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Asymmetric oxidation of enol phosphates to α-hydroxy ketones using Sharpless reagents and a fructose derived dioxirane

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ABSTRACT

The asymmetric oxidation of a variety of differently substituted, acyclic and cyclic enol phosphates using the Sharpless AD-reagents AD-mix-α and AD-mix-β, and a fructose derived chiral ketone as a catalyst, afforded the corresponding α-hydroxy ketones in high enantioselectivity and good yield. The influence of steric and electronic factors of the substrates on the facial stereoselectivity in the reported oxidations was studied.

1. Introduction

Chiral α-hydroxy ketones are important building blocks for the asymmetric synthesis of natural products.[1] Among the methods for their synthesis, the asymmetric oxidation of various enol derivatives plays an important role.[2] For this purpose, different chiral oxidizing agents, such as *N*-sulfonyl-oxaziridinides[2a] or Sharpless reagents:[3] AD-mix-α **1a** and β **1b** (Fig. 1) as well as chiral catalysts such as (salen) Met complexes, which were designed by Jacobsen[4] and modified by Berkessel,[5] have been used. The fructose-derived ketone **2** has been reported to be a very efficient catalyst for the asymmetric epoxidation of di-*trans* and trisubstituted acyclic olefins[6] and has also been applied to the oxidation of enol derivatives.[7] New catalysts, analogues of ketone **2**, were prepared by Shi for his studies of metal-free asymmetric epoxidations.[8] These chiral ketones were successfully applied to the asymmetric epoxidation of other differently substituted unsaturated compounds.[8]

As part of our interest in the application of organophosphorus derivatives in the synthesis of functionalized polycyclic compounds,[9] we have elaborated upon a methodology based on another type of enol derivative, namely enol phosphates, for an alternative synthesis of cyclic α-hydroxy carbonyl compounds.[10] Enol phosphates are known to exhibit biological activity, the most important example being phosphoenol pyruvate.[11] Bicyclic enol phosphates such as cyclophostin and cyclipostin P,[12] show a potent inhibition of acetyl cholinesterase or hormone sensitive lipases. In the last few years, diversely substituted enol phosphates have been used as versatile intermediates for the construction of complex organic molecules.[13]

Recently we have described an efficient asymmetric synthesis of chiral α-hydroxy carbonyl compounds via the oxidation of readily available acyclic and cyclic enol phosphates using Jacobsen's catalyst.[14] With the aim of improving efficiency in the asymmetric synthesis of various cyclic and acyclic α-hydroxy derivatives, we decided to extend our studies to the oxidation of enol phosphates using other chiral reagents. Initially we selected commercially available Sharpless reagents AD-mix-α-**1a** ('OsO_4·$(DHQ)_2PHAL$'), AD-mix-β-**1b** ('OsO_4·$(DHQD)_2PHAL$'), and the chiral oxidant dioxirane **3**, generated in situ from ketone **2** (Fig. 1).

2. Results and discussion

Enol phosphates are easy to prepare from simple reagents such as the corresponding alkyl aryl ketones and dialkyl- or diarylphosphorochloridates.[14] For our investigation, we selected a set of acyclic phosphates **4a**–**h** and cyclic enol phosphates **5a**–**d**, which were synthesized from the corresponding phosphorochloridates and enolate anions, generated in situ from the appropriate ketones by the action of LDA.[14b] Acyclic enol phosphates **4** were formed as single *Z*-isomers except for **4e**, which was obtained as a mixture of *Z*- and *E*-isomers in a 5:1 ratio. (Scheme 1). The *Z*-configuration of enol phosphate **4f** was established on the basis of the observation of a positive nuclear Overhauser effect (NOE); 3% increase in the area for the vinyl proton *cis* to the phenyl.[15] The *Z*-configuration of the other enol phosphates was determined by comparison of the chemical shift of the vinyl protons and the coupling constant ($^4J_{PH}$) observed for **4f** and for compounds **4a**–**d,** and **g**, **h**. Additionally a NOESY experiment was carried out on compound **4e**.[14b]

The corresponding bi- and tricyclic phosphates **5** (Fig. 2) containing an aromatic system fused with a cyclic enol phosphate moiety with an *E*-configuration, were prepared according to the procedure described above.

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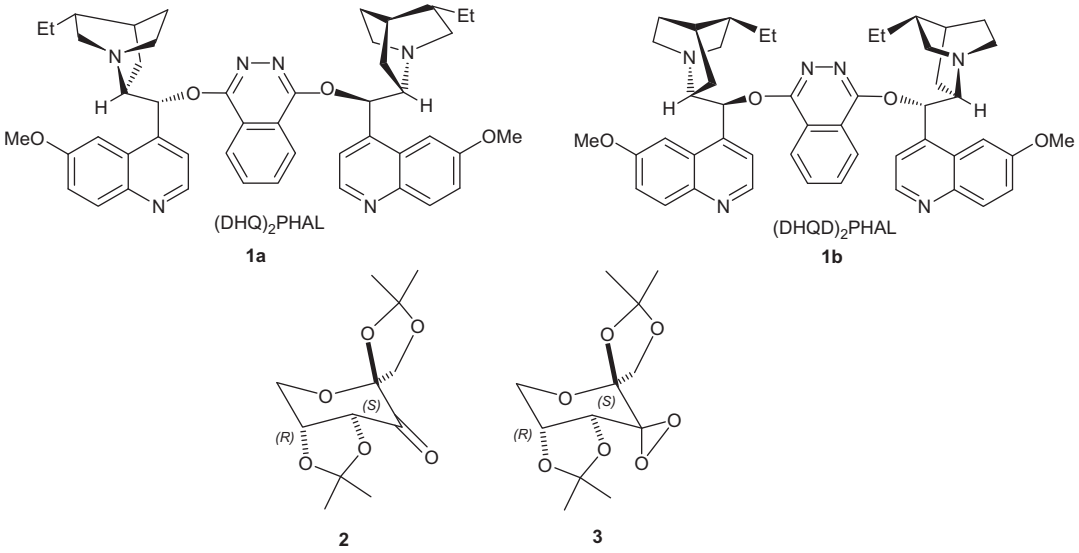
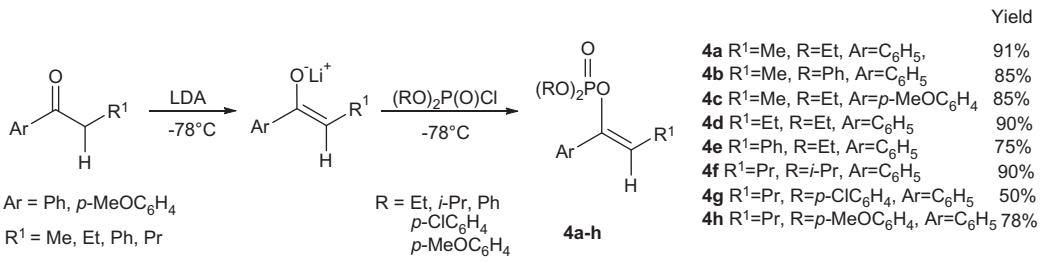


Figure 1. Ligands, fructose derived ketone, and chiral dioxirane designed for our study.



Scheme 1. General synthesis of enol phosphates **4**.

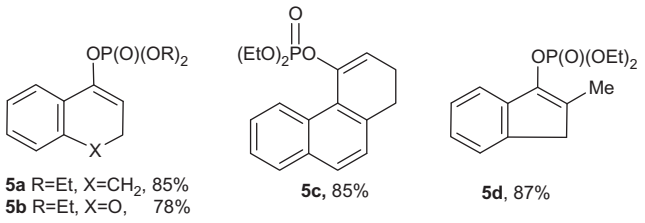
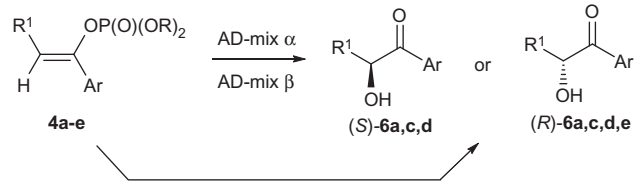


Figure 2. Cyclic *E*-enol phosphates **5**.



