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Palladium-catalyzed allylation of α-hydroxy acids

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Abstract. Mandelic and lactic acids are converted to the 1,3-dioxolan-4-ones by treatment with acetone dimethyl acetal. Deprotonation followed by treatment with an allyl acetate and a catalytic amount (1 mol%) of palladium catalyst afforded the allylated dioxolanones, which could be hydrolyzed to the corresponding α-allyl α-hydroxy acids. The lithium enolate of the dioxolanone of mandelic acid was also coupled with methallyl, cinnamyl, geranyl and (*E*)-1-methyl-2-butenyl acetates. The zinc enolate of the dioxolanone of lactic acid reacted smoothly with allyl acetate in a catalyzed reaction whereas no detectable reaction was observed when the lithium enolate was used. This appears to be the result of complications arising from the enhanced basicity of the lithium compared to zinc enolate.
Various attempts were made to achieve enantioselectivity using chiral ligands on the palladium catalyst. The zinc enolates were found to provide better results although the enantioselectivity was only modest, about 30% enantiomeric excess being the best result obtained. Chiraphos proved to be the best optically active ligand of a variety tested.

Introduction

We have reported methods for the synthesis in optically pure form of α-alkylated α-amino acids[1] and α-alkylated α-mercapto acids[2]. The amino acids are prepared by classical chemical synthesis followed by a kinetic resolution using enzyme technology developed at DSM[3], whereas a variation of the *Seebach* procedure[4] (see further) is used to obtain the α-mercapto acids.
We also wanted to develop general methods to obtain α-alkylated α-hydroxy acids, preferably in optically active form[5]. We have described an enzymatic method involving kinetic resolution by esterases for the preparation of optically active acids[6]. We describe here complementary methods for the catalytic α-allylation of α-hydroxy acids whereby the starting acids are by preference racemic.

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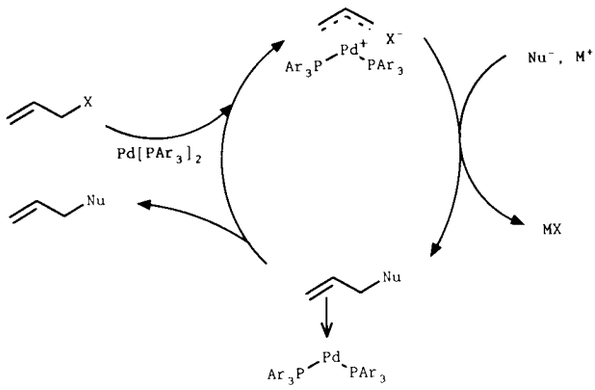
Abbreviations and Chemical Abstracts names:

BINAP = (+)(*R*)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
BPPFA (**22**) = (*S*)-1′,2-bis(diphenylphosphino)-(*R*)-α,*N*,*N*-trimethylferrocenemethanamine
BPFFOAc = (*S*)-1′,2-bis(diphenylphosphino)-(*R*)-α,*N*,*N*-trimethylferrocenemethanol, acetate
BPPM (**27**) = (2*S*,*cis*)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]-1-pyrrolidinecarboxylic acid, *tert*-butyl ester
carvyl = 5-isopropenyl-2-methyl-2-cyclohexenyl
chiraphos (**21**) = (−)(*S*,*S*)-(1,2-dimethyl-1,2-ethanediyl)bis(diphenylphosphine)
cinnamyl = (*E*)-3-phenyl-2-propenyl
DBA = dibenzylideneacetone = 1,5-diphenyl-1,4-pentadien-3-one
DIBAL = diisobutylaluminum hydride
DIOP (**20**) = (−)(4*R-trans*)-[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis(diphenylphosphine)
DMSO = dimethyl sulfoxide
DPPE = 1,2-bis(diphenylphosphino)ethane = (1,2-ethanediyl)bis(diphenylphosphine)
e.e. = enantiomeric excess
homomethphos (**24**) = (*R*)-1-(diphenylphosphino)-*N*,*N*-dimethyl-5-(methylthio)-2-pentanamine
HRMS = high-resolution mass spectra
geranyl = (*E*)-3,7-dimethyl-2,6-octadienyl
lactic acid (**1**) = 2-hydroxypropanoic acid
LDA = lithium diisopropylamide
mandelic acid (**2**) = α-hydroxybenzeneacetic acid
methallyl = 2-methyl-2-propenyl
Ph-CAPP (**26**) = (2*S*,*cis*)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]-*N*-phenyl-1-pyrrolidinecarboxamide
pivaldehyde = 2,2-dimethylpropanal
THF = tetrahydrofuran
valphos (**25**) = (*R*)-1-(diphenylphosphino)-*N*,*N*,3-trimethyl-2-butanamine

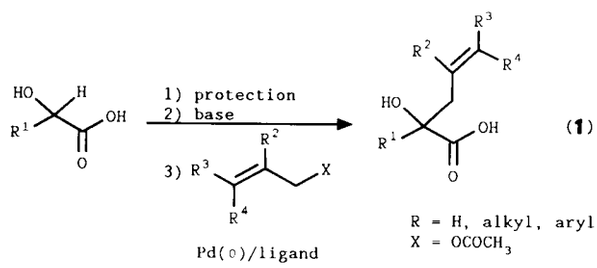
The development of catalytic allylation[7] has been, to a significant extent, the result of efforts of the *Trost* group[8]. The approach is summarized in Scheme 1. Oxidative addition[9]



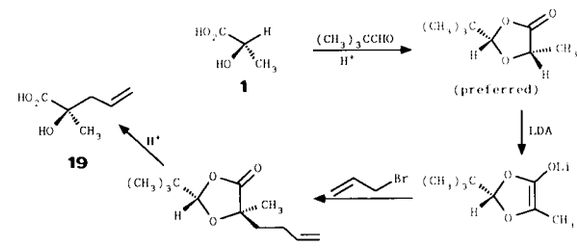
Scheme 1

to allyl acetates (or $CH_2{=}CHCH_2X$, X = OAr, O_2CR, NR_2, SO_2R or NO_2) provides the cationic complexes that are subject to nucleophilic substitution followed by reductive elimination[10]. Nucleophiles that undergo successful reaction generally have pK_a's in the range of 9–18. Malonate[11] and amines[12] are used commonly although phosphorus[13], sulfur[14a] and some oxygen nucleophiles[14b,c] also can participate in these reactions.

