The Stereoselectivity of Addition of Benzoyloxyl Radicals to Cyclohexenes

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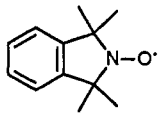
The reactions of benzoyloxyl radicals with cyclohexene and with 4-*tert*-butylcyclohexene, in the presence of the free radical scavenger 1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-yloxyl, are reported. The major reaction observed was diaxial addition; however, the diequatorial and axial/equatorial products were also significant. The overall ratio of axial to equatorial addition of benzoyloxyl radicals to the alkene was 3:2. The aminoxyl trapping reaction was more selective with a ratio of *trans* to *cis* addition of *ca.* 4:1. The stereoselectivity of the addition of benzoyloxyl radicals to cyclohexenes and of the trapping of cyclohexyl radicals is discussed in terms of steric and polar factors.

The importance of free radical chemistry for organic synthesis depends on the degree to which stereoselectivity can be controlled.[1] Factors that are known to be important in controlling the regio- and stereo-selectivity of free radical additions include steric effects, polar effects and bond strength terms.[1-3]

Some reactions are highly stereoselective. For example, the free radical addition of hydrogen bromide to cyclohexenes gives almost exclusively (95–100%) diaxial addition.[4,5] Addition to other cyclic alkenes is also highly selective to give predominantly the *trans* product.[6] The addition of thiols to cyclohexenes is less stereoselective[5-9] (about 70–90% diaxial addition) and this reduced stereoselectivity has been attributed to reversibility in some cases. Free radical additions to norbornenes give predominantly the *cis* product.[6]

While there have been numerous studies of the free radical addition of hydrogen bromide and of thiols to alkenes,[10] as far as we are aware, there have been no studies of the stereochemistry of addition of oxyl radicals to cyclohexenes.

The regio- and stereo-selectivity of the reactions of oxyl radicals with cyclic alkenes can be conveniently studied[11-14] using the radical scavenger 1,1,3,3-tetramethyl-2,3-dihydro-1*H*-isoindol-2-yloxy (**1**) which reacts with carbon-centred radicals at close to diffusion-controlled rates ($k_T \sim 1.2 \times 10^9$ dm^3 mol^{-1} s^{-1})[15] to produce stable alkoxyamines. The alkoxyamines are readily isolated and their structures determined by ^{1}H and ^{13}C NMR spectroscopy. The technique has been applied widely for the determination of the detailed mechanism of the initiation step in free radical polymerisations.[11-14]

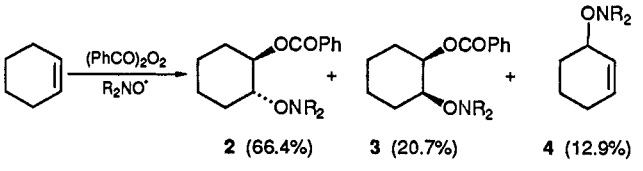


1 ≡ R_2N—O·

In this paper, we report the results of a detailed study of the addition of benzoyloxyl radicals to cyclohexene and to 4-*tert*-butylcyclohexene in the presence of the aminoxyl **1**. It will be shown that these reactions exhibit a stereoselectivity comparable to that observed in the addition of thiols to cyclohexenes. However, much of the stereoselectivity comes from the aminoxyl trapping reaction rather than the initial addition of benzoyloxyl radicals to the alkene.

Results

Initially, the reaction of benzoyloxyl radicals with cyclohexene was investigated. Benzoyloxyl radicals were generated by thermolysis of benzoyl peroxide either in neat cyclohexene or in cyclohexene/acetone mixtures.[16] Typically, a solution of benzoyl peroxide (20 mg, 0.08 mmol) and aminoxyl **1** (33 mg, 0.17 mmol) in cyclohexene (5 cm^3) was degassed, and then heated at 60 °C for 24 h. The reaction products were isolated by reverse-phase HPLC and their structures determined by ^{1}H and ^{13}C NMR spectroscopy. The cyclohexene-derived products and their relative yields are shown in Scheme 1.



2 (66.4%) **3** (20.7%) **4** (12.9%)

Scheme 1

It can be seen that the major products of the reaction are the addition products **2** and **3** (ratio *trans*:*cis* = 3.2:1). The minor product of the reaction, **4** is due to allylic hydrogen abstraction followed by trapping. It is interesting to note that when *tert*-butoxyl radicals were used instead of benzoyloxyl radicals, hydrogen abstraction was the major (98%) reaction pathway but the ratio of *trans*:*cis* addition products (3:1) was very similar to that observed here.[17] There were small solvent and temperature effects on the ratio of **2**:**3**:**4** (Table 1).