Scheme 2. Asymmetric oxidation of enol phosphates **4** with AD-mix-α and AD-mix-β.

2.1. Asymmetric oxidation of enol phosphates 4 and 5 with AD-mix-α and AD-mix-β—Sharpless AD-reaction

In the first set of experiments, we studied the asymmetric oxidation of enol phosphates according to the Sharpless AD-procedure.[3a] We examined this process using acyclic **4a**–**e** and cyclic enol phosphates **5a, b**. The reactions of **4a**–**e** were carried out with commercially available AD-mix-α and AD-mix-β which utilize the $(DHQ)_2$-PHAL[16] and $(DHQD)_2$-PHAL[16] ligands, in *t*-BuOH–H_2O (1:1) or in CH_3CN–H_2O (1:1), and methanesulfonamide as an additive, at 0 °C for 24 h. The product, α-hydroxy ketones **6** were isolated by flash chromatography (Scheme 2).

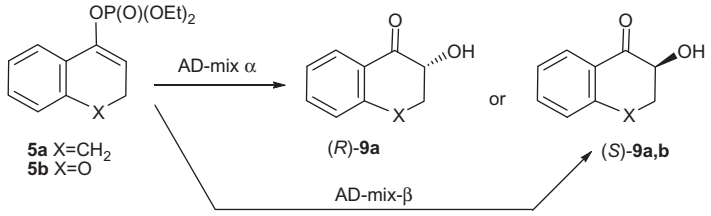
Phosphates **4a**–**d**, with an alkyl substituent β to the phosphate group, when treated with AD-mix-α or with AD-mix-β, afforded α-hydroxy ketones **6a,c,d** with an (*S*)-configuration and α-hydroxy ketones **6a,c,d** with an (*R*)-configuration, with very high enantioselectivity (92–100%) and in reasonable yields (Table 1, entries 1–4). The mixture of *Z*/*E* (5:1) enol phosphate **4e**, containing phenyl groups at both the α- and β-positions, only reacted with AD-mix-β to give (*R*)-(−)benzoin **6e** with 100% ee, albeit in very low yield. (Table 1, entry 5). The composition of the crude post-reaction mixture [(*Z*/*E* 2:1) of the remaining phosphate **4e**] revealed that only the *Z*-isomer of **4e** had reacted, although the conversion was low. Furthermore, the reaction of **4e** with AD-mix-α afforded a mixture of unidentified compounds among which only benzil [PhC(O)-C(O)Ph] was identified.

The asymmetric dihydroxylation of cyclic enol phosphate **5a**, derived from tetralone, with AD-mix-α and AD-mix-β, carried out under standard conditions, led to the formation of the corresponding 2-hydroxy tetralone **9a** in modest yields and enantioselectivity (Table 1, entries 6,7). A few attempts at the oxidation of chromanone derived enol phosphate **5b** under various conditions, were unsuccessful. However, in an experiment using double the amount of commercial AD-mix-β and sodium persulfate as a co-oxidant,[17]

Table 1
Enantioselective synthesis of α-hydroxy ketones **6**, **9** by catalytic asymmetric dihydroxylation (AD) of (*Z*)-acyclic **4a–e** and of (*E*)-cyclic enol phosphates **5a**, **b**

Entry	Substrate	Product	AD-mix-α			AD-mix-β		
			ee[a] (%)	Config[b]	Yield[c] (%)	ee[a] (%)	Config[b]	Yield[c] (%)
1	**4a**	**6a**	98.6	(*S*)-(−)	47	99	(*R*)-(+)	60
2	**4b**	**6a**	94	(*S*)-(−)	40	94	(*R*)-(+)	54
3	**4c**	**6c**	100	(*S*)-(−)	67	100	(*R*)-(+)	75
4	**4d**	**6d**	92	(*S*)-(−)	60	95	(*R*)-(+)	50
5	**4e**[d]	**6e**				100	(*R*)-(−)	14
6	**5a**[e,f]	**9a**	34	(*R*)-(+)	29			
7	**5a**[e,g]	**9a**	13	(*R*)-(+)	18	31	(*S*)-(−)	25
8	**5b**[e,g,h]	**9b**				12	(*S*)-(−)	30

[a] Determined by HPLC (Chiracel OD, see Section 4).
[b] Absolute configurations were determined by comparison of sign of the specific rotation with the literature data (see Section 4).
[c] Yield of isolated product.
[d] Ratio of isomers: (*Z*/*E* 5:1).
[e] *E* Isomers.
[f] Conditions: solvent: *t*-BuOH/H_2O.
[g] Conditions: solvent:CH_3CN.
[h] According to Marcune[17] conditions: CH_3CN, $Na_2S_2O_8$, −10 → 0° C, 1 h, +5 °C, 24 h.



Scheme 3. Asymmetric oxidation of cyclic enol phosphates **5** with AD-mix-α and AD-mix-β.

the product, 3-hydroxychroman-4-one **9b** was formed, though in 30% yield and with only 12% ee (Table 1, entry 8) (Scheme 3).

The results presented in Table 1 show that those acyclic enol phosphates **4** are suitable substrates for the AD process. The stereochemical outcome of these reactions and the high level of asymmetric induction are in agreement with those observed for (*Z*)-methyl enol ethers or the silyl enol ethers of aryl alkyl ketones studied by Sharpless et al.[3a] In order to understand this high face stereoselectivity in the AD reactions of acyclic enol phosphates **4**, the mechanistic models proposed for these processes were analyzed.

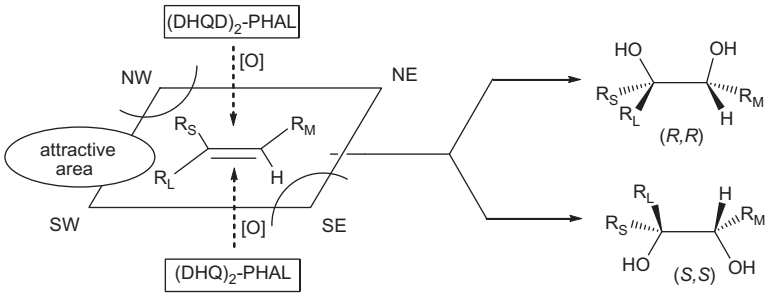
The initially proposed empirical model, a 'mnemonic device for predicting enantiofacial selection'[18] was later modified so that 'the southwest quadrant is regarded as being an attractive area, well suited to accommodate flat aromatic substituent, the northeast and southeast quadrants retain open and severely crowded, and the northwest quadrant which exhibits modest steric restriction, but can play an attractive role for some olefinic substrate'[19d] (Scheme 4).

Over the last two decades, extensive studies, including computational and kinetic investigations, have been undertaken with the aim of rationalizing some mechanistic aspects of the Sharpless asymmetric dihydroxylation reactions.[19] They allowed us to propose the updated mnemonic device which differs from the original one, indicating that only one quadrant (SE) is crowded while the NW quadrant is open and not subject to weak crowding. This model improves the predictivity, especially for trisubstituted alkenes.[19l,m]

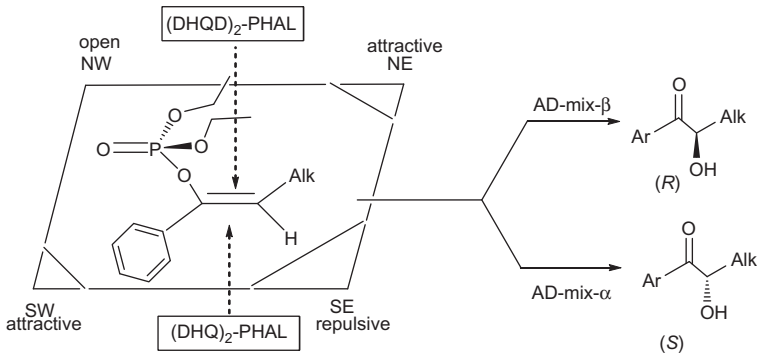
Thus, our results show that acyclic α-hydroxy ketones **6** of (*R*)- and of (*S*)-configuration were formed from (*Z*)-acyclic enol phosphates **4**, according to the updated Sharpless mnemonic.[19l,m] Enol phosphate **4** is positioned as illustrated in Scheme 5, with the phenyl substituent placed in the SW quadrant, which is assigned as the most important for attractive interactions with the catalyst ligand. The bulky phosphoryl group occupies the open northwest quadrant.

