Published in final edited form as:
Tetrahedron Asymmetry. 2009 January 30; 20(1): 1–63. doi:10.1016/j.tetasy.2009.01.002.

Recent Progress on the Stereoselective Synthesis of Cyclic Quaternary α-Amino Acids

Carlos Cativiela[a,*] and **Mario Ordóñez**[b,*]

[a]Departamento de Química Orgánica, ICMA, Universidad de Zaragoza-CSIC, 50009 Zaragoza (Spain)

[b]Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, 62209 Cuernavaca, Morelos (México)

Abstract

The most recent papers describing the stereoselective synthesis of cyclic quaternary α-amino acids are collected in this review. The diverse synthetic approaches are classified according to the size of the ring and taking into account the bond that is formed to complete the quaternary skeleton.

1. Introduction

Linear peptides are highly flexible molecules that can adopt many conformations in solution and, of these, only a few are responsible for their biological activity. The construction of novel peptide sequences with tailor made enhanced properties is one of the most challenging areas in biomimetic research. The incorporation of rigid amino acid surrogates provides very useful information on the bioactive conformation and results in beneficial physiological effects. Between these rigid amino acids the use of quaternary compounds is one of the most interesting approaches, and for this reason during the last few years many procedures towards the stereoselective synthesis of these compounds have been described. In this context, we have previously reviewed (1998 and 2000) the stereoselective synthesis of these interesting compounds,[1,2] and taking into account the great quantity of procedures reported, more recently we have published an update about the stereoselective synthesis of the acyclic α-amino acids3 that we would like to complete now with a corresponding update of the cyclic systems.

Before beginning the summary of the new procedures concerning the stereoselective synthesis of these cyclic derivatives it is worth mentioning that apart from our own contributions, during the last years some reviews focused on some particular aspects have been published in relation to the synthesis of some cyclic amino acid and derivatives,[4,5] the synthesis of heterosubstituted carbocyclic α-amino acids,[6] the synthesis of some fluorinated acyclic and cyclic amino acids, [7] the synthesis of unnatural α-amino acids[8] and the modelling and synthesis of some conformationally constrained amino acids.[9] Much more recently, the synthesis of the family of enantiomerically pure 1-amino-2-phenylcycloalkanecarboxylic acids,[10] an excellent review of 1-aminocyclopropane-carboxylic acids,[11,12] the catalytic asymmetric synthesis of α-amino acids including some quaternary derivatives,[13] the synthesis of cyclic α-amino acids and their use in the preparation of stable conformational short peptides,[14] and also some recent approaches towards the asymmetric synthesis of quaternary amino acids[15] have been reported.

*aCorresponding author. Tel. and Fax: +(34)976761210; cativiela@unizar.es. *bCorresponding author. Tel. and Fax: +(52)7773297997; palacios@ciq.uaem.mx.

Nevertheless, and in spite of all these reviews, some of which are from a general point of view and others focused on some particular aspects or families of compounds, we would like to review all methodologies in a manner that is useful to organic experimentalists.

Some data concerning the structural analysis of cyclic amino acids in small and medium size Ac_nc (1-aminocycloalkanecarboxylic acids) has been completed during these years and the synthesis and structural studies of model peptides containing these cyclic amino acids has been reported.[16–24] Apart from these classical rings, the conformational tendencies of other cyclic amino acids such as Hms(Ipr) or *O*,*O*-isopropylidene-α-hydroxymethylserine,[25] Afc or 9-amino-9-fluorenecarboxylic acid,[26,27] Daf or 9-amino-4,5-diazafluorene-9-carboxylic acid,[28,29] Adt 4-amino-1,2-dithiolane-4-carboxylic acid,[30] the axially chiral α-amino acids Bip and Bin[31–37] or the Bip system incorporating a crown ether receptor[38] have been reported. More recently, the synthesis and properties of antAib, a novel tetrasubstituted α-amino acid of the Ac_5c type possessing a fused anthracene fluorophore has also been reported.[39,40]

Theoretical calculations focused on the study of the conformational tendencies of 1-amino-cycloalkanecarboxylic acids (Ac_nc) have been reported.[41–43] Of these compounds the cyclopropane derivatives have attracted the attention of many researchers, probably due to the particular characteristics that the cyclopropane ring confers to the amino acid. When additional substituents are incorporated into the ring, two chiral centres are formed and, as a consequence, new stereoisomers are possible. In the particular case of the incorporation of one phenyl ring as a substituent (named, c_3Phe), the compound can be considered as a constrained phenylalanine and in this case several theoretical studies has been reported[44] to explain the behaviour previously described by our group.[45,46] The presence of an additional phenyl group in a different carbon atom ($c_3$diPhe) confers peculiar characteristics to the molecule these have been reported both from an experimental[47] and theoretical point of view.[48] The case of the cyclopropane derivative in which both phenyl substituents are on the same carbon atom (c_3Dip) seems particularly interesting since it has been reported that it confers important tendencies to give a γ-turn in some model peptides.[49,50] The structural tendencies of other cyclopropane derivatives such as c_3Val[51,52] or other 2-phenyl-1-aminocycloalkanecarboxylic acids such as c_5Phe[53] and c_6Phe[54–56] have also been reported. Additionally, the theoretical study of 8-aminopentacycloundecane-8-carboxylic acid has been reported.[57] Very recently, the helical screw sense exclusively governed by chiral centres in the side chain of some cyclic amino acids has been reported.[58–60]

Finally, some systematic structure-activity relationships between biological properties of peptides incorporating quaternary cyclic amino acids has also been reported.[61–63]

2. Synthesis of 1-aminocycloalkanecarboxylic acids

2.1. Using cyclic compounds as starting materials

One of the most useful methodologies to prepare 1-aminocycloalkanecarboxylic acids in a stereoselective manner involves the use of cyclic compounds (typically aldehydes but ketones for the synthesis of quaternary α-amino acids) as starting materials, although in this case the introduction of both functional groups (amino and carboxylic acid) is necessary. Of all reported methodologies, the Strecker reaction[64,65] and related synthesis have been repeatedly used. The diastereoselective Strecker reaction involves the addition of cyanide or its equivalents to the previously formed C=N bond from the corresponding ketone and a chiral amine, and subsequent hydrolysis of the nitrile group. For the Strecker reaction several chiral auxiliaries such as (*S*)-α-methylbenzylamine (α-MBA),[66] (*R*)-phenylglycinol,[67] (*R*)-phenylglycine amide,[68] (S_S)-*p*-toluene- and (S_S)-*tert*-butane-sulfinimides,[69] (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP),[70] (*S*)-1-amino-2-methoxymethyl-indoline (SAMI),[71] and 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl amine[72] have been used.

The stereoselective synthesis of 1-aminocycloalkanecarboxylic acids using this methodology have been grouped depending on the size and type of the starting carbonyl compound.

The 1-aminocyclopropanecarboxylic acids probably are the most interesting carbocyclic α-amino acids and several methodologies have been described for their stereoselective synthesis. However, to the best of our knowledge the work of Fadel *et al.*[66] is the only example reported in the literature in which, the Strecker reaction has been used for their stereoselective synthesis. In this context, reaction of cyclopropanone hemiacetal (2*S*)-**1** with the chiral amine [(*S*)-α-MBA or (*S*)-α-methoxymethylbenzylamine ((*S*)-MOMBA)] afforded the imines **2a,b**, which, by addition of NaCN gave the α-aminonitriles (1*R*,2*S*)-**3a,b** with moderate diastereoselective excess. Hydrolysis of diastereoisomerically pure (1*R*,2*S*)-**3a,b** with concentrated sulfuric acid at 0 °C, followed by hydrogenolysis over $Pd(OH)_2$/C provided the amine amide (1*R*,2*S*)-**4a**, which, by treatment with 6 N HCl at reflux, gave the (1*R*,2*S*)-1-amino-2-methylcyclopropanecarboxylic acid **5a** (*allo*-norcoronamic acid) in 85% yield (Scheme 1).

On the other hand, condensation of the cyclobutanones (±)-**6a–c**[73] with (*S*)-α-MBA in the presence of a catalytic amount of acetic acid or *p*-toluenesulfonic acid (TsOH), followed by addition of sodium cyanide[74] or trimethylsilylcyanide (TMSCN)75 in the presence of $ZnCl_2$, afforded the α-amino nitriles *cis*-**7a–c**, *trans*-**8a–c**, *cis*-**9a–c**, and *trans*-**10a–c** in moderate yield and diastereoisomeric ratio. The results are summarized in Table 1.

Hydrolysis of diastereoisomerically pure *cis*-**7b** (R = *i*-Pr) with concentrated sulfuric acid at 0 °C gave the amide **11b** in 85% yield, which, by hydrogenolysis over $Pd(OH)_2$/C, furnished the amine amide (1*S*,2*S*)-**12b** in 98% yield. Finally, hydrolysis of (1*S*,2*S*)-**12b** with 6 N HCl under reflux followed by treatment with propylene oxide in ethanol gave the α-amino acid (1*S*, 2*S*)-**13b** in 90–94% yield. Under identical conditions, *cis*-**9b** was transformed into (1*R*, 2*R*)-**13b** (Scheme 2).[74]

In a similar way, treatment of the mixture of α-amino nitriles **8–10c** with concentrated sulfuric acid at 0 °C followed by separation and subsequent hydrogenolysis with HCO_2NH_4, Pd/C conditions, and hydrolysis with concentrate HCl led to (1*R*,2*R*)-**13c**, (1*S*,2*S*)-**13c** and (1*R*, 2*S*)-**14c** as chlorohydrate salt (Scheme 3).[75]

Recently, Fadel *et al.*[76] have reported the stereoselective synthesis of (1*R*,2*R*)-1-amino-2-hydroxy-cyclobutanecarboxylic acid **13d**, a serine derivative from racemic or optically pure 2-benzyloxy-cyclobutanone **6d** (R = OBn), and (1*R*,2*R*)- and (1*S*,2*S*)-1,2-diaminocyclobutanecarboxylic acid **13e** an ornitine derivative, from racemic 2-aminocyclobutanone **6e**. For this purpose, the condensation of either (±)-or enantiopure **6d** with (*S*)-α-MBA, followed by addition of sodium cyanide gave the corresponding α-amino nitrile mixture **7**–**10d**. The formation of the four diastereoisomers **7**–**10d** using (*R*)- or (*S*)-**6d** was probably due to the partial racemization of enantiomerically pure starting ketone under Strecker conditions.[76a] On the other hand, one-pot reaction of **6e** with (*S*)-α-MBA in the presence of AcOH and NaCN afforded, under thermodynamic control, only two major stereoisomers **8e** and **10e** in 55:45 ratio and excellent yield.[76b] The results are summarized in Table 2.

Hydrolysis of diastereoisomerically pure **8d** (R = OBn) with hydrogen peroxide and ethanolic potassium hydroxide solution, followed by hydrogenolysis over $Pd(OH)_2$/C in the presence of di-*tert*-butylcarbonate [$(Boc)_2O$], afforded the amide (1*R*,2*R*)-**15d** in 69% yield. Finally, hydrolysis of (1*R*,2*R*)-**15d** with 6 M HCl under reflux gave the quaternary α-amino acid (1*R*, 2*R*)-**13d** in 74% yield as chlorohydrate salt. Under identical conditions *trans*-**8e** and *trans*-**10e** were transformed into quaternary 1,2-diamino acids (1*R*,2*R*)- and (1*S*,2*S*)-**13e** in good chemical yield (Scheme 4).[76]

On the other hand, condensation of the 2-alkylpentanones **16a–e**[77] with (*R*)-α-MBA in the presence of a catalytic amount of TsOH, followed by addition of TMSCN and $ZnCl_2$ in methanol or hexane under thermodynamically or kinetically controlled conditions, produced the four diastereoisomeric α-amino nitriles **17a–e** to **20a–e**. The results are summarized in Table 3.[78]

Hydrolysis of the mixture of α-amino nitriles **17a–e** to **20a–e** obtained using methanol as solvent with concentrate sulfuric acid, produced the diastereoisomerically pure α-amino carboxyamides **21a–e** to **24a–e**, after separation by flash chromatography and preparative HPLC. Hydrogenolysis of diastereoisomerically pure α-amino carboxyamides **21a–e**, **22a–e**, **23a–c** and **24a–c** with HCO_2NH_4 and Pd/C, followed by hydrolysis with concentrate HCl and subsequent treatment with cation exchange resin, gave the 2-alkylated 1-aminocyclopentanecarboxylic acids (1*R*,2*R*)- and (1*S*,2*S*)-**25a–e**, and (1*R*,2*S*)- and (1*S*,2*R*)-**26a–c** (Scheme 5).[78]

Condensation of the 5-bromo-1-indanone **27**, which is easily obtained from 3-bromobenzaldehyde, with (*R*)-phenylglycinol followed by addition of TMSCN and subsequent treatment with HCl, afforded the mixture of α-amino esters **28** in 61% yield and 7:1 diastereoisomeric ratio, which, under reflux in toluene gave the spiro derivatives (*S*,*R*)-**29** and (*R*,*R*)-**30** in 59% yield. Palladium-catalyzed carbonylation of diastereoisomerically pure (*S*,*R*)-**29** with $Pb(OAc)_2$ and 1,3-bis(diphenyl-phosphino) propane (dppp) in ethanol produced the derivative (*S*,*R*)-**31** in 67% yield, which, by cleavage of spiro ring with K_2CO_3 in methanol produced the diester (*S*,*R*)-**32** in 70% yield. Finally, oxidative cleavage of benzyl fragment in (*S*,*R*)-**32** with $Pb(OAc)_2$ followed by acidic hydrolysis and subsequent treatment with propylene oxide furnished the 1-aminoindane-1,5-dicarboxylic acid **33** [(*S*)-AIDA] in 65% yield and this is an antagonist of metabotropic glutamate receptors (Scheme 6).[79]

On the other hand, palladium-catalyzed phosphonylation of diastereoisomerically pure (*S*,*R*)-**29** whith diethyl phosphite produced the ethyl phosphonate (*S*,*R*)-**34** in 83% yield, which, by cleavage of spiro ring with K_2CO_3 in methanol, led to diester (*S*,*R*)-**35** in 70% yield. Finally, oxidative cleavage of benzyl fragment in (*S*,*R*)-**35** with $Pb(OAc)_2$, followed by acidic hydrolysis and subsequent treatment with propylene oxide furnished the 1-amino-5-phosphoindane-1-carboxylic acid **36** [(*S*)-APICA] in 65% yield (Scheme 7).[79]

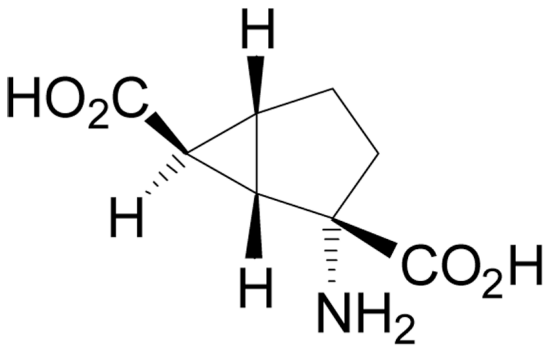
Schann *et al.*[80] reported the first stereoselective synthesis of aminopyrrolidinedicarboxylic acids **41** and **42**, which have been used in the preparation of glutamate receptor compounds.[81] Thus, the Bucherer-Bergs reaction[82] of (*S*)-**37**, readily obtained from (2*S*,4*R*)-4-hydroxyproline, with $(NH_4)_2CO_3$ and KCN in ethanol gave the spirohydantoin mixture **38** in 68–78% yield, which, by basic hydrolysis followed by treatment with $SOCl_2$ and methanol under reflux afforded, after chromatographic separation, the amino esters (2*S*,4*S*)-**39** and (2*S*,4*R*)-**40**. *N*-Boc protection of (2*S*,4*S*)-**39** and (2*S*,4*R*)-**40**, followed by cleavage of benzyl protective group by hydrogenolysis under HCO_2NH_4 and Pd/C conditions, and subsequent saponification and cleavage of Boc protective group with HCl, gave the amino acids (2*S*,4*S*)-**41** and (2*S*,4*R*)-**42**, respectively. Under identical conditions (*R*)-**37** was transformed into (2*R*,4*R*)-**41** and (2*R*,4*S*)-**42** (Scheme 8).

On the other hand, reaction of the ulose **43**, readily obtained by oxidation of diacetone-D-glucose, with ammonia in the presence of $Ti(O\textit{i}\text{-}Pr)_4$, followed by addition of TMSCN, provided the glycol-α-amino nitrile **44** in 80% yield as the only detectable stereoisomer, which, by treatment with carbon dioxide in MeOH at 75 atm/85 °C or $(NH_4)_2CO_3$ in MeOH-H_2O at 70 °C, gave the spirohydantoin **45** in 80% yield. Selective hydrolysis of one of the acetonides of **45** with 1 N HCl, followed by hydantoin ring opening with barium hydroxide and subsequent

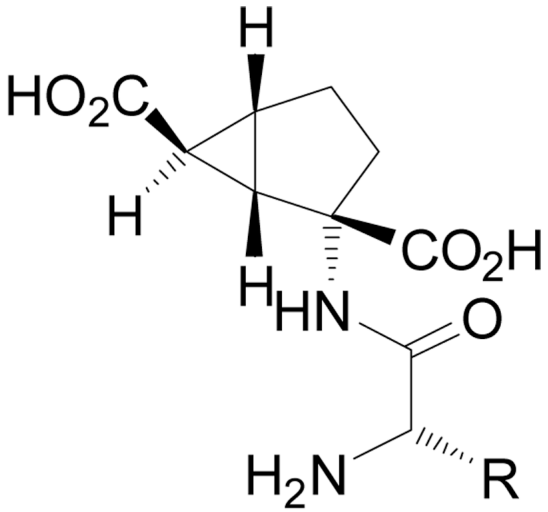
ion-exchange chromatography, furnished the quaternary glycoamino acid **46** in 55% yield in three steps (Scheme 9).[83]

Recently De Micheli *et al.*[84] reported the stereoselective synthesis of conformationally constrained α-amino acid **50**, an analogue of aspartic acid, based on the Strecker methodology. Thus, TsOH-catalyzed condensation of the ketone **47** with 4-methoxybenzylamine (PMB-NH_2), followed by addition of TMSCN in the presence of $ZnCl_2$, afforded the cyano derivative **48** as a single detectable stereoisomer. Cleavage of PMB protective group in **48** with cerium (IV) ammonium nitrate (CAN) provided the α-amino nitrile **49**, which, by hydrolysis and subsequent ion-exchange chromatography gave the conformationally constrained α-amino acid **50** in 27% overall yield (Scheme 10).

Conformationally constrained (1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane 2,6-dicarboxylic acid, also known as (LY354740),[85] is a highly potent and selective agonist for group II metabotropic glutamate (mGlu) receptors, specifically mGlu2 and mGlu3, that has been found to possess anxiolytic, antipsychotic, anticonvulsant, anti-Parkinsonian, analgesic, and neuroprotective properties in vivo.86 Additionally the peptides of type **51** are effective prodrugs of LY354740.[87] For this reason several analogues of LY354740 have been prepared.



(1*S*,2*S*,5*R*,6*S*)
LY354740



51

Monn *et al.*[88] reported the synthesis of conformationally constrained α-amino acids (+)- and (+)-**55** and (−)-**56**, which, were evaluated as mGlu receptors. In this context, reaction of the optically pure bicyclic ketone (+)-**53**, obtained from **52**,[89] with $(NH_4)_2CO_3$ and KCN in ethanol gave the spirohydantoin (+)-**54** in 28% yield after crystallization, which, by basic hydrolysis, gave the conformationally constrained α-amino acid (+)-**55** in 55% yield. In a similar way, (−)-**53** was transformed into (−)-**56** (Scheme 11).

On the other hand, Lee and Miller[90] reported the stereoselective synthesis of conformationally constrained α-diamino acid (−)-**60** starting from the cyclic ketone (−)-**57**. In this context, the intermolecular cyclopropanation of the α,β-unsaturated ketone (−)-**57** with the sulfonium ylide obtained from (ethoxycarbonylmethyl)dimethylsulfonium bromide and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), afforded the bicyclic ketone (−)-**58** in 60–73% yield,[91] which, by a Bucherer-Bergs reaction with $(NH_4)_2CO_3$ and KCN in ethanol, provided the spirohydantoin (−)-**59** in 59% yield and 96% ee. Basic hydrolysis of (−)-**59** and sequential treatment with

copper(II) carbonate, benzoyl chloride and ion-exchange chromatography, furnished the α-diamino acid (−)-**60** with >98% ee (Scheme 12).

Mann *et al.*[92] reported the synthesis of constrained cycloalkyl analogue of glutamic acid **64** with a ω-phosphonic acid function, an analogue of AP4.[93] Thus, reaction of the bicyclic ketone **61** with $(NH_4)_2CO_3$ and KCN in H_2O produced the spirohydantoins **62** and **63** in 68% yield and 4:1 ratio as an inseparable mixture of diastereoisomers, from which, by acidic hydrolysis and crystallization, the α-amino acid **64** could be obtained in 56% yield (Scheme 13).

On the other hand, reaction of the optically pure bicyclic ketone (−)-**66**, obtained in 9 steps from chiral methyl ester (1*R*,5*R*)-**65**, with ammonia in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ in methanol followed by addition of TMSCN, afforded the α-amino nitrile **67** in 80% yield and 13.1:1 diastereoisomeric ratio, which, by cristallyzation and subsequent hydrolysis with 8 N HCl and AcOH, furnished the optically pure conformationally constrained fluoro α-amino acid (+)-**68** in 94% yield (Scheme 14).[94]

Nakazato *et al.*[95,96] reported the synthesis of several conformationally constrained fluoro α-amino acids, which were evaluated as potent and selective group II metabotropic glutamate receptor antagonists. For example, reaction of the optically pure cyclic sulfates (+)-**70a,b**, obtained in 3 steps from the bicyclic ketone (−)-**69**, with sodium azide followed by treatment with sulfuric acid, gave the azide derivatives (1*R*,2*R*,3*R*,5*R*,6*R*)-**71a,b** in good yield. Catalytic hydrogenation of benzyl ester and azide functions in **71b** followed by acidic hydrolysis provided the conformationally constrained α-amino acid (1*R*,2*R*,3*R*,5*R*,6*R*)-**72** in 79% yield (Scheme 15).

On the other hand, reaction of (1*R*,2*R*,3*R*,5*R*,6*R*)-**71a** with trifluoromethanesulfonyl anhydride (Tf_2O) in pyridine afforded the derivative (−)-**73**, which, by treatment with KNO_2 in the presence of 18-crown-6 and subsequent addition of water, gave the compound (1*R*,2*R*,3*S*,5*R*,6*R*)-**74** in 80% yield. Reduction of azide group in **74** under Staudinger conditions[97] using PMe_3, followed by basic hydrolysis, produced the α-amino acid (1*R*,2*R*,3*S*,5*R*,6*R*)-**75** in 48% yield (Scheme 16).[95]

Additionally, optically pure (1*R*,2*R*,3*R*,5*R*,6*R*)-**71a** and (1*R*,2*R*,3*S*,5*R*,6*R*)-**74** have been transformed into conformationally constrained α-amino acids (1*R*,2*R*,3*R*,5*R*,6*R*)-**76** and (1*R*,2*R*,R*S*,5*R*,6*R*)-**77a,b**, respectively, which have been evaluated as potent and selective group II metabotropic glutamate receptor antagonists (Scheme 17).[95,96]

On the other hand, reaction of cyclic sulfate (1*S*,2*S*,3*R*,5*R*,6*S*)-**78a** with sodium azide, followed by treatment with sulfuric acid, gave the azide derivative (1*S*,2*R*,3*R*,5*R*,6*S*)-**79a** in 91% yield. Reaction of **79a** with benzyl trichloroacetimidates ($ArCH_2OC(=NH)CCl_3$) in the presence of a catalytic amount of trifluoromethanesulfonic acid (TfOH) afforded the corresponding ether derivatives (1*S*,2*R*,3*R*,5*R*,6*S*)-**80**. Reduction of the azide function in **80** with PMe_3 and subsequent basic hydrolysis produced the α-amino acids (1*S*,2*R*,3*R*,5*R*,6*S*)-**81** (several aryl groups were used) (Scheme 18).[96a]

Very recently, Woltering *et al.*[98] reported the stereoselective synthesis of (1*S*,2*R*,3*R*,5*R*,6*S*)-2-amino-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid **82** [(+)-HYDIA], a group II mGlu receptor. Thus, the selective ring opening of cyclic sulfate (1*S*,2*S*,3*R*,5*R*,6*S*)-**78b** with sodium azide afforded the azide derivative (1*S*,2*R*,3*R*,5*R*,6*S*)-**79b** in 62% yield. Catalytic hydrogenation of the benzyl ester and azide functions of **79b**, followed by acidic hydrolysis and subsequent treatment with propylene oxide, produced the (+)-HYDIA, **82** in 87% yield (Scheme 19).

Oxidation of the alcohol group in (1*S*,2*R*,3*R*,5*R*,6*S*)-**79b** with PCC gave the corresponding ketone (1*S*,2*R*,5*R*,6*S*)-**83** in 67% yield, and subsequent reduction with $NaBH_4$ afforded the alcohol (1*S*,2*R*,3*S*,5*R*,6*S*)-**84** in 51% as a single diastereoisomer. Catalytic hydrogenation of the benzyl ester and azide functions in **84**, followed by acidic hydrolysis and subsequent treatment with propylene oxide, produced the β-hydroxy-α-amino acid (1*S*,2*R*,3*S*,5*R*,6*S*)-**85** in 86% yield. On the other hand, treatment of **79b** with Tf_2O in pyridine provided the triflate (1*S*,2*R*,3*R*,5*R*,6*S*)-**86** in 86% yield and a subsequent S_N2 reaction using sodium azide furnished (1*S*,2*R*,3*S*,5*R*,6*S*)-**87** in 49% yield as a single diastereoisomer. Catalytic hydrogenation of the benzyl ester and azide functions of **87**, followed by acidic hydrolysis and subsequent treatment with propylene oxide produced the α,β-diamino acid (1*S*,2*R*,3*S*,5*R*,6*S*)-**88** in 79% yield (Scheme 20).[98]

Reaction of the (+)-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one **89** with $(NH_4)_2CO_3$ and KCN in H_2O produced the spirohydantoin **90** in 83% yield as the main product and hydrolysis of **90** with barium hydroxide gave the quaternary α-amino acid (−)-**91** in 67% yield. Under identical conditions, the enone (−)-**92** was transformed into the quaternary α-amino acid (+)-**94** through the spirohydantoin (+)-**93** (Scheme 21).[99]

Condensation of the 2-metoxycyclohexanone (±)-**95a** with (*S*)-α-MBA, followed by addition of TMSCN in the presence of $ZnCl_2$ in methanol, gave the α-amino nitriles mixture **96a** (*cis/trans* = 26:74 ratio) under thermodynamic control, and (*cis/trans* = 75:25) under kinetic control conditions. Hydrolysis of the mixture of α-amino nitriles *cis/trans*-**96a** with concentrate sulfuric acid produced, after chromatographic separation, the mixture of the α-amino carboxyamides *cis/trans*-**97a**, and the hydrogenolysed product (1*S*,2*R*)-**98a**. Low pressure liquid chromatography (LPLC) separation of the carboxyamides *cis/trans*-**97a** afforded the diastereoisomerically pure α-amino carboxyamide *trans*-**97a** [(1*S*,2*S*,1'*S*)-**97a**], which, by hydrogenolysis over Pd/C followed by hydrolysis with 12 M HCl and subsequent ion-exchange chromatography on a Dowex 50W column, led to (1*S*,2*S*)-1-amino-2-hydroxycyclohexanecarboxylic acid **99a**. On the other hand, acidic hydrolysis of **98a** and subsequent treatment with Dowex resin gave the quaternary α-amino acid (1*S*,2*R*)-**100a** (Scheme 22).[100]

Frahm *et al.*[101] reported the stereoselective synthesis of 1,2-diaminocyclohexanecarboxylic acids (1*R*,2*R*)- and (1*S*,2*S*)-**99b** starting from the 2-benzoylaminocyclohexanone (±)-**95b** by applying the Strecker methodology. Thus, the condensation reaction of (±)-**95b** with (*R*)-α-MBA, followed by addition of TMSCN in the presence of $ZnCl_2$ in methanol or hexane, under thermodynamic conditions, afforded the corresponding α-amino nitriles mixture *cis/trans*-**96b** in 99% yield, which, by hydrolysis with concentrate sulfuric acid at −20 °C produced, after LPLC separation, the α-amino carboxyamides (1*R*,2*R*,1'*R*)-**97b** and (1*S*,2*S*,1'*R*)-**101b** in 19 and 8% yield, respectively. Hydrogenolysis of diastereoisomerically pure **97b** and **101b** over Pd/C, followed by hydrolysis with 12 M HCl and subsequent ion-exchange chromatography gave the corresponding α,β-diamino acids (1*R*,2*R*)- and (1*S*,2*S*)-**99b** in 97% yield (Scheme 23).

On the other hand, condensation of ethyl 2-cyclohexanoneacetate (±)-**95c** with (*R*)-α-MBA, followed by addition of TMSCN in the presence of $ZnCl_2$ in methanol under kinetic or thermodynamic control, gave the α-amino nitriles mixture *cis/trans*-**96c** in 96% yield. Hydrolysis of the mixture of α-amino nitriles **96c** with concentrate sulfuric acid at −20 °C, followed by chromatographic separation and subsequent hydrogenolysis under HCO_2NH_4, Pd/C conditions produced the azabicyclo compounds (1*R*,2*S*)- and (1*S*,2*R*)-**102** (Scheme 24).[102]

Reaction of the enantiopure ketone **103**[103] with $(NH_4)_2CO_3$ and KCN, followed by treatment with $(Boc)_2O$ produced the spirohydantoins **104** and **105** in 49% yield and 5:2 dr. Basic

hidrolysis of diastereoisomerically pure **104**, obtained after chromatographic separation, afforded the quaternary α-amino acid (*S*,*S*)-**106** in 91% yield (Scheme 25).[104]

Condensation of the ketones **107a,b** with (*S*)-α-MBA, followed by addition of HCN in the presence of a catalytic amount of ZnI_2 afforded the α-amino nitriles mixture **108a,b**. Hydrolysis of **108a** with concentrate sulfuric acid furnished the α-amino carboxyamides (1*S*,1'*S*)-**109a** and (1*R*,1'*S*)-**110a** in 86% yield and 10:1 diastereoisomeric ratio. Hydrolysis of **108b** under identical conditions gave the α-amino carboxyamides (1*S*,1'*S*)-**109b** and (1*R*,1'*S*)-**110b** in 50% yield and 45:55 dr. Hydrogenolysis of diastereoisomerically pure (1*S*,1'*S*)-**109a** over Pd/C, followed by acidic hydrolysis provided the quaternary α-amino acid (*S*)-**111a** in quantitative yield. In a similar way, (1*R*,1'*S*)-**110b** was transformed into (*R*)-**111b** in quantitative yield (Scheme 26).[105]

In a similar way, condensation of the ketones **107a–c** with (*R*)-phenylglycinol, followed by addition of TMSCN afforded the α-amino nitriles mixture **112a–c**. Hydrolysis of **112a,b** with concentrate sulfuric acid produced the corresponding α-amino carboxyamides (1*S*, 1'*R*)-**113a,b** and (1*R*,1'*R*)-**114a,b** with a predominance of (1*S*,1'*R*)-**113a,b**, and small quantities of the lactones (1*S*,1'*R*)-**115a,b**. On the other hand, hydrolysis of **112c** under identical conditions gave the lactone (1*S*,1'*R*)-**115c** as the principal product, which, by treatment with dry ammonia led t o the α-amino carboxyamide (1*S*,1'*R*)-**113c**. Oxidative cleavage of the chiral auxiliary fragment in diastereoisomerically pure (1*S*,1'*R*)-**113a–c** with $Pb(OAc)_2$, followed by acidic hydrolysis and subsequent treatment with propylene oxide, provided the quaternary α-amino acids (*S*)-**111a–c** in 60–72% yield (Scheme 27).[105]

Warmuth *et al.*[106] reported the stereoselective synthesis of conformationally constrained lysine derivatives (*S*,*S*)-**122** and (*R*,*S*)-**123**. In this context, selective monoprotection of one of the carbonyl groups of the diketone **116** using 1,2-ethanedithiol in the presence of a catalytic amount of $BF_3.OEt_2$, followed by reaction with $(NH_4)_2CO_3$ and KCN, gave the corresponding spirohydantoins mixture **117** in almost quantitative yield, which, by cleavage of the thiocetal group with $AgNO_3$ and subsequent treatment with $(Boc)_2O$ in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP), produced the *N*,*N'*-bis-Boc-protected spirohydantoins mixture **118** in 79% yield. Condensation of **118** with (*R*)-phenylglycinol, followed by reduction of the imine formed with $NaBH(OAc)_3$ in THF and subsequent chromatographic separation, afforded the diastereoisomerically pure (*S*,*S*,1'*R*)-**119** and (*R*,*S*, 1'*R*)-**120** in 38 and 45% yield, respectively. Oxidative cleavage of chiral auxiliary fragment in (*S*,*S*,1'*R*)-**119** with $Pb(OAc)_2$, followed by hydrolysis with HCl and subsequent *N*-Boc-protection led to (*S*,*S*)-**121** in 62% yield, which, by hydrolysis and esterification, gave the lysine analogue (*S*,*S*)-**122** in 41% yield. In a similar way, (*R*,*S*,1'*R*)-**120** was transformed into (*R*,*S*)-**123** (Scheme 28).

