Copper-Catalysed Asymmetric 1,4-Addition of Organozinc Compounds to Linear Aliphatic Enones Using 2,2′-Dihydroxy 3,3′-Dithioether Derivatives of 1,1′-Binaphthalene

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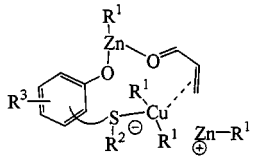
Directed *ortho* dilithiation of bis(diethylcarbamate) or bis-(MOM)-protected (S_a)-1,1′-bi(2-naphthol) followed by treatment with R_2S_2 [R = Me, Ph (X-ray structure)] or Me_2Se_2 cleanly affords the 3,3′ derivatives; the free naphthols are produced on deprotection. In the case of the bis(MOM) series, but not that of the bis(carbamates), some racemisation occurs. The ligand 2,2′-dihydroxy-3,3′-dimethylthio-1,1′-binaphthalene shows optimal performance in the addition of $ZnEt_2$ to linear aliphatic enones (*E*)-$R^1C(O)CH{=}CHR^2$. Variation of the steric demands of R^1 and R^2 generates catalytic results consistent with binding of a zinc-based Lewis acid *anti* to the ene function and with the reactive conformation being *s-cis*. With enones containing the functions R^2 = $(CH_2)_nCH(OAlkyl)_2$ (n = 0–2), the $ZnEt_2$ addition products undergo base-promoted cyclisation.

Introduction

Despite the enormous progress that has been made recently in asymmetric 1,4-additions of organozinc reagents to enones in the presence of phosphorus-ligated copper complexes, significant problems remain to be solved in this area.[1] For example, many catalysts are evaluated by their performance in the model reaction between $ZnEt_2$ and 2-cycloalkenones.[2] The primary literature indicates that outside this system, significant drops in catalyst performance can be experienced. Even the remarkable enantioselectivities achieved by the phosphoramidite ligands, for example, can suffer with variation of the organozinc reagent and − especially − the enone structure.[3] In particular, linear enones bearing only *aliphatic* substituents are challenging substrates for phosphorus-based ligands, although these fragments frequently appear in synthetic targets of biological interest.

Recently, we[4−7] and others[8] have become interested in the use of chiral organosulfur ligands in copper-catalysed additions to linear aliphatic enones in attempts to find highly selective reactions. In particular, we have designed species which contain both a thioether (capable of coordinating organocuprates) and aromatic alkoxide donors (allowing strong interaction with the terminal organozinc species). We believe that such ligands should favour organised transition states, shown diagrammatically in structure **A**, featuring binding of both the enone and a Gilman-type cuprate $[Cu(R^1)_2]^-$ [derived from the terminal organozinc species $Zn(R^1)_2$] in an ordered transition state. Coordination of strong σ-donors, such as thioethers, is predicted to result in a dramatic rate increase in conjugate addition, due to stabilisation of the putative Cu^{III} transition state through charge transfer, affording $[(ArS^{\delta+}R^2)Cu(R^1)_2$-$(enolate^{\delta-})]^-$.[9] In this paper, full details are given of our investigations of 2,2′-dihydroxy-3,3′-diorganothio-1,1′-binaphthalene ligands (**3**, Scheme 1), currently the most effective additives we have found for this chemistry.



A

Results and Discussion

Ligand Structure Studies

Preliminary investigations had indicated that the dimethyl species **3a** was able to deliver significant enantioselectivity in Cu^I-catalysed 1,4-additions of $ZnEt_2$ to (*E*)-alkyl-3-en-2-ones (up to 73% *ee*) and 2-cyclohexenone (up to 77% *ee*).[6] One obvious strategy to improve this performance is systematic variation of the nature of the YR substituent in structure **3**. We have developed directed *ortho* metallations of carbamate-protected, enantiopure 1,1′-binaphthols[10] using Snieckus-type chemistry[11] and this is shown in Scheme 1 for the (S_a) series. Treatment of the bis(carbamate) **1a** with *s*BuLi/TMEDA at −78 °C cleanly

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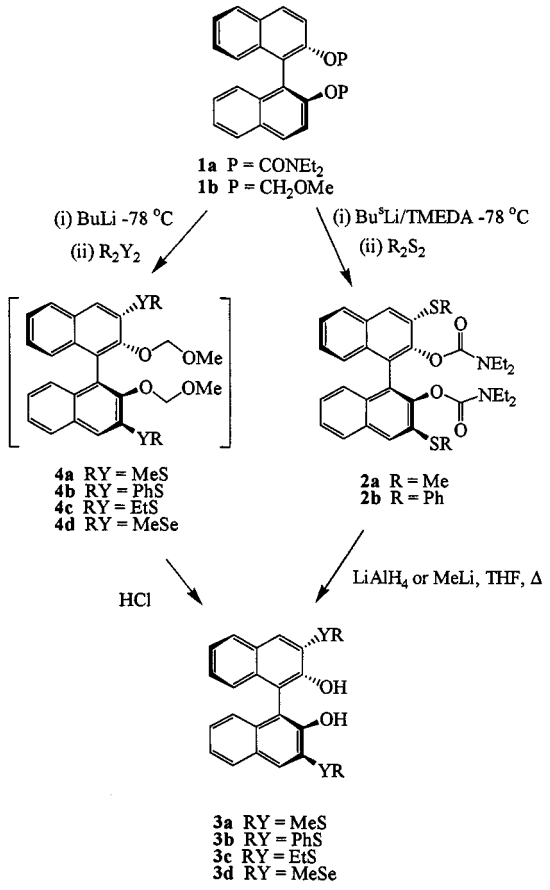
affords the dilithio species, which when intercepted with R_2S_2 (R = Me, Ph) yields the 3,3′-disubstituted compounds **2**. However, while the methylthio compound **2a** is easily deprotected with either $LiAlH_4$ or MeLi, producing **3a**, the equivalent phenyl compound **2b** reacts sluggishly and not very cleanly with these reagents. Steric protection of the carbamate may be the origin of these problems. In the search for a general solution to the synthesis of a range of **3** derivatives, dilithiation of the bis(MOM) derivative **1b** under standard conditions[11] seemed attractive. Subsequent treatment of these dilithio species with appropriate disulfides affords **4** (or dimethyl diselenide for **4d**), which can readily be directly deprotected with HCl to afford the ligands **3** in good yield.



Scheme 1

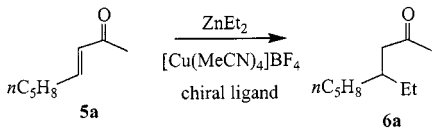
The effect of changing the soft donor site could be assayed by carrying out copper-catalysed reactions between $ZnEt_2$ and (*E*)-non-3-en-2-one **5a** in the presence of **3**/[Cu(MeCN)$_4$]BF_4[12] (Table 1). These studies immediately revealed two things: firstly, that the methylthioether **3a** seems to give the optimal performance with respect to *ee* value, and secondly, that the *ee* value obtained in the catalytic reaction using **3a** is dependent on the route by which the ligand is prepared.

The *ee* values obtained for the product **6a** suggest that the enantiopurity of **3a** is compromised when it is prepared by the MOM route (through **4a**). Thus far, we have not been able to find a chiral HPLC column that will separate the antipodes of **3a−d** (or the precursors **2a−b** and **4a−d**). In the absence of a direct assay, racemisation of species leading to **3a** had to be investigated indirectly. Firstly, to be absolutely sure that racemisation was not a feature of the carbamate route (through **2**, Scheme 1), the optical rotations of repeatedly fractionally crystallised samples of **2a−b** were measured. These optical rotations remained constant, although that of **2b** was very low ($[\alpha]_D^{25} = +3$ at $c = 5.0$). To check whether this class of molecules has any tendency to crystallise as eutectic mixtures, a crystallographic study of **2b** was undertaken. The results found that no $(R_a)/(S_a)$ co-crystallisation had taken place and that the atom connectivity expected from the double lithiation had been obtained (Figure 1). A similar study of the optical rotation of **3a** upon repeated recrystallisation gave no evidence that the material obtained from this route is less than enantiopure.

Assuming no nonlinear effect (NLE[13]) is associated with Cu^I/**3a** catalysis, the *ee* value achieved for the formation of **6a** suggests that the *ee* of **3a** derived from the MOM-protected compound (i.e. **4a**) is 88% (0.63/0.72 × 100%). As all of the derivatives **4** were deprotected under identical conditions (acid concentration and hydrolysis time), an identical deprotection was carried out on the starting material **1b**. The *ee* of the 1,1′-bi(2-naphthol) produced this way was 93%, as determined by HPLC, confirming induction of racemisation by HCl during MOM deprotection. While we cannot rule out dramatically different degrees of racemisation across the series **4a−d**, we believe that this is unlikely and that the enantiopurity of all the ligands **3** produced by this route is likely to be ≥ 88% *ee*. Given the large differences in the ligand-derived enantioselectivities (Table 1), minor differences in the ligand enantiopurity would not affect the conclusion that ligand structure **3a** is already optimal. Recently, the MOM-protected starting material **1b** was suggested as the most effective method for the synthesis of enantiopure 3,3′-bis($SiMe_3$)-substituted binol ligands.[14] No comment was made regarding racemisation during the acid deprotection of the intermediates in this synthesis.

The poor performance of seleno ligand (S_a)-**3d** was surprising, as the "soft" selenium donor should ligate and stabilise organocopper(III) intermediates more effectively than the analogous thioether. Some attempts were made to vary the reaction conditions for this ligand, with the aim of improving its enantioselectivity. In dichloromethane, the addition of $ZnEt_2$ to **5a** produces **6a** in 53% *ee*, while in Et_2O the other enantiomer of the product is produced in 20% *ee*. Use of $AlMe_3$ in THF produces a 41% *ee* for the equivalent methyl addition product. Additionally, because the loadings of the thioethers **3** in Table 1 are relatively high (20 mol-%) some catalytic reactions were studied at reduced ligand loadings of **3a** and different Cu/**3a** ratios (Table 2). Initial investigations revealed that reduction of the copper and ligand loadings to 2.5 mol-% [Cu(MeCN)$_4$]BF_4 and **3a** (5 mol-%) resulted in incomplete conversion, but significant amounts of **6a** were still formed (71% yield) with slightly reduced induction (up to 68% *ee*).[6] At these lower ligand loadings, the purity of the reagents and ligands becomes the critical factor in determining the chemical yield and enanti-

Table 1. Treatment of (*E*)-non-3-en-2-one **5** with $ZnEt_2$ in the presence of $[Cu(MeCN)_4]BF_4$ (10 mol-%) and ligands **3a**−**d** (20 mol-%)



Ligand	Chemical yield [%][a] (c.y.)	Product *ee* [%][b] (from MOM series ligands)	Product *ee* [%][b] (from carbamate series ligands)
3a	85	63 (+)-(*R*)[c]	73 (+)-(*R*)[c]
3b	58	25 (−)-(*S*)[c]	–
3c	75	12 (+)-(*R*)[c]	–
3d	68	23 (+)-(*R*)[c]	–

[a] Carried out as THF solutions at −20 °C with $[Cu^I]_{initial}$ = 23 mM; $[\mathbf{3}]_{initial}$ = 46 mM. − [b] Determined by G.C. on an oktakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin column. − [c] Stereochemistry assigned by comparison with analogous (+)-(*R*)-methyl addition compound (see later, also ref.[6]).