It was also mentioned that, 'if the substituent oriented toward NW corner is long and flexible it can wrap around and experience moderate steric stabilization from any nearby group'.[19l] This could be the case of the phosphoryl group.

Corey extended the scope of the AD reaction, using the pyridazine-linked ligand, [$(DHQD)_2$PYDZ], to the polycyclic olefinic



Scheme 4. Sharpless mnemonic device for the prediction of AD selectivity.



Scheme 5. Updated mnemonic device for the AD oxidation of acyclic enol phosphates **4**.

substrates containing an aromatic framework. Several (*R*,*R*)-polycyclic diols with an aromatic moiety were obtained with high enantioselectivity.[19g] A few years later, Marcune et al. applied a modified AD procedure to accomplish the asymmetric synthesis of cyclic α-hydroxy ketones from enol ethers of cyclic ketones.[17] The (*R*)- and (*S*)-enantiomers of 2-hydroxy tetralone **9a** and (*S*)-3-hydroxychroman-4-one **9b** were obtained using the $(DHQD)_2PHAL$ and the $(DHQ)_2PHAL$ ligands, respectively, with high enantioselectivity and in good yield. The facial stereoselectivity was found to be the same as that observed for polycyclic diols.

On the contrary, our attempt to synthesize enantiomerically enriched 3-hydroxychroman-4-one **9b** and 2-hydroxy tetralone **9a**, according to the modified AD procedure was less successful. Using our substrates, cyclic enol derivatives **5a**, **5b**, containing a phosphoryl group, the corresponding α-hydroxy ketones **9a** and **9b** were obtained in low yield and enantioselectivity. Moreover these compounds **9a**, **9b** were formed not only in low enantiomeric purity, but the sense of these asymmetric inductions was [(*S*)-configuration] opposite to that [(*R*)-configuration] observed by Marcune for the cyclic enol ethers.

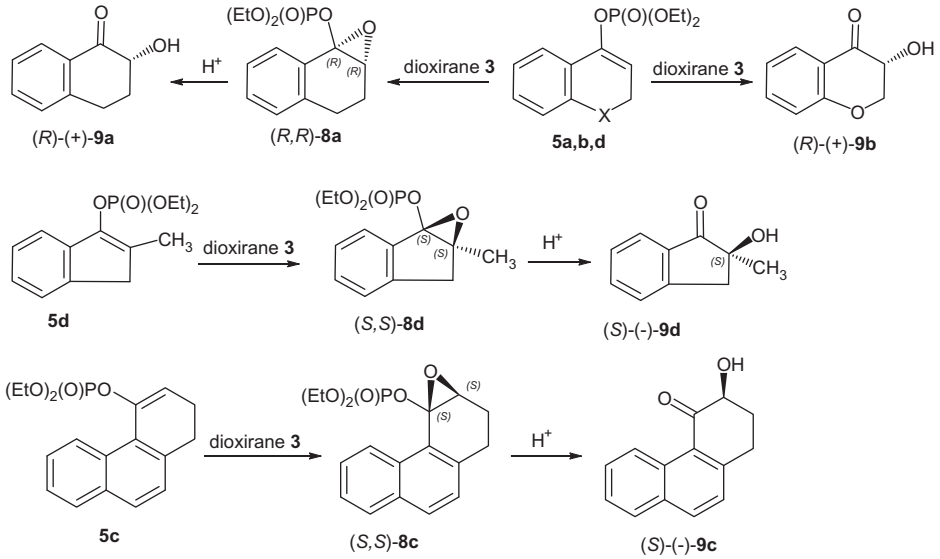
2.2. Asymmetric epoxidation of enol phosphates 4 and 5 with chiral dioxirane 3

Searching for another effective catalyst for the asymmetric oxidation of enol phosphates, in particular cyclic compounds fused with an aromatic moiety, we focused our attention on an organocatalyst—a fructose derived ketone **2**, readily available from D-fructose via a simple two step synthesis.[6,20] The chiral oxidant, dioxirane **3**, is usually generated in situ from ketone **2** and Oxone (potassium peroxomonosulfate).[6]

Adam et al. described the utility of this method for the conversion of acyclic silyl enol ethers into the corresponding optically active α-hydroxy ketones.[21] Shi et al. applied ketone **2** and its modified derivatives, for the preparation of many enantiomeric mono- and bicyclic enol epoxides.[7b,8c,f] Further transformations, under acidic or thermal conditions, afforded enantiomerically enriched α-acyloxy-, α-alkoxy, or α-aryloxy ketones. In some cases, one enantiomer of an epoxide could be converted into either enantiomer of these ketones by the choice of proper reaction conditions.[7b]

To test the utility of chiral dioxirane **3** in asymmetric oxidations, we examined the reactivity of the enol phosphate derived from chroman-4-one **5b**. (Scheme 6, Table 2).

From the reaction with excess dioxirane **3**, generated in situ from chiral ketone **2** and Oxone, the desired (*R*)-(+)-3-hydroxychroman-4-one **9b** was obtained directly in good yield and with high enantioselectivity (92% ee, Table 2, entry 2). The same process, carried out under catalytic conditions (Table 2, entry 3) afforded product **9b** with similar enantioselectivity (82% ee) albeit in lower yield. Therefore, the next set of experiments with phosphates **5a, c, d** containing cyclic, aromatic substituents, as well as with



Scheme 6. Asymmetric epoxidation of cyclic enol phosphates **5** with chiral dioxirane **3** and subsequent epoxides conversion into cyclic α-hydroxy ketones **9**.

Table 2
Enantioselective synthesis of α-hydroxy ketones **6**, **9** via enantioselective epoxidation of cyclic **5** and acyclic enol phosphates **4** with a fructose-derived dioxirane **3**[a]

Entry	Substrate (*E*) or (*Z*)	Epoxide[b]	Config[c]	Yield[d] (%)	Product	Yield[e] (%)	ee[f] (%)	Config[g].
1	**5a**	**8a**	(*R*,*R*)	50	**9a**	50	88	(*R*)-**(+)**
2	**5b**				**9b**	60	92	(*R*)-**(+)**
3	**5b**[h]				**9b**	40	83	(*R*)-**(+)**
4	**5c**	**8c**	(*S*,*S*)	48	**9c**	48	84	(*S*)-**(−)**
5	**5d**	**8d**	(*S*,*S*)	28	**9d**	25	12	(*S*)-**(−)**
6	**4a**	**7a**	(*S*,*R*)	33	**6a**	33	76	(*R*)-**(+)**
7	**4b**	**7b**	(*S*,*R*)	48	**6a**	48	68	(*S*)-**(−)**
8	**4f**	**7f**	(*S*,*R*)	55	**6f**	50	66	(*R*)-**(+)**
9	**4g**	**7g**	(*S*,*R*)	20	**6f**	18	76	(*S*)-**(−)**
10	**4h**	**7h**	(*S*,*R*)	50	**6f**	40	69	(*S*)-**(−)**

[a] General non-catalytic reaction conditions: substrate (1 equiv), ketone **2** (3 equiv), Oxone (5 equiv), and K_2CO_3 (15 equiv) in CH_3CN/aq Na_2-(EDTA) at 0 °C.
[b] Not isolated but characterized by ^{31}P and ^{1}H NMR data and compared with the literature data.[14b]
[c] The absolute configurations were tentatively assumed by comparing the absolute configurations of the resulting α-hydroxy ketones **6** and **9**, determined by the sign of the specific rotation of **6** and **9** and chiral HPLC data.[14b]
[d] By ^{31}P NMR spectroscopy of the crude reaction mixture.
[e] Yield of isolated products.
[f] Determined by chiral HPLC (Chiracel OD).
[g] Absolute configurations were determined by comparison of the sign of the specific rotation with the literature data (see Section 4).
[h] Conditions: substrate (1 equiv), ketone **2** (0.3 equiv), Oxone (1.38 equiv), and K_2CO_3 (5 equiv) in CH_3CN/buffer [0.05 M $Na_2O_4O_7$.10 H_2O in aq Na_2-(EDTA)] at 0 °C.

