Published in final edited form as:
Tetrahedron. 2009 January 3; 65(1): 17–49. doi:10.1016/j.tet.2008.09.083.

An Overview of Stereoselective Synthesis of α-Aminophosphonic Acids and Derivatives

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Abstract

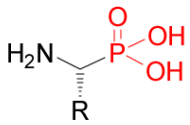
An overview of all methodologies published during the last few years focused to the stereoselective (diastereoselective or enantioselective) synthesis of α-aminophosphonic acids and derivatives is reported. The procedures have been classified according a retrosynthetic strategy and taking into account the formation of each one of the bonds connected to the chiral centre.

Keywords

α-Aminophosphonic acids; α-Aminophosphonates; Stereoselective Synthesis; Resolution; Chiral Pool

1. Introducción

α-Aminoalkylphosphonic acids **1** are structurally analogous to α-amino acids **2**, obtained by isosteric substitution of planar and less bulky carboxylic acid (CO_2H) by a tetrahedral phosphonic acid functionality (PO_3H_2). Several aminophosphonic, aminophosphinic and aminophosphonous acids have been isolated from various natural sources either as free amino acids or as constituents of more complex molecules.[1] Many natural and synthetic aminophosphonic acids, their phosphonate esters and short peptides incorporating this unit, exhibit a variety of biological properties.[2] Their diverse applications include enzyme inhibitors[3] such as synthase,[4] HIV protease,[5] rennin,[6] phosphatasa activity,[7] PTPases,[8] and potent antibiotics,[9] as antibacterial agents,[10] antiviral,[11] antifungal,[12] herbicides,[13] antitumor agents.[14] Their role for antibody generation is also well documented.[15] In addition, the incorporation of cyclic amino acids of medium ring size into key positions in peptide chains plays an important role, and constitutes the most prominent pathway to conformationally constrained peptidomimetics, a tool in modern drug discovery.[16]



α-Aminophosphonic acid, **1**

α-Amino acid, **2**

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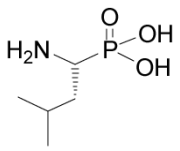
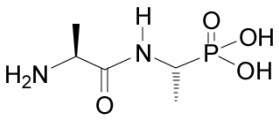
In addition, α-aminophosphonic acids and their monoalkyl esters are also of interest in hydrometallurgy in order to extract metals[17] and in diagnostic medicine as screening agents, once complexed with lanthanides and actinides.[18,19]

It is well known that the biological activity of α-aminophosphonic acids and derivatives depends on the absolute configuration of the stereogenic α carbon to phosphorous.[20] For example, (*R*)-phospholeucine **3** is a more potent inhibitor of leucine aminopeptidase than the *S* enantiomer,[21] and (*S*,*R*)-alafosfalin **4** shows higher antibacterial activity against both Gram-positive and Gram-negative microorganisms than the other three diastereoisomers.[22]



(*R*)-Phospholeucine, **3**



(*S*,*R*)-Alafosfalin, **4**

In view of the different biological and chemical applications of the α-aminophosphonic acids and derivatives, in the last 35 years the development of suitable synthetic methodologies for their preparation in optically pure form has been a topic of great interest in several research groups. In this context, several protocols for efficient asymmetric synthesis of α-aminophosphonic acids and derivatives have emerged in the recent years and several reviews have been published.[23] Now we would like to report herein an update over stereoselective synthesis of α-aminophosphonic acids and derivatives from 1998-2007. The principal synthetic strategies of α-aminophosphonic acids and derivatives optically pure can be classified in C-P bond formation using the Strecker type process, C-C bond formation derived from diastereoselective alkylation of phosphonoglycine equivalents, C-N bond formation derived from diastereoselective electrophilic amination, catalytic hydrogenation of dehydro-aminophosphonates, resolution and chiral pool processes.

2. Stereoselective synthesis of α-aminophosphonic acids and derivatives

2.1. Stereoselective C-P bond formation

The nucleophilic addition of dialkyl- or diaryl phosphite to imines or oxoiminium derivatives, the Pudovik reaction,[24] is one of the most convenient methods for the preparation of α-aminophosphonates, key intermediates in the synthesis of α-aminophosphonic acids. In this context, the stereoselective synthesis of α-aminophosphonates can be carried out by four routes: (1) addition of alkylphosphites to chiral imines readily obtained by condensation of aldehydes with chiral amines, (2) addition of alkyl phosphites to chiral imines readily obtained by condensation of chiral aldehydes with non-chiral amines, (3) addition of chiral alkyl phosphites to non-chiral imines, and (4) addition of non-chiral alkyl phosphites to non-chiral imines in the presence of a chiral catalyst (Scheme1).

2.1.1. Addition of alkyl phosphites to imines derived from chiral amines—The first synthesis of enantiomerically pure α-aminophosphonic acids was described by Gilmore and McBride in 1972.[25] They reported that the addition of diethyl phosphite to the imine (*S*)-**5a** readily obtained from condensation of benzaldehyde and (*S*)-α-methylbenzylamine [(*S*)-α-MBA], afforded the α-aminophosphonates (*R*,*S*)-**6a** and (*S*,*S*)-**7a** (X = O) with a 66:34 diastereoisomeric ratio.[26] A better diastereoselectivity was obtained when the addition of diethyl phosphite to the imine (*S*)-**5b** derived from cyclohexanecarboxaldehyde (R' = cyclohexyl) was carried out, where the diastereoisomeric ratio was 83:17.[27] Recently, Vovk *et al*.[28] found that the reaction of imine (*S*)-**5c** (R' = 4-HOC_6H_4) with an excess of sodium diethyl phosphite solution gave the α-aminophosphonates (*R*,*S*)-**6c** and (*S*,*S*)-**7c** (X = O) in

98% yield and 95% diastereoisomeric excess. On the other hand, Thompson *et al.*[29] reported that the addition of dimethyl thiophosphite (DMTP) to the imine (*R*)-**5a** (R' = C_6H_5), led to the α-aminophosphonothionates (*R*,*S*)-**6d** and (*S*,*S*)-**7d** (X = S) in 64% yield and 76:24 diastereoisomeric ratio (Scheme 2).

Hydrogenolysis of (*R*,*S*)-**6a** and (*R*,*S*)-**6c** (X = O) followed by hydrolysis with trimethylsilyl bromide (TMSBr) gave the enantiomerically pure (*R*)-α-aminophosphonic acids (Scheme 3).

This methodology has been used in the preparation of calix[4]arene α-aminophosphonic acids, which show inhibitory activity toward porcine kidney alkaline phosphatase.[28] In this context, addition of sodium salt of diethyl phosphite to iminocalix[4]arenes **9** and **12** easily obtained through of the condensation of mono- or 1,3-diformilcalix[4]arenes with (*S*)- or (*R*)-α-MBA, afforded the corresponding α-aminophosphonates **10** and **13** in 60-80% yield and 75-85% diastereoisomeric excess. Hydrogenolysis of chiral auxiliary in **10** and **13**, followed by the hydrolysis of phosphonic esters with TMSBr and methanol gave the mono- and di-α-aminophosphonic acids **11** and **14** in quantitative yield (Scheme 4).

The inhibitory activity of α-aminophosphonic acids (*R*)-**8c**, **11** and **14** toward porcine kidney alkaline phosphatase (PKAP) depends considerably on the absolute configuration at the α-carbon atoms. For example, the K_i value for (*S*)-**11** is about two times smaller than that the enantiomer (*R*)-**11**, and (*R*,*R*)-**14** binds to PKAP about 50 times stronger than the (*S*,*S*)-**14** enantiomer.

Molecular mechanics study on this type of reaction revealed that the diastereoisomeric excess values and the induced direction are controlled by the conformation of the imine substrate.[30] In imines such as (*S*)-**5**, conformations **A** and **C** are destabilized because of allylic 1,3-strain (Figure 1).[31] Thus, addition of alkyl phosphites to more stable imine **B** bearing (*S*)-α-MBA, takes place by the *re* face generating the (*R*,*S*)-**6** diastereoisomer as major product. As consequence, the imines bearing (*S*)-α-MBA give rise to (*R*)-α-aminophosphonic acids, whereas using (*R*)-α-MBA affords the (*S*)-α-aminophosphonic acids.

Petneházy *et al.*[32] found that the addition of ethyl phenylphosphinate **15** to imines (*S*)-**5a-d** at 70 °C in toluene afforded the α-aminophosphinates **16a-d** with a predominance of two of the four diastereoisomers. Hydrolysis of **16a-d** with HCl or HBr solution in glacial acetic acid gave the corresponding derivatives **17a-d**, which by hydrogenolysis led to α-aminophosphinic acids **18a-d** with good to excellent diastereoisomeric ratio (80:20 to 100:0), (Scheme 5).[33]

On the other hand, addition of diethyl phosphite to imine **19** obtained in excellent yield from condensation of (*R*)-phenylglycine *t*-butyl ester in the presence of Lewis acids such as $ZnCl_2$, $MgBr_2$ and trifluoroacetic acid (TFA), afforded the corresponding α-aminophosphonates (*R*,*R*)-**20** and (*R*,*S*)-**21** (Table 1, entries 1-4).[34] All three catalysts led to increased rates of addition, indicative of the desired imine activation, but none afforded an increase of the diastereoselectivity. The poor diastereoselectivity obtained indicated that the chelate **22** was not formed. A smaller diastereoselectivity was obtained in the addition of diethyl phosphite or dimethyl phosphite to imine **19**, derived from (*R*)-leucine benzyl ester (Table 1, entries 5-7).[35] Similar results were obtained in the reaction of imine **19** with diethyl thiophosphite (Table 1, entries 8-11). However, the addition of lithium salt of diethyl phosphite prepared by treatment of diethyl phosphite with *n*-BuLi in THF at -78→25 °C, gave the α-aminophosphonates (*R*,*R*)-**20** and (*R*,*S*)-**21** with 80% yield and high diastereoselectivity (Table 1, entry 12).

The high diastereoselectivity has been explained as result of the coordination of nucleophile with the corresponding imine **19**, generating the chelate **23**, with a *trans* relationship between

the nucleophile and the stereodirecting phenyl group, and the addition of dialkyl phosphite on the *re* face of the imine double bound (Figure 2).

A most effective diastereoselectivity in favour of diastereoisomer (*R*,*R*)-**25** was obtained in the addition of lithium salt of diethyl phosphite to aldimines **24** bearing methoxymethyl ether derived from (*R*)-2-phenylglycinol (Table 2, entries 1-10).[36] However, the addition of dimethyl thiophosphite to imine **24** gave the α-aminophosphonates (*R*,*R*)-**25** and (*S*,*R*)-**26** in moderated and reverse diastereo-selectivity (Table 2, entry 11).[29]

To explain the results obtained in the Table 2, the authors suggest a chelated intermediate **27** analogous to the structure **23** (Figure 2). Thus, the enantiofacial preference of attack on the aldimine carbon by the phosphorous atom is due to the formation of highly organized cyclic transition state **27** by chelation with the lithium cation, and the *anti* disposition of the phenyl and phosphite groups presumably directs the addition to the *re* face of the imine, affording the α-aminophosphonates (*R*,*R*)-**25** as principal products,[37] which by hydrogenolysis over Pd $(OH)_2$ afforded the enantiomerically pure (*R*)-α-aminophosphonates **28** (Scheme 6).

The intramolecular version of nucleophilic addition of phosphites to imines was reported by Dimukhametov *et al*.[38] In this context, the reaction of the chlorophosphite **30** with (*R*)-*N*-(benzylidene)-2-aminobutan-1-ol **29** gave the phosphite **31**, which after intramolecular cyclization followed of the Michaelis-Arbuzov reaction,[39] afforded the 1,4,2-oxazaphosphinanes **32** and **33** in 88% yield and 70:30 diastereoisomeric ratio, which are precursors of chiral α-aminophosphonic acids (Scheme 7).

To explain the stereochemistry of this reaction, the authors suggest that the nucleophilic attack by phosphite group on electrophilic C=N group proceeds stereospecifically by the *re*-face, generating the *R* configuration at α-C atom to phosphorous as principal product. The attack on the *si*-face is hindered, in this case the ethyl group would have to adopt an unfavorable axial position in the transition state (Figure 3).

Recently Chen *et al*.[40] reported the synthesis of the α-aminophosphonates **36a-k** derivatives of 2'-deoxyuridine **34**. In this context, nucleophilic addition of dimethyl phosphite to corresponding imines obtained from condensation of arylaldehydes with the amine **35** obtained in 4 steps from **34**, followed by treatment with ammonium fluoride provided the α-aminophosphonates **36a-k** in 55-70% yield and 60:40 diastereoisomeric ratio (Scheme 8). The configurations of the three chiral carbon atoms of **35** are known, but the newly formed chiral carbon atom resulting from the addition reaction was not established.

The chiral sulfinimides readily available[41] containing an arylsufinyl moiety constitutes a valuable target molecules in asymmetric synthesis.[42] For example,[43] the addition of lithium or sodium salt of alkyl phosphites to *p*-toluenesulfinyl imine (*S*)-**37**[44,45] gave the *N*-sulfinyl-α-aminophosphonates **38** and **39** in moderated yield and excellent diastereoselectivity with preference of (S_S,R_C)-**38** (Table 3, entries 1-12). On the other hand, the reaction of the lithium salt of bis(diethylamido) phosphite with (*S*)-**37** afforded the α-aminophosphonates (*S*s,*R*c)-**38** and (*S*s,*S*c)-**39** in good diastereoselectivity and with a preference of diastereoisomer (S_S,S_C)-**39** (Table 3, entry 13).[46]

The high diasteroselectivity obtained in the addition of the lithium salt of alkyl phosphites to *p*-toluenesulfinyl imine (*S*)-**37** may be rationalized by assuming a coordination of lithium to the nitrogen lone pair, facilitating the delivery of the phosphorus atom to the prochiral trigonal carbon center from the face opposite to the sulfinyl oxygen atom (Figure 4).[43] However, a model to explain the opposite configuration observed in the addition of bis(diethylamido) phosphite to *p*-toluenesulfinyl imine (*S*)-**37** has not yet been elucidated.[46]

Removal of *N*-sulfinyl auxiliary in the diastereoisomer (S_S,R_C)-**38** (R' = Ph, and R = OEt) by acidic hydrolysis with TFA in methanol gave the enantiomerically pure α-aminophosphonic diethyl esther (*R*)-**28**, whereas the hydrolysis with hydrochloric acid in acetic acid at reflux produced the enantiomerically pure (*R*)-phosphophenylglycine **8**. In a similar way, hydrolysis of (S_S,S_C)-**39** afforded the (*S*)-phosphophenylglycine **8** (Scheme 9).

On the other hand, addition of lithium salt of bis(diethylamido) phosphine borane complex to enantiopure *p*-toluenesulfinyl imines (*S*)-**37a-e** in THF at -78°C, afforded the corresponding derivatives (S_S,S_C)-**40a-e** as principal diastereoisomers in high yield. Treatment of (S_S,S_C)-**40a-e** with hydrochloric acid in AcOH at reflux led to enantiomerically pure (*S*)-α-aminophosphonic acids **8a-e** in good yield. In a similar way, the imines (*R*)-**37a-b** were transformed into (*R*)-α-aminophosphonic acids **8a-b** (Scheme 10).[47]

The diastereoselectivity obtained in the addition of lithium salt of bis(diethylamido) phosphine to *p*-toluenesulfinyl imines (*S*)-**37a-e** is opposite to that observed with lithium dialkyl phosphites. These results have been explained in terms of the transition state model **D**, in which the lithium cation is coordinated to the nitrogen lone pair, facilitating the delivery of the phosphorous atom to the prochiral trigonal carbon center from the less hindered face occupied by the lone pair of electrons at sulfur (Figure 5).

Recently, Gallina *et al.*[48] have described the preparation of *N*-arylsulfonylaminophosphonic acids (*R*)-**44a-i** using the addition of lithium dialkyl phosphites to enantiopure and conformationally restricted sulfinimines **41** as key step. In this context, the addition of the lithium salt of dialkyl phosphites to imine (*S*)-**41**, obtained from condensation of isobutyraldehyde with (*S*)-*p*-bromobenzene-sulfinamide,[49] afforded the mixture of (S_S,R_C)-**42a-c** and (S_S,S_C)-**43a-c** in good yield and diastereoselectivity (Scheme 11). Diastereoisomerically pure (S_S,R_C)-**42a-c** were transformed into (*R*)-α-aminophosphonic acids **44a-i**, which showed a selective inhibition of matrix metalloproteinases (MMPs).

Recently, Chen and Yuan[50] reported the nucleophilic addition of dialkyl phosphites to *N*-*tert*-butylsulfinyl imines in order to obtain enantiomerically pure α-aminophosphonic acids. The *N*-*tert*-butylsulfinyl group activates the imines for the nucleophilic addition and serves as a powerful chiral directing group and, after the addition reaction, is readily cleavaged upon treatment of the product with acid. Competitive nucleophilic attack at sulfur atom is minimized in the addition to *N*-*tert*-butylsulfinyl imines versus *N*-*p*-tolylsulfinyl imines due to the greater steric hindrance and reduced electronegativity of the *tert*-butyl group relative to the *p*-tolyl moiety.[51] Thus, the nucleophilic addition of the lithium salt of dimethyl phosphite to *N*-*tert*-butylsulfinyl imines (*S*)-**45a-p** in the presence of K_2CO_3 in dichloromethane or ethyl ether[52] at room temperature provided the phosphonates (S_S,R_C)-**46a-p** in good yield and with moderated to excellent diastereoselectivity (Table 4).

Acidic hydrolysis of diastereomerically pure (S_S,R_C)-**46a**, **46h**, and **46j-n**, with 10 N HCl under reflux followed by treatment with propylene oxide led to enantiomerically pure α-aminophosphonic acids (*R*)-**8a** and quaternary (*R*)-**47a-f**, analogues of α-methyl α-amino acids, which are of considerable interest because their incorporation into peptides results in a improvement in their rigidity,[53] resistance to protease enzymes, and often enhancement of the bioactivity[54] (Scheme 12).

Davis *et al.*[45] reported that the addition of lithium salt of diethyl phosphite to enantiopure imines (*S*)-**48a-g**, readily obtained by condensation of (*S*)-*p*-toluenesulfinamide with the appropriate ketone in the presence of $Ti(OEt)_4$, [55] 4 gave the α-aminophosphonates (S_S,R_C)-**49a-g** in good yield and excellent diasteroselectivity, except for the imine (*S*)-**48g** derived from 2-hexanone, where the α-aminophosphonates (S_S,R_C)-**49g** and (S_S,S_C)-**50g** were obtained with 82:18 dr. (Table 5).[56]

The high diastereoselectivity obtained in the addition of the lithium salt of diethyl phosphite to enantiopure *p*-toluenesulfinyl imines (*S*)-**48a-g** has been explained in terms of the transition state model **E**, in which the lithium cation is coordinated to both sulfinyl and phosphonate oxygens in a seven-membered twisted chairlake transition state, and assuming that the sulfinyl imine has the favored geometry, a plausible rationalization for the preferential formation of (S_S,R_C)-**49a-g**. By contrast the twisted-chair transition state **F** leading to the minor product (S_S,S_C)-**50a-g** has the bulky aryl and *p*-tolyl groups in the energetically unfavorable axial positions (Figure 6).

Removal of *N*-sulfinyl auxiliary in the diastereoisomerically pure (S_S,R_C)-**49b,e,f** with TFA in methanol produced the enantiomerically pure α-aminophosphonates (*R*)-**51a-c**, whereas the acidic hydrolysis of (S_S,R_C)-**49b,e,f** with 10 N HCl at reflux followed by treatment with propylene oxide gave the enantiomerically pure (*R*)-α-aminophosphonic acids **47c,g,h** (Scheme 13).

Aza-Darzens reaction of (*S*)-**37** with the lithium anion of diethyl chloromethylphosphonate **52** in THF at -78 °C, afforded the α-chloro-β-amino derivatives (S_S,1*S*,2*R*)-**53** and (S_S,1*R*, 2*R*)-**54** in good yield (72-98%) and with moderated to excellent diastereoisomeric ratio (54:46 to 92:8).[57] Identical results were obtained using diethyl bromo-, iodo- or tosylphosphonates. Reaction of diastereoisomerically pure (S_S,1*S*,2*R*)-**53** with sodium hydride gave the aziridines (S_S,2*S*,3*R*)-**55** in 64-85% yield via S_N2 inversion α to phosphorus, which by treatment with TFA provided to (2*S*,3*R*)-**56** in 70-82% yield. Catalytic hydrogenation under (Pd/C-HCO_2NH_4) conditions produced the (*S*)-α-aminophosphonates **28a-f** in 67-98% yield (Scheme 14).[58,59]

On the other hand, aza-Darzens reaction of imine (*S*)-**37a** with the lithium anion of diethyl 1-chloroethylphosphonate **57** in THF at -78 °C afforded the α-chloro-β-amino derivative (S_S, 2*R*,3*R*)-**58** in 56% yield, and the unseparable mixture of (S_S,2*S*,3*R*)-**59** and (S_S,2*S*,3*S*)-**59** in 23% yield. Reaction of diastereoisomerically pure (S_S,2*R*,3*R*)-**58** with NaH gave the aziridine (S_S,2*R*,3*R*)-**60** in 69% yield, which by treatment with TFA led to (2*R*,3*R*)-**61** in 76% yield. Finally, catalytic hydrogenation under (Pd/C-HCO_2NH_4) conditions gave the diethyl (*R*)-α-methylphosphophenylalanine diethyl esther **51d** in 92% yield. In a similar way, the mixture of **59** was converted into (*S*)-**51d** in 43% overall yield, after three steps (Scheme 15).[60]

The formation of (S_S,2*R*,3*R*)-**58** was explained through of a transition state model **G**, in which the lithium anion derived from **57** attacks the sulfiminine (*S*)-**37a** for the *si* face, whereas the *re* face is sterically shielded by the sulfinyl oxygen in the six-membered transition state (Figure 7).

Other important methodology used in the synthesis of α-aminophosphonates is the Kabachnik-Fields reaction,[61] which is an efficient three-component reaction of aldehydes or ketones, amines and phosphites under solvent free conditions.[62] The first asymmetric synthesis of α-amino-phosphonates via one-pot three-component reaction was reported by Heydari *et al.*[63] They carried out the reaction of dimethyl phosphite to imines derived from (*S*)-α-MBA prepared *in situ*, in the presence of lithium perchloratediethyl eter (LPDE), obtaining the α-aminophosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** in good yield and moderated diastereoselectivity (Table 6, entries 1-4). In a similar way, one-pot three-component reaction of dimethyl phosphite, with arylaldehydes and (*S*)-α-MBA in the presence of LPDE and trimethylsilyl chloride (TMSCl), gave the phosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** in good yield and moderated diastereoselectivity (Table 6, entries 5-8).[64]

Nucleophilic addition of phosphites to imines catalyzed by base or acids under three-component conditions is the most convenient methodology for the synthesis of α-amino-phosphonates. Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3.Et_2O$, $ZnCl_2$, and $MgBr_2$ have been used.

[65] However, these reactions cannot be carried out in one-pot reaction with carbonyl compounds, amine and dialkyl phosphite, because the imines and water that exist during the imine formation can decompose or deactivate the Lewis acids.[66] This disadvantage has been overcome by a recent procedure describe by Qian and Huang,[67] by using a combination of lanthanide triflate as catalyst in the presence of 4 Å molecular sieves or magnesium sulphate in dichloromethane as the best solvent. However, although this procedure afford excellent yields for aromatic aldehydes, only low to moderated yields were obtained for aliphatic aldehydes, which is atributed to that aromatic aldehydes have higher reactivity than aliphatic aldehydes. For example three component reaction of benzaldehyde, (*S*)-α-MBA and diethyl phosphite in the presence of catalytic amount of ytterbium triflate (10% mol) and anhydrous $MgSO_4$ at room temperature, gave the α-aminophosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** in excellent yield and 57:43 diastereoisomeric ratio. Similar results were obtained when *p*-methoxybenzaldehyde was used (Table 6, entries 9-10). The α-aminophosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** were obtained with better diastereoisomeric ratio (83:17) when three component reaction of benzaldehyde, (*S*)-α-MBA and diethyl phosphite was carried out in the presence of catalytic amount of indium(III) chloride (10% mol) in dry THF at reflux or under sonication (Table 6, entry 11).[68] The reaction of 2-formylpyridine under identical conditions led to the α-amino-phosphonates (*R*,*S*)-**6** and (*S*,*S*)-**7** in 90% yield and 78:22 diastereoisomeric ratio (Table 6, entry 12). This methodology afforded excellent yields for aliphatic and aromatic aldehydes as well as with open-chain, cyclic, and aromatic ketones.

One-pot reaction of methylcyclopropanone acetal (2*S*)-**62** obtained in two steps from commercially available methyl (*S*)-3-hydroxy-2-methylpropionate,[69] with (*S*)-α-MBA hydro-chloride and triethyl phosphite in the presence of catalytic amount of TMSCl in ethanol at 55 °C, afforded the α-aminophosphonates (1*S*2*S*)-**63** and (1*R*2*S*)-**64** in 80% yield and 87:13 diastereoisomeric ratio. The selectivity was not altered when (*R*)-α-MBA or (*S*)-1-(1-naphthyl) ethylamine were used as chiral auxiliary. Hydrogenolysis of diastereoisomerically pure (1*S*2*S*)-**63** in the presence of Pearlman's catalyst, afforded the α-aminophosphonate (1*S*2*S*)-**65** in 82% yield, which by hydrolysis with trimethylsilyl iodide (TMSI) followed by the treatment with propylene oxide gave the (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid **66** in 86% yield (Scheme 16).[70]

The diastereoselectivity obtained in the nucleophilic addition of triethyl phosphite to the iminium intermediate **67** takes place from the less hindered face (*si*-face) opposite to the methyl group on the cyclopropane with a relative *like* approach, affording (1*S*2*S*)-**63** as the principal product (Figure 8).

In a similar way, one-pot reaction of methylcyclopropanone acetal (2*S*)-**62** with (*R*)-phenylglycinol and triethyl phosphite in the presence of catalytic amount of TMSCl in ethanol at 55 °C afforded the spirophosphonates **68** and **69** in good yield, and with the *trans* isomer as the major product (ratio 89:11). Reaction of (2*S*)-**62** with (-)-norephedrine and triethyl phosphite under the same conditions gave the spirophosphonates in low yield and diastereoisomeric ratio. Hydrogenolysis of diastereoisomerically pure **68** in the presence of catalytic amount of Pearlman's catalyst, afforded the cyclic α-aminophosphonate **70** in 79% yield, which by hydrolysis with TMSI followed by the treatment with propylene oxide gave the cyclic α-aminophosphonic acid (1*S*,2*S*)-**66** in 87% yield. Under identical conditions **69** led to (1*R*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid **71** (Scheme 17).[71]

Recently Fadel *et al.*[72] described that the three-component reaction of *N*-Boc-3-piperidinone **72**, (*S*)-α-MBA (χ = H) and trimethyl phosphite in the presence of AcOH and anhydrous $MgSO_4$ at 50 °C, gave the α-aminophosphonates (*R*,*S*)-**73a** and (*S*,*S*)-**74a** in 75% yield and 60:40 dr. Similar results were obtained when (*S*)-α-methoxymethylbenzylamine (χ = OMe) was used, obtaining the α-aminophosphonates (*R*,*S*)-**73b** and (*S*,*S*)-**74b** (Scheme 18).

Cleavage of the *N*-Boc protecting group in **73a**/**74a** with TFA at room temperature followed by chromatographic separation and hydrogenolysis over $Pd(OH)_2$ of each diastereoisomer, gave the phosphonates (*R*)-**75** and (*S*)-**75** in good yield, which by hydrolysis with aqueous HCl solution followed by treatment with propylene oxide provided the enantiomerically pure α,β-diaminophosphonic acids (*R*)-**76** and (*S*)-**76** in quantitative yield (Scheme 19).[73]

On the other hand, three component reaction of several aliphatic aldehydes with (*R*)-2-phenylglycinol and dimethyl phosphite in the presence of 5 M LPDE, afforded the α-aminophosphonates (*R,R*)-**25** and (*S,R*)-**26** in excellent yield and good diastereoselectivity, predominating the diastereoisomer (*R,R*)-**25** (Table 7, entries 1-3).[63] In a similar way, reaction of aromatic aldehydes, methoxymethyl ether of (*S*)-2-phenylglycinol or (*S*)-1-methoxy-3-methyl-2-butylamine and diethyl phosphite in the presence of catalytic amount of ytterbium triflate (10% mol) and anhydrous $MgSO_4$ at room temperature, gave the α-aminophosphonates (*S,S*)-**25** and (*R,S*)-**26** in good yield and moderate diastereoselectivity in favor of diastereoisomer (*S,S*)-**25** (Table 7, entries 4-7).[67]

The high diasteroselectivity obtained using (*R*)-2-phenylglycinol has been explained on the basis of the aza analogue of the Anh-Eisenstein hypothesis,[74] where the nucleophilic attack on the imine **77** should take place antiperiplanar to the phenyl group to give the diastereoisomer (*S,R*)-**25** as principal product.[63] Whereas, the addition of diethyl phosphite to the imines derived from methoxymethyl ether of (*S*)-2-phenylglycinol or (*S*)-1-methoxy-3-methyl-2-butylamine in the presence of catalytic amount of ytterbium triflate, the authors suggest the model **78** transition state in which the $Yb(OTf)_3$ is chelated by the nitrogen and the methoxy group, and the nucleophilic attack on the imine should take place antiperiplanar to the α-*i*-Bu group (Figure 9).[67]

Very recently Kapoor *et al.*[75] reported the synthesis of α-aminophosphonates **79a-e** from (*S*)-phenylglycine and (*S*)-phenylalanine. In this context, reaction of aryl aldehydes with amino acid esters and dimethyl phosphite in the presence of antimony trichloride adsorbed on alumina as an efficient and recyclable catalyst, gave the mixture of α-aminophosphonates **79a-e** in moderated yield and diastereoisomeric ratio (Scheme 20).

Houghten *et al.*[76] have reported the preparation of α-aminophosphonates bearing peptides under three components reaction. In this context, reaction of aldehyde, resin-bound peptides **80** and dimethyl phosphite in the presence of catalytic amount of $BF_3.Et_2O$ (10% mol) gave the α-aminophosphonates **81a-n**, which by hydrolysis with HF and anisole gave the α-aminoalkyl phosphonopeptides **82a-n**. The results are showed in the Table 8.

Three-component reaction of chiral amides **83a-b** with aldehydes and dimethyl phosphite in the presence of acetyl chloride at 0 °C, afforded the α-aminophosphonates **84a-d** in moderate yield and excellent diastereoselectivity,[77] which is consistent with frontside attack of the phosphorous nucleophile on the *s-cis/E* conformation of the *N*-acylimine intermediate (Scheme 21). Hydrolysis of **84a** gave the (*S*)-phosphophenylglycine **8**.[78]

On the other hand, reaction of chiral hypophosphorous acid salt **85** obtained by addition of (*S*)-α-MBA to anhydrous hypophosphorous acid, with aldehydes at reflux in ethanol gave the corresponding *N*-protected α-aminophosphonous acids **86a-e** as a single diastereoisomer, which by treatment with bromine-water solution at 70 °C followed by addition of propylene oxide afforded the (*R*)-α-aminophosphonic acids **8** (Scheme 22). (*S*)-α-Aminophosphonic acids **8** were obtained using (*R*)-α-MBA.[79]

2.1.2. Addition of alkyl phosphites to imines derived from chiral aldehydes and ketones—In order to obtain diasteroisomeric pure phosphotreonine **89**, Bongini *et al.*

[80]reported that the nucleophilic addition of trimethylsilyldiethyl phosphite to the imine (*S*)-**87** readily obtained by condensation of (*S*)-2-triisopropylsilyoxy lactaldehyde with *N*-trimethylsilylamine, provided the β-silyloxy-β-aminophosphonate (*S*,*S*)-**88** in 85% yield and >98:2 *syn/anti* diastereoisomeric ratio. Acidic hydrolysis of (*S*,*S*)-**88** with 6 N HCl at reflux gave the phosphotreonine (*S*,*S*)-**89**. In a similar way, addition of trimethylsilyldiethyl phosphite to the imine (*R*)-**87**, followed by acidic hydrolysis afforded the (*R*,*R*)-phosphotreonine **89** (Scheme 23).

The high diasteroselectivity in the addition of trimethylsilyldiethyl phosphite to the imine (*S*)-**87** is characterized by two important features: (1) the α-silyloxy group induces high degree of *syn* diastereoselectivity, without chelating Lewis acid; (2) with increasing bulkiness of the silicon protecting group, an enhance of the *syn* diastereoselectivity was observed. Computational studies showed that a pentacoordinate silicon group may be involved in the determination of the diastereoselectivity of the reaction. It should be noted that the reaction proceeds at -78 °C, at this temperature the $(EtO)_2P\text{-}OSiMe_3$ tautomeric structure is stabilized and strongly promotes nucleophilic reactivity via a concerted [2 + 3] cycloaddition reaction (Figure 10).

Recently, Davis and Prasad reported[81] that the addition of potassium salt of diethyl- or dimethyl phosphite to enantiopure *O*-protected α-hydroxy sulfinimine (S_S,2*S*)-**90** readily obtained by condensation of (*S*)-*p*-toluenesulfinamide with the appropriate *O*-protected α-hydroxy aldehyde in the presence of $Ti(OEt)_4$, afforded the α-aminophosphonates (S_S,1*R*,2*S*)-**91a-d** in good yield and 94% de.[82] Low diastereoselectivity was obtained when the lithium or sodium salt of alkyl phosphites were used. Treatment of (S_S,1*R*,2*S*)-**91a-b** with tetrabutylamonium fluoride (TBAF) at 0 °C gave the β-hydroxy derivatives **92a-b** in 66-67% yield. Whereas, hydrolysis of (S_S,1*R*,2*S*)-**91a** with 3 N HCl at reflux led to α-amino-β-hydroxyphosphonate (1*R*,2*S*)-**93** in 72% yield, which by hydrolysis with 6 N HCl at reflux produced the α-amino-β-hydroxyphosphonic acid (1*R*,2*S*)-**94** in 61% yield (Scheme 24).

Addition of trimethyl phosphite to the oxime **95** readily obtained from condensation of *O*-benzyl hydroxylamine and 2,3,5-tri-*O*-benzyl D-arabinose,[83] afforded a mixture of D-gluco and D-manno isomers **96** and **97**, each consisting of a pair of two isomeric phosphonates (**a** and **b**). The cyclization into the phosphonates was spontaneous under these reaction conditions. Acetylation of **96a** gave the corresponding *N*-acetyl D-gluco derivative **98a**, whereas acetylation of the remaining mixture of isomers led to the other D-glucophosphonates **98b** and D-mannose analogues **99a-b**. Hydrolysis of methyl esters **98a-b** and **99a-b** and chromatographic separation followed by the hydrogenolysis of each isomer gave the *N*-acetyl-D-glucosamine phosphonate **100** and *N*-acetyl-D-mannosamine phosphonate **101** as free acids (Scheme 25).[84]

Nucleophilic addition of lithium salt of diethyl phosphite to nucleosyl imines **102** and **103** prepared from condensation of protected cytidine[85] and uridine,[86] respectively, with *p*methoxybenzylamine, for cytidine series gave the α-aminophosphonates **104** and **105** in 6:1 ratio, and for uridine series afforded **106** and **107** in 2:1 ratio. Oxidation of the *p*methoxybenzyl (PMB) protective group in the α-aminophosphonate **104** with DDQ followed by the hydrolysis of phosphono esters with TMSBr provided the α-aminophosphonic acid **108** directly in good yield. Presumably, HBr generated in situ from excess of TMSBr was sufficient to remove the TBS group. On the other hand, treatment of **106** under oxidative conditions with cerium amonium nitrate (CAN) to remove the PMB-protective group, followed by the hydrolysis of phosphono ester with TMSBr afforded the α-aminophosphonic acid **109** in good yield (Scheme 26).[87]

Addition of diethyl phosphite to *N*-benzyl nitrones derived from chiral α-alcoxy aldehydes has been a methodology used for the synthesis of polihydroxylated α-aminophosphonates. For example, Pollini *et al.*[88] reported that the nucleophilic addition of diethyl phosphite to *N*-benzyl nitrones **110a-c** readily obtained from D-glyceraldehyde, Ltreose and D-galactose, in the presence of *tert*-butyldimethylsilyl triflate (TBDMSOTf) afforded exclusively the *syn*-adducts **111a-c** in good yield, which by catalytic hydrogenation over $Pd(OH)_2/C$ in the presence of di(*tert*-butyl)dicarbonate $(Boc)_2O$ gave the α-*N*-Boc-aminophosphonates **112a-c** in moderated yield (Scheme 27).

The high diastereoselectivity obtained in the addition of diethyl phosphite to **110a** has been explained in terms of the two transition state structures **113** and **114**, in which the silicon atom of the trialkylsilyl group coordinates to both the nitrone oxygen atom and one of the oxygen atoms of the dioxolane ring (α-chelation) or (β-chelation), respectively (Figure 11). The formation of *anti* diastereoisomer suggests that the addition of diethyl phosphite occurs preferentially by the *si* face of the nitrone in the β-chelate model **114**.

On the other hand, treatment of TBDMSOTf-precomplexed nitrones **115a-c** with diethyl phosphite in THF at 20 °C, afforded the α,β-diaminophosphonates **116a-c** and **117a-c** in good yield and 95:5 dr. Catalytic hydrogenation of **116ac** over $Pd(OH)_2/C$ in the presence of $(Boc)_2O$ gave the *N*,*N*-diprotected α,β-diaminophosphonates **118a-c** in moderated yields (Scheme 28).[88]

In a similar way, treatment of *N*,*N*-diprotected α-amino nitrones **119a-d** with TBDMSOTf followed by nucleophilic addition of diethyl phosphite afforded exclusively the *syn* adducts **120a-d** in good yield. Catalytic hydrogenation of **120a-d** over $Pd(OH)_2/C$ in the presence of $(Boc)_2O$ provided the *N*,*N*-diprotected α,β-diaminophosphonates **121a-d** in moderated yield (Scheme 29).[88]

To explain the observed *syn*/*anti* stereoselectivity in the nucleophilic addition reaction of diethyl phosphite to the nitrones **115a-c** and **119a-d**, the authors have postulated two transition state structures **122** and **123** (Figure 12), in which the silicon atom of trialkylsilyl group coordinates to both the nitrone oxygen atom and the carbamate group. The difference between these conformations exists on the outside and inside positions of the medium-sized substituent. The addition of diethyl phosphite to *N*-monosubstituted derivatives **115a-c** should occur from the less-hindered side of the cyclic chelate **122** leading the *anti* products **116a-c**, whereas the addition to *N*,*N*-disubstituted α-nitrones **119a-d** should take place from the less-hindered side of the cyclic chelate **123** (*re* attack) to give exclusively the *syn* adducts **120a-d**.

2.1.3. Addition of chiral alkyl phosphites to nonchiral and chiral imines—The chiral auxiliary can be attached not only to the imine fragment but also to the phosphite residue. In this context, chiral C_3-symmetric trialkyl phosphites have been studied as starting reagents for the preparation of chiral organophosphorous compounds. For example, nucleophilic addition of tris[(1*R*,2*S*,5*R*)-menthyl] phosphite **125** readily obtained from reaction of (1*R*,2*S*,5*R*)-menthol with phopshorous trichloride, to the imine **124** in the presence of trimethylsilyl chloride afforded the α-aminophosphonates **126** in good yield and moderated diastereoselectivity (de = 50%). Hydrolysis of diastereoisomerically pure **126** with HCl in dioxane, followed by catalytic hydrogenolysis over Pd/C gave the (*R*)-phosphophenylglycine **8a** with ca. 95% ee (Scheme 30).[89]

Recently, Kolodiazhnyi *et al.*[90] reported that the addition of chiral dialkyl phosphites **127a-b** [R* = (1*R*,2*S*,5*R*)-menthyl and (1*S*)-*endo*-bornyl] to chiral imines derived from (*S*)-and (*R*)-α-MBA, is accompanied by a double asymmetric induction at the α-carbon atom. Thus, addition of **127a** to imine (*S*)-**5** at 80 °C gave the α-aminophosphonate (*R*,*S*)-**128** in 60% yield and 92%

de, whereas addition of **127a** to imine (*R*)-**5** led to α-aminophosphonate (*S*,*R*)-**128** in 50% yield and 50% de.[91] In a similar way, nucleophilic addition of chiral di-[(1*S*)-*endo*-bornyl] phosphite **127b** to (*S*)-**5** provided the α-aminophosphonate (*R*,*S*)-**129** in 60% yield and 86% de, whereas addition of **127b** to (*R*)-**5** afforded the α-aminophosphonate (*S*,*R*)-**129** in 70% yield and 60% de (Scheme 31). Hydrolysis of diastereoisomerically pure (*R*,*S*)-**128** and (*S*,*R*)-**128** with HCl in dioxane, followed by catalytic hydrogenolysis over Pd/C gave the (*S*)- and (*R*)-phosphophenylglycine **8a**, respectively.

On the other hand, addition of tris[(1*R*,2*S*,5*R*)-menth-2-yl] phosphite **125** to the imine **124** in the presence of $BF_3.OEt_2$ afforded the α-aminophosphonate **126** with 30% de. In a similar way, addition of **125** to imine (*S*)-**5** in the presence of $BF_3.OEt_2$ gave the α-aminophosphonate (*S*,*S*)-**130** with 70% de (Scheme 32).

It is noteworthy that the reaction of tris[(1*R*,2*S*,5*R*)-menthyl] phosphite **125** and di-[(1*R*,2*S*, 5*R*)-menthyl] phosphite **127a** with Schiff bases differ in steric results and led to the diastereoisomers with opposite absolute configuration at the α-carbon atom.

Reaction of chiral P-H spirophosphoranes **131** with longchain aldimines **132** is a methodology used for the synthesis of α-aminophosphonic acid amphiphiles **135** in both enantiopure forms.[92] In this context, reaction of aldimine **132** (R' = $C_{18}H_{37}$) with the spirophosphorane **131a** readily obtained from (*S*)-α-hydroxyisovaleric acid,[93] followed by the selective hydrolysis of **133** afforded the derivative **134a** with 15:85 dr. In a similar way, nucleophilic addition of spirophosphoranes **131b-d** obtained from tartaric acid esters, to the aldimines **132** (R' = $C_{18}H_{37}$, R' = $C_{16}H_{31}$, R' = $C_{12}H_{23}$) followed by the selective hydrolysis of **133** gave the derivatives **134b-f** with 55:45 dr in all cases. The lack of diastereoselectivity obtained for **134b-f**, compared with **134a**, might be due to the structural lability of spirophosphoranes **131b-f**. The absence of the carbonyl intracyclic group may also reduce the acidity and the reactivity of the P-H bond. Finally, acidic hydrolysis of diastereosiomerically pure **134a-f** afforded the α-aminophosphonic acid amphiphiles **135a-f** in both enantiopure forms (Scheme 33).

Since the chiral auxiliary might be easily removed by hydrolysis of the phosphonic ester, Martens *et al*.[94] carried out the addition of chiral BINOL-phosphite **136** to achiral 3-thiazolines **137a-e** in the presence of $BF_3.OEt_2$ obtaining tthe corresponding thiazolidinyl phosphonates **138a-e** in moderated yield and excellent diastereoselectivity. It is noteworthy that stereoselectivity of the BINOL-phosphite **136** seems to be independent of steric demands of the nearby substituents R. In contrast, the nature of more distant substituent R' of the *N*,*S*-acetalic carbon atom influences the diastereoselectivity to a larger extent (Table 9).[95]

Removal of the chiral auxiliary and cleavage of the *N*,*S*-acetal[94] might be performed by acidic hydrolysis as has benn described in the literature, thus maintaining the chiral information of the released α-aminophosphonic acid.

Swamy *et al*.[96] reported the utility of chiral cyclic chlorophosphites derived from BINOL as scaffolds for the onepot synthesis of α-aminophosphonates under solvent-free conditions. In this context, treatment of the chlorophosphite (*R*)-**139** with urethane and arylaldehydes at 80 °C, yielded the α-aminophosphonates **140a-c** in good yield and 60:40 dr, with the (*R*,*S*) diastereoisomers as principal products (Scheme 34).

In a similar way, reaction of (*R*)-**139** with benzylcarbamate and arylaldehydes, afforded the α-aminophosphonates **141a-d** and **142a-d** in good yield and diastereoisomeric ratios from 1.1:1 to 1.8:1, with the (*R*,*S*)-**141a-d** diastereoisomers as principal products (Scheme 35).[97]

On the other hand, treatment of diethyl (*R*,*R*)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate **143** readily prepared from diethyl L-tartrate and phosphorus trichloride, with

benzyl carbamate and arylaldehydes followed by the addition of H_2O, led to the α-aminophosphonates **144a-f** and **145a-f** in good yield, and diastereoisomeric ratios from 1.7:1 to 2.5:1, with the (*R*,*R*,*R*)-**144a-d** diastereoisomers as principal products. Saponification of diastereoisomerically pure **144a** and **145a** afforded the (*R*)- and (*S*)-*N*-Cbzphosphophenylglycine **146a**, respectively (Scheme 36).[97]

Using this Mannich type multicomponent reaction, Xu and Gao[98] prepared the depsiphosphonopeptides **148** and **149**, which are analogues of naturally occurring peptides. Thus, reaction of 1-carboethoxy phosphorodichloridites **147** with benzyl carbamate and benzaldehyde in anhydrous benzene, followed by the hydrolysis afforded the depsiphosphonopeptides **148** and **149** in 86% yield and 85:15 dr. Saponification of diastereoisomerically pure **148** and **149** followed by cleavage of Cbz protective group provided the enantiomerically pure (*S*)- and (*R*)-phosphophenylglycine **8**, respectively (Scheme 37).

