Copper-Catalysed, Enantioselective Desymmetrisation of *meso* Cyclic Allylic Bis(diethyl phosphates) with Organozinc Reagents

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A highly regio-, diastereo- and enantioselective desymmetrization of five-, six-, and seven-membered *meso*, cyclic allylic bis(diethyl phosphates) (**3**–**5**) with organozinc reagents was developed, using catalytic amounts (10 mol%) of $[Cu(OTf)]_2 \cdot C_6H_6$ and two different classes of chiral ligands: Schiff bases **1** and phosphoramidites **2**. Good to excellent enantioselectivities were obtained for every substrate by a subtle balance of ligand structure and experimental conditions. In particular, *ee*'s of up to 88 % were obtained for the five-membered ring substrate **3** with ligands **1cjo** and **1cjm** using Et_2Zn (94 % *ee* with Me_2Zn, 88 % *ee* with $n Bu_2Zn$). Schiff-base ligands **1** were not effective with the six- and seven-membered substrates **4** and **5**. The use of phosphoramidite ligands **2** afforded *ee*'s of up to 94 % (Et_2Zn) for the six-membered ring product **7**, and virtually only one enantiomer (*ee* $\geq$ 98 %, with Et_2Zn) for the seven-membered ring product **8**. In addition, the desymmetrisation of the conduritol derivative **10** was obtained, with *ee*'s of up to 86 %. In this case, a fully functionalised cyclohexane derivative, containing four contiguous stereocentres and a double bond, was obtained as a single diastereomer and in high enantiomeric excess from an achiral starting material.

Introduction

The substitution of allylic functionalities by hard carbon nucleophiles, such as organometallics, has recently attracted much attention and several methods have been developed to achieve regio-,[1] diastereo- and enantiocontrol. The leaving group can be displaced either in an α or γ fashion by the incoming carbon nucleophile, depending on the substrate, leaving group, organometallic reagent and metal source. Some catalytic, enantioselective protocols have recently appeared using organozinc[2] or Grignard[3] reagents, and a chiral copper complex. High *ee*'s were obtained using hindered organozinc reagents, while reactions of less hindered reagents proceeded with significantly lower enantioselectivity.[2a] Cinnamyl chlorides and bromides underwent allylic alkylation with organozinc reagents with significant enantioselectivity (up to 81 % *ee*), in the presence of copper phosphoramidite complexes.[2e,2f] The allylic substitution of 3-substituted cinnamyl diethyl phosphates with organozinc reagents, in the presence of copper pyridinyl peptide Schiff-base ligands, was also found to proceed with 78–90 % *ee* leading to the formation of asymmetric quaternary carbon centres.[2c,2d] A highly enantioselective allylic substitution of allylic chlorides by Grignard reagents (*ee* up to 96 %), catalysed by chiral copper phosphoramidite complexes, was also recently reported.[3d,3e,3f]

In the case of *meso*, cyclic allylic diol derivatives, the desymmetrisation by allylic substitution is a powerful synthetic methodology for the construction of enantiomerically enriched functionalised products.[4] This reaction can occur with α- or γ-substitution, and either with overall retention or overall inversion. In the case of α-substitution, where an allylic alcohol derivative is obtained, a second allylic substitution might occur, again in α or γ and either with retention or inversion. Based on this complex scenario, up to 15 different products may be formed (four pairs of enantiomers in the case of monosubstitution, and three pairs of enantiomers plus one *meso* compound in the case of disubstitution). The palladium-catalysed desymmetrisation of *meso*, cyclic allylic diol derivatives, pioneered by Trost and co-workers, is usually performed with soft nucleophiles and occurs with α-substitution and overall retention.[4b,4c] A somewhat related enantioselective ring opening of *meso*-oxabicyclic alkenes with organometallic reagents was reported by Lautens et al. (palladium-catalysed addition of alkylzinc reagents and Rh^I-catalysed addition of arylboronic acids),[5] and by Pineschi, Feringa and co-workers (Cu^I-catalysed addition of alkylzinc reagents).[6] In the first case, the product of γ-substitution with retention is obtained (the nucleophile

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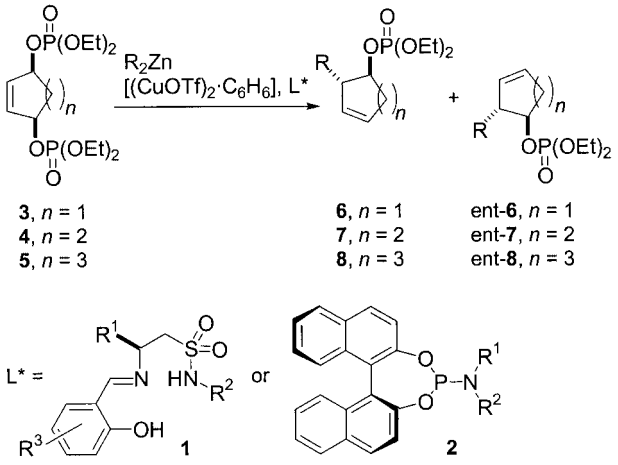
attacks from the same side of the allylic leaving group),[5] whereas in the second case the γ-substitution reaction takes place with inversion.[6]

We have recently disclosed a new highly regio-, diastereo-, and enantioselective desymmetrisation of *meso*, cyclic allylic bis(diethyl phosphates) with organozinc reagents catalysed by copper(I) complexes of chiral Schiff-base ligands **1**[7] and of chiral, binaphthol derived, phosphoramidites **2** (Scheme 1).[8]



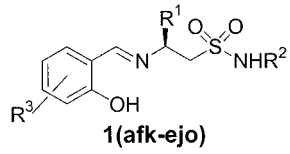
Scheme 1. Desymmetrisation of *meso*, cyclic allylic bis(diethyl phosphates) **3**–**5** with organozinc reagents catalysed by the copper(I) complexes of chiral Schiff-base ligands **1** or phosphoramidites **2**.

In the case of the five- and seven-membered ring substrates **3** and **5**, the reaction took place exclusively via γ-substitution with inversion, while in the case of the six-membered ring substrate **4**, variable amounts of the product arising from γ-substitution with retention were also obtained, depending on the ligand and the experimental conditions (vide infra). In this paper we present a full account of this work.

Results and Discussion

Desymmetrisation of Cyclic Allylic Bis(diethyl phosphates) with Chiral Schiff Bases 1

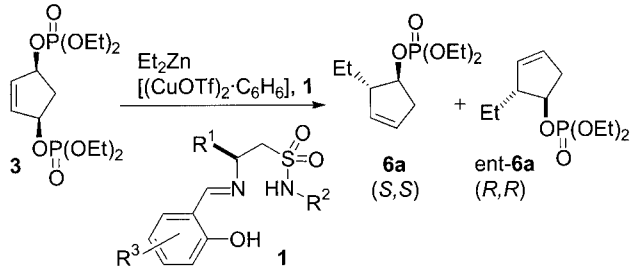
A library of 125 ligands **1** (Figure 1)[9] was screened in the copper catalysed desymmetrisation of *meso*-**3** with diethylzinc. Cu^{I} complexes were preformed in situ by stirring a 10 mol% solution of ligand **1** with 10 mol% $[CuOTf]_2 \cdot C_6H_6$ in toluene/THF (95:5) at room temperature. Diethylzinc (solution in toluene) and *meso*-4-cyclopentene-1,3-diyl bis(diethyl phosphate) (**3**) were then added to the mixture at –78 °C, and the reaction was stirred for 15 h at this temperature before quenching. The chiral copper complex appears to be essential to obtain good conversions. In fact,



a; R^1 = Me
b; R^1 = *i*Pr
c; R^1 = *i*Bu
d; R^1 = CH_2Ph
e; R^1 = *t*Bu
f; R^2 = CH_2Ph
g; R^2 = (*R*) -CH(Me)Cy
h; R^2 = (*S*) -CH(Me)Cy
i; R^2 = *i*Pr
j; R^2 = $CHPh_2$
k; R^3 = H
l; R^3 = 3,5-*t*Bu_2
m; R^3 = 3,5-Cl_2
n; R^3 = 5,6 -$(CH)_4$-
o; R^3 = 3-Ph

Figure 1. Library of 125 chiral Schiff-base ligands **1** for catalytic enantioselective desymmetrisation

Table 1. High-throughput screening of the library of ligands **1**[a]



Entry	Ligand	R^1	R^2	R^3	*ee* [%][b] (conf.) [c]	Yield [%]
1	**1cjo**	*i*Bu	$CHPh_2$	3-Ph	88 (*S*,*S*)	54
2	**1cjm**	*i*Bu	$CHPh_2$	3,5-Cl_2	88 (*S*,*S*)	47
3	**1cjl**	*i*Bu	$CHPh_2$	3,5-*t*Bu_2	74 (*S*,*S*)	42
4	**1ajm**	Me	$CHPh_2$	3,5-Cl_2	72 (*S*,*S*)	62
5	**1cjk**	*i*Bu	$CHPh_2$	H	68 (*S*,*S*)	54
6	**1cjn**	*i*Bu	$CHPh_2$	5,6-$(CH)_4$-	66 (*S*,*S*)	49
7	**1afk**	Me	CH_2Ph	H	38 (*R*,*R*)	13
8	**1bfk**	*i*Pr	CH_2Ph	H	49 (*R*,*R*)	12
9	**1ehk**	*t*Bu	(*S*)-CH(Me)Cy	H	52 (*R*,*R*)	26

[a] $[CuOTf]_2 \cdot C_6H_6$ (0.1 equiv.), ligand **1** (0.1 equiv.), Et_2Zn (2.0 equiv.), **3** (1.0 equiv.), toluene/THF: 95:5, –78 °C, 15 h. Selected results. [b] Determined by GC: MEGADEX DMEPEβ, OV 1701, 25 m, film 0.25 μm, carrier H_2 (70 kPa). [c] See main text.

the addition of Et_2Zn in the presence of $[CuOTf]_2{\cdot}C_6H_6$ and in the absence of the chiral ligand gave only starting material and minute amounts of the reaction product (8 %).

