# 7
# Asymmetric Carbonyl Olefination

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## 7.1
## Introduction and Historical Aspects

Ylides, which are among the most structurally interesting of reactive species, were first recognized as synthetically versatile reagents with the birth of the Wittig reaction in 1953 [1]. Since then, the chemistry of ylides and related carbanions with respect to carbonyl electrophiles has grown rapidly and they have now become powerful and versatile synthetic tools in organic chemistry [2]. Thus, the stereo-, regio-, and chemoselectivities can be controlled to a great extent, and Wittig-type reactions have become one of the most valuable organic transformations for the creation of a carbon–carbon bond, introducing a new $sp^2$ carbon at the carbonyl group [3]. In addition to the phosphonium ylides of Wittig reactions, chemistry based on other types of ylides [2], such as sulfonium, heteroatom, ammonium, nitrile, and pyridinium species, has also been developed in recent years. Ylides can be regarded as special carbanions, which are stabilized by a neighboring positively charged heteroatom, and which undergo nucleophilic reactions to form a new C–C bond.

In analogy with phosphorus ylides, stabilized carbanions that are adjacent to an oxidized phosphorus atom, as in a phosphate or phosphine oxide, also show characteristic nucleophilicity towards carbonyl groups [4]. The specific Wittig-type reactivity of such species has been investigated alongside the development and refinement of the chemistry of the original Wittig reactions. Nowadays, the Wittig reaction and related processes are recognized as some of the most essential transformation methods permitting carbon–carbon bond formation, and are often used as a crucial step in the total synthesis of complex molecules such as natural products [5].

It is generally accepted that reactions of carbonyl compounds occupy a central position in organic synthesis and hence in asymmetric synthesis. Thus, the development of new methods for stereoselective or stereocontrolled synthesis involving carbonyl groups has been a major subject in organic chemistry, and in particular much attention has been focused on enantioselective transformations. Efficient and practical asymmetric versions of a variety of ordinary synthetic reactions have

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been widely sought by many research groups, with a view to establishing novel asymmetric methodologies.

In spite of the importance of the Wittig and related reactions with regard to C–C bond formation, no new $sp^3$ stereogenic carbon centers are created in these types of transformations, in contrast to ordinary asymmetric reactions involving the formation of a center of chirality. For this reason, progress in the application of Wittig and related reactions to asymmetric synthesis has long been significantly slow, and it is only in the last two decades that practical methods with high efficiency for asymmetric carbonyl olefination have been developed [6]. Applications of such processes to the enantioselective construction of complex or useful molecules have only just begun to emerge.

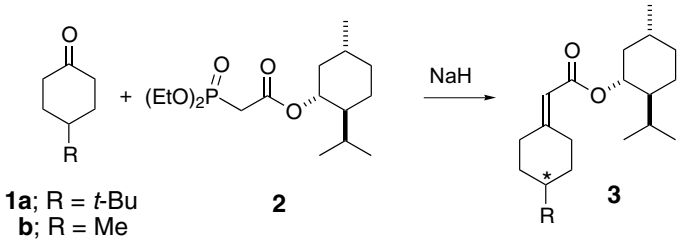
Various types of phosphorus reagents have been employed for asymmetric transformations of carbonyl compounds into alkenes [2, 4, 7–11]. Depending upon the structure of these reagents, different reaction names are given [3]. Phosphonium ylides and phosphine oxide are particularly popular, and are referred to as Wittig and Horner reagents, respectively. On the other hand, phosphonates and other phosphonic acid derivatives are termed Horner–Wadsworth–Emmons (HWE) reagents. In recent years, arsonium derivatives have often been used for similar reactions, and they are also covered herein.

Methods for the formation of carbon–carbon double bonds in an asymmetric manner through non-Wittig-type reactions [12, 13] have also been reported in recent years, including asymmetric induction by reactions with chiral sulfoxides [13], sulfones (Julia olefination) [14], sulfoximides [12a, 15], or selenides [16]; Pd-catalyzed allylic nucleophilic substitutions [17], as well as asymmetric deprotonation [18]. In the context of the topic of asymmetric carbonyl olefination, some of these asymmetric transformations are beyond the scope of this chapter, although a few of the transformations closely related to the Wittig-type reactions will be discussed in a later part of this chapter.

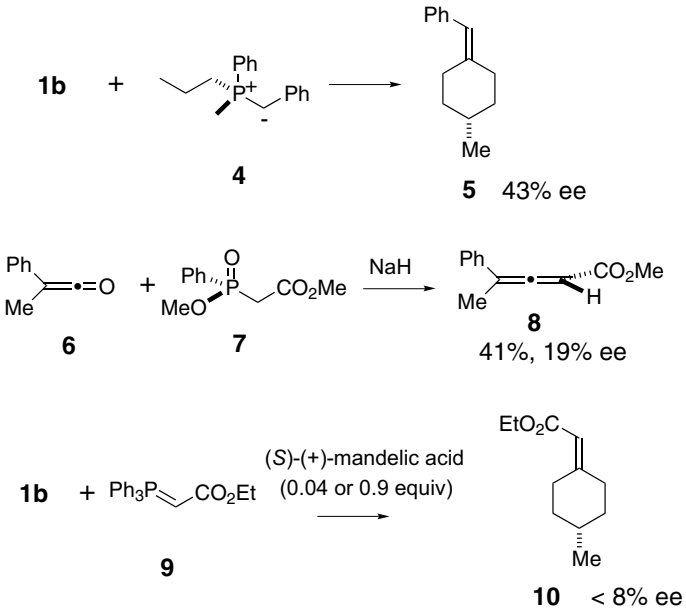
As discussed below, the strategies for asymmetric induction through olefination by Wittig-type reactions can be broadly classified into four groups. According to the type of these approaches to optically active olefinic compounds, asymmetric olefinations based on Wittig and related reactions will be reviewed in this chapter.

The historical aspect must first be mentioned here, prior to the main issue of asymmetric olefination by Wittig-type reactions. The first report concerning asymmetric Wittig-type reaction of a 4-substituted cyclohexanone appeared in 1962 [19], in which an optically active phosphonate **2** bearing *l*-menthol as a chiral auxiliary on the carboalkoxyl moiety was used (Scheme 7.1). Although the authors reported that dissymmetric olefinic products **3** were obtained in high yields in optically active form, no precise degree of asymmetric induction (diastereomeric excess) was given, and an error in the optical purities of the products was subsequently pointed out by researchers of another group [6].

A few years after this first report, a chiral non-racemic phosphonium ylide **4** having a stereogenic phosphorus center was prepared and used for asymmetric olefination (Scheme 7.2). Here, it was reported that monocarbonyl substrates **1** were converted into the olefinic products in enantiomerically enriched form, al-




**Scheme 7.1.** The first report of asymmetric carbonyl olefination.




**Scheme 7.2.** Additional early examples of asymmetric carbonyl olefination.

though again the *ee* values of the olefins were not determined, except in the case of the 4-methylcyclohexyl derivative **5** (43% *ee*) [20].

The generation of dissymmetric non-racemic 1,2-dienes, i.e. allenic compounds, from the corresponding ketene **6**, was investigated in 1975 using optically active phosphinate-type esters such as **7** incorporating a stereogenic phosphorus center [21]. Although neither the chemical nor the optical yields of allenic products such as **8** were wholly satisfactory (41–80% yield and up to 23% *ee*), this is the only example of the use of a phosphinate ester in asymmetric olefination.

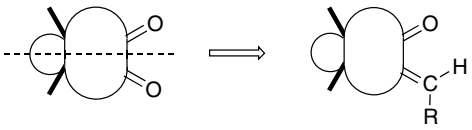
The first attempt to use a chiral catalyst in an asymmetric Wittig-type reaction was reported in 1970 [22]. A combination of the stabilized ylide **9** and a chiral organic acid as an external catalyst was evaluated in the olefination of 4-substituted cyclohexanone derivatives **1**. In this study, (*S*)-(+)-mandelic acid was found to be

most effective in the generation of non-racemic cycloalkylidene derivatives such as **10**, although the observed degree of asymmetric induction was quite low (up to 4% *ee* with 0.04 molar equivalents of catalyst) and the enhancement of the *ee* value was small even when 0.9 molar equivalents of chiral acid was used.

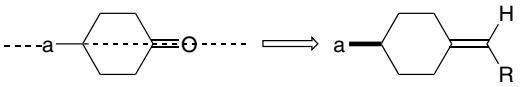
## 7.2 Strategies for Asymmetric Carbonyl Olefination

Asymmetric carbonyl olefination may be accomplished by means of any of the four general approaches outlined below, all of which are highly dependent on the structure of the carbonyl compound [7, 8, 10] (Scheme 7.3). Besides the four major approaches described here, other routes from achiral carbonyl compounds to non-racemic alkenes are available, and these topics will be mentioned separately towards the end of this chapter.

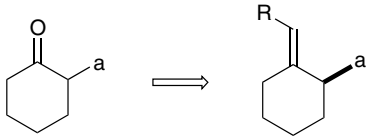
1) differentiation of enantiotopic carbonyls




2) dissymmetrization of prochiral carbonyl compounds




3) kinetic resolution of racemic carbonyl compounds




4) miscellaneous approaches

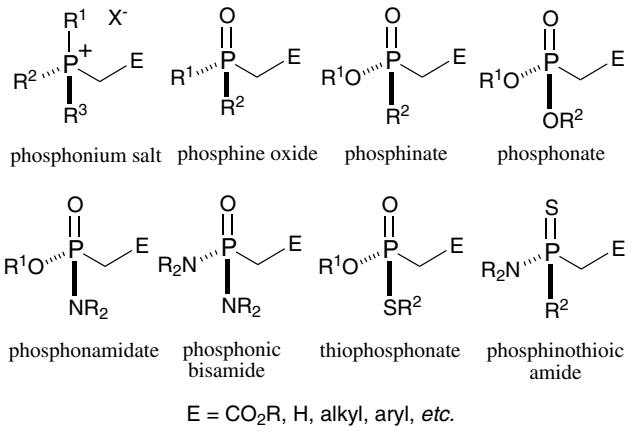
**Scheme 7.3.** Four general approaches for asymmetric carbonyl olefination.

The first approach is based on differentiation of enantiotopic carbonyl groups in symmetrical molecules such as *meso* compounds, and is therefore referred to as the desymmetrization of symmetric organic molecules. Discrimination of the $\pi$-faces of symmetrically substituted carbonyl groups constitutes the second type of approach leading to dissymmetric compounds having axial chirality, and is referred to as dissymmetrization. The third type of asymmetric carbonyl olefination

is based on the kinetic resolution of racemic carbonyl compounds, and includes dynamic resolution and parallel kinetic resolution. The final category of approaches consists of miscellaneous alternative reactions, such as the stepwise construction of optically active olefinic compounds from achiral ketonic compounds, involving asymmetric dehydration or other elimination reactions. Recently, asymmetric induction caused by non-covalent bonding interactions with external chiral ligands has attracted much attention, and all such examples of asymmetric carbonyl olefination belong to one of the four approaches as classified above. The discussion in this chapter is ordered according to the class of strategy used for the transformation to optically active olefin compounds.

## 7.3 Optically Active Phosphorus or Arsenic Reagents Used in Asymmetric Carbonyl Olefination

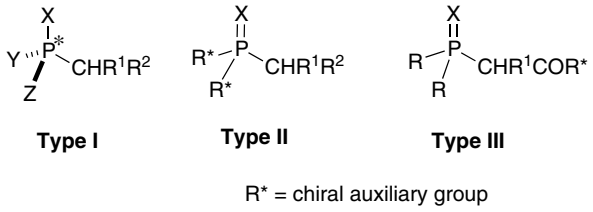
A variety of achiral phosphorus reagents has appeared as a result of extensive research work on the Wittig and related reactions by many groups, and the phosphorus Wittig-type reagents [7, 8, 10] employed in these transformations can be classified into eight groups depending upon the kind of substituents attached to the phosphorus atom and/or its oxidation state, as shown in Scheme 7.4.




**Scheme 7.4.** Wittig-type reagents used in carbonyl olefination.

Recently, chiral non-racemic organophosphorus compounds have received much attention. The major factor stimulating the extensive investigation of these compounds originates from their great practical value as ligands in catalysts for asymmetric synthesis and as efficient synthetic reagents as well as tools for the elucidation of biochemical mechanisms [9, 11, 23]. With the progress in comprehensive investigations of asymmetric carbonyl transformations, a considerable number of

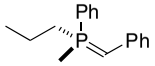
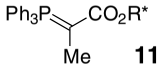
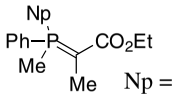
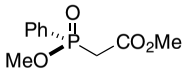
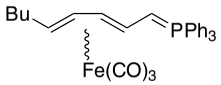
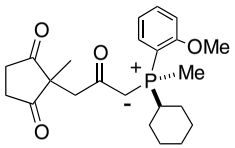
optically active chiral phosphorus reagents have emerged. The representative reagents are listed in Table 7.1, with an indication of the source of their chirality. The chiral phosphorus reagents are also divided into three main groups depending upon the location of the stereogenic chiral centers (Scheme 7.5). In type **I**, the tetrahedral phosphine atom is a stereogenic center; in type **II** it is the substituents connected to the phosphorus atom that are optically active, while in type **III** reagents the chirality exists at sites other than the phosphorus atom or its substituents, and the most widely used HWE reagents bearing an auxiliary group at the carboalkoxy moiety belong to this latter class. Although in the design of chiral phosphorus reagents, type **I** would seem to be most promising due to the proximity of the chiral center to the reaction site, the troublesome preparative work required to obtain this class of phosphorus compounds, as well as the difficulty in determining the absolute stereochemistry of the synthesized chiral phosphorus reagent, are reasons why this class of reagents has not been so widely utilized in asymmetric carbonyl olefinations. The olefination process consists of three successive steps, namely addition, ring closure to the four-membered ring, and elimination, and therefore the direct production of optically active olefinic products is possible with the chiral reagents of types **I** and **II**, through elimination of the phosphorus portion, whereas diastereomers are formed with the type **III** reagents.

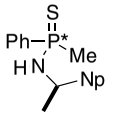
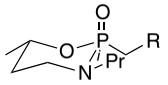
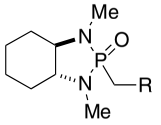
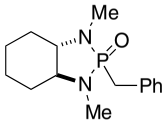
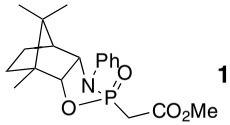
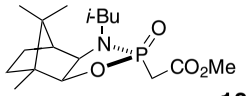



**Scheme 7.5.** Three types of chiral phosphorus reagents employed in asymmetric carbonyl olefination.

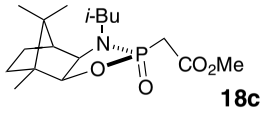
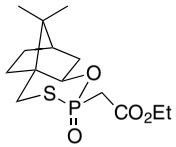
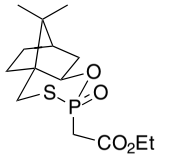
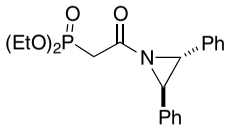
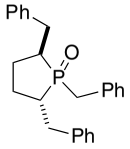
The success and applicability of these reagents is largely dependent on their potential for asymmetric induction, easy prediction of the product stereochemistry, as well as their availability and accessibility. Since the anion of a HWE reagent can be regarded as a simple carbanion stabilized by two electron-withdrawing groups, and has the advantages of higher reactivity as well as easy separation of the reacted reagent from the reaction mixture, the chiral reagents that have been most widely used to date have been HWE-type reagents [24, 25]. Chiral HWE reagents containing optically active 8-phenylmenthol or binaphthol (BINOL) as auxiliary groups are especially popular. The effective function of these two moieties in HWE reagents as chiral auxiliaries for asymmetric induction in carbonyl transformations has been documented. Thus, in spite of the lower accessibility of both enantiomers, optically active 8-phenylmenthols can efficiently control the enantio(diastereo)-selectivity of products as well. For example, an ester bearing a (−)-8-phenylmenthyl auxiliary confers a high diastereofacial bias upon the derivatized anion, which

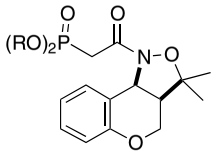
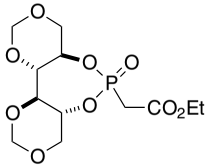
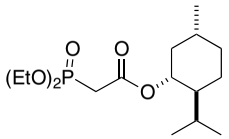
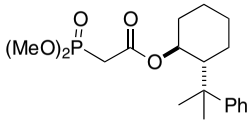
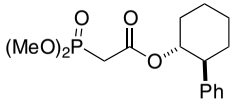
**Tab. 7.1.** Classification of chiral phosphorus or arsenic reagents used in asymmetric olefination.

| *Type of Reagents* | *Structure* | *Source of Chirality* | *Refs.* |
|---|---|---|---|
| **I**, phosphonium ylide |  **4** | (+)-(*S*)-benzyl(methyl)-phenyl-(propyl)phosphonium bromide | 20 |
| **III**, phosphonium ylide |  **11a** ; R* = (-)-menthyl<br>**b** ; R* = (-)-*sec*.octyl | (−)-menthol or (−)-*sec*.octanol | 70 |
| **I**, phosphonium ylide |  **12**<br>Np = 1-naphthyl | racemic | 70 |
| **I**, phosphinate |  **7** | methylphenylphosphinylacetic acid | 21 |
| **III**, phosphonium ylide |  **13** | racemic | 85 |
| **I**, phosphonium ylide |  **14** | (+)-(*R*)-cyclohexyl-*O*-anisyl-methylphosphine (CAMP) | 42 |

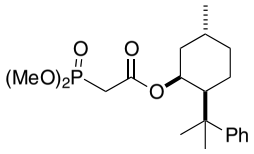
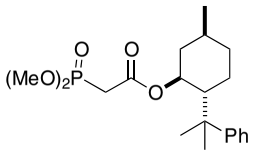
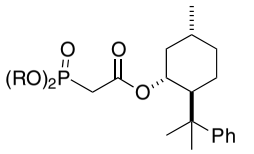
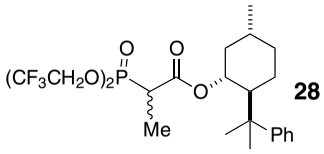
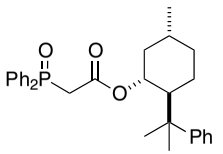
| | | | | |
|---|---|---|---|---|
| **I**, phosphinothioic amide |  | **15** Np = 1-naphthyl | (*S*)-*N*,*S*-dimethyl-*S*-phenyl-sulfoximine | 78 |
| **I**, phosphonamidate |  | **16a** ; R = Ph<br>**b** ; R = SPh | (*S*)-3-hydroxybutyrate | 54, 55 |
| **II**, phosphonic bisamide |  | **17a** ; R = Me<br>**b** ; R = Ph<br>**c** ; R = vinyl | (*R*,*R*)-1,2-diaminocyclohexane | 6, 49, 50, 52a, 66 |
| **II**, phosphonic bisamide |  | **17d** | (*S*,*S*)-1,2-diaminocyclohexane | 6, 49, 50, 66 |
| **I**, **II**, phosphonamidate |  | **18a** | camphorquinone | 55 |
| **I**, **II**, phosphonamidate |  | **18b** | camphorquinone | 55 |