Such palladium-catalyzed reactions wherein an allyl group is introduced and an optically active ligand on the metal is used to bring about optical activity, offer an attractive route to realization of the desired objective (Eqn. 1). Special



aspects in this synthesis with α-hydroxy acids as starting materials are the need to protect the hydroxy group and the use of a fairly hard enolate (the pK_a's of α-hydroxy esters should be somewhat greater than those of the corresponding unsubstituted esters – about 25 relative to H_2O for simple aliphatic esters[15]; substituents like phenyl will lower the pK_a, of course). Protection together with conformational locking is readily achieved via condensation with an aldehyde or ketone to form 1,3-dioxolan-4-ones. *Seebach* has used this approach with optically active α-hydroxy acids and pivaldehyde as the carbonyl component[4]. The *cis*-stereochemistry for the resulting 5-membered heterocycle is preferred. Although formation of an enolate leads to loss of stereogenicity adjacent to the carbonyl group, the bulky *tert*-butyl group at the newly formed stereogenic center directs the incoming electrophile to the opposite face of the enolate. This process is stoichiometric and is illustrated for the preparation of (*R*)-α-allyl-α-hydroxypropanoic acid in Scheme 2. Alkylation of α-amino[16] and α-mercapto carboxylic acids[2] has also been achieved by this approach.

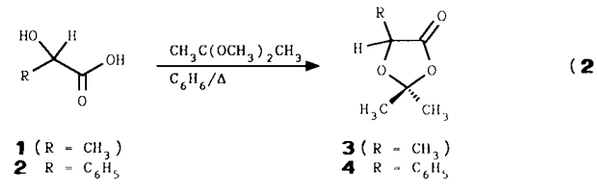


Scheme 2

In a catalytic process wherein enantioselectivity is forthcoming from the presence of optically active ligands on a transition metal, there is no need for optically active α-hydroxy acids as starting materials. Moreover the protection/conformational locking of the acid may be carried out with a cheap, achiral symmetrical ketone rather than expensive pivalaldehyde.

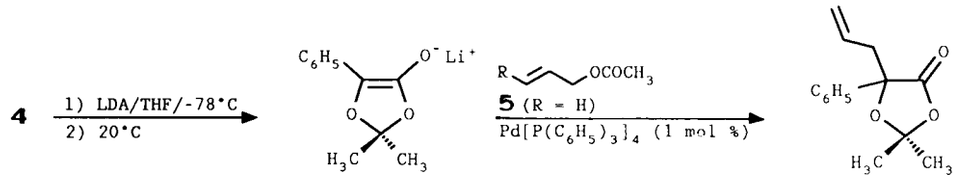
Results and discussion

Racemic lactic (**1**) and mandelic (**2**) acids were used as starting materials. Condensation with 2,2-dimethoxypropane (acetone dimethyl acetal) in benzene at reflux temperature in the absence of any additional catalyst provided **3** and **4** (Eqn. 2). Condensation of α-hydroxy acids with



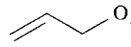
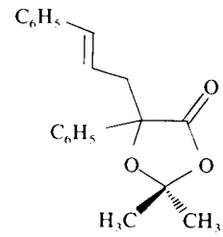
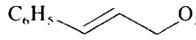
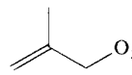
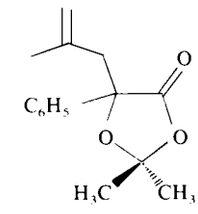
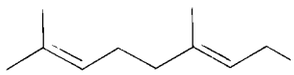
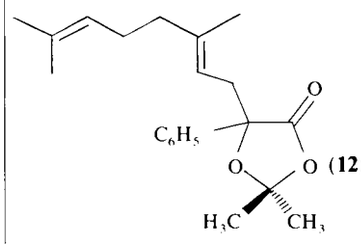
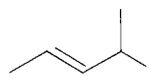
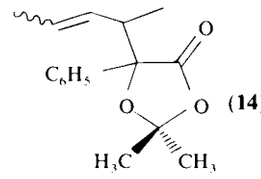
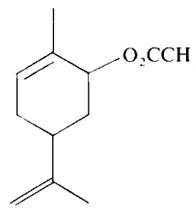
ketones requires the use of strongly acidic catalysts like sulfuric[17] or 4-toluenesulfonic acids or boron trifluoride etherate[18], resulting in more difficult work-up procedures. Deprotonation of **4** was accomplished at −78 °C in THF with lithium diisopropylamide (LDA). The resulting enolate can be warmed to room temperature without decomposition. Deprotonation of optically active **4** followed by quenching with NH_4Cl delivered completely racemic **4**. This experiment was carried out to establish that there was no unanticipatedly tight coordination or other factors that might lead to the enolate not being effectively planar and achiral.

Condensation (Scheme 3) of deprotonated **4** with the



Scheme 3

Table I Catalytic allylation of Dioxolanone **4**[a].

Entry	Allylic acetate	Catalyst	Product	Yield
1	 (**5**)	$Pd[P(C_6H_5)_3]_4$[b]	**6** 	79%
2	 (**7**)	"[c]	(**8**)	79%
3	 (**9**)	"[b]	 (**10**)	54%
4	"	$Pd(DBA)_2$/DPPE	"	82%
5	 (**11**)	$Pd[P(C_6H_5)_3]_4$[b]	 (**12**)	–
6	"	$Pd(DBA)_2$/DPPE[b]	"	70%
7	 (**13**)	"[b]	 (**14**)	78%[d]
8	 (**15**)	"[d]	–	–

[a] THF, room temperature. [b] 1 mol%. [c] 5 mol%. [d] *E*/*Z* mixture of stereoisomers (see text).

cationic π-allyl complex from allyl acetate (**5**, R = H and $Pd[P(C_6H_5)_3]_4$ (1 mol%) proceeded cleanly. At room temperature the reaction was complete within 45 min; with a 10-fold reduction in the amount of Pd complex the reaction was approximately 50% complete within 45 min. This indicates the high reactivity and good turnover of the catalyst system. In the absence of Pd complex there was no observable reaction.

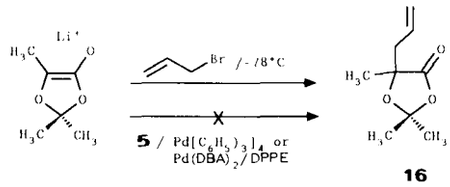
The effect of structural variation in the allylic segment was examined. Results are summarized in Table I. The regioselectivity is excellent, attack occurring within limits of detection only at the least substituted position of the allylic unit (entries 2 and 6). Stereochemistry about the double bond is preserved. The *E* stereochemistry in **12** was assigned by ^{13}C NMR, which revealed a high-field signal (δ 16.32 ppm) for the methyl group of the internal double bond. *Trost* has shown that for the *Z* configuration a δ value of about 23 ppm may be expected[19]. Retention of configuration is not observed, however, for the (*E*)-1-methyl-2-butenyl fragment (entry 7). Compound **14** consists of both possible diastereomers in 55/45 ratio, each as an *E*/*Z* mixture (ratio 2/1). All four can be identified in the NMR spectra. The reasons for loss of stereochemistry about the double bond are unclear to us. There is, of course, no question of structurally observable regioselectivity of attack in this case.

