Highly diastereoselective Diels–Alder cycloadditions of 9*R*-(1-methoxyethyl)anthracene with *p*-benzoquinone

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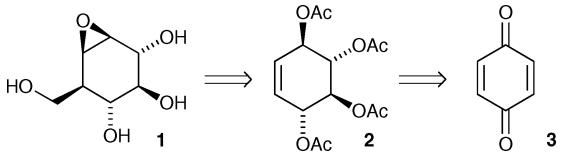
Diels–Alder cycloadditions of *p*-benzoquinone with 9*R*-(1-methoxyethyl)anthracene provides a 60 : 40 ratio of cycloadducts when heated at reflux in xylene. Mechanistic studies to explore the origins of this selectivity have shown that at lower temperatures the kinetic product predominates, giving a 96 : 4 ratio of cycloadducts.

Introduction

The importance of *p*-benzoquinone and its derivatives as synthetic building blocks have been amply demonstrated by their extensive use in natural product synthesis.[1] For example, the asymmetric synthesis of (+)-cyclophellitol **1**, an inactivator of β-glucosidase isolated from the mushroom *Phellinus* sp., has been recently described *via* a synthetic pathway relying upon a palladium-catalysed kinetic resolution of the racemic conduritol B tetraacetate **2**, easily accessed from *p*-benzoquinone **3** (Scheme 1).[2]



Scheme 1 Synthesis of (+)-cyclophellitol **1**.

Moreover, the cyclohexane epoxide backbone is a common framework found in a huge range of structurally diverse naturally occurring compounds isolated mainly from fungi and higher plants. Many of these highly oxygenated six-membered rings have attracted synthetic interest because of their varied biological properties (Fig. 1).[3]

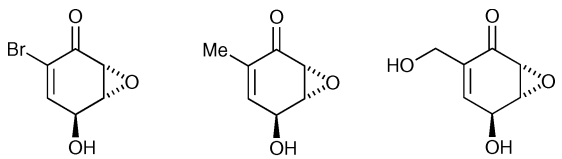
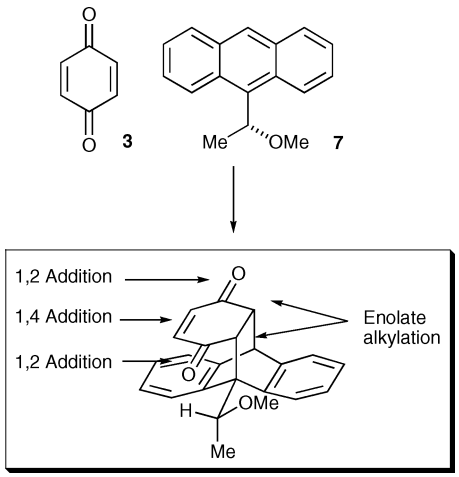


Fig. 1 Cyclohexane epoxide natural products.

For example, bromoxone **4** was isolated from the marine acorn worm[4] and showed potent anti-tumour activity against P388 cells *in vitro*, while related epiepoformin **5** and epiepoxydon **6**, inhibitors of lettuce seed germination, were isolated from an unidentified fungus separated from diseased carpemyrtle leaves of *Lagerstroemia indica*.[5] Although these three compounds have been prepared from ethyl (1*R*,2*S*)-5,5-ethylendioxy-2-hydroxycyclohexanecarboxylate, the synthetic routes are generally arduous giving low overall yields.[6]

The literature contains a large number of examples of Diels–Alder reactions with *p*-benzoquinone **3**, including reaction with cyclopentadiene,[7] cycloheptadiene,[8] butadiene,[9] *trans*,*trans*-1,4-diphenylbuta-1,3-diene,[10] and an isodicyclopentadiene derivative.[11] Given this precedent, cycloadditions of *p*-benzoquinone **3** to the 9*R*-(methoxyethyl)anthracene **7** appeared to be an attractive alternative for further development of a chiral auxiliary strategy that employs a key Diels–Alder/retro Diels–Alder reaction that we[12,13,14] and others[15] have been developing. The resulting cycloadduct would be highly functionalised and as such would offer wide scope as a key building block for the synthesis of target molecules based upon a cyclohexane backbone. A number of functional group transformations were envisaged with this substrate (Scheme 2).



Scheme 2 Diastereoselective Diels–Alder addition.

Thus, the carbonyl groups facilitate both 1,2-nucleophilic addition and enolate alkylation, while the enone may be functionalised through standard electrophilic and Michael addition reactions. The work described herein describes our investigation of the viability of the Diels–Alder reaction of anthracene derivatives

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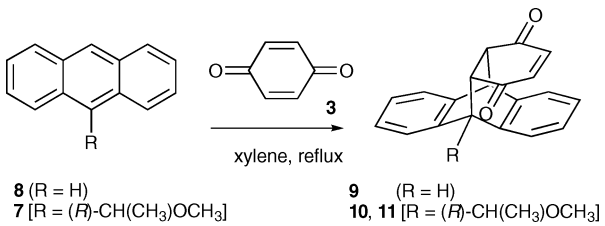
with *p*-benzoquinone and attempts to rationalise the selectivity observed.

Results and discussion

Thermal cycloadditions

An initial assay was conducted to investigate the difference in the relative reaction rates of anthracene **8** and 9-substituted methyl ether **7** with *p*-benzoquinone **3** by heating at reflux in mixed xylenes for 24 h and sampling each reaction at selected time intervals (Scheme 3, Table 1, Chart 1).



Scheme 3 Thermal Diels–Alder cycloadditions.

Table 1 Diels–Alder cycloadditions of anthracene **8** and ether **7** with *p*-benzoquinone **3** in mixed xylenes at reflux

	Conversion (%)[a]	
Time/h	**9**	**10** & **11**
1	75	14
2	81	20
5	98	32
15	100	41
24	100	60

[a] Conversion calculated from the ratio of signals for the starting material and product(s) in the ^{1}H NMR spectrum.

