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Organocatalysis of asymmetric epoxidation by iminium salts using sodium hypochlorite as the stoichiometric oxidant

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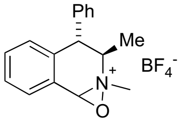
ABSTRACT

Iminium salts can provide high selectivity and high efficiency when used as organocatalysts for asymmetric epoxidation. For this purpose, they are normally used in conjunction with Oxone as the stoichiometric oxidant. Oxone, however, has limited stability, is insoluble in most organic solvents, is atom-inefficient, and produces considerable inorganic residue as the by-product of oxidation. In this paper we report for the first time the development of a reaction system driven by sodium hypochlorite as the stoichiometric oxidant.

1. Introduction

Epoxides are key building blocks in organic synthesis, and are important intermediates in the preparation of many natural products.[1,2] Lusinchi first reported in 1976 that oxaziridinium salts such as **1** are able to transfer oxygen to weakly nucleophilic substrates such as alkenes. Further research work confirmed that oxaziridinium salts could be generated *in situ* by the oxidation of the corresponding iminium salts, such as **2**, and so used as catalysts.[3] Over recent years several research groups have sought to devise methods in developing iminium salt catalysts for asymmetric epoxidation.[4]



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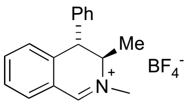

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We were the first to report iminium salt catalysts containing a chiral substituent on the iminium nitrogen atom,[5] exocyclic to the ring containing the iminium unit. Among substituents investigated to date, substituted dioxane units have proven to be optimal for both yield and induction of enantioselectivity.[6–8] Four of the most successful catalysts are the dihydroisoquinolinium salts **3** and **4**,[6,8,9] biphenyl azepinium salt **5**,[7,8,10] and binaphthalene azepinium salt **6**, the last of which provides enantiomeric excesses of up to 95%.[8,11]

The standard conditions used by many research groups for iminium salt-catalysed epoxidation employ Oxone ($2KHSO_5\cdot KHSO_4\cdot K_2SO_4$) as a stoichiometric oxidant, sodium carbonate as a base, and acetonitrile–water as the solvent mixture (Scheme 1). The presence of water is essential for Oxone solubility, and this restricts the range of temperatures at which the epoxidation can be carried out. The upper limit is determined by the stability of Oxone (around room temperature),[12] while the lower limit is determined by the freezing point of the acetonitrile–water mixture used, which is around −10 °C.[6,10] Two liquid layers are normally formed in the reaction, and there is also an undissolved inorganic content due to the reagents and by-products involved.[10,11]

We have recently prepared and utilized the tetraphenylphosphonium salt (TPPP) of monoperoxysulfate, the oxidizing component of Oxone, as an alternative stoichiometric oxidant for these systems. This reagent has the advantages that it is soluble in organic solvents, and thus allows lower temperature reactions, and that no base is required.[9] Enantioselectivities are similar or a little improved at lower temperatures. For example, iminium salt catalysts **3** and **5** mediate the epoxidation of 1-phenylcyclohexene in 41% and 59% ee, respectively, when using Oxone as the stoichiometric oxidant at 0 °C; the enantiocontrol increases a little to 45% and 67% ee, respectively, when using TPPP at −40 °C.

We have also very recently reported the use of hydrogen peroxide as a stoichiometric oxidant, very greatly reducing the amount of inorganic materials present in the reaction, and providing a ‘greener,’ more environmentally friendly reaction process.[13,14] With the hydrogen peroxide system, in the presence of an inorganic salt co-catalyst, ees are somewhat reduced below those provided by the standard oxidant system; for example, iminium salt catalysts

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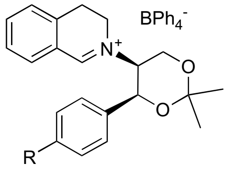
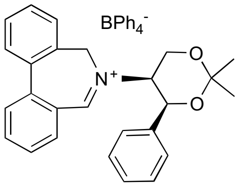


3, R = H; **4**, R = SO_2Me



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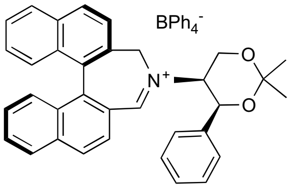