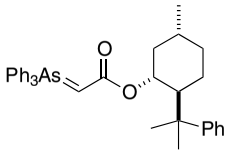
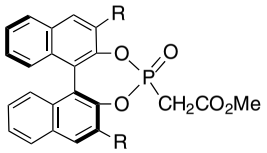
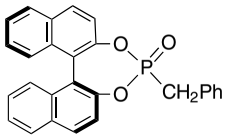
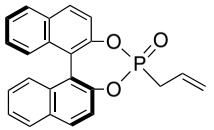
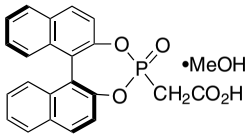
Tab. 7.1 *(continued)*

| *Type of Reagents* | *Structure* | *Source of Chirality* | *Refs.* |
|---|---|---|---|
| **I**, **II**, phosphonamidate |  **18c** | camphorquinone | 55 |
| **I**, **II**, thiophosphonate |  **19a** | (−)-10-mercaptoisoborneol | 56 |
| **I**, **II**, thiophosphonate |  **19b** | (−)-10-mercaptoisoborneol | 56 |
| **III**, phosphonate |  **20** | (*R*,*R*)-1,2-diphenylaziridine | 88 |
| **II**, phosphine oxide |  **21** | racemic | 111 |

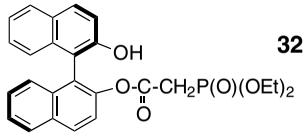
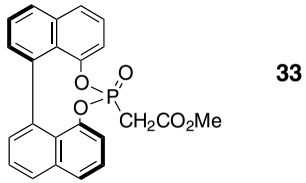
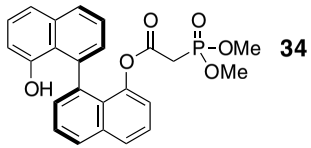
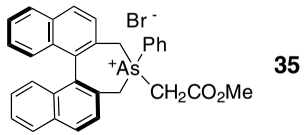
| | | | | |
|---|---|---|---|---|
| **III**, phosphonate |  | **22a** ; R = Me<br>**b** ; R = Et<br>**c** ; R = *i*-Pr<br>**d** ; R = Ph | (−)-benzopyrano[4,3-*c*]-isoxazolidine | 57 |
| **II**, phosphonate |  | **23** | D-(+)-mannitol | 92 |
| **III**, phosphonate |  | **2** | (−)-menthol | 19 |
| **III**, phosphonate |  | **24** | (+)-8-phenylnormenthol | 67 |
| **III**, phosphonate |  | **25** | (−)-*trans*-2-phenyl-1-cyclohexanol | 60 |

**Tab. 7.1** *(continued)*

| *Type of Reagents* | *Structure* | *Source of Chirality* | *Refs.* |
|---|---|---|---|
| **III**, phosphonate |  **26** | (+)-8-phenylneomenthol | 60 |
| **III**, phosphonate |  **27a** | (+)-8-phenylmenthol | 58, 59, 60 |
| **III**, phosphonate |  **27b** ; R = Me<br>**c** ; R = Et<br>**d** ; R = $^{i}$Pr<br>**e** ; R = $CF_3CH_2$<br>**f** ; R = *o*-Tolyl | (−)-8-phenylmenthol | 32, 39, 40, 45, 60, 61, 79, 80, 81, 88, 93, 96, 97, 98 |
| **III**, phosphonate |  **28** | (−)-8-phenylmenthol | 79b, 88, 93 |
| **III**, phosphine oxide |  **29** | (−)-8-phenylmenthol | 61 |

| | | | | |
|---|---|---|---|---|
| **III**, arsenium |  | **30** | (−)-8-phenylmenthol | 63, 84 |
| **II**, phosphonate |  | **31a** : R = H<br>**b** : R = Me<br>**c** : R = $SiMe_3$<br>**d** : R = Ph | (*S*)-2,2′-BINOL | 31, 33, 37, 46, 47, 68, 69, 74, 76 |
| **II**, phosphonate |  | **31e** | (*S*)-2,2′-BINOL | 8 |
| **II**, phosphonate |  | **31f** | (*S*)-2,2′-BINOL | 52b |
| **II**, phosphonate |  | **31g** | (*S*)-2,2′-BINOL | 31 |

Tab. 7.1 *(continued)*

| *Type of Reagents* | *Structure* | *Source of Chirality* | *Refs.* |
|---|---|---|---|
| **III**, phosphonate |  **32** | (*R*)-2,2′-BINOL | 8 |
| **II**, phosphonate |  **33** | (*S*)-8,8′-BINOL | 99 |
| **III**, phosphonate |  **34** | (*S*)-8,8′-BINOL | 99 |
| **II**, arsenium |  **35** | (*S*)-2,2′-BINOL | 64 |

consistently displays highly diastereoselective alkylation to give enantiomerically enriched alkylated products after the subsequent removal of the chiral auxiliary [26]. The presence of a phenyl group in the auxiliary may play an essential role in differentiating the $\pi$-faces (*si*- or *re*-face) of the anionic species of the reagent in the transition state, presumably operating through $\pi$-$\pi$ interaction with the $\pi$-systems of the enolate so as to effectively shield one of the faces from electrophilic approach of the carbonyl groups in an extended chair conformer, making it possible not only to induce a high level of diastereo- or enantioselectivity, but also to predict the stereochemistry of olefinic products (see, for example, Scheme 7.10).

On the other hand, BINOL and related derivatives [27], such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), based on a $C_2$-symmetrical biaryl system with axial chirality, have been successfully used for a variety of asymmetric transformations, including catalytic processes. The conformation of one chiral, cyclic HWE reagent, **31g**, in the solid state has been elucidated by X-ray crystallographic analysis [4, 28], which revealed the efficient chiral environment created by the two naphthalene rings [8]. In addition to the aforementioned $C_2$-symmetric chiral phosphonates of BINOL derivatives and the HWE-type reagent bearing an 8-phenylmenthol auxiliary, the corresponding arsine analogues have also recently been developed.

It was observed that a small structural change in the phosphorus reagent can lead to the opposite sense of preferential absolute stereochemistry in the products, and this will be discussed later in more detail.

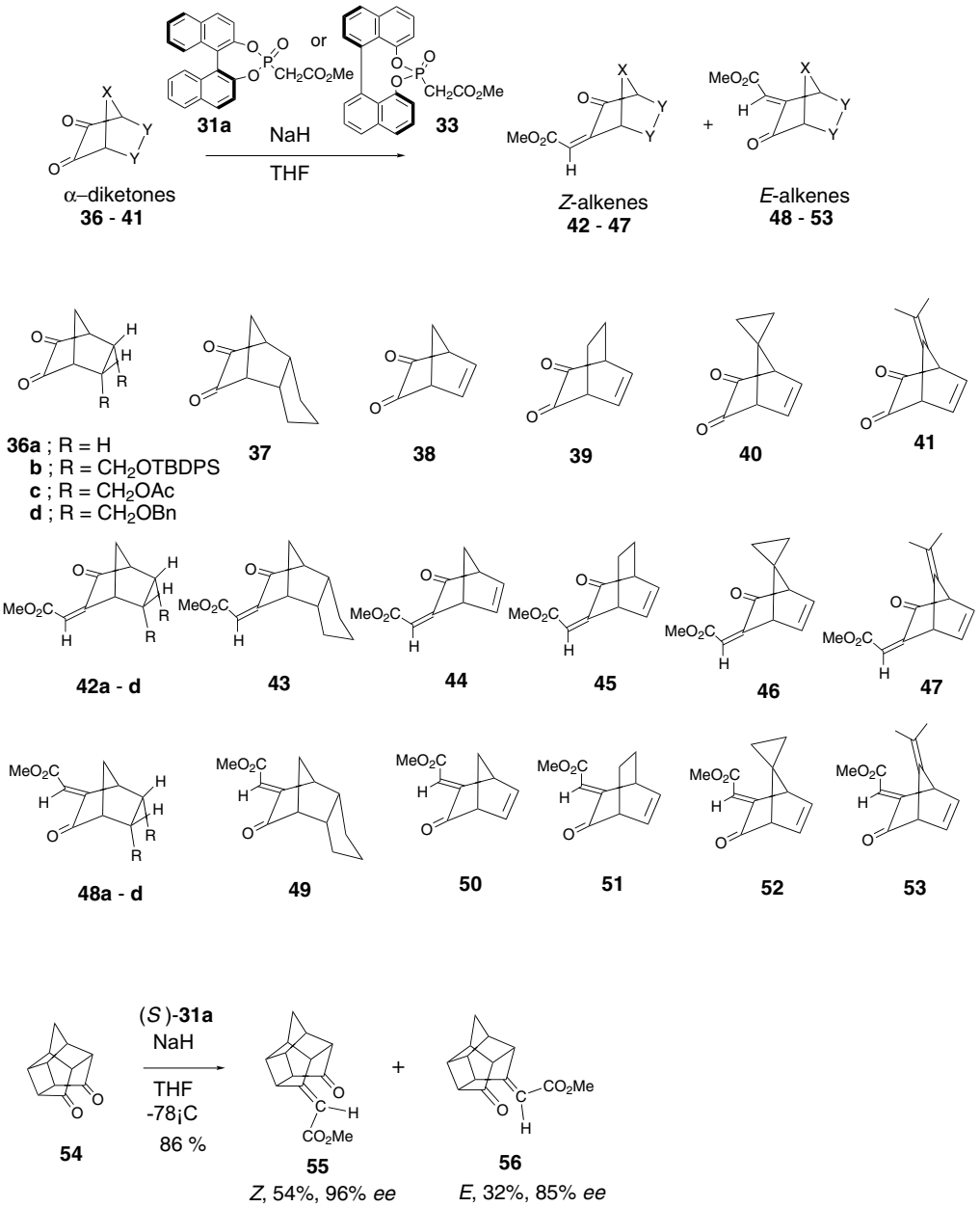
## 7.4
## Discrimination of Enantiotopic or Diastereotopic Carbonyl Groups

### 7.4.1
### Intermolecular Desymmetrization of Symmetrical Dicarbonyl Compounds

Though an approach of desymmetrization of symmetrical molecules to form optically active compounds had previously been exclusively studied in connection with the functions of biocatalysts [29], transformations by purely chemical methods rather than with the aid of enzymes or yeasts have in recent years received much attention as simple and efficient routes to synthetically useful non-racemic compounds [30]. Theoretically, differentiation between two enantiotopic or diastereotopic carbonyl groups, such as in *meso* compounds, can provide a single optically active enone in quantitative yield, if the stoichiometry is well controlled. Furthermore, this approach has the advantage that even if the minor monoalkene isomer is formed, which undergoes bis-alkylation to yield a diene much faster than the major monoalkene through kinetic resolution, the desired major monoalkene can be obtained with increased isomeric purity as a result [30]. Consequently, discrimination of enantiotopic carbonyl groups has been established as a promising and practical methodology for the preparation of functionalized molecules, specifically enones, without the need for a stoichiometric amount of a chiral reagent.

The concept of desymmetrization through intermolecular HWE reactions using chiral phosphonate reagents was independently demonstrated by two research

groups in 1993 [31, 32]. Several bicyclic α-dicarbonyl compounds **36–41** were subjected to asymmetric olefination with anions of the HWE reagents (*S*)-**31a** or (*S*)-**33** to afford the corresponding *E*- and *Z*-olefinic products in good chemical yields and with excellent enantiomeric excesses [31, 33] (Scheme 7.6 and Table 7.2). The



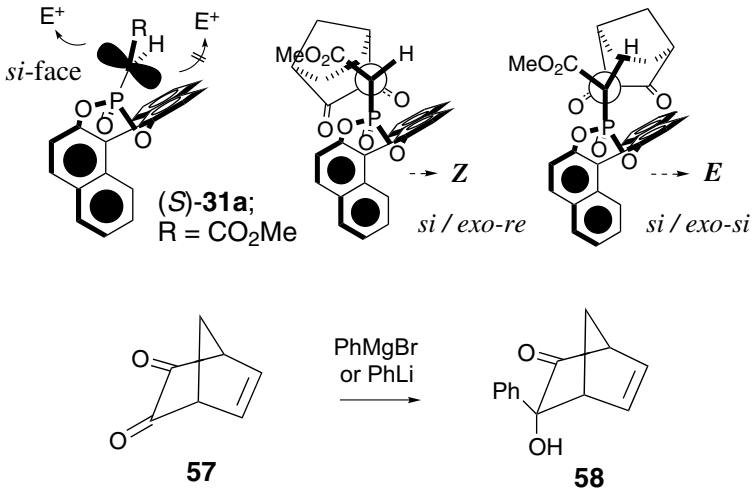

**Scheme 7.6.** Discrimination of enantiotopic carbonyls of α or γ-diketones.

**Tab. 7.2.** Asymmetric HWE reactions of **36**–**41** with **31a** or **33.**

| *Reagent* | *α-Diketones* | *Yield (%)* | *E/Z ratio* | *Products (% ee)* | |
|---|---|---|---|---|---|
| **31** | **36b** | 97 | 2/95 | **48b** (30) | **42b** (98) |
| **33** | **36b** | 59 | 1/97 | **48b** (–) | **42b** (85) |
| **31** | **36c** | 81 | 23/58 | **48c** (23) | **42c** (90) |
| **31** | **36d** | 86 | 22/64 | **48d** (7) | **42d** (73) |
| **31** | **37** | 72 | 15/57 | **49** (−1) | **43** (93) |
| **31** | **36a** | 50 | 37/13 | **48a** (84) | **42a** (88) |
| **31** | **38** | 83 | 58/25 | **50** (79) | **44** (97) |
| **31** | **40** | 97 | 62/35 | **52** (45) | **46** (97) |
| **31** | **41** | 83 | 53/30 | **53** (28) | **47** (>99) |
| **31** | **39** | 98 | 60/38 | **51** (75) | **45** (89) |

enantiotopic polycyclic γ-diketone **54** was also effectively differentiated by the chiral reagent with a base. In these reactions, a different carbonyl group is selected for the production of the respective *Z*- and *E*-isomers, so that the sense of chirality of the *Z*-product is opposite to that of the *E*-product. A higher degree of asymmetric induction is invariably observed for the *Z*-olefinic product. Furthermore, it was suggested in this investigation that reduction in optical purity of the olefinic products is caused by *E*/*Z* isomerization under the reaction conditions and/or during the work-up process.

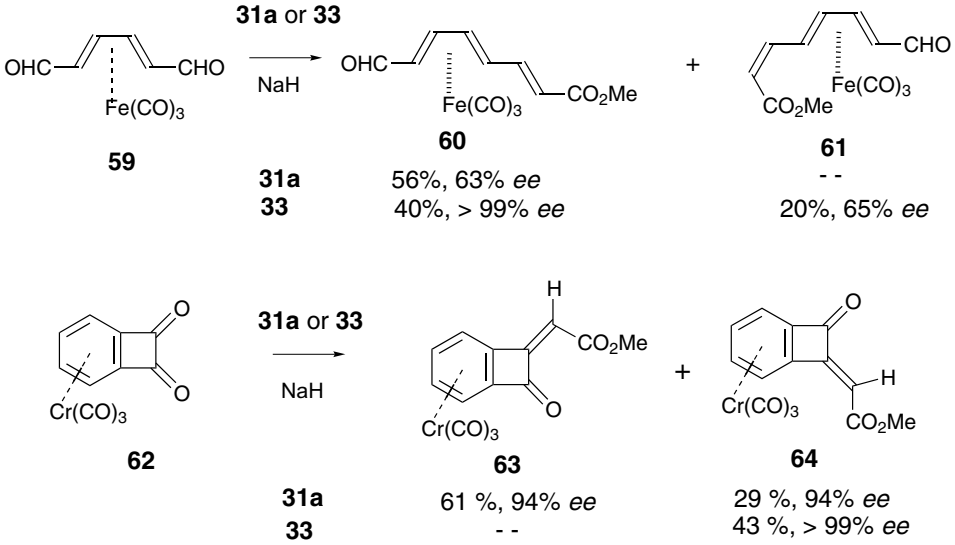
It is likely that the initial addition step in the HWE reaction is rate-determining [34] when the *Z*-isomer is the major product, and energetically favorable approach of an anion of the chiral reagent must be invoked to account for the observed stereochemistry [25, 35]. In the planar anionic species of reagent (*S*)-**31a** chelated by a metallic cation, the *re*-face is sterically hindered due to the hydrogen atom at the 3-position of the naphthyl group, and nucleophilic attack on the carbonyl from the *exo* direction is favored (Scheme 7.7), as has been proven experimentally by sepa-




**Scheme 7.7.** Mechanistic explanation for the observed stereochemistry.

rate reactions, such as the transformation of **57** to **58**, and supported by theoretical calculations [36]. The *exo* face of the two carbonyl groups corresponds to the *re*- and *si*-face, respectively. Thus, only two possible combinations of the anion and the carbonyl substrate can be drawn (*si*/*exo*-*re* and *si*/*exo*-*si*) as reasonable transition states. The former combination does not suffer from the severe electronic repulsive interactions that exist in the latter, resulting in predominant production of the *Z*-isomer. The *E*-isomer obtained from the latter combination should have the opposite sense of absolute stereochemistry to the *Z*-isomer.

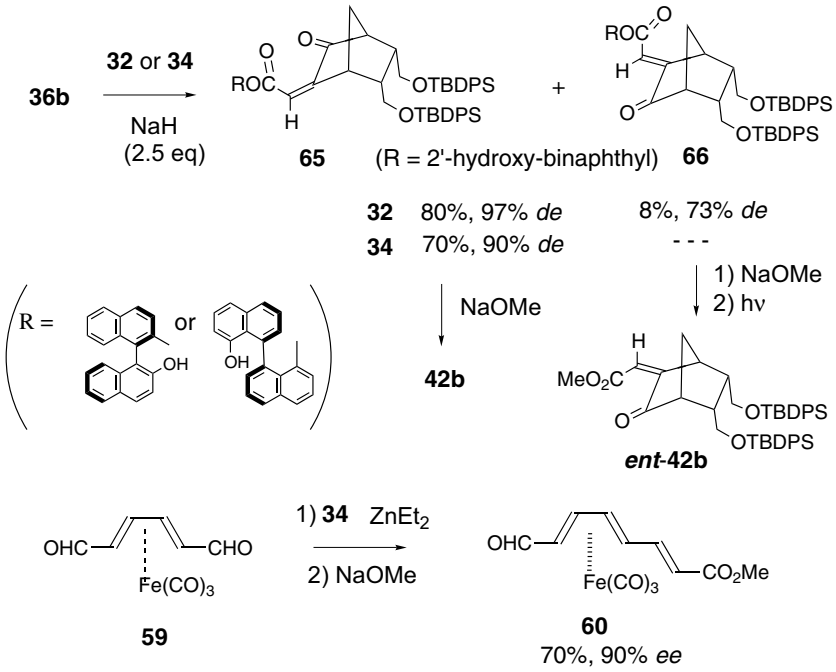
In a similar manner, asymmetric carbonyl olefination of *meso*-dicarbonyl compounds was extended to metallic arene or diene complexes [37], such as $\eta^4$-diene Fe or $\eta^6$-arene Cr complexes, to form planar complexes with high enantiomeric bias (Scheme 7.8). Since both complexation and decomplexation of these optically active compounds occur readily, these olefinic complexes are effective as stereocontrollers due to the presence of bulky metal tricarbonyl groups, and serve as useful reactants for obtaining optically active compounds of central chirality by appropriate chemical transformation.




