Asymmetric Wittig Type Reactions

Tobias Rein,*a,b,c Torben M. Pedersenc,d

a AstraZeneca R&D Södertälje, Discovery Chemistry, 15185 Södertälje, Sweden
Fax +46(8)55328892; E-mail: Tobias.Rein@astrazeneca.com
b Department of Chemistry, Organic Chemistry, Royal Institute of Technology, 10044 Stockholm, Sweden
c Department of Chemistry, Technical University of Denmark, Building 201, Kemitorvet, 2800 Kgs. Lyngby, Denmark
d Department of Chemistry, Stanford University, Stanford, California 94305, USA

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Abstract: The Wittig reaction and related methods for synthesis of C=C double bonds belong to the standard repertoire of the synthetic chemist. Studies of asymmetric versions of these reactions have been increasing in recent years and applications of such processes to complex molecule synthesis have begun to emerge. In this review, we will emphasise the recent advances in developing methods and synthetic applications of these reactions, but earlier results will be covered as well to place the recent results in context.

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Key words: asymmetric synthesis, asymmetric Wittig reactions, kinetic resolution, enantioconvergent synthesis, desymmetrization

1 Introduction

Development of new methods for stereocontrolled synthesis has been an area of key importance in organic chemistry in recent years. As a result of these efforts, powerful asymmetric versions of many ‘standard’ reactions have emerged, including reaction types, which are not obviously applicable to asymmetric synthesis since no new sp3 stereocenter is formed in the process. One such class of transformations is asymmetric versions of the Wittig and related reactions. Different types of organophosphorus reagents can be used for transformation of a carbonyl compound into an alkene. As a result of this, several different names have been associated with reactions of this type, a fact, which might cause some confusion. In this review, the nomenclature used in some earlier reviews will be followed: phosphonium ylides and phosphine oxides are referred to as Wittig reagents and Horner reagents, respectively, whereas phosphonates and other phosphonic acid derivatives are labeled Horner–Wadsworth–Emmons (HWE) reagents. Reports concerning the use of arsonium ylides for similar asymmetric condensation reactions will be covered as well. Beside Wittig type reactions, other methods for preparing C=C bonds with simultaneous asymmetric induction have been reported: e.g., via asymmetric deprotonation, by use of chiral sulfoximides, chiral sulfoxides, or chiral selenoxides, or via asymmetric palladium-catalyzed nucleophilic substitution. These methods will not be discussed further in this review, however.

In order to make a Wittig type reaction capable of giving asymmetric induction, a usual requirement is that the substrate contains either a prostereogenic unit or several symmetrically arranged stereogenic units apart from the reacting carbonyl group, since no new sp3 stereocenter can be introduced in an intermediate, before the C=C bond is finally formed; however, this approach will not be discussed further in the present review. From this viewpoint, as well as from the perspective of synthetic planning, it is convenient to classify these reactions according to the type of carbonyl compound used as substrate, and this arrangement will be used in the following discussion.

2 Reactions with Achiral Monocarbonyl Substrates

2.1 Reactions with Symmetrically Substituted Monoketones

In reactions of this type, only two different product isomers can be formed (via four discrete intermediates), and the analysis of the product distribution is therefore relatively straightforward. Perhaps for this reason, the conversion of a symmetrically substituted monoketone (usually a 4-substituted cyclohexanone) to an axially dissymmetric alkene has been the benchmark reaction by which new chiral Wittig type reagents have been tested.
The first report of asymmetric Wittig type reactions appeared nearly forty years ago, and described HWE reactions of chiral phosphonate, containing menthol as a chiral auxiliary, with 4-methyl and 4-t-butyl cyclohexanone (1a, 1b; Scheme 1). The diastereomeric alkene products 3 were obtained in high yield and in optically active form, but the exact levels of asymmetric induction were not determined.11

Scheme 1

The first use of a chiral phosphonium ylide containing a stereogenic phosphorus center was demonstrated a few years later by Bestmann and Lienert (Scheme 2).12 Reaction of ylide 4 with 4-methylcyclohexanone gave 5 in 43% ee. Several other monocarbonyl substrates gave enantiomerically enriched products in reactions with the same chiral ylide, but the specific ee’s of the products could not be determined.

Scheme 2

Bestmann and Lienert also reported the first attempt to use a chiral catalyst in an asymmetric Wittig type reaction (Scheme 3).13 Several chiral acids were investigated as catalysts for the reaction between stabilized ylide 6 and 4-substituted cyclohexanones, however mandelic acid was the most effective; the observed levels of induction were very low, even when close to stoichiometric amounts of the chiral acid were used.

Scheme 3

In 1984, Hanessian et al.14 introduced the first Wittig type reagents giving high levels of asymmetric induction. Re-

Biographical Sketches

Tobias Rein was born in Stockholm, Sweden, in 1956. He received his MSc in 1982 from the Royal Institute of Technology in Stockholm and his PhD in 1989 from the same university, where he worked under the guidance of Professor Björn Åkermark. After a postdoctoral year at the University of Texas at Austin, where he worked together with Professor Stephen F. Martin on alkaloid total synthesis, he was appointed assistant professor at the Royal Institute of Technology, Stockholm, in 1991 and associate professor at the Technical University of Denmark, Lyngby, in 1996. In September 2000 he joined the AstraZeneca R&D unit in Södertälje, Sweden, and since October 2001 he holds an adjunct professorship in organic chemistry at the Royal Institute of Technology. His research interests centers around the development of synthetic methods with applications to medicinal chemistry as well as complex molecule synthesis.