The most interesting results obtained from the library screening are shown in Table 1: good *ee*'s (up to 88 %), in favour of **6a** [(*S*,*S*)-enantiomer], were achieved using ligands **1cjo** and **1cjm**. The absolute configuration of **6a** was assigned by chiral GC after comparison of its retention time with the retention time of an enantiomerically pure sample of (*S*,*S*)-**6a**. This was synthesised by a CuCN-mediated (3.5 equiv.) allylic alkylation of (1*R*,3*S*)-(+)-*cis*-3-hydroxy-4-cyclopenten-1-yl acetate with EtMgCl (3.0 equiv.) in THF at –18 °C (via γ-substitution of the acetate with inversion),[10] followed by reaction with $(EtO)_2POCl$ (pyridine, DMAP, CH_2Cl_2).

It is interesting to note that ligands with different steric hindrance, although possessing the same absolute configuration at the stereogenic centre bearing R^1, may lead to the preferred formation of the opposite enantiomer ent-**6a** (*R*,*R*) (Table 1, Entries 7–9). An *ee* of 52 % in favour of ent-**6a** was obtained using ligand **1ehk**. As a rule of thumb, substituted salicylaldehydes [R^3 = 3,5-Cl_2; 3-Ph; 3,5-*t*Bu; 5,6-$(CH)_4$-], bulky amines (R^2 = $CHPh_2$), and relatively small substituents at the stereogenic centre (R^1 = *i*Bu, Me) favour the formation of **6a**, while unsubstituted salicylaldehydes (R^3 = H) and relatively small amines (e. g. R^2 = CH_2Ph) tend to favour the formation of ent-**6a**.

An optimisation of the reaction conditions (solvents, temperature and copper source) revealed that increasing the temperature to –60 °C did not have any detrimental effect on the enantioselectivity; conversely, complete conversion and almost quantitative yield were observed (Table 2, Entries 1–3). The reaction was also found to be rather insensitive to the oxidation state of the copper source[11] (Table 2, cf. Entries 2 and 8), while the use of more coordinating copper counterions (e. g. acac, OAc, Table 2, Entries 10–12) lowered the enantiomeric excesses. As for the solvent, the addition of a small amount of THF to toluene was found to have a beneficial effect on the enantioselectivity of the reaction (Table 2, Entry 3 vs. 7). The reaction in THF gave a lower *ee* (Table 2, Entry 6), while the use of CH_2Cl_2 or *n*-hexane inhibited the reaction completely (Table 2, Entries 4–5).

A study of the dependence of the *ee* of the reaction product on the optical purity of ligand **1cjo** was undertaken to gain a deeper insight into the reaction mechanism.[12] A range of ligands **1cjo** with increasing optical purities (0, 20, 40, 60, 80, 100 % *ee*) was screened under the optimised reaction conditions. The correlation between the % *ee* of ligand **1cjo** and the % *ee* of product **6a** is shown in Figure 2. An

Table 2. Optimisation of the enantioselective desymmetrisation of the *meso*-bis(diethyl phosphate) **3** catalysed by Cu^I complexes of ligands **1** to give **6a**[a]

Entry	Ligand	Cu	Solvent[b]	*T* [°C]	*ee* [%] (conf.)	Yield [%]
1	**1cjo**	$[CuOTf]_2{\cdot}C_6H_6$	Tol/THF, 95:5	–60	88 (*S*,*S*)	>98
2	**1cjm**	$[CuOTf]_2{\cdot}C_6H_6$	Tol/THF, 95:5	–60	88 (*S*,*S*)	>98
3	**1cjl**	$[CuOTf]_2{\cdot}C_6H_6$	Tol/THF, 95:5	–60	74 (*S*,*S*)	80
4	**1cjl**	$[CuOTf]_2{\cdot}C_6H_6$	*n*-hexane	–60	0	0
5	**1cjl**	$[CuOTf]_2{\cdot}C_6H_6$	CH_2Cl_2	–20	0	0
6	**1cjl**	$[CuOTf]_2{\cdot}C_6H_6$	THF	–60	54 (*S*,*S*)	60
7	**1cjl**	$[CuOTf]_2{\cdot}C_6H_6$	Tol	–60	67 (*S*,*S*)	75
8	**1cjm**	$Cu(OTf)_2$	Tol/THF, 95:5	–60	86 (*S*,*S*)	81
9	**1cjm**	$[CuOTf]_2{\cdot}$Tol	Tol/THF, 95:5	–60	84 (*S*,*S*)	>98
10	**1cjm**	Cu(acac)	Tol/THF, 95:5	–60	83 (*S*,*S*)	>98
11	**1cjm**	Cu(OAc)	Tol/THF, 95:5	–60	81 (*S*,*S*)	89
12	**1cjm**	$Cu(OAc)_2$	Tol/THF, 95:5	–60	78 (*S*,*S*)	91

[a] "Cu" (0.1 equiv.), ligand **1** (0.1 equiv.), Et_2Zn (2.0 equiv.), **3** (1.0 equiv.), solvent, T (°C), 15 h. [b] Tol = toluene.

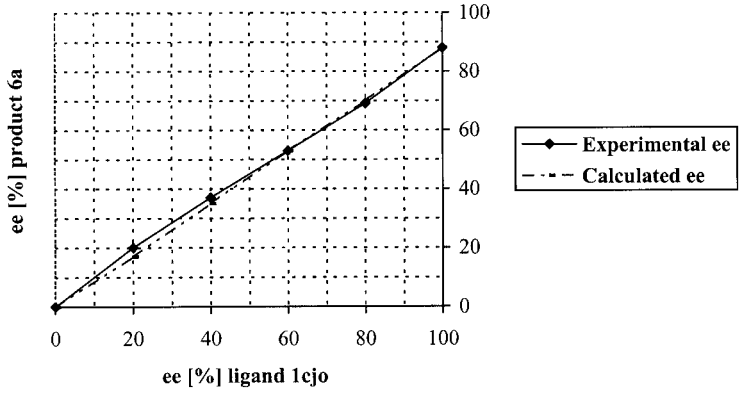
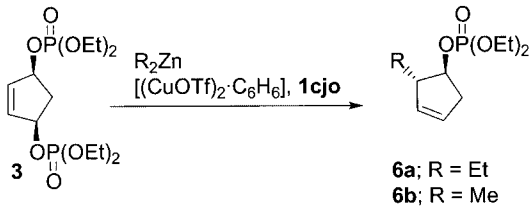


Figure 2. Correlation between the enantiomeric excess of the ligand **1cjo** and the *ee* of phosphate **6a**

Table 3. Scope of the enantioselective desymmetrisation of the *meso*-bis(diethyl phosphate) **3** catalysed by Cu^I complexes of ligands **1** (different organozinc reagents)[a]



6a; R = Et
6b; R = Me
6c; R = *n*Bu
6d; R = *i*Pr
6e; R = Ph

Entry	R	Product	*T* [°C]	*ee* [%] (conf.)	Yield [%]
1	Et	**6a**	–60	88[b] (*S*,*S*)	>98
2	Me	**6b**	–60	94[b] (*S*,*S*)	75[d]
3	*n*Bu	**6c**	–60	88[b] (*S*,*S*)	>98
4	*i*Pr	**6d**	–60	28[b] (*S*,*S*)	>98
5	Ph_2Zn (1 equiv.) + Et_2Zn (2 equiv.)	**6e**	–40	60[c] (*S*,*R*)	30 (**6e/6a**, 1.4:1)
6	Ph_2Zn (1 equiv.) + Me_2Zn (2 equiv.)	**6e**	–60	78[c] (*S*,*R*)	30 (**6e/6b**, 10:1)
7	Ph_2Zn (2 equiv.) + Me_2Zn (1 equiv.)	**6e**	–60	68[c] (*S*,*R*)	60 (**6e/6b**, 48:1)

[a] $[CuOTf]_2{\cdot}C_6H_6$ (0.1 equiv.), ligand **1cjo** (0.1 equiv.), R_2Zn (2.0 equiv.), **3** (1.0 equiv.), toluene/THF: 95:5, *T* (°C), 15 h. [b] determined by GC, MEGADEX DMEPEβ, OV 1701, 25 m, film 0.25 μm, carrier H_2 (70 kPa). [c] determined by ^1H NMR analysis of the corresponding Mosher ester, after reduction of the phosphate with $LiAlH_4$ in diethyl ether (quant. yield), and derivatization of the resulting alcohol with (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid, DCC, 4-DMAP in dichloromethane (quant. yield). [d] Reaction time = 67 h.

almost perfect linear dependence is observed; therefore, although the presence of aggregated species cannot be ruled out, the catalytic active species should contain only one ligand.