Thus, use of 50:50 cyclohexene/acetone changed the ratio to 70.0:16.3:13.6, while carrying out the neat cyclohexene reaction at 25 °C gave a ratio of 71.1:19.1:9.7 respectively. When the concentration of aminoxyl **1** was increased 15-fold (to approximately 0.5 mol dm^{-3}), the amount of hydrogen-abstraction product increased dramatically (ratio **2**:**3**:**4** = 7.7:2.2:90.1). This suggests that **4** is formed predominantly *via* hydrogen abstraction by the aminoxyl **1** rather than by benzoyloxyl radicals.[18]

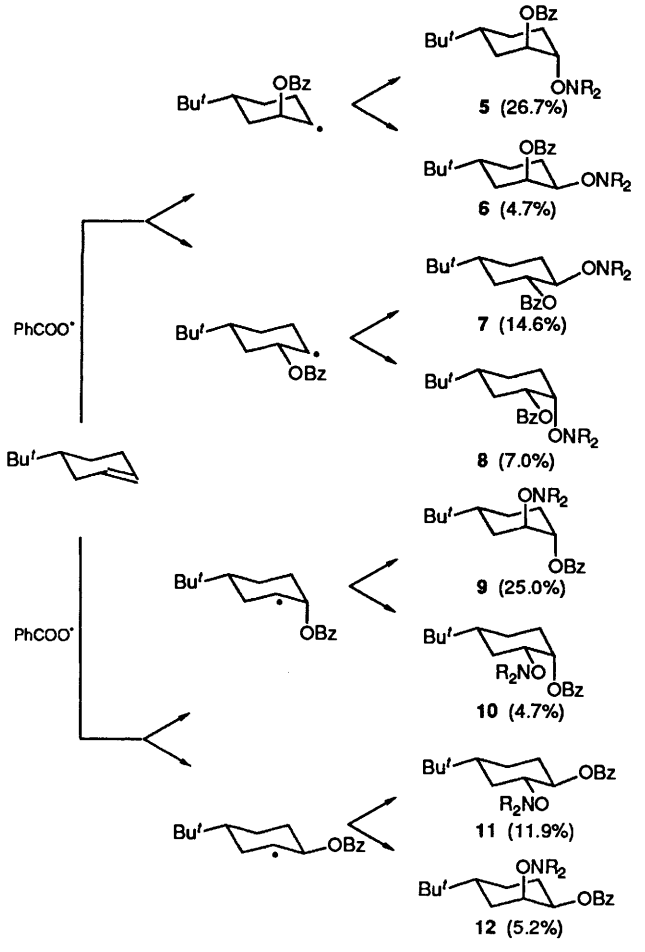
Hydrogen-abstraction from cyclohexene by **1** followed by trapping to give **4** was confirmed by carrying out a blank reaction (*i.e.* without any benzoyl peroxide initiator). Under these conditions, the hydrogen-abstraction product **4** was cleanly produced.

Although these experiments show clearly that *trans* addition is favoured over *cis* addition (by a factor of 3–4:1) they do not tell us whether the addition of benzoyloxyl radicals is stereospecific (*i.e.* whether the *trans* product is a result of axial addition followed by axial trapping, or equatorial addition followed by equational trapping *etc.*). We therefore turned our attention to the conformationally biased molecule, 4-*tert*-butylcyclohexene.

Table 1 Reaction of benzoyloxyl radicals and **1** with cyclohexene

Solvent	Bz_2O_2/ mol dm^{-3}	Aminoxyl/ mol dm^{-3}	T/°C	Reaction time/h	**2** (%)	**3** (%)	**4** (%)
Cyclohexene	0.016	0.035	60	24	66.4	20.7	12.9
Cyclohexene	0.016	0.035	25	1750[b]	71.1	19.1	9.7
Cyclohexene	0.016	0.526	60	24	7.7	2.2	90.1
Cyclohexene	0	0.329	60	24	—	—	>95
Acetone[a]	0.016	0.035	60	24	70.0	16.3	13.6

[a] Cyclohexene/acetone 1:1. [b] 73 days at RT in the dark.



Scheme 2

A solution of benzoyl peroxide (20 mg, 0.08 mmol) and aminoxyl **1** (33 mg, 0.17 mmol) in a mixture of 4-*tert*-butylcyclohexene (5 cm^3) and acetone (5 cm^3), was degassed by successive freeze–thaw cycles under vacuum, sealed, and then heated at 60 °C for 27 h.

HPLC revealed a complex mixture of addition and hydrogen-abstraction products. The six possible hydrogen abstraction products (analogous to **4**) accounted for approximately 10% of the total reaction products and were not further investigated. The addition products were separated by preparative HPLC and the structures (Scheme 2) determined by a combination of ^1H and ^{13}C NMR spectroscopy and chemical interconversions. For example, the diaxial addition product **5** was converted into the axial–equatorial product **8** by hydrolysis of the benzoate ester with sodium methoxide in methanol followed by Mitsunobu esterification[19,20] of the resulting alcohol with benzoic acid, triphenylphosphine and diisopropyl azodicarboxylate.

* 1 cal = 4.184 J.