Steric factors not surprisingly are important[20]. Geranyl acetate (**11**, entry 5) fails to react with $Pd[P(C_6H_5)_3]_4$ as catalyst but reacts well with $Pd(DBA)_2$ in combination with DPPE. Carvyl acetate (**15**, entry 8) is apparently too hindered, however, to react.

The combination $Pd(DBA)_2$/DPPE, introduced originally by *Fiaud*[21], was found also to improve the yield in the allylation of **4** with methallyl acetate (**9**, entries 3 and 4). These reactions with **9** are of special note; in our hands

stoichiometric reaction of the enolate of **4** with methallyl chloride failed to give significant amounts of **10**. Only the catalytic variant described here provided this branched material[6b].

The dioxolanone **3** derived from lactic acid was not investigated as extensively as **4**. The chief point of interest is the difference in reactivity of the enolates derived from **3** and **4**. The lithium enolate of **3** failed to react with allyl acetate with any available palladium catalyst or under any of a variety of reaction conditions. On the other hand, reaction of **3** with allyl bromide at −78°C proceeded normally to afford **16** (Eqn. 3).



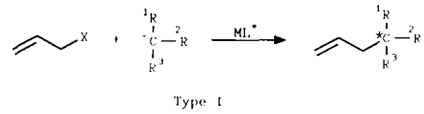
16 (3)

The lithium enolate derived from **3** should be more basic than that from **4** because the phenyl group delocalizes the charge in the latter. Examination of the reaction products from attempted catalytic allylation revealed starting material **3** as well as unidentified olefinic components formed apparently from allyl acetate (**5**), which was nearly completely consumed during the reaction. These complications may be the result of the enhanced basicity of **3** compared to **4**. Less basic enolates and enol derivatives were examined in the hope of avoiding this problem. Zinc enolates[22] and enol stannanes[23] have been used for this purpose. Use of the zinc enolate prepared by exchange of the lithium with anhydrous $ZnCl_2$ led to the formation of **16** in 73% yield when **5** and $Pd[P(C_6H_5)_3]_4$ were added at −78°C and then allowed to warm to room temperature. However, reaction at room temperature led to a poor yield of **16**. Yields with enol stannanes were also unsatisfactory. These conditions have not been explored with other allylic acetates although they have been employed in attempts to achieve enantioselective reactions (see further).

Ring opening of the allylated dioxolanones may be carried out either under acidic (ester formation) or basic (hydrolysis to free acids) conditions as shown in Scheme 4 for **6** and **16**. Compound **10**, owing to its sensitivity to acid, can only be opened under basic conditions; lactonization occurs on attempted acid-catalyzed reaction.

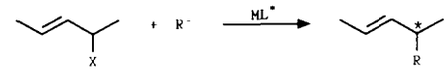
The possibilities for enantioselective allylation were examined using various chiral ligands[24] available either commercially or from previous research. Structures **20–27** given below were used in scouting experiments.

Catalytic allylation is not usually characterized by extremely high enantioselectivities although during the past few years considerable improvement has been achieved[25]. There are two basic approaches for reactions in which a single new stereocenter is created. Type-I reactions (Eqn. 4) involve



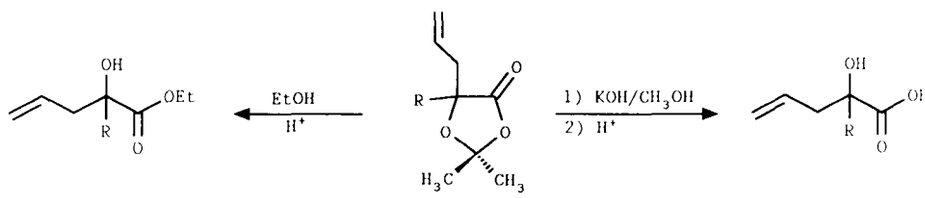
Type I (4)

generation of a stereocenter in the attacking nucleophile whereas Type-II reactions are characterized by formation of the chiral center in the π-allyl fragment (Eqn. 5).



Type II (5)

Type-II reactions can lead to quite acceptable enantiomeric excesses[10a,11,26] whereas results in Type-I reactions are in general poorer. A representative example of a Type-I reaction (the type of reaction that will be necessary in our case) is the catalytic allylation of 2-acetylcyclohexanone (**28**) to afford **29** (Eqn. 6). *Kagan* and coworkers have achieved a 7% e.e. with a Pd-DIOP catalyst[27]. The difficulty in achieving enantioselectivity is presumed to arise from approach of the nucleophile on the face of the π-allyl complex opposite to palladium. The distance between incom-

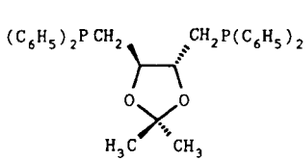


18, **19** ethyl ester

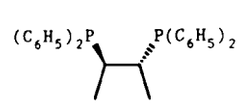
6 (R = C_6H_5)
16 (R = CH_3)

18 (R = C_6H_5)
19 (R = CH_3)

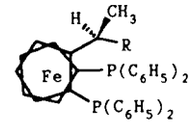
Scheme 4



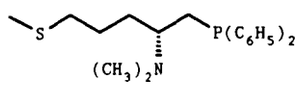
20 DIOP



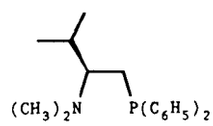
21 Chiraphos



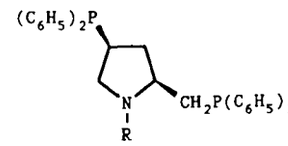
22 BPPFA [R = $N(CH_3)_2$]
23 R = $N(CH_3)CH_2CH_2OH$



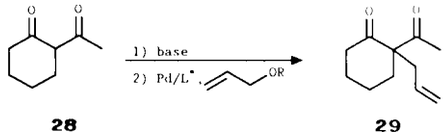
24 Homomethphos



25 Valphos

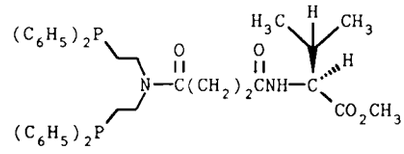


26 Ph-CAPP (R = $CONHC_6H_5$)
27 BPPM [R = $CO_2C(CH_3)_3$]



28 **29** (6)

ing nucleophile and optically active ligand is too great. By use of **30**, which is presumed to be long and flexible enough to bridge the distance between faces, a 52% e.e. of **29** could be achieved[28]. Ferrocenyl ligand **23** provided with a flexible



30

side arm afforded **29** in 81% e.e.[29]. These examples illustrate the problems in Type-I reactions and the experimental approaches that have been devised for their solution[30].