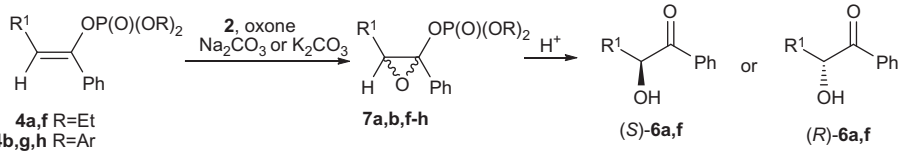
dialkyl- **4a, f** and diaryl-substituted **4b, g, h** acyclic enol phosphates, were performed under non-catalytic conditions (entries 1, 4–10). In most cases, the corresponding enol phosphate epoxides **7** and **8** were formed in good to moderate yields (Table 2, entries 1, 4, 6–9) as determined by ^{31}P NMR. The substrates **4g** and **5d** were less reactive under the epoxidation reaction conditions to give the epoxides **7g, 8d** in very low yield. (Table 2, entries 5, 10). Any attempts to isolate all of the intermediate epoxides **7, 8**, including an Et_3N-buffered silica gel column, were unsuccessful. For this reason, the crude reaction mixtures were hydrolyzed using trifluoroacetic acid in ether/H_2O solution to give α-hydroxy carbonyl derivatives **6a, f**, **9a, c, d**, which have been isolated in pure form. The degrees of conversion of all enol phosphate epoxides **7, 8** to α-hydroxy ketones **6, 9** were nearly quantitative as concluded from ^{31}P NMR data. High enantioselectivities (88–82%) were observed for the epoxidation of cyclic phosphates **5a, c** but for product **9c,** the (*S*)-configuration prevailed. Enol phosphate **5d** was converted into nearly racemic 2-hydroxy-2-methyl-indanone **9d** in low yield. The stereoselectivity of the epoxidation of the *Z* isomers of acyclic enol phosphates **4a, b, f, g, h** was good (ee 76–66%), but lower compared to the cyclic ones **5a**–**c** (ee 92–83%).[22] While the enol phosphates with alkoxy substituents on the phosphoryl group **4a,f** led to (*R*)-configured final products **6a** and **6f**, (Scheme 7, Table 2, entries 6, 8) the substrates bearing aryloxy groups at phosphorus **4b, g, h** afforded the (*S*)-enantiomers of α-hydroxy ketones **6a** and **6f**[23] (Scheme 7, Table 2, entries 7, 9, 10).

The results of the asymmetric epoxidation of acyclic **4** and cyclic enol phosphates **5**, using chiral ketone-catalyst **2**, show that the degree of enantioselectivity and absolute configuration of α-hydroxy ketones obtained, are dependent on the geometry (*E*/*Z*) and substitution pattern of the starting phosphates, which is in agreement with earlier observations by Shi[6,7b] and Adam.[21] Two mechanistic models with *spiro* or *planar* transition states were proposed for the dioxirane-mediated epoxidation of differently substituted olefins.[6] Calculations performed by Bach et al.[24] show that the optimized transition state is the *spiro*-like TS model presumably 'due to the stabilizing interaction of a dioxirane oxygen lone pair with the π^* orbital of the alkene. (In the *planar* TS, that interaction is not possible owing to its geometry)'. The electronic factors of a substituent on the olefin, such as phenyl, can lower the energy of the π^* orbital of the alkene and enhance these stabilizing interactions.[7c] Based on stereochemical analysis of a few possible *spiro* and *planar* transition states, it can be concluded that two of them, one *spiro* and one *planar*, are sterically favored. In these models, the steric repulsions of the dioxirane and olefin substituents are minimized.[7b]

The application of the *spiro* model of the TS to the *E*-configured cyclic enol phosphates **5a, b** allowed us to predict the proper (*R*,*R*) facial stereoselectivity in this epoxidation process.[6,7] Following Shi's mechanistic proposal for the epoxidation of cyclic enol ethers,[7b] the arrangement of this bicyclic system containing a phosphate group and an aromatic moiety is illustrated in Figure 3. The phosphoryl group is positioned over the fructose ring so that it can avoid the steric repulsion with the *exo*-dioxolane ring (Fig. 3a).

The α-hydroxy ketone of opposite configuration (*S*)-**9c** was formed from the enol phosphate derivative of 2,3-dihydro-phenanthren-4-one **5c**. In this case, the steric interactions of the bulkier aromatic substituent with the fructose moiety in the *spiro* transition state prevailed. (Fig. 3b). Hence, we assume that the (*S*)-configured product was formed as a result of the epoxidation according to the *planar* TS (Fig. 3c).

The *spiro* transition state model, in which the planar Ph group is directed over the plane of the dioxirane ring, can explain the (*R*,*S*) facial stereoselectivity of the epoxidation of acyclic enol phosphates **4a, f** containing a dialkoxy phosphoryl group and an alkyl substituent in the *cis* position. Hydrolysis of the resulting epoxides **7a**, **f**, with $CF_3C(O)OH$, led to the observed α-hydroxy ketones **6a**, **f** with an (*R*)-configuration (Table 2, entries 6, 8), (Scheme 8). However, in contrast to these (*R*)-α-hydroxy ketones **6a** and **6f,** the (*S*)-α-hydroxy ketones **6a** and **6f** were formed from phosphates **4b, g,**



Scheme 7. Enantioselective synthesis of acyclic α-hydroxy ketones **6** via epoxidation of acyclic enol phosphates **4**.

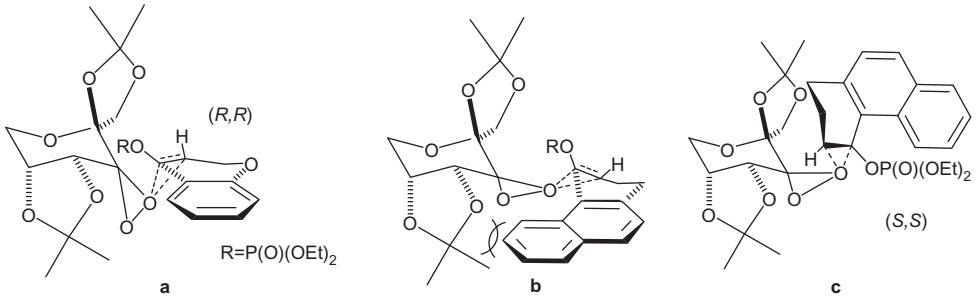
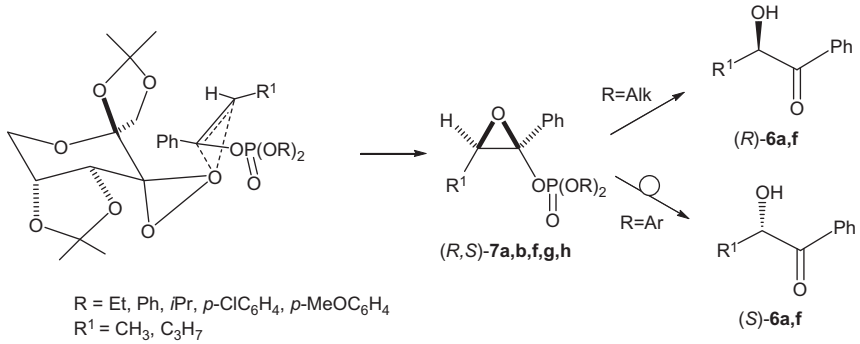


Figure 3. Proposed *spiro* and *planar* transition states for the epoxidation of cyclic enol phosphates **5** with chiral dioxirane **3**.



Scheme 8. Mechanistic proposal for the epoxidation of enol phosphates **4** by fructose derived chiral dioxirane **3**.

h bearing aryloxy phosphoryl groups (Table 2, entries 7, 9, 10). Although the absolute configurations of the enol phosphate epoxides **7a, b, f, g,** and **7h** were not determined due to their instability, the stereochemical course of these epoxidations was assumed to be the same in both cases, based on the preferred *spiro* transition state model discussed above (Scheme 8).

