Synthesis of 5-alkylidene-1,3-dioxane-4,6-diones, an easily accessible family of axially chiral alkenes: preparation in non-racemic form and platinum binding studies

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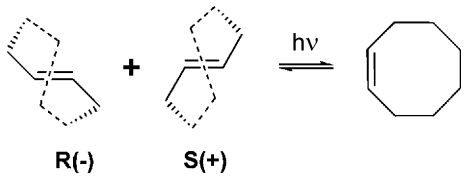
A general synthetic route to 5-alkylidene-1,3-dioxane-4,6-diones, which are a family of axially chiral alkenes, is described. Conformational issues are explored and the platinum-binding properties of these species are discussed. That these alkenes exist as stable enantiomers is established by their partial kinetic resolution upon reaction with cysteine.

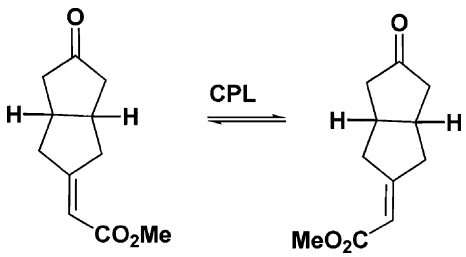
Introduction

Molecules in which one of the elements of chirality involves a carbon–carbon double bond are interesting in that interconversion of enantiomers may be achieved by alkene isomerisation. Alkenes may be isomerised through many processes including irradiation with the correct frequency of electromagnetic radiation (usually u. v.) to induce diradical formation and thus lower the barrier to rotation around the carbon–carbon bond, which upon relaxation and reformation of the alkene results in isomerisation. In many cases, instead of direct excitation of the alkene, irradiation excites another group, often a carbonyl, which then transfers excitation to the alkene, generating a species in which, again, the carbon–carbon bond is formally single, allowing rotation and thus isomerisation. In chiral molecules in which interconversion of enantiomers is achieved by double bond isomerisation, this provides a path for photochemical racemisation, or, in certain cases the use of circular polarised light allows photochemical deracemisation. Circularly polarised light is intrinsically chiral, and as such the interaction with chiral molecules is diastereoisomeric, with each enantiomeric form of circularly polarised light being absorbed to a different extent by each enantiomer of the sample, with the difference being referred to as the anisotropy factor $\Delta\varepsilon$. Thus, when irradiation of a racemic sample of substrate is carried out with a single enantiomer of circularly polarised light, the enantiomer of sample which has the highest extinction coefficient is racemised faster than its enantiomer, which leads to an excess of the lower absorbing enantiomer. As the $\Delta\varepsilon$ values for simple molecules are small, typically $\leq$1% of the absolute extinction coefficients, the enantiomeric excesses obtained in such experiments are usually very small, but they are important examples of *absolute asymmetric induction*, that is the induction of enantiomeric excesses by reactions of racemic mixtures or achiral molecules, using only the chirality of physical forces rather than chiral chemicals, and as such have implications for the origins of biological homochirality, as it has been observed that cosmic background radiation is significantly circularly polarised at many wavelengths, and thus primordial Earth experienced non-racemic irradiation prior to the development of biological chirality.[1]

The classic example of a molecule which is chiral by virtue of a double bond configuration is *trans*-cyclooctene, and this material has been shown to be capable of deracemisation by intense irradiation with circularly polarised u. v. (Scheme 1).[2] This is an unusual example, however, in that irradiation can cause not only interconversion of enantiomers, but also produces the (achiral) *cis*-isomer. More recently alkylidene cyclohexanes have emerged as one of the more interesting families of chiral molecules which can be racemised by photochemical isomerisation of an alkene,[3] and indeed, these species have also been deracemised by irradiation with circularly polarised light (Scheme 2). Amongst other prominent molecules which have been photochemically deracemised with circularly polarised light are the crowded helical tetraaryls such as the 9,9′-oxo and thioxanthenylidenes which have been studied by Feringa *et al.* (Scheme 3).[4] The aim of the present work was to develop routes which would allow rapid access to a large and varied series of molecules which would both be capable of photochemical racemisation (and potentially deracemisation) *via* double bond isomerisation, and be crystalline, in order to allow any enantiomeric excess obtained to be enhanced by



Scheme 1



Scheme 2

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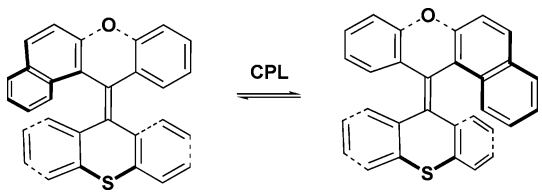


Scheme 3

in situ crystallisation. A survey of the literature was made to find the simplest routes to such species, and to find which families were typically crystalline. Substituted cyclooctenes and methylene cyclohexanes both suffer from low melting points (many are liquid at ambient temperature), and the bixanthenylidenes, while typically high melting solids, are not accessible by the simple one or two step reactions which are useful if a large series of compounds is sought, therefore attention turned to developing new families of axially chiral alkenes.

Results and discussion

A consideration of the structural features required suggested that a potentially viable route to double-bond chiral compounds amenable to rapid analogue collection was the condensation of aldehydes with an activated methylene group in a prochiral ring. The direct analogues of the alkylidene cyclohexanes accessible by this route would be the condensation products of simple analogues of dimedone, which are available *via* condensations of Michael acceptors with malonate esters, however a survey of the literature in this area suggested that the precursors for the condensations (5-monosubstituted cyclohexane-1,3-diones) were best approached by routes which varied depending upon the nature of the substituent, and in many cases would require 2 or more step syntheses of the Michael acceptors, which while trivial moved away from the desired rapid access to a range of analogues. The dioxoanalogue of dimedone, Meldrum's acid, however, seemed a good candidate for studies as condensation of Meldrum's acid with aldehydes is known and high yielding and the substitution of acetone for non-symmetrical ketones in the synthesis of Meldrum's acid analogues should allow for chirality. As two of the three components in the synthesis are carbonyl compounds, a one-pot synthesis is conceivable in which malonic acid is cyclised, then condensed with the same carbonyl compound. In order to validate this approach, therefore, and to demonstrate their chirality, a study has been undertaken of 5-alkylidene-1,3-dioxane-4,6-diones.