The catalytic allylation of **4** to form **6** was examined as model reaction. Chiral catalysts were usually prepared by mixing *in situ* the chiral ligand and $Pd(II)(O_2CCH_3)_2$. Reduction to Pd(0) occurs *in situ*[31]. This method is easier than generating separately the oxygen sensitive Pd(0) complexes. The effect of added $ZnCl_2$ is given in Table II. In all cases the lithium enolate of **4**, generated by deprotonation with LDA in THF, was used. Enantiomeric excesses were determined by derivatization of acids **18**, derived by hydrolysis of **6**, with (*S*)-2-chloropropanoyl chloride followed by ^1H NMR analysis as previously reported[5].

Although the e.e.'s are at best only modest, it is clear that better results are obtained in the presence of at least one equivalent of $ZnCl_2$. To our knowledge only two other papers on the use of zinc enolates in Type-I allylations have appeared. In both cases substantial improvements in e.e.'s were observed. *Negishi*[22] has used the zinc enolate of 3-pentanone in a reaction with 2,3-dichloropropene in the presence of Pd·**21** catalyst to obtain 6-chloro-4-methyl-6-hepten-3-one in 34% e.e. *Hayaishi* and coworkers[32] have reported the reaction of zinc enolates of α-isocyano esters with allyl acetate in the presence of Pd·**21**; an e.e. of 36% was obtained. These results emphasize the difficulties in achieving high e.e.'s in Type-I reactions.

In these experiments chiraphos[33] (**21**) was clearly more effective than DIOP (**20**). Using **21** an attempt was made to optimize the temperature conditions and Pd/ligand ratios. The data are given in Table III. Reaction is obviously slow at low temperature; the procedure of warming to room temperature is experimentally the most convenient although longer reaction at −50°C (entry 5) does provide a marginal improvement.

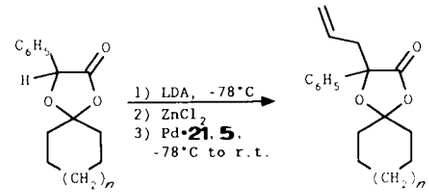
Table III Effect of temperature on the enantiomeric excess of **6**.

Entry	Pd/ligand[a]	Temp. (°C)	Time (h)	Yield **6** (%)	$[\alpha]_{578}$[b] (°)	E.e.[c]
1	1/1	−78 to r.t.	18	70	+14.1	25
2	1/2	−78 to r.t.	18	67	+12.3	22
3	1/1	−78 to −10	2.5	58	+12.2	22
4	1/1	−78	5	45	+13.4	24
5	1/1	−50	19	65	+16.7	30

[a] $Pd(DBA)_2$ and **21**. [b] c = 1, $CHCl_3$. [c] See text or method, ±2% accuracy.

Results with other ligands are not given in table form. Chirapos (**21**) proved indeed to be the best of all the ligands examined. The ability of **21** to form a "chiral pocket" has been emphasized[33c]. We are reluctant, however, to attempt at this stage to relate the stereochemistry of **21** to that of the major coupling products (the absolute configurations are known) for reasons detailed in the final paragraph. Poor results were found with **23** and **30**, which we prepared following described procedures[28,29]. In these cases the presence of long chains potentially capable of hydrogen bonding to the incoming nucleophile did not offer any advantage. Various experimental changes – reduction of Pd(II) *in situ* with DIBAL, changes in the order of addition of reagents, further variation of ligand/Pd ratios – all led to no significant improvement. Ligand **24**, which has been used with considerable success in nickel catalyzed cross couplings[34], provided scarcely any enantioselectivity at all.

Some improvement was noted on structural change of the enolate. Condensation of mandelic acid with cyclopentanone and cyclohexanone provided **31** and **32**; the results of catalytic allylation of the zinc enolates with Pd·**21** are summarized in Eqn. 7.



(7)

31 (n = 0)
32 (n = 1)

33, 71% yield, 75% e.e.
34, 67% yield, 33% e.e.

We observed no significant changes in e.e. as Pd/ligand ratios were changed (Table III, entries 1, 2) A complication in all these reactions is the possible involvement of achiral reaction paths. Although the point was not examined quantitatively it was apparent that both $Pd(O_2CH_3)_2$ and $Pd(DBA)_2$ in the absence of phosphine ligands were capa-

Table II Effect of $ZnCl_2$ on the enantiomeric excess of **6** *formed by catalytic allylation of* **4**.

Entry	Pd compd.[a]	Ligand[a]	$ZnCl_2$[b] (eqv.)	Yield **6** (%)	$[\alpha]_{578}$[c] (°)	E.e.[d]
1	$Pd(O_2CCH_3)_2$	DIOP	1[d]	75	+4.9	9
2	$Pd(O_2CCH_3)_2$	DIOP	0	70	+2.9	5
3	$Pd(DBA)_2$	chiraphos	1	70	+14.1	25
4	$Pd(DBA)_2$	chiraphos	0	65	+5.5	10
5	$Pd(DBA)_2$	chiraphos	2	[e]	[e]	[e]
6	$Pd(DBA)_2$	chiraphos	0.03	76	+6.2	11

[a] 1% relative to enolate of **4**. [b] Relative to enolate of **4**. [c] c = 1, $CHCl_3$. [d] Enantiomeric excess, ±2%, see text for method of determination. [e] No product isolated.

ble of inducing product formation. This point concerns us greatly; in the absence of absolutely unambiguous evidence that there is no competition from achiral pathways we feel that it is unwise to embark on the development of detailed stereochemical models. We hope in the future to be able to fill this picture in more completely.

In conclusion it is clear that catalytic allylation of α-hydroxy enolates (in protected, cyclic form) is possible. The catalytic route even offers access to systems not available via stoichiometric allylation. Attempts to carry out the reactions enantioselectively have only been partly successful. It has been possible, however, to define several factors that lead to enhancement of the degree of enantioselectivity. In particular the positive effect of using zinc enolate derivatives deserves emphasis.