2.1.4. Catalytic asymmetric addition of alkyl phosphites to non-chiral imines—

Catalytic enantioselective synthesis is one of the most important topics in modern synthetic chemistry because it provides the most efficient methodology to approach in the preparation of enantiomerically pure compounds.[99] In this context, Shibasaki *et al.*[100] reported the first catalytic hydrophosphonylation of imines. Thus, addition of dimethyl phosphite to imines **150a-f** in the presence of lanthanoid-potassium-BINOL complex [(*R*)-LPB] gave the (*R*)-α-aminophosphonates **151a-f** in moderated to high enantiomeric excess (Scheme 38).

Another approach for the synthesis of chiral α-amino-phosphonates is the chiral Brønsted acid catalyzed enantioselective hydrophosphonylation of non chiralimines. For example, Akiyama *et al.*[101] reported that hydrophosphonylation of imines **152a-k** catalyzed by the cyclic phosphoric acid **153**, derived from (*R*)-BINOL, afforded the (*S*)-α-aminophosphonates **154a-k** in good yield and enantioselectivity (Scheme 39).

To explain the high chiral induction, the authors propose a nine-membered transition state (Figure 13), wherein phosphonic acid (*R*)-**153** plays two roles: (1) the phosphonic acid hydrogen activates the imine as a Brønsted acid, and (2) phosphoryl oxygen activates the nucleophile by coordinating with the hydrogen of the phosphite as a Brønsted base, thereby promoting *re* facial attack to the imine and increasing the enantioselectivity by proximity effect.

On the other hand, Joly and Jacobsen[102] found that the nucleophilic addition of di(*o*-nitrobenzyl) phosphite to *N*-benzyl imines **124a-r** in the presence of chiral urea **155** as catalyst, gave the (*R*)-α-aminophosphonates **156a-r** in excellent both yield and enantioselectivity. Hydrogenolysis of **156a**, **156b** and **156f** afforded the enantiomerically enriched (*R*)-α-aminophosphonic acids **8** (Scheme 40).

Recently, Katsuki *et al.*[103] reported that the asymmetric hydrophosphonylation of aromatic aldimines **157a-h** bearing 4-methoxy-3-methylphenyl group as *N*-protecting group in the presence of complex (*R*)-Al(salalen) **158** as catalyst, gave the (*R*)-α-aminophosphonates **159a-h** in excellent yield and good enantioselectivity. When the imine carried an electron-withdrawing *p*-substituent, the enantioselectivity was improved up to 95% ee; however, the presence of an electron-donating *p*-substituent decreased to 85% ee (Scheme 41).[104]

One-pot hydrophosphonylation of aldehydes, 4-methoxy-3-methylaniline or diphenylmethylamine and dimethyl phosphite in the presence of complex (*R*)-Al(salalen) **158** as catalyst, afforded the (*R*)-α-aminophosphonates **160a-f** in good enantioselectivity (Scheme 42).[103,105]

On the other hand, addition of diethyl phosphite to *N*-Boc protected imines **161a-i** at 20 °C in the presence of quinine **162** as chiral catalyst, provided the (*R*)-α-aminophosphonates **163a-i**

in moderated yield and enantioselectivity. An enhanced in the enantioselectivity was observed when the reaction was carried out at -20 °C (Scheme 43).[106]

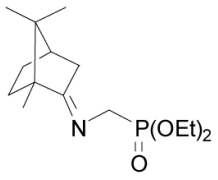
To explain the high chiral induction, the authors proposed that the imine is activated by a hydrogen bonding with the acidic hydroxyl group in the quinine, and that the phosphite-phosphonate equilibrium toward the phosphite form could attack to the eletrophilic azomethine carbon (Figure 14).[106]

In 1998 Shibasaki *et al.*[107] described for the first time the catalytic and enantioselective hydrophosphonylation of cyclic imines. In this context, nucleophilic addition of dimethyl phosphite to thiazolines **137** catalyzed by (*R*)-YbPB **164**, afforded the corresponding 4-thiazolidinyl phosphonates (*S*)-**165a-e** in good yield and enantiomeric excess (Scheme 44).

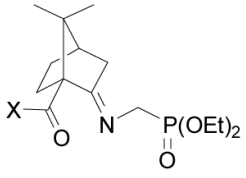
In a similar way, enantioselective hydrophosphonylation of cyclic imines **137** using cyclic phosphites, catalyzed by (*S*)-YbPB **164**, provided the 4-thiazolidinyl phosphonates (*R*)-**166a-g** in excellent enantiomeric excess and high chemical yields (Table 10).[108]

2.2. Stereoselective C-C bond formation

2.2.1. Alkylation of phosphoglycine derivatives—The chiral Schiff bases formed from esters of glycine and chiral carbonyl compounds are one of the most popular approaches for the asymmetric synthesis of α-amino acids.[109] In a similar way, the chiral Schiff bases prepared from phosphoglycine have been also used in the asymmetric synthesis of α-aminophosphonic acids. For example, the Schiff base **167** derived from (*R*)-camphor and phosphoglycine diethyl ester was used by Schöllkopf[110] for the asymmetric synthesis of α-aminophosphonic acids. On the other hand, the Schiff base **168** derived from (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one and phosphoglycine diethyl ester has been used by Roumestant *et al.*[111] for the stereoselective synthesis of α-aminophosphonic acids. Jommi *et al.*[112] reported that the chiral Schiff base **169** obtained from condensation of (+)-ketopinic acid and phosphoglycine diethyl ester is an important compound for the asymmetric synthesis of α-aminophosphonic acids. Alkylation of the oxazolidine **170** derived from (*R*)-phenylglycinol has been also used in the enantioselective synthesis of α-aminoalkylphosphonic acids.[113]



167



X = OH, *i*-PrNH, 3-HOC_6H_4NH

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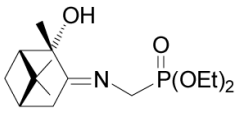
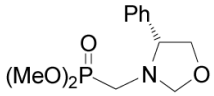


168



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In 1990 Hanessian and Bennani[114] reported the enantio-selective synthesis of α-aminoalkylphosphonic acids (*R*)-**8** via the diastereoselective alkylation of bicyclic phosphono-amide **172** which was easily prepared from (*R*,*R*)-diamine **171** (Scheme 45).

Recently, Cheng-Ye and Qian-Yi[115] reported a facile and efficient asymmetric synthesis of α-aminophosphonic acids (*R*)-**8** via the diastereoselective alkylation of bicyclic phosphonoamide **175**. Thus, treatment of (2*S*,5*S*)-**175** readily obtained from (2*S*,5*S*)-**174**

derived from (*S*)-2-anilinomethylpyrrolidine, with *n*-BuLi in THF at -78 °C followed by the addition of alkyl halide, afforded the alkylated products **176a-f** in moderated yield and with moderated to excellent diastereoselectivity (43-99%). Acidic hydrolysis of **176a-b** and **176e** gave the (*R*)-α-aminoalkylphosphonic acids **8** with excellent enantiomeric excess (Scheme 46).[116]

On the other hand, treatment of bicyclic chloromethylphosphonoamide (2*R*,5*S*)-**174** with lithium diisopropylamide (LDA) in THF at -78 °C followed by addition of alkyl iodide, afforded the alkylated products (2*R*,5*S*,9*S*)-**177a-g** in good yield (72-83%) and with low to good levels of diastereoselectivity (16-95% de). Nucleophilic displacement on chloro derivatives **177a-d** by the azide ion and subsequent treatment under Staudinger reaction[117] conditions, gave the α-aminophosphonoamides **178a-d** in good yield and diastereoselectivity (82-95% de). Acidic hydrolysis of **178a-d** led to (*R*)-α-aminophosphonic acids **8** (Scheme 47).[118,119]

Recently, Yokomatsu *et al.*[120] reported the diastereoselective synthesis of α-aminophosphonate **184** by a highly diastereoselective alkylation of phosphoglycine derivative (R_P)-**179**. In this context, treatment of (R_P)-**179** with LHMDS in THF at -78 °C followed by addition of benzyl bromide afforded the benzylated product (*R*,R_P)-**180** in 73% yield and 10:1 diastereoisomeric ratio,[121] which by hydrogenolysis over $Pd(OH)_2$/C and subsequent tosylation of free amine (*R*,R_P)-**181** gave the *N*-tosyl derivative (*R*,R_P)-**182** in 93% yield. Deprotection of ketal moiety in (*R*,R_P)-**182** with TMSCl and EtOH provided the compound (*R*,R_P)-**183** in 73% yield.[122] Finally, oxidation of (*R*,R_P)-**183** with DMSO and I_2 followed by the esterification with diazoethane led to enantiomerically pure (*R*)-α-aminophosphonate **184** in 37% yield (Scheme 48).

Recently, we have reported the first stereochemical reversal in the benzylation reaction of the phosphonoamide **185**[123] changing the LDA equivalents. In this context, the enolization of **185** with freshly LDA 2.0 equiv in THF at -78 °C, followed by the addition of benzyl bromide afforded the quaternary β-phosphonoamides (*R*,*S*)-**186** and (*S*,*S*)-**187** in 77% yield and 90:10 diastereoisomeric ratio, with predominance of (*R*,*S*)-**186**. Whereas, when the enolate of **185** was generated with LDA 2.5 equiv at -78 °C followed by the addition of benzyl bromide, gave also the quaternary β-phosphonoamides (*R*,*S*)-**186** and (*S*,*S*)-**187** in 83% yield and 20:80 dr, but now with a predominance of (*S*,*S*)-**187** (Scheme 49).[124] Quaternary β-phosphonoamides (*R*,*S*)-**186** and (*S*,*S*)-**187** could be transformed into quaternary α-aminophosphonic acids after several reactions including the Curtius rearrangement.[125]

Asymmetric Michael addition of diethyl (1-cyanoethyl)-phosphonate **188** to acrylaldehyde in the presence of $Rh(acac)(CO)_2$ and (*R*,*R*)-(*S*,*S*)-PhTRAP **189** in dry benzene, afforded the quaternary optically active (4-oxoalkyl)-phosphonate **190** in 80% yield and 92% ee, which by treatment with benzyltriphenylphosphonium ylide and subsequent hydrogenation of new formed carbon-carbon double bond led to cyano derivative **191** in 86% yield. Complete hydrolysis of **191** using 47% HBr followed by the esterification with diazomethane led to dimethyl ester **192** in 40% yield. Selective hydrolysis of carbomethoxy group in **192** and subsequent Curtius rearrangement[125] followed by the treatment with benzyl alcohol gave the quaternary α-aminophosphonate **193** in 81% yield (Scheme 50).[126]

On the other hand, asymmetric allylation of α-acetamido β-ketophosphonate **194** at -30°C with allyl acetates **195** using potassium *tert*-butoxide as base in the presence of 1 mol % of chiral catalyst prepared *in situ* from (*R*)-BINAP and $[Pd(\pi\text{-allyl})(cod)]BF_4$, afforded the α-allyl α-aminophosphonates **196a-e** in 78-87% ee. However, the allylation reaction of α-acetamido β-carbomethoxyphosphonate gave **196f** with only low enantioselectivity (Scheme 51).[127]

Recently, Jászay *et al.*[128] reported the synthesis of (*S*)-phosphoglutamic acid **200** via a catalytic enantioselective Michael addition. In this context, treatment of the achiral Schiff base **197** derived from phosphoglycine, with sodium *tert*-butoxide followed by the addition of *tert*-butyl acrylate in the presence of TADDOL **198**, produced the α-aminophosphonate **199** in 95% yield and 72% ee.[129] Acidic hydrolysis of **199** using 6 N HCl gave the (*S*)-phosphoglutamic acid[130] **200** (Scheme 52).

2.2.2. Nucleophilic addition to iminophosphonates—Catalytic enantioselective carbon-carbon bond-forming reactions have been used for the asymmetric synthesis of α-aminophosphonates. In this context, addition of silicon enolates **202a-k** derived from aromatic and aliphatic ketones, to *N*-acyl-α-iminophosphonate **201** catalyzed by the chiral copper(II) complex derived from $Cu(OTf)_2$ and diamine **203** in the presence of hexafluoroisopropyl alcohol (HFIP) at 0 °C, gave the γ-keto-α-aminophosphonates **204a-k** in good yield (70-88%) and enantioselectivity (76-94% ee), (Scheme 53).[131]

Treatment of **204g** and **204j** with concentrate HCl at reflux followed by recrystallization afforded the γ-keto-α-aminophosphonic acids **205g** and **205j**, respectively, with excellent enantioselectivity. Whereas, reaction of **204a** with zinc powder in acetic acid, followed by the hydrogenolysis over Pd/C in acetic acid and methanosulfonic acid provided the α-aminophosphonate **206** with good enantioselectivity (Scheme 54).

In a similar way, reaction of α-iminophosphonate **201** with the enamines **207** in the presence of $Cu(OTf)_2$ and chiral diamine **208** in dichloromethane at 0 °C followed by hydrolysis, provided the corresponding γ-keto-α-aminophosphonates **204** in good yield (66-82%) and enantioselectivity (76-93% ee), (Scheme 55).[132,133]

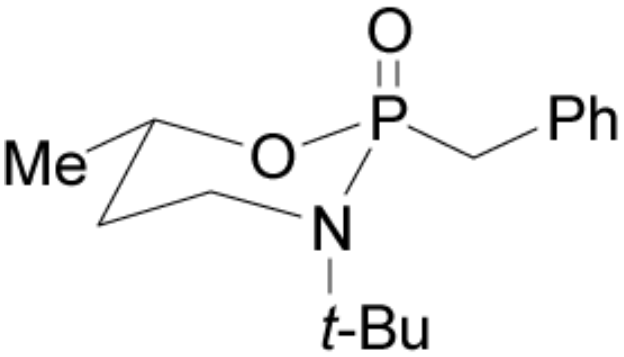
Kobayashi *et al.*[134] reported the first example of catalytic enantioselective allylations of α-iminophosphonates for the synthesis of α-allyl α-aminophosphonates **210**. In this context, allylation reaction of *N*-acyl-α-iminophosphonate **201** with the allylsilanes **209a-e** in the presence of $Cu(OTf)_2$ and the chiral diamine **203** in dichloromethane at 0 °C, led to the α-aminophosphonates **210** in good yield (66-86%) and enantioselectivity (79-89% ee), (Scheme 56).

Recently, Dodda and Zhao[135] reported the first enantioselective synthesis of α-aminopropargylphosphonates **214am** through the direct addition of terminal alkynes **212** to α-iminophosphonate **211** in the presence of a copper(I)-bisoxazoline **213** complex as chiral catalyst. In general, high yields (56-92%) and good levels of asymmetric induction (60-81% ee) were obtained (Scheme 57).

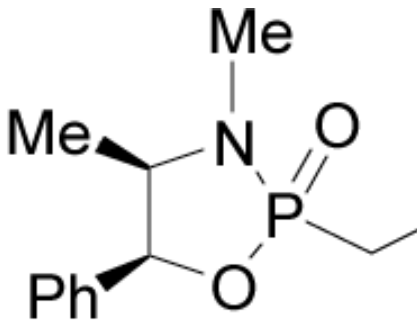
Carbon-carbon bond-forming via 1,3-dipolar cycloaddition reaction has been used for the synthesis of (*R*)- and (*S*)-phosphohomoserine **220**.[136] In this context, 1,3-dipolar cycloaddition of the nitrone (*S*)-**215** with allyl alcohol in the presence of $ZnCl_2$ or $MgBr_2$ gave the unseparable mixture of *cis*-isomers (3*S*,5*S*,1′*S*)-**216** and (3*R*,5*R*,1′*S*)-**217** in a 50:50 ratio.[137,138] Hydrogenation of diastereoisomerically pure (3*S*,5*S*,1′*S*)-**216** in the presence of $(Boc)_2O$ led to *N*Boc-aminodiol (1*S*,3*S*)-**218** in 75% yield, which by treatment with sodium metaperiodate followed by the reduction of aldehyde generated with $NaBH_4$ provided the corresponding alcohol (*S*)-**219**. Finally, acidic hydrolysis of (*S*)-**219** with 6 M HCl and subsequent treatment with propylene oxide afforded the enantiomerically pure (*S*)-phosphohomoserine **220** in 94% yield. In a similar fashion, diastereoisomerically pure (3*R*,5*R*,1′*S*)-**217** was transformed into (*R*)-phosphohomoserine **220** (Scheme 58).

2.3. Stereoselective C-N bond formation

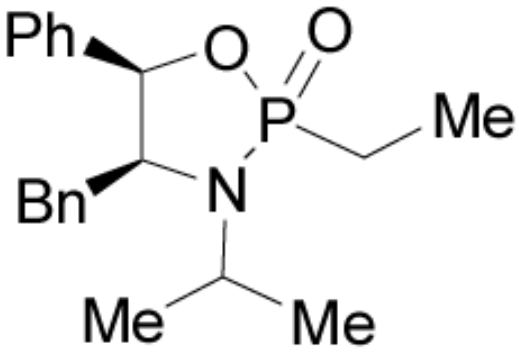
2.3.1. Stereoselective electrophilic amination—Other approach for the asymmetric synthesis of α-aminophosphonic acids is the stereoselective electrophilic amination of chiral α-phosphonates carbanions. In this context, several chiral oxazaphosphorinanes and oxazaphospholanes and diazophospholanes, derived from alkylphosphonic dichlorides and appropiated chiral amino alcohols or diamines, have been used as key substrates in the electrophilic amination. For example, Denmark *et al.*[139] reported the asymmetric synthesis of α-aminophosphonic acids from **221** via stereoselective electrophilic amination. On the other hand, chiral oxazaphospholanes **222**[140] and **223**[141] have been also used in the synthesis of α-aminophosphonic acids. Similar results have been obtained using the diazaphospholane **224**.[142]



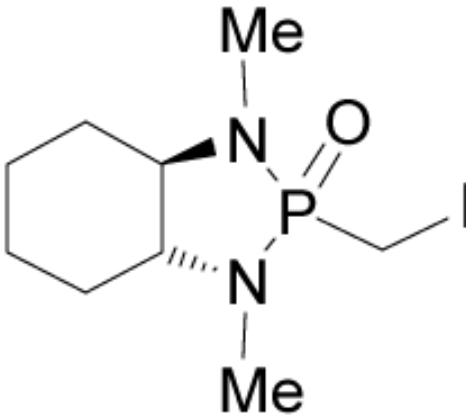
221



222



223



224

Recently, Jørgensen *et al.*[143] reported that the enantioselective α-amination of α-ketophosphonates **225** with dibenzyl azodicarboxylate in the presence of a catalyst formed by combination of chiral bisoxazoline **226** and $Zn(OTf)_2$, afforded the corresponding aminated products **227** in good yield (75-98%) and excellent enantioselectivity (85-95% ee) (Table 11).

Recently, Ruiz *et al.*[144] reported that the treatment of bislactim ether **228** with LDA in THF at -78 °C followed by the addition of trisyl-N_3, gave the phosphonates **229** and **230** derived from azidation by a complete retention of 2,5-*trans* configuration of the bis-lactim ether, and

the phosphonates **231** and **232** products of the racemization of bis-lactim **229** at position 2. The mixture of the phosphonates **229, 230, 231** and **232** was obtained in 80% yield and 7:7:1:1 ratio (Scheme 59).[145]

Mild acid hydrolysis of diastereoisomerically pure **229** with 0.25 N HCl provided the compound **233**, which by acid hydrolysis with 12 N HCl at reflux led to α-azidophosphonic acid **234**. Finally, catalytic hydrogenation of **234** over PtO_2 gave the α-aminophosphonic acid *syn*-**235** in 90% yield, an AP_4 derivative.[146] In a similar way, **230** was transformed into *anti*-**236** (Scheme 60).

2.3.2. Addition of amines to enaminophosphonates—Palacios *et al.*[147] reported that the addition of (*R*)-α-MBA (R = Me, R' = Ph) and ethyl (*S*)-valinate (R = CO_2Et, R' = *i*-Pr) to 1,2-diaza-1,3-butadiene **237** afforded the α-aminophosphonates **238** and **239**, respectively, in good yield but with very low diastereoselectivity (<10% ds), (Scheme 61). Similar results were obtained in the addition of non-chiral amines to **237**.

The same authors reported that the Michael addition of benzylamine to 1,2-diaza-1,3-butadiene **240** derived from L-lactic acid, gave the corresponding α-aminophosphonate **241** in 75% yield and 40% de. In a similar way, addition of (*S*)-valine methyl ester to **240** afforded the non-separable diastereoisomeric mixture **242** in 57% yield and moderated diastereoselectivity (Scheme 62).

Phosphonyl nitrosoalkenes are reactive intermediates as Michael aceptors toward nucleophilic reagents such as ammonia, amines and enantiomerically pure α-amino esters. For example, addition of L-valine ethyl ester hydrochloride to nitrosoalkene **243** afforded the α-aminophosphonate **244a** as nonseparable diastereoisomeric mixture in 82% yield and 28% de. In a similar way, Michael addition of L-phenylalanine methyl ester hydrochloride to **243** gave the α-aminophosphonate **244b** in 80% yield and 65% de. However, no diastereoselection was observed when L-proline methyl ester hydrochloride was added to **243**, and both diastereoisomers of **245** were obtained as an equimolecular mixture (Scheme 63).[148]

2.4. Stereoselective C-H bond formation

2.4.1. Catalytic hydrogenation of dehydroaminophosphonates—Catalytic asymmetric hydrogenation of dehydroaminophosphonates[149] type **246** is other methodology available for synthesis of optically pure α-aminophosphonic acids and derivatives. In this context, from 1985 to 1999 several catalyst have been used in the hydrogenation of **246** obtaining the α-aminophosphonates **247** in good yield and excellent levels of enantioselectivity (Scheme 64).[150]

In 2004, Imamoto *et al.*[151] described that the catalytic hydrogenation of dehydroaminophosphonate **248** in the presence of rhodium complex (*R*,*R*)-*t*-BuBisP* **249** gave the (*R*)-α-aminophosphonate **250** in 90% ee (Scheme 65).

Recently, Hu *et al.*[152] reported that the chiral phosphineaminophosphine (PEAphos) **252** readily obtained from (*S*)-MBA promoted an excellent enantioselectivities in the Rhcatalyzed asymmetric hydrogenation of dehydroaminophosphonates **251a-b**, and the corresponding (*S*)-α-amino-phosphonates **253a-b** were obtained in excellent yield and enantioselectivity (96% ee), (Scheme 66).

On the other hand, asymmetric hydrogenation of dehydroaminophosphonate **251b** in the presence of a rhodium complex derived of bis(phospholanes) **254** or BASPHOS **255**, gave the (*R*)-α-aminophosphonate **253b** in moderated enantioselectivity (20.8-78.8% ee), (Scheme 67).[153]

1-Amino-2,2,2-trifluoroethanephosphonic acid (*R*)-**260** has been obtained by a base-catalyzed [1,3]-proton shift reaction of diisobutyl 1-*N*-α-methylbenzylimino-2,2,2-trifluoroethanephosphonate **257**.[154] In this context, the reaction of chloroimine (*S*)-**256** with triisobutyl phosphite at 80 °C gave the (*S*)-α-iminophosphonate **257** in 79% yield, which by [1,3]-proton shift induced by triethylamine afforded the α-aminophosphonate (*R*)-**258** in 73% yield and 67% ee. Acidic hydrolysis of imine group in (*R*)-**258** with 2 N HCl produced the α-aminophosphonate (*R*)-**259** in 85% yield. Finally, treatment of (*R*)-**259** with concentrated hydro-chloric acid, followed by the addition of propylene oxide afforded the (*R*)-α-aminophosphonic acid **260** in 90% yield (Scheme 68).[155]

2.5. Resolutions

Optically active α-aminophosphonic acids can be also obtained by resolution. For example, reaction of dibenzoyl L-tartaric anhydride **261** with diphenyl α-aminophosphonates **262a-e** provided the amides **263a-e**. Hydrolysis of diastereoisomerically pure **263a-e** obtained by crystallization gave both enantiomers of (*S*)- and (*R*)-α-aminophosphonic acids **8** in high yields (Scheme 69).[156]

On the other hand, resolution of (±)-**264** on a 500 g-scale using simulated moving-bed chromathography on Chiracel OJ, gave the (*R*)-α-aminophosphonate **265** in 35% yield and 99% ee (Scheme 70).[157]

Biocatalytic resolution of racemic molecules has attracted the interest of synthetic chemists for several decades.[158] In this context, Yuan *et al.*[159] reported that CALB-catalyzed acylation of **266a-e** using ethyl acetate as acetylating reagent, produced the optically enriched **267a-e** and **268a-e** in good yield and enantioselectivity (Table 12).

2.6. Chiral pool

The hydroxy group in enantiomerically pure α-hydroxyalkylphosphonates can be replaced by an amino function using the Mitsunobu reaction.[160] For example, treatment of (*R*)-α-hydroxyphosphonates **269** under Mitsunobu conditions using triphenylphosphine (Ph_3P), diethyl azodicarboxylate (DEAD) and hydrazoic acid, afforded the (*S*)-α-azidophosphonates **270** with complete inversion of configuration.[161] Reduction of azido group in **270** under Staudinger reaction[117] with Ph_3P followed by the hydrolysis of the iminophosphoranes **271** gave the (*S*)-α-aminophosphonates **28** in good yield (50-88%) and enantioselectivity (40-82% ee) (Scheme 71).[162]

In a similar way, treatment of (*S*)-α-hydroxyphosphonates **272** (92-99% ee) with Ph_3P/DEAD/HN_3, gave the (*R*)-α-azidophosphonates **273** with good yield and 68-90% ee, which by reduction of azido group with Ph_3P followed by acidic hydrolysis led to the (*R*)-α-aminophosphonic acids **8** in 59-85% yield (Scheme 72).[163]

On the other hand, treatment of (*S*)-α-hydroxyphosphonates **274a-c** with Ph_3P/DEAD/HN_3 gave the (*R*)-α-azidophosphonates **275a-c** in 88-98% yield, which by reduction of azido group with PPh_3 led to the (*R*)-α-amino-phosphonates **276a-c** in 75-85% yield (Scheme 73).[164]

α-Amino-β-hydroxyphosphonic acids can be obtained from α,β-dihydroxyphosphonates via Mitsunobu azidation. For example, reaction of **277a-b** with Ph_3P/DEAD/HN_3 afforded the α-azidophosphonates **278a-b** in moderated yield, which by catalytic hydrogenation over Pd/C in the presence of $(Boc)_2O$ provided to the *N*-Boc-α-aminophosphonates **279a** and **279b** in 85 and 83% yield, respectively (Scheme 74).[165]

In a similar way, treatment of (1*S*,2*S*)-**280** with Ph_3P/DEAD and HN_3 led to α-azidophosphonate **281**, which by catalytic hydrogenation over PtO_2, followed by acidic

hydrolysis of **282** gave the (1*R*,2*S*)-phosphotreonine **283**. Under identical conditions (1*R*, 2*R*)-**280** was transformed into (1*S*,2*R*)-**283** (Scheme 75).[166]

On the other hand, reaction of (*S*)-**284** with *p*-nitrobenzenesulfonyl chloride furnished the corresponding nosylate (*S*)-**285** in 94% yield, which under Staudinger reaction gave the corresponding aziridine (*R*)-**286**. Regioselective opening of the aziridine (*R*)-**286** with TFA followed by acidic hydrolysis with hydrochloric acid and subsequent ion exchange, afforded the (*R*)-phosphoserine **287** in 59% yield (Scheme 76).[167]

Treatment of phosphoserine diethyl esther (*R*)-**288** with tosylchloride afforded the corresponding *N*-tosylate (*R*)-**289** in 74% yield, which by reaction with mesylchloride afforded the *O*-mesylate derivative (*R*)-**290** in 75% yield. Reaction of (*R*)-**290** with NaH in THF gave the aziridine-2-phosphonate (*R*)-**291** in 88% yield, which by reaction with several nucleophiles gave the α-aminophosphonates (*R*)-**292a-j** in 36-87% yield. In a similar way, the α-aminophosphonates (*S*)-**292a-j** were obtained from (*S*)-**288** (Scheme 77).[168]

On the other hand, reaction of phosphoserinate (*R*)-**288** with benzaldehyde followed by the reduction with sodium cyanoborohydride in acetic acid afforded the *N*-benzyl aminophosphonate (*R*)-**293** in 76% yield. Treatment of (*R*)-**293** with thionyl chloride and subsequent oxidation with sodium periodate in the presence of ruthenium chloride gave the sulfonamide (*R*)-**294** in 70% yield, which by reaction with several nucleophiles provided the α-aminophosphonates (*R*)-**295a-g**. In a similar way, (*S*)-**295a-g** were obtained from (*S*)-**288** (Scheme 78). [169]

Pousset and Larchevêque[170] reported that the catalytic hydrogenation of *N*-Boc-aziridine-2-phosphonates **297a-e** readily obtained from 3-amino-2-hydoxyphosphonates **296a-e** in 77-92% yield, furnished the *N*-Boc-α-aminophosphonates **298a-e** in moderated yield (5-77%) and high enantioselectivity (Scheme 79).

On the other hand, treatment of α-hydroxy phosphonate (1*R*,2*S*)-**299** with mesyl chloride in the presence of triethylamine followed by the addition of benzylamine gave the α,β-diaminophosphonate (1*S*,2*R*)-**301** in 72% yield. Transformation of (1*R*,2*S*)-**299** into (1*S*, 2*R*)-**301** with inversion of configuration takes place through the participation of the aziridium ion **300** (Scheme 80).[171]

Treatment of sulfate (*S*)-**302** readily obtained by reaction of (*S*)-1,2-propanediol, with dimethyl *t*-butoxycarbonylmethylphosphonate **303** and NaH gave the cyclopropane derivative **304** in 84% yield and 94% de. Acidic hydrolysis of **304** with formic acid afforded the carboxylic acid derivative **305** in 90% yield, which by treatment with thionyl chloride, followed by Curtius rearrangement using sodium azide and subsequent addition of benzyl alcohol, furnished the *N*-protected aminophosphonate **306** in 95% yield. Finally, hydrolysis of **306** with TMSI followed by treatment with propylene oxide led to enantiomerically pure (1*R*,2*R*)-1-amino-2-methylcyclopropanephosphonic acid **66** in 83% yield (Scheme 81).[172] The aminophosphonic acid **66** is an analogue of (1*S*,2*R*)-*allo*-norcoronamic acid.[173]

2.7. Stereoselective synthesis of azaheterocyclic phosphonic acids and derivatives

Azaheterocyclic phosphonates are considered as one of the most biologically important class of heterocyclic. In this context, in 2004 Stevens *et al.*[174] published a review about synthetic methods for azaheterocyclic phosphonates and their biological activity, and recently De Kimpe *et al.*[175] published other review on the synthesis and reactivity of C-heteroatoms-ubsituted aziridines, including C-phosphorus-substituted aziridines. Now we describe herein only some examples and an update over the stereoselective synthesis of azaheterocyclic phosphonic acids and derivatives.

2.7.1. Aziridin-2-ylphosphonic acids and derivatives—Palacios *et al.*[176,177] reported that the treatment of *O*-tosyl oximes **307a-c** with quinidine (QN) afforded the 2*H*-azirine-2-phosphonates **308a-c** in good yield (72-95%) and moderated enantioselectivity (24-72% ee). When (-)-sparteine, hydroquinidine or quinine were used as a base, **308a-c** were obtained with low enantioselectivity. Reduction of **308a-c** with $NaBH_4$ in ethanol gave the 2-phosphorylated *cis*-aziridines **309a-c** in 81-91% yield and with 20-65% ee (Scheme 82).

2.7.2. Azetidin-2-ylphosphonic acids and derivatives—Stereoselective synthesis of azetidin-2-ylphosphonates has been scarcely explored. The first asymmetric synthesis of azetidine-2-phosphonates of type **313**, **316** and **317** was reported by Couty *et al.*[178] In this context, treatment of aminophosphonate **310** derived from (*S*)-*N*-benzyl phenylglycinol,[179] with thionyl chloride in dichloromethane followed by the addition of $NaHCO_3$ gave the chloro derivative **311** in 92% yield. Reaction of **311** with LHMDS in THF afforded only the 1,3-*trans* azetidine **312** in 75% yield, which by hydrolysis of the phosphonate moiety with TMSBr followed by purification by ion-exchange chromatography led to azetidin-2-ylphosphonic acid **313** in 86% yield. In a similar way, aminophosphonates **314** and **315** derived from (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-*pseudo*-ephedrine, respectively, afforded the aminophosphonic acids **316** and **317** in good yield (Scheme 83).

2.7.3. Pyrrolidin-2-ylphosphonic acids and derivatives—Reaction of 2,5-dimethoxytetrahydrofurane **318** with (*R*)-phenylglycinol and benzotriazole (BtH) via a double Robinson-Schopf condensation,[180] afforded the bicyclic derivative (3*R*,5*S*,7a*S*)-**319** in 80% yield, which by an Michaelis-Arbuzov reaction with triethyl phosphite in the presence of $ZnCl_2$ gave the corresponding phosphonate (3*R*,5*S*,7a*S*)-**320** as a single diastereoisomer in 77% yield. Hydrogenolysis of **320** followed by acidic hydrolysis of phosphonate moiety with 6 M HCl and subsequent treatment with propylene oxide led to (*S*)-phosphoproline **321** in 89% yield (Scheme 84).[181]

On the other hand, treatment of (3*R*,5*S*,7a*S*)-**320** with *n*-BuLi followed by the addition of MeI afforded the methylated product (3*R*,5*S*,7a*S*)-**322** in 95% yield, high diastereoselectivity, and with retention of the configuration. Hydrogenolysis of **322** over Pd/H_2 gave the quaternary phosphorproline diethyl esther (*S*)-**323** in 83% yield (Scheme 85).[182]

Addition of trimethyl phosphite to the bicyclic lactam **324** readily obtained from (*R*)-phenylglycinol, in the presence of $TiCl_4$ gave the phosphonylated pyrrolidinone **325** in 86% yield and 62% de (Scheme 86).[183]

Treatment of chiral sulfinyl imines **326a-b** with lithium salt of diethyl phosphite gave the α-aminophosphonates **327a-b** in good yield and moderated diastereoselectivity. Cleavage of sulfinyl group and hydrolysis of acetal gave the aminocarbonyl derivative, which cyclized to afford the iminophosphonates **328a-b**. Finally, catalytic hydrogenation of **328a-b** led to the cyclic α-aminophosphonates **329a-b**. In a similar way, chiral sulfinyl mine **330** furnished to α-aminophosphonate (2*R*,5*S*)-**331** (Scheme 87).[184]

Davies *et al.*[185] reported the synthesis of *cis*-5-substituted pyrrolidine-2-phosphonates **339a-d** using metal carbenoid NH insertion. In this context, reaction of β-amino esters **332a-d** with lithium dimethyl methylphosphonate gave the corresponding δ-amino-β-ketophosphonates **333a-d**, which by treatment with TFA followed by the reaction with $(Boc)_2O$ afforded the derivatives **334a-d** in 80-90% yield. Reaction of **334a-d** with NaH and 4-acetamidobenzenesulfonyl azide (4-ABSA) furnished the diazo derivatives **335a-d** in excellent yield (83-91%), which by treatment with $Rh_2(OAc)_4$ led to the 3-oxo-pyrrolidine phosphonates **336a-d**. Removal of the 3-oxo group in **336a-d** by treatment with NaH followed by the addition of diethyl chlorophosphonate, and subsequent hydrogenation of **337ad** provided the cyclic

phosphonates **338a-d** in good yield. Finally, cleavage of Boc protective group in **338a-d** with TFA afforded the *cis*-5-substituted pyrrolidine 2-phosphonates **339a-d** in 68-86% yield (Scheme 88).[186]

Reaction of (2*R*,5*R*)-**336a** with NaH followed by the addition of allyl bromide[187] in the presence of 18-crown-6 gave the quaternary phosphonate (2*R*,5*R*)-**340** in 35% yield, which by treatment with TFA afforded the pyrrolidine phosphonate (2*R*,5*R*)-**341** in 76% yield as a single diastereoisomer, product derived from the retention of the configuration. Catalytic hydrogenation of **341** gave the acyclic α-amino-β-ketophosphonate (*R*)-**342** in 95% yield (Scheme 89).[188]

Reduction of L-pyroglutamic acid derivative **343** with super hydride in THF at -78 °C followed by acetylation and subsequent treatment with trimethyl phosphite in the presence of $BF_3.OEt_2$, gave the cyclic phosphonates **344** and **345** in moderated to good yield (45-80%) and diastereoselectivities from 1:1.5 to 1:1.9 (Scheme 90).[189]

Decarboxylation-phosphorylation reaction of α-amino acids afford α-aminophosphonates in good yield.[190] For example, treatment of (4*R*)-acetoxyproline derivative **346** with PhI $(OAc)_2$-I_2 under sunlight followed by the reaction with $(MeO)_3P$ in the presence of $BF_3.OEt_2$ afforded the α-aminophosphonates **347** and its epimer **348** in 64 and 15% yield, respectively (Scheme 91).[191]

A better result was obtained in the oxidative decarboxylation of **349**. In this context, anodic oxidation of **349** afforded a 1:1 mixture of **350** in 90% yield, which by treatment with trimethyl phosphite in the presence of $TiCl_4$, gave the cyclic phosphonate **351** in 80% yield and 96% de (Scheme 92).[192]

On the other hand, reaction of (3*S*,5*S*,1'*S*)-**216** with mesyl chloride in the presence of triethylamine gave the mesylated derivative (3*S*,5*S*,1'*S*)-**352** in 96% yield, which by hydrogenolysis followed by treatment of product obtained **353** with K_2CO_3 furnished (2*S*, 4*S*)-**354** in 75% yield. In a similar way, reaction of (3*R*,5*R*,1'*S*)-**217** gave (2*R*,4*R*)-**354** (Scheme 93).[137a]

On the other hand, addition of dimethyl or diethyl phosphite to the nitrone **355** at 40 °C gave the corresponding *N*-hydroxy phosphonates **356a-b** in quantitative yield. *O*,*N*Bis-deprotection in **356a-b** by hydrogenolysis over Pd/C in EtOH and aqueous 1 N HCl afforded the pyrrolidinephosphonates **357a-b** as hydrochlorides in 43 and 61% yield, respectively (Scheme 94).[193]

2.7.4. Piperidin-2-ylphosphonic acids and derivatives—Davis *et al.*[184] described the stereoselective synthesis of piperidin-2-yl-phosphonates **361a-b** from chiral sulfinyl imines **358a-b**. In this context, reaction of the imines **358ab** with lithium salt of diethyl phosphite afforded the α-aminophosphonates **359a-b** in good yield and excellent diastereoselectivity. Cleavage of sulfinyl group and acidic hydrolysis of ketal in **359a-b** gave the amino-carbonyl derivative, which by cyclization afforded the iminophosphonates **360a-b**. Finally, catalytic hydrogenation of **360a-b** led to cyclic α-aminophosphonates (2*R*,7*S*)-**361a** and (2*R*, 7*R*)-**361b** (Scheme 95).[194]

In a similar way, the cyclic α-aminophosphonate (2*R*,7*S*)-**363** was obtained in moderated yield and diastereoselectivity from chiral sulfinyl imine **362** (Scheme 96). [194]

3. Conlusion

In spite of the recognised relevance of the α-aminophosphonic acids it is obvious that there is a very important gap between the possibilities that offer these compounds in relationship with the corresponding counterparts, the α-amino acids. Nevertheless, during the last years these α-aminophosphonic acids are gaining importance step by step so, in this way, numerous papers have been published on their stereoselective synthesis. Authors of this report have covered all advances related to the synthesis of these important compounds and, although there is a long way to cover many of these procedures are already competitive in such a way that many of them can be applied to the synthesis on these compounds in enantiomerically pure form and in a multigram scale, being persuaded that all these efforts will contribute to the future advance in the interest of these important compounds.

Acknowledgments

This work was carried out with the financial support of CONACYT-MEXICO (Projects 62271) and financial support from the Ministerio de Educación y Ciencia-FEDER (project CTQ2007-62245) and Gobierno de Aragón (group E40 and project MI041/2007) is gratefully acknowledged. This project has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under contract number N01-CO-12400. The content of this publication does not necessarily reflect the view of the policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organization imply endorsement by the U.S. Government. This research was supported (in part) by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research. We thank to Ana Isabel Jiméenez and Victoria Labastida for their valuable help.

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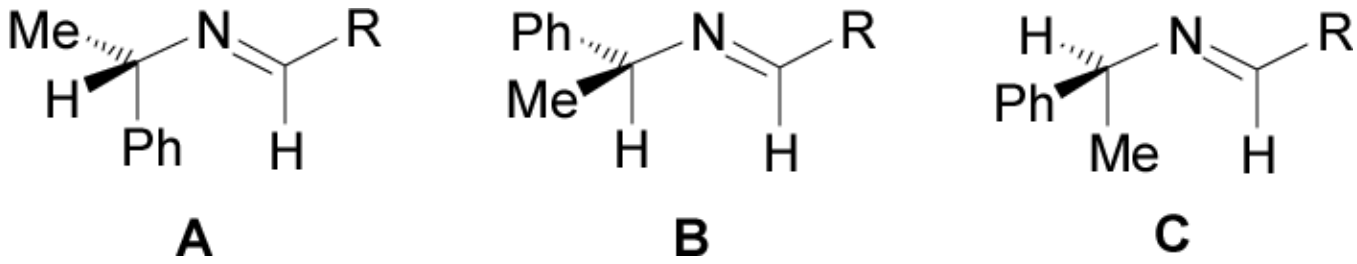


Figure 1.
Conformers for imine (*S*)-**5**.

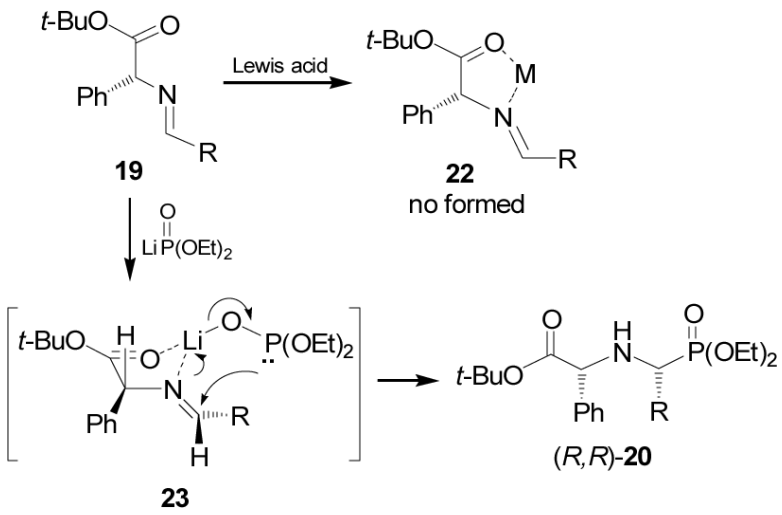


Figure 2.
Proposed of addition of $LiP(O)(OEt)_2$to **19**.

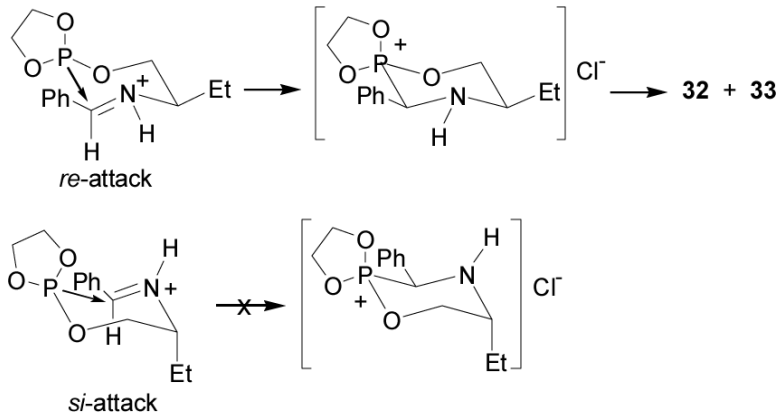


Figure 3.
Intramolecular cyclization of **31.**

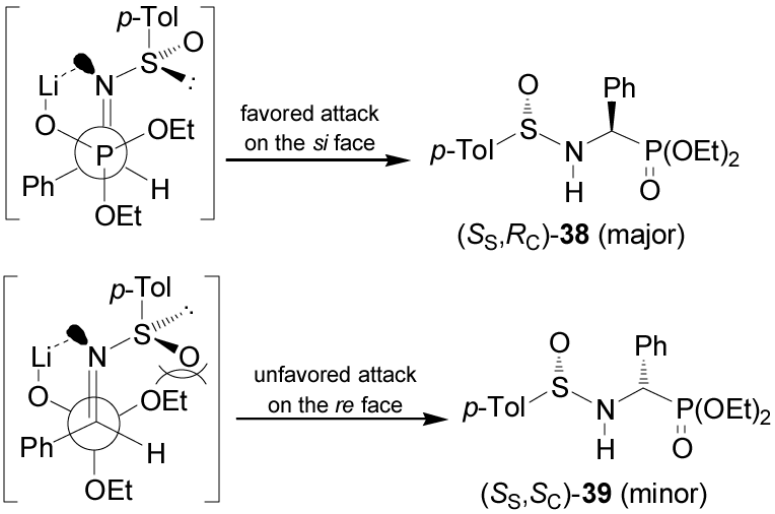


Figure 4.
Addition of $LiP(O)(OEt)_2$ to imine (*S*)-**37**.