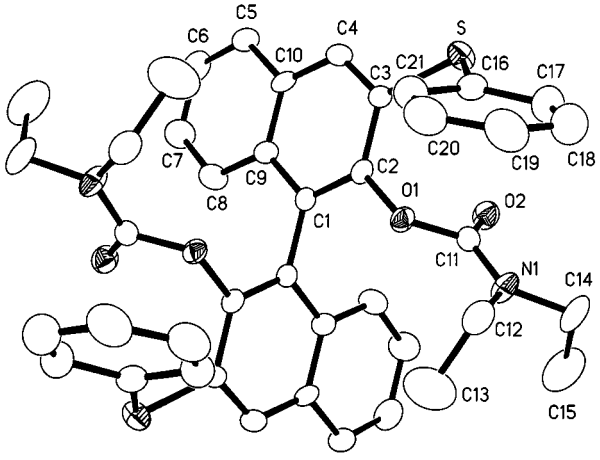


Figure 1. Molecular structure of **2b** shown with 30% probability ellipsoids; hydrogen atoms have been omitted for clarity; selected bond lengths [Å] and angles [°]: S−C(3) 1.774(6), S−C(16) 1.767(6), O(1)−C(2), O(1)−C(11), N(1)−C(11), 1.337(8), N(1)−C(12) 1.463(8), N(1)−C(14) 1.474(8); C(3)−S−C(16) 106.8(3), C(2)−O(1)−C(11) 116.2(4), O(2)−C(11)−N(1) 127.2(6)

oselectivity. Typically, a range of chemical yield (c.y.) and *ee* values are obtained, and these are shown in Table 2 together with the effects of temperature and solvent change on the reaction.

Enone Structure Studies

For linear enones, free rotation produces *s-cis* (**5c**) and *s-trans* (**5t**) (Scheme 2). Exchange between these two conformers is of key importance in asymmetric catalysis, as it exchanges the *Re*/*Si* faces of the enone (the stereochemical descriptors of the front-side faces at the β carbon atom are shown in Scheme 2). The presence of zinc-derived Lewis acids ZnX_2 (X = Et, alkoxide) in the asymmetric conjugate reaction complicates the situation, as this may bind the carbonyl lone pair either *syn* or *anti* to the ene function (while ionic Lewis acids, such as Li^+, bind carbonyl groups with little spatial preference, "softer" Lewis acids bind the carbonyl group while preserving its sp^2 hybridisation; that is, M−O=C ≈ 120°[15,16]). The relative populations of the four species **5c,a**, **5c,s**, **5t,a**, and **5t,s** in the "loaded" state of the catalyst therefore directly affect the *Re*/*Si* ratio and hence the *ee* value provided by the catalyst. Considerable information is available both on carbonyl group Lewis acid binding[15] and on the mechanism of organocuprate additions[9] to enones. To the best of our knowledge, however, few attempts had been made to apply this information to asymmetric copper-catalysed additions of organozinc compounds.

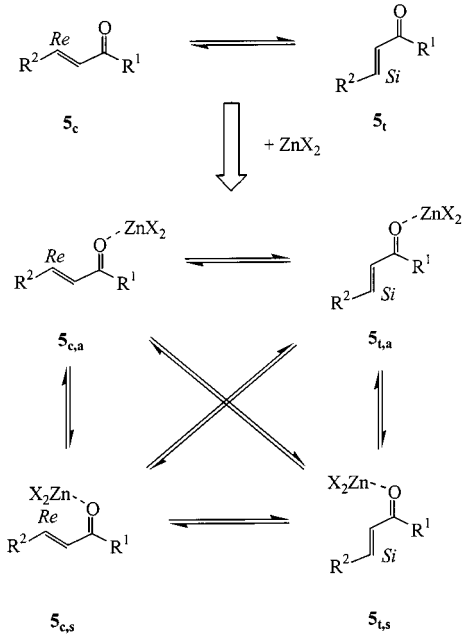
To obtain information on the nature of the asymmetric transition state attained with ligand **3a**, a series of enones (**5a**−**l**) were prepared by either crossed-aldol or Wittig methods. The structures of these compounds were expected to favour one of the species **5c,a**, **5c,s**, **5t,a**, and **5t,s** significantly. Although many of these species are known, great care was taken to obtain pure (*E*) samples rather than the (*E*)/(*Z*) mixtures occasionally produced by the literature routes. These species were treated with $ZnEt_2$ in the presence of $[Cu(MeCN)_4]BF_4$ and stereochemically pure (S_a)-**3a** under identical conditions (Scheme 3, Table 3). To ensure complete reproducibility in these mechanistic studies, the loading of **3a** was kept high. Additionally, because of the racemisation associated with the MOM route, all **3a** used in subsequent studies was prepared from the bis(carbamate) **1a**. The preference for zinc-derived Lewis acids to bind *syn* (**5c,s** or **5t,s**) or *anti* (**5c,a** or **5t,a**) to the ene function was investigated first. We reasoned that as the size of R^1 is increased any tendency for a ZnX_2 fragment to bind *anti* should be suppressed.

The behaviour of enones **5a**−**c** is consistent with binding of the zinc Lewis acid *anti* to the ene functions, as in structures **5c,a** and **5t,a** (Scheme 2). Reduction in the enone reactivity and selectivity through an increase in the steric demand of R^1 would not be expected if *syn* binding is a major contribution. Unsaturated esters normally present ground states possessing a (*Z*) configuration about the =C−OR ester bond and are therefore expected to be poor substrates if *anti* carbonyl group binding is a requirement. This proved

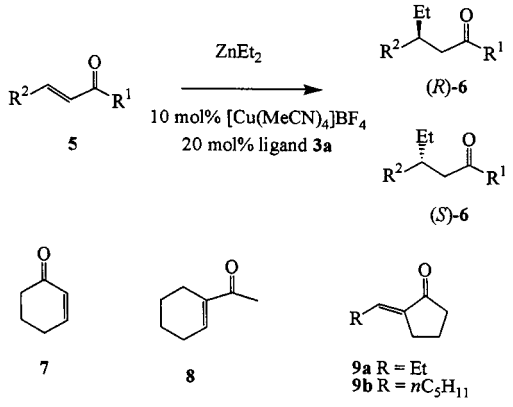
Table 2. Treatment of (*E*)-non-3-en-2-one **5** with ZnR_2 in the presence of $[Cu(MeCN)_4]BF_4$ and ligand **3a**

Ligand loading [mol-%] (conc.[a])	CuI loading [mol-%] (conc.[a])	Conditions	Product c.y. (*ee*) [from MOM series ligands] [%][b]	Product c.y. (*ee*) [from carbamate series ligands] [%][b]
5 (46 mM)	2.5 (23 mM)	R = Et, THF, −20 °C	–	71 (68)
8 (36 mM)	4 (18 mM)	R = Et, THF, −20 °C	–	54 (65)
8 (36 mM)	8 (36 mM)	R = Et, THF, −20 °C	58 (62)	–
8 (19 mM)	4 (9 mM)	R = Et, THF, −20 °C	44 (61)	–
8 (65 mM)	4 (33 mM)	R = Et, THF, −20 °C	52 (61)	–
20 (46 mM)	10 (23 mM)	R = Et, THF, 0 °C	71 (64)	–
20 (46 mM)	10 (23 mM)	R = Et, THF, −50 °C	32 (43)	–
20 (46 mM)	10 (23 mM)	R = Et, toluene, −20 °C	20 (12[c])	–
20 (46 mM)	10 (23 mM)	R = Et, CH_2Cl_2, −20 °C	32 (43)	–
20 (46 mM)	10 (23 mM)	R = Me, THF, −20 °C	< 16 (58)	–
20 (46 mM)	10 (23 mM)	R = CH_2TMS, THF, −20 °C	n.r.[d]	–

[a] nitial concentrations. – [b] Determined by GC on an oktakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin column. Unless stated otherwise, the (+)-(*R*) isomer was predominant by comparison with analogous (+)-(*R*)-methyl addition compound (see later, also ref.[6]). – [c] (−)-(*S*) isomer. – [d] No reaction.



Scheme 2

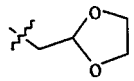


Scheme 3

to be the case: **5d** is completely unreactive, although this might simply be due to the known low reactivity of unsaturated esters in copper-catalysed conjugate addition. Compound **5e** is expected to show complete *anti* binding, due to the presence of the chelate. The result is somewhat ambiguous. While the presence of a clean catalytic reaction reinforces the idea of *anti* coordination in this case, as the (−)-**6e** antipode is isolated, in all other cases (+)-**6** is formed when (S_a)-**3a** is used. We have assigned the (+)-**6** stereoisomers the (*R*) configuration on the basis of the facts that the (+) enantiomer also corresponds to (*R*) in the analogous methyl addition compound and that the (+/−) elution behaviour for the methyl and ethyl compounds is the same under a range of different chiral GC conditions. Thus, for enones other than **5e**, the ligand (S_a)-**3a** affords the (*R*)-**6** conjugate addition product. For **5e**, either the presence of the heteroatom alters the sign of the optical rotation, or more probably the presence of a chelating substrate changes the asymmetric transition state, reversing the selectivity.

The propensity for the linear enones to react in an *s-cis* vs. *s-trans* conformation could be examined using enones **5f−g**. We supposed that, because of our design strategy (cf. structure **A**), that transition states featuring *s-cis* conformations would be much more susceptible to steric clashes caused by increasing the size of substituent R^2 than those proceeding from the alternative *s-trans* conformer (clearly this is a simplification, as conformers $\mathbf{5_{c,s}}$ and $\mathbf{5_{t,s}}$ will also be affected to some degree, but in view of the lack of literature data this simple model was pursued to see if the results were consistent with structure **A**). Additionally, because of the proposed close proximity of the zinc and copper centre substrates, processing of ether-like oxygen atoms may be able to adopt binding motifs not available to simple enones. Comparing runs using **5a**, **5f**, and **5g**, it can clearly be seen that, as the steric imposition on the transition state increases, the chemical yield falls (nC_5H_{11}, 85%; *i*Pr, 59%; CH_2*i*Pr, 43%) but the *ee* value rises (nC_5H_{11}, 73%; *i*Pr, 77%; CH_2*i*Pr, 79%), indicating increased congestion in the transition state. Enone **5h** fails to react, indicating that the chiral cleft in the catalyst structure cannot accommodate R^2 =

Table 3. Asymmetric conjugate addition of $ZnEt_2$ to enones **5a−l** and **8−9** catalysed by $[Cu(MeCN)_4]BF_4$ (10 mol-%) and (S_a)-**2b** (20 mol-%) in THF at −20 °C

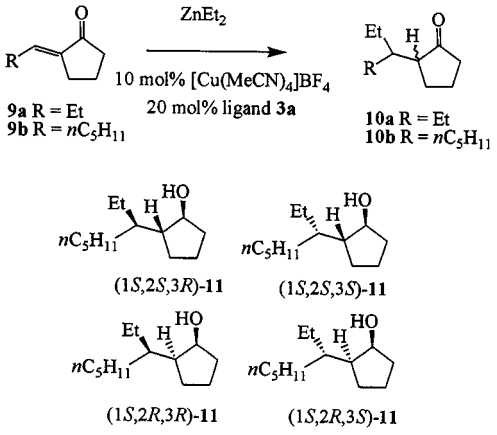
Enone	R^{1}[a]	R^{2}	c.y. **6** [%][b]	*ee* **6** [%][b][c]
5a	Me	nC_5H_{11}	85	72 (+)-(*R*)
5b	*i*Pr	nC_5H_{11}	61	39 (+)-(*R*)
5c	*t*Bu	nC_5H_{11}	0	–
5d	OMe	nC_5H_{11}	0	–
5e	CH_2OMe	nC_5H_{11}	65	24 (−)[d]
5f	Me	*i*Pr	59	77 (+)-(*R*)
5g	Me	CH_2-*i*Pr	43	79 (+)-(*R*)
5h	Me	*t*Bu	0	–
5i	Me	$CH(OMe)_2$	52	18 (+)-(*R*)[e]
5j	Me	$CH_2CH(OEt)_2$	58	70 (+)-(*R*)[e]
5k	Me		59	52 (+)-(*R*)[e]
5l	Me	$CH_2CH_2CH(OEt)_2$	65	69 (+)-(*R*)[e]
7	–	–	78	77 (−)-(*S*)[f]
8	–	–	0	–
9a	–	–	54	–[g]
9b	–	–	55	72−86[h]

[a] Carried out as THF solutions at −20 °C with $[Cu^{I}]_{initial}$ = 23 mM; $[\mathbf{3}]_{initial}$ = 46 mM. – [b] Determined by GC on an oktakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin column. – [c] Stereochemistry assigned by comparison with analogous (+)-(*R*)-methyl addition compound (see later, also ref.[6]). – [d] Absolute stereochemistry not clear. – [e] Determined on derived aldehyde. – [f] Stereochemistry based on known optical rotation. – [g] 1:1 mixture of diastereomers at C(2); no stereocentre generated by conjugate addition. – [h] 1:1 mixture of diastereomers at C(2); *ee* determined by ^{13}C NMR of the alcohol **11** by CBS reduction.