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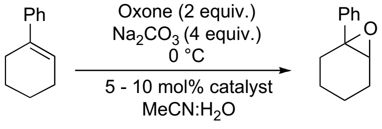
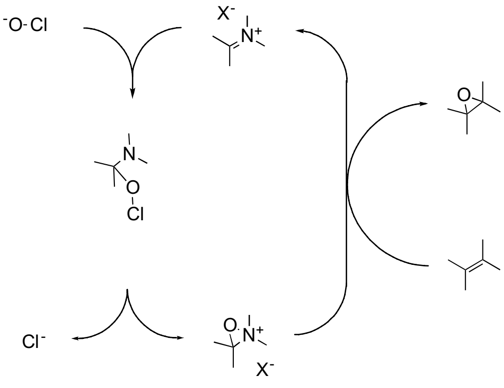


Scheme 1.



Scheme 3.

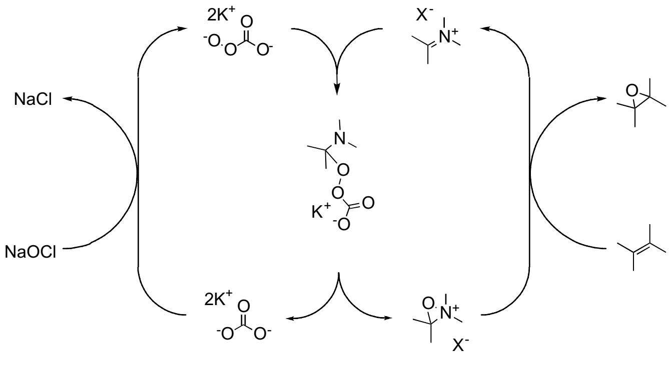
3 and **5** mediate the epoxidation of 1-phenylcyclohexene in 31% and 56% ee. Hydrogen peroxide is, however, poorly stable and loses its efficacy over a period of time, and can be hazardous to use and transport in high concentrations.[15] Given these facts, and having established that the observed enantiocontrol in the iminium salt-catalysed asymmetric epoxidation is influenced by the oxidant, we sought an alternative that could sustain the enantioselectivities attained with the standard oxidant.

2. Results and discussion

2.1. Initial observations

During our work with hydrogen peroxide, we observed that carbonate salts co-catalysed the epoxidation effectively, with no background epoxidation being observed when reactions were carried out at temperatures of up to 5 °C. We suggested that a double catalytic cycle may operate in these processes, with percarbonate providing an intermediate oxidizing stage.[16] We conjectured that sodium hypochlorite might provide an alternative stoichiometric oxidant for our iminium salt-catalysed systems by generating a percarbonate oxidant *in situ* in the presence of a carbonate salt.

Sodium hypochlorite is inexpensive, relatively safe, and has high oxygen content. In the form of commercial bleach it can oxidize electron-deficient alkenes, such as enones and conjugated esters, to their corresponding epoxides with the addition of catalytic base,[17] but does not generally directly oxidize electron-rich alkenes to their corresponding epoxides.[18] Bleach has been used as an oxidant in asymmetric epoxidation using a range of catalysts including chiral salen complexes,[19] manganese porphyrin complexes,[20] and quaternary ammonium salts.[21] There is also precedent for the use of other hypochlorite oxidants such as potassium hypochlorite for oxygen transfer,[22,23] for example, oxidations of alcohols to ketones,[24] aldehydes to acid chlorides,[25] ketones to carboxylic acids,[26] sulfides to sulfoxides,[27] phosphines and phosphites to phosphine oxides and phosphates.[28] Donohoe has reported the use of *tert*-butyl hypochlorite as an oxidant for catalytic asymmetric aminohydroxylation,[29] and Corey has reported asymmetric epoxidation catalysed by dihydrocinchonidinium salts using potassium hypochlorite as oxidant.[21b]



Scheme 2.

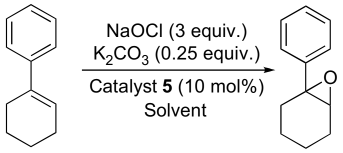
Sodium hypochlorite itself does not directly epoxidize simple alkenes under our reaction conditions: blank reactions in the presence of potassium carbonate, but in the absence of an iminium salt catalyst, show no conversion to the epoxide over 24 h.

