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Cycloalkenyl Halide Substitution Reactions of Enantiopure Arene *cis*-Tetrahydrodiols with Boron, Nitrogen and Phosphorus Nucleophiles

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Abstract: Enantiopure arene *cis*-tetrahydrodiols of bromobenzene and iodobenzene have been obtained in good yields, from chemoselective hydrogenation (rhodium-graphite) of the corresponding *cis*-dihydrodiol metabolites. Palladium-catalysed substitution of the halogen, by hydrogen, boron, nitrogen and phosphorus nucleophiles, in the acetonide derivatives, has yielded highly functionalised products for application in synthesis with potential as scaffolds for chiral ligands.

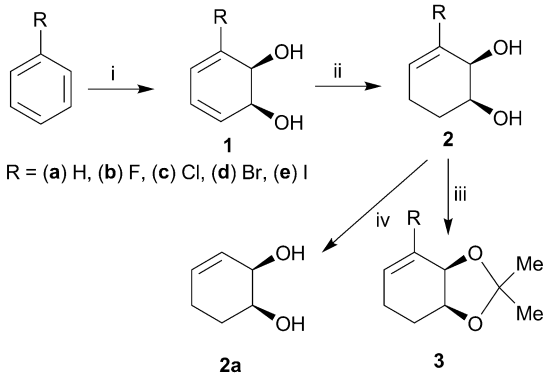
Keywords: catalytic hydrogenation; chemoenzymatic synthesis; *cis*-dihydrodiols; *cis*-tetrahydrodiols

Introduction

A wide range of benzene substrates can be efficiently dihydroxylated to yield *cis*-dihydrodiol bioproducts, for example, **1a–e**, using toluene dioxygenase (TDO)-expressing mutant strains of the bacterium *Pseudomonas putida,* e.g., UV4 or 39/D, and *E. coli* recombinant strains, e.g., JM109(pDTG601) or JM109-(pKST11), as biocatalyst sources (Scheme 1).[1]

These multi-functionalised *cis*-dihydrodiols have great potential as chiral intermediates in organic synthesis. One of the advantages of this biocatalytic process is that single biotransformations can be readily scaled up to produce large quantities (multi-grams to kilograms) of enantiopure *cis*-dihydrodiols **1** (e.g., R = F, Cl, Br, I). Although, a small number of *cis*-dihydrodiols **1** has been extensively used in the synthesis of natural products,[2–4] to date, their full potential in the synthesis of chiral ligands has not been realised. The current feasibility study has been carried out in this context.

While mono-halogenated *cis*-dihydrodiols **1b–e**, (Scheme 1) have added to the pool of chiral precursors available for synthesis, they are often unstable at room temperature, readily dehydrating to form phenols, which, in turn, catalyse further decomposition. To minimise decomposition, *cis*-dihydrodiols **1b–e** must be stored below 0 °C. This instability presents problems for storage and safe transportation. Regioselective hydrogenation of the unsubstituted alkene bond of *cis*-dihydrodiol metabolites of mono-substituted benzenes, e.g., **1b–e**, can, in principle, give very



Scheme 1. *Reagents and conditions:* (i) *P. putida* UV4/O_2 (R = **1a–e**); (ii) Rh/graphite, H_2, MeOH, (R = **1b–e**); (iii) 2,2-dimethoxypropane, acetone, PTSA, (R = **1d**, **1e**); (iv) H_2, Pd/C, Et_3N, MeOH (R = **1e**).

stable *cis*-tetrahydrodiol adducts **2b–e**.[5–9] The adducts still contain the original two chiral centres and much of the original functionality and have the advantage of being stable at room temperature. In practice, selective alkene reduction of *cis*-dihydrodiols **1a–e** gave a mixture of products depending on the nature of substituent R and the conditions used. In addition to the reduction of the 5,6-alkene bond, the other metal-catalysed side reactions include oxidation to a catechol, hydrogenolysis and loss of water to form a phenol. Even in the absence of hydrogen, 10% Pd-C catalyses a concomitant oxidation and reduction of *cis*-dihydrodiols **1** (R = F, Me, *t*-Bu, CN, CF_3) to catechols and tetrahydrodiols **2** in 30–45% yields.[10]

Recently we published[11] our results on the partial and exhaustive hydrogenation of a range of dienes **1**, employing a variety of heterogeneous catalysts. Rh/graphite, in methanol as solvent, was found to be the catalyst of choice. Its use significantly reduced the formation of phenol and catechol by-products. Halogenated *cis*-dihydrodiols **1b–e**, (Scheme 1), were found to be more challenging substrates for selective alkene reduction, as in addition to the usual aromatisation side reaction, hydrogenolysis of the carbon-halogen bond was also observed. Thus, the reduced yield of *cis*-tetrahydrodiols **2d** and **2e** made the otherwise synthetically versatile bromo- and iodo-*cis*-dihydrodiol derivatives, **1d** and **1e**, less attractive chiral precursors.[6–9] In this context, earlier studies[6,9] showed that partial catalytic hydrogenation of *cis*-dihydrodiols **1c** and **1d** using Rh/Al_2O_3 catalyst in THF or EtOH solvent resulted in good yields (85%) of adducts **2c**, **2d** with minimal evidence of hydrogenolysis of the carbon-halogen bond or aromatisation occurring. However, when these reaction conditions were applied to, arguably the most useful, *cis*-dihydrodiol **1e**, yields of adduct **2e** never exceeded[9] 55% and purification of the crude reaction mixture proved to be quite difficult. The main impurities found in the mixture resulted from the significant degree of aromatisation, hydrogenolysis and total hydrogenation reactions. An alternative non-catalytic approach to the partial reduction of *cis*-dihydrodiols **1**, using dimide was developed by Hudlicky et al.[12] This methodology was successfully applied to a range of mono-substituted benzene *cis*-dihydrodiols **1**, with reported yields in the range 60–95%. The major objectives of the current study were: (i) to develop a robust scalable catalytic method for the synthesis of the versatile *cis*-tetrahydrodiols **2d** and **2e** and (ii) to substitute the cycloalkenyl bromine or iodine atoms in these compounds with boron, nitrogen and phosphorus atoms, as initial steps leading to the development of a much wider range of *cis*-tetrahydrodiols **2** and derivatives with potential as chiral ligands.