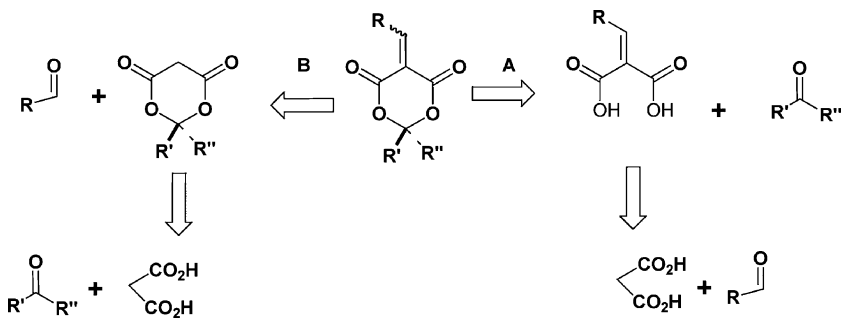
5-Alkylidene-1,3-dioxane-4,6-diones

There are a small range of examples of non-symmetrical examples of 5-alkylidene-1,3-dioxane-4,6-diones known[5] (there are many examples of the symmetrical materials derived from Meldrum's acid), but there is no general method for their synthesis and a literature search found no mention of their chirality. Thus it was decided that a small range of alkylidene substituted non-symmetrical analogues of Meldrum's acid should be synthesised in order to assess the ease of synthesis, stability and crystallinity of these species and to allow their chirality to be confirmed.

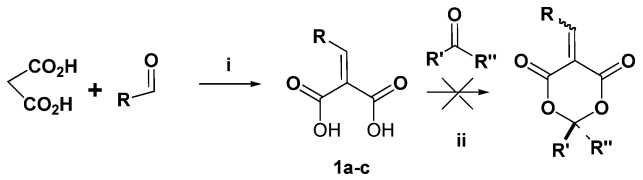
There are two obvious routes to such materials: A) the synthesis of alkylidene malonic acid derivatives, followed by cyclisation to the non-symmetrical acetals; and B) the synthesis first of cyclic malonate acetals, followed by their condensation with carbonyl compounds (Scheme 4).

The first of these routes was attempted with condensation of malonic acid with a variety of aromatic aldehydes giving the alkylidene malonic acids **1a–c** in acceptable to good yields (given the availability of the starting materials no optimisation was considered). These alkylidene malonic acids proved, however, to be reluctant to condense with aldehydes or ketones to give the desired products. A variety of reaction conditions, reagents and catalysts were screened in an attempt to obtain cyclisation, concentrating on Brønsted acids (TsOH, H_2SO_4, TFA) and standard dehydrating reagents/conditions (Dean–Stark or acetic anhydride), but in all cases the major products were either starting materials or decomposition products, with no evidence of successful cyclisation (we were able to compare crude spectra with the spectra of the desired materials obtained later to confirm this conclusion) (Scheme 5). It is possible that the lack of conformational freedom in the alkylidene malonic acids is responsible for this reluctance to cyclise. It is assumed that the ring-closing step would involve generation of an oxonium ion by acid catalysed dehydration of an intermediate hemiacetal, followed by nucleophilic attack at the sp^2 carbon. Although by the Baldwin-style analysis this is a 6-*endo*-trig cyclisation which is formally favoured, there may be insufficient conformational flexibility in the highly unsaturated backbone which would form the ring to allow the carboxylate to approach the sp^2 carbon at the Burgi–Dunitz angle.

In the light of the failure to obtain the desired species from this approach, attention turned to the initial condensation to the unsymmetrical Meldrum's acid derivatives, followed by condensation to the alkylidene species, which should suffer from no untoward stereoelectronic effects. The condensation of Meldrum's acid itself with aldehydes and ketones is well known and a huge range of



Scheme 4



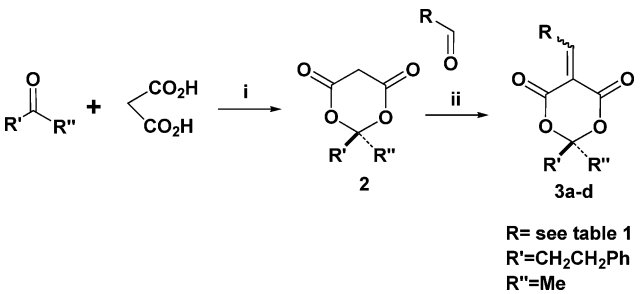
Scheme 5 (i) NH_4OAc, EtOH; (ii) various conditions.

such derivatives is known, however substituting the *gem*-dimethyl group of Meldrum's acid with a non-symmetrical substitution pattern was necessary for chiral products. The condensation of malonic acid with aromatic aldehydes has been reported to give the cyclic acetals[6] however in the present study the reaction of equimolar ratios of aromatic aldehydes with malonic acid never gave this desired product cleanly, although a double condensation did give useful materials (see below). The major product from the reactions of aromatic aldehydes with malonic acid under the high temperature conditions recommended for the cycloacetalisation, in fact was in most cases the relevant cinnamic acid derivative. These materials are formed from the condensation used previously to give the alkylidene malonic acids, followed by thermal decarboxylation. In order to retard the Knoevenagel condensation to the alkylidene species, attention turned to the use of ketones. In order to maintain crystallinity it was felt that an aromatic substituent was desirable, and a methylene group was also likely to be useful in order that diastereotopicity could be observed in the ^{1}H NMR, which could confirm the chirality of the products. The attempted condensation of malonic acid with acetophenone following the literature method which had proven to be the highest yielding route to Meldrum's acid[7] gave none of the desired product (from NMR and mass spectroscopy of the crude reaction mixtures). The literature[8] suggested that the condensation of malonic acid with aromatic ketones gives not the 1,3-dioxane-4,6-diones but instead tends to condense *via* nucleophilic attack at the ketone, often followed by dehydration and decarboxylation to the unsaturated acid. Therefore, benzyl acetone was selected as an aliphatic ketone which has both an aromatic substituent and methylene groups, while the carbonyl group is more similar to acetone than the carbonyl of an aromatic ketone. (A range of alkylidene malonates derived from benzyl acetone have been prepared on solid supports as intermediates in solid-phase synthesis[9] however they were not liberated from the support in this form and no comment was made on chirality.) The condensation of benzyl acetone with malonic acid was investigated under a variety of conditions, with the product mixtures varying greatly with temperature, pH and reagents. Eventually it was found that a variation of a literature[7] procedure for Meldrum's acid provided the most reliable route to 2-methyl-2-(2-phenylethyl)-1,3-dioxane-4,5-dione **2**, whereby excess malonic acid was reacted with benzyl acetone in the presence of acetic anhydride and sulfuric acid. The excess malonic acid is easily removed by filtration of a solution of the crude reaction product in dichloromethane, and after evaporation the cyclic acetal slowly crystallises from the by-products in good yield. Interestingly this material is very susceptible to hydrolysis and must be stored under anhydrous conditions, in stark contrast to Meldrum's acid itself, which while having some hydrolytic instability is much more robust than the benzyl derivative considered here.