Condensation of the ketone (±)-**124** with (*S*)-α-MBA in the presence of $TiCl_4$, followed by addition of TMSCN in the presence of $AlCl_3$ afforded, after separation, the corresponding α-amino nitriles **125a** and **125b** in 31 and 39% yield, respectively. Reaction of the enantiomerically pure ketone (+)-**124** under identical conditions, gave the α-amino nitrile **125a** in 68% yield as a single stereoisomer. Hydrolysis of the benzyl ester, nitrile and *N*-debenzylation in the diastereoisomerically pure **125a** with HCl and acetic acid at 160 °C, followed by addition of diazomethane gave the dimethyl ester (−)-**126** in 49% yield and this was transformed into dibenzyl ester (−)-**127** by ester exchange reaction with benzyl alcohol in the presence of $Ti(O\textit{i}\text{-}Pr)_4$. Finally, cleavage of the benzyl groups in (−)-**127** under hydrogenolysis over $Pd(OH)_2/C$ produced the conformationally constrained glutamic acid derivative (−)-**128** in 68% yield. Under identical conditions, **125b** was transformed into (+)-**128** (Scheme 29).[107]

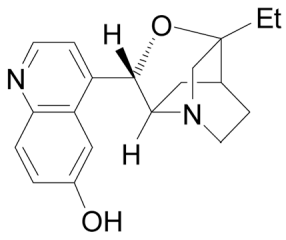
In some cases the intramolecular Strecker reaction has been used as an interesting methodology focused on the synthesis of quaternary α-amino acids. For example, intramolecular condensation of the ketones **95d–g** in the presence of TFA afforded the ketimine mixture **129d–g** and **131d–g**, presumably under a rapid equilibrium through the enamines **130d–g**. Addition of NaCN/TFA (condition A) or TMSCN/$ZnCl_2$ (condition B) to the imine mixture **129d–g** and **131d–g** gave the α-amino nitriles (1*S*,6*S*)-**132d–g** and (1*S*,6*R*)-**133d–g** in moderate to excellent yield and with low to good diastereoselective ratio. The cyanide addition to the ketimines having an alkyl side chain gave a small amount of the (1*R*)-stereoisomers. The results are summarized in Table 4.[108]

Oxidation of (1*S*,6*S*)-**132d** (R = Bn) with 1,4-diazabicyclo[2.2.2]octane (DABCO) and *tert*-butyl hypochlorite (*t*-BuOCl), followed by hydrolysis with concentrate HCl gave the (1*R*,2*S*)-1-amino-2-hydroxycyclohexanecarboxylic acid **100a** in 92% yield. On the other hand, oxidation of (1*S*,6*R*)-**133g** (R = *t*-Bu) with ozone and subsequent hydrolysis with concentrate HCl afforded the (1*R*,2*R*)-**99a** in 90% yield (Scheme 30).[108]

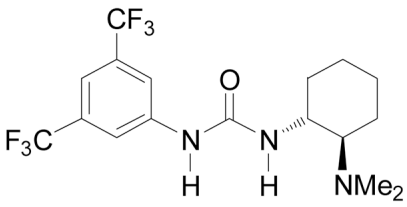
This methodology has also been used in the stereoselective synthesis of several quaternary α-amino acids.[109]

The electrophilic α-amination of carbonyl compounds is a conceptually attractive method for the synthesis of nitrogenated compounds by C–N bond formation.[110] In this context, apart from Strecker and related reactions, it has been reported that cyclic quaternary α-amino acids can be alternatively obtained through electrophilic amination reactions starting from molecules containing a carbonyl functionality. For example, Pellacani *et al.*[111] reported that the α-amination of enamine **134** bearing (*R*)-α-MBA, with ethyl *N*-[(4-nitrobenzenesulphonyl)oxy] carbamate ($NsONHCO_2Et$) as electrophilic aminating reagent, gave the quaternary α-amino derivative **136** in 95% yield and 60% ee, through the aziridine intermediate **135**. The stereochemistry of **136** was not reported (Scheme 31).

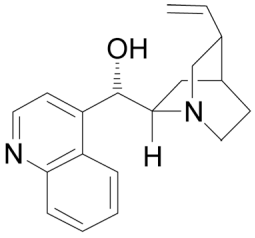
On the other hand, the α-amination of α-keto esters **137** using azodicarboxylates as the electrophilic aminating reagent, in the presence of 5–20 mol% of chiral catalyst such as β-isocupreidine **138**[112] (a constrained quinidine-derivative), the urea **139**,[113] cinchonine **140**,[114] chiral guanidine **141** with a seven-membered-ring structure,[115] palladium complex **142**,[116] and (*S*,*S*)-ip-pybox **143**,[117] afforded the corresponding α-aminated derivatives **144** in good yield and excellent levels of enantioselectivity, which are important precursors of quaternary cyclic α-amino acids. The results are summarized in Table 5.



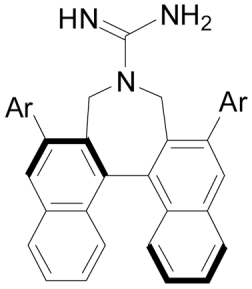
138



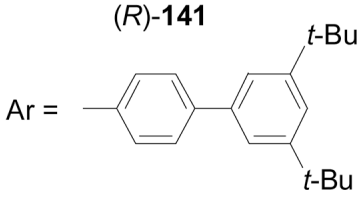
139

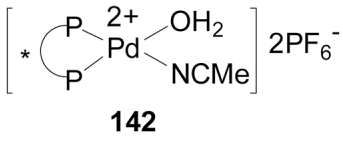


140

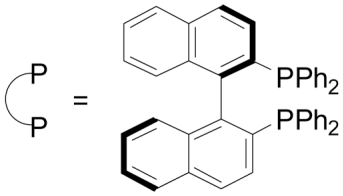


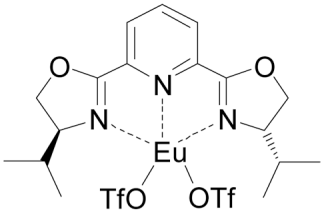
(*R*)-**141**





142





(*S*,*S*)-ip-pybox **143**

Asymmetric organocatalysis utilizes organic molecules to induce chirality in various C-C, C–N, and C–O bond-forming reactions.[118] For example, the enantioselective catalytic α-amination of the carboxaldehydes **145a–c** with dibenzyl azodicarboxylate in the presence of (*R*)-proline (20 mol%) produced the corresponding α-aminated products **146a–c** in good yield and >99% ee. Oxidation of the aldehyde group in **146a,b** with $NaClO_2$, followed by esterification with (trimethylsilyl)-diazomethane ($TMSCHN_2$) gave the esters **147a,b** in 82% yield (Scheme 32).[119]

Hydrolysis of **147b** with pyridine and trifluoroacetic anhydride (TFAA), followed by N-N bond cleavage with SmI_2 and subsequent treatment with propylene oxide gave the (*S*)-AIDA **33** in 70% yield. On the other hand, palladium-catalyzed phosphonylation of **147a** furnished the ethyl phosphonate **148** in 77% yield, which, by hydrolysis followed by N-N bond cleavage and subsequent treatment with propylene oxide led to (*S*)-APICA **36** in 80% yield. (Scheme 33).[119]

Very recently, Shibasaki *et al.*[120] reported the catalytic asymmetric α-amination of the succinimide **149**. Thus, reaction of **149** with di-*tert*-butyl azodicarboxylate in the presence of a catalytic amount of (*R*)-**150** derived from D-valine, La(O*i*-Pr)$_3$ and *N*,*N*-dimethylacetamide (DMA) in chloroform at 0 °C, afforded the corresponding α-aminated product (*R*)-**151** in quantitative yield and 92% ee (condition A). Identical results were obtained using a catalytic amount of (*R*)-**150**, and readily available and much less expensive $La(NO_3)_3$ and H-D-Val-O*t*-Bu in ethyl acetate at 0 °C.[121] Treatment of **151** with HCl(g) in toluene, followed by cleavage of the N-N bond by hydrogenation over Raney-Ni and recrystallization led to the enantiomerically pure (*R*)-3-amino-3-ethoxycarbonyl-pyrrolidin-2,5-dione **152** in 66% yield

(Scheme 34). The quaternary α-amino derivative **152** is a key intermediate in the synthesis of AS-3201 (Ranirestat), a highly potent aldose reductase inhibitor.[122]

Other methodology focused on the stereoselective synthesis of cyclic α-amino acids starting from cyclic carbonyl compounds is the amidation reaction, which, is carried out using nitrogen as the nucleophilic reagent. For example, Satoh *et al.*[123] reported the synthesis of the cyclic quaternary α-amino acids (*R*)- and (*S*)-**157** through the selective ring-opening of diastereoisomerically pure sulfinyloxiranes (2*S*,3*R*,R_S)-**154** and (2*R*,3*R*,R_S)-**155**. In this context, reaction of the β-tetralone with the lithium α-sulfinyl carbanion generated from enantiomerically pure (*R*)-chloromethyl *p*-tolyl sulfoxide and lithium diisopropylamide (LDA), afforded the adduct **153** as a mixture of two diastereoisomers in 82% yield, which, by treatment with *t*-BuOK gave the sulfinyloxiranes (2*S*,3*R*,R_S)-**154** and (2*R*,3*R*,R_S)-**155** in 93% yield and 3:1 dr. These compounds were separated by column chromatography. Treatment of diastereoisomerically pure (2*S*,3*R*,R_S)-**154** with sodium azide, followed by oxidation of the resulting aldehyde intermediate with a methanolic solution of iodine and KOH, produced the azido methyl ester (*R*)-**156** in 82% yield, which, by catalytic hydrogenation, led to enantiomerically pure (*R*)-**157** in 98% yield. In a similar way, (2*R*,3*R*,R_S)-**155** was transformed into (*S*)-**157** (Scheme 35).

Recently, Honda *et al.*[124] in order to obtain the (*R*)-deoxydysibetaine and 4-*epi*-dysibetaine, they carried out the addition of the lithium salt of chloroform to the ketone **158**, which is readily obtained from (*R*)-4-hydroxyproline, to give the alcohol **159** in 74% yield and high diastereoselectivity, which, by treatment with DBU and sodium azide in the presence of 18-crown-6 under modified Corey-Link reaction,[125] gave the dimethyl ester **161** in 56% yield through the intermediate epoxide **160**. Reduction of azide group in **161** with H_2 over Raney-Ni, followed by protection of resulting primary amine with $(Boc)_2O$, furnished the protected quaternary α-amino acid **162** in 75% yield, and subsequent treatment with SmI_2 in THF-HMPA or THF-DMEA afforded the δ-lactam[126] (*R*)-**163** in >90% yield (Scheme 36).

2.2. Construction of the ring by cyclization reactions

Due to the wide range of methodologies reported to the construction of the cyclic by C-C bond formation, we have decided to organize this section according to the size of the ring to be prepared. Since the Grubbs reaction is common to different cycles it can be considered independently.

Enantiomerically pure epichlorohydrins have been used as bifunctional electrophiles for the asymmetric synthesis of aminocyclopropanecarboxylic acids. For example, treatment of chiral glycine equivalent **165** obtained from enantiopure **164**, with 2.1 equiv. of sodium bis (trimethylsilyl)amide (NaHMDS), followed by addition of (*R*)-epichlorohydrin gave the cyclopropane as derivative **166** in 69% yield. Hydrolysis of **166** afforded the (1*R*,2*R*)-1-amino-2-(hydroxymethyl)cyclopropanecarboxylic acid **167** in 59% yield. On the other hand, Swern-oxidation of **166**, followed by reductive amination – performed with aniline and $NaBH_3CN$ – produced the compound **168** in good yield. Subsequent hydrolysis furnished the diamino acid (1*R*,2*S*)-**169** in 62% yield. Under identical conditions, the alkylation of **165** with (*S*)-epichlorohydrin and subsequent reactions produced the quaternary α-amino acids (1*R*, 2*S*)-**170** and (1*R*,2*R*)-**171** (Scheme 37).[127]

In a similar way, alkylation of chiral glycine equivalent (*S*)-**173**, obtained in four steps from carboxylic acid (*S*)-**172**, with (*R*)-epichlorohydrin gave the cyclopropane derivative **174**, which under identical conditions to those described in Scheme 37 was transformed into quaternary α-amino acids (1*S*,2*R*)-**170** (X = OH) and (1*S*,2*S*)-**171** (X = NHPh). Alkylation of (*S*)-**173** with (*S*)-epichloro-hydrin afforded the cyclopropane derivative **175**, which was transformed into quaternary α-amino acids (1*R*,2*S*)-**170** and (1*R*,2*R*)-**171** (Scheme 38).[128]

On the other hand, treatment of **174** with 1-phenyl-3-(trifluoroacetyl)urea **176** and diisopropyl azodicarboxylate (DIAD) under Mitsunobu[129] conditions afforded the urea **177** in 65% yield, which, by cleavage of the trifluoroacetyl group with aqueous K_2CO_3, led to compound **178** in 76% yield. Finally, hydrolysis of **178** produced the quaternary diamino acid (1*S*,2*S*)-**179** in 24% yield (Scheme 39).[128]

Recently, Acher *et al.*[130] reported the utility of (1*S*,2*R*)- and (1*R*,2*R*)-1-amino-2-(hydroxymethyl) cyclopropanecarboxylic acid derivatives **180** and **185**[131] in the synthesis of (1*S*,2*R*)- and (1*R*,2*R*)-1-amino-2-phosphonomethylcyclopropanecarboxylic acids **184** and **186** (APCPr),[132] which were evaluated at the recombinant group III metabotropic glutamate receptor. Thus, the bromination of (1*S*,2*R*)-**180** with CBr_4 and polymer bond PPh_3 in the presence of triethylamine led to bromo derivative (1*S*,2*R*)-**181** in 56% yield. In order to prevent the cyclopropane cleavage in the next Arbuzov reaction,[133] the Boc protective group was replaced by a more electron-withdrawing trifluoroacetyl group, obtaining (1*S*,2*R*)-**182** in 95% yield. Arbuzov reaction of **182** with trimethyl phosphite gave the corresponding phosphonate (1*S*,2*R*)-**183** in 51% yield, which, by hydrolysis, followed by ion exchange chromatography, produced the optically pure (1*S*,2*R*)-**184**, APCPr in 96% yield. Under identical conditions, (1*R*,2*R*)-**185** was transformed into (1*R*,2*R*)-**186**, APCPr (Scheme 40).

Carboni *et al.*[134] reported the application of Belokon's Ni(II) complex (*S*)-**187** (a glycine equivalent) in the diastereoselective synthesis of (1*S*,2*R*)- and (1*R*,2*S*)-allonorocoronamic acid **5a** through a double alkylation. In this context, treatment of Ni(II) complex (*S*)-**187** with potassium *tert*-butoxide followed by addition of sulfate (*S*)-**188** gave the corresponding enolate **189**, which, by intramolecular alkylation, afforded the cyclopropane derivative (*S*,1*S*, 2*R*)-**190** in 70% yield. Acidic hydrolysis of **190** followed by ion exchange chromatography produced the (1*S*,2*R*)-allonorcoronamic acid **5a** in 96% yield. Alkylation of Ni(II) complex (*S*)-**187** with the sulfate (*R*)-**188**, followed by hydrolysis, gave the (1*R*,2*S*)-allonorcoronamic acid **5a** (Scheme 41).

Recently, Fox *et al.*[135] reported the catalytic stereoselective synthesis of (1*R*,2*S*)-dehydrocoronamic acid methyl ester **196**, through a double alkylation of glycine anion equivalents **191a,b**. Thus, asymmetric allylic alkylation of **191a,b** with 3,4-epoxy-1-butene in the presence of a catalytic amount of (*S*,*S*)-**192**-$(allylPdCl)_2$ complex, afforded the allyl derivatives mixture **193a,b** in quantitative yield and 3:2 dr, which, by mesylation followed by treatment with NaH or potassium *tert*-butoxide in THF, gave the cyclopropanes **194a,b** and dihydroazepines **195a,b**. Hydrolysis of the mixture of **194a** and **195a** followed by separation led to (1*R*,2*S*)-**196** in 14% yield and 88% ee (Scheme 42).[136]

Reaction of 2,3-epoxy-1,1,1-trifluoropropane **197** with the sodium salt of **198** gave the γ-hydroxy nitrile derivative **199** in 73% yield and 30% de, which, by reaction with tosyl chloride (TsCl) followed by treatment with NaH and subsequent recrystallization, afforded the diastereoisomerically pure cyclopropyl cyanide (1*S*,2*S*)-**200** in 70% yield. Oxidative degradation of the pyrrole ring of **200** with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ produced the α-amino nitrile (1*S*,2*S*)-**201** in 71% yield. Subsequent hydrolysis with HCl furnished the optically pure trifluoronorcoronamic acid (1*S*,2*S*)-**202** in 67% yield (Scheme 43).[137]

In a similar way, reaction of **197** with the sodium salt of **203** gave the γ-hydroxy nitrile **204**, which, by reaction with TsCl followed by treatment with sodium hydride and subsequent recrystallization, furnished the diastereoisomerically pure cyclopropyl cyanide (1*R*,2*S*)-**205** in 70% yield. Hydrolysis of nitrile function of **205** with hydrogen peroxide under basic conditions produced the amide (1*R*,2*S*)-**206** in 79% yield, which, by Hoffman rearrangement[138] followed by oxidative degradation of aromatic ring of **207** with $NaIO_4$ in the presence of a catalytic

amount of $RuCl_3$, produced the optically pure *N*-Boc-trifluoronorcoronamic acid (1*R*,2*S*)-**208** in 30% yield (Scheme 44).[137]

Synthesis of optically pure 1-aminocycloalkanecarboxylic acids starting from α-amino acids is another methodology that has been used. For example, Donkor *et al.*[139] reported the synthesis of all four diastereoisomers of *N*-Cbz-2,3-methanoleucine from L- and D-valine. Deamination of L-valine with $NaNO_2/H_2SO_4$ followed by reduction of the carboxylic acid with $LiAlH_4$ produced the corresponding diol (*S*)-**209** in 42% yield. This compound was transformed into cyclic sulfate (*S*)-**210** in 91% yield. Reaction of (*S*)-**210** with the sodium dimethyl malonate afforded the cyclopropane derivative (*R*)-**211** in 84% yield and selective hydrolysis with KOH and subsequent Curtius rearrangement[140] with diphenylphosphorazide (DPPA) in the presence of triethylamine (TEA), followed by addition of benzyl alcohol, gave the diprotected α-amino acid (1*S*,2*R*)-**212** in good yield. Finally, hydrolysis of (1*S*,2*R*)-**212** with KOH gave (1*S*,2*R*)-**213** in 91% yield (Scheme 45).

On the other hand, selective hydrolysis of (*R*)-**211** with KOH followed by treatment with hydrazine gave the compound **214**, which, by reaction with $NaNO_2/H_2SO_4$ and subsequent esterification with diazomethane provided the azide derivative **215**. Curtius rearrangement of **215** followed by hydrolysis with KOH furnished (1*R*,2*R*)-**216** (Scheme 46). Under indentical conditions the diastereoisomers (1*R*,2*S*)-**213** and (1*S*,2*S*)-**216** were obtained from D-valine.[139]

Frick *et al.*[141] reported the stereoselective synthesis of protected 2,3-methano amino acids (1*S*,2*S*)-**224** and (1*R*,2*R*)-**225**, which are analogues of ornithine and glutamic acid, respectively. Initially, treatment of **218**, obtained from epoxide **217**,[142] with 3,5-dinitrobenzoic acid under Mitsunobu conditions gave the corresponding 3,5-dinitrobenzoate **219** in 91% yield. This compound was reacted with NaH to give the cyclopropane derivative **220** in 81% yield. Cleavage of the benzyl protective group with H_2 over Pd/C followed by treatment with TFA furnished the lactone (1*R*,6*R*)-**221** in 97% yield. The synthesis of the lactone (1*S*,6*S*)-**221** was reported by Frick *et al.*[142] (Scheme 47).

Reaction of (1*S*,6*S*)-**221**[142] with ethyl chloroformate followed by treatment with sodium azide and subsequent Curtius rearrangement of the corresponding azide under heating and the addition of benzyl alcohol, produced the *N*-Cbz-amino derivative (1*S*,6*S*)-**222** in 90% yield, which, by hydrolysis with LiOH and subsequent esterification with MeI, afforded the protected amino acid (1*S*,2*S*)-**223** in 93% yield. Reaction of (1*S*,2*S*)-**223** with methanesulfonyl chloride (MsCl), followed by reaction with sodium azide and subsequent reduction of the azido group with H_2 over Pd-$BaSO_4$ in the presence of $(Boc)_2O$, gave the protected 2,3-methanoornithine analogue (1*S*,2*S*)-**224** in 79% yield (Scheme 48).[141]

Under identical conditions to those described in the scheme 48, (1*R*,6*R*)-**221** was transformed into (1*R*,2*R*)-**223** in good yield and subsequent oxidation with pyridine-SO_3 followed by treatment with sodium chlorite gave, the methyl 2,3-methanoglutamate derivative (1*R*,2*R*)-**225** in 80% (Scheme 49).[141]

Chiral didehydroamino acid derivatives from a cyclic glycine template have been used in the stereoselective synthesis of cyclopropane amino acid derivatives through diastereoselective cyclopropanation reactions by using Corey's ylide. For example, reaction of (*S*)-oxazinone **227**, obtained in four steps from (*S*)-2-hydroxyisovaleric acid **226**, with acetaldehyde and propanaldehyde in the presence of K_2CO_3 and tetrabutylammonium bromide (TBAB), produced the didehydroamino acid derivatives (*S*)-**228a,b** with high selectivity in 50–55% yield. Treatment of these compounds with Corey's dimethylsulfoxonium methylide gave the cyclopropanation products **229a,b** in moderate yield and 9:1 diastereoisomeric ratio. Hydrolysis of diastereoisomerically pure **229a,b** with HCl afforded the (1*S*,2*R*)-*allo*-

norcoronamic acid **5a** in 60% yield and (1*S*,2*R*)-*allo*-coronamic acid **5b** in 67% yield (Scheme 50).[143]

On the other hand, condensation of the protected (*S*)-pyrazine-2-one **231**, obtained in three steps from (*S*)-α-aminoketone **230**, with acetaldehyde and propanaldehyde furnished the *Z*-α,β-unsaturated compounds (*S*)-**232a,b** in 88 and 86% yield, respectively. Treatment of these compounds with Corey's dimethylsulfoxonium methylide gave the cyclopropanation products **233a,b** in moderate yield and 23:1 dr. Hydrolysis of diastereoisomerically pure **233a** with HCl afforded the enantiomerically pure (1*S*,2*R*)-*allo*-norcoronamic acid **5a** in 24% yield (Scheme 51).[144]

Didehydroamino acid derivatives from cyclic glycine templates have also been used in the stereoselective synthesis of cyclopropane amino acid derivatives, through diastereoselective cyclopropanation reactions with phosphorus or sulfur ylides. For example, addition of $Me_2C(Li)PPh_3$ and $(CD_3)_2CD_2(Li)SO$ to the dehydroalanine (*S*)-**234** afforded the spiro derivatives (3*S*,6*S*)-**235a,b** in excellent yield and diastereoselectivity (>98:2), which, by treatment with TFA, gave the diketopiperazines (3*S*,6*S*)-**236a,b** in good yield. Finally, hydrolysis of **236a,b** with 6 M HCl followed by esterification with $SOCl_2$/MeOH produced the corresponding methyl ester hydrochloride salts (*S*)-**237a,b** in excellent yield (Scheme 52).[145]

Enantioselective organocatalytic intermolecular cyclopropanation of protected dehydroalanine **238** with the ammonium ylide generated from reaction of *tert*-butyl bromoacetate with catalytic amounts of quinine derivatives **239** or **240** and Cs_2CO_3 as a base, afforded the cyclopropane compound (+)-**241** in 97% ee using **239** as a catalyst, and (−)-**241** in 90% ee using **240** as a catalyst (Scheme 53).[146]

On the other hand, condensation of (*R*)-**242** with benzylamine, followed by addition of TMSCN afforded a mixture of α-amino nitriles (1*R*,2*S*)-**243** and (1*S*,2*S*)-**244** in 75% yield and 85:15 diastereoisomeric ratio. Protection of the amino function of diastereoisomerically pure (1*R*,2*S*)-**243** with methyl chloroformate (MocCl) gave (1*R*,2*S*)-**245** in 98% yield, which, by selective cleavage of the *tert*-butyldimethylsilyl (TBS) protective group with acetic acid and subsequent reaction with PPh_3 and chloroform or bromoform, led to the derivatives (1*R*,2*S*)-**246a,b** in excellent yield. Intramolecular alkylation of (1*R*,2*S*)-**246a** with KOH-DMF or potassium *tert*-butoxide in THF gave the cyclopropylaminonitrile (1*S*,2*R*)-**247** in 82% yield and >98:2 dr, which, by treatment with hydrogen peroxide under basic conditions, furnished the amide (1*S*,2*R*)-**248** in 87% yield (Scheme 54).[147]

Wanner *et al.*[148] reported the synthesis of all four stereoisomers of 1-amino-2-(hydroxymethyl)-cyclobutanecarboxylic acid (1*S*,2*S*)- and (1*R*,2*R*)-**13f**, (1*S*,2*R*)- and (1*R*,2*S*)-**14f** through a double alkylation of the chiral glycine equivalent (*R*)-**173**. In this context, reaction of (*R*)-**173** with *s*-BuLi in THF at −78 °C, followed by addition of but-3-enyl triflate, afforded the alkylated products **249a** and **249b** in 69% yield and 95.5:4.5 dr. The use of other bases and 4-bromobut-1-ene as the alkylating reagent gave both low yield and diastereoselectivity. Oxidation of the terminal double bond of the butenyl side chain in **249a,b** with a catalytic amount of OsO_4 in combination with Me_3NO as a co-oxidant, followed by selective protection of primary hydroxy group with *tert*-butyldimethylsilyl chloride (TBSCl) and subsequent selective replacement of secondary hydroxy group with PPh_3 and I_2, produced the iodohydrins **250a–d** in good overall yield and 4:4:1:1 dr. Reaction of **250a–d** with phosphazenic base (*t*-BuP_4) gave the corresponding cyclobutane derivatives, which, by treatment with tetrabutylammonium fluoride (TBAF) and subsequent separation by preparative HPLC, furnished the hydroxyl derivatives **251a–d** in good yield and 48:31:18:3 dr. Finally, hydrolysis of diastereoisomerically pure **251a** led to (1*S*,2*S*)-**13f** in 71% yield. In a similar way,

251b afforded (1*S*,2*R*)-**14f** in 76% yield. The diastereoisomers (1*R*,2*R*)-**13f** and (1*R*,2*S*)-**14f** were obtained from (*S*)-**173** (Scheme 55).

Dialkylation of *N*-(diphenylmethylene)glycine ethyl ester **191a** with 1,4-diiodo derivative (*S*)-**253**, obtained in 4 steps from (*S*)-malic acid dimethyl ester **252**, afforded the cyclopentane derivative mixture **254** in 2:1 dr. Hydrolysis of **254** with 2 M HCl followed by treatment with $(Boc)_2O$ and subsequent chromatographic separation, gave the diprotected quaternary α-amino acids (1*S*,3*S*)-**255** and (1*R*,3*S*)-**256** in 36 and 19% yield, respectively, and these were used in the preparation of the thymine derivatives **257** and **258** (Scheme 56).[149]

On the other hand, reduction of dicarboxylic acid (*S*,*S*)-**259** with $LiAlH_4$, followed by treatment with I_2 and PPh_3, afforded the diiodide **260** in 83% yield. Dialkylation of ethyl isocianoacetate with **260**, followed by hydrolysis and subsequent treatment with $(Boc)_2O$, gave the ethyl 1-*N*-Boc-aminocyclopentanecarboxylate **261** in 59% yield. Ozonolysis of **261** followed by treatment with $NaBH_4$ and subsequent oxidation of the resulting diol with oxone gave the dicarboxylic acid **262** in 25% overall yield. On the other hand, hydrogenation of **261** over Pd/C produced the diprotected quaternary α-amino acid **263** in 99% yield. Finally, ozonolysis of **261** followed by treatment with benzylamine and subsequent reduction with $NaBH_3CN$ produced the compound **264** in 53% yield (Scheme 57).[150]

Ma *et al.*[151] reported the stereoselective synthesis of (*S*)-1-aminoindane-1,6-dicarboxylic acid **269** and related analogues, through the intramolecular acylation of enantiopure α,α-disubstituted amino acid (*S*)-**266**. In this context, the protection of (*R*)-phenylglycine with methyl chloroformate followed by condensation with benzaldehyde dimethyl acetal, afforded the *cis*-oxazolidinone (2*R*,4*S*)-**265**, which, by alkylation with *tert*-butyl bromoacetate followed by hydrolysis, produced the carboxylic acid (*S*)-**266**. Reaction of (*S*)-**266** with PCl_5 followed by treatment with $AlCl_3$ gave the acylated product (*S*)-**267** in 92% yield, and this was hydrogenated over Pd/C to provide the cyclic α-amino acid (*S*)-**268** in 94% yield. Sequential iodination with $I_2/Hg(OTf)_2$, palladium-catalyzed carbonylation under $Pd(OAc)_2$/CO/MeOH conditions, and hydrolysis led to (*S*)-**269** in 40% overall yield (Scheme 58).