Torben M. Pedersen was born in Fredericia, Denmark in 1972. He received his MSc in chemistry from the Technical University of Denmark in 1997, and his PhD in 2001 from the same university. During his PhD work, which was performed under the supervision of associate Professor Tobias Rein and Professor David Tanner, he worked in the area of asymmetric synthesis and organometallic chemistry. He pursued one year of his doctoral studies at the University of Notre Dame, USA, working on natural product synthesis under the guidance of Professor Paul Helquist. He is currently conducting postdoctoral studies at Stanford University, USA, under the direction of Professor Paul A. Wender. His research interests include development of methodology for asymmetric synthesis, total synthesis of complex molecules and organometallic chemistry.
actions of phosphonic bisamides of type 8 with 4-substituted cyclohexanones (Scheme 4) as well as enantiomerically pure or racemic chiral monoketones (Sections 3 and 4.1, respectively) were studied, and in several cases products (e.g., 10) of >96% isomeric purity were obtained. Furthermore, the synthetic utility of the obtained products was demonstrated by transformation into different acyclic building blocks containing remote methyl-substituted stereocenters, via sequential ene reaction and C=C double bond cleavage. In some reactions, the intermediate β-hydroxyphosphonamide 9 was isolated and characterized by X-ray analysis. The X-ray structures nicely support the mechanistic model given by Hanessian et al., in which the phosphonamide anion attacks the equatorial face of the carbonyl substrate via an arrangement as shown in Scheme 4, in a kinetically controlled addition step.2c

Scheme 4

Reagents 8 have subsequently been applied by Schuster et al.15 to the preparation of enantiomerically enriched disymmetric alkenes (e.g., 12) from 4-substituted cyclohexanones or bicyclo[3.3.0]octan-3,7-diones (Scheme 5). The product alkenes were studied as possible chiroptical triggers for a liquid crystal based optical switch.

Scheme 5

Reagents of type 14, which are related to 2 (Scheme 1) but contain other chiral alcohols as auxiliaries, were independently introduced by Gais et al.16 and Rehwinkel et al.17 in 1988, within the context of synthetic approaches to prostacyclin analogues (Section 3). Gais et al. studied reactions of 14a with the symmetric ketone 13, and found that alkene 15 could be obtained with high diastereoselectivity (Scheme 6).

Scheme 6

NMR studies revealed that the anion Li-14a exists in a chelated form, in which the si face of the nucleophilic carbon is shielded. The stereoselectivity of the reaction was rationalized as resulting from either kinetic control in the addition step, with addition to the least hindered, convex face of the carbonyl group, or a difference in the rate of elimination from diastereomeric intermediates, or a combination of both. A study of the temperature dependence of the reaction stereoselectivity was performed, but since a linear correlation was found and since the stereoselectivity was not influenced by the degree of conversion, no distinction between the two mechanistic alternatives could be made.

The first use of chiral phosphonic acid derivatives containing a stereogenic phosphorus center in asymmetric Wittig type reactions was reported in 1990 by Koizumi et al.18 The chiral 1,3,2-oxathiaphosphorinanes 16a and 16b, which have opposite configuration at phosphorus, were derived from 10-mercaptoisoborneol, and could be separated by chromatography. Reactions with 4-r-butylcyclohexanone gave only low levels of induction (Scheme 7). Interestingly, reagents 16a and 16b favored opposite enantiomers of the product.

Scheme 7
An interesting approach to asymmetric Wittig reactions was demonstrated by Toda and Akai. Inclusion complexes of the stabilized ylide 6, a symmetrically substituted cyclohexanone (e.g., 18), and a chiral host were reacted in the solid state (Scheme 8). The chiral host 19 proved to be the most effective, providing the dissymmetric alkene products (e.g., 20) in up to 57% ee.

![Scheme 8](image)

Denmark et al. have reported two types of chiral phosphonamidate reagents, both containing carbon stereocenters as well as a stereogenic phosphorus center, and demonstrated their use in asymmetric HWE reactions. The best activator was found to be trityl triflate, and the phosphonium ion. The stereoselectivities were highest only by a phenyl or a phenylthio group, required electrophilic activation of the elimination step for the overall reaction to proceed (Scheme 9).20a

![Scheme 9](image)

The best activator was found to be trityl triflate, and the elimination step is believed to proceed via the O-trityl phosphonium ion. The stereoselectivities were highest when the initial addition step is irreversible. Under these optimized conditions, reagents 21 gave the desired symmetric alkene products in good yield and excellent enantioselectivities. The phenylthio substituted alkene (e.g., 22) can be further utilized in highly stereoselective Ni-catalyzed couplings with Grignard reagents, thus potentially giving access to a variety of substituted, enantio- and diastereomerically enriched alkene.

Phosphonamidate reagents containing an anion-stabilizing carbomethoxy group gave alkenes directly under mild conditions, without extra activation (Scheme 9). Of the different isomeric reagents studied, compound 23, in which the camphor ring system and the carbomethoxymethylene substituents are placed cis relative to each other on the central 5-membered ring, gave the best stereoselectivities (78–86% ee). This reagent was evaluated in kinetic resolutions as well (Section 4.1).