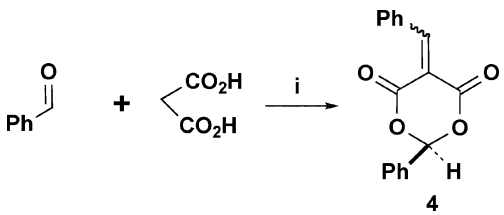
Table 1 Yields of 5-alkylidene-1,3-dioxane-4,6-diones

	R	R′	R″	Yield (%)	Mpt/°C
3a	Ph	CH_2CH_2Ph	H	43	107–108
3b	4-NO_2–C_6H_4	CH_2CH_2Ph	H	37	146–149
3c	2-NO_2–C_6H_4	CH_2CH_2Ph	H	66	89–91
3d	4-MeO–C_6H_4	CH_2CH_2Ph	H	66	91–93
3e	$CH(CH_3)_2$	CH_2CH_2Ph	H	33	79–81
4	Ph	Ph	H	21	146–148

With a robust route to a crystalline non-symmetrical Meldrum's acid derivative, **2** the Knoevenagel condensations of this material with a variety of ketones were studied. These reactions proceeded smoothly with benzaldehyde, a variety of substituted benzaldehydes (2-nitro, 4-nitro, 4-methoxy) and with isobutyraldehyde. All these products were highly crystalline and while the yields were generally better with the substituted aromatic aldehydes, even with benzaldehyde and isobutyraldehyde yields of around 50% were obtained after crystallisation of the products from the reaction mixtures (Scheme 6; Table 1). Given the few steps involved in the preparation of these species no attempt was made to optimise the yields, or even to recover more of the product than was simply delivered by crystallisation. To demonstrate that this approach could provide a one-pot route to alkylidene malonates, malonic acid and an excess of benzaldehyde were reacted under the conditions used for the synthesis of **1**, and the derived alkylidene malonate was recovered by crystallisation, albeit in a low yield (Scheme 7; Table 1). Although all of the ketone-derived species were synthesised from benzyl acetone, as these synthetic approaches work equally well for the chiral materials derived from benzyl acetone and the acetone derivatives, it seems likely that this chemistry would be applicable to derivatives of a wide range of aliphatic ketones, giving a vast scope to the species available.



Scheme 6 (i) H_2SO_4, Ac_2O; (ii) NH_4OAc.



Scheme 7 (i) H_2SO_4, Ac_2O

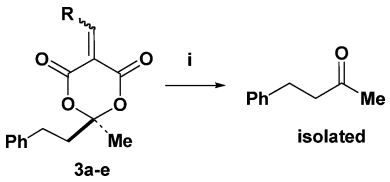
These species proved to be considerably less susceptible to hydrolysis than the parent compound, in fact surviving prolonged exposure to water in a 2-phase system (see below). This hydrolytic stability is, presumably, the reversal of the Burgi–Dunitz angle

argument which precluded the formation of these species by cyclocondensation. In the same way that although malonic acid easily cyclo-condenses with ketones, alkylidene malonic acids seem to have insufficient conformational flexibility to allow the ring closure step to take place. It is likely that, while the methylene species is susceptible to hydrolysis, the alkylidene analogues are too rigid to allow an oxygen lone pair to align *anti* periplanar to the carbon–oxygen bond (*i.e. syn* periplanar with the σ* orbital) which must be broken in hydrolysis.

With a range of 5-alkylidene-1,3-dioxane-4,6-diones in hand which had been designed to show chirality, their ^{1}H NMRs were examined for evidence of diastereotopicity in the signals from the methylene groups. Rather than the simple pairs of triplets predicted by first-order coupling for the methylene groups of the 2-phenylethyl substituent, a pair of complex multiplets were observed. However, this could not be attributed to molecular chirality as the same phenomenon is observed in these signals in the precursor **2** which formally has a plane of symmetry and is thus necessarily achiral. The non-first order nature of this region of the spectrum was unexpected, and could reflect a preferred twisted conformation of the six-membered ring with a *trans* arrangement of carbonyls in which the plane of symmetry associated with the *cis* form is lost (Fig. 1). In the solid state at least, however, many analogues, and indeed Meldrum's acid itself exist in the *cis* form[10] and thus the complex NMR is more likely to be the result of anisogamy, *i.e.* magnetic nonequivalence due to different coupling constants to the vicinal proton barriers in the chain.

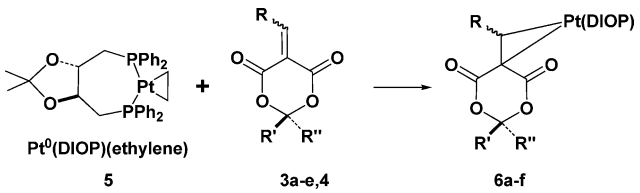
Fig. 1 Conformers of 1,3-dioxane-1,6-diones.

As this complex system is observed even in the achiral unsubstituted species, the use of NMR measurements to characterise molecular chirality was inappropriate. Although the molecules must necessarily exist as a pair of enantiomers, it was thought possible that they may be unstable to racemisation through an addition–elimination mechanism. The extremely polarised nature of the alkene, due to its conjugation with two carbonyls could lower the barrier to rotation, or a mechanism for racemisation could operate whereby polar solvents, or lone pairs of other molecules, act as nucleophiles in a Michael-addition–retro-Michael sequence, allowing racemisation. Given the possibility therefore that these species may not exist as stable enantiomers it was essential to investigate their stability, and as NMR was unsuitable, other methods were examined. None of the chiral HPLC columns tested (Chirocel OD, OJ) gave any separation between enantiomers, and it became apparent that GC was leading to decomposition. Mass spectra recorded at temperatures similar to the GC conditions showed that a fragmentation had occurred at high temperature (this was also observed in refluxing xylene) whereby the parent ketone (benzyl acetone) is eliminated from the ring. In the mass spectrum cationic fragments are observed correlating to the mass of the remaining portion of the molecule. In experiments, however, these fragments are lost as a mixture of decomposition products, and only benzyl acetone is observed as a discrete product of the fragmentation (Scheme 8).



Scheme 8 (i) Xylene reflux.

As chiral stationary phase chromatography seemed unsuitable for establishing the stability of the enantiomers, attention turned to NMR chiral shift reagents. As it was expected that the esters of the alkylidene malonates would have a reasonable negative character and thus hydrogen-bonding ability, attempts were made to resolve the enantiomers with the use of the Eu-based shift reagent Eu(HFC)$_3$. Although at certain ratios of shift reagent to substrate there was evidence that single peaks were becoming split, it was impossible to achieve separation between peaks which would allow a determination of the kinetic parameters for racemisation, and thus establish the stability of the new chiral system. As these chiral shift reagents seemed to be unsuitable for the molecules in question, attention turned to a different kind of chiral metal complex which has been used in e. e. determinations of unsaturated systems. Parker *et al.* showed[11] that it is possible to use the phosphorus NMR signals of homochiral platinum DIOP complexes to determine the e. e. of coordinated alkenes. Ethylene(DIOP)Pt^0 reacts with a wide range of alkenes with displacement of ethylene to give the alkene Pt complex. In the case of chiral alkenes, the resultant complexes exist as mixtures of diastereoisomers, which are seen as inequivalent in the ^{31}P NMR allowing the determination of the e. e. of the alkenes. The ^{31}P spectra are often complex, as unsymmetrically substituted alkenes lead to the ^{31}P nuclei in each molecule being inequivalent and coupling to each other, in addition to the Pt–P coupling in that fraction of the sample containing the spin-active Pt nucleus, thus giving 12 signals per diastereoisomer. Fortunately the large spectral range of ^{31}P NMR usually leads to well separated signals allowing determination of e. e. In the case of 5-alkylidene-1,3-dioxane-4,6-diones, the case is further complicated by the existence of two inequivalent faces of the alkene, doubling the number of isomers which can result from the complexation (Scheme 9).