On the other hand, treatment of (*S*)-**268** with acetyl chloride catalyzed with $AlCl_3$, followed by Baeyer-oxidation using *m*-chloroperbenzoic acid (*m*-CPBA) and subsequent hydrolysis, produced the phenol derivative (*S*)-**270** in good yield. Iodination of (*S*)-**270** with I_2/pyridine followed by palladium-catalyzed carbonylation using $Pd(OAc)_2$/CO/EtOH afforded the diester (*S*)-**271** in 55% overall yield, and this compound was hydrolysed with TMSI to give the conformationally constrained (*S*)-**272** in 75% yield. Additionally, iodination of (*S*)-**270** followed by palladium-catalyzed phosphonylation with $Pd(PPh_3)_4/HP(O)(OEt)_2$ afforded the phosphonate (*S*)-**273** in 58% yield, which, by hydrolysis with TMSI, gave the phosphonic acid (*S*)-**274** in 82% yield (Scheme 59).[151]

Asymmetric Strecker reaction of 4-methylbenzaldehyde with (*R*)-phenylglycinol and NaCN, followed by hydrolysis and subsequent intramolecular esterification with TsOH afforded the corresponding lactone mixture **275** in 57% yield. Alkylation of **275** with *tert*-butyl bromoacetate and subsequent opening of the lactone ring with Et_3N/MeOH, produced the alkylated products (*S*,*R*)-**276** and (*R*,*R*)-**277** in 65% yield and 4:1 dr. Cleavage of the chiral auxiliary of diastereo-isomerically pure (*S*,*R*)-**276** with $Pd(OAc)_4$/NaOAc, followed by acidic hydrolysis and subsequent protection of the resulting amino group with methyl chloroformate led to (*S*)-**278** in 75% yield. Subsequent intramolecular acylation with oxalyl chloride and $AlCl_3$ gave (*S*)-**279** in 93% yield. Benzylic bromination of (*S*)-**279** with *N*-bromosuccinimide (NBS) catalyzed with 2,2'-azoiso-butyronitrile (AIBN) produced the bromo derivative (*S*)-**280** in 87% yield. This compound was oxidised with Ag_2O and $AgNO_3$ and subsequent esterification with MeI/K_2CO_3 furnished the diester (*S*)-**281** in 64% yield. Reduction of the

ketone function of (*S*)-**281** by Pd/C-catalyzed hydrogenation gave (*S*)-**282** in 97% yield, which, by hydrolysis with 6 N HCl and subsequent treatment with propylene oxide afforded the (*S*)-AIDA **33** in 78% yield (Scheme 60).[151]

The alkylidene carbene C–H insertion is another strategy for the enantioselective synthesis of conformationnaly constrained α-amino acids. For example, reaction of (*R*)-**283**, obtained in six steps from L-serine, with lithium (trimethylsilyl)diazomethane generated *in situ* by treatment of (trimethylsilyl)diazomethane with *n*-BuLi, gave the alkylidene carbene **284**, which, through a 1,5-C–H insertion reaction, produced the spiro compound (*S*)-**285** in 62% yield. Catalytic hydrogenation of (*S*)-**285** over Pd/C afforded the hydrogenated product (1*S*, 3*R*)-**286** in 79% yield as a single diastereoisomer, which, by cleavage of the acetonide function with BF_3.2AcOH furnished the alcohol (1*S*,3*R*)-**287** in 60–70% yield. Finally, Dess-Martin periodinane oxidation of (1*S*,3*R*)-**287** followed by treatment with sodium chlorite afforded the (1*S*,3*R*)-*N*-Boc-2,5-methanoleucine **288** in 70% yield and >95% ee (scheme 61).[152]

In a similar way, treatment of (*R*)-**289**, obtained from L-serine, with lithium (trimethylsilyl)-diazomethane led to a 1,5-C–H insertion reaction that gave the spiro compound (*S*)-**290** in 69% yield. Catalytic hydrogenation of this compound over Pd/C produced (1*S*,3*R*)-**291** in 79% yield and >10:1 dr. Selective cleavage of TBS protective group in (1*S*,3*R*)-**291** with HF/MeCN led to diol (1*S*,3*R*)-**292** in 81% yield, which, by oxidation of hydroxy groups with $RuCl_3/NaIO_4$ followed by treatment with HCl and subsequent ion exchange chromatography, afforded the quaternary α-amino acid (1*S*,3*R*)-ACPD, **293** in 49% yield (scheme 62).[153]

Treatment of **295a,b**, obtained from (*R*)-glyceraldehyde dimethyl acetal **294**, with NBS in MeCN afforded the bicyclic lactone **297** in 42% yield. This product is probably obtained through the oxidation of **295** to the imine intermediate **296** followed by an intramolecular attack of the free OH group on the carbon-nitrogen double bond. Hydrolysis of bicyclic lactone **297** with HCl and subsequent cleavage of the TBS protective group gave the quaternary α-amino acid methyl ester **298** (Scheme 63).[154,155]

Alkylation of commercially available (*R*)-bislactim ether **299** with the dibromide **300** and *n*-BuLi in THF at −78 °C afforded the alkylated product (2*R*,5*S*)-**301** in 95% yield and 93:7 dr, which, by treatment with diluted *n*-BuLi, furnished the corresponding spiro derivative (2*R*, 5*R*)-**302** in 99% yield as a single diastereoisomer. Hydrolysis of (2*R*,5*R*)-**302** gave the methyl ester of 2-amino-tetraline-2-carboxylic acid (*R*)-**157** in 98% yield (Scheme 64).[156]

Jørgensen *et al.*[157] reported the first highly enantioselective catalytic alkylation of ketimines, a methodology used for the synthesis of quaternary α-amino acids. In this context, addition of ketene acetal **304** to the ketimine **303** in the presence of a catalytic amount of (*R*,*R*)-Ph-pybox-$Zn(OTf)_2$ **305** afforded the Mannich base **306** in 98% yield and 93% ee. Selective *N*-protection of **306** with $(Boc)_2O$ gave the compound **307** in 78% yield, which, by treatment with Cs_2CO_3, produced the δ-lactone **308** in 79% yield by spontaneous cyclization of the resulting phenol function (Scheme 65).

On the other hand, the first direct organocatalytic enantioselective Mannich reaction of the ketimine **309** with several aldehydes in the presence of a catalytic amount of the chiral amine **310**, afforded the corresponding Mannich products **311a–h** and **312a–h** in good yield and with moderate to excellent diastereoisomeric ratio (4:1 to >20:1), with a predominance of **311a–h**. These compounds can be used as intermediates in the synthesis of quaternary α-amino acids (Scheme 66).[158]

Olefin metathesis is a fundamental chemical reaction involving the rearrangement of carbon–carbon double bonds and can be used to couple, cleave, ring-close, ring-open, or polymerize olefinic molecules. The widely accepted view that olefin metathesis revolutionized the

different fields of synthetic chemistry led to the award of the 2005 Nobel Prize in Chemistry to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock "for the development of the metathesis method in organic synthesis".159 The ring closing metathesis (RCM) synthetic methodology has also been used in the stereoselective synthesis of different size of cyclic α-amino acids,[160] and in this review we present this methodology as an independient section. For example, Ru(II)-catalyzed ring-closing metathesis reaction of dialkylated compounds **313a,b**, obtained from bislactim ether (*R*)-**299**, in 1,2-dichloroethane (DCE) gave the spiro derivatives **314a,b**, which, by dihydroxylation of the five and six-membered-rings with a catalytic amount of OsO_4 in combination of morpholine *N*-oxide (NMO) afforded the diols **315a,b** and **316a,b**. Treatment of the diols **315a,b** with methyl iodide and sodium hydride, followed by hydrolysis with TFA, produced the conformationally constrained cyclic α-amino acids methyl esters **317a,b**. Hydrolysis of diol **315a** with TFA, followed by acetylation, gave the acetylated α-amino acid methyl ester **318a** (Scheme 67).[161]

Ring closing metathesis of dialkylated derivatives **313a–d** in the presence of a catalytic amount of Grubbs second generation catalyst $PhCH{=}RuCl_2(IMes)(PCy_3)$ under microwave assisted heating, gave the corresponding spiro compounds with five-, six- and seven-membered rings containing a double bond **314a–d** in 63–99% yield. Hydrolysis of the bis-lactim ether of **314a–d** with TFA at room temperature or under microwave conditions, followed by treatment with $(Boc)_2O$ afforded the *N*-Boc protected quaternary amino acid ethyl esters **319a–d** in good yield, which, by basic hydrolysis under microwave assisted heating, produced the amino acids **320a–d** in 76–93% yield (Scheme 68).[162]

Cascade Ru(II)-catalyzed ring closing metathesis reaction of **321a,b** produced the RCM products **322a,b** in excellent yield. In a similar way, reaction of **323a–c**, obtained from **321a,b**, under identical conditions furnished the conformationally constrained amino acids **324a–c** in good yield (Scheme 69).[163,164]

Diels-Alder reaction of **324a,b,d** with diethyl acetylenedicarboxylate (DEAD) followed by aromatization with MnO_2 gave the conformationally constrained α-amino acids **325a,b,d** in good yield (Scheme 70).[164]

On the other hand, ring closing metathesis reaction of triyne **327**, readily obtained from **326**, in the presence of a catalytic amount of $PhCH{=}RuCl_2(PCy_3)_2$ in toluene at 85 °C gave the product (2*R*,7*R*)-**328** in 58% yield.[165] Ring closing metathesis reaction of triyne **326** in the presence of a catalytic amount of $PhCH{=}RuCl_2(PCy_3)_2$ in toluene at 85 °C gave **329** in 90% yield,[165,166] and a quantitative yield was obtained when the reaction of **326** was carried out under microwave assisted heating. Identical results were obtained using $PhCH{=}RuCl_2(IMes)(PCy_3)_2$ as a catalyst.[166] Hydrolysis of **329** with 0.1 M TFA gave the constrained α-amino acid methyl ester (2*R*,7*R*)-**330** in 35% yield (Scheme 71).[167]

Ring closing metathesis reaction of tetraene **331** in the presence of 10 mol% of $PhCH{=}RuCl_2(PCy_3)_2$ in toluene at 85 °C in order to obtain the spirane **332** was unsatisfactory, probably due to a sterically congested substrate. The more reactive $PhCH{=}RuCl_2(IMes)(PCy_3)$ catalyst also failed to effect the spiroannulation of **331**. However, ring closing metathesis reaction of less bulky tetraene **333**, obtained by hydrolysis of **331**, under identical conditions gave the spiranes **334** and **335** in 73% yield and 3:2 isomeric ratio (Scheme 72).[168]

On the other hand, Ru(II)-catalyzed ring closing metathesis reaction of diastereoisomerically pure **336** gave the cyclic α-amino acid methyl ester **337** in 96% yield (Scheme 73).[169]

Chemoselective allylation of imino ester **338** with allylzinc bromide afforded the diene **339** in 95% yield as a single diastereoisomer, which, by ring closing metathesis reaction in the presence of Grubbs first generation catalyst $PhCH{=}RuCl_2(PCy_3)_2$, gave the cyclic amino ester

340 in 92% yield and >98% de. Cleavage of the benzyl group in **340** under $H_2/Pd(OH)_2$ conditions provided the amino ester **341** in almost quantitative yield, which, by treatment with TBAF and subsequent ion-exchange chromatography, furnished the quaternary α-amino acid **342** in 70% yield (Scheme 74).[170]

Undheim *et al.*[171] reported the stereoselective synthesis of rigidified homoserine analogues **350** and **351** through the ring closing metathesis reaction. In this context, reaction of hydroxy derivative **343** in the presence of a catalytic amount of $PhCH=RuCl_2(PCy_3)_2$ in DCE at 65 °C gave the spiro compound **344** in 72% yield. Swern oxidation of **344** produced the α,β-unsaturated ketone **346** in 74% yield. On the other hand, oxidation of **343** under Swern conditions furnished the ketone **345** in 79% yield, which, by ring closing metathesis reaction in the presence of a catalytic amount of $PhCH=RuCl_2(PCy_3)_2$ in benzene at 70 °C, afforded the spiro derivative **346** in 37% yield. Conjugate addition of lithium dimethylcuprate to **346** furnished **347** in 91% yield and high diastereoselectivity (Scheme 75).

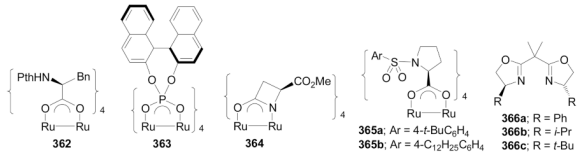
Reduction of the carbonyl group of **347** with $NaBH_4$ in methanol afforded the alcohols **348** and **349** in 37 and 57% yield, respectively. Hydrolysis of diastereoisomerically pure **348** with 0.1 M TFA gave the amino ester **350** in 38% yield, whereas the hydrolysis of **349** under identical conditions afforded the dipeptide **351** in 77% yield (Scheme 76).[171]

Møller and Undheim[172] reported the synthesis of spiro derivatives **354** and **357** by palladium-mediated 5-*exo*-*trig*-spiroannulation and these compounds are precursors of functionalized cyclic quaternary α-amino acids. Thus, the lithiation of **352** followed by addition of 2,3-dibromopropene gave the diene **353** in 60% yield and >98% de and treatment of **353** with a catalytic amount of $Pb(OAc)_2$ in the presence of PPh_3/Ag_2CO_3 afforded the spiro compound **354** in 60% yield. In a similar way, reaction of **355**, obtained from **352**,[172b] produced the spiro derivative **356** in 60% yield and treatment with a catalytic amount of $NiCl_2$(dppp) and MeMgBr led to compound **357** in 64% yield (Scheme 77).

On the other hand, aldol reaction of **358a,b** using Cs_2CO_3 as a base in acetonitrile, afforded the spiroannulated compounds **359a,b** in 49 and 63% yield, respectively, and subsequent hydrolysis with 0.1 M TFA gave the amino esters **360a,b** in 56 and 59% yield, respectively (Scheme 78). Using this methodology the α-amino acid methyl esters **360c–f** were obtained from the appropriate substrates.[173]

2.3. Cicloadditions and related reactions

Direct incorporation of an “amino acid synthetic equivalent” into an alkene by transition metal catalyzed diazo decomposition has also been used for the synthesis of quaternary 1-amino-cyclopropanecarboxylic acids.[174,175] For example, the asymmetric catalytic cyclopropanation of styrene with α-nitro-α-diazocarbonyl compounds **361a–d** in the presence of a catalytic amount of **362–366** as a chiral catalyst, afforded the cyclopropane derivatives *trans*- and *cis*-**367a–d** in good selectivity *trans:cis*, but with low enantioselectivity.[176] The results are summarized in Table 6.



Moreau and Charette[177] reported the catalytic asymmetric cyclopropanation of styrene with iodonium ylides derived from nitroacetates. For example, reaction of phenyliodonium with methyl nitroacetate gave the corresponding phenyliodonium ylide **368**, which, by

cyclopropanation reaction with styrene in the presence of a catalytic amount of isopropilidene bis(4-phenyl-2-oxazoline) **366a** and $AgSbF_6$, afforded the methyl 1-nitrocyclopropyl carboxylate **367a** in 79% yield and excellent diastereo- and enantioselectivity (similar results were obtained using others alkyl and aryl alkenes). Reduction of the nitro group of **367a** with Zn/HCl in 2-propanol furnished the aminoester **369** in 89% yield (Scheme 79).

On the other hand, reaction of chiral carbenes **370a,b** with terminal olefins in toluene under reflux produced the corresponding cyclopropanes **371a,b** and **372a,b** as a mixture of both *cis* diastereoisomers in low yield and 2:1 and 1.5:1 diastereoisomeric ratio, respectively, with a predominance of **371a,b** (Scheme 80).[178]

Reaction of (*Z*)-**373** with (−)-menthol in the presence of bis-(dibutylchlorotin)oxide gave the aminoacrylate (*Z*)-**374** in 78% yield and subsequent treatment with diazomethane in dichloromethane produced the Δ^1-pyrazolines **375a** and **375b** in 93% yield and 1.8:1 dr, (reversal of diastereoselectivity was observed when (+)-menthol was used as chiral auxiliary). Heating of diastereoisomerically pure **375a** and **375b** at 150 °C afforded the constrained cysteines derivatives (1*S*,2*S*)- and (1*R*,2*R*)-**376**, respectively, in good yield and diastereoselectivity. Saponification of (1*S*,2*S*)-**376** with NaOH in methanol gave the carboxylic acid (1*S*,2*S*)-**377** in 44% yield (Scheme 81).[179]

1,3-Dipolar cycloaddition of α,β-unsaturated compound **379**, obtained from Horner-Wadsworth-Emmons reaction of (*S*)-**294** and the phosphonate **378**, with diazomethane followed by photolysis of the resultant pyrazoline gave the cyclopropane derivative **380** in 87% yield.[180] Hydrolysis of the acetonide in **380** with HCl afforded the corresponding diol, which was oxidised with $NaIO_4$ produced the aldehyde (1*R*,2*S*)-**381** in good yield. Reduction of **381** with $NaBH_4$ and subsequent saponification of methyl ester gave (1*R*,2*S*)-**382** in good yield. Finally, cleavage of the *N*-Boc protective group in (1*R*,2*S*)-**382** followed by treatment with propylene oxide provided the α-aminocyclopropanecarboxylic acid (1*R*,2*S*)-**170** in excellent yield (Scheme 82).[181]

Reaction of aldehyde (1*S*,2*R*)-**381** with *N*-methylglycine and [60]fullerene afforded the fulleropyrrolidine **384** in 25% yield, through the 1,3-dipolar cycloaddition of the *in situ* produced azomethine ylide **383**. Cleavage of the *N*-Boc protective group of **384** with TMSI in chloroform led to compound **385** in 89% yield (Scheme 83).[182]

On the other hand, 1,3-dipolar cycloaddition of diazomethane to α,β-unsaturated compound **386** followed by photolysis of the resultan pyrazoline gave the cyclopropane derivative **387** in 48% yield, which, by saponification of the methyl ester and cleavage of the acetonide using pyridinium *p*-toluenesulfonic acid (PPTS), gave the keto amino acid (1*R*,2*R*,1'*R*,3'*R*)-**388** in 35% yield. In a similar way, reaction of **389** with diazomethane followed by photolysis produced the diprotected quaternary α-amino acid (1*S*,2*S*,1'*S*,3'*R*)-**390** in 45% yield (Scheme 84).[183]

Recently, Avenoza *et al.*[184] reported the asymmetric [2+2] cycloaddition of 2-acylaminoacrylates **391** with donor olefins **392** in the presence of a catalytic amount of sterically hindered aluminum aryloxides, such as methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide) (MABR) and methylaluminoxane (MAO) as a Lewis acid. These reactions gave the constrained protected serine analogues c_4Ser(OBn) **393a–h** and **394**.[185] The results are summarized in Table 7. The best diastereoselectivity was obtained in the reaction of vinyl ether bearing (1*R*,2*S*)-2-phenylcyclohexyl gragment as a chiral auxiliary (entries 3, 6 and 9).

Recently, Tanaka *et al.*[186] reported the synthesis of α,α-disubstituted α-amino esters **396a–g** by Rh-catalyzed [2+2+2] cycloaddition of 1,6-diynes **395a–g** with protected dehydroamino ester **391c**. In all cases the compounds **396a–g** were obtained in good yield and with good

enantioselectivity and, in the case of unsymmetrical 1,6-diynes, moderate regioselectivity was observed. The results are summarized in Table 8.

Pyne *et al.*[187] reported the synthesis of conformationally constrained cyclopentenylglutamate analogues in a regioselective and diastereoselective manner using a formal [3+2] cycloaddition reaction of chiral dehydroamino esters. For example, [3+2] cycloaddition of ylide **398a** generated *in situ* from ethyl 2,3-dienoate **397a**, with the chiral dehydroamino ester (*R*)-**399** gave the mixture of the two regioisomers **400a** and **401a** in 17 and 49% yield, respectively, after column chromatographic separation. In a similar way, cycloaddition of **398b,c**, obtained from **397a,b**, with (*R*)-**399** afforded the spiro compounds **400b,c** in 38 and 78% yield, respectively, as a single diastereoisomers. Hydrolysis of optically pure **400a–c** with HCl followed by ion-exchange chromatography and subsequent treatment with HCl produced the conformationally constrained amino acids **402a–c** in good yield as chlorohydrate salt. In a similar way, **401a** was transformed into the quaternary α-amino acid (*S*)-**403** (Scheme 85).

Reaction of dehydroamino ester **404** with ethyl butynoate **405** in the presence of PPh_3 gave the cycloadducts **406** and **407** in 87% yield and 60:40 dr, which, by successive selective hydrolysis of the $N{=}CPh_2$ group, *N*-Cbz protection, preparative HPLC separation and hydrolysis of the esters, afforded the cyclic glutamic acid analogues (*R*)- and (*S*)-**402a** in good yield (Scheme 86).[187]

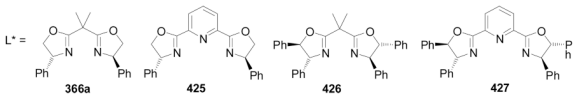
Diels-Alder reaction of (*S*)-**228c** with cyclopentadiene at room temperature gave, after flash chromatography, the cycloadduct *endo*-**408** in 85% yield and 15% of other diastereoisomers, and with cyclohexa-1,3-diene at 90 °C afforded the cycloadduct *endo*-**409** in 88% yield and 12% of other diastereoisomers. Hydrolysis of the imine moiety of the cycloadducts *endo*-**408** and *endo*-**409**, followed by catalytic hydrogenation of double bound C=C and subsequent hydrolysis of the ester function with 6 N HCl, produced the constrained α-amino acids (*S*)-**410** and (*S*)-**411**, respectively, in good yield (Scheme 87).[144,188]

In a similar way, Diels-Alder reaction of (*S*)-**232c** with cyclopentadiene and cyclohexa-1,3-diene gave, after flash chromatography, the cycloadducts *endo*-**412** and *endo*-**413** as the main diastereoisomers, respectively. Catalytic hydrogenation of these compounds over Pd/C, followed by hydrolysis with 6 N HCl and subsequent ion-exchange chromatography, furnished the α-amino acids (*S*)-**410** and (*S*)-**411** in moderate yield (Scheme 88).[144]

Diels-Alder cycloaddition of chiral methylene piperazine-2,5-diones **414a–g** with cyclopentadiene gave the four diastereoisomers *exo*-**415a–g**, *exo*-**416a–g**, *endo*-**417a–g** and *endo*-**418a–g** in low to moderate yield and with good *exo/endo* selectivity. The results are summarized in Table 9.[189]

Diels-Alder cycloaddition of chiral acrylates **419a,b**, bearing (+)- or (−)-menthyl as a chiral auxiliary, with cyclopentadiene in the presence of $EtAlCl_2$ or $Mg(ClO_4)_2$ under thermal or ultrasound conditions, gave the four diastereoisomers *exo*-**420a,b**, *exo*-**421a,b**, *endo*-**422a,b** and *endo*-**423a,b** in moderate to good yield, good *exo/endo* selectivity, and good enantioselectivity. The results are summarised in Table 10.[190]

On the other hand, enantioselective Diels-Alder cycloaddition of achiral acrylate **424** with cyclopentadiene in the presence of a catalytic amount of chiral ligands **366a**, **425**, **426**, and **427**, and $Mg(ClO_4)_2$ or $Ce(OTf)_4.H_2O$, gave the spiro compounds mixture of two *endo*-**428a,b** and two *exo*-**429a,b**, both with poor enantioselectivity.[190,191] The results are summarised in Table 9.



Recently, Pellegrino *et al.*[192] reported that the Diels-Alder cycloaddition of acylaminoacrylate **430**, bearing the (−)-8-phenylmenthyl group as a chiral auxiliary, with cyclopentadiene in the presence of a catalytic amount of $Mg(ClO_4)_2$ under ultrasound conditions gave the adducts *exo*-**431a,b** and *endo*-**432a,b** in 87% yield and 7:1 dr, with a predominance of *exo*-**431a** (only trace amount of the second *exo*-**431b** (0.3%) and *endo***432b** (0.9%) isomers were detected). Hydrogenation of the C=C double bond of diastereoisomerically pure *exo*-**431** followed by selective hydrolysis with Na_2CO_3 and subsequent oxidation of alcohol group, led to the β-keto ester *exo*-**433** in excellent yield. This compound was used in the synthesis of *cis*-3-carboxycyclopentylglycine (1*S*,3*R*,1'*S*)-**434a** and its epimer (1*S*,3*R*,1'*R*)-**434b** (Scheme 89).

The same authors[193] reported that Diels-Alder cycloaddition of chiral aminoacrylate **391a**, bearing the (−)-8-phenylmenthyl group as a chiral auxiliary, with cyclopentadiene in the presence of a catalytic amount of $Mg(ClO_4)_2$ under ultrasound conditions. This reaction gave the norbornenes *exo*-**435** and *endo*-**436** in 84% yield, a ratio of 83:17 and with high diastereoselectivity (*exo* 97% and *endo* 96%). Selective hydrolysis of major *exo*-**435** produced the enantiopure constrained α-amino acid *exo*-**437** in 79% yield (Scheme 90).

On the other hand, oxidative cleavage of the C=C double bond of norbornene *exo*-**435** with potassium permanganate furnished (1*S*,2*R*,4*S*)-**438** in 81% yield and selective hydrolysis of the ester function under basic conditions provided the tricarboxylic acid (1*S*,2*R*,4*S*)-**439** in 80% yield. Finally, hydrolysis of amide function of (1*S*,2*R*,4*S*)-**439** with 6 M HCl gave the quaternary α-amino acid (1*S*,2*R*,4*S*)-**440** in 83% yield. In a similar way, (1*R*,2*S*,4*R*)-*endo*-**436** was transformed into quaternary α-amino acid (1*S*,2*S*,4*R*)-**441** (Scheme 91).[193,194]

Dihydroxylation of C=C double bond in the norbornene *exo*-**435** with NMO in the presence of a catalytic amount of osmium tetroxide afforded the diol *exo*-**442**,[195] which, by cleavage of C_5–C_6 bond with sodium periodate, gave the bisaldehyde (1*S*,2*R*,4*S*)-**443**. Reductive amination of bisaldehyde **443** with *p*-methoxybenzylamine ($PMBNH_2$) and sodium triacetoxyborohydride as a reducing agent, provided the derivative (1*S*,5*S*,6*S*)-*exo*-**444**, which, by treatment with sodium in methanol produced the constrained α-amino acid (1*S*,5*S*,6*S*)-*exo*-**445** in 57% overall yield. In a similar way, (1*R*,2*S*,4*R*)-*endo*-**436** was transformed into quaternary α-amino acid (1*R*,5*R*,6*S*)-*endo*-**446** (Scheme 92).[196]

On the other hand, reductive amination of bisaldehydes (±)-**447a,b** using (*R*)-α-MBA and sodium triacetoxyborohydride afforded, after chromatographic separation, the azabiciclo derivatives (1*R*,5*R*,6*R*,1'*R*)-*exo*-**448a**, (1*S*,5*S*,6*S*,1'*R*)-*exo*-**448b**, (1*R*,5*R*,6*S*,1'*R*)-*endo*-**449a** and (1*S*,5*S*,6*R*,1'*R*)-*endo*-**449b** in 25%, 28%, 12% and 10% yield, respectively. Cleavage of the benzyl group by hydrogenolysis over Pd/C on diastereoisomerically pure *exo*-**488a,b** and *endo*-**489a,b**, followed by hydrolysis with 6 N HCl gave the constrained α-amino acids (1*R*,5*R*,6*R*)-*exo*-**450**, (1*S*,5*S*,6*S*)-*exo*-**450**, (1*R*,5*R*,6*S*)-*exo*-**451** and (1*S*,5*S*,6*R*)-*exo*-**451** in good yield (Scheme 93).[197]

2.4. Resolution procedures

2.4.1. Chemical resolution—Mash *et al.*[198] reported the synthesis of 2-amino-4-bromo-7-methoxyindane-2-carboxylic acid (*S*)-**461** by chemical resolution. In this context, a double alkylation of ethyl glycinate **452a** with 2,3-bis(bromomethyl)-4-bromoanisole **453** afforded the racemic compound (±)-**454**, which, by hydrolysis of imine function furnished the corresponding α-amino ester (±)-**455** in 33% yield. Coupling of (±)-**455** with the *N*-Boc-phenylalanine (*S*)-**456** in the presence of benzotriazol-1-yloxy-tris(dimethylamino)

phosphonium hexafluorophosphate (BOP) gave a 50:50 mixture of the dipeptides (*R*,*S*)-**457** and (*S*,*S*)-**458** in 93% yield and these were separated by column chromatography. Cleavage of the *N*-Boc protective group of diastereoisomerically pure (*S*,*S*)-**458** with TFA produced the dipeptide (*S*,*S*)-**459**, which was treated with phenylisothiocyanate and triethylamine to furnish the corresponding thiourea (*S*,*S*)-**460** in 71% yield. Finally, hydrolysis of (*S*,*S*)-**460** with HCl provided the quaternary α-amino acid (*S*)-**461** in 83% yield (Scheme 94). The α-amino acid (*S*)-**461** has been used in the synthesis of piperazine-2,5-diones.

Monn *et al.*[199] reported the synthesis of heterobicyclic α-amino acids (−)- and (+)-**465a,b** by resolution and these compounds were evaluated as agonist for group II mGlu receptors. In this context, reaction of furan or thiophene with ethyl diazoacetate in the presence of $Rh_2(OAc)_4$ produced the bicyclic adducts (±)-**462a,b** in (20–40%) yield. Reaction of (±)-**462a,b** with $(NH_4)_2CO_3$ and KCN, followed by saponification, gave the (±)-carboxylic acids **463a,b** in 72% yield. These compounds were resolved by selective crystallization of either the (*R*)- or (*S*)-phenylglycinol salts (−)-**464** or (+)-**464**, respectively. Hydrolysis of diastereoisomerically pure salts (−)-**464a,b** and (+)-**464a,b** followed by ion-exchange chromatography furnished the optically pure (−)- and (+)-**465a,b** in good yield (Scheme 95).

The diastereoisomer (−)-**465b** has been transformed into sulfoxides **469** and **470** as well as sulfone **472**, and these compounds were evaluated as potent, selective, and orally bioavailable agonist for mGlu2/3 receptors. Thus, esterification of (−)-**465b** with thionyl chloride in methanol followed by treatment with $(Boc)_2O$ gave the methyl ester **466** in 79% yield, which, by oxidation with *m*-CPBA afforded the sulfoxides mixture **467** and **468** in 5% and 85% yield, respectively. Hydrolysis of diastereoisomerically pure **467** and **468** produced the quaternary α-amino acids **469** and **470** in 65% and 69% yield, respectively. On the other hand, oxidation of sulfoxide function in **467** with *m*-CPBA provided the corresponding sulfone **471** in 84%, which, by hydrolysis afforded the quaternary α-amino acid **472** in 71% yield (Scheme 96).[200]

On the other hand, Bucherer-Bergs reaction of 6-bromo-2-tetralone **473** with $(NH_4)_2CO_3$ and KCN gave the spirohydantoin **474** in 81% yield, which, by cleavage of the hydantoin ring and esterification, afforded the methyl (±)-2-amino-6-bromotetraline-2-carboxylate **475** in 54% yield. Resolution of (±)-**475** as the L-mandelic acid salt produced the ammonium salt (*S*,*S*)-**476** in 25% yield and treatment with $(Boc)_2O/Et_3N$, followed by basic hydrolysis, produced the constrained *N*-Boc α-amino acid (*S*)-**477** in 77% yield. This compound was converted in four steps into (2*S*)-*N*-Boc-amino-6-(diethylphosphono)tetraline-2-carboxylic acid **478** (Scheme 97).[201]

Treatment of (±)-**480**, which is readily obtained from (±)-**479**, with (*S*)-phenylalanine cyclohexylamide **481** in *N*-methylpyrrolidin-2-one (NMP) at 90 °C, followed by column chromatography separation, produced the diastereoisomerically pure (1*S*,2*S*,1'*S*)-**482a** and (1*R*,2*R*,1'*S*)-**482b** in 36 and 35% yield, respectively. Subsequent hydrolysis and treatment with propylene oxide furnished the 1-amino-2-hydroxycyclohexanecarboxylic acid (1*S*,2*S*)- and (1*R*,2*R*)-**99a** in good yield (Scheme 98).[202]

In a similar way, treatment of (±)-**483** with (*S*)-2-acetoxypropanoyl chloride (*S*)-**484** in the presence of triethylamine, followed by column chromatography separation, gave the diastereoisomerically pure (1*S*,2*R*,1'*S*)-**485** and (1*R*,2*S*,1'*S*)-**486** in 40 and 50% yield, respectively. Hydrogenation of (1*S*,2*R*,1'*S*)-**485** and (1*R*,2*S*,1'*S*)-**486** over Pt/C, followed by hydrolysis and subsequent treatment with propylene oxide, led to (1*S*,2*R*)- and (1*R*,2*S*)-**100a** in good yield (Scheme 99).[202]

Recently, Gelmi *et al.*[194] reported the synthesis of the four diastereoisomers of constrained α-amino acids *exo*-**437** and *exo*-**487** by resolution. In this context, treatment of (±)-*exo*-**437** with (*R*)-α-MBA gave the corresponding diastereoisomeric salts, hydrolysis of which afforded, after

crystallization, the enantiomerically pure (1*R*,2*R*,4*R*)-**437** and (1*S*,2*S*,4*S*)-**437** in 31 and 37% yield, respectively. In a similar way, the resolution of (±)-*endo*-**487** gave the enantiomerically pure (1*R*,2*S*,4*R*)-**487** and (1*S*,2*R*,4*S*)-**487** in 42 and 40% yield, respectively (Scheme 100).