Results and Discussion

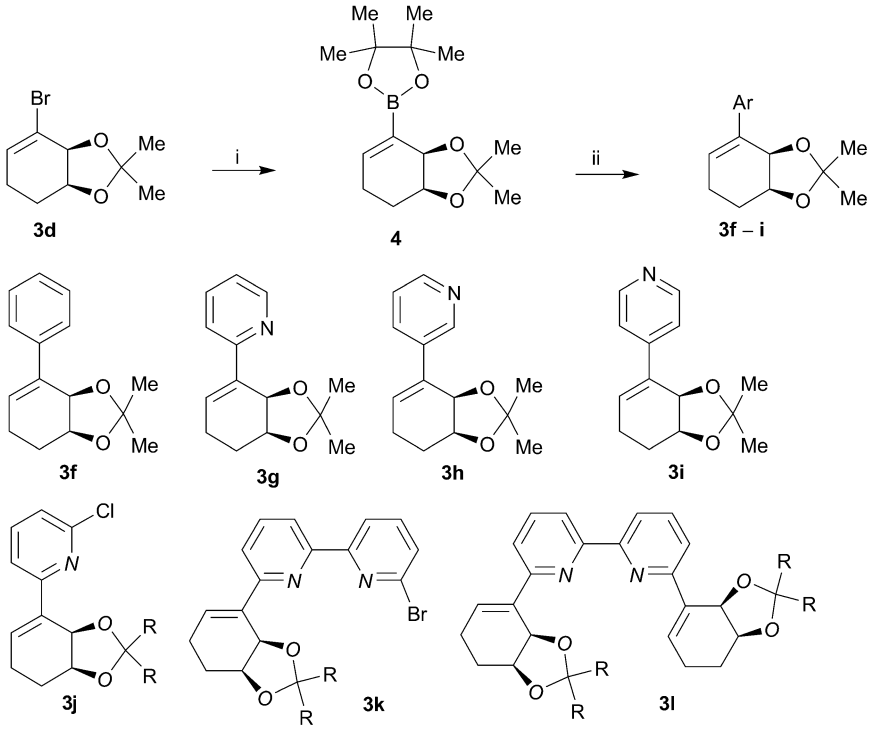
The initial phase of the study involved a systematic search for optimal conditions for the regioselective catalytic hydrogenation of halo-substituted dienes **1b–e** (Scheme 1). Optimal partial hydrogenation conditions were established, by monitoring (GC-MS analysis) the reaction mixture obtained on stirring a methanol solution (50 mL) of *cis*-dihydrodiol **1b–e** (250 mg) in the presence of 5 wt% Rh-graphite catalyst (25 mg) under a hydrogen atmosphere (1.4 bar) in a stirred tank reactor. Under these conditions (Rh/*cis*-dihydrodiol ratio 0.005), the partial hydrogenations of the *cis*-dihydrodiols **1b** and **1c** were found to be complete within 15 min; the reaction rate was much slower (120 min) for the partial hydrogenation of bromo derivative **1d**. Optimal conditions for hydrogenation of iodo *cis*-dihydrodiol **1e** to *cis*-tetrahydrodiol **2e** in methanol required a higher pressure of hydrogen (8 bar), and elevated catalyst loading (Rh/*cis*-dihydrodiol ratio 0.015). Employing these conditions, low levels of aromatisation and hydrogenolysis by-products were observed and *cis*-tetrahydrodiol **2e** was obtained in isolated yields of up to 90%. The partial hydrogenations of *cis*-dihydrodiols **1b–e**, under these stated optimal conditions, have been carried out up to a 5-g scale. However, appropriate equipment and catalyst recycling should, in principle, readily produce much larger quantities of diols **2b–e**. These results show vast improvements in terms of: (i) the reduced rhodium catalyst to substrate ratio and (ii) isolated yields of the useful and stable bromo and iodo *cis*-tetrahydrodiols **2d** and **2e**.

Cycloalkenyl bromides and iodides are versatile functionalities and can be manipulated to introduce a range of additional atoms or groups into the molecule by transition metal-catalysed substitution reactions. *cis*-Tetrahydrodiols **2c–e** have been used as synthetic precursors for arene oxide[6] and *trans*-dihydrodiol[6] mammalian metabolites and fungal bioproducts (e.g., cladospolide).[13] Substitutions of the bromine atom in compound **3d** by an alkyl group[8] or a tributyltin group[14] are among the relatively few reported examples of halide group substitution in *cis*-tetrahydrodiol derivatives. Recently, Banwell,[3] Hudlicky[4] and Gonzalez[15] have demonstrated that cycloalkenyl bromides derived from **1d** readily undergo Suzuki–Miyaura cross-coupling reactions with arylboronic acids and potassium alkynyltrifluoroborates. These coupling reactions were used in the synthesis of amabiline, lycorine, nobilisitine A, narciclasine, pancratistatin analogues and conduritol alkyne conjugates. Cycloalkenyl halides **2d** and **2e**, available in good yields from our improved reduction procedure, were also subjected to a series of metal-catalysed substitution reactions, to evaluate their synthetic potential.

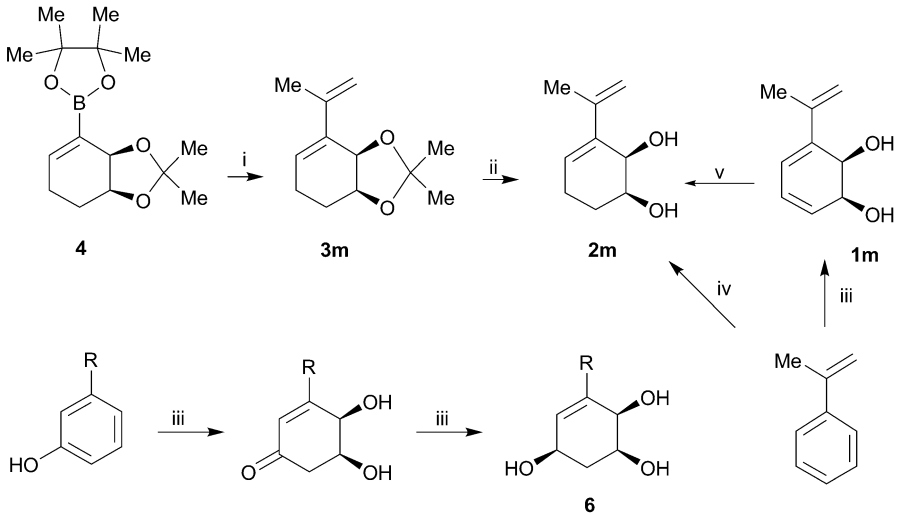
Initially, replacement of the halogen atom with hydrogen (hydrogenolysis) was investigated for cycloalkenyl halides **2d** and **2e**. Treatment of cycloalkenyl iodide **2e** in methanol with hydrogen (1 bar), in the presence of a 5% Pd/C catalyst and a trace of triethylamine, gave the enantiopure benzene *cis*-tetrahydrodiol derivative **2a** ($[\alpha]_D$: −109, MeOH, 76%, Scheme 1). This method provides an alternative route for the synthesis of (1*S*,2*R*)-*cis*-1,2-cyclohex-3-enediol **2a**. The opposite enantiomer (>98% *ee*) of compound **2a** was isolated in relatively low yield (<15%), from a mixture of bioproducts, resulting from a TDO-catalysed biotransformation (*P. putida* UV4) of 1,3-cyclohexadiene[16] (Scheme 1). Surprisingly cycloalkenyl bromide **2d**, under the same reaction conditions (H_2, Pd/C, triethylamine), gave achiral *cis*-1,2-dihydroxycyclohexane as the sole reaction product.

Treatment of *cis*-tetrahydrodiols **2d** and **2e** with 2,2-dimethoxypropane gave the corresponding acetonides **3d** and **3e**. The halogen atoms in compounds **3d** and **3e** can be effectively replaced with boron, nitrogen and phosphorus nucleophiles, under mild conditions using palladium catalysis, to give a new range of versatile chiral intermediates (Scheme 2, Scheme 3, Scheme 4 and Scheme 5). Although similar transformations have been extensively studied for aryl bromides,[17] there still remains a great deal of work to be carried out on the substitution reactions of cycloalkenyl bromides (or iodides) containing additional functional groups. Preliminary experiments, during the synthesis of cycloalkenylboronic ester derivatives of acetonides **3d** and **3e**, involved halogen-lithium exchange followed by trapping the cycloalkenyllithium with triisopropyl borate. However, this approach proved to be unreliable, and the yields were generally less than 35%. Using this procedure, for the borylation reactions of aryl halides, poor reproducibility was reported by other researchers, particularly, when the organolithium intermediate was unstable.[18] Our efforts were then focused on the palladium-catalysed substitution of the cycloalkenyl bromide with boron nucleophiles, as first described by Murata for the synthesis of arylboronic acids[19] and later by Murata and Ishiyama for the synthesis of alkenylboronic acids[20] (Scheme 2).

