

Recent Advances in Asymmetric Wittig-Type Reactions*

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Reactions in which no new sp^3 stereocenters are formed can nevertheless be used for asymmetric synthesis if substrates are employed which contain either a stereogenic unit or another prostereogenic unit apart from the reacting functional group. In this way, asymmetric versions of such powerful reactions as the Wittig reaction and its variants can be developed. Recently, the interest in this class of asymmetric reactions has grown, and several useful new reagents and methods have been reported. In this review, a short discussion of different substrate types is followed by an overview of the results obtained in various asymmetric Wittig-type reactions.

Despite the profound importance of the Wittig reaction and its variants in synthetic chemistry, there still remain mechanistic details which have not been completely elucidated. In some cases, however, structure determinations on intermediates isolated from asymmetric alkenylation reactions have given mechanistic insights. These observations are discussed, and an attempt is also given to rationalize results obtained in reactions involving reagents in which 8-phenylmenthol has been used as a chiral auxiliary.

Finally, the possibilities for developing catalytic asymmetric Wittig-type reactions are briefly discussed.

The area of asymmetric organic synthesis has attracted increasing attention during recent years, and many powerful new asymmetric reaction processes have been reported.¹ However, only a limited number of studies aimed at the development of asymmetric Wittig-type reactions have been published to date, despite the profound importance non-asymmetric versions of such reactions have in synthetic organic chemistry.^{2,3} In part, this discrepancy might originate from the fact that no new sp^3 stereocenter is formed in a Wittig-type reaction; thus, for asymmetric induction to be possible, there are some restrictions as to which substrates can be used. Nevertheless, the interest in this class of asymmetric reaction has grown recently as evidenced by an increasing number of publications, and applications of such reactions in approaches to more challenging synthetic targets have also begun to emerge. In this review, an overview of the results obtained in the area to date is given, as well as some reflections on the directions in which this field of research might move in the future.

Depending on the particular type of phosphorous functionality used in the reagent, different reaction types have been associated with different names. In asymmetric reactions, both phosphonium ylids,^{4–12} phosphonates,^{13–23} phosphonic bisamides,^{24,25} phosphonamidates,^{26,27} thiophosphonates,²⁸ phosphinates,^{29,30} phosphinothioic amides³¹ and phosphine oxides^{16,32} have been utilized as reagents (Fig. 1). The name Wittig reagents is normally reserved for phosphonium ylids; in this review, we follow the example set in a recent review² and refer to phosphonates as Horner–Wadsworth–Emmons (HWE) reagents, whereas phosphine oxides are labeled as Horner reagents. Other phosphonic acid derivatives (phosphonic bisamides and phosphonamidates) will also be referred to as HWE reagents.

Beside Wittig-type reactions, other methods for preparing C=C double bonds with simultaneous asymmetric induction have also been reported (e.g., via asymmetric deprotonation,³³ by use of chiral sulfoximides,^{34,35} chiral sulfoxides,³⁶ or chiral selenoxides,^{37–40} via asymmetric palladium-catalyzed nucleophilic substitution,^{41–43} by kinetic resolution via asymmetric dihydroxylation,⁴⁴ or by classical resolution of a racemate⁴⁵). However, these methods will not be discussed in any detail in this review.

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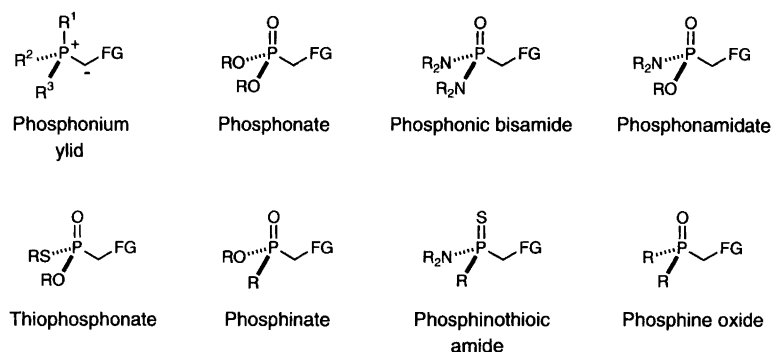


Fig. 1. Different classes of Wittig-type reagent which have been used in asymmetric reactions. FG = H, alkyl, aryl, or functional group.

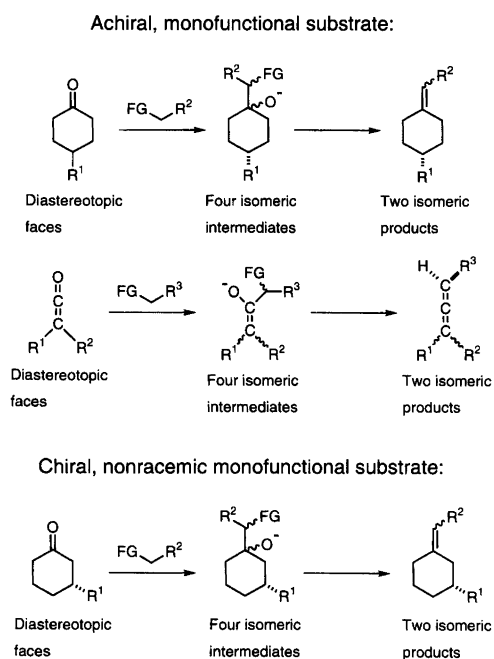
Asymmetric Wittig-type reactions: an overview of results obtained to date

Since no new sp^3 stereocenter is formed in Wittig-type reactions, it is usually required that the substrate contains either a stereogenic or a prostereogenic unit apart from the carbonyl group, to make the process capable of giving asymmetric induction (an exception to this rule occurs, however, if additional stereocenters can be introduced before the C=C bond is finally formed³²). In Schemes 1 and 2, different possible situations are illustrated. As shown in Scheme 1, in cases where only one carbonyl group is available for reaction, two isomeric products can form via four isomeric intermediates. If two enantiotopic carbonyl groups are present, however, the situation becomes more complex: eight isomeric

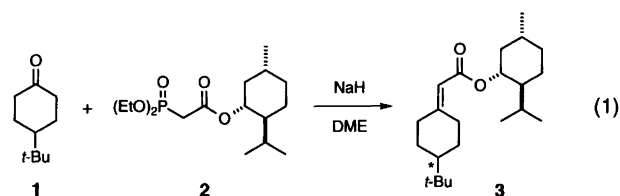
intermediates can form, and as a result four isomeric products might be obtained.