Reaction of *N*-protected amino acids RCO-Bin-OH (±)-**488a,b** with (*S*)-**481** in the presence of *N*-hydroxybenzotriazole (BtOH) and *N*-ethyl-*N*'-dimethylaminopropylcarbodiimide hydrochloride (EDC) in CH_2Cl_2, followed by column chromatography separation, afforded the diastereoisomerically pure (*R*,*S*)-**489a,b** and (*S*,*S*)-**490a,b** in good yield. Hydrolysis of diastereoisomerically pure (*R*,*S*)-**489a,b** and (*S*,*S*)-**490a,b**, followed by esterification with MeOH/HCl, furnished the H-Bin-OMe (*R*)- and (*S*)-**491** in good yield (Scheme 101).[203]

On the other hand, reaction of racemic diesters (±)-*cis*-**492** with commercially available (1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone **493** in the presence of $BF_3.OEt_2$ afforded the corresponding Schiff bases (*S*)-*cis* and (*R*)-*cis*-**494**. Crystallization of the diastereoisomeric mixture gave (*S*)-*cis*-**494** as a single diastereoisomer. The remaining diastereoisomer (*R*)-*cis*-**494** could not be isolated from mother liquor either by crystallization or by chromatography on silica gel. However, (*R*)-*cis*-**494** could be converted into the (*S*)-*cis*-**494** diastereoisomer by thermal equilibration. Hydrolysis of diastereoisomerically pure (*S*)-*cis*-**494** followed by treatment with $(Boc)_2O$ furnished the enantiomerically pure *N*-Boc-protected methyl ester (*S*)-*cis*-**495**. Under identical conditions, *N*-Boc-protected methyl ester (*S*)-*trans*-**497** was obtained from (±)-*trans*-**496** (Scheme 102).[204]

Treatment of racemic Boc-$[OH]_2$-Bip-OMe (±)-**498** with the ditosylate (*R*)-**499** in the presence of Cs_2CO_3 in DMF at 60 °C gave the methyl esters *N*-Boc-[20-C-6]-(*R*)-Bip-OMe (*R*,*R*)-**500** and *N*-Boc-[20-C-6]-(*S*)-Bip-OMe (*R*,*S*)-**501** in 25 and 26% yield, respectively. Cleavage of ether function of (*R*,*R*)-**500** with large excess of BBr_3 followed by esterification with thionyl chloride and methanol, produced the (*R*)-binaphthol and H-$[OH]_2$-Bip-OMe (*R*)-**502** (Scheme 103).[205,206]

On the other hand, epoxidation of **319a** with *m*-CPBA afforded the epoxides **503** and **504** in 59% yield and 85:15 dr. Desymetrization of the major epoxide isomer **503** with *s*-BuLi in the presence of (−)-sparteine gave the allyl alcohol (1*S*,4*R*)-**505** in 14% yield and 33% ee, which, by hydrogenation over Pd/C provided the alcohol (1*S*,3*R*)-**256** in 71% yield. Treatment of (1*S*,3*R*)-**256** with acetic acid under Mitsunobu conditions produced the alcohol (1*S*,3*S*)-**255** in 58% yield and subsequent mesylation followed by reaction with NaCN and hydrolysis with 6 M HCl led to (1*S*,3*R*)-ACPD **293** in 45% yield. In a similar way, (1*S*,3*R*)-**256** was transformed into (1*S*,3*S*)-ACPD **506** in 34% overall yield (Scheme 104).[207]

Recently, Varie *et al.*[208] reported a pilot-plant desymetrization of the cyclic *meso*-epoxide **507a** using a chiral lithium amide prepared from (*R*,*R*)-diamine **508** and *n*-BuLi to give the allyl alcohol (1*S*,4*R*)-**509** in 72% yield and 99.3% ee. However, treatment of *meso*-epoxide **507b** under identical conditions gave the allyl alcohol (1*S*,4*S*)-**510** in only 3% yield and 48% ee (Scheme 105).

2.4.2. Enzymatic resolution—Enzymatic hydrolysis of prochiral bis(2,2,2-trifluoroethyl)-2,2-dimethylcyclopropane-1,1-dicarboxylate **511** with pig liver esterase (PLE) gave the (*R*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxycarbonyl)-cyclopropane-1-carboxylic acid (*R*)-**512** in 62% yield and >95% ee, which, by Curtius rearrangement with diphenylphosphoryl azide (DPPA), followed by work-up with ethanol gave the diprotected α-amino acid (*S*)-**513** in 34% yield. Finally, basic hydrolysis of (*S*)-**513** produced the (*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (*S*)-**514** in 75% yield and >84% ee (Scheme 106).[209]

Recently, Beaulieu *et al.*[210] reported the pilot plant large-scale synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid methyl ester (1*R*,2*S*)-**196** from (±)-*trans*-**515** using inexpensive esterase enzyme (Alcalase) as a resolution agent. In this context, treatment of (±)-*trans*-**515**, obtained in three steps from **452b**, with a large excess of Alcalase under Na_2HPO_4 buffer conditions at pH 8.1–8.2 produced (1*R*,2*S*)-**515** in 49% yield and 97% ee, and (1*S*,2*R*)-**516** in with 99% ee, after separation.[211] Hydrolysis of (1*R*,2*S*)-**515** with HCl gave the (1*R*,2*S*)-**516** in 64% yield as hydrochloride salt with >97% ee (Scheme 107). The vinyl-ACCA derivative (1*R*,2*S*)-**196** is an important building block for the preparation of HCV protease inhibitors.[212]

Kirihara *et al.*[213] reported an efficient synthesis of (*R*)- and (*S*)-1-amino-2,2-difluorocyclopropanecarboxylic acid **521** by lipase-catalyzed desymetrization of diol **517** or diacetate **522**. Thus, lipase-catalyzed transesterification of prochiral diol **517** with vinyl acetate as the acyl donor in the presence of lipase PS from *Pseudomonas cepacia* in benzene and diisopropyl ether, afforded the corresponding mono-acetylated product (*R*)-**518** in 97% yield and 91.3% ee. Oxidation of (*R*)-**518** followed by treatment with DPPA and subsequent work-up with *tert*-butyl alcohol and Et_3N under reflux gave the carbamate (*R*)-**519** in 51% yield. Cleavage of the acetyl group of (*R*)-**519** produced the *N*-protected aminoalcohol (*R*)-**520** in 66% yield and >99% ee, which, by oxidation followed by hydrolysis led to (*R*)-**521** in 99% yield (Scheme 108).

On the other hand, lipase-catalyzed deacetylation of the prochiral diacetate **522** with lipase PS in a mixed solvent of acetone and phosphate buffer gave the corresponding mono-acetylated product (*S*)-**518** in 86% yield and 91.7% ee, which, under identical conditions to those described in the Scheme 108, was transformed into (*S*)-1-amino-2,2-difluorocyclopropanecarboxylic acid **521** as hydrochloride salt (Scheme 109).[213]

Catalytic hydrolysis of (±)-**523** with lipase CALB from *Pseudomonas cepacia* in a mixed solvent of acetone and phosphate buffer gave the corresponding mono-acid (3a*S*,5*S*,6a*S*)-**524** and the residual diester (3a*R*,5*R*,6a*R*)-**523**, both with >99% ee. Hydrolysis of (3a*S*,5*S*,6a*S*)-**524** and (3a*R*,5*R*,6a*R*)-**523** furnished the constrained α-amino acids (3a*S*,5*S*,6a*S*)-**525** and (3a*R*,5*R*,6a*R*)-**525** in 60 and 74% yield, respectively (Scheme 110).[214]

In a similar way, hydrolysis of (±)-**526** using lipase proleather (Subtilysin Carlsberg) in acetone and phosphate buffer gave the monoacid (3a*R*,5*S*,6a*R*)-**527**, the product derived from the hydrolysis of methyl ester linked to position 5, and the residual diester (3a*S*,5*R*,6a*S*)-**526**, both with >99% ee. Similar results were obtained with papain-catalyzed hydrolysys of (±)-**526**, but with reversal of the stereochemistry. Hydrolysis of (3a*R*,5*S*,6a*R*)-**527** and (3a*S*,5*R*,6a*S*)-**526** led to the constrained α-amino acids (3a*R*,5*S*,6a*R*)-**528** and (3a*S*,5*R*,6a*S*)-**528** in 78 and 64% yield, respectively (Scheme 111).[214,215]

On the other hand, the pig liver esterase (PLE) enzymatic desymetrization of diacetate **529** afforded the monoacetate (*S*)-**530** with 80% ee along with diol **531**. The monoacetate (*S*)-**530** was transformed in three steps into diprotected alkyne (*S*)- and (*R*)-**532**. Addition of the carbanion derived from (*S*)-**532** to the lactone **533** gave the compound **534** in 68% as a 1:1 mixture of anomers. Partial reduction of the alkyne followed by the spiroketalization and subsequent cleavage of the silyl protecting groups with TBAF, acetylation and HPLC separation, produced the spiro derivative **535** in 53% overall yield. Reduction of the azide and olefin fuctional groups and simultaneous removal of (DMB) protective group in **535** in the presence of acetic anhydride furnished the acetamide **536** in 59% yield. Oxidation of **536** with Dess-Martin periodinane and $NaClO_2$ gave the α-*N*-acetylgalactosaminylserine derivative **537** in 89% yield. In a similar way, (*R*)-**532** was transformed into derivative **538** (Scheme 112).[216]

Metathesis reaction of **539**, which is readily obtained by dialkylation of dimethyl malonate with 4-bromo-1-butene, in the presence of Grubbs catalyst gave the cycloheptene **540** in 98% yield. Epoxidation of this compound with *m*-CPBA followed by hydrolysis with sulfuric acid afforded the cycloheptane-*trans*-1,2-diol (±)-**541** in 80% yield. Kinetic resolution of (±)-**541** with Amano AK in vinyl acetate produced the diol (4*R*,5*R*)-**541** and the monoacetate (4*S*, 5*S*)-**542** in 43% and 33% yield, respectively, both with >99% ee. Methylation of (4*R*, 5*R*)-**541** with MeI and Ag_2O produced the dimethoxy compound (4*R*,5*R*)-**543** in quantitative yield and selective hydrolysis with NaOH, followed by Curtius rearrangement and subsequent workup with benzyl alcohol, furnished the cyclic amino acid (4*R*,5*R*)-**544** in 92% yield (Scheme 113).[217]

2.4.3. HPLC resolution—Semipreparartive chiral HPLC resolution of (±)-**546**, obtained in four steps from α,β-dehydroamino acid derivative **545**, using a mixture of 10-undecenoate/3,5-dimethylphenylcarbamate of amylose covalently attached to allylsilica gel (CSP-2) as a chiral stationary phase, afforded the enantio-merically pure (2*R*,3*R*)- and (2*S*,3*S*)-**546**. Hydrolysis of each enantiomer gave the constrained cyclopropane analogues of phenylalanine $c_3$diPhe (2*R*, 3*R*)- and (2*S*,3*S*)-**547** in excellent yield as hydrochloride salt (Scheme 114).[218]

In a similar way, chiral HPLC resolution of (±)-**549**, obtained in three steps from α,β-dehydroamino acid derivative **548**, using a mixture of 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose linked to allylsilica gel (CSP-1) as a chiral stationary phase, afforded the enantiomerically pure (*R*)- and (*S*)-**549**, which, by cleavage of the benzoyl group with hydrazine followed by hydrolysis gave the constrained cyclopropane analogues of valine c_3Val (*R*)- and (*S*)-**514** in excellent yield as hydrochloride salt (Scheme 115).[219]

Chiral HPLC resolution of *trans*-c_4Phe (±)-**550**, using CSP-1 as a chiral stationary phase and a mixture of hexane/2-propanol/chloroform (95/3/2) as eluent afforded the enantiomerically pure (1*S*,2*R*)- and (1*R*,2*S*)-**550**. Hydrolysis of each enantiomer gave the constrained cyclobutane analogues of phenylalanine (1*S*,2*R*)-*N*-Boc-c_4Phe-OH (1*S*,2*R*)-**551** and (1*R*,2*S*)-*N*-Boc-c_4Phe-OH (1*R*,2*S*)-**551** in excellent yield. Under identical conditions, (±)-**552** gave (1*R*,2*R*)-*N*-Cbz-c_4Phe-OH (1*R*,2*R*)-**553** and (1*S*,2*S*)-*N*-Cbz-c_4Phe-OH (1*S*,2*S*)-**553** in excellent yield (Scheme 116).[220]

Chiral HPLC resolution of *cis*-*N*-(1-cyano-2-phenylcyclopentyl)benzamide (±)-**554** using CSP-1 as a chiral stationary phase and a mixture of hexane/2-propanol/acetone (95/3/2) as eluent afforded the enantiomerically pure (1*R*,2*R*)- and (1*S*,2*S*)-**554**, hydrolysis of which produced the constrained cyclopentane analogues of phenylalanine (1*R*,2*R*)-c_5Phe and (1*S*, 2*S*)-c_5Phe **555** in excellent yield as hydrochloride salt. Finally, reaction of (1*R*,2*R*)- and (1*S*, 2*S*)-**555** with TMSCl, followed by addition of benzyl chloroformate (CbzCl) furnished the (1*R*,2*R*)-*N*-Cbz-c_5Phe-OH and (1*S*,2*S*)-*N*-Cbz-c_5Phe-OH **556** in 60 and 65% yield, respectively. In a similar way, (±)-**557** afforded the (1*R*,2*S*)-c_5Phe and (1*S*,2*R*)-c_5Phe **558** in 95 and 92% yield, respectively, and these compounds were transformed into (1*R*,2*S*)-*N*-Boc-c_5Phe-OH and (1*S*,2*R*)-*N*-Boc-c_5Phe-OH **559** (Scheme 117).[221]

Natalini *et al.*[222] reported the preparative resolution of 1-aminoindane-1,5-dicarboxylic acid (±)-AIDA **33** by chiral ligand-exchange chromatography (CLEC), using (*S*)-*N*,*N*-dimethylphenylalanine as the chiral selector in the movile phase, obtaining the enantiomerically pure (*S*)- and (*R*)-AIDA **33** with high ee (Scheme 118).

On the other hand, chiral HPLC resolution of methyl *cis*-1-benzamido-2-phenylcyclohexane-carboxylate (±)-**560** using CSP-2 as a chiral stationary phase and a mixture of hexane/2-propanol/chloroform (96/1/3) as eluent to afford enantiomerically pure (1*R*,2*R*)- and (1*S*, 2*S*)-**560**, which, by hydrolysis with HCl under reflux, produced the constrained cyclohexane

analogues of phenylalanine (1*R*,2*R*)-c_6Phe and (1*S*,2*S*)-c_6Phe **561** in quantitative yield as chlorhydrate salt. Finally, reaction of (1*R*,2*R*)- and (1*S*,2*S*)-**561** with TMSCl, followed by addition of CbzCl, provided the (1*R*,2*R*)-*N*-Cbz-c_6Phe-OH and (1*S*,2*S*)-*N*-Cbz-c_6Phe-OH **562** in 70 and 80% yield, respectively. (Scheme 119).[223]

Esterification of (1*R*,2*R*)- and (1*S*,2*S*)-**561** with thionyl chloride and methanol, followed by coupling with protected aspartic acid (*S*)-*N*-Cbz-Asp(O*t*-Bu)-OH using *i*-BuOCOCl in the presence of NMM, produced the protected dipeptides (*S*,1*R*,2*R*)-**563** and (*S*,1*S*,2*S*)-**564** in 90% yield. Subsequent deprotection with TFA, followed by hydrogenolysis over Pd/C, led to the optically pure aspartame analogues H-(*S*)-Asp-(1*R*,2*R*)-c_6Phe-OMe, (*S*,1*R*,2*R*)-**565** (sweet) and H-(*S*)-Asp-(1*S*,2*S*)-c_6Phe-OMe, (*S*,1*S*,2*S*)-**566** (bitter), in 96 and 98% yield, respectively (Scheme 120).[224]

On the other hand, chiral HPLC resolution of *trans*-*N*-(1-cyano-2-phenylcyclohexyl)acetamide *trans*-(±)-**567** using CSP-1 as a chiral stationary phase and a mixture of hexane and 2-propanol (93:7) as eluent, gave the enantiomerically pure (1*R*,2*S*)- and (1*S*,2*R*)-**567**, which, by hydrolysis with HCl under reflux, produced the constrained cyclohexane analogues of phenylalanine (1*R*,2*S*)-c_6Phe and (1*S*,2*R*)-c_6Phe **568** as chlorhydrate salts in 92 and 98% yield, respectively. Finally, reaction of (1*R*,2*S*)- and (1*S*,2*R*)-**568** with $(Boc)_2O$ in tetramethylammonium hydroxide (TMAH) furnished the (1*R*,2*S*)-*N*-Boc-c_6Phe-OH and (1*S*,2*R*)-*N*-Boc-c_6Phe-OH **569** in 50 and 46% yield, respectively (Scheme 121).[225]

Enantiomerically pure (1*R*,2*S*)- and (1*S*,2*R*)-**568** were transformed into optically pure aspartame analogues H-(*S*)-Asp-(1*R*,2*S*)-c_6Phe-OMe (*S*,1*R*,2*S*)-**570** (sweet) and H-(*S*)-Asp-(1*S*,2*R*)-c_6Phe-OMe (*S*,1*S*,2*R*)-**571** (bitter) under identical conditions to those described above (Scheme 122).[226]

3. Synthesis of azacycloalcane-2-carboxylic acids

2.1. Using cyclic compounds as starting materials

One of the most useful procedures to the stereoselective synthesis of these compounds involves alkylation reactions using the non-quaternary cyclic amino acids as starting materials whenever stereochemical control can be achieved. For example, Wulff *et al.*[227] reported the highly diastereoselective alkylation of enantiopure aziridine-2-carboxylic acid ethyl esters **572** and **573**[228] with complete retention of the stereochemistry. In this context, treatment of **572** with LDA at −78 °C in 1,2-dimethoxyethane (DME) and diethyl ether, followed by addition of several alkylating agents, afforded the alkylated compounds **574a–j** as single stereoisomers and in good yields with complete retention of the stereochemistry. Similar results were obtained in the methylation of **573** (R = Ph), with the methylated product **575** obtained with high diastereoselectivity and in 91% yield.[229] Treatment of **575** with triflic acid and anisole produced the trisubstituted aziridine **576** in 84% yield (Scheme 123).

This methodology has been extensively used for the stereoselective synthesis of α-alkylprolines. Since most of the examples have been collected in a recent review, [230] we only report here the most recents papers. Sommer and Williams[231] reported the stereoselective synthesis of ^{13}C-labeled α-alkyl-β-methylproline ethyl ester (2*R*,3*S*)-**579**, a key intermediate in the elaboration of paraherquamides E, F and related derivatives, through the stereocontrolled allylation of β-methylproline ethyl ester (2*S*,3*S*)-**577**. In this context, treatment of β-methylproline ethyl ester (2*S*,3*S*)-**577**, obtained from expensive 1-^{13}C-(*S*)-isoleucine, with KHMDS at −78 °C followed by addition of allyl iodide **578** afforded the α-allylated product (2*R*,3*S*)-**579** in 88% yield as a single diastereoisomer. Identical results were obtained in the allylation of (2*R*,3*S*)-**580**, obtained in several steps from (*R*)-α-MBA and the cheap 1-^{13}C-ethyl

bromoacetate. The stereochemistry obtained in the allylation of (2*S*,3*S*)-**577** and (2*R*,3*S*)-**580** is influenced strongly by the methyl group in the β-position on the proline ring (Scheme 124).

Very recently, Chandan and Moloney[232] reported the synthesis of 2,2,5-trisubstituted pirrolidines **585a–c** from allylic pyroglutamates **581a–c** by Ireland-Claisen ester rearrangement. Thus, treatment of **581a–c** with LiHMDS and Al(*i*-OPr)$_3$ in the presence of quinine under Kazmaier's conditions,[233] gave the rearrangement products **582a–c** in good yield as single diastereo-isomers through the transition state **A**. Interestingly, the Claisen rearrangement only occurred in the presence of quinine. Esterification of **582a–c** with MeOH and TsOH, followed by treatment with Lawesson's reagent afforded the thiolactams **583a–c**, which, by an Eschenmoser sulfide contraction[234] with diethyl bromomalonate and sodium bicarbonate, produced the enamines **584a–c** in good yield. Finally, reduction of enamine function in **584a–c** with sodium cyanoborohydride provided the corresponding 2,2,5-trisubstituted pirrolidines **585a–c** in good yield as single diastereoisomers (Scheme 125).

In 1981, Seebach *et al.*[235] reported a methodology that formally allows the direct α-alkylation of L-proline without loss of the optical purity and with retention of the configuration, thus constituying a showcase of their concept of *self-reproduction of chirality*.[236] In recent years this methodology has been used for the stereoselective synthesis of quaternary proline analogues. For example, treatment of the oxazolidinone (3*S*,7a*R*)-**586**, readily obtained from L-proline,[237] with LDA in THF at −78 °C followed by addition of 3-bromoprop-1-yne gave the α-alkylated product (3*S*,7a*R*)-**587** in 24% yield as a single diastereoisomer. Subsequent cleavage of the oxazolidinone moiety with TMSCl in methanol under microwave conditions, followed by treatment with CbzCl, furnished the *N*-Cbz protected α-propargyl proline (*R*)-**588** in 73% yield. Cycloaddition of (*R*)-**588** with the appropriate azide derivative, followed by treatment with $CuSO_4$ and Cu(0) under microwave conditions, afforded the corresponding triazoles (*R*)-**589a–d** in 62–79% yield (Scheme 126).[238]

On the other hand, aldol reaction of the oxazolidinone (3*S*,7a*R*)-**590**, readily obtained from L-proline,235b,c with the Garner's aldehyde[239] (*R*)-**591** afforded the aldol products **592** and **593** in 58% yield and 4:1 dr. Dess-Martin oxidation of **592** followed by reduction with $NaBH_4$ gave **593** in 43% yield and this was used in the synthesis of (2*S*,3*S*,4*R*,7*R*,9*S*)-kaitocephalin.[240] Under identical conditions, aldol reaction of (3*S*,7a*R*)-**590** with the aldehyde (*S*)-**591** gave **594** and **595** in 51% yield and 2:3 dr. Oxidation of **594** followed by reduction with $NaBH_4$ gave **595** in 31% yield and this was used in the synthesis of (2*R*,3*S*,4*R*,7*R*,9*S*)-kaitocephalin[241] (Scheme 127).

Aldol reaction of enantiopure *trans*-**596** with Garner's aldehyde (*S*)-**597**[242] afforded the aldol products in 60% yield as a complex mixture, indicating a mis-matched double stereodifferentiation, whereas the same reaction using the aldehyde (*R*)-**597** gave the aldol product **598** in 40–50% yield as a single diastereoisomer, which, confirm a matched double stereodifferentiation. On the other hand, treatment of *trans*-**596** with LDA in THF at −78 °C, followed by addition of *N*-acylimidazole (*S*)-**599**, gave the corresponding β-keto ester **600** in 40–50% yield as a single diastereoisomer, which, by reduction of the keto function with DIBAL at −78 to 25 °C, gave the β-hydroxy ester **601** in 86–93% yield and >30:1 dr. The latter compound is an epimer of **598** and is a key compound for the synthesis of (2*R*,3*S*,4*R*,7*R*,9*S*)-kaitocephalin (Scheme 128).[243]

Recently, we reported[244] a versatile methodology for the synthesis of (2*R*,3a*S*,7a*S*)-2-methyl-octahydroindole-2-carboxylic acid **605**. Treatment of (*S*,*S*,*S*,*R*)-**603**, obtained in three steps from (*S*)-indoline-2-carboxylic acid **602**, with LDA in THF at −78 °C followed by addition of several alkyl electrophiles produced the alkylated products **604a–c** in good yield. In these compounds both the trichloromethyl group and the newly introduced substituent are *cis* to each

other on the *exo* side of the bicyclic constituted by the two five-membererd rings, as in the pioneering investigations by Seebach.[235b] Hydrolysis of (*S*,*S*,*S*,*R*)-**604a** with 6 N HCl in acetic acid gave the α-methylated indoline (2*R*,3a*S*,7a*S*)-**605** in 92% yield as the hydrochloride salt (Scheme 129).

Treatment of enantiopure **606** with LDA followed by addition of several alkyl halides produced the 3,3-disubstituted bicyclic derivatives **608a–f** in good yield and with >95% diastereoselectivity, through the exocyclic lithium enolate **607** (Scheme 130).[245]

Symmetry-breaking enolization reaction of *meso*-diester **610**, obtained in three steps from dipicolinic acid **609**, with the chiral *bis*-lithium amide base **611** followed by addition of several alkylating reagents afforded the alkylated compounds **612a–f** in good yield and with >98% ee (Scheme 131).[246]

Hou *et al.*[247] have reported the synthesis of (*R*)- and (*S*)-2-alkyl pipecolic acids **617a–e** by diastereoselective alkylation of (*R*)-5-phenylmorpholin-2-one **613**. In this context, commercially available (*R*)-phenylglycinol was transformed in three steps into (*R*)-**613** in 34% overall yield, and treatment of this compound with NaHMDS followed by the addition of 1,4-diiodobutane gave the iodide derivative (*R*,*R*)-**614** in 65% yield as a single diastereoisomer. Cleavage of Boc protective group of (*R*,*R*)-**614** with TFA and subsequent cyclization under basic conditions produced the (4*R*,9a*R*)-oxazin-2-one **615** in 65% yield. Treatment of **615** with KHMDS followed by addition of several alkyl halides afforded the corresponding alkylated compounds (4*R*,9a*S*)-**616a–d** and (4*R*,9a*R*)-**616e** in good yield and diastereoselectivity. Hydrogenation of (4*R*,9a*S*)-**616a–d** and (4*R*,9a*R*)-**616e** in the presence of Pearlman's catalyst gave the 2-substituted pipecolic acids (*S*)-**617a–c** and (*R*)-**617e** in quantitative yield (Scheme 132).

On the other hand, Porzi and Sandri[248] reported the synthesis of unnatural dipeptides (2*S*, 2'*S*)-**622** and (3*S*,2'*S*)-**623** through an alkylation-cyclization reaction using the mono-lactim ether (*S*)-**618** as starting material. In this context, treatment of (*S*)-**618** with LiHMDS, followed by addition of 1-chloro-4-iodobutane and α, α'-dibromo-*o*-xylene afforded the monoalkylated products **619a,b** in moderate yield and 98:2 dr, which, by heating in DMF, gave the bicyclic derivatives **620a,b** in good yield. Reaction of **620a,b** with LiHMDS and subsequent addition of methyl iodide produced the methylated compounds **621a,b** in 80–85% yield and with 1,4-*trans* induction. Successive cleavage of the benzyl group with Li/NH_3, treatment with Et_3OBF_4 and acidic hydrolysis furnished the dipeptides (2*S*,2'*S*)-**622** and (3*S*,2'*S*)-**623a** in 65% yield (Scheme 133).

3.2. Construction of the ring by cyclization reactions

The following paragraphs cover all current methodologies for cyclcization reactions and these are arranged into several according to the strategy involved. The first want involves the N-C bond formation starting from quaternary acyclic compounds in which the stereocentre has been previously formed. For example, nosylation reaction of methyl α-alkylserinates **624a–c** with *o*-NsCl and excess of $KHCO_3$ in acetonitrile under reflux provided the *N*-nosyl aziridines **625a–c** in good yield (Scheme 134).[249]

On the other hand, treatment of (*R*)-5-phenylmorpholin-2-one **613** with NaHMDS, followed by addition of several alkylating reagents, gave the corresponding alkylated compounds (*R*,*R*)-**626a–f** in 49–79% yield as single diastereoisomers. Treatment of these compound with KHMDS and subsequent addition of 1,4-diiodobutane (the alkylation of **626e–f** did not proceed), followed by cleavage of Boc protective group with TFA and subsequent cyclization under basic conditions produced the (4*R*,9a*R*)-oxazin-2-one **627a–d** in 56–67% yield.

Hydrogenation of **627a–d** in the presence of Pearlman's catalyst gave the 2-substituted pipecolic acids (*R*)-**617a–c** in quantitative yield (Scheme 135).[247]

In a similar way, treatment of (*S*)-**618** with LiHMDS followed by the addition of allyl bromide provided **628** in 85% yield and 85:15 dr,[250] which, by alkylation using LiHMDS as a base and α,α'-dibromo-*o*-xylene as an alkylating reagent, afforded the dialkylated derivative (3*R*, 6*S*)-**629** in 80% yield. Heating of (3*R*,6*S*)-**629** in DMF produced the bicyclic derivative **630** in 85% yield and treatment of this compound under identical conditions to those described for **621a,b**, gave (3*R*,2'*S*)-**631** in 67% yield (Scheme 136).[248]

Maruoka *et al.*[251] reported the catalytic enantioselective synthesis of tetrahydroisoquinoline- and dihydroisoquinoline-3-carboxylic acid derivatives **634a–c** and **636a,c** by a phase-transfer alkylation-cyclization process. Thus, treatment of Shiff bases **632a–c**, obtained from *p*-chlorobenzaldehyde and the appropriate α-amino acid *tert*-butyl esters, with α,α'-dibromo-*o*-xylene and 50% KOH in the presence of C_2-symmetric chiral quaternary ammonium salt (*S*,*S*)-3,4,5-F_3-Ph-NAS-Br **633**, followed by hydrolysis with citric acid and subsequent treatment with excess of $NaHCO_3$, produced the (3*R*)-3-alkyl-1,2,3,4-tetrahydroisoquinolines derivatives **634a–c** in moderate yield and good enantioselectivity. In a similar way, alkylation of **632a,c** with **635** in the presence of **633**, followed by hydrolysis with HCl and subsequent treatment with excess of $NaHCO_3$, produced the (3*R*)-3-alkyl-3,4-dihydroisoquinoline derivatives **636a,c** in good yield and enantioselectivity (Scheme 137).

Formation of the C–N bond can be achieved by cyclization of carbenoid intermediates. For example, intramolecular cyclization of enantiopure carbenoids **637a,b**, obtained from (*R*)-**299**, in the presence of a catalytic amount of $Rh_2(OAc)_4$ in CH_2Cl_2 gave the bicyclic compounds **638a,b** with complete chemoselectivity at the adjacent annular nitrogen and a preference for carbon-carbon double bond additions or C–H insertions. Hydrolysis of **638a,b** with 3 M HCl, followed by treatment with $(Boc)_2O$ and triethylamine, produced the protected dipeptides **639a,b** (Scheme 138).[252]

In a similar way, intramolecular cyclization of enantiopure carbenoids (2*S*,5*R*)-**640a,b** in the presence of a catalytic amount of $Rh_2(OAc)_4$, afforded the bicyclic compounds **643a,b** as the main products and **644a,b**, probably due to isomerization at C-5 through the intermediates **641** and **642**. Chemoselective opening ring of the iminoether function in the diastereoisomerically pure **643a,b** with 3 M HCl, followed by treatment with $(Boc)_2O$ and triethylamine, produced the corresponding dipeptides (2*S*,2'*R*)-**645a,b** in moderated yield. Under identical conditions the enantiopure carbenoids (2*R*,5*R*)-**646a,b** were transformed into the dipeptides (2*R*,2'*S*)-**645a,b** (Scheme 139).[253]

Other protocol reported by our group involved the large scale reduction of enantiopure ketone 648,[254] obtained in several steps from **647** by a Diels-Alder reaction. In this context, reduction of **648** with K-selectride in THF at −78 °C afforded the mixture of alcohols (axial **649** and equatorial **650**) in 98% yield and an 85:15 ratio. Treatment of these compounds with MsCl and triethylamine followed by base-promoted internal nucleophilic displacement with sodium hydride and DMF, gave the 7-azabicyclo[2.2.1]heptane derivative **651** in 75% yield (Scheme 140).[255]

Cleavage of the acetonide function of **651** with PPTS in acetone-water provided the corresponding diol **652** in 67% yield, which, by oxidation with $NaIO_4$ and $RuCl_3$ followed by hydrolysis with 6 N HCl gave the (1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptane-1,2-dicarboxylic acid as hydrochloride salt **653** in 75% yield. On the other hand, oxidation of **652** with $NaIO_4$ furnished the aldehyde (1*S*,2*R*,4*R*)-**654** in 90% yield, which, by Wittig reaction with $RCH{=}PPh_3$, provided the vinyl derivatives (1*S*,2*R*,4*R*)-**655a–e** in 75–99% yield. The vinyl derivative **655a** was also obtained through the two-step Corey-Winter[256] procedure. In this

context, reaction of diol **652** with *N*,*N*'-thiocarbonyldiimidazole (TDCI) provided the thiocarbonate **656** in 83% yield. Treatment of **656** with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (DMPDAP) led to **655a** in 86% yield. Finally, hydrogenation of C=C double bond of **655a–e** over $Pd(OH)_2$ followed by hydrolysis with 6 N HCl afforded the (1*S*, 2*R*,4*R*)-proline derivatives **657a–d** in good yield (Scheme 141).[257]

Additionally, the aldehyde (1*S*,2*R*,4*R*)-**654** has been used in the synthesis of 7-azanorbornane β-susbtituted prolines.[258] For example, reduction of aldehyde function in (1*S*,2*R*,4*R*)-**654** with $NaBH_4$ followed by treatment with MsCl and triethylamine produced the corresponding mesylate (1*S*,2*R*,4*R*)-**658**, which, by nucleophilic substitution, afforded the compounds (1*S*, 2*R*,4*R*)-**659a–e** in 60–100% yield. Hydrolysis of (1*S*,2*R*,4*R*)-**659a,b,d** with 6 M HCl provided the amino acids (1*S*,2*R*,4*R*)-**660a,b,d** in quantitative yield and these can be considered as (2*S*,3*R*)-3-methylproline, (2*S*,3*R*)-3-methylthio-methylproline and (2*S*,3*R*)-3-carboxymethylproline analogues. Additionally, (1*S*,2*R*,4*R*)-**659e** was transformed into amino compounds (1*S*,2*R*,4*R*)-**661a–d** (Scheme 142).