Scheme 9

The reaction of 5-(4-nitrobenzylidene)-2-methyl-2-(phenylethyl)-1,3-dioxane-4,6-dione **3b** with Pt^0 (DIOP)ethylene in d_6-benzene gave a spectrum with 32 peaks, 16 centred around 7.5 ppm and 16 symmetrically separated around the central peaks at −8 ppm and 23 ppm, assigned to the ^{195}Pt satellites (Fig. 2). By a consideration of the ratios of signal intensities, a certain degree of assignment of the signals was possible. As the sample was racemic,

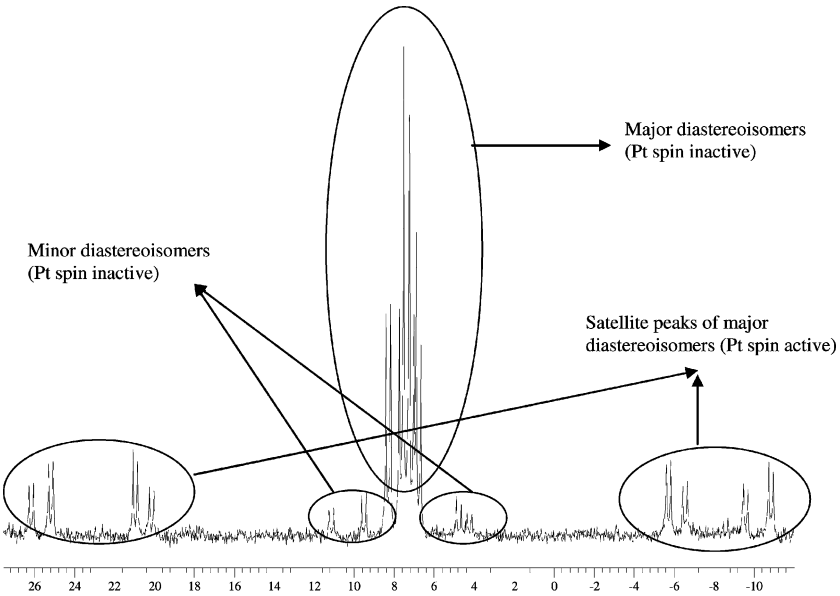


Fig. 2 ^{31}P NMR spectrum of **3b** coordinated to Pt–DIOP.

and it is common for little kinetic resolution to be observed in these complexations, it was expected that the ratio of diastereoisomers resulting from the reaction of the enantiomerically pure DIOP complex with the racemic alkene would be close to unity. However, it was expected that there could be a large degree of selectivity of which face of the alkene is complexed, as one face will experience more steric strain as a result of the conformation of the six-membered ring being distorted by the non-symmetrical substitution in the 5-position. The typical configuration of these rings is largely planar with the 5-carbon out of the plane of the ring in an envelope-type conformation.[12] One of the substituents is in a pseudo-equatorial position, far from the ring and with no role in blocking the coordination of the alkene, while the other is in a pseudoaxial position which will experience diaxial type interactions with the lone-pairs of the 1,3 oxygens, and will interact with incoming complexes to retard coordination of that face of the alkene. It is reasonable to suppose that the favoured conformation will have the larger group in the pseudoequatorial position, and thus it is likely to be the face of the alkene which is *syn* to the smaller substituent (in this case the methyl group) which is more hindered, and therefore coordination of Pt occurs predominantly on the same face as the phenethyl group. As each of the isomers thus formed should give two doublets, correlated pairs of peaks were easily assigned by their mutual J_{PP}. The remaining sets of peaks were assigned as pairs of diastereoisomers on the basis of intensities, with the isomers resulting from facial differentiation in complexation being in an approximate 10 : 1 ratio, and with these sets, the pairs of diastereoisomers reflecting the racemic nature of the sample apparently being in a 10 : 11 ratio. The assumption behind these assignations is that the relaxation times of the isomers will be similar and thus the ^{31}P line intensities can be taken as almost quantitative. In this context it would appear that there has been some slight kinetic resolution in the complex formation to give the 10 : 11 ratio, however this could be calculated for in e. e. determination on a non-racemic sample. A tentative assignment of individual ^{31}P nuclei in each complex can be made from the magnitude of the value of $J_{Pt,P}$ in each case. The magnitude of $J_{M,P}$ in complexes is highly dependent on the *trans* influence, with π acidic ligands leading to low values.[13] This effect is particularly pronounced in square planar complexes and given that one of the carbon atoms in the complex has two ester groups, it is likely to be highly π acidic and thus gives very low values for $J_{P,P}$. These assignments are summarised in Table 2.

Table 2 ^{31}P NMR data for the main facial isomer (minor facial isomer sidebands are too weak to accurately measure Pt–P data)

Diastereoisomer	δp/ppm	δp′/ppm	$J_{P,P'}$/Hz	$J_{Pt,P}$/Hz	$J_{Pt,P'}$/Hz
Major	7.12	7.62	27	4326	3228
Minor	8.28	6.77	27	4326	3231

P and P′ have been determined from the magnitude of J_{Pt-P} as the ^{31}P nuclei *trans* to the benzylidene carbon and C5 of the ring respectively. The low value of J_{PP} (27 Hz compared to 59 to 72 Hz in similar complexes) is again considered more likely to be a result of the extremely electron deficient system lowering Fermi contact through the P–Pt–P system, rather than the variation in bond angles which usually explains variations in P–M–P coupling. In this case the fact that in comparison with literature examples[12] the P–M–P system is unaltered, and only the *trans* ligand varies between our systems and the literature examples militates against this line of reasoning. Other spectra were less clearly resolved than this example, with apparently only one isomer being observed in the case of **3d** and **4**. These complexes were of very low solubility and it is more likely that preferential crystallisation of one isomer led to this observation than kinetic resolution in complex formation. Conformational isomerism (hindered rotation around the C–C bond between the alkene and the 2-nitrophenyl group) is assumed to lead to the doubling of the peaks for **3c**.