Two possible catalytic cycles are illustrated in Schemes 2 and 3 for the proposed process. Hypochlorite may generate percarbonate, which then acts as the oxygen transfer agent, followed by oxaziridinium ion formation (Scheme 2); such a double catalytic cycle involving a second mediator does not, however, appear to have been previously proposed for other processes involving hypochlorite. Alternatively, hypochlorite may add directly to the iminium unit (Scheme 3). Both pathways involve expulsion of a leaving group to generate the oxaziridinium intermediates, potentially as a pair of diastereoisomers, each of which may induce asymmetric oxygen transfer to a substrate. These diastereoisomers would be expected to display different enantioselectivities in any such reaction; the observed ee in each case may therefore be an aggregate resulting from oxidation by the two isomers.

Initial experiments carried out at room temperature using aqueous sodium hypochlorite (3 equiv) as stoichiometric oxidant, potassium carbonate (0.25 equiv) as mediator, and iminium salt catalyst **5** (10 mol %) in an acetonitrile medium induced asymmetric epoxidation of 1-phenylcyclohexene with up to 50% ee (Scheme 4). We were encouraged by this observation to investigate the parameters affecting this potentially attractive reaction system.

2.2. The effect of inorganic mediator on asymmetric epoxidation

Mixtures containing iminium salt **5** and sodium hypochlorite in the presence of an alkene substrate but in the absence of an



Scheme 4.

inorganic mediator showed no conversion to the corresponding epoxides. Therefore sodium hypochlorite, like hydrogen peroxide under similar conditions, is unable to drive the epoxidation process, and thus presumably does not oxidize iminium salts to oxaziridinium salts, in the absence of inorganic mediator. We therefore investigated the effects on the reactions of several added mediators in reactions carried out over 24 h (Table 1).

Rewardingly, the reactions proceeded smoothly when a mediator was included, and the enantioselectivity observed was largely independent of the type of mediator (HCO_3^-, CO_2^{2-} or OH^-) used to promote the reaction. Experiments containing a very low proportion of mediator (0.01 equiv) showed minimal conversion to the epoxide. When the proportion of mediator was increased to 0.25 equiv, the reaction furnished 1-phenylcyclohexene oxide with 68% ee with K_2CO_3, 60% ee with $NaHCO_3$, and 67% ee with KOH. For any mediator, the ee remained constant when the mediator was added in greater proportion than 0.1 equiv. We concluded that, in those cases using carbonates as bases, percarbonate may be generated, and this may mediate the generation of oxaziridinium ion. The large variation in conversions and generally rather smaller effect on ees with change of mediator may reflect that conversion mirrors rate of reaction, which is dependent on ease of generation of the oxaziridinium species, and this would be affected by factors such as the multiphase structure, ion association, identity of the peroxy nucleophile generated; while by contrast the ee should be less variable, unless there is a large variation in the direction of attack on the iminium salt using different inorganic mediators.

2.3. The effects of solvent and temperature

As potassium carbonate appeared to offer the best ees, together with margins for improvement in both conversions and ees, we chose this mediator for further studies. Several solvents were investigated, with reactions carried out at room temperature and 0 °C using catalyst **5** (Table 2).

The results presented in Table 2 show that acetonitrile facilitates complete conversion to the epoxide in less than 24 h in the absence of the iminium salt catalyst, perhaps as a result of peroxyimidic acid formation. No such background epoxidation was seen over the same period when using dichloromethane or chloroform as the reaction solvent. Interestingly, in the presence of catalyst **5**, the epoxide was obtained in 50% ee at rt and 56% ee at 0 °C in acetonitrile solvent, despite the ready background reaction, the presence of the iminium salt catalyst presumably offering a lower energy pathway for reaction, leading to asymmetric epoxidation. When using dichloromethane as the reaction solvent, iminium salt catalyst **5** induces epoxidation with 60% ee at rt and 68% ee at 0 °C. Oxygen transfer, for example from percarbonate, to the iminium ion may take place at the solvent–solvent interface. Alternatively, the iminium salts may act as phase transfer agents, the oxidation to oxaziridinium species then taking place in the aqueous phase before return of the oxaziridinium ion to the organic phase. Assuming that hypochlorite would largely be contained in the aqueous phase, the oxaziridinium species would then become the dominant oxidant in the organic phase.

