz–Scheffer epoxidation, undergo exclusive *cis*-epoxidations in high yield by our method (expt. 24). Furthermore, the potentially valuable reagent,[9] phenylsulphonyl oxirane, unavailable by other epoxidation methods owing to its further reaction with the reagents,[10] is easily made by the current method (expt. 23). Still[11] has introduced potassium hydride and t-butyl hydroperoxide in THF for the epoxidation of α,β-unsaturated ketones. This reagent is non-stereospecific in the epoxidation of analogous esters and sulphones. Thus di-t-butyl maleate yields the epoxide of di-t-butyl fumarate (30%), while a 60 : 40 ratio of *trans* to *cis*-epoxide (60% overall yield) results when expt. 24 was conducted using Still's method.

(ii) From the few examples studied (expts. 3 and 4) the reaction is, as expected, specific for electrophilic double bonds as opposed to nucleophilic ones.

(iii) Apart from the undesired cleavage of the t-butyl hydroperoxide by the organolithium (easily countered by use of 1.5 mol. equiv. of the hydroperoxide and 1.1 mol. equiv. of the organolithium) the chief problem lies with transesterification of methyl esters by the liberated lithium n-butoxide and t-butoxide. This reaction is in accord with our recently noted ready transesterification by lithium alkoxides.[12] Ester exchange of methyl esters may be ameliorated by using methyl-lithium which appears milder in terms of cleavage and generates lithium methoxide if cleavage does occur [equation (2)]. Conversely if a t-butyl epoxyester is desired, use of t-butyl-lithium enhances this process (expt. 19). In general it is best to use a higher ester than methyl for optimum yields and preferably a bulky ester. If mixed epoxy-esters are produced they may be methanolysed without epoxide cleavage with methanol and an acid catalyst (expt. 12).

(iv) Initial experiments with (*R*)-menthyl‡ esters (expts. 2, 10, 11, 14, 17, and 20—22) showed moderate chiral discrimi-

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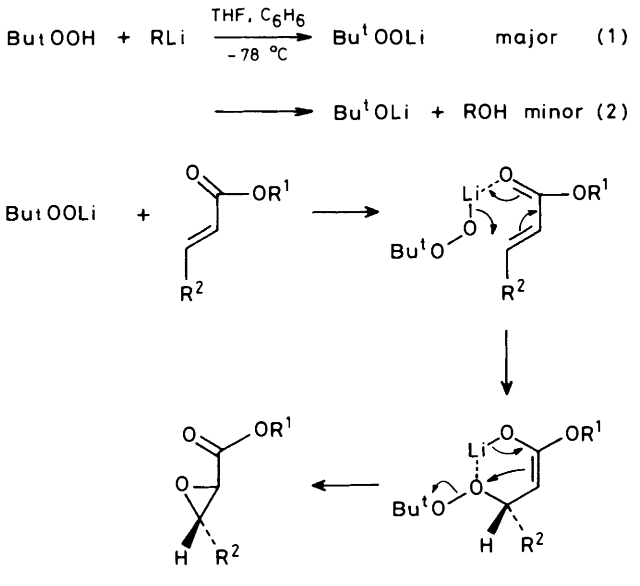
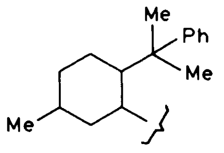
‡ (*R*)-Menthyl is the radical formed by loss of the 1-hydroxy group in (1*R*, 2*S*, 5*R*)-(−)-2-isopropyl-5-methylcyclohexan-1-ol.

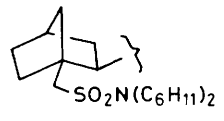


Scheme 1



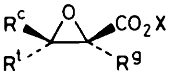
8 - PM

(**1**) = HO - 8 - PM

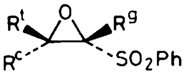


COSA

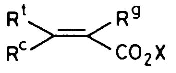
(**2**) = HO - COSA



(A)



(B)



(**3**) $R^g = PhCH_2, R^c = R^t = H$
(**4**) $R^g = H, R^c = R^t = Me$
(**5**) $R^g = R^c = H, R^t = Pr^n$
(**6**) $R^g = R^c = H, R^t = Pr^i$

nation (19—41% diastereoisomeric excesses, d.e.s) and interesting trends: (a) Little benefit accrues from reactions conducted below −20 °C (expt. 2). (b) Dimenthyl fumarate undergoes epoxidation in good yield, also yielding minor amounts of transesterified esters as by-products. However, this trans-esterification occurs largely after epoxidation since the d.e.s of all the esters are similar (expt. 14). β-Alkyl substituents (unlike an α-methyl group) exert a beneficial effect upon the chiral discrimination (28—35% d.e.; *cf.* 25% d.e. for menthyl acrylate). A β-phenyl group raises the d.e. to 41% (expt. 17). (c) Armed with these data we are now examining various established efficient chiral auxiliaries such as 8-phenylmenthol (8-PM, **1**)[13] and Oppolzer's camphorsulphonamide derived alcohol (COSA, **2**).[14] Using the former, bis(8-PM) fumarate underwent epoxidation at ambient temperature with 55% d.e. (expt. 15), while the corresponding acrylate at −20 °C gave 40% d.e. (expt. 5) readily raised by one recrystallisation to 70%. COSA acrylate at −20 °C gave 65% d.e. (expt. 6). We are currently looking into better auxiliaries and the use of double asymmetric induction[15] employing chiral hydroperoxides to raise the diastereofaciality of the process to more acceptable levels. This method would then be a complementary asymmetric epoxidation to that of Sharpless.[16]

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