Attempts, using bis(pinacolato)diborane as borylating agent, gave the desired pinacol boronic ester **4** 69% along with 15–20% of the unreacted cycloalkenyl bromide precursor **3d**; the reaction could not be driven to completion. The alternative reagent, pinacolborane, was found to be a more robust and cheaper borylating agent. It gave the required cycloalkenylboronic ester **4** as the sole product in 80% yield. The ^{13}C NMR spectrum of cycloalkenylboronic ester **4** shows a distinctive boron-substituted broad cycloalkenyl signal ($\delta = 129.8$) of very low intensity, due to a



Scheme 2. *Reagents and conditions*: (i) pinacolborane, Et_3N, $PdCl_2$(dppf), dioxane, 80 °C, 80%; or bis(pinacolato)diborane, PhOK, $PdCl_2(Ph_3P)_2$, Ph_3P, toluene, 50 °C, 69%; (ii) $PdCl_2(Ph_3P)_2$, THF, H_2O, KOAc, Et_3N, 80 °C, bromobenzene, 2-, 3- or 4-bromopyridine, 65–85% or with 6,6′-dibromo-2,2′-dipyridine, 28–53%.



Scheme 3. *Reagents and conditions:* (i) 2-bromopropene, $PdCl_2$(dppf), THF, H_2O, KOAc, Et_3N, 80 °C, 67%; (ii) TFA, water, THF, 40 °C, 12 h, 85%; (iii) *P. putida* UV4/O_2; (iv) Strain S107B1/O_2; (v) Pd/C, H_2.

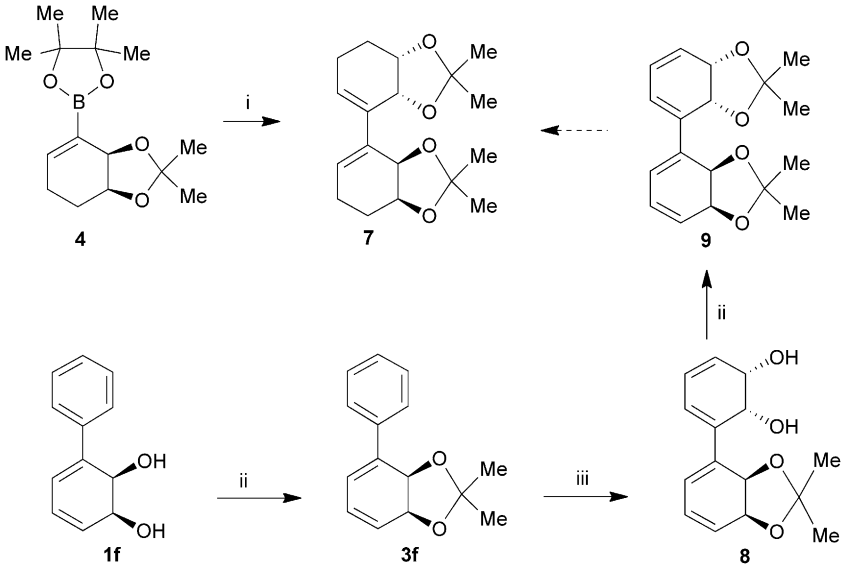
large quadrupolar effect of the boron atom. This effect was observed[21] in the ^{13}C NMR spectra of cycloalkenylboranes and provides a reliable indicator of the presence of a boron atom in compound **4**. As anticipated, cycloalkenylboronic ester **4** underwent efficient Suzuki–Miyaura cross-coupling[22] with bromobenzene, 2-bromo-, 3-bromo- and 4-bromopyridines, to give the corresponding cross-coupled products **3f–i** with yields in the range 68–85%, (Scheme 2). This method of synthesising *cis*-tetrahydrodiols **3g–i** provides an attractive alternative to use of the TDO-catalysed *cis*-dihydroxylation (*P. putida* UV4) of 2-, 3- and 4-phenylpyridines to form the corresponding *cis*-dihydrodiols **1g–i** (yield $<5\%$) and their subsequent partial hydrogenations. Biphenyl dioxygenase (BPDO), present in a mutant strain (B8/36) of *Sphingomonas yanoikuyae*,[23] gave a better yield (31% to 59%) of the biaryl *cis*-dihydrodiols **1g–i**.

The sequence in Scheme 2 provides an alternative route to acetonide **3j** (R = Et) which has recently been used in the synthesis of a series of 2,2′-bipyridines, e.g., **3l** (R = Et), for use as potential chiral ligands.[24] The method was also successfully applied to the coupling of 2,2′-dibromo-2,2′-dipyridine with two molecules of cycloalkenylboronic ester **4** to furnish the corresponding chiral bipyridine **3l** (R = Me, 28% yield) along with monosubstituted derivative **3k** (53% yield) which could be recycled. Thus, an attractive convergent route to a range of potential chiral ligands **3l** has been developed. Compound **3k** can be used to synthesise unsymmetrical derivatives.

Omori et al. isolated[25] a novel *cis*-tetrahydrodiol metabolite **2m** of α-methylstyrene, usisng an unidentified bacterial strain, S107B1, (Scheme 3). This biotransformation was somewhat unusual; it appeared to involve an endocyclic *cis*-dihydroxylation of α-methylstyrene to yield *cis*-dihydrodiol **1m** and a subsequent chemoselective biocatalytic hydrogenation of the 5,6-alkene bond. Recently, we have also observed similar consecutive bio-oxidation/reduction reactions with *meta*-subsituted phenols, (Scheme 3). The *m*-phenols undergo *cis*-dihydroxylation to yield cyclohexenone-*cis*-diol metabolites and further reduction of the keto group to form a new family of arene *cis*-tetrahydrotriol (*cis*-cyclohexenetriol) metabolites **6** (Scheme 3).[26]

The relative stereochemistry of the bioproduct **2m** was earlier correctly assigned by ^1H NMR spectroscopy but the absolute stereochemistry of the two chiral centres was not determined.[25] Attempts to synthesise *cis*-tetrahydrodiol **2m** by selective catalytic hydrogenation of *cis*-dihydrodiol metabolite **1m** of known absolute stereochemistry[27] gave in our hands an inseparable mixture of products, including diene **2m** (Scheme 3). As an alternative approach, chemoenzymatic synthesis *via* cyclic boronate **4** was then tested. Chiral boronate **4** underwent efficient Suzuki–Miyura cross-coupling with the volatile sterically hindered 2-bromopropene, to yield the conjugated diene **3m** in 67% yield (Scheme 3). Deprotection of the acetonide group furnished *cis*-tetrahydrodiol **2m** with an $[\alpha]_D$: −101 (*c* 0.3, MeOH). This compares well with the reported[25] value, $[\alpha]_D$: −105 (*c* 0.8, MeOH), and hence confirms that the metabolite **2m** resulting from enzyme-catalysed *cis*-dihydroxylation/hydrogenation of α-methylstyrene was enantiopure and of the (1*S*,2*R*) absolute configuration. This is another example of synthesis *via* the cyclic boronate **4** which is much better than using *cis*-dihydrodiol precursors (**1m**→**2m**).