In the following discussion, the different results presented have been arranged according to the type of substrate used.

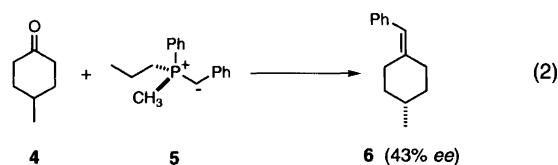
Achiral, monofunctional substrates. The possibility to convert a prochiral ketone to an axially dissymmetric alkene has been investigated by several groups.^{4-7,13-16,24-28} In particular, 4-substituted cyclohexanones have been used as model substrates in this context, but other symmetrically substituted ketones have also been tested.^{4,7,14} In the very first published examples of asymmetric Wittig-type reactions,¹³ cyclohexanones (e.g., **1**) were reacted with the chiral phosphonate **2** derived from menthol [eqn. (1)]

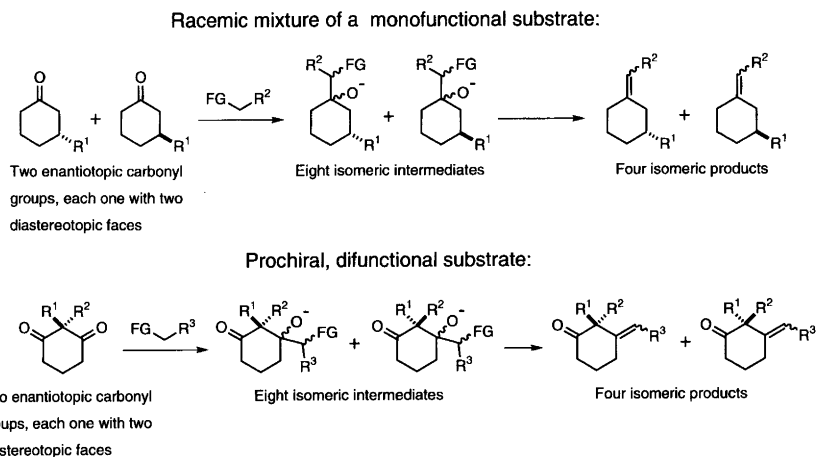


Scheme 1. Number of possible isomeric intermediates and products which can be obtained from an achiral, monofunctional substrate and from a chiral, non-racemic monofunctional substrate. FG = phosphorus-based functional group.



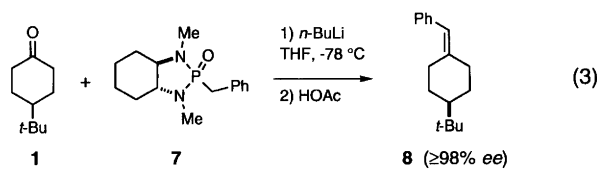
to give the product esters in diastereomerically enriched form (there is some doubt²⁴ as to the level of asymmetric induction obtained, however). Bestmann and Lienert reported the first use of a chiral, non-racemic phosphonium ylid containing a stereogenic phosphorus center in a Wittig reaction.⁴ They obtained alkene **6** in 43% *ee* from 4-methylcyclohexanone (**4**) by use of reagent **5** [eqn. (2)].



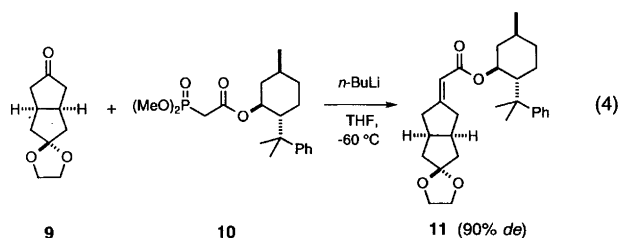


Scheme 2. Number of possible isomeric intermediates and products which can be obtained from a racemic mixture of a monofunctional substrate and from a prochiral, difunctional substrate. FG = phosphorus-based functional group.

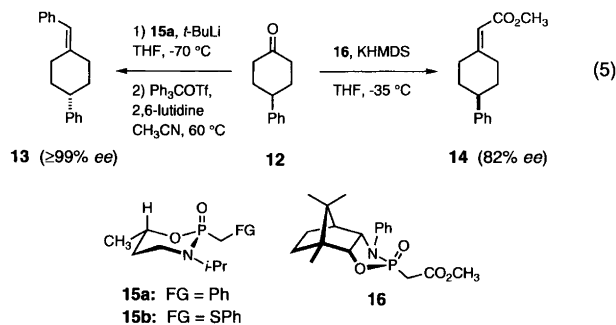
Reagent **7** and related phosphonic bisamides, which were introduced by Hanessian,^{24,25} were the first reagents reported to give high levels of enantioselectivity [eqn. (3)];



in several reactions, chiral alkenes of $>98\%$ ee were obtained. Such products have been used further by Hanessian in the preparation of a variety of building blocks containing methyl-substituted stereocenters.⁴⁶ In 1988, Gais¹⁴ and Rehwinkel¹⁵ independently studied reactions with reagent **10**, prepared from (1*S*, 2*R*, 5*S*)-8-phenylmenthol, and related chiral phosphonoacetates (including the enantiomeric reagent **28a**, see below). As shown by Gais,¹⁴ reaction of **10** with the *meso*-ketone **9** gave the desired chiral alkene **11** with high selectivity [eqn. (4)].