The chiral Horner reagent 27 was introduced by Furuta and Iwamura, who compared it with HWE reagents 14b and 25b; all these reagents contain (–)-8-phenylmenthol as a chiral auxiliary (Scheme 10).

![Scheme 10](image)

Reactions with 4-tert-butylocyclohexanone as well as kinetic resolutions (Section 4.1) were investigated, and the interesting observation was made that even though the levels of enantioselection were only modest, the major products obtained from phosphonate 14b on the one hand and from phosphine oxide 27 on the other hand were of opposite absolute configuration, despite the fact that the same enantiomer of the chiral auxiliary was employed in both cases. Thus, the substituents at phosphorus can clearly have an impact not only on the level but also on the mode of stereoselection. The mechanistic factors causing this outcome remain to be elucidated, but it can be speculated that either a difference in enolate geometry of the phosphorus reagent or a difference in rate-determining step of the reaction can explain these results.

Abiko and Masamune have reported the preparation and use of chiral HWE reagents 28, containing a benzopyrano-[4,3-c]-isoxazolidine as chiral auxiliary, in reactions with 4-substituted cyclohexanones (Scheme 11).

The products (e.g., 29) were obtained with 80–92% de, and pure diastereomers could be obtained in high yield after chromatography or recrystallization. The stereoselectivity was rationalized as originating from an irreversible attack of the phosphonate anion, for which minimization of dipole-dipole repulsions favors the conformation.
shown, on the equatorial face of the ketone carbonyl, followed by a rapid elimination. An added advantage of this particular auxiliary is that the initial HWE product could be converted to an allylic alcohol, an unsaturated aldehyde, or an unsaturated ketone in a single step, via reaction with lithium borohydride–ethanol, DIBAL-H or a Grignard reagent, respectively.

Several recent papers have addressed the possibilities for effecting asymmetric induction in a Wittig type reaction without relying on a covalently bonded source of chirality (see also the approach by Toda and Akai\(^ {19} \)). Kumamoto and Koga investigated the use of chiral amino alkoxides as bases in HWE reactions between stabilized phosphonates and 4-4-ipentylcyclohexanone, \(^ {23} \) and found that 33 could be obtained in up to 52% ee when the alkoxide 31 was used as base (Scheme 12).

\[ {\text{Cyano phosphonate 30 gave better results than the more commonly used phosphonoacetate. With respect to the mechanism, it was shown that the intermediate 32 at least partially reverts to starting material under the reaction conditions, indicating that the asymmetric induction in this system results from a difference in the rate of elimination from diastereomeric intermediate complexes rather than kinetic control in the addition step.}} \]

In a related study, Tomioka et al. demonstrated that promising levels of enantioselectivity could be reached in reactions between phosphonates and 4-cyclohexanones if the lithiated phosphonate (e.g., 34) was precomplexed with a chiral ligand (Scheme 13).\(^ {24} \) Of the ligands investigated, 35 gave the best enantioselectivity. Since the HWE reagents used contain only weakly anion-stabilizing functional groups, the intermediate adducts (e.g., 36) were isolated and the elimination performed in a separate step, by refluxing with NaOAc in propionic acid.

\[ {\text{Scheme 13}} \]

Sano has reported\(^ {25} \) that the chiral diamine 38 in combination with Sn(II) triflate and N-ethyl piperidine can serve to promote an asymmetric HWE reaction between phosphonate 37 and 4-4-ipentyl cyclohexanone, to give trisubstituted alkene 39 with good enantioselectivity (Scheme 14).

\[ {\text{Scheme 14}} \]

Even though the chiral co-reactants 31, 35 and 38 were used in stoichiometric amounts in the studies discussed above, the results obtained indicate possibilities for developing a catalytic asymmetric Wittig type reaction. Apart from the pioneering investigation of chiral acid catalysts by Bestmann and Lienert,\(^ {13} \) only one additional catalytic system has been demonstrated. Arai et al.\(^ {26} \) recently showed that 4-4-ipentylcyclohexanone could be converted to the dissymmetric alkene 17 in up to 57% ee by reaction with triethylphosphonoacetate in the presence of chiral
phase transfer catalysts (e.g., 41) derived from cinchonine (Scheme 15).

Scheme 15

Use of rubidium hydroxide as base gave the best enantioselectivities, and due to the basic reaction conditions, reesterification of the acid obtained as part of the initial product mixture was necessary in order to obtain maximum yield of the desired product. The low catalytic turnover of this system makes the system impractical from a preparative point of view, but the results serve as important proof of the concept.

Despite their higher reactivity, arsonium ylides have been much less studied in olefination reactions compared to phosphonium ylides. The first use of a chiral arsonium reagent in an asymmetric Wittig type reaction appeared in 1997, when Dai et al.27 demonstrated that the chiral ylide 43, containing 8-phenylmenthol as the chiral auxiliary, gave diastereoselectivities of 47–80% in conversions of 4-substituted cyclohexanones to dissymmetric alkenes (e.g., 46) (Scheme 16). Under the reaction conditions investigated (n-BuLi, THF, –78 °C), the corresponding phosphonates28 containing the same chiral auxiliary gave lower selectivity.