The Suzuki–Miyaura cross-coupling reaction of cycloalkenylboronate **4** was found to be remarkably tol-



Scheme 4. *Reagents and conditions:* (i) **3d**, $PdCl_2(Ph_3P)_2$, THF, H_2O, KOAc, Et_3N, 80 °C, 83%; (ii) 2,2-dimethoxypropane, acetone, PTSA, 75%; (iii) *S. yaniokuyae* B8/36/O_2.

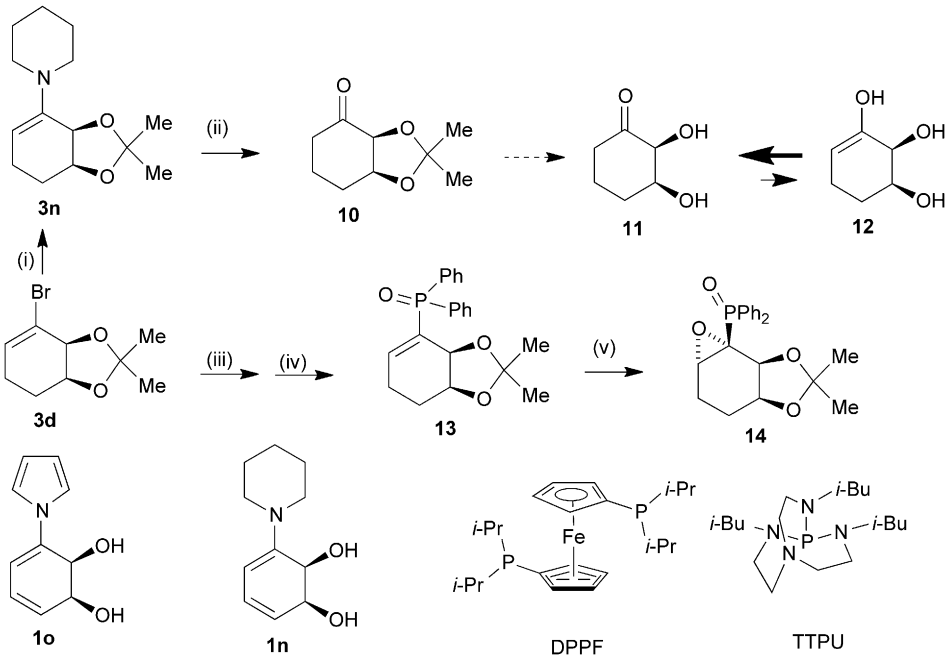
erant of steric hindrance; it efficiently coupled with cycloalkenyl bromide **3d** to give the C_2 symmetrical diene **7** in 83% yield (Scheme 4). In our laboratories, we had carried out the chemoenzymatic synthesis of this type of compound using two separate biotransformations.[28] In the first enzymatic step, biphenyl was metabolised to give diol **1f**, which was then converted into acetonide **3f′**. This decreased its hydrophilicity, and thus rendered it more susceptible to a second biocatalytic dihydroxylation of the intact aromatic ring. The resulting acetonide diol **8** was converted into diacetonide **9**.[28] In our opinion, the cross-coupling methodology (**4**→**7**) has advantages over the linear sequence (**2f**→**3f**→**8**→**9**→**7**) involving two BPDO-catalysed biotransformations.

Due to the pioneering work of Buchwald and Hartwig[29] the Pd-catalysed substitution of an aryl halide, with a nitrogen nucleophile, has become a standard reaction routinely used in organic synthesis. Similar reactions using copper catalysts are also gaining prominence[30] but the corresponding reactions with cycloalkenyl halides[31–33] or triflates,[34] or trifluoroborate salts[35] have not been as widely studied, possibly, because the reaction products are not as stable as in the aromatic series. Substitution of the bromine atom in compound **3d** by a nitrogen atom (secondary amine) has the potential to give an enamine. e.g., **3n**, which can be reacted further with electrophiles or hydrolysed to the ketone (Scheme 5).

Employing Verkade's general procedure[31] cycloalkenyl bromide **3d**, on reaction with piperidine, yielded the known enantiopure ketone **10** *via* the transient enamine intermediate **3n**,[36] during an attempted purification of the reaction product by flash chromatography. Acetonide **10** is a configurationally stable form of the stereochemically labile diol **11**[37] which is a keto-tautomer of *cis*-tetrahydrophenol **12**. Conversion of cycloalkenyl bromides to ketones by hydrolysis is often done under harsh reaction conditions.[38] The above experiment gives a mild method for carrying out this conversion on acid-sensitive substrates. Furthermore, while the *N*-substituted *cis*-dihydrodiol **1o** has recently been isolated as a metabolite of *N*-phenylpyrrole using TDO,[23] to date, it has not been possible to isolate a *cis*-dihydrodiol metabolite from aniline or *N*-alkyl-substituted anilines. Thus the synthesis of chiral enamine derivatives, e.g., **3n**, from the corresponding *cis*-tetrahydrodiol precursor, *via* partial hydrogenation of the corresponding *cis*-dihydrodiols, e.g., **1n**, was not an option.

Chiral phosphine ligands are employed in many catalytic asymmetric transformations, often producing products with high *ee* values. However, these ligands are generally difficult to prepare, requiring multistep syntheses with air-sensitive intermediates.[39] As the next stage of our programme of utilising enantiopure *cis*-tetrahydrodiols **2**, to devise new synthetic routes to chiral ligands,[24,40] our efforts were directed towards the synthesis of chiral phosphines. It is well known that arylphosphines couple with aryl halides under metal catalysis,[41] usually palladium,[42,43] nickel[44] and more recently copper.[45] Examples of phosphorus coupling to cycloalkenyl bromides[46] and triflates[34] are rarer and have only recently been properly explored.[47]

Diphenylphosphine efficiently coupled to the chiral cycloalkenyl bromide **3d** (Scheme 5), under palladium catalysis using the DPPF ligand.[33,43] To simplify pu-



Scheme 5. *Reagents and conditions:* (i) $Pd_2(dba)_3$, NaOPh, piperidine, TTPU, toluene 80 °C; (ii) SiO_2, 57% two steps; (iii) $Pd_2(dba)_3$, Cs_2CO_3, Ph_2PH, DPPF, toluene, 80 °C; (iv) 30% H_2O_2, 84% two steps; (v) LiOOH, toluene, 80 °C, 78%.

rification, the cycloalkenyl phosphine was characterised as the phosphine oxide **13**, by using an oxidative work-up. Further chirality and functionality was introduced into cycloalkenyl phosphine oxide **13** through epoxidation with lithium hydroperoxide[48] to give a very stable single diastereoisomeric epoxide **14** (78% yield). The relative stereochemistry at the new chiral centres was readily determined from the vicinal proton and phosphorus coupling constants (15.2 and 5.2 Hz), confirming that the phosphorus atom was in an axial position.[49] In compounds **13** and **14** the two phenyl groups attached to phosphorus are diastereotopic, the proton and carbon NMR spectra of both depicted a complex pattern of signals, but this, allied to the phosphorus coupling, provided convincing evidence of their structural assignments.