**Scheme 7.8.** Asymmetric carbonyl olefinations to give planar chiral alkenes.

Like the chiral reagents (*S*)-**31** and (*S*)-**33** having optically active 2,2′- or 8,8′-BINOL as auxiliaries at the phosphorus moiety, the chiral reagents (*S*)-**32** and (*R*)-**34** with the same auxiliaries at the carboalkoxyl portion also showed a similar selectivity towards symmetrical *meso*-dicarbonyl substrates, yielding the corresponding alkenes with high diastereoselectivity [8] (Scheme 7.9).

The enantiotopic aldehyde groups in the dialdehyde **67** were also efficiently discriminated by the chiral phosphonate **27b** to give monoolefination products with

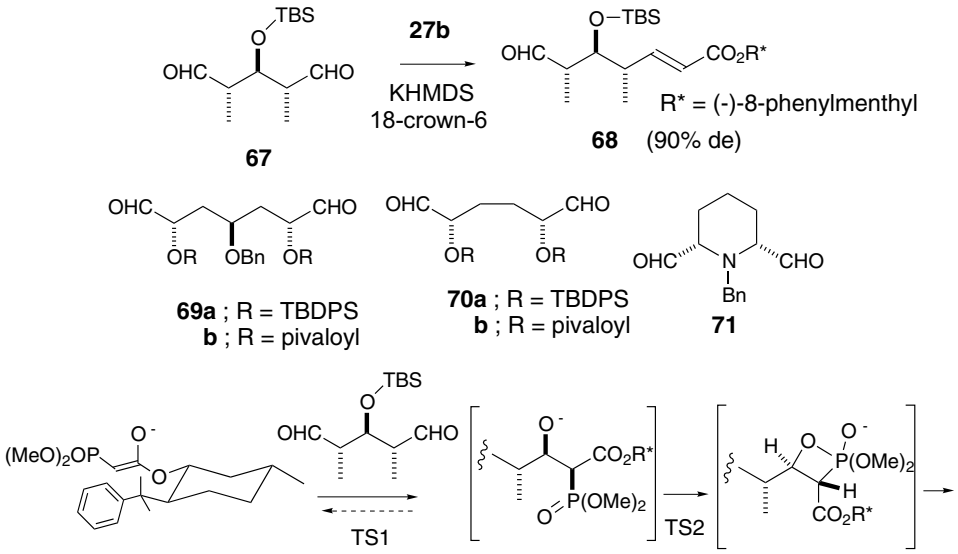



**Scheme 7.9.** Diastereoselective asymmetric carbonyl olefinations.

good diastereoselectivities (64–94% *de*) and high *E*-selectivity [32, 38] (Scheme 7.10). Various dialdehydes **69–71** were subjected to the asymmetric olefination and some of the products corresponded to partial structures of naturally occurring macrolides and could be used as building blocks for their total synthesis. It seemed likely that the reaction proceeded under thermodynamic control to give the (*E*)-alkenes, in spite of the reaction conditions of KHMDS, 18-crown-6, and THF, which tend to maximize kinetic control. Later, rationalization of product selectivity in this asymmetric transformation through the use of a new method for creating a transition state force field, based on quantum chemical normal-mode analysis, was reported [39, 40]. Here, two transition states for the addition step (TS1) and for the subsequent ring closure to an oxaphosphetane (TS2) were considered. According to this molecular mechanics study, the observed high *E*-selectivity was proposed to be caused by a greatly increased influence of TS2 due to a sterically demanding substrate, for example the dialdehyde **69**, blocking the path through the intermediate leading to the *Z*-product.

### 7.4.2
### Intramolecular Discrimination Reactions

The most serious problems associated with the Wittig-type reactions stem from sensitivity to steric hindrance and enolization of the carbonyl substrates under the

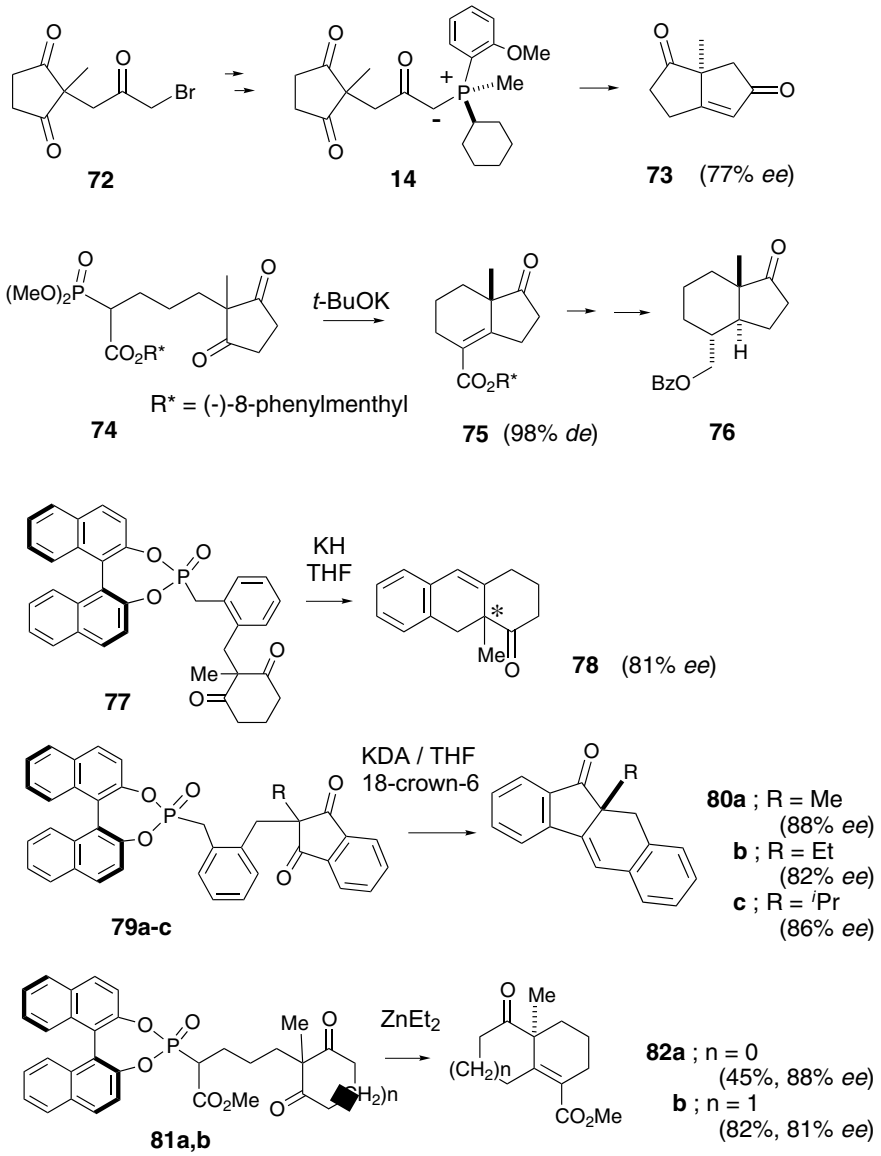



**Scheme 7.10.** Differentiation of enantiotopic dialdehydes.

basic conditions employed. On the other hand, an intramolecular process resulting in the construction of new ring systems can solve the problem of steric hindrance to some extent, because such a process is more entropically favored than an intermolecular one, especially when an energetically preferred 5- or 6-*exo*-trig process occurs. Intramolecular Wittig-type reactions [41] are effective not only for the construction of cyclopentene or cyclohexene derivatives, but also for larger ring systems.

The first example of the use of prochiral polycarbonyl compounds as substrates based on this idea appeared in 1980 [42, 43]. In this study, after examination of several chiral phosphorus ylides derived from triketone **72**, the most effective stereogenic phosphine was found to be *R*-(+)-CAMP (cyclohexyl *o*-anisylmethyl phosphine), which gave the cyclized diketone **73** (bis-nor-Wieland–Miescher ketone) with 77% *ee* (Scheme 7.11). The cyclized optically active ketone **73** was a useful chiral building block for the construction of some interesting polyquinan (polycondensed cyclopentanoid) natural products, such as coriolin [42]. Here, the stereoselectivity in discrimination of the two diastereotopic carbonyl groups was rationalized on the basis of a reversible initial nucleophilic addition step, but later another research group suggested that the initial step is likely to be irreversible even in the case of stabilized ylides [44].

A few additional examples of the use of intramolecular asymmetric HWE reactions to construct fused polycyclic ring systems containing a quaternary carbon have also been reported. The hydrindenone derivative **75** was successfully synthesized from the 1,3-cyclopentadione derivative **74** with high diastereoselectivity (98% *de*) [45]. The product **75**, containing a tetrasubstituted olefinic linkage, was




**Scheme 7.11.** Intramolecular discrimination of carbonyl groups forming new five- or six-membered rings.

converted to compound **76**, which is useful as a new building block for 10,25-dihydroxyvitamin $D_3$. In a similar manner, novel dihydronaphthalene derivatives **78** and **80** [46], perhydroindanones **82a**, and perhydronaphthalenones **82b** [47] having a quaternary stereogenic carbon and/or a tetrasubstituted double bond have

been enantioselectively prepared through differentiation of the diastereotopic carbonyl groups. A possible mechanistic explanation was given in these reports.

## 7.5 Discrimination of Enantiotopic or Diastereotopic Carbonyl $\pi$-Faces

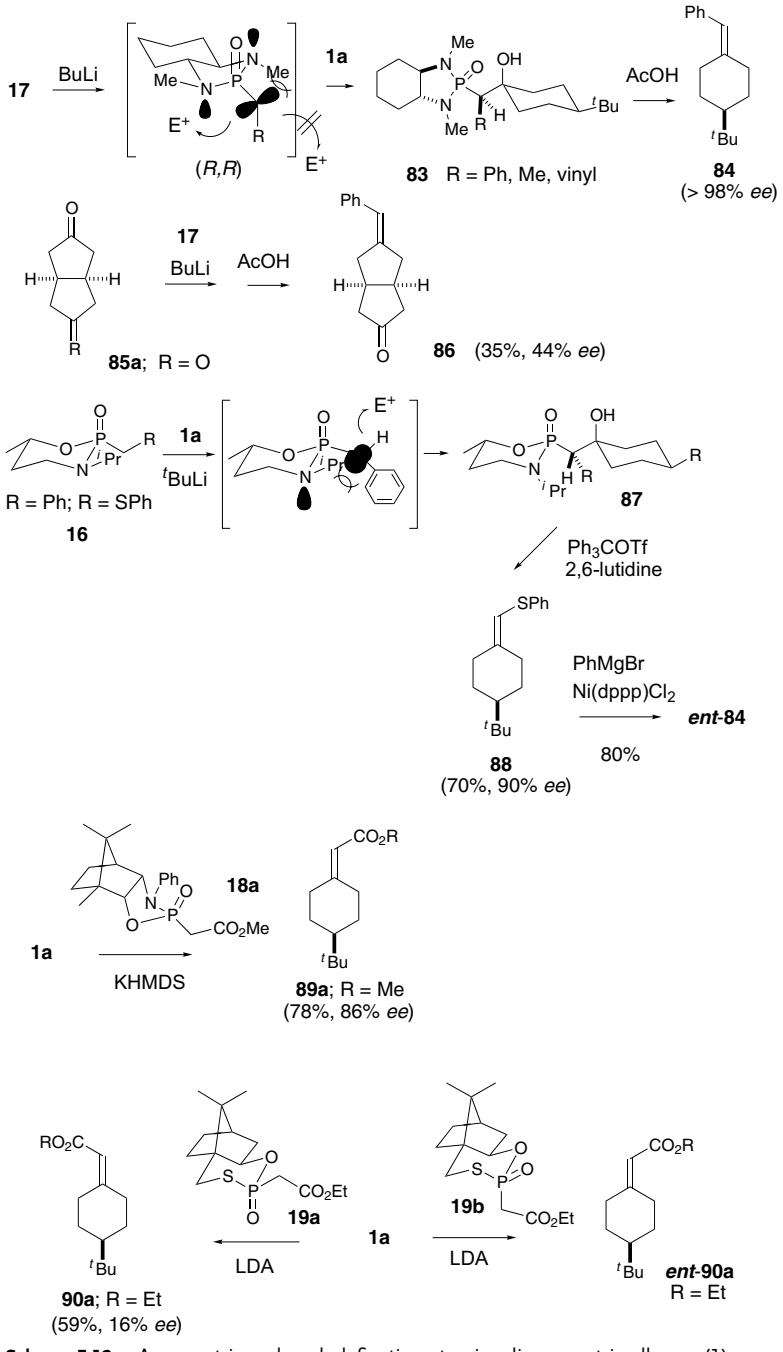
### 7.5.1 Reactions with Prochiral Carbonyl Compounds

Some cycloalkylidene compounds possessing axial chirality but no asymmetric center are known to be optically active, and the first such compound to be identified was 4-methylcyclohexylideneacetic acid, obtained in 1909 through resolution with the alkaloid brucine [48]. Using symmetrically substituted monoketones as substrates, asymmetric carbonyl olefination causes dissymmetrization to give olefinic products with axial chirality. Since only two isomeric products are formed through four diastereomeric intermediates in this process, this transformation has often been used as a benchmark in evaluating newly developed chiral Wittig-type reagents. As already mentioned in the introduction, reactions of this kind became the first examples of asymmetric carbonyl olefinations.

After a couple of investigations of this approach using symmetrical 4-substituted cyclohexanone derivatives as substrates, a brilliant piece of work was reported in 1984 [6], in which a new chiral phosphonic bis(amide) of type **17** was exploited and used for the asymmetric carbonyl olefination of symmetrical ketones **1a** and **85a** (Scheme 7.12). The chiral molecules used here, *trans*-1,2-diaminocyclohexane derivatives, are well-known as effective chiral reagents and as ligands for catalysts used in asymmetric synthesis and molecular recognition [49, 50, 66]. Due to the $C_2$ symmetry of the diamine, the stereoelectronic requirements of the two nitrogen atoms attached to the phosphorus atom in a cyclic rigid core, and the overall topology of the resulting enantiomerically pure alkyl phosphonamides, the corresponding stabilized $\alpha$-carbanions exhibit diastereofacial bias in their reactions with carbonyl electrophiles. In the case of the phosphonic bis(amide)-type reagent **17**, the intermediate anionic species do not undergo the subsequent elimination simultaneously, but can be isolated as the carbinols **83**, treatment of which with AcOH in a separate step results in elimination to give the olefinic products **84**. The product stereochemistry is thought to be governed by the initial kinetically controlled addition step of the anion. Later, the reagent **17** was successfully applied to the preparation of axially chiral dissymmetric alkenes, such as **86**. Interestingly, the olefinic products were examined as possible chiroptical triggers for a liquid-crystal based optical switch [51].

Reagents of this type have also proved to be effective for asymmetric Michael additions [52].

Another chiral phosphoramidate **16**, which possesses stereogenic centers at both phosphorus and carbon atoms, was examined in asymmetric HWE olefination reactions [53]. By fine-tuning of the N-substituents in the structure of the auxiliary,




**Scheme 7.12.** Asymmetric carbonyl olefinations to give dissymmetric alkenes (1).

the *cis*-*N*-isopropyl phosphoramidate was found to give the best results. As with the phosphonic bis(amide) **17**, an additional elimination step to obtain the olefin **88** from the rather stable intermediate **87** was required [54]. This conversion was best achieved by the action of trityl triflate, and probably proceeded through the *O*-trityl phosphonium ion. Overall, the process of asymmetric olefination using a combination of reagents of this type furnished dissymmetric olefins with high enantioselectivity and in good chemical yield (Scheme 7.12). Furthermore, a closely related asymmetric conversion employing an alternative reagent of this class provided a convenient method for the preparation of a variety of substituted optically active dissymmetric alkenes through stereoselective Ni-catalyzed coupling with Grignard reagents [53].

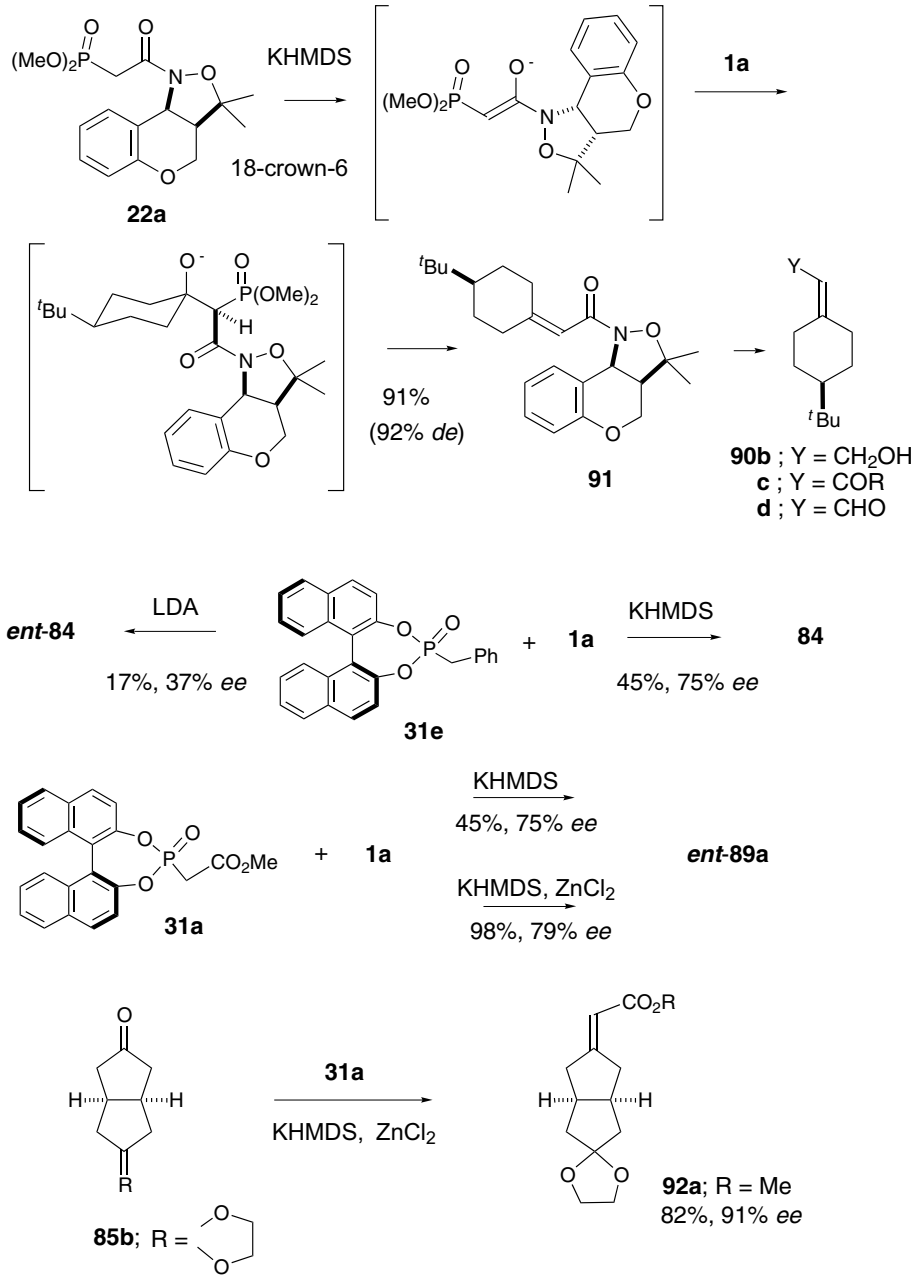
In the case of phosphoramidate reagents bearing an anion-stabilized carboalkoxy group such as **18**, simultaneous elimination from the intermediate occurs, leading directly to the alkene without any further treatment. The well-designed compound **18a**, which contains a camphor ring and a carbomethoxymethylene group, gave a high asymmetric induction of up to 86% *ee* [55].