Discussion

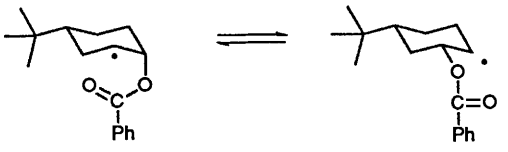
The Benzoyloxyl Radical Addition Step.—It can be seen from Scheme 2 that the preferred mode of addition of the benzoyloxyl radical to the alkene is axial (axial:equatorial = 3:2), although the stereoselectivity observed is not as high as that observed for bromine or thiyl radical addition.[4–9] The high stereoselectivity observed for bromine radical addition (axial:equatorial ≥20:1) has been attributed to the formation of a bromine-bridged, radical intermediate[4,21] while the preference for axial addition by thiyl radicals (*ca.* 2-4:1) has been explained[5] in terms of conformational energy factors and reversibility of the thiyl radical addition step. Le Bel *et al.*[5] have argued that the initial axial preference by thiyl radicals is at least 9:1 and can be rationalised in terms of axial attack giving rise to a cyclohexyl radical having a chair conformation, while equatorial attack would give rise to a (higher energy) twist-boat radical intermediate, *i.e.* torsional effects determine the preferred mode of addition. We believe that similar arguments cannot be used to explain the modest axial: equatorial preference observed for the addition of benzoyloxyl radicals to 4-*tert*-butylcyclohexene.

By analogy with the addition of alkyl radicals to alkenes,[22] the addition of alkoxyl or acyloxyl radicals to alkenes would be expected to be strongly exothermic as the C–O bond being formed (~86 kcal mol^{-1}),[23,*] is much stronger than the π-bond being broken (146 − 83 = 63 kcal mol^{-1}).[23] According to the Hammond postulate,[24] the transition state should lie very early on the reaction coordinate, so that the stability of the cyclohexyl radical intermediate formed would be expected to play little or no part in determining the axial *vs.* equatorial preference of the benzoyloxyl radical. This contrasts with the bromine and thiyl radical addition processes, which would be expected to be far less exothermic due to the much weaker C–Br and C–S bonds being formed (68 and 65 kcal mol^{-1}) respectively,[23] and which would therefore have more advanced transition states. Evidence in support of an early transition state for benzoyloxyl radical addition comes from a study of its reaction with styrene in the presence of **1**. In this study,[25,16] a substantial amount of the head addition product was obtained, indicating that the product radical stability (primary *vs.* secondary benzylic) did not exert a major influence on the addition process.

The addition of benzoyloxyl radicals to alkenes, unlike their reaction with aromatic substrates, is believed to be irreversible.[18a] The present data are also consistent with irreversible addition of benzoyloxyl radicals. Thus, if the addition process were reversible, the selectivity, *i.e.* the ratio of *trans*:*cis* addition, might be expected to increase with increasing aminoxyl concentration. From Table 1, it can be seen that this was not the case. The ratio of *trans*:*cis* addition was solvent dependent, but varied little with the aminoxyl concentration. Moreover, the ratio obtained for cyclohexene (4.3) was virtually identical to that obtained for 4-*tert*-butylcyclohexene (4.4, both with acetone as cosolvent).

One other process that could influence the ratio of axial: equatorial addition is 1,2-benzoyloxy migration (Scheme 3).

Although such radical rearrangements are well known,[26]



Scheme 3

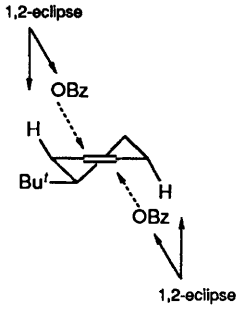


Fig. 1

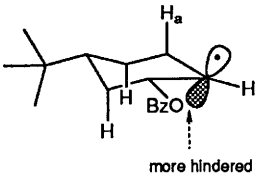


Fig. 2

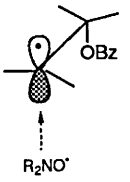


Fig. 3

they occur at quite slow rates[27] ($k = 10^2$–10^4 s^{-1} at 75 °C) and would not be expected to compete under the reaction conditions employed here with the very fast (almost diffusion-controlled) trapping by the aminoxyl **1**. The insensitivity of the ratio of *trans*:*cis* addition products to aminoxyl concentration, together with the almost identical results obtained with both cyclohexene and *tert*-butylcyclohexene, do not support a 1,2-benzoyloxy migration.

We believe that the modest axial preference observed for benzoyloxyl radical addition to 4-*tert*-butylcyclohexene is a result of small steric effects and that the pseudo-axial hydrogens on C-3 and C-6 primarily govern the orientation of addition. Addition to C-2 from above the plane, or to C-1 from below the plane leads to an unfavourable 1,2-hydrogen/benzoyloxyl radical eclipsing interaction (Fig. 1), thus hindering the (equatorial) approach of the incoming group. Such an explanation was considered and rejected by LeBel[5] for the addition of thiyl radicals to cyclohexenes, although steric approach control was regarded as an important factor by Bordwell *et al.*[9]

Presumably both steric effects and torsional effects can determine the preferred mode of addition, with the balance of these two factors being dependent on the position of the transition state along the reaction coordinate. The lower stereoselectivity and expected earlier transition state for benzoyloxyl radical addition compared with bromine or thiyl radical addition would suggest that torsional effects are more important for the latter than for the former.