Experimental

General remarks

Melting points were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope and are uncorrected. Boiling points at the reported pressure are those observed on distillation generally with a Kugelrohr apparatus.

^{1}H NMR spectra were recorded on a Hitachi Perkin–Elmer R-24B NMR spectrometer (at 60 MHz) or, when indicated, on a Varian VXR-300 MHz spectrometer (at 300 MHz). Chemical shifts are for 60 MHz spectra denoted in δ units (ppm), relative to tetramethylsilane (TMS) as an internal standard at δ 0 ppm. For 300-MHz spectra the ^{1}H NMR chemical shifts are determined relative to the solvent ($CDCl_3$) and have been converted to the TMS scale using δ($CDCl_3$) 7.26 ppm. ^{13}C NMR spectra were recorded on a Nicolet NT-200 (at 50.32 MHz), or a Varian VXR-300 (at 75.43 MHz) spectrometer. Chemical shifts are denoted in δ units (ppm) relative to δ($CDCl_3$) 76.91 ppm. Splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet), br (broad).

Optical rotations were measured on a Perkin–Elmer 241 polarimeter at room temperature.

Elemental analyses were performed in the Microanalytical Department of this laboratory.

Mass spectra (HRMS) were recorded on an AEI-MS-902 mass spectrometer.

Tetrahydrofuran was distilled prior to use from the deep blue solution resulting from reaction of sodium and benzophenone. All other reagents and solvents were purified and dried where necessary following standard procedures. The solvents were distilled before use and were stored on molecular sieves (3 or 4 Å). Lithium diisopropylamide (LDA) was prepared by the addition of one equivalent of a 1.6M *n*-butyllithium solution in hexane to a solution of one equivalent of diisopropylamine in THF at −50°C. All reactions involving Li enolates were carried out under a N_2 atmosphere. Anhydrous zinc chloride was prepared according to a literature procedure[35] involving treatment with thionyl chloride. Water from commercial lactic acid was removed by azeotropic distillation with toluene using a Dean–Stark trap. Dry lactic acid polymerizes slowly on standing and should be used rapidly.

Ligands

DIOP (**20**), BINAP, chiraphos (**21**) and BPPM (**27**) were purchased from Aldrich. BPPFA (**22**) was obtained from Strem Chemicals. BPPFOAc was a product from Kanto Chemicals. (*S*)-Homomethphos (**24**) and valphos (**25**) were prepared as described[36]. Ph-CAPP (**26**) was prepared according to a literature procedure[37].

Tetrakis(triphenylphosphine)palladium(0) $[Pd(PPh_3)]_4$ was prepared according to a literature procedure[38]. From $PdCl_2$ (1.9 g, 10.7 mmol), triphenylphosphine (15.0 g, 57.2 mmol) in DMSO (135 ml) and hydrazine hydrate (2.25 g, 45 mmol) was obtained 10.1 g, (82% yield) of $Pd(PPh_3)_4$ as a yellow crystalline compound.

Pd(DBA)$_2$[39] was prepared from Na_2PdCl_4 (2.5 g, 8.5 mmol) and DBA (6.3 g, 27 mmol) in MeOH (50 ml). After addition of sodium acetate (2.2 g, 27 mmol), 4.7 g (97% yield) of $Pd(DBA)_2$ was obtained as a dark brown crystalline compound.

Cinnamyl acetate (**7**)[40] was prepared from cinnamyl alcohol (4.0 g, 30 mmol) in pyridine (10 ml) and acetyl chloride (3.6 g, 45 mmol). After Kugelrohr distillation (135°C, 13 mm Hg), 4.1 g (78% yield) of **7** as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 3H), 4.73 (dd, 2H), 6.24–6.34 (m, 1H), 6.66 (d, 1H, *J* 15.8 Hz), 7.28–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 20.76 (q), 64.82 (t), 122.86 (d), 126.31 (d), 127.78 (d), 128.31 (d), 133.91 (d), 135.90 (s), 170.53 (s).

Methallyl acetate (**9**) was prepared following a procedure described in the literature[40] from a solution of methallyl alcohol (4.4 g, 60 mmol) in pyridine (15 ml), which was cooled to 5°C and to which acetyl chloride (3.6 g, 45 mmol) was added dropwise. After stirring for 15 min the mixture was poured into water (10 ml) and extracted with ether (3 × 20 ml). The combined ether layers were washed with 3N HCl (3 × 30 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded the product as a yellow oil which was purified by distillation to give **9** (4.9 g, 72% yield) as a colorless oil; b.p. 123–124°C. ^{1}H NMR ($CDCl_3$): δ 1.73 (s, 3H), 2.08 (s, 3H), 4.50 (s, 2H), 4.97 (s, 2H).

Geranyl acetate (**11**)[40] was prepared from geraniol (5.0 g, 30 mmol), acetic anhydride (5.0 g, 50 mmol) and pyridine (4.0 ml). There was obtained 4.9 g (83% yield) of **11** after Kugelrohr distillation (130°C, 22 mm Hg) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.57 (s, 3H), 1.67 (s, 6H), 2.07 (s, 7H), 4.60 (d, 2H, *J* 7.1 Hz), 5.00–5.50 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 16.29 (q), 17.51 (q), 20.86 (q), 25.50 (q), 26.16 (t), 39.39 (t), 61.25 (t), 118.15 (d), 123.60 (d), 131.64 (s), 142.07 (s), 170.94 (s).

(E)-1-Methyl-2-butenyl acetate (**13**) was synthesized from (*E*)-3-penten-2-ol (23 mmol), acetic anhydride (3.6 g, 35 mmol) and pyridine (4.0 ml). Distillation of the residue afforded **13** (2.2 g, 75% yield) as a colorless oil; b.p. 135–137°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (d, 3H, *J* 6.2 Hz), 1.60 (d, 3H), 1.92 (s, 3H), 5.18–5.22 (m, 1H), 5.34–5.41 (m, 1H), 5.56–5.66 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 17.25 (q), 19.91 (q), 20.96 (q), 70.69 (d), 127.62 (d), 130.42 (d), 169.80 (s).