Two chiral phosphonic acid derivatives **19a**,**b**, containing a stereogenic phosphorus atom connected to a mercaptoisoborneol moiety, were prepared as a mixture, and were then chromatographically separated. Their ability in asymmetric carbonyl olefination was examined in the reaction with 4-*tert*-butylcyclohexanone **1a** [56]. The two lithium carbanions reacted with the carbonyl group of the substrate to give opposite enantiomers **90a**, although no remarkable degree of asymmetric induction was observed (up to 16% *ee*).

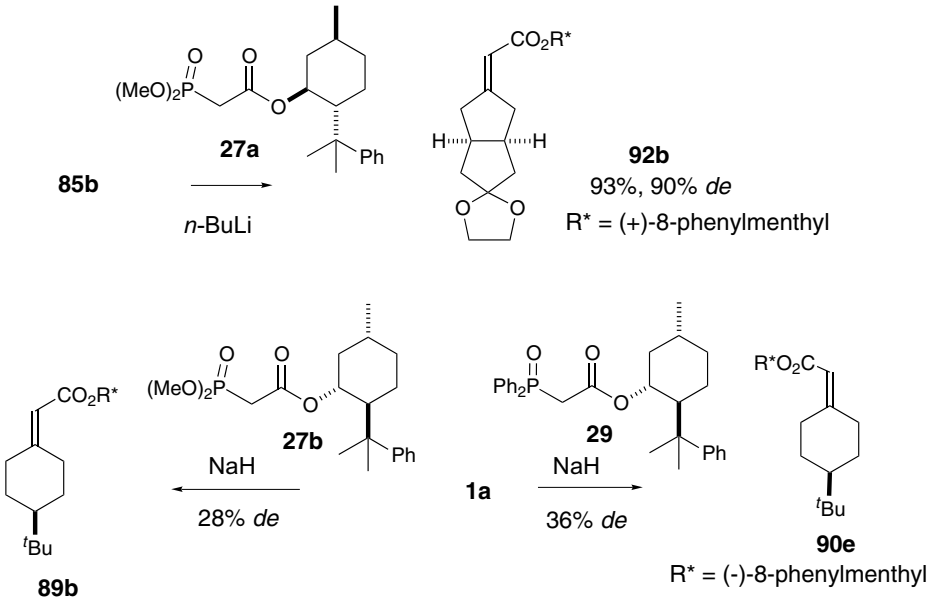
Chiral benzopyrano[4,3-*c*]isoxazolidine was incorporated into HWE phosphonate reagent **22a** and employed in asymmetric carbonyl olefinations of 4-substituted cyclohexanones to give the condensed products in good chemical yields and with high diastereoselectivity (Scheme 7.13); the products were efficiently converted to the corresponding allylic alcohol **90b**, unsaturated ketone **90c**, and unsaturated aldehyde **90d** by simple treatment with $LiBH_4$, a Grignard reagent, or DIBAL-H, respectively [57]. Again, both initial irreversible attack of the anion on the carbonyl from the equatorial direction and subsequent rapid elimination were considered in rationalizing the observed stereochemistry.

The chiral phosphonates **31a**,**e**, possessing optically active BINOL as an auxiliary, also demonstrated their ability as asymmetric inducers in the dissymmetrization of carbonyl compounds. In order to achieve both high enantioselectivity and good chemical yield, addition of zinc chloride was quite effective in these transformations [8]. It is known that bicyclo[3.3.0]octane derivatives usually adopt either W-, S-, or V-shaped conformations, and the observed stereochemistry of the alkene **92a** was best explained by considering an initial approach of the nucleophile to the W-shaped bicyclo[3.3.0]octanone in the direction in which steric interaction between the reagent and the substrate is minimized.

The reagents most widely applied to the dissymmetrization of ketones are chiral HWE phosphonate reagents possessing an 8-phenylmenthyl auxiliary on their carboalkoxy portion. Using reagents of this type, high diastereoselectivity has been achieved [58–60] (Scheme 7.14), and this may be due to the presence of the phenyl




**Scheme 7.13.** Asymmetric carbonyl olefinations to give dissymmetric alkenes (2).

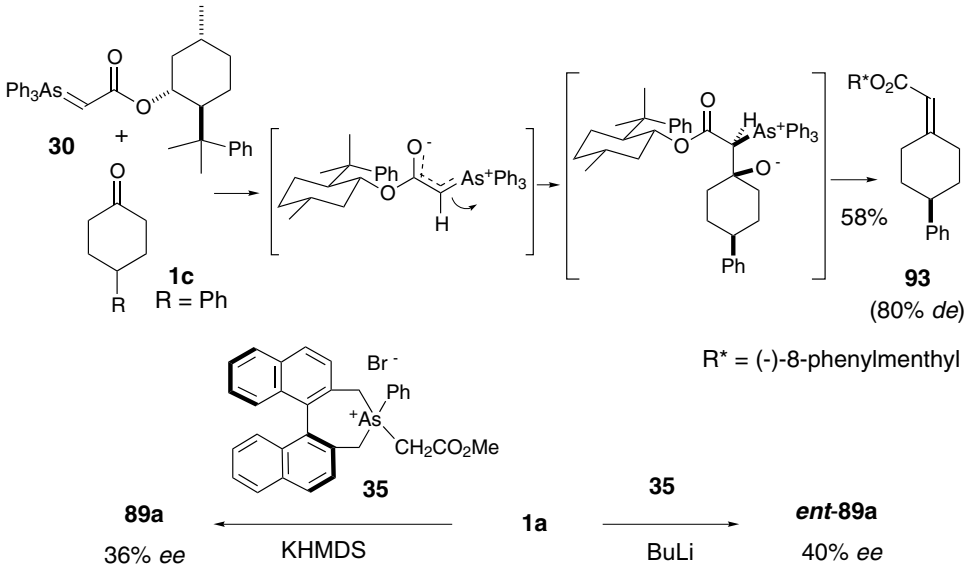



**Scheme 7.14.** Asymmetric carbonyl olefinations to give dissymmetric alkenes (3).

group in the chiral 8-phenylmenthyl auxiliary, which plays an important role in the addition of the phosphonate carbanion by effectively shielding one of the diastereotopic faces from approach of the electrophile.

The Horner-type reagent **29** has also been used for the same asymmetric carbonyl olefination [61], and the results were compared with those obtained using the corresponding HWE chiral reagent **27b**. The level of asymmetric induction with the Horner-type reagent **29** was not so remarkable, but the absolute stereochemistry of the olefinic product was opposite to that obtained from the reaction with the HWE reagent **27b**, despite the use of the same chiral auxiliary with the same absolute stereochemistry at the carboalkoxy moiety. These experiments clearly indicate that the substituents at phosphorus can significantly affect not only the level but also the mode of enantio- or diastereoselectivity. Consideration of the differences in the enolate geometry or in the rate-determining step of the aforementioned reaction (TS1 or TS2, *vide supra*) might lead to a reasonable explanation for the observed results.

Generally, arsonium ylides [62] are more reactive but less accessible than phosphonium ylides. Recently, the chiral arsonium reagent **30** has appeared, and has been applied in asymmetric Wittig-type carbonyl olefinations. This first chiral arsonium reagent also bears 8-phenylmenthyl as a chiral auxiliary on its carboalkoxy portion [63], and gave moderate chemical yields and diastereoselectivities in the conversion of 4-substituted cyclohexanone derivatives to axially chiral non-racemic alkylidene cyclohexanes under the same reaction conditions as used for the related reactions with phosphorus reagents (Scheme 7.15). On the other hand, the corre-




**Scheme 7.15.** Asymmetric carbonyl olefinations to give dissymmetric alkenes (4).

sponding HWE-type arsonium reagent exhibited lower diastereoselectivity. The observed stereochemistry of the products can again be rationalized by considering the initial nucleophilic attack to occur on the equatorial face of the cyclohexyl carbonyl group under kinetically controlled conditions from one of the favorable π-faces of the reagent created by the specific circumstance associated with the 8-phenylmenthyl auxiliary.

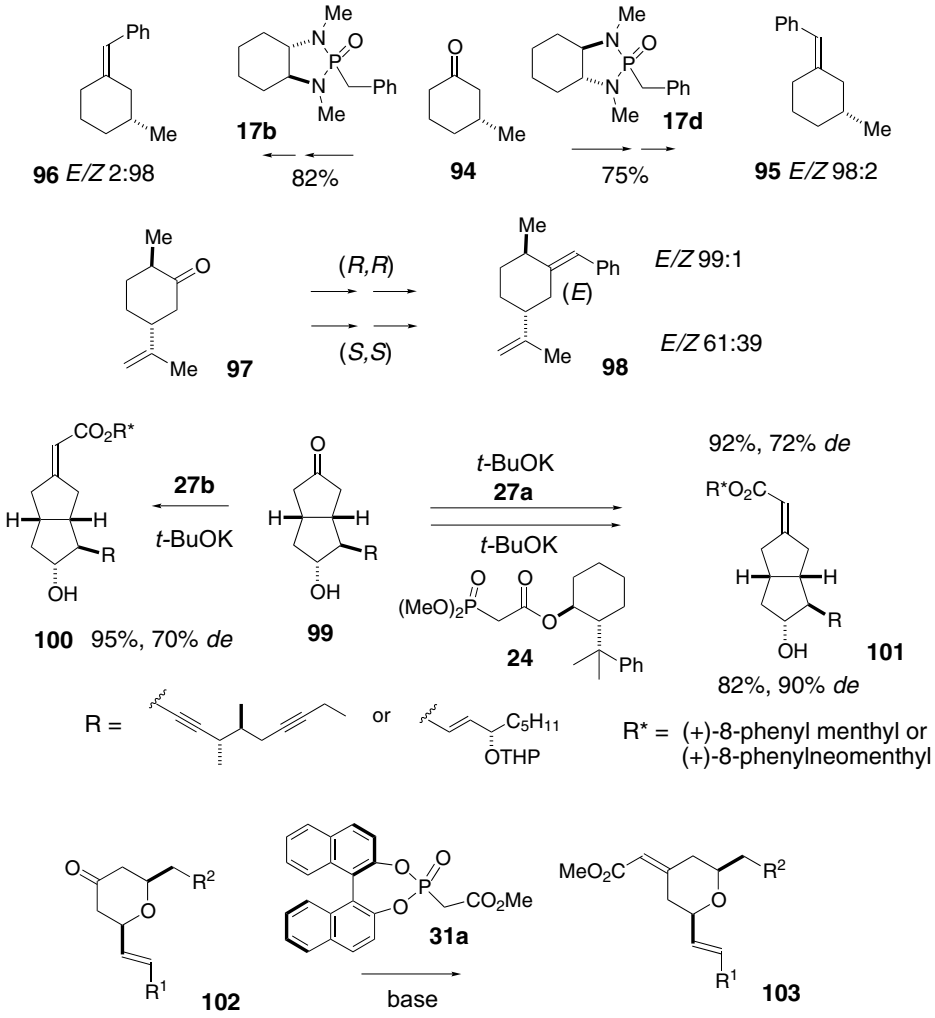
Recently, a novel $C_2$-symmetric chiral arsine **35** has been prepared from (*S*)-BINOL and employed in the enantioselective olefination of 4-substituted cyclohexanones to give the alkenes with moderate enantioselectivities of up to 40% *ee*. Moreover, a reversal in the stereochemistry of the products was observed simply by changing the counter cation of the base from lithium to potassium [64].

### 7.5.2
### Reactions with Chiral Non-Racemic Carbonyl Compounds

Since double asymmetric synthesis often represents a promising transformation method for obtaining organic compounds in high optical purity [65], this method has been applied to the highly stereoselective conversion of a chiral unsymmetrical ketone to an alkene with a single geometry. In this context, the phosphoramides **17** were demonstrated to afford *E*- or *Z*-olefinic products **95** and **96** from (3*R*)-cyclohexanone (**4**) with excellent stereoselectivity, depending upon which enantiomer of the reagent was employed [66]. In the reaction with (2*R*,5*R*)-dihydrocarvone **97**, contrasting results were observed in that complete stereoselectivity in

favor of the *E*-isomer **98** was achieved as a result of a matched combination and little selectivity was shown in the mismatched one.

The anions of the HWE reagents **27a**,**b** were reacted with the chiral monoketone **99** to afford the corresponding *Z*- and *E*-olefins **100** and **101** with high diastereomeric excesses, depending upon which enantiomer of the chiral phosphonate was employed. The olefinic products thus obtained served as key intermediates in the synthesis of prostacyclin derivatives [59, 60]. A closely related chiral reagent, **24**, bearing 8-phenylnormenthol [67], both enantiomeric forms of which are readily accessible, provided an improved diastereoselectivity in favor of the *E*-isomer **101** (Scheme 7.16).




**Scheme 7.16.** Asymmetric olefinations with non-racemic chiral carbonyl compounds.

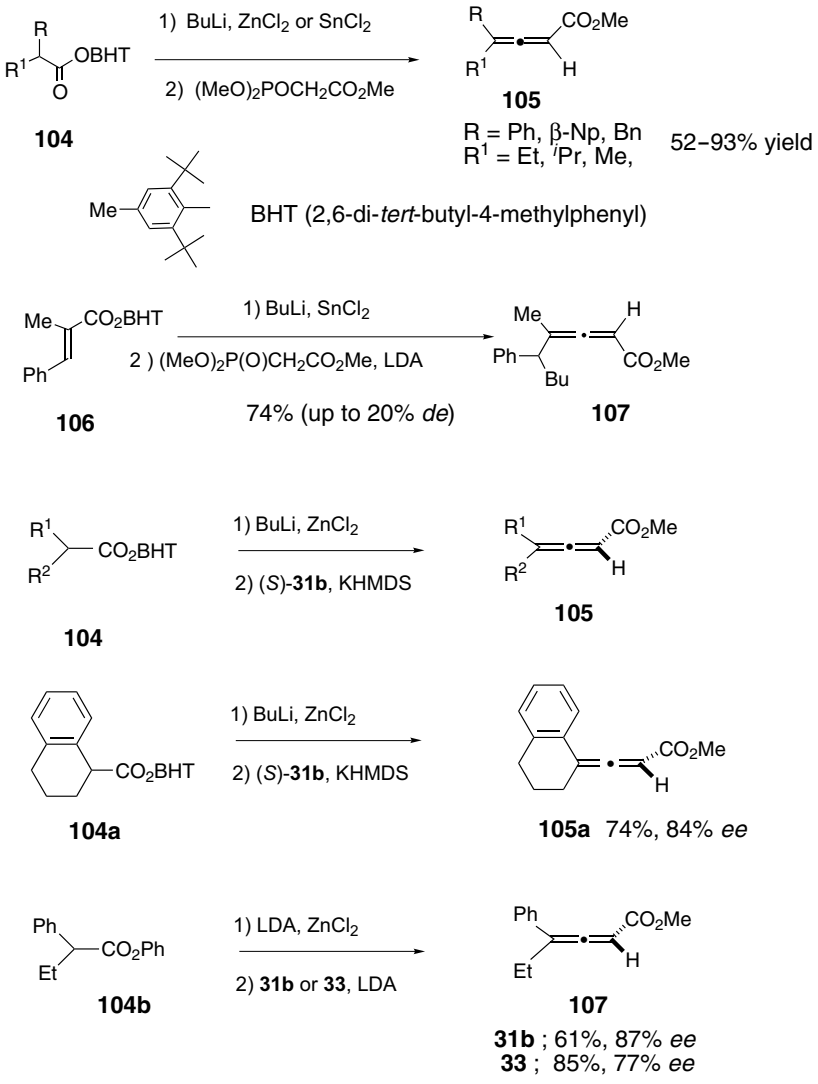
Recently, by selection of the appropriate enantiomer of the chiral HWE reagent **31a**, the concept of double asymmetric induction in an asymmetric carbonyl olefination step has been applied in controlling the geometry of the alkenic intermediate **103** in the total synthesis of structurally complex macrolides [68, 69] (*vide infra*).

### 7.5.3
### Reactions with Prochiral Ketenes to give Dissymmetric Allenes

The idea that the facile condensation reaction between the non-enolizable and sterically less hindered carbonyl group of a ketene with a Wittig-type reagent provides a possible means of assembling compounds with axial chirality has long been recognized. Several attempted reactions based on this idea were reported during the 1960s. However, these early investigations had only limited success in that only low *ee* values were obtained [20, 70]. The most serious problem associated with the preparation and manipulation of ketenes is their inherently high reactivity and lability, which often leads to polymerizations or undesired side reactions and hence to a significant reduction in the chemical yield of the desired products. Therefore, general methods for the preparation of optically active allenic compounds have relied on transformation from propargyl derivatives having built-in stereogenic chiral centers [16d, 71].

In order to solve these troublesome problems of ketenes and to develop a new preparative method based on carbon–carbon bond formation, exploratory experiments were carried out. The most practical and successful protocol proved to be a one-pot procedure involving HWE olefination of in situ generated ketenes with a phosphonate reagent. By using this convenient one-pot procedure, which was first developed for the preparation of racemic conjugate allenecarboxylate (alka-2,3-dienoate) derivatives [72], troublesome handling of labile ketenic compounds can be avoided. Thus, treatment of the anion of the HWE reagent with in situ generated ketenes from enolates of 2,6-di-*tert*-butyl-4-methylphenyl (BHT) esters **104** gave the desired allenecarboxylates **105** in high yields. Thereafter, by using α,β-unsaturated BHT esters as substrates, tandem Michael–HWE reactions were performed [73]. Thus, the Michael-initiated ketenes, generated in situ from organolithium reagents and α,β-unsaturated BHT esters such as **106**, were effectively reacted with the anion of an achiral HWE reagent to give δ-branched allenecarboxylates **107** and derivatives thereof in good yields, although the diastereoselectivity was poor (Scheme 7.17).

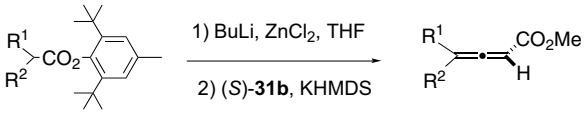
These reactions were successfully applied to the enantioselective preparation of axially chiral allenecarboxylates [74]. In these one-pot transformations, replacement of the metallic counter cation by a somewhat less electropositive one, such as $Zn^{2+}$ or $Sn^{2+}$, was found to be effective in controlling the nucleophilicity of the reagents and hence led to improved chemical yields. Additionally, the substituent at the 3-position of the naphthalene ring of the HWE reagent **31** significantly affects the degree of asymmetric induction, and a methyl substituent was found to give the best results. Treatment of BHT esters **104** as ketene precursors with a base in the presence of zinc ions generated the ketene, which was subsequently reacted




**Scheme 7.17.** Preparation of allenic compounds from ketenes.

with the anion of chiral phosphonate **31b** to form a dissymmetric allenecarboxylate in good chemical yield and with satisfactory optical purity (Table 7.3). A simple phenyl ester such as **104b** can also serve as a substrate for effective asymmetric transformation in place of the BHT esters [75] of lower availability [76]. Conjugated allenecarboxylates are interesting building blocks showing a versatile reactivity, and the selective transfer of axial chirality in these molecules to central chirality by ap-

**Tab. 7.3.** Preparation of optically active allenecarboxylates with the anion of (S)-**31b.**




| *BHT esters* | | *allenecarboxylate* | |
|---|---|---|---|
| ***R*¹** | ***R*²** | ***yield (%)*** | ***% ee (config.)*** |
| Ph | Me | 94 | 62 (*Ra*) |
| $^{i}$Pr | Ph | 71 | 81 (*Sa*) |
| cyclo-Hex | Ph | 81 | 79 (*Sa*) |
|  | | 74 | 84 (*Ra*) |
| 2-Naphthyl | Et | 91 | 72 (*Ra*) |
| $Ph_2CH$ | Me | 85 | 61 (*Ra*) |

propriate transformation provides an efficient preparative method for a variety of optically active compounds.

