Preparation of Scalemic P-Chiral Phosphines and Their Derivatives

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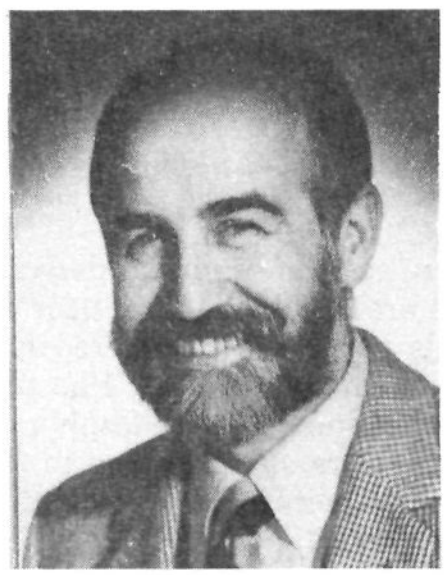
Contents



K. Michał Pietrusiewicz was born in Poland in 1946. He received his M.Sc. from the Technical University of Łódź in 1969 and Ph.D. from the Center of Molecular and Macromolecular Studies of the Polish Academy of Sciences in Łódź in 1976. In the same year he joined the group of Ernest L. Eliel at the University of North Carolina for a year and a half postdoctoral training, and during 1983–84 he stayed one year with Barry M. Trost at the University of Wisconsin as a Fullbright Fellow. From 1969 to present he has been at the Center of Molecular and Macromolecular Studies of the Polish Academy of Sciences in Łódź where he currently holds the rank of Associate Professor. His research interests embrace organic and organometallic synthesis and stereochemistry with special focus on the C–P organophosphorus systems.

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I. Introduction

The early expectation that nonsymmetrically substituted phosphorus compounds can be resolved into the two enantiomeric forms was first verified experimentally in 1911 by Meisenheimer and Lichtenstadt,[1] and the work of these authors marks the beginning of history of the optically active organophosphorus compounds possessing a chirality center at phosphorus. The driving force for the synthesis of these compounds evolved over the years from the original intrinsic interest in the preparation of optically active P-chiral systems and in the basic studies of their stereochemistry, to the rapidly growing utility of such compounds in various actively developing fields including among others chemotherapy,[2,3] pest control,[4,5] bioorganic chemistry,[6,7] asymmetric synthesis,[8] and asymmetric catalysis.[9–12] Despite the fact that P-chiral organophosphorus compounds could not be found in the natural pool of chirality and that synthesis of such compounds in the enantiomeric forms has continued to pose a considerable challenge,[13,14] the field has grown enormously in the last three decades and it has come to the point where it is already difficult to review it in a comprehensive way as the whole. In this paper we review the methods which have been developed for the preparation of *scalemic*[15] P-chiral phosphines, i.e., compounds in which the central phosphorus atom is connected with three carbons or at least two carbons and one hydrogen atom

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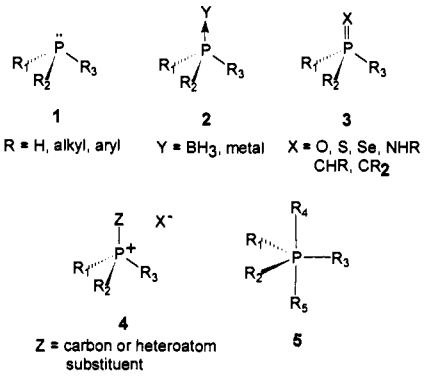
(e.g., 1) and of those of their higher oxidation level derivatives in which this distinction is held (e.g., 2–5).



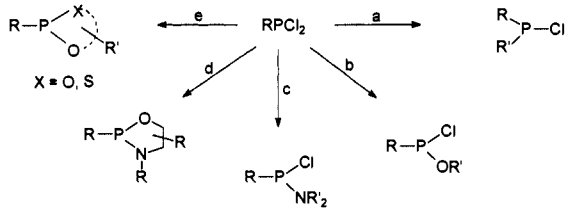
By this token, scalemic P-chiral derivatives of phosphorus acids are excluded, except for P-chiral phosphinous acids which are considered here as chalcogenides of secondary phosphines. Phosphines and their derivatives containing both phosphorus and carbon chirality centers are also included in the survey but those which owe their chirality solely to the backbone dissymmetry are excluded. A brief outline of methods of selective C–P bond formation given in section II contains only those of which find most frequent use in synthesis of nonsymmetrically substituted phosphines and their derivatives, and which are potentially general. A comprehensive treatment of procedures for C–P bond making has recently been published.[16]

An attempt has been made to cover the literature until September 1993. Previously published reviews and monographs in which various aspects of synthesis and use of scalemic P-chiral phosphines and their derivatives have been discussed are listed as refs 12, 13, 14, and 17–23.

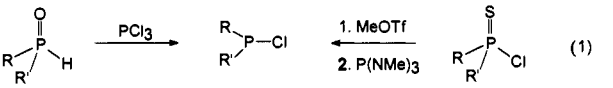
II. Synthesis of Racemic P-Chiral Phosphines and Their Derivatives

Notwithstanding the fact that nonsymmetrically substituted phosphines and their derivatives have been dealt with in laboratory practice well over 100 years[24] the early difficulties and labor expense associated with their synthesis have remained to be concerned with until today. In principle, to mount three different carbon substituents on phosphorus one needs to start from simple PX_3 or $O{=}PX_3$ (X = Cl, Br, OR, etc.) molecules and to carry out selective step by step displacement of the X groups at P. This can in principle be realized directly, but relay methods utilizing the corresponding mixed chloro, ester or/and amide derivatives to secure chemoselective displacements are often found to be more practical. Also, many alkyl and aryl dichlorophosphines have been made readily[25] or commercially available and nowadays the synthesis of nonsymmetrical phosphines is usually considered with $RPCl_2$ as the starting point (Scheme 1). For the direct selective displacement of only one Cl atom in $RPCl_2$ by an R′ group to yield nonsymmetrical monochlorophosphine (path a) use of sterically crowded or heavy metal (or both) organometallics is usually required.[25–27] In favorable cases the desired monochlorophosphines can be cleanly obtained from nonsymmetrical secondary

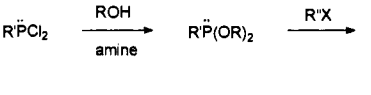
Scheme 1

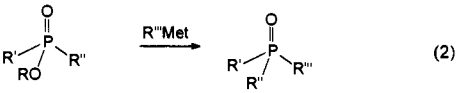


phosphine oxides[28] or thiophosphorochloridates[29] provided that those substrates are readily available (eq 1).



To overcome the aforementioned limitations methods to usefully differentiate substituents at phosphorus enabling subsequent chemoselective displacements have been developed. Some of the frequently utilized routes are sketched in Scheme 1. Moderately bulky alcohols or thiols (paths b and e),[30] secondary amines (path c),[31] or amino alcohols (path d)[32,33] can all serve the purpose reasonably well, but the amide routes secure usually the most satisfactory results in terms of selectivity and of facility of purification of intermediates. When nonsymmetrical phosphine oxide is the synthetic target it is usually most convenient to convert dichlorophosphine into a dialkyl (cyclic or acyclic) phosphonite and to use Michaelis–Arbusov reaction for the clean introduction of the second C–P bond and subsequent displacement with an organometallic reagent for the third (eq 2).[34] The Michaelis–

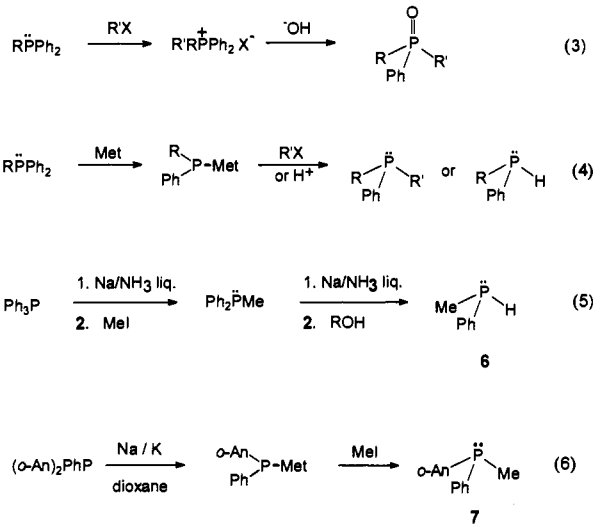




Arbusov and Michaelis–Becker processes are also very useful for the formation of the third C–P bond provided that the corresponding precursor, i.e., nonsymmetrical phosphinite or secondary phosphine oxide is relatively readily accessible.[16]

A conceptually different synthetic approach to nonsymmetrical phosphines and their derivatives is based on desymmetrization of more readily available symmetrical phosphines. One early developed route[1,35] in which symmetrical phosphine is first quaternized and then one of the two alike substituents in the resulting phosphonium salt is hydrolytically removed to yield nonsymmetrical phosphine oxide is exemplified in eq 3. In a more recent desymmetrization approach use has been made of the fact that alkali metals are able to reductively cleave P–aryl bonds[36–40] but typically not P–alkyl bonds.[41] Thus, on treatment with alkali metal a symmetrical alkyldiphenylphosphine gives prochiral phosphide anion which after quenching with an alkyl halide or a proton donor yields directly nonsymmetrical tertiary or secondary phosphine (eq 4). Li, Na, K, and Na/K alloy in ethereal solvents or in liquid NH_3 can be used to this effect.[42] The method is especially well suited for desymmetrization of 1,ω-bis(diphenylphos-

phino)alkanes[43,44] for which double terminal P–Ph bond cleavage occurs very cleanly and can be accelerated by ultrasound irradiation.[43] It has been also found practical to desymmetrize triphenylphosphine by stepwise cleavage of two phenyl residues intercepted by methylation to obtain in one-pot methylphenylphosphine (6) in remarkable 77% yield (eq 5).[45] Importantly, as exemplified by the synthesis of 7 (eq 6),[46] when different aryl groups are present in triarylphosphine a selective cleavage[39] can also be effected and the method for its simplicity will probably gain more practical importance in the future.

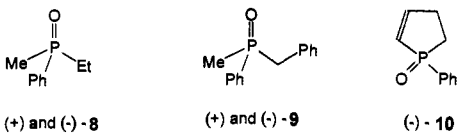


III. Methods of Preparation of Scalemic P-Chiral Phosphines and Their Derivatives

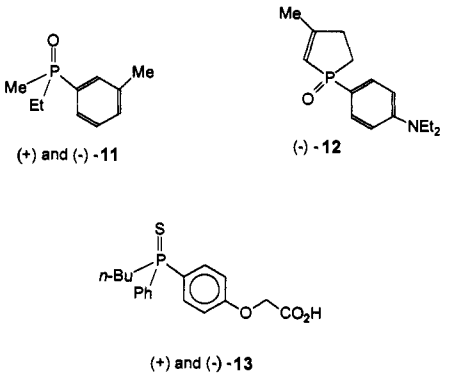
A. Resolution of Racemates

1. Direct Resolutions

a. With Resolving Agents. The first known optically active organophosphorus compound, ethylmethylphenylphosphine oxide (8), was obtained by direct resolution of the racemate using (+)-bromocamphorsulfonic acid for the formation of separable diastereomeric salts.[1] Although not without difficulty and in the time span of 15 years the two diastereomeric salts were isolated in the pure forms by fractional crystallization from EtOAc and EtOAc/ether and yielded ultimately both enantiomers of 8 in good optical purity.[35] In the same laboratory benzylmethylphenylphosphine oxide (9) was similarly resolved with camphorsulfonic acid as the resolving agent.[35] Although historically important and reproducible,[47] this resolution method relying on protonation of the weakly basic phosphoryl oxygen has, in fact, never been used to successfully resolve any other simple P-chiral phosphine oxide besides 8 and 9. Recently attempted resolution of phospholene oxide 10 with (−)-dibenzoyltartaric acid (DBTA) was only partially successful and afforded (−)-10 of only ca. 65% ee and in very low yield.[48] The method can be very useful, however, for aiding some otherwise difficult separations of diastereomeric P-chiral compounds[49,50] as well as for resolution of the backbone chiral diphosphorus systems such as NORPHOS[51] and BINAP.[52]



Toda and co-workers[53] recently found that 2,2′-dihydroxy-1,1′-binaphthyl (binaphthol) is also able to form crystalline complexes with phosphine oxides and they used this observation to fully resolve oxides 8 and 11 with (+)- and (−)-binaphthol. Attempted resolution of other phosphine oxides by this method was however unsuccessful.

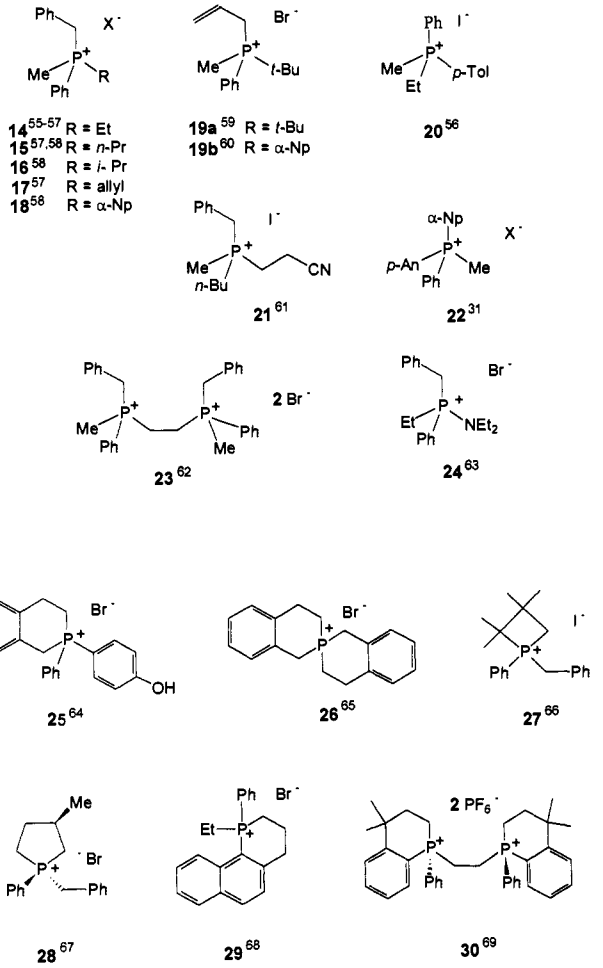


The two other known direct resolutions of P-chiral phosphine chalcogenides relied on functions other than P=X. Ostrogovich and Kerek[54] reported resolution of phospholene oxide 12 through its ammonium salts with (+)-9-bromocamphorsulfonic acid, and Davies and Mann[26] resolved sulfide 13 which gave separable salts with (+)- and (−)-1-phenylethylamine. In the latter case, since sulfur in the P=S group is too weak a protic base the introduction of an added functionality for the purpose of resolution proved prerequisite. It is probably for this reason why no further examples of direct resolution of phosphine sulfides could be found in the literature.

The first successful resolution of a simple P-chiral phosphonium salt was reported by McEwen and coworkers[55] in 1959. These authors were able to resolve benzylethylmethylphenylphosphonium iodide (14) using silver hydrogen dibenzoyltartrate (Ag-DBHT) as the resolving agent and this methodology quickly gained more general use and importance. The acyclic phosphonium salts resolved in this way are listed in Chart 1 as 14–24. In fact, the resolution of cyclic phosphonium salts has a somewhat longer history; however, the early resolution of 25[64] could not be later repeated and, the second resolved phosphonium salt 26,[65] even though cyclic, was P-chiral. The cyclic phosphonium salts resolved to date include 25–30.[64-69]

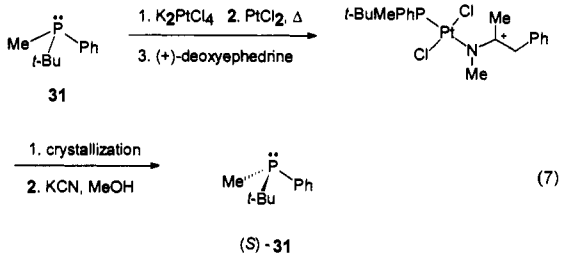
Typically, the resolution of phosphonium salts either cyclic or acyclic was performed by combining the racemate with the silver salt of a chiral acid and recrystallization of the resulting mixture of diastereomeric salts from hydroxylic solvents or acetone. Usually the two enantiomers of the resolving agent had to be employed to obtain both enantiomers of the phosphonium salt although occasionally both diastereomeric salts could be drawn efficiently in the pure form from a single pairing. Enantiomeric silver menthoxyacetates,[68] silver or potassium hydrogen di-

Chart 1

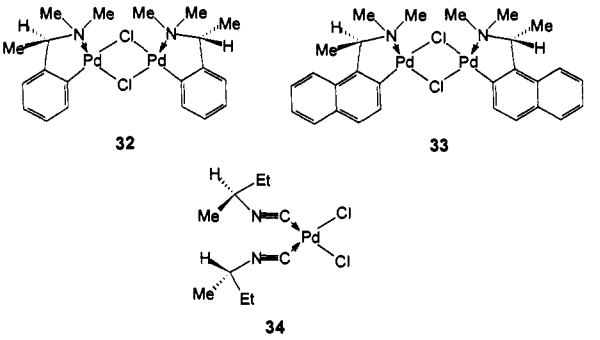


benzoyltartrates[55–57,61,63,69,70] and silver camphorsulfonates[67] were used successfully as the resolving agents. In some instances the corresponding free acids could also be used.[58,64] In a modified version of this resolution protocol the pairs of diastereomeric phosphonium hydrogen dibenzoyltartrates were obtained from racemic P-chiral ylids by protonation with (−)-DBTA.[58]

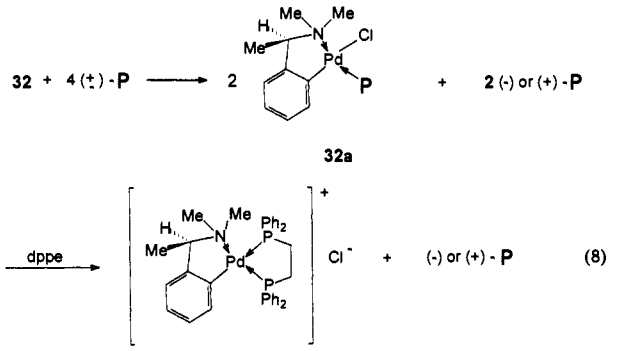
The availability of resolved P-chiral phosphonium salts had a great impact on the development of phosphorus stereochemistry as they served as the chiral probes in the studying the steric course of reactions occurring at P and, even more importantly, as the primary source of scalemic phosphines at that time.[57] Direct resolution as a means to obtain scalemic phosphines emerged as a practical alternative only 10 years after the enantiomeric tertiary phosphines obtained by electroreductive cleavage of the resolved quaternary salts[57] were proved for the first time to be configurationally stable in the useful range of temperatures. In the meantime, however, in 1967 Wittig et al.[71] partially resolved a triarylphosphine via kinetic resolution (cf. section III.A.4), and in 1968 Chan,[72] by adapting the method developed by Cope for resolution of strained olefins and sulfoxides,[73] succeeded in partially resolving *tert*-butylmethylphenylphosphine (**31**) through its diastereomeric platinum(II) complexes with (+)-deoxyephedrine (eq 7). The *tert*-butylmethylphenylphosphine oxide obtained by *in situ* oxidation of the liberated phosphine was of ca. 44% ee.



In early 1970s two groups developed general procedures for direct resolution of phosphines via their diastereomeric transition metal complexes. One of those procedures which was developed by Otsuka and co-workers[74] relies on chiral palladium(II) complexes **32–34** derived from enantiomeric 1-phenylethylamines,

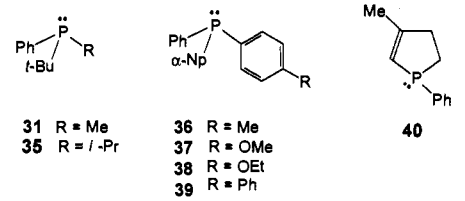


1-naphthylethylamines, and *sec*-butylisonitrile as the resolving agents (only one enantiomer of each complex shown). A general procedure of such resolution utilizing typically only 0.5 equiv of the resolving agent is given in eq 8, and the resolved phosphines **31** and **35–40** are



listed in Chart 2. Although, as it appeared, matching of the suitable complex with the phosphine was frequently required, the method proved efficient and reasonably general and provided direct access to the resolved phosphines of high enantiomeric purity. Typically, the unreacted excess phosphine remaining in solution provided material highly enriched in one enantiomer whereas the other enantiomer was usually recoverable from the precipitated crystalline complex of type **32a**. Even though the studied resolutions looked at first glance like the classical examples of kinetic resolutions it was found more probable, however, that they were driven by precipitation of the less soluble of the two diastereomeric complexes equilibrating quickly in solution via ligand exchange rather than by a difference in complexation rates of the two phosphine enantiomers. Interestingly, in one case, i.e., **40**, the resolution was effected not in the complexation step

Chart 2

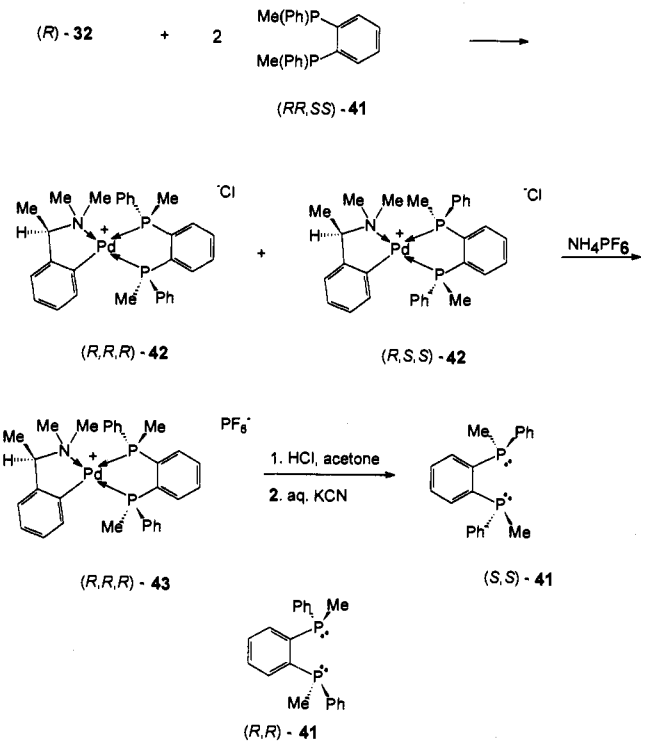


31 R = Me
35 R = *i*-Pr

36 R = Me
37 R = OMe
38 R = OEt
39 R = Ph

40

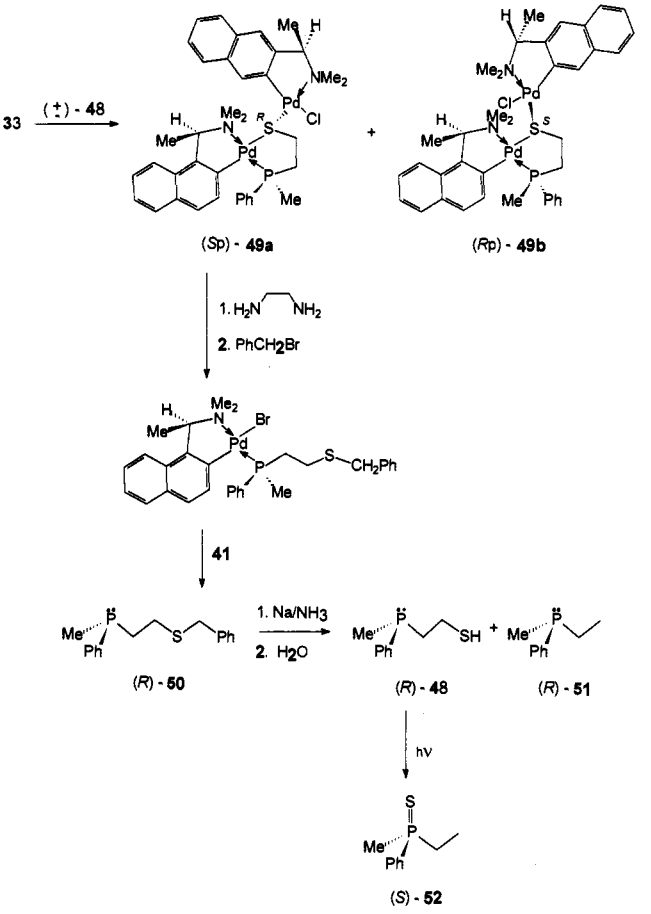
Scheme 2



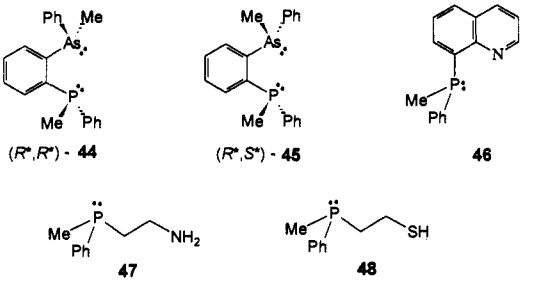
but instead during liberation of the phosphine from the metal by treatment with achiral dppe.

Complexes **32** and **33** were found by Wild and coworkers[45,75-78] to be especially well suited for the resolution of bidentate phosphines. Their remarkably efficient resolution of *o*-phenylenebis(methylphenylphosphine) (**41**) by the chloro-bridged dimer (*R*)-**32** is detailed in Scheme 2.[45] Nearly complete precipitation of a single complex **43** followed by effective two-step decomplexation allowed the isolation of the optically pure (*S*,*S*)-**41** in 85% overall yield and recovery of the optically pure (*R*,*R*)-**41** from the mother liquors in even higher 90% overall yield. In one preparative run more than 5 g of each enantiomer was drawn from 11.6 g of the racemate. In the same way related bidentate ligands (*R**,*R**)-**44** and (*R**,*S**)-**45** were resolved[75] although in the case of the "meso"-type (*R**,*S**)-**45** the complex **33** had to be used. Complex **33** proved also to be highly effective in a similar large-scale resolution of phosphine **46** as well as in resolution of **47**[77] and **48** (Scheme 3).[78] Interestingly, in the two latter cases the resolved optically pure phosphines were liberated from Pd by treatment with racemic **41**. The resolution of thiol phosphine **48**[78] went through the diastereomeric dipalladium complexes of type **49** in which, after separation, the external Pd was displaced with ethylene diamine and the freed thiolato-S atom was alkylated with benzyl bromide. After subsequent liberation the resulting *S*-benzyl phosphine was treated with Na/NH_3

Scheme 3



to afford optically pure **48** in 80% yield; the remaining 20% being also optically pure ethylmethylphenylphos-

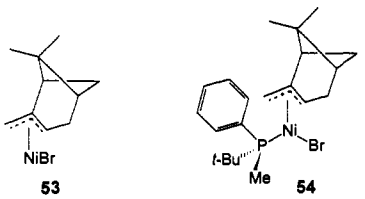


phine (**51**). Interestingly, the phosphine **48** bearing free thiol group in the β position was found to be photochemically unstable and rearranged on exposure to light into optically pure ethylmethylphenylphosphine sulfide (**52**) with complete retention of configuration.