The examples of substitution reactions of cycloalkenyl bromide **3d** mentioned above have been used to demonstrate the synthetic value of the *cis*-tetrahydrodiols; the corresponding cycloalkenyl iodide **3e** was also found to undergo similar reactions. This study, which contains representative examples of the cycloalkenyl bromide/iodide substitution reactions, is now being extended to the synthesis of a wider range of products with potential as chiral ligands.

Conclusions

It has been demonstrated that: (i) highly functionalised chiral cycloalkenyl halides **3d** and **3e** can be readily prepared by a TDO-catalysed biotransformation of the corresponding halobenzene substrates and that efficient chemoselective catalytic hydrogenation can be achieved in good yield (85–90%) without significant aromatisation or hydrogenolysis occurring, (ii) the cycloalkenyl halides can be efficiently substituted directly with hydrogen, boron, nitrogen and phosphorus nucleophiles. The novel cyclic boronate **4** undergoes subsequent cross-coupling reactions to give enantiopure products in good yields, e.g., compounds **3f–m** and **7** of synthetic value, for natural product and chiral ligand syntheses.

Experimental Section

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded using 300 MHz (Bruker DPX 300) and at 500 MHz (Bruker DRX 500) NMR spectrometers, in $CDCl_3$ solvent unless stated otherwise. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard and coupling constants are given in Hertz. Spectra splitting patterns are designated as s singlet, d doublet, t triplet, q quartet, m multiplet and br broad. Mass spectra were recorded using a Double Focusing Triple Sector VG Auto Spec, and accurate molecular masses were determined by the peak matching method using perfluorokerosene as standard reference and were accurate to within ±0.006 a.m.u. Analytical TLC was carried out on Merck Kielselgel 60_{254} plates and the spots visualised using a Hanovia Chromatolite UV lamp. Flash chromatography and preparative

layer chromatography (PLC) was performed using Merck Kieselgel 60 (230–400 mesh) and $PF_{254/366}$ respectively. *cis*-Dihydrodiols **1** (R = F, Cl, Br or I) and authentic samples of the corresponding *cis*-tetrahydrodiols **2** (R = F, Cl, Br or I) were available from earlier studies.[9]

The initial parallel screening of the hydrogenation reactions was performed in a Baskerville multi-cell autoclave reactor containing a 10 × 10 mL vessel system capable of hydrogen pressures up to 100 bar and temperatures up to 200 °C. Six different heterogeneous catalysts (5 wt% Pd, Pt, Ir, Ru, Rh and Pd-Pt [1:1] on graphite) were employed to determine the relationship between catalyst properties and performance in hydrogenation of *cis*-dihydrodiols **1**. All catalysts were obtained from Johnson Matthey. Catalysis was preformed in protic (water, methanol) and aprotic (toluene, tetrahydrofuran) solvents. Optimal reaction conditions for the partial hydrogenation of monohalogenated *cis*-dihydrodiols **1** (R = F, Cl, Br, I) were determined in a Hazard Evaluation Laboratory (HEL) stirred tank reactor. The reactor was first heated to 25 °C, and the system was purged with hydrogen. After that the hydrogen pressure was introduced as required and the stirrer set at 1400 rpm. These parameters were maintained throughout the experiment. Under these conditions the reactions were under kinetic control. All the reactions were performed in duplicate and the results averaged. Typical conditions were: 250 mg of *cis*-dihydrodiol, 25 mg of 5 wt% Rh/G, in methanol (50 mL), 1.4 bar of H_2 pressure at 25 °C. The minimum times for completion of the partial hydrogenation under these conditions (0.005 = Rh/substrate) for *cis*-dihydrodiols **1** were (R = F, 10 min), (R = Cl, 15 min) and (R = Br, 120 min). The partial hydrogenation of *cis*-dihydrodiol **1** (R = I) required the use of a higher pressure of hydrogen (8 bar) and an increased catalyst loading (0.015 = Rh/substrate and was complete after 21 min. Employing these conditions yields of up to 90% of *cis*-tetrahydrodiols **2** (R = F, Cl, Br or I) were obtained.

(1*S*,2*R*)-1,2-Dihydroxycyclohex-3-ene (2a)

A solution of *cis*-diol **2e** (250 mg, 1.04 mmol) in methanol (10 mL) containing triethylamine (300 μL, 2.16 mmol) was magnetically stirred in the presence of 5% Pd/C (25 mg), under a hydrogen atmosphere (1 atm), at room temperature. The progress of the reaction was monitored by TLC (EtOAc-hexane, 1:1). When nearly all of *cis*-diol **2e** had been consumed (*ca:* 3 h), the reaction was terminated by filtering off the catalyst. The filtrate was concentrated and the residue purified by preparative layer chromatography (PLC) (EtOAc-hexane, 1:1) to give *cis*-diol **2a** as a colourless oil; yield: 92 mg (76%); $[\alpha]_D$: −109 (*c* 1.1, $CHCl_3$). The spectroscopic data of *cis*-diol **2a** were in agreement with the literature data.[27]

(1*S*,2*S*)-1,2-Dihydroxy-3-fluorocyclohex-3-ene (2b)

White crystalline solid; m.p. 101–103 °C (from $CHCl_3$/hexane); $[\alpha]_D$: −79 (*c* 1.34, MeOH); anal. found: C 54.3, H 6.8; $C_6H_9O_2F$ requires: C 54.5, H 6.9%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.74 (2H, m, 6-H, 6′-H), 2.06 (1H, m, H-5), 2.21 (1H, m, 5′-H), 3.88 (1H, m, 1-H), 4.27 (1H, m, 2-H), 5.41 (1H, m, 4-H); ^{13}C NMR (100 MHz): δ = 19.68 (d, *J* = 7.9 Hz), 25.45 (d, *J* = 1.8 Hz), 66.41 (d, *J* = 23.9 Hz), 68.65 (d, *J* = 8.6 Hz), 106.06 (d, *J* = 14.3 Hz), 157.09 (d, *J* = 256.5 Hz); LR-MS (EI): *m/z* = 132 (M^+, 7%), 113 (17), 95 (16), 88 (100), 69 (21), 41 (50). (1*S*,2*S*)-1,2-Dihydroxy-3-chlorocyclohex-3-ene (**2c**), (1*S*,2*S*)-1,2-dihydroxy-3-bromocyclohex-3-ene (**2d**) and (1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohex-3-ene (**2e**) were found to have identical physical properties and spectroscopic characteristics to those reported earlier.[9]

(1*S*,2*S*)-1,2-Isopropylidenedioxy-3-bromocyclohex-3-ene (3d)

To a solution of (1*S*,2*S*)-1,2-dihydroxy-3-bromocyclohex-3-ene **2d** (5.00 g, 26.0 mmol) in a mixture of acetone (15 mL) and 2,2-dimethoxypropene (10 mL) was added *p*-toluenesulfonic acid (25 mg, 0.13 mmol). After stirring the mixture at room temperature overnight, most of the solvent was removed under reduced pressure, water (20 mL) was added, and the reaction mixture extracted with Et_2O (2 × 50 mL). The Et_2O extract was washed with water (20 mL), dried (Na_2SO_4) and concentrated. Purification of the concentrate by flash chromatography (EtOAc-hexane, 1:4) gave compound **3d** as a white crystalline solid; yield: 5.37 g (89%); m.p. 41 °C (Et_2O); $[\alpha]_D$: +80.7 (*c* 0.8, $CHCl_3$); HR-MS: *m/z* = 216.9864, calcd. for $C_8H_{10}O_2{}^{79}Br$ $(M-Me)^+$: 216.9867; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (3H, s, Me), 1.45 (3H, s, Me), 1.80–1.83 (1H, m, 5-H), 2.03–2.07 (2H, m, 5-H, 6-H), 2.27–2.33 (1H, m, 6-H), 4.41 (1H, m, 1-H), 4.50 (1H, d, *J* = 5.3 Hz, 2-H), 6.23 (1H, dd, *J* = 5.7, 2.5 Hz, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.45, 23.41, 25.51, 26.64, 73.26, 75.56, 108.31, 121.34, 131.21; LR-MS (EI): *m/z* = 219 (M^+−Me, ^{81}Br, 38%), 217 (40), 159 (36), 157 (34), 43 (100).