*t*Bu. These results suggest that an *s-cis* conformation is favoured, as originally suggested by Feringa,[1] and further experiments support this idea. The addition of $ZnEt_2$ to cyclohexenone (**7**) catalysed by Cu^{I}/(S_a)-**3a** affords the (*S*) addition product (77% *ee*).[17] As **7** can only react from *s-trans* transition states, this reversal of enantiofacial selectivity strongly points to an *s-cis* transition state for the linear enones **5**. The *s-trans* and *s-cis* conformers of enone **8** are expected to be almost isoenergetic. It fails to react, indicating that certain *s-trans* conformers cannot be accessed in the mechanism of action of this catalysts. Finally, enones **9a−b** could be used as enforced *s-cis* enones. As the literature preparations of **9** predate NMR instrumentation, it is vital to ensure that the proposed (*E*) configuration is correct if it is to be used for mechanistic studies. Fortunately, the presence in compound **9b** of a set of small (1.95−2.72%) but conclusive nuclear Overhauser effects between the ring 3-CH_2 group and the allylic and homoallylic methylene groups of the nC_5H_{11} substituent confirmed the (*E*) assignment presumed in the original literature.[18] Compounds **9** react smoothly with $ZnEt_2$ to produce **10**, reinforcing the suggestion that catalysts derived from **3a** act on the acyclic substrates **5** through an *s-cis* configuration.

After quenching with $HCl_{(aq)}$, the product enolates derived from **9** afford ketones with a stereogenic centre at C(2) (Scheme 4). As this centre arises through unselective protonation, it is attained in a stereorandom manner. Compound **9a** thus affords a 1:1 mixture of enantiomers **10a**, even though no chiral centre is generated by the conjugate addition; they can be separated by chiral GC. While we could also separate the equivalent diastereomers of **10b** on a variety of chiral GC columns, we could not resolve the four separate stereoisomers. The conjugate addition product of **10b** also proved to be rather resistant to *ee* determination by chemical derivatisation. Attempts to prepare acetals or imines from **10b** using enantiopure diols or amines also proved ineffective. In a final attempt to determine the enantioselectivity for the addition of $ZnEt_2$ to **9b** (Table 3), **10b** was reduced with BH_3·THF in the presence of (*R*)-CBS catalyst. Recent evidence indicates that substrates closely related to **10b** are reduced with very high *ee* values and that these give resolved NMR spectra.[19] In the case of **10b**, CBS reduction was expected to generate the stereoisomers **11**. Indeed, the ^{13}C NMR spectrum showed a clear splitting of peaks belonging to the major and minor isomer of the asymmetric conjugate addition product. To corroborate this result, the same asymmetric addition was performed using (R_a)-**3a** instead of (S_a)-**3a** and the addition product reduced under identical conditions as **10b**. According to the ^{13}C NMR spectra, ethyl addition gave an *ee* in the range of 72−86%, depending on which pair of peaks was measured, assuming that the CBS reduction occurs with almost complete enantioselectivity.

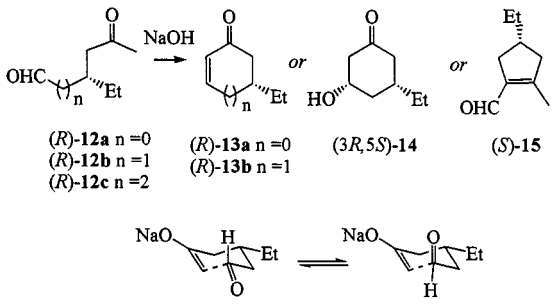
The possibility of tridentate (Cu−alkene, Zn−carbonyl, and Zn−additional donor) binding of enones could be examined using substrates **5i−l** (Table 3). As the structure of the active catalyst in this system is not known, there may be more than one zinc Lewis acid site present if the catalyst is aggregated or if both naphtholate units in ligand **3** are capped by a ZnEt unit. Additional binding of the enone through an acetal oxygen atom is expected to change the nature of the transition state. The shortest tethered acetal **5i** clearly experiences such a fate, but the outcome is highly detrimental to the enantioselectivity and the addition pro-



Scheme 4

ceeds with very low induction (18% *ee*). The higher homologues do not apparently bind the zinc Lewis acid site(s) through their acetal functions and the chemical yields and enantioselectivities achieved (Table 3) are comparable to those of their hydrocarbon analogues. In all cases **5i−l**, the initial product acetals undergo facile hydrolysis to the aldehydes **12**.

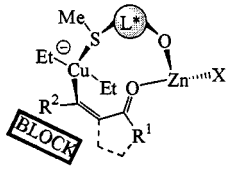
We reasoned that aldehydes **12** might have some potential as intermediates in prostenoid and homoprostenoid synthesis. Treatment of ethereal solutions of **12** with 6 M NaOH resulted in ring closure but dehydration was facile. For **12a**, none of the 3-ethyl-4-hydroxycyclopentanone aldol product was isolated, only the enone **13a** being obtained. Few direct routes to such enones are available,[20] but the route is not practical in this case, due to the low *ee* value of the starting material **6i** and potential stereochemical lability of the chiral centre. However, GC analysis of **13a** indicated that no further racemisation had occurred during the base-promoted cyclisation. Carrying out the ring closure of **12b** at 0 °C, it was possible to isolate a small amount of **14** (5%), along with the dehydrated **13b** as the major product (87%). Isolated (3*R*,5*S*)-**14** proved resistant to dehydration on standing in $CDCl_3$ for at least 3 months. This behaviour, together with its ^1H NMR spectrum, is consistent with isolation of the all-equatorial isomer. The ratio of **13b/14** from this reaction may reflect the diastereoselectivity in the cyclisation (Scheme 5); the derived axial alcohol spontaneously eliminates, producing **13b**. The products isolated in this base-promoted chemistry are formed under thermodynamic control. For example, the cyclisation of **13c** results only in the unusual unsaturated aldehyde (*S*)-**15**: No 7-membered ring product is isolated. (The change in the stereochemical descriptor is a consequence of the CIP priority rules, and not of the chemical transformation.)



Scheme 5

Conclusion

Ligand optimisation studies have indicated that the 3,3′-bis(SMe) derivative **3a** derived from the carbamate **1a** is the most effective with respect to enantioselectivity. Variation of the enone structure has revealed that the catalyst derived from (S_a)-**3a** causes linear enones to adopt an *s-cis* conformation with a zinc-derived Lewis acid bound to the carbonyl lone pair *anti* to the ene function. While precise features of the asymmetric transition state are not yet completely clear, a working mnemonic is given by structure **B**. The nature of the steric block that is the apparent cause of the enantioselectivity is not yet clear; a naphthyl ring is one likely candidate.



B

Experimental Section

General: Infrared spectra were recorded using a Nicolet Avatar 360 FT-IR infrared spectrophotometer. − ^1H and ^{13}C NMR spectra were recorded either with Jeol (GX 270) or with Bruker (AM 400, AV400, DRX500) spectrometers at ambient temperature, using tetramethylsilane as standard; *J* values are given in Hz. − Mass spectra were obtained with AIMS902 (electron impact, EI, or chemical ionisation CI), VG-ZAB (EPSRC service, Swansea), or 70E VG (fast atom bombardment, FAB) machines. − Elemental analyses were performed using a CE-440 elemental analyser. − Optical rotations were measured with Jasco, DIP370 Digital or AA-10 Polarimeter instruments in units of 10^{-1} °·cm^2·g^{-1} (*c* in g/100 cm^3). − Chemical yield (c.y.) and enantiomeric excess (*ee*) analysis of the catalysis were carried out with a Varian 3380 gas chromatograph, using either LIPODEX A (ex. Macherey−Nagel[21]), octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin (6-Me-2,3-pe-γ-CD),[22] or oktakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin (2,6-Me-3-pe-γ-CD)[23] columns using undecane as an internal standard. Details of the chromatographic separations are given in Table 4. − Tetrahydrofuran (THF) was distilled from Na/benzophenone under argon. Diethyl ether and hexane were dried with sodium wire. Catalytic reactions were carried out under argon, using standard Schlenk techniques. Column chromatography and TLC analyses were performed on silica gel, Rhône Poulenc Sorbsil and Merck Kieselgel 60 $F_{254+366}$, respectively. Light petroleum ether refers to the fraction with b.p. 40−60 °C.

Table 4. Assay of the enantiomeric excesses (*ee*) of the conjugate addition products resulting from $ZnEt_2$ addition

Enone	Product	Column	Programme	Elution order [min.] (hand)
5a	**6a**	6-Me-2,3-pe-γ-CD[a]	75 °C isothermal	29.1 (−)-(*S*)[b] 30.2 (+)-(*R*)[b]
5b	**6b**	2,6-Me-3-pe-γ-CD[c]	95 °C isothermal	16.2 (−)-(*S*)[b] 17.7 (+)-(*R*)[b]
5e	**6e**	2,6-Me-3-pe-γ-CD[c]	95 °C isothermal	28.7 (−) 31.0 (+)[d]
5f	**6f**	6-Me-2,3-pe-γ-CD	65 °C isothermal	18.3 (−)-(*S*)[b] 19.0 (+)-(*R*)[b]
5g	**6f**	2,6-Me-3-pe-γ-CD	65 °C isothermal	25.4 (−)-(*S*)[b] 26.2 (+)-(*R*)[b]
5i[e]	**12a**	6-Me-2,3-pe-γ-CD	75 °C isothermal	17.2 (−)-(*S*)[b] 21.1 (+)-(*R*)[b]
5j, **5k**[e]	**12b**	6-Me-2,3-pe-γ-CD	75 °C isothermal	27.1 (−)-(*S*)[b] 28.3 (+)-(*R*)[b]
5l[e]	**12c**	6-Me-2,3-pe-γ-CD	75 °C isothermal	64.2 (−)-(*S*)[b] 67.4 (+)-(*R*)[b]

[a] Oktakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin (ref.[22]). − [b] Based on comparison of the optical rotation sign with that of the analogous methyl addition compound, the absolute stereochemistry of which has been determined (ref.[6]). − [c] Oktakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin (ref.[23]). − [d] Absolute stereochemistry not clear. − [e] Determined on aldehyde after hydrolysis.