2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-one (**4**) was prepared by refluxing a mixture of mandelic acid (**2**) (15.2 g, 0.10 mol), 2,2-dimethoxypropane (12.5 g, 0.12 mol) and benzene (100 ml) for 2 h with azeotropic removal of methanol. The resulting solution was concentrated under reduced pressure and the residue was purified by Kugelrohr distillation (150°C, 20 mm Hg) to give 18.8 g (98% yield) of **4** as a colorless oil, which solidified on standing; m.p. 42.5–43.5°C. ^{1}H NMR ($CDCl_3$) δ 25.78 (q), 26.90 (q), 75.86 (d), 110.66 (s), 126.19 (d), 128.43 (d), 128.66 (d), 134.20 (d), 171.20 (s). Anal. calcd. for $C_{11}H_{12}O_3$: C 68.74, H 6.29; found: C 68.68, H 6.36%.

2,2-Dimethyl-5-methyl-1,3-dioxolan-4-one (**3**) was prepared from lactic acid (**1**, 14.7 g, 0.16 mol) and 2,2-dimethoxypropane (22.1 g, 0.21 mol), following the procedure described above. Kugelrohr distillation at 50°C (50 mm Hg) of the crude product afforded 17.7 g (88% yield) of **3** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (d, 3H), 1.54 (s, 3H), 1.61 (s, 3H), 4.48 (q, 1H).^{13}C NMR ($CDCl_3$): δ 16.91 (q), 25.08 (q), 26.95 (q), 69.94 (d), 109.83 (s), 173.34 (s). Anal. calcd. for $C_8H_{10}O_3$: C 55.37, H 7.74; found: C 55.01, H 7.72%.

General procedure for the Pd-catalyzed allylation of dioxolanone **4**

A 3.0-mmol run is described: A solution of **4** (3.0 mmol) in THF (3 ml) was added to a solution of LDA (3.3 mmol) in THF/hexane (3/2.5 ml) at −78°C. The mixture was allowed to warm to room temperature and a solution in a second flask by mixing an allylic acetate (3.1 mmol) with either $Pd(PPh_3)_4$ (34.7 mg, 30 μmol) or $Pd(DBA)_2$ (17.2 mg, 30 μmol) and DPPE (12.0 mg, 20 μmol) in THF (2 ml) was added using syringe techniques. After stirring (for time see below) a precipitate formed. The mixture was poured into a half saturated ammonium chloride solution (10 ml) followed by extraction with ether (3 × 15 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuum to afford the allylated dioxolanone, which was purified by either chromatography, distillation or crystallization. Details for individual compounds are given below.

2,2-Dimethyl-5-allyl-5-phenyl-1,3-dioxolan-4-one (**6**). From **4** (0.58 g, 30 mmol), $Pd(PPh_3)_4$ (34.7 mg, 30 μmol) and allyl acetate (**5**) (0.31 g, 3.1 mmol) was obtained, after stirring for 45 min, product **6**, which was purified by flash chromatography (SiO_2; CH_2Cl_2/hexane 1/1) to afford 0.53 g (79% yield) of **6** as a colorless oil; b.p. 110°C, 0.1 mm Hg. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H), 1.60 (s, 3H), 2.53–2.72 (m, 2H), 5.03–5.12 (m, 2H), 5.60–5.73 (m, 1H), 7.18–7.57 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 27.60 (q), 27.70 (q), 45.82 (t), 83.12 (s), 110.05 (s), 120.09 (t), 124.61 (d), 127.85 (d), 128.20 (d), 131.17 (d), 139.55 (s), 172.27 (s). Anal. calcd. for $C_{14}H_{16}O_3$: C 72.39, H 6.94; found: C 72.13, H 7.04%.

2,2-Dimethyl-5-phenyl-5-(3-phenylallyl)-1,3-dioxolan-4-one (**8**). A mixture of **4** (0.58 g, 3.0 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol) and cinnamyl acetate (**7**, 0.55 g, 3.1 mmol) afforded after 5 h allylated dioxolanone **8**. The residue was taken up in ether and filtered over silica in a funnel to remove the Pd compounds. After removal of the solvent, the resulting slightly yellow oil was recrystallized from absolute ethanol to give **8** (0.69 g, 75% yield) as a white solid; only the *E* isomer was formed; m.p. 92–93°C. 1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s), 1.57 (s), 2.66–2.90 (m, 2H), 6.02–6.14 (m, 1H), 6.42 (d, 1H, *J* 15 Hz), 7.12–7.64 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 27.64 (q), 45.00 (t), 83.35 (s), 110.21 (s), 122.46 (d), 124.58 (d), 126.02 (d), 127.30 (d), 127.88 (d), 128.23 (d), 128.31 (d), 135.07 (d), 136.71 (s), 139.46 (s), 172.32 (s). Anal. calcd. for $C_{20}H_{20}O_3$: C 77.90, H 6.54; found: C 77.67, H 6.62%.

2,2-Dimethyl-5-methallyl-5-phenyl-1,3-dioxolan-4-one (**10**). *(a)* A mixture of **4** (1.16 g, 6.0 mmol), $Pd(DBA)_2$ (34.4 mg, 60 μmol), DPPE (24.0 mg, 60 μmol) and methallyl acetate (**9**, 0.75 g, 6.6 mmol) gave after stirring for 3 h, **10** which was purified by Kugelrohr distillation (84°C, 0.02 mm Hg) to yield 1.20 g (82% yield) of **10** as a colorless oil. ^1H NMR (C_6D_6, 300 MHz): δ 1.16 (s, 3H), 1.45 (s, 3H), 1.83 (s, 3H), 2.67 (d, 1H, *J* 14.0 Hz), 2.93 (d, 1H, *J* 14.0 Hz), 5.00 (s, 1H), 5.04 (s, 1H), 7.16–7.30 (m, 3H), 7.85–7.89 (m, 2H). ^{13}C NMR (C_6D_6): δ 22.63 (q), 23.50 (q), 25.64 (q), 47.17 (t), 82.07 (s), 107.66 (s), 114.57 (t), 123.27 (d), 126.06 (d), 126.53 (d), 138.10 (s), 138.73 (s), 170.41 (s), Anal. calcd. for $C_{15}H_{18}O_3$: C 73.15, H 7.37; found: C 73.34, H 7.44%.
(b) From **4** (0.58 g, 3.0 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol) and **9** (0.35 g, 3.1 mmol) was obtained after stirring for 18 h and after Kugelrohr distillation (110°C, 0.05 mm Hg), 0.40 g (54% yield) of **10**.