(3a*S*,7a*R*)-2,2-Dimethyl-7-(4,4,5,5-tetramethyl [1,3,2] dioxaborolan-2-yl)-3a,4,5,7a-tetrahydrobenzo-[1,3]dioxole (4)

Method A: A mixture of cycloalkenyl bromide **3d** (466 mg, 2 mmol), palladium dichlorobistriphenylphosphine (42 mg, 0.06 mmol), triphenylphosphine (32 mg, 0.12 mmol), bis(pinacolato)diborane (558 mg, 2.20 mmol) and sodium phenoxide (348 mg, 3.0 mmol) in toluene (20 mL), under nitrogen was heated at 50 °C for 10 h in a Schlenk tube. After addition of water (10 mL) to the reaction mixture it was extracted with EtOAc, the extract washed with brine, dried (Na_2SO_4) and concentrated. Column chromatography (EtOAc-hexane, 1:4) of the concentrate gave a mixture of compound **4** (yield: 387 mg, 69%) and unreacted cycloalkenyl bromide **3d**.

Method B: A mixture of cycloalkenyl bromide **3d** (466 mg, 2 mmol), $PdCl_2$(dppf) (50 mg, 0.07 mol), triethylamine (0.82 mL) and pinacolborane (0.44 mL) in dry dioxane (10 mL) was heated at 80 °C for 12 h, under nitrogen, in a Schlenk tube. The solvent was then removed under reduced pressure, water (40 mL) was added and the reaction mixture extracted with EtOAc (3 × 50 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. PLC purification of the concentrate (EtOAc-hexane, 1:4) gave compound **4** as a clear oil; yield: 448 mg (80%); $[\alpha]_D$: +66.5 (*c* 1.0, $CHCl_3$); HR-MS: *m/z* = 280.1876, calcd. for $C_{15}H_{25}BO_4$ (M^+): 280.1872; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (12H, s), 1.36 (3H, s), 1.62–1.68 (1H, m), 1.83–2.11 (1H, m), 2.32–2.42 (1H, m), 4.27–4.34 (1H, m), 4.64 (1H, d,

$J=5.3$ Hz), 6.73 (1H, t, $J=3.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=21.99$, 25.25 (t), 27.21, 28.22, 72.94, 83.66, 108.55, 129.77, 145.74; LR-MS (EI): $m/z=281$ (15%), 280 (100), 279 (30).

General Procedure 1 for Suzuki–Miyaura Reactions

A solution of 2,2-dimethyl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3a,4,5,7a-tetrahydrobenzo[1,3] dioxole (**4**, 420 mg, 2.00 mmol), palladium dichloro-*bis*-triphenylphosphine (56 mg, 0.079 mmol), potassium acetate (300 mg, 3.0 mmol), triethylamine (1.2 mL, 1.5 mmol) and cycloalkenyl or aromatic bromide (2.5 mmol) in THF/water (6:1, 7 mL) was heated at 80 °C for 12 h. Water (10 mL) was added to the reaction mixture and it was extracted with EtOAc (3×25 mL), the extract washed with brine, dried (Na_2SO_4) and concentrated. PLC of the concentrate (EtOAc-hexane, 1:4) gave the cycloalkenyl/aromatic substituted product.

General Procedure 2 for Suzuki–Miyaura Cross-Coupling of Pyridines

A solution of bromopyridine (316 mg, 2 mmol), $PdCl_2$(dppf) (80 mg, 0.11 mmol), triethylamine (0.82 mL, 5.8 mmol), potassium acetate (213 mg, 2.2 mmol) and pinacolborane **4** (0.49 g, 3.8 mmol) in a mixture of THF and water (4:1, 10 mL) was heated at 80 °C for 12 h under nitrogen in a Schlenk tube. After working up the reaction mixture, as described for procedure 1, the crude product obtained was purified by PLC (EtOAc-hexane, 1:4).

(3a*S*,7a*R*)-2,2-Dimethyl-7-phenyl-3a,4,5,7a-tetrahydrobenzo[1,3]dioxole (3f)

Following general procedure 1, compound **3f** was obtained, as a solid, yield: 85%; m.p. 68–70 °C; $[\alpha]_D$ +62 (*c* 1, $CHCl_3$); HR-MS: $m/z=230.1303$, calcd. for $C_{15}H_{18}O_2$ (M^+): 230.1307; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.34$ (3H, s), 1.35 (3H, s), 1.70–1.83 (1H, m), 1.96–2.23 (1H, m), 2.0–2.21 (1H, m), 2.42–2.48 (1H, m), 4.33–4.35 (1H, m), 4.85 (1H, d, $J=5.4$ Hz), 6.23 (1H, t, $J=4.4$ Hz), 7.17 (1H, t, $J=7.4$ Hz), 7.25 (2H, t, $J=7.7$ Hz), 7.44 (2H, d, $J=6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=22.14$, 26.36, 27.0, 28.28, 73.07, 72.80, 108.64, 126.43, 127.58, 129.12, 136.03, 140.26; LR-MS (EI): $m/z=31$ (20%), 230 (100).

(3a*R*,7a*S*)-2-(2,2-Dimethyl-3a,6,7,7a-tetrahydrobenzo[1,3]dioxol-4-yl)-pyridine (3g)

Following general procedure 2 with 2-bromopyridine compound **3g** was prepared, as a solid, yield: 82%; m.p. 98–108 °C; $[\alpha]_D$: +70.4 (*c* 1.0, $CHCl_3$); HR-MS: $m/z=231.1251$, calcd. for $C_{14}H_{17}NO_2$ (M^+): 231.1259; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.31$ (3H, s), 1.37 (3H, s), 1.70–1.74 (1H, m), 1.85–1.89 (1H, m), 2.0–2.16 (1H, m), 2.32–2.46 (1H, m), 4.38–4.42 (1H, m), 5.09 (1H, d, $J=5.5$ Hz), 6.84 (1H, t, $J=4.4$ Hz), 7.09 (1H, td, $J=4.8$, 1.0 Hz), 7.46 (1H, d, $J=7.8$ Hz), 7.58 (1H, td, $J=7.8$, 2.0 Hz), 8.52 (1H, d, $J=4.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=22.06$, 26.18, 26.97, 28.56, 72.51, 74.26, 108.85, 120.9, 122.65, 132.65, 136.94, 149.48, 157.56; LR-MS (EI): $m/z=232$ (30%), 231 (100).