Ligand Preparations

(S_a)-2,2′-Bis(*N*,*N*-diethylcarbamoyloxy)-3,3′-diphenylthio-1,1′-binaphthalene [(S_a)-2b] via Carbamate 1a: A solution of *s*BuLi in hexanes (1.3 M; 8.7 mL, 11.3 mmol) was added dropwise over 9 min to a stirred solution of (S_a)-**1a** (2.5 g, 5.16 mmol) and TMEDA (1.5 mL, 10.3 mmol) in dry THF (30 mL) at −78 °C under an inert gas. The reaction was stirred for a further 5 min, diphenyl disulfide (2.49 g, 11.4 mmol) was then added, and the reaction mixture was stirred for 1 h at −78 °C. The mixture was then brought to ambient temperature and quenched with saturated aqueous NH_4Cl solution, the volatiles were removed under high vacuum, the residue was extracted into dichloromethane, the layers were separated and the organic fraction was dried with $MgSO_4$. Column chromatography (EtOH/dichloromethane, 1:49) followed by crystallisation from dichloromethane/light petroleum ether gave colourless crystals (38%); m.p. 145−146 °C; $[\alpha]_D^{29} = +3$ (c = 5.0 in $CHCl_3$). − $C_{42}H_{40}N_2S_2O_4$ (700.9): calcd. C 72.0, H 5.75, N 4.0, S 9.15; found C 72.1, H 5.8, N 4.1, S 9.3. − δ_H (400 MHz, 50 °C, $CDCl_3$) = 0.5−0.9 (12 H, br m, CH_2CH_3), 2.87 (4 H, br s, CH_2CH_3), 3.04 (4 H, br s, CH_2CH_3), 7.21−7.37 (12 H, br m, Ar), 7.47 (4 H, br m, Ar), 7.66 (2 H, br d, J 8.0, 5-H), 7.79 (2 H, br s, 4-H). − δ_C (100.4 MHz, $CDCl_3$, 55 °C) = 12.8, 13.4, 41.8, 42.0, 125.9, 126.0, 126.3, 127.0, 127.3, 129.2, 130.6 br, 131.9 br, 132.8, 135.4 br, 146.4, 152.5. − $\tilde{\nu}$ (KBr disc) [cm^{-1}] = 3060w (Ar C−H), 2980w, 2940w, 1720vs (C=O), 1280s, 1220s, 1160s, 750s. − MS (EI); *m*/*z* (%): 700 (2) [M^+], 591 (4), 100 (100), 72 (72) {found (HRMS, EI) for [M^+] 700.2430, $C_{42}H_{40}N_2O_4S_2$ requires 700.2430}. − Attempted deprotection of **2b** (1.50 g, 2.15 mmol) either with MeLi/LiBr complex [21.5 mmol; on **2b** as a diethyl ether solution (11 mL), 16 h reflux] or with $LiAlH_4$ [8.86 mmol; on **2b** as a THF solution, 16 h reflux] failed to give clean formation of **3b**.

General Procedure for Lithiation of 2,2′-Bis(methoxymethoxy)-1,1′-binaphthalene (1b), Treatment with R_2Y_2 (RY = MeS, EtS, PhS, and MeSe) Followed by in situ Deprotection: *n*BuLi (1.75 mL of a 2.5 M hexane solution, 4.38 mmol) was added at room temperature under nitrogen to a solution of **1b** (0.54 g, 1.43 mmol) in anhydrous diethyl ether. The solution was stirred (3 h) at ambient temperature. The dilithio species was cooled (0 °C) and a solution of R_2Y_2 (5.00 mmol) in THF (20.0 mL) added. The resulting solution was allowed to warm to room temperature (4 h) and was then quenched with $NH_4Cl_{(aq)}$. The volatiles were removed under vacuum and the residue extracted with dichloromethane in the usual way. The resulting solution was dried ($MgSO_4$) and concentrated to yield **4** as oils. − Crude **4** was dissolved in the minimum amount of dichloromethane and treated with a solution of methanol (20 mL), to which concentrated HCl (3 mL, 37% w/w) had been added. The mixture was stirred (16 h), the solvent removed and the residue extracted into dichloromethane. After washing with brine and drying of the organic layer, the solvent was removed. Crude **3a** was isolated by recrystallisation from ethanol; **3b** was obtained as a powder after column chromatography (diethyl ether/light petroleum ether, 1:1); **3c** was isolated as an oil after chromatography (diethyl ether/light petroleum ether/dichloromethane, 1:1:2).

(R_a)-3,3′-Diphenylthio-1,1′-binaphthalene-2,2′-diol [(R_a)-3b]: 54%, nominally > 88% *ee*; m.p. 58−60 °C; $[\alpha]_D^{21} = +143$ (c = 1.01 in $CHCl_3$). − δ_H (400 MHz, $CDCl_3$): 6.32 (s, 2 H, OH), 7.16−7.38 (m, 16 H, Ar), 7.81 (d, J = 8.9 Hz, 2 H, 5-H), 8.15 (s, 2 H, 4-H). − δ_C (67.8 MHz, $CDCl_3$): 114.7, 121.1, 124.2, 124.7, 126.8, 127.8, 128.1, 128.5, 129.2, 129.4, 134.4, 134.8, 136.1, 150.9. − $\tilde{\nu}$ (KBr disc) [cm^{-1}] = 3398s br (OH), 3052w (Ar C−H),1617m, 1581m, 1420m, 1267m, 755m, 742s. − MS (EI); *m*/*z* (%): 502 (100) [M^+] {found (HRMS, EI) for [M^+] 502.1077, $C_{32}H_{22}O_2S_2$ requires 502.1061}.

(R_a)-3,3′-Diethylthio-1,1′-binaphthalene-2,2′-diol [(R_a)-3c]: 64%, nominally > 88% *ee*; oil; $[\alpha]_D^{21} = +99$ (c = 1.00 in $CHCl_3$). − δ_H (400 MHz, $CDCl_3$) = 1.34 (t, J = 7.4 Hz, 6 H, CH_2Me), 2.93, (q, J = 7.4 Hz, 4 H, CH_2Me), 6.55 (s, 2 H, OH), 7.12 (d, 2 H, J = 6.8 Hz plus small unresolved long-range couplings, 8-H), 7.23 (ddd, 2 H, J = 1.4, 6.8, 8.2 Hz, 6-H or 7-H), 7.31 (ddd, 2 H, J = 1.2, 6.8, 8.2 Hz, 6-H or 7-H), 7.81 (d, 2 H, J = 8.2 Hz plus small unresolved long-range couplings, 5-H), 8.12 (s, 2 H, 4-H). − δ_C (67.8 MHz, $CDCl_3$) = 14.6, 30.0, 113.9, 123.0, 124.0, 124.6, 127.2, 127.8, 129.0, 133.8, 134.3, 150.9. − $\tilde{\nu}$ (KBr disc) [cm^{-1}] = 3517m br, 3398s br (2 × OH), 3052m, 2973s, 2926s, 2873m (4 × C−H), 1620m, 1496s, 1450s, 1418s, 1270s, 1146s, 749s. − MS (EI); *m*/*z* (%): 502 (100) [M^+] {found (HRMS, EI) for [M^+] 406.1059, $C_{24}H_{22}O_2S_2$ requires 406.1061}.

(R_a)-3,3′-Dimethylseleno-1,1′-binaphthalene-2,2′-diol [(R_a)-3d]: 61%, nominally > 88% *ee*; m.p. 169 °C; $[\alpha]_D^{21}$ = +114 (*c* = 0.56 in $CHCl_3$). − $C_{22}H_{18}O_2Se_2$ (472.3): calcd. C, 55.9, H 3.8; found C 55.6, H 4.1. − δ_H (400 MHz, $CDCl_3$) = 2.41 (s, 6 H, SeMe), 5.98 (s, 2 H, OH), 7.10 (d, 2 H, *J* = 6.8 Hz plus small unresolved long-range couplings, 8-H), 7.25 (ddd, 2 H, *J* = 1.3, 6.8, 8.2 Hz, 6-H or 7-H), 7.33 (ddd, 2 H, *J* = 1.3, 6.8, 8.2 Hz, 6-H or 7-H), 7.81 (d, 2 H, *J* = 8.2 Hz plus small unresolved long-range couplings, 5-H), 8.05 (s, 2 H, 4-H). − δ_C (67.8 MHz, $CDCl_3$) = 7.6, 112.3, 121.6, 124.2, 124.6, 127.0, 127.4, 129.7, 132.3, 132.9, 150.6. − $\tilde{\nu}$ (KBr disc) [cm^{-1}] = 3508s, 3410s br, 3339s (3 × OH), 3053w (Ar C−H), 2919w, 1570m, 1495m, 1419m, 1384m, 1203m, 1198m, 1174m, 1136s, 750s. − MS (EI); *m*/*z* (%): 473 (42) [M^+, ^{80}Se], 471 (100) [found (HRMS, EI) for [M^+] 473.9658, $C_{22}H_{18}O_2Se_2$ requires 473.9637].

Enone Preparations and Characterisation of the Conjugate Addition Products: Enones **5a**, **5f**, and **7−8** are commercially available. The remaining substrates were prepared by either aldol or Wittig−Horner/Wadsworth−Emmons techniques. Except for **5i**, the formation of only the (*E*) isomer was confirmed by the presence of a large vicinal coupling. For **5i**, an approximate 3:1 (*E*)/(*Z*) ratio was obtained; the (*E*) component was separated by column chromatography.

Enone Preparation by Aldol Condensation (Substrates 5b−d, 5g−h): R^1COMe (R^1 = *i*Pr, *t*Bu, OMe, Me; 10.0 mmol) was added at −80 °C to a solution of LDA [prepared from *i*Pr_2NH (1.5 mL, 10.5 mmol) and *n*BuLi (4.4 mL of 2.5 M hexane solution, 11.0 mmol), 30 min, 0 °C] in THF (20 mL) and the mixture was stirred for 20 min. The resulting enolate was treated with R^2CHO (*n*C_5H_{11}, *i*Pr, CH_2*i*Pr, *t*Bu) and the mixture was stirred for another hour at −80 °C. After standard workup and removal of the volatiles, the crude β-hydroxycarbonyl compound was dissolved in ether (20 mL) and treated with conc. HCl (2 mL). The resultant enone was isolated by flash chromatography (eluent: diethyl ether/light petroleum ether, 1:5). For **5d**, the initial aldol product was treated sequentially with $MeSO_2Cl$ and DBU to effect dehydration.