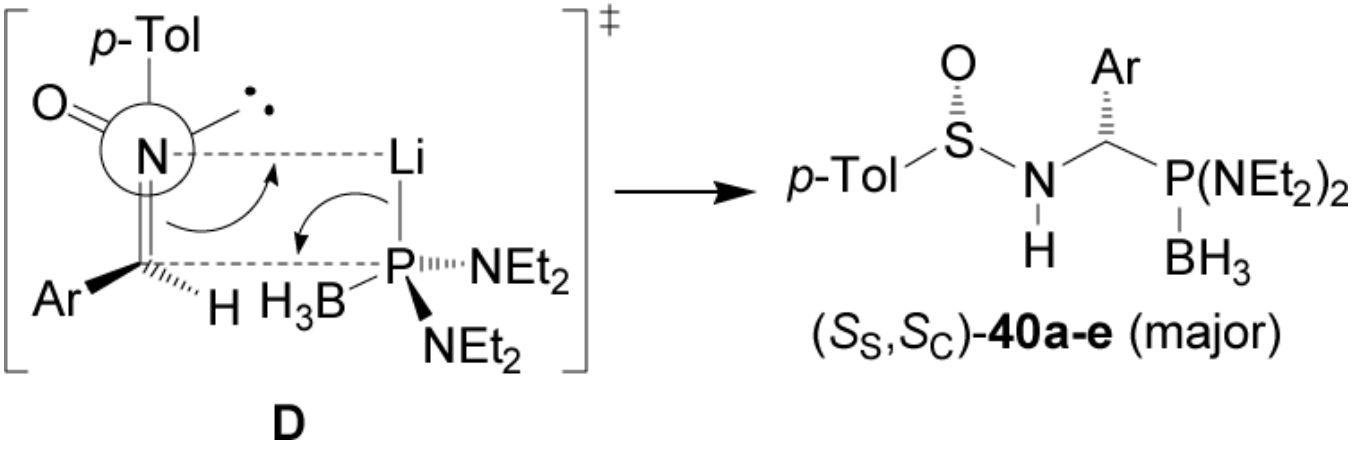


Figure 5.
Transition state for the formation of (S_S,S_C)-**40**.

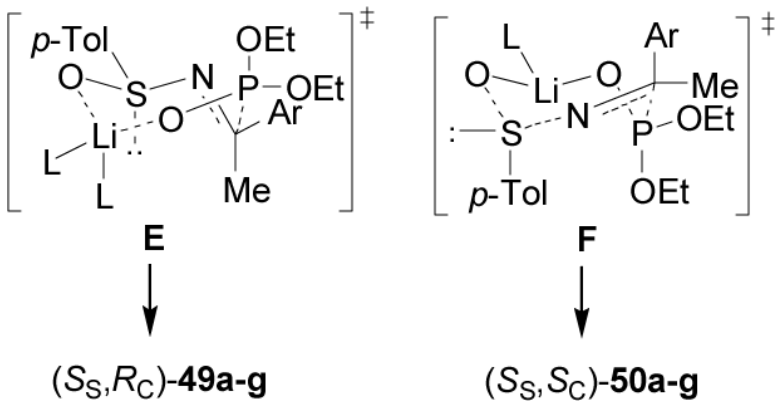


Figure 6.
Rationalization for the formation of (S_S,R_C)-**49a-g**.

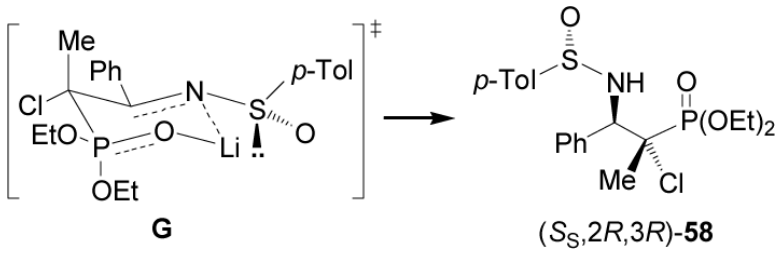


Figure 7.
Proposed predominant transition state for phosphonate addition to sulfinimine **37a.**

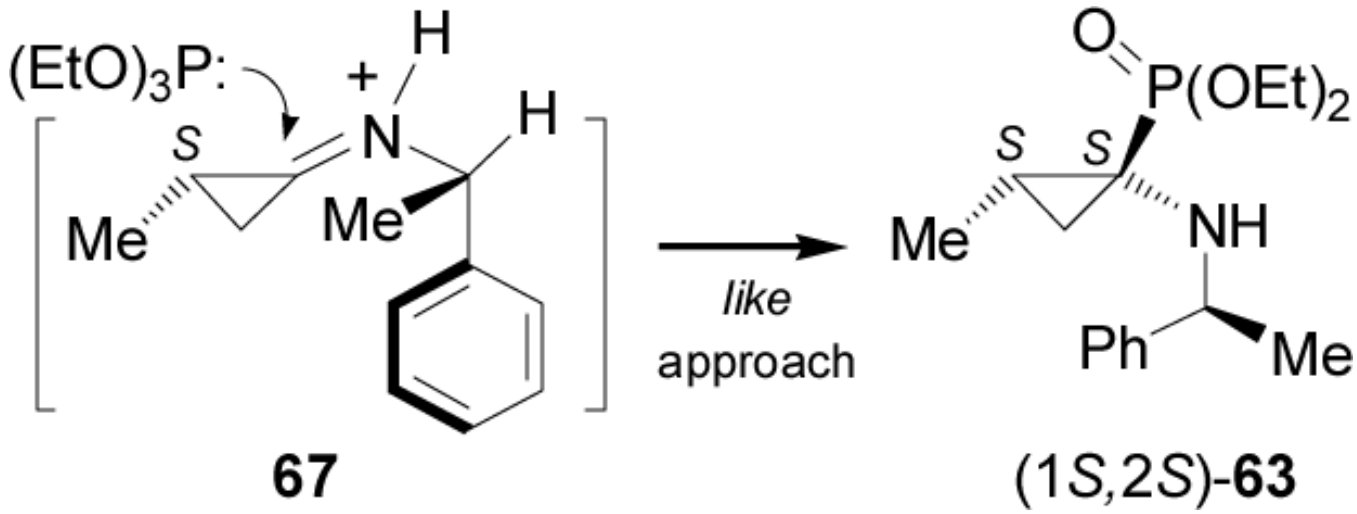


Figure 8.
Model proposed for addition of $(EtO)_3P$ to **67**.

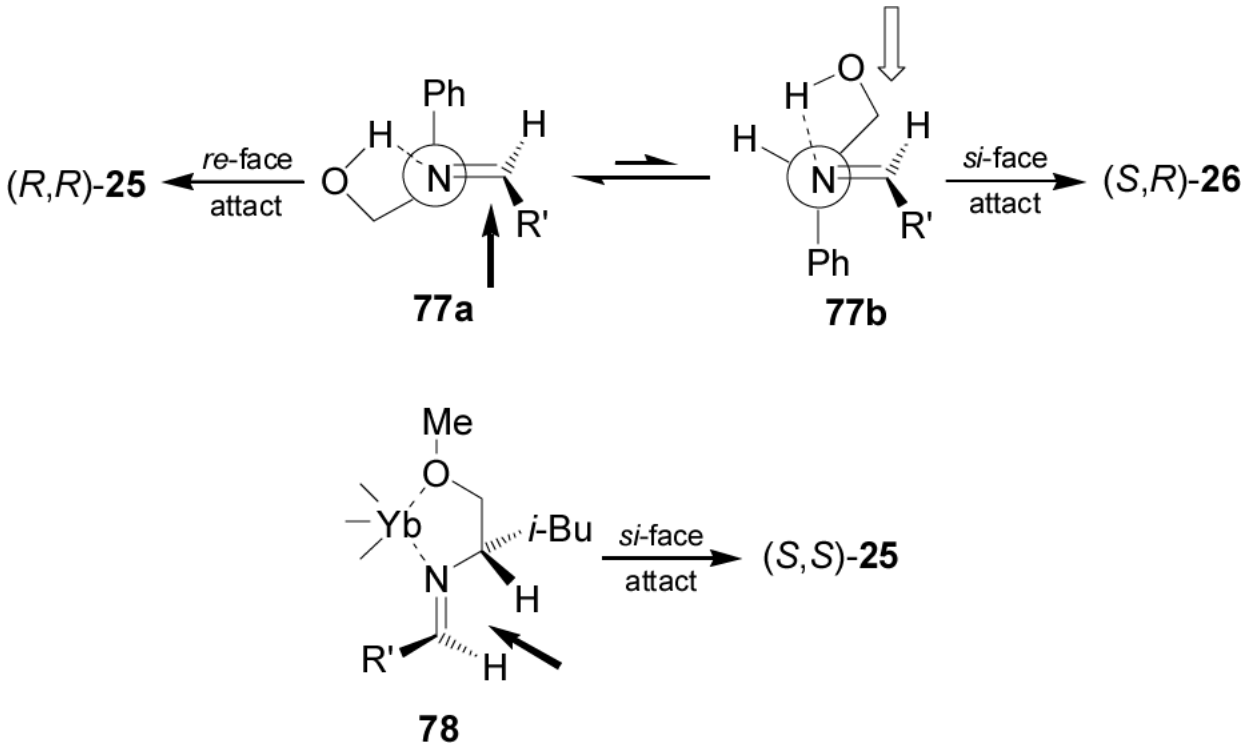


Figure 9.
transition state in the formation of **25** and **26**.

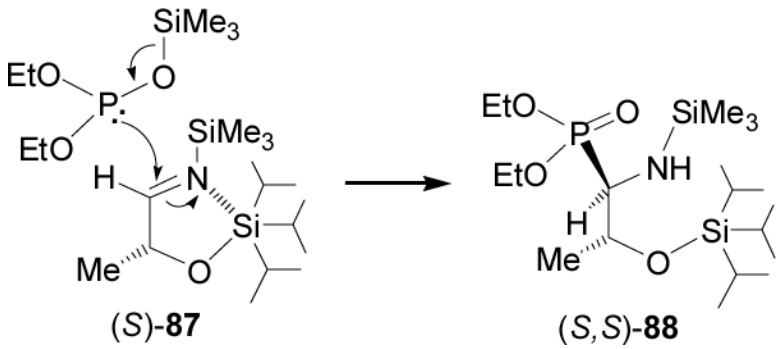


Figure 10.
Transition state prosed for addition of $(EtO)_2POSiMe_3$ to (*S*)-**87**.

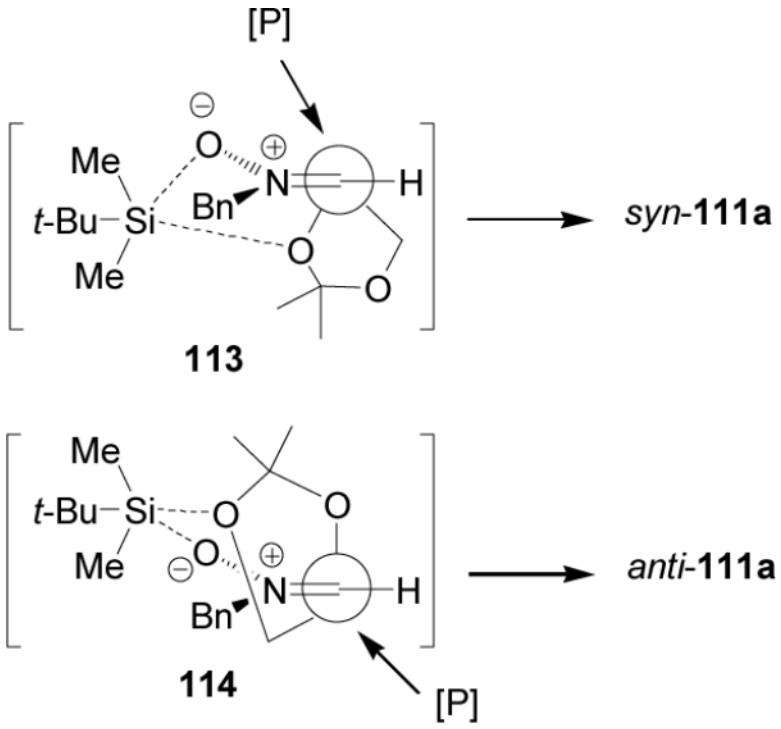


Figure 11.
Models for the addition of $HP(O)(OEt)_2$ to **110a**.

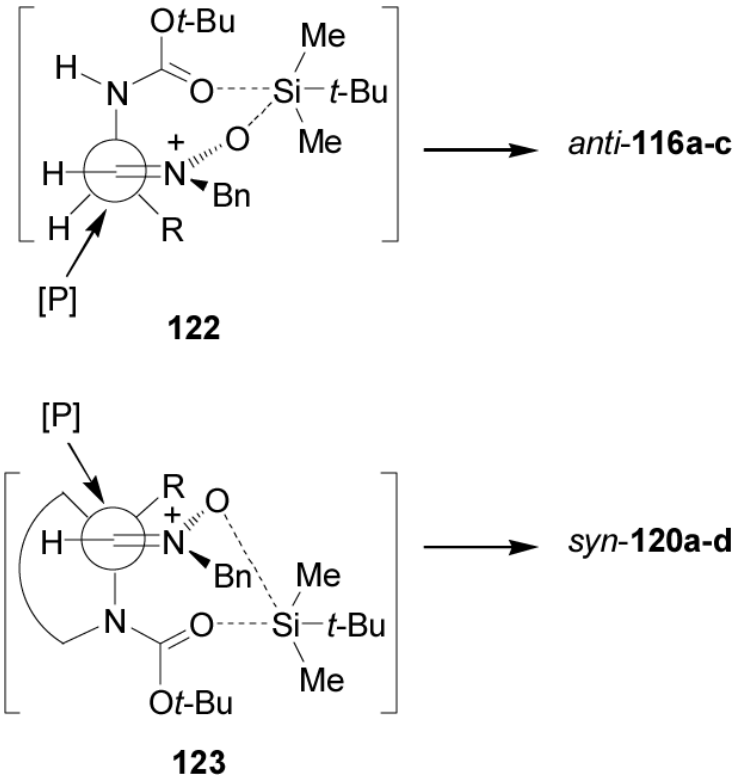


Figure 12.
Models for the addition of $HP(O)(OEt)_2$ to nitrones.

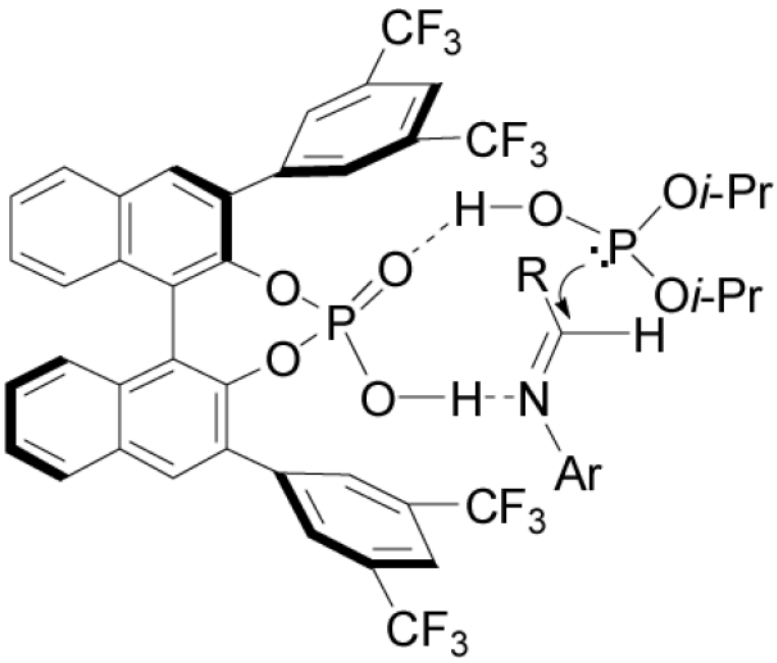


Figure 13.
Plausible reaction mechanism of **152a-k**.

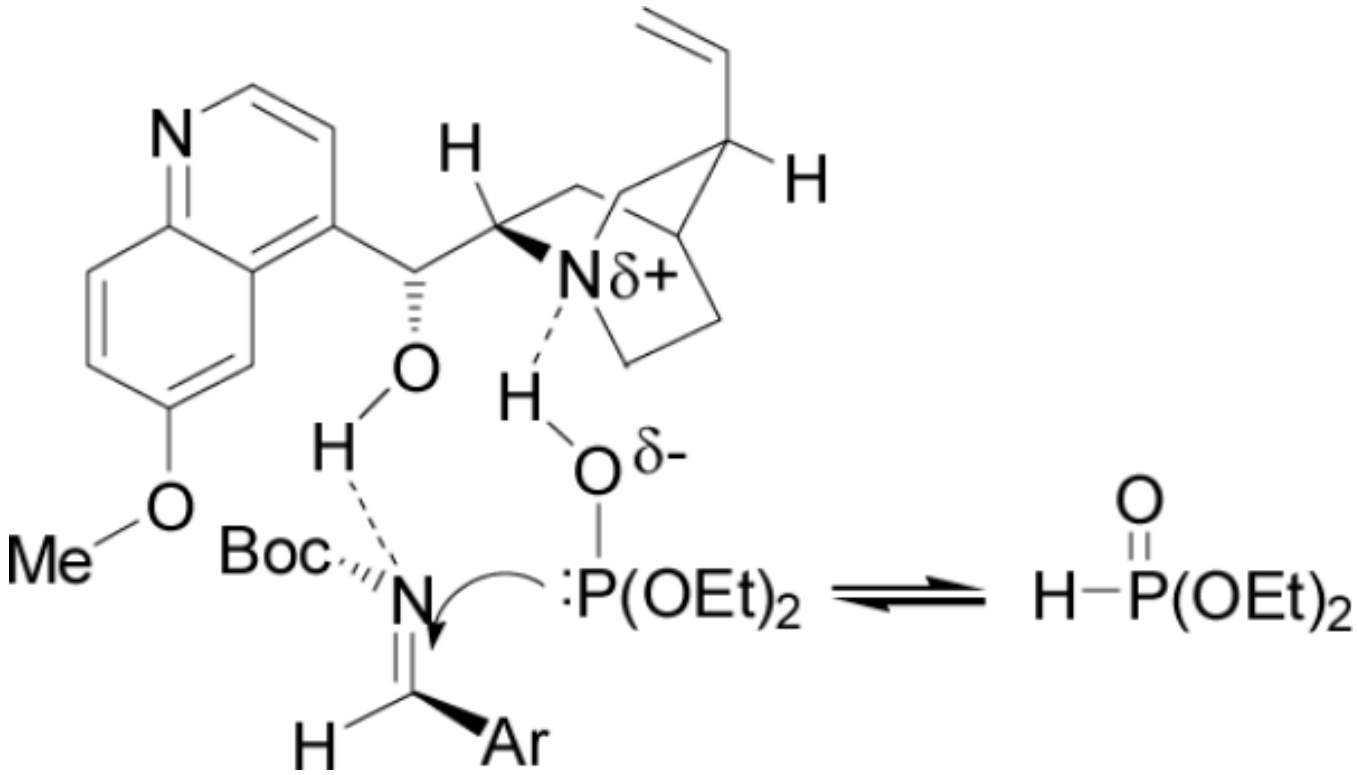
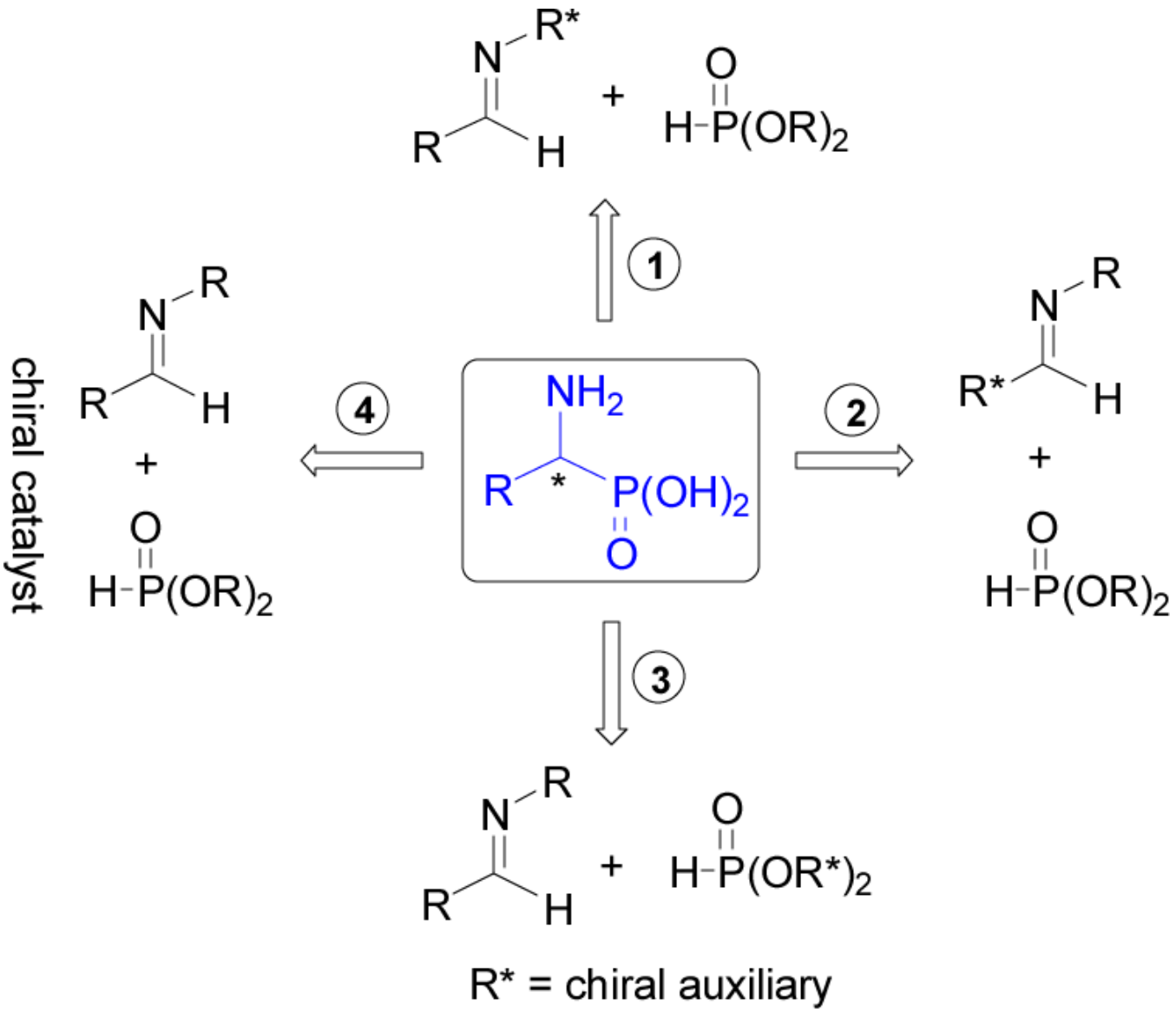
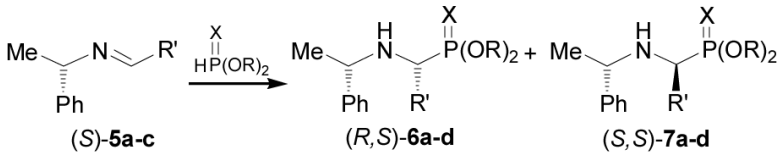


Figure 14.
Proposed mechanism for the addition of $(EtO)_2P(O)H$ to **161** catalyzed by quinine.



Scheme 1.

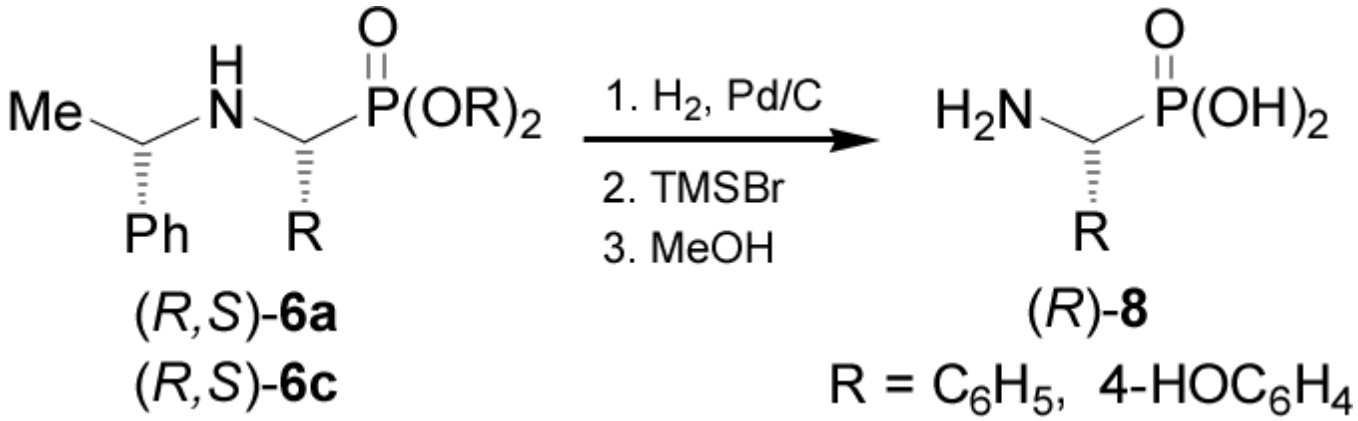


(*S*)-**5a-c** (*R,S*)-**6a-d** (*S,S*)-**7a-d**

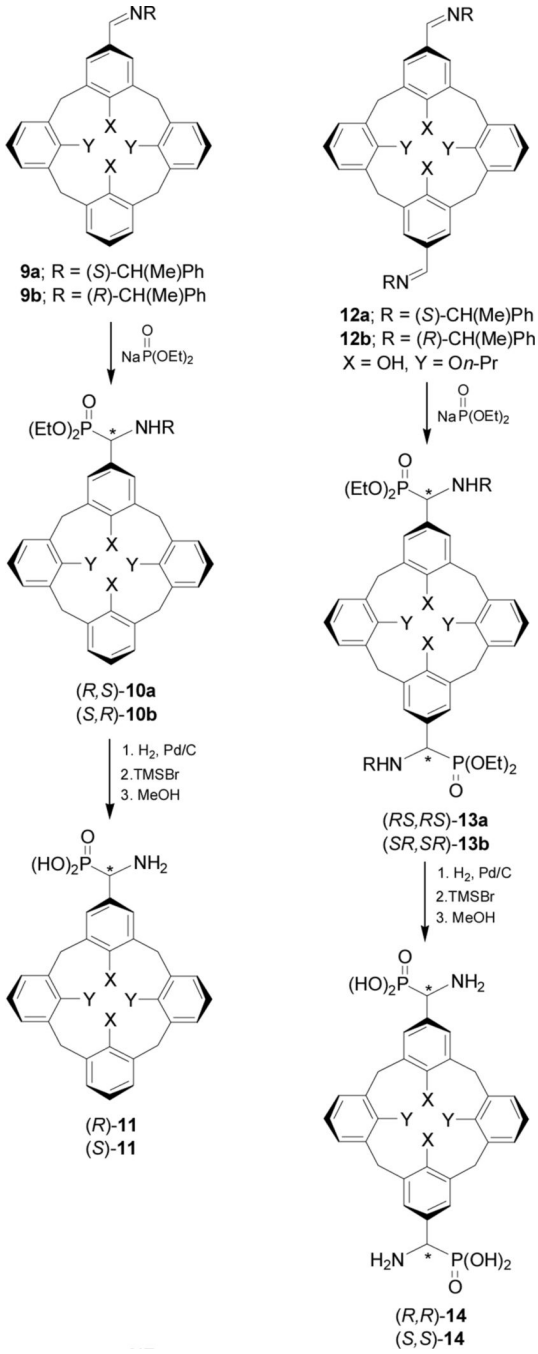
	R	X	R'	yield (%)	(*R*,*S*) : (*S*,*S*)
a	Et	O	C_6H_5	[a]	66 : 34
b	Et	O	*c*-Hexyl	77	83 : 17
c	Et	O	4-HOC_6H_4	98	97.5 : 2.5
d	Me	S	C_6H_5	64	76 : 24

[a]Yield was not reported

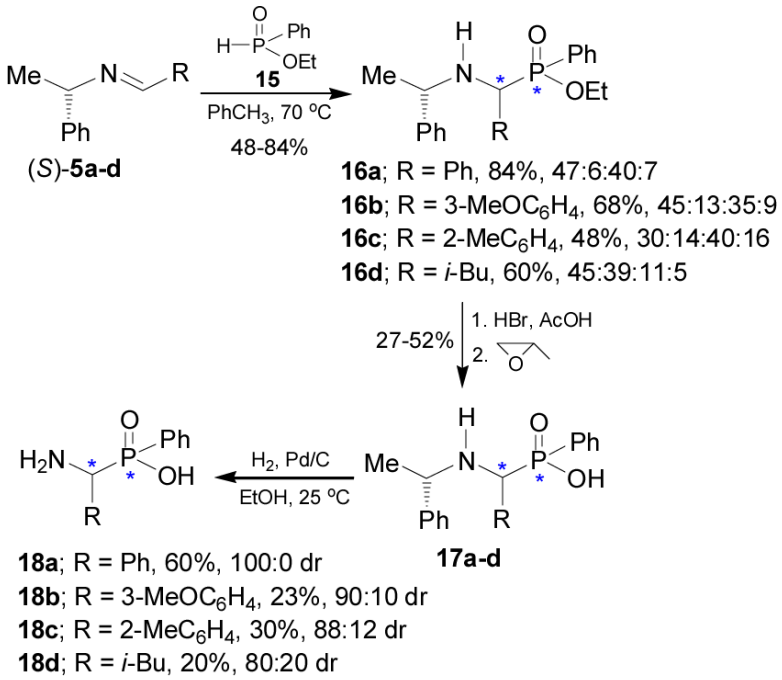
Scheme 2.



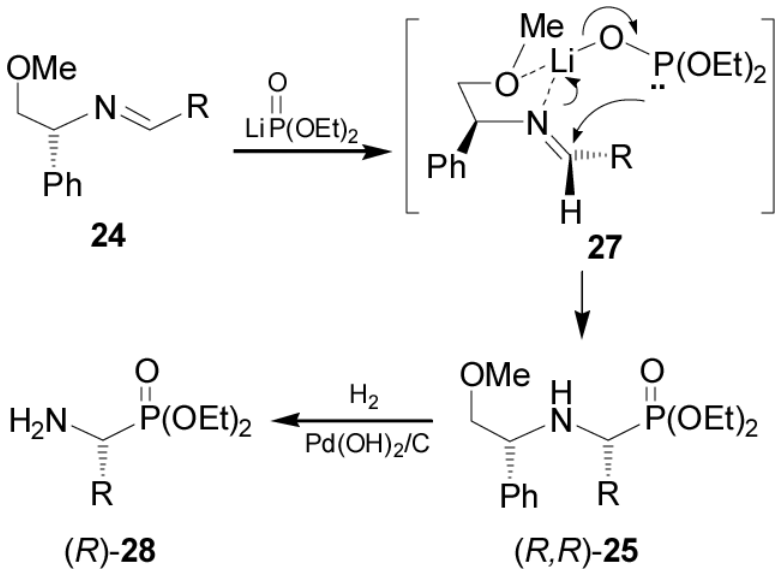
Scheme 3.



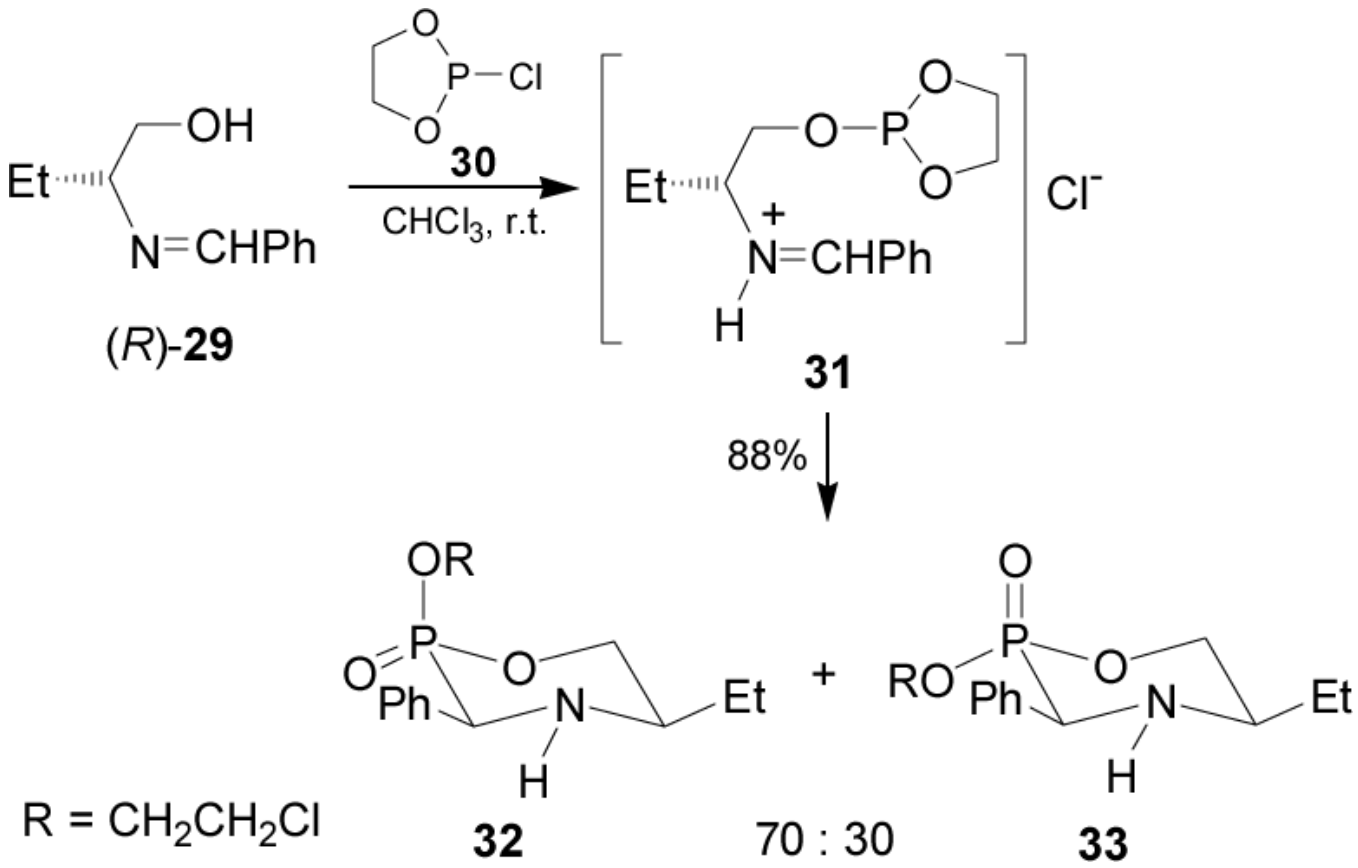
Scheme 4.



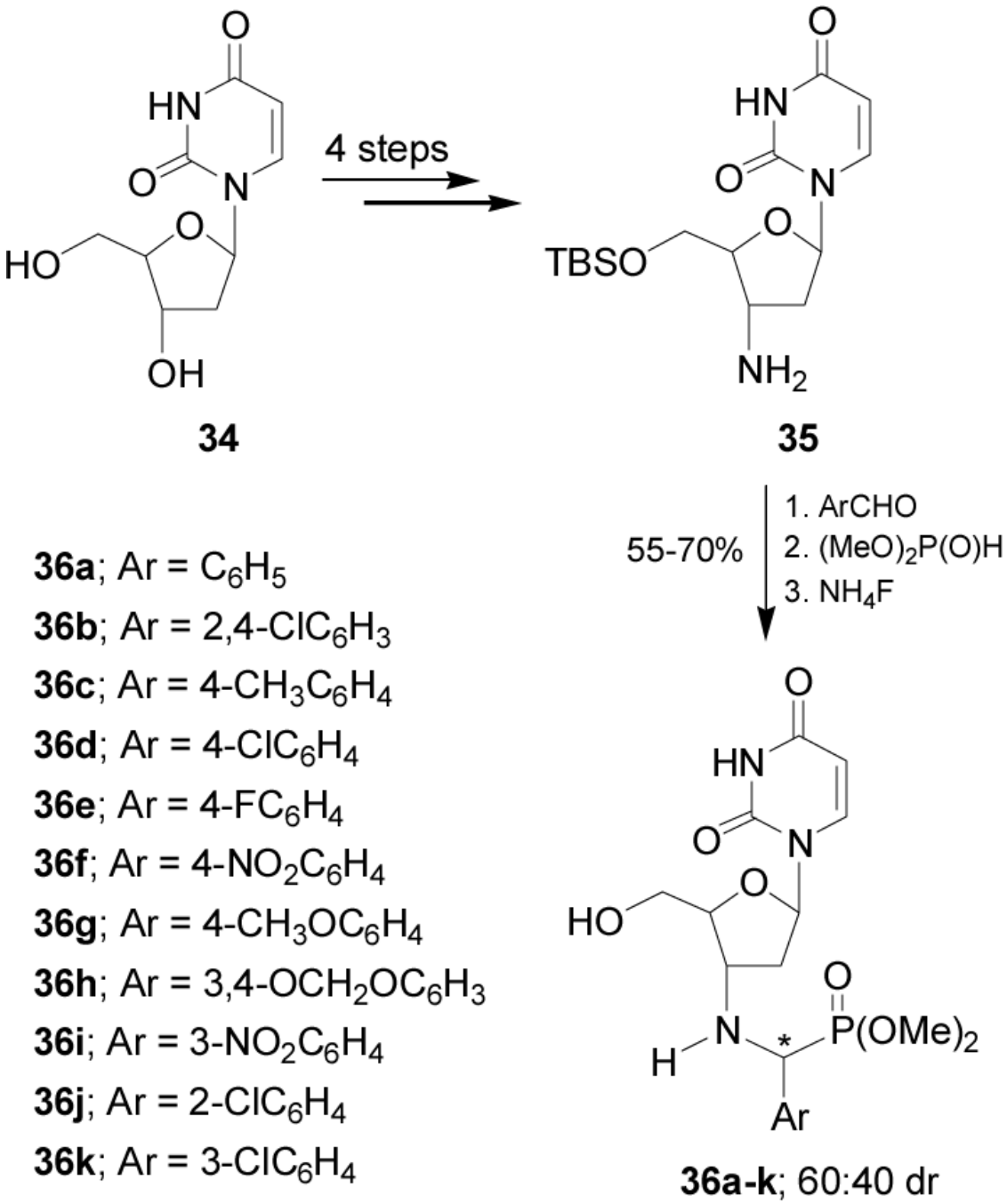
Scheme 5.



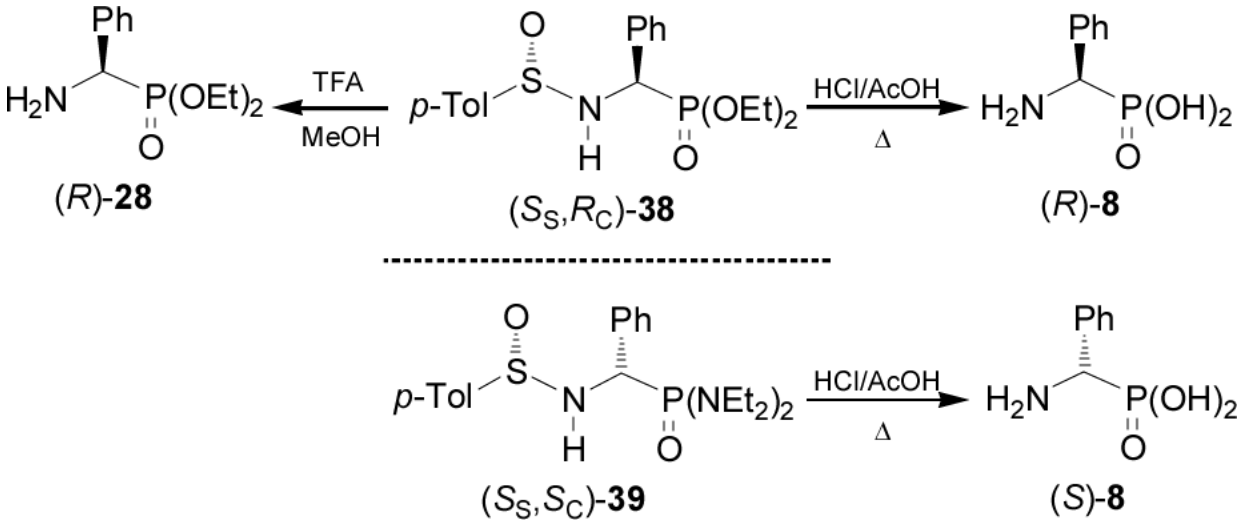
Scheme 6.



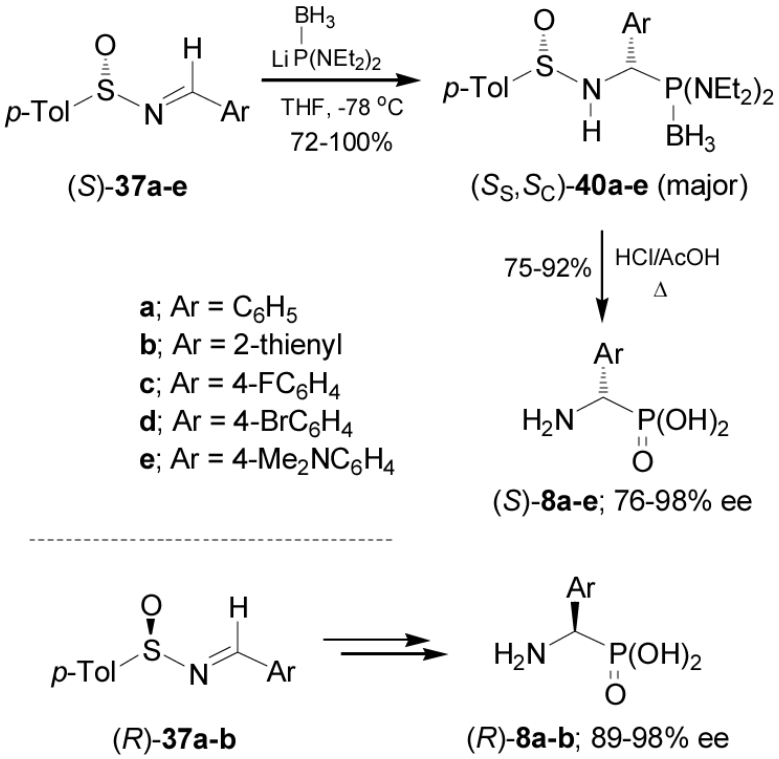
Scheme 7.



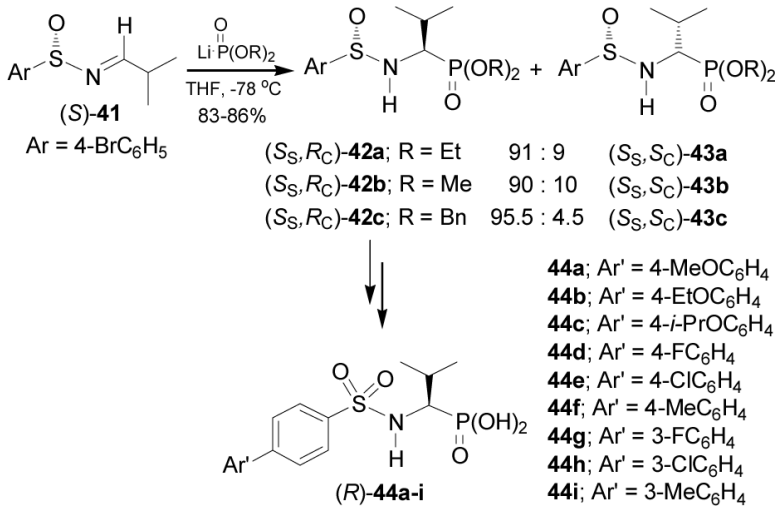
Scheme 8.



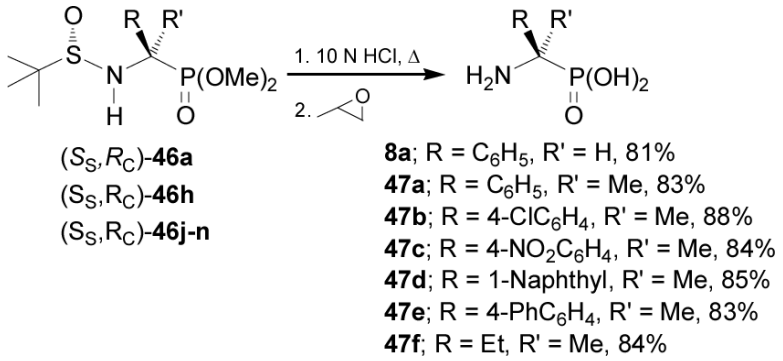
Scheme 9.