In order to justify our conclusion that the phenethyl group would take up the pseudoequatorial position, thus rendering the face of the double bond *syn* to the methyl group more

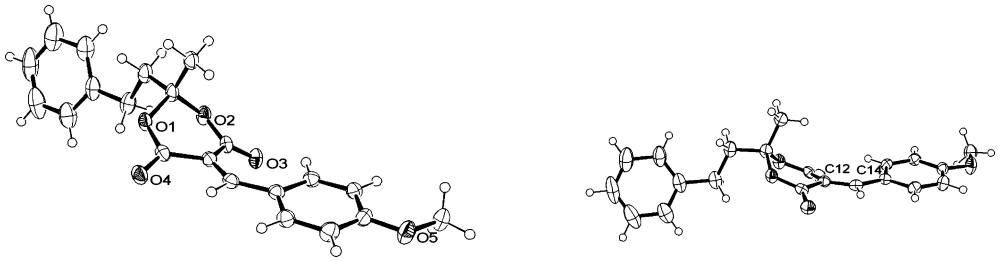
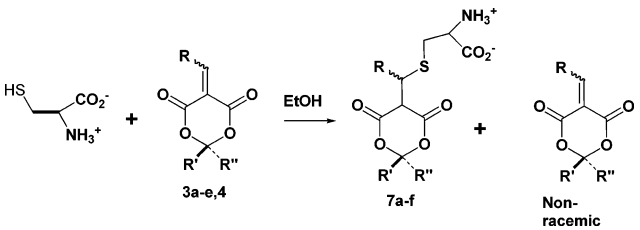


Fig. 3 ORTEP[14] views (50%) of **3d** showing molecular structure, and how the methyl group sterically hinders the C12=C14 double bond.

hindered, the X-ray crystal structure of one of the compounds, **2d** the methoxyphenyl substituted example, was determined. The structure (Fig. 3) clearly shows the carbonyls in a *cis* conformation, with the envelope formed by the C-5 having the phenethyl group in a pseudoequatorial position and thus the methyl group causes severe hindrance of the *syn* face of the double bond.

Although there was now crystallographic evidence that the alkylidene malonate esters adopted necessarily chiral conformations, and the Pt^0 complexes appeared to be capable of allowing differentiation of enantiomers by the formation of diastereoisomers in the ^{31}P NMR, this is not evidence of the existence of stable enantiomers which do not easily interconvert, which would render the new family of chiral species useless. In order to investigate the stability of the enantiomers towards interconversion, a partial kinetic resolution was attempted. As the alkene of the alkylidene malonates is conjugated with two ester groups, it seemed likely to be reactive towards the addition of nucleophiles. A series of chiral nuclophiles was screened for reaction with alkylidene malonates. The only one which gave an irreversible reaction appeared to be L-cysteine. The adducts formed upon reaction of L-cysteine with a series of alkylidene malonates were insoluble in all but the most polar of organic solvents and were hydroscopic and unstable, however they were shown to be the required Michael addition products in the more easily handleable cases by NMR and mass spectrometry, although full characterisation was not achieved. A series of attempts was made to achieve kinetic resolution of the alkylidene malonates by simply reacting half an equivalent of L-cysteine in ethanol with the alkylidene malonates, then purifying the unreacted alkylidene malonate using the extreme insolubility of these compounds by evaporation of the reaction mixture followed by dissolution in chlorinated solvents and filtering off both the adducts, and any unreacted amino acid. The results of these attempts were mixed, with in some cases optical activity being observed in the alkylidene malonates, and in other cases racemic material being recovered. Attempts to standardise the procedures failed to give reproducible results, and this was assigned to the low solubility of both the reactants in ethanol, which leads to irreproducibility in the ratios of each reactant in solution due to difficult-to-control variables such as rate of stirring and particle size. Varying the solvent from alcohols gave no reaction at all, presumably as in non-polar organics the amino acid is completely insoluble. In highly polar organics the nucleophilicity of the L-cysteine may be moderated (or retro-Michael promoted) and when the reaction was attempted in a two phase system with the alkylidene malonate in an organic phase, rapidly stirred with a solution of cysteine, very little or no reaction was observed and no optical activity was observed in the unreacted alkylidene malonates. Although these results were disappointing in that reproducible kinetic resolution was not achieved (thus no data for optical rotations are given in the experimental section), samples of optically enriched alkylidene malonates were in fact obtained for all of the species examined (Scheme 10).



Scheme 10

The optical activity could be incontrovertibly assigned to the alkylidene malonates as, along with them showing perfect spectral purity, in all cases the sign of the optical rotation observed was negative, while both L-cysteine and the adducts have positive optical rotations. The stability of these species towards racemisation was established by following the optical activity over long periods of time, at elevated temperatures and in a variety of solvents. Along with the possibility that the high degree of polarisation of the alkene could render its natural barrier to rotation (racemisation) low, the possibility exists that polar solvents may catalyse the racemisation. It was possible to demonstrate that the natural barrier to rotation is high enough for these to be considered as true atropisomers, fulfilling the Oki criteria,[15] and going much further in that no loss of optical rotation was observed over many days in solution at ambient temperature. In order to demonstrate that polar solvents do not racemise these compounds by a Michael-addition–retro-Michael sequence, they were heated in acetone and ethanol with no loss of optical rotation being observed. Attempts to determine the e. e.s of the optically enriched samples using the Pt^0 method failed, with apparently racemic spectra being recorded, presumably an indication of a very low degree of enantiomeric excess resulting from poor kinetic resolution.

Conclusion

It has been demonstrated that 5-alkylidene-1,3-dioxane-4,6-diones are an easily accessible family of axially chiral alkenes which show barriers to racemisation which allow them to be considered as stable enantiomers.

Experimental

General experimental

All starting materials and reagents were purchased from commercial suppliers and used as supplied unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 MHz at 400 MHz (proton) and 160 MHz (carbon), or an APX 250 at 250 MHz and 100 MHz respectively. ^{31}P NMR were recorded on a Jeol at 121 MHz. IR spectra were recorded on a Perkin Elmer 1600 FT IR as thin films or nujol mulls; mass spectra were recorded on a VG Fisons Platform II or at the EPSRC national mass spectrometry service in Swansea (HRMS). Elemental analyses were performed by Warwick Analytical Services (University of Warwick).