In order to investigate the scope of this new reaction, different organozinc reagents were tested with bis(diethyl phosphate) **3**, using the best ligand from the previous screening (**1cjo**) (Table 3). In the case of dimethylzinc, the reaction gave exclusively the product arising from γ-substitution with inversion (**6b**),[13] in reasonably good yield (75 %) and excellent enantiomeric excess (94 % *ee*) (Table 3, Entry 2). Other dialkylzinc reagents were also tested: nBu_2Zn gave results comparable to Et_2Zn (quantitative yield and 88 % *ee* for product **6c**, Entry 3),[13] whereas iPr_2Zn afforded product **6d** in a modest 28 % *ee* (quantitative yield, Entry 4).[13] Allylic phenylation was achieved by reaction of bis(diethyl phosphate) **3** with a mixture of diphenylzinc and dimethylzinc or diethylzinc.[14] It is interesting to note that: i) no conversion was obtained using diphenylzinc; ii) the combination of diphenylzinc and diethylzinc, which is highly effective in the transfer of a phenyl group to aldehydes,[14a] gave a 1.4:1 ratio of the phenyl (**6e**) and ethyl adduct (**6a**) (Table 3, Entry 5); iii) the combination of diphenylzinc and dimethylzinc, which is highly effective in the copper catalysed conjugate phenylation of enones,[14b] gave the transfer of the phenyl group selectively (Table 3, Entry 6). Final optimisation of the diphenylzinc/dimethylzinc ratio (2:1) gave product (**6e**),[13] arising from γ-substitution with inversion, in moderate yield (60 %) and fair *ee* (68 %) (Table 3, Entry 7).

Reaction of diethylzinc with *cis*-2-cyclohexene-1,4-diyl bis(diethyl phosphate) (**4**) gave the γ-substitution products originating from either inversion (**7a**) or retention (**9**) with good diastereoselectivity (81:19–4:96) depending on the solvent and the ligand used (Table 4, Entries 1–5). Compound **7a** was formed in low enantiomeric excess, while compound **9** was always isolated as a racemic mixture. In the case of *cis*-2-cycloheptene-1,4-diyl bis(diethyl phosphate) (**5**), only the product arising from γ-substitution with inversion (**8a**) was detected, with moderate enantiomeric excess (up to 56 %) (Table 4, Entries 6–9).

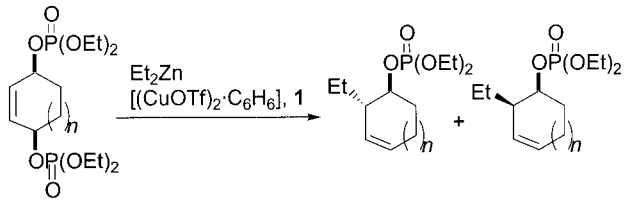
At present we do not have a convincing rationale for these unexpected results. A possible reason for the striking different stereochemical behaviour of the cycloalkene derivatives **3** and **5** with respect to **4** might be related to their symmetry. Indeed, while the cyclopentene derivative **3** and the cycloheptene derivative **5** can exist and react in a C_S-conformation (plane-symmetric), the cyclohexene derivative **4** is better described as a mixture of readily interconverting enantiomers.

The enantiomeric excess and the absolute configuration of phosphate **8a** (*S*,*S*) were determined by ^1H NMR spectroscopy after reduction to the corresponding alcohol ($LiAlH_4$, diethyl ether) and formation of the Mosher ester [(*R*)-(+)-α-Methoxy-α-(trifluoromethyl) phenylacetic acid, DCC, 4-DMAP in dichloromethane][15] (see details in the Experimental Section).

Desymmetrisation of Cyclic Allylic Bis(diethyl phosphates) with Phosphoramidite Ligands 2

Phosphoramidites of general structure **2** (Figure 3) serve as very effective ligands in a number of catalytic asymmetric

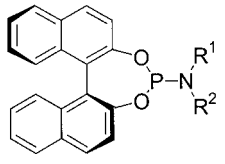
Table 4. Enantioselective desymmetrisation of *meso*-bis(diethyl phosphate) **4** and **5** catalysed by Cu^I complexes of ligands **1**[a]



Entry	Substrate	Ligand	Solvent	*T* [°C]	**7a/9**	*ee* [%]	Yield [%]
1	**4**	**1cjm**	Tol/THF, 95:5	–78	22:78	8 (**7a**)[b]	62
2	**4**	**1cjo**	Tol	–78	16:84	<5 (**7a**)[b]	74
3	**4**	**1cjo**	THF	–78	81:19	<5 (**7a**)[b]	43
4	**4**	**1ajk**	Tol	–30	77:23	21 (**7a**)[b]	45
5	**4**	**1ajk**	Tol/THF, 95:5	–78	7:93	7 (**7a**)[b]	47
6	**5**	**1cjm**	Tol/THF, 95:5	–60	–	27 (**8a**)[c]	21
7	**5**	**1cjo**	Tol/THF, 95:5	–60	–	13 (**8a**)[c]	35
8	**5**	**1cfk**	Tol/THF, 95:5	–60	–	41 (**8a**)[c]	45
9	**5**	**1cjk**	Tol/THF, 95:5	–60	–	56 (**8a**)[c]	47

[a] $[CuOTf]_2{\cdot}C_6H_6$ (0.1 equiv.), ligand **1** (0.1 equiv.), Et_2Zn (2.0 equiv.), **4** or **5** (1.0 equiv.), solvent, *T* (°C), 15 h. [b] Determined by GC: MEGADEX DMEPEβ, OV 1701, 25 m, film 0.25 μm, carrier H_2 (70 kPa), after reduction of the phosphate ester to the corresponding alcohol with $LiAlH_4$ in diethyl ether (quant. yield) (see details in the Experimental Section). [c] Determined by ^1H NMR analysis of the Mosher esters, after reduction of the phosphate ester to the corresponding alcohol with $LiAlH_4$ in diethyl ether (see details in the Experimental Section).

carbon–carbon bond forming reactions.[16] These include the already mentioned copper-catalysed ring opening of oxabicyclic alkenes[6] and allylic alkylation,[2e,2f,3c–3e,17] the conjugate addition of dialkylzincs to enones,[18] unsaturated esters[19] and nitro alkenes,[20] the ring opening of vinyl epoxides,[21] the desymmetrisation of methylidene cycloalkene oxides,[22] and the rhodium-catalysed conjugate addition of arylboronic acids.[23]



2a; $R^1 = R^2$ = Me
2b; $R^1 = R^2$ = (*R*)-CH(Me)Ph
2c; $R^1 = R^2$ = (*S*)-CH(Me)Ph
2d; R^1 = (*R*)-CH(Me)Ph, R^2 = *i*Pr
2e; $R^1 = R^2$ = *i*Pr
2f; R^1 = (*R*)-CH(Me)Ph, R^2 = H

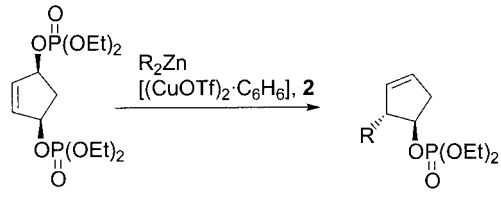
Figure 3. Structure of the phosphoramidite ligands **2**

Copper complexes of ligands **2a**–**f** were obtained in situ by stirring copper(I) triflate with 2.0 equiv. of the appropriate ligand in toluene (45 min, room temp.). Reaction of *meso*-4-cyclopentene-1,3-diyl bis(diethyl phosphate) (**3**), with 2.0 equiv. of Et_2Zn in the presence of 10 mol% of the copper-phosphoramidite complexes afforded the product arising from γ-sustitution with inversion ent-**6a** [(*R*,*R*)-enantiomer] in variable yields and enantiomeric excesses (Table 5). In particular, the screening of the ligands revealed that good yields and enantiomeric excesses were obtained when phosphoramidite ligands with bulkier secondary amine substituents were used (Table 5, Entries 1–6). Varying the temperature with the best ligand (**2b**) (Table 5, Entries 7–9), the enantiomeric excess was increased to 87 % at –40 °C (Entry 7). Dimethylzinc was considerably less reactive than diethylzinc: reactions at –40 °C or –20 °C gave poor conversions (10–20 %) associated with very good *ee*'s (90–92 %) (Table 5, Entries 10,11). When the reaction was run at 0 °C, ent-**6b** was obtained with a fair conversion (54 %), still associated with a good *ee* (87 %, Table 5, Entry 12). Other dialkylzinc reagents were also tested: nBu_2Zn gave a lower *ee* compared to Et_2Zn (ent-**6c**, 72 % *ee*, Entry 13), whereas iPr_2Zn afforded product ent-**6d** in a very poor 12 % *ee* (Entry 14).

Reaction of *meso*-2-cyclohexene-1,4-diylbis(diethyl phosphate) (**4**) with Et_2Zn afforded variable proportions of products ent-**7a** and **9** arising from γ-substitution with either inversion (ent-**7a**) or retention (**9**) (Table 6).