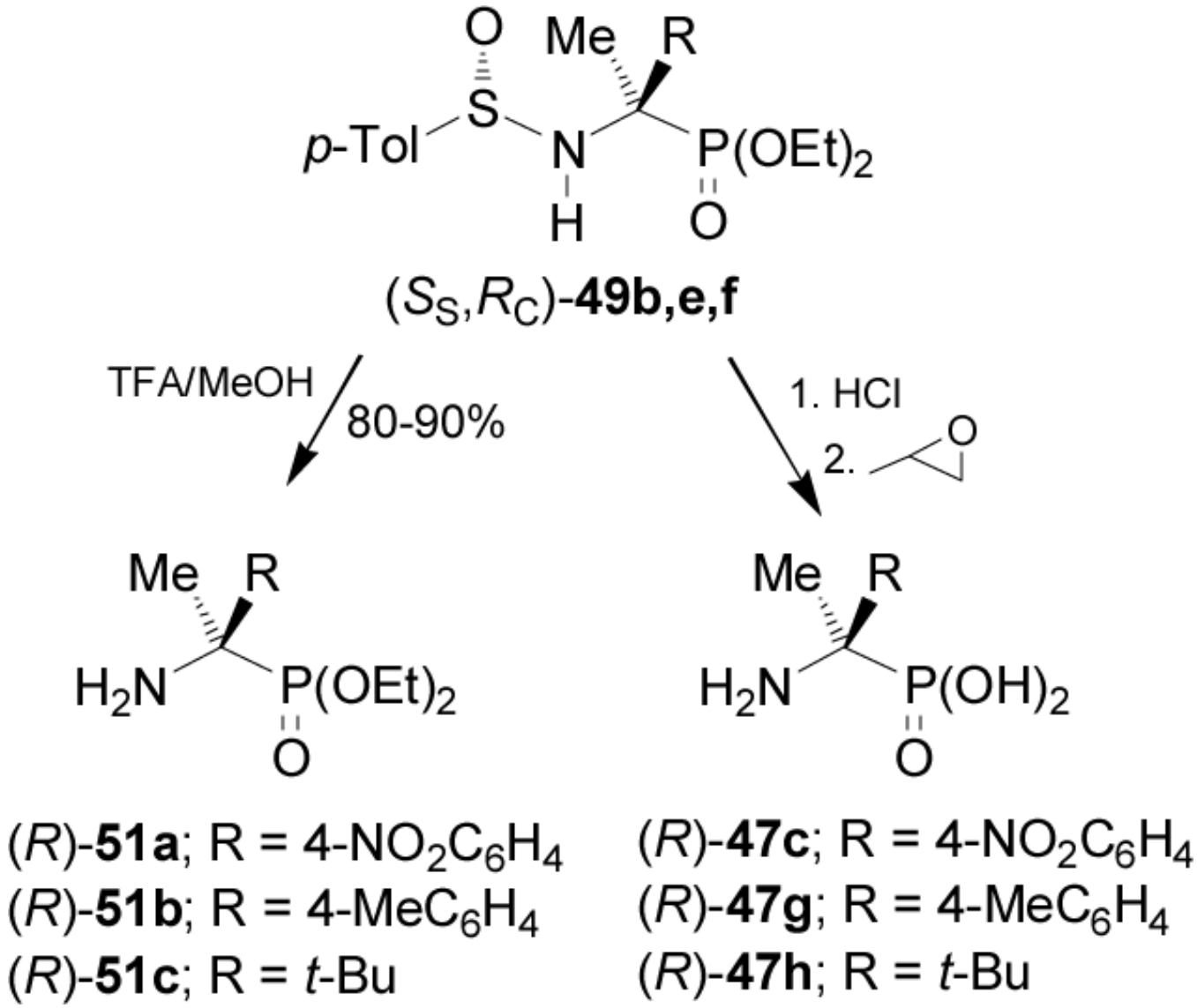
Scheme 10.



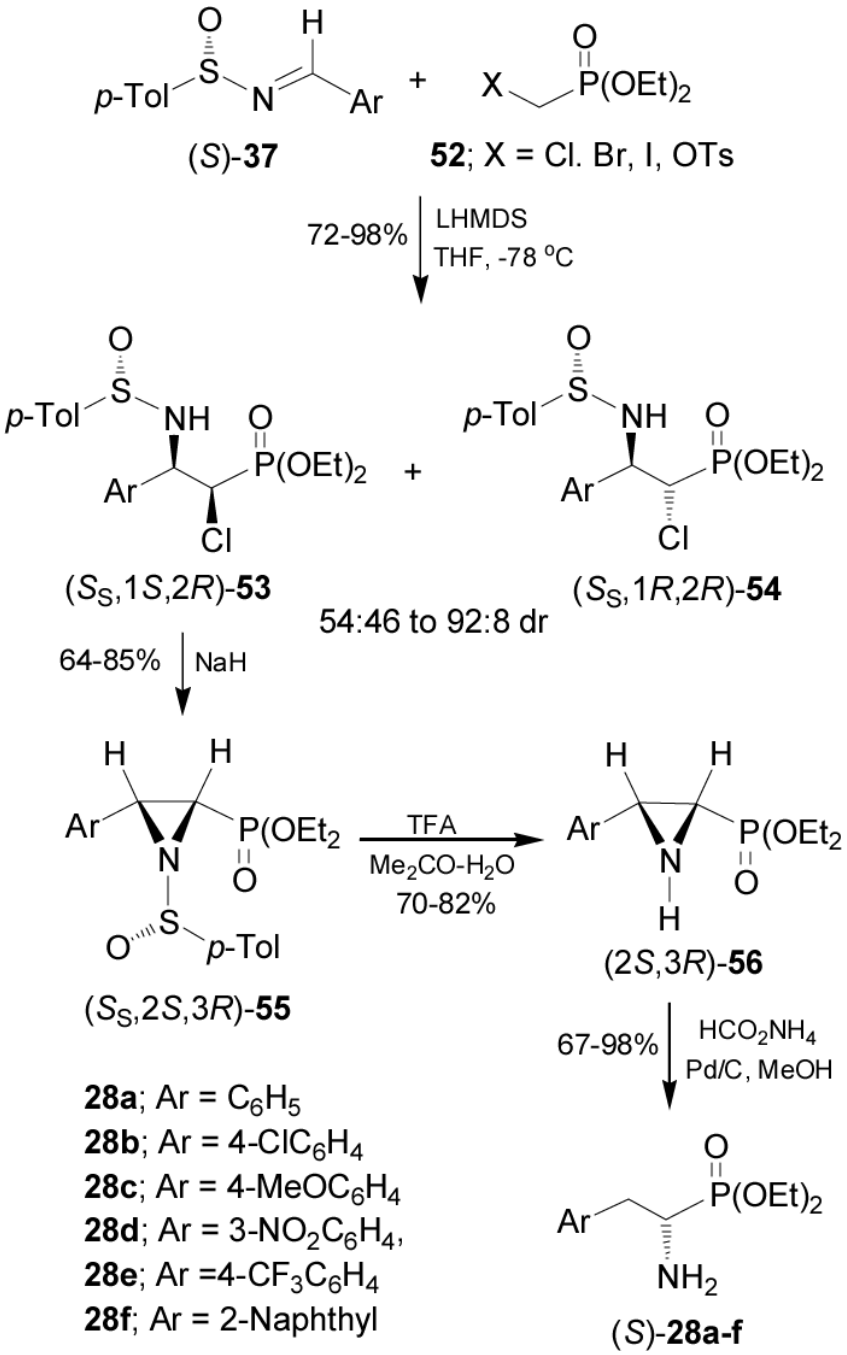
Scheme 11.



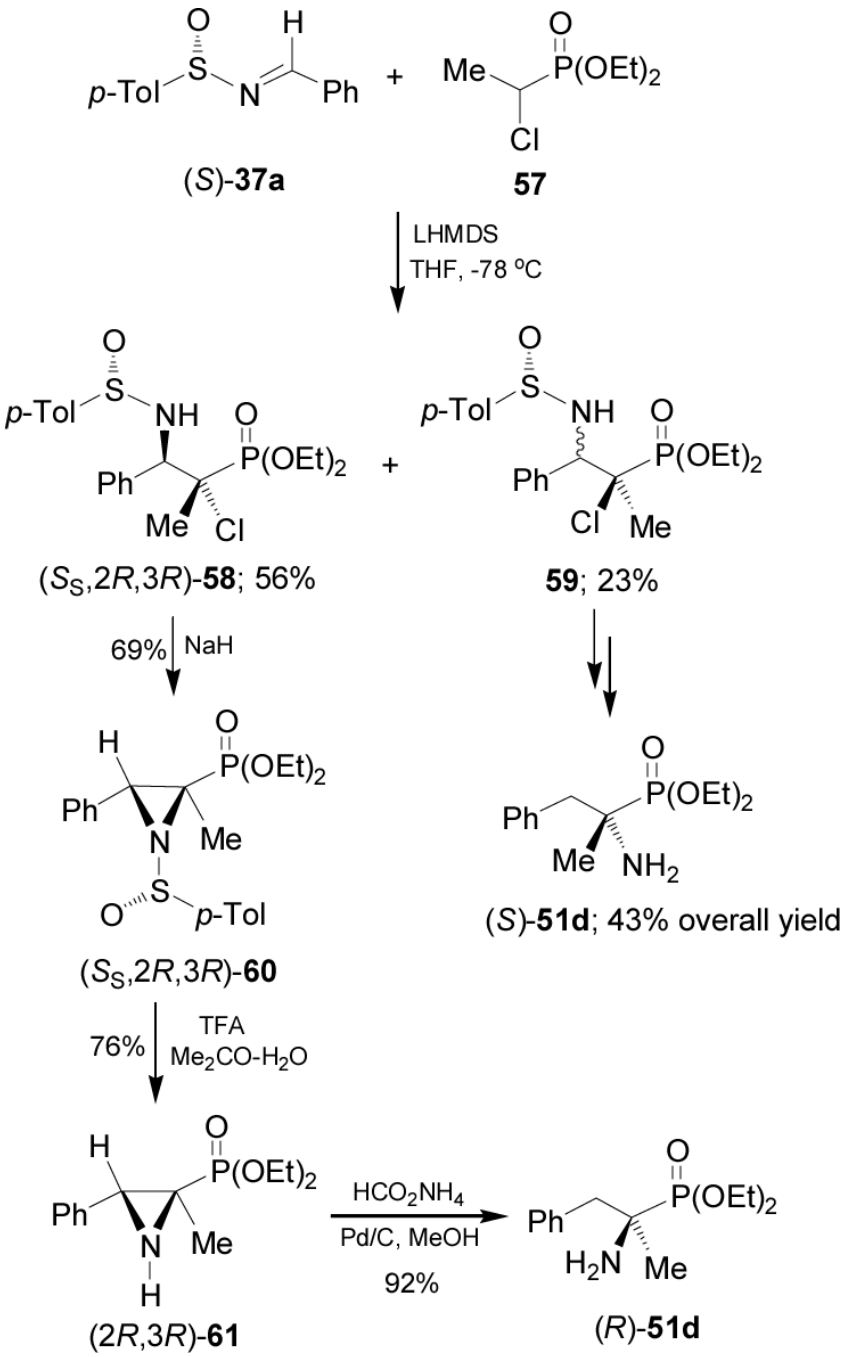
Scheme 12.



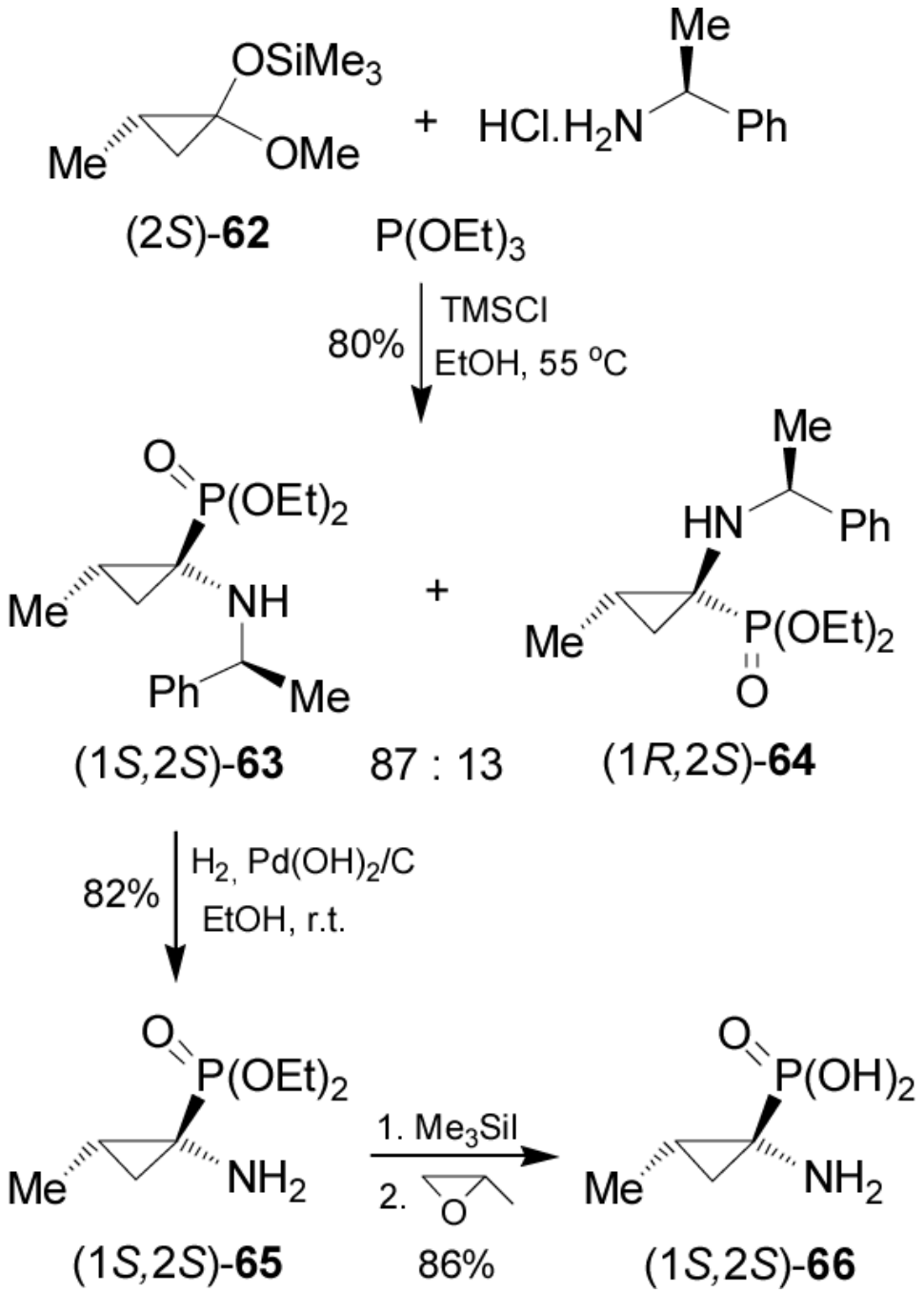
Scheme 13.



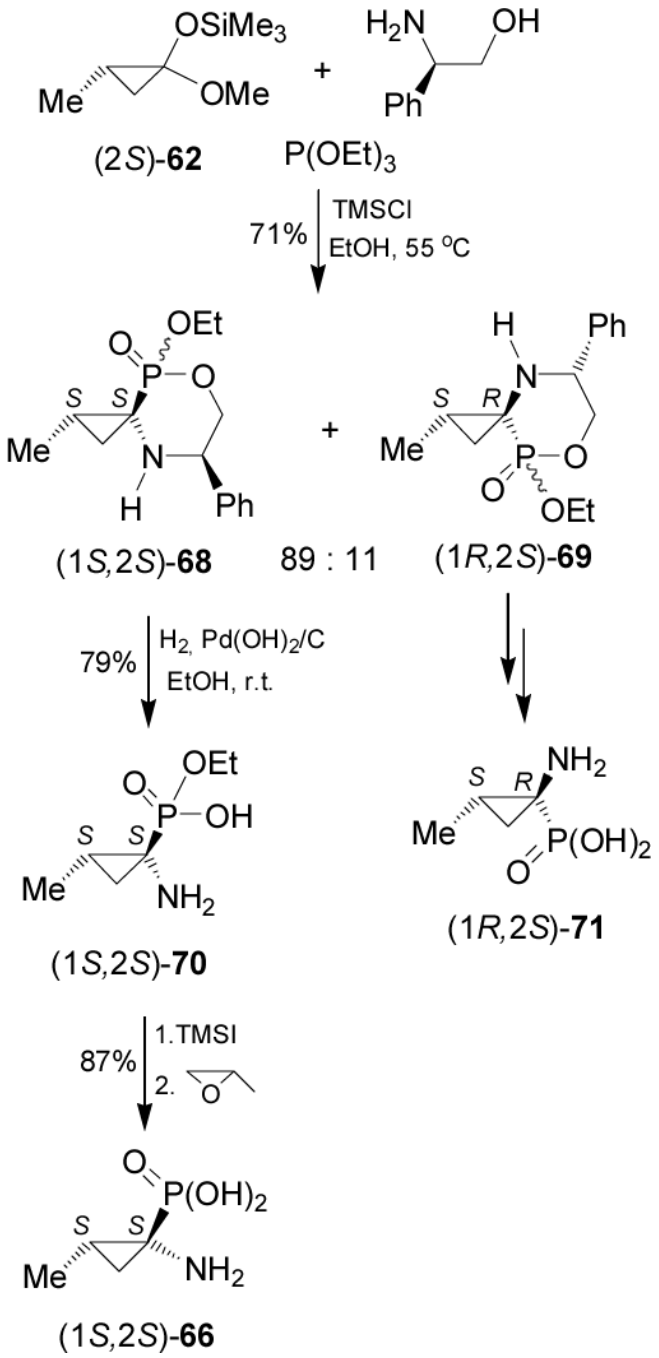
Scheme 14.



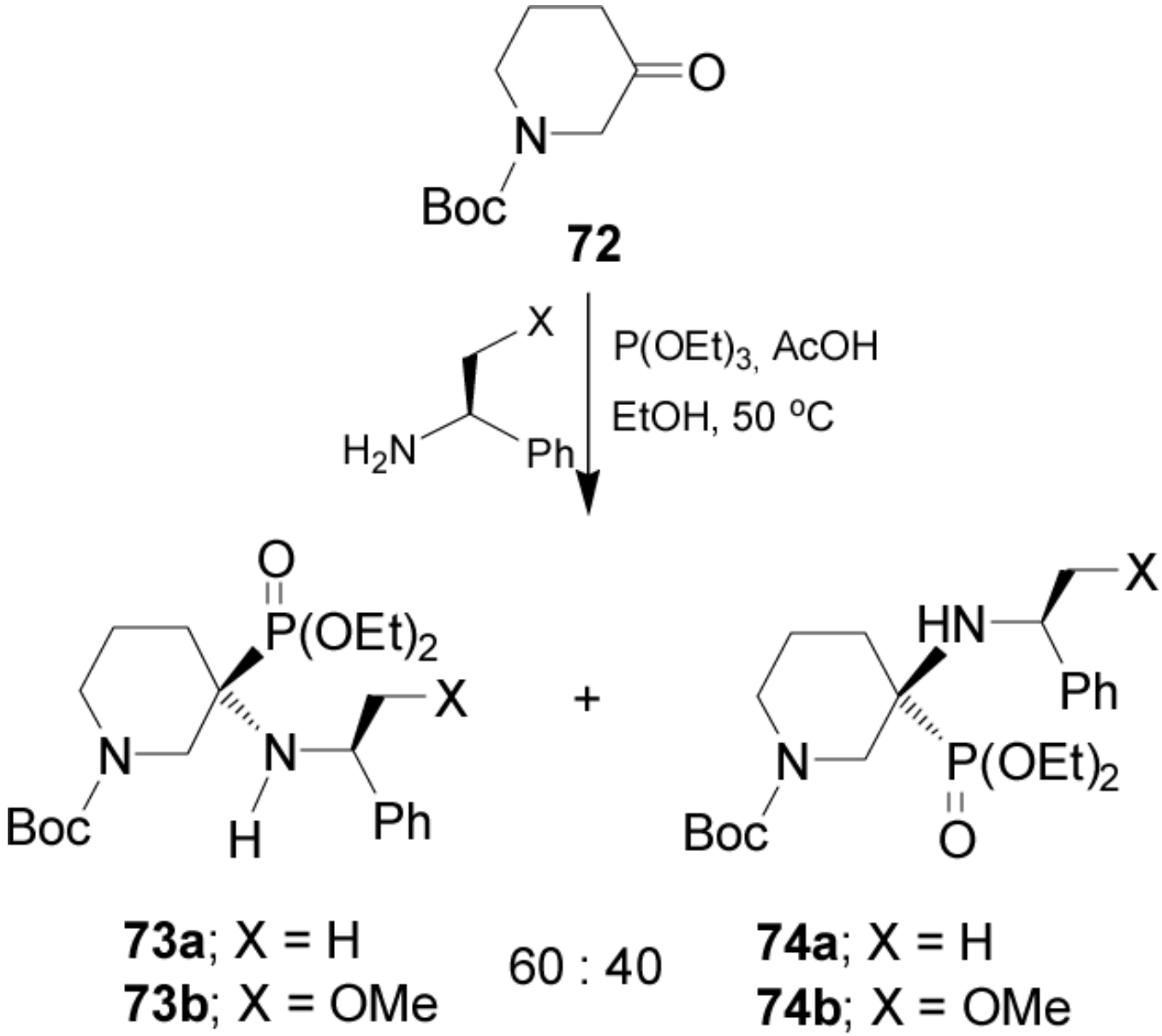
Scheme 15.



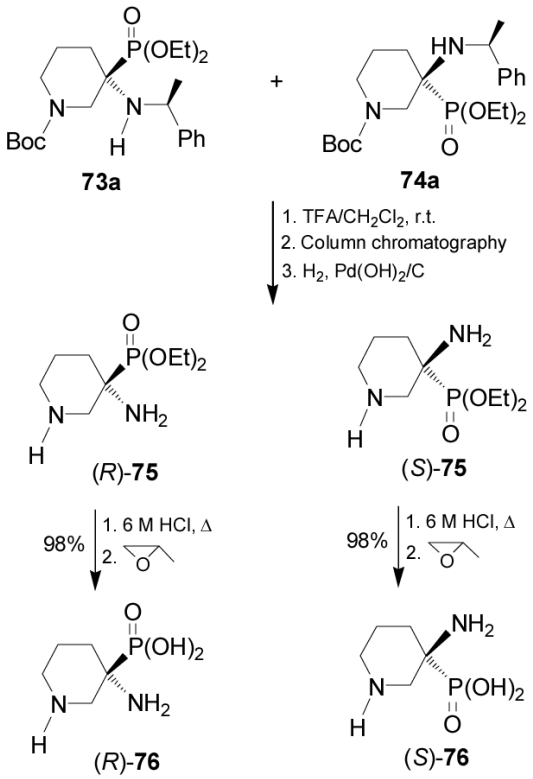
Scheme 16.



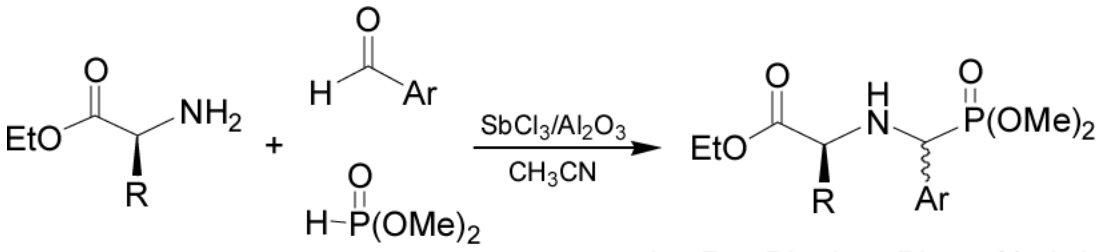
Scheme 17.



Scheme 18.

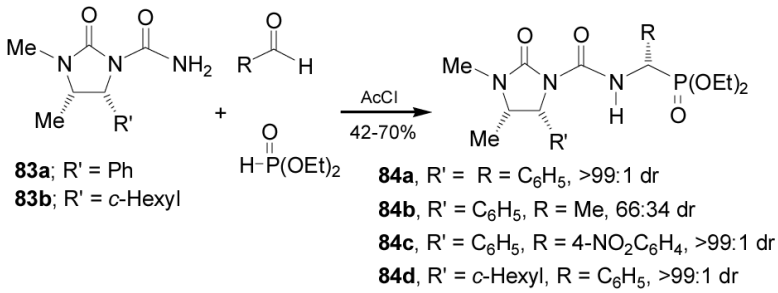


Scheme 19.

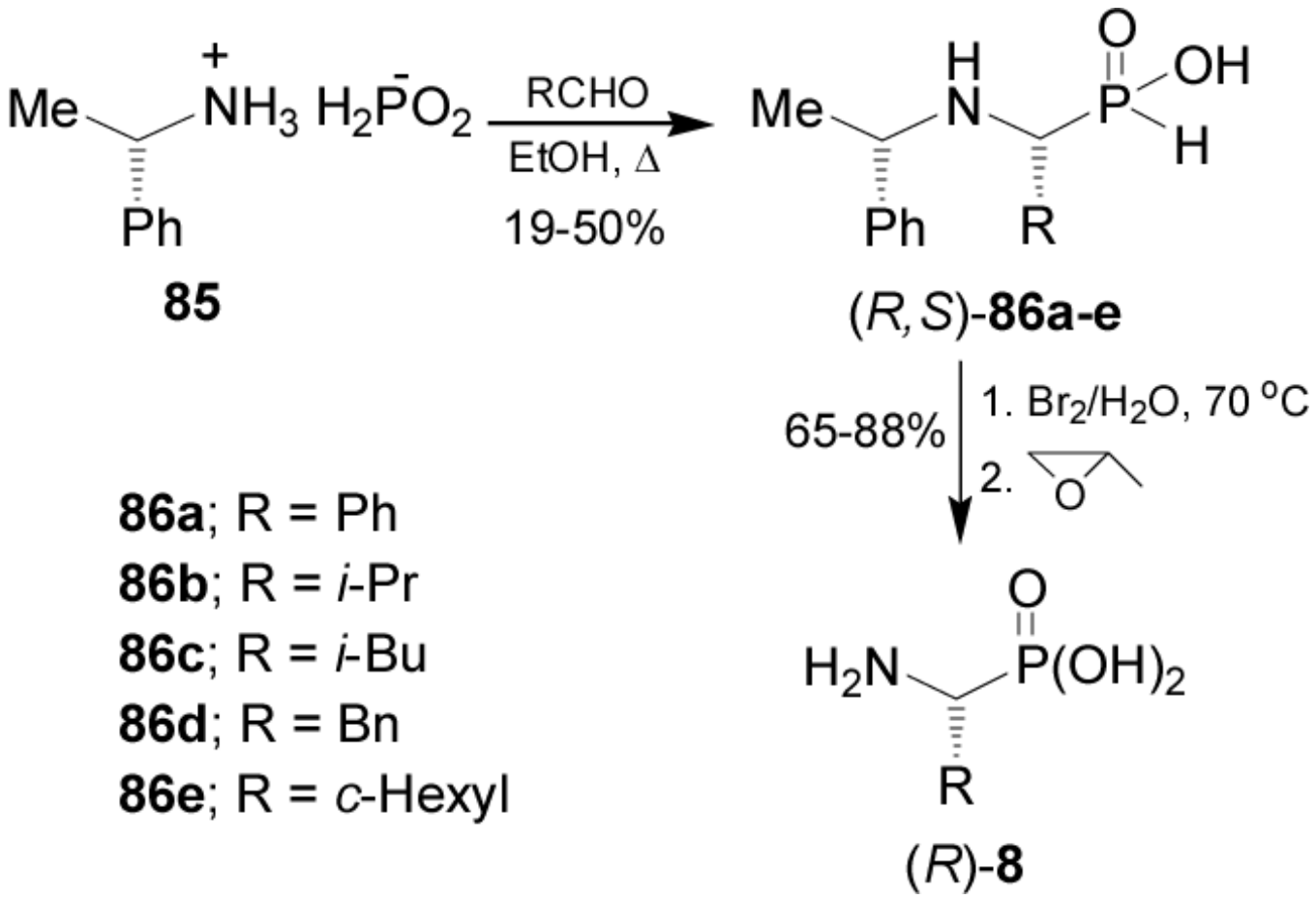


79a; R = Ph, Ar = Ph, 74%, 9:1
79b; R = Ph, Ar = 4-ClC_6H_4, 78%, 9:1
79c; R = Ph, Ar = 4-$NH_2C_6H_4$, 73%, 9:1
79d; R = Bn, Ar = Ph, 68%, 3:2
79e; R = Bn, Ar = 4-ClC_6H_4, 65%, 3:2

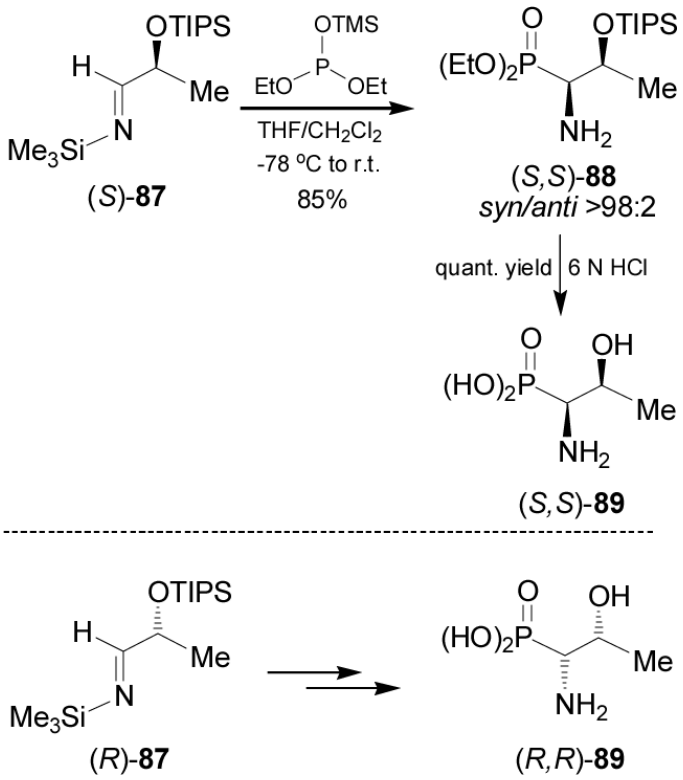
Scheme 20.



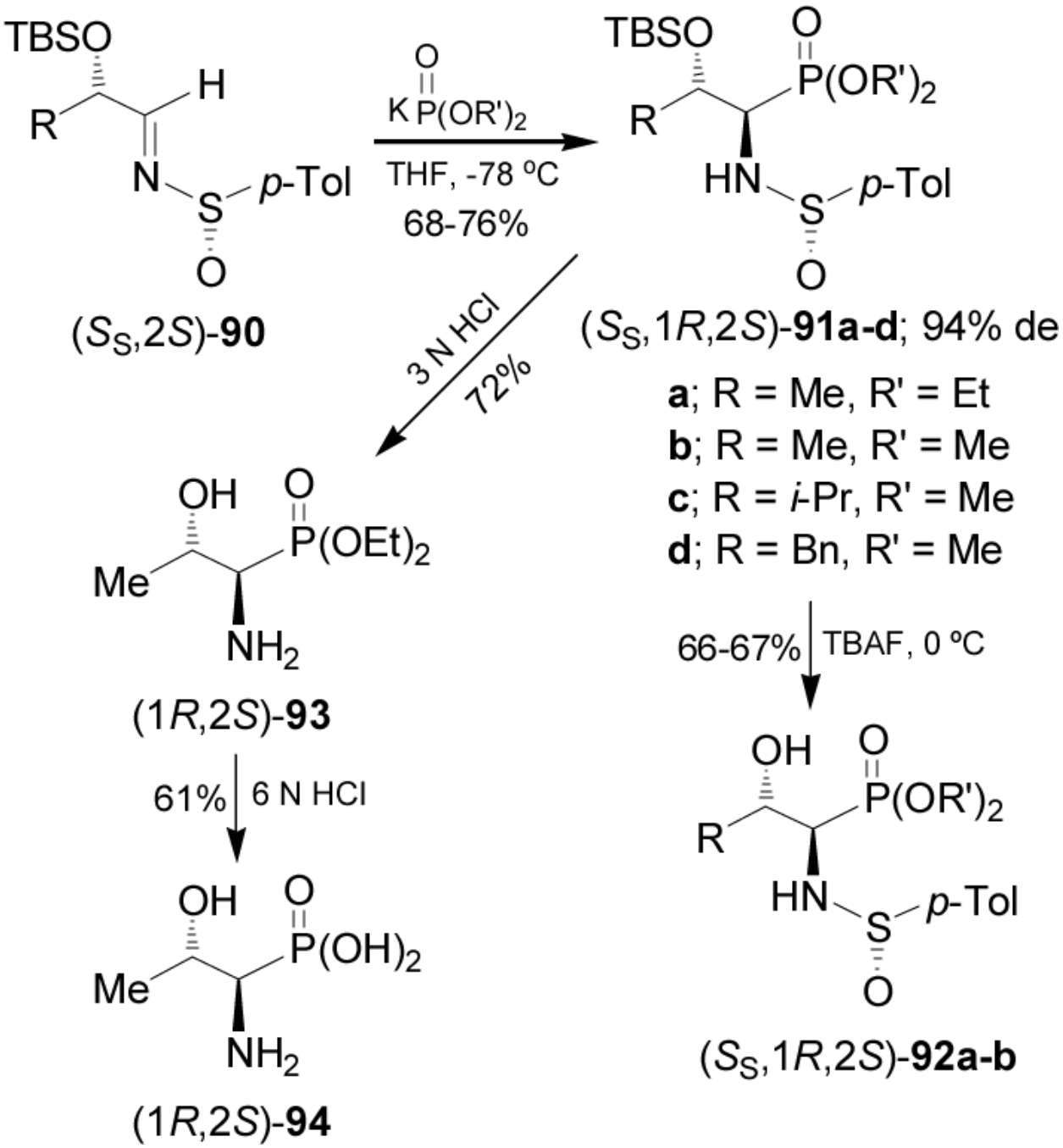
Scheme 21.



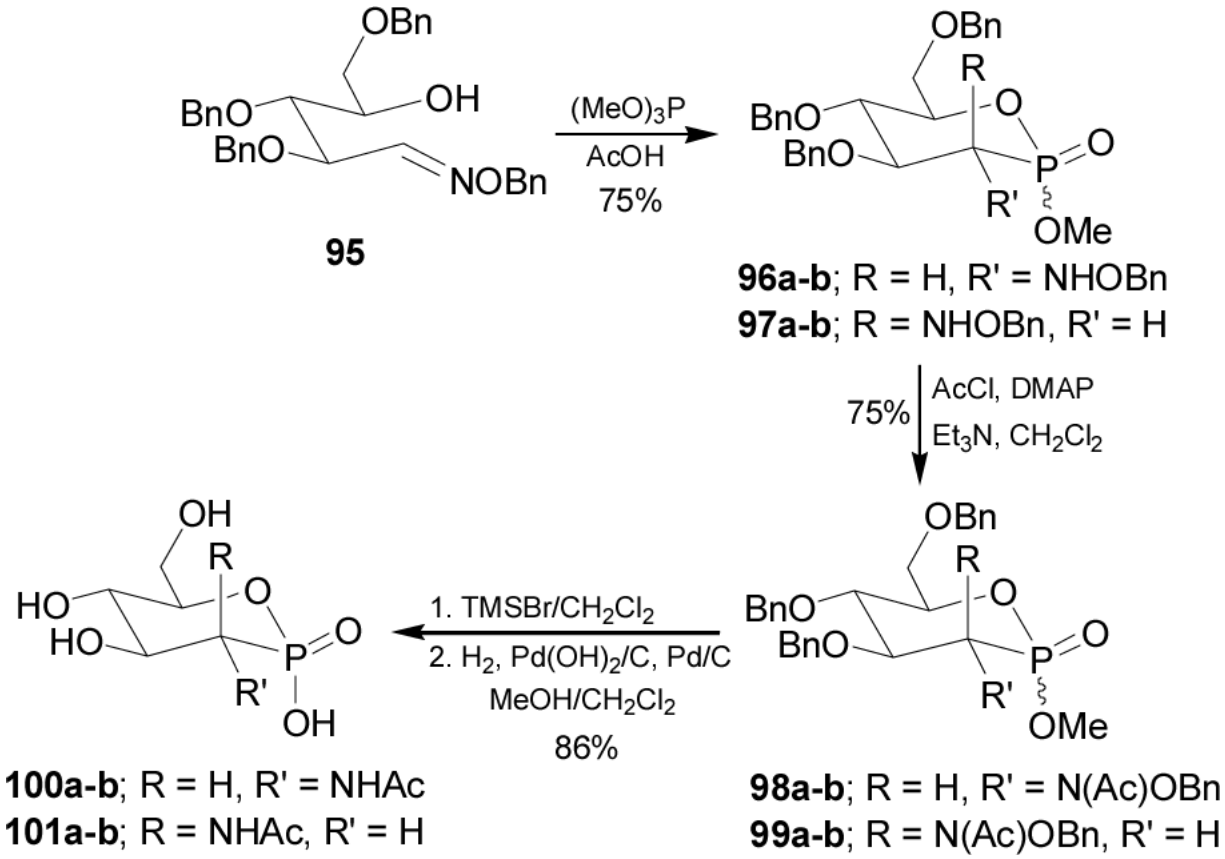
Scheme 22.



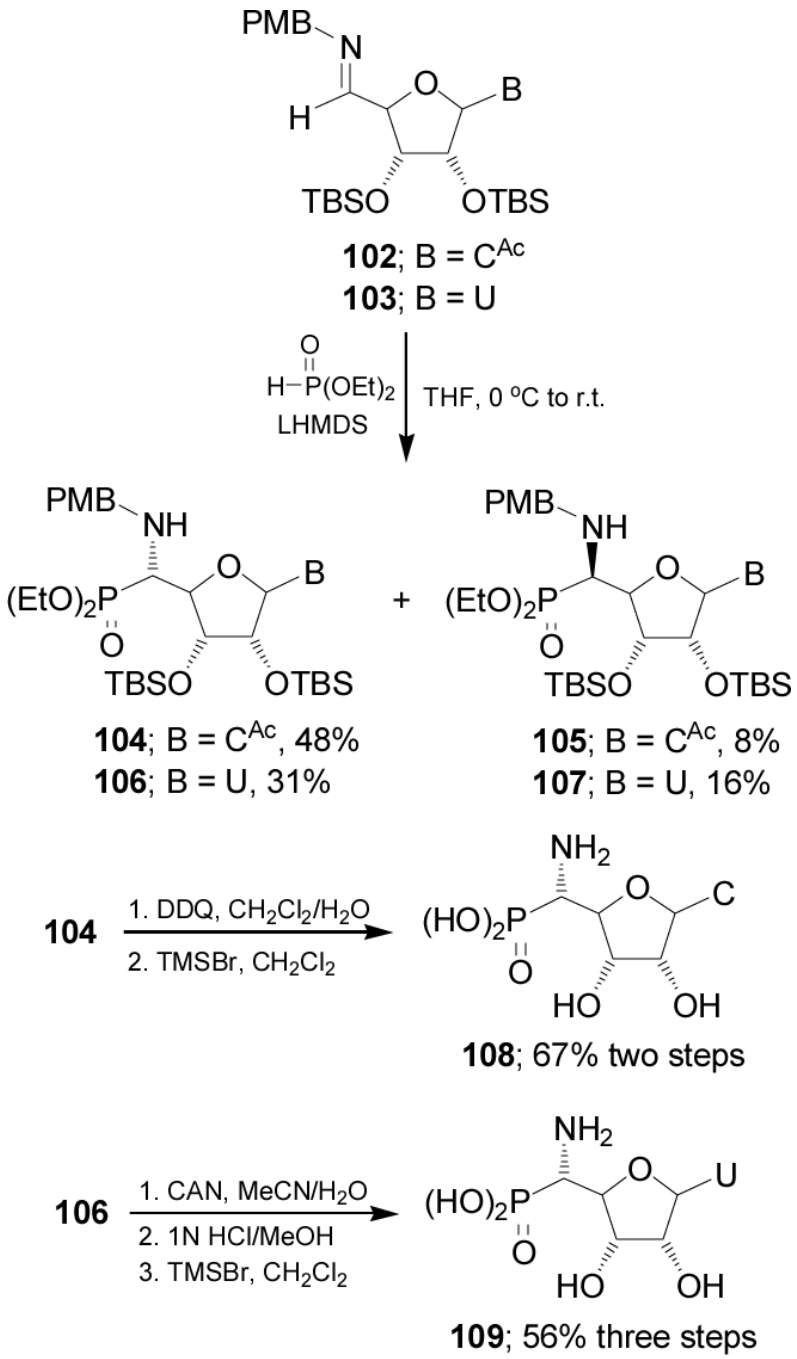
Scheme 23.



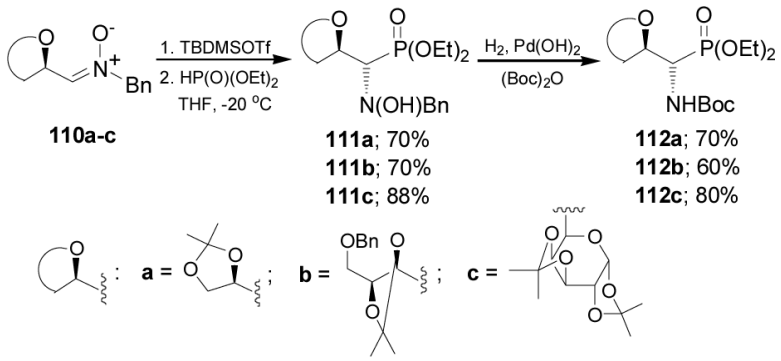
Scheme 24.



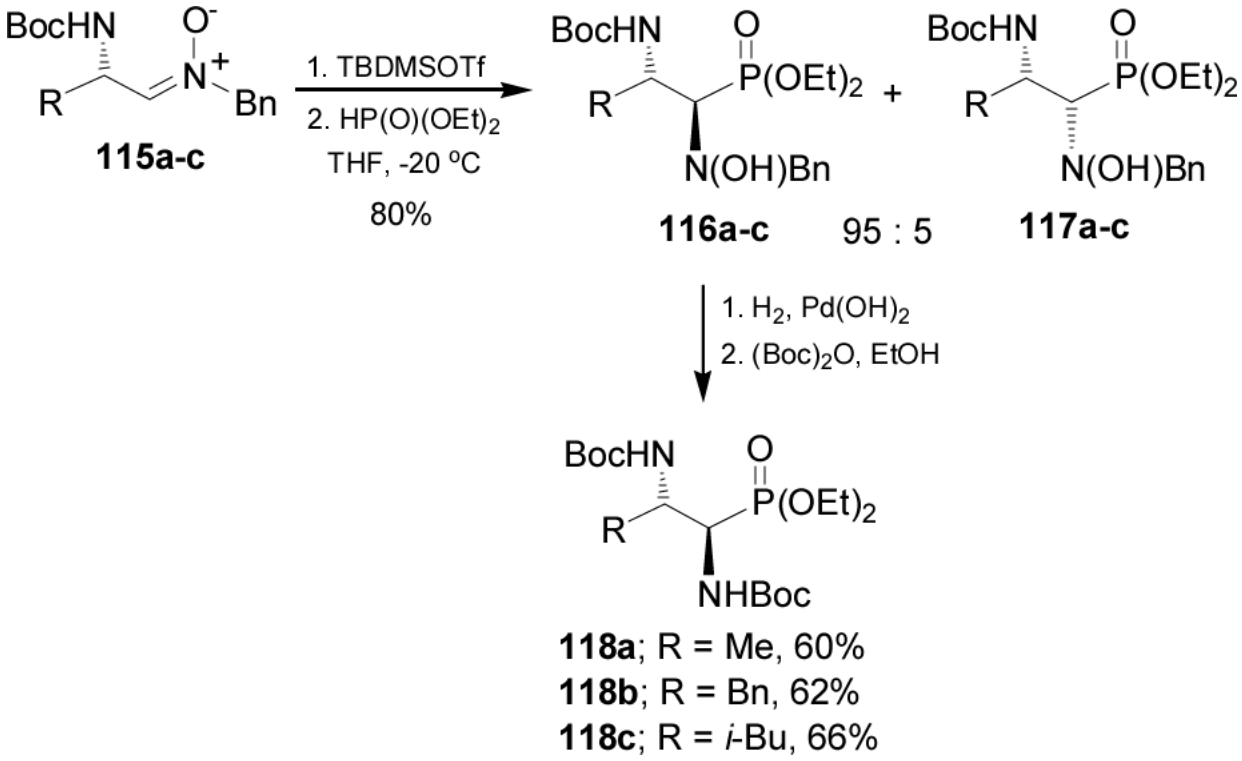
Scheme 25.



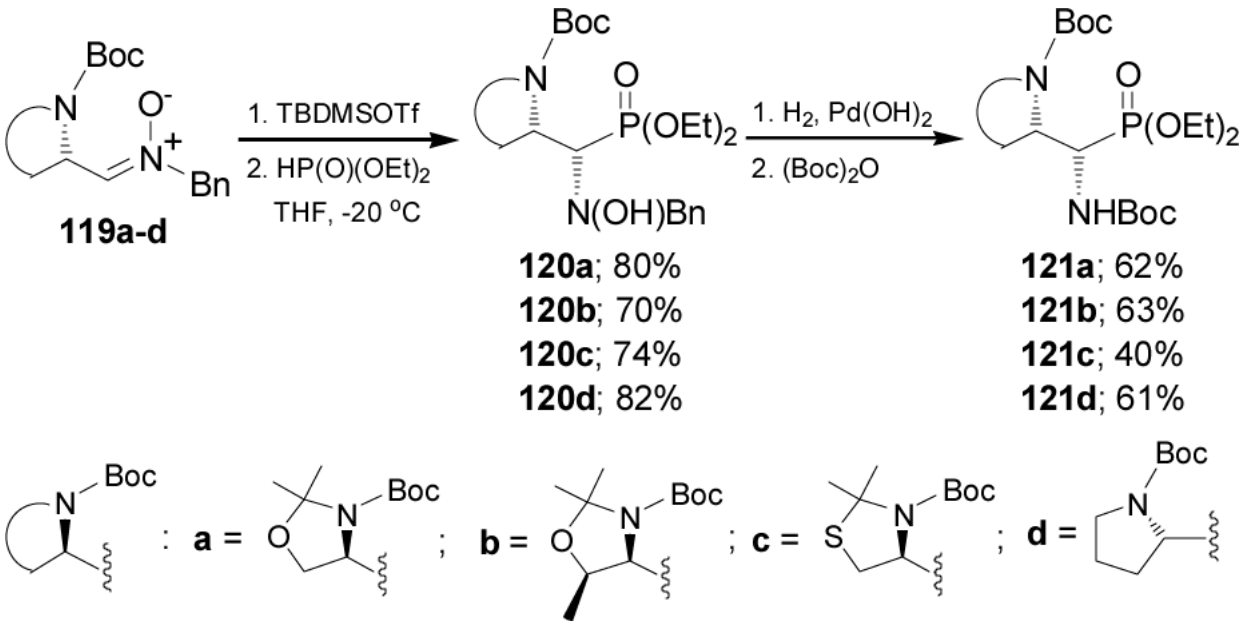
Scheme 26.