It can be concluded that the general utility of palladium complexes **32** and **33** in resolution of P-chiral phosphines is already well established. Structures of several intermediate diastereomerically pure phosphine palladium complexes were confirmed by X-ray measurements which also provided the important configurational assignments. Complexes **32** and **33** were also used with success for resolution of some P-achiral axially dissymmetric phosphines[79] although they failed to resolve C_3-symmetric phosphines.[60] The diastereomerism that ensued on interactions of such complexes with scalemic phosphines could also be utilized for determination of the optical purity of the latter.[78,81]

Another fairly general resolution procedure which relied on separation of diastereomeric metal complexes

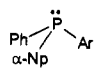
derived from (+)-(1*R*,5*R*)-π-pinenyl nickel halides **53**[82] and racemic phosphines was developed by the Mühlheim group.[83] Several aryldialkyl- and trialkylphosphines were resolved in this way via diastereomeric complexes of type **54**[84] of which one diastereomer could



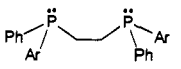
53 **54**

be usually quite readily obtained by fractional crystallization. Frequently, the phosphines resolved by this procedure were not liberated from the metal since the diastereomerically enriched (or pure) phosphine-modified Ni complexes of type **54** could be utilized directly as components of the chiral catalytic systems for asymmetric oligomerization of olefins.[85]

A similar procedure avoiding liberation of the resolved phosphine was also developed by Yoshikuni and Bailar[86] for the preparation of chirally modified cationic bis(phosphine)rhodium complexes of type $[Rh(COD)(P^*)_2]^+$. In this case the preformed racemic complexes were resolved as the corresponding α-bromocamphor-π-sulfonates $[Rh(COD)(P^*)_2]BCS^*$ by fractional precipitation from ether. Obtained in this way Rh complexes containing completely resolved mono- and bidentate phosphines **55–59** were used, after exchange of bromocamphorsulfonate counterion with Cl^-, PF_6^-, or ClO_4^-, as chiral catalysts for asymmetric hydrogenation.

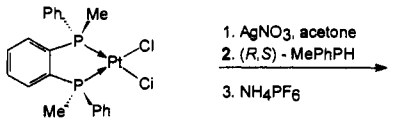


55 Ar = o-Tol
56 Ar = *p*-Tol

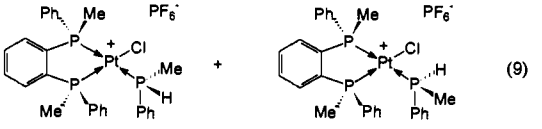


57 Ar = o-Tol
58 Ar = *p*-Tol
59 Ar = α-Np

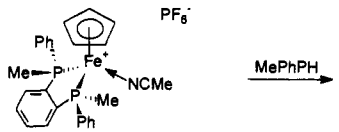
Into the same category of resolutions of phosphines by metal complexes which did not end up with liberation of the resolved phosphine fall the resolutions of secondary methylphenylphosphine (**6**) reported by Wild and co-workers.[87,88] In these studies platinum and iron cationic complexes of type **60**[87] and **62**[88] were introduced as effective resolving agents in which, interestingly, bis(phosphine) (*S*,*S*)-**41** which was obtained earlier via the palladium route served as the chiral auxiliary ligand. The resolution involving the platinum complex is shown in eq 9.[87] In this case the two diastereomeric methylphenylphosphine complexes **61** were formed in a 1:3 ratio and the pure major isomer (*S*,*S*,*S*)-**61** was obtained as the CH_2Cl_2 solvate by crystallization from CH_2Cl_2–Et_2O.[88] Its structure and absolute configuration was established by X-ray. In a very similar way the two separable iron complexes were obtained in a 1:1 ratio (eq 10). It is difficult to judge the origin of the selectivity observed in the formation of the studied complexes since the phosphine can undergo racemization under the experimental conditions and the two diastereomeric complexes can interconvert readily under the catalysis of traces of Cl^- or adventitious water. As demonstrated in racemic models, complexes **62** could also serve to resolve ethylphenylphosphine and benzylphenylphosphine and are very likely to find wider



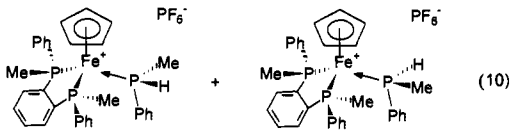
(*S*,*S*) -**60**



(*S*,*S*,*R*) - **61** (1 : 3) (*S*,*S*,*S*) - **61** (9)



(*S*,*S*) - **62**

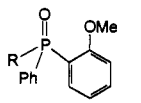


(*S*,*S*,*R*) - **63** (3.5 : 1) (*S*,*S*,*S*) - **63** (10)

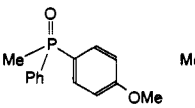
use as convenient resolving agents for secondary phosphines.[88] Also importantly, secondary phosphines in complexes **61** and **63** can be deprotonated and subsequently alkylated with complete retention of configuration at the metal-bound phosphorus.[88]

One unsuccessful attempt of resolution of a singular cyclic phosphine through complexation with chiral nickelocenes is on record.[89]

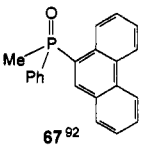
b. By Chromatography. Since the advent of high-performance chromatographic techniques and development of a range of chiral stationary phases (CSPs) resolution of racemic mixtures by chromatographic methods has become a viable alternative to the existing classical methods of resolutions.[90] Early analytical studies[91-93] on chiral phosphine derivatives focused mainly on phosphine oxides and typically required the presence of π-basic, usually condensed aromatic, substituents in their structures (e.g., **64–71**) since interac-



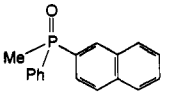
64[93] R = Me
65[93] R = Et



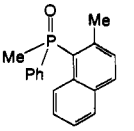
66[93]



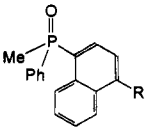
67[92]



69[92]



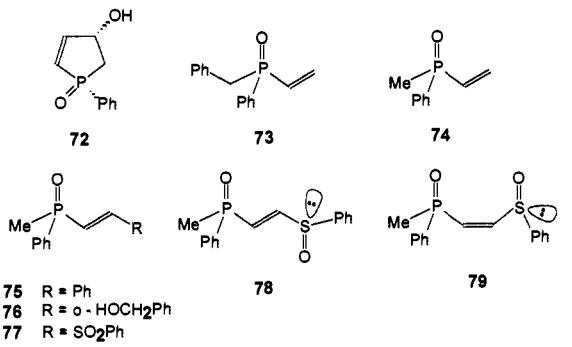
70[92]



71[91-93]
R = H, Me, OH, OEt, OCH_2CO_2Et

tions based solely on the P=O dipole were considered not efficient enough. These and later also many other structurally diversified diaryl and monoaryl phosphine derivatives have been resolved using various CSPs including poly(trityl methacrylate),[91] Pirkle's CSPs,[92,94,95] cellulose triacetate,[96,97] CSPs based on *N*,*N*′-(3,5-dinitrobenzoyl)-*trans*-1,2-diaminocyclohexane (DACH-DNB),[98] cyclodextrines,[93] as

well as commercially available chiral columns such as Chiracel, Daicel, Chiralpack, etc. Most recently, a range of vinyl phosphine oxides of diversified functional pattern, either cyclic or acyclic, and of *E* or *Z* geometry (e.g., **72–79**), have been resolved analytically on DACH-DNB columns.[98]

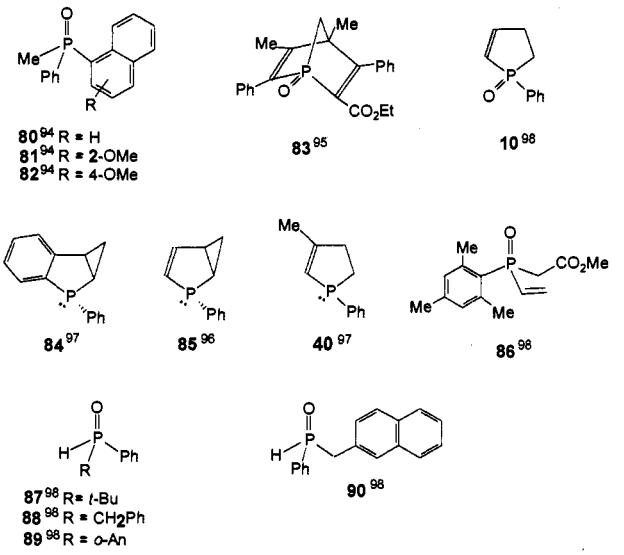


72 **73** **74**

75 R = Ph
76 R = o-$HOCH_2Ph$
77 R = SO_2Ph

78 **79**

The number of successful, although not always complete, semipreparative and preparative chromatographic resolutions of P-chiral phosphines and their derivatives is also continuously growing.[94-98] Structures **80–90** specify the examples available to date. This



80[94] R = H
81[94] R = 2-OMe
82[94] R = 4-OMe

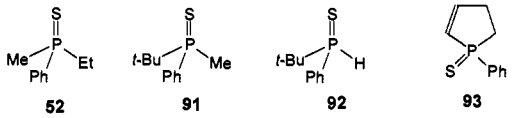
83[95] **10**[98]

84[97] **85**[96] **40**[97] **86**[98]

87[98] R = *t*-Bu
88[98] R = CH_2Ph
89[98] R = *o*-An

90[98]

collection includes for the first time secondary phosphine oxides[98] and phosphines,[95,97] even though the latter had to be isolated ultimately as oxides. It is also worthy of stressing that secondary phosphine oxides give uniformly excellent separations on a DACH-DNB column, which offered in the cited cases **87–90** enantioselectivity factors up to $\alpha = 3.04$. About 30 mg of each enantiomer of **90** of more than 99% ee was obtained by Gasparrini and co-workers[98] in just two repetitive runs on this column. Further work by this group demonstrated also that simple tertiary and secondary phosphine sulfides (e.g., **52**, **91–93**), as well as their



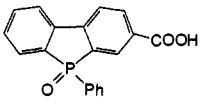
52 **91** **92** **93**

selenide and borane counterparts can be resolved on the same DACH-DNB CSP which apparently begins to emerge as the CSP of choice for chromatographic resolutions of phosphine derivatives.

The number and the range of phosphine derivatives resolved to date on chiral columns augur well for the further dynamic development of the method with more preparative separations rapidly becoming available.

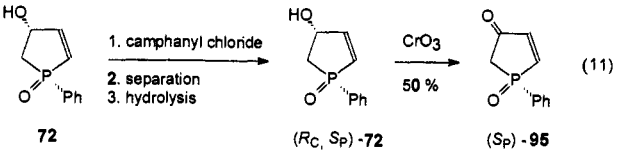
2. Resolution via Covalent Diastereomers

In 1961 Campbell and Way[99] reported the resolution of dibenzophosphole oxide **94** via its diastereomeric amides derived from enantiomeric (+)- and (−)-1-phenylethylamines. All the previous attempts by the authors to resolve this oxide by salt formation with the same amines as well as with many other scalemic bases failed.



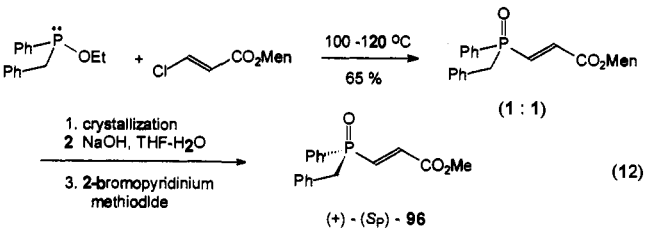
94

On the way to enantiomeric 4-oxo-1-phenyl-2-phospholene 1-oxide (**95**) Bodalski and co-workers[100] resolved its 4-hydroxy precursor **72** through the corresponding diastereomeric esters with (−)-ω-camphanic acid. One of the esters was obtained in pure form by fractional crystallization from benzene–hexane and, after hydrolysis, was subsequently converted into the desired ketophospholene oxide **95** (eq 11). The absolute configuration of the resolved (+)-**72** was established by X-ray.



72 (R_C, S_P)-**72** (S_P)-**95** (11)

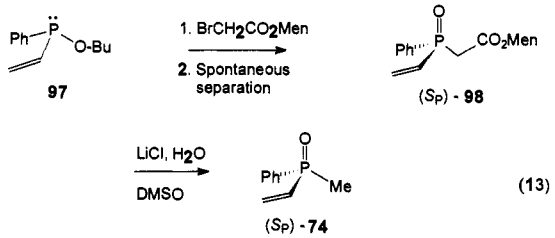
Aside from the above two resolutions of preformed racemic mixtures of functionalized phosphine derivatives, all the resolutions discussed in this section involve a more practical, one-step-saving procedure in which the covalently bound auxiliary was introduced to the phosphine structure simultaneously with the formation of the last of the required C–P bonds. Such a procedure seems to have been employed for the first time in the preparation of the optically active phosphinyl acrylate **96** shown in eq 12.[101] Reaction of ethyl



(+) - (S_P) - **96** (12)

benzylphenylphosphinite with (−)-menthyl 2-chloroacrylate directly provided a 1:1 mixture of P-epimeric menthyl *trans*-2-phosphinylacrylates of which one epimer could be isolated in pure form by a series of crystallization from acetone. Subsequent transesterification afforded (−)-(*S*)-**96** in which phosphorus remained the sole stereogenic center.

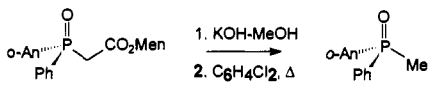
In a related Arbusov approach (eq 13)[102,103] butyl phenylvinylphosphinite (97) was allowed to react with (−)-menthyl bromoacetate (99) to afford equimolar mixture of menthyl (phenylvinylphosphinyl)acetates [(R_PS_P)-98]. Quite fortuitously, one diastereomer



97 (S_P)-98 (S_P)-74 (13)

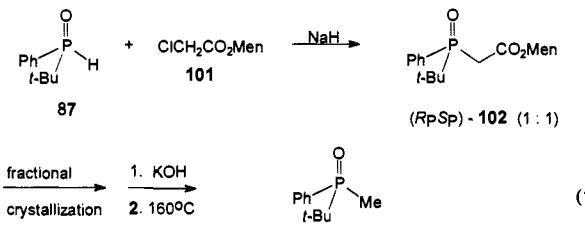
spontaneously crystallized out from the crude reaction mixture upon its cooling to room temperature. Collected by filtration and recrystallized from benzene diastereomerically pure (S_P)-98 was then conveniently freed from the carbomenthoxy auxiliary by a one-step decarbalkoxylation yielding enantiomerically pure (S_P)-74.[103] The procedure is well suited for the large-scale preparation; from one batch ca. 25 g of (S_P)-98 and consequently ca. 7 g of (S_P)-74 can readily be obtained.

In exactly the same way (S_P)-100 can be isolated in pure form by treatment of the corresponding oily post-Arbusov mixture containing the two P-epimers in equal amounts with chilled pentane or benzene–hexane.[104] Practically pure (S_P)-100 precipitates in the cold and is collected as somewhat oily crystals requiring a single recrystallization from benzene–hexane. Interestingly, albeit in a time span of years, a purified 1:1 mixture of diastereomers 100 constituting thick lucid oil was also found to spontaneously deposit (S_P)-100 as huge blocks, leaving practically pure (R_P)-100 as an oil. As exemplified in eq 14, decarbalkoxylation of the separated diastereomers 100 affords the corresponding enantiomers of PAMP oxide 64 directly. A crystalline diastereomer of 100 of the (R_P) configuration was also obtained by this procedure by using (+)-99 derived from D-menthol as the chiral auxiliary.[104]



(S_P)-100 (S_P)-64 (14)

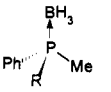
In the analogous preparation of enantiomeric *tert*-butylmethylphenylphosphine oxides developed by Imamoto and Johnson,[105] a mixture of the corresponding P-epimeric menthyl phosphinylacetates was obtained by the Michaelis-Becker reaction of secondary phosphine oxide 87 with (−)-menthyl chloroacetate (101) (eq 15). After facile separation of (R_P)-102 and (S_P)-



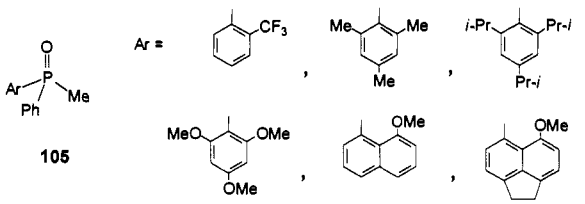
87 101 (R_PS_P)-102 (1 : 1)

(R) and (S)-103 (15)

102 by fractional crystallization the carbomenthoxy auxiliary was removed in this case by means of hydrolysis of the individual diastereomers with KOH in methanol, followed by thermal decarboxylation of the resulting acids. Both enantiomers of 103 could be obtained readily in gram quantities, and the procedure proved to be general. In the same way the corresponding phosphine boranes 104[106] as well as a whole series of arylmethylphenylphosphine oxides 105[105] of high optical purity were obtained from the more easily accessible diastereomer of the corresponding pairs of menthyl phosphinylacetates. The absolute configurations of oxides 105 were not established. A potential mnemonic for assignment of configuration at phosphorus in menthyl phosphinylacetates has been recently discussed.[104]

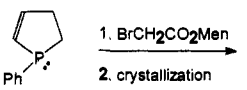


(R)-104a R = *t*-Bu
(S)-104b R = *o*-An

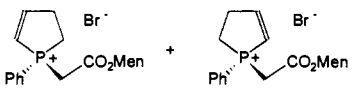


105

(−)-Menthyl acetate residue appears to also act successfully as the "covalent" resolving unit in quaternary phosphonium salts (eq 16).[107] Both (R_P)-107



106



(R_P)-107 (S_P)-107 (16)

and (S_P)-107 were isolated with remarkable ease in diastereomerically pure forms from one batch in gram quantities by crystallization from EtOAc and EtOAc–EtOH. If this facility of separation also recurs in other pairs of P-epimeric menthoxycarbonylmethylphosphonium salts, as it was already the case in the phosphine oxide series,[102-105] the developed procedure may likely gain practical importance for the oxidative resolution of phosphines due to expected facility of removal of the auxiliary menthyl acetate moiety through the stereochemically well-behaved Wittig reaction. In the cited case both salts gave the corresponding virtually enantiomerically pure enantiomers of 1-phenyl-2-phospholene 1-oxide (10) quantitatively.[107]

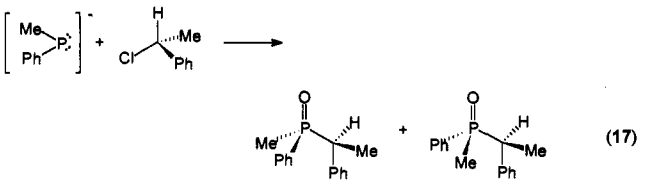
3. Self-Resolving Systems

Resolutions of phosphorus stereogenic centers in compounds grouped in this section were also realized by means of a covalently bound auxiliary, but they are different from those discussed in the previous section in that the chiral, typically C-chiral, unit introduced to the phosphine structure for the purpose of resolution was this time meant to be retained in the target

structure. Compounds resolved in this way remain internally diastereomeric, and as such they are frequently relatively easily assigned their configuration as well as are readily monitored for any changes of their stereochemical integrity at phosphorus. Also, in their P^{III} forms they are useful as chiral ligands which are especially well suited for studies of potential cooperativity between inducing factors related to backbone- and phosphorus-based ligand chirality in asymmetric catalysis.

Preparation of phosphines and their derivatives of this kind requires, however, that at least one of their three C–P bonds is formed under the circumstances that the auxiliary C-chiral subunit is already present in the organophosphorus precursor or in the reagent structure. Thus, a distereoselective asymmetric creation of a P-stereogenic center in such syntheses is in principle possible and the occurrence of this phenomenon in several of the preparations discussed below has been observed. Nevertheless, even in those fortunate cases, almost without exception, access to individual diastereomers of the desired C,P-chiral phosphine derivative had to rely ultimately on separation.

In 1975 Naylor and Walker[108] reported that alkylation of sodium methylphenylphosphide with (+)-1-phenylethyl chloride followed by oxidation of the crude products by H_2O_2 led to the formation of a 63:37 mixture of oxides **108** of which the major **108a** could be isolated pure by chromatography on silica gel (eq 17).



(17)

(*S*P, *S*C) - **108a** (*R*P, *S*C) - **108b**

Using the same methodology and scalemic neomenthyl and menthyl chlorides Fisher and Mosher[109] synthesized menthyl and neomenthyl phosphines **109**, **111** and **113**, **115**. Of these **109** and **111** were separated via their oxides **110** and **112** from which the individual phosphines were recovered by reduction with phenylsilane which gave **111** with complete and **109** with predominant retention of configuration.

109 X = lp
110 X = O

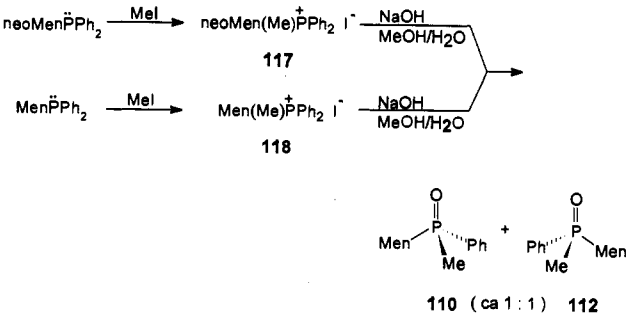
111 X = lp
112 X = O

113 X = lp
114 X = O

115 X = lp
116 X = O

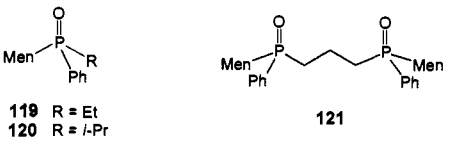
The same four diastereomeric phosphines and their oxides were prepared later on a large scale by Valentine and co-workers.[110] These authors succeeded in separation of all the four oxides by crystallization and they demonstrated also that Si_2Cl_6 was the best reagent for stereoselective conversion of these oxides into phosphines. For the preparation of menthylphosphine oxides a new and potentially general route was developed which was based on hydrolytic cleavage of P-prochiral phosphonium cations[1,35] derived from *either* diphenylneomenthyl- or diphenylmenthylphosphine (Scheme 4).[110] By this route diastereomers of novel oxides **119** and **120** and bis(oxide) **121** were also

Scheme 4



110 (ca 1 : 1) **112**

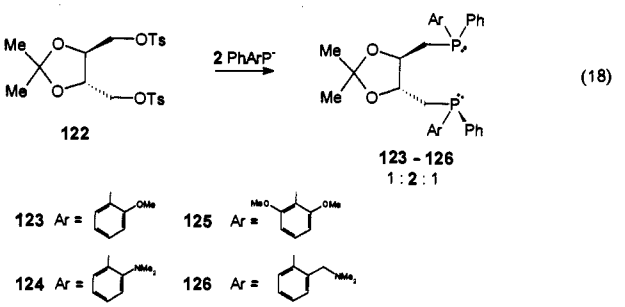
prepared, but except for (R_P,S_P)-**121**, they were not separated. Only little or no selectivity was observed in the studied decompositions of P-prochiral phosphonium salts **117** and **118**.



119 R = Et
120 R = *i*-Pr

121

Alkylations of phosphide anions with bifunctional scalemic alkylating agent **122** derived from tartaric acid were studied by Burgess and co-workers[111] in the course of their work on P-chiral analogs of DIOP. The systems studied are shown in eq 18. No carbon-to-phosphorus



(18)

122

123 - 126
1 : 2 : 1

123 Ar =

125 Ar =

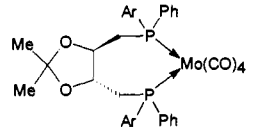
124 Ar =

126 Ar =

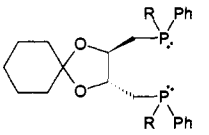
induction was observed in any of the alkylations studied and, by default, the 1:2:1 mixtures of the three diastereomeric bis(phosphines) had to be dealt with in each case. Even though careful crystallization was helpful in aiding isolation of the C_1 isomer of **123**, for all the other separations the stereoisomeric mixtures of bis(phosphines) had to be converted into the corresponding mixtures of their molybdenum tetracarbonyl complexes of type **127** which proved eventually separable by flash chromatography. After separation, it was found convenient to liberate the free ligands reductively by treating the individual molybdenum complexes with sodium naphthalenide at −78 °C. Due to overreduction, liberation of bis(phosphine) **125** was only partially successful. Separation of **126** was not reported.