The second reported methodology involves the formation of a C_α-C_β bond. In this case the stereoselectivity of the cyclization reaction depends on the chirality of the non-quaternary α-amino acid used as starting material, wherever the chirality of the stereocentre can be remembered to some extent (memory of chirality). This methodology has been repeatedly used for the stereoselective synthesis of four-, five-, six- and seven-membered rings. These results have been collected in recent reviews,[259] and we therefore only describe here the most recents papers. For example, Kawabata *et al*.[260,261] reported the four-membered cyclization for the straightforward synthesis of cyclic amino acids with tetrasubstituted stereocentres from chiral α-amino acids through memory of chirality. In this context, treatment of **662a,b** with KHMDS in DMF at −60 °C furnished the four-membered compounds **663a,b** with good enantioselectivity and retention of configuration, while that the use of lithium 2,2,6,6-tetramethylpiperidine (LTMP) as a base in THF at −20 °C led to **663a,b** with good enantioselectivity but with inversion of the configuration. Treatment of (*R*)-**663a** with methanolic NaOMe followed by cleavage of the *N*-Boc protective group with 4 N HCl gave the azetidine derivative (*R*)-**664** in 56% yield (Scheme 143).

In a similar way, treatment of **665** and **666** with KHMDS in DMF at −60 °C provided the piperidine derivative **667** in 84% yield and 97% ee, and the azepane **668** in 31% yield and 83% ee (**666** was recovered). The stereochemical course of the cyclization was with retention of the configuration (Scheme 144).[260]

Recently, Kawabata *et al.*[262] reported that the asymmetric cyclization of **662a–c** (n = 2), **669a–c** (n = 3), and **665a–c** (n = 4) using powdered KOH as an efficient base in DMSO at 20 °C afforded the four- five- and six-membered compounds **663a–c**, **670a–c** and **667a–c**, respectively, in good yield and excellent enantioselectivity. The results are summarised in Table 12.

This protocol has been used in the synthesis of Fmoc-cyclic amino acid **671**, which is expected to be an useful building block for conformationally constrained peptides of biological interest. In this context, treatment of isoleucine derivative **669d** with powdered KOH in DMSO at 20 °C afforded the cyclic product **670d** in 94% yield as a single diastereoisomer, which, by hydrolysis with HCl and subsequent *N*-Fmoc protection, led to the proline derivative **671** in 53% yield (Scheme 145).[262]

Very recently, Kawabata *et al*.[263] reported the asymmetric intramolecular alkylation of β-alcoxy-α-amino esters through memory of chirality methodology. In this context, treatment of serine derivatives **672a**, **673a–f** and **674a** with CsOH as an efficient base in DMSO at 20 °C

afforded the cyclization products **675a**, **676a–f** and **677a** in 13–89% yield and enantioselectivities in the range 82 to 94%. The results are summarized in Table 13.

Memory of chirality in intramolecular conjugate addition of enolates is another metholodogy used for the asymmetric synthesis of nitrogen heterocycles with contiguous quaternary stereocentres. For example, treatment of α,β-unsaturated derivatives **678a,b** with KHMDS in DMF-THF at −78 °C gave the piperidine derivatives **679a,b** as a single detectable diastereoisomers in moderate yield. Seven-membered ring cyclization of α,β-unsaturated compound **678c** proceeded to give **679c** in 91% ee, albeit in only 19% yield (Scheme 146).[264] Compounds **679a–c** are precursors of conformationally constrained L-glutamate analogues.

On the other hand, treatment of α,β-unsaturated compound **680** with KHMDS in DMF-THF at −78 °C gave the tetrahydroisoquinoline derivative **681** as a single diastereoisomer in 95% ee and 94% yield.[261,264] Treatment of **680** with LTMP in THF at 0 °C led to *ent*-**681** as a single diastereoisomer in 91% ee and 62% yield (Scheme 147).[261]

The third methodology reported involves the cyclization by C-C bond formation, starting from the corresponding quaternary α-amino acids previously obtained with both chain appropriately functionalized. For example, ring closing metathesis of dialkylated derivative (*R*)-**683**, obtained in three steps from **682**,[265] in the presence of a catalytic amount of $PhCH{=}RuCl_2(PCy_3)_2$ in benzene under reflux gave the corresponding six-membered derivative (*R*)-**684** in 94% yield. Subsequent hydrogenation of the C=C double bond over Pd/C afforded the α-quaternary pipecolic acid derivative (*R*)-**685** in 95% yield (Scheme 148).[266]

Finally, the one-pot aza-Darzens reaction has been reported as a competitive alternative for the synthesis of aziridine carboxylic acids. For example, aza-Darzens reaction[267] of (*S*)-sulfinimine **686a** with the lithium α-bromoenolate generated from methyl α-bromopropianate **687** and LiHMDS in THF at −78 °C, afforded the corresponding aziridines (S_S,2*R*,3*S*)-**688** and (S_S,2*S*,3*S*)-**689** in 55 and 21% yield, respectively. Oxidation of diastereoisomerically pure (S_S,2*R*,3*S*)-**688** with *m*-CPBA gave the *N*-tosyl aziridine (2*R*,3*S*)-**690** in excellent yield. On the other hand, reaction of diastere-oisomerically pure (S_S,2*R*,3*S*)-**688** with MeMgBr provided the aziridine (2*R*,3*S*)-**691** in 92% yield (Scheme 149).[268]

In a similar way, the one-pot reaction of (*S*)-sulfinimines **686b,c** with the lithium α-bromoenolate generated from methyl 3-benzyloxy-2-bromopropionate **692**[269] and LiHMDS in THF at −78 °C, produced the aziridines (S_S,2*S*,3*S*)-**693b** and (S_S,2*R*,3*S*)-**694b** (R = Ph) in 70% yield and 95:5 dr, and the aziridines (S_S,2*S*,3*S*)-**693c** and (S_S,2*R*,3*S*)-**694c** (R = *E*-MeCH=CH) in 79% yield and 15:85 dr. Selective cleavage of *N*-sulfinyl bond in (S_S,2*S*,3*S*)-**693b** with TFA gave the aziridine (2*S*,3*S*)-**695b** in 76% yield, whereas the treatment of (S_S,2*R*,3*S*)-**694c** with excess of MeMgBr provided the aziridine (2*R*,3*S*)-**696c** in 86% yield (Scheme 150).[270]

3.3. Cycloadditions and related reactions

This strategy has been elegantly used to the synthesis of different types of prolines and derivatives and it is especially useful in the synthesis of polysubstituted (polyfunctional) prolines. Nevertheless, most of the published papers have been gathered in our recent review.[230] As a result we only include here the reports that have appeared very recently. For example, Xie *et al.*[271] reported a practical asymmetric synthesis of highly substituted proline derivatives **698** and **700** on a multi-kilogram scale. In this context, [3+2] cycloaddition reaction of methyl acrylate with the enantiopure imine (*S*)-**697a**, readily obtained by condensation of L-leucine *tert*-butyl ester with 2-thiazole-carboxaldeyde, in the presence of a catalytic amount of hydroquinine, AgOAc, and molecular sieves, produced the proline derivative **698** in 85:15 enantiomeric ratio (er). Treatment of the resulting compound with (*R*)-1,1'-binaphthyl-2,2'-

dehydrogenphosphate in 2-propanol and subsequent crystallization gave **698** in 99.9:0.1 er and 57% overall yield. In asimilar way, [3+2] cycloaddition reaction of (*S*)-**697a** with methyl vinyl ketone in the presence of a catalytic amount of cinchonidine and AgOAc gave the proline derivative **699** as a mixture of α/β epimers in 98:2 ratio, which, by treatment with 10 mol% of DBU, gave the β epimer **700** as the main product with 73:27 er (Scheme 151).

Very recently, Kobayashi *et al*.[272] reported the [3+2] cycloaddition reaction of different imines (±)-**701** with several acrylates **702** in the presence of a catalytic amount of the bisoxazolines **703a–e** and Ca(O*i*-Pr)$_2$ in THF and molecular sieves. The substituted pyrrolidine derivatives **704** were obtained in high yields and with high diastereoselectivities and enantioselectivities (Scheme 152)

The [3+2] cycloaddition reaction was used by Kobayashi *el at.*[272] in the synthesis of optically pure pyrrolidine cores of hepatitis C virus RNA-dependent polymerase inhibitors and potentially effective antiviral agents. In this context, [3+2] cycloaddition reaction of *tert*-butyl acrylate with the enantiopure imines (*R*)-**697a,b** in the presence of a catalytic amount of the bisoxazolines **703a,b** and Ca(O*i*-Pr)$_2$ in THF and molecular sieves, produced the pyrrolidine derivatives **705a,b** in high yield with perfect diastereoselectivities and high enantioselectivities (Scheme 153).

Another approach to generate enantiomerically enriched polysubstitutted prolines or pyrrolidine derivatives is the 1,3-dipolar cicloaddition between electrophilic alkenes and stabilized or nonstabilized dipolarophiles, respectively. This strategy allows the creation of up four stereogenic centres in only one step and gives high regioselectivity and *endo*/*exo*-diastereoselectivities. For example, Nájera *et al.*[273] reported the stereoselective synthesis of polysubstituted prolines (2*R*,4*R*,5*S*)- and (2*S*,4*S*,5*R*)-**707** by a 1,3-dipolar cicloaddition, In this context, the cycloaddition reaction between the racemic imino ester (±)-**697b** with acrylate bonded to methy (*S*)-lactate **706** in the presence of a catalytic amount of AgOAc and KOH in toluene, afforded the polysubstituted proline (2*R*,4*R*,5*S*)-**707** in 77% yield and 96% de. In similar way, reaction of (±)-**697b** with acrylate bonded to methy (*R*)-lactate **706** gave the polysubstituted proline (2*S*,4*S*,5*R*)-**707** in 88% yield and 96% de. (2*R*,4*R*,5*S*)-**707** And (2*S*, 4*S*,5*R*)-**707** were transformed into (2*R*,4*R*,5*S*)- and (2*S*,4*S*,5*R*)-**708**, two promising potential drugs, particularly for the hepatitis C virus RNA-dependent polymerase inhibitors and potential effective antiviral agents (Scheme 154).

Recently, Nájera *et al.*[274] reported that the catalytic enantioselective 1,3-dipolar cycloaddition reaction of racemic benzylideneiminoglycinates **709a–d** with *tert*-butyl acrylate in the presence of a catalytic amount of (S_a,*R*,*R*)-**710**, $AgClO_4$ and triethylamine or 1,4-diazabicyclo [2.2.2]octane (DABCO) as a base, afforded the corresponding prolines **711a,b** and **712c,d** with high enantiomeric ratio (Scheme 155).[275]

1,3-Dipolar cycloaddition reaction of racemic methyl *N*-benzylidenealaninate **713** with the vinyl sulfone in the presence of copper(I)/click ferrophos complex **714** and CuOAc, produced the quaternary methyl prolinate derivative **715** in 83% yield and 93% ee (Scheme 156).[276]

Very recently, Carretero *et al.*[277] reported the stereoselective synthesis of 3-pyrrolines **719a,b** by asymmetric 1,3-dipolar cycloaddition reaction. Thus, the reaction of racemic methyl *N*-benzylidene-alaninates **713a,b** with *trans*-1,2-bisphenylsulfonyl ethylene **716** in the presence of a catalytic amount of $Cu(MeCN)_4PF_6$, Fesulphos (*R*)-**717** and Et_3N, afforded the quaternary methyl prolinate derivatives **718a,b** in good yield and with good enantioselectivity. Subsequent treatment of these compounds with Na(Hg) gave the quaternary derivatives **719a,b** in 85 and 77% yield, respectively. (Scheme 157).

Cyclopropanation reaction of a cyclic dehydroaminoacid derivative allowed the synthesis of new constrained quaternary pipecolic derivatives. Thus, the reaction of (*S*)-2,3-didehydropipecolate **721**, obtained in five steps from *N*,*N*-diprotected L-lysine methyl ester **720**, with dimethylsulfoxonium methylide afforded the 2,3-methano-6-methoxypipecolate (2*S*,3*R*)-**722** in 73% yield and treatment with $NaBH_4$ in formic acid gave the 2,3-methanopipecolate (2*S*,3*R*)-**723** in 75% yield and 85% ee. Finally, hydrolysis of (2*S*,3*R*)-**723** with TMSI produced the (2*S*,3*R*)-methanopipecolic acid **724** in 50% yield (Scheme 158).[278]

3.4. Resolution procedures

3.4.1. Chemical resolution—Reaction of alcohol (±)-**726**, obtained from (±)-**725**,[279] with (*R*)-methoxytrifluorophenylacetic acid [(*R*)-MTPA] in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and DMAP, followed by crystallization, gave the diastereoisomeric esters (1*S*,2*S*,4*R*,2′*R*)-**727** and (1*R*,2*R*,4*S*,2′*R*)-**728** in 95% yield and >95% optical purity. Hydrolysis of **727** and **728** with methanolic NaOMe followed by hydrolysis with 6 N HCl at 60 °C furnished the enantiomerically pure (1*S*,2*S*,4*R*)-**729** and (1*R*,2*R*,4*S*)-**729**, respectively, and these are analogues of 3-hydroxyproline (Scheme 159).[280]

3.4.2. HPLC Resolution—Preparative HPLC resolution of β-lactam (±)-**730** on CSP-1 as a chiral stationary phase gave the β-lactams (*S*)- and (*R*)-**730** with 85 and 92% enantiomeric purity. Subsequent saponification of these compounds provided the conformationally constrained amino acids (*S*)- and (*R*)-**731**. On the other hand, reduction of the amide function of (*S*)- and (*R*)-**730** with Ph_2SiH_2 and $RhH(CO)(PPh_3)_3$ followed by cleavage of PMB protective group under H_2 and $Pd(OH)_2$, provided the optically pure Phe-derived conformationally constrained amino esters (*S*)- and (*R*)-**732** (Scheme 160).[281]

Preparative HPLC resolution of (±)-**733**, obtained from **545**, on CSP-1 as a chiral stationary phase gave the enantiomerically pure (1*S*,2*S*,4*R*)-**733** and (1*R*,2*R*,4*S*)-**733**, which, were separately treated with 6 N HCl to give the enantiomerically pure proline-phenylalanine chimeras (1*S*,2*S*,4*R*)- and (1*R*,2*R*,4*S*)-**734** in 95% yield. Oxidative cleavage of the phenyl substituent on the azabicyclic ring of (1*S*,2*S*,4*R*)- and (1*R*,2*R*,4*S*)-**733** produced the corresponding carboxylic acids (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-**735** in 45% yield. Hydrolysis of these compounds provided the enantiomerically pure (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-3-carboxyproline analogues **736** in 95% yield. On the other hand, the conversion of the carboxylic acid function of (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-**735** into methyl alcohols (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-**737** was carried out by treatment with isobutylchloroformate (IBCF) and triethylamine followed by reduction with $NaBH_4$. Finally, Dess-Martin oxidation of the alchohol function of (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-**737** gave the corresponding aldehyde derivatives (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-**738** in 80% yield, and these proved to be a versatile synthetic intermediate in the preparation of a wide variety of β-substituted azabicyclic prolines (Scheme 161).[282]

3.5. Miscellaneus and notes added in proofs

Several other special cyclization procedures useful for very particular cases have been reported. For example, the Pictet-Spengler cyclization of *N*-sulfonyl-β-phenylethylamines **739a,b** with menthyl α-chloro-α-phenylseleno propionate **740** in the presence of $SnCl_4$ gave the corresponding 1,2,3,4-tetrahydrosioquinoline-1-carboxylates derivatives **741a,b** in moderate yield and good diastereo-selectivity after crystallization (Scheme 162).[283]

Pictet-Spengler cyclization of quaternary oxazolidines **742a–d** in the presence of $TiCl_4$ and Et_3N provided the corresponding tetrahydroisoquinolines **743a–d** with good regioselectivity, which, by cleavage of the benzyl functionality under H_2 and $Pd(OH)_2$, gave the quaternary amino acids **744a–d** in 30–96% yield (Scheme 163).[284]

On the other hand, Pictet-Spengler cyclization of quaternary *N*-Boc-*N*-MOM-α-methyl- and α-allyltrytophan derivatives **746a,b**, obtained from alkylation of **745**, with HCl in ethyl acetate afforded the corresponding tryptoline derivatives **747a,b** in good yield, where the MOM protective group serves as a formaldehyde equivalent (Scheme 164).[285]

Reaction of enantiopure quaternary α-amino acid derivative **748** with paraformaldehyde in formic acid followed by treatment with H_2O and TsOH provided the lactone *cis*-**752** and the hydroxy ester *trans*-**753** in 50 and 32% yield, respectively. The transformation from **748** to *cis*-**752** and *trans*-**753** should occur through the chairlike *N*-tosyliminium intermediate **749** followed by cyclization to give the secondary cation **750**, which, is stabilized by the ester carbonyl group to produce the dioxycarbenium ion **751**. Finally, the hydrolysis of **751** followed by treatment with TsOH gave the lactone *cis*-**752** and the hydroxy ester *trans*-**753** (Scheme 165).[286]

Clayden *et al.*[287] reported the synthesis of α-methyl kainic acid (an α-methylproline 3,4-disubstituted system) by the stereospecific lithiation-dearomatizing cyclization of the chiral benzamide (*R*,*R*)-**754**. Thus, reaction of the benzamide (*R*,*R*)-**754** with *tert*-BuLi at −78 °C followed by treatment with 0.5 M HCl produced the corresponding bicyclic compound **755** as a single stereo- and regioisomer in 70% yield. Conjugated addition of Me_2CuLi to **755** followed by cleavage of the benzyl fragment with CAN and subsequent treatment with $(Boc)_2O$ gave **756** in 66% yield, which, in turn was transformed into α-methyl kainic acid after 12 steps (Scheme 166).

Finally, during the corrections of this review, Makosza *et al.*[288] reported the stereoselective synthesis of (2*R*)-4-nitroarylprolines **759a–c** through oxidative nucleophilic substitution of hydrogen in nitroarenes using the chiral carbanion of L-proline derivative (3*S*,7a*R*)-**590**, applying the self-reproduction of chirality methodology. Thus, treatment of (3*S*,7a*R*)-**590** with KHMDS in THF-DMF at −78 °C followed by the addition of corresponding nitroarene, afforded the σ^H adduct **757**, which, by oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) gave the 4-nitroaryl derivatives **758a–c** as a single detectable diastereoisomeres with 29–72% yield (reaction with 2-fluor, 2-chloro and 2-methylnitrobenzene failed). Hydrolysis of (3*S*,7a*R*)-**758a–c** with HBr and subsequent treatment with propylene oxide led to the (2*R*)-4-nitroarylprolines **759a–c** with 55–85% yield (Scheme 167).

Concluding remarks

In this review, we have covered recent progress in the development of new synthetic methodologies for the preparation of cyclic α,α-dialkylamino acids and we have also discussed extensions to well established synthetic routes. The use of cyclic compounds as starting materials is one of the most convenient procedures reported.

The construction of the cycle using cyclization or cycloaddition reactions both in a diastereo-selective or enantioselective manner is one excellent alternative. All of these strategies can be completed with the use of resolution procedures (chemical, enzymatic or chromatographic) that have emerged as another good alternative.

All of these methodologies give the synthetic organic chemist the opportunity to select the most appropriate way to obtain the desired cyclic α,α-dialkylamino acid in enantiomerically pure form on both a laboratory scale and a multigram scale.

Abbreviations

Ac	acetyl
AcOH	acetic acid
ACCA	1-aminocyclopropanecarboxylic acid
acac	acetylacetone
ACPD	1-amino-1, 3-cyclopentane dicarboxic acid
Adt	4-amino-1,2-dithiolane-4-carboxylic acid
Afc	*O*,*O*-isopropylidene-α-hydroxymethylserine
AIBN	2,2'-azoisobutyronitrile
AIDA	1-aminoindane-1,5-dicarboxylic acid
APCPr	1-amino-2-phosphonomethylcyclopropanecarboxylic acid
APICA	1-amino-5-phosphoindane-1-carboxylic acid
AP4	L-2-amino-4-phosphonobutanoic acid
BINAP	2,20-bis(diphenylphosphanyl)-1,10-binaphthyl
BINOL	1,10-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
BtH	benzotriazole
BuLi	butyl lithium
Bz	benzoyl
CALB	*Candida antarctica* lipase B
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CLEC	chiral ligand-exchange chromatography
Daf	9-amino-9-fluorenecarboxylic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAM	di-*p*-anisylmethyl
DBDA	dibenzyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	diethyl acetylenedicarboxylate
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMA	*N*,*N'*-dimethylacetamide

DMB	3,4-dimethoxybenzyl
DMAP	4-dimethylaminopyridine
DMEA	dimethylethanolamine
DME	1,2-dimethoxyethane
DMF	*N*,*N*'-dimethylformamide
DMPDAP	1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine
DMSO	dimethylsulfoxide
DPPA	diphenylphosphorazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereoisomeric ratio
EDA	ethylenediamine
EDC	*N*-ethyl-*N*'-dimethylaminopropylcarbodiimide hydrochloride
ee	enantiomeric excess
er	enantiomeric ratio
HMPA	hexamethylphosphoramide
HOBt	*N*-hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
HYDIA	amino-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid
IBCF	isobutylchloroformate
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LPLC	Low pressure liquid chromatography
LTMP	lithium 2,2,6,6-tetramethylpiperidide
KHMDS	potasium bis(trimethylsilyl)amide
MABR	methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide)
MAO	methylaluminoxane
MBA	methylbenzylamine
m-CPBA	*m*-chloroperbenzoic acid
MOM	methoxymethyl
MOMBA	methoxymethylbenzylamine
MS	molecular sieves
Ms	methanesulfonyl (mesyl)
MTPA	methoxytrifluorophenylacetic acid
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine

NMO	morpholine *N*-oxide
NMP	*N*-methylpyrrolidin-2-one
Ns	nitrobenzenesulphonyl
PCC	pyridinium chlorochromate
PLE	pig liver esterase
PMB	*p*-methoxybenzyl
mGlu	metabotropic glutamate
PPTS	pyridinium *p*-toluenesulfonic acid
RCM	ring closing metathesis
rt	room temperature
SAMI	(*S*)-1-amino-2-methoxymethylindoline
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
TBAB	tetrabutylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TDCI	*N*,*N'*-thiocarbonyldiimidazole
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMAH	tetramethylammonium hydroxide
TMSCl	trimethylsilyl chloride
TMSI	trimethylsilyl ioide
TMSCN	trimethylsilylcyanide
TMSE	trimethylsilylethyl
Tol	tolyl
TsOH	*p*-toluenesulfonic acid
Ts	*p*-toluenesulfonyl (tosyl)

Acknowledgments

This work was carried out with the financial support of CONACYT-MEXICO (Projects 62271 and 44126) 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 as 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 or the policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations 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.

References

1. Cativiela C, Díaz-de-Villegas MD. Tetrahedron: Asymmetry 1998;9:3517–3599.
2. Cativiela C, Díaz-de-Villegas MD. Tetrahedron: Asymmetry 2000;11:645–732.
3. Cativiela C, Díaz-de-Villegas MD. Tetrahedron: Asymmetry 2007;18:569–623.
4. Undheim K. Amino Acids 2008;34:357–402. [PubMed: 17476570]
5. Park K-H, Kurth MJ. Tetrahedron 2002;58:8629–8659.
6. Gelmi ML, Pocar D. Org. Prep. Proced. Int 2003;35:141–205.
7. Qiu X-L, Meng W-D, Qing F-L. Tetrahedron 2004;60:6711–6745.
8. Perdih A, Dolenc MS. Curr. Org. Chem 2007;11:801–832.
9. Galeazzi R, Mobbili G, Orena M. Curr. Org. Chem 2004;8:1799–1829.
10. Lasa M, Cativiela C. Synlett 2006:2517–2533.
11. Brackmann F, de Meijere A. Chem. Rev 2007;107:4493–4537. [PubMed: 17944521]
12. Brackmann F, de Meijere A. Chem. Rev 2007;107:4538–4671. [PubMed: 17944522]
13. Nájera C, Sansano JM. Chem. Rev 2007;107:4584–4671. [PubMed: 17915933]
14. (a) Tanaka M. Chem. Pharm. Bull 2007;55:349–358. [PubMed: 17329870] (b) Maity P, König B. Biopolymers (Pept. Sci.) 2007;90:8–27.
15. (a) Vogt H, Bräse S. Org. Biomol. Chem 2007;5:406–430. [PubMed: 17252120] (b) Nájera C. Synlett 2002:1388–1493.
16. Arduin M, Spagnolo B, Calò G, Guerrini R, Carrà G, Fischetti C, Trapell C, Marzola E, McDonald J, Lambert DG, Regoli D, Salvadori S. Bioorg. Med. Chem 2007;15:4434–4443. [PubMed: 17490886]
17. Prasad S, Mathur A, Jaggi M, Singh AT, Mukherjee R. J. Pept. Sci 2007;13:544–548. [PubMed: 17617800]
18. Vijayalakshmi S, Rao RB, Karle IL, Balaram P. Biopolymers 2000;53:84–98. [PubMed: 10644953]
19. Saviano M, Iacovino R, Menchise V, Benedetti E, Bonora GM, Gatos M, Graci L, Formaggio F, Crisma M, Toniolo C. Biopolymers 2000;53:200–212. [PubMed: 10679624]
20. Saviano M, Iacovino R, Benedetti E, Moretto V, Banzato A, Formaggio F, Crisma M, Toniolo C. J. Pept. Sci 2000;6:571–583. [PubMed: 11147716]
21. Moretto A, Formaggio F, Crisma M, Toniolo C, Saviano M, Iacovino R, Vitale RM, Benedetti E. J. Pept. Res 2001;57:307–315. [PubMed: 11328488]
22. Romanelli A, Garella I, Menchise V, Iacovino R, Saviano M, Montesarchio D, Didierjean C, di Lello P, Rossi F, Benedetti E. J. Pept. Sci 2001;7:15–26. [PubMed: 11245201]
23. Datta S, Rathore RNS, Vijayalakshmi S, Vasudev PG, Rao RB, Balaram P, Shamala DN. J. Pept. Sci 2004;10:160–172. [PubMed: 15113088]
24. Ohwada T, Kojima D, Kiwada T, Futaki S, Sugiura Y, Yamaguchi K, Nishi Y, Kobayashi Y. Chem. Eur. J 2004;10:617–626.
25. Wolf WM, Stasiak M, Leplawy MT, Bianco A, Formaggio F, Crisma M, Toniolo C. J. Am. Chem. Soc 1998;120:11558–11566.
26. Savrda J, Mazaleyrat J-P, Wakselman M, Formaggio F, Crisma M, Toniolo C. J. Pept. Sci 1999;5:61–74. [PubMed: 10100122]
27. Crisma M, Formaggio F, Mezzato S, Toniolo C, Savrda J, Mazaleyrat J-P, Wakselman M. Lett. Pept. Sci 2000;7:123–131.
28. Mazaleyrat J-P, Wakselman M, Formaggio F, Crisma M, Toniolo C. Tetrahedron Lett 1999;40:6245–6248.
29. Peggion C, Crisma M, Formaggio F, Toniolo C, Wright K, Wakselman M, Mazaleyrat J-P. Biopolymers 2002;63:314–324. [PubMed: 11877741]
30. Aschi M, Lucente G, Mazza F, Mollica A, Morera E, Nalli M, Paradisi MP. Org. Biomol. Chem 2003;1:1980–1988. [PubMed: 12945783]
31. Formaggio F, Crisma M, Toniolo C, Tchertanov L, Guilhem J, Mazaleyrat J-P, Gaucher A, Wakselman M. Tetrahedron 2000;56:8721–8734.