Table 1
Asymmetric epoxidation of 1-phenylcyclohexene using different mediators[a]

Entry	Base	Conversion[b]/%	ee/%[c]
1	—	2	0
2	K_2CO_3	50	68
3	K_2CO_3[d]	53	66
4	K_2CO_3[e]	71	69
5	K_2CO_3[f]	32	66
6	KOH	13	67
7	K_2HPO_4	27	63
8	$NaHCO_3$	92	60
9	KF	14	<5
10	TBAF	89	16

[a] Epoxidation conditions: iminium salt **5** (10 mol %), aq sodium hypochlorite (6 equiv), mediator (0.25 equiv), dichloromethane, 0 °C, 24 h.
[b] Conversions were evaluated by GC analysis based upon alkene and epoxide content.
[c] Enantiomeric excesses were determined by chiral GC analysis; the major enantiomer was the (1*S*,2*S*)-epoxide.
[d] Epoxidation conditions: as (a) but using mediator (0.40 equiv).
[e] Epoxidation conditions: as (a) but using mediator (1.00 equiv).
[f] Epoxidation conditions: as (a) but without solvent.

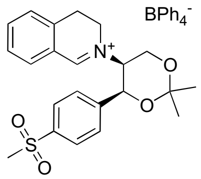
Table 2
Asymmetric epoxidation of 1-phenylcyclohexene using catalyst **5** in various solvents[a]

Entry	Solvent	Temp/°C	Catalyst	Time/h	Conversion[b]/%	ee[b]/%
1	Acetonitrile	rt	—	24	100	<5
2	Dichloromethane	rt	—	24	0	—
3	Chloroform	0	—	24	0	—
4	Acetonitrile	rt	**5**	2	100	50
5	Dichloromethane	rt	**5**	2	100	60
6	Acetonitrile	0	**5**	4	100	56
7	Dichloromethane	0	**5**	24	50	68
8	Chloroform	0	**5**	24	47	48

[a] Epoxidation conditions: iminium salt catalyst **5** (10 mol %), aq sodium hypochlorite (3 equiv), K_2CO_3 (0.25 equiv), solvent, alkene substrate (1 equiv).
[b] Conversions and enantiomeric excesses were determined by chiral GC analysis; the major enantiomer was the (1*S*,2*S*)-epoxide.

It seems likely that the decreased enantiocontrol in the acetonitrile reaction was due to background epoxidation, rather than a genuine solvent effect. Use of chloroform, however, clearly results in poorer induced enantioselectivity, although chloroform does not promote background epoxidation. We have previously observed excellent enantiocontrol when using chloroform as the solvent under non-aqueous conditions, with TPPP as stoichiometric oxidant.[8,9]

In previous work we observed that, when epoxidizing *trans*- and tri-substituted alkenes, the use of iminium salt catalyst **4**, a sulfone derivative of catalyst **3**, gave high levels of enantiocontrol. More interestingly, this catalyst in some cases displayed reversal of the sense of induced enantioselectivity when chloroform was used as solvent in place of dichloromethane.



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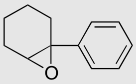
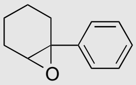
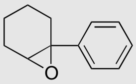
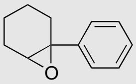
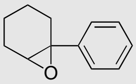
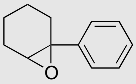
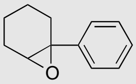
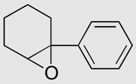
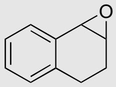
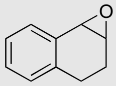
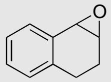
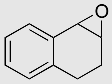
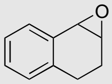
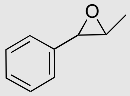
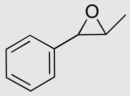
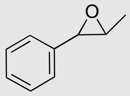
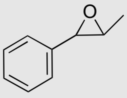
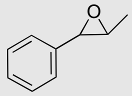
With the new sodium hypochlorite system giving good enantiocontrol when used in conjunction with chloroform and iminium salt catalyst **5** (up to 47% ee), we next tested iminium salts **3**, **4** and **5** under these conditions with three representative alkene substrates (Table 3).