The Aminoxyl Trapping Step.—The overall stereochemistry of the addition reaction is determined not only by the benzoyloxyl radical addition step but also by the stereoselectivity of the aminoxyl trapping reaction. It can be seen from Scheme 2 that when the benzoyloxy group is axial, the preferred mode of trapping by aminoxyl **1** is also axial (axial:equatorial trapping = 5.5:1). Conversely, when the benzoyloxy group is equatorial, the preferred mode of trapping by the aminoxyl is equatorial (equatorial:axial trapping = 2.2:1). The overall ratio of *trans*:*cis* addition was 4.4:1, very close to the ratio observed with cyclohexene in acetone (4.3:1).

The stereoselectivity of attack on the 4-*tert*-butylcyclohexyl radical has been discussed in terms of torsional effects and steric effects. Torsional effects favour axial attack, while steric effects favour equatorial attack.[1] However, as found in the present study, axial substituents β to the radical centre cause a shift in the direction of axial attack, while equatorial substituents direct the reaction towards equatorial attack.[1]

In the following discussion, it is assumed that the preferred conformation of the 4-*tert*-butylcyclohexyl radical is one in which there is a hyperconjugative interaction between the half-filled orbital and the adjacent C–H bond (C–H_a in Fig. 2).[29,30] When the benzoyloxy group is equatorial, axial trapping by the bulky aminoxyl **1** is presumably hindered by 1,3-diaxial interactions (Fig. 2).

However, when the benzoyloxy group is axial, equatorial trapping by the nitroxide results in a 1,2-eclipsing interaction (Fig. 3). Moreover, the 1,2-eclipsing interaction may be accompanied by an unfavourable dipolar repulsion between the aminoxy and benzoyloxy groups. Presumably these two factors strongly outweigh the 1,3-diaxial interactions inherent in axial trapping so that the latter becomes the preferred pathway. Similar dipolar repulsion arguments might also enhance the preferred equatorial trapping when the benzoyloxy group is equatorial.

Reversibility of the aminoxyl trapping reaction is not expected to be significant under the reaction conditions employed here. Previous work[31–33] has established that alkoxyamines with structures closely related to those in the present study, are thermally stable under these conditions.

Conclusions

The addition of benzoyloxyl radicals to cyclohexenes occurs with only modest stereoselectivity, with axial addition being favoured over equatorial addition by about 3:2. Steric factors are thought to be responsible for this preference. Trapping of the resulting cyclohexyl radical by the aminoxyl **1** occurred with higher stereoselectivity, the *trans* product being favoured by about 4:1. A combination of steric and polar factors are thought to be responsible for the preferential formation of the *trans*-addition product.

Experimental

^1H and ^{13}C NMR spectra (proton-noise decoupled; off-resonance decoupled) were recorded on either a Bruker CXP-300 spectrometer (at 300.06 and 75.46 MHz), or a Bruker WM-250 spectrometer (at 25.12 and 62.80 MHz). Some ^1H NMR spectra were run on a Bruker spectrometer at 500 MHz. (H. Stendar, M. J. Gallagher) at the University of New South Wales. Spectra were run for compounds in deuteriated chloroform with tetramethylsilane as an internal standard. *J* Values are in Hz. The 1 H NMR spectra of the adducts **2**–**12** were quite complex usually requiring proton decoupling experiments, DEPT, and COSY relay experiments to confirm assignments. The four

strong methyl signals of the isoindoline moiety had chemical shifts that overlapped those of the cyclohexyl ring protons, so that determination of coupling constants and connectivity were difficult even at 500 MHz. Double quantum-filtered two-dimensional COSY was unable to suppress completely these strong methyl resonances and spurious cross-peaks (due to residual signals) were still obtained. Another complication arose because the signal from the methine hydrogen on the carbon bearing the aminoxy group (*e.g.* 4-H in **5**) generally appeared as a broad hump, particularly at 250 and 300 MHz. This may have been due to the correspondence of the time scales of the stereomutation process (pyramidal inversion and N–O bond rotation) in these isoindolines[34] and the NMR experiment.

The most important signals for the assignment of relative stereochemistry were the two 1 H multiplets at approximately δ 4 and δ 5. From previous work[14,17] it was known that the chemical shift of protons on carbons bearing the aminoxy moiety lie in the range 3.6–4.2 ppm, whereas protons on carbon bearing a benzoyloxy group appear at about 5.1 ppm.[35] In those cases where one or both of these 1 H multiplets were not completely resolved, it was generally possible to make an unequivocal assignment based on the peak width. For example, the *cis*-addition product **3** displayed poorly resolved multiplets at δ 4.01 and δ 5.50, but both multiplets were less than 15 Hz in width. This implies that no more than one large (diaxial) coupling (typically about 10 Hz) is possible, thus excluding the *trans* structure **2**).

Similarly, the resonance at δ 5.15 in **7** occurred as a complex six-line multiplet of width 25.4 Hz, implying two diaxial couplings. Irradiation of the δ 3.95 resonance in **7** caused the δ 5.15 signal to collapse to a slightly broadened doublet of doublets ($\sim$10 Hz and 5 Hz), corresponding to a diaxial and an axial/equatorial coupling. (Distinguishing between very similar structures such as **7** and **11** was more difficult and required extensive decoupling experiments.[36])

The coupling constants reported here are observed coupling constants based on a first-order analysis of the spectra. The substitution pattern for all carbons was confirmed by either DEPT or off-resonance spectra for all compounds isolated. For the minor products isolated, some carbons were not observed due to the small amount of sample and poor signal/noise ratio. T denotes the isoindoline moiety of the aminoxyl trap.