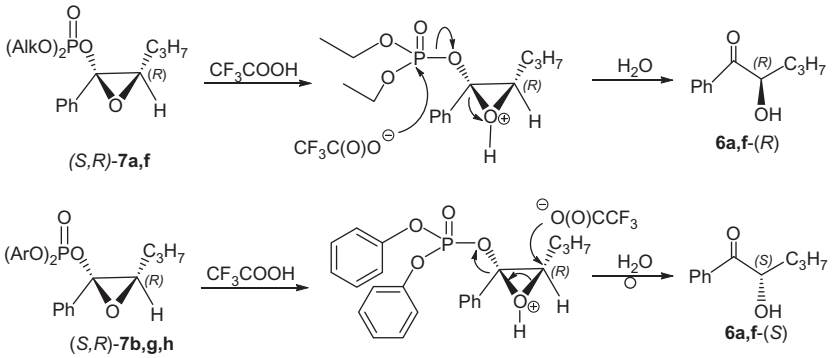
Therefore, it seems reasonable to assume that a reversal of configuration leading to (*S*)-α-hydroxy ketones **6a, f,** takes place over the course of the acidic hydrolysis of the enol diaryloxyphosphate epoxides **7b, g,** and **h**.

Two tentatively considered mechanisms for the hydrolysis of enol phosphate epoxides **7** are shown in Scheme 9.

Under the acidic conditions of this reaction, it is the *O*-protonated epoxide which undergoes hydrolysis. In the case of dialkoxy phosphoryl epoxides, attack of an anion at the phosphorus atom facilitates the cleavage of the phosphorus-oxygen bond. Consequently, α-hydroxy ketones (*R*)-**6a,f** of retained configuration are formed. The presence of bulky aryloxy substituents at the phosphorus atom in compounds **7b, g**, and **7h** can impede the attack of the $CF_3C(O)O^-$ anion at this atom. Hence, the reaction occurs at the less substituted carbon atom. Subsequent hydrolysis affords α-hydroxy ketone (*S*)-**6a,f** with inversion of configuration at that carbon. It should be also mentioned that an analogous phenomenon was observed in the asymmetric oxidation of aryloxy substituted enol phosphates using Jacobsen's catalyst.[14]

3. Conclusion

We have demonstrated that readily available enol phosphates **4** and **5** are good synthons for the stereoselective synthesis of differently substituted α-hydroxy carbonyl derivatives. It has been shown that Sharpless AD reagents **1a** and **1b**, are complementary to fructose-derived ketone **2** in the asymmetric oxidation of (*Z*)-acyclic enol phosphates **4** and of (*E*)-cyclic enol phosphates **5** respectively. AD-mix-α **1a** and AD-mix-β **1b** have appeared to be very effective reagents for the enantioselective oxidation of acyclic enol phosphates **4** giving α-hydroxy ketones with excellent ees. In turn cyclic enol phosphates **5**, containing an aromatic moiety have



Scheme 9. Proposed courses of the hydrolysis of acyclic enol phosphate epoxides **7**.

been easily epoxidized with high enantioselectivity using simple organic catalyst, a fructose derived ketone **2** and Oxone as the oxidant. The corresponding enantioselective α-hydroxy cyclic ketones were obtained in good yields. This epoxidation of acyclic enol phosphates affords enantiomerically enriched enol phosphate epoxides. The acidic hydrolysis of these epoxideslends to both enantiomers of acyclic α-hydroxy ketones, depending on AlkO or ArO groups on the phosphorus atom. The synthetic scope of both asymmetric oxidations: the osmium catalyzed AD reactions and epoxidation reactions using an organic catalyst is extended by conversion of (*Z*) and (*E*)-enol phosphates into the pool of versatile substrates.

4. Experimental

4.1. General

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AC 200 Spectrometer at 200.13, 50.32, and 81.02 MHz, respectively (using $CDCl_3$ as a solvent) unless otherwise noted. IR spectra were measured on an Ati Mattson Infinity FTIR 60. MS spectra (EI, CI, and HRMS) were recorded on a Finnigan MAT 95 spectrometer. Optical rotation values were measured in a 100 mm cell on Perkin Elmer 241 MC under Na lamp radiation. The enantiomer ratios were determined by HPLC analysis on the commercially available column Chiracel OD under the conditions specified. Flash chromatography separations were performed on silica gel columns (Merck, Kieselgel 70–230 mesh) with the indicated eluent. Chemicals, solvents, AD-mix-α, and AD-mix-β were obtained from commercial sources and distilled or dried according to standard methods.

4.2. Synthesis of materials

Enol phosphates **4a**–**f**,**h**, **5a**,**c**,**d** were prepared according to the literature.[14b] Racemic epoxides **7a,b,f–h, 8a,c,d** and racemic α-hydroxy ketones **6a**–**f, 9a,c,d** were prepared as described.[14b] The products, enantiomerically enriched α-hydroxy ketones **6** and **9** were characterized by comparison of their data with those of known samples[14b] or by their spectroscopic data.

4.2.1. Phosphoric acid bis-(4-chloro-phenyl) ester 1-phenyl-pent-1-enyl ester 4g. General procedure

To a solution of freshly prepared LDA (9 mmol) in THF (100 mL) at −78 °C was added butyl phenyl ketone (1.2 g, 7.6 mmol) in THF (20 mL) and the mixture was stirred under an Ar atmosphere for 1.5 h. Next, a solution of di-(4-chloro-phenyl)-phosphorochloridate (3 g, 9 mmol) in THF (20 mL) was added dropwise at the same temperature. The mixture was stirred and allowed to warm slowly to room temperature. After 2 h of stirring at ambient temperature, the solvent was evaporated, the residue was dissolved in ether, washed with saturated NH_4Cl and water, and dried ($MgSO_4$). Evaporation of the solvent afforded the crude reaction mixture, which was analyzed by ^{1}H and ^{31}P NMR spectroscopy. Pure enol phosphate was obtained by column chromatography with petroleum ether/EtOAc (6:4) as a single isomer, yellow oil (1.8 g, 50%); R_f 0.75, (50% EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.32 (m, 5H, Ph), 7.25 (dt, 4H, *J* 6, 3 Hz, 4-ClC_6H_4), 7.02 (d, 4H, *J* 8.1 Hz, 4-ClC_6H_4), 5.62 (dt, 1H, *J* 7, 1.5 Hz, C=CH), 2.22 (dq, 2H, *J* 7.5, 2.6 Hz, CH_2), 1.43 (sext, 2H, *J* 7.5 Hz, CH_2), 0.88 (t, 3H *J* 7.5 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.9, 145.9 (d, *J* 9.6 Hz), 134.9 (d, *J* 9.8 Hz), 130.9, 129.9, 129.7, 128.5, 128.3, 125.5, 121.3 (d, *J* 4.8 Hz) 118.6 (d, *J* 6.6 Hz), 28,1, 22.2, 13.8; ^{31}P NMR (81 MHz, $CDCl_3$) δ −17.1; IR (KBr, cm^{-1}) 3095, 2960, 2931, 2870, 1588, 1486, 1301, 1196, 1092, 957, 830; HRMS calculated for $C_{23}H_{21}Cl_2O_4P$ [M^+] 462.0554; found for 462.0549.