Scheme 16

It was postulated that 43 preferentially reacts via the arrangement shown (in analogy to other reagents containing the same chiral auxiliary), in which one face of the nucleophilic center is shielded by the auxiliary, and adds to the equatorial face of the ketone to give intermediate 45. The formation of small amounts of the minor product diastereomer was explained as resulting either from attack of the nucleophile on the less accessible face of the carbonyl substrate or via partial epimerization of the arsine-substituted stereocenter in the intermediate.

The same arsonium ylide has recently been employed in kinetic resolutions of racemic, axially chiral aldehydes (Section 4.1).

2.2 Synthesis of Chiral Allenes from Ketenes or Acid Halides

Comparatively little attention has been given to the possibilities for preparing a chiral allene via an asymmetric Wittig type reaction. The first examples were demonstrated by Tömösközi and Bestmann, who reacted stabilized ylides 47, containing a chiral alcohol unit as an auxiliary, with acid chlorides and obtained enantiomerically enriched allenes 50 (Scheme 17).29 The absolute configuration of the products was postulated to be the one shown; neither the level of asymmetric induction nor the product yields were reported, however. The mechanism of the reaction involves a dual role for the phosphonium ylide, acting first as a nucleophile and then as a base to promote formation of an intermediate of type 49.

Scheme 17

In a similar fashion, the same authors subsequently demonstrated the possibility to kinetically resolve a racemic phosphonium ylide by reaction with a chiral, enantiomerically enriched acid chloride to give a chiral allene (Section 4.2).

Beside acid halides, ketenes can be used as substrates for preparation of enantiomerically enriched allenes via an asymmetric Wittig type reaction. This opportunity was first investigated by Musierowicz et al. who used the phosphinate ester 51, containing a stereogenic phosphorus center, as the chiral reactant (Scheme 18).30 The chiral allenes 53 were obtained in up to 23% ee, and the mechanism was postulated to involve a reversible addition step followed by rate-determining elimination with formation of the major product isomer via intermediate 52.
have been obtained by Fuji et al. for the preparation of enantiomeric excesses up to 84% reagents in asymmetric Wittig type reactions.

In a synthetic setting where it is desired to convert a chiral, unsymmetric ketone to an alkene, control of the alkene geometry can be problematic if the intrinsic stereochemical bias of the substrate is either low or favoring the undesired product isomer. This problem can be overcome by applying double asymmetric synthesis, i.e. using a chiral Wittig type reagent with strong enough directing power to overcome any undesired stereochemical influence of the substrate. Three of the reagent types discussed earlier have been tested in such a context. The phosphonamides, developed by Hanessian et al. (Scheme 4) were shown to give either E- or Z-product from (3R)-cyclohexanone with excellent selectivity, depending on which enantiomer of the reagent was used. On the other hand, in reactions with (2R,5R)-dihydrocarvone, the matched combination gave almost complete selectivity favoring the E-product whereas the mismatched case resulted in a 61:39 E:Z ratio, as a result of the influence of the 2-methyl substituent.

The HWE reagents 14a,b (Scheme 6) were applied independently by the groups of Gais to the stereocontrolled synthesis of alkenes which served as key intermediates in syntheses of prostacyclin analogues. Rehwinkel et al. found that ketone 56 could be converted to (E)-57 or (Z)-57 with essentially identical diastereoselectivity depending on which enantiomer of the chiral phosphonate was used (Scheme 20). Gais et al. subsequently reported that reagent 58 gives the corresponding E-product with improved diastereoselectivity (90% de) under slightly modified reaction conditions. An advantage with the latter reagent is that the corresponding chiral auxiliary, 8-phenylmenthol, is equally readily available in both enantiomeric forms, in contrast to 8-phenylmenthol.

3 Reactions with Chiral, Nonracemic Monoketones

In a more recent study, enantiomeric excesses up to 84% have been obtained by Fuji et al. for the preparation of allenes (e.g., 55) via reaction of ketones with chiral HWE reagents of type 54 (Scheme 19).

These chiral phosphonates were originally introduced by Fuji et al. within the context of desymmetrization of meso-dicarbonyl compounds (Section 7). The ketones were generated in situ from 2,6-di-t-butyl-4-methylphenyl (BHT) esters, by treatment with n-BuLi/ZnCl₂. The phosphonate anion is postulated to be present as a Zn chelate in which the 2,2'-binaphthol unit shields one face of the enolate, and the stereoselectivity is believed to originate from preferential attack on the least hindered face of the ketene carbonyl in an irreversible addition step.

By far the most complex applications reported to date of double asymmetric synthesis using chiral Wittig type reagents concern total syntheses of the bryostatins, a group of structurally complex macrolides with a range of interesting biological activities and clinical potential as antitumor agents. Two recently reported total syntheses, of bryostatin 2 by Evans et al. and of bryostatin 3 by Nishiyama et al., have both made use of Fuji’s chiral HWE reagent (R)-54a to control the alkene geometry of the exocyclic unsaturated enoate at C13-C30 (bryopyran numbering). In both syntheses, this alkene unit was introduced at a late stage, by reaction with a very complex tet-
rhapydropyran-4-one substrate of type 59 (Scheme 21). Both groups found that the intrinsic substrate influence favored the desired product, but only to a small extent; by use of the appropriate enantiomer of reagent 54a, the selectivity could be increased. It was postulated that the stereoselection results from kinetic control in the addition step.