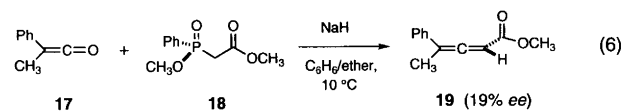


More recently, Denmark has demonstrated that the chiral phosphonamidates **15**²⁶ and **16**²⁷ can be used for the preparation of differently functionalized dissymmetric alkenes in high ee [eqn. (5)].



The phenylthio functionality introduced by use of reagent **15b** is, in turn, useful for incorporating new substituents into the alkene. A chiral thiophosphonate²⁸ and a Horner reagent derived from 8-phenylmenthol¹⁶ (reagent **35**, see below) have also been tested in reactions with 4-substituted cyclohexanones, but gave low selectivities.

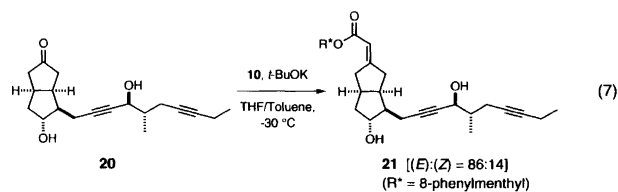
To date, attempts to prepare chiral alkenes by reaction of chiral Wittig-type reagents with ketenes or acid chlorides have given only modest levels of asymmetric induction.^{8,9,29,30} In one of the few documented cases the chiral phosphinate ester **18** gave the chiral allene **19**, unfortunately in only 19% ee [eqn. (6)].³⁰



This also constitutes one of the few examples of use of a chiral phosphinate.^{29,30}

Chiral, non-racemic monofunctional substrates. When preparing an alkene from an unsymmetrical, chiral ketone, use of a chiral reagent can offer improved possibilities for control of the double bond geometry in the product. These reactions constitute examples of double asymmet-

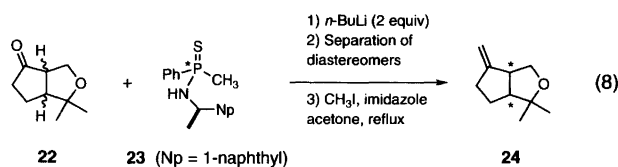
ric synthesis:⁴⁷ if the influence of the chiral reagent can override the intrinsic (and often low) stereochemical preference of the substrate, either *E* or *Z* products can be obtained by use of the appropriate enantiomer of the reagent. In approaches to prostacyclin analogs, Gais¹⁴ and Rehwinkel¹⁵ employed this technique to prepare **21** and similar key intermediates with good double bond selectivity [eqn. (7)]:



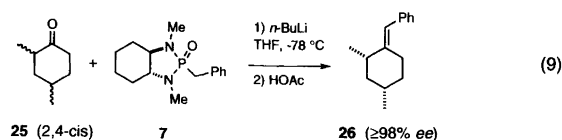
use of an achiral phosphonate ($R^* = \text{Me}$) instead of the chiral reagent **10** gave much lower selectivity. Hanessian's phosphonic bisamide reagents (e.g., **7**) have also proved useful in similar processes.^{24,25}

Kinetic resolution of racemic monofunctional substrates.

By reacting a chiral, racemic carbonyl compound with a chiral Wittig-type reagent, kinetic resolution of the substrate might be observed. This is a more demanding process than the ones previously exemplified, since the chiral reagent in this case has to distinguish between two enantiotopic carbonyl groups (one in each enantiomer of the substrate), and between two diastereotopic faces at each carbonyl group. The first documented attempt at performing kinetic resolution of a chiral, racemic ketone, through reaction with the chiral phosphinate **18**,²⁹ met with limited success. An early example of a successful kinetic resolution was provided by Johnson and coworkers,³¹ who prepared both enantiomers of the monoterpene **24** from the racemic ketone **22** by reaction with the chiral phosphinothioic amide **23** [eqn. (8)];

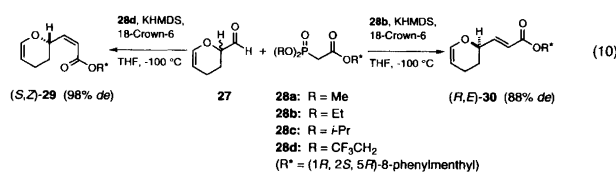


absolute configuration at phosphorus in **23** not reported]. The success of this approach relied on the efficient chromatographic separation of the isolable diastereomeric β -hydroxyphosphinothioic amides. More recently, several examples of efficient kinetic resolution of racemic ketones have been reported: reagent **7** has been utilized for kinetic resolution of 2-substituted cyclohexanones with excellent selectivity [eqn. (9)],²⁵

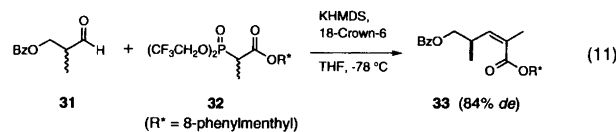


and resolutions of 3-substituted cyclohexanones through reactions with phosphonamide **16** have also been reported.²⁷

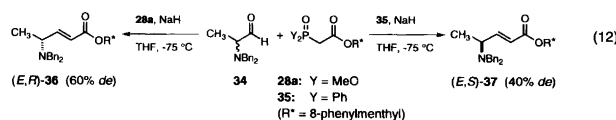
The first example of kinetic resolution of a racemic aldehyde was demonstrated by Rein and Reiser.¹⁷ In reactions with aldehyde **27**, it was found that an appropriate choice of the R group in the chiral phosphonates **28** gave access to either (*S,Z*)-**29** or (*R,E*)-**30** with good to excellent diastereoselectivities [eqn. (10)].