Crystallographic data for **3d**: $C_{21}H_{20}O_5$, crystal system monoclinic; space group P_{21}/a; $a = 9.6549(2)$, $b = 12.9703(3)$, $c = 14.7696(4)$ Å, $\alpha = 90$, $\beta = 108.6430(10)$, $\gamma = 90$; $Z = 4$; $T = 150(2)$ K; $\mu = 0.095$ mm^{-1}; $\lambda = 0.71069$ Å (MoKα); $F(000)$ 744; $3.14 < \theta < 27.48$; 20365 reflections, 3980 unique [R(int) = 0.0826]; $R1 = 0.0524$, $wR2 = 0.1052$ [$I > 2\sigma(I)$]; $R1 = 0.0899$, $wR2 = 0.1171$ (all data).†

3-(4-Methoxyphenyl)-2-carboxy-2-propenoic acid (1a). The synthesis of 3-(4-methoxyphenyl)-2-carboxy-2-propenoic acid (**1**) was performed following a procedure described in the literature.[16] A mixture of *p*-anisaldehyde (9.0 mL, 55 mmol), malonic acid (11.44 g, 110 mmol) and ammonium acetate (0.04 g, 0.52 mmol) in ethanol (25 mL) was stirred under nitrogen at room temperature for 7 days. The solvent was then evaporated until dryness, the solid residue was dissolved in ethyl acetate, extracted then with sodium hydroxide, precipitated with hydrochloric acid and finally a solid was collected by filtration to give 5.46 g (44.7%) of **1a**.[17] δH (400 MHz, CD_3OD) 3.75 (s, 3H, CH_3O), 6.85 (dd, 2H, ^3J = 7.1 Hz, ^4J = 1.7 Hz, Ar-H2,6), 7.45 (dd, 2H, ^3J = 7.1 Hz, ^4J = 1.7 Hz, Ar-H3,5), 7.55 (s, 1H, CH=C). Mp 207–209 °C (lit.[17] 204–205 °C).

3-(4-Nitrophenyl)-2-carboxy-2-propenoic acid (1b). The synthesis of 3-(4-nitrophenyl)-2-carboxy-2-propenoic (**2**) acid was performed following a procedure similar to the one described in the literature.[17] A mixture of *p*-nitrobenzaldehyde (2.02 g, 13.37 mmol), malonic acid (2.87 g, 27.57 mmol) and ammonium acetate (0.01 g, 0.13 mmol) in ethanol (25 mL) was stirred under nitrogen at room temperature for 14 days. The solvent was then evaporated until dryness, and the solid residue was dissolved in ethyl acetate. The product was extracted with sodium hydroxide, precipitated with hydrochloric acid and collected by filtration to give 1.35 g (42.6%) of **1b**.[17] δH (400 MHz, CD_3OD) 7.65 (s, 1H, CH=C), 7.70 (d, 2H, ^3J = 8.7 Hz, Ar-H2,6), 8.2 (d, 2H, ^3J = 8.8 Hz, Ar-H3,5). Mp 242–244 °C.

3-(2-Nitrophenyl)-2-carboxy-2-propenoic acid (1c). The synthesis of 3-(2-nitrophenyl)-2-carboxy-2-propenoic acid (**3**) was performed following a procedure similar to that described in the literature.[17] A mixture of *o*-nitrobenzaldehyde (14.70 g, 128 mmol), malonic acid (26.62 g, 256 mmol) and ammonium acetate (0.10 g, 1.3 mmol) in ethanol (40 mL) was stirred under nitrogen at room temperature for 5 days. The solvent was evaporated until dryness and the solid residue was dissolved in ethyl acetate. The product was extracted then with sodium hydroxide, precipitated with hydrochloric acid and collected by filtration to give 1.35 g (42.6%) of **1c**.[17] δH (400 MHz, CD_3OD) 7.80 (d, 1H, ^3J = 8.0 Hz, ArH-6), 7.90 (dd, 1H, ^3J = 8.0 Hz, ^3J = 7.0 Hz, ArH-5), 8.00 (dd, 1H, ^3J = 8.0 Hz, ^3J = 7.0 Hz, Ar H-4), 8.40 (s, 1H, CH=C), 8.50 (d, 1H, ^3J = 8.0 Hz, ArH-3). Mp 151–154 °C.

2-Methyl-2-(2-phenylethyl)-1,3-dioxane-4,6-dione (2). The synthesis of 2-methyl-2-(2-phenylethyl)-1,3-dioxane-4,6-dione (**2**) was performed following a similar procedure to that described in the literature.[7] A mixture of 4-phenyl-2-butanone (45 mL, 300 mmol), malonic acid (20.8 g, 200 mmol) and sulfuric acid (0.6 mL, 12 mmol) was added to a Schlenk, under nitrogen. It was stirred for 15 min at room temperature and acetic anhydride (24 mL, 250 mmol) was then added very slowly. The mixture was stirred at room temperature for 18 hours. The solvent was evaporated until dryness, and the remaining solid was dissolved in dichloromethane, filtered, and recrystallised from ethyl acetate and petrol to give 5.39 g (11.5%) of **2**. δH (400 MHz, $CDCl_3$) 1.75 (s, 3H, CH_3), 2.29 (m, 2H, CH_2–CH_2–Ph), 2.86 (m, 2H, CH_2–CH_2–Ph), 3.60 (s, 2H, CH_2(CO)$_2$), 7.10 (m, 3H, PhH-3,4,5), 7.25 (m, 2H, Ph-2,6). δC (101 MHz, $CDCl_3$): δ 26.53, 29.46, 36.64, 42.59, 107.64, 126.91, 128.69, 129.13, 140.12, 163.27. ν_{max}: 1781, 1744 cm^{-1}. Mp 85–87 °C. $C_{13}H_{14}O_4$ requires C 66.66 H 6.02 found C 65.99 H 6.04%.

5-Benzylidene-2-methyl-2-phenylethyl-1,3-dioxane-4,6-dione (3a). A mixture of **4** (0.47 g, 2 mmol), benzaldehyde (0.24 mL, 2.4 mmol) and ammonium acetate (1.5 mg, 0.002 mmol) in ethanol (10 mL) was stirred at room temperature for 18 h. A white solid was collected by filtration and washed with cold ethanol, to afford 0.276 g (43%) of **3a**. δH (400 MHz, $CDCl_3$) 1.75 (s, 3H, CH_3), 2.23 (m, 2H, CH_2–CH_2–Ph), 2.82 (m, 2H, CH_2–CH_2–Ph), 7.15 (m, 3H, CH_2PhH-3,4,5), 7.23 (app. t, 2H, ^3J = 6.5 Hz), 7.42 (m, 2H, CHPhH-3,5), 7.51 (app. t, 1H, ^3J = 7.0 Hz, CHPhH-4), 7.99 (app. d, 2H, ^3J = 7.72 Hz, CHPhH-2,6), 8.39 (s, 1H, CH=C). δC (101 MHz, $CDCl_3$): δ 26.68, 29.61, 42.57, 105.97, 115.06, 126.78, 128.75, 129.08, 129.18, 132.06, 134.13, 134.22, 140.52, 158.83, 160.13, 163.72. Mp 107 °C. m/z (EI/CI MS) 173.9, 91.1, 43.2. $C_{20}H_{18}O_4$ requires C 74.52, H 5.63, N 0.00; found C 74.31, H 5.69, N 0.07%.