Two other P-chiral analogs of DIOP, i.e., **128** are also on record[112] but details of their synthesis are not available. Similarly, use of self-resolving phosphines **129** and **130** was reported by Wilke and co-workers.[85,113]

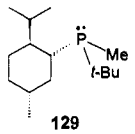
An approach which relies on reactions of scalemic phosphides with achiral electrophiles has also found considerable utility in the preparation of self-resolving P-chiral systems. It was first used by King and coworkers[114] to obtain diphosphine **131** by reacting



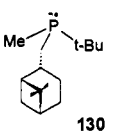
127



128 R = CH_2Ph, Cy

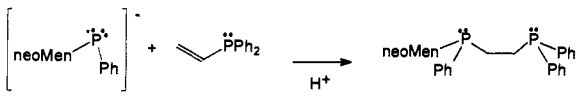


129



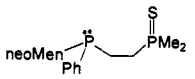
130

neomenthylphenylphosphine with diphenylvinylphosphine in the presence of potassium *tert*-butoxide (eq 19). Diphosphine **131** was formed as a 1:1 mixture of

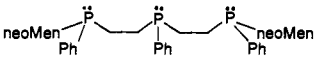


131 (1:1)

(19)



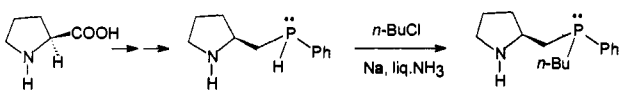
132



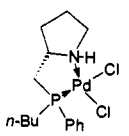
133

the two diastereomers but subsequent repeated recrystallizations furnished both diastereomers in pure form albeit in low yield. Similarly derived menthyl counterparts of **131** failed to crystallize, and crystalline sulfides **132** (1:1) and triphosphines **133** could not be separated.

In the same way Kinoshita and co-workers[115] prepared proline-derived aminophosphines **134** as a 1:1 mixture (eq 20) and resolved them later successfully via



134 (1:1)



135

(20)

complexes **135** with $PdCl_2$. Interestingly, recrystallization of the diastereomeric complexes from chloroform–ethanol gave two different crystal forms, blocks and needles, which were separated by hand picking. Aminophosphines **134** resolved in this way were established their absolute configurations by X-ray of **135**, but they were not liberated.

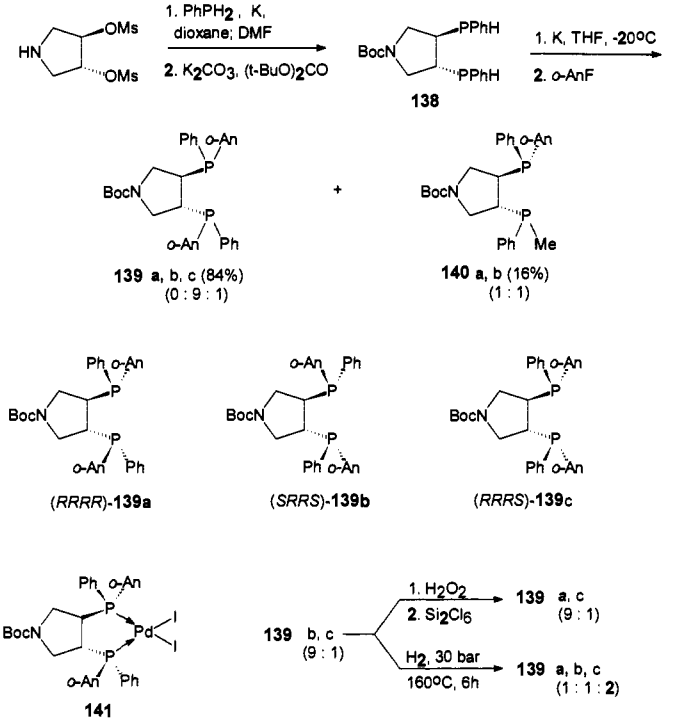
Horner and Simons[49] described alkylations of scalemic phosphides **136** derived from (*S*)-1-phenylethylamine by 1,2-dichloroethane (eq 21). The resulting mixtures of stereoisomeric bis(phosphines) **137a** were subsequently converted into oxides but their separation was not performed.

136

137
R = Me, Ph

(21)

Scheme 5



138

139 a, b, c (84%)
(0 : 9 : 1)

140 a, b (16%)
(1 : 1)

(*RRRR*)-**139a**

(*SRRS*)-**139b**

(*RRRS*)-**139c**

141

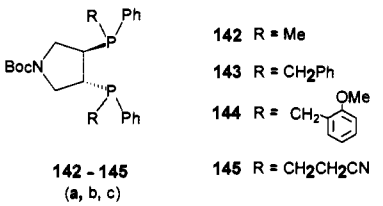
139 b, c (9 : 1)

139 a, c (9 : 1)

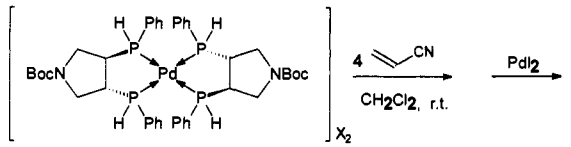
139 a, b, c (1 : 1 : 2)

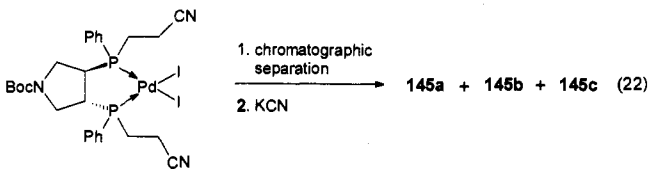
Recently, in a series of papers Nagel and coworkers[116–119] reported several successful alkylations and arylations of bis(phosphides) derived from tartaric acid based pyrrolidine 3,4-bis(secondary phosphines) of type **138**. The developed general synthetic protocol is exemplified in Scheme 5.[116] The starting bis(phosphides) were obtained either by deprotonation of the corresponding bis(secondary phosphines) as shown or by phenyl cleavage from the corresponding bis(diphenylphosphinyl)pyrrolidines.[117] In the example cited in Scheme 5 potassium metal and *o*-fluoroanisole were found to constitute the best combination of reagents in terms of both the yield and the selectivity, the concomitant formation of 16% of **140** as the sideproducts notwithstanding. By contrast, a reverse approach involving alkylation of prochiral *o*-anisylphenyl phosphide with scalemic 3,4-bis(mesyloxy)pyrrolidines gave the desired bis(phosphines) **139** in a statistical 1:1:2 ratio and in only <10% yield. For the purpose of resolution, the isomeric bis(phosphines) **139b,c** were converted into their air-stable and colored complexes with PdI_2, **141**, which could be subsequently separated readily by chromatography to provide after decomplexation with KCN good yields of the major **139b** as well as small amounts of **139c**. As it turned out to be a rule, diiodopalladium complexes of C_1-symmetric bis(phosphines), e.g., **139c**, could be readily separated from those containing C_2-symmetric bis(phosphines), e.g., **139a** or **139b**, whereas separations of the latter two appeared not possible. In this situation, in order to get straightforward access to larger quantities of **139c** and to **139a** the originally formed 9:1 mixture of **139b,c** was, before complexation, equilibrated thermally to a 1:1:2 mixture of **139a–c** or, respectively, inverted to a 9:1 mixture of **139a,c**, by the procedures summarized at the bottom of Scheme 5. By using the same synthetic protocol and the same isomerization and separation techniques three further bis(phosphines) **142–145** were also obtained, each in the three individual forms, and

were all assigned their absolute configurations.[117,118]

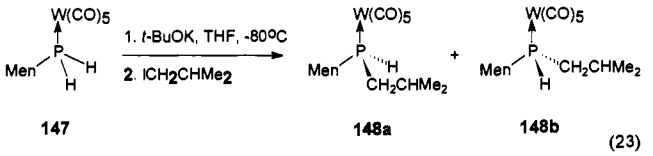


The selectivity observed in the studied alkylations was found to depend on several factors including N-substituent, electrophile, and metal, but nevertheless, it was usually biased to favor decidedly the formation of either (*RRRS*)-**e** or (*SRRS*)-**b** isomers. Interestingly, this preference is changed in favor of the formation of (*RRRR*)-**a** isomer when the alkylation is performed on the phosphine bound to a metal, as in the cationic palladium complex **146**. This alternate approach was used by Nagel and co-workers to synthesize **142** as well as stereoisomeric (cyanoethyl)phosphines **145** (eq 22).[119] In the same study **146** was also allowed to react with methyl acrylate and with two epoxides, but the resulting products were not characterized individually.



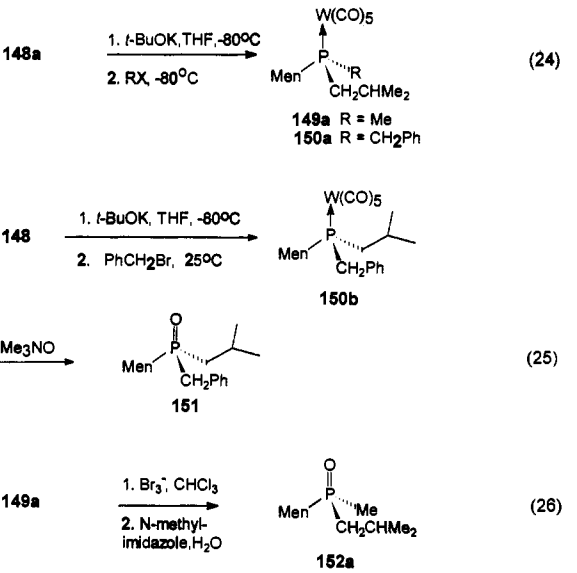


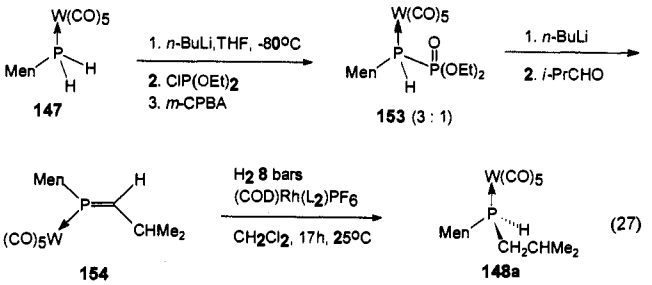
Mathey and co-workers[120] recently reported that scalemic primary and secondary phosphines coordinated to tungsten can be reacted with electrophiles in a highly stereoselective manner. As shown in eq 23,



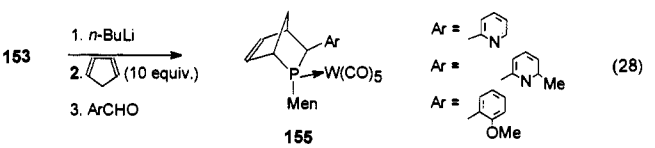
deprotonation and subsequent alkylation of (menthylphosphine)pentacarbonyltungsten **147** with *i*-BuI gives two diastereomeric secondary phosphine complexes **148a** and **148b** as either 7:3 or 3:7 mixture depending on the reaction temperature. Further alkylation of **148a** at −80 °C with MeI or $PhCH_2Br$ proceeded with complete stereospecificity and afforded **149a** and **150a**, respectively, with retention of configuration (eq 24). However, at room temperature, regardless of which mixture of **148** was used, the benzylation reaction led always to the preferential formation of **150b** (80% de) (eq 25). Diastereomerically pure **150b** was obtained by crystallization and was oxidatively decomplexed to yield **151** with full retention of configuration. Similarly, **149a** gave diastereomerically pure **152a** (eq 26).

In the main stream of the above studies[120] phosphide anion derived from (menthylphosphine)pentacarbonyltungsten **147** (or its molybdenum analog) was phosphorylated to give scalemic phospha-Wittig reagent **153** which in turn served to synthesize several novel P-chiral menthylphosphine derivatives. Reaction of **153** with isobutyraldehyde yielded intermediate prochiral phosphaalkene **154** which was subsequently hydrogenated over L_2Rh^+ catalyst to give stereoselectively **148a** (eq 27). When L_2 was dppe, the diastereomeric excess of

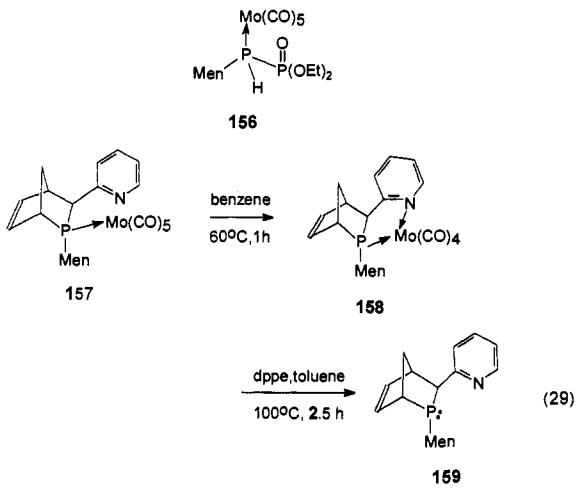




148a over **148b** was >90%, whereas with L_2 = (−)-chiraphos only **148a** was obtained. When **153** was allowed to react with a series of aryl aldehydes in the presence of excess cyclopentadiene the intermediate phosphaalkenes were trapped *in situ* to afford in each case a single phosphanorbornene derivative **155** (eq 28).

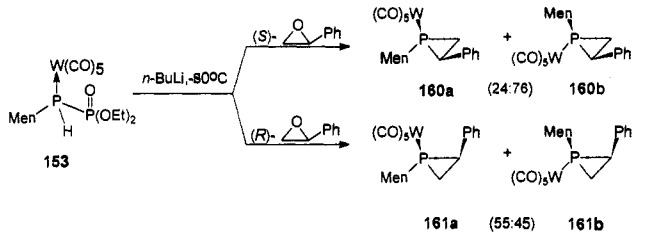


As has been rigorously established, both the hydrogenation and the [2 + 4] cycloadditions with cyclopentadiene took place on the *si* face of the phosphaalkene complexes. By a somewhat modified procedure and starting from the corresponding molybdenum reagent **156**, complex **157** was also obtained, again as a single stereoisomer. This complex was unstable and readily lost one CO to give more stable chelate **158** from which, however, the optically pure phosphine **159** could be ultimately liberated in more than 20% overall yield (based on the complexed menthylphosphine) (eq 29).

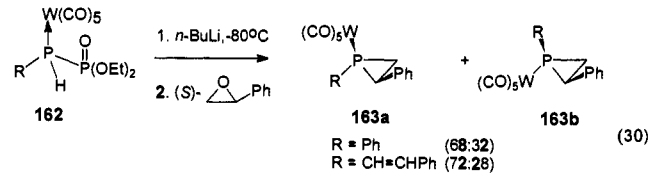


By reacting phospha-Wittig reagent **153** with enantiomeric styrene oxides the same authors[121] were able to synthesize and fully separate all four stereoisomeric menthylphosphirane complexes **160a,b** and **161a,b** (Scheme 6). As for the doubly asymmetric processes,

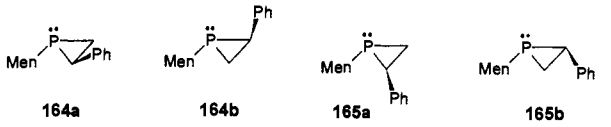
Scheme 6



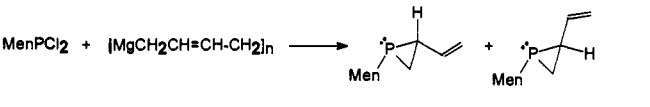
the reactions turned out to be only moderately stereoselective. Importantly, however, they were completely stereospecific with respect to the carbon configuration as total inversion of configuration at the oxirane carbon was observed. From the analysis of the product composition and stereochemistry it became apparent that the asymmetric induction by the *P*-menthyl group had not been effective. Besides clarifying the mechanistic picture of the phosphirane formation,[121] these observations led the authors to expect that the use of enantiomeric styrene oxides as the only chiral auxiliaries would be equally effective in creating asymmetry at P. The two pertinent examples are given in eq 30.



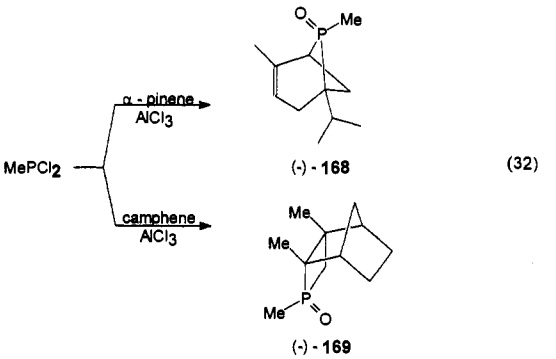
By using the same methodology, phosphirane molybdenum complexes corresponding to **160a,b**, **161a,b**, and **163a,b** (R = *t*-Bu) were also synthesized with very similar selectivity.[122] This time however, after separation the complexes were treated with dppe to yield free phosphiranes **164a,b** and **165a,b**, which were fully characterized and used as ligands for asymmetric catalysis. In the case of P–*t*-Bu derivatives the liberated phosphiranes were *in situ* transformed into cationic rhodium complexes to be used directly in hydrogenation experiments.



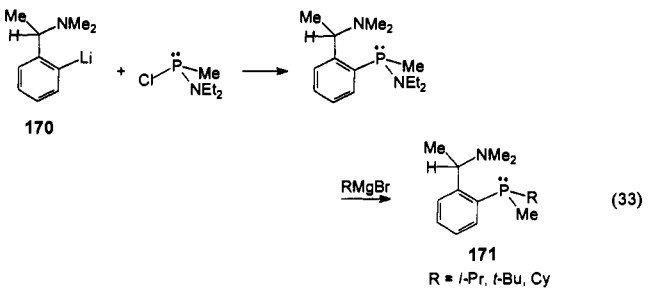
Ring-substituted *P*-menthylphosphiranes were also synthesized by Richter[123] in a straightforward manner involving treatment of dichloromenthylphosphine with magnesium butadiene at lowered temperature (eq 31). The phosphiranes were formed in this case as a mixture of four diastereomers **166a,b** and **167a,b** with a cis/trans ratio of 9:1. One of the cis isomers **166** constituted 82% of the whole mixture and the level of asymmetric induction in its formation was estimated to be ca. 82%.



In a similarly straightforward although mechanistically different manner Vilkas and co-workers[124,125] were able to convert simple achiral dichloromethylphosphine into P-chiral phosphetane oxides **168**[124] and **169**[125] incorporated into a terpenoid framework (eq 32). In spite of the multistep skeleton rearrangements involved, these syntheses provided, in one pot, the diastereomerically pure products in 30% yield.

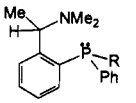


Reactions of aminochlorophosphines with scalemic aryllithium reagents **170** derived from enantiomeric 1-phenylethylamines were utilized by Horner and Simons[49] for the synthesis of several C,P-chiral aryldialkyl and alkyldiaryl phosphines **171** (eq 33). All of



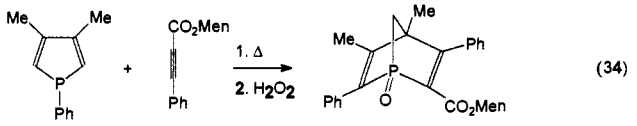
these diastereomeric phosphines, as well as **172** obtained in analogous manner, were resolved via their oxides with the aid of tartaric or perchloric acid and were then

reduced back to individual P-epimeric phosphines with $SiHCl_3$. Four triarylphosphines were also prepared in this way but they could not be resolved. Still another internally diastereomeric phosphine of the same type, i.e., (S_C,S_P)-**173**, was resolved by Tsuji and co-workers,[50] again with the help of (*R*)-tartaric acid. Its absolute configuration was assigned on the basis of X-ray analysis of its Pd(II) complex.[126]



172 R = Me
173 R = *n*-Bu

Cycloaddition reactions of an organophosphorus compound to a chiral auxiliary as a means of formation of self-resolving cycloadducts were employed by two groups. Mathey and co-workers[95] used a [2 + 4] cycloaddition of phosphole **174** to menthyl and bornyl phenylpropiolates to obtain diastereomeric 1-phosphanorbornadienes of type **175** (eq 34). In the menthyl

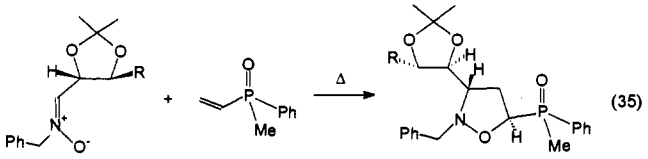


(34)

174 **175**

series the depicted oxidized major product was separated from its minor regioisomer on silica gel and was then resolved by HPLC into two individual P-epimeric oxides which were finally reduced back to phosphines by $SiHCl_3$–pyridine. The corresponding epimers in the bornyl series were not resolved.

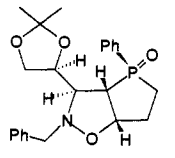
Brandi et al.[127] studied 1,3-dipolar cycloadditions of chiral nitrones to vinylphosphine oxides, and they were able to demonstrate that these processes can occur in a highly stereoselective manner, especially, in their doubly asymmetric version (cf. section III.C.2.c). However, when scalemic nitrones **176** were allowed to react with racemic vinyl phosphine oxide **74**, in both cases one of the cycloadducts was formed in useful predominance i.e., **177** (73% and 95%, respectively) (eq 35),



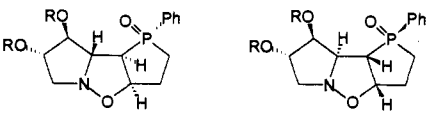
(35)

176 R = H, Me **74** **177** (major)

even though all the eight possible stereoisomeric products could be identified in the reaction mixtures before isolations of **177**. Analogous reaction of **176** (R = H) with racemic phospholene oxide **10** gave two products of type **178** (only major shown), which were separated and individually identified to originate from the opposite enantiomers of **10**, each thus in 100% stereoselectivity.[128] In complete accord with this picture, a small amount of unreacted **10** enriched in the slower reacting enantiomer (−)-(*R*)-**10** was also isolated. This particular observation inspired the authors to a more detailed study[129] on kinetic resolution of (±)-**10** by scalemic cyclic nitrones which will be discussed in section III.A.4. In the context of this section it should be recalled, however, that besides effectively resolving phospholene derivatives, those cycloadditions were also highly efficient as the asymmetric transformations affording stereoisomeric scalemic tricyclic P-chiral phosphine derivatives, e.g., **179a** and **179b** containing six contiguous stereogenic centers of defined absolute stereochemistry in the highly stereoselective manner (cf. eq 46, section III.A.4).[129] The two stereoisomers **179a** and **179b** which were typically formed in unequal amounts (in up to 10:1 ratio depending on the bulkiness of R) could be separated with ease by crystallization.

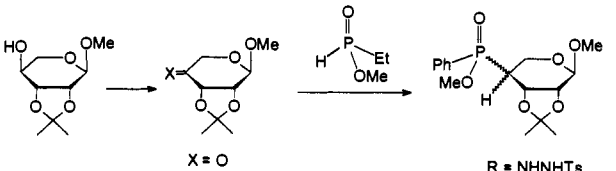


178 (major)



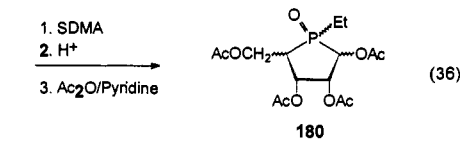
179a **179b**

Transformations of carbohydrates which led to self-resolving phosphasugars were described largely by Inokawa and Yamamoto and co-workers.[130-140] In the key step of their typically employed double Abramov-type route a sugar-bonded phosphinate was selectively reduced by dihydrobis(2-methoxyethoxy)aluminate (SDMA) to a secondary phosphine oxide which was subsequently allowed to undergo intramolecular Abramov reaction with the sugar carbonyl function placing phosphorus in the hemiacetal ring. Two examples are shown in eqs 36[130] and 37.[131] Although in all such



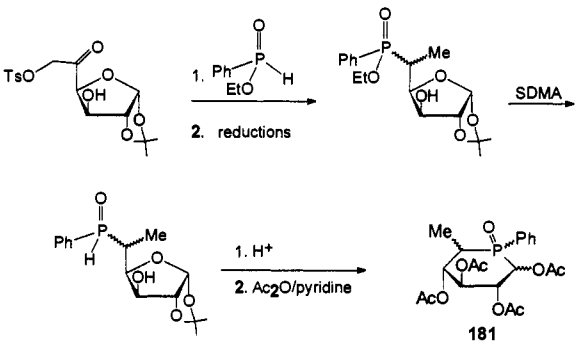
X = O
X = NHNHTs

R = NHNHTs
R = H



(36)

180

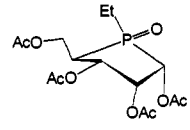


(37)

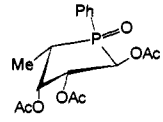
181

preparations, mixtures of two to seven stereoisomeric products of type **180** or **181** were usually formed with little selectivity and their separations were tedious and

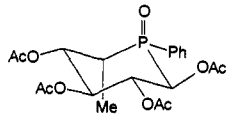
difficult, in many instances the authors were able to isolate individual isomers and to assign their absolute stereochemistry by means of detailed NMR and/or X-ray analysis. Those which were crystalline and were studied by the X-ray diffraction technique have been selected to serve as examples (182–189). In one study[137] an unusual enantiomerically pure phosphine **190** was isolated as a crystalline side product in 2.7% yield.