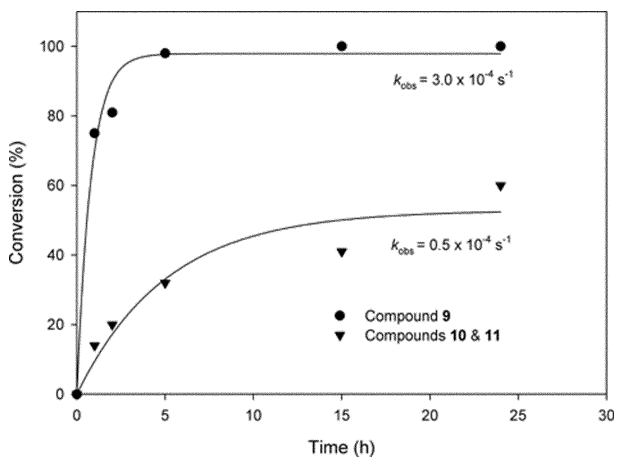
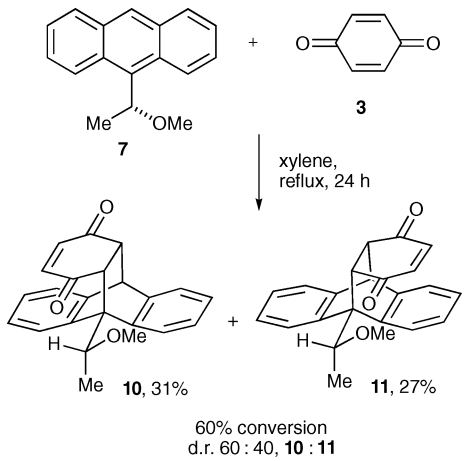


Chart 1 Reactions rates of anthracene **8** and ether **7** with *p*-benzoquinone **3**.

From the rate profiles, the methoxyethyl substituent at the 9-position of anthracene causes a six fold decrease in the apparent reaction rate, k_{obs}, when compared with anthracene **8**. This could be a consequence of the substituted anthracene ring system not adopting a fully planar conformation in the transition state and therefore diminishing π-stacking interactions with the dienophile. However, given that maleic anhydride and *N*-methylmaleimide in toluene or benzene react more slowly with anthracene **8** than with ether **7**,[12] it is perhaps more likely that the apparently slow reaction rate here is based on the existence of a competing retro Diels–Alder reaction.

The stereochemical outcome of the thermal cycloaddition of *p*-benzoquinone **3** with the ether **7** was then considered (Scheme 4).



Scheme 4 Diastereoisomers formed from the cycloaddition reaction.

Analysis of the crude ^{1}H NMR spectrum indicated a conversion of 60% from starting material into a mixture of the two possible diastereoisomers **10** and **11** in an approximate ratio of 60 : 40, respectively, determined by integration of the appropriate signals. Separation by flash column chromatography afforded both diastereoisomers in a 31 and 27% yield, respectively, and their relative stereochemistry was confirmed by single crystal X-ray diffraction (Fig. 2).

Cycloadduct **10** crystallised as a hemi-dichloromethane solvate with the dichloromethane on a twofold axis and clearly shows the orientation of the methoxy group away from the carbonyl with the methyl substituent antiperiplanar to the ring system which is in good agreement with the previous elucidated structures of the cycloadducts from maleic anhydride and *N*-methylmaleimide.[12] By contrast the conformation of the 9-substituent in isomer **11** locates the methoxy group antiperiplanar to the newly formed ring system with the methyl substituent oriented away from the carbonyl, possibly due to strong steric and electrostatic repulsions. It is also noteworthy to mention the shallow boat conformation of the 2-ene-1,4-dione ring in structure **10**, in which C15–C16 and C19–C20 bonds are coplanar (rms deviation 0.011 Å). The two carbonyl moieties represented by the sets of atoms C15/C19/C17/O1 and C16/C20/C18/O2 (rms deviation 0.007 and 0.010 Å, respectively) are bent away from the underlying phenyl ring with dihedral angles with the previous plane C15/C16/C20/C19 of 25.0 and 13.1°, respectively. This conformation is similar to that reported for the crystal structure of the addition product **9** from the reaction of *p*-benzoquinone and anthracene.[16] Somewhat surprisingly the six-membered diketone ring in structure **11** adopts a flat conformation in which all atoms involved (C15/C16/C17/C18/C19/C20) fall in a plane (rms deviation 0.049 Å). The carbonyl groups O1/C17 and O2/C18 have now dihedral angles with this plane of 4.0 and 10.1°,

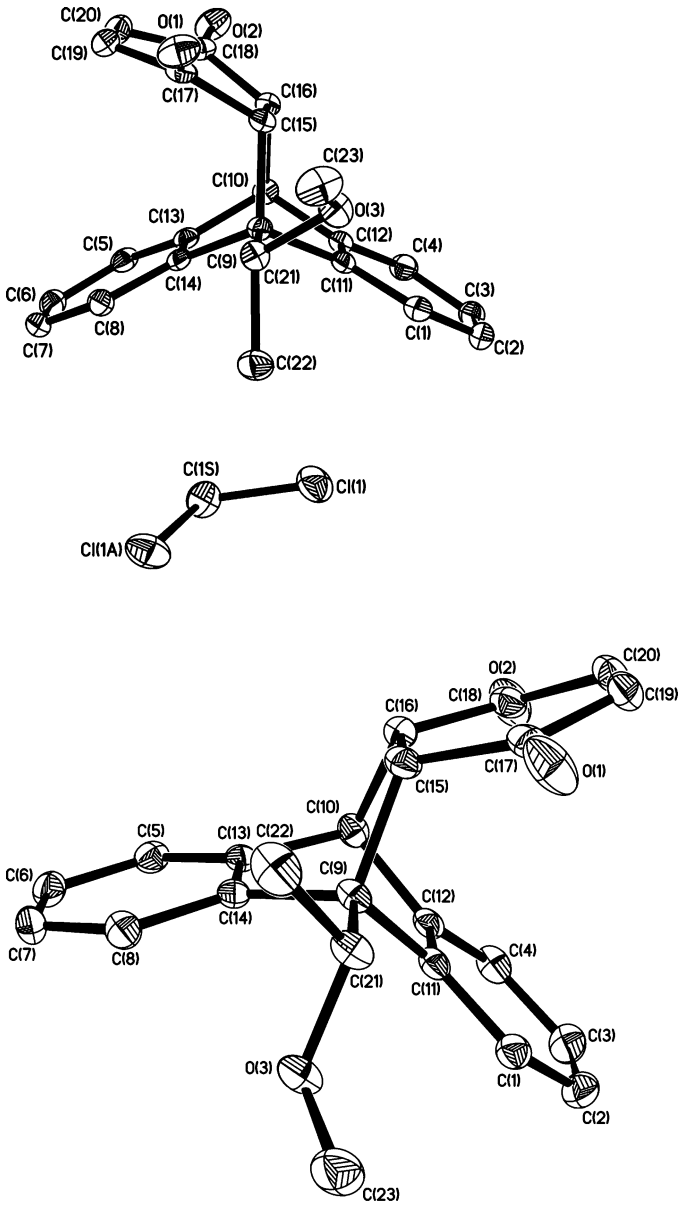
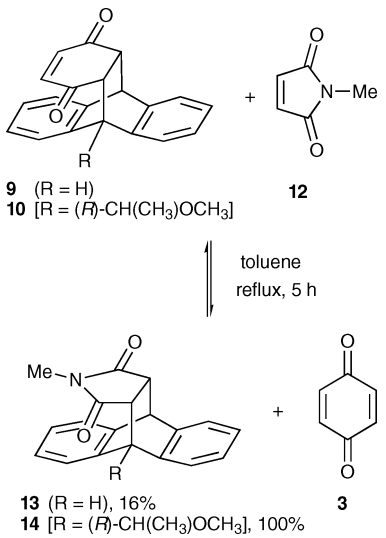