Very recently, it has also been shown that the related chiral phosphonopropionate reagent **32** can be used in kinetic resolution of racemic aldehydes¹⁸ to give (*Z*)-trisubstituted alkenes (e.g., **33**) with high levels of asymmetric induction [eqn. (11)].

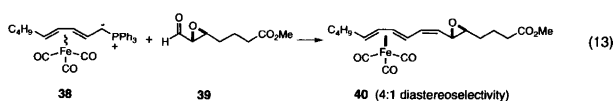


Furuta and Iwamura have also employed chiral reagents derived from 8-phenylmenthol in kinetic resolutions of aldehydes.¹⁶ They made the interesting observation that in kinetic resolutions of (\pm)-*N,N*-dibenzylalaninal (**34**), the phosphonate **28a** and the phosphine oxide **35** both gave *E*-alkenes as main products, but with opposite absolute configuration at the allylic stereocenter: **28a** gave predominantly (*E,R*)-**36**, while **35** afforded (*E,S*)-**37**, in both cases with moderate diastereoselection [eqn. (12)].

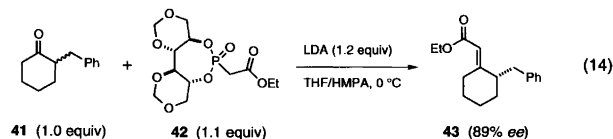


Kinetic resolution of racemic Wittig reagents. Two examples of kinetic resolution of a racemic phosphonium ylid by reaction with a chiral carbonyl compound have been reported.^{9,10} In an early study,⁹ Bestmann found that racemic phosphonium ylids could be reacted with optically active acid chlorides to give chiral allenes, although the levels of asymmetric induction obtained were only modest. In a more recent case,¹⁰ the chiral

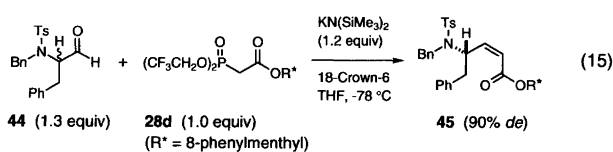
aldehyde **39** was reacted with the racemic phosphonium ylid **38**, which contains a stereogenic η^4 -dienyl-Fe(CO)₃ unit, to give alkene **40** as the main product [eqn. (13)].



Dynamic kinetic resolution. An inherent limitation of standard kinetic resolutions is that the racemic substrate has to be present in at least a twofold excess in order to enable complete conversion of the chiral reagent into a single product isomer. On the other hand, if reactions conditions can be found under which the enantiomers of the substrate equilibrate rapidly, it becomes theoretically possible to obtain a quantitative yield of a single product from only stoichiometric amounts of substrate. Such dynamic kinetic resolutions⁴⁸ have recently been reported both for racemic ketone¹⁹ and aldehyde²⁰ substrates by use of chiral HWE reagents. Narasaka and Gras showed¹⁹ that reaction of equimolar amounts of racemic 2-benzylcyclohexanone (**41**) and phosphonate **42** (derived from mannitol), in the presence of a small excess of LDA, provided the (*S,E*)-alkene **43** in 89% *ee* [eqn. (14)].



The possibility to use protected α -amino aldehydes (e.g., **44**) as substrates for dynamic kinetic resolutions was demonstrated by Rein and Reiser [eqn. (15)].²⁰

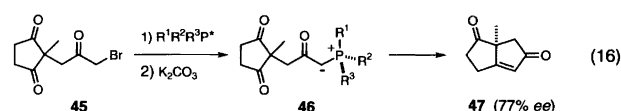


Consequently, this strategy also offers an entry to γ -aminoalkenes formally derived from unnatural amino acids. The resulting alkene products, which should be of general interest as synthetic building blocks (e.g., for the preparation of new peptidomimetics),⁴⁹ were obtained in up to 94% *de*. It should be noted that in some cases the selectivities obtained in these dynamic resolutions were significantly higher than in the corresponding standard kinetic resolutions.

Difunctional substrates. If a compound containing two enantiotopic carbonyl groups is used as the substrate, a chiral Wittig-type reagent might give selective reaction at one of the carbonyl groups, a process which then will

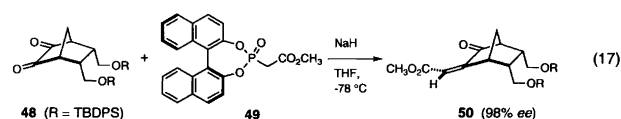
also result in asymmetric induction. Such reactions are conceptually related to the kinetic resolutions described earlier, in that the chiral reagent needs to differentiate between two enantiotopic functional groups and between two diastereotopic faces at the reacting group.^{50,51} One principal difference, however, is that when bifunctional substrates are used, the initially formed monoaddition products can sometimes react further to form bisaddition products. Since the diastereomeric monoaddition products will usually react at different rates in this second reaction, the ratio between the remaining monoaddition isomers will change depending on the extent to which bisaddition products have been formed.⁵²

In the first reported case of an asymmetric Wittig-type reaction in which a substrate containing two enantiotopic carbonyl groups was used,^{11,12} Trost and Curran converted triketone **45** into the bicyclic product **47** via an intramolecular Wittig reaction of the stabilized ylid **46** [eqn. (16)].

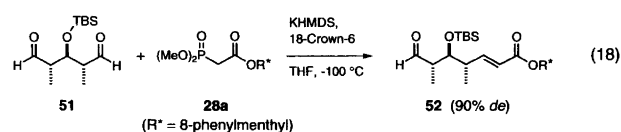


In this case, the asymmetric induction originated from the stereogenic phosphorus center; several chiral phosphines were examined, with (+)-(*R*)-CAMP (cyclohexyl-*o*-anisylmethyl phosphine) giving the highest selectivity (77% *ee*). Compound **47** has served as a key building block in preparation of polycyclopentanoid natural products.⁵³

The possibility to achieve high selectivities in related intermolecular processes was recently independently demonstrated by Fuji²² and Rein,²¹ using diketone and dialdehyde substrates, respectively. Fuji utilized the binaphthol-derived, chiral HWE reagent **49**,²² and obtained the (*Z*)-monoaddition product **50** in 98% *ee* and excellent yield from the α -diketone **48** [eqn. (17)].