32. Formaggio F, Peggion C, Crisma M, Toniolo C, Tchertanov L, Guilhem J, Mazaleyrat J-P, Goubard Y, Gaucher A, Wakselman M. Helv. Chim. Acta 2001;84:481–501.
33. Mazaleyrat J-P, Wright K, Gaucher A, Wakselman M, Oancea S, Formaggio F, Toniolo C, Setnička V, Kapitán J, Keiderling TA. Tetrahedron: Asymmetry 2003;14:1879–1893.
34. Mazaleyrat J-P, Wright K, Gaucher A, Toulemonde N, Wakselman M, Oancea S, Peggion C, Formaggio F, Setnička V, Keiderling TA, Toniolo C. J. Am. Chem. Soc 2004;126:12874–12879. [PubMed: 15469284]
35. Mazaleyrat J-P, Wright K, Gaucher A, Toulemonde N, Dutot L, Wakselman M, Broxterman QB, Kaptein B, Oancea S, Peggion C, Crisma M, Formaggio F, Toniolo C. Chem. Eur. J 2005;11:6921–6929.
36. Dutot L, Gaucher A, Wright K, Wakselman M, Mazaleyrat J-P, Oancea S, Peggion C, Formaggio F, Toniolo C. Tetrahedron: Asymmetry 2006;17:363–371.
37. Gaucher A, Dutot L, Barbeau O, Wakselman M, Mazaleyrat J-P, Peggion C, Oancea S, Formaggio F, Crisma M, Toniolo C. Tetrahedron: Asymmetry 2006;17:30–39.
38. Mazaleyrat J-P, Goubard Y, Azzini M-V, Wakselman M, Peggion C, Formaggio F, Toniolo C. Eur. J. Org. Chem 2002:1232–1247.
39. Lohier J-F, Wright K, Peggion C, Formaggio F, Toniolo C, Wakselman M, Mazaleyrat J-P. Tetrahedron 2006;62:6203–6213.
40. Wright K, Lohier J-F, Wakselman M, Mazaleyrat J-P, Peggion C, Formaggio F, Toniolo C. Biopolymers (Pept. Sci.) 2007;88:797–806.
41. Gómez-Catalán J, Alemán C, Pérez JJ. Theor. Chem. Acc 2000;103:380–389.
42. Casanovas J, Zanuy D, Nussinov R, Alemán C. Chem. Phys. Lett 2006;429:558–562.
43. Alemán C, Zanuy D, Casanovas J, Cativiela C, Nussinov R. J. Phys. Chem. B 2006;110:21264–21271. [PubMed: 17048955]
44. Alemán C, Jiménez AI, Cativiela C, Pérez. JJ, Casanovas J. J. Phys. Chem. B 2002;106:11849–11858.
45. Jiménez AI, Vanderesse R, Marraud M, Aubry A, Cativiela C. Tetrahedron Lett 1997;38:7559–7562.
46. Jiménez AI, Cativiela C, Aubry A, Marraud M. J. Am. Chem. Soc 1998;120:9452–9459.
47. Jiménez AI, Cativiela C, Marraud M. Tetrahedron Lett 2000;41:5353–5356.
48. Casanovas J, Jiménez AI, Cativiela C, Pérez JJ, Alemán C. J. Org. Chem 2003;68:7088–7091. [PubMed: 12946154]
49. Jiménez AI, Ballano G, Cativiela C. Angew. Chem. Int. Ed 2005;44:396–399.
50. Casanovas J, Jiménez AI, Cativiela C, Pérez JJ, Alemán C. J. Phys. Chem. B 2006;110:5762–5766. [PubMed: 16539522]
51. Jiménez AI, Marraud M, Cativiela C. Tetrahedron Lett 2003;44:3147–3150.
52. Peggion C, Formaggio F, Crisma M, Toniolo C, Jiménez AI, Cativiela C, Kaptein B, Broxterman QB, Saviano M, Benedetti E. Biopolymers 2003;68:178–191. [PubMed: 12548622]
53. Casanovas J, Jiménez AI, Cativiela C, Nussinov R, Alemán C. J. Org. Chem 2008;73:644–651. [PubMed: 18081347]
54. Jiménez. AI, Cativiela C, Gómez-Catalán J, Pérez JJ, Aubry A, París M, Marraud M. J. Am. Chem. Soc 2000;122:5811–5821.
55. Gómez-Catalán J, Jiménez AI, Cativiela C, Pérez JJ. J. Pept. Res 2001;57:435–446. [PubMed: 11437947]
56. Lasa M, Jiménez AI, Zurbano MM, Cativiela C. Tetrahedron Lett 2005;46:8377–8380.
57. Bisetty K, Corcho FJ, Canto J, Kruger HG, Pérez JJ. J. Pept. Sci 2006;12:92–105. [PubMed: 15952237]
58. Tanaka M, Demizu Y, Doi M, Kurihara M, Suemune H. Angew. Chem. Int. Ed 2004;43:5360–5363.
59. Royo S, De Borggraeve WM, Peggion C, Formaggio F, Crisma M, Jiménez AI, Cativiela C, Toniolo C. J. Am. Chem. Soc 2005;127:2036–2037. [PubMed: 15713068]
60. Tanaka M, Anan K, Demizu Y, Kurihara M, Doi M, Suemune H. J. Am. Chem. Soc 2005;127:11570–11571. [PubMed: 16104711]
61. Grieco P, Lavecchia A, Cai M, Trivedi D, Weinberg D, MacNeil T, Van der Ploeg LHT, Hruby VJ. J. Med. Chem 2002;45:5287–5294. [PubMed: 12431055]

62. Horvat Š, Mlinarić-Majerski K, Glavaš-Obrovac L, Jakas A, Veljković J, Marczi S, Kragol G, Roščić M, Matković M, Milostić-Srb A. J. Med. Chem 2006;49:3136–3142. [PubMed: 16722632]
63. Ruzza P, Cesaro L, Tourwé D, Calderan A, Biondi B, Maes V, Menegazzo I, Osler A, Rubini C, Guiotto A, Pinna LA, Borin G, Donella-Deana A. J. Med. Chem 2006;49:1916–1924. [PubMed: 16539378]
64. Strecker D. Ann. Chem. Pharm 1850;75:27–45.
65. For specific reviews of the Strecker reaction and analogous synthesis, see: (a) Vachal, P.; Jacobsen, EN. In Comprehensive Asymmetric Catalysis. Jacobsen, EN.; Pfaltz, A.; Yamamoto, H., editors. Berlin: Springer; 2004. p. 117 (b) Ohfune Y, Shinada T. Bull. Chem. Soc. Jpn 2003;76:1115–1129. (c) Gröger H. Chem. Rev 2003;103:2795–2828. [PubMed: 12914481] (d) Enders D, Shilvock JP. Chem. Soc. Rev 2000;29:359–373. (e) Mori, A.; Inoue, S. In Comprehensive Asymmetric Catalysis. Jacobsen, EN.; Pfaltz, A.; Yamamoto, H., editors. Vol. vol. II. Berlin: Springer; 1999. p. 983
66. (a) Fadel A, Khesrani A. Tetrahedron: Asymmetry 1998;9:305–320. (b) Fadel A. Synlett 1993:503–505. (c) Subramanian PK, Woodard RW. Synth. Commun 1986;16:337–342. (d) Weinges K, Gries K, Stemmle B, Schrank W. Chem. Ber 1977;110:2098–2105.
67. (a) Tang G, Tian H, Ma D. Tetrahedron 2004;60:10547–10552. (b) Ma D, Tian H, Zou G. J. Org. Chem 1999;64:120–125. [PubMed: 11674092] (c) Ma D, Tang G, Tian H, Zou G. Tetrahedron Lett 1999;40:5753–5756. (d) Chakraborty TK, Hussain KA, Reddy GV. Tetrahedron 1995;51:9179–9190.
68. Boesten WHJ, Seerden J-PG, Lange B, Dielemans HJA, Elsenberg HLM, Kaptein B, Moody HM, Kellogg RM, Broxterman QB. Org. Lett 2001;3:1121–1124. [PubMed: 11348174]
69. (a) Avenoza A, Busto JH, Corzana F, Peregrina JM, Sucunza D, Zurbano MM. Synthesis 2005:575–578. (b) Davis FA, Lee S, Zhang H, Fanelli DL. J. Org. Chem 2000;65:8704–8708. [PubMed: 11112592] (c) Davis FA, Portonovo PS, Reddy RE, Chiu Y. J. Org. Chem 1996;61:440–441. [PubMed: 11666956] (d) Bravo P, Capelli S, Meille SV, Seresini P, Volonterio A, Zanda M. Tetrahedron: Asymmetry 1996;7:2321–2332. (e) Davis FA, Reddy RE, Portonovo PS. Tetrahedron Lett 1994;35:9351–9354.
70. (a) Ros A, Díez E, Marqués-López E, Martín-Zamora E, Vázquez J, Iglesias-Sigüenza J, Pappalardo RR, Alvarez E, Lassaletta JM, Fernández R. Tetrahedron: Asymmetry 2008;19:998–1004. (b) Enders D, Moser M. Tetrahedron Lett 2003;44:8479–8481.
71. Choi JY, Kim YH. Tetrahedron Lett 1996;37:7795–7796.
72. (a) Kunz H, Sager W, Pfrengle W, Schanzenbach D. Tetrahedron Lett 1988;29:4397–4400. (b) Kunz H, Sager W. Angew. Chem. Int. Ed 1987;26:557–559.
73. For the synthesis of chiral 2-alkylcyclobutanones of type **6**, see: Hazelard D, Fadel A. Tetrahedron: Asymmetry 2005;16:2067–2070.
74. Truong M, Lecornué F, Fadel A. Tetrahedron: Asymmetry 2003;14:1063–1072.
75. Volk F-J, Wagner M, Frahm AW. Tetrahedron: Asymmetry 2003;14:497–502.
76. (a) Hazelard D, Fadel A, Girard C. Tetrahedron: Asymmetry 2006;17:1457–1464. (b) Hazelard D, Fadel A, Guillot R. Tetrahedron: Asymmetry 2008;19:2063–2067.
77. For the synthesis of ketones of type **16**, see: (a) Cornubert R, Borrel C. Bull. Soc. Chim. Fr 1930;47:301–322. (b) Wiehl W, Frahm AW. Chem. Ber 1986;119:2668–2677. (c) Reetz MT, Maier WF. Angew. Chem 1978;90:50.
78. (a) Meyer U, Breitling E, Bisel P, Frahm AW. Tetrahedron: Asymmetry 2004;15:2029–2037. (b) Wede J, Volk F-J, Frahm AW. Tetrahedron: Asymmetry 2000;11:3231–3252.
79. Ma D, Tian H, Zou G. J. Org. Chem 1999;64:120–125. [PubMed: 11674092]
80. Schann S, Menet C, Arvault P, Mercier G, Frauli M, Mayer S, Hubert N, Triballeau N, Bertrand H-O, Acher F, Neuville P. Bioorg. Med. Chem. Lett 2006;16:4856–4860. [PubMed: 16828551]
81. For the preparation of peptides from **41** and **42**, see: Levins CG, Schafmeister CE. J. Org. Chem 2005;70:9002–9008. [PubMed: 16238339]
82. (a) Bucherer HT, Brandt W. J. Prakt. Chem 1934;140:129–150. (b) Bucherer HT, Steiner W. J. Prakt. Chem 1934;140:291–316. (c) Ware E. Chem. Rev 1950;46:403–470. (d) Rousset A, Lasperas M, Taillades J, Commeyras A. Tetrahedron 1980;36:2649–2661. (e) Sarges R, Goldstein SW, Welch WM, Swindell AC, Siegel TW, Beyerpp TA. J. Med. Chem 1990;33:1859–1865. [PubMed: 2113948] For recent applications, see: (f) Pesquet A, Daïch A, Van Hijfte L. J. Org. Chem 2006;71:5303–5311.

[PubMed: 16808520] (g) Averina EB, Yashin NV, Grishin YK, Kuznetsova TS, Zefirov NS. Synthesis 2006:880–884.

83. (a) Nguyen Van Nhien A, Ducatel H, Len C, Postel D. Tetrahedron Lett 2002;43:3805–3808. (b) Postel D, Nguyen Van Nhien A, Villa P, Ronco G. Tetrahedron Lett 2001;42:1499–1502.
84. Conti P, Pinto A, Roda G, Tamborini L, Arosio D, De Micheli C. Synthesis 2007:2145–2148.
85. For the synthesis of LY354740, see: Ohfune Y, Demura T, Iwama S, Matsuda H, Namba K, Shimamoto K, Shinada T. Tetrahedron Lett 2003;44:5431–5434. (b) Monn JA, Valli MJ, Massey SM, Hansen MM, Kress TJ, Wepsiec JP, Harkness AR, Grutsch JL, Writht RA, Johnson BG, Andis SL, Kingston A, Tomlinson R, Lewis R, Griffey KR, Tizzano JP, Schoepp DD. J. Med. Chem 1999;42:1027–1040. [PubMed: 10090786] (c) Monn JA, Valli MJ, Massey SM, Writht RA, Salhoff CR, Johnson BG, Howe T, Alt CA, Rhodes GA, Robey RL, Griffey KR, Tizzano JP, Kallman MJ, Helton DR, Schoepp DD. J. Med. Chem 1997;40:528–537. [PubMed: 9046344] (d) Ohfune Y, Demura T, Iwama S, Matsuda H, Namba K, Shimamoto K, Shinada T. Tetrahedron Lett 2003;44:5431–5434.
86. Gereau, RW.; Swanson, GT., editors. The Glutamate Receptors. Portland, OR: Humana Press Inc.; 2008.
87. (a) Fennell JW, Semo MJ, Wirth DD, Vaid RK. Synthesis 2006:2659–2664. (b) Bueno AB, Collado I, de Dios A, Domínguez C, Martín JA, Martín LM, Martínez-Grau MA, Montero C, Pedregal C, Catlow J, Coffey DS, Clay MP, Dantzig AH, Lindstrom T, Monn JA, Jiang H, Shoepp DD, Stratford RE, Tabas LB, Tizzano JP, Wright RA, Herin MF. J. Med. Chem 2005;48:5305–5320. [PubMed: 16078848] (c) Coffey DS, Hawk MK, Pedersen SW, Vaid RK. Tetrahedron Lett 2005;46:7299–7302.
88. Dominguez C, Prieto L, Valli MJ, Massey SM, Bures M, Wright RA, Johnson BG, Andis SL, Kingston A, Schoepp DD, Monn JA. J. Med. Chem 2005;48:3605–3612. [PubMed: 15887967]
89. For the synthesis of **52**, see: Monn JA, Valli MJ, Massey SM, Wright RA, Salhoff CR, Johnson BG, Howe T, Alt CA, Rhodes GA, Robey RL, Griffey KR, Tizzano JP, Kallan MJ, Helton DR, Schoepp DD. J. Med. Chem 1997;40:528–537. [PubMed: 9046344]
90. Lee W, Miller MJ. J. Org. Chem 2004;69:4516–4519. [PubMed: 15202910]
91. For the cyclopropanation using sulfonium ylides, see: (a) Zhang F, Moher ED, Zhang TY. Tetrahedron Lett 2007;48:3277–3279. (b) Aggarwal VK, Grange E. Chem. Eur. J 2006;12:568–575. (c) Domínguez C, Ezquerra J, Prieto L, Espada M, Pedregal C. Tetrahedron: Asymmetry 1997;8:511–514.
92. Bessières B, Schoenfelder A, Verrat C, Mann A, Ornstein P, Pedregal C. Tetrahedron Lett 2002;43:7659–7662.
93. (a) Sibille P, López S, Brabet I, Valenti O, Oueslati N, Gaven F, Goudet C, Bertrand H-O, Neyton J, Marino MJ, Amalric M, Pin J-P, Acher FC. J. Med. Chem 2007;50:3585–3595. [PubMed: 17602546] (b) Reyes-Rangel G, Marañon V, Avila-Ortiz CG, Anaya de Parrodi C, Quintero L, Juaristi E. Tetrahedron 2006;62:8404–8409. (c) Fernández MC, Díaz A, Guillín JJ, Blanco O, Ruiz M, Ojea V. J. Org. Chem 2006;71:6958–6974. [PubMed: 16930050] and references therein.(d) Fernández MC, Quintela JM, Ruiz M, Ojea V. Tetrahedron: Asymmetry 2002;13:233–237. (e) Jiao X, Chen W, Hu B. Synth. Commun 1992;22:1179–1186.
94. Tan L, Yasuda N, Yoshikawa N, Hartner FW, Eng KK, Leonard WR, Tsay F-R, Volante RP, Tillyer RD. J. Org. Chem 2005;70:8027–8034. [PubMed: 16277324]
95. Nakazato A, Sakagami K, Yasuhara A, Ohta H, Yoshikawa R, Itoh M, Nakamura M, Chaki S. J. Med. Chem 2004;47:4570–4587. [PubMed: 15317467]
96. (a) Yasuhara A, Sakagami K, Yoshikawa R, Chaki S, Nakamura M, Nakazato A. Bioorg. Med. Chem 2006;14:3405–3420. [PubMed: 16431115] (b) Yasuhara A, Nakamura M, Sakagami K, Shimazaki T, Yoshikawa R, Chaki S, Ohta H, Nakazato A. Bioorg. Med. Chem 2006;14:4193–4207. [PubMed: 16487713]
97. (a) Gololobov YG, Kasukhin LF. Tetrahedron 1992;48:1353–1406. (b) Tian WQ, Wang YA. J. Org. Chem 2004;69:4299–4308. [PubMed: 15202883] and references therein.
98. Woltering TJ, Adam G, Huguenin P, Wichmann J, Kolczewski S, Gatti S, Bourson A, Kew JNC, Richards G, Kemp JA, Mutel V, Knoflach F. ChemMedChem 2008;3:323–335. [PubMed: 18058780]
99. Martins FJC, Viljoen AM, Kruger HG, Fourie L, Roscher J, Joubert AJ, Wessels PL. Tetrahedron 2001;57:1601–1607.

100. Fondekar KP, Volk F-J, Frahm AW. Tetrahedron: Asymmetry 1999;10:727–735.
101. Fondekar KP, Volk F-J, Khaliq-uz-Zaman SM, Bisel P, Frahm AW. Tetrahedron: Asymmetry 2002;13:2241–2249.
102. Bisel P, Fondekar KP, Volk F-J, Frahm AW. Tetrahedron 2004;60:10541–10545.
103. For the synthesis of **103**, see: Pellicciari R, Natalini B, Luneia R, Marinozzi M, Roberti M, Rosato GC, Sadeghpour BM, Synyder JP, Monahan JB, Moroni F. Med. Chem. Res 1992;2:491–496.
104. Warmuth R, Munsch TE, Stalker RA, Li B, Beatty A. Tetrahedron 2001;57:6383–6397.
105. Gupta S, Das BC, Schafmeister CE. Org. Lett 2005;7:2861–2864. [PubMed: 15987155]
106. Stalker RA, Munsch TE, Tran JD, Nie X, Warmuth R, Beatty A, Aakeröy CB. Tetrahedron 2002;58:4837–4849.
107. Ito H, Saito A, Kakuuchi A, Taguchi T. Tetrahedron 1999;55:12741–12750.
108. (a) Shinada T, Kawakami T, Sakai H, Matsuda H, Omezawa T, Kawasaki M, Namba K, Ohfune Y. Bull. Chem. Soc. Jpn 2006;79:768–774. (b) Namba K, Kawasaki M, Takada I, Iwama S, Izumida M, Shinada T, Ohfune Y. Tetrahedron Lett 2001;42:3733–3736.
109. For reviews, see: Ohfune Y, Shinada T. Eur. J. Org. Chem 2005:5127–5143. and references therein. (b) ref. [65b].
110. Reviews: (a) Janey JM. Angew. Chem., Int. Ed 2005;44:4292–4300. (b) Erdik E. Tetrahedron 2004;60:8747–8782. (c) Greck C, Drouillat B, Thomassiang C. Eur. J. Org. Chem 2004:1377–1385. (d) Genet, J-P.; Greck, C.; Lavergne, CD. Modern Amination Methods. Ricci, A., editor. Weinheim: Wiley-VCH; 2000. ch. 3 (e) Greck C, Genet J-P. Synlett 1997;7:741–748. (f) Krohn, K. Organic Synthesis Highlights. Weinheim: VCH; 1991. p. 45-53.
111. Felice E, Fioravanti S, Pellacani L, Tardella PA. Tetrahedron Lett 1999;40:4413–4416.
112. Saaby S, Bella M, Jørgensen KA. J. Am. Chem. Soc 2004;126:8120–8121. [PubMed: 15225045]
113. Xu X, Yabuta T, Yuan P, Takemoto Y. Synlett 2006:137–140.
114. Pihko PM, Pohjakallio A. Synlett 2004:2115–2118.
115. Terada M, Nakano M, Ube H. J. Am. Chem. Soc 2006;128:16044–16045. [PubMed: 17165751]
116. Kang YK, Kim DY. Tetrahedron Lett 2006;47:4565–4568.
117. Comelles J, Pericás A, Moreno-Mañas M, Vallribera A, Drudis-Solé G, Lledós A, Parella T, Roglans A, Santiago García-Granda S, Roces-Fernández L. J. Org. Chem 2007;72:2077–2087. [PubMed: 17315933]
118. For recent reviews, see: (a) Chem. Rev 2007;107 special issue on organocatalysis. (b) Enders D, Grondal C, Hüttl MRM. Angew. Chem., Int. Ed 2007;46:1570–1581. (c) Gaunt MJ, Johansson CCC, McNally A, Vo NT. Drug Discovery Today 2007;12:8–27. [PubMed: 17198969] (d) Acc. Chem. Res 2004;37 special issue on organocatalysis. (e) Dalko PI, Moisan L. Angew. Chem., Int. Ed 2004;43:5138–5175. (f) Dalko, PI., editor. Enantioselective Organocatalysis: Reactions and Experimental Procedures. New York: Wiley-VCH; 2007. (g) Berkessel, A.; Gröger, H., editors. Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis. New York: Wiley-VCH; 2005.
119. Suri JT, Steiner DD, Barbas CF III. Org. Lett 2005;7:3885–3888. [PubMed: 16119923]
120. Mashiko T, Hara K, Tanaka D, Fujiwara Y, Kumagai N, Shibasaki M. J. Am. Chem. Soc 2007;129:11342–11343. [PubMed: 17722933]
121. Mashiko T, Kumagai N, Shibasaki M. Org. Lett 2008;10:2725–2728. [PubMed: 18522392]
122. (a) Giannoukakis N. Expert Opin. Invest. Drugs 2008;12:575–581. (b) Kurono M, Fujii A, Murata M, Fujitani B, Negoro T. Biochem. Pharmacol 2006;71:338–353. [PubMed: 16324683] (c) Giannoukakis N. Curr. Opin. Invest. Drugs 2006;7:916–923. (d) Negoro T, Murata M, Ueda S, Fujitani B, Ono Y, Kuromiya A, Suzuki K, Matsumoto J-I. J. Med. Chem 1998;41:4118–4129. [PubMed: 9767647] (e) Ishii A, Kotani T, Nagaki Y, Shibayama Y, Toyomaki Y, Okukada N, Ienaga K, Okamoto K. J. Med. Chem 1996;39:1924–1927. [PubMed: 8627616] (f) Lee YS, Pearlstein R, Kador PF. J. Med. Chem 1994;37:787–792. [PubMed: 8145228] (g) Kador PF, Kinoshita JH, Sharpless NE. J. Med. Chem 1985;28:841–849. [PubMed: 3925146]
123. (a) Satoh T, Hirano M, Kuroiwa A, Kaneko Y. Tetrahedron 2006;62:9268–9279. (b) Satoh T, Hirano M, Kuroiwa A. Tetrahedron Lett 2005;46:2659–2662.
124. Katoh M, Hisa C, Honda T. Tetrahedron Lett 2007;48:4691–4694.

125. (a) Domínguez C, Ezquerra J, Baker SR, Borrelly S, Prieto L, Espada M, Pedregal C. Tetrahedron Lett 1998;39:9305–9308. (b) Corey EJ, Link JO. J. Am. Chem. Soc 1992;114:1906–1908.
126. For the transformation of proline derivatives into δ-lactams, see: (a) Katoh M, Inoue H, Suzuki A, Honda T. Synlett 2005:2820–2822. (b) Katoh M, Mizutani H, Honda T. Tetrahedron Lett 2005;46:5161–5163. (c) Honda T, Takahashi R, Namiki H. J. Org. Chem 2005;70:499–504. [PubMed: 15651792] (d) Katoh M, Matsune R, Nagase H, Honda T. Tetrahedron Lett 2004;45:6221–6223.
127. Achatz O, Grandl A, Wanner KT. Eur. J. Org. Chem 1999:1967–1978.
128. Koch C-J, Šimonyiová S, Pabel J, Kärtner A, Polborn K, Wanner KT. Eur. J. Org. Chem 2003:1244–1263.
129. (a) Mitsunobu O. Synthesis 1981:1–28. (b) Castro BR. Org. React 1983;29:1–162. (c) Hughess DL. Org. React 1992;42:335–356. (d) Hughess DL. Org. Prep. Proced. Int 1996;28:127–164. (e) Dodge JA, Jones SA. Rec. Res. Dev. Org. Chem 1997;1:273–283. (f) Dembinski R. Eur. J. Org. Chem 2004:2763–2772. (g) Dandapani S, Curran DP. Tetrahedron 2002;58:3855–3864. (h) Lipshutz BH, Chung DW, Rich B, Corral R. Org. Lett 2006;8:5069–5072. [PubMed: 17048845]
130. Sibille P, López S, Brabet I, Valenti O, Oueslati N, Gaven F, Goudet C, Bertrand H-O, Neyton J, Marino MJ, Almalric M, Pin J-P, Acher FC. J. Med. Chem 2007;50:3585–3595. [PubMed: 17602546]
131. For the synthesis of **180** and **185**, see: (a) Burgess K, Ho K-K. Tetrahedron Lett 1992;33:5677–5680. (b) Burgess K, Ho K-K. J. Org. Chem 1992;57:5931–5936.
132. For the synthesis of racemic **184** and **186**, see: Johnson RL, Rao KSSP. Bioorg. Med. Chem. Lett 2005;15:57–60. [PubMed: 15582410]
133. Bhattacharya AK, Thyagarajan G. Chem. Rev 1981;81:415–430.
134. Debache A, Collet S, Bauchat P, Danion D, Euzenat L, Hercouet A, Carboni B. Tetrahedron: Asymmetry 2001;12:761–764.
135. Fox ME, Lennon IC, Farina V. Tetrahedron Lett 2007;48:945–948.
136. For the epimerization of (1*R*,2*S*)-*N*-Boc-dehydrocoronamic acid methyl ester catalyzed by ruthenium carbenes, see: Zeng X, Wei X, Farina V, Napolitano E, Xu Y, Zhang L, Haddad N, Yee NK, Grinberg N, Shen S, Senanayake CH. J. Org. Chem 2006;71:8864–8875. [PubMed: 17081017]
137. (a) Katagiri T, Irie M, Uneyama K. Org. Lett 2000;2:2423–2425. [PubMed: 10956512] (b) Katagiri T, Uneyama K. Chirality 2003;15:4–9. [PubMed: 12467035]
138. (a) Wallis ES, Lane JF. Org. React 1946:267–306. (b) Gogoi P, Konwar D. Tetrahedron Lett 2007;48:531–533. and references therein.
139. Donkor IO, Zheng X, Han J, Miller DD. Chirality 2000;12:551–557. [PubMed: 10861954]
140. (a) Lebel H, Leogane O. Org. Lett 2006;8:5717–5720. [PubMed: 17134255] (b) Lebel H, Leogane O. Org. Lett 2005;7:4107–4110. [PubMed: 16146363] (c) Marinescu L, Thinggaard J, Thomsen IB, Bols M. J. Org. Chem 2003;68:9453–9455. [PubMed: 14629171] (d) Scriven EF, Turnbull K. Chem. Rev 1988;88:297–368. (e) Smith PAS. Org. React 1946;3:337–449.
141. Frick JA, Klassen JB, Rapoport H. Synthesis 2005:1751–1756.
142. Chang HS, Bergmeier SC, Frick JA, Bathe A, Rapoport H. J. Org. Chem 1994;59:5336–5342.
143. (a) Chinchilla R, Falvello LR, Galindo N, Nájera C. J. Org. Chem 2000;65:3034–3041. [PubMed: 10814194] (b) Abellán T, Chinchilla R, Galindo N, Guillena G, Nájera C, Sansano JM. Eur. J. Org. Chem 2000:2689–2697.
144. (a) Abellán T, Balbino M, Nájera C, Sansano JM. Tetrahedron 2001;57:6627–6640. (b) Abellán T, Nájera C, Sansano JM. Tetrahedron: Asymmetry 2000;11:1051–1055. (c) Abellán T, Chinchilla R, Galindo N, Nájera C, Sansano JM. J. Heterocyclic Chem 2000;37:467–479.
145. Buñuel E, Bull SD, Davies SG, Garner AC, Savory ED, Smith AD, Vickers RJ, Watkin DJ. Org. Biomol. Chem 2003;1:2531–2542. [PubMed: 12956073]
146. Papageorgiou CD, Cubillo de Dios MA, Ley SV, Gaunt MJ. Angew. Chem. Int. Ed 2004;43:4641–4644.
147. Badorrey R, Cativiela C, Díaz-de-Villegas MD, Gálvez JA. Tetrahedron: Asymmetry 2000;11:1015–1025.
148. Koch C-J, Höfner G, Polborn K, Wanner KT. Eur. J. Org. Chem 2003:2233–2242.

149. Howarth NM, Wakelin LPG, Walker DM. Tetrahedron Lett 2003;44:695–698.
150. Tanaka M, Anan K, Demizu Y, Kurihara M, Doi M, Suemune H. J. Am. Chem. Soc 2005;127:11570–11571. [PubMed: 16104711]
151. Ma D, Ding K, Tian H, Wang B, Cheng D. Tetrahedron: Asymmetry 2002;13:961–969.
152. Gabaitsekgosi R, Hayes CJ. Tetrahedron Lett 1999;40:7713–7716.
153. Bradley DM, Mapitse R, Thompson NM, Hayes CJ. J. Org. Chem 2002;67:7613–7617. [PubMed: 12398480]
154. Soengas RG, Estévez JC, Estévez RJ. Tetrahedron: Asymmetry 2003;14:3955–3963.
155. For the synthesis of racemic quaternary tetrahydrofuran α-amino acids derivatives, see: Maity P, Zabel M, König B. J. Org. Chem 2007;72:8046–8053. [PubMed: 17877403]
156. Solladié-Cavallo A, Martín-Cabrejas LM, Caravatti G, Lang M. Tetrahedron: Asymmetry 2001;12:967–969.
157. Saaby S, Nakama K, Lie MA, Hazell RG, Jørgensen KA. Chem. Eur. J 2003;9:6145–6154.
158. Zhuang W, Saaby S, Jørgensen KA. Angew. Chem. Int. Ed 2004;43:4476–4478.
159. For recent reviews, see: Schrodi Y, Pederson RL. Aldrichimca Acta 2007;40:45–52. (b) Adv. Synth. Catal 2007;349:1–268. Olefin Metathesis Special Issue. (c) Chauvin Y. Angew. Chem., Int. Ed 2006;45:3740–3747. (d) Schrock RR. Angew. Chem. Int. Ed 2006;45:3748–3759. (e) Grubbs RH. Angew. Chem. Int. Ed 2006;45:3760–3765. (f) Nicolaou KC, Bulger PG, Sarlah D. Angew. Chem. Int. Ed 2005;44:4490–4527. (g) Grubbs RH. Tetrahedron 2004;60:7117–7140.(h) Grubbs, RH., editor. Handbook of Metathesis. Vol. Vols 1–3. Weinheim: Wiley-VCH; 2003. (i) Connon SJ, Bhechert S. Angew. Chem. Int. Ed 2003;42:1900–1923. (j) Schrock RR, Hoveyda AH. Angew. Chem. Int. Ed 2003;42:4592–4633. (k) Trnka TM, Grubbs RH. Acc. Chem. Res 2001;34:18–29. [PubMed: 11170353] (l) Buchmeiser MR. Chem. Rev 2000;100:1565–1604. [PubMed: 11749276] (m) Fürstner A. Angew. Chem. Int. Ed 2000;39:3012–3043.
160. (a) Krikstolaitytè S, Hammer K, Undheim K. Tetrahedron Lett 1998;39:7595–7598. (b) Hammer K, Rømming C, Undheim K. Tetrahedron 1998;54:10837–10850. (c) Hammer K, Undheim K. Tetrahedron: Asymmetry 1998;9:2359–2368.
161. Hammer K, Wang J, Falck-Pedersen ML, Rømming C, Undheim K. J. Chem. Soc., Perkin Trans 1 2000:1691–1695.
162. Jam F, Tullberg M, Luthman K, Grøtli M. Tetrahedron 2007;63:9881–9889.
163. Undheim K, Efskind J. Tetrahedron 2000;56:4847–4857.
164. Efskind J, Römming C, Undheim K. J. Chem. Soc., Perkin Trans 1 2001:2697–2703.
165. Hoven GB, Efskind J, Rømming C, Undheim K. J. Org. Chem 2002;67:2459–2463. [PubMed: 11950288]
166. Efskind J, Undheim K. Tetrahedron Lett 2003;44:2837–2839.
167. Undheim K, Efskind J, Hoven GB. Pure Appl. Chem 2003;75:279–292.
168. Andrei M, Efskind J, Undheim K. Tetrahedron 2007;63:4347–4355.
169. Trost BM, Dogra K. J. Am. Chem. Soc 2002;124:7256–7257. [PubMed: 12071719]
170. (a) Fustero S, Sánchez-Roselló M, Rodrigo V, del Pozo C, Sanz-Cervera JF, Simón-Fuentes A. Org. Lett 2006;8:4129–4132. [PubMed: 16928091] (b) Fustero S, Sánchez-Roselló M, Rodrigo V, Sanz-Cervera JF, Piera J, Simón-Fuentes A, del Pozo C. Chem. Eur. J 2008;14:7019–7029.
171. Krikstolaityté S, Sackus A, Rømming C, Undheim K. Tetrahedron: Asymmetry 2001;12:393–398.
172. (a) Møller B, Undheim K. Eur. J. Org. Chem 2003:332–336. (b) Efskind J, Rømming C, Undheim K. J. Chem. Soc., Perkin Trans. 1 1999:1677–1684.
173. Andrei M, Undheim K. Tetrahedron: Asymmetry 2004;15:53–63.
174. For the non-asymmetric cyclopropanation of α-nitro-α-diazocarbonyl derivatives, see: Wurz RP, Charette AB. J. Org. Chem 2004;69:1262–1269. [PubMed: 14961679] Charette AB, Wurz RP, Ollivier T. Helv. Chim. Acta 2002;85:4468–4484.
175. For review on the chiral catalyst for asymmetric transformations of vinyl- and aryldiazoacetates, see: Davies HML. Eur. J. Org. Chem 1999:2459–2469.