Fig. 2 X-Ray structures of diastereoisomers **10** and **11**, respectively. Ellipsoids shown at 50% probability.

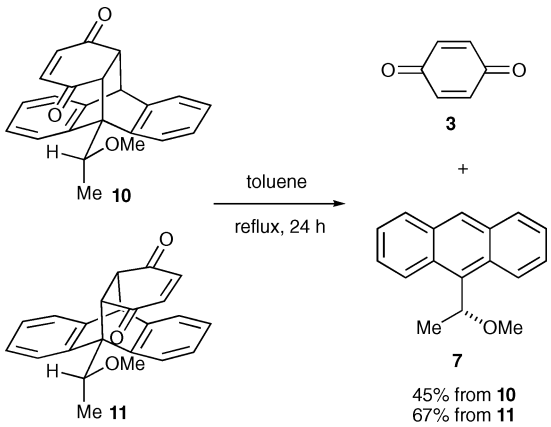
respectively, this resulting in a considerably more constrained conformation of the rigid bicyclic system.

The reversibility of the Diels–Alder reactions of the cycloadduct **9** and the isolated single diastereoisomer **10** were investigated by refluxing with equimolar amounts of *N*-methylmaleimide **12** in toluene for 5 h (Scheme 5). Analysis indicated the appearance of the crossover cycloadducts **13** and **14** in 16 and 100% conversion, respectively, as determined by integration of the appropriate signals in the ^{1}H NMR spectra. Such results confirmed the existence of a retro Diels–Alder reaction in equilibrium with the forward cycloaddition which thus explained their relative rates of formation noted earlier.

Additionally, both isolated single diastereoisomers **10** and **11** were resubjected to the original cycloaddition conditions in toluene (Scheme 6).



Scheme 5 Reversibility of Diels–Alder reaction.



Scheme 6 Reversibility of Diels–Alder reaction.

Both cycloadducts **10** and **11** were found to partially cleave back producing the ether **7** in 45 and 67% yields, respectively. Such results confirmed a lower stability associated with benzoquinone-derived cycloadducts **10** and **11** under thermal conditions in comparison to maleate-based cycloadducts, which show very little cycloreversion.[13] The increased amount of cleavage obtained for the *syn*-diastereoisomer **11** is also in agreement with what would be predicted from the X-ray crystal structure, owing the more constrained conformation adopted when compared to the *anti*-cycloadduct **10**. Interestingly, the crude mixture from the cleavage reaction of the *anti*-cycloadduct **10** was an 80 : 20 mixture of **10** : **11**, which indicated that the reaction was not totally equilibrated under the conditions given and illustrated the slow forward process taking place with this diastereoisomer at this temperature. Similarly, the reaction of the *syn*-cycloadduct **11** also returned increased amounts of the initial diastereoisomer as a 35 : 65 mixture of **10** : **11**. These results confirmed an equilibrium for this reaction taking place under the conditions studied.

The facile reversibility encountered in the Diels–Alder reaction of the ether **7** and *p*-benzoquinone **3** suggests an explanation of the diastereoselectivity based on the thermodynamic stability of the products. Molecular modelling studies of the ground state conformations were carried out for the two addition products

Table 2 Molecular modelling of diastereoisomers **10** and **11**

Cycloadduct	ΔH_f	Calculated K_{eq}[a]	Predicted dr[b]	Observed dr[b]
10	−20.24	0.77	61 : 39	60 : 40
11	−20.04			

[a] Obtained from the calculated energy differences at 110 °C. [b] Ratio (*anti* : *syn*).

10 and **11**. The predicted equilibrium constant for the two diastereoisomers obtained from their calculated heats of formation agree reasonably well with the observed experimental results (Table 2).

Investigation of the mechanism of the Diels–Alder reaction

The poor diastereoselectivity observed for the Diels–Alder reaction of the ether **7** to *p*-benzoquinone **3** was intriguing when compared to the highly diastereoselective systems (>98% de) found with maleate-type dienophiles.[12] This was further confounded by measuring oxygen–oxygen distances between the methoxy group and the proximal carbonyl group as well as appropriate bond angles (ω) in the X-ray crystal structure of addition product **10** (3.1 Å, 111.1°) and comparing to these of the addition products of ether **7** with maleic anhydride (3.5 Å, 114.1°) and *N*-methylmaleimide (3.5 Å, 112.7°) (Fig. 3).

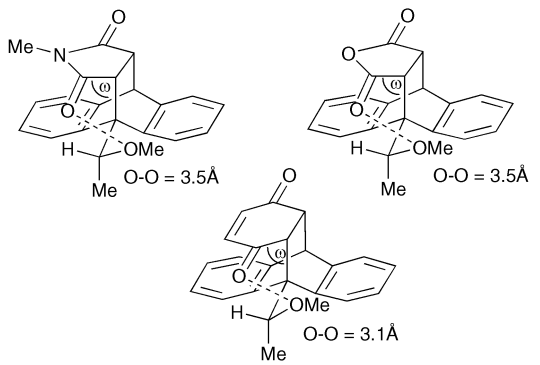
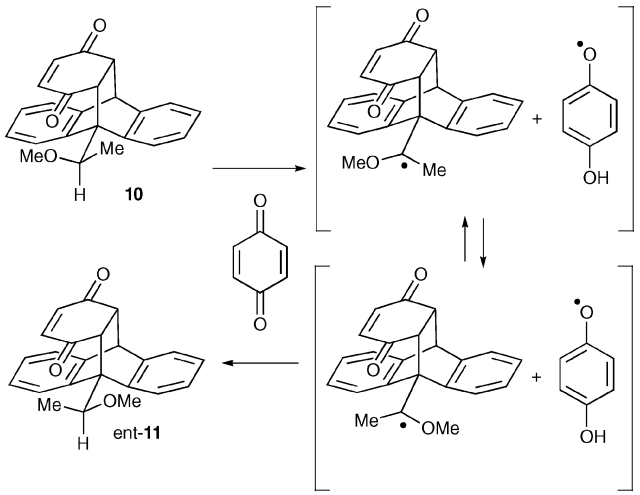


Fig. 3 Atom distances taken from X-ray crystallographic information.