In particular, small ligands (e. g. **2a**, Entry 1) and higher reaction temperatures (cf. Entries 7–9, 10–11) afforded larger proportions of product **9**, whereas ligands bearing bulkier amine substituents and lower temperatures favoured the formation of product ent-**7a**. An enantiomeric excess of 82 % was obtained for the product arising from γ-substitution with inversion (ent-**7a**), using ligand **2b** at –60 °C, albeit in rather low yield (Entry 2). Increasing the reaction temperature to –40 °C improved both the yield (77 %) and the enantiomeric excess (90 %, Entry 7). Interestingly, ligand **2c** comprising (*S*)-BINOL and the (*S*,*S*)-diamine moiety, afforded a very promising 76 % *ee* at –60 °C (Entry 3), which could be improved to 94 %, with 69 % yield, raising the temperature to –40 °C (Entry 10). It should be noted that this is one of the few cases where the matched combination arises in **2** from (*S*)-BINOL and the (*S*,*S*)-diamine.[21,22] Product **9**, on the other hand was always isolated as a racemic mixture. The absolute configuration of ent-**7a** was determined after reduction to the corresponding

Table 5. Desymmetrisation of the *meso*-bis(diethyl phosphate) **3** using phosphoramidite ligands **2**[a]



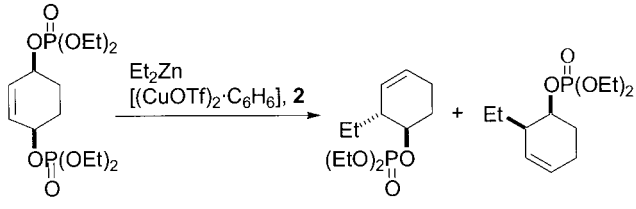
3

ent-**6a**; R = Et
ent-**6b**; R = Me
ent-**6c**; R = *n*Bu
ent-**6d**; R = *i*Pr

Entry	Ligand	R	*T* [°C]	Product	*ee* [%][c] (conf.)[d]	Yield [%][b]
1	**2a**	Et	–60	ent-**6a**	24 (*R*,*R*)	10
2	**2b**	Et	–60	ent-**6a**	74 (*R*,*R*)	>98
3	**2c**	Et	–60	ent-**6a**	60 (*R*,*R*)	20
4	**2d**	Et	–60	ent-**6a**	58 (*R*,*R*)	30
5	**2e**	Et	–60	ent-**6a**	10 (*R*,*R*)	65
6	**2f**	Et	–60	ent-**6a**	0	13
7	**2b**	Et	–40	ent-**6a**	87 (*R*,*R*)	>98
8	**2b**	Et	–20	ent-**6a**	84 (*R*,*R*)	>98
9	**2b**	Et	0	ent-**6a**	81 (*R*,*R*)	>98
10	**2b**	Me	–40	ent-**6b**	92 (*R*,*R*)	10
11	**2b**	Me	–20	ent-**6b**	90 (*R*,*R*)	20
12	**2b**	Me	0	ent-**6b**	87 (*R*,*R*)	54
13	**2b**	*n*Bu	–40	ent-**6c**	72 (*R*,*R*)	52
14	**2b**	*i*Pr	–60	ent-**6d**	12 (*R*,*R*)	>98

[a] $[CuOTf]_2 \cdot C_6H_6$ (0.05 equiv.), ligand **2** (0.2 equiv.), R_2Zn (2.0 equiv.), **3** (1.0 equiv.), *T* (°C), toluene, 15 h. [b] GC yield. [c] Determined by GC: MEGADEX DMEPEβ, OV 1701, 25 m, film 0.25 μm, carrier H_2 (70 kPa). [d] The absolute configuration of **6a**–**6d** was determined as described above in the main text and in ref.[13]

Table 6. Desymmetrisation of *meso*-bis(diethyl phosphate) **4** using phosphoramidite ligands **2**[a]



4 ent-**7a** **9**

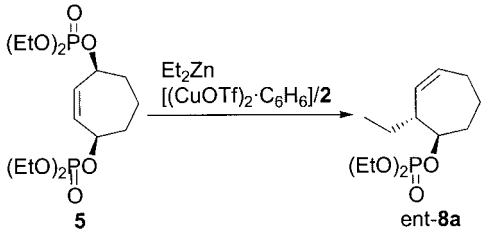
Entry	Ligand	*T* [°C]	ent-**7a**/**9**	*ee* [%] (ent-**7a**)[b] (conf.)[c]	Yield [%][d]
1	**2a**	–60	31:69	35 (*R*,*R*)	13
2	**2b**	–60	76:24	82 (*R*,*R*)	35
3	**2c**	–60	87:13	76 (*R*,*R*)	16
4	**2d**	–60	79:21	68 (*R*,*R*)	3
5	**2e**	–60	69:31	48 (*R*,*R*)	10
6	**2f**	–60	–	–	0
7	**2b**	–40	87:13	90 (*R*,*R*)	77
8	**2b**	–20	67:33	84 (*R*,*R*)	89
9	**2b**	0	44:56	52 (*R*,*R*)	85
10	**2c**	–40	85:15	94 (*R*,*R*)	69
11	**2c**	–20	68:32	93 (*R*,*R*)	88

[a] $[CuOTf]_2 \cdot C_6H_6$ (0.05 equiv.), ligand **2** (0.2 equiv.), Et_2Zn (2.0 equiv.), **4** (1.0 equiv.), *T* (°C), toluene, 15 h. [b] Determined by GC: MEGADEX DMEPEβ, OV 1701, 25 m, film 0.25 μm, carrier H_2 (70 kPa), after reduction of the phosphate ester to the corresponding alcohol with $LiAlH_4$ in diethyl ether (quant. yield). [c] The absolute configuration was determined by comparison of the optical rotation value $[\alpha]_D$ of the corresponding alcohol with the literature value (see details in the Experimental Section). [d] Isolated yield.

alcohol (see details in the Experimental Section) and comparison of the optical rotation ($[\alpha]_D$) with the literature value.[21]

Reaction of the seven-membered-ring substrate **5** (Table 7) afforded only the product arising from γ-substitution with inversion (ent-**8a**) with excellent enantiomeric excess (> 98 %) and isolated yield (85–86 %) using ligands **2b** and **2c** (Entries 4,5).

Table 7. Desymmetrisation of the *meso*-bis(diethyl phosphate) **5** using phosphoramidite ligands **2**[a]



Entry	Ligand	*T* [°C]	*ee* [%][b] (conf.)[c]	Yield [%][d]
1	**2a**	–60	n. d.	5
2	**2b**	–60	98 (*R*,*R*)	81
3	**2c**	–60	>98 (*R*,*R*)	75
4	**2b**	–40	>98 (*R*,*R*)	85
5	**2c**	–40	>98 (*R*,*R*)	86

[a] $[CuOTf]_2{\cdot}C_6H_6$ (0.05 equiv.), ligand **2** (0.2 equiv.), Et_2Zn (2.0 equiv.), **5** (1.0 equiv.), *T* (°C), toluene, 15 h. [b] Determined by ^1H NMR analysis of the Mosher esters, after reduction of the phosphate ester to the corresponding alcohol with $LiAlH_4$ in diethyl ether (see details in the Experimental Section). [c] The absolute configuration was determined by ^1H NMR analysis of the Mosher ester (see details in the Experimental Section). [d] Isolated yield.

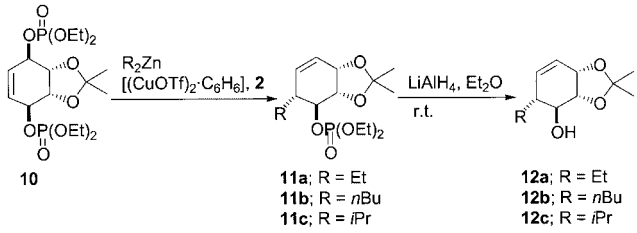
This is a case of very remarkable chemo-, regio-, diastereo- and enantio-control, where the potential competition of several reaction pathways might in principle lead up to 15 different reaction products (see above, in the Introduction section) and only one is obtained.

Desymmetrisation of the Conduritol Derivative 10

When ligands **1** were used in the desymmetrisation of bis(diethyl phosphate) **10**, no reaction took place. On the contrary, the use of ligands **2** allowed the synthesis of the compound derived from γ-substitution with inversion (**11**) with a variety of organozinc reagents (Table 8).

Phosphates **11** were then reduced to the corresponding alcohols **12** ($LiAlH_4$ in Et_2O) and the *ee*'s were measured by injection in a GC equipped with a chiral capillary column (see details in the Experimental Section). In particular, good *ee*'s (up to 86 %) were obtained for the addition of diethylzinc using ligand **2b**, albeit in poor yields (31 %; Table 8, Entry 2). The yield could be improved (52 %, 74 % considering the recovered starting material; Table 8, Entry 3) using a longer reaction time (72 h). Reaction with nBu_2Zn and iPr_2Zn were generally less selective (Table 8, Entries 9, 10). The absolute configuration of phosphates **11** (1*S*,2*R*,5*S*,6*S*) was tentatively assigned by analogy with the stereochemistry of the six-membered-ring phosphate ent-**7a**.[24] The desymmetrisation of the bis(diethyl phosphate) **10** is particularly interesting since a fully functionalised cyclohexane derivative, containing four contiguous stereocentres and a double bond, was obtained as a single diastereomer and in high enantiomeric excess (up to 86 %) from an achiral starting material.

Table 8. Desymmetrisation of *meso*-bis(diethyl phosphate) **10** using phosphoramidite ligands **2**[a]



Entry	Ligand	R	*T* (°C)	Product	*ee* [%][b]	Yield [%][c]
1	**2a**	Et	–60	**12a**	60	71
2	**2b**	Et	–60	**12a**	86	31
3	**2b**	Et	–60	**12a**	86	52[d]
4	**2c**	Et	–60	**12a**	2	23
5	**2a**	Et	–40	**12a**	54	60
6	**2b**	Et	–40	**12a**	65	78
7	**2a**	Et	–20	**12a**	58	93
8	**2b**	Et	–20	**12a**	54	90
9	**2b**	*n*Bu	–60	**12b**	56	15
10	**2b**	*i*Pr	–60	**12c**	20	60

[a] $[CuOTf]_2{\cdot}C_6H_6$ (0.05 equiv.), ligand **2** (0.2 equiv.), Et_2Zn (2.0 equiv.), **10** (1.0 equiv.), *T* (°C), toluene, 15 h. [b] Determined by GC: MEGADEX DMEPEβ, OV 1701, 25 m, film 0.25 μm, carrier H_2 (70 kPa), after reduction of the phosphate ester to the corresponding alcohol **12** with $LiAlH_4$ in diethyl ether (quant. yield) (see details in the Experimental Section). [c] Isolated yield. [d] Reaction time 72 h.