The enantioselectivity observed by using the chiral HWE reagent (*S*)-**31b** is best understood by consideration of the favorable transition state rather than the stability and reactivity of the phosphoxetane intermediate. Thus, the addition of $Zn^{2+}$ ions leads to a rigidly chelated phosphate anion bound by $Zn^{2+}$, as depicted in Figure 7.1, where the axially dissymmetric binaphthyl group dictates the orientation of the approach to the electrophile from the less hindered *si*-face of the reagent (route **a**). Assuming $R^1 > R^2$ in terms of bulkiness, it is likely that the nucleophile approaches the LUMO of the ketene carbonyl from the face including the less bulky $R^2$, so as to avoid the more severe steric repulsive interaction with $R^1$. Consequently, the substituent at the 3-position of the naphthalene ring exerts its influence as the bulkiness of the $R^2$ group increases.

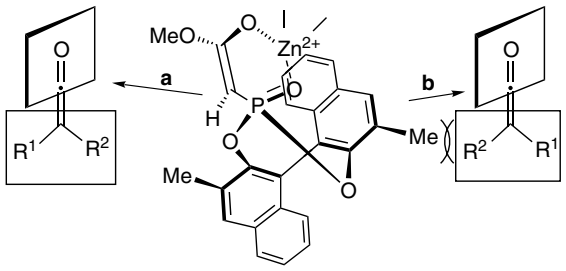


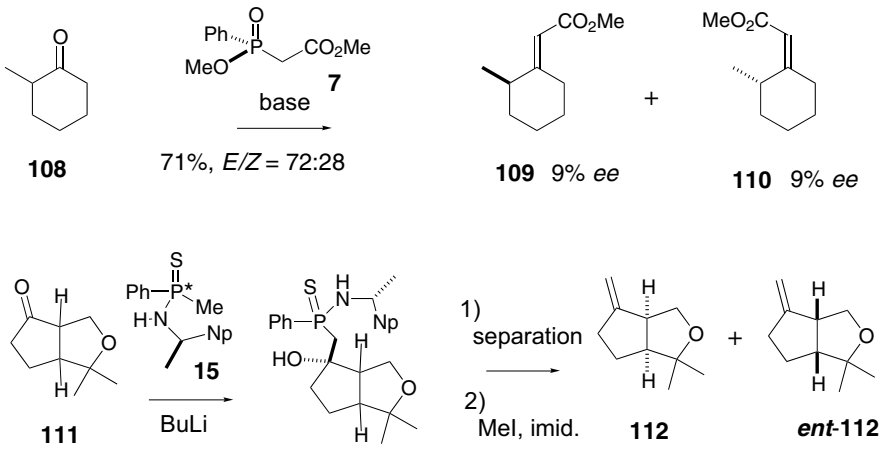

**Fig. 7.1.** Possible mechanistic explanation for the observed enantioselectivity in the asymmetric HWE reaction with (*S*)-**31b**.

## 7.6
## Kinetic Resolution

### 7.6.1
### Resolution of Racemic Carbonyl Compounds

When there exists a considerable difference in activation energy between diastereomeric transition states derived from each enantiomer of a racemic compound and a chiral reactant, kinetic resolution [77] becomes possible based on the difference in relative reaction rates, to give enantiomerically enriched product together with recovery of starting material in non-racemic form. In some aspects, this concept resembles the discrimination of enantiotopic carbonyl groups discussed above, and indeed both transformations are realized with biocatalysts, such as enzymes or yeasts. Although kinetic resolution has an inherent and practical problem in that theoretically only up to 50% of chemical yield can be obtained, this chemical approach to optically active compounds has been widely used as one of the most convenient resolution methods for racemates. Thus, for complete conversion to a single alkene in an asymmetric carbonyl olefination, at least a twofold excess of the racemic carbonyl substrate is necessary for the reaction with the chiral Wittig-type reagent. An early study [21] along these lines, employing the chiral phosphinate reagent **7**, demonstrated that the reaction of racemic 2-methylcyclohexanone **108** resulted in both the *E*- and *Z*-olefinic compounds **109** and **110** with low enantiomeric excess (Scheme 7.18), and it was found that the absolute configurations at the stereocenters were opposite to each other, suggesting preferential reaction with the opposite enantiomer for the production of the two stereoisomers in this kinetic resolution process.

The asymmetric olefination of the racemic ketone **111** with the anion of the phosphinothioic amide **15** can be regarded as an example of kinetic resolution;




**Scheme 7.18.** Early examples of asymmetric olefination through kinetic resolution.

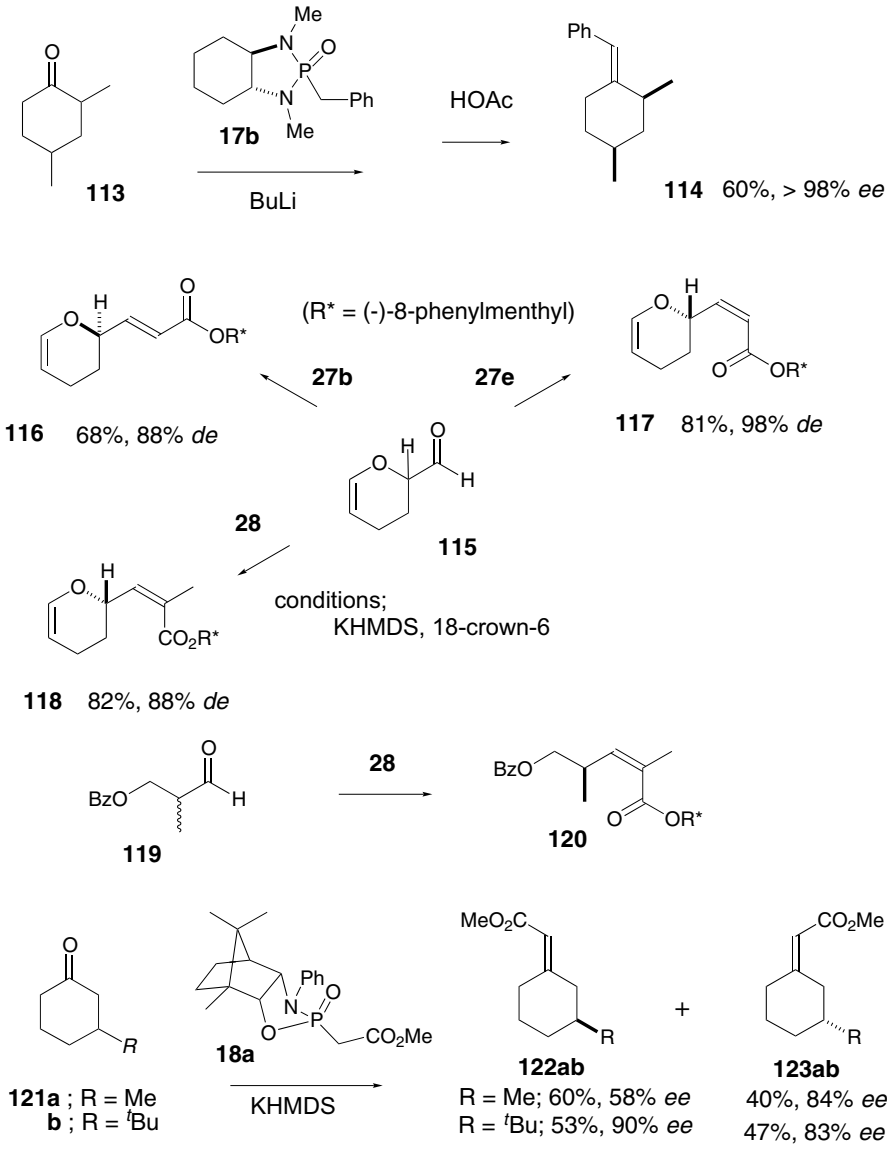
however, the transformation involving the enantioselective preparation of both enantiomers of the irridoid monoterpene hop ethers **112** from the corresponding diastereomers relied on successful separation of the diastereomeric intermediates, formed in a 3:2 ratio, rather than on a difference in their relative rates of formation [78].

Some years later, the first investigations [19, 49, 66] of the preparative value of this method were carried out by using chiral reagents **17**. In the reaction of two equivalents of racemic *cis*-2,4-dimethylcyclohexanone **113** with the anion of chiral phosphonate **17b**, kinetic resolution took place to give the *E*-alkene **114** with excellent enantioselectivity in 60% yield based on the reagent employed, after treatment of the adduct with AcOH (Scheme 7.19).

Later, the method of kinetic resolution was extended to aldehyde substrates [79, 80]. Here, acrolein dimer **115** was used as a racemic substrate, and 2.1–3 equivalents thereof was efficiently resolved to give the corresponding *E*- or *Z*-alkenes with high levels of diastereoselectivity by reactions with a series of chiral phosphates **27** or **28**. In this study, the change in structure of the connecting groups to the phosphorus atom significantly affected the *E*/*Z* selectivity of the olefinic products. Since modification at the phosphonate moiety allowed control of the product stereochemistry, it was possible to synthesize either (*R*, *E*)- or (*S*, *Z*)-alkenes in good yields and with high diastereomeric excesses. It is noteworthy that optically active *E*- and *Z*-alkenes were produced from different enantiomers of the racemic substrates, as in the preferential discrimination of opposite carbonyl groups in the differentiation of enantiotopic carbonyl groups mentioned above. The trisubstituted *Z*-alkenes **118** and **120** were prepared in this way using phosphate **28** [79b].

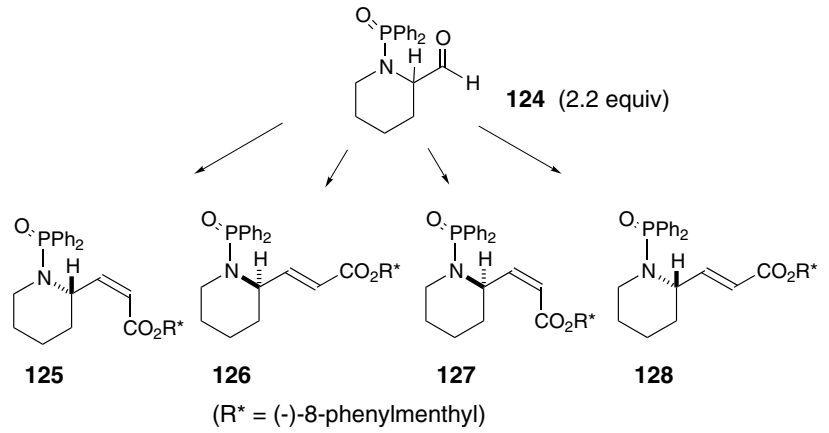
In a similar way, racemic 3-substituted cyclohexanones **121** were reacted with the anion of the chiral phosphoamidate reagent **18a** to give two isomeric optically active alkenes, that is (*S*, *E*)- and (*R*, *Z*)-alkenes possessing the opposite absolute configuration at the homoallylic carbon centers, with high enantiomeric excess [55].

In a closely related study on kinetic resolution, it was shown that not only the structure of the chiral phosphorus reagent, but also the structure of the racemic carbonyl substrates and the reaction conditions significantly affect the product stereoselectivity. All four possible isomeric alkenes **125–128** could be preferentially obtained from the racemic *N*-diphenylphosphoryl-protected aldehyde **124** as the major products by appropriate selection of the base, the solvent, and the substituent R on the phosphonates **27** and **28** (geometric selectivities from 66:34 to 98:2; diastereomer ratios between 93:7 and >99:1) (Scheme 7.20) [81]. Mechanistically, a switch between Felkin–Anh–Eisenstein and chelation control [82] at the transition state of addition to the aldehyde occurs, depending upon the reaction conditions used, and the combination with the influence of substrate stereocenters is responsible for the bias in the product distribution. Insight into the mechanism of the reaction between the chiral reagents and the aldehyde substrates was gained from a molecular mechanics modeling study, which supported the hypothesis of kinetic stereoselectivity in the addition step, as previously assumed by many research groups. Preferential production of an alkene from one of the eight ($2^3$) the-

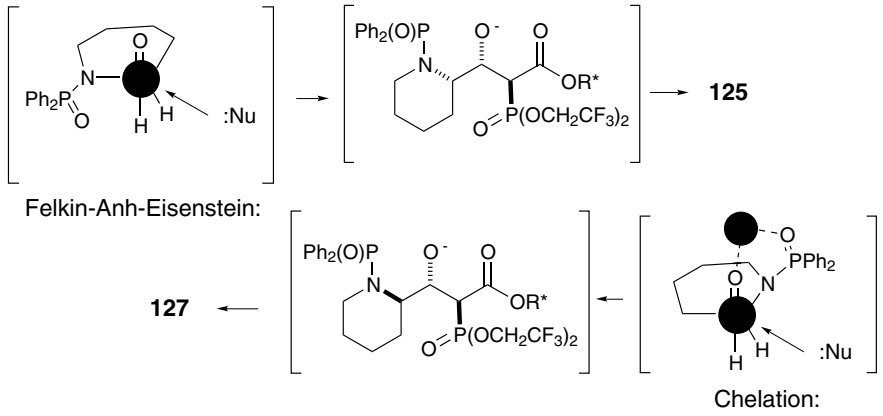



**Scheme 7.19.** Asymmetric carbonyl olefinations through kinetic resolution.

oretically possible intermediates, as well as the formation of the opposite absolute configuration at the allylic stereocenter of the products from a reaction involving kinetic resolution, can be rationalized by considering the following factors. Thus, the selectivity is determined by the influence of three major factors: the chiral auxiliary, the nature of the R group connected to the phosphorus atom, and the α-stereocenter in the substrate. The chiral auxiliary dictates the face of the phospho-




| Alkenes | **125** | **126** | **127** | **128** |
|---|---|---|---|---|
| Reagents | **27e** | **27f** | **27e** | **27b** |
| Base | KHMDS / 18-crown-6 | KHMDS / 18-crown-6 | NaHMDS | KHMDS |
| Solvent | THF or EtCN | THF | $CH_3CN$ | THF |




**Scheme 7.20.** Preferential formation of one of the four possible diastereomers.

nate enolate that is attacked, hence the absolute configuration at C-2. The R group on the phosphonate and the substrate $\alpha$-stereocenter affect the relative configurations at C-2 and C-3, and C-3 and C-4, which determine the $E/Z$ stereochemistry of the alkene and the absolute stereochemistry induced by the chiral reagent, respectively (Figure 7.2). Additionally, a modeling study indicated considerable effect of the substrate stereocenter not only on the addition step but also on the elimination in some cases.

Asymmetric olefination based on kinetic resolution was then directed to the use

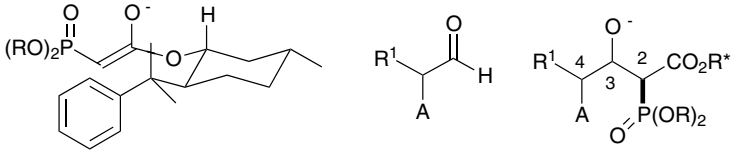
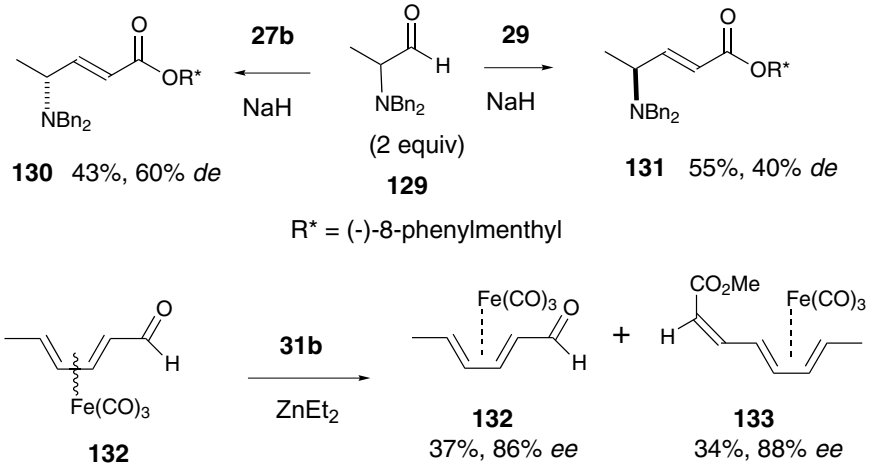


**Fig. 7.2.** Mechanistic consideration of the reaction with reagents **27**.

of α-amino aldehyde **129** as a substrate (Scheme 7.21), whereby the preferential production of opposite enantiomers **130** and **131** was again observed by a small modification of the structure of the chiral reagent using the same enantiomer as a chiral auxiliary, yielding (*R*, *E*)- and (*S*, *E*)-alkenes with **27b** and **29**, respectively [61]. This method constitutes a complementary route to optically active non-proteinogenic amino acid derivatives of great interest [83].

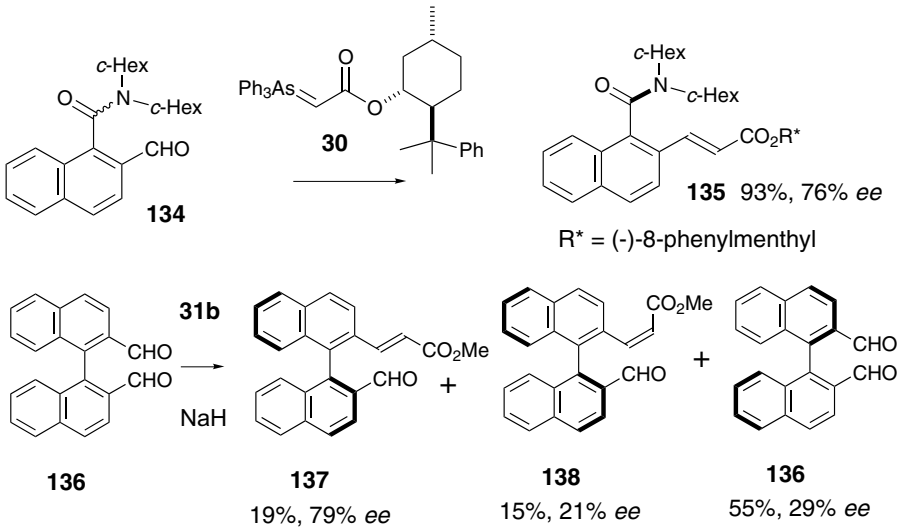


**Scheme 7.21.** Additional examples of kinetic resolution of racemic aldehydes.

An example of kinetic resolution of a racemic aldehyde of the $\eta^4$-Fe complex **132** was reported to give the corresponding *Z*-olefin **133** together with the starting aldehyde with a satisfactory level of optical purity [37]. Provided that the conjugated aldehyde exists in the *s-trans* conformation, the initial rate-determining nucleophilic attack from the *si*-face of the reagent anion is energetically favored, and this addition occurs on the less hindered *anti* side of the iron carbonyl groups in the substrate. Consequently, the anion may approach the *re*-face of the aldehyde carbonyl rather than the *si*-face, leading to the preferential formation of the observed product **133** along with recovery of the non-racemic **132**.