The similar distances and bond angles noted suggest that comparable electronic and/or steric factors should be involved in the transition states of the respective cycloadditions if the reactions proceeded through the same reaction mechanism, which vastly contrast with the observed difference in the selectivity.

Initial thoughts to account for the stereochemical outcome were based upon a possible epimerisation of the stereogenic centre of the addition products **10** and/or **11** through radical abstraction of the methine proton and epimerisation (Scheme 7). Such an argument was supported by the previous use of *p*-benzoquinone **3** as a reagent for the oxidation of aryl conjugated allylic alcohols under similar conditions to those used herein (xylene, 120 °C).[17] However, this was ruled out by subjecting the isolated single diastereoisomer **10** to thermal cleavage as described earlier (Scheme 6), which led to the ether derivative **7** with a specific rotation identical to the starting material.

This led us to consider an alternative reaction may be proceeding. Although the synthetic potential of cycloaddition reactions was outlined by Diels and Alder long ago,[18] the mechanistic interpretation of these reactions is still controversial in some respects.[19] The choice between the concerted and the stepwise mechanism by radical or zwitterionic intermediates cannot always be made easily. Recently many kinetic studies of substituent and solvent effects have appeared.[20] In addition, electron-transfer processes *via* charge-transfer interactions between anthracene dienes and dienophiles, including *p*-benzoquinone, in the transition state of Diels–Alder reactions have recently been reported.[21,22] Such a stepwise process would naturally lead to poor stereocontrol, especially if initial attack occurred at the position distal to the stereodirecting group.



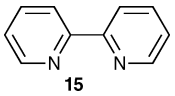
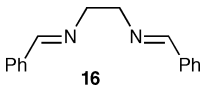
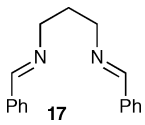
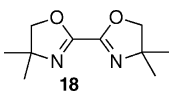
Scheme 7 Possible epimerisation by radical abstraction.

However, direct experimental evidence to demonstrate the existence of a charge transfer complex was difficult to determine using *in situ* UV/Vis measurements of the reactions. Attempts to detect the semiquinone radical anion were carried out as described in the literature,[23] by measuring the change in initial absorbance of different concentrations of ether **7** and *p*-benzoquinone **3** at various wavelengths with a UV/Vis spectrometer in deaerated chloroform at 298 K, but unfortunately no absorption maxima could be observed around the area expected for this species (λ_{max} = 422 nm)[22] presumably due to the very short lifetimes of such radical species. Although this cannot rule out a possible stepwise reaction mechanism, further work would be needed to demonstrate the existence of an intermediate charge transfer complex.

Lewis acid catalysed Diels–Alder reactions

Following recent examples in the literature, which reported remarkable selectivity for Diels–Alder additions catalysed by a new family of Lewis acid complexes derived from pyridyl-*bis*(oxazoline) ligands and samarium and gadolinium triflates,[24] attempts to enhance the selectivity of the Diels–Alder cycloadditions of ether **7** and *p*-benzoquinone **3** were carried out under similar conditions. A ligand–metal triflate survey was performed by heating reactants at 70 °C in CH_3CN in a range of different ligands (bipy **15**, BEN **16**, *N*,*N*′-dibenzylidenepropane-1,3-diamine **17** and 4,4′,5,5′-tetrahydro-4,4,4′,4′-tetramethyl-2,2′-bioxazole **18**) and metal triflates (Mg^{2+}, Cu^{2+}, Sc^{3+}, Y^{3+}, La^{3+}, Gd^{3+}). The highest reactivity was observed when the bisoxazole ligand **18** was used in combination of Cu^{2+} and Y^{3+} as catalyst systems for periods of 16 h (Table 3). However, exposing the reaction under longer

Table 3 Lewis acid catalysed Diels–Alder cycloadditions of ether **7** with *p*-benzoquinone **3**[a]

	Conversion (%) (ratio of diastereoisomers *anti* : *syn*)[b]				
M(OTf)$_n$–ligand	Blank	 **15**	 **16**	 **17**	 **18**
Blank	11 (98 : 8)	NA	NA	NA	NA
$Mg(OTf)_2$	NA	11 (97 : 3)	11 (98 : 2)	11 (100 : 0)	9 (96 : 4)
$Cu(OTf)_2$	NA	11 (100 : 0)	11 (95 : 5)	13 (96 : 4)	35 (87 : 13)
$Sc(OTf)_3$	NA	12 (85 : 15)	14 (86 : 14)	16 (81 : 19)	16 (81 : 19)
$Y(OTf)_3$	NA	12 (88 : 12)	14 (87 : 13)	15 (90 : 10)	20 (87 : 13)
$La(OTf)_3$	NA	11 (90 : 10)	9 (90 : 10)	10 (100 : 0)	15 (90 : 10)
$Gd(OTf)_3$	NA	7 (100 : 0)	11 (96 : 4)	9 (97 : 3)	10 (95 : 5)

[a] Reactions performed with ether **7** and *p*-benzoquinone **3** in a 1 : 1 ratio in CH_3CN at 70 °C for 16 h. [b] Calculated from the integral of the signals corresponding to starting material and addition products in the ^{1}H NMR spectrum.

reaction times (48 h) led to decomposition of the starting materials. On the other hand, encouraging results were obtained for those background reactions in the absence of catalyst when heated in CH_3CN at 70 °C, achieving a 56% conversion after 48 h and a 93 : 7 ratio in favour of diastereoisomer **10**.

Thermal additions at lower temperature

These preliminary results led to a more detailed study into the role of the temperature in the outcome of the Diels–Alder reaction of ether derivative **7** and *p*-benzoquinone **3**. Reactants were heated in toluene at different temperatures for 48 h and the conversions and relative ratios of diastereoisomers **10** and **11** were determined by integration of the appropriate signals in the ^{1}H NMR spectra of the crude material (Table 4).