(*E*)-2-Methyldec-4-en-3-one (5b): Yield 82%. − δ_H ($CDCl_3$, 400 MHz) = 0.89 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*), 1.10 (d, *J* = 6.9 Hz, 3 H, CH*Me*$_2$), 1.23−1.35 (m, 4 H, 2 × CH_2 of *n*C_5H_{11}), 1.35−1.50 (m, 2 H, CH_2 of *n*C_5H_{11}), 2.20 (dq, 2 H, *J* = 1.5, 7.5 Hz, =CH*CH*$_2$), 2.81 (sept, 1 H, *J* = 6.9, *CH*Me_2), 6.15 (dt, *J* = 15.7, 1.5 Hz, 1 H, CO*CH*=), 6.87 (dt, *J* = 15.7, 7.0 Hz, 1 H, CH_2*CH*=). − δ_C ($CDCl_3$, 67.8 MHz) = 13.9 (CH_2*Me*), 18.5 (CH*Me*$_2$), 22.4, 27.8, 31.3, 32.4 (4 × CH_2 of *n*-C_5H_{11}), 38.4 (*CH*Me_2), 128.3 (CO*CH*=), 147.3 (CH_2*CH*=), 204.1 (CO). − MS (EI); *m*/*z* (%): 168 (7) [M^+], 140 (8), 125 (100). − These properties and others (b.p., IR spectrum) are consistent with literature data for **5b**.[24]

(*E*)-2,2-Dimethyldec-4-en-3-one (5c): Yield 71%. − δ_H ($CDCl_3$, 400 MHz) = 0.85 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*), 1.11 (s, 9 H, *t*Bu), 1.24−1.34 (m, 4 H, 2 × CH_2 of *n*C_5H_{11}), 1.40−1.48 (m, 2 H, CH_2 of *n*C_5H_{11}), 2.16 (dq, 2 H, *J* = 1.5, 7.1 Hz, =CH*CH*$_2$), 6.46 (dt, *J* = 15.3, 1.5 Hz, 1 H, CO*CH*=), 6.90 (dt, *J* = 13.3, 7.0 Hz, 1 H, *CH*=CH_2). − δ_C ($CDCl_3$, 67.8 MHz) = 13.9 (CH_2*Me*), 22.3 (CH_2), 26.1 (*t*Bu), 27.8, 31.3, 32.4 (3 × CH_2 of *n*C_5H_{11}), 38.0 (*C*Me_3), 124.0 (CO*CH*=), 147.5 (CH_2*CH*=), 204.1 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2992m, 2959s, 2861s (3 × C−H), 1711s, 1691s (2 × C=O), 1625m (C=C), 1477m, 1467m, 1366m, 1084m, 990. − MS (EI); *m*/*z* (%): 165 (100) [M^+ − *t*Bu] [found (HRMS, FAB) for [M^+] 182.1665, $C_{12}H_{22}O$ requires 182.1671]. − Compound **5c** has been described in the literature[25,26] but no spectroscopic or physical data were reported.[27]

Methyl (*E*)-Oct-2-enoate (5d): Yield 65%. − δ_H ($CDCl_3$, 400 MHz) = 0.87 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*), 1.24−1.37 (m, 4 H, 2 × CH_2 of *n*C_5H_{11}), 1.41−1.49 (m, 2 H, CH_2 of *n*C_5H_{11}), 2.19 (dq, 2 H, *J* = 1.6, 7.0 Hz, =CH*CH*$_2$), 3.71 (s, 3 H, OMe), 5.81 (dt, *J* = 15.6, 1.6 Hz, 1 H, CO*CH*=), 6.97 (dt, *J* = 15.6, 7.0 Hz, 1 H, CH_2*CH*=). − δ_C ($CDCl_3$, 67.8 MHz) = 13.8 (CH_2*Me*), 22.3, 27.5, 31.1, 32.0 (4 × CH_2 of *n*C_5H_{11}), 51.1 (OMe), 120.7 (CO*CH*=), 149.6 (CH_2*CH*=), 167.0 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2960s, 2926s, 2858s (3 × C−H), 1717s (C=O), 1659s (C=C), 1458m, 1436m, 1379m, 1272s, 1205s, 1175s, 1129m, 1045m, 988. − MS (EI); *m*/*z* (%): 156 (3) [M^+], 125 (29), 87 (100). − These properties[27] and others (b.p.[28]) are consistent with literature data for **5d**.

(*E*)-6-Methylhept-3-en-2-one (5g): Yield 73%. − δ_H ($CDCl_3$, 400 MHz) = 0.93 (d, *J* = 6.7 Hz, 6 H, CH*Me*$_2$), 1.78 (sept, 1 H, *J* = 7.1, 6.7 Hz, *CH*Me_2), 2.11 (2 H, apparent dt, *J* = 1.4, 7.1 Hz, 7.4, *CH*$_2$CHMe_2), 2.24 (s, 3 H, CO*Me*), 6.07 (dt, *J* = 15.9, 1.4 Hz, 1 H, CO*CH*=), 6.78 (dt, *J* = 15.9, 7.4 Hz, 1 H, CH_2*CH*=). − δ_C ($CDCl_3$, 67.8 MHz) = 22.2 (2 C, CH*Me*$_2$), 26.6 (CO*Me*), 27.7 (*CH*Me_2), 41.5 (CH_2), 132.1 (CO*CH*=), 147.4 (CH_2*CH*=), 198.7 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2958s. 2930s, 2871s (3 × C−H), 1720sh, 1697sh, 1674s (C=O), 1627s (C=C), 1466m, 1362m, 1252m, 982m. − MS (FAB); *m*/*z*: 126 (8) [M^+], 111 (31), 84 (36), 69 (100) {found (HRMS, FAB) for [M^+] 126.1042, $C_8H_{14}O$ requires 126.1045}. − These properties and others (b.p.) are consistent with literature data for **5g**.[29]

(*E*)-5,5-Dimethylhex-3-en-2-one (5h): Yield 75%. − δ_H ($CDCl_3$, 400 MHz) = 1.08 (s, 9 H, *t*Bu), 3.23 (s, 3 H, CO*Me*), 5.98 (d, 1 H, *J* = 16.2, CO*CH*=), 6.77 (d, 1 H, *J* = 16.2, *t*Bu*CH*=). − δ_C ($CDCl_3$, 67.8 MHz) = 26.9 (CO*Me*), 28.6 (C*Me*$_3$), 33.6 (*C*Me_3), 126.3 (CO*CH*=), 157.9 (CH_2*CH*=), 199.8 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2964s, 2869s (2 × C−H), 1699s, 1678s (2 × C=O), 1623s (C=C), 1478m, 1464m, 1361s, 1255s, 984m. − MS (EI); *m*/*z* (%): 126 (16) [M^+], 111 (100) {found (HRMS, EI) for [M^+] 126.1039, $C_8H_{14}O$ requires 126.1045}. − These properties and others (b.p.) are consistent with literature data for **5h**.[29]

Enone Preparation by Wittig−Horner/Wadsworth−Emmons Methodology (Substrates 5e, 5i−l): Appropriate aldehydes (4.00 mmol) were refluxed in THF (10 mL) in the presence of either Ph_3P=CH(COMe)[30] (4.00 mmol) or the ylide derived from $(MeO)_2$-P(O)CH_2COCH_2OMe[31] and K_2CO_3 in toluene for **5e**. The resultant enones were isolated by flash chromatography (eluent: diethyl ether/light petroleum ether, 1:1).

(*E*)-1-Methoxynon-3-en-2-one (5e): Yield 78%. − δ_H ($CDCl_3$, 400 MHz) = 0.89 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*), 1.24−1.38 (m, 4 H, 2 × CH_2 of *n*C_5H_{11}), 1.42−1.51 (m, 2 H, CH_2 of *n*C_5H_{11}), 2.21 (dq, 2 H, *J* = 1.5, 6.9 Hz, =CH*CH*$_2$), 3.42 (s, 3 H, OMe), 4.16 (s, 2 H, *COCH*$_2$). − 6.25 (dt, *J* = 15.9, 1.5 Hz, 1 H, CO*CH*=), 6.97 (dt, *J* = 15.9, 6.9 Hz, 1 H, CH_2*CH*=). − δ_C ($CDCl_3$, 67.8 MHz) = 13.7 (CH_2*Me*), 22.2, 27.4, 31.1, 32.4 (4 × CH_2 of *n*C_5H_{11}), 59.0 (OMe), 76.4 (CH_2O), 125.8 (CO*CH*=), 148.7 (CH_2*CH*=), 196.7 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2970m, 2932s, 2874s (3 × C−H), 1701s (C=O), 1654s (C=C), 1458m, 1420m, 1384m, 1200m, 1126m. − MS (EI); *m*/*z* (%): 170 (4) [M^+], 147 (27), 125 (36) [M^+ − CH_2OMe] {found (HRMS, EI) for [M^+] 170.1260, $C_{10}H_{18}O_2$ requires 170.1307; for [M^+ − CH_2OMe] 125.0963, $C_8H_{14}O$ requires 125.0966}.

(*E*)-5,5-Dimethoxypent-3-en-2-one (5i): Yield 82%. − δ_H ($CDCl_3$, 400 MHz) = 2.28 (s, 3 H, CO*Me*), 3.35 (s, 6 H, OMe), 4.95 [1 H, dd, *J* = 1.3, 4.1 Hz, *CH*$(OMe)_2$] 6.32 (dd, *J* = 16.2, 1.3 Hz, 1 H, CH*CH*=), 6.56 (dd, *J* = 16.2, 4.1 Hz, 1 H, CO*CH*=). − δ_C ($CDCl_3$, 67.8 MHz) = 27.1 (CO*Me*), 52.8 (2 C, OMe), 100.9

[*CH*(OMe)$_2$], 132.7 (CO*CH*= or CH*CH*=), 140.9 (CO*CH*= or CH*CH*=), 198.2 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2994m, 2938s, 2832s (3 × C−H), 1701s, 1682s (2 × C=O), 1642m (C=C), 1360s, 1257s, 1131s (C−O), 1057s, 982. − MS (EI); *m*/*z* (%): 144 (1) [M$^+$], 129 (35), 113 (100). − $C_7H_{12}O_3$ (144.2): calcd. C 58.32, H 8.39; found C 58.13, H 8.39. − Compound **5i** has been described in the literature but no spectroscopic or physical data were reported.[32]

(*E*)-7,7-Diethoxyhex-3-en-2-one (5j): Yield 55% (two steps, starting from alcohol). − δ_H (400 MHz, $CDCl_3$) = 1.19 (t, *J* = 7.1 Hz, 6 H, OCH$_2$*Me*), 2.26 (s, 3 H, CO*Me*), 2.54 (ddd, 2 H, *J* = 7.1, 5.5 Hz, 1.5, *CH*$_2$CH=), 3.49 (dq, 2 H, *J* = 9.4, 7.1 Hz, OCH$_{2\alpha}$), 3.63 (dq, 2 H, *J* = 9.4, 7.1 Hz, OCH$_{2\beta}$), 4.58 [1 H, t, *J* = 5.5, *CH*(OEt)$_2$], 6.10 (dt, *J* = 16.1, 1.4 Hz, 1 H, CO*CH*=), 6.73 (dt, *J* = 16.1, 7.1 Hz, 1 H, CH$_2$*CH*=). − δ_C ($CDCl_3$, 67.8 MHz) = 15.1 (2 C, CH$_2$*Me*), 26.7 (CO*Me*), 37.1 (*CH*$_2$CH=), 61.5 (2 C, O*CH*$_2$Me), 101.2 [*CH*(OEt)$_2$], 133.4 (CO*CH*=), 142.6 (CH$_2$*CH*=), 198.4 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2977s, 2930m, 2882m (3 × C−H), 1700m, 1677s (2 × C=O), 1630m (C=C), 1372m, 1360m, 1255m, 1126s (C−O), 1062s, 978m. − MS (EI); *m*/*z* (%): 142 (1) [M$^+$ − EtOH], 113 (29), 103 (100) {found (HRMS, EI) for [M$^+$ − EtOH] 141.0916, $C_8H_{13}O_2$ requires 141.0916}.