2,2-Dimethyl-5-geranyl-5-phenyl-1,3-dioxolan-4-one (**12**). *(a)* Dioxolanone **4** (0.58 g, 3.0 mmol), $Pd(DBA)_2$ (17.2 mg, 30 μmol), DPPE (12.0 mg, 30 μmol) and geranyl acetate (**11**, 0.59 g, 3.0 mmol) yielded after stirring for 18 h and Kugelrohr distillation (100°C, 0.02 mm Hg), 0.69 g (70%) of **12** as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.00 (s, 3H), 1.18 (s, 6H), 1.25 (s, 3H), 1.27 (s, 3H), 1.57–1.69 (m, 2H), 2.18–2.37 (m, 2H), 4.64–4.70 (m, 1H), 4.76–4.82 (m, 1H), 6.86–7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 16.32 (q), 17.54 (q), 25.56 (q), 26.33 (q), 27.76 (q), 37.79 (t), 40.34 (t), 83.77 (s), 109.96 (s), 116.85 (d), 123.87 (d), 124.67 (d), 127.72 (d), 128.12 (d), 131.35 (s), 139.96 (s), 140.45 (s), 172.71 (s). The elemental analysis results were not satisfactory. Anal. calcd. for $C_{21}H_{28}O_3$: C 76.79, H 8.59; found: C 75.60, H 8.62%. Attempts to determine the exact mass were unsuccessful owing to the failure to obtain a parent peak. Geranyl alcohol is known to be very difficult to purify.

2,2-Dimethyl-5-(1-methyl-2-butenyl)-5-phenyl-1,3-dioxolan-4-one (**14**). From 0.58 g (3.0 mmol) of **4**, $Pd(DBA)_2$ (17.2 mg, 30 μmol), DPPE (12.0 mg, 30 μmol) and (*E*)-1-methyl-2-butenyl acetate (**13**, 0.40 g, 3.1 mmol) there was obtained, after stirring for 18 g, **14** which was purified by Kugelrohr distillation (100°C, 0.01 mm Hg) to give 0.61 g (78% yield) of **14** as a colorless oil. The product consisted of mixture of diastereomers (*E*/*Z* 2/1; diastereomeric ratio 55/45). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.77, 1.10 (2 d, 3H, *J* 7.0 Hz), 1.38, 1.43 (2 s, 3H), 1.49, 1.69 (2 m, 3H), 1.65, 1.68 (2 s, 3H), 2.69–2.80 (m, 1H), 5.09–5.23 (m, 1H), 5.39–5.66 (m, 1H), 7.21-7.64 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.83 (q), 15.66 (q), 17.66 (q), 17.86 (q), 27.00 (q), 27.19 (q), 27.69 (q), 27.90 (q), 45.94 (q), 46.26 (q), 85.74 (s), 86.09 (s), 109.92 (s), 125.09 (d), 125.18 (d), 127.43 (d), 127.49 (d), 127.52 (d), 127.61 (d), 127.78 (d), 127.91 (d), 127.99 (d), 128.04 (d), 128.27 (d), 129.12 (d), 130.59 (d), 136.08 (d), 138.40 (s), 138.83 (s), 172.63 (s). Anal. calcd. for $C_{16}H_{20}O_3$: C 73.82, H 7.74; found: C 73.71, H 7.76%.

2,2,5-Trimethyl-5-allyl-1,3-dioxolan-4-one (**16**). *(a)* To a solution of LDA (3.3 mmol) in THF/hexane (3/2.5 ml) was added a solution of **3** (0.39 g, 3.0 mmol) in THF (3 ml) at −78°C. The mixture was allowed to warm to about −40°C and then again cooled to −78°C. A solution of anhydrous $ZnCl_2$ (0.42 g, 3.1 mmol) in THF (3 ml) was added and the mixture was allowed to warm to −10°C in *ca.* 30 min. Then the mixture was cooled again to −78°C and a solution of $Pd(PPh_3)_4$ (34.7 mg, 30 μmol) and allyl acetate (**5**, 0.31 g, 3.1 mmol) in THF (2 ml) was added dropwise. The mixture was allowed to warm to room temperature, stirred overnight and worked up as described in the general procedure. Kugelrohr distillation (60°C, 15 mm Hg) of the crude reaction product afforded **16** (0.73 g, 73% yield) as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.42 (s, 3H), 1.52 (s, 6H), 2.4 (d, 2H), 4.8–6.0 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 24.52 (q), 27.94 (q), 28.60 (q), 42.98 (t), 79.89 (s), 109.42 (s), 119.87 (t), 131.43 (d), 174.69 (s). Anal. calcd. for $C_9H_{14}O_3$: C 63.52, H 8.29; found: C 63.40, H 8.31%.
(b) A solution of 0.39 g (3.0 mmol) of **3** in THF (3 ml) was treated with LDA (3.3 mmol) and subsequently with anhydrous $ZnCl_2$ (0.31 g, 3.1 mmol) as described above. The enolate solution was allowed to warm to room temperature and a solution of $Pd(PPh_3)_4$ (34.7 mg, 30 μmol) and **5** (0.31 g, 3.1 mmol) in THF (2 ml) was added. After the addition was complete the solution became turbid. Stirring was continued for another 30 min. and the reaction was worked up as usual to afford 0.16 g (31% yield) of **16**. No starting material could be recovered. In reactions wherein $ZnCl_2$ was not added no **16** was detected but some **3** was recovered. No **5** remained but unidentified olefinic absorptions were observed in the NMR spectrum.

2-Hydroxy-2-phenyl-4-pentenoic acid (**18**). Dioxolanone **6** (0.46 g, 2.0 mmol) was added at room temperature to a solution of KOH (0.34 g, 6.0 mmol) in CH_3OH (5 ml). The mixture was stirred overnight after which time the solvent was removed in vacuum. The residue was dissolved in water (5 ml) and acidified with 6N HCl. The precipitate that formed was taken up in ether and the organic layer was separated. The aqueous layer was extracted with ether (2 × 10 ml). Drying of the combined organic layers ($MgSO_4$) and evaporation of the solvent in vacuum afforded **18** (0.37 g, 96% yield) as a white crystalline compound. Although this material is quite pure, the product can be recrystallized from ether/pentane (1/1) to give 0.35 g (91% yield) of **18** as fine white needles, m.p. 106.5–108°C. ^1H NMR $CDCl_3$, 300 MHz): δ 2.78–3.01 (2 dd, 2H), 5.18–5.20 (m, 2H), 5.70–5.82 (m, 1H), 7.25–7.38 (m, 3H), 7.56–7.63 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 43.95 (t), 77.75 (s), 120.17 (t), 125.38 (d), 128.05 (d), 128.29 (d), 131.55 (d), 140.09 (s), 179.00 (s). Anal. calcd. for $C_{11}H_{12}O_3$: C 68.74, H 6.29; found: C 68.77, H 6.25%.