Conclusions

In summary, we have developed a highly regio-, diastereo- and enantioselective desymmetrisation of five-, six-, and seven-membered *meso*, cyclic allylic bis(diethyl phosphates) **3**–**5** with organozinc reagents, using catalytic amounts of $[Cu(OTf)]_2 \cdot C_6H_6$ and two different classes of chiral ligands: Schiff bases **1** and phosphoramidites **2**. Good to excellent enantioselectivities were attained for every single substrate by a subtle balance of ligand structure and experimental conditions. In fact, *ee*'s of up to 88 % were obtained for the five-membered ring substrate **3** with ligands **1cjo** and **1cjm** in the case of Et_2Zn (94 % *ee* with Me_2Zn and 88 % with nBu_2Zn). The Schiff-base ligands were not effective with the six- and seven-membered substrates **4** and **5**. The use of phosphoramidite ligands **2**, on the other hand, afforded *ee*'s of up to 94 % for the six-membered ring product ent-**7**, and virtually only one enantiomer (*ee* ≥ 98 %) for the seven-membered ring product ent-**8**. In addition, desymmetrisation of the conduritol derivative **10** was obtained, with *ee*'s of up to 86 %. In this case, a fully functionalised cyclohexane derivative, containing four contiguous stereocentres and a double bond, was obtained as a single diastereomer and in high enantiomeric excess from an achiral starting material. Work is in progress to expand the scope of this desymmetrisation methodology using other organometallic reagents.

Experimental Section

General Remarks: All reactions were carried out in flame-dried glassware with magnetic stirring under argon. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH_2Cl_2 (CaH_2), THF (Na), Et_2O (Na), toluene (Na). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} precoated glass plates (0.25 mm thickness). Visualisation was accomplished by irradiation with a UV lamp and/or staining with a ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 μm. Proton NMR spectra were recorded on a 400 MHz spectrometer. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3\delta$ = 7.26 ppm). Carbon NMR spectra were recorded on a 400 MHz (100 MHz) spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ^{31}P NMR spectra were recorded on a 400 MHz (162 MHz) spectrometer with complete proton decoupling. Infrared spectra were recorded with a standard Infrared spectrophotometer; peaks are reported in cm^{-1}. Optical rotation values were measured with an automatic polarimeter with a 1-dm cell at the sodium D line. Gas chromatography was performed with a GC instrument equipped with a flame ionisation detector, temperature and pressure control. When the enantiomeric excesses were determined by chiral GC, a MEGADEX DMEPEβ, OV 1701 capillary column (25 m, film 0.25 μm) was used, with a racemic sample as reference. The following compounds were synthesised as originally reported: *meso*-2-cyclohexene-1,4-diol,[25] *meso*-2-cycloheptene-1,4-diol,[25] *meso*-5,6-(isopropylidenedioxy)cyclohex-2-ene-1,4-diol.[26,27] *cis*-4-Cyclopentene-1,3-diol was purchased from Aldrich and used as received.

General Procedure for the Preparation of *meso*-Bis(diethyl phosphates) 3, 4, 5, 10:[28] *n*BuLi (1.6 M in hexanes, 4.70 mL, 7.5 mmol) was added dropwise to a cooled (–40 °C) solution of the *meso*-diol (3.00 mmol) in THF/TMEDA (4:1, 20 mL). The solution was stirred for 15 min before diethyl chloro phosphate (1.29 g, 7.5 mmol) was added via a syringe. The resulting mixture was stirred at –40 °C for 1 hour and slowly warmed to 0 °C, quenched with brine, and extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and volatiles were removed under reduced pressure. The crude residue was purified by flash chromatography (eluent: ethyl acetate/methanol, 94:6) to give the *meso*-bis(diethyl phosphates) **3**, **4**, **5**, **10** as colourless oils.

***meso*-4-Cyclopentene-1,3-diyl Bis(diethyl phosphate) (3):** Yield: 1.027 g (90 %). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.17–6.16 (m, 2 H), 5.25–5.19 (m, 2 H), 4.16–4.08 (m, 8 H), 2.98–2.88 (m, 1 H), 2.04 (dt, *J* = 14.6, *J* = 4.3 Hz, 1 H), 1.35 (t, *J* = 7.0 Hz, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9 (CH), 134.8 (CH), 79.0 (CH), 78.9 (CH), 63.7 ($2CH_2$), 63.6 ($2CH_2$), 39.4 (CH_2), 15.9 ($4CH_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.81 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2985, 1645, 1373, 1261, 1164, 1027, 989, 804 cm^{-1}. MS (FAB, glycerol): *m*/*z* (%) = 373 (60) $[M + H]^+$, 219 (100) $[M – (EtO)_2P(O)OH + H]^+$, 191 (25) $[M – (EtO)_2P(O)OH – (C_2H_4) + H]^+$, 163 (45) $[M – (EtO)_2P(O)OH – 2(C_2H_4) + H]^+$. HRMS (EI, 70 eV): *m*/*z* calcd. for $C_{13}H_{26}O_8P_2$: 372.1103 $[M]^+$; found: 372.1111.

***meso*-2-Cyclohexene-1,4-diyl Bis(diethyl phosphate) (4):** Yield: 0.996 g (86 %). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.93 (m, 2 H), 4.78–4.72 (m, 2 H), 4.06 (dq, *J* = 7.3, *J* = 7.3 Hz, 8 H), 2.04–1.94 (m, 2 H), 1.93–1.83 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.6 (2CH), 77.7 (2CH), 63.7 ($4CH_2$), 26.0 ($2CH_2$), 16.1 ($4CH_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.24 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2985, 1644, 1396, 1261, 1164, 1027, 989, 817 cm^{-1}. MS (FAB, glycerol): *m*/*z* (%) 409 (10) $[M + Na]^+$, 387 (40) $[M + H]^+$, 233 (100) $[M – (EtO)_2P(O)OH + H]^+$, 155 (95) $[(EtO)_2P(O)OH + H]^+$, 127 (50) $[(EtO)P(O)(OH)_2 + H]^+$, 99 (90) $[P(O)(OH)_3 + H]^+$. HRMS (EI, 70 eV) *m*/*z* calcd. for $C_{14}H_{29}O_8P_2$: 387.1338 $[M + H]^+$; found: 387.1378.

***meso*-2-Cycloheptene-1,4-diyl Bis(diethyl phosphate) (5):** Yield: 1.057 g (88 %). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.79 (br. s, 2 H), 4.91–4.82 (m, 2 H), 4.12–4.04 (m, 8 H), 2.04–1.94 (m, 2 H), 1.72–1.63 (m, 2 H), 1.31 (t, *J* = 8.0 Hz, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.9 (2CH), 77.4 (2CH), 63.7 ($4CH_2$), 33.8 ($2CH_2$), 22.4 (CH_2), 16.0 ($4CH_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.53 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2985, 1646, 1396, 1263, 1164, 1027, 989, 804 cm^{-1}. MS (FAB, glycerol): *m*/*z* (%) = 401 (20) $[M + H]^+$, 247 (50) $[M – (EtO)_2P(O)OH + H]^+$, 155 (100) $[(EtO)_2P(O)OH + H]^+$, 127 (25) $[(EtO)P(O)(OH)_2 + H]^+$, 99 (45) $[P(O)(OH)_3 + H]^+$. HRMS (EI, 70 eV) *m*/*z* calcd. for $C_{15}H_{30}O_8P_2$: 400.1316 $[M]^+$; found: 400.1446.

***meso*-Bis(diethyl phosphate) 10:** Yield: 1.224 g (89 %). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.93 (br. s, 2 H), 4.78–4.72 (m, 2 H), 4.31–4.23 (m, 2 H), 4.20–4.11 (m, 8 H), 1.51 (s, 3 H) 1.39–1.36 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.6 (2CH), 109.6 (C), 76.5 (2CH), 75.4 (2CH), 64.1 (J_{PC} = 4 Hz, $4CH_2$), 27.0 (CH_3), 24.9 (CH_3), 26.0 ($2CH_3$), 16.0 (J_{PC} = 7 Hz, $2CH_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.55 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2986, 2935, 2911, 1735, 1717, 1445, 1396, 1384, 1263, 1165, 1028, 972 cm^{-1}. MS (FAB, glycerol): *m*/*z* (%) = 459 (45) $[M + H]^+$, 305 (100) $[M – (EtO)_2P(O)OH + H]^+$, 155 (65) $[(EtO)_2P(O)OH + H]^+$, 127 (30) $[(EtO)P(O)(OH)_2 + H]^+$, 99 (60) $[P(O)(OH)_3 + H]^+$. HRMS (EI,

70 eV) *m*/*z* calcd. for $C_{17}H_{33}O_{10}P_2$: 459.1549 $[M + H]^+$; found: 459.1563.

General Procedure for the Screening of the Library of Ligands 1 in the Enantioselective Desymmetrisation of *meso*-Bis(diethyl phosphates) 3, 4, 5: Ligand **1** (0.017 mmol) was dissolved in dry toluene (1.2 mL) and dry THF (0.1 mL) in a flame-dried flask, under argon. $[Cu(OTf)]_2{\cdot}C_6H_6$ (4.3 mg; 0.0085 mmol) was subsequently added. The resulting yellowish solution was stirred at room temp. for 45 min. The reaction mixture was cooled to –78 °C, and treated with Et_2Zn (1.1 M solution in toluene; 0.310 mL, 0.340 mmol) and, after 10 min, with a solution of *meso*-bis(diethyl phosphate) (0.170 mmol) in toluene (0.390 mL). The reaction mixture was stirred at –78 °C for 15 h, then quenched with a saturated aqueous NH_4Cl solution (1 mL) and diluted with ethyl acetate (1 mL). The organic phase was separated and filtered through celite. *n*-Decane (0.033 mL, 0.170 mmol) was added and the crude reaction mixture (1 μL) was then injected into a GC instrument equipped with a chiral capillary column for determination of conversions and enantiomeric excesses.