176. (a) Charette AB, Wurz RP. J. Mol. Catal. A: Chem 2003;196:83–91. For cobalt-catalyzed asymmetric cyclopropanation of alkenes with α-nitrodiazoacetates, see: (b) Zhu S, Perman JA, Zhang XP. Angew. Chem. Int. Ed 2008;47:1–5.
177. Moreau B, Charette AB. J. Am. Chem. Soc 2005;127:18014–18015. [PubMed: 16366547]
178. Barluenga J, Aznar F, Gutiérrez I, García-Granda S, Llorca-Baragaño MA. Org. Lett 2002;4:4273–4276. [PubMed: 12443076]
179. Clerici F, Gelmi ML, Pocar D, Pilati T. Tetrahedron: Asymmetry 2001;12:2663–2669.
180. For the origin of the π-facial diastereoselection of this reaction, see: Muray E, Alvarez-Larena A, Piniella JF, Branchadell V, Ortuño RM. J. Org. Chem 2000;65:388–396. [PubMed: 10813946]
181. Rifé J, Ortuño RM. Tetrahedron: Asymmetry 1999;10:4245–4260.
182. Illescas B, Rifé J, Ortuño RM, Martín N. J. Org. Chem 2000;65:6246–6248. [PubMed: 10987969]
183. Moglioni AG, García-Expósito E, Alvarez-Larena A, Branchadell V, Moltrasio GY, Ortuño RM. Tetrahedron: Asymmetry 2000;11:4903–4914.
184. Avenoza A, Busto JH, Canal N, Peregrina JM, Pérez-Fernández M. Org. Lett 2005;7:3597–3600. [PubMed: 16048351]
185. For the synthesis of non-chiral 1-aminocyclobutanecarboxylic acid 2-substituted via [2+2] cycloaddition of 2-aminoacrylates, see: Avenoza A, Busto JH, Mata L, Peregrina JM, Pérez-Fernández M. Synthesis 2008:743–746. (b) Jiménez-Osés G, Corzana F, Busto JH, Pérez-Fernández M, Peregrina JM, Avenoza A. J. Org. Chem 2006;71:1869–1878. [PubMed: 16496971] (c) Avenoza A, Busto JH, Canal N, Peregrina JM. J. Org. Chem 2005;70:330–333. [PubMed: 15624942] (d) Avenoza A, Busto JH, Peregrina JM, Pérez-Fernández M. Tetrahedron 2005;61:4165–4172. (e) Avenoza A, Busto JH, Canal N, Peregrina JM. Chem. Commun 2003:1376–1377.
186. Tanaka K, Takahashi M, Imase H, Osaka T, Noguchi K, Hirano M. Tetrahedron 2008;64:6289–6293.
187. Ung AT, Schafer K, Lindsay KB, Pyne SG, Amornraksa K, Wouters R, Van der Linden I, Biesmans I, Lesage ASJ, Skelton BW, White AH. J. Org. Chem 2002;67:227–233. [PubMed: 11777464]
188. Chinchilla R, Falvello LR, Galindo N, Nájera C. Tetrahedron: Asymmetry 1999;10:821–825.
189. Burkett BA, Chai CLL. Tetrahedron Lett 2001;42:2239–2242.
190. Abbiati G, Clerici F, Gelmi ML, Gambini A, Pilati T. J. Org. Chem 2001;66:6299–6304. [PubMed: 11559178]
191. For the Diels-Alder cycloaddition of **424** with cyclopentadiene, see: Clerici F, Gelmi ML, Pellegrino S, Pilati T. J. Org. Chem 2003;68:5286–5291. [PubMed: 12816490] (b) Clerici F, Gelmi ML, Gambini A. J. Org. Chem 2001;66:4941–4944. [PubMed: 11442431] (c) Clerici F, Gelmi ML, Gambini A. J. Org. Chem 2000;65:6138–6141. [PubMed: 10987950]
192. Caputo F, Clerici F, Gelmi ML, Pellegrino S, Pilati T. Tetrahedron: Asymmetry 2006;17:61–67.
193. Caputo F, Clerici F, Gelmi ML, Pellegrino S, Pocar D. Tetrahedron: Asymmetry 2006;17:1430–1436.
194. Gelmi ML, Caputo F, Clerici F, Pellegrino S, Gianaccini G, Betti L, Fabbrini L, Schmid L, Palego L, Lucacchini A. Bioorg. Med. Chem 2007;15:7581–7589. [PubMed: 17900912]
195. For the application of diol *exo*-**442** in the synthesis of cyclopentylglycine derivatives, see: Pellegrino S, Clerici F, Gelmi ML. Tetrahedron 2008;64:5657–5665.
196. Caputo F, Cattaneo C, Clerici F, Gelmi ML, Pellegrino S. J. Org. Chem 2006;71:8467–8472. [PubMed: 17064021]
197. Gelmi ML, Cattaneo C, Pellegrino S, Clerici F, Montali M, Martini C. J. Org. Chem 2007;72:9811–9814. [PubMed: 17988151]
198. Williams LJ, Jagadish B, Lansdown MG, Carducci MD, Mash EA. Tetrahedron 1999;55:14301–14322.
199. Monn JA, Valli MJ, Massey SM, Hansen MM, Kress TJ, Wepsiec JP, Harkness AR, Grutsch JL Jr, Wright RA, Johnson BG, Andis SL, Kingston A, Tomlinson R, Lewis R, Griffey KR, Tizzano JP, Schoepp DD. J. Med. Chem 1999;42:1027–1040. [PubMed: 10090786]
200. Monn JA, Massey SM, Valli MJ, Henry SS, Stephenson GA, Bures M, Hérin M, Catlow J, Giera D, Wright RA, Johnson BG, Andis SL, Kingston A, Schoepp DD. J. Med. Chem 2007;50:233–240. [PubMed: 17228865]

201. Oishi S, Kang S-U, Liu H, Zhang M, Yang D, Deschamps JR, Burke TR Jr. Tetrahedron 2004;60:2971–2977.
202. Avenoza A, Barriobero JI, Cativiela C, Fernández-Recio MA, Peregrina JM, Rodríguez F. Tetrahedron 2001;57:2745–2755.
203. Mazaleyrat J-P, Boutboul A, Lebars Y, Gaucher A, Wakselman M. Tetrahedron: Asymmetry 1998;9:2701–2713.
204. Ridvan L, Buděšínsky M, Tichý M, Maloň P, Závada J, Podlaha J, Císařová I. Tetrahedron 1999;55:12331–12348.
205. (a) Mazaleyrat J-P, Wright K, Azzini M-V, Gaucher A, Wakselman M. Tetrahedron Lett 2003;44:1741–1745. (b) Wright K, Lohier J-F, Wakselman M, Mazaleyrat J-P, Formaggio F, Peggion C, De Zotti M, Toniolo C. Tetrahedron 2008;64:2307–2320.
206. For the application of derivatives of (*R*)-**502** in the assignment of the absolute configuration of β-amino acids, see: Dutot L, Wright K, Gaucher A, Wakselman M, Mazaleyrat J-P, De Zotti M, Peggion C, Formaggio F, Toniolo C. J. Am. Chem. Soc 2008;130:5986–5992. [PubMed: 18399631]
207. Hodgson DM, Thompson AJ, Wadman S, Keats CJ. Tetrahedron 1999;55:10815–10834.
208. Varie DL, Beck C, Borders SK, Brady MD, Cronin JS, Ditsworth TK, Hay DA, Hoard DW, Hoying RC, Linder RJ, Miller RD, Moher ED, Remacle JR, Rieck JA III. Org. Proc. Res. Develop 2007;11:546–559.
209. Salgado A, Huybrechts T, Eeckhaut A, Van der Eycken J, Szakonyi Z, Fülöp F, Tkachev A, De Kimpe N. Tetrahedron 2001;57:2781–2786.
210. Beaulieu PL, Gillard J, Bailey MD, Boucher C, Duceppe J-S, Simoneau B, Wang X-J, Zhang L, Grozinger K, Houpis I, Farina V, Heimroth H, Krueger T, Schnaubelt J. J. Org. Chem 2005;70:5869–5879. [PubMed: 16018680]
211. For the epimerization of **515**, see: Zeng X, Wei X, Farina V, Napolitano E, Xu Y, Zhang L, Haddad N, Yee NK, Grinberg N, Shen S, Senanayake CH. J. Org. Chem 2006;71:8864–8875. [PubMed: 17081017]
212. For selected examples, see: Shu C, Zeng X, Hao M-H, Wei X, Yee NK, Busacca CA, Han Z, Farina V, Senanayake CH. Org. Lett 2008;10:1303–1306. [PubMed: 18293994] (b) Liverton NJ, Holloway MK, McCauley JA, Rudd MT, Butcher JW, Carroll SS, DiMuzio J, Fandozzi C, Gilbert KF, Mao S-S, McIntyre CJ, Nguyen KT, Romano JJ, Sthlhut M, Wan B-L, Olsen DB, Vacca JP. J. Am. Chem. Soc 2008;130:4607–4609. [PubMed: 18338894] (c) Randolph JT, Zhang X, Huang PP, Klein LL, Kurtz KA, Konstantinidis AK, He W, Kati WM, Kempf DJ. Bioorg. Med. Chem. Lett 2008;18:2745–2750. [PubMed: 18375121] (d) Naud J, Lemke C, Goudreau N, Beualieu E, White PD, Llinàs-Brunet M, Forgione P. Bioorg. Med. Chem. Lett 2008;18:3400–3404. [PubMed: 18448339] (e) Poirier M, Aubry N, Boucher C, Ferland J-M, LaPlante S, Tsantrizos YS. J. Org. Chem 2005;70:10765–10773. [PubMed: 16355998]
213. Kirihara M, Kawasaki M, Takuwa T, Kakuda H, Wakikawa T, Takeuchi Y, Kirk KL. Tetrahedron: Asymmetry 2003;14:1753–1761.
214. Roda G, Conti P, De Amici M, He J, Polavarapu PL, De Micheli C. Tetrahedron: Asymmetry 2004;15:3079–3090.
215. For the aplication of quaternary α-amino acids **525** and **528** as ionotropic and metabotropic glutamate receptor subtypes, see: Conti P, De Amici M, Grazioso G, Roda G, Pinto A, Hansen KB, Nielsen B, Madsen U, Bräuner-Osborne H, Egebjerg J, Vestri V, Pellegrini-Giampietro DE, Sibille P, Acher FC, De Micheli C. J. Med. Chem 2005;48:6315–6325. [PubMed: 16190758]
216. (a) Lane JW, Halcomb RL. J. Org. Chem 2003;68:1348–1357. [PubMed: 12585874] (b) Lane JW, Halcomb RL. Tetrahedron 2001;57:6531–6538.
217. Tanaka M, Demizu Y, Nagano M, Hama M, Yoshida Y, Kurihara M, Suemune H. J. Org. Chem 2007;72:7750–7756. [PubMed: 17713957]
218. Jiménez AI, López P, Oliveros L, Cativiela C. Tetrahedron 2001;57:6019–6026.
219. Jiménez AI, López P, Cativiela C. Chirality 2005;17:22–29. [PubMed: 15515045]
220. Lasa M, López P, Cativiela C. Tetrahedron: Asymmetry 2005;16:4022–4033.
221. Cativiela C, Lasa M, López P. Tetrahedron: Asymmetry 2005;16:2613–2623.
222. Natalini B, Marinozzi M, Bade K, Sardella R, Thomsen C, Pellicciari R. Chirality 2004;16:314–317. [PubMed: 15069662]

223. Alías M, Cativiela C, Jiménez AI, López P, Oliveros L, Marraud M. Chirality 2001;13:48–55. [PubMed: 11135415]
224. Avenoza A, París M, Peregrina JM, Alías M, López MP, García JI, Cativiela C. Tetrahedron 2002;58:4899–4905.
225. Cativiela C, López P, Lasa M. Eur. J. Org. Chem 2004:3898–3908.
226. Alías M, Lasa M, López MP, García JI, Cativiela C. Tetrahedron 2005;61:2913–2919.
227. Patwardhan AP, Pulgam VR, Zhang Y, Wulff WD. Angew. Chem. Int. Ed 2005;44:6169–6172.
228. For the synthesis of aziridine-2-carboxylic acids alkyl esters, see: (a) Hansen KB, Finney NS, Jacobsen EN. Angew. Chem., Int. Ed. Engl 1995;34:676–678. (b) Osborn H, Sweeney MIJ. Tetrahedron: Asymmetry 1997;8:1693–1715. (c) Muller P, Fruit C. Chem. Rev 2003;103:2905–2919. [PubMed: 12914485] (d) Bew SP, Hughes DL, Savic V, Soapi KM, Wilson MA. Chem. Commun 2006:3513–3515.
229. Lu Z, Zhang Y, Wulff WD. J. Am. Chem. Soc 2007;129:7185–7194. [PubMed: 17497860]
230. Calaza MI, Cativiela C. Eur. J. Org. Chem 2008:3427–3448.
231. Sommer K, Williams RM. Tetrahedron 2008;64:7106–7111.
232. Chandan N, Moloney MG. Org. Biomol. Chem 2008;6:3664–3666. [PubMed: 18843394]
233. Kazmaier U, Mues H, Krebs A. Chem. Eur. J 2002;8:1850–1855.
234. Elliott MC, Wood JL, Wordinghan SV. Trends Heterocycl. Chem 2005;10:7395.
235. (a) Seebach D, Naef R. Helv. Chim. Acta 1981;64:2704–2708. (b) Seebach D, Boes M, Naef R, Schweizer WJ. J. Am. Chem. Soc 1983;105:5390–5398. (c) Beck AK, Blank S, Job K, Seebach D. Sommerfeld. Org. Synth 1995;72:62–73.
236. Seebach D, Sting AR, Hoffmann M. Angew. Chem., Int. Ed. Engl 1996;35:2708–2748.
237. For the preparation of α-alkyl prolines from alkylation of (3*S*,7a*R*)-**586**, see: (a) Bittermann H, Gmeiner P. J. Org. Chem 2006;71:97–102. [PubMed: 16388623] (b) Bittermann H, Böckler F, Einsiedel J, Gmeiner P. Chem. Eur. J 2006;12:6315–6322. (c) See also ref. [230]
238. Pisaneschi F, Cordero FM, Lumini M, Brandi A. Synlett 2007:2882–2884.
239. (a) Garner P, Park J-M. J. Org. Chem 1987;52:2361–2364. (b) Garner P, Park J-M. Org. Synth 1992;70:18–28. (c) Marshall JA, Beaudoin S. J. Org. Chem 1996;61:581–586. [PubMed: 11666978]
240. Okue M, Kobayashi H, Shin-ya K, Furihata K, Hayakawa Y, Seto H, Watanabe H, Kitahara T. Tetrahedron Lett 2002;43:857–860.
241. Watanabe H, Okue M, Kobayashi H, Kitahara T. Tetrahedron Lett 2002;43:861–864.
242. Dondoni A, Perrone D. Org. Synth 2000;77:64–77. (b) Ref. [216]
243. Vaswani RG, Chamberlin AR. J. Org. Chem 2008;73:1661–1681. [PubMed: 18225916]
244. Sayago FJ, Calaza MI, Jiménez AI, Cativiela C. Tetrahedron 2008;64:84–91.
245. Alonso DA, Nordin SJM, Andersson PG. Org. Lett 1999;1:1595–1597.
246. Goldspink NJ, Simpkins NS, Beckmann M. Synlett 1999:1292–1294.
247. Hou D-R, Hung S-Y, Hu C-C. Tetrahedron: Asymmetry 2005;16:3858–3864.
248. Balducci D, Grandi A, Porzi G, Sandri S. Tetrahedron: Asymmetry 2005;16:1453–1462.
249. Palomo C, Aizpurua JM, Balentová E, Jiménez A, Oyarbide J, Fratila RM, Miranda JI. Org. Lett 2007;9:101–104. [PubMed: 17192095]
250. Balducci D, Porzi G, Sandri S. Tetrahedron: Asymmetry 2004;15:1085–1093.
251. Ooi T, Takeuchi M, Maruoka K. Synthesis 2001:1716–1718.
252. Andrei M, Efskind J, Viljugrein T, Römming C, Undheim K. Tetrahedron: Asymmetry 2004;15:1301–1313.
253. Andrei M, Römming C, Undheim K. Tetrahedron: Asymmetry 2004;15:1359–1370.
254. Buñuel E, Cativiela C, Díaz-de-Villegas MD. Tetrahedron: Asymmetry 1996;7:1431–1436.
255. Buñuel E, Gil AM, Díaz-de-Villegas MD, Cativiela C. Tetrahedron 2001;57:6417–6427.
256. (a) Corey EJ, Winter RAE. J. Am. Chem. Soc 1963;85:2677–2678. (b) Corey EJ, Carey FA, Winter RAE. J. Am. Chem. Soc 1965;87:934–935. (c) Corey EJ, Hopkins PB. Tetrahedron Lett 1982;23:1979–1982.

257. Gil AM, Buñuel E, Díaz-de-Villegas MD, Cativiela C. Tetrahedron: Asymmetry 2003;14:1479–1488.

258. (a) Gil AM, Orús E, López-Carrillo V, Buñuel E, Cativiela C. Tetrahedron: Asymmetry 2005;16:3115–3123.(b) Gil, AM.; Buñuel, E.; Cativiela, C.; Attanasi, OA.; Spinelli, D. Targets in Heterocyclic Systems. Chemistry and Properties (Volume 8). Cambridge: Royal Society of Chemistry; 2005. p. 56-86.

259. (a) Zhao H, Hsu DC, Carlier PR. Synthesis 2005:1–16. (b) Kawabata T, Fuji K. Top. Stereochem 2003;23:175–205. (c) Kawabata T, Chen J, Suzuki H, Nagae Y, Kinoshita T, Chancharunee S, Fuji K. Org. Lett 2000;2:3883–3885. [PubMed: 11101444] (d) Fuji K, Kawabata T. Chem. Eur. J 1998;4:373–376. (e) Kawabata T, Wirth T, Yahiro K, Suzuki H, Fuji K. J. Am. Chem. Soc 1994;116:10809–10810.

260. Kawabata T, Kawakami S, Majumdar S. J. Am. Chem. Soc 2003;125:13012–13013. [PubMed: 14570459]

261. Kawabata T, Matsuda S, Kawakami S, Monguchi D, Moriyama K. J. Am. Chem. Soc 2006;128:15394–15395. [PubMed: 17132004]

262. Kawabata T, Moriyama K, Kawakami S, Tsubaki K. J. Am. Chem. Soc 2008;130:4153–4157. [PubMed: 18303890]

263. Moriyama K, Sakai H, Kawabata T. Org. Lett 2008;10:3883–3886. [PubMed: 18698782]

264. Kawabata T, Majundar S, Tsubaki K, Monguchi D. Org. Biomol. Chem 2005;3:1609–1611. [PubMed: 15858636]

265. Gardiner J, Abell AD. Tetrahedron Lett 2003;44:4227–4230.

266. Gardiner J, Abell AD. Org. Biomol. Chem 2004;2:2365–2370. [PubMed: 15305220]

267. For the one-pot aza-Darzens reaction of sulfinimines with lithium α-bromoenolates, see: (a) Davis FA, Liang C-H, Liu H. J. Org. Chem 1997;62:3796–3797. (b) Davis FA, Liu H, Zhou P, Fang T, Reddy GV, Zhang Y. J. Org. Chem 1999;64:7559–7567.

268. Davis FA, Deng J, Zhang Y, Haltiwanger RC. Tetrahedron 2002;58:7135–7143.

269. Anelli PL, Beltrami A, Lolli M, Uggeri F. Synth. Commun 1993;23:2639–2645.

270. Davis FA, Zhang Y, Rao A, Zhang Z. Tetrahedron 2001;58:6345–6352.

271. Agbodjan AA, Cooley BE, Copley RCB, Corfield JA, Flanagan RC, Glover BN, Guidetti R, Haigh D, Howes PD, Jackson MM. Matsuoka RT, Medhurst KJ, Millar A, Sharp MJ, Slater MJ, Toczko JF, Xie S. J. Org. Chem 2008;73:3094–3102. [PubMed: 18358046]

272. Tsubogo T, Saito S, Seki K, Yamashita Y, Kobayashi S. J. Am. Chem. Soc 2008;130:13321–13332. [PubMed: 18783222]

273. Nájera C, Retamosa MG, Sansano JM, Cozar A, Cossío FP. Eur. J. Org. Chem 2007:5038–5049.

274. Nájera C, Retamosa MG, Sansano JM. Angew. Chem. Int. Ed 2008;47:6055–6058.

275. For the synthesis of highly substituted conformationally constrained and spiro nitroprolines via Ag (I) catalyzed 1,3-cycloadditions, see: Grigg R, Kilner C, Sarker MAB, Orgaz de la Cierva C, Dondas HA. Tetrahedron 2008;64:8974–8991.

276. Fukuzawa S-I, Oki H. Org. Lett 2008;10:1747–1750. [PubMed: 18373347]

277. López-Pérez A, Adrio J, Carretero JC. J. Am. Chem. Soc 2008;130:10084–10085. [PubMed: 18613686]

278. Matsumura Y, Inoue M, Nakamura Y, Talib IL, Maki T, Onomura O. Tetrahedron Lett 2000;41:4619–4622.

279. Avenoza A, Cativiela C, Busto JH, Fernández-Recio MA, Peregrina JM, Rodríguez F. Tetrahedron 2001;57:545–548.

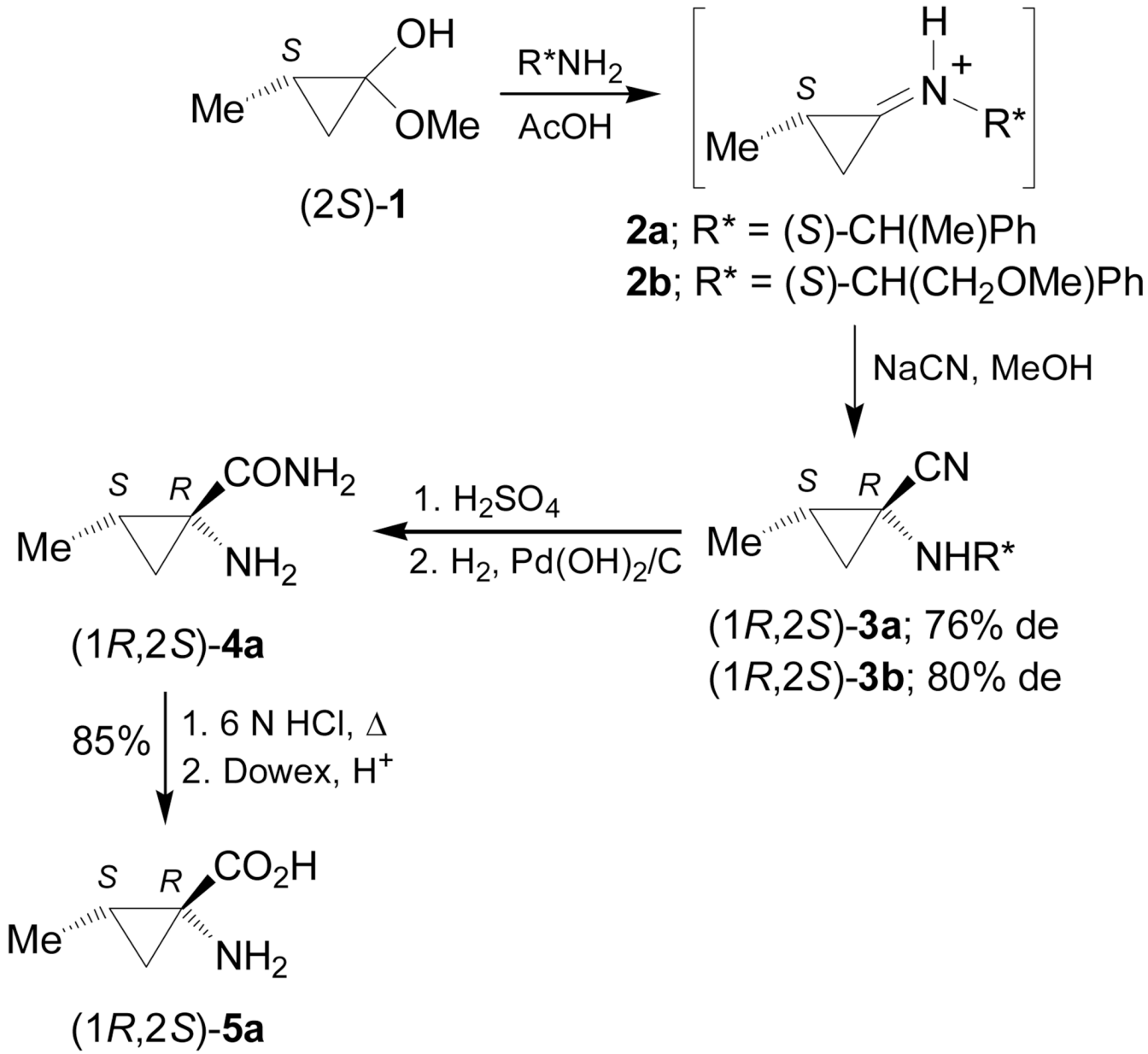
280. Avenoza A, Barriobero JI, Busto JH, Cativiela C, Peregrina JM. Tetrahedron: Asymmetry 2002;13:625–632.

281. Gerona-Navarro G, Bonache MA, Alías M, Pérez-de-Vega MJ, García-López MT, López P, Cativiela C, Gonzalez-Muñiz R. Tetrahedron Lett 2004;45:2193–2196.

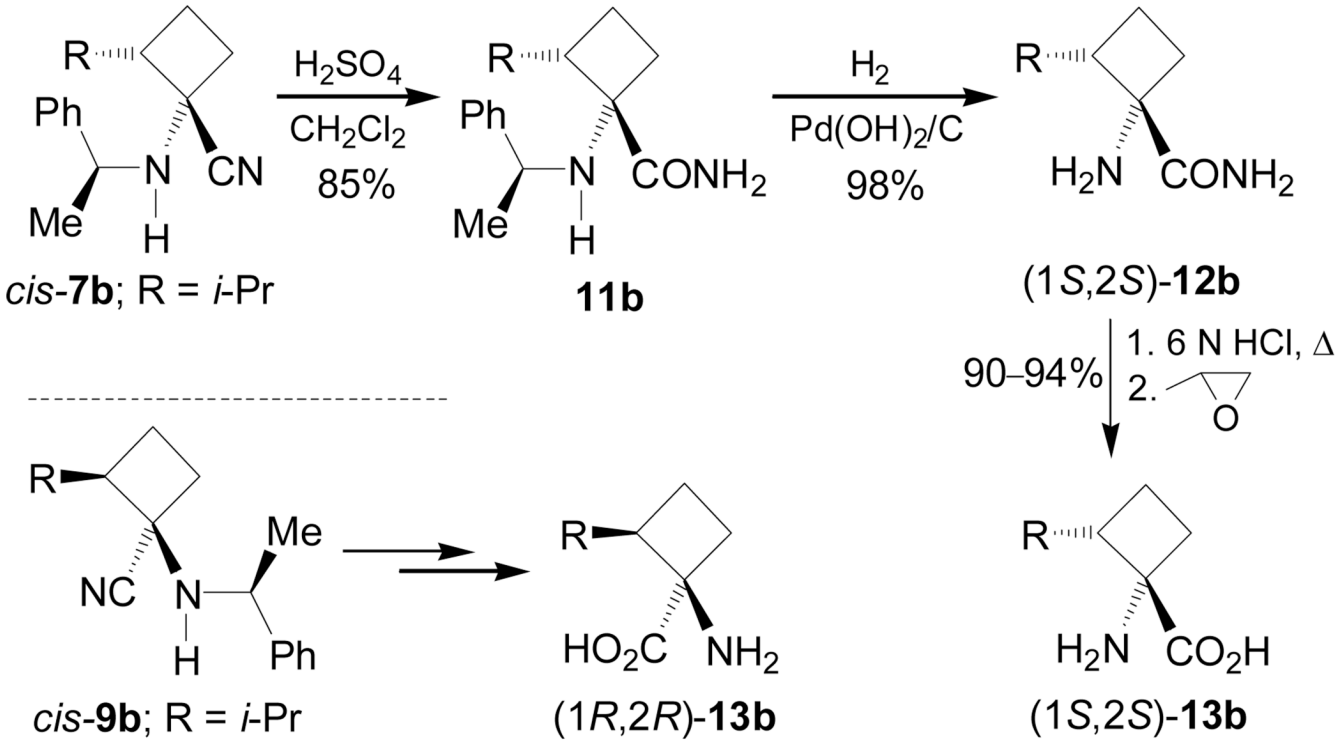
282. (a) Gil AM, Buñuel E, López P, Cativiela C. Tetrahedron: Asymmetry 2004;15:811–819. (b) (a) Gil AM, Buñuel E, Cativiela C. Arkivoc 2007;iv:157–159.

283. Silveira CC, Bernardi CR, Braga AL, Kaufman TS. Tetrahedron Lett 1999;40:4969–4972.

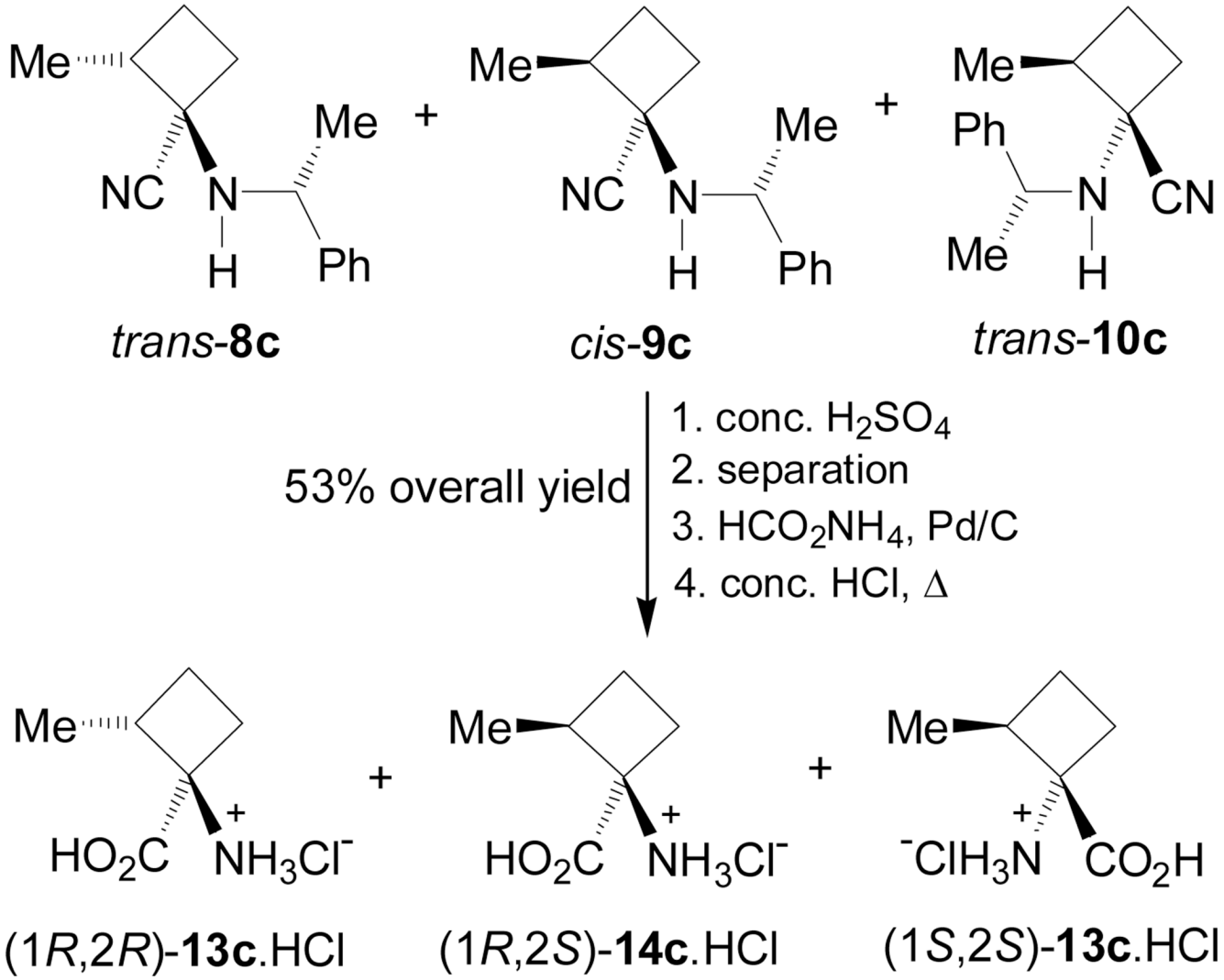
284. Alezra V, Bonin M, Micouin L, Husson H-P. Tetrahedron Lett 2001;42:2111–2113.
285. Kawabata T, Oztürk O, Suzuki H, Fuji K. Synthesis 2003:505–508.
286. Rutjes FPJT, Veerman JJN, Meester WJN, Hiemstra H, Schoemaker HE. Eur. J. Org. Chem 1999:1127–1135.
287. Clayden J, Knowles FE, Menet CJ. Tetrahedron Lett 2003;44:3397–3400.
288. Makosza M, Sulikowski D, Maltsev O. Synlett 2008:1711–1713.