5-(4-Nitrobenzylidene)-2-methyl-2-(phenylethyl)-1,3-dioxane-4,6-dione (3b). A mixture of *p*-nitrobenzaldehyde (0.75 g, 5 mmol), **2** (1 g, 4.3 mmol) and ammonium acetate (0.003 g, 0.004 mmol) in ethanol (10 mL) was stirred under nitrogen at room temperature for 3 hours. A yellow solid was then collected by filtration and recrystallised from ethanol, to afford 0.59 g (37%) of **3b**. δH (400 MHz, $CDCl_3$) 1.75 (s, 3H, CH_3), 2.20 (m, 2H, CH_2–CH_2–Ph), 2.75 (m, 2H, CH_2–CH_2–Ph), 7.15 (m, 3H, PhH-3,4,5), 7.20 (m, 2H, Ph-H2,6), 8.00 (d, 2H, ^3J = 7.0 Hz, ArH-2,6), 8.25 (dd, 2H, ^3J = 7.0 Hz, ^4J = 1.8 Hz, Ar-H3,5), 8.40 (s, 1H, CH=C). δC (101 MHz, $CDCl_3$) 26.97, 29.59, 42.66, 106.69, 118.78, 123.98, 126.91, 128.72, 129.14, 133.52, 137.80, 140.21, 149.92, 155.13,

† CCDC reference number 611771. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608785j

159.29, 162.55. Mp 146–149 °C. ν_{max}: 1729, 1529, 1350 cm^{-1}. $C_{20}H_{17}NO_6$ requires C 65.39, H 4.66, N 3.81; found C 65.22, H 4.64, H 3.78%. *m/z* (EI) 367.

5-(2-Nitrobenzylidene)-2-methyl-2-(phenylethyl)-1,3-dioxane-4,6-dione (3c). A mixture of *o*-nitrobenzaldehyde (0.76 g, 5 mmol), **2** (1.0 g, 4.3 mmol) and ammonium acetate (0.003 g, 0.004 mmol) in ethanol (6 mL) was stirred under nitrogen at room temperature for 18 hours. A yellow solid was then collected by filtration and recrystallised from ethanol, to give 1.03 g (66%) of **3c**. δH (400 MHz, $CDCl_3$) 1.75 (s, 3H, CH_3), 2.22 (m, 2H, CH_2–CH_2–Ph), 2.83 (m, 2H, CH_2–CH_2–Ph), 7.15 (m, 3H, PhH-3,4,5), 7.24 (dd, 2H, ^3J = 7.1 Hz, ^4J = 1.8 Hz, PhH-2,6), 7.42 (d, 1H, ^3J = 7.7 Hz, ArH-6), 7.60 (m, 1H, ArH-5), 7.68 (m, 1H, ArH-4), 8.24 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.1 Hz), 8.76 (s, 1H, CH=C). δC (101 MHz, $CDCl_3$): δ 27.02, 29.57, 42.63, 106.83, 118.04, 125.28, 126.82, 128.74, 129.08, 130.27, 130.67, 131.34, 134.25, 140.35, 146.69, 156.46, 159.36, 161.919. Mp 89–91 °C. ν_{max} 1777, 1743, 1531, 1336 cm^{-1}. $C_{20}H_{17}NO_6$ requires C 65.39, H 4.66, N 3.81; found C 65.12, H 4.64, N 3.72%. *m/z* (APCI) 368 (M + 1), 266 (M − 102), 220 (M − 148).

5-(4-Methoxybenzylidene)-2-methyl-2-(phenylethyl)-1,3-dioxane-4,6-dione (3d). A mixture of *p*-anisaldehyde (1.12 mL, 10 mmol), **2** (2 g, 8.6 mmol) and ammonium acetate (0.006 g, 0.008 mmol) in ethanol (10 mL) was stirred under nitrogen at room temperature for 24 h. A bright yellow solid was then collected by filtration and recrystallised from ethanol, to give 2.00 g (66%) of **3d**. δH (400 MHz, $CDCl_3$) 1.68 (s, 3H, CH_3), 2.22 (m, 2H, CH_2–CH_2–Ph), 2.80 (m, 2H, CH_2–CH_2–Ph), 3.83 (s, 3H, OCH_3), 6.93 (dd, 2H, ^3J = 7.1 Hz, ^4J = 1.8 Hz, ArH-3,5), 7.18 (m, 3H, PhH-3,4,5), 7.22 (m, 2H, PhH-2,6), 8.17 (dd, 2H, ^3J = 7.1 Hz, ^4J = 1.8 Hz, ArH-2,6), 8.35 (s, 1H, CH=C). δC (101 MHz, $CDCl_3$) 26.52, 29.62, 42.51, 56.13, 105.54, 111.04, 114.81, 125.13, 126.70, 128.76, 129.04, 138.20, 140.69, 158.61, 160.88, 164.53, 165.14. Mp 91–93 °C. ν_{max}: 1722 cm^{-1}. $C_{21}H_{20}O_5$ requires C 71.58, H 5.72; found C 71.41, H 5.61%. *m/z* (EI) 352.2.

5-Isobutylidene-2-methyl-2-(2-phenylethyl)-1,3-dioxane-4,6-dione (3e). A mixture of isobutanone (0.91 mL, 10 mmol), **2** (0.94 g, 4.00 mmol) and ammonium acetate (0.003 g, 0.004 mmol) dissolved in 10 mL of ethanol was stirred under nitrogen at room temperature for 18 hours. A white solid was collected by filtration and recrystallised from ethanol to give 0.46 g (33%) of **3e**. δH (250 MHz, $CDCl_3$) 1.08 (d, 3H, ^3J = 6.6 Hz, 1/2 × CH(CH_3)$_2$), 1.11 (d, 3H, ^3J = 6.6 Hz, 1/2 × CH(CH_3)$_2$), 1.67 (s, 3H, C(CH_3)(2-Ph–Et)), 2.15 (m, 2H, CH_2–CH_2–Ph), 2.78 (m, 2H, CH_2–CH_2–Ph), 3.71 (dh, 1H, J = 10.6 Hz, 6.6 Hz, CH(CH_3)$_2$), 7.10 (m, 3H, PhH-3,4,5), 7.20 (m, 2H, PhH-2,6), 7.65 (d, 1H, J = 10.6 Hz, CH=C). δC (101 MHz, $CDCl_3$) 21.54, 21.86, 26.78, 29.52, 30.01, 42.57, 106.19, 116.55, 126.77, 128.71, 129.06, 140.50, 160.03, 162.55, 174.38. Mp 79–81 °C. ν_{max}: 1731 cm^{-1}. *m/z* (ES) 288.2 (M). $C_{17}H_{20}O_4$ requires C 70.83, H 6.91, N 0.00; found C 70.29, H 6.97, N 0.09%.