(*E*)-5-(1,3-Dioxolan-2-yl)pent-3-en-2-one (5k): Yield 63% (two steps, starting from alcohol). − δ_H (400 MHz, $CDCl_3$) = 2.26 (s, 3 H, CO*Me*), 2.60 (ddd, 2 H, *J* = 1.4, 4.6 Hz, 6.8, =CH*CH*$_2$), 3.84−4.03 (m, 4 H, OCH$_2$CH$_2$O), 5.00 (t, *J* = 4.6 Hz, 1 H, *CH*CH$_2$), 6.17 (dt, *J* = 16.0, 1.4 Hz, 1 H, *CH*CO), 6.78 (dt, *J* = 10.0, 6.8 Hz, 1 H, =*CH*CH$_2$). − δ_C ($CDCl_3$, 67.8 MHz) = 26.7 (CO*Me*), 37.0 (*CH*$_2$CH=), 64.9 (2 C, O*CH*$_2$), 102.3 [*CH*(OCH$_2$)$_2$], 133.9 (CO*CH*=), 141.1 (CH$_2$*CH*=), 198.1 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2968m, 2889s (2 × C−H), 1715m, 1676s 1677s (2 × C=O), 1631 (C=C), 1363m, 1257m, 1137s (C−O), 1036m, 977m. − MS (CI); *m*/*z* (%): 155 (33) [M$^+$ − H], 87 (100) {found (HRMS, FAB) for [M$^+$ + H] 157.0865, $C_8H_{13}O_3$ requires 157.0865}.

(*E*)-7,7-Diethoxyhept-3-en-2-one (5l): Yield 58% (two steps, starting from alcohol). − δ_H (400 MHz, $CDCl_3$) = 1.13 (t, *J* = 7.1 Hz, 6 H, OCH$_2$*Me*), 1.68−1.73 (m, 2 H, =CHCH$_2$*CH*$_2$), 2.16 (s, 3 H, CO*Me*), 2.21−2.27 (m, 2 H, *H*$_2$CH=), 3.38−3.46 (m, 2 H, OCH$_{2\alpha}$), 3.53−3.62 (m, 2 H, OCH$_{2\beta}$), 4.42 (t, *J* = 5.6 Hz, 1 H, *CH*(OEt)$_2$], 6.01 (dt, *J* = 16.0, 1.5 Hz, 1 H, CO*CH*=), 6.76 (dt, *J* = 16.0, 6.8 Hz, 1 H, CH$_2$*CH*=). − δ_C ($CDCl_3$, 67.8 MHz) = 15.1 (2 C, CH$_2$*Me*), 26.7 (CO*Me*), 27.5 (*CH*$_2$CH$_2$CH=), 37.1 (*CH*$_2$CH=), 61.2 (2 C, O*CH*$_2$Me), 101.9 [*CH*(OEt)$_2$], 131.2 (CO*CH*=), 147.5 (CH$_2$*CH*=), 198.4 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2975s, 2930m, 2879m (3 × C−H), 1698m, 1676s (2 × C=O), 1628m (C=C), 1444m, 1361m, 1254m, 1128s (C−O), 1062s, 979m. − MS (EI); *m*/*z* (%): 155 (12) [M$^+$ − OEt], 123 (16), 111 (23), 109 (30), 95 (46) {found (HRMS, FAB) for [M$^+$ − EtOH]155.1062, $C_9H_{15}O_2$ requires 155.1072}.

Preparation of the Precursor Aldehydes: For enones **5j**−**l**, the required aldehydes were obtained from (EtO)$_2$CH(CH$_2$)$_n$CH=CH$_2$ (*n* = 0, 1) or 2-vinyl-[1,3]dioxolane (5.00 mmol) by hydroboration under literature conditions to give the known alcohols.[32−34] The alcohols (1.16 mmol) were oxidised under Swern conditions [DMSO (181 mg, 2.32 mmol), oxalyl chloride (0.15 mL, 1.73 mmol) and NEt_3 (0.56 mL, 4.06 mmol)]. The derived aldehydes,[32,33,35] proving rather reactive, were used directly as crude products in the organophosphorus couplings. The aldehyde (MeO)$_2$CHCHO is commercially available.

(*E*)-2-Propylidenecyclopentanone (9a): Synthesis by literature methods.[36,37] Yield 50%. − δ_H (400 MHz, $CDCl_3$) = 1.05 (t, *J* = 7.6 Hz, 3 H, CH$_2$*Me*), 1.92 (2 H, quint, *J* = 7.5, central CH$_2$ of ring), 2.15 (2 H, apparent tquint, *J* = 7.6, 1.5 Hz, *CH*$_2$CH=), 2.32 (t, *J* = 7.5 Hz, 2 H, CO*CH*$_2$ in ring), 2.58 (2 H, tdt, *J* = 7.3, 2.5 Hz, 1.3), 6.51 (1 H, *J* = 7.6, 2.5 Hz, =CH). − (δ_C ($CDCl_3$, 67.8 MHz): 11.8 (CH$_2$*Me*), 18.8 (CH$_2$ of ring), 22.0 (=CH*CH*$_2$), 25.6 (CH$_2$ of ring), 27.9, 29.5, 31.4 (3 × CH$_2$ of *n*C_5H_{11}), 37.6 (CO*CH*$_2$ of ring), 135.7 (CO*C*=), 136.5(CH$_2$*CH*=), 206.3 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2966s, 2877s (2 × C−H), 1717s (C=O), 1651m (C=C), 1462m, 1410m, 1286m, 1225m, 1202m, 1142m, 993s, 732m. − MS (CI); *m*/*z* (%): 124 (27) [M$^+$], 95 (22) {found (HRMS, CI) for [*M*$^+$] 124.0885, $C_8H_{12}O$ requires 112.0888}.

(*E*)-2-Hexylidenecyclopentanone (9b): Synthesis by literature methods.[36,37] Yield 50%. − δ_H (400 MHz, $CDCl_3$) = 0.88 (t, *J* = 6.9 Hz, 3 H, CH$_2$*Me*), 1.23−1.35 (m, 4 H, 2 × CH$_2$ of *n*C_5H_{11}), 1.40−1.49 (m, 2 H, CH$_2$ of *n*C_5H_{11}), 1.92 (2 H, quint, *J* = 7.5, central CH$_2$ of ring), 2.13 (2 H, apparent qt, *J* = 7.5, 1.5 Hz, *CH*$_2$CH=), 2.43 (t, *J* = 7.5 Hz, 2 H, CO*CH*$_2$ in ring), 2.57 (2 H, tdt, *J* = 7.5, 2.7 Hz, 1.5), 6.54 (1 H, *J* = 7.5, 2.7 Hz, =CH). − δ_C ($CDCl_3$, 67.8 MHz) = 13.9 (CH$_2$*Me*), 19.7 (CH$_2$ of ring), 22.4 (CH$_2$ of *n*C_5H_{11}), 26.6 (CH$_2$ of ring), 27.9, 29.5, 31.4 (3 × CH$_2$ of *n*C_5H_{11}), 38.5 (CO*CH*$_2$ of ring), 136.3 (CH$_2$*CH*=), 137.1 (CO*CH*=), 207.1 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2950s, 2853s (2 × C−H), 1723s (C=O), 1654m (C=C), 1460m, 1231m, 1185m, 974s. − MS (FAB); *m*/*z*: 167 (84) [M$^+$ + H], 112 (100) {found (HRMS, FAB) for [M$^+$ + H] 167.1439, $C_{11}H_{19}O$ requires 167.1436}. − These properties and others (b.p.) are consistent with literature data for **9b**. The results of an NOE study between the ring 3-CH$_2$ and the methylene functions of the C_5H_{11} chain are consistent with isolation of only the (*E*) double-bond isomer.

Structural Confirmation of the Isolated 1,4-Addition Products: The conjugate addition products were isolated directly from the catalytic reactions by flash chromatography. Because of the small scale of the reactions and the presence of undecane, internal standard accurate analytical or [α]$_D$ values could not be obtained in all cases.

(+)-4-Ethylnonan-2-one (6a): δ_H (400 MHz, $CDCl_3$) = 0.82 (t, *J* = 7.4 Hz, 3 H, *Me* of C^5-Et), 0.87 (t, *J* = 6.8 Hz, 3 H, Me of *n*C_5H_{11}), 1.18−1.39 (m, 10 H, 4 × *CH*$_2$ of *n*C_5H_{11} and *CH*$_2$ of C^5-Et), 1.85 (apparent sept, 1 H, *J* = 6.3, *CH*Et), 2.12 (s, 3 H, CO*Me*), 2.33 (2 H, *J* = 7.8, CO*CH*$_2$). − δ_C ($CDCl_3$, 67.8 MHz) = 12.8 (*Me* of C^5-Et), 16.0 (*Me* of *n*-C_5H_{11}), 24.6, 28.2, 28.3 (2 × CH$_2$ of *n*C_5H_{11} and C^5-Et), 32.3 (*CH*Et), 34.1, 35.4 (2 × CH$_2$ of *n*C_5H_{11}), 37.3 (CO*Me*), 50.5 (CO*CH*$_2$), 211.4 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2959s, 2927s, 2873m, 2858m (4 × C−H), 1717s (C=O), 1462m, 1355m, 1165m. − MS (EI); *m*/*z* (%): 171 (100) [M$^+$ + H], 141 (18) [M$^+$ − Et], 112 (19), 99 (18) {found (HRMS, EI) for [M$^+$] 170.1761, $C_{11}H_{22}O$ requires 170.1761}. − These properties are consistent with literature structure and data.[6]

(+)-5-Ethyl-2-methyldecan-3-one (6b): δ_H (400 MHz, $CDCl_3$) = 0.83 (t, *J* = 7.4 Hz, 3 H, *Me* of C^5-Et), 0.86 (t, *J* = 6.9 Hz, 3 H, Me of *n*C_5H_{11}), 1.06 (d, *J* = 6.9 Hz, 6 H, CH*Me*$_2$), 1.12−1.35 (m, 10 H, 4 × *CH*$_2$ of *n*C_5H_{11} and *CH*$_2$ of C^5-Et), 1.87 (apparent sept, 1 H, *J* = 6.3, *CH*Et), 2.34 (2 H, ABX, *J* = 7.7, 6.3 Hz, CO*CH*$_2$), 2.57 (sept, 1 H, *J* = 6.9, *CH*Me$_2$). − δ_C ($CDCl_3$, 67.8 MHz) = 11.1 (*Me* of C^5-Et), 14.3 (*Me* of *n*-C_5H_{11}), 18.5 (CH*Me*$_2$), 22.9, 26.6, 26.65, 32.4, 33.8 (5 × CH$_2$ of *n*C_5H_{11} and C^5-Et), 35.2 (*CH*Et), 41.4 (*CH*Me$_2$), 45.4 (CO*CH*$_2$), 215.6 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2961s, 2928s, 2874m, 2855m (4 × C−H), 1713s (C=O), 1460m, 1383m, 1045m. − MS (FAB); *m*/*z* (%): 198 (10) [M$^+$], 155 (55), 86 (68), 71 (100) {found (HRMS, FAB) for [M$^+$] 198.1984, $C_{13}H_{26}O$ requires 198.1987}.