As the temperature of the reaction was increased, the amount of addition products obtained was seen to decrease. These results were somewhat surprising since it was expected for thermal cycloadditions to show an increased reactivity at elevated temperatures of reaction, as anticipated for the additions of anthracene **8**. This apparent anomalous reactivity could be explained by the retro Diels–Alder reaction for these compounds being more facile at high temperatures. Interestingly, the reactions at lower temperature showed a higher selectivity in favour of the *anti*-diastereoisomer, which agrees with the previous reactions carried out in CH_3CN. Subsequently, the highest diastereoselectivity (96 : 4) was obtained at the lowest temperature (70 °C), which also gave the highest conversion (67%). These were, therefore, accepted as the optimised conditions for the Diels–Alder reaction of ether **7** and *p*-benzoquinone **3**. In addition, slow cooling of the reaction mixture caused precipitation of product crystals making the purification step by flash column chromatography unnecessary and affording the desired cycloadduct **10** in an enhanced 62% yield and >98% de This optimised procedure, under the new conditions, fulfilled the crucial requirement of high diastereoselectivity in the addition step and widely enhanced the potential of the described methodology.

To investigate the extent of the retro Diels–Alder reaction under these optimised conditions, both isolated single diastereoisomers **10** and **11** were subjected to thermal cleavage by heating at 70 °C in toluene for 48 h in the presence and absence of *N*-methylmaleimide **12** (1 eq.) (Table 5). Interestingly, only cycloadduct **10** could be partially cleaved back at this temperature affording similar conversions to both ether **7** and maleimide adduct **14**. The outcome of this retro Diels–Alder reaction (22–29%) is in agreement with the unconverted ether **7** observed previously for the forward process (33%), which indicates a complete re-equilibration of both reactions after 48 h. In addition, the diastereoisomer returned was identical to starting material **10**, which confirms that only the kinetic product **10** is formed under these reaction conditions.

The enhanced conversion and selectivity obtained in the cycloaddition of ether **7** and *p*-benzoquinone **3** at low temperatures (70 °C) in conjunction with the decreased competing retro Diels–Alder reaction observed for both addition products **10** and **11**, now suggested an explanation based upon kinetic control being

Table 4 Diels–Alder cycloaddition of ether **7** with *p*-benzoquinone **3** at different temperatures[a]

Temperature (°C)	Conversion (%)[b]	dr[c]
70	67	96 : 4
80	52	93 : 7
90	46	88 : 12
100	45	82 : 18
110	31	58 : 42

[a] Reactions performed with ether **7** and *p*-benzoquinone **3** in a 1 : 1 ratio in toluene at specified temperature for 48 h. [b] Ratio calculated by integration of the signals corresponding to starting material and addition products **10** and **11** in the ^{1}H NMR spectrum. [c] Ratio calculated by integration of the signals corresponding to each diastereoisomer **10** : **11**, respectively.

Table 5 Retro Diels–Alder exchange reactions of adducts **10** and **11**[a]

	Conversion to **7** (%)[b] No maleimide	Conversion to **14** (%)[b] 1 eq. *N*-methyl maleimide
10	29	22
11	0	0

[a] Reactions performed with ether **7** with and without *N*-methyl maleimide in a 1 : 1 ratio in toluene at 70 °C for 48 h. [b] Ratio calculated by integration of the signals corresponding to starting material and addition products in the ^{1}H NMR spectrum.

more satisfactory to explain the diastereoselectivity. Therefore, a similar rationalisation to those previously used in the additions of maleate dienophiles could be used to explain the facial selectivity in Diels–Alder reactions of *p*-benzoquinone **3** at low temperature (70 °C). Subsequently, the dienophile would preferentially approach the ether **7** by the opposite face to the methyl group, and the selectivity would be established through minimisation of electrostatic repulsions between the dienophile carbonyl oxygen and the methoxy group of the diene to yield the *anti*-cycloadduct **10** (Fig. 4).[15]

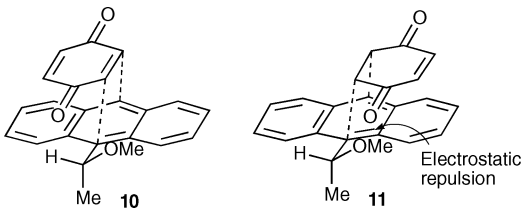


Fig. 4 Models for diastereoselection.

Thermal additions of cyclohexenone derivatives

Attempts at the thermal Diels–Alder reaction of ether **7** with the new range of cyclohexenone derivatives **19**–**22** (Fig. 5) were performed by both heating the reactants at 160 °C in a Fischer-Porter apparatus at 20 bar in toluene for 48 h and also by the optimised conditions (toluene, 70 °C, 48 h).

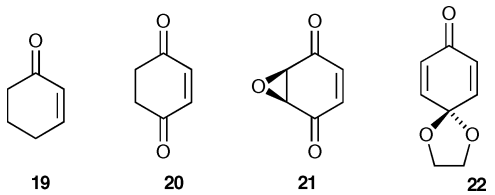


Fig. 5 Other cyclohexenone dienophiles.

However, quite disappointingly, only unreacted starting materials could be observed in all the cases. These results, which are in agreement with similar studies in the literature,[25] indicated that the absence of a second ketone functionality and/or double bond moiety make the enone derivatives **19**–**22** less reactive than *p*-benzoquinone **3**. Experiments examining the reactivity of substituted benzoquinones are currently underway.

Conclusion

We have successfully developed a highly diastereoselective cycloaddition protocol for accessing densely functionalised benzoquinone building blocks. The potential application of this methodology to the synthesis of structurally related targets is enormous and is currently under investigation.

Experimental

All solvents used were freshly dried over sodium except CH_2Cl_2 which was dried over $LiAlH_4$. Et_3N was distilled over KOH. *p*-Benzoquinone was recrystallised from petrol 60–80. A xylenes mixture was used in all reactions in xylene unless otherwise stated. Glassware was flame dried and cooled *in vacuo* before use and all reactions were carried out under nitrogen unless otherwise stated. TLC was carried out using Merk aluminium TLC sheets (silica gel 60 F_{254}). Visualisation of the TLC plates was carried out using a UV lamp or by dipping in $KMnO_4$ then exposure by heating. Flash column chromatography was carried out with Fluorochem Limited Silica Gel 40–63u 60A.