The kinetic resolution of racemate **134** possessing axial chirality was examined with the chiral arsonium ylide **30**, which afforded the non-racemic atropisomer **135** with a satisfactory *de* of up to 76% [84]. In this reaction, dynamic kinetic resolution was operative to some extent (*vide infra*). The same kind of kinetic resolution

through discrimination of axial chirality of the racemic substrate **136** was also examined with the axially chiral phosphorus reagent **31b**; this gave the optically active atropisomers **136–138** with satisfactory enantiomeric purity, although the yields were low (Scheme 7.22).



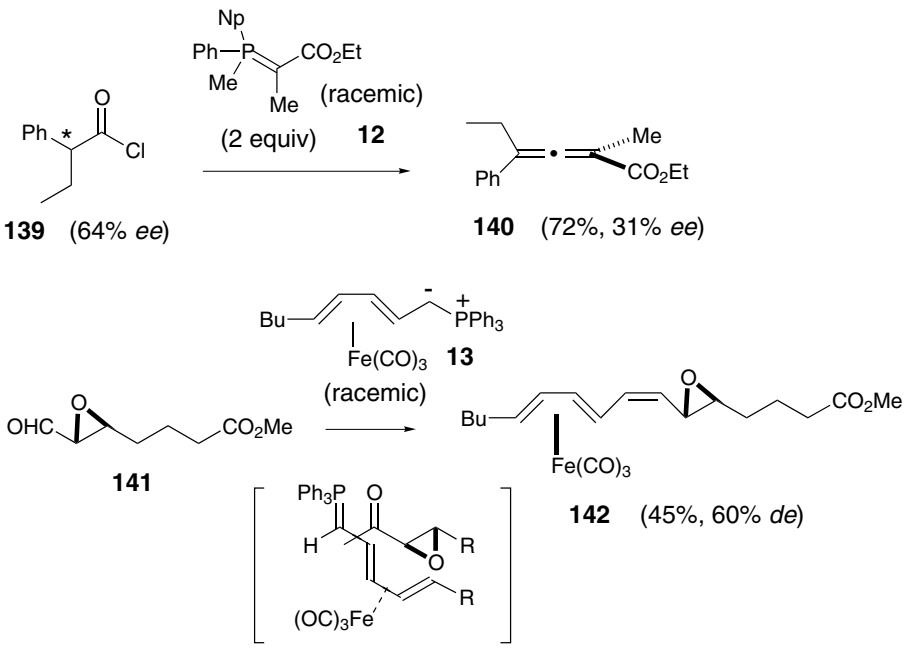

**Scheme 7.22.** Kinetic resolution of racemic aldehydes to give axially chiral compounds.

### 7.6.2
### Resolution of Racemic Phosphorus Reagents

Kinetic resolution of a racemic Wittig-type reagent through reaction with a chiral carbonyl substrate constitutes a reverse strategy to that described above. A preliminary report described the reaction of the racemic stabilized phosphonium ylide **12** with an optically active alkanoyl chloride **139** to furnish a chiral allenic compound **140**, albeit with only a modest level of stereoselectivity [70]. More recently, the optically active epoxy aldehyde **141** was treated with racemic phosphonium ylide **13** having a $\eta^4$-dienyl $Fe(CO)_3$ group to afford the *Z*-alkene **142** with 60% *de* in moderate chemical yield [85] (Scheme 7.23). These two examples are clearly suggestive of kinetic resolution of the ylide, with a matched double asymmetric induction leading to preferred formation of the major isomer, and a mismatched combination suffering from serious non-bonded interactions leading to the minor products.

### 7.6.3
### Parallel Kinetic Resolution

Although kinetic resolution is an established method for the preparation of chiral compounds, it requires a large difference in the rate constants of the enantiomers of the substrate in order to obtain the product and recovered starting material with

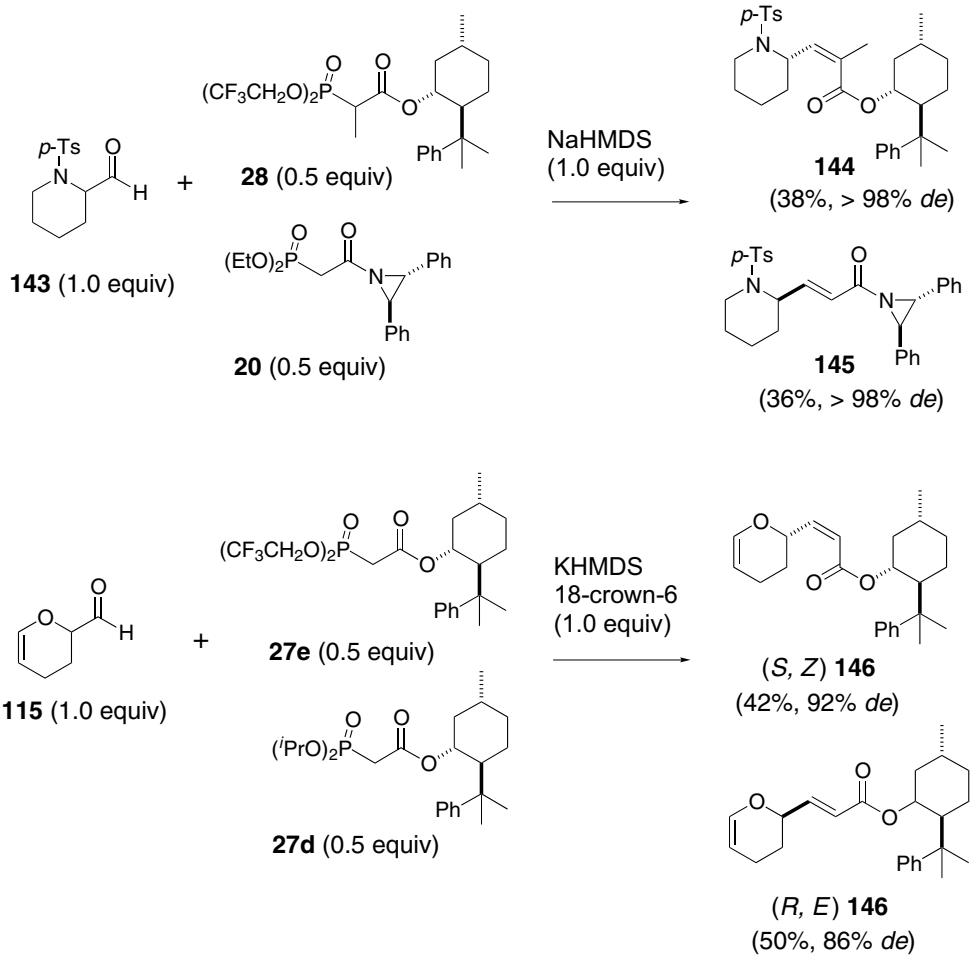



**Scheme 7.23.** Kinetic resolution of racemic reagents.

high optical purity and in good chemical yield. Therefore, an exceptionally high selectivity factor $s$ ($s = k$(fast-reacting enantiomer)/$k$(slow-reacting enantiomer) is required to meet these conditions (for example, $s = 500$, 98% *ee* in 50% yield for both the slow- and fast-reacting enantiomers). Clearly, there will be a continuous increase in the relative concentration (and therefore the relative rate of reaction) of the less reactive substrate as the faster-reacting substrate is consumed. To overcome this concentration effect, a new strategy for the optical resolution of racemic substrates, termed "Parallel Kinetic Resolution (PKR)", has recently been proposed [86, 87] and developed as an improved version of simple kinetic resolution.

Under PKR conditions, two enantiomeric substrates are simultaneously converted into two structurally and configurationally different chiral products by reaction with chiral reagents or catalysts. It has been shown that to achieve the same selectivity, the selectivity factor $s$ can be significantly lower for PKR than for a traditional kinetic resolution. As yet, there has been only one report of an asymmetric HWE reaction under PKR conditions [88], in which one equivalent of racemic aldehyde **143** was converted into alkene products **144** and **145** by reaction with half an equivalent each of two chiral phosphonates **28** and **20** bearing different chiral auxiliaries (Scheme 7.24). These alkene products, **144** and **145**, were readily separable as a result of the difference in polarity between the two auxiliaries. It was clearly shown that the diastereoselectivities of the alkene products were dramatically improved compared to those obtained in the respective individual kinetic resolutions, especially in the case of alkene **145**.

The alternative approach to PKR using asymmetric HWE reactions, in which




**Scheme 7.24.** Asymmetric carbonyl olefinations through parallel kinetic resolution.

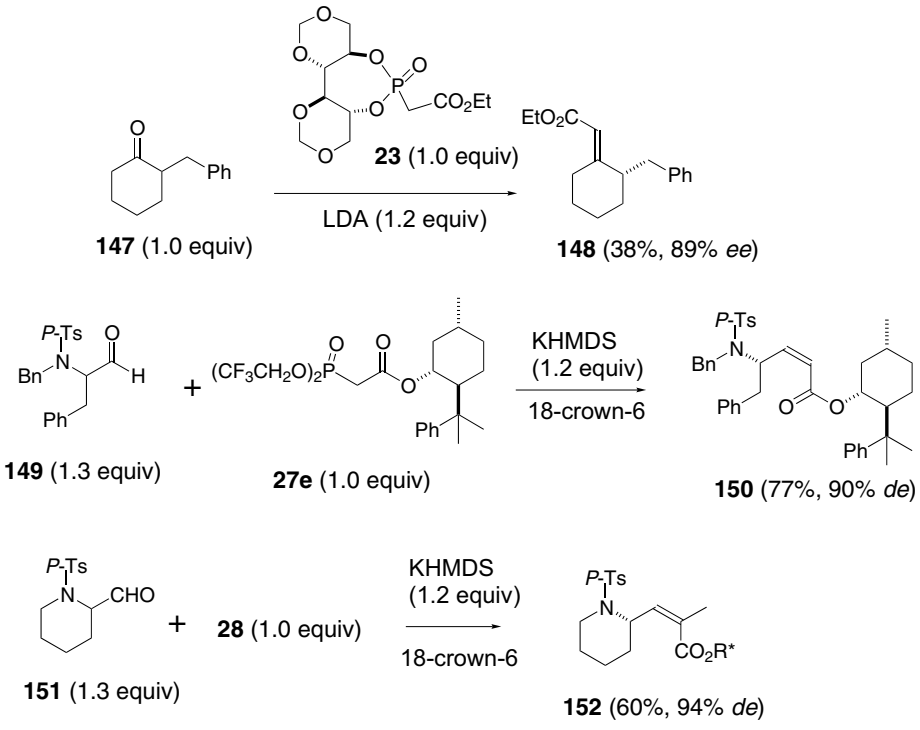
one *E*- and one *Z*-selective reagent bearing the same auxiliary are used in combination, has been examined in the reactions of acrolein dimer **115** and phosphonates **27e** and **27d**. The products, (*R*, *E*)- and (*S*, *Z*)-**146**, were obtained with synthetically useful diastereoselectivities and in excellent chemical yields. Moreover, the alkene products could be readily separated by chromatographic means.

## 7.7
## Dynamic Resolution

Kinetic resolution has long been recognized as an effective tool for the preparation of enantiomerically enriched compounds, but the inherent drawback of this methodology is that the maximum yield of one enantiomer is 50%. In addition, the

enantiomeric purity of the recovered substrate and product is profoundly affected by the extent of conversion. This limitation can be overcome if the stereogenic center of a racemic substrate can racemize rapidly during the course of the reaction, which can, in principle, lead to quantitative conversion of the substrate into a single stereoisomer of the product [89, 90].

Several efforts have been made to prepare chiral alkene products by the use of an asymmetric Wittig-type reaction in a dynamic process [91]. The dynamic kinetic resolution of racemic 2-benzylcyclohexanone (**147**) with an equimolar amount of chiral cyclic phosphonate **23**, prepared from mannitol, afforded the chiral (*E*, *S*)-alkene product **148** with excellent optical purity in good chemical yield [92] (Scheme 7.25). In the presence of excess LDA, racemization of the substrate led to recovery of the starting ketone with low optical purity. Molecular mechanics calculations aimed at evaluating conformational and constitutional equilibria of the oxyanion obtained by addition of the phosphonate carbanion to the carbonyl group of **147** were performed to clarify the stereoselectivity. The three energetically most favored isomers from the eight possible diastereomers considered theoretically were selected. It was shown that two of these three isomers, that have much better molecular geometries than the other, undergo ring closure to the oxaphosphetane and then to the alkene **148**. This result indicates that the stereoselectivity is not only controlled by the direction of addition of the phosphonate carbanion to the




**Scheme 7.25.** Examples of dynamic kinetic resolution.

carbonyl group, but also by the relative rates for the ring closure and elimination to give the products.

Another example of this category is the first dynamic kinetic resolution of a racemic α-amino aldehyde [93]. It has been shown that the *N*-tosyl-protected aldehyde **149** reacts with a near equimolar amount of chiral phosphonate **27e** to afford vinylogous amino acid esters (*R*, *E*)-**150** with excellent diastereoselectivity and chemical yield. Similarly, the *N*-tosyl-protected piperidine **151** was converted into the trisubstituted alkene **152** with good diastereoselectivity and in high chemical yield by reaction with chiral phosphonate **28**. In several cases, it has been shown that the selectivity obtained under dynamic conditions exceeds that obtained by a traditional kinetic resolution. The HWE products obtained appear to be attractive precursors for non-proteinogenic amino acids [83] as well as various alkaloids.

The aforementioned transformation of racemic **134** to **135** belongs to the category of dynamic kinetic resolution [84] (Scheme 7.22). It was shown that the diastereoselectivity of the alkene product is lower than that of the product obtained from the corresponding simple kinetic resolution (*vide supra*).

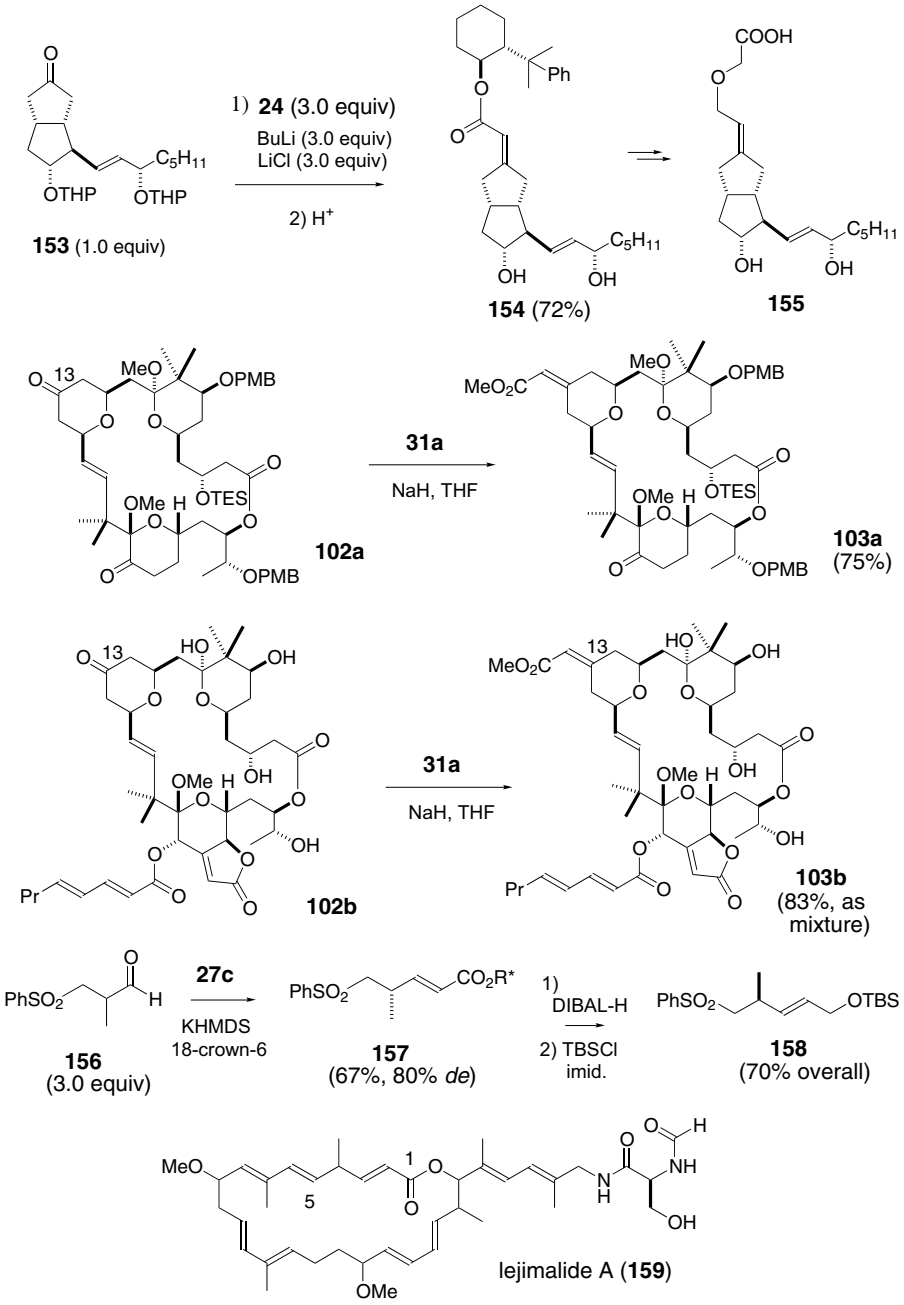
## 7.8 Further Application of Asymmetric Wittig-Type Reactions in Enantioselective Synthesis

### 7.8.1 Use of Asymmetric Wittig-Type Reactions in the Total Synthesis of Natural Products

The usefulness of the Wittig and related reactions in facilitating crucial carbon–carbon bond-formation steps in multi-step chemical syntheses has been demonstrated by many examples of the construction of useful complex molecules such as natural products. Some successful constructions of optically active functionalized building blocks with chiral HWE reagents for the total synthesis of natural products have already been discussed in this chapter [12a, 45, 59–61, 78], and additional examples, which have recently been reported, are mentioned here.

The first example is the stereoselective introduction of the α side chain into 3-oxacarbacyclin and 3-oxaisocarbacyclin molecules by reaction with chiral HWE reagents. Reaction of the THP-protected ketone **153** with three equivalents of chiral phosphonate **24** in the presence of LiCl gave an *E*/*Z* mixture of the α,β-unsaturated ester (*E*:*Z* = 95:5) [67] (Scheme 7.26). The desired *E*-isomer **154** was isolated after deprotection of the THP groups and converted into the 3-oxacarbacyclin **155** as well as 3-oxaisocarbacyclin [94].