Mass spectra were recorded on a Kratos MS-25 spectrometer or on a V9 micromass instrument (CSIRO, Melbourne). Microanalyses were carried out by the Microanalytical Service, University of Queensland or by the Australian Microanalytical Service, AMDEL, Melbourne.

Analytical HPLC studies were carried out with either an analytical Ranin Instruments Dynamax-60A 8 mm 250 × 4.6 mm C18 or a semi-preparative Whatman Partisil 10-ODS-3 500 × 10 mm C18 column using an ETP Kortec K35M Dual Piston HPLC pump and either a Soma S-310A-11 or an ETP Kortec K95 variable wavelength UV detector set at 270 nm. The columns were protected with Uptight 2 cm guard columns filled with Whatman 30–38 μm glass beads coated with C_{18} groups.

Peak areas were determined by integration of the HPLC chromatogram. Allowance for differing chromophores was made either by determining the extinction coefficients, at 270 nm, of the isolated products, or by the re-injection of solutions of known concentration to assess peak response ratios for the UV detector. The adjusted peak areas were converted into relative product yields and normalised to 100%.

The reaction products were isolated using preparative reversed-phase HPLC on a Ranin Instruments Dynamax-60A 8 mm 250 × 21.4 mm C18 preparative column. Compounds were detected by the Soma detector fitted with a 1 mm preparative cell. Solvent flow rates were variable depending upon the methanol–water ratio and the back pressure developed. The solvents were pumped at pressures less than 2000 psi by a Gilson 330 pump fitted with a 25 cm^3 min^{-1} preparative head and an 803C manometric module. In some instances two preparative columns were linked together with a coupling piston effectively to make a 500 × 21.4 mm column. Final purification of the isolated products was achieved with a Whatman semi-preparative column.

Cyclohexene was fractionally distilled at atmospheric pressure, passed through basic alumina and stored over 3 Å molecular sieves. 4-*tert*-Butylcyclohexene was prepared by a literature procedure[37] b.p. 97–100 °C (100 mmHg), RI 1.4583 [lit.,[38] b.p. 65–66 °C (20 mmHg), RI 1.4584]. Benzoyl peroxide was purified by recrystallisation from chloroform/methanol, m.p. 106–107 °C (lit.,[39] 104–106 °C). 1,1,3,3-Tetramethyl-2,3-dihydro-1*H*-isoindol-2-yloxyl **1** was prepared, by the method of Griffiths *et al.*,[12] m.p. 128–129 °C.

Reaction of Benzoyl Peroxide with Cyclohexene.—Typical preparative procedure. A solution of benzoyl peroxide (200 mg, 0.83 mmol) and aminoxyl **1** (330 mg, 1.74 mmol) in a mixture of cyclohexene (5 cm^3) and acetone (5 cm^3) was degassed by several freeze–thaw cycles under vacuum ($< 10^{-2}$ mm Hg) and sealed *in vacuo* in a glass vessel. The reaction mixture was heated in an oil bath at 60 °C for 24 h, concentrated to approximately 1 cm^3 under high vacuum and the products separated by HPLC using 90:10 methanol/water. The following products (in order of elution from the HPLC column) were obtained as oils.

3-(1,1,3,3-*Tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-*cyclohexene* (**4**). This material was identical by HPLC, ^1H and ^{13}C NMR spectroscopy to an authentic sample.[17] ε_{270} = 858 dm^3 mol^{-1} cm^{-1}.

cis-2-*Benzoyloxy*-1-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)*cyclohexane* (**3**). δ_C 21.1 (C-5), 23.2 (C-4), 25.3 (Me T), 27.6 (C-6), 28.6 (C-3), 29.9 (Me T), 68.4 (C-1, C-3 T), 72.8 (C-1), 82.2 (C-2), 121.6 (C-4, C-7 T), 127.4 (C-5, C-6 T), 128.4 (C-3 Bz), 129.8 (C-4 Bz), 131.2 (C-1 Bz), 132.8 (C-2 Bz), 145.4 (C-3a, C-7a T), 166.1 (C=0); δ_H 1.31 (s, 3 H, Me), 1.34 (s, 3 H, Me), 1.45 (s, 3 H, Me), 1.53 (s, 3 H, me), 1.40–1.56 (m, 5 H, ring), 1.90 (m, 1 H, ring), 2.01 (m, 1 H, ring), 2.18, (m, 1 H, ring), 4.01 (m, 1 H, 1-H ring), 5.50 (m, 1 H, 2-H ring), 7.04 (m, 2 H, ArH); 7.22 (m, 2 H, ArH), 7.44 (m, 2 H, ArH), 7.53 (m, 1 H, ArH), 8.11 (m, 2 H, ArH); ε_{270} = 1273 dm^3 mol^{-1} cm^{-1} (Found: MH^+ 394.2370. $C_{25}H_{31}NO_3H$ requires 394.2382).