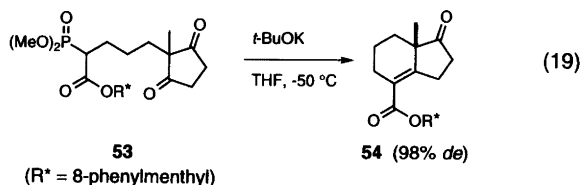
In reactions between the chiral phosphonate **28a** and two differently substituted *meso*-dialdehydes (e.g., **51**),²¹ Rein and Kann obtained (*E*)-monoaddition products with good diastereoselectivity [eqn. (18)].



Subsequent work has shown that if phosphonate **28d** is used instead of **28a**, monoaddition products with (*Z*)-

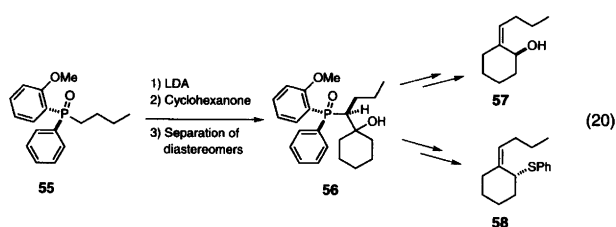
geometry are produced with equally high levels of asymmetric induction.⁵⁴ Alkene **52** and related compounds should find further use in the syntheses of various polypropionate natural products.

In an elegant application²³ of the use of 8-phenylmenthol-derived phosphonates, Mandai constructed the bicyclic compound **54** from the chiral precursor **53** (which, in turn, was prepared from **28a**) via an intramolecular HWE reaction [eqn. (19)].



Compound **54** is a potentially useful building block for vitamin D₃ analogs. The fact that in this case a tetrasubstituted alkene is formed with excellent selectivity and in good yield is a demonstration of the synthetic power of the HWE reaction.

Non-prochiral substrates. In some cases, the initial adduct formed by reaction of a Wittig-type reagent with a carbonyl compound is stable enough to be isolated. This opens the possibility of introducing additional stereocenters into the molecule before performing the final elimination step, in which the C=C bond is formed. Warren has studied several variations on this theme; in the example illustrated,³² intermediate **56** was produced from the chiral Horner reagent **55** and cyclohexanone, and then further converted into alcohol **57** and sulfide **58** [eqn. (20)].



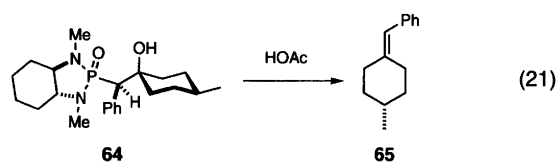
Mechanism: several important questions remain to be answered

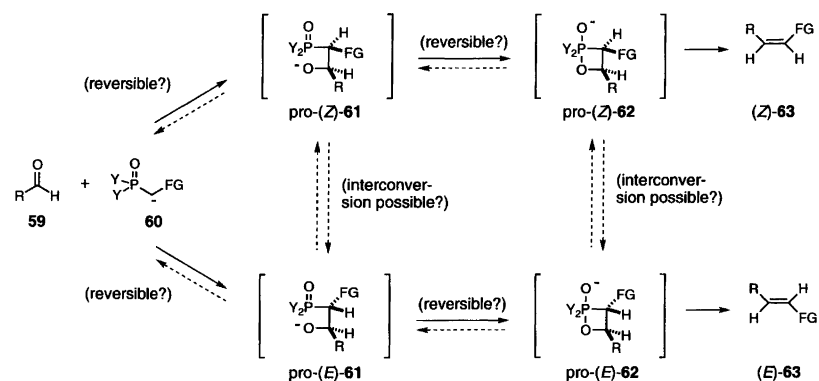
Although the Wittig reaction and its variants have been extensively used by synthetic chemists for more than 30 years, there still are several details concerning the mechanism which remain to be elucidated, even for the parent (i.e., non-asymmetric) reactions. Consequently, for most of the asymmetric reactions reported so far, detailed proof concerning the reasons for the observed selectivities has not yet been obtained; nevertheless, in these cases, a 'working hypothesis' based on certain given assumptions can often be formulated, in the absence of more rigorous proof. A detailed discussion about the mechanism of the general Wittig reaction and its variants is beyond the

scope of this article; for more information, the reader is referred to two excellent reviews.^{2,3} Here, we will limit the discussion to selected asymmetric processes.

In the vast majority of the published asymmetric Wittig-type reactions in which high levels of induction have been observed, HWE reagents have been utilized. Scheme 3 illustrates the general mechanism for reactions involving such reagents.^{2,3} The mechanism for the Horner variant (involving phosphine oxides, Y = alkyl or aryl) is closely related; in the currently favored mechanism for the Wittig reaction, however, oxaphosphetanes are formed directly from the starting materials, without the involvement of betaine intermediates (i.e., intermediates corresponding to **61** in Scheme 3).^{2,3,55} When rationalizing the stereochemical outcome of these reactions – either the asymmetric or non-asymmetric versions – a crucial point of course concerns the reaction step in which the relative and absolute configurations of the stereocenters in the product are determined. This, in turn, will depend on whether the initial addition step is reversible or not. For the Wittig reaction, accumulated evidence favors the view that the initial addition step (formation of an oxaphosphetane) is usually irreversible, both when non-stabilized, semi-stabilized or stabilized ylids are employed.^{2,3} When HWE or Horner reagents are used, on the other hand, the relative rates of the addition, retroaddition and elimination steps will be influenced by several factors, such as the presence or absence of a strongly anion-stabilizing functional group [e.g., C(=O)OR], the nature of the substituents at phosphorus, the reaction conditions (temperature, solvent, and type of metal counter-ion present), and the substrate structure.^{2,3} Often, a subtle balance between these factors will determine the overall result of the reaction.⁵⁶ Furthermore, there is the additional possibility that intermediates *pro*-(Z)-**61** and *pro*-(E)-**61** [or *pro*-(Z)-**62** and *pro*-(E)-**62**] might interconvert directly without reverting to starting materials,⁵⁷ if there remains a reasonably acidic proton on the phosphoryl-substituted carbon.