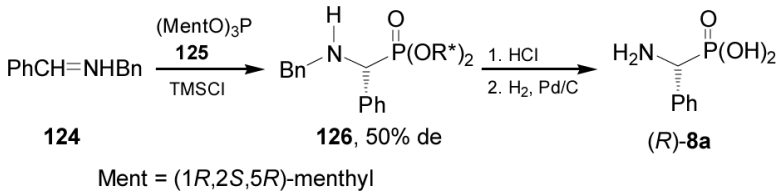
Scheme 27.



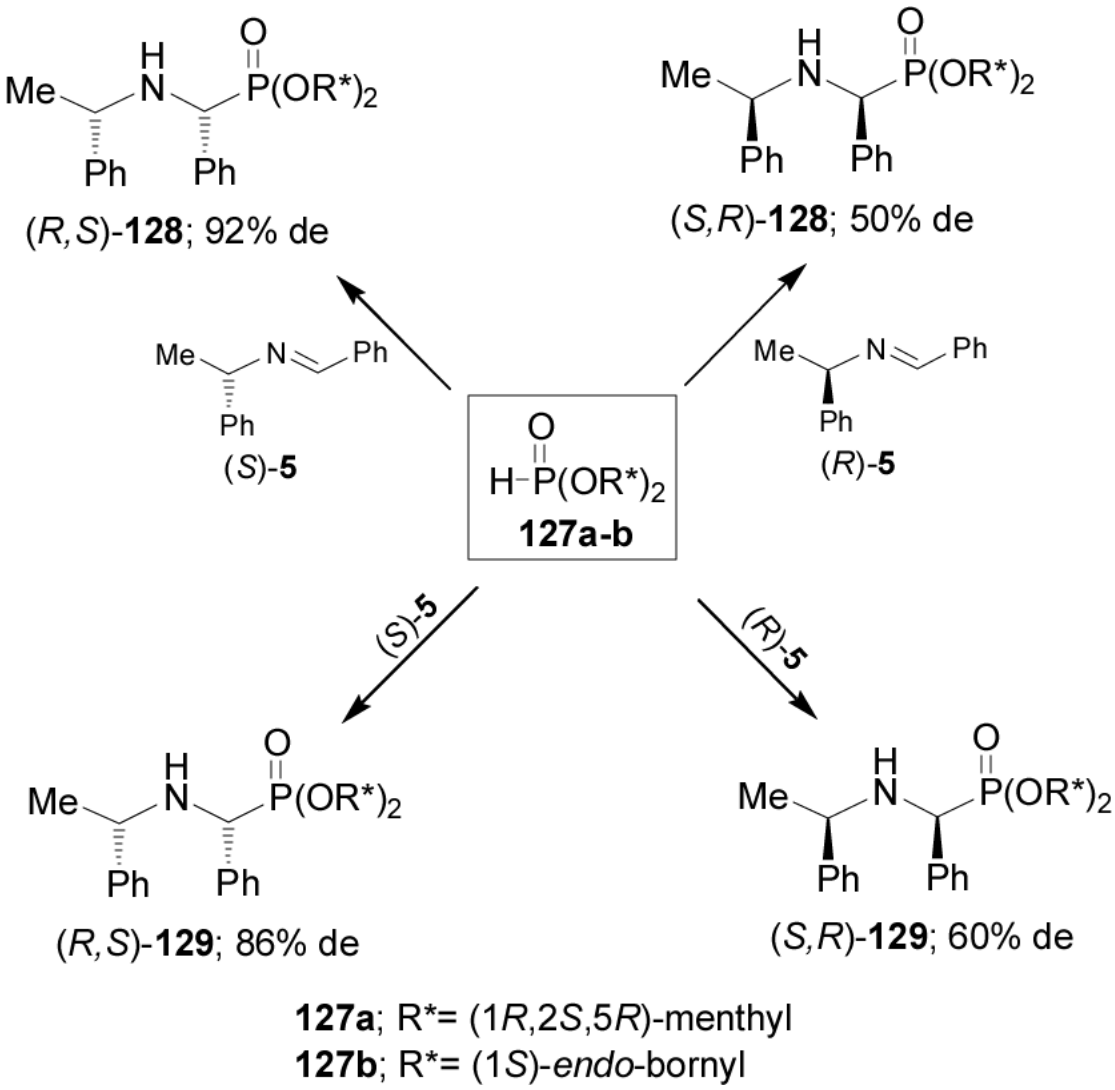
Scheme 28.



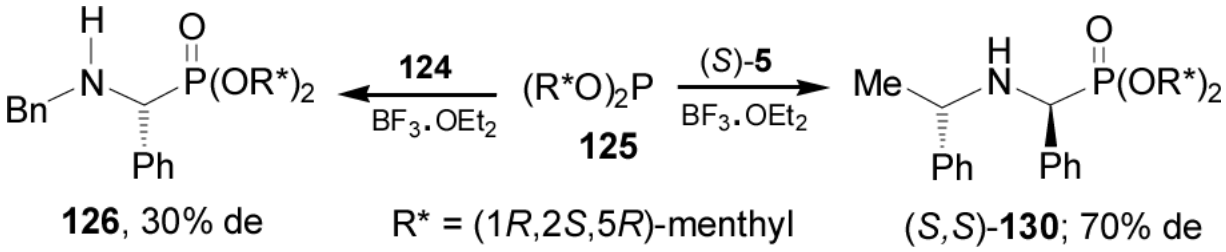
Scheme 29.



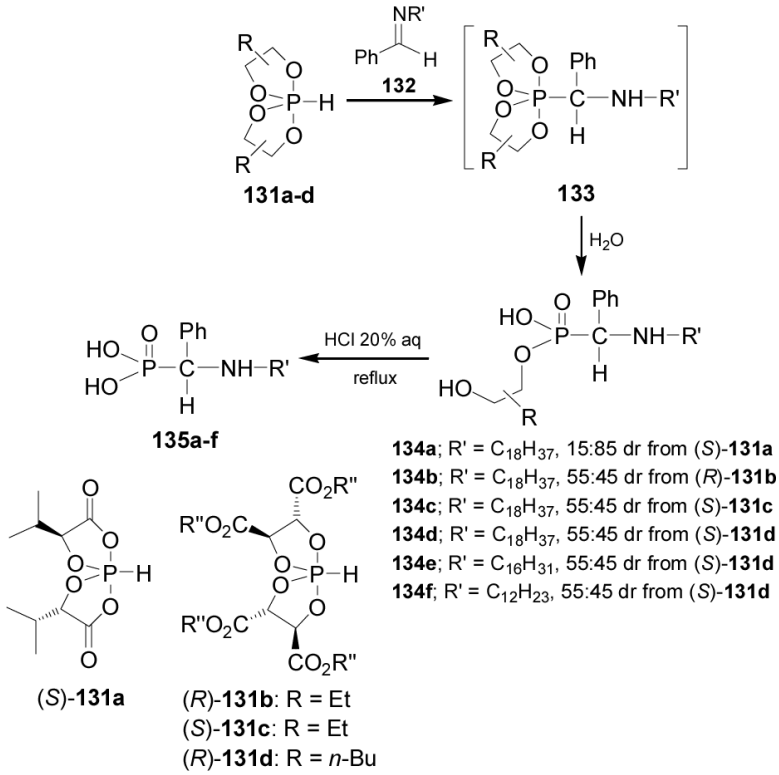
Scheme 30.



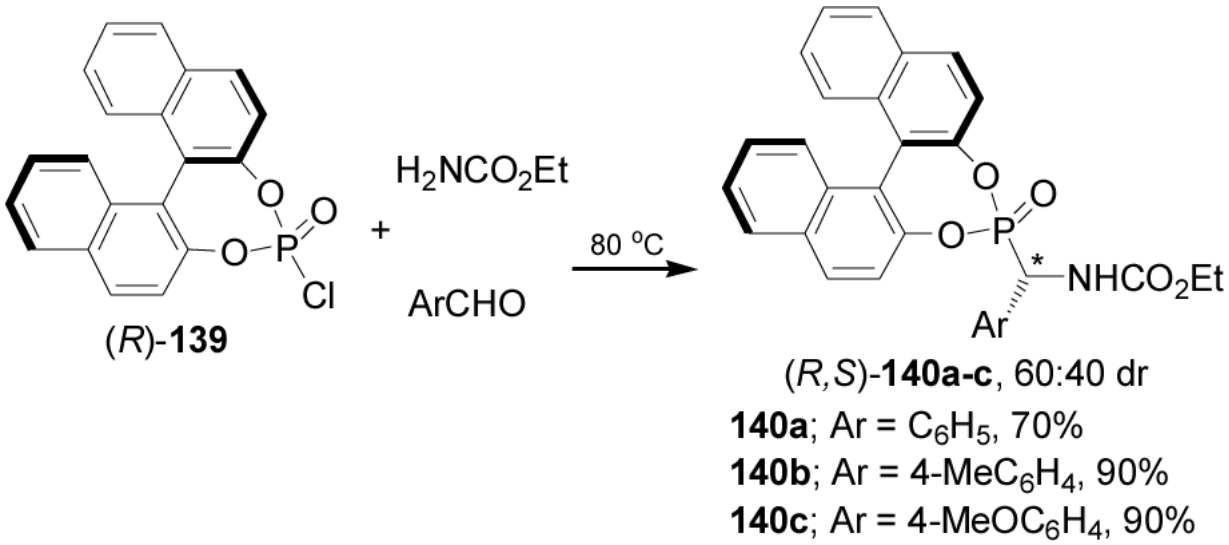
Scheme 31.



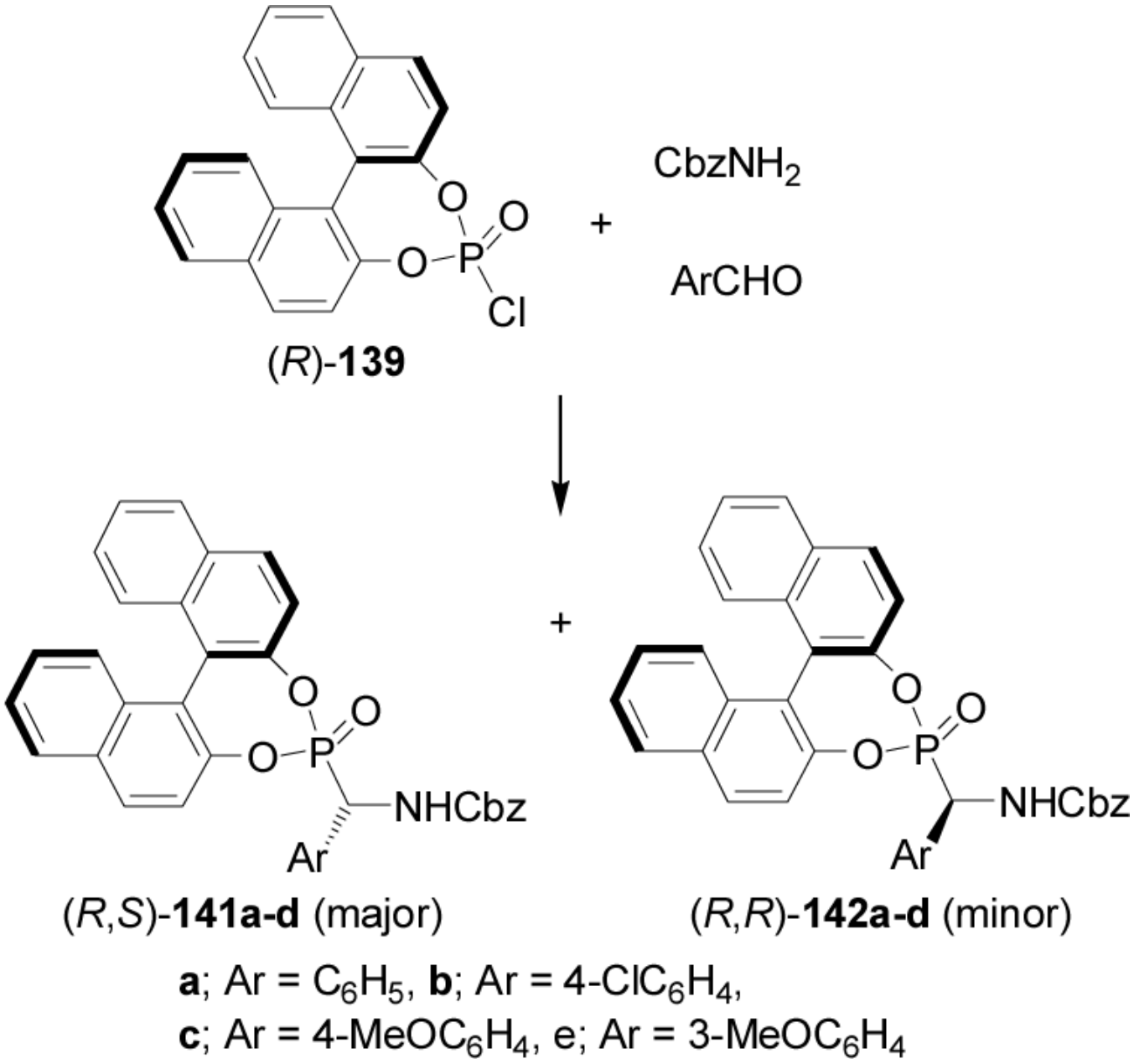
Scheme 32.



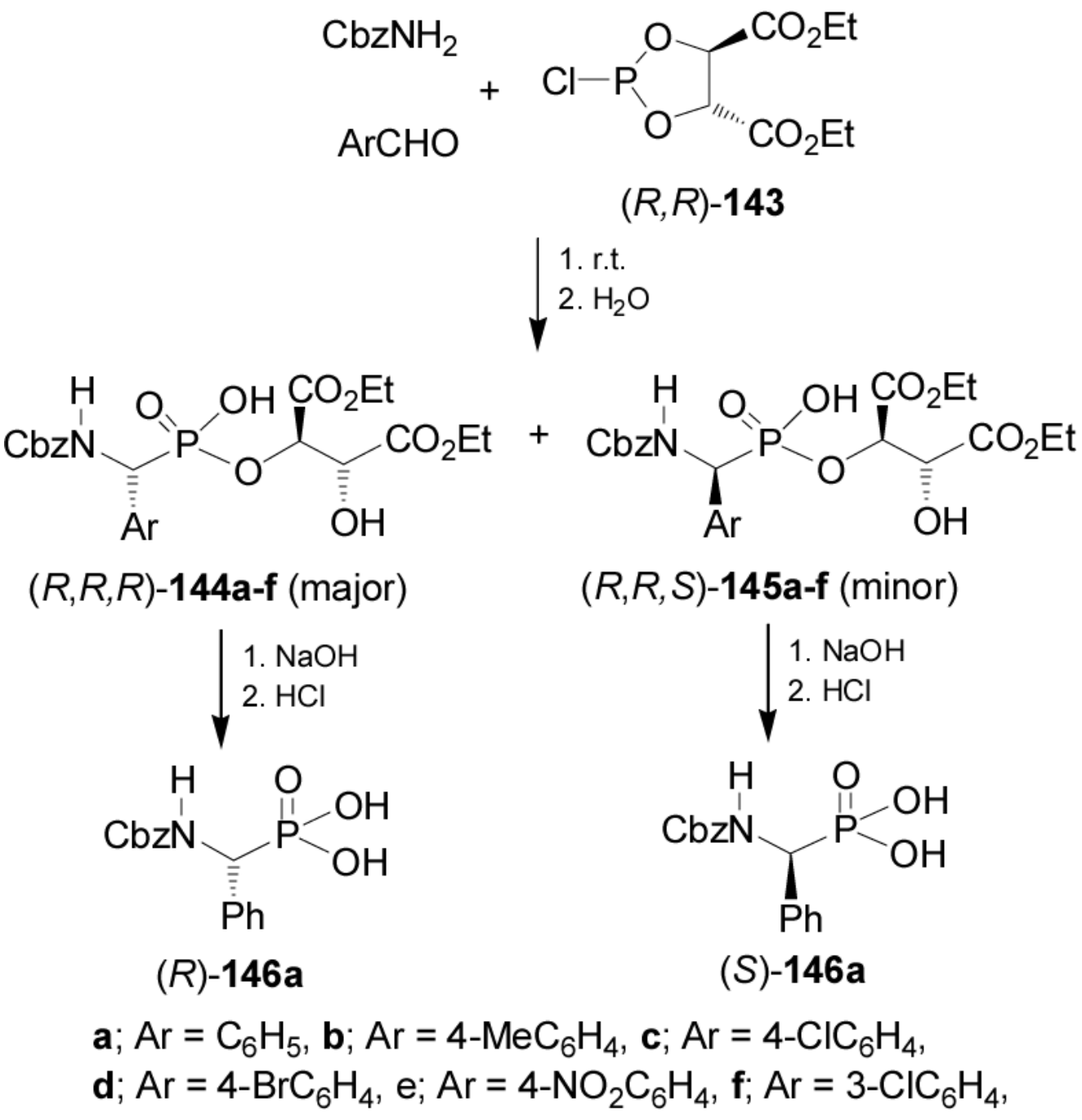
Scheme 33.



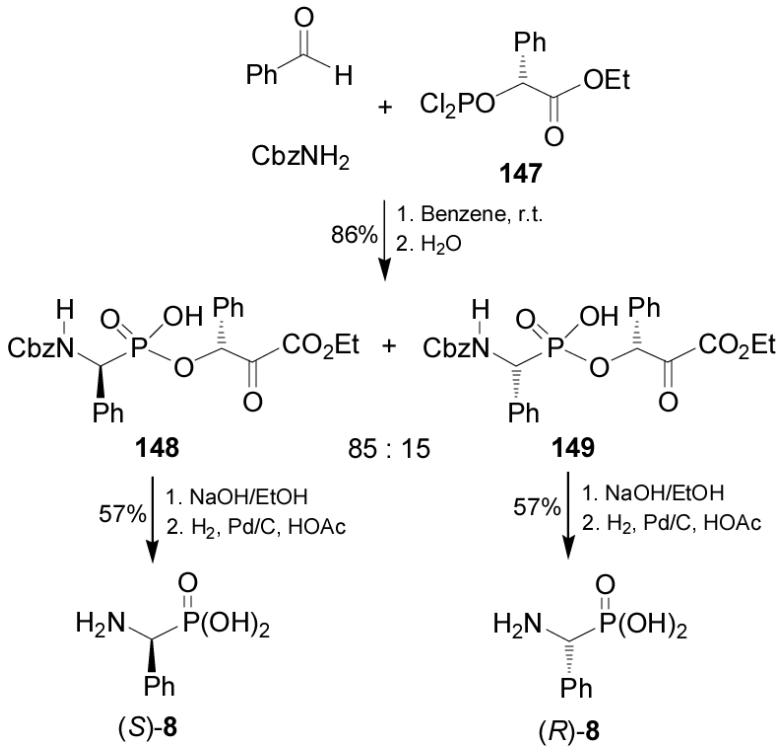
Scheme 34.



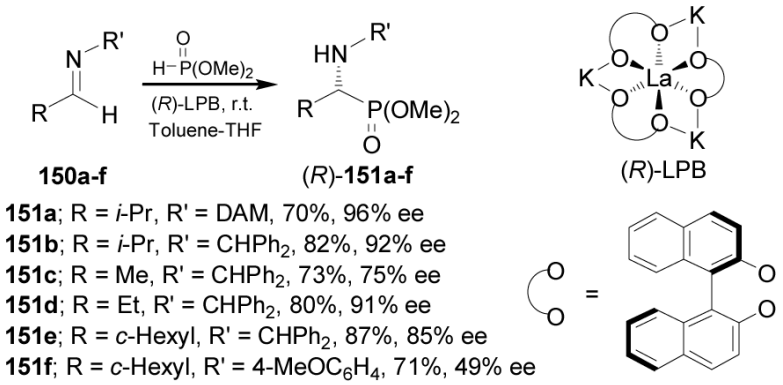
Scheme 35.



Scheme 36.



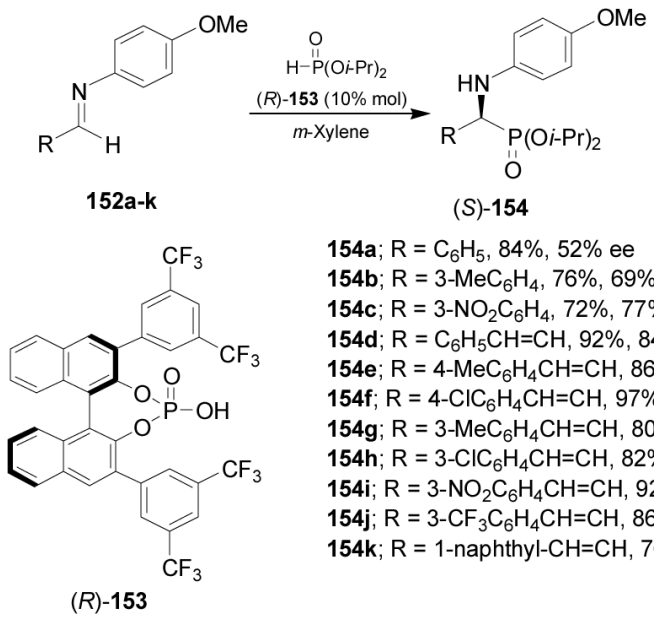
Scheme 37.



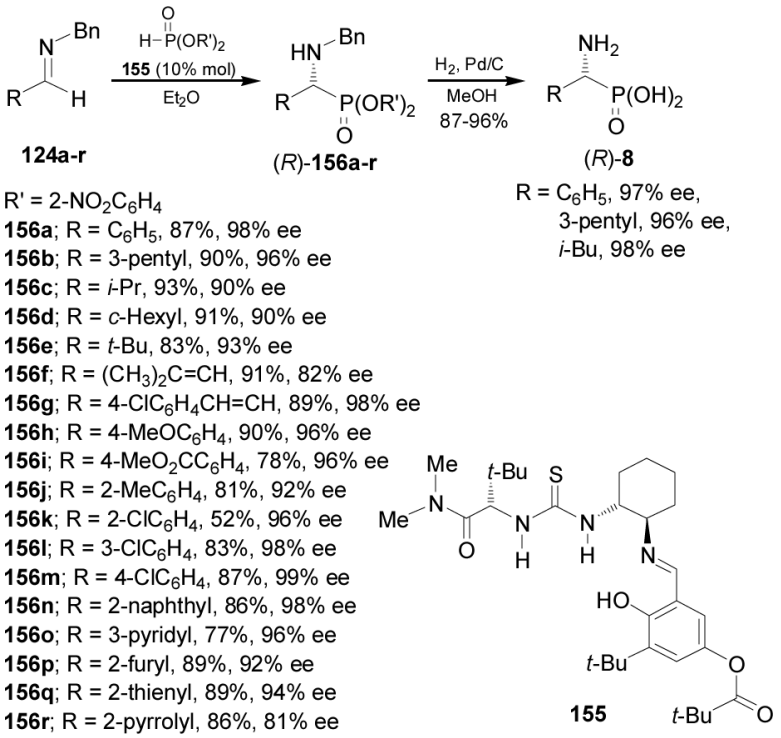
150a-f (*R*)-**151a-f** (*R*)-LPB

151a; R = *i*-Pr, R' = DAM, 70%, 96% ee
151b; R = *i*-Pr, R' = $CHPh_2$, 82%, 92% ee
151c; R = Me, R' = $CHPh_2$, 73%, 75% ee
151d; R = Et, R' = $CHPh_2$, 80%, 91% ee
151e; R = *c*-Hexyl, R' = $CHPh_2$, 87%, 85% ee
151f; R = *c*-Hexyl, R' = 4-$MeOC_6H_4$, 71%, 49% ee

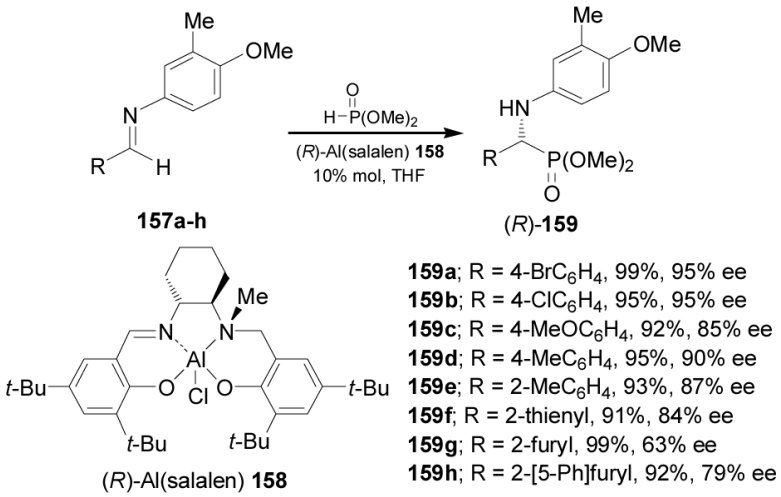
Scheme 38.



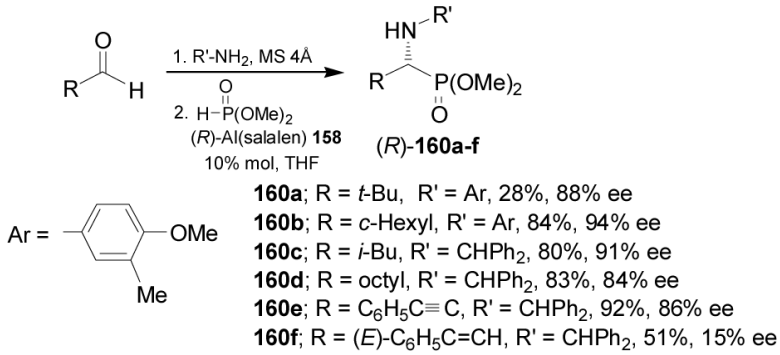
Scheme 39.



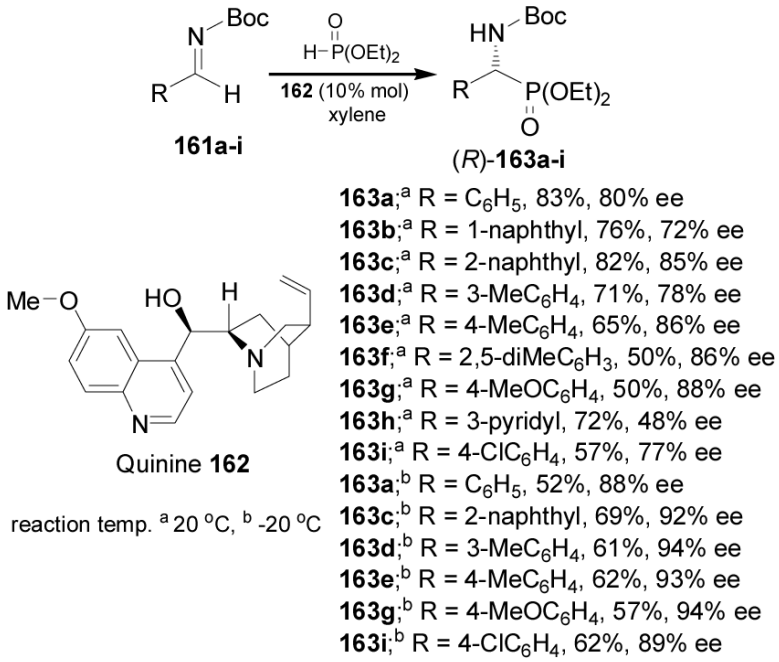
Scheme 40.



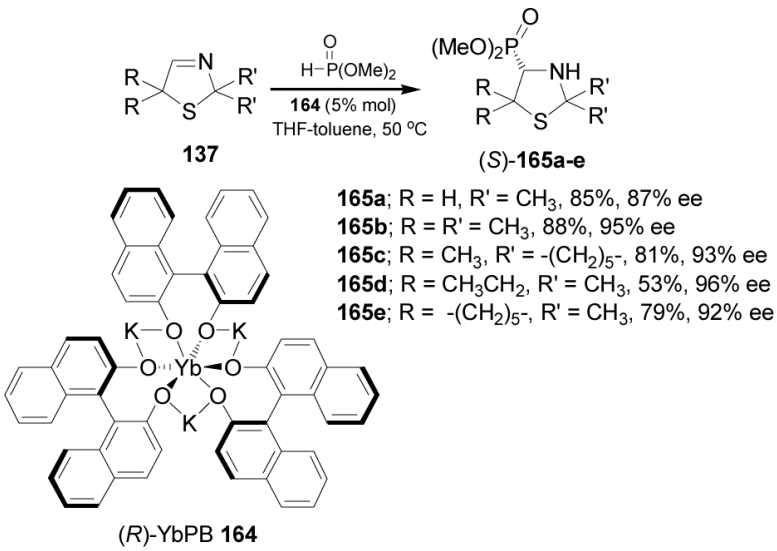
Scheme 41.



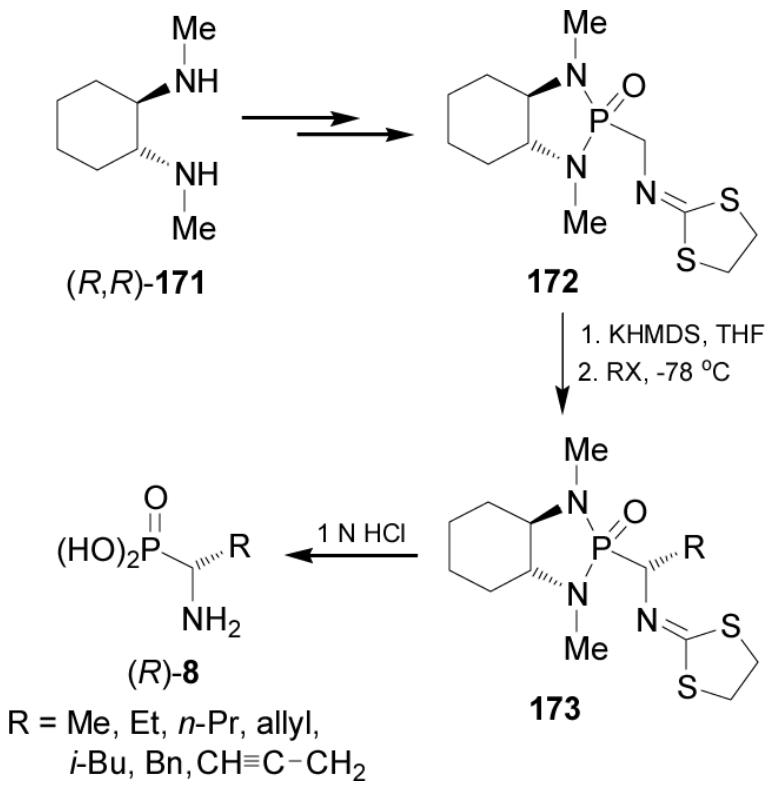
Scheme 42.



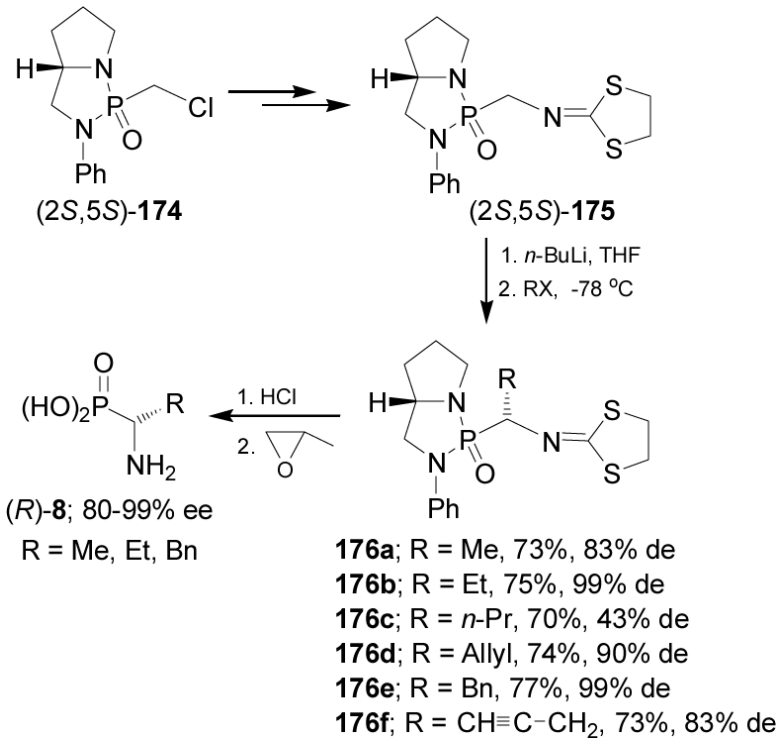
Scheme 43.



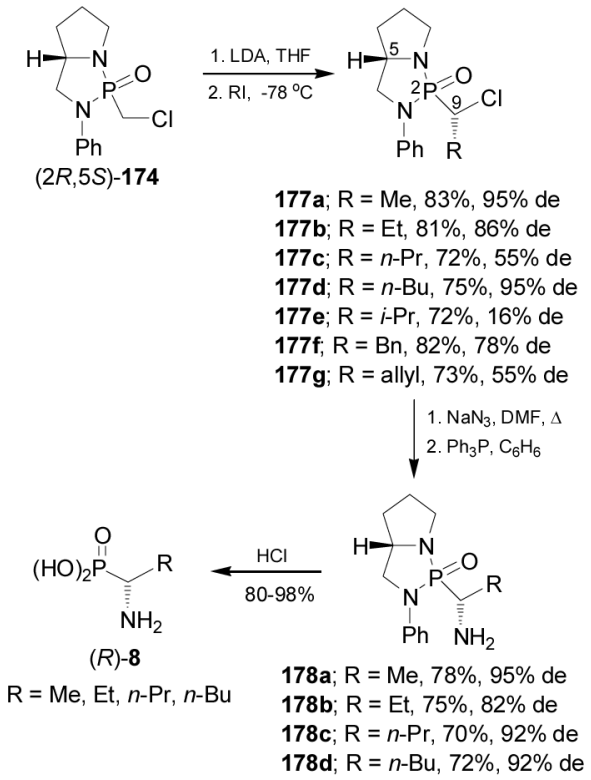
Scheme 44.



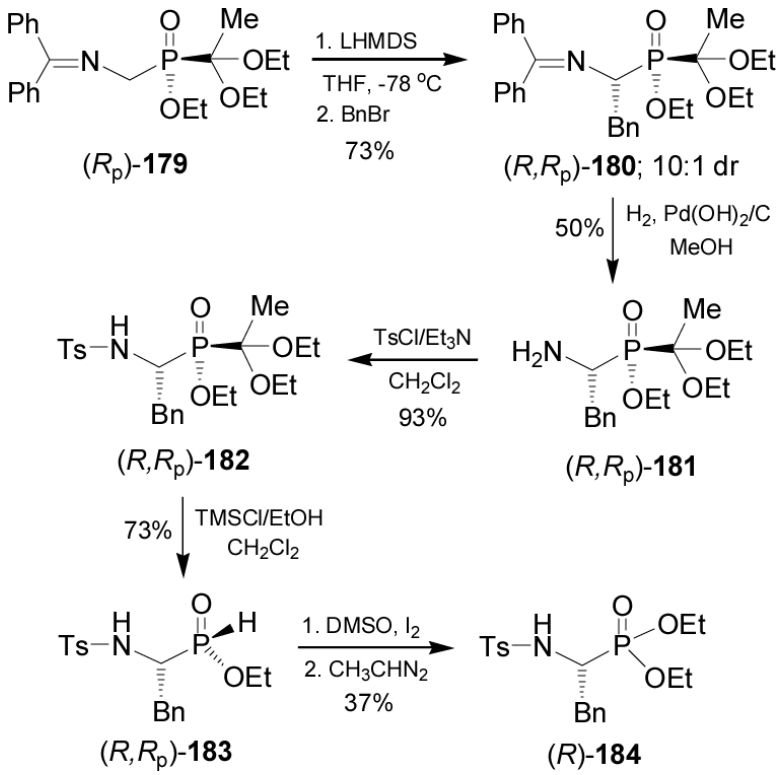
Scheme 45.



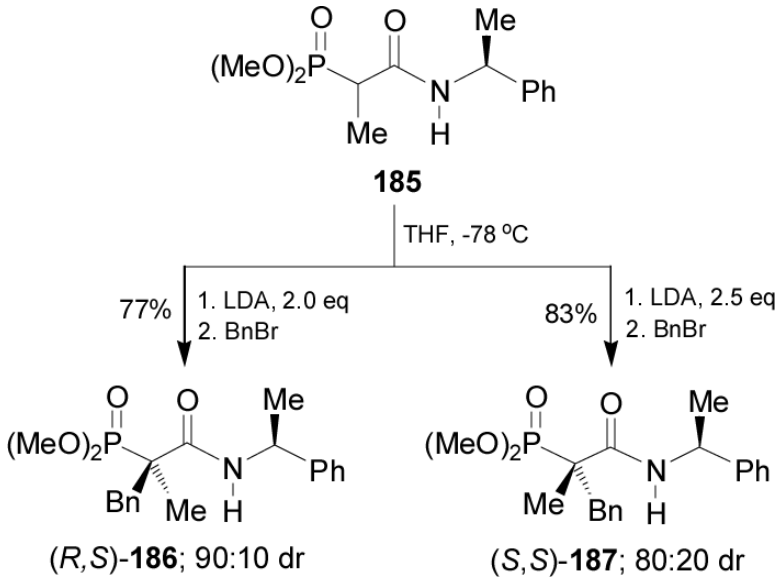
Scheme 46.



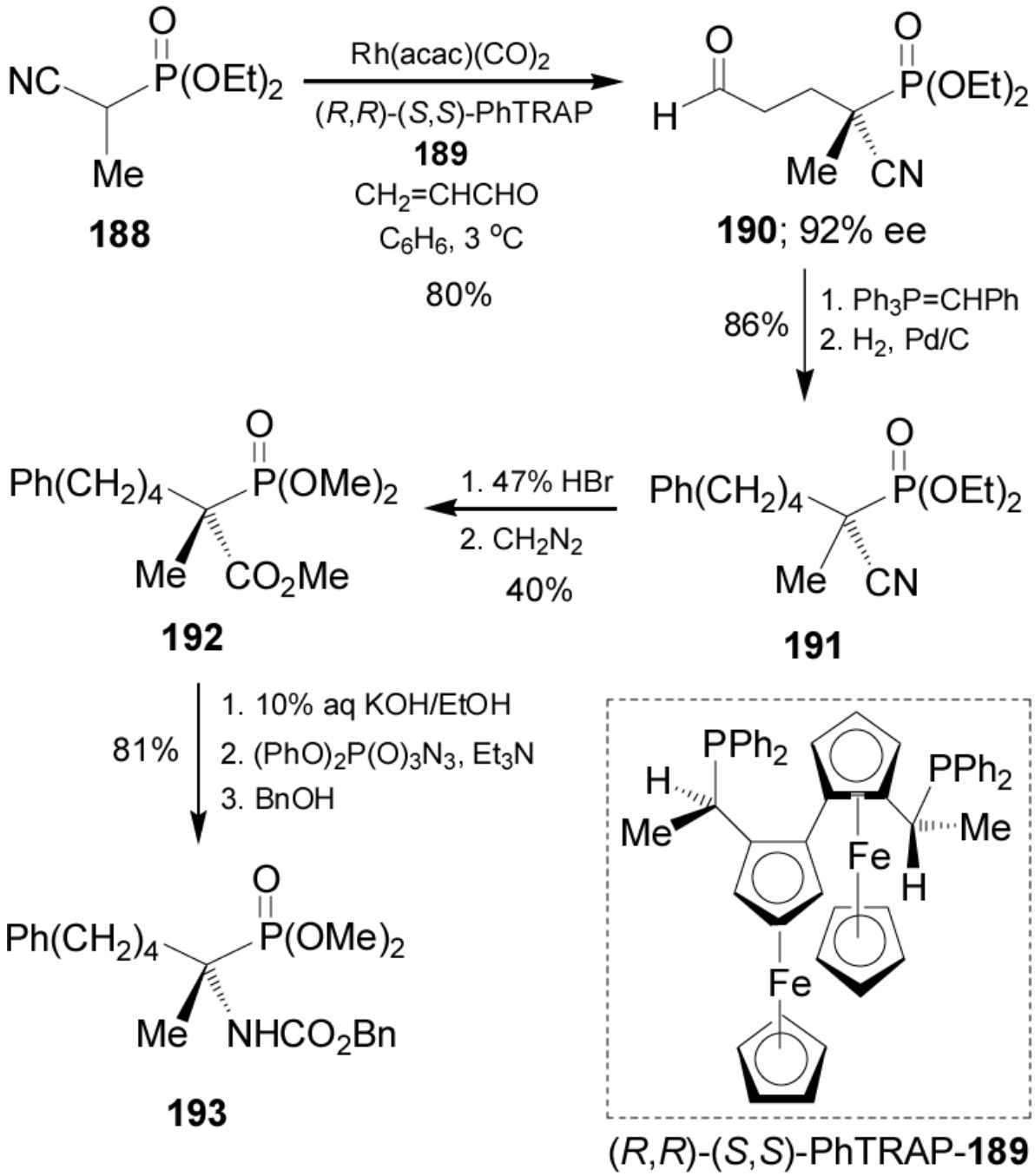
Scheme 47.



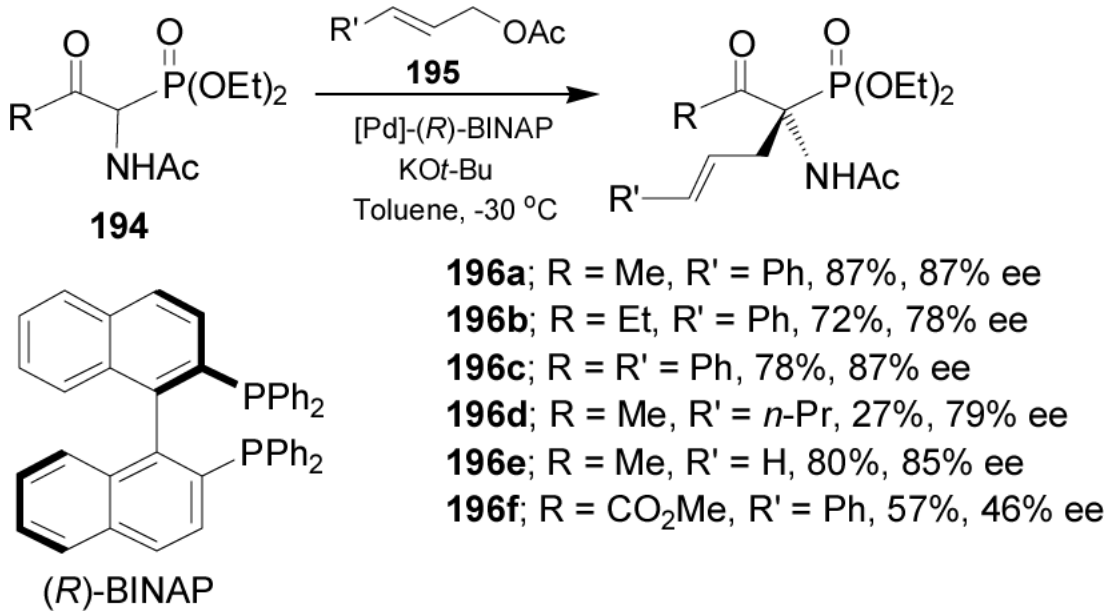
Scheme 48.



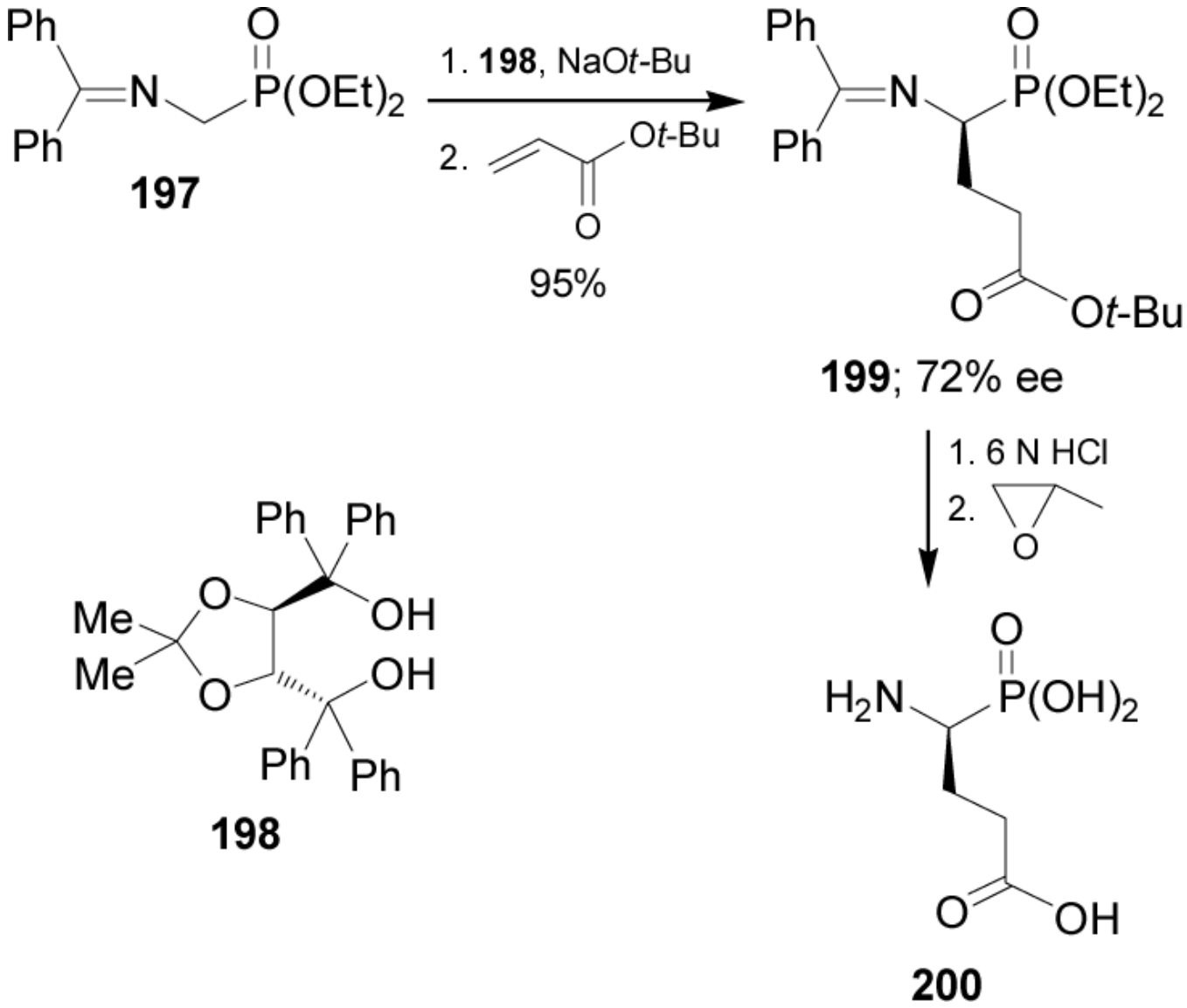
Scheme 49.