trans-2-*Benzoyloxy*-1-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)*cyclohexane* (**2**). δ_C 22.9 (C-5), 23.1 (C-4), 25.0 (Me T), 25.3 (Me T), 29.7 (C-6), 30.1 (Me T), 30.3 (C-3), 30.5 (Me T), 67.2 (C-1 T), 68.1 (C-3 T), 74.0 (C-1), 81.9 (C-2), 121.4 (C-4 T), 121.6 (C-7 T), 127.1 (C-5, C-6 T), 128.2 (C-3 Bz), 129.7 (C-4 Bz), 131.0 (C-1 Bz), 132.6 (C-2 Bz), 145.6 (C-3a, C-7a T), 165.9, (C=0); δ_H 1.28 (s, 3 H, Me), 1.33 (s, 3 H, Me), 1.53 (s, 3 H, Me), 1.64 (s, 3 H, Me), 1.35–1.55 (m, 4 H, ring), 1.75 (v br t, 2 H, ring),2.14 (m, 1 H, ring), 2.39 (m, 1 H, ring), 4.01 (ddd, 1 H, ^3J 10.1, 9.0, 4.3, 1-H ring), 5.22 (ddd, 1 H, ^3J, 10.1, 9.0 4.3, 2-H ring), 7.07 (m, 2 H, ArH), 7.21 (m, 2 H, ArH), 7.44 (m, 2 H, ArH), 7.54 (m, 1 H, ArH), 8.11 (m, 2 H, ArH) (Found: C, 76.4; H, 7.6; N, 3.3. $C_{25}H_{31}NO_3$ requires C, 76.3; H, 7.9; N, 3.6%).

Reaction of Benzoyl Peroxide with 4-tert-*Butylcyclohexene.*—The general procedure was similar to that used for cyclohexene except that the reaction mixture was partially purified by flash column chromatography on Kieselgel-60 (adducts eluted with hexane) prior to separation by HPLC (100% methanol). Products **7** and **8** could not be completely resolved in a single run and were isolated by repeated separations on the Whatman semi-preparative system. The minor products **6** and **10** could not be completely separated however. The ^1H NMR spectrum

of the eluted peak indicated a 1:1 mixture (clear from the two 9 H singlets of the *tert*-butyl groups). The following products (in order of elution from the HPLC column) were obtained as oils.

3-trans-*Benzoyloxy*-4-trans-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-tert-*butylcyclohexane* (**6**) *and* 4-cis-*Benzoyloxy*-3-trans-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-tert-*butylcyclohexane* (**10**). δ_C 20.5 (Me T), 25.3 (Me T), 27.1 (Me_3 C), 27.4 (Me_3 C), 28.0, 30.3, 31.8, 34.6 (ring carbons), 40.9 [C-2, (**6**)], 46.4 [C-5, (**10**)], 71.7, 72.0 [C-4 (**6**), C-3 (**10**)]; 83.3, 83.8 [C-3 (**6**), C-4 (**10**)], 121.5 (C-4, C-7 T), 121.6 (C-5, C-6 T), 127.6 (C-5, C-6 T), 128.4 (C-3 Bz), 129.6 (C-4 Bz), 129.7 (C-4 Bz), 131.0 (C-1 Bz), 132.8 (C-2 Bz); δ_H 0.82 (s, 9 H, Me_3C), 0.93 (s, 9 H, Me_3 C), 1.1–2.4 (m, 38 H, Me, T and ring H), 3.92 [v br s, 2 H, 4-H (**6**) and 3-H (**10**)], 5.61, 5.68 [m, 1 H each 3-H (**6**) and 4-H (**10**)], 7.05 (m, 4 H, ArH), 7.22 (m, 4 H, ArH), 7.53 (m, 6 H, ArH), 8.09 (m, 4 H, ArH) (Found: C, 77.3; H, 9.0; N, 3.2. $C_{29}H_{39}NO_3$ requires C, 77.5; H, 8.7; N, 3.1%).

4-trans-*Benzoyloxy*-3-cis-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-tert-*butylcyclohexane* (**11**). δ_C 24.8 (Me T), 25.1 (Me_3C), 25.2 (Me T), 27.7 (Me_3C), 29.9 (Me T), 30.5 (Me T), 32.4 (C-6), 45.9 (C-5), 67.0 (C-1 T), 68.3 (C-3 T), 75.7 (C-3), 83.8 (C-4), 121.2 (C-4 T), 121.6 (C-7 T), 128.2 (C-3 Bz), 129.7 (C-4 Bz), 130.6 (C-1 Bz), 132.7 (C-2 Bz), 145.5 (C-3a T), 145.9 (C-7a T), 166.1 (C=O); δ_H 0.89 (s, 9 H, Me_3 C), 1.15 (s, 3 H, Me), 1.25 (s, 3 H, Me), 1.50 (s, 3 H, Me), 1.60 (s, 3 H, Me), 0.95–1.20 (m, 2 H, ring H); 1.35–1.55 (m, 2 H, ring H), 1.75 (m, 1 H, ring H), 2.20 (m, 1 H, ring H), 2.67 (m, 1 H, ring H), 3.99 (dt, 1 H, *J* 10, 10, 3.8, 3-H), 5.03 (dt, 1 H, *J* 10, 10, 3.8, 4-H), 6.90 (m, 2 H, ArH); 7.17 (m, 2 H, ArH), 7.45 (m, 2 H, ArH), 7.57 (m, 1 H, ArH), 8.10 (m, 2 H, ArH) (Found: C, 77.5; H, 8.7; N, 2.9. $C_{29}H_{39}NO_3$ requires C, 77.5; H, 8.7; N, 3.1%).