(−)-4-Ethyl-1-methoxynonan-2-one (6e): δ_H (400 MHz, $CDCl_3$) = 0.84 (t, *J* = 7.5 Hz, 3 H, *Me* of C^5-Et), 0.86 (t, *J* = 6.8 Hz, 3 H, Me of *n*C_5H_{11}), 1.15−1.38 (m, 10 H, 4 × *CH*$_2$ of *n*C_5H_{11} and *CH*$_2$

of C^5-Et), 1.88 (apparent sept, 1 H, J = 6.4, *CH*Et), 4.69 (2 H, ABX, J = 7.3, 6.4 Hz, CO*CH*$_2$), 3.40 (s, 3 H, OMe), 3.98 (s, 2 H, *CH*$_2$OMe). − δ_C ($CDCl_3$, 67.8 MHz) = 10.7 (*Me* of C_4-Et), 14.0 (*Me* of nC_5H_{11}), 22.6, 26.2, 26.3, 32.0, 33.4 (5 × CH_2 of nC_5H_{11} and C_5-Et), 34.9 (*CH*Et), 43.2 (CO*CH*$_2$CH), 59.2 (OMe), 78.0 (CO*CH*$_2$OMe), 208.7 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2959s, 2929s, 2852m (3 × C−H), 1708s (C=O), 1462m, 1406m, 1285m, 1192m, 935m. − MS (FAB); *m*/*z* (%): 200 (3) [M^+], 155 (79) [M^+ − *CH*$_2$OMe], 85 (37), 71 (100) {found (HRMS, FAB) for [M^+] 200.1775, $C_{12}H_{24}O_2$ requires 200.1776}.

(+)-4-Ethyl-5-methylhexan-2-one (6f): δ_H (400 MHz, $CDCl_3$) = 0.82 (d, J = 6.7 Hz, 3 H, CH*Me*$_{2\alpha}$), 085 (d, J = 6.7 Hz, 3 H, CH*Me*$_{2\beta}$), 0.86 (t, J = 7.5 Hz, 3 H, *Me* of C^4-Et), 1.15−1.26 (m, 1 H, *CH*$_{2\alpha}$Me), 1.29−1.40 (m, 1 H, *CH*$_{2\beta}$Me), 1.67−1.81 (m, 2 H, *CH*Me$_2$ and *CH*Et), 2.14 (s, 3 H, CO*Me*), 2.25 (dd, J = 16.2, 7.3 Hz, 1 H, CO*CH*$_{2\alpha}$), 2.38 (dd, J = 16.2, 5.4 Hz, 1 H, CO*CH*$_{2\beta}$). − δ_C ($CDCl_3$, 67.8 MHz) = 12.0 (*Me* of C^4-Et), 18.7 (CH*Me*$_{2\alpha}$), 19.8 (CH*Me*$_{2\beta}$), 24.2 (*CH*$_2$Me), 29.5, 30.5 (*CH*Me$_2$ and *CH*Et), 41.4 (COMe), 45.3 (CO*CH*$_2$), 209.7 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2961s, 2933s, 2894m, 2875m (4 × C−H), 1719s (C=O), 1466m, 1369m, 1355m, 1166m. − MS (ES); *m*/*z* (%): 142 (1) [M^+], 99 (19), 84 (64), 69 (52), 58 (55), 43 (100) {found (HRMS, EI) for [M^+ + H] 143.1436, $C_9H_{19}O$ requires 143.1436}. − This compound has been described in the literature but no spectroscopic or physical data have been reported.[4,38,39]

(+)-4-Ethyl-6-methylheptan-2-one (6g): δ_H (400 MHz, $CDCl_3$) = 0.85 (t, J = 7.5 Hz, 3 H, *Me* of C^4-Et), 0.86 (d, J = 6.0 Hz, 3 H, CH*Me*$_{2\alpha}$), 088 (d, J = 6.3 Hz, 3 H, CH*Me*$_{2\beta}$), 1.01 (dt, J = 13.6, 6.8 Hz, 1 H, *CH*$_{2\alpha}$-*iPr*), 1.16 (dt, J = 13.6, 6.8 Hz, 1 H, *CH*$_{2\beta}$-*iPr*), 1.22−1.38 (m, 2 H, *CH*$_2$Me), 1.59 (1 H, J = 6.8, *CH*CH$_2$Me) 1.88−1.98 (m, 1 H, *CH*Me$_2$), 2.13 (s, 3 H, CO*Me*), 2.31 (apparent sept, 2 H, ABX, J = 7.1, 6.8 Hz, CO*CH*$_2$). − δ_C ($CDCl_3$, 67.8 MHz) = 10.5 (*Me* of C^4-Et), 22.6 (CH*Me*$_{2\alpha}$), 22.8 (CH*Me*$_{2\beta}$), 25.1 (*CH*Me$_2$ or *CH*Et), 26.4 (*CH*$_2$Me), 29.5, 30.5 30.3 (COMe), 32.9 (*CH*Me$_2$ or *CH*Et), 43.2 (*CH*$_2$-*i*Pr), 48.4 (CO*CH*$_2$), 209.1 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2960s, 2915s, 2896m, 2871m (4 × C−H), 1710s (C=O), 1459m, 1362m, 1162m. − MS (ES); *m*/*z* (%): 156 (1) [M^+], 98 (38), 69 (58), 58 (100) {found (HRMS, FAB) for [M^+] 156.5111, $C_{10}H_{20}O$ requires 156.1514}.

4-Ethyl-5,5-dimethoxypentan-2-one (6i) and (+)-2-Ethyl-4-oxopentanal (12a): The initial kinetic acetal (**6i**) was observed if the reaction mixture was quenched with buffer (pH =7). − δ_H (400 MHz, $CDCl_3$) = 0.88 (t, J = 7.5 Hz, 3 H, *Me* of C^4-Et), 1.27 (1 H, dquint, J = 13.8, 7.5 Hz, *CH*$_{2\alpha}$Me), 1.49 (ddq, 1 H, J = 13.8, 5.2 Hz, 7.5, CH$_{2\beta}$Me), 2.14 (s, 3 H, CO*Me*), 2.20−2.31 (m, 2 H, CO*CH*$_{2\alpha}$ and *CH*Et), 2.53−2.59 (m, 1 H, CO*CH*$_{2\beta}$), 3.32 (s, 3 H, OMe$_\alpha$), 3.35 (s, 3 H, OMe$_\beta$), 4.16 [d, J = 5.2 Hz, 1 H, *CH*(OMe)$_2$]. − After deprotection with dil. HCl (2.0 M), the aldehyde (**7a**) displayed a ^{1}H NMR spectrum consistent with that in the literature:[40] δ_H (400 MHz, $CDCl_3$) = 0.95 (t, J = 7.5 Hz, 3 H, *Me* of C^4-Et), 1.51−1.61 (m, 1 H, *CH*$_{2\alpha}$Me), 1.70−1.81 (m, 1 H, CH$_{2\beta}$Me), 2.19 (s, 3 H, CO*Me*), 2.40−2.48 (m, 1 H, CO*CH*$_{2\alpha}$), 2.82−2.92 (m, 2 H, CO*CH*$_{2\beta}$ and *CH*Et), 9.71 (s, 1 H, CHO). − The compound could not be isolated analytically pure and was cyclised directly (see later).

4-Ethyl-5,5-diethoxyhexan-2-one (6j) and (+)-3-Ethyl-5-oxohexanal (12b): The initial kinetic acetal (**6j**) was observed if the reaction mixture was quenched with buffer (pH = 7). − δ_H (400 MHz, $CDCl_3$) = 0.85 (t, J = 7.4 Hz, 3 H, *Me* of C^4-Et), 1.16 (t, J = 7.1 Hz, 3 H, O*CH*$_2$Me) overlapped by 1.16 (t, J = 7.1 Hz, 3 H, O*CH*$_2$Me), 1.28−1.39 (m, 2 H, *CH*$_2$ of C^4-Et), 1.46−1.53 (m, 1 H, CH*CH*$_{2\alpha}$CH), 1.58−1.64 (m, 1 H, CH*CH*$_{2\beta}$CH), 2.01 (1 H, apparent sept, J = 6.3, C*H*Et), 2.11 (s, 3 H, CO*Me*), 2.40 (2 H, ABX, 16.4, 6.6, CO*CH*$_2$), 3.40−3.50 (m, 2 H, O*CH*$_2$Me), 3.56−3.66 (m, 2 H, O*CH*$_2$Me), 4.52 (t, J = 6.0 Hz, 1 H, C*H*[OEt]$_2$). − Deprotection with dil. HCl (2.0 M) provided the aldehyde. − $[\alpha]_D^{22}$= +70 (c = 0.57, $CHCl_3$). − δ_H (400 MHz, $CDCl_3$) = 0.91 (t, J = 7.4 Hz, 3 H, *Me* of C^4-Et), 1.32−1.46 (m, 2 H, *CH*$_2$Me), 2.14 (s, 3 H, CO*Me*), 2.26−2.38 (m, 5 H, CHO*CH*$_2$*CHCH*$_2$CO), 9.74 (s, 1 H, CHO). − MS (FAB); *m*/*z* (%): 142 (1) [M^+], 113 (14), 99 (26), 83 (20), 59 (23), 58 (100) {found (HRMS, FAB) for [M^+]142.0996, $C_8H_{14}O_2$ requires 142.0994}. − Compound **12b** was also obtained from catalytic reactions using **5k**.

(+)-4-Ethyl-6-oxoheptanal (12c): $[\alpha]_D^{22}$ = +9 (c = 0.33, $CHCl_3$). − δ_H (400 MHz, $CDCl_3$) = 0.82 (t, J = 7.4 Hz, 3 H, *Me* of C^4-Et), 1.18−1.37 (m, 2 H, *CH*$_2$Me), 1.49−1.63 (m, 2 H, CHOCH$_2$*CH*$_2$), 1.86 (1 H, apparent sept, J = 6.4, *CH*Et), 2.10 (s, 3 H, CO*Me*), 2.28 (dd, 1 H, J = 6.9, 16.7 Hz, CO*CH*$_{2\alpha}$), 2.35−2.42 (m, 3 H, CHO*CH*$_2$ and CO*CH*$_{2\beta}$), 9.72 (t, J = 1.7 Hz, 1 H, CHO). − δ_C ($CDCl_3$, 67.8 MHz) = 10.6 (*Me* of C^4-Et), 25.4, 26.0 (2 × CH_2), 30.4 (*CH*Et), 34.3 (COMe), 41.2, 47.7 (2 × CH_2), 202.2 (CHO), 208.4 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2963m, 2931m, 2876w (3 × C−H), 1717s (2 × C=O), 1412m, 1357m, 1163m. − MS (FAB); *m*/*z* (%): 156 (2) [M^+], 113 (21), 98 (31), 81 (26), 58 (100) {found (HRMS, FAB) for [M^+] 156.1152, $C_9H_{16}O_2$ requires 156.1150}. − The precursor acetal (**6l**) was not isolated or characterised.