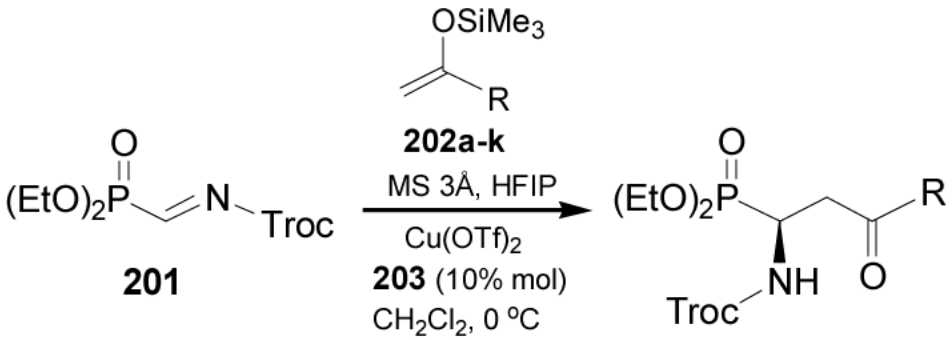
Scheme 50.

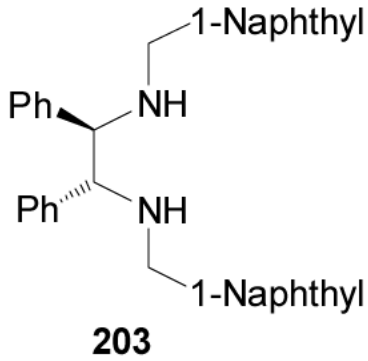


Scheme 51.



Scheme 52.

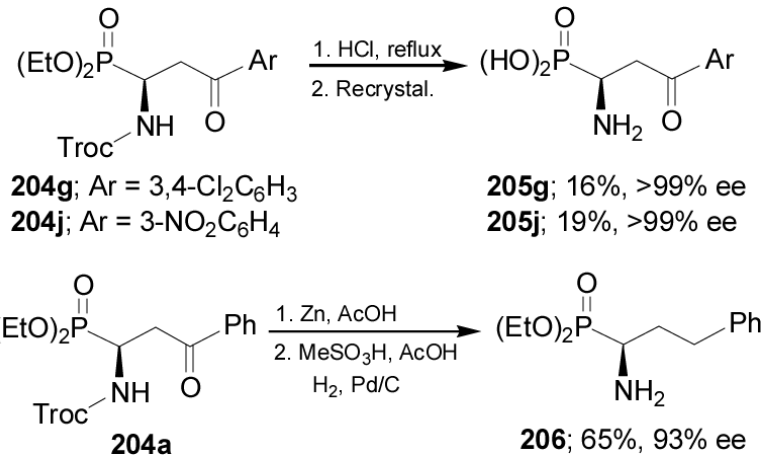




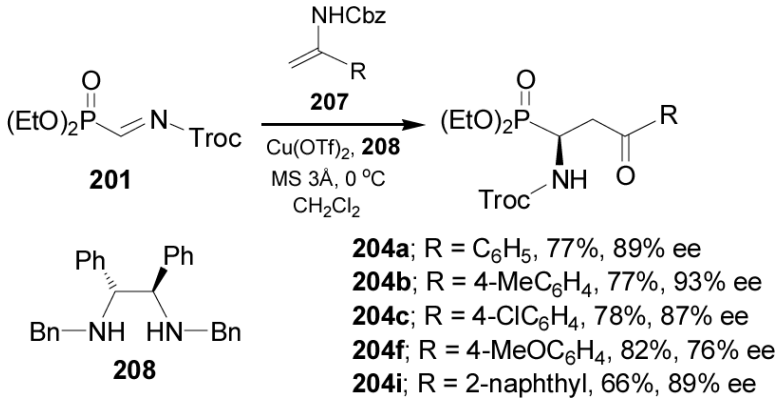
203

204a; R = C_6H_5, 86%, 91% ee
204b; R = 4-MeC_6H_4, 82%, 85% ee
204c; R = 4-ClC_6H_4, 71%, 91% ee
204d; R = 4-BrC_6H_4, 86%, 86% ee
204e; R = 4-IC_6H_4, 80%, 89% ee
204f; R = 4-$MeOC_6H_4$, 82%, 76% ee
204g; R = 3,4-$Cl_2C_6H_3$, 83%, 92% ee
204h; R = 1-naphthyl, 79%, 92% ee
204i; R = 2-naphthyl, 84%, 87% ee
204j; R = 3-$NO_2C_6H_4$, 88%, 94% ee
204k; R = Me, 70%, 89% ee

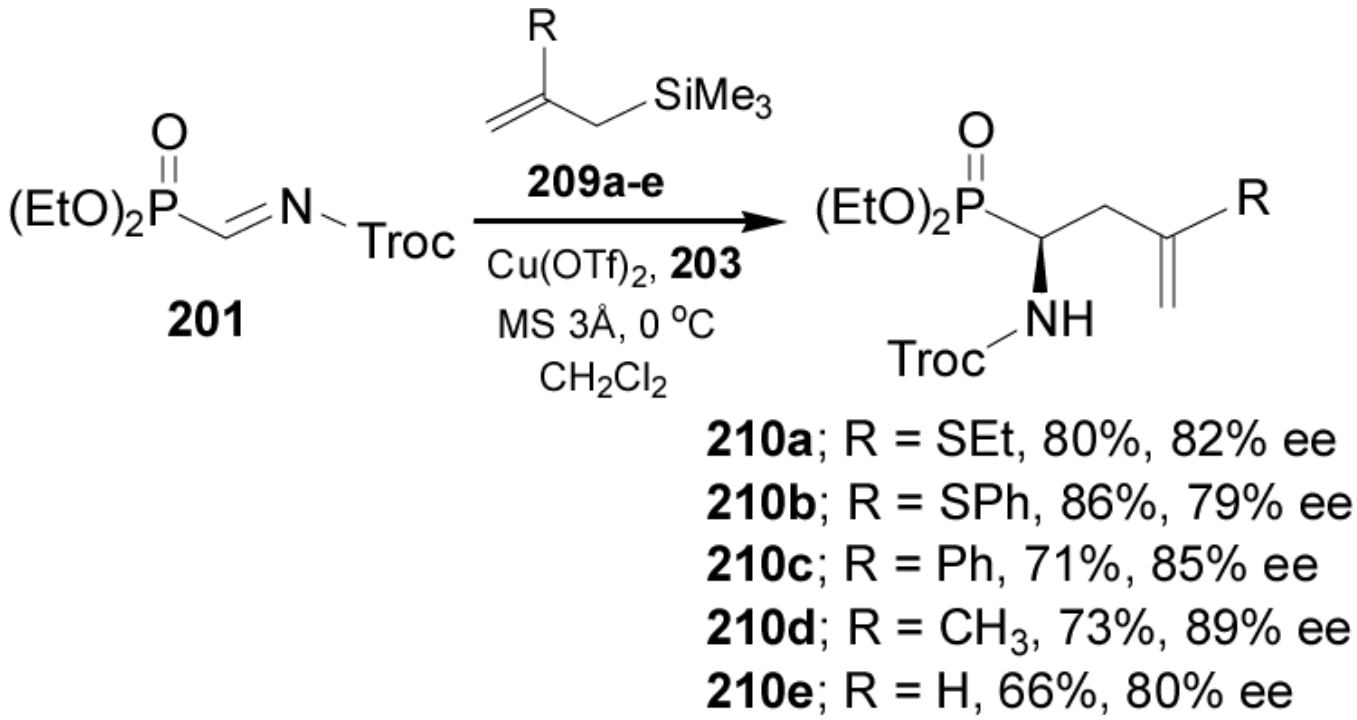
Scheme 53.



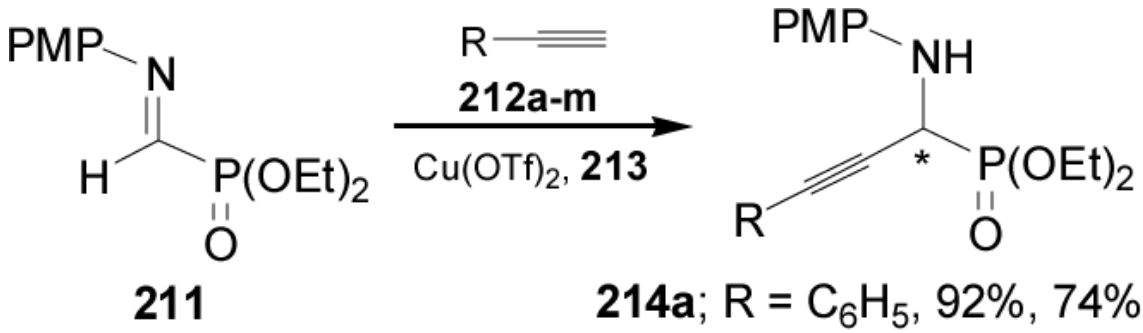
Scheme 54.

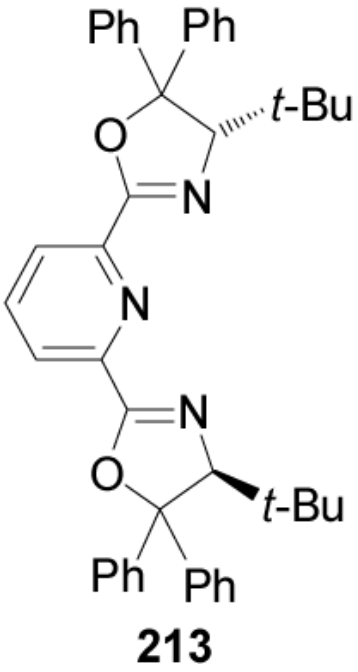


Scheme 55.



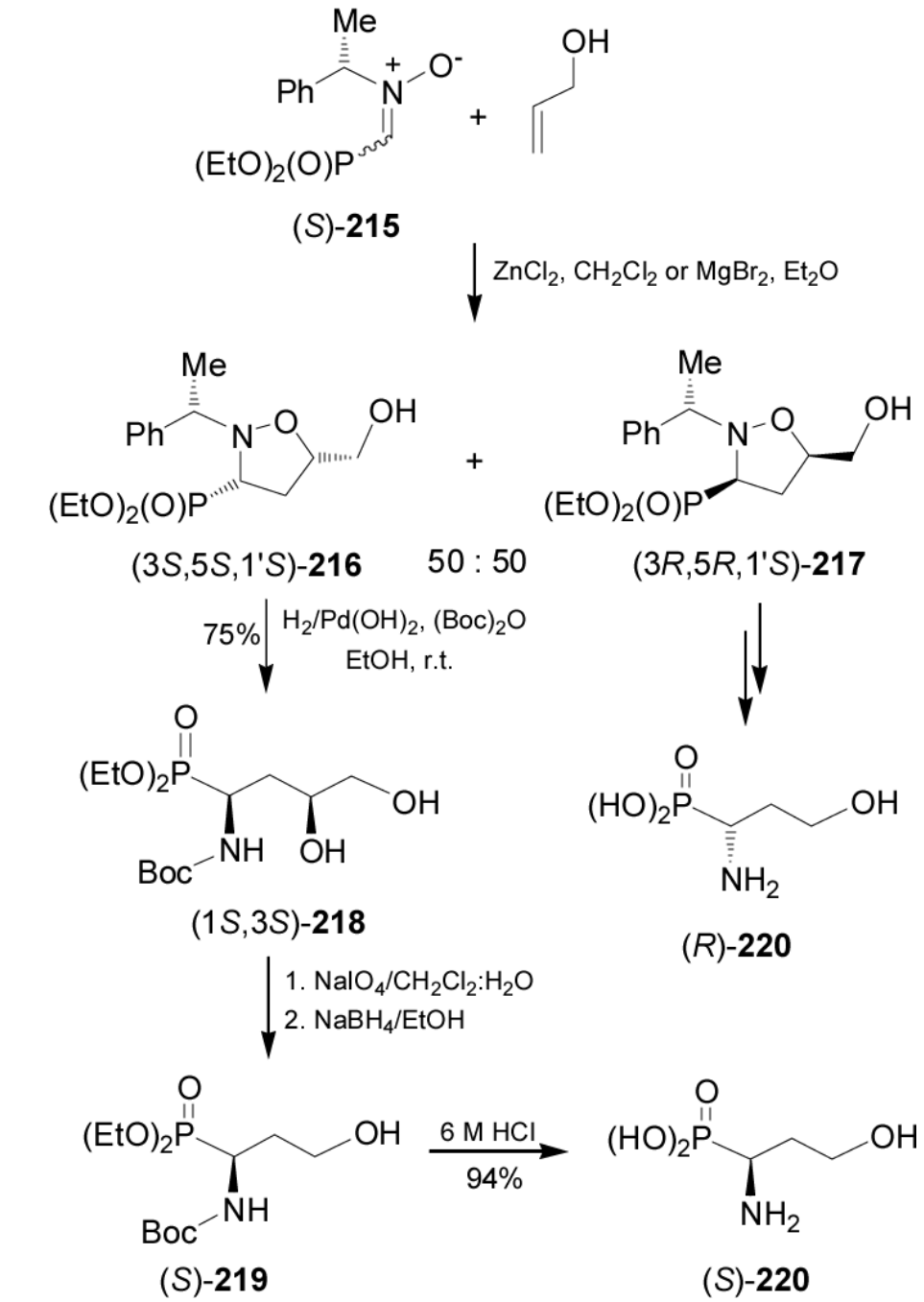
Scheme 56.



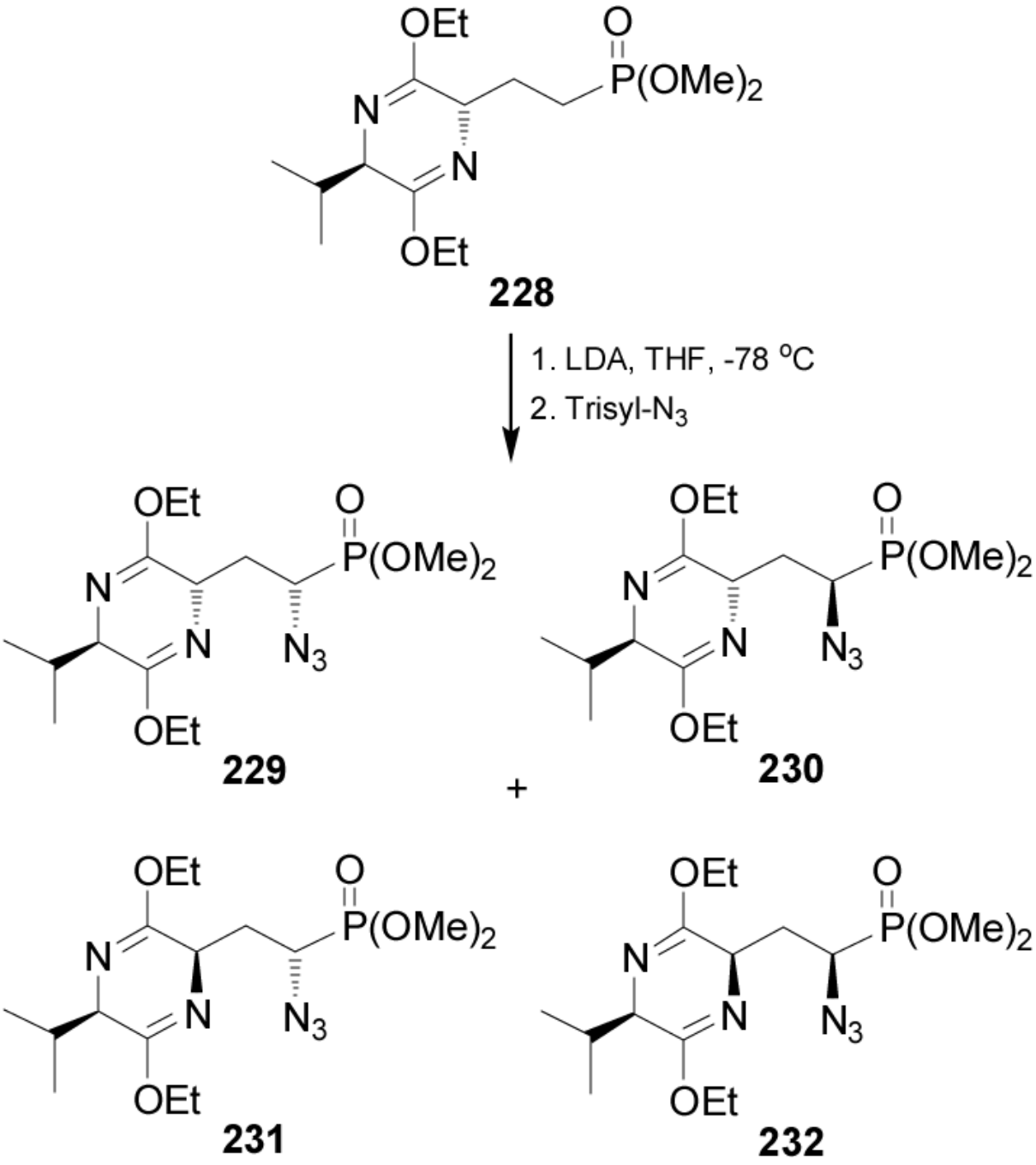


214a; R = C_6H_5, 92%, 74% ee
214b; R = 4-BrC_6H_4, 88%, 74% ee
214c; R = 2-BrC_6H_4, 85%, 68% ee
214d; R = 4-ClC_6H_4, 90%, 74% ee
214e; R = 4-FC_6H_4, 91%, 68% ee
214f; R = 4-$CF_3C_6H_4$, 81%, 75% ee
214g; R = 4-$CH_3C_6H_4$, 86%, 75% ee
214h; R = 3-$CH_3C_6H_4$, 80%, 74% ee
214i; R = 4-$CH_3OC_6H_4$, 88%, 70% ee
214j; R = 3,5-$F_2C_6H_3$, 82%, 81% ee
214k; R = 1-Naphthyl, 72%, 60% ee
214l; R = $CH_3(CH_2)_4$, 69%, 64% ee
214m; R = $PhCH_2CH_2$, 56%, 67% ee

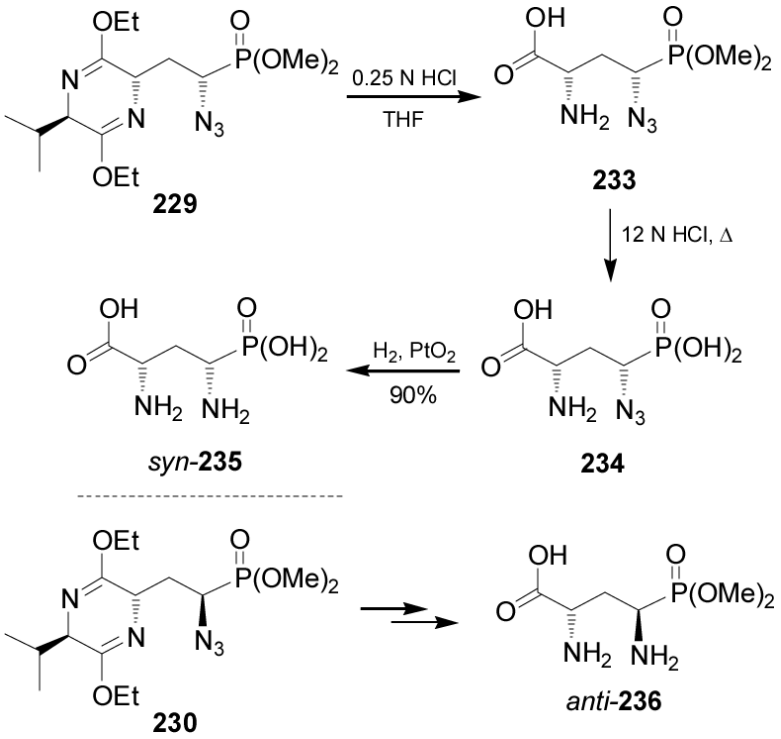
Scheme 57.



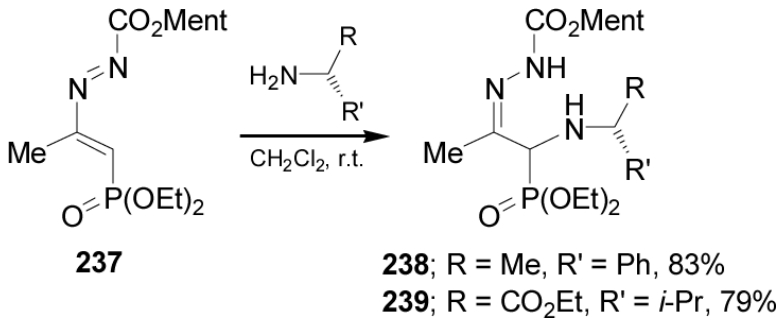
Scheme 58.



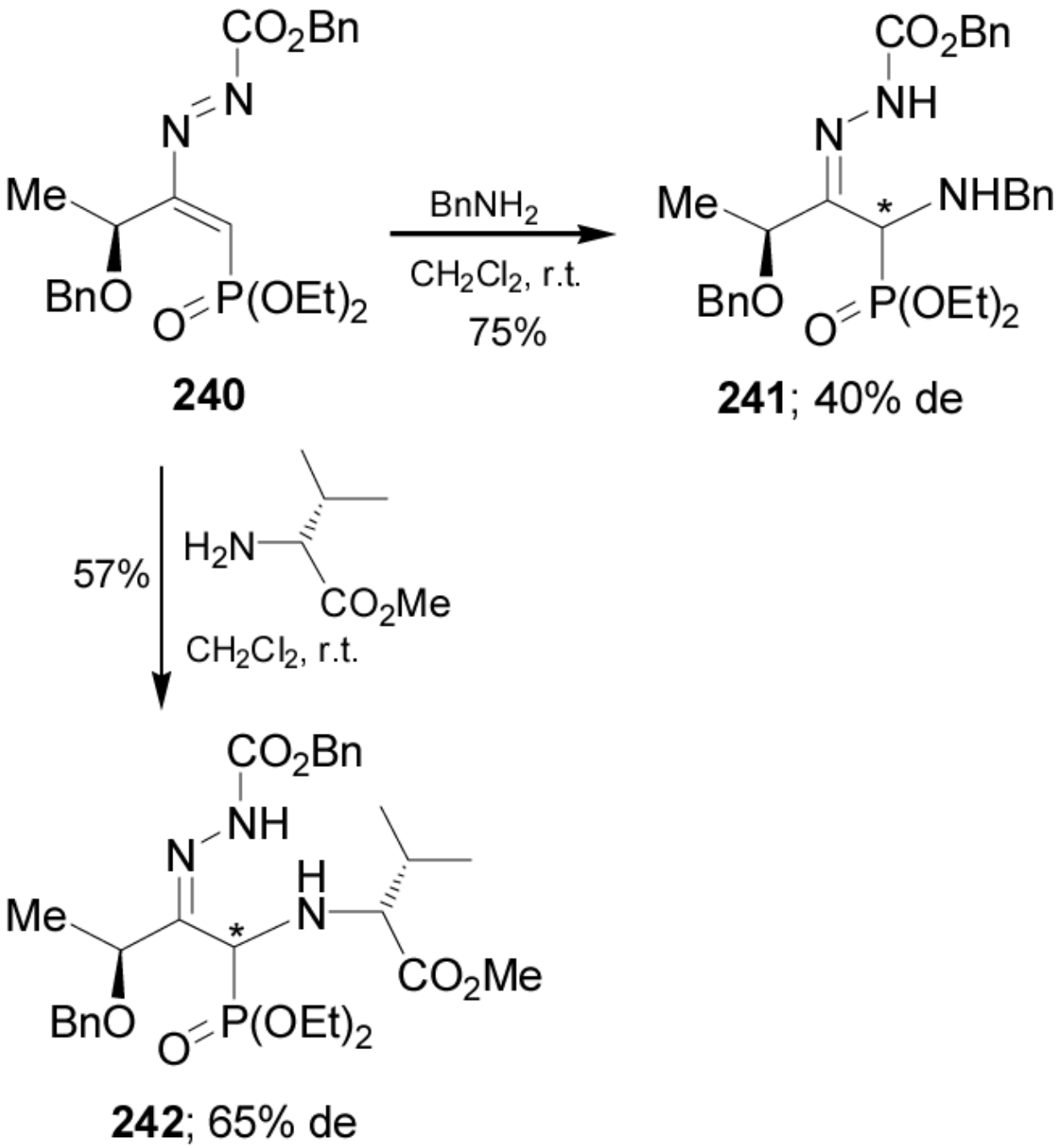
Scheme 59.



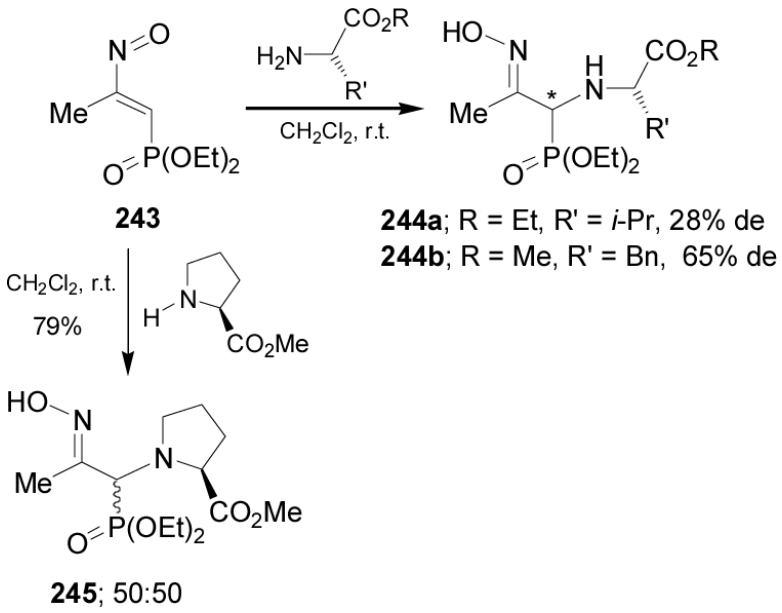
Scheme 60.



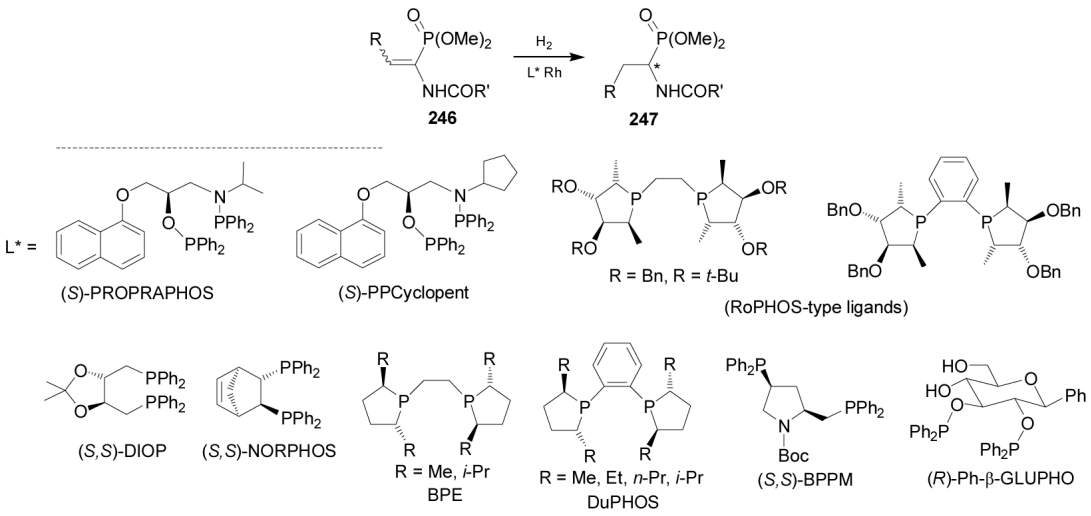
Scheme 61.



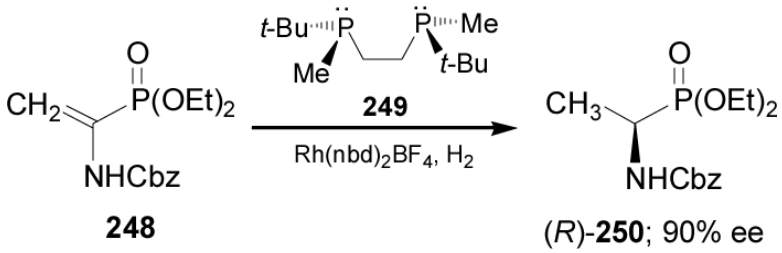
Scheme 62.



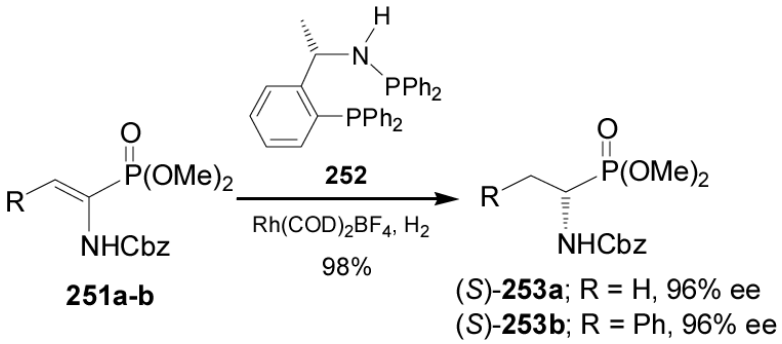
Scheme 63.



Scheme 64.

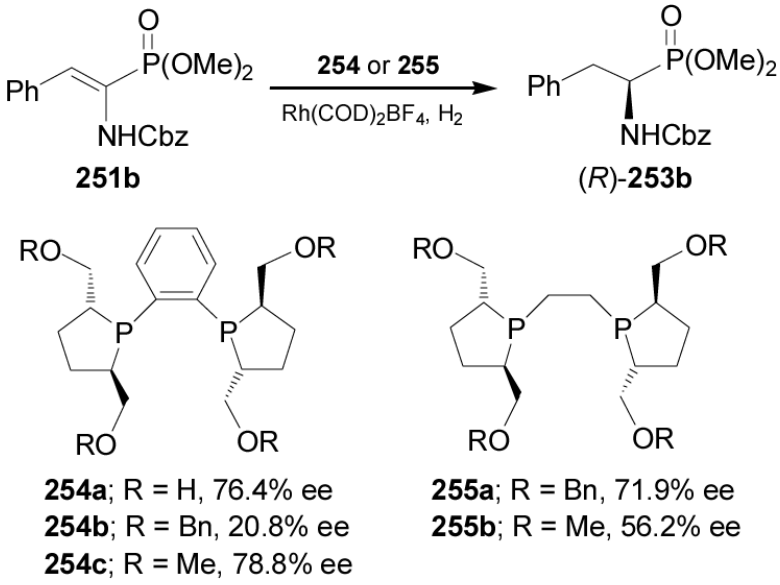


Scheme 65.

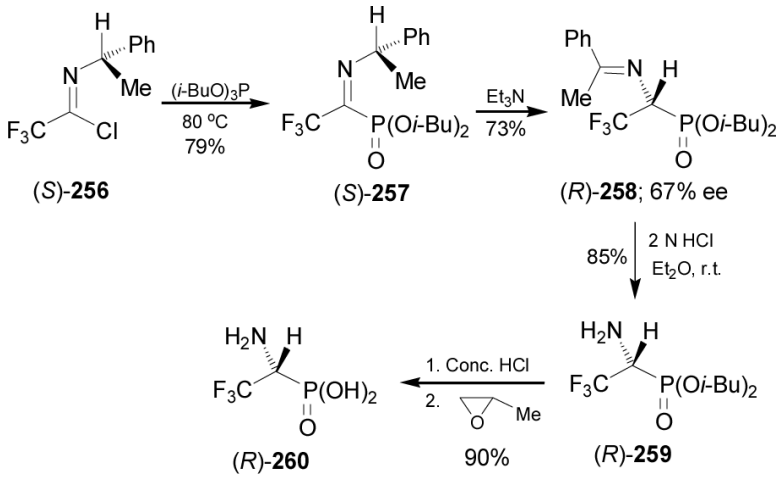


251a-b

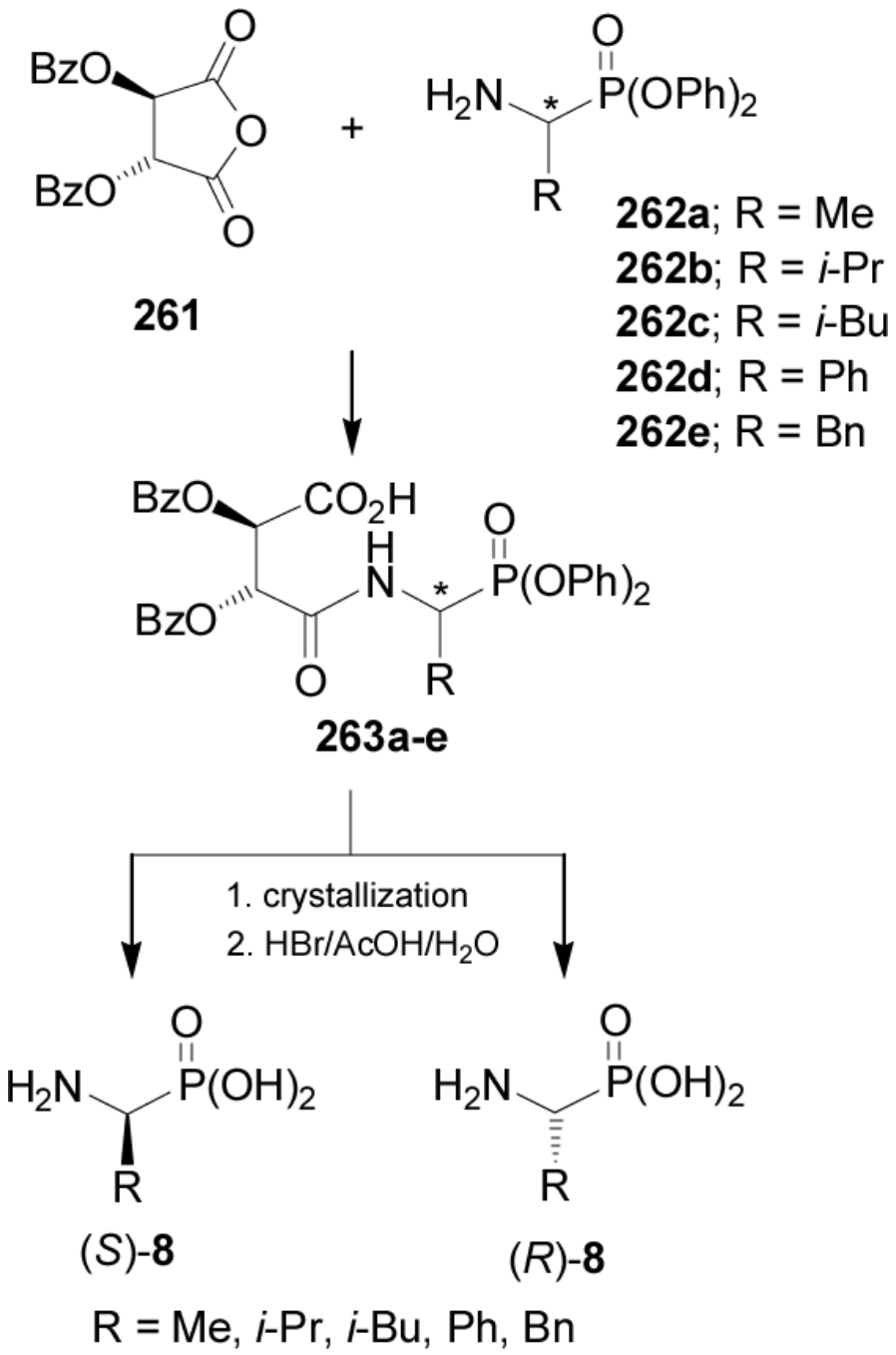
Scheme 66.



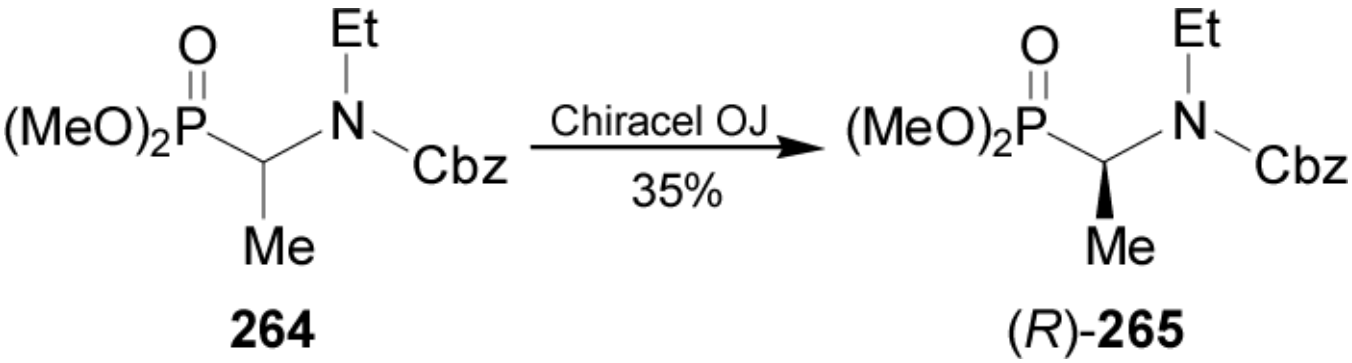
Scheme 67.



Scheme 68.

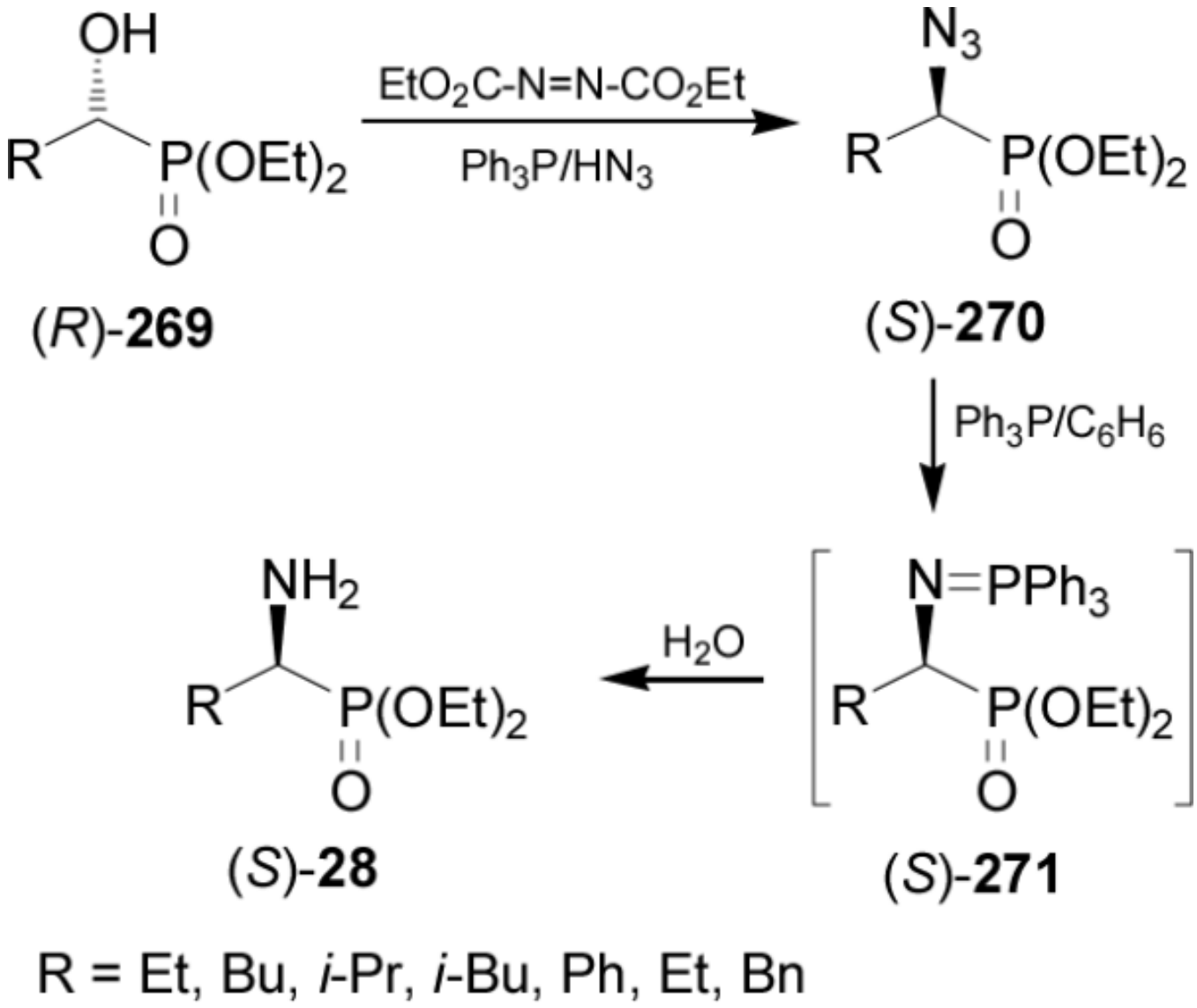


Scheme 69.

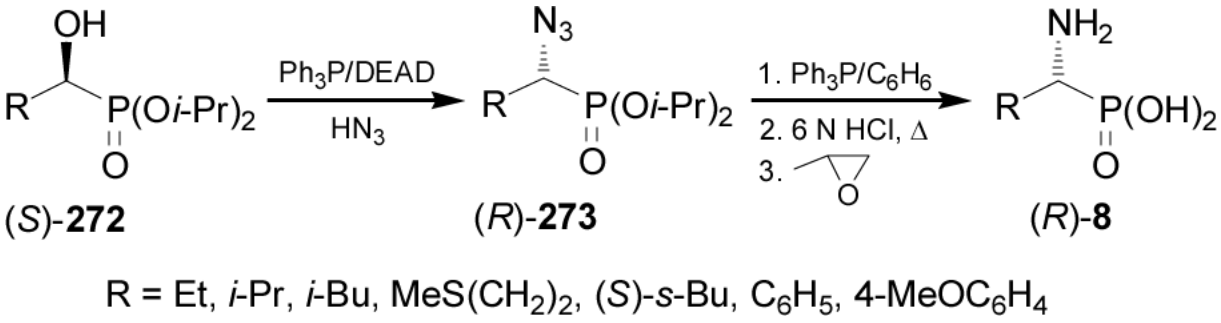


264 (*R*)-**265**

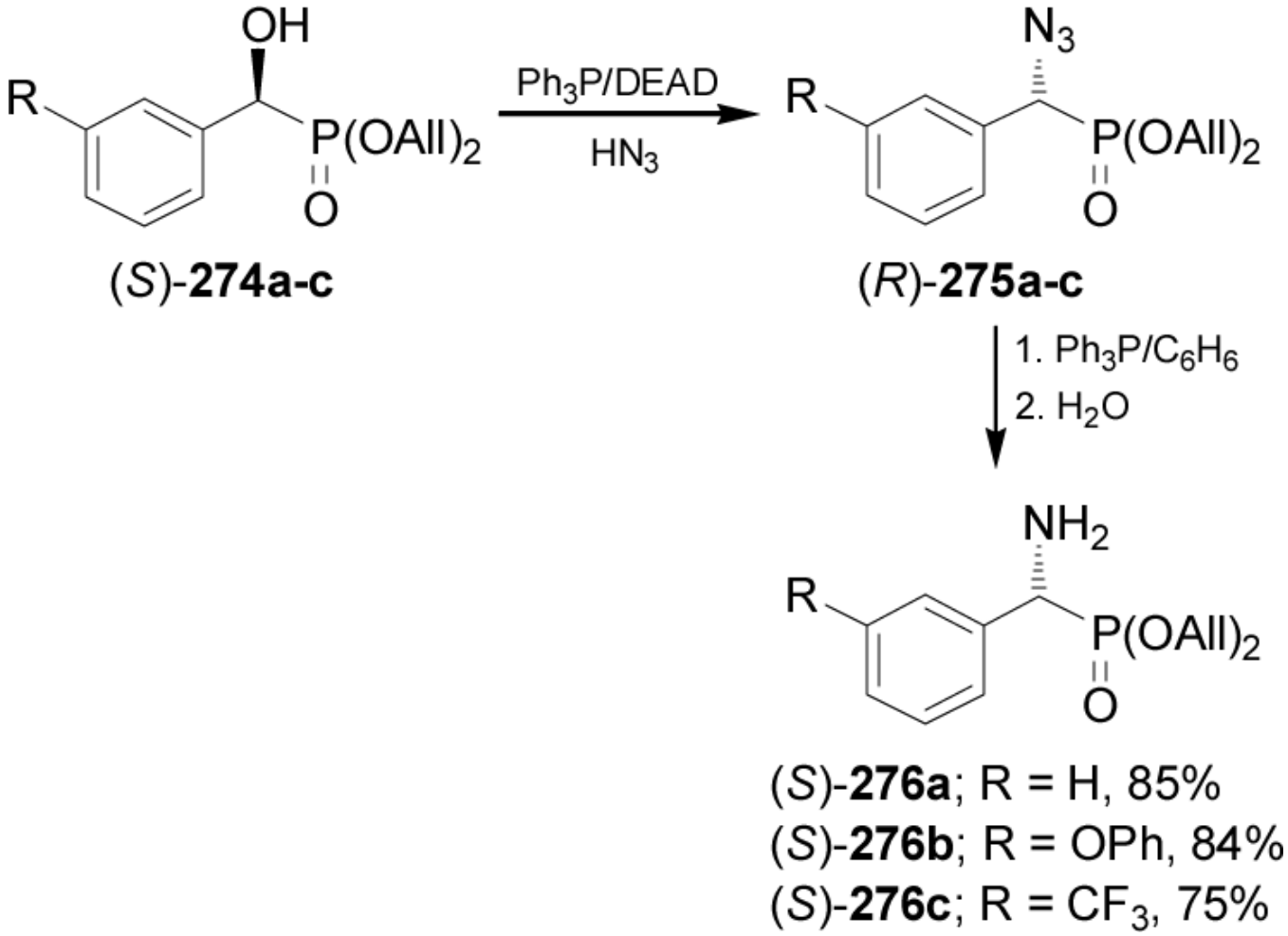
Scheme 70.