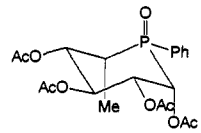
182[132]



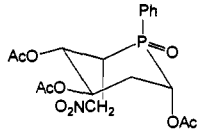
183[133]



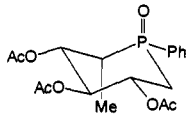
184[131]



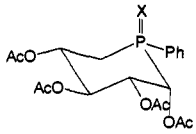
185[131]



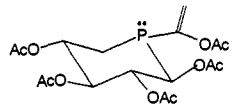
186[134]



187[135]

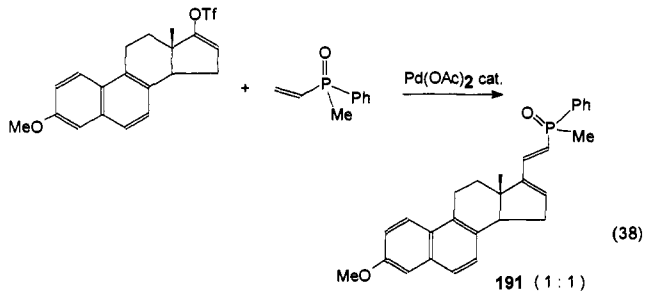


188[136] X = O
189[136] X = S



(-) - **190**[137]

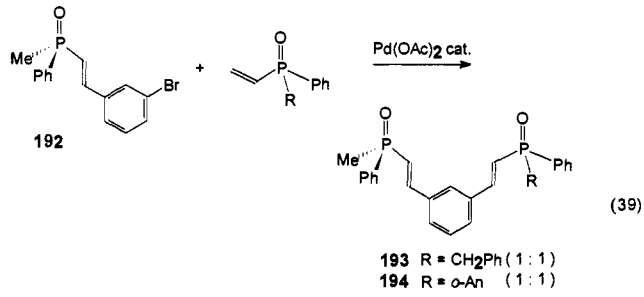
A single example in which steroid chirality was meant to resolve phosphorus stereogenic center in a butadienyl phosphine oxide **191** has been reported very recently (eq 38).[141]



(38)

191 (1 : 1)

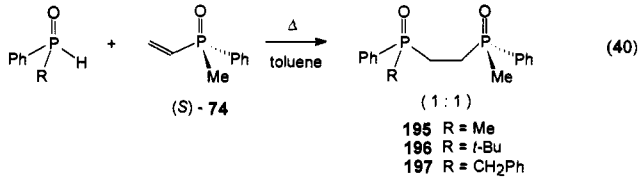
In the same study[141] and utilizing the same Heck-type chemistry two other self-resolving systems **193** and **194** were also prepared (eq 39). It should be noted, however, that these systems are distinct from all the previous ones discussed in this section in that, in these cases, instead of employing carbon chirality, an existing phosphorus stereogenic center in **192** serves to resolve another. This principle was earlier applied successfully in resolution of symmetrical and nonsymmetrical 1,2-bis(phosphinyl)ethanes **195–197**[142] and 1,2-bis(phosphinyl)ethenes **199** and **200**.[143] Both these systems were promptly accessible by straightforward thermal additions of racemic secondary phosphine oxides to enantiomerically pure acceptors (–)-**74** or (–)-**198** (eqs 40 and 41). All of them were separated by chromatography and were assigned their configuration on the basis of comparisons of their NMR and physical data and an X-ray study.[144]



(39)

192

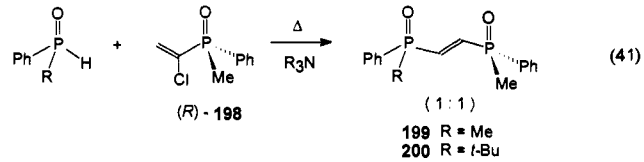
193 R = CH_2Ph (1 : 1)
194 R = *o*-An (1 : 1)



(40)

(*S*) - **74**

(1 : 1)
195 R = Me
196 R = *t*-Bu
197 R = CH_2Ph



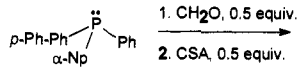
(41)

(*R*) - **198**

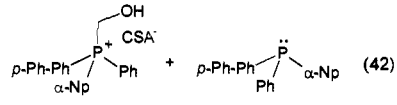
(1 : 1)
199 R = Me
200 R = *t*-Bu

4. Kinetic Resolutions

The first kinetic resolution of a phosphine is due to Wittig and co-workers[71] who succeeded in partially resolving *p*-biphenylyl-1-naphthylphenylphosphine (**201**) by means of its quaternization with half-molar amounts of paraformaldehyde and (+)-camphor-10-sulfonic acid (eq 42). The unreacted half of the phosphine was found



(±) - **201**

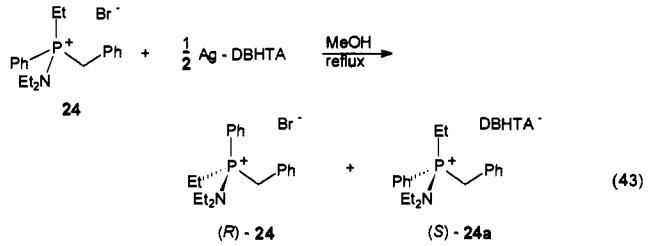


(42)

(+) - **202** (–) - **201**

to be enriched in the (–)-enantiomer and the other half, which was recovered from the hydroxymethylphosphonium salt **202** by treatment with Et_3N contained accordingly the (+)-enantiomer in excess. As it has been later revealed,[74] the optical purity of enantiomeric phosphines **201** resolved in this way was however only modest. When the three components were used in a 1:1:1 ratio, the separation of the resulting diastereomeric phosphonium salts was unsuccessful.

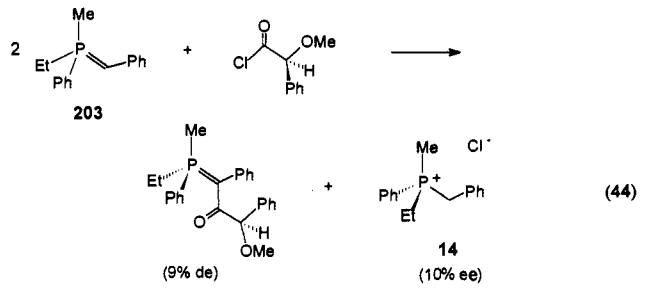
Kinetic resolution of a preformed aminophosphonium salt **24** (eq 43) was developed by Horner and Jordan[63] to complement their own classical 1:1 resolution of **24** with potassium hydrogen dibenzoyltartrate, in which they succeeded in isolation of only one, the less soluble, phosphonium hydrogentartrate of the *R* configuration.[63] This time the half of the salt containing exchanged counterion (**24a**) being poorly soluble in hydroxylic



(43)

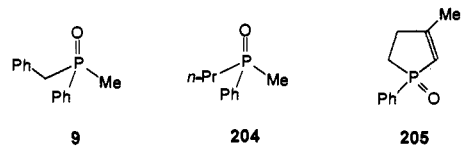
solvents was readily separated and was found to contain the lacking phosphonium cation of the *S* configuration.

Bestmann and Tömösközi[145] studied the kinetic resolution in "umylidierung" reactions of racemic ylides (e.g., **203**) with scalemic acid chlorides and related chiral reagents. An example is given in eq 44. The calculated optical yield in the case shown was 11.5%, and the highest in the study 15.4%. Several variations of this approach were also tested, however, with little if no success, with respect to the resolution of the P-center.

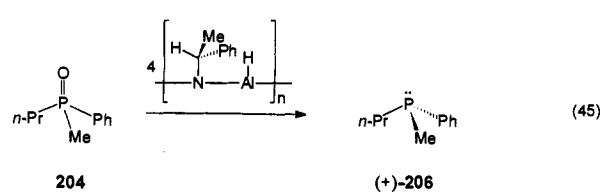


(44)

Attempts to kinetically resolve phosphines through their partial oxidation with scalemic peracids or scalemic amine oxides met with very little success.[146] The reverse approach, relying on reduction of racemic phosphine oxides with scalemic reducing agents, led to more promising results. Two groups[147,148] studied reductions of oxides **9**, **204**, and **205** by scalemic alanes derived from AlH_3 and (−)-1-phenylethylamine[147] or, $LiAlH_4$ and (*S*)-2-(anilinomethyl)pyrrolidine.[148] The

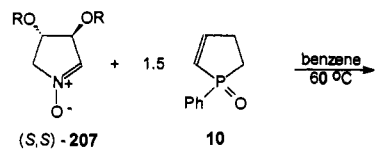


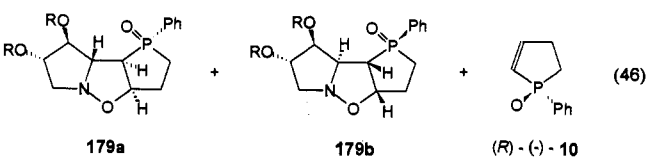
phosphines obtained in this way from oxides **9** and **204** had 6.8%[148] and 21.5%[147] ee, respectively. The results for phospholene oxide **205** were obscured as under the reaction conditions it underwent concomitant partial reduction of the double bond leading to the formation of nonseparable mixtures of unsaturated and diastereomeric saturated cyclic phosphines. Interestingly, as indicated in eq 45 showing the most successful experiment, as much as 4-fold excess of the hydride was used and the reduction was driven to nearly complete conversion of the phosphine oxide.[147] These conditions strongly imply that the mechanism of dynamic kinetic resolution was in operation in the studied cases as it is well known that phosphine oxides racemize rapidly in the presence of aluminum hydrides *prior* to reduction.[149]



(45)

Very recently an efficient kinetic resolution of 1-phenyl-2-phospholene 1-oxide (**10**) by means of its 1,3-dipolar cycloadditions with chiral scalemic nitrones was developed by Brandi and co-workers.[129] Crucial to this development were previous observations that **10** is approached by nitrones exclusively in the exo mode and only from the P=O bearing side.[114,150] The resolution process is exemplified in eq 46. In the

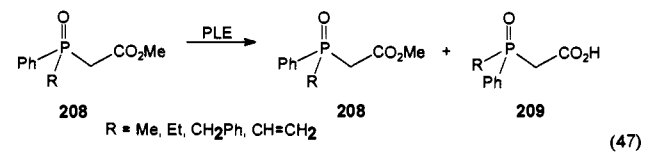




(46)

experiment shown, involving nitrone **207** possessing sterically demanding alkoxy groups (R = *t*-Bu), the unreacted (−)-*R*-**10** was isolated in 27% yield (to be compared with 33.3% theoretical yield after virtually complete conversion of the nitrone) and it was determined to be of remarkable 96% enantiomeric purity. The process proved similarly effective in resolution of phospholene sulfide **93** and is likely to become of more general utility. Enantiomerically pure nitrones **207** are readily available from tartaric acid,[151] and those possessing bulky OH protecting groups, e.g., R = *t*-$BuPh_2$-Si, offer resolutions with stereoselectivity factors $s = k_R/k_S$ higher than 10.[129]

Finally, enzymatic kinetic resolution of P-chiral phosphine derivatives has also been very recently accomplished. In one preliminary study[152] a short series of simple phosphinylacetates **208** (e.g., R = Me, Et, CH_2Ph, $CH{=}CH_2$; eq 47) was successfully resolved via PLE-catalyzed hydrolysis which afforded in the studied cases the unreacted esters **208** and the acids **209** of up to >98% enantiomeric purity.



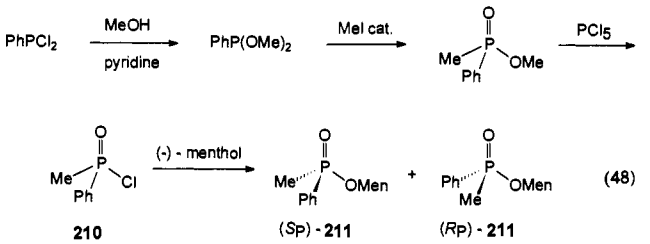
(47)

B. Stereoselective Synthesis

1. Via Single Displacement at P

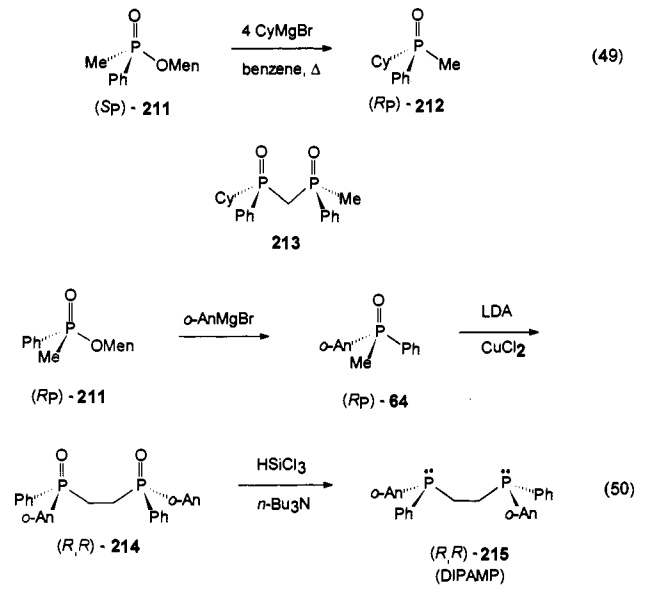
A search for flexibility and generality greater than just resolving individual racemic mixtures led to the development of synthetic methods potentially permitting preparations of series of scalemic phosphines or their derivatives from one precursor. Such an approach required, however, that a suitable *P-resolved* precursor possessing one or more potential leaving groups would be available and, that it would be possible to create new C–P bonds at its resolved P-center *stereoselectively*.

The pioneering work in this area is due to Nudelman and Cram[153] and to Mislow and co-workers,[34,154] who were the first to demonstrate that unsymmetrically substituted menthylphosphinates, RR'P(O)OMen, could be separated readily into the diastereomeric forms and subsequently reacted with Grignard reagents to afford scalemic tertiary phosphine oxides with a high degree of stereospecificity. A typical procedure for the preparation of P-chiral menthyl phosphinates is exemplified by Mislow's synthesis of menthyl methylphenylphosphinates (211) shown in eq 48.[34] Separation of the



(48)

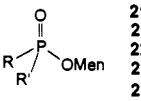
diastereomeric products 211 was effected by fractional crystallization from hexane at 5 °C. A readily crystallized diastereomer (S_P)-211, could be obtained in excellent yield especially when recycling of mother liquors via racemic 210 is repeatedly performed. Isolation of (R_P)-211, although possible, proved inefficient. In the same work,[34] a further three pairs of diastereomeric menthyl phosphinates were similarly obtained and separated, and together with 211 provided a pool of substrates for the subsequent Grignard syntheses of scalemic phosphine oxides and their configurational intercorrelations. As rigorously established in this work, the substitution reactions of menthyl phosphinates with organometallic reagents occur with inversion of configuration at phosphorus. Preparation of (*R*)-cyclohexylmethylphenylphosphine oxide (212) shown in eq 49 provides an early example.[34] Interestingly, in this synthesis a small amount of nonsymmetrical bis(phosphinyl)methane 213 (6%) was also isolated. Another important preparation is shown in eq 50.[155]



(49)

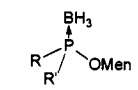
(50)

Although in general, the reactions of this type had to be carried out with an excess of a Grignard reagent under somewhat stringent conditions and were found to be very sensitive to variations of groups at phosphorus, oxygen, and magnesium, the method became of general use for its flexibility and high level of stereospecificity usually attainable. Many more diastereomeric pairs of menthyl phosphinates, i.e., **216–229**, were resolved by the group of Mislow[34,156,157] and

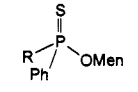


216 [156] R, R' = Me, Et
217 [34] R, R' = Me, Cy
218 [34] R, R' = Ph, *n*-Pr
219 [34] R, R' = Ph, β-Np
220 [159] R, R' = Me, *o*-An
221 [158] R, R' = Me, *p*-An
222 [158] R, R' = Me, *o*-H_2NPh
223 [158] R, R' = Me, p-Me_2NPh
224 [160] R, R' = Me, *p*-*t*-BuPh
225 [161] R, R' = Me, CH_2Ph
226 [162] R, R' = Ph, Et
227 [157] R, R' = Ph, *i*-Pr
228 [163] R, R' = Ph, $PhCH_2$
229 [164] R, R' = Ph, *o*-An

Horner[158] as well as by others,[155,159–164] albeit not without difficulties. Frequently only one diastereomer could be obtained in the pure form and several examples of unsuccessful attempts are also on record.[158,165] Alternative routes to the resolved menthyl phosphinates were thus developed in addition to procedures aimed to provide P-resolved phosphinates possessing simpler, chiral or achiral, alkyl residues in the ester group.[33,166] The corresponding phosphine boranes **230**[106] and **231**[106] and phosphinothioates **232**[170] and **233**[162] were also successfully resolved.

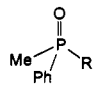


230 [106] R, R' = Me, Ph
231 [106] R, R' = Ph, *o*-An

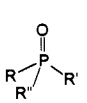


232 [170] R = Me
233 [162] R = Et

With the exception of phosphinothioates **232** and **233**, all the listed phosphinates were subjected to reactions with organometallic reagents which furnished eventually an impressive range of structurally diversified phosphine oxides (and boranes), frequently of high optical purity, and in several cases in both enantiomeric forms. The structures of scalemic phosphine oxides and boranes prepared by this method are specified below (**8**, **9**, **66**, **69**, **204**, **234–237**, and **104b**, **258–260**).



8 [34] R = Et
9 [34] R = $PhCH_2$
66 [34] R = *p*-An
69 [34] R = β-Np
204 [34] R = *n*-Pr
234 [171] R = Allyl
235 [172] R = *n*-Bu
236 [34] R = α-$NpCH_2$
237 [34] R = α-$NpCH_2CH_2$
238 [173] R = *m*-An
239 [34] R = *p*-PhPh
240 [174] R = *p*-Tol
241 [174] R = *p*-CF_3Ph
242 [160] R = *p*-*t*-BuPh
243 [165] R = *o*-Me_2NPh
244 [165] R = *o*-MeSPh
245 [165] R = *o*-EtPh
246 [173] R = *o*-Me-*p*-An

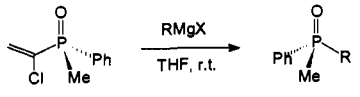


247 [156] R, R', R'' = Me, *n*-Pr, Et
248 [156] R, R', R'' = Me, *n*-Pr, Cy
249 [158] R, R', R'' = Me, *n*-Pr, *p*-An
250 [158] R, R', R'' = Me, *i*-Pr, *p*-An
251 [158] R, R', R'' = Me, *n*-Pr, *p*-Me_2NPh
252 [158] R, R', R'' = Me, *n*-Pr, *o*-H_2NPh
253 [158] R, R', R'' = Me, *n*-Pr, *o*-Me_2NPh
254 [158] R, R', R'' = Me, *n*-Pr, *o*-MePh
255 [160] R, R', R'' = Me, *t*-BuPh, $PhCH_2$
256 [156] R, R', R'' = Ph, β-Np, *o*-An
257 [156] R, R', R'' = Ph, β-Np, *p*-An

104b [173] R = *o*-An
258 [173] R = *o*-Me-*p*-An
259 [173] R = *m*-An
260 [173] R = *p*-An

Many of these products were later reduced to provide the corresponding scalemic phosphines. For example, syntheses of a long series of ortho-substituted aryl phosphine ligands by Horner and co-workers[158,165] relied on this methodology as did the Monsanto syntheses of CAMP[175] and DIPAMP[155] ligands (cf. eq 50). In the latter syntheses access to larger quantities of the difficulty accessible (*vide supra*) R_P epimer of **211** prerequisite for the formation of the *R,R* enantiomer of DIPAMP (required in the Monsanto L-DOPA process) was secured by crystallization of the Mislow diastereomeric mixture of **211** (1:1) from 50% solutions in α- or β-pinene by selective seeding.[175] Alternatively, (R_P)-**220** could be used to obtain intermediate **64** of the desired *R* configuration in its reaction with PhMgBr. It was disclosed[159] that in the preparation of **220** the desired R_P diastereomer is formed predominantly (4:1) and could be readily separated from the minor S_P diastereomer (cf. however, ref 158).

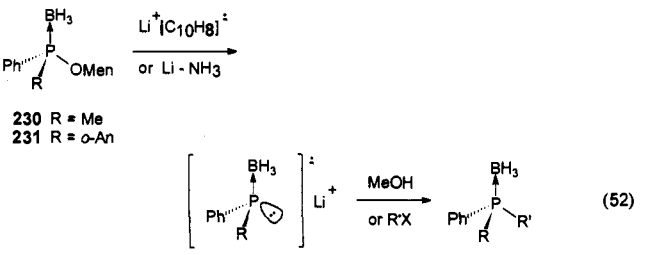
As mentioned before, the displacement of OMen group in menthyl phosphinates by Grignard reagents has been very sensitive to structural factors, and judicious matching of starting phosphinates with Grignard reagents has been often prerequisite for the overall success. Several attempts to improve the procedure have been made. It was discovered[156] early that organolithium reagents can be used successfully to effect the desired displacement, and typically, these reagents offer milder conditions and better yields but sometimes at the cost of lower optical purity of the resulting phosphine oxide. Groups different than menthyl in the phosphinate reagents were rarely tested. Some examples will be seen in the following two sections. In one early work[153] use of cholesterol as the auxiliary proved successful. In turn, Naso and co-workers[176] were able to demonstrate that 1-chlorovinyl group in (*R*)-**198** can also serve as the very effective leaving group for substitutions by aryl and vinyl Grignard reagents (eq 51). The studied displacements were established to provide virtually optically pure phosphine oxides of inverted configuration at phosphorus. The enantiomerically pure starting (*R*)-**198** is readily available from (*S*)-**74**.[143]



64 R = *o*-An
66 R = *p*-An
69 R = β-Np
75 R = CH=CHPh
239 R = *p*-PhPh
240 R = *p*-Tol
261 R = 2-Thienyl
262 R = CH=CHSiMe$_3$

(51)

The well-established utility of resolved menthyl phosphinates in the synthesis of scalemic phosphine oxides and boranes via substitution reactions with organometallic reagents has been recently further expanded due to the work of Imamoto and co-workers.[177,178] These authors discovered that the ester P–O bond in menthyl phosphinates can also be cleaved in a stereoselective manner reductively. The cleavage can be effected under very mild conditions with typical one-electron reducing agents such as $LiNH_3$, sodium or lithium naphthalenide, lithium biphenylide, and lithium 4,4′-di-*tert*-butylbiphenylide (LDBB). As the authors demonstrated in the phosphine borane series (eq 52),[177] quenching of the reaction mixture with an alkyl halide or methanol provides the corresponding scalemic

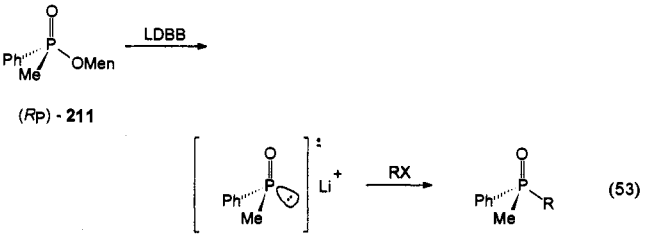


230 R = Me
231 R = *o*-An

104b R, R' = *o*-An, Me
263 R, R' = Me, CH_2Ph
264 R, R' = Me, H
265 R, R' = *o*-An, H

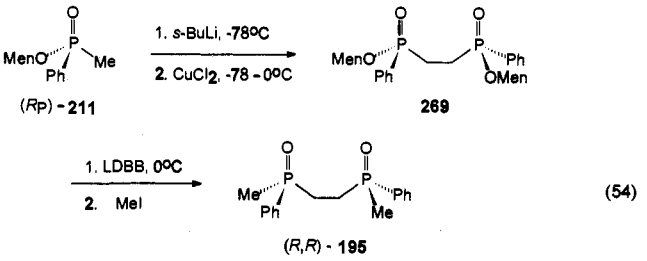
(52)

tertiary **104b**, **263** or secondary **264**, **265** phosphine borane, respectively. As shown in eqs 53 and 54[178]



9 R = $PhCH_2$
266 R = *n*-Hex
267 R = *p*-MeOPhCH_2
268 R = $PhCH_2OCH_2$

(53)

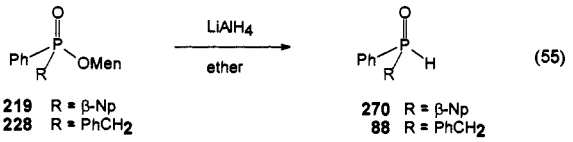


(54)

analogous reactions of menthyl phosphinate (R_P)-**211** and bis(phosphinate) (R_P,R_P)-**269** with LDBB and benzyl bromide and methyl iodide gave phosphine oxides **9**, **266–268** and bis(phosphine oxide) (*R,R*)-**195**, respectively. The corresponding *S* enantiomers of **9** and **195** were also obtained by this route. The cleavage of the OMen group was found to take place with almost complete preservation of stereochemical integrity at phosphorus and consequently resulted in the formation of the displacement products with *retention* of configuration, in contrast to the Mislow procedure which leads to the displacements products of inverted configurations. Hence, the two procedures are complementary.