![Scheme 21](image)

**Scheme 21**

4 **Kinetic Resolution**

4.1 **Resolution of Racemic Monocarbonyl Compounds**

When a chiral racemic monocarbonyl compound is reacted with a chiral Wittig type reagent, the possibility for kinetic resolution exists. This process is more complicated compared to the methods described above since, in this case, the chiral reagent has to distinguish between two enantiotopic carbonyl groups (one in each enantiomer of the substrate), each of which has two diastereotopic faces.

In the standard type of resolution, the racemic carbonyl substrate needs to be present in at least a twofold excess in order to allow complete conversion of the chiral Wittig type reagent to a single product isomer. The first kinetic resolution of a racemic ketone by an asymmetric Wittig type reaction was documented by Musierowicz et al., who reacted chiral phosphinate 51 with 2-substituted cycloalkanones (e.g., 61). Even though the enantiomeric selectivities obtained were low, the interesting observation was made that the major E and Z products formed from 2-methylcyclohexanone possessed opposite absolute configuration at the allylic stereocenter, and thus originated from opposite enantiomers of the substrate (Scheme 22).

![Scheme 22](image)

**Scheme 22**

In another early study, described by Johnson et al., the racemic ketone 63 was reacted with resolved phosphinothioic amide dianion 64 (Scheme 23; the absolute configuration at phosphorus in 64 was not reported), to give two separable diastereomeric intermediates which after elimination afforded the respective enantiomer of the iridoid monoterpene hop ether (65). This strategy relied on the chromatographic separation of the intermediate β-hydroxyphosphinothioic amides, rather than a difference between the rates of their formation, since the intermediates were formed in a ratio of 3:2.39

![Scheme 23](image)

**Scheme 23**

Phosphonamides 8 were the first chiral HWE reagents capable of effecting preparatively useful kinetic resolutions.40 For example, kinetic resolution of racemic cis-2,4-dimethylhexanone 66 gave alkene 67 with excellent selectivity (Scheme 24).40

![Scheme 24](image)

**Scheme 24**

Danish and Rivera showed that 3-substituted cyclohexanones (e.g., 68) could be resolved by reaction with chiral phosphonamidate 23. Alkenes 69 were formed with rather low geometric selectivity, but the enantiomeric excess of each geometric isomer was good; again, the major E and Z isomers were formed from opposite enantiomers of the substrate (Scheme 25).

![Scheme 25](image)

**Scheme 25**

Somewhat surprisingly, kinetic resolution of a racemic aldehyde was not reported until 1994, when Rein et al. showed that acrolein dimer could be efficiently resolved by reaction with chiral phosphonates 25.41 Reagent 14b gave good diastereoselectivities, but a low E:Z ratio. By switching to reagents 25a-c, containing modified phosphonate groups, it was possible to prepare either (R,E)-71 or (S,Z)-71 in useful yields and with high diastereomeric excess (Scheme 26). Note that the major
E- and Z-products were formed from different enantiomers of the substrate.

This strategy was further extended by using chiral phosphonopropionate 25e to produce chiral Z-trisubstituted alkenes (e.g., 72) with high diastereoselectivity via kinetic resolution of racemic aldehydes (Scheme 26).43

Furuta and Iwamura studied kinetic resolutions of 2-phenylacetaldehyde and N,N-dibenzylalaninal (73) using phosphonates 14b and 25b as well as the corresponding diphenylphosphine oxide 27 (Scheme 27).21 In analogy with results obtained in reactions with 4-t-butylcyclohexanone (Scheme 10), 14b and 27 reacted with opposite enantiomer preference, to give (R,E)-7440,42 and (S,E)-74,40,42 respectively, even though both reagents contain the same enantiomer of the chiral auxiliary.

Molecular mechanics modeling of the reactions between reagents 14b/25 and different mono- and dialdehyde substrates have contributed to a more detailed mechanistic picture (Scheme 30).48 The modeling study supported the hypothesis that the kinetic stereoselectivity in the addition step results from the combined influence of three factors: the chiral auxiliary, the R group in the phosphonate, and the α-stereocenter(s) in the substrate. The chiral auxiliary determines the face selectivity of the phosphonate enolate 80, and thus the absolute configuration at C2 in intermediate 82; the phosphoryl R group determines the relative configuration at C2 and C3, and thus the alkene geometry of the product; and the substrate α-stereocenter determines the relative configuration at C3 and C4. Only for one of the eight possible diastereomeric intermediates will all three of these factors act in synergy. This analysis also nicely explains the generally observed trend that for a given combination of reagent and substrate, the E- and Z-products are usually formed with opposite absolute configuration at the allylic stereocenter.39

Rein et al. demonstrated the first application of kinetic resolution of an aldehyde to natural product synthesis by the preparation of a subunit of iejimalide A, a member of a group of marine macrolides showing high cytotoxic activity (Scheme 28).44 Reaction of racemic 3-sulfonyl aldehyde 75 with the chiral E-selective phosphonate 25a afforded unsaturated ester 76 as a 9:1 mixture of diaste-
Depending on the structure of the reactants and the reaction conditions, either the initial addition step, the subsequent elimination or both can influence the stereoselectivity. A somewhat surprising result of the modeling was that the influence of the substrate stereo-center in several cases seemed to be at least as large in the elimination step as in the addition.