4.2.2. Phosphoric acid 2*H*-chromen-4-yl ester diethyl ester 5b

[25] Yellow oil (78%); R_f 0.5, (50% EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (dd, 1H, *J* 7.6, 1.5 Hz, CH), 7.14 (dt, 1H, *J* 7.6, 1.5 Hz, CH), 6.87 (dt, 1H, *J* 7.6, 1.0 Hz, CH), 6.76 (dd, 1H, *J* 8.1, 1.0 Hz, CH), 5.59 (dt, 1H, *J* 4.0, 1.5 Hz, C=CH), 4.87 (dd, 2H, *J* 4.0, 2.0 Hz, CH_2), 4.19 (dd, 4H, *J* 7.0 Hz, OCH_2CH_3), 1.33 (t, 6H, *J* 7.0 Hz, OCH_2CH_3), ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.1 (d, *J* 7.2 Hz), 152.0, 130.6, 127.1, 123.4, 122.7, 115.6, 70.4, 64.1, 64.0, 13.7, 13.6; ^{31}P NMR (81 MHz, $CDCl_3$) δ −6.15; IR (film, cm^{-1}) 3078, 2985, 2911, 1609, 1478, 1465, 1237, 1218, 1034, 982, 762; *m*/*z* (EI) 284 (25), 255 (21), 227 (16), 146 (100), 120 (69); HRMS calc for $C_{13}H_{17}O_5P$ [M^+] 284.0813; found for 284.0805;

4.3. General procedure for the Sharpless AD reactions of acyclic enol phosphates 4a–e and cyclic enol phosphate 5a with AD-mix-β and AD-mix-α (Table 1)

A mixture of AD-mix-β or AD-mix-α (1.4 g) and $MeSO_2NH_2$ (95 mg, 1 mmol) in *t*-BuOH-H_2O (5 mL/5 mL) was stirred at room temperature until the mixture became nearly homogeneous. Then it was cooled to 0 °C and to this mixture, the appropriate enol phosphate (1 mmol) was added at once. The heterogeneous mixture was stirred vigorously at 0 °C for 16 h (ice bath). Then the reaction was quenched at 0 °C by the addition of sodium sulfite (1 g) and the mixture was stirred for 1 h. After the addition of CH_2Cl_2 (30 mL) and separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (40 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give a crude product, which was purified by flash chromatography (silica gel, gradient of EtOAc/hexane) to give the pure acyclic α-hydroxy ketones **6a,c–e**, which were characterized by ^{1}H NMR.[14b] The enantiomeric excess was determined by HPLC with a Chiracel OD-H column. All runs were carried out at room temperature. The absolute configurations of products **6a,c–e,** and **9a** were determined by the comparison of the sign of the specific rotation with the literature data: **6a**,[26] **6c**,[27] **6d**,[26] **6e**,[26] **9a**[28] and additionally by comparison of HPLC data.[14]

4.3.1. 2-Hydroxy-1-phenyl-1-propan-1-ones(*S*)-(−)- and (*R*)-(+)-6a (Table 1, entry 1)

(*S*)-(−)-**6a,** colorless liquid, HPLC conditions: 5% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 16.3 (*S*), t_R [min] 17.6 (*R*); $[\alpha]_D^{20} = -96.4$ (*c* 0.7, $CHCl_3$), lit. (*S*)-(−)-**6a**: $[\alpha]_D^{20} = -80.9$ (*c* 2.0, $CHCl_3$), ee = 95%;[26a] (*R*)-(+)-**6a,** 5% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 20.7 (*S*), t_R [min] 22.7 (*R*); $[\alpha]_D^{20} = +55.4$ (*c* 0.1, $CHCl_3$), lit. (*R*)-(+)-**6a**: $[\alpha]_D^{20} = +82.2$ (*c* 2.0, $CHCl_3$), ee = 96%.[26c]

4.3.2. 2-Hydroxy-1-phenyl-1-propan-1-ones(*S*)-(−) and (*R*)-(+)-6a (Table 1, entry 2)

(*S*)-(−)-**6a**, HPLC conditions: 4% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 14.4 (*S*), t_R [min] 15.8 (*R*); $[\alpha]_D^{20} = -82.5$ (*c* 0.6, $CHCl_3$); (*R*)-(+)-**6a,** 4% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 17.8 (*S*), t_R [min] 19.5 (*R*); $[\alpha]_D^{20} = +55$ (*c* 0.35, $CHCl_3$).

4.3.3. 2-Hydroxy-1-(4-methoxyphenyl)-1-propan-1-ones(*S*)-(−)- and (*R*)-(+)-6c (Table 1, entry 3)

(*S*)-(−)-**6c,** colorless liquid, **HPLC** conditions: 0.7% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 43.2 (*S*); $[\alpha]_D^{20} = -79$ (*c* 0.7, $CHCl_3$), lit. (*S*)-(−)-**6c**: $[\alpha]_D^{20} = -33.4$ (*c* 1.0, MeOH);[27] (*R*)-(+)-**6c**, 0.7% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 47.7 (*R*); $[\alpha]_D^{20} = +59$ (*c* 0.5, $CHCl_3$).

4.3.4. 2-Hydroxy-1-phenyl-1-butan-1-ones(*S*)-(−)- and (*R*)-(+)-6d (Table 1, entry 4)

(*S*)-(−)-**6d,** colorless liquid, HPLC conditions: 4% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 11.8 (*S*), t_R [min] 14.5 (*R*); $[\alpha]_D^{20} = -34.4$ (*c* 0.7, $CHCl_3$), lit. (*S*)-(−)-**6d**: $[\alpha]_D^{20} = -30.8$ (*c* 2.24, $CHCl_3$),

ee = 95%;[26a] (*R*)-(+)-**6d,** 4% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 12.0 (*S*), t_R [min] 13.9 (*R*); $[\alpha]_D^{20} = +31.2$ (*c* 0.7, $CHCl_3$), lit. (*R*)-(+)-**6d**: $[\alpha]_D^{20} = +40.5$ (*c* 0.3, $CHCl_3$), ee = 81%.[14b]

4.3.5. 2-Hydroxy-1,2-diphenyl-ethanone(*R*)-(−)-6e (Table 1, entry 5)

(*R*)-(−)-**6e,** white solid, mp 140 °C, HPLC conditions: 5% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 36.6 (*R*); $[\alpha]_D^{20} = -142$ (*c* 0.7, $CHCl_3$), lit. (*S*)-(+)-**4d**: $[\alpha]_D^{20} = +114.9$ (*c* 1.5, acetone), ee = 95%.[26]

4.3.6. 2-Hydroxy-3,4-dihydro-*2H*-naphthalen-1-one(*R*)-(+)-9a (Table 1, entry 6)

(*R*)-(+)-**9a,** colorless liquid, HPLC conditions: 0.3% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 36.3 (*R*), t_R [min] 41.0 (*S*); $[\alpha]_D^{20} = +11$ (*c* 0.7, $CHCl_3$).

4.3.7. 2-Hydroxy-3,4-dihydro-*2H*-naphthalen-1-ones(*R*)-(+)- and (*S*)-(−)-9a (Table 1, entry 7)

(*R*)-(+)-**9a**, HPLC conditions: 0.3% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 28.1 (*R*), t_R [min] 29.9 (*S*); (*S*)-(−)-**9a** 0.3% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 52.3(*R*), t_R [min] 60.8 (*S*); $[\alpha]_D^{20} = -11.2$ (*c* 0.3, $CHCl_3$); lit. (*S*)-(−)-**9a:** $[\alpha]_D^{20} = -8.6$ (*c* 1.0, CH_2Cl_2), ee = 99%.[28]

4.4. Procedure for Sharpless AD reactions with cyclic enol phosphate 5b. Preparation of (*S*)-3-hydroxy-2,3-dihydro-4*H*-chromen-4-one 9b.[17]

A mixture of AD-mix-β (2.8 g), $MeSO_2NH_2$ (130 mg, 1.5 mmol), and $Na_2S_2O_8$ (375 mg, 1.5 mmol) was dissolved in CH_3CN (10 mL) and water (10 mL) and stirred at 0 °C for 15 min. To this slurry was added the enol phosphate of chromanone **5b** (284 mg, 1 mmol) and the mixture was stirred overnight at 0 °C. Next methyl *t*-butyl ether (10 mL) and brine (8 mL) were added. After separation, the aqueous layer was extracted with MTBE (10 mL), washed with water, and the combined organic layers were dried with Na_2SO_4. After evaporation of the solvent, the yellow oil was purified by flash chromatography (silica gel, gradient of EtOAc/hexane) to give product **9b** as a white crystalline solid; 49 mg, 30%; $[\alpha]_D^{20} = -8.8$ (*c* 0.7, $CHCl_3$), R_f (50% EtOAC/hexane) 0.7; mp 57–59 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (1H, dd, *J* 7.8, 1.5 Hz, Ar), 7.52 (1H, dt, *J* 7.8, 1.5 Hz, Ar), 7.06 (1H, t, *J* 7.6 Hz, Ar), 6.98 (1H, d, *J* 8.3 Hz, Ar), 4.71–4.57 (2H, AB part of ABX, CH_2), 4.20–4.05 (1H, X part of ABX, CH), 2.5 (1H, br s, OH); *m*/*z* (CI, isobutane) 165 (100, MH^+); Enantiomeric excess was determined by HPLC, Chiracel OD-H: (*S*)-(−)-**9b,** ee 12%, (Table 1, entry 8), HPLC conditions: 0.7% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 34.6(*R*), t_R [min] 39.9 (*S*), lit. (*S*)-(−)-**9b**: $[\alpha]_D^{20} = -57$ (*c* 2.0, $CHCl_3$), ee = 100%[31]