2-(1-Ethylpropyl)cyclopentanone (10a): Isolated as a 1:1 mixture of enantiomers at C-2. − δ_H (400 MHz, $CDCl_3$) = 0.84, (t, J = 7.4 Hz, 3 H, Me), 0.89 (t, J = 7.4 Hz, 3 H, Me), 1.19 (m, 3 H), 1.50−1.79 (m, 4 H), 1.98−2.11 (m, 3 H), 2.15−2.22 (m, 1 H), 2.28−2.37 (m, 1 H). − δ_C ($CDCl_3$, 67.8 MHz) = 13.7, 14.2 (2 × CH_2*Me*), 22.6, 25.8, 26.2, 26.5 (4 × CH_2, 2 × *C*H$_2$Me, C-3, C-4), 41.2 (C-5), 42.5 (*exo*-CH), 53.7 (ring-CH), 223.0 (CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2963s, 2935s, 2876m (3 × C−H), 1734s (C=O), 1462m, 1407w, 1380w, 1272w, 1150m, 919w, 734m. − MS (CI); *m*/*z* (%): 309 (100) [M^+ − dimer], 154 (11) [M^+], 137 (35), 125 (10), 84 (18) {found (HRMS, CI) for [M^+ + H] 155.1416, $C_{10}H_{19}O$ requires 155.1436}.

(−)-2-(1-Ethylhexyl)cyclopentanone (10b): Isolated as a 1:1 mixture of diastereomers at C-2, *ee* of the addition determined by ^{13}C NMR of CBS-reduced **10b** (see below). − $[\alpha]_D^{25}$ = −0.3 (c = 1.6, $CHCl_3$). − δ_H (400 MHz, $CDCl_3$) = 0.83, 0.86, 0.875, 0.88 (4 closely overlapping methyl ssignals each 3 H, t, J = 7.4, *Me* of C^4-Et and *Me* of nC_5H_{11}); the rest of the spectrum is not informative and composes an envelope of signals in the range 1.15−2.40. − δ_C ($CDCl_3$, 67.8 MHz) = 12.2, 12.6, 14.3 (2 C) [4 × CH$_2$*Me*], 21.0, 22.8, 22.9, 24.5, 24.6, 24.65, 25.4, 27.3, 27.8, 31.6, 32.2, 32.3, 32.4 (14 × CH_2, including overlapping signals), 39.1, 39.2 (2 × CH), 39.6 (2 C, 2 × CH_2), 52.2, 50.6 (2 × CH), 222.2 (2 C, CO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2959s, 2927s, 2874m, 2855m, (4 × C−H), 1735s (C=O), 1465m, 1406w, 1378w, 1271w, 1150m. − MS (EI); *m*/*z* (%): 196 (1) [M^+], 167 (1) [M^+ − Et], 125 (4) [M^+ − pentyl], 84 (100) [pentanone] {found (HRMS, EI) for [M^+] 196.1831, $C_{13}H_{24}O$ requires 196.1827}.

Reduction of 10b by BH_3·THF with (*R*)-CBS Catalysis and *ee* Determination: BH_3·THF (1 M in THF, 0.44 mL, 0.44 mmol) was added at room temperature to a solution of (*R*)-methyloxazaborolidine (1 M in toluene, 0.44 mL, 0.44 mmol) in dry dichloromethane. After the mixture had been stirred for 1 h, a solution of **10b** (0.44 mmol) in dry dichloromethane (0.5 mL) was added over a period of 20 min by syringe pump. The solution was stirred overnight, quenched with methanol and stirred for a further hour. The volatiles were removed under vacuum and the crude product puri-

fied by flash chromatography (diethyl ether/pentane, 1:3) to give alcohol **11** (74%). Isolated as a 1:1 mixture of diastereomers at C-2, *ee* value of the ethyl addition determined by ^{13}C NMR: 72−86%, depending on which pair of peaks was measured. − δ_H (400 MHz, $CDCl_3$) = 0.81, 0.85, 0.87, 0.90 (4 closely overlapping methyl signals each 3 H, t, J = 7.3, *Me* of C^4-Et and *Me* of nC_5H_{11}), 3.95 and 4.23 (1 H, 2 × m, C^1-H); the rest of the spectrum was not informative, comprising an envelope of signals in the range 1.15−1.90. − δ_C ($CDCl_3$, 67.8 MHz) = 9.8, 11.0 (CH_3, minor isomer: 9.4, 11.5), 14.2 (CH_3), 21.6, 22.8, 23.0, 23.1, (minor isomer: 24.5), 25.2 (minor isomer: 25.5), (minor isomer: 26.6) 26.9, (minor isomer: 27.1) 27.3, (minor isomer: 27.9) 28.1, 30.2, 30.3, 31.3, 32.4, 32.5, 34.8, 36.0 (8 × CH_2, including overlapping signals), (minor isomer: 37.7) 37.8, 41.4 (CH), 49.1, (minor isomer: 51.3) 51.4 (CH), 73.8, (minor isomer: 76.2) 76.9 (C-1). − MS (FAB); *m*/*z* (%): 181 (5) [M^+ − OH], 85 (13) [cyclopentanol] {found (HRMS, FAB) for [M^+ − OH] 181.1927, $C_{13}H_{25}$ requires 181.1956}.

Details of Chromatographic Separations of Enantiomers: The *ee* assays on compounds **6a−l** and **12a−b** were carried out by GC with a Varian 3380 machine, using helium carrier gas and the columns and conditions given in Table 4. The injector and detector port temperatures were 150 and 200 °C respectively.

Base-Promoted Cyclisations of 12a−c Affording (13a−b, 14, and 15): Diethyl ether solutions of (*R*)-**12a−c** (0.26 mmol, 0.26 M) were stirred overnight with 6 M NaOH (1.0 mL) at ambient temperature. Normal extractive workup followed by flash chromatography afforded **10−11** in 80−85% yield. Treatment of (*R*)-**12b** at 0 °C (12 h) afforded (*R*)-**13b** (87%), together with (3*R*,5*S*)-**14** (5%).

4-Ethylcyclopent-2-enone (13a): Yield 80% (18% *ee*). − δ_H (400 MHz, $CDCl_3$) = 0.98 (t, J = 7.4 Hz, 3 H, CH_2*Me*), 1.46 (ddq, 1 H, J = 13.5, 5.2 Hz, 7.4, $CH_{2\alpha}$Me), 1.61 (ddq, 1 H, J = 13.5, 6.1 Hz, 7.5, $CH_{2\beta}$Me), 1.97 (dd, J = 18.8, 2.1 Hz, 1 H, CO$CH_{2\alpha}$), 1.97 (dd, J = 18.8, 6.3 Hz, 1 H, CO$CH_{2\beta}$), 2.88 (m, 1 H, C*H*Et), 6.16 (dd, J = 5.7, 2.1 Hz, 1 H, =CH), 7.63 (dd, J = 5.7, 2.5 Hz, 1 H, =CH). −MS (CI); *m*/*z* (%): 100 (49) [M^+], 82 (100) {found (HRMS, CI) for [M^+] 110.0732, $C_7H_{10}O$ requires 110.0732}. − These values are consistent with **12a** generated by a different route.[41]

(+)-(*R*)-5-Ethylcyclohex-2-enone (13b): Yield 87% (70% *ee*). − δ_H (400 MHz, $CDCl_3$) = 0.93 (t, J = 7.4 Hz, 3 H, CH_2*Me*), 1.38−1.45 (m, 2 H, CH_2Me), 1.95−2.17 (3 H, $CHCH_2$CH=), 2.40−2.48 (m, 1 H, CO$CH_{2\alpha}$), 2.50−2.56 (m, 1 H, CO$CH_{2\beta}$), 6.01 (1 H, apparent dt, J = 10.0, 1.5 Hz, CO*CH*=), 6.97 (ddd, 1 H, J = 2.1, 5.5 Hz, 10.0). − δ_C ($CDCl_3$, 67.8 MHz) = 11.0 (CH_2*Me*), 28.5 (CH_2 ring or CH_2Me), 31.9 (CH_2 ring or CH_2Me), 36.8 (*CH*Et), 44.1 (CH_2 ring or CH_2Me), 129.7 (=CH), 150.0 (=CH), 199.2 (CO). − MS (CI); *m*/*z* (%): 124 (53) [M^+], 96 (67), 82 (100) {found (HRMS, CI) for [M^+] 124.0889, $C_8H_{12}O$ requires 124.0888}. − The chiroptical properties are as described in the literature.[42]

(+)-(*S*)-4-Ethyl-2-methylcyclopent-1-enecarbaldehyde (*S*)-(15): Yield 85% (69% *ee*); $[\alpha]_D^{25}$= +5 (c = 0.435, $CHCl_3$). − δ_H (400 MHz, $CDCl_3$) = 0.89 (t, J = 7.3 Hz, 3 H, CH_2*Me*), 1.39 (2 H, apparent quint, J = 7.3, CH_2Me), 2.11 (s, broadened by long-range coupling, 3 H, =C*Me*), 2.14−2.26 (m, 2 H, ring CH_2), 2.63−2.76 (m, 2 H, ring CH_2), 9.96 (s, 1 H, CHO). − δ_C ($CDCl_3$, 67.8 MHz) = 12.3 (CH_2*Me*), 14.3 (=C*Me*), 28.9, 35.9 (2 × CH_2), 37.4 (*CH*Et), 46.8 (CH_2), 188.2 (CHO). − $\tilde{\nu}$ (thin film) [cm^{-1}] = 2959m, 2923m, 2878w, 2853w (4 × C−H), 1666s (C=O), 1383m, 1218m. − MS (FAB); *m*/*z* (%): 138 (63) [M^+], 109 (92), 68 (100) {found (HRMS, FAB) for [M^+] 138.1046, $C_9H_{14}O$ requires 138.1045}.

(3*R*,5*S*)-3-Ethyl-5-hydroxycyclohexanone (3*R*,5*S*)-(14): Yield 5% (70% *ee*). − δ_H (400 MHz, $CDCl_3$) = 0.93 (t, J = 7.4 Hz, 3 H, CH_2*Me*), 1.39−1.49 (m, 2 H, CH_2Me), 1.51−1.64 (m, 2 H, C^4H_2), 1.73 (d, J = 3.9 Hz, 1 H, OH), 1.94 (dt, 1 H, J = 1.1, 14.0 Hz, C^6H_{ax}), 2.22 (m, 1 H, C^3H_{ax}), 2.33 (ddd, 1 H, J = 1.1, 11.4 Hz, 13.5, C^2H_{ax}), 2.38 (ddt, 1 H, J = 14.1, 3.9 Hz, 2.0, C^6H_{eq}), 2.73 (ddt, 1 H, J = 13.5, 4.8 Hz, 2.0, C^2H_{eq}), 3.93 (m, 1 H, C^5H_{ax}).

X-ray Crystallography of (*S*$_a$)-2b: Colourless prisms were grown from dichloromethane/light petroleum ether, $C_{42}H_{40}O_4N_2S_2$, M = 700.9, orthorhombic, space group $P2_12_12$, a = 12.154(8), b = 16.732(3), c = 9.286(6) Å, V = 1888(3) Å^3, Z = 2, D_c = 1.23 g cm^{-3}, μ(Mo-K_α) = 1.75 cm^{-1}, F(000) = 740, T = 296 K, prism 0.50 × 0.25 × 0.25 mm. Measurements were made as previously described,[43] using a Rigaku AFC6S diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71069 Å) using ω-2θ scans for 2152 unique reflections. A direct-method solution was applied using MITHRIL.[44] Full-matrix, least-squares anisotropic refinement on F^2 was applied to all non-hydrogen atoms to give R = 0.067, wR = 0.059 for 1416 independently observed reflections [$F_o^2 > 1\sigma(F_o^2)$, $2\theta_{max}$ = 52.0°] and 226 variables. Goodness of fit 1.11, max. shift/error in final cycle 0.01, max./min. peak in final difference map 0.33, −0.29 e·Å^3. Crystallographic data (excluding structure factors) for (*Sa*)-**2b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152542. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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