Kinetic resolution of substrates containing stereogenic elements other than $sp^{3}$-hybridized carbon have been reported in two recent studies. Tanaka et al. demonstrated that chiral phosphonate 54b could be used for kinetic resolution of racemic aldehyde 83, containing a stereogenic \[\text{Fe(CO)}_3\] unit (Scheme 31). Both the product enolate 84 and the recovered aldehyde (2\(R\))-83 were obtained with good enantiomeric excess. In analogy to the suggested mechanism for other reactions using the same reagent, it was postulated that the chiral auxiliary favors nucleophilic addition from one face of the chiral enolate, in an irreversible addition step. It was suggested that the aldehyde reacts via its $S$-\textit{trans} conformer, with the diene-\textit{Fe(CO)}\(_3\) unit disfavoring attack at one face of the carbonyl due to steric interactions with the chiral auxiliary in the phosphonate.

The use of a chiral arsonium ylide for the atroposelective kinetic resolution of racemic, axially chiral \(N,N\)-dialkyl 2-formyl-1-\textit{naphthamides} (e.g., 85) has been reported by Dai and Lau (Scheme 32). Reaction with 8-phenylmenthol derived arsonium ylide 43 gave access to the chiral alkenene 86 with good diastereoselectivity. Based on studies of the influence of changes in reaction conditions on stereoselectivity, the authors hypothesized that the substrate reacts predominantly via a non-chelated form to give the (5)-isomer as the major product. Due to rapid epimerization of the product at room temperature, its absolute configuration has not been determined; therefore, this hypothesis remains to be verified.
Scheme 33

In a more recent study,54 chiral epoxy aldehyde 91 was reacted with racemic phosphonium ylide 90, possessing a stereogenic \( \eta^4 \)-diene-\( \text{Fe(CO)}_3 \) unit. This resulted in formation of alkene 92 as a 4:1 mixture of diastereomers, thus showing that the ylide had undergone kinetic resolution (Scheme 34).

Scheme 34

Individual experiments confirmed that the major isomer was formed as the result of a matched double asymmetric reaction, whereas the minor product was the result of a mismatched combination. It was postulated that the ylide possesses a transoid conformation and reacts via nucleophilic attack from the face \( \text{anti} \) to the \( \eta^4 \)-diene-\( \text{Fe(CO)}_3 \) unit; furthermore, it was assumed that the attack on the carbonyl group occurred \( \text{anti} \) to the epoxide moiety. The difference in reaction rate between the enantiomeric ylides would then result from strong non-bonded interactions in the mismatched combination.

5 Dynamic Resolution

One obvious drawback with the standard type of kinetic resolution is the inherently limited material throughput: based on the racemic substrate, a maximum yield of 50% can be obtained, since the substrate needs to be present in at least a twofold excess in order to allow complete conversion of the chiral reagent into the desired product isomer. It is therefore highly desirable to define reaction conditions which make dynamic resolution possible, by favoring a rapid equilibration of the enantiomers during the reaction.55 This would, in principle, allow quantitative conversion of a stoichiometric amount of racemic substrate into a single stereoisomer of the product. Although the scope of asymmetric Wittig type reactions in this context has only begun to be explored, it has been demonstrated that both ketones and aldehydes can function as substrates for dynamic resolution. Narasaka and Gras showed that reaction of equimolar amounts of racemic 2-benzylcyclohexanone (93) and chiral phosphonate 94, derived from mannitol, provided chiral alkene 95 in high ee when the reaction was carried out in the presence of an excess of LDA (Scheme 35).56 The substrate equilibration was relatively slow under these conditions, however, since recovered substrate was not fully racemized.

Scheme 35

Molecular mechanics calculations were performed on the different possible intermediate diastereomeric oxyanions, to serve as a basis for rationalization of the stereoselectivity. It was found that three of the eight possible diastereomers were much lower in energy than the others. Two of these were precursors of the main observed product, and these two were also calculated to undergo elimination most readily. For this system, the calculations thus indicated that the stereochemistry of the product is determined by the relative rates of elimination from different intermediate, reversibly formed oxyanions.

The first examples of dynamic kinetic resolutions of racemic aldehydes were reported by Rein et al. (Scheme 36).57 Reaction of close to equimolar amounts of racemic \( \alpha \)-amino aldehydes (e.g., 96) with chiral phosphonates of type 14b/25 afforded vinylogous amino acid esters 97 with up to 94% diastereoselectivity. It is noteworthy that the stereoselectivity in some cases was improved significantly under the dynamic resolution conditions, as compared to the corresponding standard kinetic resolution.58 The products should have synthetic potential as building blocks for e.g. peptidomimetics.59

Scheme 36

The mechanistic factors contributing to the stereoselectivity of this process are believed to be the same as described previously (Section 4.1) for reactions involving reagents 14b and 25.48 Dai and Lau attempted dynamic resolution of the axially chiral aldehyde 85 by reaction with ylide 43, but the observed stereoselectivity was considerably lower than in the corresponding kinetic resolution (Scheme 32).51
6 Other Strategies Based on Resolution of Enantiomers