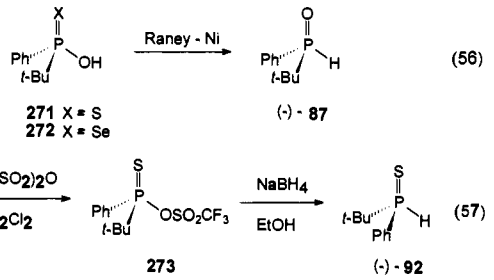
The reductive removal of the OMen group from the resolved menthyl phosphinates as a potential route to scalemic secondary phosphine oxides was already tested in the past;[163,179] however, those early attempts met with only very little success. The resulted secondary phosphine oxides **88** and **270** (eq 55), albeit optically active, were obtained in very low optical yields due to extensive racemization caused by $LiAlH_4$ used as the reducing agent.[149,160]

The synthesis of a secondary phosphine oxide of high optical purity by reductive means was later shown to be possible by Michalski and Skrzypczyński[181] who reacted to this effect resolved phosphinothioic acid **271** and phosphinoselenoic acid **272** with Raney nickel (eq



(55)

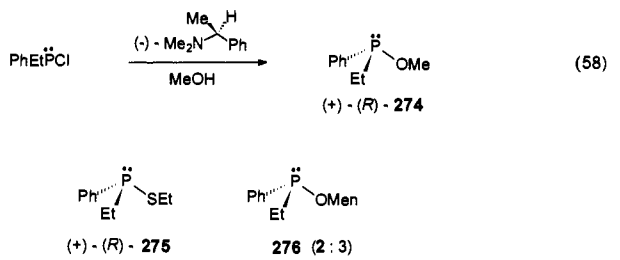
56). The corresponding scalemic secondary phosphine sulfide **92** was also prepared from the same phosphinothioic acid via mixed anhydride **273** (eq 57).[182]



(56)

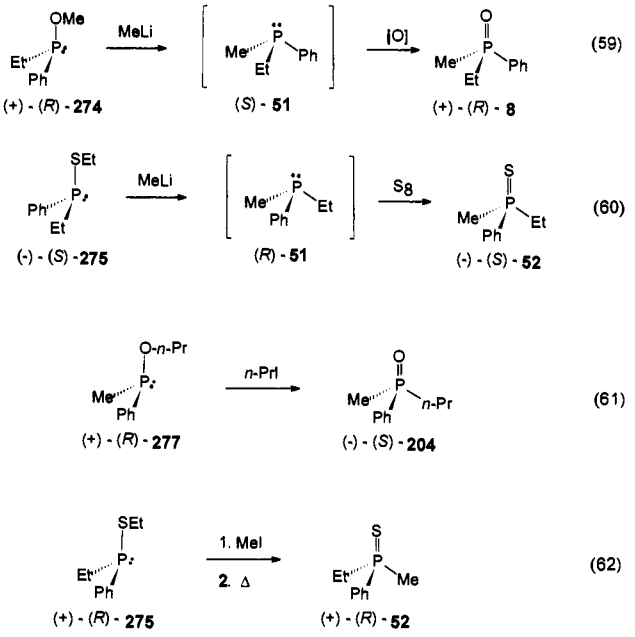
(57)

The idea behind many of the above syntheses of scalemic tertiary phosphine oxides was to provide ultimately an access to scalemic tertiary phosphines. Methods for stereoselective reductions of phosphine chalcogenides to phosphines as well as for liberation of phosphines from their borane complexes have accordingly been developed and they will be discussed in section III.C.2. Direct synthesis of scalemic phosphines by displacement procedures similar to those developed for phosphine oxides could have been considered as a viable alternative only after P-resolved esters of trivalent phosphorus acids were proved to be configurationally reasonably stable[183] and convenient routes to them were provided.[184] Mikołajczyk and co-workers[184] were able to obtain several partially P-resolved alkyl phosphinites and thiophosphinites via an asymmetric route which is typified in eq 58. Albeit not having been



(58)

very efficient as an asymmetric (or doubly asymmetric in the case of menthol) process, it provided access to the first simple scalemic phosphinites (e.g., **274–276**) which could be used to study stereochemistry of displacement of ester groups in trivalent phosphorus compounds.[152,185] It was then unequivocally established that substitution of phosphinite ester or thioester group by organolithium reagents occurs with high stereoselectivity and with inversion of configuration at phosphorus. It was also demonstrated that Michaelis–Arbusov reactions of such esters cleanly afford the expected phosphine chalcogenide with retention of configuration at phosphorus. The pertinent syntheses which served in cited work also for chemical correlations are exemplified in eqs 59–62.[188] The same authors later prepared[187] diastereomerically pure menthyl ethylphenylphosphinite (**276**) by the procedure shown in eq 63 and used it together with (R_P)-**279** (analogously



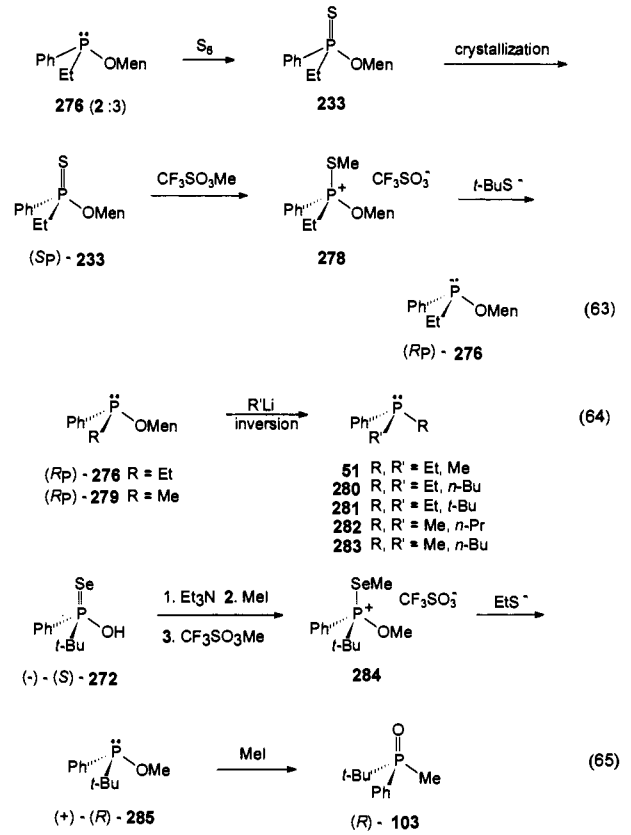
(59)

(60)

(61)

(62)

prepared from the corresponding diastereomerically pure (S_P)-**232**)[170] for reactions with organolithium reagents to directly obtain phosphines **51** and **280–283** of very high optical purity (eq 64).[187] In the closely related manner enantiomerically pure (*S*)-**272** afforded methyl *tert*-butylphenylphosphinite (**285**) of high optical purity, from which in turn, phosphine oxide (*R*)-**103** of ca. 78% ee was obtained by treatment with MeI (eq 65).[188]



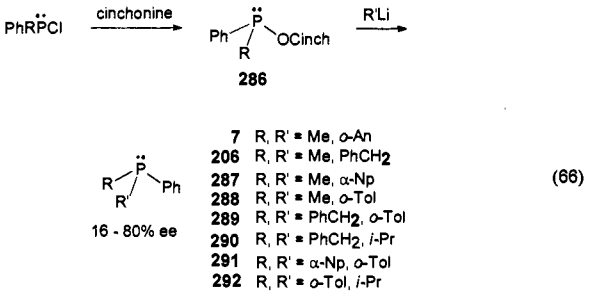
(63)

(64)

(65)

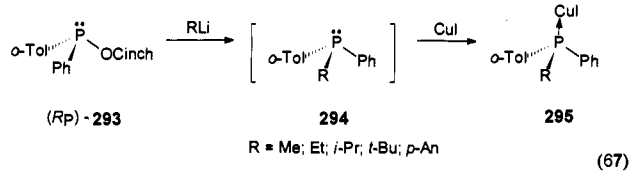
Another synthetic procedure leading directly to phosphines of high optical purity was developed by Chodkiewicz and co-workers[189] and it is based on

reactions of cinchonine phosphinites **286** with organolithium reagents. The procedure is operationally straightforward and takes advantage of the fact that diastereomeric cinchonine phosphinites **286** formed by condensing chlorophosphines with cinchonine are frequently found highly enriched in one of the diastereomers. Treatment of such diastereomeric mixtures without separation by organolithium reagents leads to scalemic phosphines of up to 80% ee (eq 66). In one



(66)

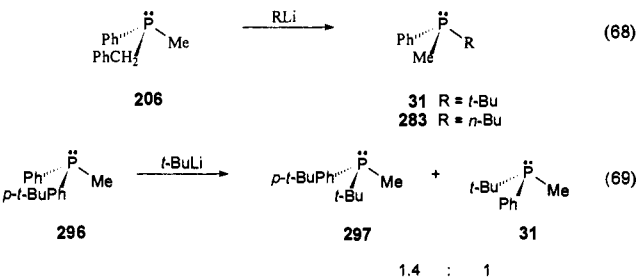
case, i.e., **293**, the major (R_P) diastereomer was obtained in the pure form by crystallization of its CuCN complex from DMSO–*N*-methylmorpholine (1:1) and was used to synthesize a series of scalemic phosphines **294** of very high optical purity.[190] These phosphines were conveniently isolated via their easy to handle complexes with CuI **295** (eq 67). The free phosphines can be



(67)

liberated from the Cu^I complexes by treatment with alkaline cyanide or, alternatively, can be oxidized to the corresponding oxides by H_2O_2 in benzene.

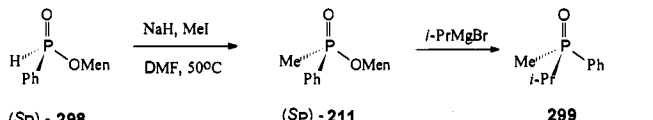
Finally, the single displacement procedure also can be used to transform stereoselectively one resolved phosphine into another. Kyba[172] demonstrated early that displacement of the benzyl group in (+)-**9** with *t*-BuLi and *n*-BuLi reagents led to phosphines **31** and **283** with clean inversion of configuration (eq 68). Analogous displacements in **296** (eq 69) gave in turn **297** and **31** in comparable amounts and, importantly, again with complete inversion of configuration in both products.[160] This particular observation led the author to conclude that the nucleophilic substitution at P^{III} is a classical S_N2 process not involving any P^V pentacoordinate intermediates.



(68)
(69)

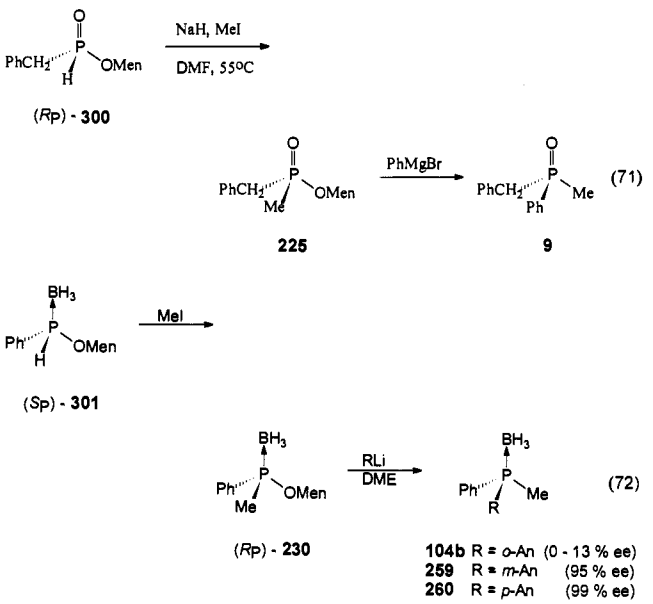
2. Via Two Consecutive Displacements at P

In an attempt to broaden the scope of their synthetic methodology based on Grignard reactions of P-resolved menthyl phosphinates Mislow and co-workers[160] developed also a procedure which allows sequential introduction of two carbon substituents on phosphorus. The authors were able to separate partially the diastereomers of menthyl phenylphosphinate (**298**) and to demonstrate that they can be stereospecifically alkylated with primary and secondary halides with retention of configuration. The resulting scalemic menthyl phosphinates could then be transformed into tertiary phosphine oxides via Grignard displacement as before. The route is exemplified in eq 70. Both



(70)

enantiomers of **299** could be obtained from a single H-phosphinate precursor by reverting the order of introduction of the two alkyl substituents.[160] Although stereochemically sound and potentially flexible (recently also Pd catalyzed arylation of menthyl H-phosphinates with either retention and inversion of configuration has also become possible[164]) the method has found little use probably because the separation of diastereomerically pure precursors proved difficult, in the early cases. The two recent applications of this method are shown in eqs 71[161] and 72.[106] Even though

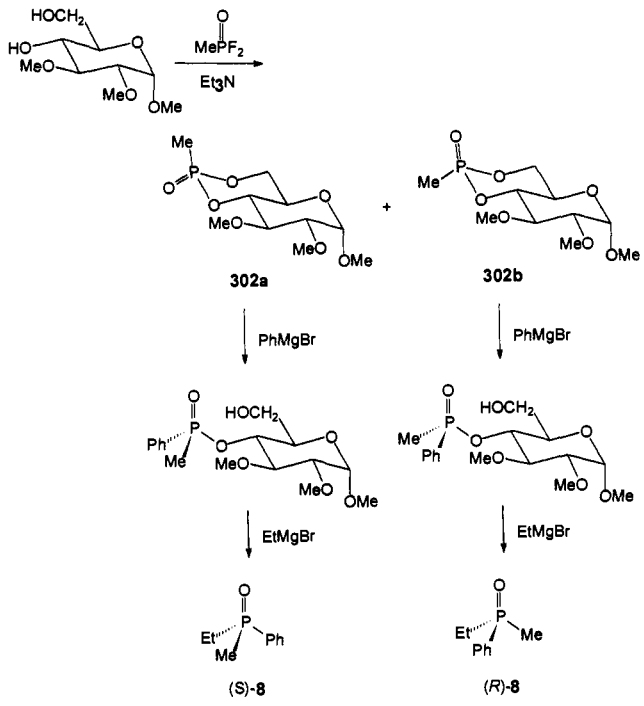


(71)
(72)

in the former synthesis the S_P diastereomer of the starting menthyl benzylphosphinate (**300**) was readily available in high yield and in the pure form, the depicted preparation of (−)-(*S*)-**9** was only partially successful due to considerable racemization in the Grignard substitution step. Also in the related synthesis of boranes **104b**, **259**, and **260** shown in eq 72 the substitution step was found to be sensitive to the steric bulk of the organometallic reagent. The reaction proceeded with excellent stereoselectivity with meta- and para-substituted aryllithium reagents but with the ortho-substituted one the resulted tertiary phosphine oxide **104b** was practically racemized.[106,173]

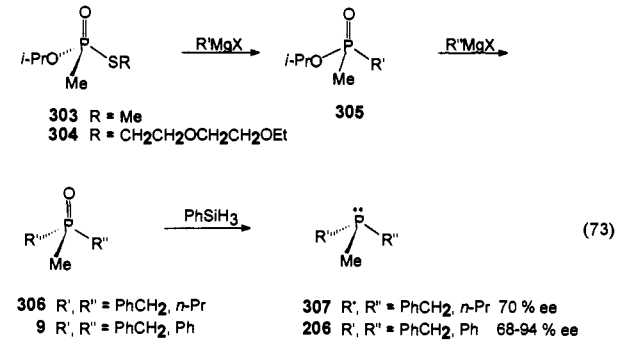
In many instances however, as demonstrated in the previous section, nucleophilic substitution of an ester

Scheme 7



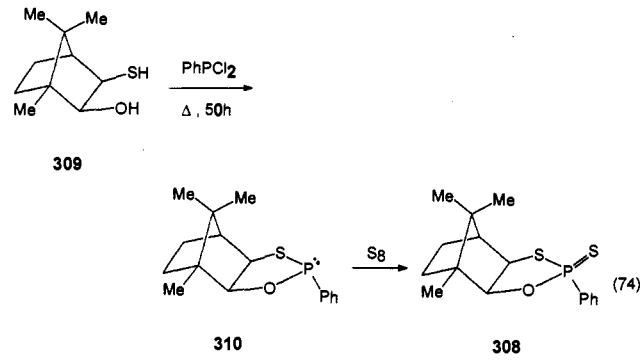
group in P^{IV} derivatives could be performed with very high stereoselectivity and these observations led to expectations that two sequential substitutions could also provide a means for stereoselective synthesis of scalemic phosphine derivatives. For such an approach resolved P-chiral precursors possessing two leaving groups potentially different in their leaving group ability were prerequisite. In the pioneering study Inch and co-workers[191] used resolved P-chiral glucopyranosyl bicyclic phosphonates **302** in which a primary and a secondary hydroxyl group served for the phosphonate formation (Scheme 7). The two diastereomeric P-chiral phosphonates **302a** and **302b** were readily separated by chromatography and were each individually subjected to two consecutive Grignard reactions which afforded enantiomeric ethylmethylphenylphosphine oxides (**8**) of high optical purity. Interestingly, it was the primary alcohol residue which was displaced first. Both displacement steps occurred with inversion. Although fully satisfactory in the cited case the developed procedure was found to suffer from similar limitations as seen already for substitutions of menthyl phosphinates, with the overall success depending on the nature of the reagents and the groups attached to P as well as on the carbohydrate stereochemistry. For example, when the two Grignard reagents in the cited synthesis were used in the reversed order the substitution failed in the second step. Also, analogous cis-fused galactopyranosyl phosphonates failed to ring open with Grignard reagents.

In a conceptually related manner Moriyama and Bentrude[192] were able to convert enantiomerically pure thiophosphonates **303** and **304** into phosphine oxides **306** and **9** via their selective displacement reactions with two Grignard reagents in succession (eq 73). The selected substrates were however distinct from the previous ones as well as from all the others discussed in this section in that they did not contain any auxiliary chiral group in their structure besides phosphorus. The resolved thiophosphonates could be readily prepared



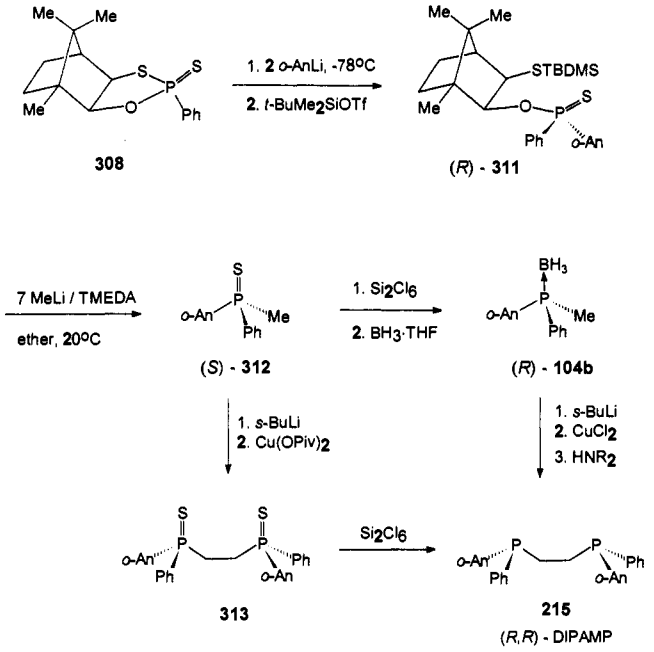
by straightforward S-alkylation of enantiomerically pure *O*-isopropylmethylphosphorothioic acid.[193] Interestingly, the reaction of phosphorothioate **304** containing chelating ester residue with PhMgBr was found to occur with predominant inversion of configuration at phosphorus. More expectedly, the reaction of *S*-methyl ester **303** with $PhCH_2MgCl$ yielded the pertinent phosphinate **305** with predominant retention of configuration. In the second displacement steps the expected inversion of configuration at phosphorus took place. Reduction of oxides **306** and **9** with phenylsilane provided scalemic phosphines **307** and **206**, respectively, with retention of configuration.

Similar O vs S distinction of the two ester leaving groups at the resolved P-center was utilized by Corey and co-workers[194] in their double displacement route to DIPAMP (**215**). The developed route commences with a cyclic thiophosphonate **308** available stereospecifically in a potentially general one-flask procedure from camphor derivative **309**, via thermodynamically favored *exo*-P–Ph oxathiaphospholidine **310** (eq 74).

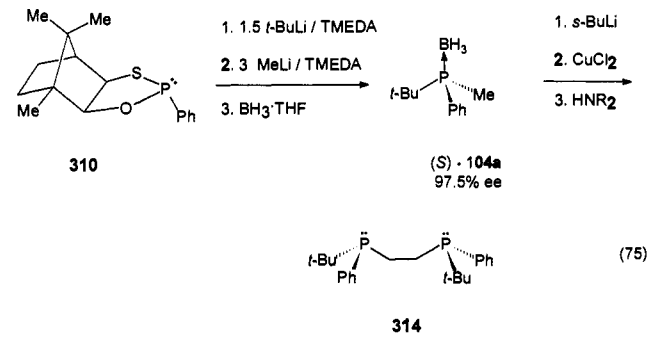


As detailed in Scheme 8, treatment of **308** with *o*-anisyllithium and further reaction with *tert*-butyldimethylsilyl (TBDMS) triflate provided thiophosphinate **311** with clean retention of configuration at phosphorus. Subsequent reaction of **311** with an excess of methyllithium followed by treatment with $BF_3{\cdot}Et_2O$ and extractive isolation gave crystalline PAMP sulfide (**312**) of fully inverted configuration at phosphorus. Final conversion of **312** into enantiomerically pure (*R*,*R*)-DIPAMP (**215**) was accomplished by two alternative and equally successful routes involving either direct coupling of sulfide **312** or, coupling of the derived borane (*R*)-**104b**. Also, as demonstrated in the synthesis of phosphine borane (*S*)-**104a** and diphosphine **314** shown in eq 75,[194] the developed displacement protocol could be applied directly to oxathiaphospholidine **310** with comparably satisfactory stereochemical results. The transformation **310** → **104a**

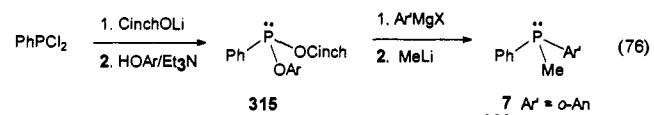
Scheme 8



involved one displacement with retention and one with inversion, analogously to **308** → **312**.



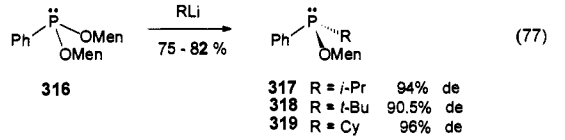
The first sequential double displacement route which led directly to scalemic phosphines was developed by Chodkiewicz[190] and was based on diastereomerically enriched nonsymmetrical alkylarylphosphonites **315** (or their CuSCN complexes) as convenient precursors (eq 76). Such compounds of high diastereomeric purity



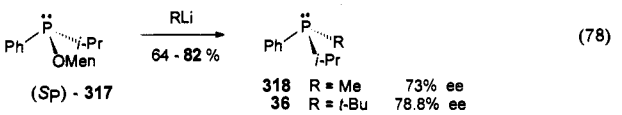
CinchOH = cinchonine or cinchonidine

could be obtained in one pot starting from $PhPCl_2$, cinchonine or cinchonidine, and the corresponding phenol, and were conveniently isolated via their equimolar complexes with cuprous salts, from which they could be recovered by treatment with alkaline cyanide. The two consecutive displacement reactions of **315** by an aryl Grignard reagent and methyllithium went stereospecifically with inversion of configuration at phosphorus and yielded phosphines **7** and **288** of high optical purity. The S_P phosphines were obtained in the cinchonine series, but with cinchonidine the corresponding R_P enantiomers were prepared.

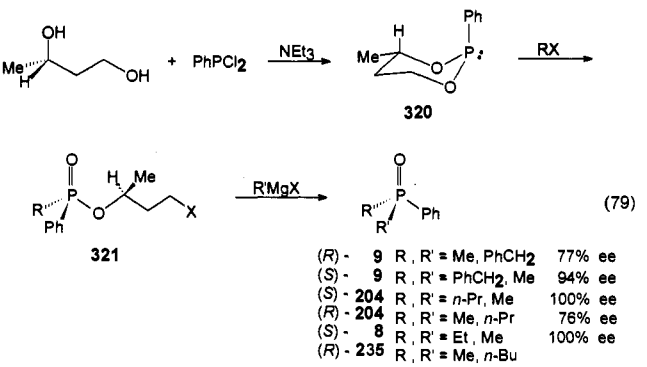
An asymmetric variant of direct phosphine synthesis via the double displacement route was developed by Neuffer and Richter.[197] In their approach a P-prochiral dimenthyl phosphonite **316** was allowed to react with alkyllithiums at low temperature and was found to yield P-resolved menthyl alkylphenylphosphinites **317–319** of very high diastereomeric purity (eq 77). Analogous



dibornyl phosphonites were also tested but they gave considerably lower inductions (69% de). For the second displacements phosphinite **317** was selected and was shown to afford scalemic phosphines **36** and **318** of markedly lower optical purity than the starting **317** (eq 78). The observed loss of the optical purity at phosphorus during displacement of the menthoxy group in **317** by organolithium reagents was somewhat unexpected as in the closely related systems **276**, **279** practically complete stereoselectivity was recorded for such displacements (cf. eq 64).[187] It should be noted however, that the two systems differed somewhat in steric crowding around phosphorus and, importantly, they were also diastereomerically distinct, i.e., they were of the opposite configurations at phosphorus.

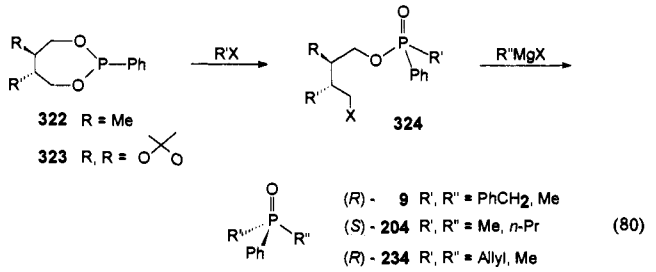


A cyclic phosphonite **320** offering different reactivity of its primary and secondary ester residues was utilized by Suga and co-workers[198] in their two-step synthesis of scalemic phosphine oxides. The starting phosphonite **320** was readily obtained from (−)-butane-1,3-diol and was found to constitute practically one diastereomer after distillation (eq 79). In the first step of the synthesis, instead of the previously seen nucleophilic displacements, the Michaelis-Arbusov reaction was employed and resulted in the regio- and stereoselective (retention) cleavage of the primary carbon–oxygen bond. The resulting phosphinates **321** were then reacted with 5 mol excess of Grignard reagents to afford the shown tertiary phosphine oxides of high optical purity (76–100%), albeit in modest yield (10–57%).



In another work from the same laboratory[199] scalemic phosphonites **322** and **323** of C_2-symmetry were used

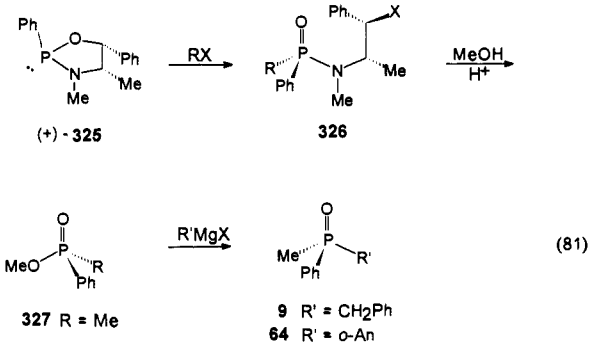
as substrates. These substrates were in fact P-achiral but they offered instead a possibility for the creation of the phosphorus stereogenic center via an asymmetric transformation in the first Michaelis–Arbusov step (eq 80). With some electrophiles excellent inductions were



(80)

de facto achieved, e.g., 100% with benzyl iodides bearing nitro or cyano group in the para position, but with those which were structurally compatible with the conditions of the subsequent displacement step only modest inductions were accessible. These are reflected in the enantiomeric purities (18–45% ee) of the phosphine oxides **9**, **204**, and **234** as well as of the corresponding phosphines which were eventually obtained. Interestingly, the same phosphines obtained analogously from bicyclic phosphonite **323** by this procedure were found to be of the opposite configuration and of a much lower optical purity (2.4–12% ee).