Optimised Procedure for the Enantioselective Desymmetrisation of *meso*-Bis(diethyl phosphates) 3, 4, 5, Using Ligands 1: Ligand **1** (0.108 mmol) was dissolved in dry toluene (7.62 mL) and dry THF (0.635 mL) in a flame-dried flask, under argon. $[Cu(OTf)]_2{\cdot}C_6H_6$ (27.2 mg; 0.054 mmol) was subsequently added. The resulting yellowish solution was stirred at room temp. for 45 min. The reaction mixture was cooled to –60 °C, and treated with R_2Zn (R = Et, 1.1 M in toluene, 1.96 mL, 2.16 mmol; R = Me, 2.0 M in toluene, 1.08 mL, 2.16 mmol; R = *n*Bu 1.0 M in heptane, 2.16 mL, 2.16 mmol; R = *i*Pr 1.0 M in toluene, 2.16 mL, 2.16 mmol) and, after 10 min, with a solution of *meso*-bis(diethyl phosphate) (1.08 mmol) in toluene (2.5 mL). The reaction mixture was stirred at –60 °C for 15 h, then quenched with a saturated aqueous NH_4Cl solution (10.0 mL). After extraction with Et_2O, the organic phase was dried with Na_2SO_4, volatiles were removed under reduced pressure and the crude reaction mixture was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 55:45).

Optimised Procedure for the Enantioselective Desymmetrisation of *meso*-Bis(diethyl phosphates) 3, 4, 5, 10, Using Phosphoramidite Ligands 2: A solution of $[Cu(OTf)]_2{\cdot}C_6H_6$ (27.2 mg, 0.054 mmol) and chiral ligand **2** (0.216 mmol) in anhydrous toluene (10.0 mL) was stirred at room temp. for 45 min. The colourless solution was cooled to the required temperature and a solution of *meso*-bis(diethyl phosphate) (1.08 mmol) in toluene (3.0 mL) was slowly added. After 5 min, R_2Zn (R = Et, 1.1 M in toluene, 1.96 mL, 2.16 mmol; R = Me, 2.0 M in toluene, 1.08 mL, 2.16 mmol; R = *n*Bu 1.0 M in heptane, 2.16 mL, 2.16 mmol; R = *i*Pr 1.0 M in toluene, 2.16 mL, 2.16 mmol) was added and the resulting solution was stirred at that temperature for 15 h. The mixture was quenched with a saturated aqueous NH_4Cl solution (15.0 mL). After extraction with Et_2O, the organic phase was dried with Na_2SO_4, volatiles were removed under reduced pressure and the crude reaction mixture was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 55:45).

Characterisation of the Individual Compounds Resulting from the Desymmetrisation Reactions

Diethyl (1*S*,2*S*)2-Ethylcyclopent-3-enyl Phosphate (6a): Yield: 267 mg (99 %). $[\alpha]_D^{25}$ = +75.5 (*c* = 1.2, $CHCl_3$, 88 % enantiomeric excess). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.69–5.62 (m, 2 H), 4.70–4.64 (m, 1 H), 4.14–4.04 (m, 4 H), 2.79–2.67 (m, 2 H), 2.53–2.45 (m, 1 H), 1.53–1.29 (m, 8 H), 0.94 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.4 (CH), 127.2 (CH), 82.7 (CH), 63.5 ($2CH_2$), 54.5 (CH), 39.8 (CH_2), 25.4 (CH_2), 16.0 ($2CH_3$), 11.6 (CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.35 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2963, 2932, 2876, 1459, 1445, 1393, 1370, 1263, 1167, 1028, 821 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 249 (40) $[M + H]^+$, 155 (100) $[(EtO)_2P(O)OH + H]^+$, 95 (10) $[M – (EtO)_2P(O)OH + H]^+$. HRMS (EI, 70 eV) *m*/*z* calcd. for $C_{11}H_{22}O_4P$: 249.1256 $[M + H]^+$; found 249.1260. The *ee* was determined by GC on a chiral stationary phase [column: see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C]. t_R = 1.81 min (*n*-decane), 34.1 min (1*R*,2*R* enantiomer), 34.6 min (1*S*,2*S* enantiomer), 54.6 min (**3**).

Diethyl (1*S*,2*S*)2-Methylcyclopent-3-enyl Phosphate (6b): Yield: 190 mg (75 %). $[\alpha]_D^{25}$ = +54.0 (*c* = 0.92, $CHCl_3$, 94 % enantiomeric excess). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.59 (br. s, 2 H), 4.69–4.54 (m, 1 H), 4.15–4.05 (m, 4 H), 2.84–2.72 (m, 2 H), 2.54–2.45 (m, 1 H), 1.37–1.31 (m, 6 H), 1.05 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.3 (CH), 126.4 (CH), 84.6 (CH), 63.5 ($2CH_2$), 47.2 (CH), 39.4 (CH_2), 17.6 (CH_3), 16.1 ($2CH_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.35 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2960, 2927, 2892, 1465, 1458, 1393, 1370, 1262, 1167, 1029, 824 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 155 (60) $[(EtO)_2P(O)OH + H]^+$, 127 (45) $[(EtO)P(O)(OH)_2 + H]^+$, 99 (65) $[P(O)(OH)_3 + H]^+$, 80 (30) $[M – (EtO)_2P(O)OH + H]^+$, 43 (90), 28 (100). The *ee* was determined by GC with a chiral stationary phase [column: see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C]. t_R = 1.81 min (*n*-decane), 25.2 min (1*R*,2*R* enantiomer), 25.5 min (1*S*,2*S* enantiomer), 54.6 min (**3**).

Diethyl (1*S*,2*S*)2-Butylcyclopent-3-enyl Phosphate (6c): Yield: 292 mg (98 %). $[\alpha]_D^{25}$ = –8.8 (*c* = 0.28, $CHCl_3$, 88 % enantiomeric excess). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.73–5.62 (m, 2 H), 4.73–4.65 (m, 1 H), 4.15–4.05 (m, 4 H), 2.82–2.73 (m, 2 H), 2.55–2.46 (m, 1 H), 1.47–1.26 (m, 12 H), 1.05 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.2 (CH), 127.4 (CH), 83.6 (CH), 63.9 ($2CH_2$), 53.4 (CH), 40.2 (CH_2), 32.8 (CH_2), 30.0 (CH_2), 23.2 (CH_2), 16.5 ($2CH_3$), 14.3 (CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.35 ppm. IR (solution in $CHCl_3$) $\tilde{\nu}_{max.}$ = 3044, 2974, 2962, 2929, 2872, 1444, 1426, 1419, 1262, 1247, 1196, 1189, 1097, 1032, 1020 cm^{-1}. MS (FAB, glycerol): *m*/*z* (%) = 277 (28) $[M + H]^+$, 155 (100) $[(EtO)_2P(O)OH + H]^+$, 127 (40) $[(EtO)_2P(O)(OH) + H]^+$, 123 (28) $[M – (EtO)_2P(O)OH + H]^+$, 99 (70) $[P(O)(OH)_3 + H]^+$. The *ee* was determined by GC with a chiral stationary phase [column: see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 70 °C, 0.8 °C/min to 130 °C]. t_R = 1.81 min (*n*-decane), 25.1 min (1*R*,2*R* enantiomer), 25.6 min (1*S*,2*S* enantiomer), 52.1 min (**3**).

Diethyl (1*R*,2*R*)2-Isopropylcyclopent-3-enyl Phosphate (ent-6d): Yield: 270 mg (96 %). $[\alpha]_D^{25}$ = +9.9 (*c* = 1.08, $CHCl_3$, 12 % enantiomeric excess). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.71–5.63 (m, 2 H), 4.83–4.75 (m, 1 H), 4.14–4.06 (m, 4 H), 2.74 (dd, *J* = 17.8, *J* = 5.2 Hz, 1 H), 2.70–2.68 (m, 1 H), 2.51 (d, *J* = 17.8 Hz, 1 H), 1.76–1.64 (m, 1 H), 1.36–1.32 (m, 6 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.2 (CH), 128.3 (CH), 81.6 (CH), 63.9 ($2CH_2$), 60.4 (CH), 41.0 (CH_2), 30.5 (CH), 20.9 (CH_3), 19.9 (CH_3), 16.5 ($2CH_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.35 ppm. IR (film): $\tilde{\nu}_{max.}$ = 3060, 2960, 2908, 2873, 1466, 1444, 1389, 1369, 1262, 1167, 1100, 1029 cm^{-1}. HRMS (ESI) *m*/*z* calcd. for $C_{12}H_{23}NaO_4P$ 285,1232 $[M + Na]^+$; found : 285,1225. The *ee* was determined by GC on a chiral stationary phase [column: see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C]. t_R = 1.81 min (*n*-decane), 39.9 min (1*R*,2*R* enantiomer), 40.9 min (1*S*,2*S* enantiomer), 54.6 min (**3**).

Diethyl (1*S*,2*R*)2-Phenylcyclopent-3-enyl Phosphate (6e): Yield: 192 mg (60 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 5 H), 5.93–5.87 (m, 1 H) 5.81–5.75 (m, 1 H), 4.83–4.78 (m, 1 H), 4.11–3.95 (m, 5 H), 2.88 (dd, J = 17.4, J = 5.2 Hz, 1 H), 2.59 (d, J = 17.4 Hz, 1 H), 1.26 (t, J = 7.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.7 (CH), 129.0 (CH), 128.5 (CH), 127.5 (CH), 126.9 (CH), 85.3 (CH), 63.5 ($2CH_2$), 58.5 (CH), 39.7 (CH_2), 16.1 ($2CH_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.59 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}_{max.}$ = 3035, 2897, 1581, 1520, 1477, 1423, 1254, 1040, 928 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 155 (25) $[(EtO)_2P(O)OH + H]^+$, 142 (100) $[M – (EtO)_2P(O)OH + H]^+$, 127 (15) $[(EtO)P(O)(OH)_2 + H]^+$, 99 (20) $[P(O)(OH)_3 + H]^+$. The enantiomeric excess of compound **6e** was determined after reduction of the phosphate ester with $LiAlH_4$ in diethyl ether (quant. yield), and derivatization of the resulting alcohol with (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid, DCC, 4-DMAP in dichloromethane (quant. yield). The ratio between the two diastereomeric Mosher esters was assessed by ^{1}H NMR spectroscopy.