4.5. General epoxidation procedure. Method A (under non-catalytic conditions)

4.5.1. Preparation of (*R*)-(+)-3-hydroxy-2,3-dihydro-4*H*-chromen-4-one 9b[17,31] from 5b

Aqueous Na_2(EDTA) (1×10^{-4} M, 10 mL) and a catalytic amount of $Bu_4N^+OH^-$ were added to a solution of enol phosphate **5b** (284 mg, 1 mmol) in acetonitrile (15 mL) with stirring at 0 °C. A mixture of Oxone (3 g, 5 mmol) and K_2CO_3 (2.1 g, 15 mmol) was mixed, and a small amount of this mixture was added to the reaction mixture to bring the pH to ~8, after which ketone **2** (770 mg, 3 mmol) was added portionwise over 1 h. Simultaneously, the rest of the Oxone and bicarbonate mixture was added over 50 min. After completion of the addition of both components, the reaction mixture was stirred for 1 h at 0 °C. Next, it was diluted with water (35 mL) and the organic layer was separated. The residue was extracted with hexanes (3×20 mL) and next with diethyl ether (2×20 mL). This organic layer was washed with brine (10 mL) and water (20 mL), dried (Na_2SO_4), and evaporated. The crude mixture, analyzed by ^{1}H and ^{31}P NMR, was found to contain α-hydroxy chromanone **9b** together with the ketone **2.** Careful separation of this mixture by flash chromatography (Hexane/EtOAc 9/1) afforded pure **9b** as a white solid (98 mg, 60% yield); $[\alpha]_D^{20} = +82$ (*c* 0.85, $CHCl_3$), R_f (50% EtOAC/hexane) 0.7; mp 58.5 °C; the enantiomeric excess was determined by HPLC, (Chiracel OD-H): (*R*)-(+)-**9b,** ee 92%, HPLC conditions: (Table 2, entry 2), 0.7% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 34.3(*R*), t_R [min] 40.4 (*S*).; lit. (*R*)-(+)-**9b**: $[\alpha]_D^{20} = +71.25$ ($CHCl_3$), ee = 83%.[17]

4.5.2. (*R*)-(+)-2-Hydroxy-3,4-dihydro-2*H*-naphthalen-1-one 9a[14b,28] (Table 2, entry 1)

Epoxide **8a** was prepared according to the general epoxidation procedure (method A) from phosphoric acid 3,4-dihydro-naphthalen-1-yl ester diethyl ester **5a** and dioxirane **3** to provide crude compound **8a**.[14b] ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77–7.72 (m, 1H, Ar), 7.28 (d, 2H, *J* 4.4 Hz, Ar), 7.11 (t, 1H, *J* 4.4 Hz, Ar), 4.53 (dd, 1H, *J* 5.5, 1.6 Hz, POCOC(*H*)), 4.20 (quint, 4H, *J* 7.0, OCH_2CH_3), 2.72–2.61 (m, 2H, CH_2), 2.40–2.30 (m, 1H, CH_2), 1.98–1.70 (dd, 1H, *J* 13.0, 6.2, CH_2), 1.38 (d, 6H, *J* 7.0, OCH_2CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ 6.09. Epoxide **8a** was hydrolyzed with $CF_3C(O)OH$ in Et_2O/H_2O solution at 0 °C[14b] to the title compound **9a**. The enantiomeric excess was determined by HPLC (Chiracel OD-H), (*R*)-(+)-**9a** entry 1;0.3% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 50.9 (*R*), t_R [min] 60.9 (*S*); $[\alpha]_D^{20} = +14.7$ (*c* 0.6, $CHCl_3$).

4.5.3. (*S*)-(−)-2,3-Dihydro-3-hydroxy-1*H*-phenanthren-4-one 9c[14b] (Table 2, entry 4)

Epoxide **8c** was prepared according to the general epoxidation procedure (method A) from phosphoric acid 1,2-dihydro-phenanthren-4-yl ester diethyl ester **5c** and dioxirane **3** to provide crude compound **8c**; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.36 (d, 1H, *J* 8.0, Ar), 7.74–7.60 (m, 2H, Ar), 7.47–7.33 (m, 2H, Ar), 7.18–7.14 (m, 1H, Ar), 4.05 (quint, 4H, *J* 7.1, OCH_2CH_3), 3.55 (dq, 1H, *J* 8.4, 2 Hz, POCOC(*H*)), 3.26–3.19 (m, 1H), 2.84–2.42 (m, 3H), 1.38 (d, 6H, *J* 7.1, OCH_2CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ −5.8. Epoxide **8c** was hydrolyzed with $CF_3C(O)OH$ in Et_2O/H_2O solution at 0 °C[14b] to the title compound **9c** (yellow oil). The enantiomeric excess was determined by HPLC (Chiracel OD-H), (*S*)-(−)-**9c,** entry 4; 5% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 21.6 (*S*), t_R [min] 26.3 (*R*); $[\alpha]_D^{20} = -20$ (*c* 0.8, $CHCl_3$); lit. (*R*)-(+)-**9c**: $[\alpha]_D^{20} = +17.5$ (*c* 0.4, $CHCl_3$), ee = 81%[14b]

4.5.4. (*S*)-(−)-2-Hydroxy-2-methyl 1-indanone 9[3b,14b], (Table 2, entry 5)

Epoxide **8d** was prepared according to the general epoxidation procedure (method A) from phosphoric acid diethyl ester 2-methyl-3*H*-inden-1-yl ester **5d** and dioxirane **3** to provide crude compound **8d**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75–7.71 (m, 1H, Ph), 7.27–7.22 (m, 2H, Ph), 7.19–7.13 (m, 1H, Ph), 4.21 (d sextet, 4H, *J* 7.1, 1.2 Hz, OCH_2CH_3), 2.94 (AB, 2H, *J* 18.1 Hz, POCOC(CH_3)CH_2), 1.76 (s, 3H, CH_3), 1.34 (t, 6H, *J* = 7.1 Hz, OCH_2CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ −4.5. Epoxide **8d** was hydrolyzed with $CF_3C(O)OH$ in Et_2O/H_2O solution at 0 °C[14b] to the title compound **9d** (white solid, mp 46 °C). The enantiomeric excess was determined by HPLC (Chiracel OD-H), (*S*)-(−)-**9d,** entry 5; 1.6% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 29.1.(*S*), t_R [min] 32.9 (*R*); $[\alpha]_D^{20} = -3.7$ (*c* 0.4, $CHCl_3$); lit. (*S*)-(−)-**9d**: $[\alpha]_D^{20} = -22.7$ (*c* 1.62, $CHCl_3$), ee = 85%.[3b]

4.5.5. (*R*)-(+)-2-Hydroxy-1-phenyl-1-propan-1-one 6a[14b,26] (Table 2, entry 6)

Epoxide **7a** was prepared according to the general epoxidation procedure (method A) from phosphoric acid diethyl ester 1-phenyl-propenyl ester **4a** and dioxirane **3** to provide crude compound

7a ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.42 (m, 2H, Ph), 7.38–7.30 (m, 3H, Ph), 4.05, 4.06 (d sextet, 4H, *J* 7.2, 1.2 Hz,, OCH_2CH_3), 3.01 (dq, 1H, *J* 5.3,1.8 Hz, POCOC(*H*), 1.66 (d, 3H, *J* 5.3 Hz, CH_3), 1.24, 1.14 (2t, 6H, *J* 7.2 Hz, OCH_2CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ −3.9. Epoxide **7a** was hydrolyzed with $CF_3C(O)OH$ in Et_2O/H_2O solution at 0 °C[14b] to the title compound **6a**. The enantiomeric excess was determined by HPLC (Chiracel OD-H), (*R*)-(+)-**6a,** entry 6: 5% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 18.8 (*S*), t_R [min] 21.1 (*R*); $[\alpha]_D^{20} = +73.3$ (*c* 0.4, $CHCl_3$).