Melting points were measured on a Gallenkamp apparatus and are uncorrected. Specific rotations were performed on a Optical Activity LTD. AA-10 automatic polarimeter at 589 nm (Na D-line) and measured at 20 °C unless otherwise stated. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. All infrared spectra were recorded on a Perkin Elmer Spectrum RX/FT-IR system with a DuraSampl IR II ATR accessory. 250 and 300 MHz ^{1}H NMR were carried out on a AC-250 or Avance 300 instrument respectively supported by an Aspect 200 or Aspect 300 data system. 100 MHz ^{13}C NMR were carried out on a Bruker AMX-400 spectrometer. 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR were carried out on JEOL (Japan Electron Optical Limited) λ 500 MHz spectrometer. Residual proton signals from the deuterated solvents were used as references [chloroform (^{1}H 7.25 ppm, ^{13}C 77 ppm)]. Coupling constants were measured in Hz. Mass spectra were recorded on a Micromass Autospec M spectrometer. Elemental microanalysis was performed using a Perkin Elmer 2400 CHNS/0 Series II elemental analyzer. Elemental analysis for some cycloadducts was calculated taking into account the percentage of CH_2Cl_2 in the product crystals since removal was proved to be difficult. These arguments were also supported by the appearance of solvent molecules in the X-ray crystal structures. Chlorine analysis was determined by the classical wet method of elemental anion analysis using the Schöniger oxygen flask combustion method. UV-Vis spectra were recorded on a Varian Cary 50 spectrometer.

Data collected were measured on a Bruker Smart CCD area detector with Oxford Cryosystems low temperature system. Single crystals of compounds **10** and **11** were grown by liquid diffusion from dichloromethane–petrol (40–60), mounted in inert oil and transferred to the cold gas stream of the diffractometer.

Minimised structures were generated using molecular modelling calculations with Quantum CAChe software (version 3.2, Oxford Molecular Ltd) by first minimising using MM3 parameters, followed by PM3 parameters.

The following compounds were prepared by following established literature procedures: **7**,[12] **16**,[26] **17**,[27] **18**.[28]

General procedure for the thermal Diels–Alder reactions of compounds 7 and 8 with *p*-benzoquinone 3

A solution of anthracene **7** or **8** (3.0 mmol) and *p*-benzoquinone (4.6 mmol) in dry degassed solvent (5 cm^3) was heated at reflux and a sample removed at a specified time interval as appropriate. Removal of the solvent produced the desired cycloadduct (conversion calculated from ^{1}H NMR spectrum).

Preparation of 4a, 9,9a,10-tetrahydro-9,10-[1′,2′]-benzenoanthracene-1,4-dione (9)[29]

Anthracene **8** (0.5 g, 2.8 mmol) and *p*-benzoquinone **3** (0.45 g, 4.2 mmol) were heated under reflux in xylene (5 cm^3) for 5 h. The hot solution was poured into a beaker and cooled overnight

at 5 °C. The solid formed was filtered, washed with cold xylene (20 cm^3) and petrol 40–60 (20 cm^3) and the solvent evaporated to yield the title compound **9** (0.65 g, 81%) as yellow crystals: mp 231–233 °C (from petrol 40–60) (lit.,[30] 227–232 °C); δ_H (250 MHz; $CDCl_3$; Me_4Si) 3.14 (2H, s, COC*H*), 4.86 (2H, s, 9-H and 10-H), 6.31 (2H, s, C=C*H*), 7.05–7.11 (2H, m, ArC*H*), 7.16–7.20 (4H, m, ArC*H*), and 7.38–7.41 (2H, m, ArC*H*).

Preparation of (4a*R*,9a*S*)-4a,9,9a,10-tetrahydro-9-[(1*R*)-1-methoxyethyl]-9,10[1′,2′]-benzenoanthracene-1,4-dione (10) and (4a*S*,9a*R*)-4a,9,9a,10-tetrahydro-9-[(1*R*)-1-methoxyethyl]-9,10[1′,2′]-benzenoanthracene-1,4-dione (11)

(*R*)-9-(1-Methoxyethyl)anthracene **7** (0.71 g, 3.0 mmol) and *p*-benzoquinone **3** (0.50 g, 4.6 mmol) were heated at reflux in dry degassed xylene for 24 h. Removal of the solvent gave a mixture of two diastereoisomers in a 60 : 40 ratio (60% conversion calculated from ^{1}H NMR spectrum). Separation of the diastereoisomers was carried out by flash column chromatography (from 50 to 100% CH_2Cl_2–petrol 40–60). Compound **10** (31%) as yellow crystals: mp 164–166 °C (from CH_2Cl_2–petrol 40–60); $[a]_D^{22}$ −140.0 (*c* 1 in $CHCl_3$); (found: C, 80.1; H, 5.7. Calc. for $C_{23}H_{20}O_3$: C, 80.2; H, 5.85%); ν_{max} (ATR)/cm^{-1} 1663 (CO), 1458 (C=C); δ_H (250 MHz; $CDCl_3$; Me_4Si) 1.81 (3H, d, *J* 6.2, CH_3CH), 3.01 (1H, dd, *J* 2.4 and 8.9, COC*H*), 3.46 (1H, d, *J* 8.9, COC*H*), 3.69 (3H, s, OCH_3), 4.44 (1H, q, *J* 6.2, CH_3C*H*), 4.61 (1H, d, *J* 2.4, PhC*H*CH), 6.02 (2H, s, 2 × C=C*H*), 7.06–7.24 (6H, m, ArC*H*), 7.35–7.40 (1H, m, ArC*H*), 7.93–7.97 (1H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.5 (*C*H_3), 50.1 (*C*H), 51.1 (*C*H), 52.0 (*C*H), 56.4 (9-C and O*C*H_3), 74.0 (CH_3*C*H), 123.4 (Ar*C*H), 123.5 (Ar*C*H), 125.1 (Ar*C*H), 125.8 (Ar*C*H), 126.4 (Ar*C*H), 126.6 (Ar*C*H), 126.7 (Ar*C*H), 127.1 (Ar*C*H), 138.1 (*C*=C), 138.4 (Ar*C*), 138.8 (Ar*C*), 139.8 (Ar*C*), 141.3 (C=*C*), 142.7 (Ar*C*), 197.8 (*C*O), 199.2 (*C*O); *m*/*z* (ES^+) 367.1294 (M + Na^+, 100%. $C_{23}H_{20}O_3Na$ requires 367.1310), 259 (15), 205 (8).