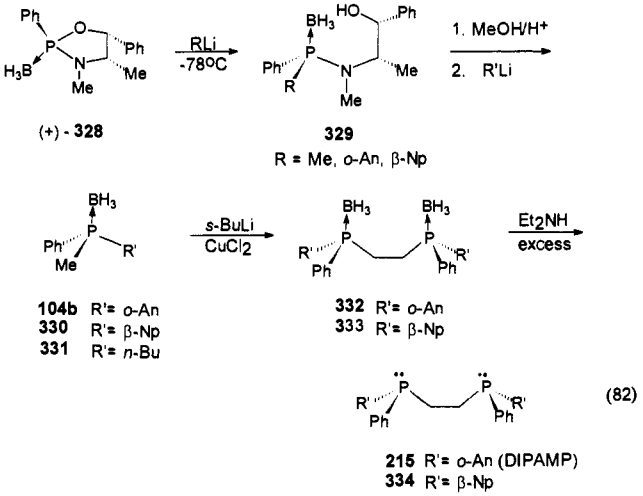
A synthesis of phosphine oxides of high enantiomeric purity via Michaelis–Arbusov–Grignard reaction sequence was also developed by Jugé and Genet[200] (eq 81). In their study diastereomerically pure 1-



(81)

phenyloxaazaphospholidine **325**[201] available directly from $PhP(NEt_2)_2$ and (−)-ephedrine was used as the P-resolved substrate. Reactions of **325**[201] with alkyl halides gave the expected phosphinamides **326** with retention of configuration but also with some loss of configurational homogeneity at the phosphorus center.[202] After having had their diastereomeric purity corrected by recrystallization these phosphinamides were further subjected to acid-catalyzed methanolysis to provide methyl alkylphenylphosphinates, **327**, of more than 96% ee. Reaction of phosphinate **327** (R = Me) with Grignard reagents afforded the desired phosphine oxides **9** and **64** of 95 and 92% ee, respectively. When $PhCH_2Cl$ was employed in the first step and MeMgBr in the second, the enantiomer of **9** of 77% ee was obtained from the same oxazaphospholidine **325**. By utilizing known routes the authors also converted **64** into the corresponding phosphine **7** (PAMP) and diphosphine **215** (DIPAMP) as well as similarly prepared their enantiomers starting from the corresponding (−)-oxazaphospholidine derived from (+)-ephedrine.

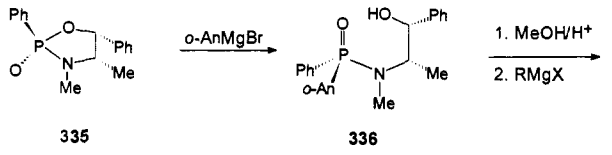
Further work from the same laboratory[203] demonstrated that the corresponding oxazaphospholidine borane complex **328** could be conveniently obtained as a diastereomerically pure crystalline product in one step in up to 80% yield. This structural modification enabled the authors to replace the Michaelis–Arbusov step of the previous synthesis with a nucleophilic displacement by RLi. As shown in eq 82 low-temperature reactions of alkyl and aryllithium reagents with **328** yielded cleanly the corresponding phosphinamide boranes **329** by selective P–O bond cleavage occurring with predominant (>92%) retention of configuration at phosphorus.[204] Quantitative metha-



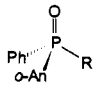
(82)

nolysis of these intermediates followed by reactions of the resulting phosphinite boranes with different organolithium reagents (both steps occurring with inversion of configuration) afforded scalemic phosphine boranes **104b**, **330**, and **331** of 85–100% ee. When required, these products could be further purified to virtually enantiomeric purity by recrystallization from hexane. Liberation of the corresponding enantiomerically pure phosphines from these borane complexes by treatment with excess of Et_2NH, as well as coupling reactions to the corresponding bis(phosphine boranes) **332** and **333**, and their subsequent decomplexation to bis(phosphines) **215** and **334**, were also reported. It should be noted that this route (cf. also the procedure of Scheme 8) provides probably the best source of the renowned PAMP and DIPAMP ligands[11] available to date. By this route the two ligands were prepared on a 0.4 mol scale in 70% and 40% overall yield, respectively, calculated on ephedrine. It has also been demonstrated that good overall yields of PAMP borane **104b** could be obtained even when the two intermediates and the corresponding phosphinite boranes are used in their crude forms. As in the previous case, the antipodal phosphines could be also prepared from the same phosphine borane **328** by changing the order of replacements by the two organolithium reagents or, alternatively, by starting from (−)-**328** prepared from the commercially available (+)-ephedrine.

Interestingly, Brown and co-workers[205] have independently developed the oxide version of this route (eq 83). The starting oxazaphospholidine **335** oxide was conveniently obtained by a *t*-BuOOH oxidation of crude



335 336



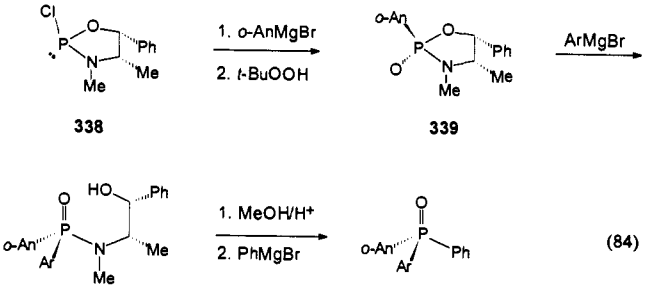
64 R = Me 94 % ee
65 R = Et > 95 % ee
337 R = *p*-An 95 % ee

(83)

oxaazaphospholidine **325** derived in this work directly from commercially available $PhPCl_2$ and (−)-ephedrine, despite the caveat published earlier by Richter.[201] The required high diastereomeric purity of crude oxazaphospholidine **325** was secured in this case by efficient thermal equilibration of the two P-epimers prior to oxidation.[205] Interestingly, these authors also noted that crude **325** could be converted readily into a stable crystalline borane. For the conversion of oxazaphospholidine oxide **335** into the desired tertiary phosphine oxides use of Grignard reagents for the two displacements proved advantageous. As rigorously established on the basis of the X-ray data for **335** and **336**, the ring P–O bond cleavage in **335** by a Grignard reagent occurred again with clean retention of configuration at phosphorus. Acid-catalyzed methanolysis of **336** and the second C–P bond formation went both with inversion providing phosphine oxides **64**, **65**, and **337** of high enantiomeric purity and of the configuration shown. In this study the *S* enantiomer of **64** was obtained by reduction of (*R*)-**64** with $HSiCl_3/Et_3N$ (inversion) followed by oxidation of the resulting phosphine by *t*-BuOOH (retention). Attempts to synthesize a valuable scalemic *o*-anisylphenylvinylphosphine oxide by this route by using vinylmagnesium bromide in the second displacement step were unsuccessful.

3. Via Three Consecutive Displacements at P

In the extension of their study on the use of ephedrine as the chiral auxiliary for synthesis of scalemic P-chiral phosphine oxides Brown and co-workers[206] also developed a procedure in which three sequential displacements at phosphorus were performed to provide the three C–P bonds. The required scalemic precursor of high diastereomeric purity possessing three distinct leaving groups at the resolved P-center was obtained again directly by simply reacting PCl_3 with (−)-ephedrine and allowing for thermal equilibration of the two P-epimers **338** formed originally in a 1:1 ratio. Use of *P*-chlorooxaazaphospholidine **338** thus obtained for the synthesis of triarylphosphine oxides is summarized in eq 84. Even though the stereoselectivity of chloride displacement in **338** by *o*-anisylmagnesium bromide was found to be only modest, the diastereomerically pure oxide **339** could be obtained in good 61% isolated yield by judicious combinations of equilibration and flash chromatography techniques. At this point the syntheses merged the route discussed above and were demonstrated to provide an efficient means of preparation of nearly enantiomerically pure triarylphosphine oxides **256**, **337**, and **340** of the shown configuration. It was confirmed once more than the stereospecific ring opening of oxaazaphospholidine oxides by Grignard reagents proceeds with retention of configuration at



338 339

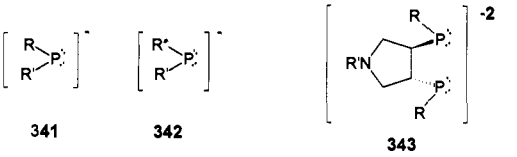
256 Ar = β-Np
337 Ar = *p*-An
340 Ar = *m*-An

(84)

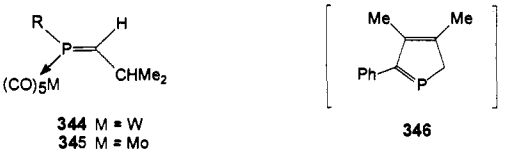
phosphorus. Again, it did not appear possible to prepare scalemic diarylvinylphosphine oxides by this route, irrespective of the stage of the introduction of the vinyl group.

4. Asymmetric Synthesis

In the preparations of phosphines and their derivatives discussed in the previous sections of this chapter several processes were utilized which could in principle lead to an asymmetric creation of a phosphorus stereogenic center during the formation of the *last* of the required three C–P bonds. Typically, these have been briefly commented upon already during the presentation of the pertinent synthetic routes and will be only summarized here. Except for dichlorophosphines and P-prochiral phosphonium salts which are not listed, all the other P-prochiral substrates tested in asymmetric transformations are visualized below in general structures **341**–**348**.

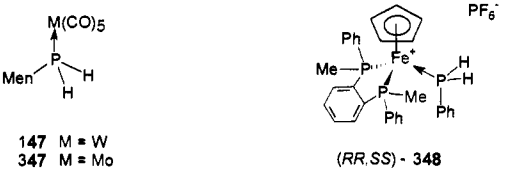


341 342 343



344 M = W
345 M = Mo

346



147 M = W
347 M = Mo

(*RR,SS*)-348

Two asymmetric reactions of dichlorophosphines which led *directly* to the P-resolved phosphine oxides or phosphines are on record. One of them is the one-pot conversion of methyldichlorophosphine into completely P-resolved polycyclic phosphine oxides via its electrophilic reactions with scalemic terpenoid olefins developed by Vilkas and co-workers[124,125] (cf. eq 32), and the other, the reaction of scalemic menthyldichlorophosphine with achiral butadienylmagnesium, which was shown by Neuffer and Richter[123] to lead predominantly to one of the *cis*-2-vinylphosphiranes with ca. 82% induction (cf. eq 31).

In the study involving alkaline cleavage of scalemic P-prochiral phosphonium salts (cf. Scheme 4) Valentine and co-workers[110] observed that neomenthyldiphenylethylphosphonium iodide yielded two diastereomeric menthylethylphenylphosphine oxides in a 7:5 ratio and that in decomposition of analogous 1,4-bis(phosphonium)butane there was ca. 2:1 preference for formation of one epimeric phosphorus configuration as compared to the other.

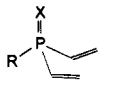
Alkylations of P-prochiral phosphides were utilized by several groups but in all the cases, except for the 26% induction achieved early by Naylor and Walker[108] (cf. eq 17), no asymmetry was induced despite the fact that many of such reactions involving either phosphides of type **341** and scalemic electrophiles[109-111] or, reversely, scalemic phosphides of type **342** and achiral electrophiles[49,114,115] were carried out. Notable exceptions to this rule are the reactions of scalemic C_2-symmetric bis(phosphides) **343** with various electrophiles found by Nagel and co-workers[116-119] to yield frequently one (usually *S,R,R,S*) of the three possible products in high predominance, i.e., up to 90% of the total isomeric mix (cf. Scheme 5). It appears that in such reactions involving pyrrolidines of the shown *R,R* configuration, creation of the S_P center in the first of the two consecutive asymmetric processes is strongly favored.

Phosphenes are P-prochiral and in the form of their tungsten and molybdenum complexes of type **344** and **345** were found by Mathey and co-workers[120] amenable to asymmetric transformations. First attempted enantiodifferentiating asymmetric hydrogenations of **344** (R = Cy, Ph) over chiral catalysts led only to racemic secondary phosphine complexes. However, later judicious placement of a menthyl auxiliary on phosphorus as in **154** [**344** (R = Men)] promoted a highly diastereoselective (9:1) hydrogenation reaction over achiral catalysts and, ultimately, a completely diastereoselective process under the influence of chiral catalysts (cf. eq 27).

Asymmetric Diels–Alder cycloadditions of complexed scalemic phosphenes of type **154** and **345** (R = Men) with cyclopentadiene were found to be also 100% diastereoselective and afforded exclusively 2-phosphanorbornenes possessing endo menthyl group (cf. eq 28). A free phosphene, e.g., **346**, generated *in situ* at elevated temperature for its Diels–Alder reactions with scalemic propiolates gave the expected 1-phosphanorbornadienes but apparently with no induction (cf. eq 34).[95]

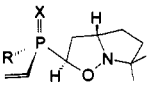
Asymmetric monoalkylation of primary phosphines in their complexes with metals have been realized. Mathey and co-workers[120] were able to demonstrate that reaction of isobutyl iodide with menthylphosphine complexed to tungsten (**147**) and to molybdenum (**347**) is a distereoselective process (40% de) as are analogous acylations by phosphorochloridates (ca. 50% de for **147**, and ca. 60% de for **347**) (cf. eq 27). Similar alkylations of phenylphosphine in cationic iron complexes of type **348**, studied by Wild and co-workers,[88,207] were also found to be diastereoselective to the extent of ca. 60% de. These latter alkylations were performed on racemic **348** but the enantiomerically pure complex prerequisite for the asymmetric synthesis is also available.[88]

Very recently asymmetric syntheses of scalemic P-chiral phosphine derivatives which could be performed without C–P bond making or breaking have also emerged as a viable possibility. Brandi and co-workers[208] were able to demonstrate that 1,3-dipolar cycloadditions of prochiral divinylphosphine derivatives **349** to a model five-membered ring nitrone lead to highly diastereomerically enriched monoadducts of type **350** of up to 92% de (e.g., **350**, R = *t*-Bu, X = S) and of predictable stereochemistry at phosphorus.[208,209] Although the nitrone used in this study was achiral, enantiomerically pure five-membered ring nitrones derived from tartaric acid have been made in the meantime readily accessible.[151]



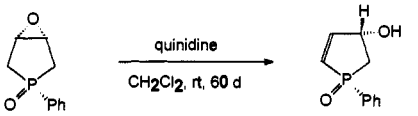
349

X = O, S
R = *t*-Bu, Ph, 2,4,6-Me_3Ph



350

A procedure for asymmetric creation of phosphorus stereogenic center in a cyclic phosphine oxide **351** by enantioselective desymmetrization catalyzed by chiral base has been developed (eq 85).[210] Inductions achieved are as yet moderate, but the developed procedure affords hydroxy phospholene **72** enriched in the enantiomer opposite to that available previously by resolution.[100]

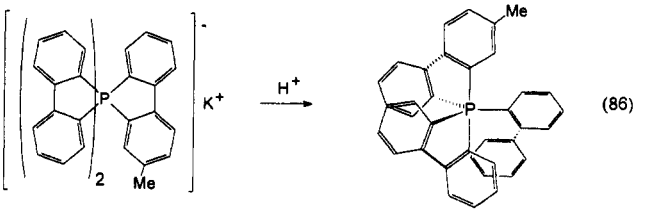


(85)

351

(-)-(*R*)-**72**
43.4% ee

Finally, an example of preparation of scalemic pentaarylphosphorane can be cited here thanks to the work of Hellwinkel[211] who succeeded in synthesizing enantiomeric **353** according to eq 86. Treatment of



(86)

352

$[\alpha]_{578}$ = ± 1870°

353

$[\alpha]_{578}$ = ± 94°

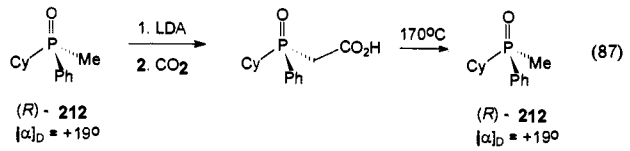
resolved propeller-shaped anion **352** with acid resulted in the formation of three chiral spirophosphoranes of which only **353** was found to be optically active, even though it itself constituted a mixture of two rapidly equilibrating pseudorotational isomers (only one shown). It remains an open, although rhetorical, question whether optical activity of **353** should be associated with chirality of its phosphorus stereogenic center or, rather with the overall propeller shape of the molecule, as in **352**. In fact, the observed dramatic drop of the rotatory power on going from **352** to **353** might be judged in favor of the former possibility. Alternatively, however, slightly unequal contribution of the two possible pseudorotamers having opposite sense of propeller chirality, and/or their not necessarily exactly equal rotatory strength, could also be considered likely

to lead to the observed differences in the two $[\alpha]_{578}$ magnitudes. All in all, **353** is P-chiral and, therefore, its synthesis from P-achiral precursor **352** is, by principle, asymmetric.

C. Transformations of Resolved P-Chiral Phosphines and Their Derivatives

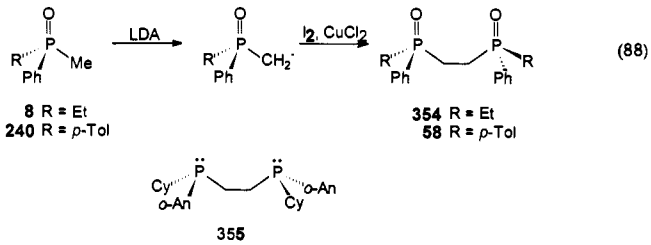
1. Modifications of Carbon Substituents

a. Via α-Carbanions. Certainly of prime importance to the development of methodologies discussed in this section should be considered the observation published in 1968 by Mislow and co-workers[34] that deprotonation of a P–Me group in phosphine oxides occurs with preservation of configurational integrity of the neighboring phosphorus stereogenic center (eq 87). Analo-



(87)

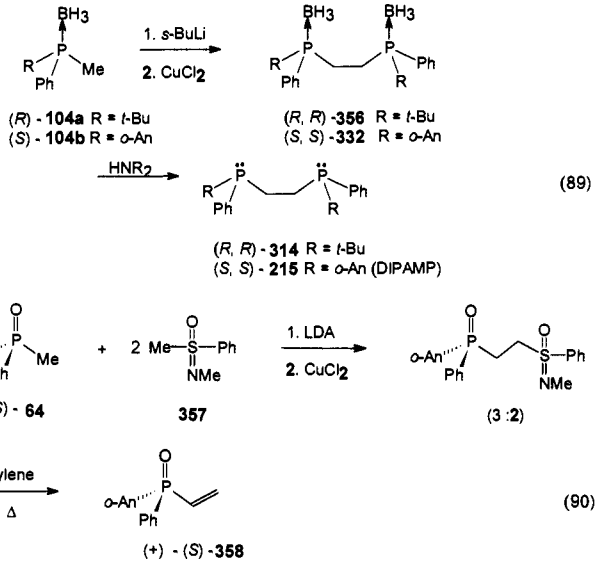
gous behavior of P-chiral methyl phosphines had been recorded even earlier by Horner et al.[212] but that has not found preparative application as yet. In fact, also in the case of P-chiral phosphine oxides a more common synthetic use of their α-carbanions had to await the 1980s except, for one important application. In 1973 Mislow and co-workers[213] discovered that simple scalemic P–Me phosphine oxides **8** and **240** can be oxidatively coupled via their α-anions to yield directly the corresponding resolved symmetrical P-chiral 1,2-bis(phosphinyl)ethanes **354** and **58** (eq 88). This coupling



(88)

procedure was soon successfully utilized by Monsanto group[155,214] in their preparation of industrially important bis(phosphines) **355** (DICAMP)[214] and **215** (DIPAMP)[155] (cf. eq 50), and it was also later adapted by other groups to synthesize several scalemic symmetrical bis(phosphine chalcogenides)[178,194,200,215] as well as bis(phosphine boranes),[106,194,203,216] frequently in both enantiomeric forms. A synthesis of two bis(phosphines) via bis(phosphine boranes) developed by Imamoto and co-workers[106] is shown in eq 89. In one case a mixed coupling of (*S*)-**64** with methylsulfoximine **357** was realized[215] in order to introduce α-unsaturation into the phosphine oxide structure (eq 90).

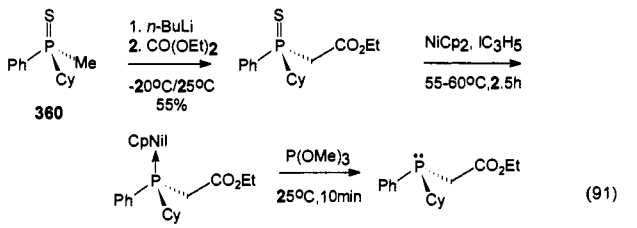
Reactions of α-carbanions derived from scalemic P-chiral phosphine derivatives with electrophiles were utilized by several groups to mount an added α-functionality or to simply construct a new alkyl group. Mathey and Mercier[217] synthesized scalemic functionalized phosphine **359** via acylation of (−)-phosphine sulfide **360** carbanion with diethyl carbonate as shown in eq 91. Johnson and Imamoto[215] used similar acylation of oxide **64** to introduce an α-carbalkoxy group required



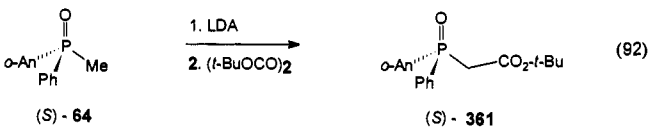
(89)

(90)

as a temporary activator for further synthetic transformations (eq 92). Analogous reactions of methyl



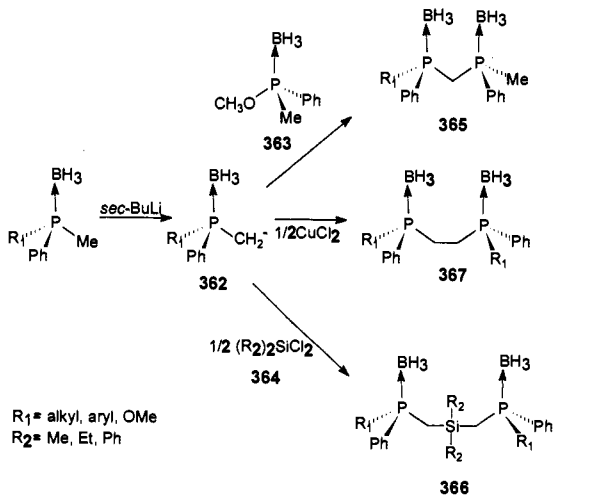
(91)



(92)

phosphine borane carbanions **362** with methoxyphosphine borane **363** and with dichlorosilanes **364** were reported by Jugé and co-workers[216] to yield cleanly the corresponding 1,1- and 1,3-bis(phosphine) systems **365** and **366**, respectively, in addition to the known coupling to **367** (Scheme 9). Finally, an intramolecular acylation

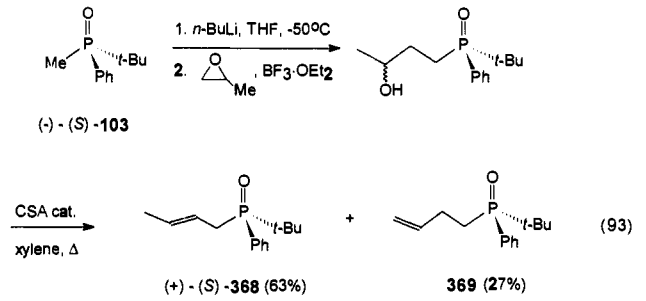
Scheme 9



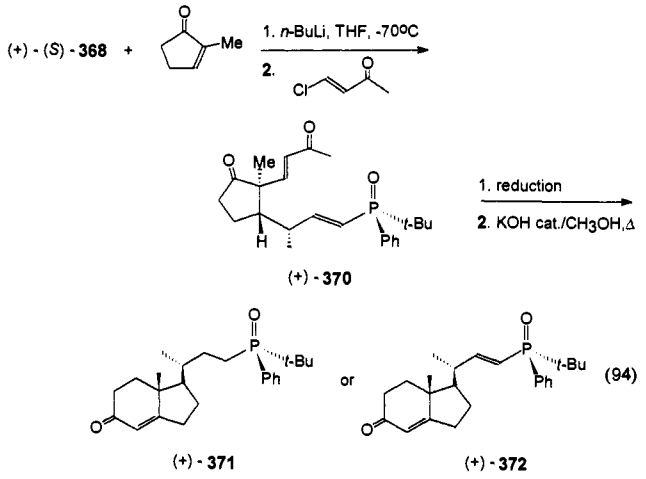
of an α-carbanion which provided a means for the fused phospholane ring closure in a recent synthesis of

enantiomeric 17-phosphasteroids is also on record (*vide infra*, Scheme 13).

Haynes et al.[218] demonstrated that reactions of α-carbanions of enantiomeric *tert*-butylmethylphenylphosphine oxides (**103**) with propylene oxide followed by dehydration gave access to useful 2-butenyl derivatives **368** (eq 93, only *S* enantiomer shown). Further deprotonation of enantiomeric **368** gave in turn delocalized carbanions which were shown to react with 2-methylcyclopentenone with complete regio- and stereoselectivity to give **370** and to afford ultimately enantiomeric hydrindenones of type **371** or **372** related to vitamin D (eq 94, only *S* series shown).



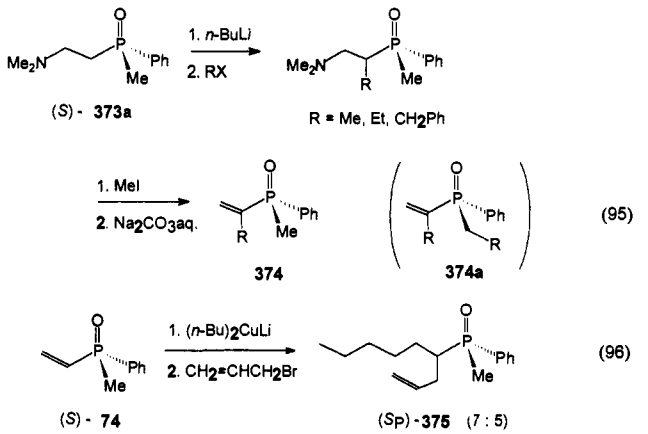
(93)



(94)

Two procedures have also been developed to enable direct regioselective α-alkylation of phosphine oxides at the methylene site instead of at the methyl present in the same molecule. Pietrusiewicz and Zabłocka[219] demonstrated that 2-dimethylamino substituent in simple alkylmethylphosphine oxides can be employed to direct a base toward regioselective deprotonation of the neighboring methylene instead of the otherwise kinetically more preferred methyl and used this observation to convert (−)-(*S*)-**373a** into a series of virtually optically pure 1-substituted vinylphosphine oxides **374** according to eq 95. Small amounts of products **374a** resulting from a double α,α′ alkylation were also isolated in these syntheses. Apparently the amine director effectively controls only the first site of the alkylation.