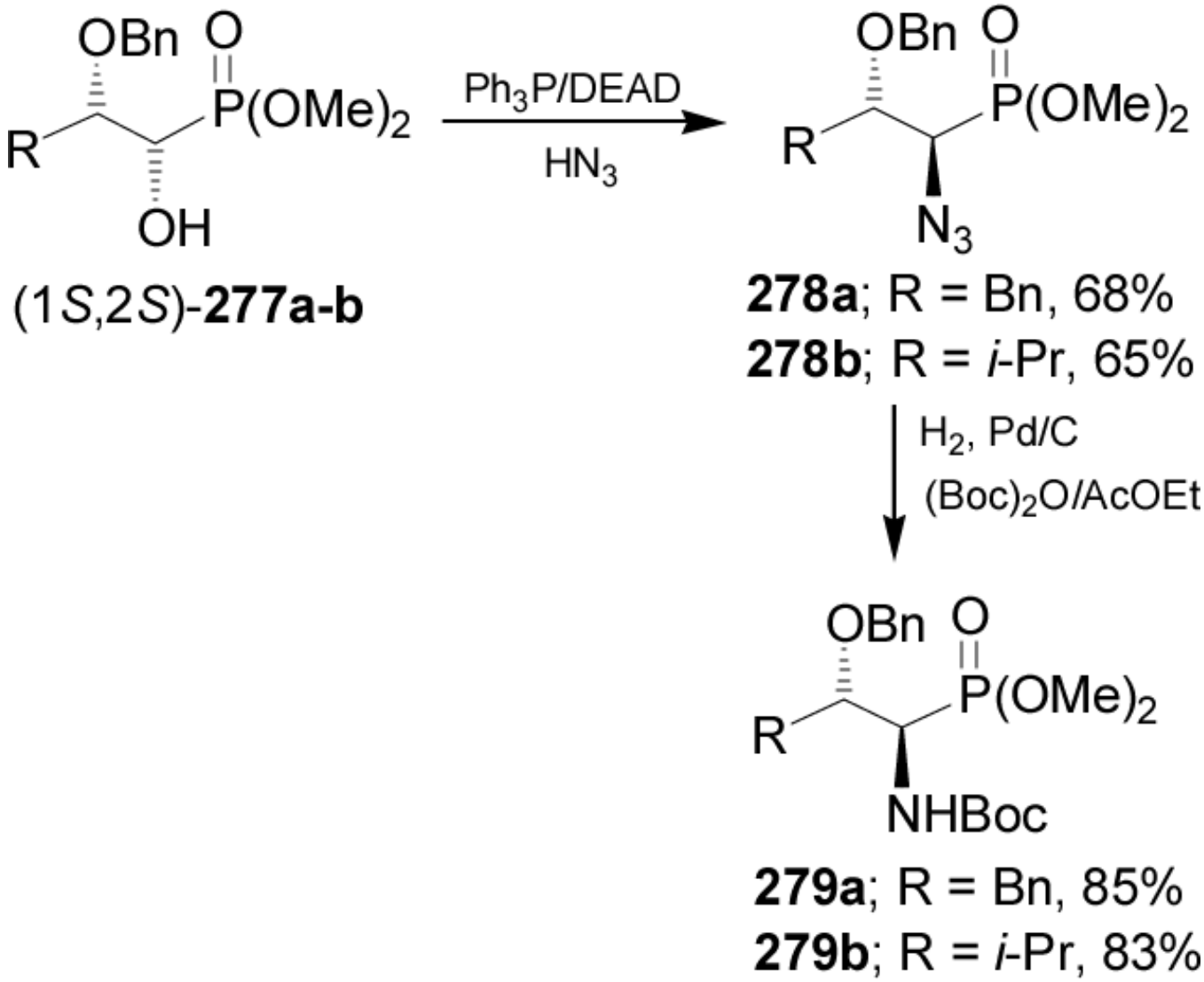
Scheme 71.



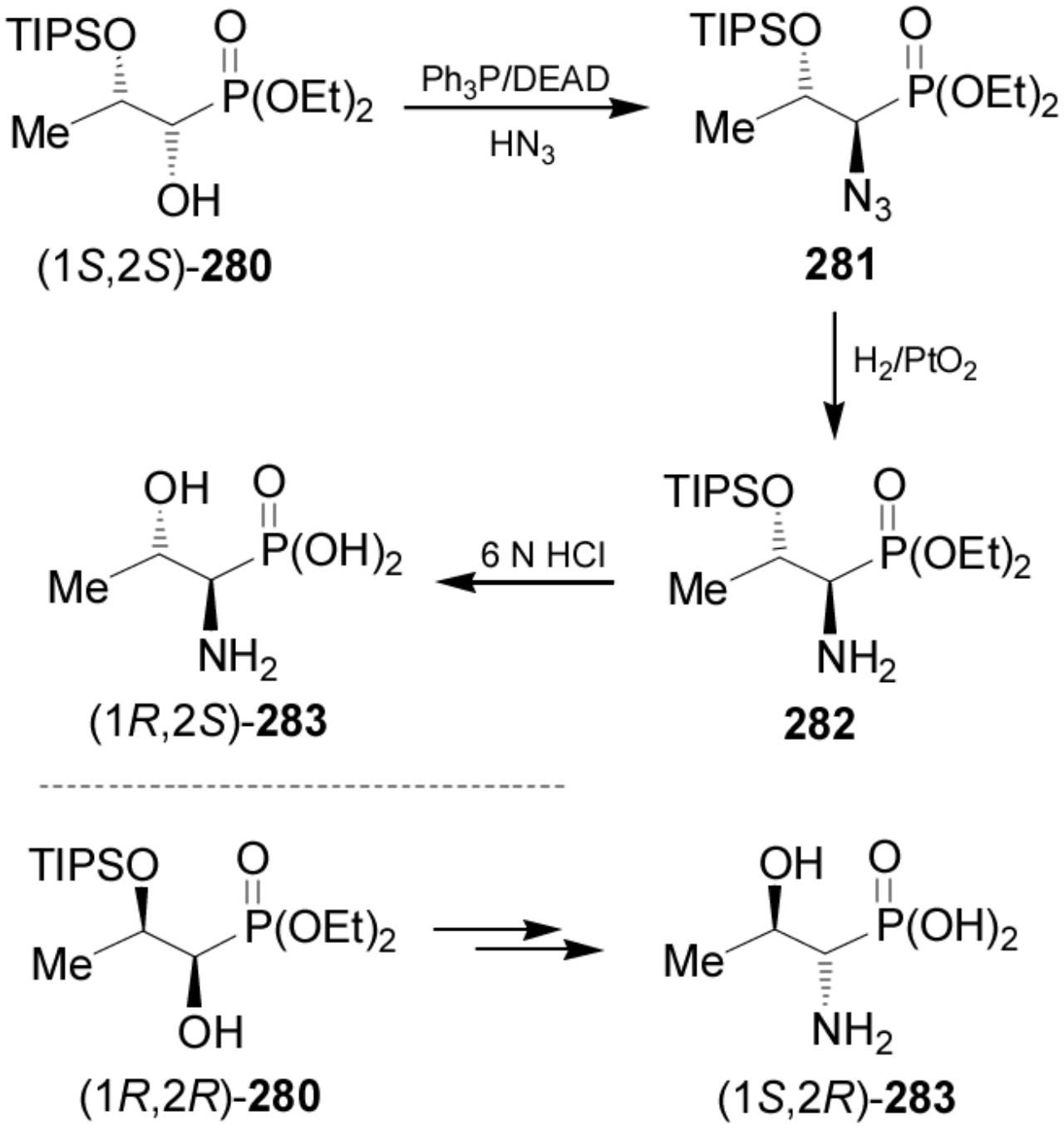
Scheme 72.



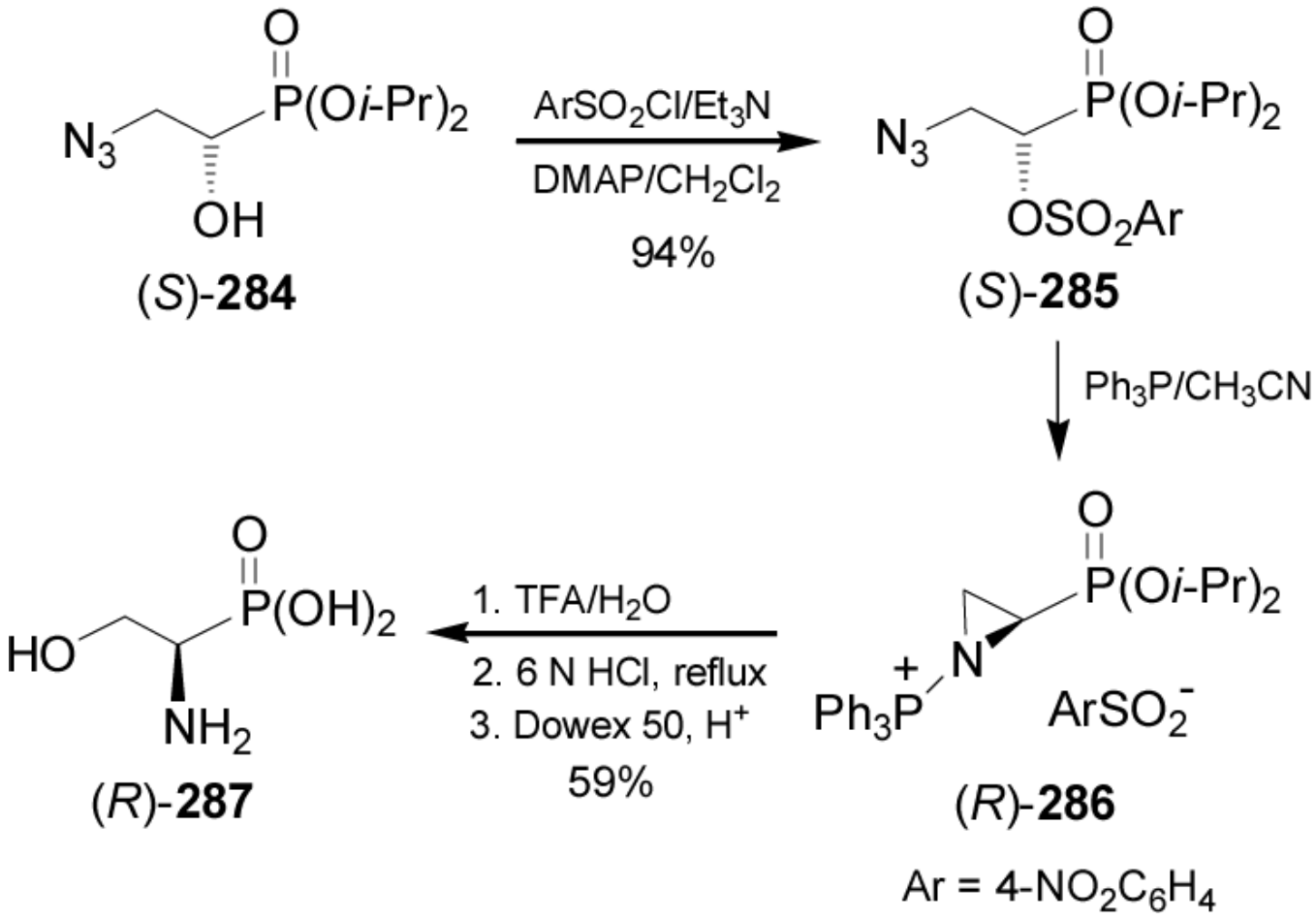
Scheme 73.



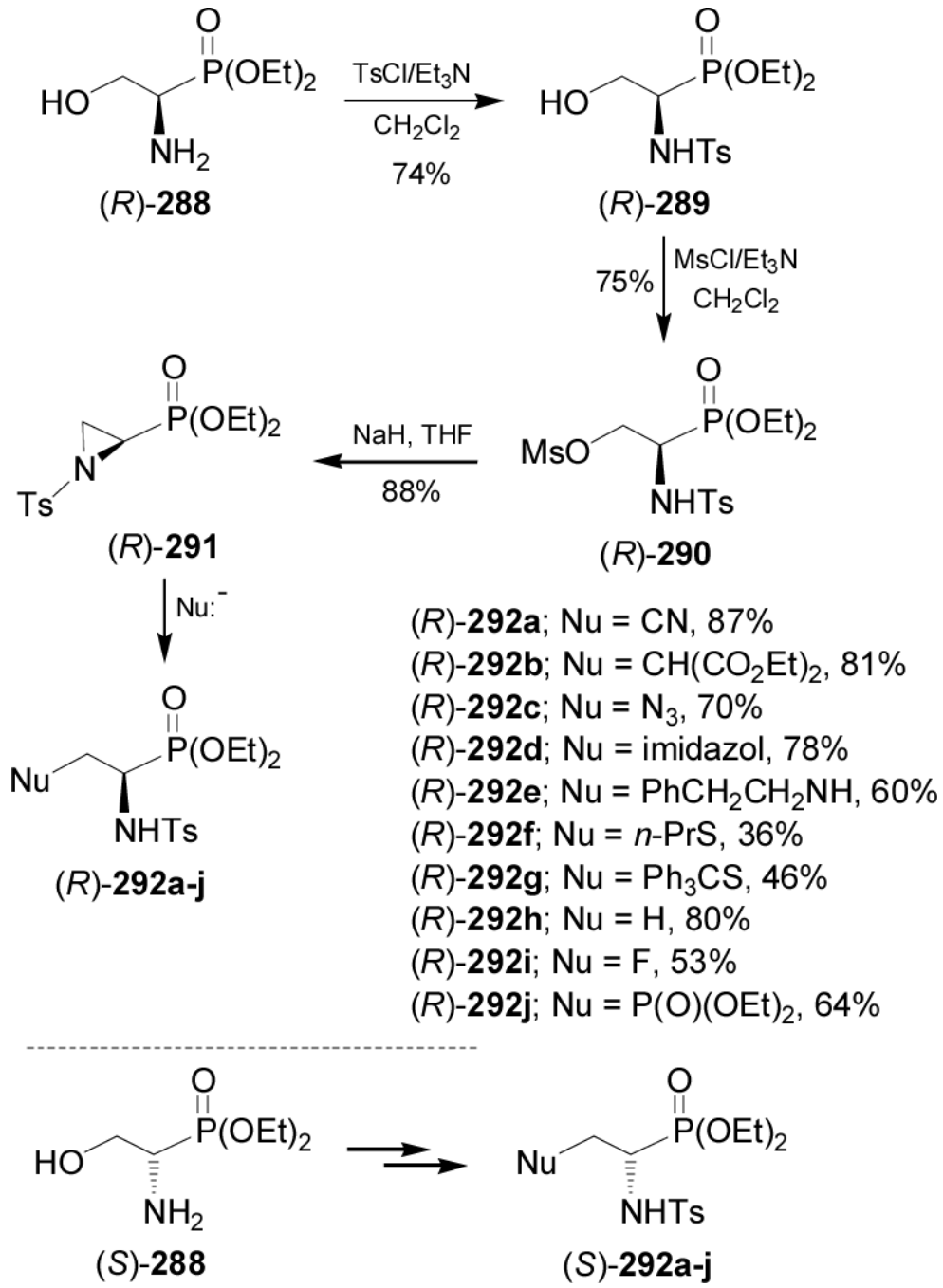
Scheme 74.



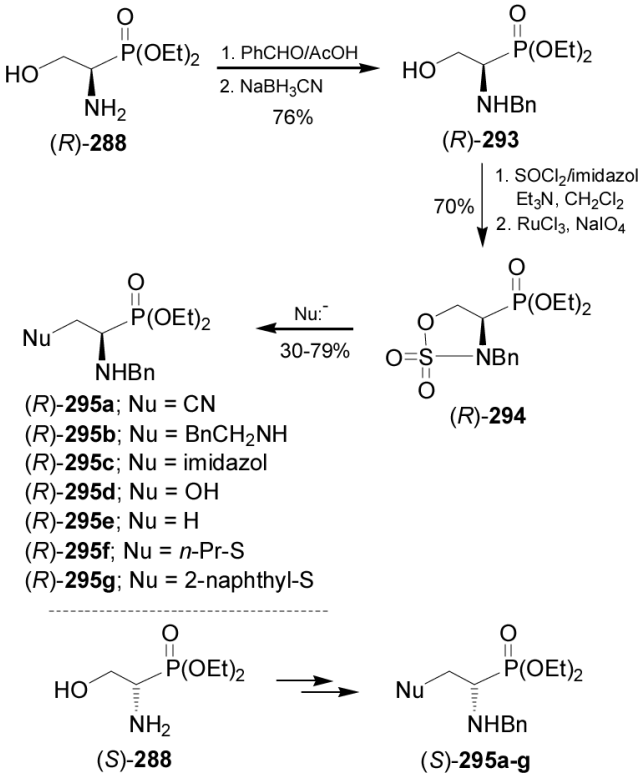
Scheme 75.



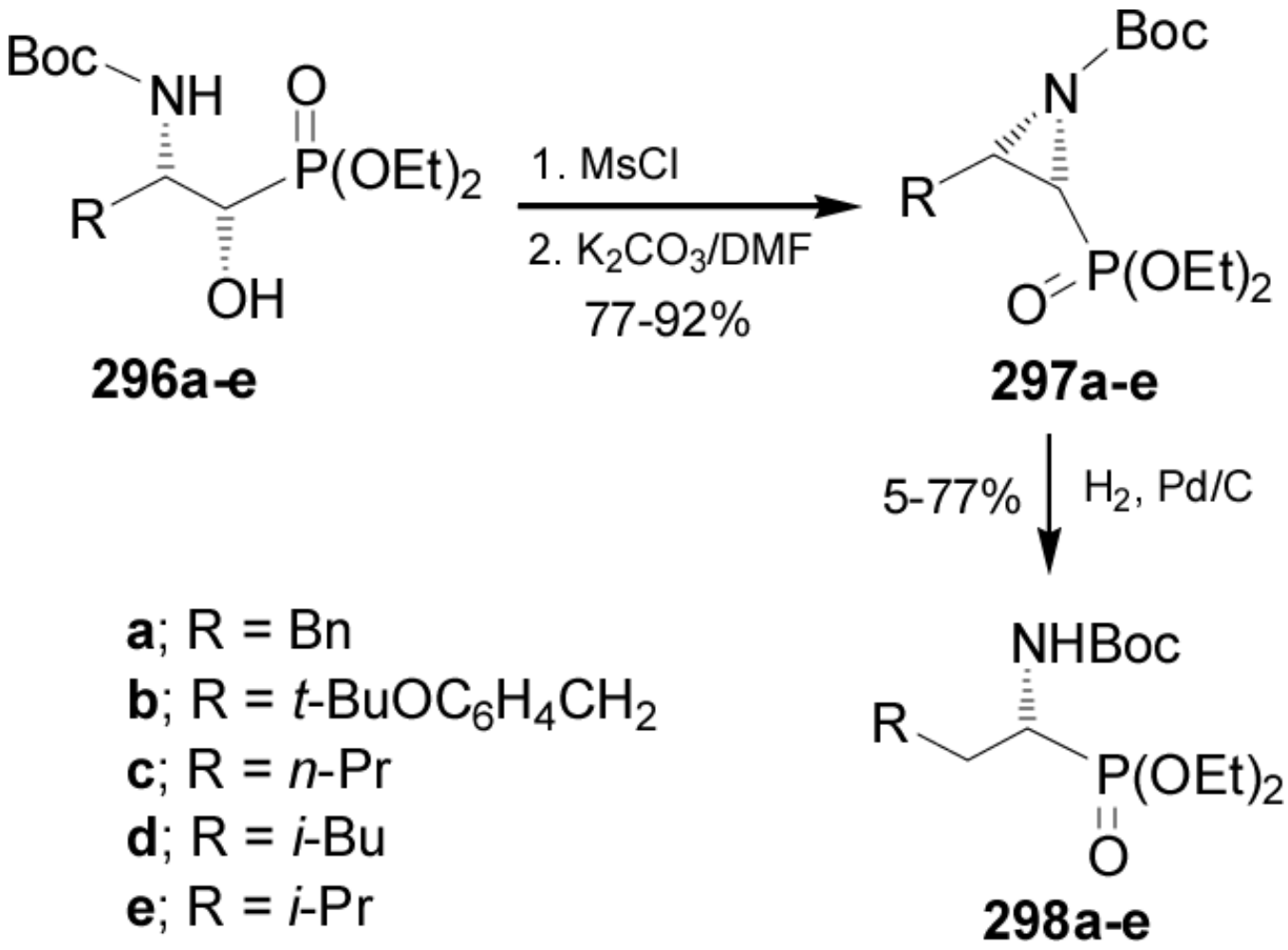
Scheme 76.



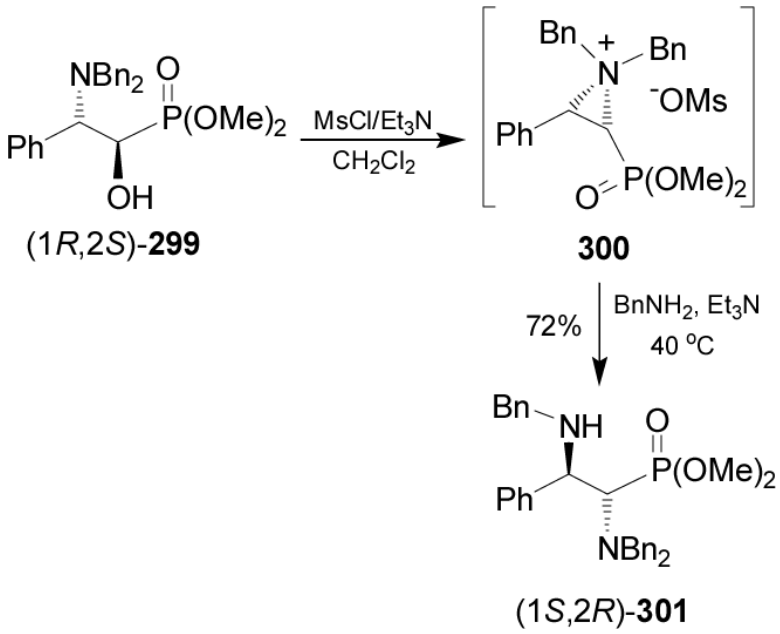
Scheme 77.



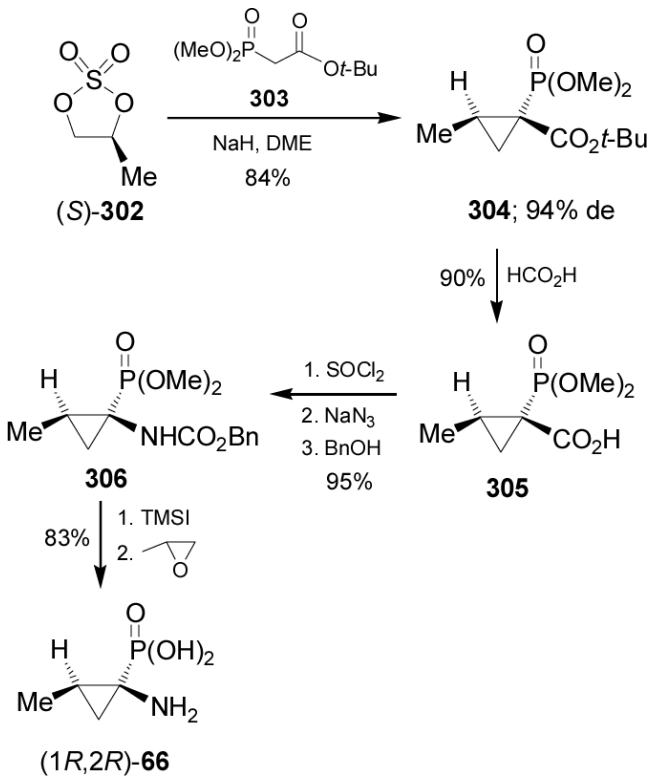
Scheme 78.



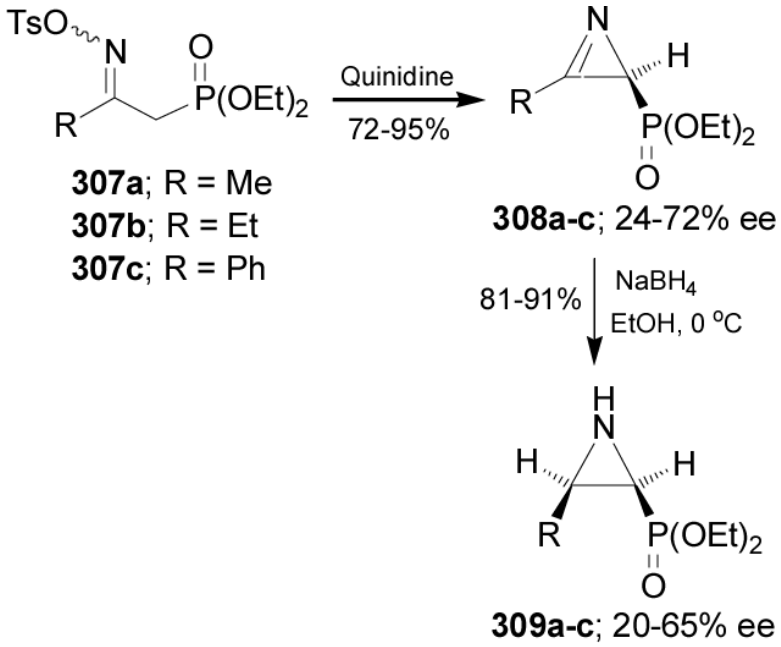
Scheme 79.



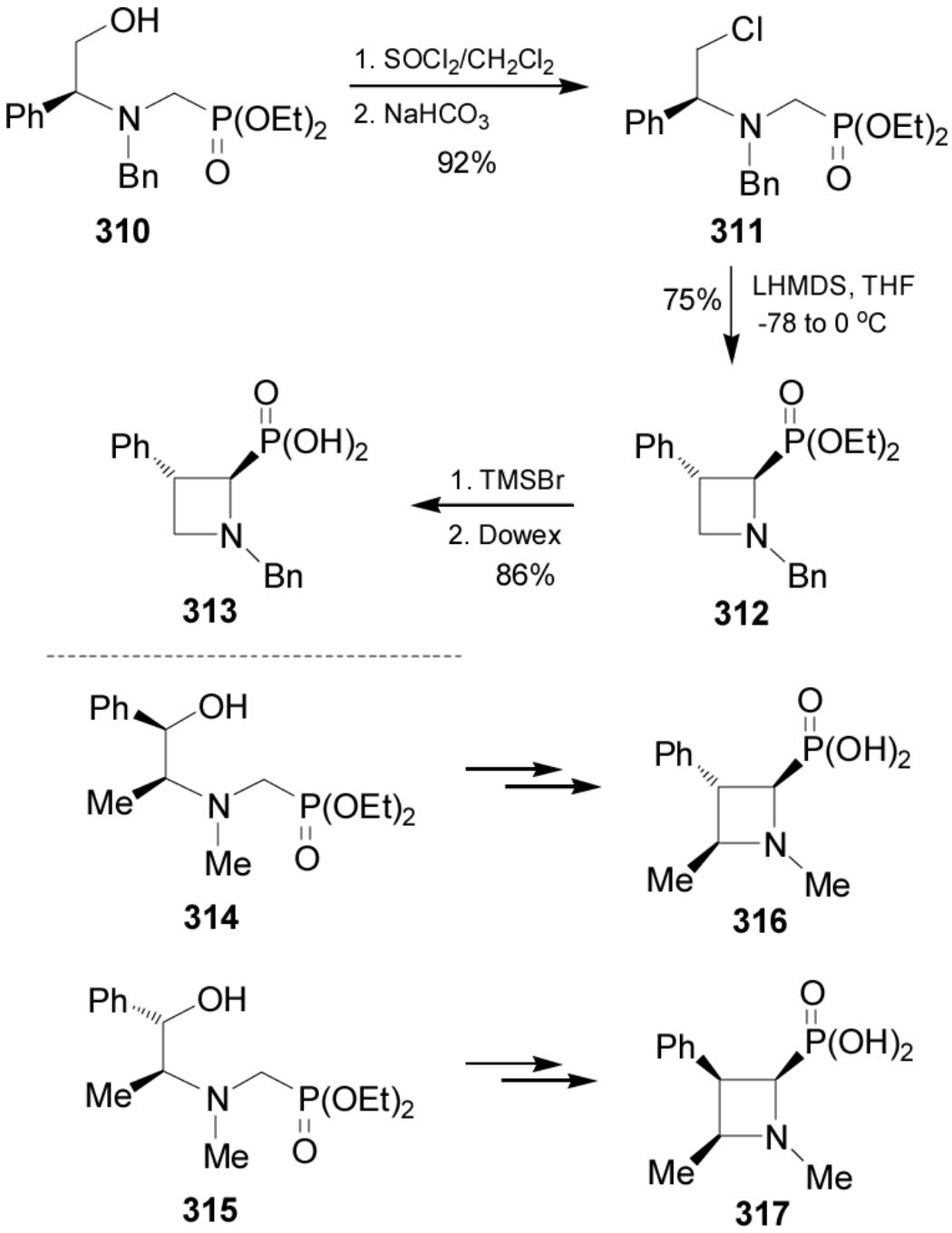
Scheme 80.



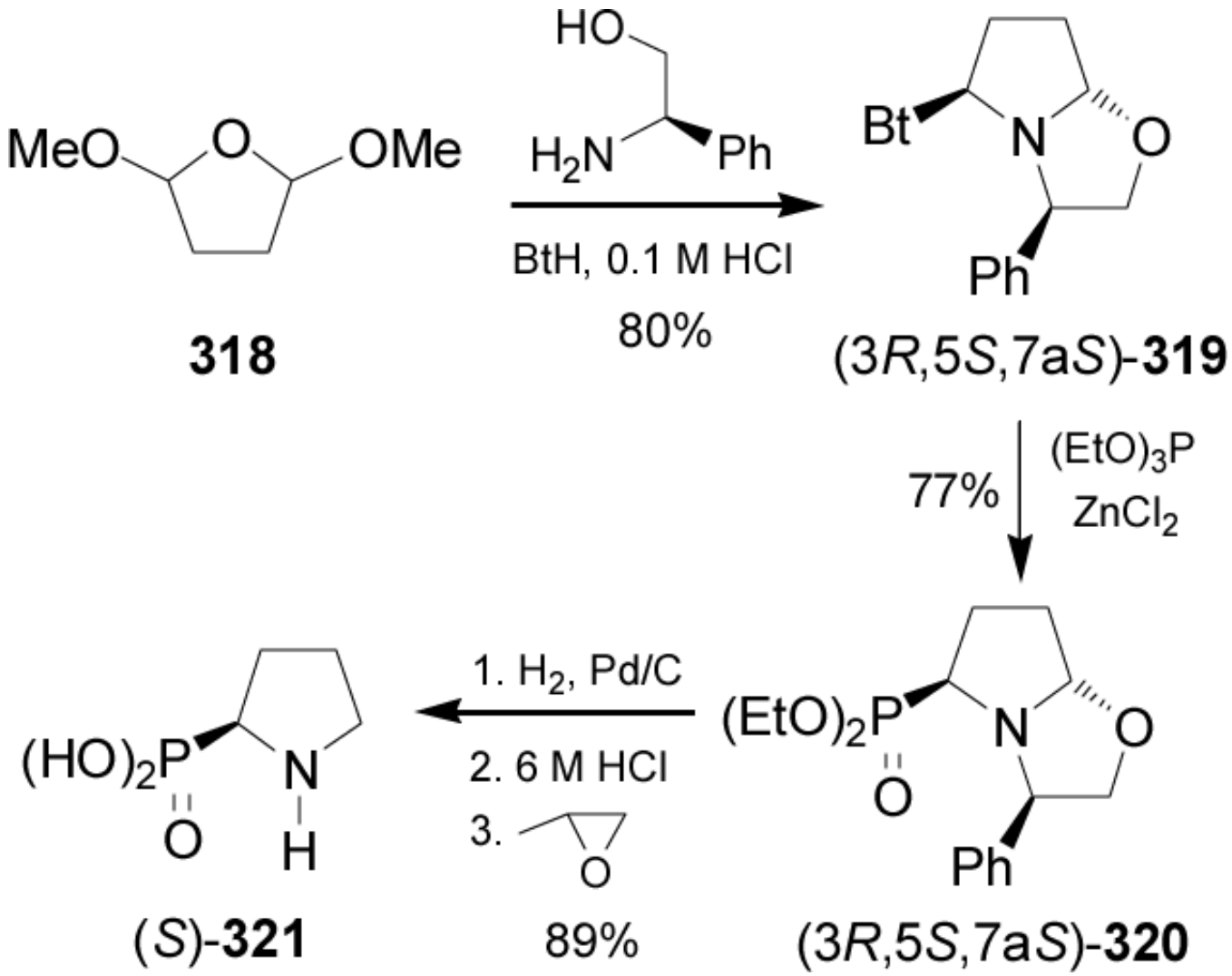
Scheme 81.



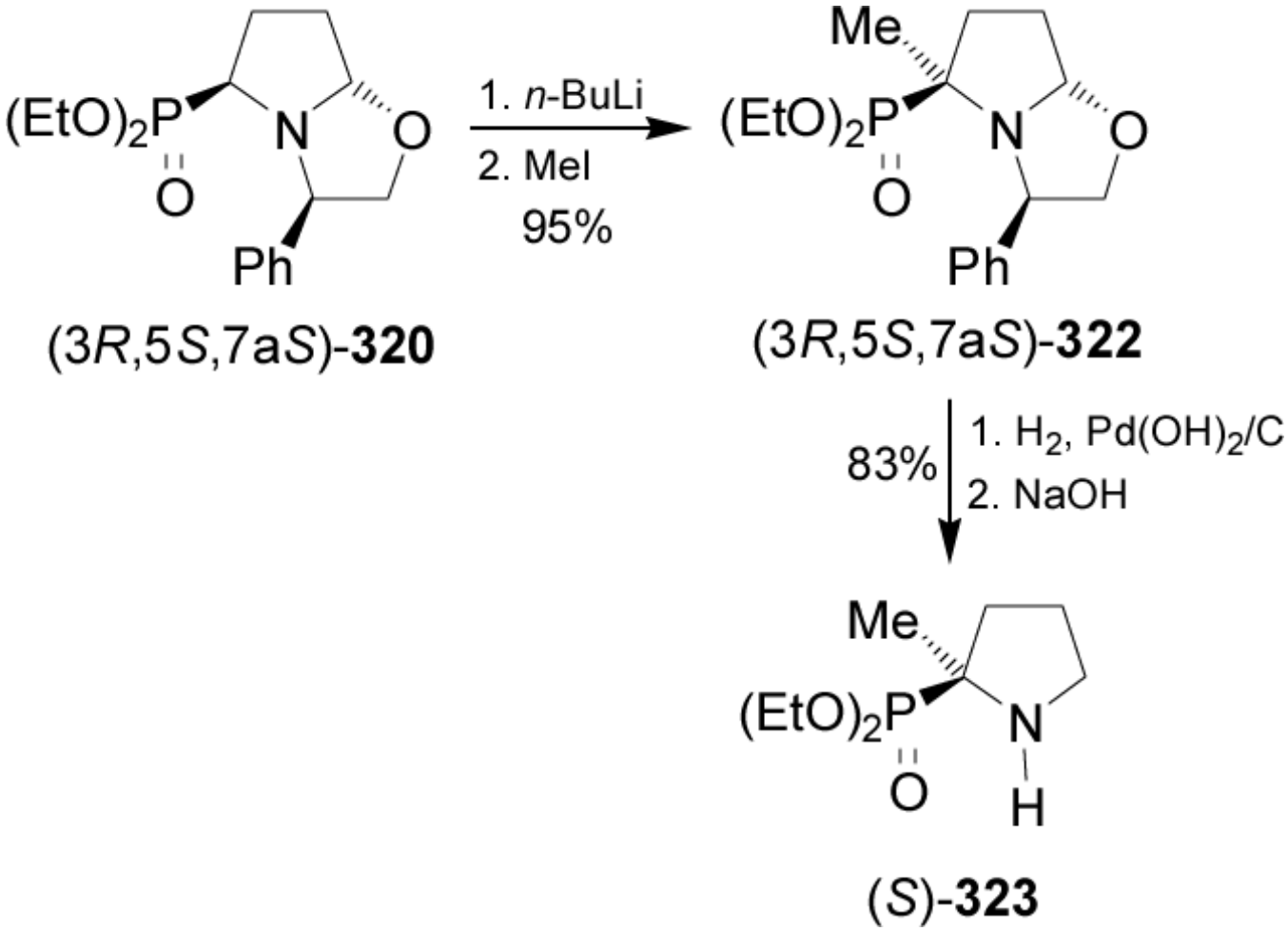
Scheme 82.



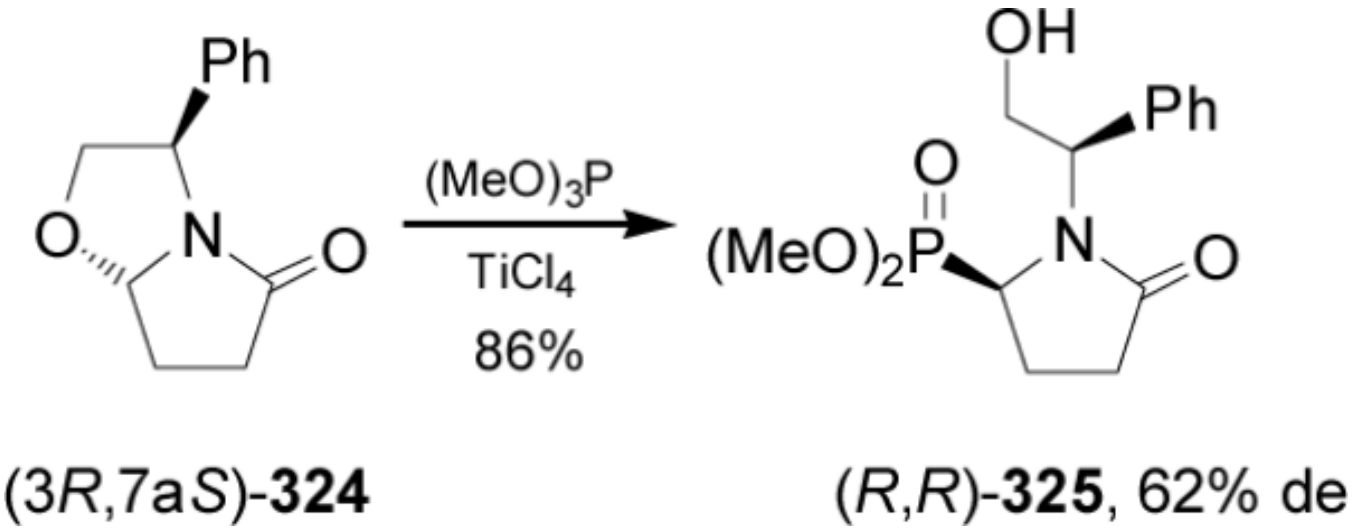
Scheme 83.



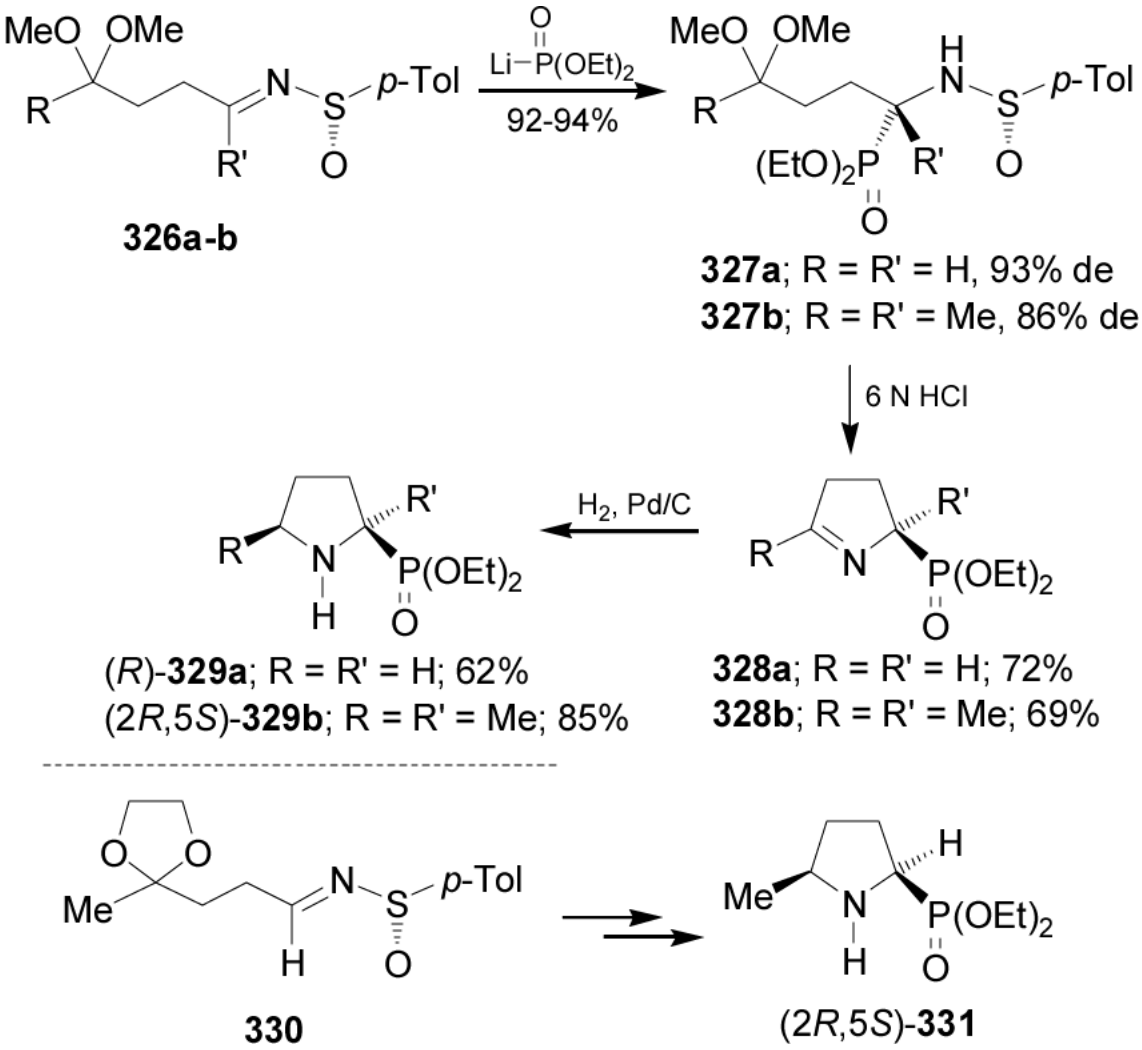
Scheme 84.