Iminium salt catalyst **5** in dichloromethane gave the best reaction profile when using sodium hypochlorite as the oxidant, giving up to 68% conversion and up to 71% ee for 2,3-dihydronaphthalene oxide. Decreased enantioselectivities were

Table 3
Asymmetric epoxidation of unfunctionalized alkenes[a]

Catalyst	Epoxide	Solvent	Conversion[c]/%	ee[b]/%	Major enantiomer[d]
3		MeCN	49	17	(−)-1*S*,2*S*
3		CH_2Cl_2	10	49	(−)-1*S*,2*S*
4		MeCN	100	28	(−)-1*S*,2*S*
4		CH_2Cl_2	50	17	(−)-1*S*,2*S*
4		$CHCl_3$	60	19	(−)-1*S*,2*S*
5		MeCN	100	55	(−)-1*S*,2*S*
5		CH_2Cl_2	50	68	(−)-1*S*,2*S*
5		$CHCl_3$	47	48	(−)-1*S*,2*S*
3		MeCN	9	21	(−)-1*S*,2*R*
3		CH_2Cl_2	23	33	(−)-1*S*,2*R*
4		$CHCl_3$	13	46	(−)-1*S*,2*R*
5		MeCN	24	66	(−)-1*S*,2*R*
5		CH_2Cl_2	68	71	(−)-1*S*,2*R*
3		MeCN	34	8	(−)-1*S*,2*S*
3		CH_2Cl_2	42	9	(+)-1*R*,2*R*
4		$CHCl_3$	44	8	(+)-1*R*,2*R*
5		MeCN	20	14	(−)-1*S*,2*S*
5		CH_2Cl_2	98	13	(−)-1*S*,2*S*

[a] Epoxidation conditions: iminium salt catalyst (10 mol %), sodium hypochlorite (6 equiv), K_2CO_3 (0.25 equiv), solvent, 0 °C, 24 h.
[b] Enantiomeric excesses were determined by chiral GC analysis.
[c] Conversions were evaluated by GC analysis.
[d] Absolute configurations of the major enantiomers were determined by comparison of optical rotations with those reported in the literature.

observed when using either acetonitrile or chloroform as the solvent. Under these conditions, use of chloroform as solvent with iminium salt catalyst **4** generally gave the same sense of induced enantioselectivity as did both catalysts **3** and **5** in dichloromethane.

Iminium salt catalyst **6** induces up to 95% ee under our original Oxone-mediated conditions.[11] When catalyst **6** was used under the sodium hypochlorite conditions, however, little conversion to the epoxide was observed, due to decomposition of the binaphthalene-based catalyst under the reaction conditions.

3. Conclusions

Commercial sodium hypochlorite in the presence of a carbonate salt has been shown to be a useful stoichiometric oxidant in iminium salt-catalysed asymmetric epoxidation, inducing similar enantioselectivities to the standard Oxone-mediated conditions.

4. Experimental section

4.1. General experimental detail

All infrared spectra were obtained using a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer; thin film spectra were acquired using sodium chloride plates. All ^1H and ^{13}C NMR spectra were measured at 400.13 and 100.62 MHz, respectively, using a Bruker DPX 400 MHz spectrometer, in deuteriochloroform solution unless otherwise stated, using TMS (tetramethylsilane) as the internal reference. Mass spectra were recorded using a Jeol SX102 instrument utilizing electron-impact (EI), fast atom bombardment (FAB), or by the EPSRC national mass spectrometry service at the University of Wales, Swansea. Optical rotation values were measured with an Optical Activity polAAar 2001 instrument, operating at λ=589 nm, corresponding to the sodium D line, at the temperatures indicated. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminium-backed plates coated with Merck Kieselgel 60 F_{254} silica gel. TLC plates were visualized by UV radiation at a wavelength of 254 nm or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate. Reactions requiring anhydrous conditions were carried out using glassware dried overnight at 150 °C, under a nitrogen atmosphere unless otherwise stated. Reaction solvents were used as obtained commercially unless otherwise stated. Light petroleum (bp 40–60 °C) was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium chloride. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran and diethyl ether were distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical. Acetone was dried over pelleted Linde 4 Å molecular sieve, and distilled under a nitrogen atmosphere. Enantiomeric excesses were determined either by ^1H NMR spectroscopy in the presence of europium(III) tris[3-(heptafluropropylhydroxymethylene)-(+)-camphorate] as the chiral shift reagent, by chiral HPLC using a Chiracel OD column on a TSP Series P200 instrument, with a TSP Series UV100 ultraviolet absorption detector set at 254 nm and a Chromojet integrator, or by chiral GC using a Chiraldex B-DM column on a Fisons GC8000 series instrument at 120 °C with a head pressure of 20 psi, using a flame ionization detector and a CE Instruments ChromeCard data station.