4.5.6. (*S*)-(−)-2-Hydroxy-1-phenyl-1-propan-1-one 6a[14b,26] (Table 2, entry 7)

Epoxide **7b** was prepared according to the general epoxidation procedure (method A) from phosphoric acid diphenyl ester 1-phenyl-propenyl ester **4b** and dioxirane **3** to provide crude compound **7b**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54–7.06 (m, 15H, Ph, OPh), 3.09 (dq, 1H, *J* 5.3,1.8 Hz, POCOC(*H*), 1.62 (d, 3H, *J* 5.3 Hz, CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ −15.1. Epoxide **7b** was hydrolyzed with $CF_3C(O)OH$ in Et_2O/H_2O solution at 0 °C[14b] to the title compound **6a**. The enantiomeric excess was determined by HPLC (Chiracel OD-H), (*S*)-(−)-**6a,** entry 7: 4% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 17.3 (*S*), t_R [min] 19.3 (*R*); $[\alpha]_D^{20} = -55.2$. (*c* 1, $CHCl_3$).

4.5.7. (*R*)-(+)-2-Hydroxy-1-phenyl-1-pentan-1-one 6f[29,30] (Table 2, entry 8)

Epoxide **7f** was prepared according to the general epoxidation procedure (method A) from phosphoric acid diisopropyl ester 1-phenyl-pent-1-enyl ester **4f** and dioxirane **3** to provide crude compound **7f**, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.45 (m, 3H, Ph), 7.36–7.28 (m, 2H, Ph), 4.62 (m, 2H, $OCH(CH_3)_2$), 2.85 (br t, 1H, *J* 6.0 Hz, (POCOC(*H*)), 1.82–1.74 (m, 2H, CH_2), 1.53–1.46 (m, 2H, CH_2), 1.26 (br t, 6H, *J* 6.0 Hz, $OCH(CH_3)_2$Hz), 0.93 (t, 3H, *J* 7.0 Hz, CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ −6.2. Epoxide **7f** was hydrolyzed with $CF_3C(O)OH$ in Et_2O/H_2O solution at 0 °C[14b] to the title compound **6f** (colorless liquid). The enantiomeric excess of **6f** was determined by HPLC (Chiracel OD-H), 3% *i*-PrOH in hexane, 0.3 mL/min; t_R [min] 19.0 (*S*), t_R [min] 25.5 (*R*); $[\alpha]_D^{20} = +11.0$. (*c* 0.2, $CHCl_3$); lit.[14b] (*R*)-(+)-**6f**: $[\alpha]_D^{20} = +17.3$ (*c* 1.3, $CHCl_3$), ee = 68% from **4h**; lit.[31] (*R*)-acetate derivative of **6f** $[\alpha]_D^{20} = -2.3$ (*c* 0.5, acetone).

4.5.8. (*S*)-(−)-2-Hydroxy-1-phenyl-1-pentan-1-one 6f[29,30] (Table 2, entry 9)

Epoxide **7g** was prepared according to the general epoxidation procedure (method A) from phosphoric acid bis-(4-chloro-phenyl) ester 1-phenyl-pent-1-enyl ester **4g** and dioxirane **3** to provide crude compound **7g** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.31 (m, 5H, Ph), 7.22–7.19 (m, 4H, 4-ClC_6H_4), 6.95 (d, 4H, *J* 8.6 Hz, 4-ClC_6H_4), 3.30 (br s, 1H, (POCOC(*H*)), 2.08 (dq, 2H, *J* 7.6, 2.5 Hz, CH_2), 1.43 (dd, 2H, *J* 7.1, 2.5 Hz, CH_2), 0.77 (t, 3H *J* 7.1 Hz, CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ −15.9. Epoxide **7g** was hydrolyzed with $CF_3C(O)OH$ in Et_2O/H_2O solution at 0 °C[14b] to the title compound **6f**. The enantiomeric excess of **6f** was determined by HPLC (Chiracel OD-H), 3% *i*-PrOH in hexane, 0.3 mL/min; t_R [min] 19.7 (*S*), t_R [min] 27.3 (*R*); $[\alpha]_D^{20} = -10.2$. (*c* 0.14, $CHCl_3$); lit.[14b] (*S*)-(−)-**6f**: $[\alpha]_D^{20} = -19.9$ (*c* 2.4, $CHCl_3$), ee = 88% from **4f**; lit.[30] (*S*)-acetate derivative of **6f** $[\alpha]_D^{20} = +1.9$ (*c* 0.8, acetone).

4.5.9. (*S*)-(−)-2-Hydroxy-1-phenyl-1-pentan-1-one 6f[29,30] (Table 2, entry 10)

Epoxide **7h** was prepared according to the general epoxidation procedure (method A) from phosphoric acid bis-(4-methoxy-phenyl) ester 1-phenyl-pent-1-enyl ester **4h** and dioxirane **3** to provide crude compound **7h**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.37 (m, 2H, Ph), 7.30–7.28 (m, 3H, Ph), 7.07–6.92 (m, 4H, 4-$MeOC_6H_4$), 6.87–6.73 (m, 4H, 4-$MeOC_6H_4$), 3.6 (s, 6H, MeO), 2.94 (dt, 1H, *J* 6.0, 1.9 Hz, (POCOC(*H*)), 1.80 (q, 2H, *J* 7.1 Hz, CH_2), 1.52 (br t, 2H, *J* 7.1 Hz, CH_2), 0.92 (t, 3H *J* 7.0 Hz, CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ −14.8. Epoxide **7h** was hydrolyzed with $CF_3C(O)OH$ in Et_2O/H_2O solution at 0 °C[14b] to the title compound **6f**. The enantiomeric excess of **6f** was determined by HPLC (Chiracel OD-H), 3% *i*-PrOH in hexane, 0.3 mL/min; t_R [min] 19.3 (*S*), t_R [min] 25.8 (*R*); $[\alpha]_D^{20} = -14.1$ (*c* 0.34, $CHCl_3$); lit.[14b] (*R*)-(+)-**6f**: $[\alpha]_D^{20} = +17.3$ (*c* 1.3, $CHCl_3$), ee = 68% from **4h**.

4.6. General epoxidation procedure Method B (under catalytic conditions). Preparation of (R)-(+)-3-hydroxy-2,3-dihydro-4*H*-chromen-4-one 9b from 5b

The mixture of buffer (0.05 M $Na_2B_4O_7$ 10 H_2O in 4×10^{-4} M aqueous Na_2(EDTA), 10 mL), enol phosphate **5b** (284 mg, 1 mmol), $Bu_4N^+OH^-$ (cat.), and ketone **2** in acetonitrile (15 mL) was cooled to 0 °C with stirring. Next, a solution of Oxone (0.85 g, 1.38 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 8 mL) and a solution of K_2CO_3 (0.8 g, 5.8 mmol) in water (7 mL) were placed in two separate funnels. These solutions were added dropwise for 1.5 h to the reaction mixture (pH ~10) after which the reaction was quenched by the addition of hexane and water. The mixture was extracted with hexane (2×10 mL) and then with diethyl ether (2×20 mL), washed with brine, and dried over Na_2SO_4. After evaporation of the solvents, the crude mixture was analyzed by ^{1}H and ^{31}P NMR. Separation of the mixture by flash chromatography (Hexane/EtOAc 9/1) gave α-hydroxy chromanone **9b** as a white solid (65 mg, 40% yield). $[\alpha]_D^{20} = +30$ (*c* 0.2, $CHCl_3$), R_f (50% EtOAC/hexane) 0.7; mp 58–60 °C; Enantiomeric excess was determined by HPLC, Chiracel OD-H: (*R*)-(+)-**9b**, ee 83%, HPLC conditions: (Table 2, entry 3) 0.7% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 33.9(*R*), t_R [min] 40.1 (*S*).

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