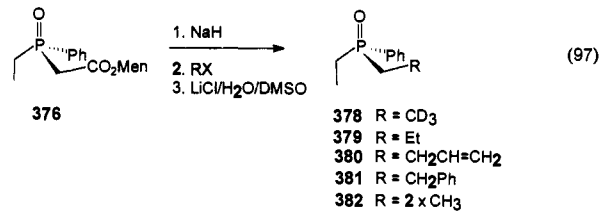
Another possibility to control the site of metalation is to generate an α-metalated species through the addition of lithium diorganocuprate across a conjugated vinyl group present in phosphine oxide structure.[103,220] Equation 96 provides an example, in which *in situ* quenching of α-carbanion derived in such a way from (*S*)-**74** is shown to lead directly to α-branched phosphine oxide **375**.[103]



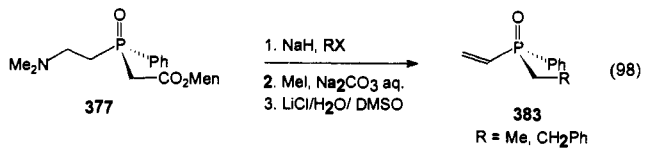
(95)

(96)

As shown in eqs 97[103] and 98,[219] when an additional activating group is present in the resolved phosphine oxide structure, as in phosphinylacetates **376**[103] and **377**,[219] the α-deprotonation–alkylation procedure becomes even more facile and, when combined with subsequent decarbalkoxylative workup of the alkylated products, can serve to conveniently synthesize various structurally modified phosphine oxides (e.g., **378–383**) from single diastereomeric precursors.



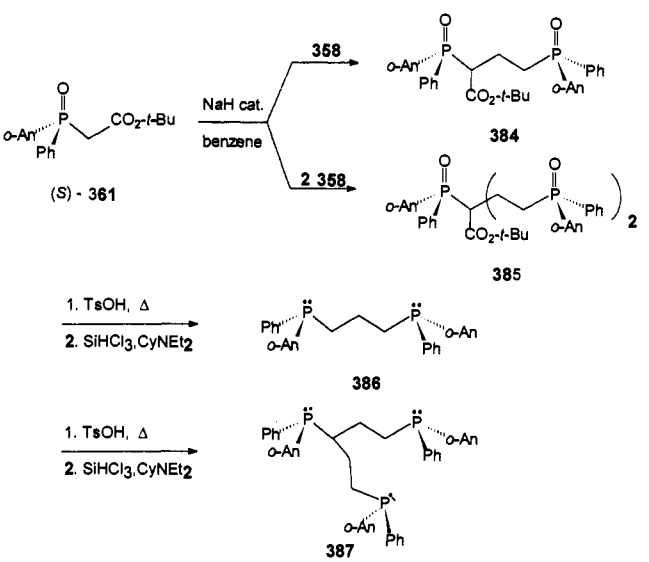
(97)



(98)

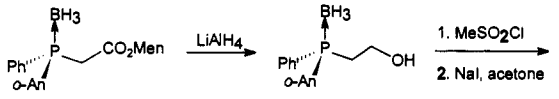
Using Michael-type chemistry Johnson and Imamoto[215] carried out single and double alkylation of enantiomerically pure phosphinylacetate **361** by (−)-(*S*)-*o*-anisylphenylvinylphosphine oxide (**358**) to obtain bis- and tris(phosphine oxides) **384** and **385**, respectively (Scheme 10). The oxides were subsequently decar-

Scheme 10

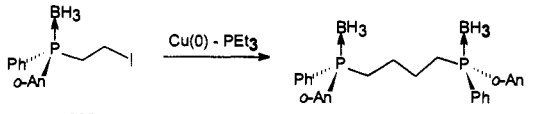


boxalkylated and deoxygenated by routine procedures to give novel P-chiral bi- and tridentate ligands **386** and **387**, respectively, of known absolute configurations.

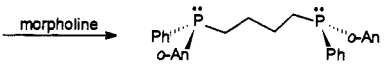
In one case not involving α-carbanion, reduction of acetate group in phosphinoacetate borane **388** opened access to 2-iodo phosphine borane **389** which could be coupled to bis(phosphine borane) **390** and yield ultimately P-chiral 1,4-bis(phosphinyl)ethane **391** (eq 99).[106]



(Sp)-**388**



389 **390**

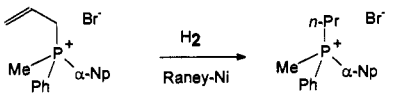


(99)

(*S,S*)-**391**

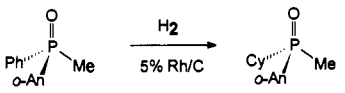
b. Via Backbone Unsaturation. Backbone unsaturation was shown to be very useful as a handle for structural modifications of the resolved phosphine derivatives, especially in cases when introduction of the unsaturated substituent and/or resolution of the unsaturated derivative was more facile then that of its saturated counterpart.

Hydrogenations of resolved allyl-[60] and cyclohexen-3-ylphosphonium[60,221] salts as well as phenyl-,[175] vinyl-,[103] and cyclohexen-4-ylphosphine oxides[103] were used occasionally as a means to obtain the corresponding alkyl or cyclohexyl substituted P-chiral derivatives. Two examples of such straightforward transformations which were utilized in the course of configurational correlation of the early resolved phosphine **201** and in the synthesis of CAMP ligand are shown in eqs 100[60] and 101,[175] respectively.



(100)

(+)-(*R*)-**19b** (+)-(*R*)-**392**

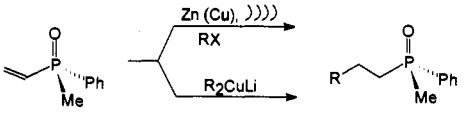


(101)

(+)-(*R*)-**64** (+)-(*R*)-**393**

The above-mentioned hydrogenations of isolated double bonds lacked in principle generality and, in fact, the major development in the discussed area of synthetic efforts has been achieved mainly through the use of resolved α,β-unsaturated phosphine oxides **74**,[103] **98**,[102,103] and **358**,[215] which offered a large variety of possibilities

Scheme 11



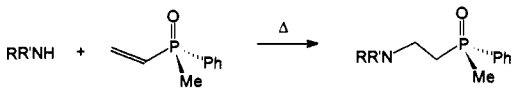
74

204 R = Me
394 R = *t*-Bu
395 R = *s*-Bu
396 R = *i*-Bu
397 R = *n*-Bu
398 R = *i*-Pr
399 R = $CHMeCH_2CHMe_2$

for their structural modifications on the basis of the versatile chemistry of their activated vinyl groups.

Michael-type additions of simple carbon nucleophiles to (−)-**74** were used to obtain a series of enantiomerically pure alkylmethylphenylphosphine oxides **204** and **394**–**399** with elongated or branched alkyl residues.[103,222] This could be effected either by mediacy of lithium diorganocuprates[103] or, alternatively, alkyl halides, zinc–copper couple and sonication[222] (Scheme 11). The two procedures are complementary; the former serves better in the additions of primary alkyl groups, whereas the latter gives better yields with secondary and tertiary ones.

In analogous fashion noncatalyzed additions of secondary and primary amines to **74** afforded a series of P-chiral (2-aminoethyl)phosphine oxides **373a–j** (eq 102).[223] In one case the resulting amino phosphine oxide (**373a**) was converted into the corresponding sulfide by stereoretentive reduction and sulfuration.

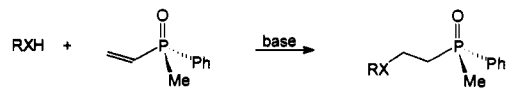


(102)

74 **373a-j**

a R, R' = Me, Me
b R, R' = Et, Et
c R, R' = $-CH_2CH_2OCH_2CH_2-$
d R, R' = Me, Cy
e R, R' = Me, $CH_2CH_2NMe_2$
f R, R' = H, Et
g R, R' = H, CH_2Ph
h R, R' = H, $CH_2CH_2NH_2$
i R, R' = H, (*S*)-CHMePh
j R, R' = H, (*R*)-CHMePh

Base-catalyzed additions of thiols and alcohols to **74** gave a series of virtually enantiomerically pure [2-(alkylthio)ethyl]- and (2-alkoxyethyl)phosphine oxides **400** which could also be reduced to the corresponding phosphines by $PhSiH_3$ with retention of configuration (eq 103).[224]



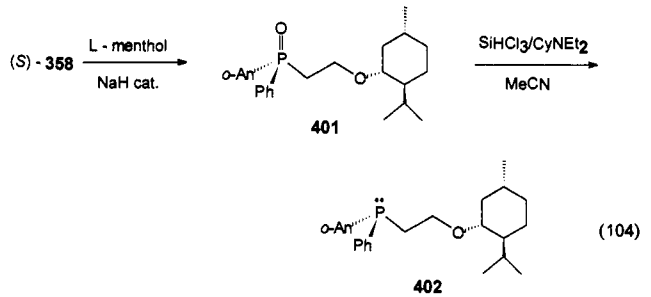
(103)

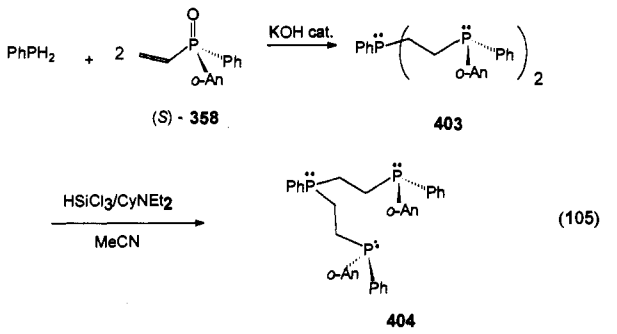
(*S*)-**74** **400**

RXH = EtSH, *n*-BuSH, MeO_2CCH_2SH, PhSH, *o*-HO_2C-PhSH, MeOH, $MeOCH_2CH_2OH$, L-menthol

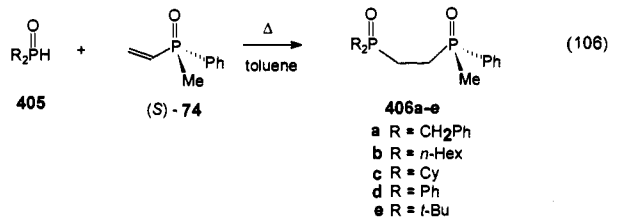
In a study by Johnson and Imamoto[215] addition of (−)-menthol to **358** was used to prepare (2-menthoxyethyl)phosphine oxide **401** which was subsequently reduced with inversion of configuration to a useful C,P-chiral phosphine ligand **402** (eq 104). In the same study phenylphosphine was successfully reacted with 2 equiv of (*S*)-**358** to obtain bisadduct **403** which by treatment with $SiHCl_3$–$CyNEt_2$ was further transformed into

unique tripodal ligand **404** possessing two resolved phosphorus stereogenic centers (eq 105).



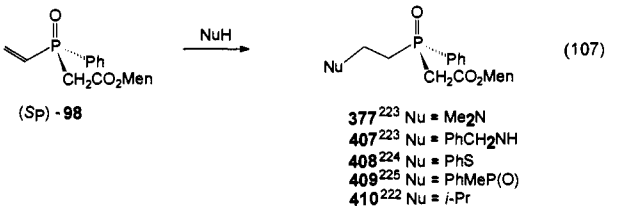


For the Michael-type additions of phosphorus-centered nucleophiles to (*S*)-**74** secondary phosphine oxides **405** were found to be the reagents of choice.[142] With these nucleophiles use of thermal conditions and nonpolar solvents proved advantageous as after heating of equimolar mixtures of **74** and **405** in boiling toluene for ca. 4 h poorly soluble adducts **406** typically crystallized out from the reaction mixture upon cooling and could be isolated pure by filtration (eq 106). Analogous



additions of nonsymmetrical secondary phosphine oxides to **74** leading to self-resolving 1,2-bis(phosphinyl)ethanes have already been discussed in section III.A.3 (cf. eq 40).

Many of the aforementioned additions of carbon- and heteroatom-centered nucleophiles to (*S*)-**74** were frequently paralleled by analogous model additions to (S_P)-**98** which served primarily as a diastereomeric check to establish whether the starting configurational homogeneity of the P-center in the vinyl phosphine oxide is fully retained under the studied conditions (eq 107).[222-225] Nevertheless, a series of resolved dia-



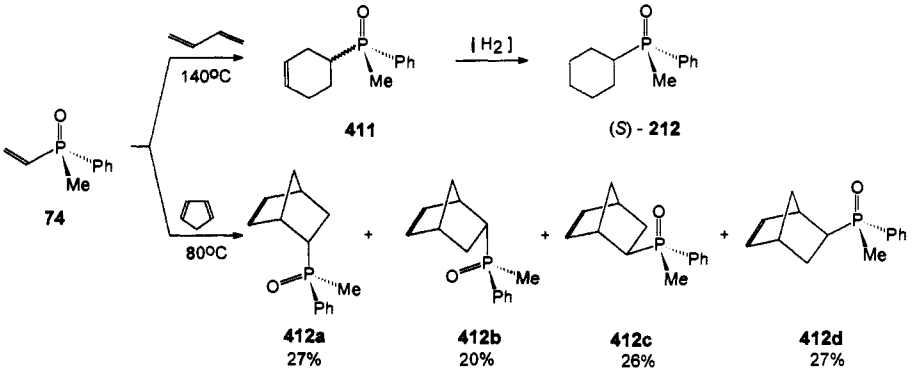
stereomerically pure phosphine oxides **377** and **407–410** was made available in this way; in the case of **409** the two P-epimers were separated by preparative TLC.

Utility of (*S*)-**74** as a dienophile for [2 + 4] cycloadditions was briefly studied[103,226] and provided a means for conversion of its vinyl group into the carbocyclic substituents (Scheme 12). No phosphorus-to-carbon induction was observed in the formation of **411**.[103] For the reaction of **74** with cyclopentadiene 22% induction level in the endo approach and nearly zero in the slightly preferred exo approach were assessed.[226] Higher inductions in cycloadditions to cyclopentadiene were shown accessible with oxide **358** under Lewis acid catalysis conditions, but **358** used in these studies was racemic.[227] Interestingly, as revealed in the X-ray study of the major endo product (S_{C_2})-**412a**[226] the preferred reactive conformation of **74** in the endo approach was *s*-trans. This is in sharp contrast with the observations that in 1,3-dipolar cycloadditions[208,209] (*vide infra*) and in its ground state[228] **74** as well as many other vinylphosphine chalcogenides[229,230] favored uniformly the *s*-cis conformation.

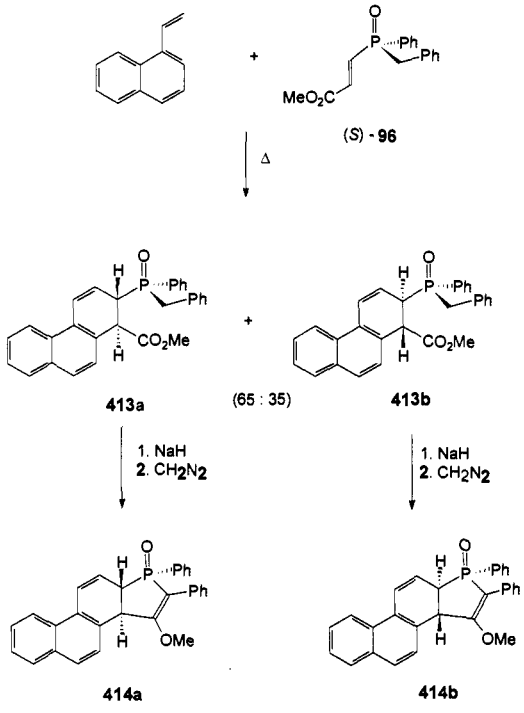
In one case (Scheme 13),[231] for the purpose of synthesizing enantiomeric P-chiral phosphasteroids doubly activated vinylphosphine oxide (*S*)-**96** was reacted with 1-vinylnaphthalene and was found to give a 65:35 mixture of only two diastereomeric cycloadducts **413**. The regioselectivity in this cycloaddition appeared to have been fully controlled by the ester group. The two cycloadducts were separated by fractional crystallization and were individually converted into the resolved desired P-chiral 17-phosphasteroids **414a** and **414b** by intramolecular acylation.

The aforementioned 1,3-dipolar cycloadditions of **74** were studied by Brandi et al.[127,208,232,233] Reaction of (*S*)-**74** with a five-membered ring nitrone **415** afforded

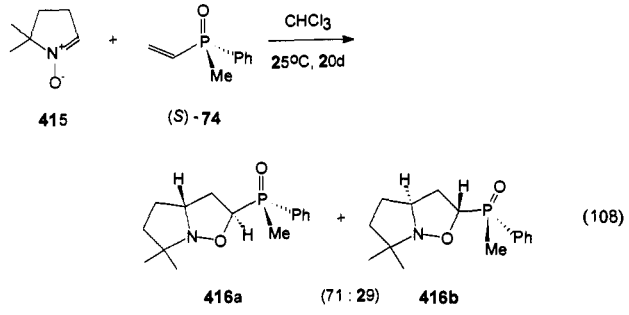
Scheme 12



Scheme 13



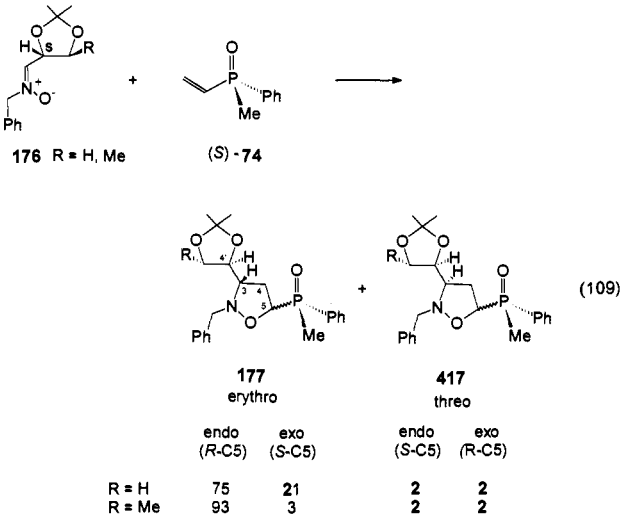
two isoxazolidinyl phosphine oxides **416a,b** in a 71:29 ratio (eq 108).[209,232] Even though the authors were able



(108)

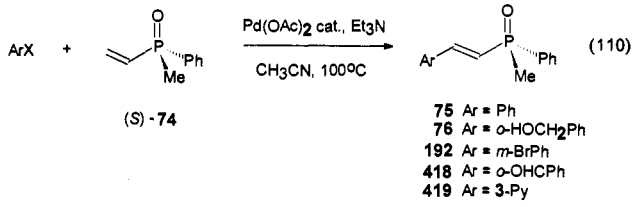
to separate this mixture into the two individual C-epimers they sought a more stereoselective process in which chirality transfer from phosphorus to carbon could be more effective. As demonstrated in the same study utilizing the same **415** as the model nitrone, the level of phosphorus-to-carbon induction in such cycloadditions could be raised considerably higher (up to 92% de) by proper adjustment of the size of the substituents and the chalcogen atom at phosphorus.[208] In those favorable cases however, the employed vinylphosphine derivatives were either not available in a scalemic form or were achiral. The desired highly diastereoselective production of scalemic isoxazolidine phosphine oxides from (*S*)-**74** was finally achieved through a doubly asymmetric process.[127] (*S*)-**74** was found to constitute matched pairs of reactants with chiral nitrones **176** of the *S* configuration which cooperated effectively in favor of the formation of the erythro,endo products **177** of the S_{C_3},R_{C_5} configuration (eq 109).[127]

Very recently use of (*S*)-**74** for structural transformations in which its double bond could be preserved was reported.[141] Palladium-catalyzed Heck coupling reactions of (*S*)-**74** with various aryl and vinyl halides were demonstrated to lead expeditiously to the expected



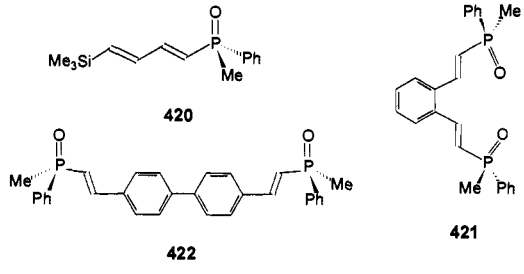
(109)

styryl- (**75**, **76**, **192**, **418**, **419**) and butadienyl- (**420**) phosphine oxides with complete preservation of configurational integrity at the phosphorus center (eq 110).

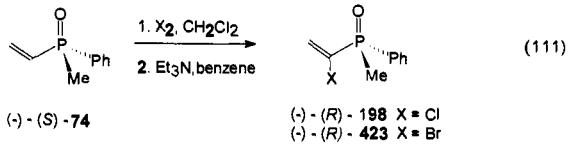


(110)

The process is of wide scope and several unprotected organic functions can be introduced into the vinylphosphine oxide structure in this way. The reaction also served well in the synthesis of scalemic diphosphorus systems **421** and **422** in which the two configurationally homogeneous phosphinyl residues occupied either proximal or distal positions, respectively.



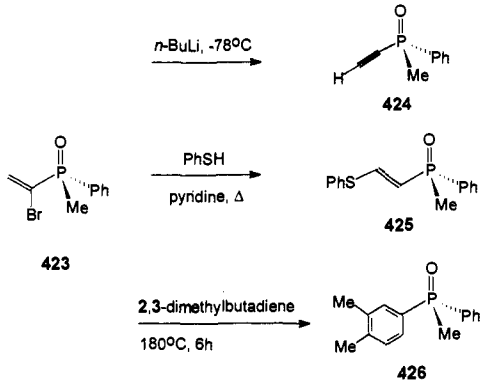
In another study,[143] halogenation and dehydrohalogenation of (*S*)-**74** was shown to provide α-halovinyl oxides (*S*)-**198** and (*R*)-**423**, valuable precursors to other phosphine oxides *per se* (eq 111). Use of (*R*)-**198** for



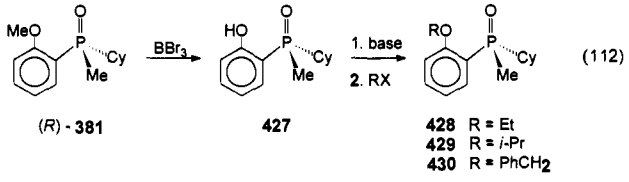
(111)

preparation of other vinyl and aryl phosphine oxides have already been discussed in sections III.A.3 and III.B.1 (cf. eqs 41 and 51). In turn the utility of (*R*)-**423** in some addition–elimination reactions is exemplified in Scheme 14.[234]

Scheme 14



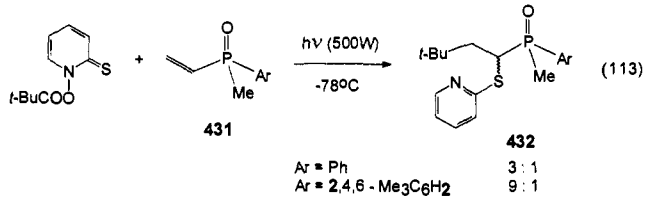
Finally, synthesis of a series of CAMP analogs **428–430** by alkylation procedure shown in eq 112[175] exemplifies transformations not involving unsaturation.



(112)

c. Asymmetric Transformations. Modifications of carbon substituents in resolved P-chiral phosphine derivatives can in principle lead to inductions originating from P → C chirality transfer. As could be judged already from several of the transformations discussed above an efficient process for such a chirality transfer has not been yet developed. From the point of view of preparation of fully resolved C,P-chiral phosphine derivatives this deficiency translates into a necessity of separating mixtures of diastereomeric products in all the pertinent cases.