Diethyl (1*R*,2*R*)2-Ethylcyclohex-3-enyl Phosphate (ent-7a): Yield: 167 mg (59 %). $[\alpha]_D^{25}$ = –63.0 (*c* = 0.95, $CHCl_3$, 94 % enantiomeric excess). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71–5.64 (m, 1 H), 5.57–5.50 (m, 1 H), 4.40–4.29 (m, 1 H), 4.17–4.07 (m, 4 H), 2.26–2.01 (m, 4 H), 1.87–1.76 (m, 1 H), 1.67–1.56 (m, 1 H), 1.45–1.31 (m, 7 H), 0.95 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.8 (CH), 126.4 (CH), 77.8 (CH), 63.5 ($2CH_2$), 43.2 (CH), 27.7 (CH_2), 25.0 (CH_2), 23.3 (CH_2), 16.1 ($2CH_3$), 10.5 (CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.47 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2964, 2873, 1655, 1515, 1465, 1250, 1022, 805 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 262 (2) $[M]^+$, 155 (100) $[(EtO)_2P(O)OH + H]^+$, 127 (95) $[(EtO)P(O)(OH)_2 + H]^+$, 108 (40) $[M – (EtO)_2P(O)OH]^+$, 99 (98) $[P(O)(OH)_3 + H]^+$, 79 (80) $[M – (EtO)_2P(O)OH – Et]^+$. HRMS (EI, 70 eV) *m*/*z* calcd. for $C_{12}H_{23}O_4P$: 262.1334 $[M]^+$; found: 262.1314.

Diethyl (1*R,2*S**)2-Ethylcyclohex-3-enyl Phosphate (9):** Yield: 28 mg (10 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71–5.64 (m, 1 H), 5.57–5.50 (m, 1 H), 4.40–4.29 (m, 1 H), 4.17–4.07 (m, 4 H), 2.26–2.01 (m, 4 H), 1.87–1.76 (m, 1 H), 1.67–1.56 (m, 1 H), 1.45–1.31 (m, 7 H), 0.95 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.8 (CH), 126.4 (CH), 77.8 (CH), 63.5 ($2CH_2$), 43.2 (CH), 27.7 (CH_2), 25.0 (CH_2), 23.3 (CH_2), 16.1 ($2CH_3$), 10.5 (CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.47 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2966, 2876, 1648, 1508, 1458, 1259, 1027, 802 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 262 (2) $[M]^+$, 155 (100) $[(EtO)_2P(O)OH + H]^+$, 127 (95) $[(EtO)P(O)(OH)_2 + H]^+$, 108 (50) $[M – (EtO)_2P(O)OH]^+$, 99 (98) $[P(O)(OH)_3 + H]^+$; 79 (95) $[M – (EtO)_2P(O)OH – Et]^+$. HRMS (EI, 70 eV) *m*/*z* calcd. for $C_{12}H_{23}O_4P$: 262.1334 $[M]^+$; found: 262.1304.

Diethyl (1*R*,2*R*)2-Ethylcyclohept-3-enyl Phosphate (ent-8a): Yield: 256 mg (86 %). $[\alpha]_D^{25}$ = –34.0 (*c* = 0.95, $CHCl_3$, ≥ 98 % enantiomeric excess). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (ddt, J = 11.3, J = 6.2, J = 1.7 Hz, 1 H), 5.47–5.38 (m, 1 H), 4.31–4.22 (m, 1 H), 4.15–4.05 (m, 4 H), 2.52–2.43 (m, 1 H), 2.29–2.20 (m, 1 H), 2.34–2.25 (m, 2 H), 1.98–1.87 (m, 1 H), 1.80–1.61 (m, 2 H), 1.52–1.37 (m, 2 H), 1.36–1.29 (m, 6 H), 0.93 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.9 (CH), 131.0 (CH), 79.2 (CH), 63.4 ($2CH_2$), 45.8 (CH), 36.4 (CH_2), 27.9 (CH_2), 24.5 (CH_2), 23.0 (CH_2), 16.1 ($2CH_3$), 11.0 (CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.68 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2978, 1653, 1392, 1262, 1166, 1033, 997, 870 cm^{-1}. MS (FAB, glycerol): *m*/*z* (%) = 277 (25) $[M + H]^+$, 155 (100) $[(EtO)_2P(O)OH + H]^+$, 127 (55) $[(EtO)P(O)(OH)_2 + H]^+$, 123 (70) $[M – (EtO)_2P(O)OH + H]^+$, 99 (85) $[P(O)(OH)_3 + H]^+$.

Diethyl (1*S*,2*R*,5*S*,6*S*)-2-Ethyl-5,6-(isopropylidenedioxy)cyclohex-3-enyl Phosphate (11a): Yield: 188 mg (52 %). $[\alpha]_D^{25}$ = –21.0 (*c* = 1.3, $CHCl_3$, 86 % enantiomeric excess). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (dt, J = 12.0, J = 4.0 Hz, 1 H), 5.79–5.74 (m, 1 H), 4.63–4.61 (m, 1 H), 4.33–4.26 (m, 1 H), 4.23–4.10 (m, 5 H), 2.25–2.20 (m, 1 H), 1.87–1.77 (m, 1 H), 1.52 (s, 3 H), 1.51–1.43 (m, 1 H), 1.48 (s, 3 H), 1.47–1.43 (m, 6 H) 0.91 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.0 (CH), 123.6 (CH), 109.7 (C), 79.2 (CH), 77.6 (CH), 63.7 ($2CH_2$, J_{CP} = 6 Hz), 28.1 (CH_3), 26.1 (CH_3), 22.8 (CH_2), 16.1 ($2CH_3$), 10.7 (CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.43 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2986, 2935, 2876, 1457, 1381, 1372, 1259, 1219, 1170, 1026, 976 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%) 335 (1) $[M + H]^+$, 319 (40) $[M – CH_3]^+$, 155 (100) $[(EtO)_2P(O)OH + H]^+$, 127 (55) $[(EtO)P(O)(OH)_2 + H]^+$, 99 (25) $[P(O)(OH)_3 + H]^+$. HRMS (EI, 70 eV) *m*/*z* calcd. for $C_{15}H_{28}O_6P$: 335.1624 $[M + H]^+$; found: 335.1668.

Diethyl (1*S*,2*R*,5*S*,6*S*)-2-Butyl-5,6-(isopropylidenedioxy)cyclohex-3-enyl Phosphate (11b): Yield: 59 mg (15 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (dt, J = 10.0, J = 3.0 Hz, 1 H), 5.79–5.74 (m, 1 H), 4.64–4.58 (m, 1 H), 4.34–4.25 (m, 1 H), 4.22–4.08 (m, 5 H), 2.31–2.22 (m, 1 H), 1.83–1.18 (m, 18 H), 0.92 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.2 (CH), 123.4 (CH), 109.7 (C), 79.6 (CH), 77.3 (CH), 78.2 (CH), 63.6 ($2CH_2$), 40.2 (CH), 29.7 (CH_2), 28.1 (CH_2), 28.0 (CH_3), 26.1 (CH_3), 22.7 (CH_3), 16.0 ($2CH_3$), 13.8 (CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.32 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2961, 2924, 2855, 1596, 1436, 1265, 1145, 1022, 799 cm^{-1}. HRMS (ESI) *m*/*z* calcd. for $C_{17}H_{31}O_6PNa$ 385.1756 $[M + Na]^+$; found : 385.1732.

Diethyl (1*S*,2*R*,5*S*,6*S*)-2-Isopropyl-5,6-(isopropylidenedioxy)cyclohex-3-enyl Phosphate (11c): Yield: 225 mg (60 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (dt, J = 10.0, J = 3.0 Hz, 1 H), 5.81–5.74 (m, 1 H), 4.64–4.57 (m, 1 H), 4.39–4.29 (m, 1 H), 4.24–4.07 (m, 5 H), 2.27–2.15 (m, 2 H), 1.55 (s, 3 H), 1.38 (s, 3 H), 1.37–1.29 (m, 6 H), 1.04 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.3 (CH), 124.4 (CH), 109.6 (C), 78.2 (CH), 78.15 (CH), 77.95 (CH), 72.9 (CH), 63.6 (CH_2), 63.4 (CH_2), 46.0 (CH), 28.0 (CH_3), 26.1 (CH_3), 25.4 (CH_3), 20.9 (CH_3), 16.1 (CH_3), 16.0 (CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.41 ppm. IR (film): $\tilde{\nu}_{max.}$ = 2961, 2924, 2850, 1635, 1274, 1029 cm^{-1}. HRMS (ESI) *m*/*z* calcd. for $C_{16}H_{29}O_6PNa$ 371.1600 $[M + Na]^+$; found : 371.1578.

General Procedure for the Reduction of Phosphate Esters 7a and ent-7a, 8a and ent-8a, 11a-c: To a stirred solution of the phosphate ester (0.10 mmol) in dry Et_2O (1.66 mL), LAH (22.17 mg, 0.60 mmol) was added portionwise at room temp. The solution was stirred for 20 min before quenching with water (SLOWLY!). The solution was filtered through a small cotton plug and volatiles were carefully removed under reduced pressure.