6.1 Parallel Kinetic Resolution

Parallel kinetic resolution (PKR)\(^60\) is a useful and complementary strategy by which complete conversion of both enantiomers of a racemate into useful chiral products can be effected. In PKR, the enantiomers of the substrate form different, non-enantiomeric products; this can be accomplished by reacting the racemate either with a single reagent displaying different reactivity towards the two enantiomers, or simultaneously with two different chiral reagents having opposite enantiomer preference. The substrate enantiomers need to react with similar rates, and if two reagents are used these need to operate effectively under the same reaction conditions. In contrast to a dynamic resolution, PKR will thus produce two different chiral products, having opposite absolute configuration at the stereocenter(s) originating from the substrate. Therefore, PKR should prove particularly useful for applications in which both the obtained products can be of further utility in the same synthetic context, either as building blocks for two different subunits of the same overall synthetic target, or for providing access to both enantiomeric series of the same target (e.g., subunits of a natural product of unknown absolute configuration). An advantage of PKR reactions is that these can, just as dynamic resolutions, give increased stereoselectivities compared to the individual standard kinetic resolutions.

To date, only one paper describing PKR by use of asymmetric Wittig type reactions has been reported.\(^61\) Two different approaches were described. In the first one, one equivalent of racemic aldehyde \(98\) was reacted with half an equivalent each of the two phosphonates \(25e\) and \(99\), containing different chiral auxiliaries (Scheme 37). The alkene products obtained, \(100\) and \(101\), were thus structurally different and could be separated on the basis of the difference in physical properties imparted by the different chiral auxiliaries. It is noteworthy that the diastereoselectivity of \(101\) was improved considerably in the PKR compared to the one obtained in the corresponding individual kinetic resolution.

In the second approach, PKR was accomplished using one \(E\)- and one \(Z\)-selective reagent containing the same chiral auxiliary. In this case, the strategy relied on the observation made in earlier work\(^48\) that \(E\)- and \(Z\)-selective phosphonates containing the same chiral auxiliary generally react with opposite enantiomer preference. Reaction of one equivalent of racemic aldehyde \(70\) with half an equivalent each of reagents \(25b\) and \(25c\) gave products \((R,E)-71\) and \((S,Z)-71\) in high combined yield and with good diastereoselectivities. The products could be readily separated by chromatography.

For substrates not capable of undergoing efficient dynamic resolution, the use of an enantioconvergent reaction sequence (i.e., conversion of both enantiomers of a racemate to the same chiral end product via isomeric synthetic intermediates) offers an alternative opportunity to increase material throughput compared to standard kinetic resolution. The first example of use of asymmetric HWE reactions for enantioconvergent synthesis was reported very recently.\(^62\) The overall stereoconvergence was accomplished by combining the asymmetric HWE reaction with a subsequent Pd-catalyzed allylic substitution (Scheme 38). In the illustrated example, reaction of racemic aldehyde \(102\) with chiral phosphonate \(25d\) afforded a close to 1:1 mixture of alkenes \((R,E)-103\) and \((S,Z)-103\), both with good to excellent diastereoselectivity. When this mixture was subjected to the dimethyl malonate anion in combination with a Pd(0) catalyst, \(E\)-product \(104\) was obtained in good overall yield and with good stereoselectivity. A key part of the strategy is that the allylic substitution proceeds with opposite stereospecificity from the two intermediate HWE products, i.e., \((R,E)-103\) reacts with retention of configuration whereas \((S,Z)-103\) reacts with inversion of configuration, with respect to both the allylic stereocenter and the geometry of the C=C double bond. It was shown that C, N and O nucleophiles work well in the Pd-catalyzed substitution. The utility of this strategy was further demonstrated by its application to a synthesis of the C(12)-C(20) fragment of the iejimalides (Scheme 28).\(^62\)
7 Desymmetrization of Prochiral Dicarbonyl Substrates

In a reaction between a chiral Wittig type reagent and a prochiral dicarbonyl compound, the reagent has to distinguish between two enantiotopic carbonyl groups as well as between diastereotopic faces at the reacting carbonyl. In this respect, this process resembles kinetic resolution of a racemate. Nevertheless, there are important differences as well. Complete conversion of the substrate to a single product is possible, but the stoichiometry must be controlled in order to suppress formation of bis-alkene products. On the other hand, apart from reducing the yield of the desired monoalkene, the formation of bis-alkenes can also have a positive effect. One can expect the initially formed monoalkene to undergo a kinetic resolution upon forming bis-alkene products. The minor monoalkene isomers, formed via reaction at the less reactive carbonyl group in the substrate, could be expected to form bis-alkenes faster. Thus, allowing a limited fraction of the initial product to react further to bisalkenenes can serve to increase the isomeric purity of the desired monoalkene.