2-Hydroxy-2-methyl-4-pentenoic acid (**19**). Following the same procedure as described above, 0.51 g (3.0 mmol) of **16** was hydrolyzed in a solution of KOH (0.51 g, 9.0 mmol) in CH_3OH (10 ml) to afford after Kugelrohr distillation (70°C, 0.1 mm Hg) **19** (0.37 g, 95% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.48 (s, 3H), 2.41–2.55 (2 dd, 2H), 5.17 (m, 2H), 5.72–5.86 (m, 1H), 6.5–8.2 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 25.17 (q), 44.30 (t), 74.57 (s), 119.85 (t), 131.60 (d), 180.70 (s). Anal. calcd. for $C_6H_{10}O_3$: C 55.37, H 7.75; found: C 55.24, H 7.80%.

General procedure for a Pd-catalyzed asymmetric allylation of dioxolanone **4**

To a solution of LDA (3.3 mmol) in THF/hexane (3/2, 5 ml) was added at −78°C a solution of 0.58 g of **4** (3.0 mmol) in THF (3 ml). The mixture was cooled to −78°C and a solution of anhydrous $ZnCl_2$ (0.42 g, 3.1 mmol) prepared in another flask in THF (3 ml) was added. The mixture was allowed to warm to −10°C in 30 min. Meanwhile in another flask, a solution of a Pd compound (3–5 mol%), a chiral ligand (3–5 mol%) and **5** (0.31 g, 3.1 mmol) was prepared and stirred at room temperature for 15 min. This solution was subsequently added dropwise to the solution of the enolate which had been cooled to −78°C. The mixture was allowed to warm to room temperature and stirred overnight. After workup, as described above for the non-asymmetric allylation, the crude reaction product was purified by flash chromatography (SiO_2; CH_2Cl_2/hexane 1/1) to afford (optically active) **6** as a colourless oil.

3-Phenyl-1,4-dioxaspiro[4.4]nonan-2-one (**31**). A mixture of mandelic acid (4.56 g, 30 mmol) and cyclopentanone (2.52 g, 30 mmol) and a catalytic amount of 4-toluenesulfonic acid in toluene (50 ml) was refluxed for 2 h with azeotropic removal of the water formed. The resulting solution was washed with water (2 × 50 ml), dried ($MgSO_4$) and concentrated in vacuum to afford, after Kugelrohr distillation (115 °C, 0.05 mm Hg) **31** (4.58 g, 70% yield) as a colorless oil which crystallized on standing. ^{1}H NMR ($CDCl_3$): δ 1.5–2.2 (m, 8H), 5.3 (s, 1H), 7.4 (s, 5H).

3-Phenyl-1,4-dioxaspiro[4.5]decan-2-one (**32**). This compound was synthesized analogously to **31**. From mandelic acid (4.56 g, 30 mmol) and cyclohexanone (2.94 g, 30 mmol) there was obtained after Kugelrohr distillation (160 °C, 0.03 mm Hg), 5.28 g (76% yield) of **32** as a colorless oil, which crystallized on standing. 1H NMR ($CDCl_3$): δ 1.2–1.8 (m, 10H), 5.3 s, 1H), 7.2 (s, 5H).

3-Allyl-3-phenyl-(,4-dioxaspiro[4.4]nonan-2-one (**33**). Again following the general procedure, 0.65 g (3.0 mmol) of **31** gave after addition of 1 equivalent of $ZnCl_2$, with **5** (0.31 g, 3.1 mmol), $Pd(DBA)_2$ (51.8 mg, 90 μmol) and chiraphos (38.4 mg, 90 μmol) and after flash chromatography (SiO_2; CH_2Cl_2/hexane 1/1) of the crude reaction product, 0.55 g (71% yield) of **33** as a colorless oil; $[\alpha]_{578}$ + 14.0° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.56–1.72 (m, 6H), 1.94–2.00 (m, 2H), 2.54–2.70 (m, 2H), 5.00–5.06 (m, 2H), 5.56–5.61 (m, 1H), 7.16–7.25 (m, 3H), 7.48–7.55 (m, 2H).^{13}C NMR ($CDCl_3$). δ 22.15 (t), 23.07 (t), 37.38 (t), 37.90 (t), 45.05 (t), 83.11 (s), 119.82 (s), 120.01 (t), 124.71 (d), 127.97 (d), 28.25 (d). 131.02 (d), 138.78 (s), Anal. calcd. for $C_{16}H_{18}O_3$: C 74.37, H 7.02; found: C 74.14, H 6.94%.
Hydrolysis of **33** in KOH/MeOH gave (*R*)-2-hydroxy-2-phenyl--4-pentenoic acid (**18**), $[\alpha]_{578}$ − 6.8° (*c* 1, $CHCl_3$), e.e. 25% as determined by ^{1}H NMR[3].

3-Allyl-3-phenyl-1,4-dioxaspiro[4.5]decan-2-one (**34**). Following the general procedure for the asymmetric allylation described above, 0.69 g (3.0 mmol) of **32** was allylated, after addition of 1 equivalent of $ZnCl_2$, with **5** (0.31 g, 3.1 mmol) in the presence of $Pd(DBA)_2$ (51.8 mg, 90 μmol) and chiraphos (38.4 mg, 90 μmol). After work up, the crude reaction product was purified by flash chromatography (SiO_2; CH_2Cl_2/hexane 1/1) to give 0.54 g (67% yield of **34** as a colorless oil; $[\alpha]_{578}$ + 14.0° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36–1.88 (m, 10H), 2.60–2.76 (m, 2H), 5.08–5.14 (m, H), 5.65–5.78 (m, 1H), 7.24–7.36 (m, 3H), 7.59–7.63 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.85 (t), 24.29 (t), 36.98 (t), 37.06 (t), 45.88 (t), 82.61 (s), 110.82 (s), 119.98 (t), 124.51 (d), 127.76 (d), 128.11 (d), 131.26 (d), 139.74 (s), 172.37 (s). Anal. calcd. for $C_{17}H_{20}O_3$: C 74.97, H 7.40; found: C 75.25, H 7.29%.
Hydrolysis of **34** in KOH/MeOH afforded (*R*)-2-hydroxy-2-phenyl--4-pentenoic acid (**18**), $[\alpha]_{578}$ − 9.2° (*c* 1, $CHCl_3$), e.e. 33%, as determined by ^{1}H NMR.

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