3-cis-*Benzoyloxy*-4-trans-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-tert-*butylcyclohexane* (**7**). δ_C 24.9 (Me T), 27.5 (Me_3C), 31.6 (C-6), 32.4 (C-1), 32.7 (C-2), 46.0 (C-5), 75.8 (C-4), 84.5 (C-3), 121.4 (C-4 T), 122.0 (C-7 T), 127.5 (C-5, C-6 T), 128.4 (C-3 Bz), 129.8 (C-4 Bz), 132.8 (C-2 Bz), 166.2 (C=O); δ_H(500 MHz) 0.89 (s, 9 H, Me_3C), 1.16 (s, 3 H, Me), 1.24 (s, 3 H, Me), 1.48 (s, 3 H, Me), 1.60 (s, 3 H, Me), 1.27 (m, 1 H, 2_{ax}-H), 130 (dt, 1 H, ^3J 13.4, 13.1, 3.1, 5_{ax}-H), 1.40–1.60 (m, 2 H, 1-H, 6_{ax}-H), 1.83 (dqt, 1 H, 6_{eq}-H), 2.15 (m, 1 H, 2_{eq}-H), 2.65 (dq, 1 H, *J* 12.9, 3 × 4.0), 3.95 (m, 1 H, 4-H), 5.15 (m, 1 H, 3-H), 7.04 (m, 2 H, ArH), 7.45 (m, 2 H, ArH), 7.56 (m, 1 H, ArH), 8.13 (m, 2 H, ArH) (Found: C, 77.3; H, 8.7; N, 2.9. $C_{29}H_{39}NO_3$ requires C, 77.5; H, 8.7; N, 3.1%).

3-cis-*Benzoyl*-4-cis-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-tert-*butylcyclohexane* (**8**). δ_C 25.5 (Me T), 26.2 (C-6), 27.7 (Me_3C), 30.5 (C-1), 40.2 (C-2), 76.1 (C-4), 80.6 (C-3), 127.4 (C-5, C-6 T), 128.3 (C-3 Bz), 130.0 (C-4 Bz), 130.9 (C-1 Bz), 132.9 (C-2 Bz), 166.7 (C=O); δ_H(500 MHz) 0.99 (s, 9 H, Me_3C), 1.39 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.52 (s, 3 H, Me), 1.20–1.60 m, 3 H, ring H), 1.84 (t, 2 H, *J* 10, 2-H), 2.43 (dq, 1 H, *J* 14.4, 3 × 3.4, 5_{eq}-H), 4.33 (v br s, 1 H, 4-H), 5.08 (m, 1 H, 3-H), 7.01 (d, 1 H, *J* 6.8, ArH), 7.10 (d, 1 H, *J* 0.3 Hz, ArH), 7.20 (m, 2 H, ArH), 7.46 (t, 2 H, *J* 8.6, ArH), 7.56 (t, 1 H, *J* 7.3, ArH), 8.15 (d, 2 H, *J* 7.6, ArH) (Found: C, 77.7; H, 8.6; N, 3.4. $C_{29}H_{39}NO_3$ requires C, 77.5; H, 8.7; N, 3.1%).

4-trans-*Benzoyloxy*-3-trans-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-tert-*butylcyclohexane* (**12**). This compound was the least stable of all the adducts, decomposing slowly in $CDCl_3$ even at −30 °C to form a compound with no benzoate moiety. A good ^{13}C NMR spectrum could not be obtained for **12** as it decomposed during the overnight acquisition. δ_H(500 MHz) 0.94 (s, 9 H, Me_3C), 1.26 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.45 (s, 3 H, Me); 1.26 (m, 1 H, ring H), 1.29 (m, 1 H, ring H), 1.68 (tt, 1 H, *J* 12.5, 12.5, 3.7, 3.7, 1-H), 1.83 (dq, 1 H, *J* 12.0, 3.8, 3.7, 3.7, 5_{eq}-H), 1.93, (dqt, 1 H, *J* 13.4, 4 × 3.4, 6_{eq}-H), 2.10 (dq, 1 H, *J* 12.7, 12.5, 12.5, 3.7, 5_{ax}-H), 2.43 (dq, 1 H, *J* 14.1, 3.6, 3.5, 3.4, 2_{eq}-H), 4.42 v br s, 1 H, 3-H), 5.02 (dt, 1 H, *J* 12.3, 3.7, 3.6 Hz, 4-H), 7.00 (d, 1 H, *J* 7, ArH), 7.09 (d, 1 H, *J* 7, ArH), 7.20 (m, 2 H, ArH), 7.45 (t, 2 H, *J* 7.7, ArH), 7.57 (t, 1 H, *J* 7.4, ArH); 8.14 (d, 2 H, *J* 7.7, ArH) (Found: C, 77.3; H, 9.0; N, 3.5. $C_{29}H_{39}NO_3$ requires C, 77.5; H, 8.7; N, 3.1%).