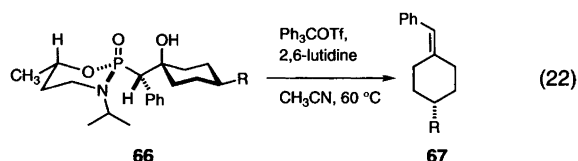
When strongly anion-stabilizing groups are not present in the HWE reagent, the initial adducts can often be isolated; elimination to form the final alkene product is then performed as a separate synthetic operation. In reactions involving the Hanessian reagent **7**, structure determinations on the intermediate adducts have provided mechanistic insights. Compound **64** was isolated as the initial product from a reaction between **7** and 4-methylcyclohexanone,²⁵ and upon subsequent treatment with acetic acid afforded the alkene **65** [eqn. (21)].





Scheme 3. General mechanism for the HWE reaction. Y=RO or R₂N; FG=H, alkyl, aryl, or functional group.

As indicated by the structure of **64**, the *Si* face of the anion of **7** has attacked the equatorially oriented face of the carbonyl group. The structure of the intermediate observed in the kinetic resolution of (\pm)-2-methylcyclohexanone with reagent **7**²⁵ can be rationalized by identical arguments. Analogously, in reactions between phosphoramidate **15** and 4-substituted cyclohexanones,²⁶ the formation of the alkenes **67** was explained as occurring via a *syn*-elimination from the intermediate adduct **66** [eqn. (22)];

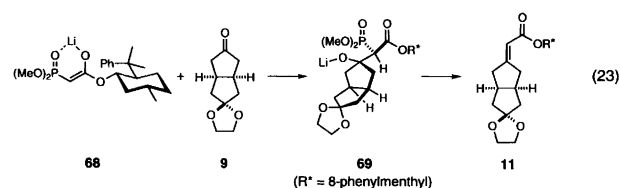


this, in turn, would form by attack of the *Re* face of the anion of **15** on the equatorial face of the ketone. Optimization of the reaction conditions showed that the elimination step was best performed using a trityl salt as promoter. In contrast, treatment of the intermediate **66** with a potassium base afforded the alkene in low enantiomeric purity along with recovered reagent **15**, thus indicating that under conditions in which the initial addition step is reversible only poor product selectivities can be obtained. The stereochemistry of the products formed from phosphoramidate **16** can be explained by similar arguments²⁷ if one assumes that the initial addition step is irreversible under the reaction conditions employed.

To explain the outcome of the reactions in which the chiral phosphonate **42** was used,¹⁹ Narasaka and Gras performed molecular mechanics calculations on the different possible intermediate diastereomeric oxyanions. They concluded that out of eight possible diastereomeric intermediates, three were much lower in energy than the others; of these three, two were precursors to the observed main product, and elimination was calculated to occur most readily from these two oxyanions. Thus, in this case it was postulated that the addition step is reversible, and that the product stereochemistry is determined by

the relative rates of elimination from the different diastereomeric intermediates.

In several of the reported reactions in which chiral phosphonates are used, 8-phenylmenthol esters are used as chiral auxiliaries. Because of the many parameters which can influence the product stereochemistry, detailed analyses of these reactions are quite complex, and rigorous proof concerning several aspects are still lacking. Nevertheless, we will put forth an attempt at rationalizing some of these results, although the line of argument should be considered only as a 'working hypothesis'. In one of the reports concerning reagent **10**,¹⁴ the (*Z*)-enolate **68** [eqn. (23)]



was illustrated as a likely^{2,58} intermediate. Furthermore, the fact that products with similar stereochemistry were formed both from the lithium¹⁴ and the potassium¹⁵ enolates indicates that both these enolates have the same geometry [the (*Z*)- and (*E*)-enolates should show opposite facial selectivities owing to the influence of the chiral auxiliary]. The main product from reaction with *meso*-ketone **9** can then be explained as originating by attack of the (*Z*)-enolate **68**, from its least shielded face, on the most accessible face of **9** to give intermediate **69**, followed by *syn*-elimination of dialkylphosphate anion [eqn. (23)]. Given the reaction conditions used, it is reasonable to assume kinetic control in the addition step,⁵⁶ and the influence of the 8-phenylmenthol unit on the facial selectivity of the phosphonate is analogous to other reported reactions involving 8-phenylmenthol esters.⁵⁹ By similar reasoning, compound **54**²³ [eqn. (19)] would form by attack of the (*Z*)-enolate derived from **53**, from its least shielded face, on one of the carbonyl faces projecting towards the connecting chain, followed by *syn*-elimination [note that in this reaction, the (1*S*, 2*S*,

5*R*-enantiomer of 8-phenylmenthol was utilized]. Attack from the same face of the enolate on the most accessible face of the other carbonyl group would give an intermediate which is incapable of undergoing *syn*-elimination.