(3a*R*,7a*S*)-3-(2,2-Dimethyl-3a,6,7,7a-tetrahydrobenzo[1,3]dioxol-4-yl)-pyridine (3h)

Employing general procedure 2 with 3-bromopyridine compound **3h** was obtained as an oil, yield: 68%; $[\alpha]_D$: +74 (*c* 1.6, $CHCl_3$); HR-MS: $m/z=231.1291$, calcd. for $C_{14}H_{17}NO_2$ (M^+): 231.1259; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.41$ (3H, s), 1.42 (3H, s), 1.78–1.90 (1H, m), 2.06–2.11 (1H, m), 2.23–2.36 (1H, m), 2.48–2.52 (1H, m), 4.41–4.50 (1H, m), 4.87 (1H, d, $J=5.6$ Hz), 6.37 (t, $J=4.4$ Hz), 7.23–7.26 (1H, m) 7.84 (1H, dt, 8.0, 2.0), 8.50 (1H, dd, $J=4.9$, 1.7 Hz), 8.77 (1H, d, $J=2.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=22.16$, 25.83, 26.59, 28.43, 72.90, 74.12, 109.42, 123.48, 130.51, 133.87, 136.01, 148.08, 148.0; LR-MS (EI): $m/z=232$ (20%), 231 (100), 230.9 (50).

(3a*R*,7a*S*)4-(2,2-Dimethyl-3a,6,7,7a-tetrahydrobenzo[1,3]dioxol-4-yl)-pyridine (3i)

Following general procedure 2 with 4-bromopyridine gave compound **3i** as an oil, yield: 76%; $[\alpha]_D$: +36 (*c* 0.5, $CHCl_3$); HR-MS (ES), $m/z=232.1334$, calcd. for $C_{14}H_{18}NO_2$ $(M+H)^+$: 232.1338; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.39$ (3H, s), 1.44 (3H, s), 1.72–1.84 (1H, m), 1.86–1.97 (1H, m), 2.0–2.21 (1H, m), 2.32–2.46 (1H, m), 4.45–4.47 (1H, m), 4.91 (1H, d, $J=5.9$ Hz), 6.58 (1H, t, $J=4.4$ Hz), 7.46 (1H, d, $J=6.0$ Hz), 8.59 (1H, d, $J=5.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=21.99$, 25.47, 26.53, 28.22, 71.93, 73.67, 109.56, 120.99, 132.43, 134.16, 147.62, 150.23; LR-MS (EI): $m/z=$ 232 (20%), 231 (100).

6-Bromo-6′-[(3a*R*,7a*S*)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl]-2,2′-bipyridine (3k) and 6,6′-Bis[(3a*R*,7a*S*)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl]-2,2′-bipyridine (3l)

Using general procedure 2 with 6,6-dibromo-2,2′-bipyridyl (0.5 equiv.) gave a mixture of compounds **3k** and **3l** which was separated by PLC (EtOAc-hexane, 1:4).

Compound **3k**: oil, yield: 28%; $[\alpha]_D$: +45, (*c* 1.0, $CHCl_3$); HR-MS (ES): $m/z=$ =461.2444, calcd. for $C_{14}H_{18}NO_2$ $(M+H)^+$: 461.2440; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.43$ (6H, s), 1.49 (6H, s), 1.83–2.03 (4H, m), 2.17–2.30 (2H, m), 2.42–2.55 (2H, m), 4.47 (2H, ddd, $J=6.41$, 6.41, 3.90 Hz), 5.25 (2H, d, $J=5.7$ Hz), 7.17 (2H, t, $J=4.3$ Hz), 7.55 (2H, d, $J=7.9$ Hz), 7.78 (2H, t, $J=7.9$ Hz), 8.39 (2H, d, $J=7.7$ Hz) ^{13}C NMR (100 MHz): $\delta=20.82$, 24.66, 25.33, 26.96, 70.69, 72.60, 107.34, 118.18, 119.02, 130.96, 134.06, 136.20, 154.24, 154.30; LR-MS (EI): $m/z=460$ (2%), 445 (4), 402 (85), 344 (100), 315 (65).

Compound **3l**: light yellow oil, yield: 53%; $[\alpha]_D$: +28.8 (*c* 0.66, $CHCl_3$); HR-MS (ES): $m/z=387.0708$, calcd. for $C_{14}H_{18}NO_2$ [M^+]: 387.0708; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.35 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.81 (1H, m, 7′-H), 1.91 (1H, dddd, $J=13.3$, 6.6, 6.6, 5.1 Hz, 7-H), 2.16 (1H, ddddd, $J=14.7$, 8.6, 5.1, 5.1 2.1 Hz, 6′-H), 2.41 (1H, m, H-6), 4.4 (1H, ddd, $J=5.7$, 5.7, 2.9 Hz, H-7a), 5.17 (1H, dt, $J=5.7$, 1.4 Hz, H-3a), 7.05 (1H, dd, $J=4.8$, 4.1 Hz, 5-H), 7.39 (1H, dd, $J=7.7$, 1.0 Hz), 7.50 (1H, dd, $J=7.9$, 0.9 Hz), 7.57 (1H, t, $J=7.8$ Hz), 7.71(1H, t, $J=8.0$ Hz), 8.20 (1H, dd, $J=7.8$, 1.0 Hz), 8.40 (1H, dd, $J=7.7$, 1.0 Hz): ^{13}C NMR (125 MHz,

$CDCl_3$): δ = 21.89, 25.74, 26.46, 28.07, 71.73, 73.65, 108.53, 119.61, 119.82, 120.87, 127.82, 132.41, 135.11, 137.64, 139.04, 141.43, 153.39, 155.78, 157.73. LR-MS: (ES): *m/z* = 797 [(2M+Na)$^+$, 20%], 409 [(M+Na)$^+$, 60], 387 [(M+H)$^+$, 100], 331 (70).

(3a*S*,7a*R*)-7-Isopropenyl-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[1,3]dioxole (3m)

Applying general procedure 1 with 2-bromopropene compound **3m** was obtained as an oil; yield: 67%; $[\alpha]_D$: +74 (*c* 0.8, $CHCl_3$); HR-MS: *m/z* = 194.1305, calcd. for $C_{12}H_{18}O_2$ (M^+): 194.1307; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.98 (1H, t, *J* = 4.4 Hz), 5.20 (1H, s), 4.95 (1H, s), 4.69 (1H, d, *J* = 5.7 Hz), 4.23 (1H, dt, *J* = 5.5, 0.9 Hz), 2.28–2.19 (1H, m), 2.05–1.98 (1H, m), 1.84 (3H, s), 1.73- 1.63 (2H, m), 1.35 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.16, 23.42, 26.36, 27.28, 28.56, 73.01, 74.02, 108.62, 142.24, 145.38; LR-MS (EI) *m/z* = 194 (7%), 194 (100), 171 (5).

(1*S*,2*R*)-3-Isopropenylcyclohex-3-ene-1,2-diol (2m)

A mixture of acetonide **3m** (58 mg, 0.3 mmol), THF (1.2 mL), TFA (0.15 mL) and water (0.3 mL) was heated at 40 °C until the starting material had reacted completely (12 h). The crude product obtained after removal of the solvents was purified by PLC (EtOAc-hexane, 1:1) to give diol **2m** as an oil, yield: 39 mg (85%); $[\alpha]_D$: −101 (*c* 0.3, MeOH), lit.[25] $[\alpha]_D$: −105 (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.89 (1H, dd, *J* = 4.7, 3.20 Hz), 5.20 (1H, s), 4.95 (1H, s), 4.43 (1H, d, *J* = 2.6 Hz), 3.79–3.62 (1H, m), 2.27–2.26 (2H, m), 1.84 (3H, s), 1.71–1.58 (2H, m).