4.2. General procedure for formation of racemic epoxides (used as standards for ee determinations)

The alkene was dissolved in dichloromethane (10 mL per gram of alkene) and cooled to 0 °C. *m*-CPBA (2 equiv) was added as a solution in dichloromethane (10 mL per gram of *m*-CPBA). The reaction mixture was allowed to reach ambient temperature, and stirred until complete consumption of the substrate was observed by TLC. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL per gram of alkene) and the layers separated. The organic layer was washed with aqueous NaOH (1.0 M) (10 mL per gram of alkene) and dried ($MgSO_4$). Solvents were removed under reduced pressure. The pure epoxide was obtained after column chromatography, eluting with ethyl acetate/light petroleum (1:99).

4.3. General procedure for catalytic asymmetric epoxidation of alkenes mediated by iminium salts using sodium hypochlorite as stoichiometric oxidant

Potassium carbonate (0.25 equiv) and the iminium salt catalyst (10 mol %) were added to acetonitrile (21 mL per gram of alkene), and the mixture cooled to −5 °C. The alkene substrate was added to this solution, and the mixture stirred to reach equilibrium at the reaction temperature, typically 0 °C. Aqueous sodium hypochlorite (3 equiv, approx. 14% solution) was added. The reaction was vigorously stirred and was monitored by TLC. Once complete consumption of alkene had occurred, or after 24 h, ice-cold brine was added, and the mixture diluted with ice-cooled diethyl ether (200 mL per gram of alkene). The aqueous phase was washed four times with diethyl ether, and the organic layers were combined and dried ($MgSO_4$). Filtration and evaporation of the solvents gave the crude epoxide product. The pure epoxide was obtained after column chromatography eluting with ethyl acetate/light petroleum (1:99).

4.3.1. *1-Phenylcyclohexene oxide*[30]

Colourless oil; ν_{max} (neat)/cm^{-1} 3084, 1602, 1495, 1446, 1359, 1249, 1173, 1132, 1079, 1030, 993, 974; δ_H (250 MHz, $CDCl_3$) 1.22–1.35 (1H, m), 1.53–1.64 (3H, m), 1.99–2.06 (2H, m), 2.16–2.18 (1H, m), 2.26–2.32 (1H, m), 3.10 (1H, t, *J* 2.0 Hz), 7.28–7.44 (5H, m); δ_C (62.5 MHz, $CDCl_3$) 19.8, 20.1, 24.7, 28.2, 60.1, 61.8, 125.3, 127.1, 128.2, 142.8. GC retention times: 30.2 min (major), 32.6 min (minor).

4.3.2. *trans-β-Methyl styrene oxide*[31]

Colourless oil; ν_{max} (neat)/cm^{-1} 3061, 2994, 1604, 1496, 1450, 1258, 1149, 9563, 853, 742, 700, 619; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 5.4 Hz), 3.32–3.40 (1H, m), 3.57 (1H, d, *J* 4.3 Hz), 7.24–7.39 (5H, m); δ_C (100 MHz, $CDCl_3$) 18.1, 59.7, 59.7, 125.7, 127.7, 128.3, 135.84. GC retention times: 12.3 min (major), 12.6 min (minor).

4.3.3. *1,2-Dihydronaphthalene oxide*

Colourless oil; ν_{max} (neat)/cm^{-1} 3059, 3028, 2930, 2850, 1602, 1493, 1316, 1129, 1088, 1030, 964; δ_H (400 MHz, $CDCl_3$) 1.62–1.72 (1H, m), 2.29–2.37 (1H, m), 2.47 (1H, dd, *J* 5.6 and 15.6 Hz), 2.64–2.70 (1H, m), 3.66 (1H, t, *J* 4.0 Hz), 3.79 (1H, d, *J* 4.4 Hz), 7.02 (1H, d, *J* 7.2 Hz), 7.09–7.25 (2H, m), 7.34 (1H, d, *J* 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 22.2, 24.8, 55.2, 55.5, 126.5, 128.80, 128.83, 129.9, 132.9, 137.1. GC retention times: 18.9 min (major), 21.3 min (minor).

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