5-Benzylidene-2-phenyl-1,3-dioxane-4,6-dione (4). A mixture of benzaldehyde (11.4 mL, 112.5 mmol), malonic acid (10.4 g, 100 mmol) and sulfuric acid (0.30 mL, 6 mmol) was stirred at 0 °C for 15 min. Acetic anhydride (12 mL, 125 mmol) was then added very slowly and the mixture was stirred at room temperature for 18 h. A white solid was collected by filtration and it was recrystallised from ethyl acetate and petrol to obtain 2.26 g (21%) of **4**.[17] δH (400 MHz, $CDCl_3$) 6.70 (s, 1H, sp^{3}CHPh), 7.40 (m, 5H, sp^{3}CHPhH-2–6), 7.50 (m, 3H, C=CHPhH-3,4,5), 7.95 (dd, 2H, ^3J = 8.0 Hz, ^4J = 1.4 Hz, C=CHPhH-2,6), 8.30 (s, 1H, C=CH). δC(101 MHz) 97.11, 116.1, 126.85, 129.30, 131.16, 131.85, 133.26, 134.11, 134.56, 159.58, 161.25, 164.55. Mp 146–148 °C. *m/z* (ES) 280.2 (M^+).

General procedure for deracemisation of benzylidene malonates. A mixture of the benzylidene malonate (2.18 mmol) and L-cysteine (0.132 g, 1.09 mmol) in 20 mL of ethanol was stirred at room temperature for 18 h. The solvent was then evaporated and the solid residue was dissolved in 200 mL of CH_2Cl_2. The product was collected in the filtrate, by evaporation of the DCM, and its purity was confirmed by ^{1}H NMR and the optical rotation recorded in dichloromethane solution. The observed rotations were inconsistent, but when non-zero were always negative. The adducts were insoluble in dichloromethane. Examination of the insoluble fraction by NMR showed mixtures of adducts, the acids derived from hydrolysis of the dioxane ring, and other unidentified materials. Homogeneous products were never isolated and partial characterisation is listed below.

Deracemisation of 5-(4-nitrobenzylidene)-2-methyl-2-(phenylethyl)-1,3-dioxane-4,6-dione (3b). Adduct: HRMS calculated mass for $C_{23}H_{24}N_2O_8S$ [M + H]$^+$ 489.1326; measured mass [M + H]$^+$ 489.1324.

Deracemisation of 5-benzylidene-2-phenyl-1,3-dioxane-4,6-dione (4). Following the above procedure for deracemisation, a second reasonably homogeneous product was observed in the dichloromethane-insoluble material, apparently a mixture of two diastereoisomeric acids derived from hydrolysis of the adducts. Diastereoisomer A (55%): δH (400 MHz, $CDCl_3$) 3.20 (dd, 1H, ^2J = 10.2 Hz, ^3J = 4.5 Hz, CHHS), 3.36 (dd, 1H, ^2J = 10.2 Hz, ^3J = 7.1 Hz CHHS), 4.30 (dd, 1H, ^3J = 4.5 Hz, ^3J = 7.0 Hz, CHCH$_2$S), 7.39 (m, 3H, PhH-3,4,5), 7.51 (app. d, 2H,^3J = 7.3 Hz, Ph-H2,6). Diastereoisomer B (45%): δH (400 MHz, $CDCl_3$) 3.13 (dd, 1H, ^2J = 9.9 Hz, ^3J = 9.0 Hz), 3.42 (dd, 1H, ^2J = 10.0 Hz, ^3J = 7.1 Hz), 3.96 (dd, 1H, ^3J = 8.7 Hz, ^3J = 7.2 Hz), 7.39 (m, 3H), 7.58 (d, 2H, ^3J = 8.2 Hz). HRMS calculated for $C_{20}H_{19}NO_6S$ (adduct) [M − H] 400.0860; measured mass [M − H] 400.0864.

General procedure for coordination of Pt(0)–(*S*)–DIOP ethene to benzylidene malonates. Pt(0)–(*S*)–DIOP ethene (40 mg, 0.055 mmol) was dissolved in C_6D_6 (0.7 mL). To the solution was then added an excess of benzylidene malonate and the mixture was shaken well for 2 min and the ^{31}P NMR recorded immediately. Low solubility of complexes derived from **3d**, **4** led to lack of observation of ^{195}Pt satellites. Conformational isomerism (hindered rotation around the C–C bond between the alkene and the 2-nitrophenyl group) is assumed to lead to the doubling of the peaks for **3c**.

5-Benzylidene-2-methyl-2-phenylethyl-1,3-dioxane-4,6-dione (3a). δP (121 MHz, C_6D_6) 10.22 (J = 35.5 Hz), 9.32 (J = 35.5 Hz), 8.39 (J = 35.5 Hz), 7.99 (J = 32.5 Hz), 7.24 (J = 35.5 Hz), 5.29 (J = 35.5 Hz).

5-(4-Nitrobenzylidene)-2-methyl-2-(phenylethyl)-1,3-dioxane-4,6-dione (3b). δP (121 MHz, C_6D_6) 7.12 (J_{PP} = 27 Hz, J_{PtP} = 4326 Hz), 7.62 (J_{PP} = 27 Hz, J_{PtP} = 3228 Hz), 8.28 (J_{PP} = 27 Hz, J_{PtP} = 4326 Hz), 6.77 (J_{PP} = 27 Hz, J_{PtP} = 3231 Hz). *m/z* (ES). Theoretical isotope model $[M + H]^+$ 1060.3 (62%), 1061.3 (100%), 1062.3 (97%), 1063.3 (42%), 1064.3 (25%), 1065.3 (10%); observed data 1060.3 (30%), 1061.3 (73%), 1062.4 (100%), 1063.5 (27%), 1064.5 (10%). Theoretical isotope model $[M + Na]^+$ 1082.2 (62%), 1083.2 (100%), 1084.2 (98%), 1085.3 (41%), 1086.3 (25%), 1087.3 (10%); observed data 1082.3 (27%), 1083.2 (85%), 1084.4 (62%), 1085.3 (20%).

5-(2-Nitrobenzylidene)-2-methyl-2-(phenylethyl)-1,3-dioxane-4,6-dione (3c). δP (121 MHz, C_6D_6) 8.52 (J = 29.6 Hz), 8.05 (J = 29.6 Hz), 7.50 (J = 26.7 Hz), 7.05 (J = 29.6 Hz), 6.80 (J = 29.6 Hz), 5.24 (J = 29.6 Hz).

5-(4-Methoxybenzylidene)-2-methyl-2-(phenylethyl)-1,3-dioxane-4,6-dione (3d). δP (121 MHz, C_6D_6) 9.72 (J = 35.5 Hz), 8.42 (J = 35.5 Hz).

5-Benzylidene-2-phenyl-1,3-dioxane-4,6-dione (4). δP (121 MHz, C_6D_6) 10.89 (J = 32.6 Hz), 6.84 (J = 32.6 Hz).

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