Compound **11** (27%) as yellow crystals: mp 166–168 °C (from CH_2Cl_2–petrol 40–60); $[a]_D^{22}$ +120.0 (*c* 1 in $CHCl_3$); (found: C, 73.95; H, 5.5; Cl, 7.0. Calc. for $C_{23}H_{20}O_3 \cdot 0.395\ CH_2Cl_2$: C, 74.3; H, 5.6; Cl, 7.4%); ν_{max} (ATR)/cm^{-1} 1661 (CO), 1457 (C=C); δ_H (250 MHz; $CDCl_3$; Me_4Si) 1.97 (3H, d, *J* 6.4, CH_3CH), 3.12–3.27 (2H, m, COC*H* and COC*H*), 3.61 (3H, s, OCH_3), 4.37 (1H, q, *J* 6.4, CH_3C*H*), 4.58 (1H, d, *J* 2.1, PhC*H*CH), 6.08 (2H, d, *J* 1.2, 2 × C=C*H*), 7.08–7.21 (6H, m, ArC*H*), 7.36–7.39 (1H, m, ArC*H*), 7.89–7.92 (1H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.0 (*C*H_3), 50.3 (*C*H), 50.9 (*C*H), 52.0 (*C*H), 55.1 (9-C), 56.8 (O*C*H_3), 76.8 (CH_3*C*H), 123.6 (Ar*C*H), 124.2 (Ar*C*H), 125.1 (Ar*C*H), 126.3 (Ar*C*H), 126.7 (Ar*C*H), 127.0 (Ar*C*H), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 139.0 (*C*=C), 139.3 (Ar*C*), 140.3 (Ar*C*), 141.1 (Ar*C*), 141.6 (C=*C*), 143.6 (Ar*C*), 198.3 (*C*O), 199.2 (*C*O); *m*/*z* (EI^+) 344.1416 (M^+, 0.15%. $C_{23}H_{20}O_3$ requires 344.1412), 236 (96), 235 (94), 221 (100), 205 (39), 178 (30).

Crystal structure determination of compound 10†

Crystal data. $C_{23.50}H_{21}ClO_3$, M = 386.85, monoclinic, a = 13.5591(16), b = 9.7766(12), c = 27.715(3) Å, U = 3639.8(8) Å^3, T = 150(2) K, space group C2/c, Z = 8, μ(Mo Kα) = 0.233 mm^{-1}, 12893 reflections measured, 4210 unique (R_{int} = 0.0443) which were used in all calculations. The final $wR(F_2)$ was 0.1205 (all data).

Crystal structure determination of compound 11†

Crystal data. $C_{23}H_{20}O_3$, M = 344.39, monoclinic, a = 16.221(8), b = 7.386(4), c = 28.003(13) Å, U = 3250(3) Å^3, T = 150(2) K, space group C2/c, Z = 8, μ(Mo Kα) = 0.092 mm^{-1}, 17536 reflections measured, 3733 unique (R_{int} = 0.0704) which were used in all calculations. The final $wR(F_2)$ was 0.1525 (all data).

General procedure for the competition experiment between cycloadducts 8, 10 and 11 with *N*-methylmaleimide 12 under thermal conditions

A solution of cycloadduct (0.16 mmol) and *N*-methylmaleimide **12** (0.02, 0.18 mmol) was heated under reflux for 5 h in dry degassed toluene (5 cm^3). Removal of the solvent produced the desired cycloadduct (conversion calculated from ^{1}H NMR spectrum). ^{1}H NMR data for cycloadducts **13** and **14** were in accordance with the literature.[31,12]

General procedure for the retro Diels–Alder reactions of compounds 10 and 11 under thermal conditions

A solution of adduct **10** or **11** (0.05 g, 0.2 mmol) in dry toluene (5 cm^3) was heated under reflux for 24 h. Removal of the solvent produced ether **7** in 47 and 70% conversion and unreacted cycloadducts **10** and **11** in 80 : 20 and 35 : 65 ratios, respectively (conversions and ratios calculated from ^{1}H NMR). Purification by flash column chromatography (50% CH_2Cl_2–petrol 40–60) afforded (*R*)-9-(1-methoxyethyl)anthracene **7** in 45 and 67% yields, respectively, each of >98% ee.

Attempted procedure for detection of the semiquinone radical anion using *in situ* UV/Vis measurements

A $CHCl_3$ solution (0.8 cm^3) containing *p*-benzoquinone **3** (10^{-4} M) and different concentrations of (*R*)-9-(1-methoxyethyl)anthracene **7** (0.1, 0.25, 0.5, 1 and 2 eq.) in a square plastic cuvette (1 mm) was deaerated by bubbling with nitrogen gas for 5 min. A wavelength scan was then carried out (200–400 nm) using a UV/Vis spectrometer but only the absorption maxima corresponding to *p*-benzoquinone **3** (242 nm) and (*R*)-9-(1-methoxyethyl)anthracene **7** (243, 258, 331, 348, 366 and 385 nm) were observed in all the cases.

General procedure for the Lewis acid catalysed Diels–Alder reactions of ether 7 with *p*-benzoquinone 3

(*R*)-9-(1-Methoxyethyl)anthracene **7** (20 mg, 0.08 mmol) and *p*-benzoquinone **3** (14 mg, 0.12 mmol) were added to a pre-stirred solution either in the presence or absence of ligand (20% mol) and metal triflate (20% mol) in dry degassed CH_3CN (2 cm^3). The resulting mixture was heated at 70 °C for 16 h and allowed to cool to rt. The solution was filtered through silica gel with CH_2Cl_2 washing (10 cm^3) and the solvent removed (conversions calculated from the ^{1}H NMR spectra).

† CCDC reference numbers 601816–601817. For crystallographic data in CIF format see DOI: 10.1039/b603819k

Improved method for the preparation of (4a*R*,9a*S*)-4a,9,9a,10-tetrahydro-9-[(1*R*)-1-methoxyethyl]-9,10[1′,2′]-benzenoanthracene-1,4-dione 10 with enhanced diastereoselectivity

(*R*)-9-(1-Methoxyethyl)anthracene **7** (0.70 g, 3.0 mmol) and *p*-benzoquinone **3** (0.50 g, 4.6 mmol) were heated at 70 °C in toluene (5 cm^3) for 48 h. Slow cooling produced yellow crystals of the title compound **10** (0.63 g, 62%) (>98% de from ^{1}H NMR spectrum) which were filtered, washed with petrol 40–60 (3 × 5 cm^3) and dried *in vacuo*.

General procedure for the retro Diels–Alder reactions of compounds 10 and 11 at 70 °C

A solution of cycloadduct (0.16 mmol) in the presence and absence of *N*-methylmaleimide **12** (0.02, 0.18 mmol) in dry degassed toluene (5 cm^3) was heated at 70 °C for 48 h. Removal of the solvent produced the desired cycloadduct (conversion calculated from ^{1}H NMR spectrum).