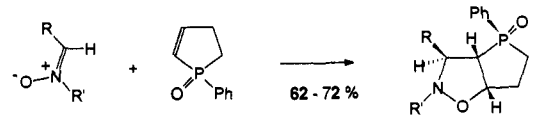
As seen above, alkylations of acyclic α-carbanions were merely selective and offered only 2:1 diastereomeric ratio in the best case, i.e., in the alkylation of (R_P)-**376** with benzyl bromide (cf eqs 96 and 97).[103] Somewhat more promising appear to be related radical processes (eq 113), but these were studied only on



(113)

racemic models.[235] Diels–Alder cycloadditions of (*S*)-**74** and (*S*)-**98** similarly were slightly effective in terms of asymmetric induction,[103,226] although again studies with model racemic **358** gave somewhat more promising results.[227]

1,3-Dipolar cycloaddition of (*S*)-**74** to a cyclic nitrone **415** (cf. eq 108) with its 71:29 product ratio[232] gave a much better starting point for further developments, and in fact, the pertinent model studies on acyclic organophosphorus dipolarophiles have already been advanced.[208] It appears however, that the ultimate dipolarophile for efficient P → C chirality transfer in 1,3-dipolar cycloadditions is phospholene oxide **10**. As shown in eq 114, **10** gives, with cyclic as well as acyclic nitrones **433**, a single product **434** of well-defined and predictable stereochemistry.[128,150] Although the cited reactions were made only with racemic **10**, the process is of immediate utility for production of optically pure cycloadducts of type **434** as the optically pure **10** is now readily available in both enantiomeric forms from the corresponding cyclic phosphonium salts **107** (cf. eq 16). On the same basis, a very recently developed completely stereoselective reaction of **435** shown in eq 115 secures prompt access to enantiomeric diphosphines of type **436**.[236]



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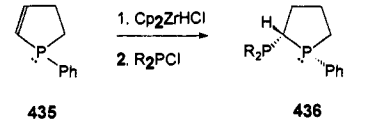
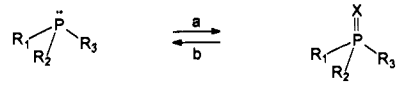


(115)

2. Interconversions Involving the Phosphorus Stereogenic Center

Once synthesized or resolved P-chiral phosphines can themselves serve as a convenient source of almost any of their higher oxidized derivatives, e.g., phosphine chalcogenides, phosphine imines, phosphonium salts, ylides, etc., and vice versa. Such transformations of scalemic phosphines and of their derivatives have been in fact exploited almost to their full potential in numerous synthetic and mechanistic studies, chemical correlations as well as in applications of scalemic P-chiral compounds in other areas. These in turn resulted in the preparation of a multitude of scalemic phosphines and their derivatives, typically in small amounts and of variable optical purities, and those will not be reviewed here. Instead, a brief survey of methods and stereochemistries available for such transformations is given.

a. Oxidations of Phosphines (Eq 116, Path a)



(116)

Stereochemical course of oxidation of phosphines depends to a large extent on the choice of oxidizing agents and reaction conditions. Oxidation processes in which configuration at phosphorus is either fully retained or fully inverted have been developed. Oxidation of phosphines with clean retention of configuration is best achieved with peroxy compounds such as H_2O_2,[57,70] *t*-BuOOH,[237] $Me_3SiOOSiMe_3$,[238,239] and *m*-CPBA.[240,241] O_2[70] and O_3[240] give similar results but aerial oxidations usually lead to impure products. Oxidation of phosphines with a very high degree of inversion can be accomplished with I_2–H_2O[242] (or, in general, halogen or pseudohalogen–water systems),[242] HNO_3,[243] and Me_2SeO.[241] Oxidations with other reagents leading to phosphine oxides with retention, e.g., *t*-BuOOAc,[237] N_2O_4,[243] amine oxides,[244] or with inversion, e.g., hydroxylamines,[245] EtOOEt,[246] positive halogen compounds,[247] *t*-BuOCl,[237] or $BrCH(CO_2Et)_2$,[246] are usually

Table 1. Stereospecific Oxidation of Methylphenyl-*n*-propylphosphine

reagent	conditions	stereochemical result	ref
H_2O_2	H_2O, rt	retention (100%)	70
EtOOEt	THF-H_2O (4:1), rt	inversion (81%)	246
EtOOEt	EtOH, rt	racemization	246
$Me_3SiOOSiMe_3$	benzene, rt	retention (95%)	238
PhC(O)OOC(O)Ph	benzene, rt	racemization (77%)	249
t-BuOOH	pentane, 0 °C	retention (100%)	237
t-BuOOAc	benzene, 80 °C	retention (94%)	237
t-BuOCl	CH_2Cl_2–MeOH, −78 °C	inversion (84%)	237
O_3	CH_2Cl_2, −60 °C	retention (100%)	240
m-CPBA	CH_2Cl_2, −5 to 0 °C	retention (100%)	240
$PhSO_2H$	different solvents, rt	racemization (49–94%)	249
Me_2SeO	$CHCl_3$, rt, 15 min	inversion (98%)	241
HNO_3 conc	H_2O, rt, 30 min	inversion (100%)	243
N_2O_4	CH_2Cl_2, rt, 30 min	retention (predominant)	243
NH_2OH	EtOH–H_2O (10:1), 2 h	inversion (82%)	245
Me_3NO	toluene, 110 °C, 3 h	retention (93.5%)	244
Me_2PhNO	MeOH, 60 °C, 30 min	retention (94%)	244
Cl_3CCHO	THF–H_2O, 0 °C	racemization (>95%)	248
I_2 (or Br_2, BrCN)	MeCN–H_2O (10:1) 0 to 5 °C	inversion (100%)	242
$BrCH(CO_2Et)_2$	THF–H_2O (5:1), rt	inversion (83%)	246

less stereospecific and are frequently greatly affected by the choice of the oxidation conditions.[61,237,242,246] Reagents like chloral,[248] dibenzoyl peroxide,[249] or phenylsulfinic acid[249] cause racemization. Representative oxidation procedures utilizing scalemic methylphenyl-*n*-propylphosphine as a model are listed in Table 1.

Oxidation of phosphines by elemental sulfur or selenium as well as by other sulfurizing agents affords the corresponding phosphine chalcogenides with full preservation of stereochemical integrity at phosphorus.[61,250] Similarly, transformation of phosphines into phosphine imines by treatment with RN_3 is also completely stereospecific and gives products with retention of configuration.[250]

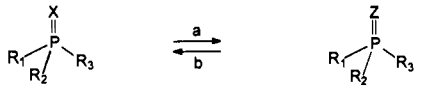
b. Reductions of Phosphine Chalcogenides (Eq 116, Path b)

Reliable methods have also been developed to stereospecifically convert phosphine oxides into phosphines with either retention or inversion of configuration at phosphorus. Interestingly, in either case silane-reducing agents are the reagents of choice. Thus, $HSiCl_3$,[251] $HSiCl_3$–pyridine,[251,252] and $PhSiH_3$[253] give phosphines with retention of configuration, whereas combination of $HSiCl_3$ with more basic amines, e.g., $HSiCl_3$–Et_3N,[251,252] or use of Si_2Cl_6[252,254] affords reduction products with 100% inversion. Four-membered-ring phosphine oxides constitute an exception and undergo reductions with the latter two reagents with clean retention of configuration.[255,256] It should be kept in mind, however, that with these reductants some losses of stereochemical integrity at phosphorus have also been observed on few occasions,[23,110] and that a general principle for securing maximum selectivity appears to be the use of low reaction temperatures and the shortest possible reaction times (preferably only minutes in case of Si_2Cl_6) to minimize exposure of the resulting phosphine to the reducing agents and their oxidation products.[257]

Reductions of phosphine oxides with $LiAlH_4$[149] and $LiAlH_4$–$CeCl_3$[106] give totally racemized products with the exception of *t*-Bu-substituted phosphine oxides which are reduced with $LiAlH_4$ with predominant retention.[258] By contrast, phosphine sulfides and phosphine selenides are reduced to phosphines by $LiAlH_4$[259,260] as well as by Si_2Cl_6[261] with complete retention of configuration.

Representative examples of stereospecific reductions of phosphine chalcogenides are collected in Table 2.

c. Interconversions of Phosphine Chalcogenides (Eq 117)



(117)

Direct conversion of phosphine sulfides and phosphine selenides into phosphine oxides with retention of configuration at phosphorus can be accomplished with $KMnO_4$,[70,250,260] whereas use of Me_2SO–H^+,[262,263] Me_2SO–I_2,[264] or $Me_3SiOOSiMe_3$[239] leads to products with 100% inversion. Other reagents such as H_2O_2,[265] Me_2SeO,[241] Ph_2SeO,[266] $(EtO)_2SeO$,[267] N_2O_4,[243] HNO_3,[260] O_3,[268] and cyclohexene oxide–CF_3CO_2H,[269] give variable results with predominant inversion being more often the case.

Stereospecific reverse transformation of phosphine oxides into phosphine sulfides can be accomplished with B_2S_3 which affords products of retained configuration.[270] More commonly used P_2S_5 was found to cause racemization.[247]

Mutual conversions of phosphine sulfides and phosphine selenides can be accomplished by sequential treatment of these chalcogenides with CF_3CO_2Me and, correspondingly, with NaSH or NaSeH, which leads to transformed products with predominant retention of configurations (83–84% ee).[271]

Typical procedures for stereospecific interconversions among phosphine chalcogenides in the model methylphenyl(*n*-propyl)phosphine system are gathered in Table 3.

Phosphine imines can be transformed into phosphine oxides either via aza-Wittig process which gives products with clean retention of configuration, or hydrolytically, by treatment with MeI–H_2O, to obtain products of inverted configuration.[250] Direct reverse conversion is also possible and can be effected by treatment of phosphine oxides with tosyl isocyanate. As applied to scalemic systems the process can be considered useful only for small ring phosphine oxides which give the

Table 2. Stereospecific Reduction of Scalemic Phosphine Chalcogenides

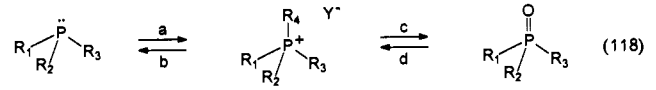
phosphine chalcogenide	reagent	conditions	stereochemical result	ref(s)
n-Pr(Ph)P(O)Me (**204**)	$PhSiH_3$	neat, rt → 80–100 °C, 1 h	retention (100%)	253
	Si_2Cl_6	benzene, 80 °C, 5 min	inversion (100%)	252
	$LiAlH_4$	THF, rt, >6 h	racemization	149
$PhCH_2(Ph)P(O)Me$ (**9**)	$PhSiH_3$	benzene, 80 °C, 15 h	retention (100%)	192
	Si_2Cl_6	benzene, 70 °C, 10 min	inversion (98%)	252
	$HSiCl_3$	benzene, 80 °C	retention (100%)	251, 252
	$HSiCl_3$–pyridine	benzene, 80 °C, 1–2 h	retention (50%)	251, 252
	$HSiCl_3$–NEt_3	benzene, 80 °C, 1–2 h	inversion (100%)	251, 252
o-An(Ph)P(O)Me (**64**)	$HSiCl_3$–NEt_3	benzene, rt, 18 h	inversion (97%)	205
t-Bu(Ph)P(O)Me (**103**)	$LiAlH_4$	THF, 66 °C, 4 d	retention (87%)	258
1-phenyl-2,2,3,4,4-pentamethylphosphetane oxide	$HSiCl_3$–NEt_3	benzene, 80 °C, 3–15 h	retention (100%)	255
	Si_2Cl_6	benzene, rt, 5 min	retention (100%)	256
1-phenyl-3-methylphospholane oxide	$PhSiH_3$	neat, rt → 80–100 °C, 1 h	retention (100%)	253
Men(Ph)P(O)Me (**112**)	$PhSiH_3$	neat, 95 °C, 4 h	retention (90%)	110
	Si_2Cl_6	benzene, 80 °C, 10 min	inversion (100%)	110
	$HSiCl_3$–NEt_3	neat, 75 °C, 90 min	inversion (80%)	110
o-An(Ph)P(O)CH_2CH_2OMen (**401**)	$HSiCl_3$–$NCyEt_2$	MeCN, rt, 1 h	inversion (100%)	215
o-An(Ph)P(O)CH_2CO_2Men (**100**)	$PhSiH_3$	benzene, 80–100 °C, 4 d	racemization	104
Me(Ph)P(O)CH_2CH_2P(O)(Ph)Me (**195**)	$PhSiH_3$	benzene, 80 °C, 4 d	retention (100%)	225
o-An(Ph)P(O)CH_2CH_2P(O)(Ph)*o*-An (**214**)	$HSiCl_3$–$N(n\text{-}Bu)_3$	MeCN, 70 °C, 3 h	inversion (100%)	155
o-An(Ph)P(S)CH_2CH_2P(S)(Ph)*o*-An (**313**)	Si_2Cl_6	benzene, 80 °C, 30 min	retention (100%)	194
Cy(Ph)P(S)CH_2CO_2Et	$NiCp_2$–$C_3H_6I/P(OMe)_3$	rt, 10 min	retention	217, 302
o-An(Ph)P(S)Me (**312**)	Si_2Cl_6	benzene, 80 °C, 30 min	retention (100%)	194
n-Pr(Ph)P(S)Me (**438**)	$LiAlH_4$	THF, 66 °C, minutes	retention (100%)	259
n-Pr(Ph)P(Se)Me (**439**)	$LiAlH_4$	THF, 66 °C, minutes	retention (100%)	260

Table 3. Stereochemistry of P=X to P=Z Conversions in the Model Methylphenyl-*n*-propylphosphine System

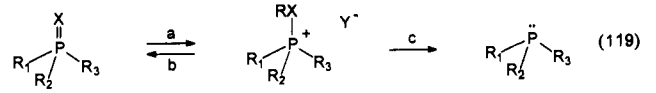
conversion	reagent	conditions	stereochemical result	ref
P=O → P=S	B_2S_3	benzene, 80 °C, 20–30 h	retention (86%)	270
	P_2S_5	benzene, 80 °C, 2.5 h	racemization	247
P=S → P=O	$KMnO_4$	H_2O–pyridine, rt	retention	250
	H_2O_2	EtOH, reflux, 20 min	inversion (16%)	265
	H_2O_2	dioxane–CF_3COOH, 50 °C	inversion (64%)	265
	HNO_3	H_2O, rt	retention	243
	N_2O_4	CH_2Cl_2, rt	retention	243
	$Me_3SiOOSiMe_3$	benzene, rt	inversion (16%)	239
	DMSO	DMSO–H^+, rt, 7 d	inversion (100%)	263
	DMSO	DMSO–I_2 cat., rt	inversion (100%)	264
	Me_2SeO	$CHCl_3$, rt	inversion (72%)	241
P=S → P=Se	CF_3SO_3Me–NaSeH	CH_2Cl_2, rt, –60 °C	retention (92%)	271
P=Se → P=O	$KMnO_4$	H_2O–pyridine, rt	retention	260
	H_2O_2	EtOH, reflux, 5 min	retention (65%)	265
	H_2O_2	H_2O, rt	inversion (83%)	265
	HNO_3	H_2O, rt	inversion	260
	N_2O_4	CH_2Cl_2, rt	inversion	260
	DMSO	DMSO–I_2 cat., rt	inversion (83%)	264
	Me_2SeO	benzene, rt	inversion (100%)	241
	Ph_2SeO	$CHCl_3$, rt	inversion (82%)	266
P=Se → P=S	CF_3SO_3Me–NaSeH	CH_2Cl_2, rt, –60 °C	retention (91%)	271

corresponding *N*-tosylphosphine imines stereospecifically with complete retention of configuration.[272] Acyclic systems are racemized.[273]

d. Phosphonium Salt Formation and Cleavage (Eqs 118 and 119)



(118)



(119)

Quaternization of scalemic phosphines by alkyl halides proceeds cleanly with retention of configuration.[57,250,274] Somewhat surprisingly, a high degree of retention can also be attained in analogous metal-catalyzed arylation reactions,[275] in spite of the highly elevated temperatures and prolonged reaction times required.[276] By quaternization of the phosphorus center in scalemic aminophosphines the corresponding aminophosphonium salts are analogously obtained with complete retention of configuration.[277,278]

Transformations of quaternary phosphonium salts into phosphines can be accomplished in a variety of ways depending largely on the salt structure and is typically facile and highly stereospecific when groups like $PhCH_2$, $CH_2{=}CHCH_2$, $HOCH_2$, $HOCH_2CH_2$, $NCCH_2CH_2$, MeS, MeSe, *t*-Bu, or at least Ar, are present in the cation. Nucleophiles or bases such as CN^-,[279] EtS^-,[186] $(Me_2N)_3P$,[280] and Et_3N,[71] are useful for the cleavage when attack on the substituent and not the phosphorus atom is desired. Alternatively, electrochemical reductions[57,70,281] or reductions with $LiAlH_4$ can be applied[258,277] although the successful use of the

Table 4. Stereochemistry of Alkali Hydroxide Cleavage of Phosphonium Salts to Phosphine Oxides

phosphonium salt	leaving group	reaction medium	stereochemical result	ref(s)
	Acyclic			
$Me(Ph)(PhCH_2)(Et)P^+I^-$	$PhCH_2$	$MeOH-H_2O$	inversion (100%)	56, 283
$Me(Ph)(PhCH_2)(n\text{-}Pr)P^+Br^-$	$PhCH_2$	$EtOH-H_2O$ (3:1)	inversion (100%)	282
		H_2O	inversion (100%)	282
$Me(Ph)(PhCH_2)(i\text{-}Pr)P^+Br^-$	$PhCH_2$	$EtOH-H_2O$ (3:1)	inversion (99%)	282
		H_2O	inversion (98%)	293
$Me(Ph)(PhCH_2)(Cy)P^+Br^-$	$PhCH_2$	$EtOH-H_2O$ (3:1)	inversion (92%)	282
		H_2O	inversion (100%)	293
$Me(Ph)(PhCH_2)(t\text{-}Bu)P^+I^-$	$PhCH_2$	$EtOH-H_2O$ (3:1)	retention (68%)	285, 294
		H_2O	retention (58%)	285, 294
$Me(Ph)(PhCH_2)(CH_2C(CH_3)_3)P^+I^-$	$PhCH_2$	$EtOH-H_2O$ (3:1)	inversion (100%)	282
		H_2O	inversion (100%)	293
$Me(Ph)(PhCH_2)(p\text{-}An)P^+Br^-$	$PhCH_2$	$EtOH-H_2O$ (3:1)	inversion (87%)	282
		H_2O	inversion (93%)	293
$Me(Ph)(PhCH_2)(p\text{-}Tol)P^+Br^-$	$PhCH_2$	$EtOH-H_2O$ (3:1)	inversion (96%)	282
		H_2O	inversion (79%)	293
$Me(Ph)(PhCH_2)(\alpha\text{-}Np)P^+Br^-$	$PhCH_2$	$EtOH-H_2O$ (3:1)	inversion (70%)	282
		H_2O	inversion (64%)	293
$Me(Ph)(n\text{-}Pr)(\alpha\text{-}Np)P^+Br^-$	α-Np	$EtOH-H_2O$ (3:1)	retention (87%)	282
		H_2O	retention (70%)	295
$Me(Ph)(n\text{-}Pr)(\beta\text{-}Np)P^+Br^-$	β-Np	$EtOH-H_2O$ (3:1)	retention (69%)	282
		H_2O	retention (55%)	295
$Me(Ph)(n\text{-}Pr)(mesityl)P^+Br^-$	mesityl	H_2O	retention (52%)	282
$Me(Ph)(n\text{-}Pr)(o\text{-}Tol)P^+Br^-$	o-Tol	H_2O	retention (64%)	282
$Me(Ph)(n\text{-}Pr)(p\text{-}Tol)P^+Br^-$	p-Tol	$EtOH-H_2O$ (3:1)	retention (72%)	282
		H_2O	retention (56%)	282
	Ph	$EtOH-H_2O$ (3:1)	retention (100%)	282
		H_2O	retention (68%)	282
$Me(Ph)(n\text{-}Pr)(Et)P^+I^-$	Ph	H_2O	retention (55%)	282
$Me(Ph)(n\text{-}Pr)(Cy)P^+Br^-$	Ph	$EtOH-H_2O$ (3:1)	retention (86%)	282
		H_2O	inversion (61%)	294
$Me(Ph)(n\text{-}Pr)(allyl)P^+Br^-$	allyl	$EtOH-H_2O$ (3:1)	inversion (93%)	282
		H_2O	inversion (96%)	295
$Me(Ph)(t\text{-}Bu)(allyl)P^+Br^-$	allyl	$EtOH-H_2O$ (3:1)	retention (100%)	294
		H_2O	retention (49%)	294
	Cyclic			
cis-1,2,2,3,4,4-hexamethyl-1-benzylphosphetanium bromide	$PhCH_2$	H_2O	retention (100%)	66, 255
trans-1,2,2,3,4,4-hexamethyl-1-benzylphosphetanium bromide	$PhCH_2$	H_2O	retention (100%)	66, 255
cis-1,3-dimethyl-1-benzylphospholanium bromide	$PhCH_2$	H_2O	retention (100%)	287, 288
trans-1,3-dimethyl-1-benzylphospholanium bromide	$PhCH_2$	H_2O	retention (100%)	287, 288
cis-1-phenyl-3-methyl-1-benzylphospholanium bromide	$PhCH_2$	H_2O	retention (100%)	67, 289
trans-1-phenyl-3-methyl-1-benzylphospholanium bromide	$PhCH_2$	H_2O	retention (100%)	67, 289
cis-1-phenyl-4-methyl-1-benzylphosphorinanium bromide	$PhCH_2$	H_2O	inversion (52%)	286
trans-1-phenyl-4-methyl-1-benzylphosphorinanium bromide	$PhCH_2$	H_2O	retention (78%)	286
cis-1-phenyl-4-methyl-1-benzylphosphepanium bromide	$PhCH_2$	H_2O	inversion (100%)	290
trans-1-phenyl-4-methyl-1-benzylphosphepanium bromide	$PhCH_2$	H_2O	inversion (100%)	290

latter reagent is limited only to sterically encumbered phosphonium cations bearing *t*-Bu groups.[258] In all such transformations retention of configuration at phosphorus is usually greatly predominating or is complete, especially in the cases where the phosphorus atom is not directly attacked.

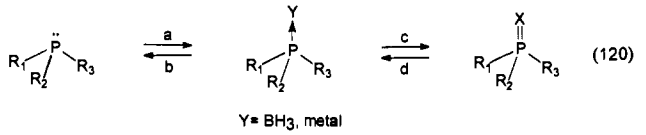
Base-catalyzed hydrolysis of phosphonium salts directly gives phosphine oxides. The stereochemical pattern of the process is rather complex[282] but phosphonium salts bearing good leaving groups such as $PhCH_2$ can be hydrolyzed stereospecifically[283] with virtually complete inversion of configuration at phosphorus.[56,57,284] With bulky groups[285] or aryls either predominant retention or extensive racemization is usually observed.[282] Also, frequently, the process differs in its stereochemical preference in acyclic[56,57,282,284] and in cyclic,[67,286-290] especially small ring,[66,255,291,292] systems. Representative stereochemical results of the base-catalyzed hydrolysis of acyclic and cyclic phosphonium salts are collected in Table 4.

Transformations of phosphonium salts into phosphine oxides with 100% retention of configuration at phosphorus can be successfully effected via Wittig reactions of the derived ylides with aldehydes.[56,284,296,297]

Phosphonium cations bearing one heteroatom-centered ligand can be obtained directly from phosphine chalcogenides by alkylation of the chalcogen atom with strong alkylating agents.[186,188,256,298] Such transformations do not affect stereochemistry at phosphorus and, accordingly, net retention is uniformly the result. Similar alkylation of phosphine imines with alkyl halides gives promptly aminophosphonium salts.[250,277,278] These phosphonium salts can be reduced to the corresponding phosphines with retention of configuration with $LiAlH_4$.[277] Cathodic reductions result instead in a C–P bond cleavage and lead to the corresponding aminophosphines.[278] In the case of alkylthio and alkylselenophosphonium salts nucleophilic displacements at S and Se by RS^- or $(Me_2N)_3P$ provide phosphines with full preservation of stereochemical integrity at phosphorus.[186,280] Base-catalyzed hydrolysis of heteroatom-substituted phosphonium salts yields phosphine oxides with complete inversion of configuration in acyclic systems,[277,298] whereas clean retention

results in hydrolysis of alkoxyphosphetanium salts.[256]

e. Complex Formation and Decomplexation (Eq 120).



(120)

Phosphines form complexes with metals as well as with borane with complete preservation of their stereochemical integrity at phosphorus. These complexes are typically obtained by mixing phosphines with appropriate metal derivatives or with $THF{\cdot}BH_3$ or $Me_2S{\cdot}BH_3$. Treatment of phosphine boranes with an excess of Et_2NH or morpholine gives back phosphines with complete retention of configuration.[106] Liberation of phosphines from their complexes with metals is similarly achieved by simply providing a better complexing agent than phosphine. Several such procedures have been exemplified already in section III.

Direct reductive conversion of phosphine oxides into phosphine borane complexes can be realized through the use of $LiAlH_4$–$NaBH_4$–$CeCl_3$ reducing system but only racemic complexes are obtained.[106] Phosphine sulfides can be directly transformed into phosphine nickel complexes by treatment with the nickelocene–allyl iodide system.[299] In this case however, formation of the complexes occurs with complete retention of stereochemical integrity at phosphorus as does subsequent liberation of phosphines from these complexes by treatment with $P(OMe)_3$ (cf. eq 9).[300]

Examples of oxidative decomplexation of phosphines with retention of configuration at phosphorus can be found in eqs 25 and 26. For examples of oxidative cleavage of phosphine copper complexes with either retention or inversion of configuration at phosphorus, see refs 190 and 301, respectively. Procedures for reductive transformations of phosphine sulfides into phosphine complexes with iron or molybdenum are also available but their stereochemical course has not been yet established.[302]

IV. Concluding Remarks

This review has summarized the methods available for the synthesis of scalemic P-chiral phosphines and their derivatives. The development of methods in their full array ranging from classical resolutions to enantiodifferentiating asymmetric synthesis continues at a fast pace and much further progress can be expected in the near future, especially in the area of chromatographic resolutions and asymmetric transformations of readily available P-chirons.

Scalemic P-chiral phosphines and their derivatives are now available in a whole diversity of structural types and functional patterns which promise that their utility will expand quickly in new directions in the areas of coordination chemistry and asymmetric synthesis and catalysis. The absolute configuration at phosphorus in the majority of scalemic phosphines and their derivatives synthesized to date is known, and convenient chromatographic[303] and NMR[81,192,304–309] methods for measurement of their enantiomeric purities have been developed. Also important, viable routes to P-chiral diphosphines with cyclic and acyclic carbon spacers of almost any size have been paved and are likely to lead to the development of novel highly efficient transition metal catalysts incorporating intuitively desirable metal–adjacent phosphorus chirality. Asymmetric processes based on the chirality transfer from phosphine ligands present in the transition metal catalysts have been developed to the level securing access to scalemic products of >95% ee,[22,311,312] and some of them have already gained industrial significance, e.g., Monsanto L-DOPA process,[313] Anic and Monsanto Aspartame processes,[314] Syntex Naproxen process,[315] Takasaga L-menthol process,[315] etc. With the notable early exception of the Monsanto L-DOPA process utilizing P-chiral DIPAMP ligand,[11] in all the other highly efficient asymmetric catalyzes developed to date C-chiral ligands, most frequently possessing a C_2 symmetry axis, were employed. Current intensive search for novel efficient ligands for asymmetric catalysis follows these successful leads and focuses mainly on the C_2-symmetric phosphines,[316–318] and on ligands bearing pendant functionalities capable of providing remote secondary interactions with the substrate.[319] The time has come for the P-chiral ligands to merge the stream and to bring in the P-chirality factor into play again.

V. Glossary of Abbreviations

An	anisyl
Ar	aryl
m-CPBA	*m*-chloroperbenzoic acid
Cy	cyclohexyl
dppe	1,2-bis(diphenylphosphino)ethane
Hex	hexyl
lp	lone pair
mesityl	2,4,6-trimethylphenyl
Met	metal
Men	menthyl
neoMen	neomenthyl
Np	naphthyl
Piv	pivaloyl
Py	pyridyl
rt	room temperature
Tol	tolyl

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