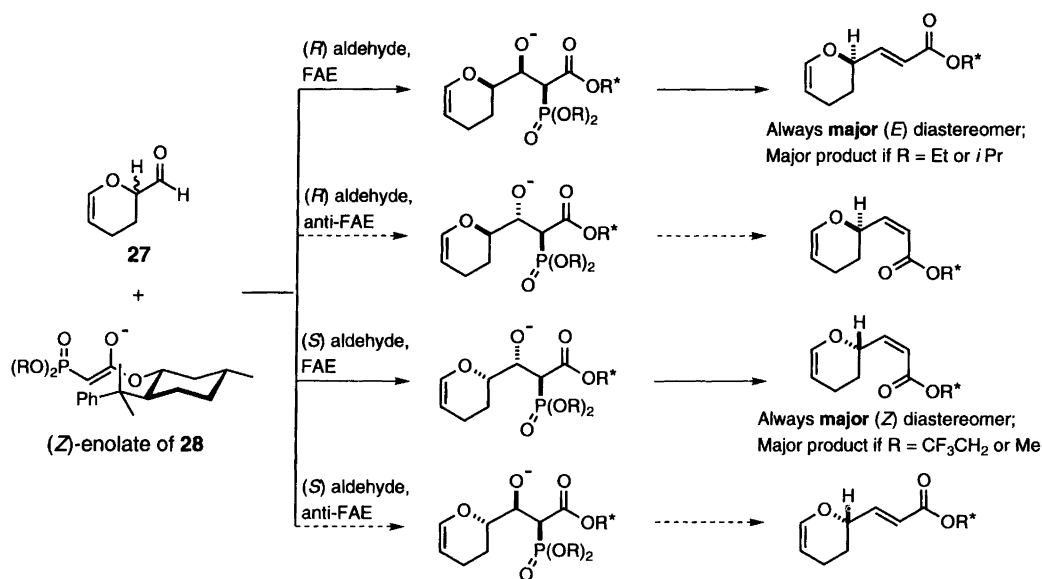
When considering the case of kinetic resolution of aldehyde **27** with reagents **28** [eqn. (10)],¹⁷ eight possible diastereomeric intermediates (four from each enolate form of the phosphonate) must be evaluated. It has been postulated that in reactions with bis(trifluoroethyl) phosphonates, the elimination step is fast relative to the initial addition, and thus that the intermediates are formed under kinetic control.⁶⁰ Under the reaction conditions used, with a strongly dissociated cation (potassium-18-crown-6), it is also reasonable to assume that the influence of the stereocenter in the aldehyde operates as described by the Felkin-Anh-Eisenstein (FAE) model,⁶¹ since aldehyde chelates should not be involved. In non-symmetric HWE reactions, bis(trifluoroethyl) phosphonates are known to give predominant formation of (*Z*)-alkenes,^{2,3,60} and accordingly these reagents must favor formation of a particular *relative* configuration of the two stereocenters which are to engage in the *syn*-elimination of the phosphoryl and oxyanion substituents, even though the specific reason for this stereochemical preference still is unclear. As illustrated in Scheme 4, this analysis predicts that the (*S,Z*)-diastereomer, which would form via FAE attack on the (*S*)-aldehyde enantiomer by the (*Z*)-enolate of the phosphonate, should be the main product from phosphonate **28d**. Furthermore, the major (*E*)-diastereomer formed from reagent **28d** should have the *R* configuration at the allylic stereocenter, as a result of FAE attack on the (*R*)-aldehyde. Both these predictions are indeed in agreement with the experimental outcome [in this context, it should also be mentioned that Denmark, using reagent **16**,²⁷ and

Musierowitz, using reagent **18**,²⁹ have observed cases of kinetic resolution where the major (*Z*)- and (*E*)-alkene products originate from opposite enantiomers of the racemic substrate].

It is also important to observe that the (*S,Z*)- and (*R,E*)-diastereomers are the major products formed from all four different phosphonates **28** employed in the reactions with aldehyde **27**. Consequently, the product patterns obtained from the phosphonates **28a-c** (R = Me, Et, *i*-Pr) can be explained by assuming reaction via the (*Z*)-enolate and kinetic control in the addition step for these reagents as well, at least under the particular conditions used. The differences in (*E*):(*Z*)-selectivity between reagents **28d** and **28a** on the one hand, and reagents **28b** and **28c** on the other, would then have to originate from differences in the respective kinetic preferences for formation of *pro*-(*Z*)- or *pro*-(*E*)-intermediates.

A similar analysis of the products expected to arise from reactions of racemic **27** with the corresponding (*E*)-enolates of reagents **28** predicts that, owing to the expected reversed facial selectivity of the enolate, this combination should instead favor formation of the (*R,Z*)- and (*S,E*)-alkenes. In practice, these compounds are the minor product diastereomers observed from all reagents **28**.

It should be noted that in all reactions with 8-phenylmenthol-derived HWE reagents studied so far by the authors of this article,^{17,18,20,21} the major (*Z*)- and (*E*)-alkene products obtained from a given substrate have opposite absolute stereochemistry at the allylic stereocenter. In addition, the major product diastereomers are generally those which are expected to arise from FAE attack on the substrate enantiomers by a (*Z*)-enolate of the phosphonate. The only exceptions to this rule observed to date occur when α -methyl aldehydes are used as substrates; a similar discrepancy has been noted



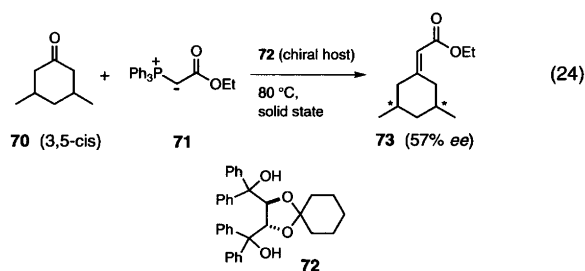
Scheme 4. Analysis of the products expected from the kinetic resolution of aldehyde **27** by reaction with the (*Z*)-enolate of reagent **28**. R = Me, Et, *i*-Pr or CF₃CH₂; R* = 8-phenylmenthyl.