References

1 T. Suzuki, K. Kubomura and H. Takayama, *Chem. Pharm. Bull.*, 1991, **39**, 2164–2166; M. Canto, P. de March, M. Figueredo, J. Font, S. Rodríguez, A. Álvarez-Larena and J. F. Piniella, *Tetrahedron: Asymmetry*, 2002, **13**, 455–459; S. Sankararaman and M. Srinivasan, *Org. Biomol. Chem.*, 2003, **1**, 2388–2392.
2 B. M. Trost and E. J. Hembre, *Tetrahedron Lett.*, 1999, **40**, 219–222.
3 K. Miyashita and T. Imanishi, *Chem. Rev.*, 2005, **105**, 4515–4536; J. Marco-Contelles, M. T. Molina and S. Anjum, *Chem. Rev.*, 2004, **104**, 2857–2899; C. Thebtaranonth and Y. Thebtaranonth, *Acc. Chem. Res.*, 1986, **19**, 84–90.
4 T. Higa, R. K. Okuda, R. M. Severns, P. J. Scheuer, C.-H. He, X. Changfu and J. Clardy, *Tetrahedron*, 1987, **43**, 1063–1070.
5 H. Nagasawa, A. Suzuki and S. Tamura, *Agric. Biol. Chem.*, 1978, **42**, 1303–1304.
6 For example, see: T. Tachihara and T. Kitahara, *Tetrahedron*, 2003, **59**, 1773–1780.
7 Y.-C. Yang and T.-Y. Luh, *J. Org. Chem.*, 2003, **68**, 9870–9873; R. Rathore and J. K. Kochi, *J. Org. Chem.*, 1995, **60**, 4399–4411.
8 G.-A. Craze and I. Watt, *J. Chem. Soc., Perkin Trans. 2*, 1981, 175–184.
9 O. Diels and K. Alder, *Chem. Ber.*, 1929, **62**, 2087–2090.
10 F. P. Ballisteri, E. Maccarone, G. Perrini, G. A. Tomaselli and M. Torre, *J. Chem. Soc., Perkin Trans. 2*, 1982, 273–277.
11 L. A. Paquette, T. M. Kravetz and L.-Y. Hsu, *J. Am. Chem. Soc.*, 1985, **107**, 6598–6603.
12 J. C. C. Atherton and S. Jones, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2166–2173.
13 J. C. C. Atherton and S. Jones, *Tetrahedron Lett.*, 2002, **43**, 9097–9100.
14 S. Jones and I. Ojea-Jimenez, *Polycylic Aromat. Compd.*, 2005, **25**, 1–12; S. Jones and R. A. Bawa, *Tetrahedron*, 2004, **60**, 2765–2770; J. C. C. Atherton and S. Jones, *Tetrahedron Lett.*, 2001, **42**, 8239–8241; S. Jones and J. C. C. Atherton, *Tetrahedron: Asymmetry*, 2001, **12**, 1117–1119.
15 K. L. Burgess, M. S. Corbett, P. Eugenio, N. J. Lajkiewicz, X. Liu, A. Sanyal, W. Yan, Q. Yuan and J. K. Snyder, *Bioorg. Med. Chem.*, 2005, **13**, 5299–5309; A. Sanyal, Q. Yuan and J. K. Snyder, *Tetrahedron Lett.*, 2005, **46**, 2475–2478; K. L. Burgess, N. J. Lajkiewicz, A. Sanyal, W. Yan and J. K. Snyder, *Org. Lett.*, 2005, **7**, 31–34; M. S. Corbett, X. Liu, A. Sanyal and J. K. Snyder, *Tetrahedron Lett.*, 2003, **44**, 931–935; A. Sanyal and J. K. Snyder, *Org. Lett.*, 2000, **2**, 2527–2530.
16 H. Adams, I. Ojea-Jimenez and S. Jones, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2004, **60**, o690–o691.
17 M. G. Kulkarni and S. Mathew, *Tetrahedron Lett.*, 1990, **31**, 4497–4500.
18 R. Huisgen, R. Grashey and J. Sauer, in *The Chemistry of Alkenes*, ed. S. Patai, Interscience, London and New York, 1964, ch. 11; O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98–122.
19 J. Sauer, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 16–33; R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403–419; R. A. Firestone, *Tetrahedron*, 1977, **33**, 3009–3039.
20 G. Kresze, J. Firl, H. Zimmer and U. Wollnik, *Tetrahedron*, 1964, **20**, 1605–1611; M. E. Burrage, R. C. Cookson, S. S. Gupte and I. D. R. Stevens, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1325–1334; M. Lotfi and R. M. G. Roberts, *Tetrahedron*, 1979, **35**, 2137–2141.
21 S. Fukuzumi and J. K. Kochi, *Tetrahedron*, 1982, **38**, 1035–1049; S. Fukuzumi, K. Ohkubo and T. Okamoto, *J. Am. Chem. Soc.*, 2002, **124**, 14147–14155.
22 S. Fukuzumi and T. Okamoto, *J. Am. Chem. Soc.*, 1993, **115**, 11600–11601.
23 S. Fukuzumi, T. Okamoto and K. Ohkubo, *J. Phys. Chem. A*, 2003, **107**, 5412–5418.
24 D. A. Evans and J. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 10162–10163.
25 I. Gerstenberger, M. Hansen, A. Mauvais, R. Wartchow and E. Winterfeldt, *Eur. J. Org. Chem.*, 1998, 643–650.
26 A. Toth, C. Floriani, M. Pasquali, A. Chiesi-Villa, A. Gaetani-Manfredotti and C. Guastini, *Inorg. Chem.*, 1985, **24**, 648–653.
27 A. Simion, C. Simion, T. Kanda, S. Nagashima, Y. Mitoma, T. Yamada, K. Mimura and M. Tashiro, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2071–2078.
28 G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *J. Am. Chem. Soc.*, 2004, **126**, 15195–15201.
29 M. R. Wasielewski, M. P. Niemczyk, D. G. Johnson, W. A. Svec and D. W. Minsek, *Tetrahedron*, 1989, **45**, 4785–4806.
30 C. F. Wilcox and F. D. Roberts, *J. Org. Chem.*, 1965, **30**, 1959–1963.
31 J. Rigaudy, J. Baranne-Lafont, A. Defoin and N. K. Cuong, *Tetrahedron*, 1978, **34**, 1473–1476.