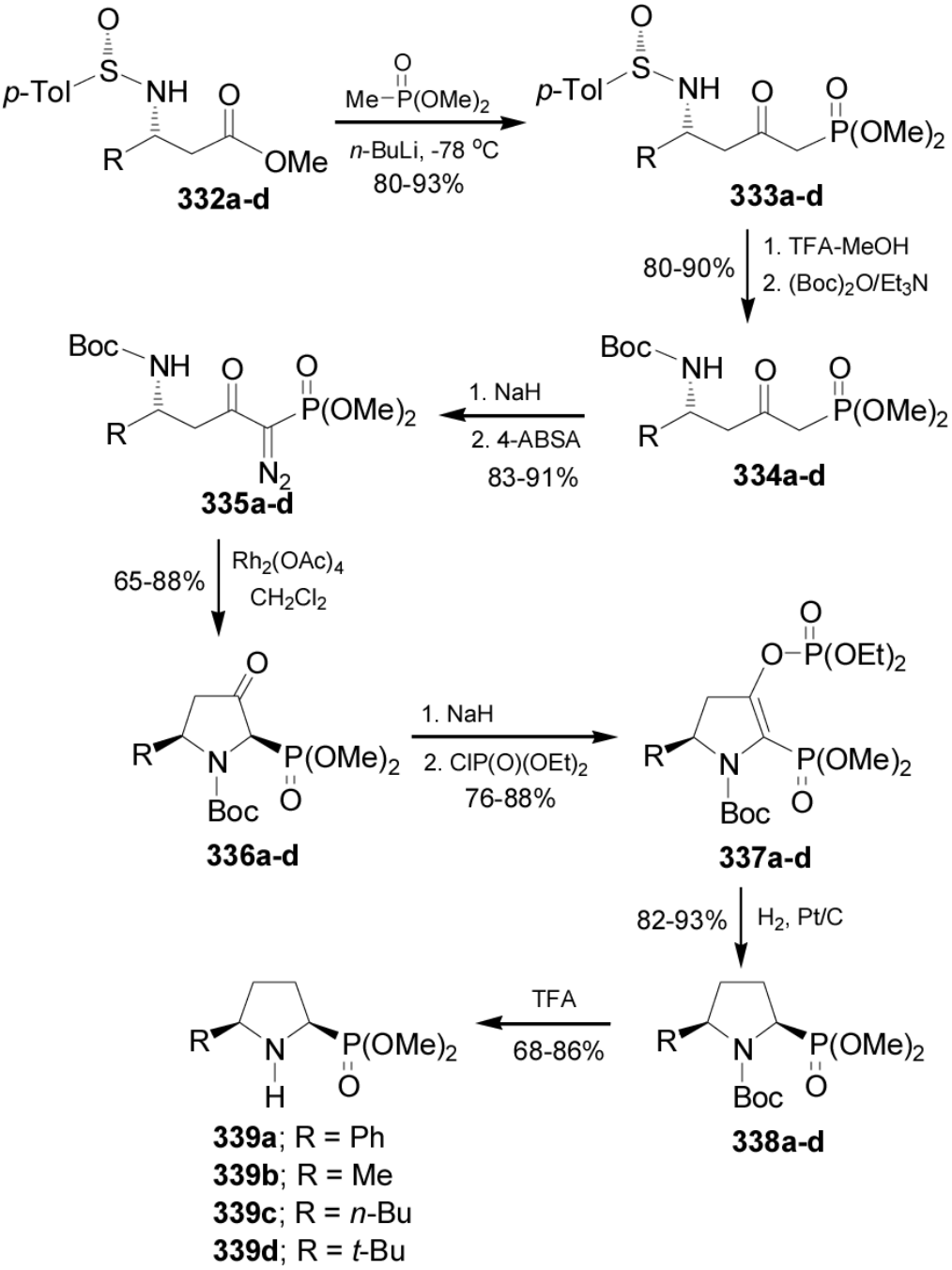
Scheme 85.



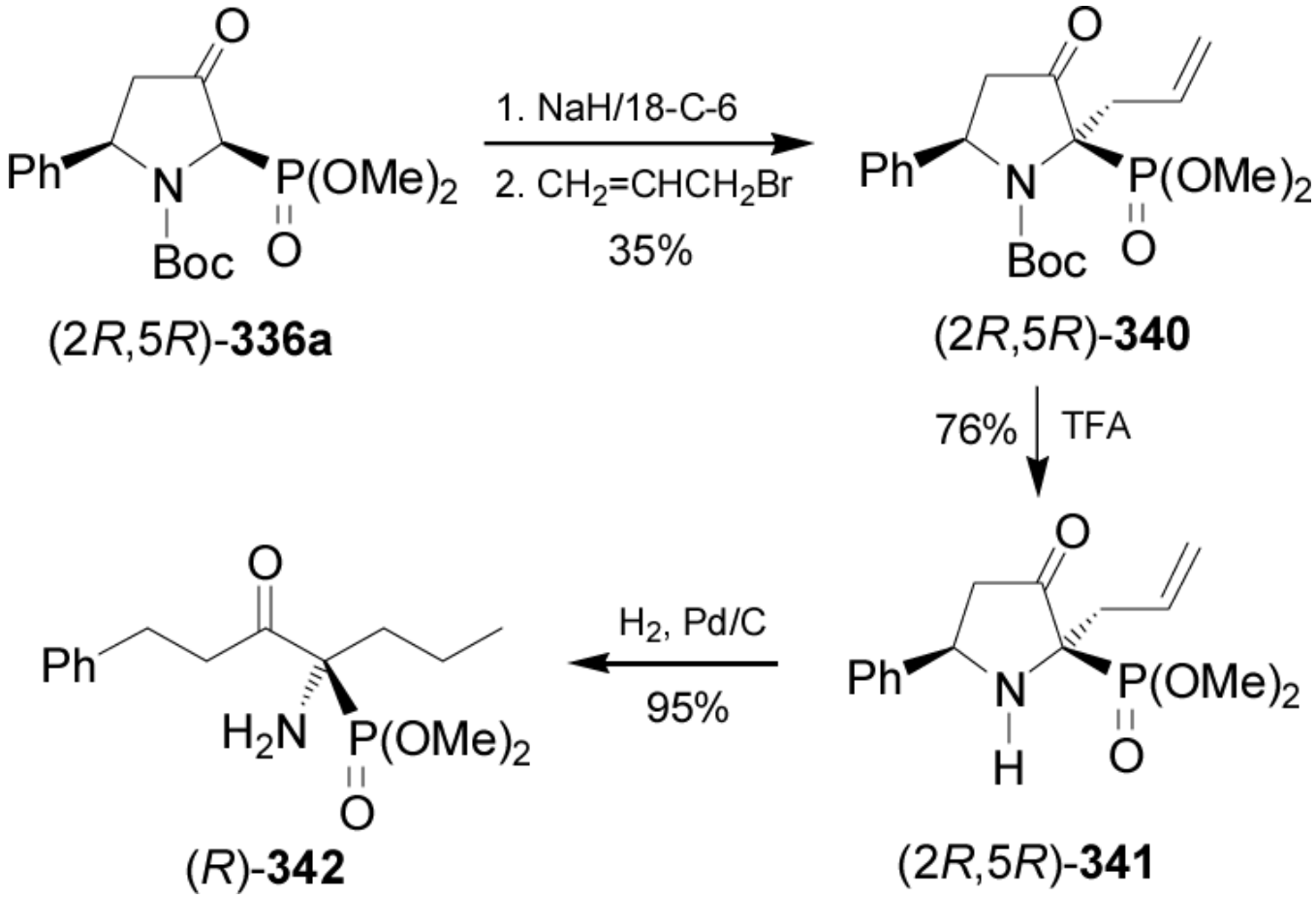
Scheme 86.



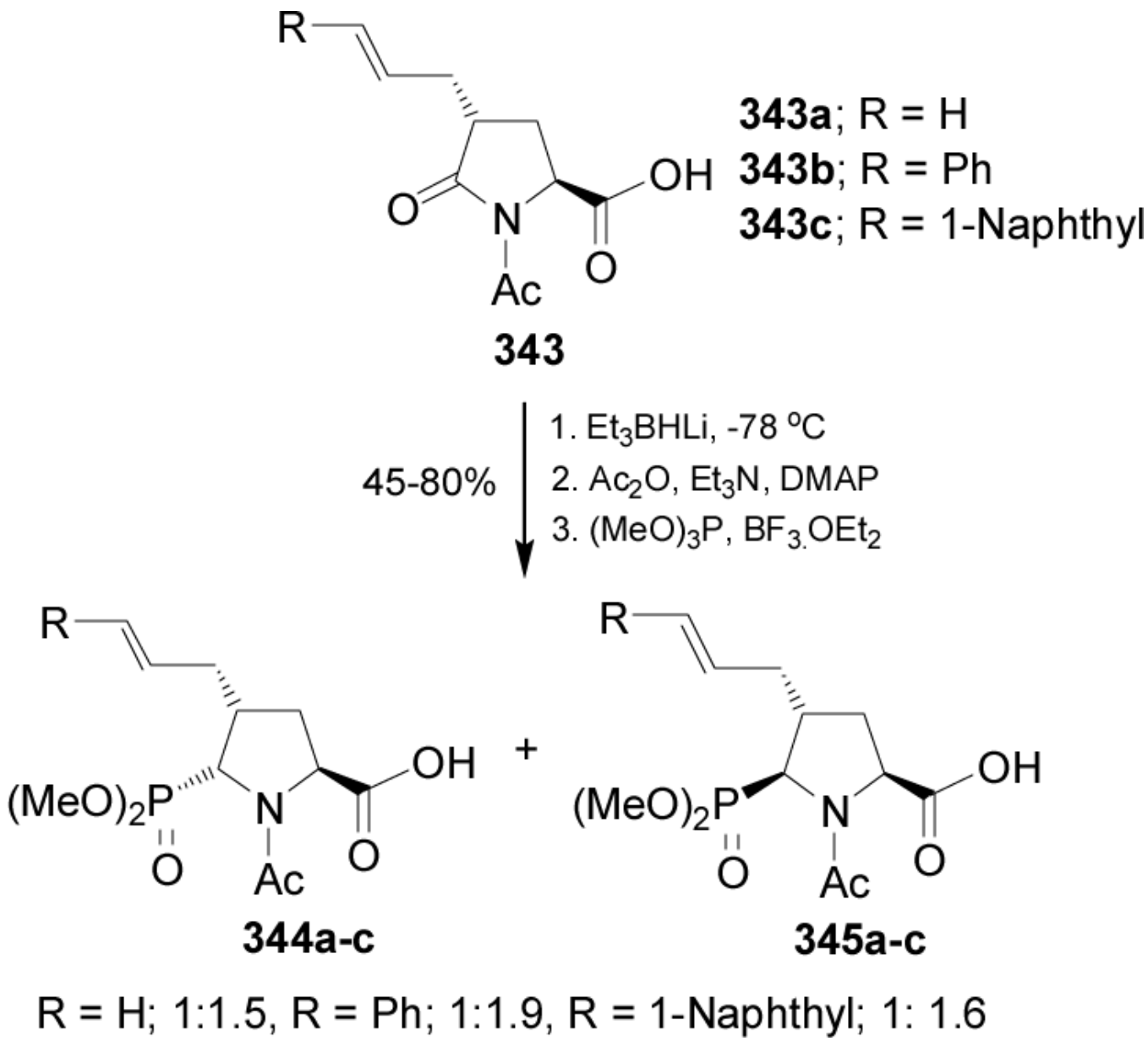
Scheme 87.



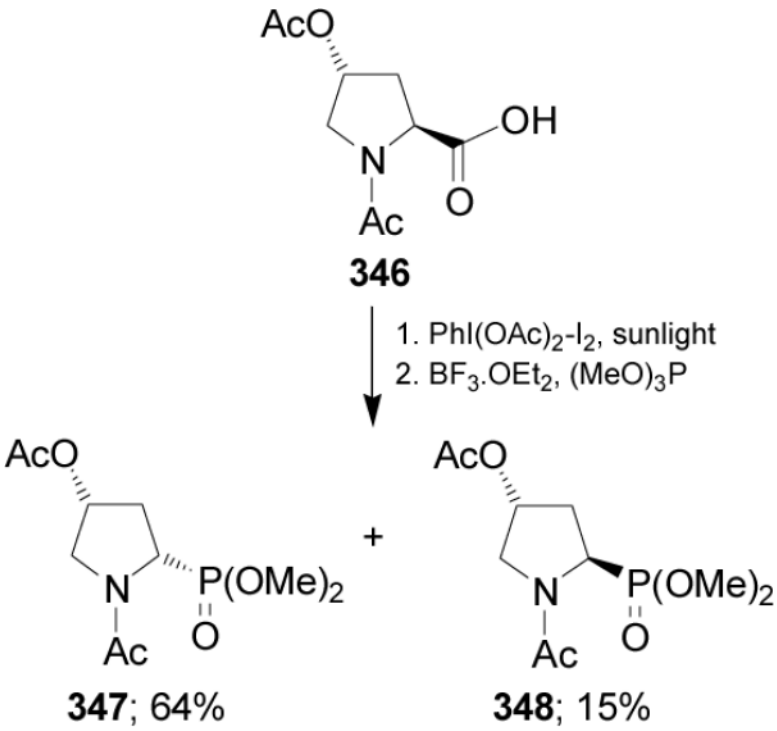
Scheme 88.



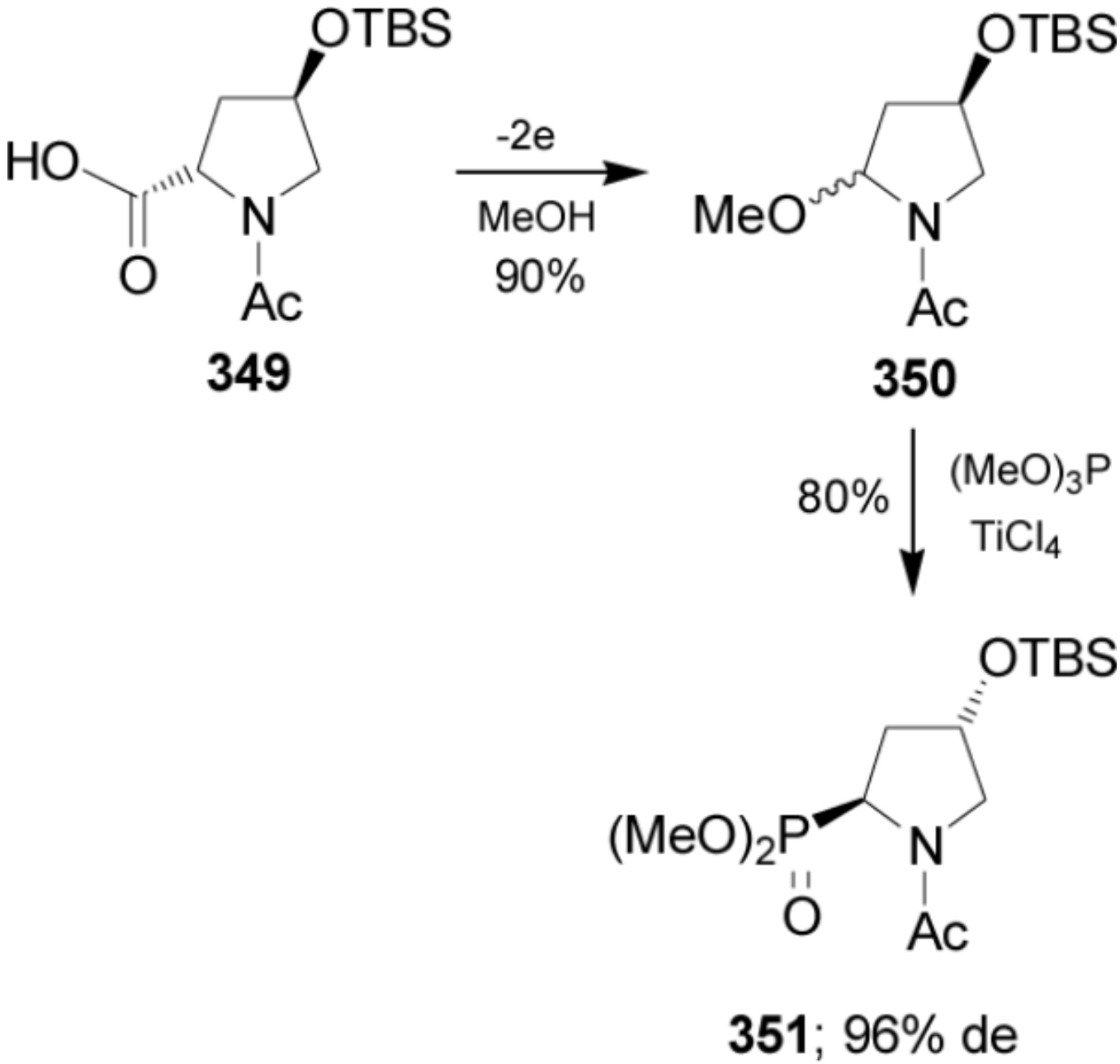
Scheme 89.



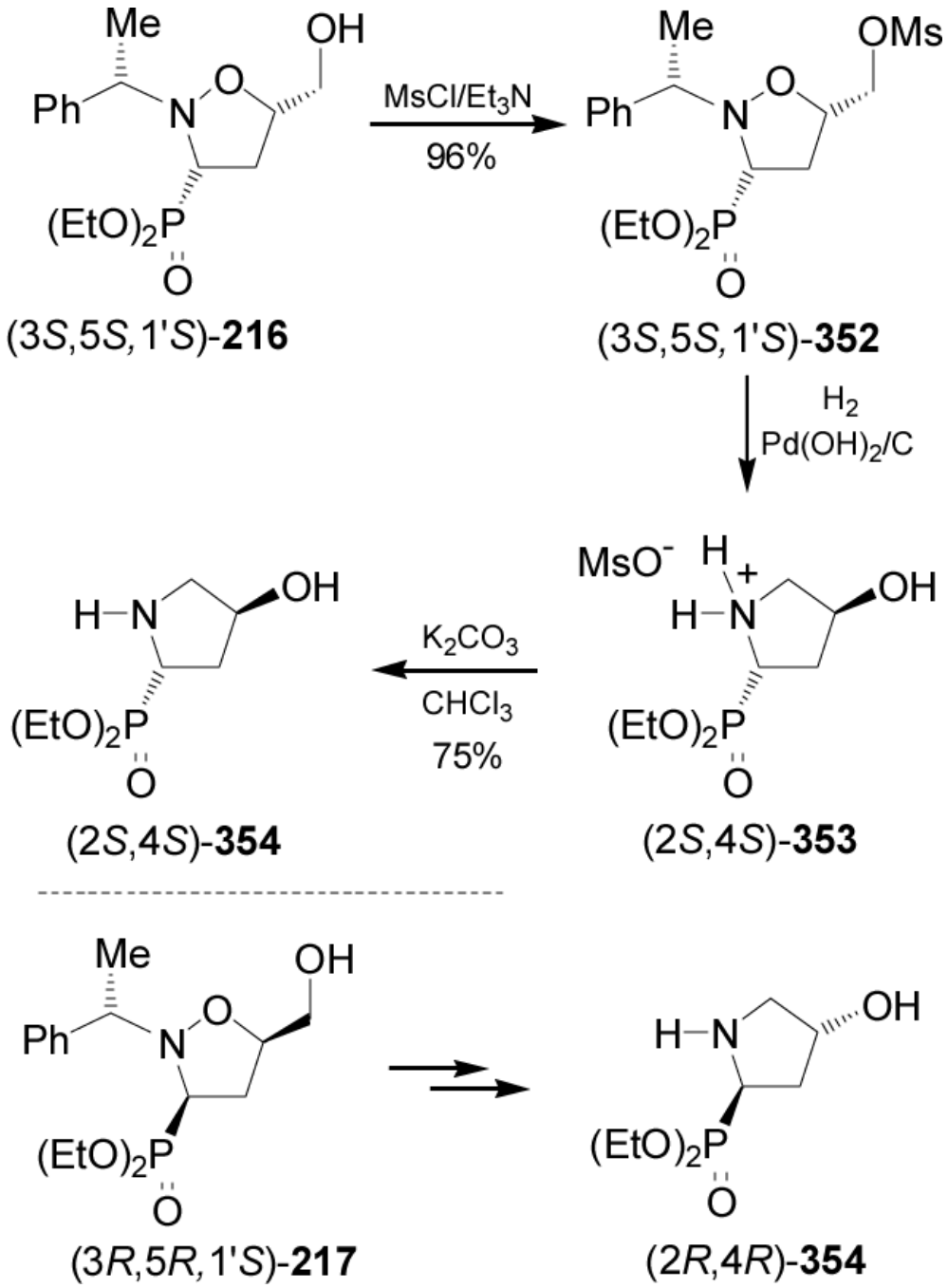
Scheme 90.



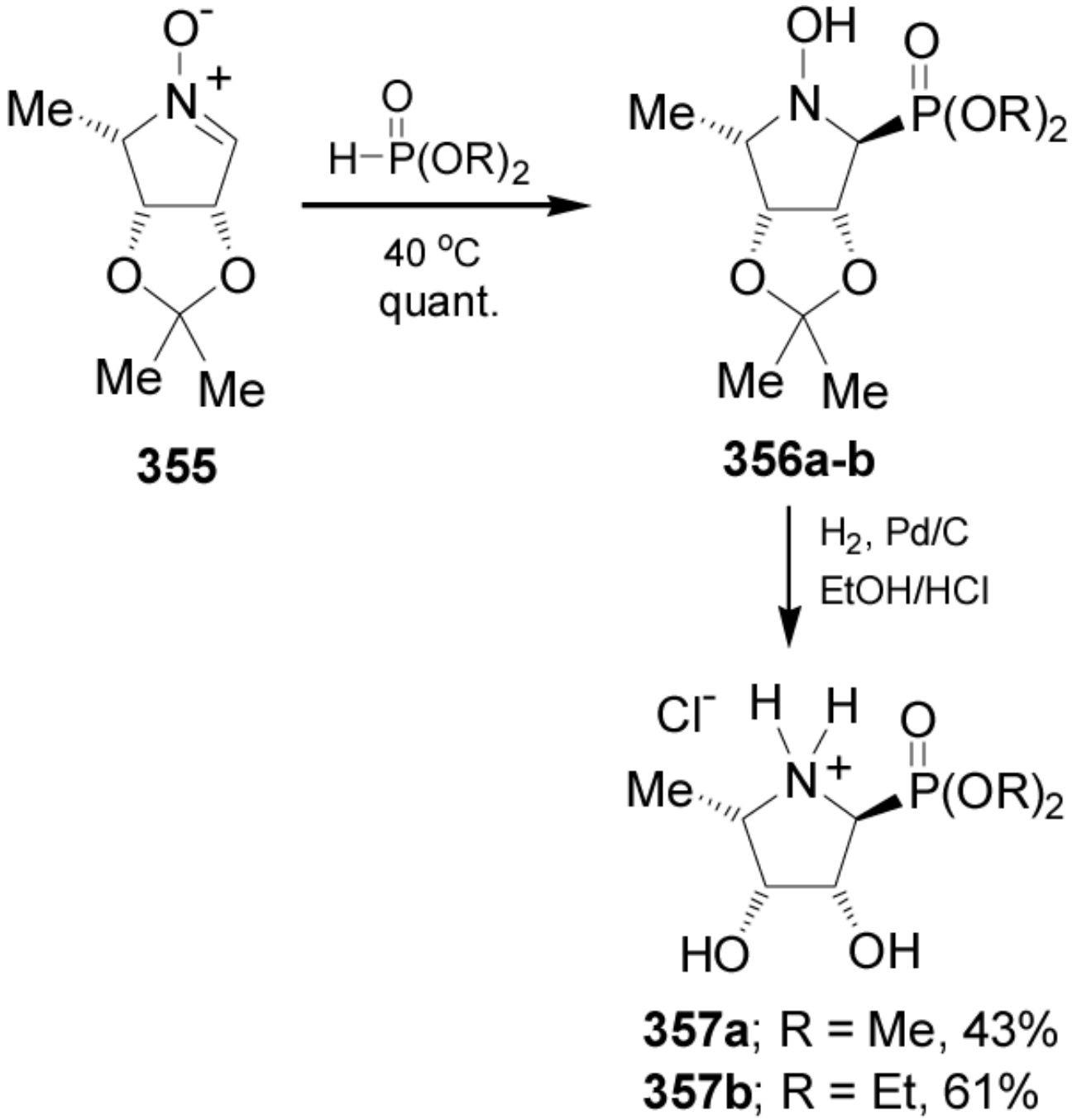
Scheme 91.



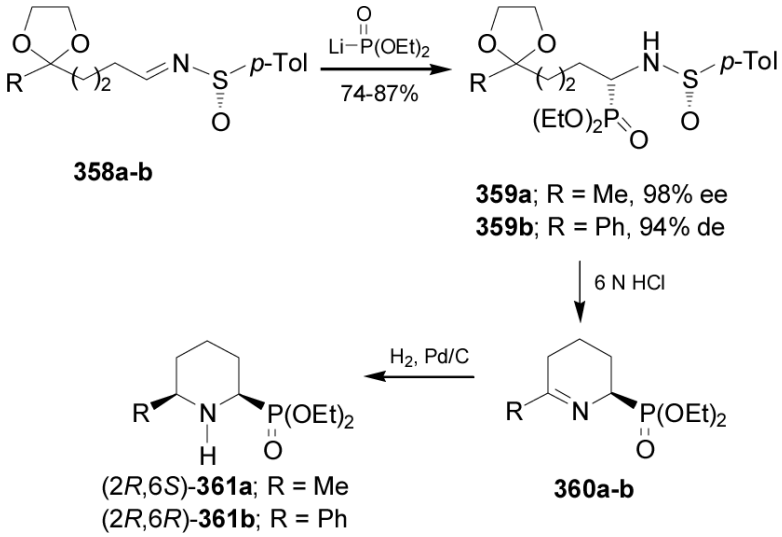
Scheme 92.



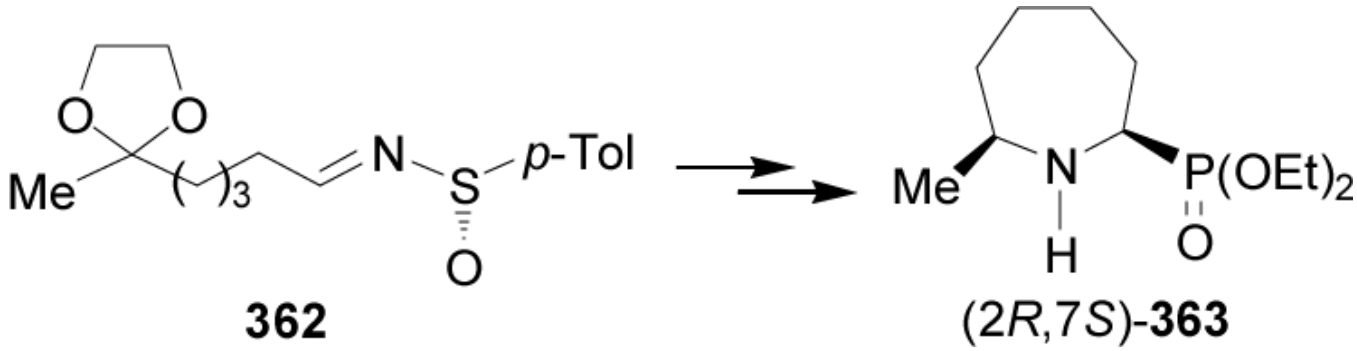
Scheme 93.



Scheme 94.



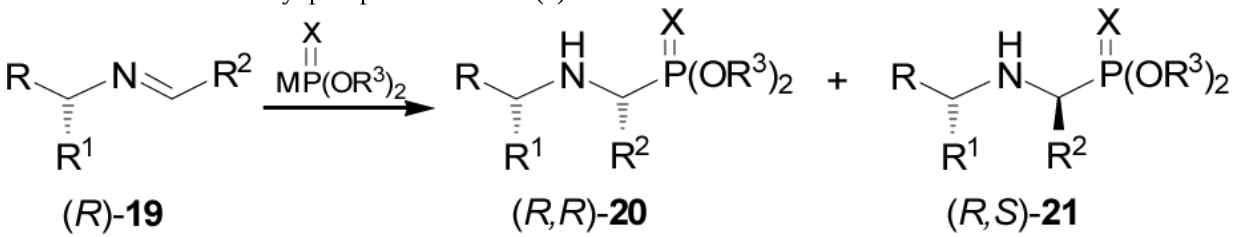
Scheme 95.



Scheme 96.

Table 1

Addition of the salt of alkyl phosphites to imines (*S*)-**19**.



Entry	R	R^1	R^2	R^3	X	Conditions	Yield (%)	20 : 21	Ref.
1	CO_2t-Bu	Ph	*c*-Hexyl	Et	O	Toluene/r.t.	87[a]	69 : 31	34
2	CO_2t-Bu	Ph	*c*-Hexyl	Et	O	Toluene/r.t.	84[b]	74 : 26	34
3	CO_2t-Bu	Ph	*c*-Hexyl	Et	O	Toluene/r.t.	40[c]	69 : 31	34
4	CO_2t-Bu	Ph	*c*-Hexyl	Et	O	Toluene/r.t.	46[d]	57 : 43	34
5	CO_2Bn	*i*-Bu	Ph	Et	O	Neat/100 °C	78	50 : 50	35
6	CO_2Bn	*i*-Bu	Ph	Me	O	Neat/100 °C	73	50 : 50	35
7	CO_2Bn	*i*-Bu	2-Furyl	Me	O	Neat/100 °C	74	50 : 50	35
8	CO_2Me	Me	Ph	Me	S	Toluene/r.t.	17[e]	47 : 53	29
9	CO_2Me	CH_2OH	Me	Me	S	Toluene/r.t.	33[e]	45 : 55	29
10	CO_2Me	CH_2OH	*i*-Pr	Me	S	Toluene/r.t.	15[e]	70 : 30	29
11	CO_2Me	CH_2OH	Ph	Me	S	Toluene/r.t.	62[e]	27 : 73	29
12	CO_2t-Bu	Ph	*c*-Hexyl	Et	O	*n*-BuLi/THF	80	98 : 02	34

[a] 120 h

[b] 7 h in the presence of $ZnCl_2$

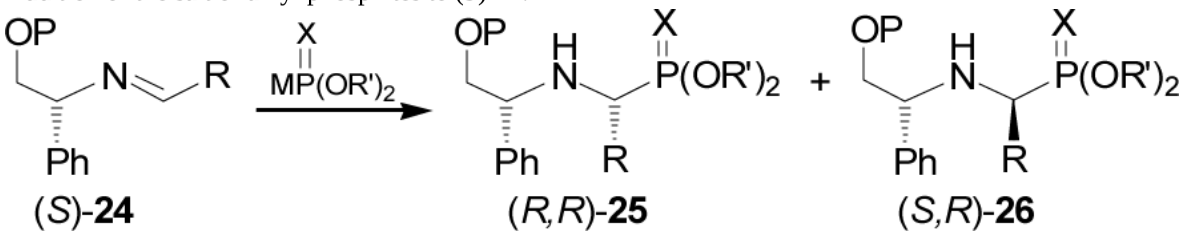
[c] 48 h in the presence of $MgBr_2$

[d] 48 h in the presence of TFA

[e] The configuration of chiral auxiliar was (*S*) and the products were (*S*,*S*)-**20** and (*S*,*R*)-**2**.

Table 2

Addition of the salt of alkyl phosphites to (*S*)-**24**.

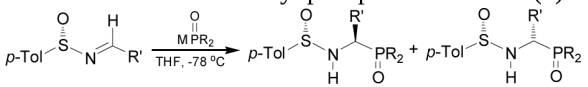


(*S*)-**24** (*R,R*)-**25** (*S,R*)-**26**

Entry	P	R	R'	X	Conditions	Yield (%)	25 : 26	Ref.
1	Me	*c*-Hexyl	Et	O	*n*-BuLi/THF	68	49 : 1	36
2	Me	*c*-HexylCH_2	Et	O	*n*-BuLi/THF	70	114 : 1	36
3	Me	*i*-Pr	Et	O	*n*-BuLi/THF	82	55 : 1	36
4	Me	*i*-Bu	Et	O	*n*-BuLi/THF	81	114 : 1	36
5	Me	Me	Et	O	*n*-BuLi/THF	77	41 : 1	36
6	Me	*n*-Hexyl	Et	O	*n*-BuLi/THF	78	49 : 1	36
7	Me	Ph	Et	O	*n*-BuLi/THF	90	7.3 : 1	36
8	Me	CH_2OBn	Et	O	*n*-BuLi/THF	36	49 : 1	36
9	Me	CH_2CH_2SMe	Et	O	*n*-BuLi/THF	69	55 : 1	36
10	Me	$CH_2CH_2CO_2t$-Bu	Et	O	*n*-BuLi/THF	37	49 : 1	36
11	H	Ph	Me	S	Toluene/ r.t.	76	1 : 3	29

Table 3

Addition of the salt of alkyl phosphites to imines (*S*)-**37**.



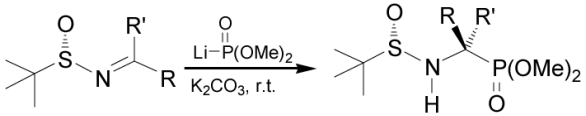
(*S*)-**37** (S_S,R_C)-**38** (S_S,S_C)-**39**

Entry	R	R'	M	Yield (%)	38 : 39	Ref.
1	OEt	C_6H_5	Li	85	92 : 08	43a
2	OEt	C_6H_5	Na	80	96 : 04	43a
3	OEt	4-$MeOC_6H_4$	Li	50	92 : 08	43a
4	OEt	4-$MeOC_6H_4$	Na	50	95 : 05	43a
5	OEt	*n*-Pr	Li	78	92 : 08	43b
6	O*i*-Pr	C_6H_5	Li	82	74 : 26	46b
7	O*i*-Pr	4-$MeOC_6H_4$	Li	55	93 : 07	46b
8	O*i*-Pr	*n*-Pr	Na	86	99 : 01	43b
9	OMe	C_6H_5	Na	*a*	88 : 12	46a
10	OMe	C_6H_5	Li	*a*	94 : 06	46a
11	OMe	2-furyl	Li	*a*	94 : 06	46b
12	OMe	2-thienyl	Li	*a*	95 : 05	46b
13	NEt_2	C_6H_5	Li	*a*	10 : 90	46a

[a]75-80% yield.

Table 4

Addition of lithium dimethyl phosphite to (*S*)-**45a-p**.

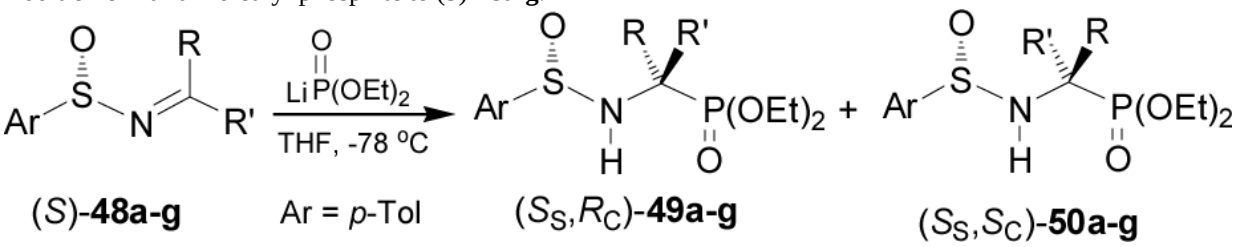


(*S*)-**45a-p** (S_S,R_C)-**46a-p**

Product	R	R'	Solvent	Yield (%)	de (%)
46a	C_6H_5	H	CH_2Cl_2	81	81.8
46b	4-$MeOC_6H_4$	H	CH_2Cl_2	78	85.2
46c	4-MeC_6H_4	H	CH_2Cl_2	81	80.2
46d	4-ClC_6H_4	H	CH_2Cl_2	82	72.4
46e	Et	H	CH_2Cl_2	80	77.0
46f	*i*-Pr	H	CH_2Cl_2	79	85.1
46g	*t*-Bu	H	CH_2Cl_2	77	86.9
46h	C_6H_5	Me	Et_2O	85	>95
46i	4-MeC_6H_4	Me	Et_2O	82	>95
46j	4-ClC_6H_4	Me	Et_2O	85	>95
46k	4-$NO_2C_6H_4$	Me	Et_2O	81	>95
46l	1-Naphtyl	Me	Et_2O	83	>95
46m	4-PhC_6H_4	Me	Et_2O	80	>95
46n	Et	Me	CH_2Cl_2	73	72.4
46o	*n*-Bu	Me	CH_2Cl_2	75	>95
46p	*t*-Bu	Me	CH_2Cl_2	73	>95

Table 5

Addition of lithium diethyl phosphite to (*S*)-**48a-g**.

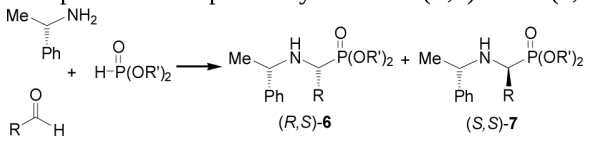


(*S*)-**48a-g** Ar = *p*-Tol (S_S,R_C)-**49a-g** (S_S,S_C)-**50a-g**

Sulfinimine	R	R'	Yield (%)	49 : 50
48a	Me	4-MeOC_6H_4	73	>99 : 1
48b	Me	4-MeC_6H_4	91	>99 : 1
48c	Me	C_6H_5	92	>99 : 1
48d	Et	C_6H_5	93	>99 : 1
48e	Me	4-$NO_2C_6H_4$	93	>99 : 1
48f	Me	*t*-Bu	97	>99 : 1
48g	Me	*n*-Bu	71	82 : 18

Table 6

One-pot three-component synthesis of (*R*,*S*)-**6** and (*S*,*S*)-**7**.

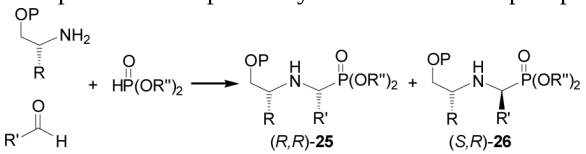


Entry	R	R'	Conditions	Yield (%)	6 : 7	Ref
1	*i*-Pr	Me	A	95	79 : 21	63
2	*t*-Bu	Me	A	96	82 : 18	63
3	*c*-Hexyl	Me	A	92	80 : 20	63
4	Bn	Me	A	90	83 : 17	63
5	Ph	Et	B	95	75 : 25	64
6	4-ClC_6H_4	Et	B	97	78 : 22	64
7	4-$NO_2C_6H_4$	Et	B	96	80 : 20	64
8	$PhCH{=}CH_2$	Et	B	93	70 : 30	64
9	Ph	Et	C	92	57 : 43	67
10	4-$MeOC_6H_4$	Et	C	88	57 : 43	67
11	Ph	Et	D	90	83 : 17	68
12	2-Py	Et	D	90	78 : 22	68

Conditions: **A**. LPDE, **B**. LPDE/TMSCl, **C**. $Yb(OTf)_3/MgSO_4$, **D**. $InCl_3$

Table 7

One-pot three-component synthesis of α-aminophosphonates (*R*,*S*)-**25** and (*S*,*S*)-**26**.

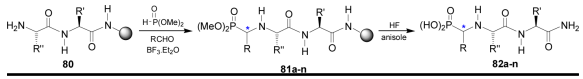


Entry	P	R	R'	R”	Conditions	Yield (%)	25 : 26	Ref.
1	H	Ph	*i*-Pr	Me	2.0 M, LPDE, -15 °C	90	88 : 12	63
2	H	Ph	*t*-Bu	Me	2.0M,LPDE, -15 °C	95	91 : 09	63
3	H	Ph	*c*-Hexyl	Me	2.0 M, LPDE, -15 °C	94	90 : 10	63
4	Me	Ph	Ph	Et	$Yb(OTf)_3/MgSO_4$	95	78 : 22	67 *a*
5	Me	Ph	4-$MeOC_6H_4$	Et	$Yb(OTf)_3/MgSO_4$	91	78 : 22	67 *a*
6	Me	*i*-Bu	Ph	Et	$Yb(OTf)_3/MgSO_4$	82	74 : 26	67 *a*
7	Me	*i*-Bu	4-$MeOC_6H_4$	Et	$Yb(OTf)_3/MgSO_4$	81	74 : 26	67 *a*

[a]The configuration of chiral auxiliary was (*S*) and the principal product was the diastereoisomer (*S*,*S*)-**25**.

Table 8

One-pot preparation of α-aminophosphonopeptides **82a-n**.

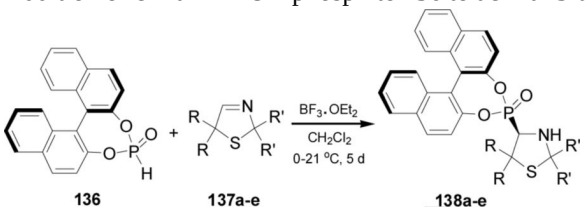


Compound	R	R'	R”	Yield (%)	ratio[a]
82a	Ph	Bn	Bn	85	80 : 20
82b	Ph	Bn	HO_2CCH_2	79	40 : 60
82c	Ph	Bn	$-(CH_2)_3-$	82	90 : 10
82d	Ph	Bn	Me	83	34 : 66
82e	Pr	Bn	Me	88	20 : 80
82f	Pr	Bn	HO_2CCH_2	86	n.d.
82g	Pr	Bn	Bn	92	n.d.
82h	Bu	Bn	*i*-Pr	80	40 : 60
82i	Bu	Me	Bn	71	n.d.
82j	Ph	Me	Bn	53	n.d.
82k	Pr	Me	Bn	65	n.d.
82l	Bu	H	Bn	88	63 : 37
82m	*i*-PrC6H_4	Bn	$-(CH_2)_3-$	75	20 : 80
82n	*i*-PrC6H_4	Bn	Me	70	44 : 56

[a] Stereochemistry was not assigned (n.d. = not determined).

Table 9

Addition of chiral BINOL-phosphite **136** to achiral 3-thiazolines **137a-e**.

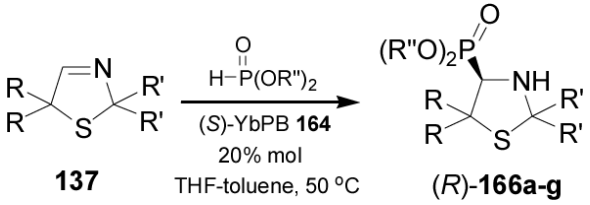


136 **137a-e** **138a-e**

Product	R/R	R'/R'	Yield (%)	dr
138a	Me/Me	Me/Me	47	83 : 17
138b	Me/Me	-$(CH_2)_5$-	47	>95 : 5
138c	-$(CH_2)_5$-	Me/Me	37	80 : 20
138d	-$(CH_2)_5$-	-$(CH_2)_5$-	68	>95 : 5
138e	H/H	-$(CH_2)_5$-	30	>95 : 5

Table 10

Catalytic and enantioselective hydrophosphonylation of **137**.

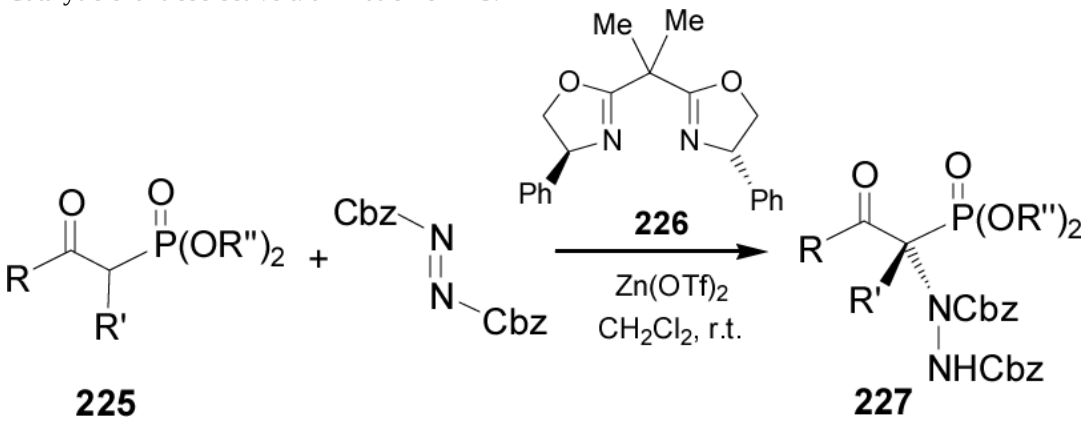


137 (*R*)-**166a-g**

Product	R/R	R'/R'	R"/R"	Yield (%)	ee (%)
166a	Me/Me	Me/Me	-$(CH_2)_3$-	99	97
166b	Me/Me	Me/Me	-$CH_2C(CH_3)_2CH_2$-	90	92
166c	Me/Me	Me/Me	-$CH_2CH{=}CHCH_2$-	87	93
166d	Me/Me	-$(CH_2)_5$-	-$(CH_2)_3$-	61	97
166e	Me/Me	-$(CH_2)_5$-	-$CH_2C(CH_3)_2CH_2$-	82	98
166f	-$(CH_2)_5$-	Me/Me	-$(CH_2)_3$-	85	97
166g	-$(CH_2)_5$-	Me/Me	-$CH_2C(CH_3)_2CH_2$-	69	96

Table 11

Catalytic enantioselective α-amination of **225**.

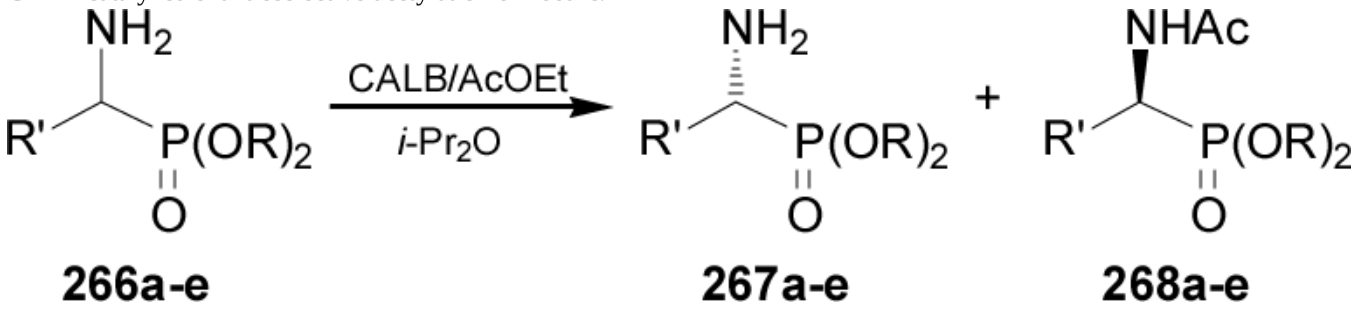


225 **227**

Entry	R	R'	R”	Yield (%)	ee (%)
1	Ph	Me	Et	85	92
2	2-Naph	Me	Et	93	92
3	Bn	Me	Et	60	95
4	Me	Me	Et	75	85
5	Ph	Allyl	Et	85	98
6	Ph	Me	Me	97	94
7	-$(CH_2)_3$-		Et	98	95
8	-$(CH_2)_4$-		Et	98	94

Table 12

CALB-catalyzed enantioselective acetylation of **266a-e**.



266a-e **267a-e** **268a-e**

			267		**268**	
Substrate	**R**	**R'**	**Yield (%)**	**ee (%)**	**Yield (%)**	**ee (%)**
266a	Et	Me	41	99.7	48	90
266b	*n*-Pr	Me	42	90	42	98
266c	*i*-Pr	Me	44	96	43	98
266d	Et	Et	73	18	10	100
266e	Et	CF_3	*a*	--	--	--

[a] No reaction