4-cis-*Benzoyloxy*-3-trans-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-tert-*butylcyclohexane* (**9**). δ_C 20.9 (C-6), 25.4 (Me), 26.5 (Me_3C), 27.1 (C-1), 27.3 (Me_3C), 30.2 (Me), 32.1 (C-2), 41.5 (C-5), 68.1 (C-1, C-3 T), 71.3 (C-3), 78.0 (C-4), 121.6 (C-4, C-7 T), 127.4 (C-5, C-6 T), 128.4 (C-3 Bz), 129.7 (C-2 Bz), 131.0 (C-4 Bz), 132.9 (C-1 Bz), 145.0 (C-3a, C-7a T), 165.7 (C=O); δ_H(500 MHz) 0.9 (s, 9 H, Me_3C), 1.43 (s, 3 H, Me), 1.45 (s, 3 H, Me), 1.55 (s, 3 H, Me), 1.62 (s, 3 H, Me), 1.45–1.82 (m, 5 H, ring H), 2.01 (dd, 1 H, *J* 13.9, 2.3, 5_{eq}-H), 2.21 (d, 1 H, *J* 13.2, 2_{eq}-H), 4.09 (v br s, 1 H, 3-H), 5.56 (q, 1 H, *J* 2.7, 4-H), 7.11 (br s, 2 H, ArH), 7.24 (m, 2 H, ArH), 7.46 (t, 2 H, *J* 7.7, 7.8, ArH), 7.57 (t, 1 H, *J* 7.7, 7.4, ArH), 8.06 (d, 2 H, *J* 7.7, ArH) (Found: C, 77.7; H, 9.0; N, 3.1. $C_{29}H_{39}NO_3$ requires C, 77.5; H, 8.7; N, 3.1%).

3-cis-*Benzoyloxy*-4-trans-(1,1,3,3-*tetramethyl*-2,3-*dihydro*-1H-*isoindol*-2-*yloxy*)-tert-*butylcyclohexane* (**5**). δ_C 21.1 (C-6), 25.5 (Me), 26.3 (Me_3C), 27.3 (C-1), 27.6 (Me_3C), 20.1 (Me), 32.3 (C-5), 41.0 (C-2), 68.0 (C-1, C-3 T), 70.1 (C-4), 80.5 (C-3), 121.7 (C-4, C-7 T), 127.4 (C-5, C-6 T), 128.4 (C-3 Bz); 129.6 (C-2 Bz), 132.9 (C-4 Bz), 145.9 (C-3a, C-7a T) (the benzoate *ipso* and carbonyl carbons were not observed after 7200 scans); δ_H(500 MHz) 0.95 (s, 9 H, Me_3C), 1.41 (s, 3 H, Me), 1.43 (s, 3 H, Me), 1.57 (s, 3 H, Me), 1.65 (s, 3 H, Me), 1.47–1.70 (m, 4 H, ring H), 1.96 (dt, 1 H, *J* 13.7, 3.9, 3.7, 2_{ax}-H); 2.02 (m, 1 H, 2_{eq}-H), 2.20 (d, 1 H, *J* 11.2, 5_{eq}-H); 4.19 (v br s, 1 H, 4-H), 5.46 (q, 1 H, *J* 2.9, 3-H); 7.11 (m, 2 H, ArH), 7.24 (m, 2 H, ArH), 7.46 (t, 2 H, *J* 7.7, ArH), 7.57 (t, 1 H, *J* 7.4, ArH), 8.05 (d, 2 H, *J* 7.7, ArH) (Found: C, 77.2; H, 8.9; N, 3.1. $C_{29}H_{39}NO_3$ requires C, 77.5; H, 8.7; N, 3.1%).

Conversion of **5** *into* **8**.—The diaxial addition product (**5**, 10 mg) was dissolved in methanol (5 cm^3) containing sodium methoxide (15 mg). The mixture was stirred at room temperature for 72 h. The resulting alcohol was isolated by semi-preparative HPLC and dried under high vacuum for 24 h. This material was then dissolved in dry DMF (100 mm^3) containing benzoic acid (10 mg, ~4.7 equiv.) and triphenylphosphine (23 mg, ~5 equiv.) cooled to 0 °C and treated with diisopropyl azodicarboxylate (20 mm^3, ~6 equiv.) under an Ar atmosphere. The mixture was allowed to stand at RT for 24 h and the product analysed by HPLC. The resulting benzoate ester was identical to the equatorial–axial product **8** by HPLC.

A similar procedure (but using THF instead of DMF for the Mitsunobu reaction) converted the diequatorial addition product (**7**) into the axial–equatorial product (**6**) (although **6** and **10** could not be completely separated, one component ran slightly faster on HPLC. It was this faster running component that was identical to the product obtained from **7** after Mitsunobu inversion.)

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