In the total synthesis of bryostatins, chiral HWE reagents have been used for the stereocontrolled transformation of the C13 ketone to the C13–C30-unsaturated enoate [68]. The reaction of macrocycle **102a** with chiral phosphonate **31a** provided the α,β-unsaturated ester of *Z*-stereochemistry, **103a**, with a diastereoselectivity of *Z*/*E* = 85:15 (75% isolated yield of the *Z*-isomer, **103a**). The obtained *Z*-isomer **103a** was successfully converted into bryostatin by several subsequent chemical




**Scheme 7.26.** Some examples of the application of asymmetric carbonyl olefination to natural product synthesis.

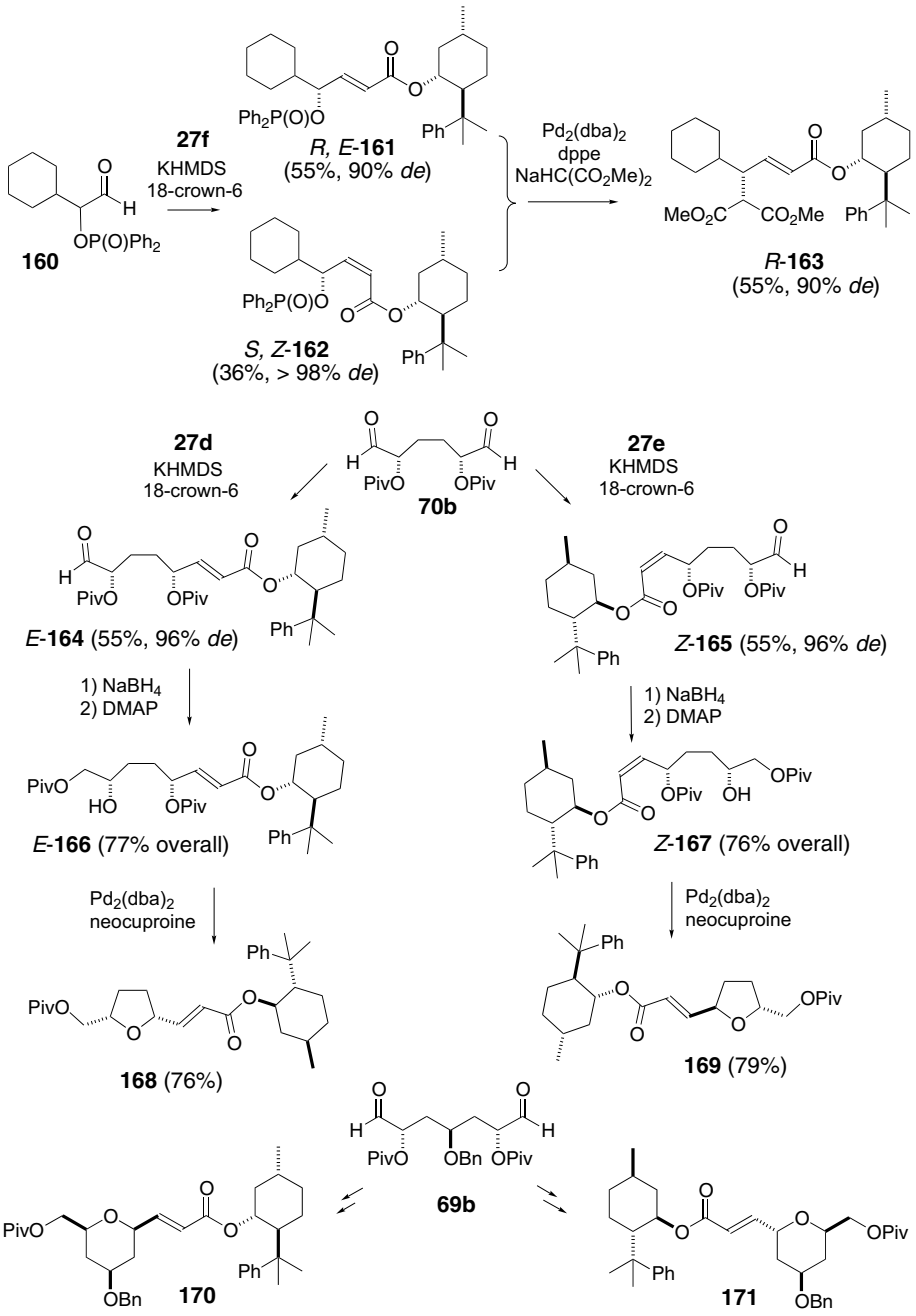
transformations. Similarly, another research group reported that the C13 ketone of compound **102b** was transformed into a mixture of $\alpha,\beta$-unsaturated esters containing the *Z*-isomer **103b** in 83% yield ($Z/E = 89{:}11$) by using the same phosphonate **31a** as a key step in the total synthesis of bryostatin [69].

Kinetic resolution of racemic aldehyde **156** was employed in the construction of the subunit of iejimalide A (**159**), a marine macrolide exhibiting high cytotoxicity. Thus, the chiral *E*-alkene **157** was obtained with 80% *de* using **27c**, and then converted into the C(1)–C(5) fragment of iejimalide A [80, 95].

### 7.8.2 Sequential HWE and Pd-Catalyzed Allylic Substitutions

The preparation of the same chiral target molecule from both enantiomers of a racemate via the isomeric synthetic intermediates (enantioconvergent reaction sequence) has been studied as an interesting and useful synthetic method. In the case of asymmetric carbonyl olefination, the success of such an enantioconvergent strategy is highly dependent on the combination of an asymmetric HWE reaction and subsequent Pd-catalyzed allylic substitution. Reaction of the racemic aldehyde **160**, bearing a diphenylphosphonyl group as a protecting group for the alcohol, which acts as a leaving group in the subsequent Pd-catalyzed allylic substitution reaction, with the anion of the chiral phosphonate **27f** afforded a near equimolar mixture of alkenes (*R*, *E*)-**161** and (*S*, *Z*)-**162**, with good to excellent diastereoselectivity (Scheme 7.27). In the subsequent step, the mixture of alkenes was subjected to Pd-catalyzed allylic substitution with carbon nucleophiles. Thus, reaction of the $\eta^3$-allylpalladium complex derived from alkene mixture (*R*, *E*)-**161** and (*S*, *Z*)-**162** with sodium dimethylmalonate gave a single, optically active product (*E*)-**163** in good overall yield and with satisfactory diastereoselectivity [96]. This stereoconvergent strategy relied on opposite stereoselectivities of the allylic substitutions of (*R*, *E*)-**161** and (*S*, *Z*)-**162**, the substrates reacting with inversion and retention of configuration, respectively. This strategy has also been applied for the preparation of the chiral building blocks in the synthesis of iejimalides (**159**).

The construction of chiral tetrahydrofuran (THF) and tetrahydropyran (THP) derivatives as building blocks for the total synthesis of natural products containing these moieties, such as mucocin, has also been successfully achieved by application of the asymmetric HWE reaction with subsequent cyclization (Pd-catalyzed intramolecular allylic substitution) strategy. Thus, desymmetrization of the *meso*-dialdehyde **70b**, derived from *cis*-2-cyclohexane-1,4-diol, with the chiral phosphonates **27d** and **27e** gave the (*E*)-alkene **164** and (*Z*)-alkene **165**, respectively, with excellent diastereoselectivities. Reduction of the remaining aldehyde groups in these alkenes and subsequent acyl group migration gave the allylic carboxylates (*E*)-**166** and (*Z*)-**167**, respectively. Intramolecular Pd(0)-catalyzed allylic substitution of (*E*)-**166** in the presence of neocuproine as a ligand gave the optically active THF derivatives **168** with excellent stereoselectivities and overall retention of configuration at the allylic stereocenter. On the other hand, the ring closure of (*Z*)-**167**




**Scheme 7.27.** Examples of asymmetric sequential HWE and Pd-catalyzed allylic substitutions.

proceeded under conditions of moderate heating to give the optically active THF derivatives **169** with overall inversion of configuration [97].

In an analogous manner to the route to the THF derivatives described above, the chiral THP derivatives **170** and **171** were successfully prepared from the *meso*-dialdehyde **69b** by asymmetric HWE reaction followed by Pd-catalyzed intramolecular cyclization [98].

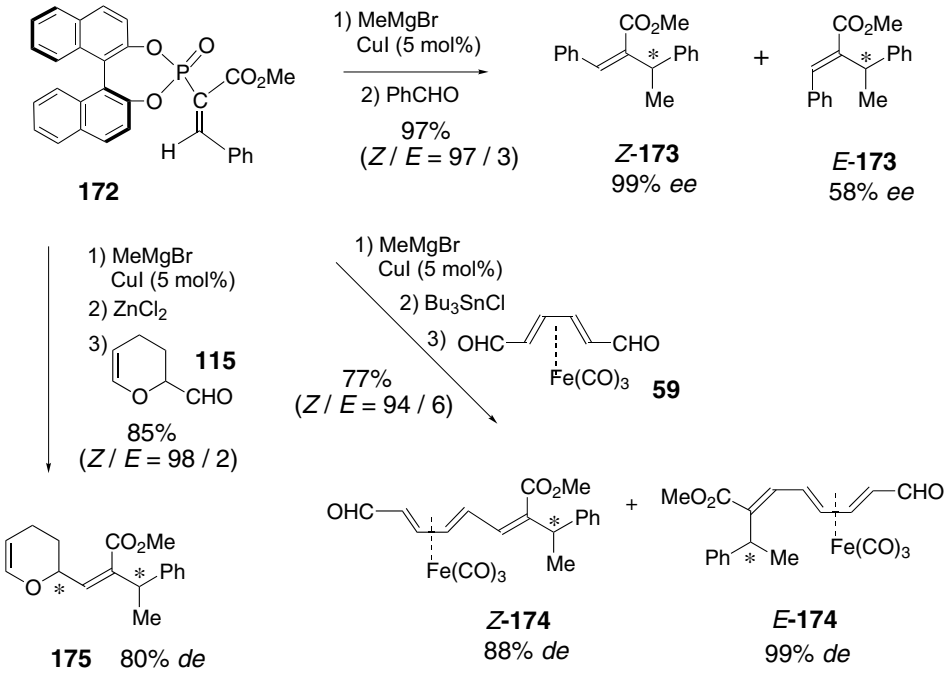
### 7.8.3
### Tandem Michael–HWE Reaction

Recently, asymmetric carbonyl olefination has been introduced into tandem-type reaction sequences for the construction of one or two asymmetric centers in a reaction involving the formation of two carbon–carbon bonds in a one-pot procedure [99]. Thus, the tandem Michael–HWE reaction was carried out starting from a substrate of the arylidene derivative **172**, which was derived from a chiral HWE reagent hitherto used for asymmetric olefination. The enolate derived from the initial Michael addition was reacted with benzaldehyde to give $\alpha,\beta$-unsaturated ester **173** with high enantiomeric excess. When the dialdehyde **59** was reacted as an electrophile in the second step, double asymmetric induction took place to afford both the (*Z*)- and (*E*)-alkenes **174** with high diastereoselectivity. Furthermore, dynamic kinetic resolution was observed in the tandem reaction with acrolein dimer **115** to yield the $\alpha,\beta$-unsaturated ester **175** having two stereogenic carbon centers in the branched substituents in more than 50% yield (85%) (Scheme 7.28). A change of the metal counterion to $Sn^{2+}$ or $Zn^{2+}$ was quite effective to achieve both high diastereoselectivity and good chemical yield in these interesting asymmetric transformations.

## 7.9
## Asymmetric Carbonyl Olefinations Without Usage of Optically Active Phosphorus Reagents

Recently, asymmetric induction mediated by external chiral ligands that are not covalently bonded to the reagent has attracted much attention, and it is believed that the information obtained from these studies will prove useful in developing a novel system for efficient catalytic asymmetric transformation. In order to explore the possibilities, a variety of reaction systems capable of effective asymmetric induction at a specific site in the course of a reaction have been devised, and several investigations have also been directed towards Wittig-type olefination. An early study using an optically active organic acid with stabilized ylides [22] was unfruitful, as discussed in the introductory section.

The HWE reactions of 4-*tert*-butylcyclohexanone (**1a**) with reagent **176** in the presence of the alkoxide of chiral amino alcohol **178** as a base resulted in the formation of dissymmetric alkene **179** in good yield with up to 52% *ee* [100] (Scheme 7.29). In this study, it was suggested that the addition step is reversible and that the

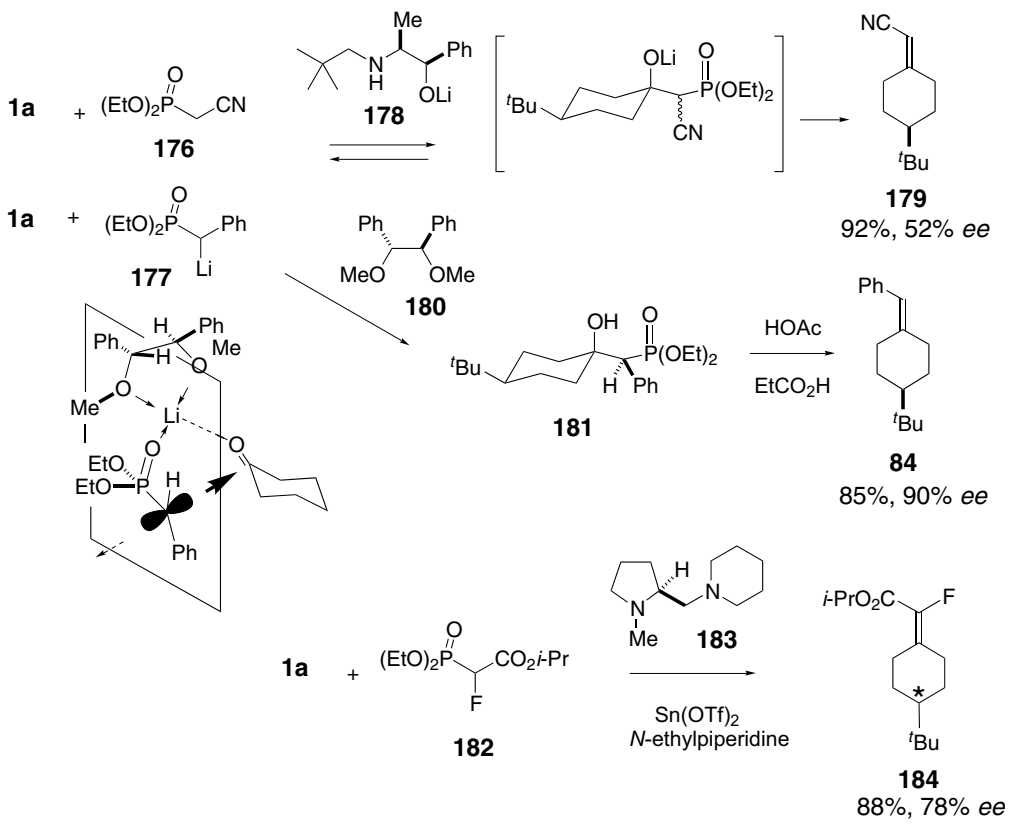



**Scheme 7.28.** Asymmetric tandem Michael–HWE reactions.

origin of asymmetric induction is probably a difference in elimination rate from the diastereomeric intermediates. In a closely related study, the lithiated achiral HWE reagent **177** was reacted with 4-*tert*-butylcyclohexanone (**1a**) in an asymmetric manner in the presence of chiral ligand **180** to give the isolable adduct **181**, from which the alkene **84** was obtained with a high level of optical purity in a discrete elimination step [101].

When the achiral phosphonate **182** was reacted with the ketone **1a** in the presence of Sn(II) triflate and *N*-ethylpiperidine, the chiral diamine **183** was shown to act as a good asymmetric inducer in generating the tetrasubstituted dissymmetric alkene **184** with a high level of enantiomeric excess [35j, 102]. In order to achieve high levels of asymmetric induction, stoichiometric amounts of ligands in relation to the external chiral source were required in all of the aforementioned asymmetric carbonyl olefinations.

The use of a substoichiometric amount (20 mol%) of an external chiral source was first demonstrated in the asymmetric olefination of a 4-substituted cyclohexanone [103] by using a chiral phase-transfer catalyst **186** derived from cinchonine; here, a combination of the chiral phase-transfer catalyst and rubidium hydroxide as a base was essential in generating the dissymmetric alkene **187** with 57% *ee* after a re-esterification step (Scheme 7.30). Though the problem of low turnover still has to be solved, this result provided an informative concept for the



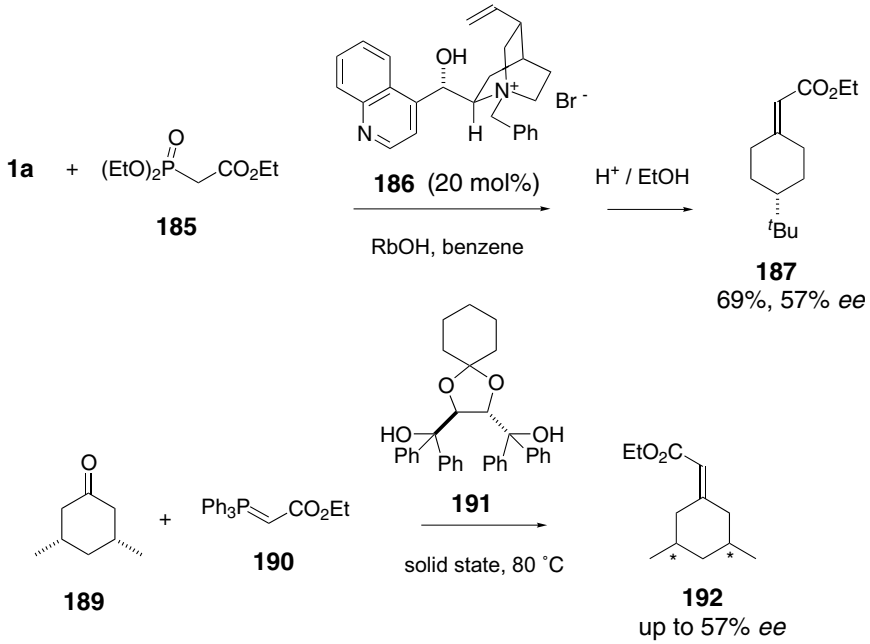

**Scheme 7.29.** Examples of asymmetric olefinations mediated by external chiral ligands.

development of new catalytic asymmetric olefination methods based on achiral Wittig-type reagents.

Besides the use of chiral bases or catalysts in solution, a rather interesting and unique approach that belongs to the present category involves the utilization of inclusion complexes of the stabilized ylides [104]. In the solid state, an achiral stabilized ylide such as **190** is reacted with a symmetrically substituted prochiral cyclohexanone such as **189** in the presence of a chiral host molecule. The best result was obtained using the chiral host molecule **191**, which gave the dissymmetric alkene **192** with up to 57% *ee*.