The first example of use of a prochiral dicarbonyl compound as substrate for desymmetrization by an asymmetric Wittig type reaction was reported by Trost and Curran in 1980. They demonstrated the concept in an intramolecular setting (Scheme 39). Reaction of bromide 105 with a chiral phosphine 54a to form the corresponding phosphonium salt, followed by ring closure of the intermediate stabilized ylide 106 by an intramolecular Wittig reaction, afforded the bicyclic product 108 (bis-nor-Wieland–Miescher-ketone) in up to 77% ee. The desymmetrization concept was independently extended to intermolecular reactions by Fuji et al. and Rein et al. The chiral phosphonate 54a (Scheme 19) was introduced by Fuji within the context of desymmetrization of meso-diketones. Reaction of 54a with diketone 109 gave Z-alkene 110 in excellent yield and enantioselectivity (Scheme 40).

Some related bicyclic meso-diketones were tried as substrates as well, and gave consistently high ee for the Z-product but variable E,Z-selectivity. The rationalization of the stereoselectivity was analogous to what has been suggested for reactions of these reagents with other substrates. In an irreversible addition step, the phosphonate enolate reacts from the face unshielded by the chiral auxiliary, and adds to the less hindered (exo) face of the reacting carbonyl group in the diketone. It was determined that the Z- and E-products were formed via attack at opposite carbonyl groups in the substrate, in analogy with the trend observed in kinetic resolutions (Section 4.1).

Recently, the range of substrates examined with these reagents has been extended to meso-dicarbonyl substrates containing aryl-Cr(CO)₃ or diene-Fe(CO)₃ units (Scheme 41). The chromium complex 111 gave Z-alkene 112 with high ee and in useful yield, along with some E-alkene of lower enantiomeric purity.
Reagents related to 54 have recently been applied to the construction of fused ring systems via intramolecular HWE reactions.2f Rein et al. have demonstrated the utility of meso-dialdehydes as substrates for asymmetric HWE reactions.68 Reagents 14b and 25 have proven generally useful for transforming meso-dialdehydes into either Z- or E-alkenes with good to excellent levels of asymmetric induction and geometric selectivity. Substrates which have given high selectivities include examples with carbon, nitrogen or oxygen substitution at the α-stereocenters (Figure). In these reactions, the alkene geometry of the product can usually be controlled by choice of an appropriate group R1 in the phosphoryl unit, in analogy with conventional non-asymmetric HWE reactions. The mechanism behind the stereoselectivity follows the general trend presented earlier,48 and also from dialdehyde substrates, E- and Z-products are formed from opposite enantiotopic carbonyl groups. The products obtained from 113 have potential utility in syntheses of several marine macrolides, whereas desymmetrization of 114 and related N-containing dialdehydes can be envisioned as key steps in approaches to a range of interesting alkaloids.

Figure

Synthetic approaches to chiral tetrahydrofuran (THF) and tetrahydropyran (THP) derivatives, based on the combination of an asymmetric HWE reaction with a subsequent stereoselective ring closure, have recently been presented by Rein and Vares (Scheme 42).69 Desymmetrization of meso-dialdehyde 115b by reaction with reagents 25b and 25c gave intermediates 117 and 120, respectively, which were transformed in two steps to compounds 118 and 121. Ring closure by palladium-catalyzed allylic substitution69 then afforded THF derivatives 119 and 122 as pure diastereomers.

In a similar fashion, THP derivatives 123 and 124 were obtained via desymmetrization of meso-dialdehyde 116b (Scheme 43). This strategy has been extended to give access to chiral THP derivatives possessing other substitution patterns, by using other reaction types (intramolecular hetero-Michael addition or epoxide opening)69b for effecting the ring closure.

The use of chiral HWE reagents containing 8-phenylmenthol as the chiral auxiliary have been elegantly applied to the synthesis of vitamin D₃ analogs by Mandai et al. (Scheme 44).70 The bicyclic intermediate 126 was prepared from 125 by a highly diastereoselective intramolecular HWE reaction. Further transformations then afforded 127, which can serve as a building block for the CD ring subunit of vitamin D₃ analogues. It is noteworthy that a tetrasubstituted alkene is formed with excellent stereoselectivity in this application of asymmetric HWE reactions. The mechanism behind this stereoselectivity can be explained in analogy with reactions of other HWE reagents containing the same auxiliary.
**Asymmetric Wittig Type Reactions**

8 Future Perspectives, Concluding Remarks

Although the first report of an asymmetric Wittig type reaction appeared forty years ago, the synthetic potential of these transformations has begun to be evaluated in more detail only during the last decade. Several different conceptual variations have by now been demonstrated in practice, and successful examples of the use of a range of substrate types have been presented, giving access to various types of chiral, functionalized building blocks from achiral or racemic precursors. The full scope of these processes along these lines. A prerequisite for such a development will be a continued elucidation of mechanistic details: advances have been made in recent years, e.g., in our understanding of asymmetric HWE reactions using chiral phosphonates, but to enable the design of new, even more efficient processes, a more detailed understanding of the factors contributing to the stereoselection will be necessary.

A particular challenge remaining to be solved is the development of efficient catalytic asymmetric procedures. An early attempt at using a chiral acid catalyst gave low levels of asymmetric induction. A chiral phase transfer catalyst has recently been introduced, but this system suffers from slow turnover. Protocols based on stoichiometric amounts of non-covalently attached ligands or inclusion complexes have been developed, but the question of how to turn these into truly catalytic processes with respect to the source of chirality remains unanswered. Further development of these or other approaches into efficient, catalytic asymmetric Wittig type reactions remains a highly desirable goal.

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(1) Present address.