(1*S*,2*S*)-2-Ethylcyclohex-3-enol and (1*R*,2*R*)-2-Ethylcyclohex-3-enol: Yield: Quantitative. Spectral and analytical data were in complete agreement with the literature.[21] The *ee* was determined by GC on a chiral stationary phase [see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C 10 min, 10 °C/min to 200 °C]. t_R = 7.9 min and 8.3 min (*cis*-2-ethylcyclohexen-3-ol enantiomers, 1:1), 8.4 min (1*S*,2*S* enantiomer), 8.9 min (1*R*,2*R* enantiomer).

(1*R*,2*R*)-2-Ethylcyclohept-3-enol: Yield: Quantitative. $[\alpha]_D^{25}$ = –41.0 (*c* = 0.93, $CHCl_3$, ≥ 98 % enantiomeric excess). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92–5.85 (m, 1 H), 5.49–5.45 (m, 1 H), 3.58–3.54 (m, 1 H), 2.36–2.28 (m, 1 H), 2.13–2.05 (m, 3 H), 1.80–1.61 (m, 3 H), 1.54–1.41 (m, 3 H), 0.96 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.0 (CH), 132.0 (CH), 71.3 (CH), 47.3 (CH), 38.3 (CH_2), 28.1 (CH_2), 24.4 (CH_2), 23.2 (CH_2),

11.1 (CH_3) ppm. IR (film): $\tilde{\nu}_{max.}$ = 3367, 2963, 2930, 2874, 1648, 1445, 1378, 1259, 1024, 908 cm^{-1}.

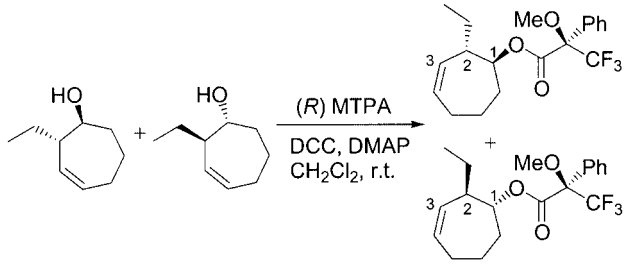
(1*S*,2*R*,5*S*,6*R*)-2-Ethyl-5,6-(isopropylidenedioxy)cyclohex-3-enol (12a): Yield: Quantitative. $[\alpha]_D^{25}$ = –33.0 (*c* = 0.4, CH_2Cl_2, 86 % enantiomeric excess). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.87 (dt, *J* = 10, *J* = 3.2 Hz, 1 H), 5.82–5.80 (m, 1 H), 4.63–4.60 (m, 1 H), 3.96 (dd, *J* = 9.3, *J* = 6.4 Hz, 1 H), 3.36 (t, *J* = 9.3 Hz, 1 H), 2.06–1.97 (m, 1 H), 1.90–1.80 (m, 1 H), 1.52 (s, 3 H), 1.43–1.33 (m, 1 H), 1.40 (s, 3 H), 0.98 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.6 (CH), 123.7 (CH), 80.4 (CH), 73.1 (CH), 73.0 (CH), 42.1 (CH), 28.6 (CH_3), 26.0 (CH_3), 23.3 (CH_2), 10.4 (CH_3) ppm. IR (film): $\tilde{\nu}_{max.}$ = 3589, 3046, 2960, 1433, 1380, 1258, 1216, 1057, 865, 824 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 198 (2) $[M]^+$, 197 (5) $[M – H]^+$, 183 (100) $[M – CH_3]^+$, 123 (85), 111 (30), 95 (65). HRMS (EI, 70 eV) *m*/*z* calcd. for $C_{11}H_{18}O_3$: 198.1256 $[M]^+$; found: 198.1276. The *ee* was determined by GC on a chiral stationary phase [see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C]. t_R = 23.1 min (7 %), 23.4 min (93 %).

(1*S*,2*R*,5*S*,6*R*)-2-Butyl-5,6-(isopropylidenedioxy)cyclohex-3-enol (12b): Yield: Quantitative. $[\alpha]_D^{25}$ = –1.8 (*c* = 0.24, $CHCl_3$, 56 % enantiomeric excess). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (dt, *J* = 9.1, *J* = 2.6 Hz, 1 H), 5.83–5.78 (m, 1 H), 4.65–4.58 (m, 1 H) 3.97 (dd, *J* = 8.9, *J* = 6.4 Hz, 1 H), 3.40 (dt, *J* = 9.3, *J* = 2.6 Hz, 1 H), 2.15–2.05 (m, 1 H), 1.88–1.76 (m, 1 H), 1.53 (s, 3 H), 1.51–1.19 (m, 9 H), 0.98 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9 (CH), 122.8 (CH), 79.9 (CH), 73.1 (CH), 72.6 (CH), 40.4 (CH), 29.9 (CH_2), 28.4 (CH), 28.2 (CH_2), 25.9 (CH), 22.9 (CH_2), 14.0 (CH_3) ppm. IR ($CHCl_3$ solution): $\tilde{\nu}_{max.}$ = 3031, 2975, 2896, 1521, 1424, 1243, 1037, 928 cm^{-1}. HRMS (ESI) *m*/*z* calcd. for $C_{13}H_{22}NaO_3$ 249,1467 $[M + Na]^+$; found 249,1459; the *ee* was determined by GC on a chiral stationary phase [see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 20 min, 20 °C/min, 200 °C]. t_R = 24.68 min (22 %), 24.79 min (78 %).

(1*S*,2*R*,5*S*,6*R*)-2-Isopropyl-5,6-(isopropylidenedioxy)cyclohex-3-enol (12c): Yield: Quantitative. $[\alpha]_D^{25}$ = –0.6 (*c* = 0.20, $CHCl_3$, 20 % enantiomeric excess). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.94 (dt, *J* = 10.0, *J* = 3.1 Hz, 1 H), 5.86–5.76 (m, 1 H), 4.66–4.57 (m, 1 H), 3.98 (dd, *J* = 8.8, *J* = 6.4 Hz, 1 H), 3.48 (t, *J* = 8.8 Hz, 1 H), 2.30–2.16 (m, 2 H), 2.10–2.04 (m, 1 H), 1.54 (s, 3 H), 1.42 (s, 3 H), 1.04 (d, *J* = 7.0 Hz, 3 H), 0.83 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.5 (CH), 124.7 (CH), 110.0 (C), 80.9 (CH), 73.3 (CH), 71.7 (CH), 46.6 (CH), 30.4 (CH), 29.1 (CH_3), 26.5 (CH_3), 26.1 (CH_3), 21.4 (CH_3), 17.0 (CH_3) ppm. IR ($CHCl_3$ solution): $\tilde{\nu}_{max.}$ = 3012, 2895, 1521, 1424, 1236, 1046, 928 cm^{-1}. HRMS (ESI) *m*/*z* calcd. for $C_{12}H_{20}NaO_3$ 235,1310 $[M + Na]^+$; found : 235,1305; the *ee* was determined by GC on a chiral stationary phase [see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 20 min, 20 °C/min, 200 °C]. t_R = 23.66 min (40 %), 23.89 min (60 %).

Synthesis of the Mosher Esters of (1*S*,2*S*)- and (1*R*,2*R*)-2-Ethylcyclohept-3-enol and Determination of Their Absolute Configuration

(1*R*,2*R*)-2-ethyl-cyclohept-3-enyl (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionate and (1*S*,2*S*)-2-Ethylcyclohept-3-enyl (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionate: (Scheme 2). To a stirred solution of racemic 2-ethylcyclohept-3-enol (5 mg, 0.036 mmol) in dry CH_2Cl_2 (1.0 mL) was added 4-DMAP (8.7 mg, 0.07 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl) phenylacetic acid (16.4 mg, 0.07 mmol) and DCC (45 mg, 0.22 mmol). The solution was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the crude reaction mixture was subjected to column chromatography (petroleum ether/ethyl acetate, 98:2) to deliver a 1:1 mixture of the diastereisomeric Mosher esters, (*R*,*R*,*R*) and (*S*,*S*,*R*) (12.0 mg, 94 %) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.56 (m, 4 H, Ph), 7.43–7.39 (m, 6 H, Ph), 5.92–5.83 (m, 2 H, CH =), 5.49–5.42 (m, 1 H, CH =, *R*,*R*,*R*), 5.40–5.36 (m, 1 H, CH =, *S*,*S*,*R*), 5.20–4.90 (m, 2 H), 3.60–3.59 (m, 3 H, OMe, *S*,*S*,*R*), 3.57–3.56 (m, 3 H, OMe, *R*,*R*,*R*), 2.62–2.52 (m, 2 H), 2.26–2.02 (m, 6 H), 1.90–1.70 (m, 4 H), 1.56–1.43 (m, 2 H) 1.41–1.18 (m, 4 H), 0.91 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$, *R*,*R*,*R*), 0.80 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$, *S*,*S*,*R*) ppm.



Scheme 2

For determination of the enantiomeric excess of 2-ethylcyclohept-3-enol, the ^1H NMR spectrum of the purified Mosher esters (as an unbalanced mixture of the two diastereoisomers) was recorded. For determination of the absolute configuration, the esters were assumed to adopt a conformation with the H–C–O–(C=O)–C–CF_3 fragment in one plane.[29] The signals assigned to the methyl group of the ethyl substituent at C-2 and to the vinylic proton at C-3 appeared at higher field in the (*S*,*S*,*R*) diastereomeric ester than the signals of the corresponding protons in the (*R*,*R*,*R*) diastereomer.[29]

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