(3a*R*,3′a*R*,7a*S*,7′a*S*)-2,2,2′,2′-Tetramethyl-3a,6,7,7a,3′a,6′,7′,7′a-octahydro[4,4′]bi{benzo[1,3]dioxolyl} (7)

Using general procedure 1 with cycloalkenyl bromide **3d**, gave compound **7** as a white solid; yield: 83%; m.p. 89–92 °C; $[\alpha]_D$: +30 (*c* 1.2, $CHCl_3$); HR-MS: *m/z* = 306.1831, calcd. for $C_{18}H_{26}O_4$ (M^+): 306.1856; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (6H, s), 1.34 (6H, s), 1.66–1.94 (4H, m), 1.96–2.12 (2H, m), 2.21–2.43 (2H, m) 4.35–4.37 (2H, m), 4.75 (2H, d, *J* = 5.8 Hz), 6.28 (2H, t, *J* = 4.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.35, 26.26, 27.07, 28.69, 71.93, 74.22, 108.69, 128.09, 134.96; LR-MS (EI): *m/z* = 306 (100%), 279 (30).

(3a*S*,7a*S*)-2,2-Dimethyltetrahydrobenzo[1,3]dioxol-4-one (10)

A stirred mixture of (1*S*,2*S*)-1,2-isopropylidenedioxy-3-bromocyclohex-3-ene **3d** (186 mg, 0.80 mmol), $Pd_2(dba)_3$ (3.6 mg, 8 μmol), sodium *tert*-butoxide (176 mg, 1.12 mmol), TTPU (16 μmol, 5.4 μL) and piperidine (0.88 mmol, 86.4 μL) in toluene (8 mL) was heated at 80 °C for 18 h in a Schlenk tube. The solvent was removed under vacuum and the residue purified by flash chromatography (EtOAc-hexane, 2:1→EtOAc) to furnish the title compound **10** as a clear oil, yield: 77 mg (57%). The spectroscopic data of compound **10** were in good agreement with the literature data.[36] $[\alpha]_D$: + 58.4 (*c* 0.51, $CHCl_3$), lit[36] $[\alpha]_D$ (*ent*): −63.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.54–4.56 (1H, m), 4.22 (1H, d, *J* = 5.4 Hz), 2.41–2.47 (1H, m), 2.13–2.27 (2H, m), 1.84–1.93 (3H, m), 1.38 (3H, s), 1.33 (3H, s).

(3a*S*,7a*S*)-7-(Diphenylphosphinoyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[1,3]dioxole (13)

(1*S*,2*S*)-1,2-Isopropylidenedioxy-3-bromocyclohex-3-ene **3d** (1.5 g, 6.4 mmol), $Pd_2(dba)_3$ (87.9 mg, 0.19 mmol), Cs_2CO_3 (4.17 g, 12.8 mmol) and DPPF (80.2 mg, 0.38 mmol) were added to a Schlenk tube containing a magnetic stirring bar. Toluene (40 mL) and diphenylphosphine (1.03 mL, 6.7 mmol) were added and the resulting mixture heated with stirring at 80 °C for 44 h. After cooling the reaction mixture to ambient temperature, aqueous hydrogen peroxide solution (30%, 50 mL) was added. The mixture was diluted with water (100 mL) and then extracted with CH_2Cl_2 (2×50 mL). The combined organic extract was concentrated and the residue purified by flash chromatography (EtOAc-hexane, 1:1) to give compound **13** as a colourless oil, yield: 1.9 g (83%); $[\alpha]_D$: +29 (*c* 1.0, CH_2Cl_2); HR-MS (ES): *m/z* = 355.1463, calcd. for $C_{21}H_{24}O_3P$ (M+H)$^+$: 355.1457; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.68 (4H, m), 7.35–7.46 (6H, m), 6.80 (1H, dt, *J* = 18.7, 4.1 Hz), 4.54 (1H, t, *J* = 5.3 Hz), 4.24 (1H, dd, *J* = 10.0, 4.5 Hz), 2.34 (1H, ddd, *J* = 17.2, 8.0, 3.9 Hz), 2.17–1.99 (1H, m), 1.73–1.87 (2H, m), 1.17 (3H, s), 1.14 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.3 (d, *J* = 7.0 Hz), 131.8 (d, *J* = 101.5 Hz), 131.2 (d, *J* = 10.2 Hz), 131.1 (d, *J* = 9.9 Hz), 130.7 (d, *J* = 2.5 Hz), 130.7 (d, *J* = 2.3 Hz), 130.6 (d, *J* = 99.3 Hz), 130.0 (d, *J* = 103.4 Hz), 127.2 (d, *J* = 12.2 Hz, 2C), 107.6, 72.0 (d, *J* = 8.1 Hz), 69.0 (d, *J* = 7.7 Hz), 26.4, 24.6, 24.5, 21.4 (d, *J* = 13.3 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 30.57.

(1a*S*,3a*S*,6a*S*,6b*R*)-6b-(Diphenylphosphinoyl)-5,5-dimethylhexahydro-1,4,6-trioxacyclopropa[*e*]indene (14)

Lithium *tert*-butyl peroxide (0.05 M solution in toluene, 314 μL, 0.15 mmol) was added to a solution of (3a*S*,7a*S*)-7-(diphenylphosphinoyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[1,3]dioxole **13** (35.4 mg, 0.1 mmol) in toluene (1 mL) at 0 °C. The cooling was removed and the reaction mixture stirred at ambient temperature for 16 h. Water (30 mL) was added and the mixture extracted with CH_2Cl_2 (2×20 mL). The combined extract was concentrated and the residue purified by flash chromatography (EtOAc-hexane, 1:1) to give compound **14** as a gum, yield: 28.9 mg (78%); $[\alpha]_D$: +20 (*c* 1.0, CH_2Cl_2); HR-MS: *m/z* = 393.1247, calcd. for $C_{21}H_{23}NaO_4P$ (M+Na)$^+$: 393.1232; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (2H, dd, *J* = 11.8, 8.0 Hz), 7.77 (2H, dd, *J* = 11.3, 8.1 Hz), 7.36–7.48 (6H, m), 4.85 (1H, dd, *J* = 7.1, 3.7 Hz), 3.96 (1H, dd, *J* = 15.2, 7.3 Hz), 2.96 (1H, dd, *J* = 5.2, 2.2 Hz), 2.07–1.89 (2H, m), 1.74–1.56 (2H, m), 1.35 (3H, s), 1.11 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.2 (d, *J* = 2.5 Hz), 131.1 (d, *J* = 2.4 Hz), 131.0 (d, *J* = 8.9 Hz), 130.9 (d, *J* = 9.7 Hz), 129.9 (d, *J* = 101.5 Hz), 127.4 (d, *J* = 102.6 Hz), 127.3 (d, *J* = 12.0 Hz), 127.1 (d, *J* = 12.2 Hz), 107.1, 71.4 (d, *J* = 8.2 Hz), 68.3 (d, *J* = 11.4 Hz), 55.7 (d, *J* = 105.8 Hz), 55.2, 26.2, 24.0, 21.8, 19.6. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 30.11.

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