(and rationalized) by Roush in aldol reactions involving this particular class of substrate.⁶²

Finally, the results obtained by Furuta and Iwamura¹⁶ [eqn. (12)] using reagents **28a** and **35** will be commented upon briefly. The fact that these reagents gave the same alkene geometry but opposite absolute stereochemistry at the allylic stereocenter in products **36** and **37** can be rationalized if the assumption is made that the anion of the phosphine oxide **35** also adds to the carbonyl substrate under kinetic control, in analogy with Scheme 4, but via the (*E*)-enolate instead of the (*Z*)-enolate. Alternatively, the addition step might instead be reversible with this reagent, in which case the predominant formation of (*E,S*)-**37** must depend on some factor (so far unknown) which favors elimination from the relevant diastereomeric precursor(s). It is somewhat puzzling that in the same study,¹⁶ the major diastereomers of the (*Z*)- and (*E*)-alkenes obtained by kinetic resolution of 2-phenylpropanal with reagent **28a** have the same configuration at the allylic stereocenter, and thus are produced from the same enantiomer of the substrate. This could indicate that the (*E*)-product is formed via reversible addition and rate-determining elimination under the specific set of reaction conditions examined by the authors, whereas the (*Z*)-alkene is produced via kinetic control in the addition step.

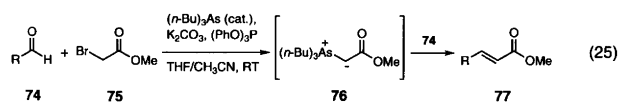
Opportunities for asymmetric catalysis?

Of the methods published to date for performing asymmetric Wittig-type reactions, almost all have been based on the use of covalently attached chiral auxiliaries for achieving asymmetric induction. A challenging, but highly desirable, goal would be the development of efficient methods based on catalytic asymmetric induction. Only two previous reports^{5,7} have explored the possibility of using compounds which are not covalently attached to the substrate or the reagent as the source of asymmetric induction. In an early paper,⁵ Bestmann and Lienert studied the influence of chiral acids on the reaction between a stabilized ylid and 4-substituted cyclohexanones; the highest enantioselectivity observed was lower than 10%, however. Using a completely different concept, Toda and Akai reacted the stabilized ylid **71** with the inclusion compound of *meso*-ketone **70** and the chiral host **72**⁷ in a solid state reaction, and obtained alkene **73** (absolute configuration not determined) in 57% *ee* [eqn. (24)].



Even though no efficient asymmetric catalyst has yet been developed for any variant of Wittig-type reactions, several methods for catalyzing the parent non-asymmetric versions have been reported in the literature. Beside proton acids,^{5,63–66} Li salts,⁶⁷ crown ethers^{68–71} and phase transfer reagents (tetraalkylammonium salts,^{68,72–75} TDA-1,⁷⁶ or even the Wittig-type reagents themselves^{77,78}) can also act as catalysts. In addition, various inorganic solid-phase promoters/catalysts [e.g., KOH,⁷⁹ K₂CO₃ or KHCO₃,^{80,81} alumina or KF–alumina,⁸² MgO or ZnO,⁸³ Cs₂CO₃,⁸⁴ Ba(OH)₂^{85–87}] have been employed under solid–liquid two-phase conditions. Furthermore, several reagents have been found to enhance the rate of the elimination step of the general mechanism: trityl salts promote the formation of alkenes from β-hydroxy phosphonamidates²⁶ [eqn. (22)], elimination from β-hydroxy phosphonothioate esters is catalyzed by Ag^I salts,⁸⁸ and lithium ion promotes alkene formation from the oxaphosphetane intermediate in a Wittig reaction.⁸⁹

One other, conceptually different, method for catalyzing a Wittig type reaction should be mentioned here. Shi and Huang have designed a system in which a catalytic amount of Bu₃As is used to generate the stabilized arsonium ylid **76** *in situ* from a 2-bromo ester,⁹⁰ the ylid and the carbonyl substrate **74** then react to give the expected⁹¹ alkene product **77** and Bu₃As(=O). The latter compound is converted back into the arsine by reaction with (PhO)₃P present in the medium, to complete the catalytic cycle [eqn. (25)].



Thus, several opportunities would seem to exist for the development of asymmetric catalysts for Wittig-type reactions, by appropriate modifications of existing non-asymmetric catalysts. A key point of concern in this context is of course that the catalyst has to exert an influence on the particular reaction step in which the product stereochemistry is determined. To enable a more rational design both of new chiral reagents and of possible asymmetric catalysts, additional detailed information concerning different mechanistic alternatives would be most welcome, in particular for reactions involving HWE reagents.

Concluding remarks

After the pioneering initial studies of asymmetric Wittig-type reactions performed by Janszó¹³ and Bestmann^{4–6,8,9} more than twenty years ago, many different research groups have contributed to the development of the area, and several highly selective processes have been reported. In particular, the activity in the field has increased strongly during recent years. Nevertheless, for most of the different substrate types that have been

shown to be useful, the synthetic scope has just begun to be evaluated. For example, the possibilities efficiently to differentiate two enantiotopic carbonyl groups (either in a difunctional substrate or in a racemic monofunctional substrate) by intermolecular reactions have been clearly demonstrated, but the range of structural variations that will permit high selectivities to be obtained remains to be defined. In addition, the concept of dynamic kinetic resolution holds great promise, but also in this case further investigations are needed to evaluate which classes of substrate can undergo such a process. However, already the selection of examples reported to date indicate that these reactions should have considerable synthetic potential. An important topic for further studies will be a continued investigation of the finer details of the reactions mechanisms, as an increased understanding of such details would strongly aid the development of new, even more efficient reagents and processes. A particularly attractive – and also challenging – goal is the design of asymmetric catalysts for Wittig-type reactions. The authors of this article firmly believe that future studies in the area will bring many exciting new discoveries, and that these methods will continue to develop into powerful tools for the practising synthetic organic chemist.

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