## 7.10
## Asymmetric Carbonyl Olefination by Non-Wittig-Type Routes

Asymmetric carbonyl olefination methods by routes other than the Wittig and related olefination reactions are available, and some precedents belonging to this



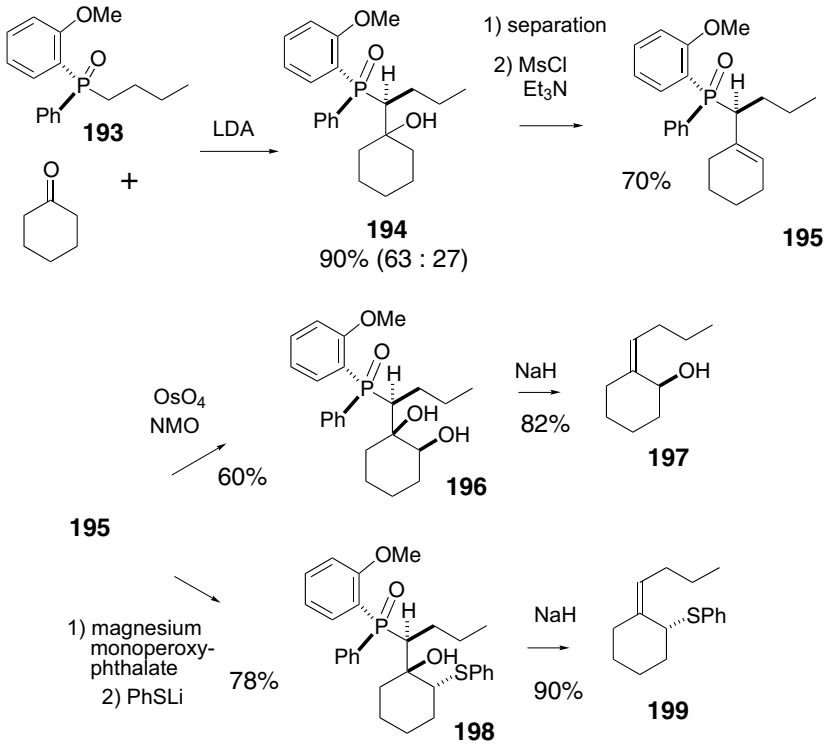

**Scheme 7.30.** Additional examples of asymmetric olefinations mediated by external chiral PTC or host molecules.

category will be emphasized in this section. There are some reports dealing with reactions in which carbon–carbon bond-forming reactions are not directly involved in simultaneous asymmetric induction, but where the overall process from the carbonyl compounds can be regarded as an asymmetric olefination. Consequently, a few of these approaches to dissymmetric alkenes will be briefly described here.

An example of asymmetric construction of alkylidenecyclohexane derivatives using an optically active chiral Horner-type reagent **193** has been reported [105]. At first glance, this transformation might appear to belong to Wittig-type asymmetric olefinations, but is essentially independent of the hitherto discussed strategies in spite of the use of a phosphorus reagent. Thus, in the overall transformation process to alkenes, an additional $sp^3$ unit was incorporated into **196** and **198** prior to Horner-type elimination to give **197** and **199**, respectively (Scheme 7.31).

In a total synthesis of the ginseng sesquiterpene (−)-*β*-panasinsene, ketone methylenation with optical resolution was reported [12a]. Thus, a kinetic resolution was operative in the reaction of the lithium carbanion of chiral sulfoximide **201** with the racemic ketone **200**, giving a separable mixture of two compounds, (+)-**202** and (+)-**203**. The latter diastereomer was converted to the natural product.

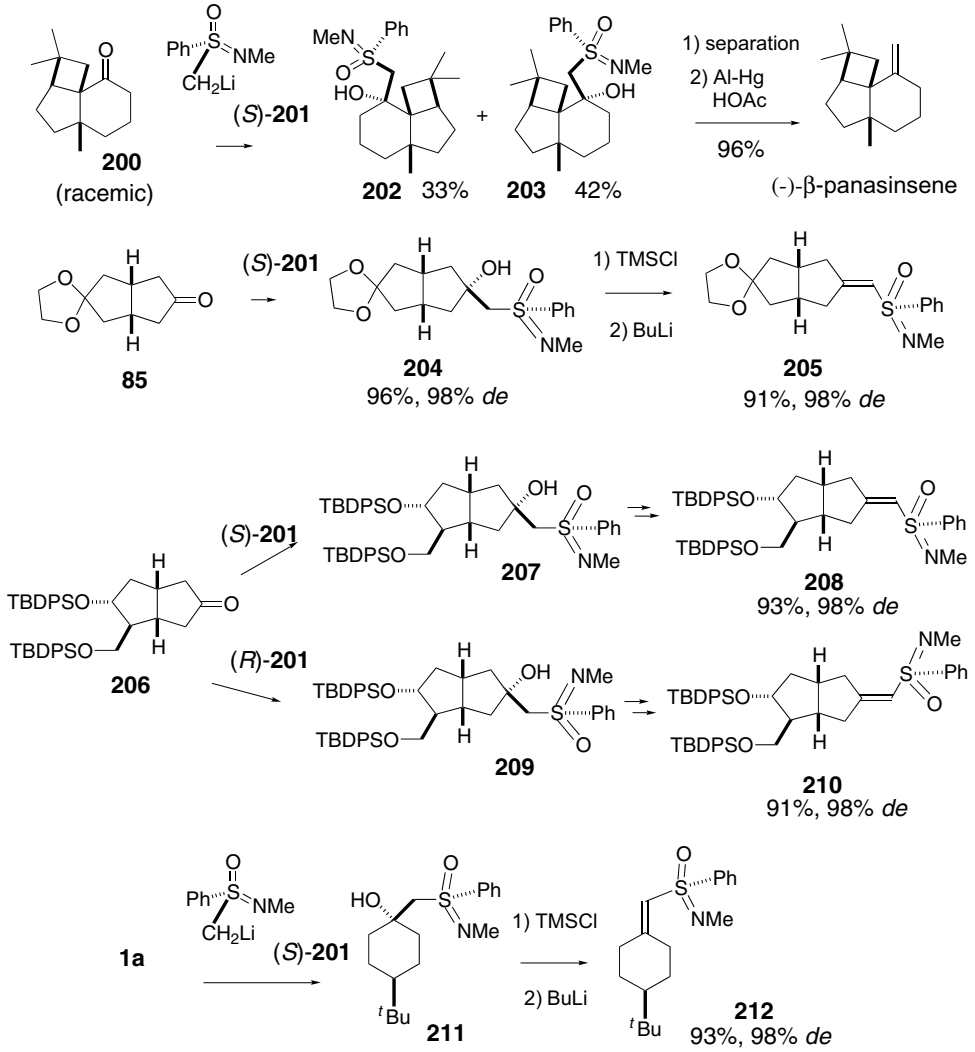
By using the same lithium salt (*S*)-**201**, asymmetric elimination to give **205** with high diastereotopic differentiation without loss of chirality was reported [15] (Scheme 7.32). This asymmetric carbonyl olefination allowed the selective synthesis of both the (*Z*)- and (*E*)-alkenylsulfoximides **208** and **210**, which are useful




**Scheme 7.31.** Miscellaneous examples of asymmetric carbonyl olefinations (1).

precursors for carbaprostacyclin derivatives. A possible explanation for the observed asymmetric elimination was provided, together with a proposed model intermediate from which elimination would be more rapid. The same chiral carbanion (s)-**201** was also used in asymmetric elimination to give 1-alkenylsulfoxide **212** with axial and central chirality through the adduct **211**.

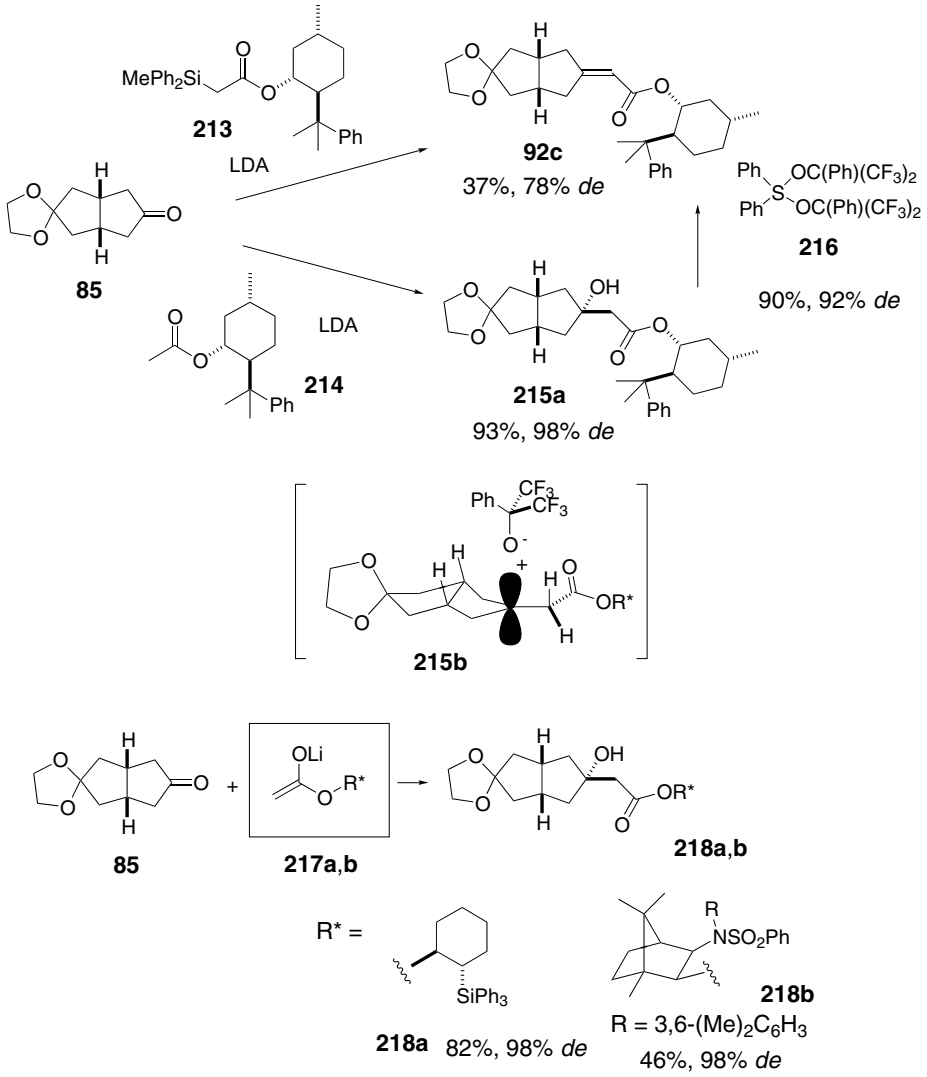
The Peterson reaction of an $\alpha$-silanyl carbanion with a carbonyl compound has been widely utilized as a powerful alternative and complementary synthetic tool for the preparation of substituted alkenes [106], but little effort has been devoted to the asymmetric version of this useful reaction. The Peterson reaction of the bicyclic ketone **85** with the silyl enolate of **213** bearing an 8-phenylmenthol moiety as a chiral auxiliary proceeded with the same sense and degree of asymmetric induction as the corresponding HWE reactions giving the alkene **92c** as described above [60]. The stereochemistry of the reaction can be rationalized in terms of a high substrate- and auxiliary-induced facial selectivity in the addition of an *E*-configured silyl enolate to the carbonyl group [59]. In the closely related transformations with the lithium enolates of 8-phenylmenthylacetate **214**, as well as its analogous enolates **217a, b**, the corresponding $\beta$-hydroxy esters **215a, 218ab** were obtained, which were dehydrated with moderate to high diastereoselectivity upon treatment with Martin's sulfurane **216** to give the alkene **92c** and the corresponding alkenes




**Scheme 7.32.** Miscellaneous examples of asymmetric carbonyl olefinations (2).

(Scheme 7.33). The dehydration proceeds according to an E1-mechanism, and the carbenium ions exist as contact ion pairs with the base $[OC(Ph)(CF_3)_2]^-$ as the counter ion; the H-atom, the empty p-orbital, and the p-orbital of the carbonyl are most likely aligned in a mutually periplanar fashion, as in **215b**. Attack of the base on the pro-*R* H atom leads to the *Z*-alkene from the transition state that is hindered neither by the auxiliary nor by the bicyclic ring system. This successful extension of the two-step asymmetric olefination of prochiral cycloalkanone derivatives proved to offer an additional route to axially chiral alkenes.

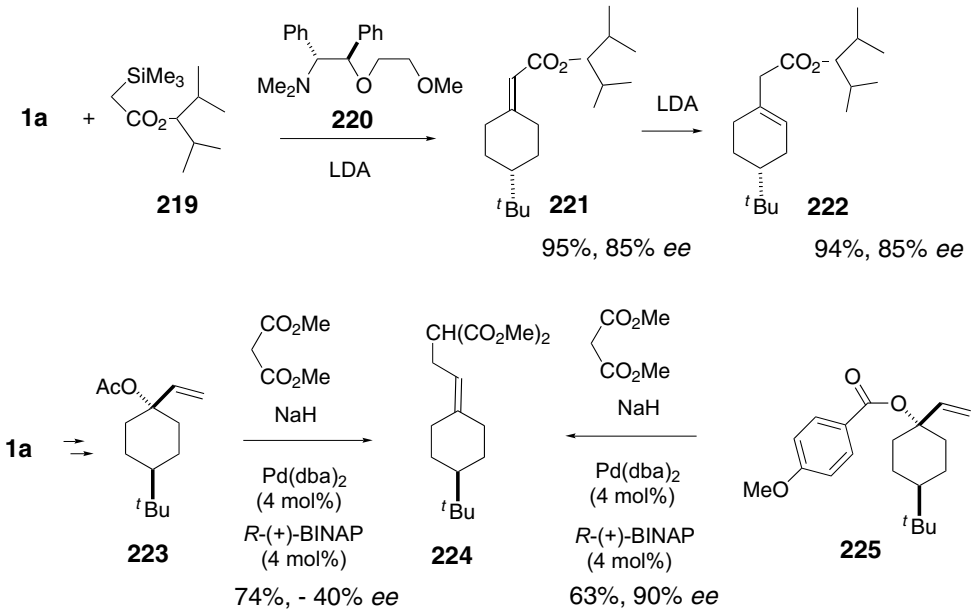
Asymmetric Peterson reaction of symmetrically substituted cyclohexanone derivatives with the lithium enolate of silanylacetate **219** in the presence of chiral




**Scheme 7.33.** Miscellaneous examples of asymmetric carbonyl olefinations (3).

ligand **220** has recently been demonstrated to give the corresponding alkylidene derivatives **221** with enantioselectivities of up to 85% [107]. An external chiral tridentate amino diether was used for this asymmetric transformation, where three equivalents of the lithium enolate–chiral ligand complex was necessary for satisfactory asymmetric induction. Stereospecific transfer of axial chirality to central chirality in **222** was achieved by treatment of non-racemic alkylidene derivatives **221** with LDA (Scheme 7.34).

Although elimination of chiral sulfoxides [13] or selenoxides [16], as well as asymmetric deprotonation [18] with chiral bases, offer alternative routes to axially




**Scheme 7.34.** Miscellaneous examples of asymmetric carbonyl olefinations (4).

chiral non-racemic alkenes, the starting compounds in these transformations are not necessarily carbonyl compounds or their equivalents. Therefore, these reactions will not be emphasized in this chapter.

On the other hand, the approach based on Pd-catalyzed asymmetric synthesis of axially chiral alkenes must be briefly discussed here, since the starting esters of allylic alcohol can be essentially derived from carbonyl compounds through nucleophilic addition of the vinyl anion or its equivalent followed by esterification. An early study of this asymmetric transformation showed that *trans*-4-*tert*-butyl-1-vinylcyclohexyl acetate (**223**) gave optically active (up to 40% *ee*) dimethyl 2-(4-*tert*-butylcyclohexylidene)methylmalonate (**224**) through Pd-catalyzed allylic substitution with sodium dimethylmalonate in the presence of 4 mol% of a chiral phosphine ligand such as (*R*)-(+)-BINAP [17a]. The enantioselectivity was greatly improved by both electronic and steric tuning of the structure of the benzoate substrate. Use of allylic benzoates such as **225**, bearing electron-donating *p*-substituents, in this case a methoxy group, led to efficient asymmetric induction of up to 90% *ee* under the same reaction conditions [17c].

## 7.11
## Concluding Remarks and Future Perspectives

Since the pioneering contributions of a few early investigations, work on asymmetric olefination has been extensively developed over the past 20 years, and in

particular many exciting and useful applications of this transformation have been conceived only in the last decade. As can be seen from the foregoing discussion, it is fair to say that this field of chemistry has only just been born.

Despite the inherent low atom economy of the Wittig and related reactions from the viewpoint of so-called green chemistry [108], asymmetric transformation with this class of phosphorus reagents seems to be quite an attractive method since the reactions proceed with concomitant elimination of the phosphorus groups, resulting either in the direct production of optically active olefinic compounds or, more usually, a separable mixture with a high diastereomeric excess in a stereochemically predictable manner.

Most optically active olefinic products possess axial or planar chirality, which can be easily converted into central chirality by further appropriate chemical transformation without any serious loss of optical purity. The products obtained by the discrimination of enantiotopic carbonyl groups or kinetic resolution already have central chirality as well as reactive functional groups such as olefinic or unsaturated carbonyl systems. Consequently, asymmetric olefination provides an efficient methodology for the construction of useful chiral synthons; applications along these lines in the asymmetric construction of useful and complex chiral molecules have just started and will be extensively investigated in the future.

Though several different approaches to optically active olefinic compounds through asymmetric Wittig and related transformations have hitherto been demonstrated, their success still depends on appropriate choice of the carbonyl compounds used as substrates. This restriction often limits the applicability of asymmetric olefination in the construction of complex chiral molecules. Moreover, the substituents and functionalities on both the substrates and the reagents have a significant influence on the degree and success of the asymmetric induction, the course of the stereochemistry, as well as the reactivity of the ylides or carbanions. The nature of the metallic cation and the reaction conditions, including the nature of the solvent, might also affect the stereochemistry and yields of the olefinic products. In this context, more detailed and extensive mechanistic investigations are required for a full understanding of the aforementioned phenomena, which, in turn, should lead to the further development of asymmetric olefination methodologies based on new designs and concepts. More detailed mechanistic studies should also help to predict the stereochemistry of the olefinic products. Apart from the few examples of established chiral phosphorus reagents employed for asymmetric olefinations, improved availability of chiral sources is necessary for economic and practical reasons; efforts to overcome these limitations are sure to make asymmetric olefination an attractive and useful methodology for the creation of optically active compounds.

External catalysts play a role not only in rate enhancement but also in creating favorable bias in the stereochemistry at the transition state. Consequently, the design of catalyst systems occupies an essential and central position in the future study of asymmetric transformations, including olefination. The use of external chiral sources with a combination of achiral or racemic reagents has been developed in recent years, and this approach holds promise for the future development

of efficient asymmetric catalytic procedures. As yet, however, the reported reaction systems still suffer from slow turnovers. Since the asymmetric methods studied to date have utilized expensive and difficult to obtain chiral sources, a reduction in the amount of such chiral sources to catalytic levels would be highly desirable for practical application to asymmetric transformations. The development of asymmetric reactions requiring only catalytic amounts of the chiral source, and that generate the product with predictable stereochemistry should make asymmetric olefination more popular and familiar. There are some publications in which catalytic cycles are proposed for catalytic Wittig-type reactions [109, 110]. In these studies, novel arsenium or telluride reagents have been designed and used to give olefinic compounds in high yields. It seems likely that the establishment of novel redox systems along with the design of chiral catalysts and reagents will be central to achieving catalytic asymmetric olefination through Wittig-type reactions.

In conclusion, it is clear that the development and successful investigation of chiral catalyst systems for this class of asymmetric transformation is still in its infancy, and there is no doubt that the establishment of effective catalytic systems of economic value remains a challenging goal for future research. Major investigations on asymmetric olefination are thus sure to unfold.

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