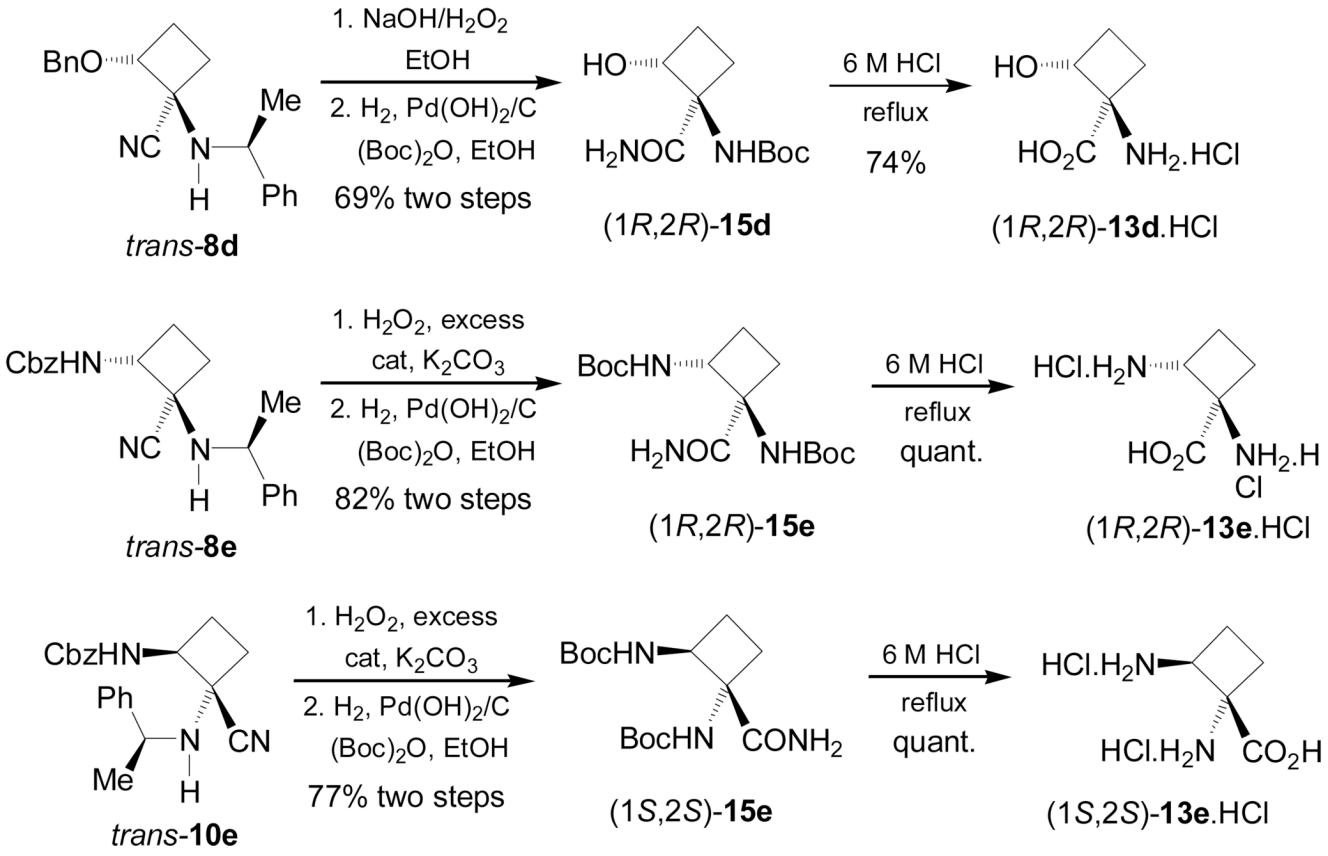
Scheme 1.



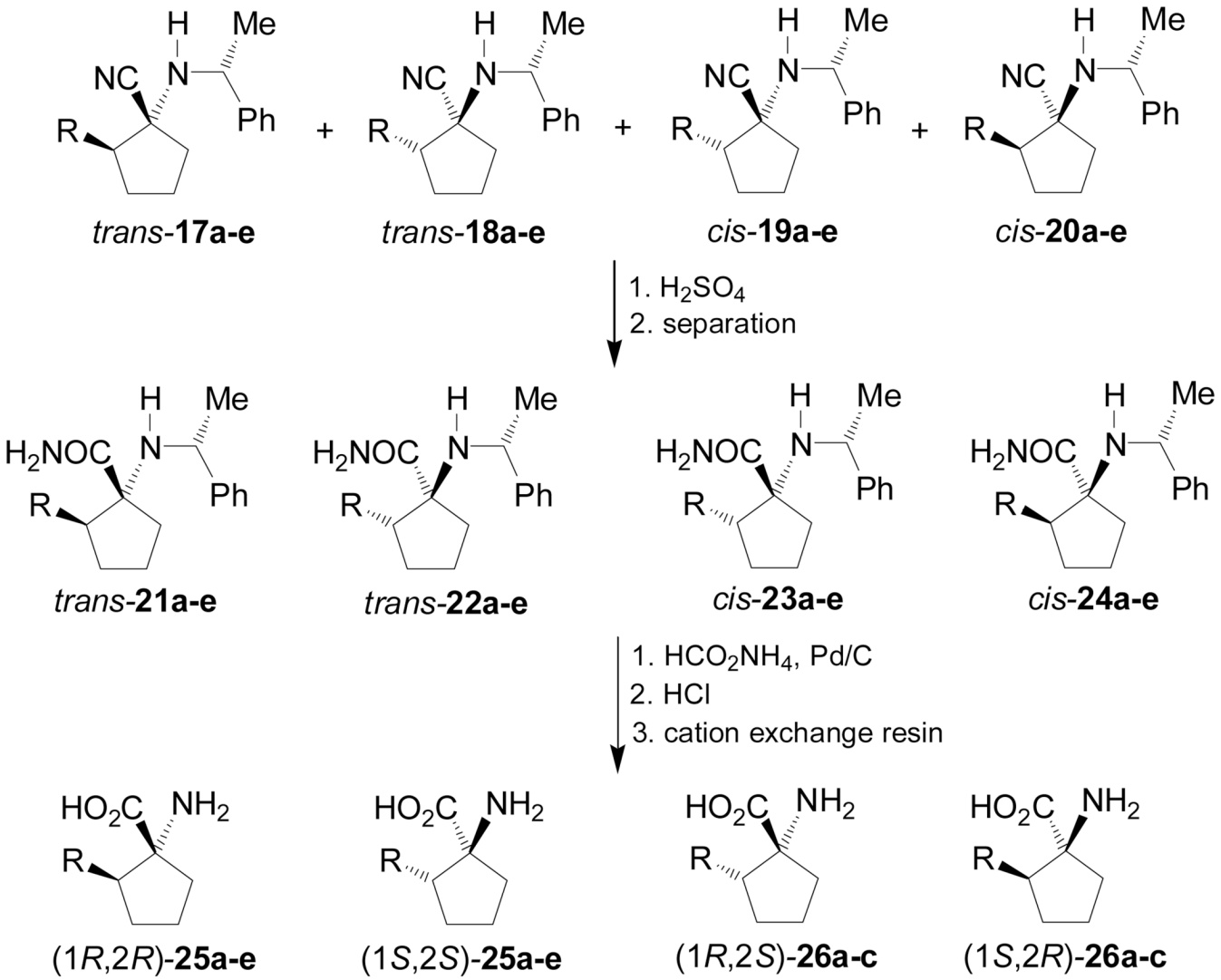
Scheme 2.



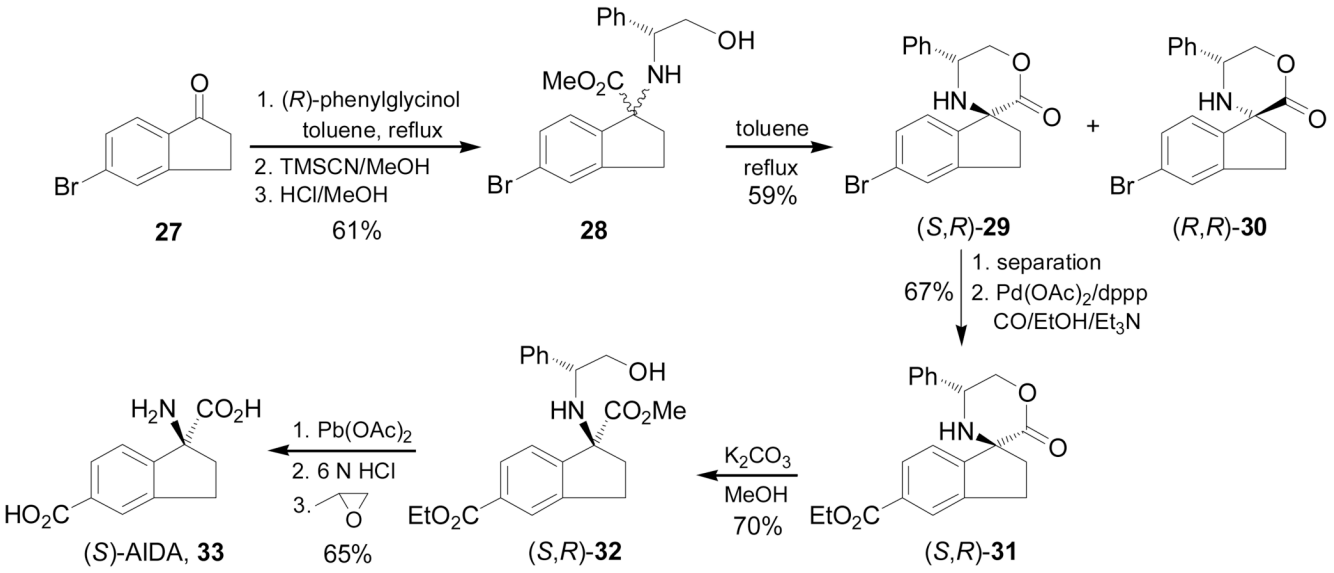
Scheme 3.



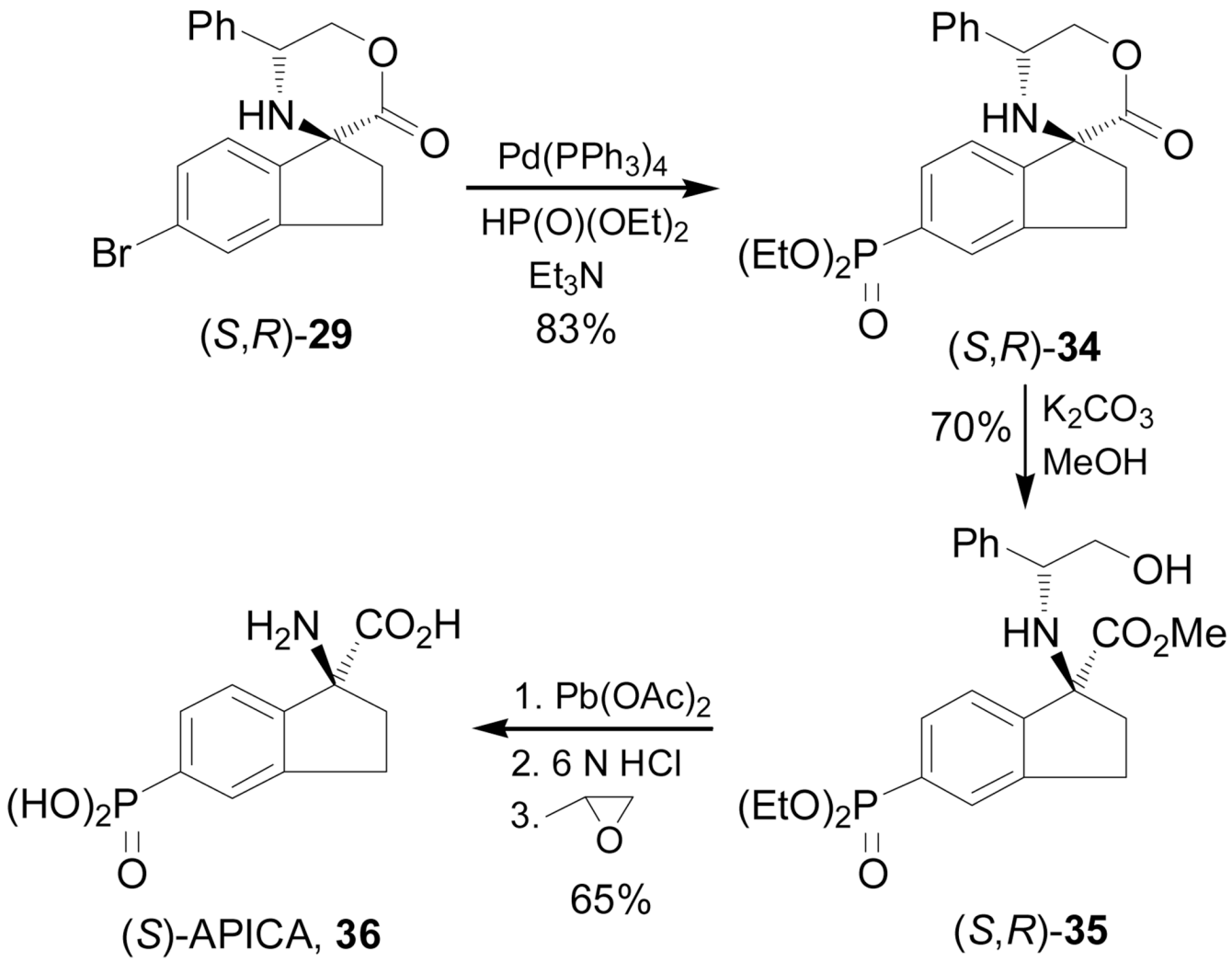
Scheme 4.



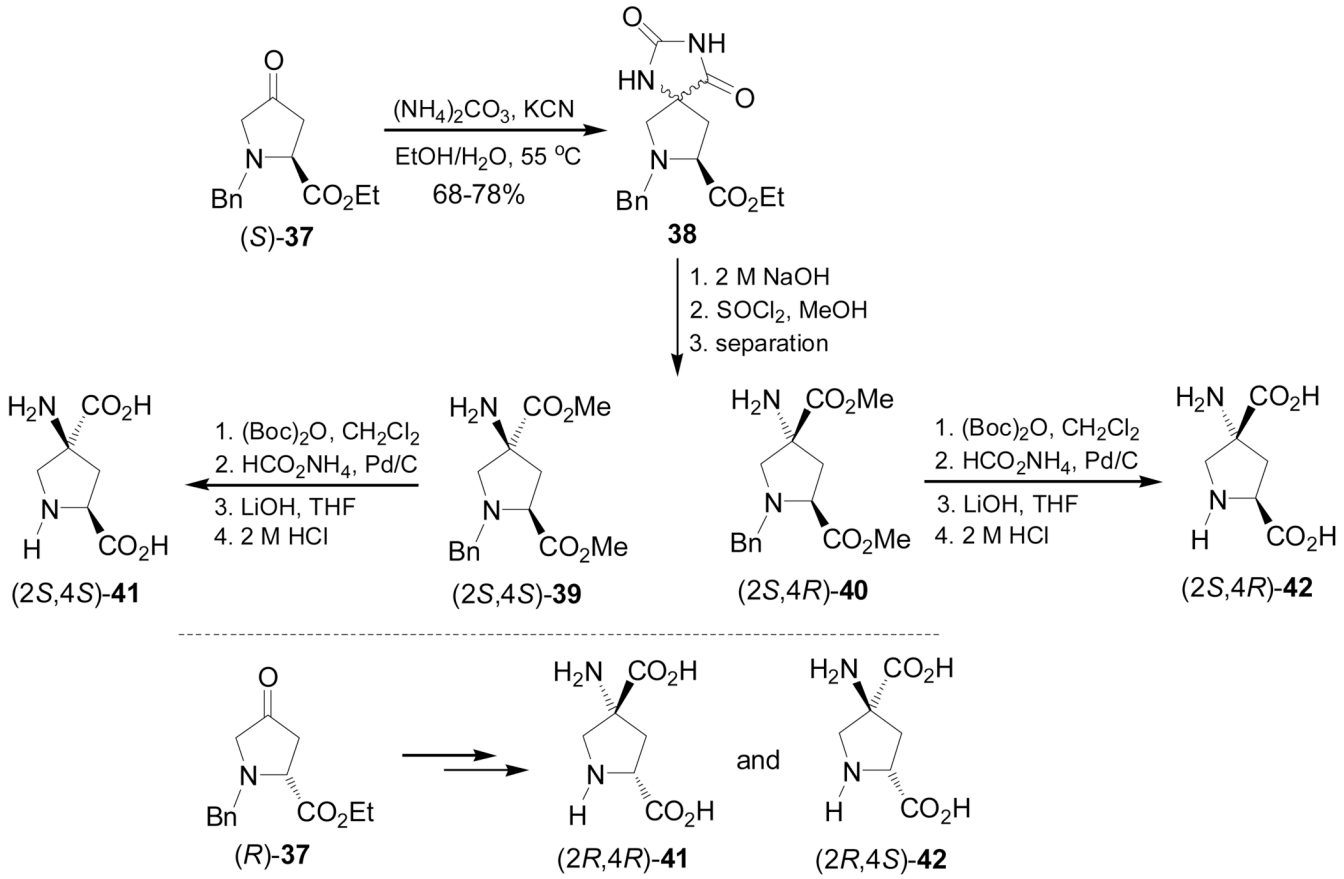
Scheme 5.



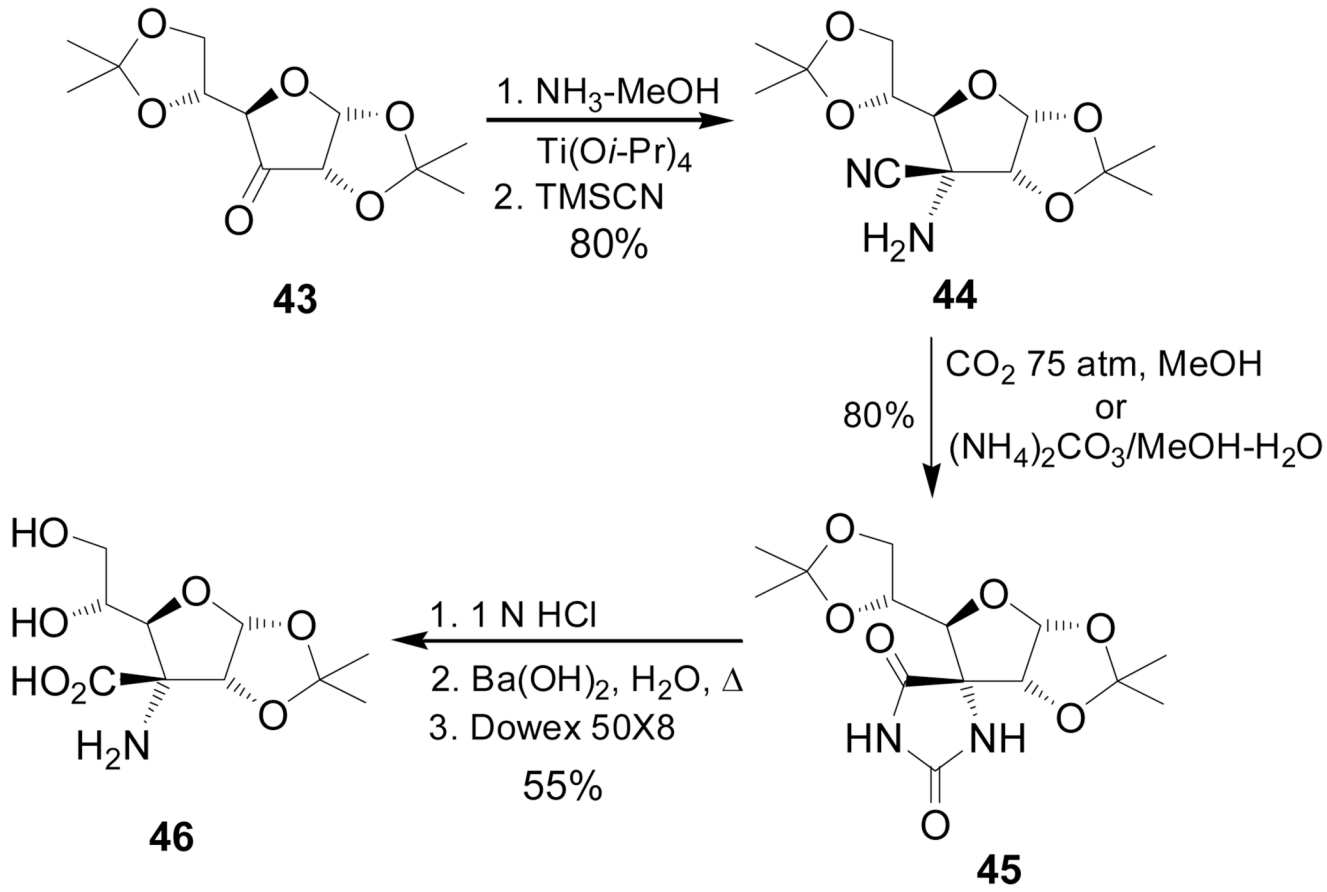
Scheme 6.



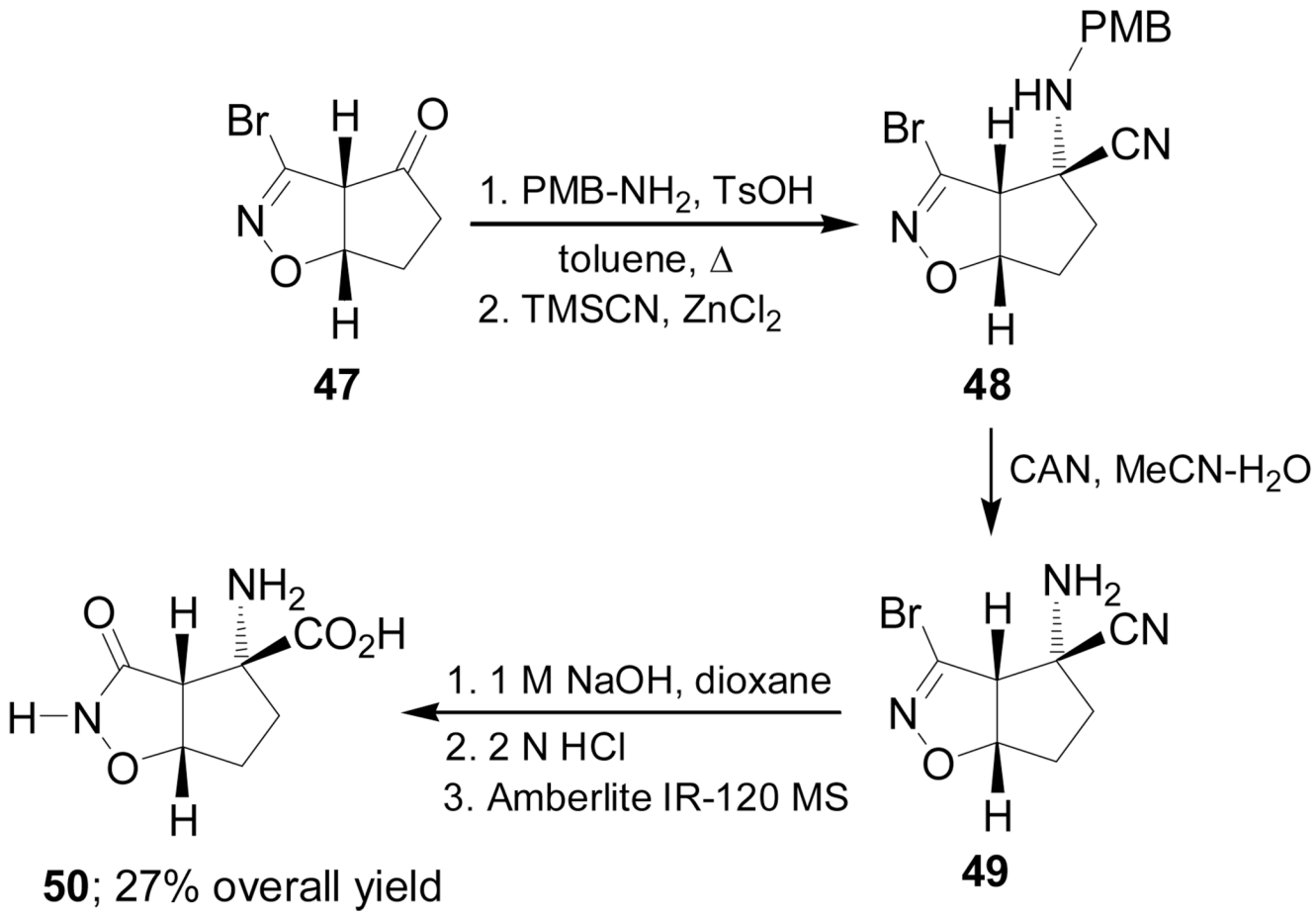
Scheme 7.



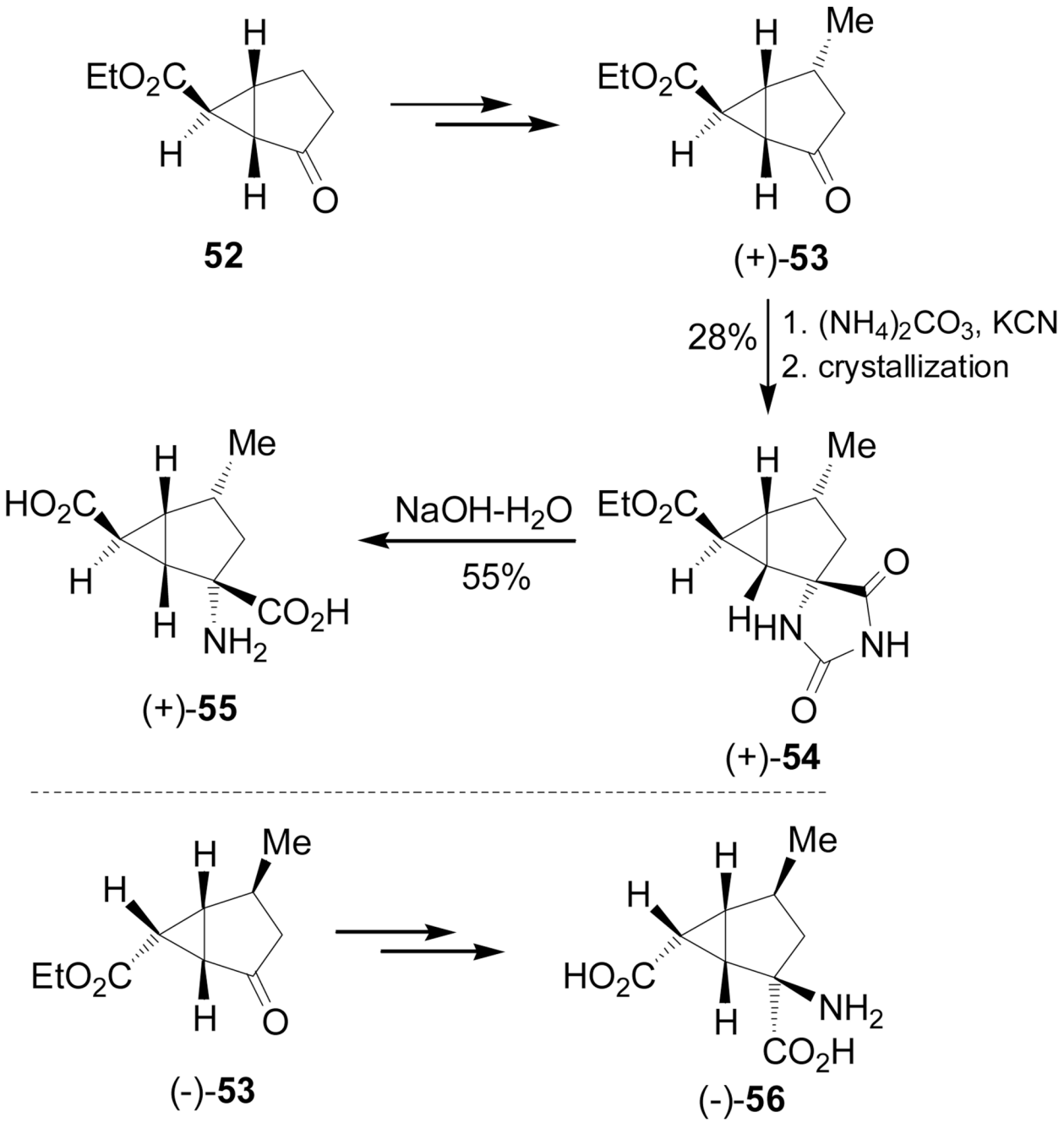
Scheme 8.



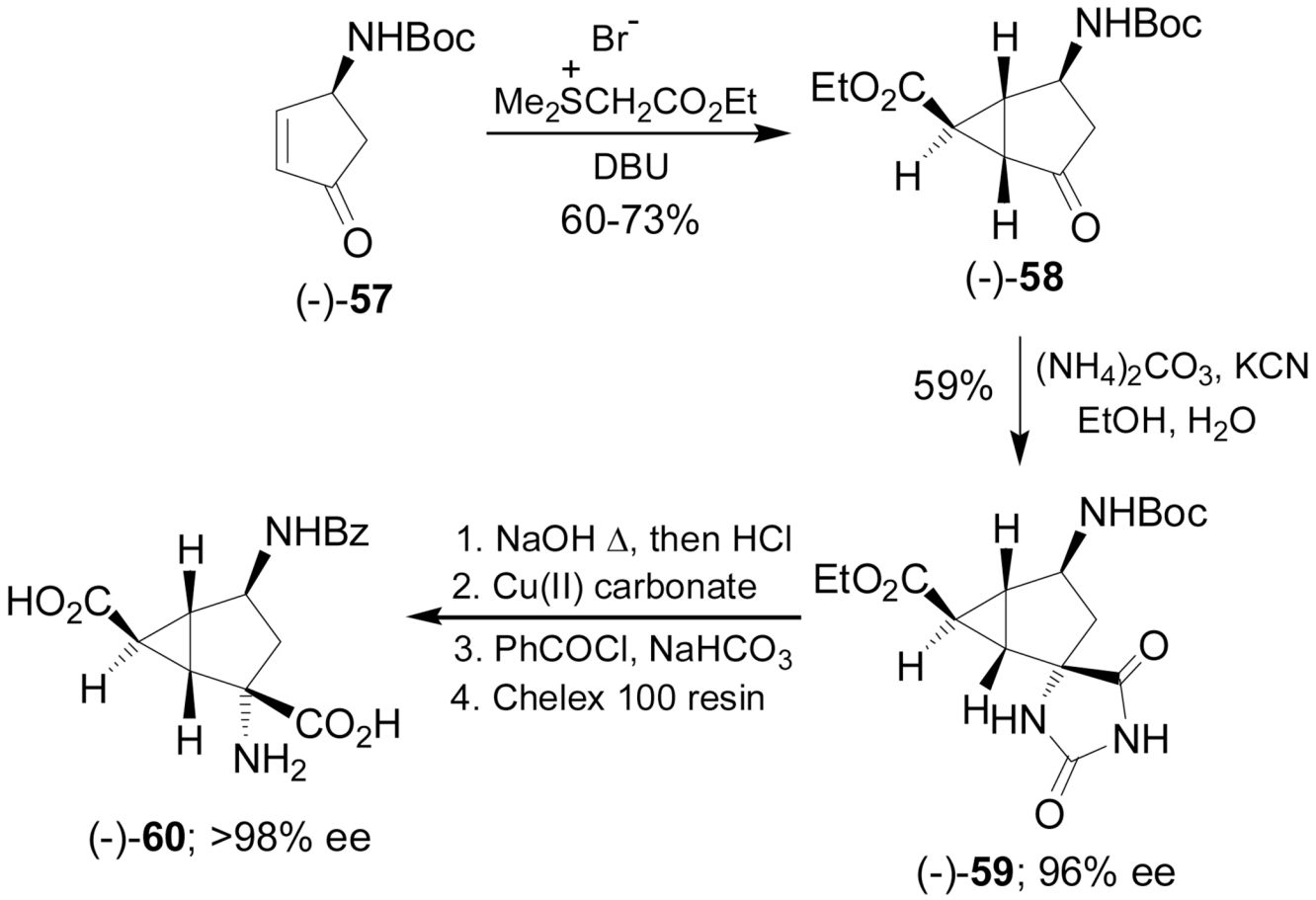
Scheme 9.



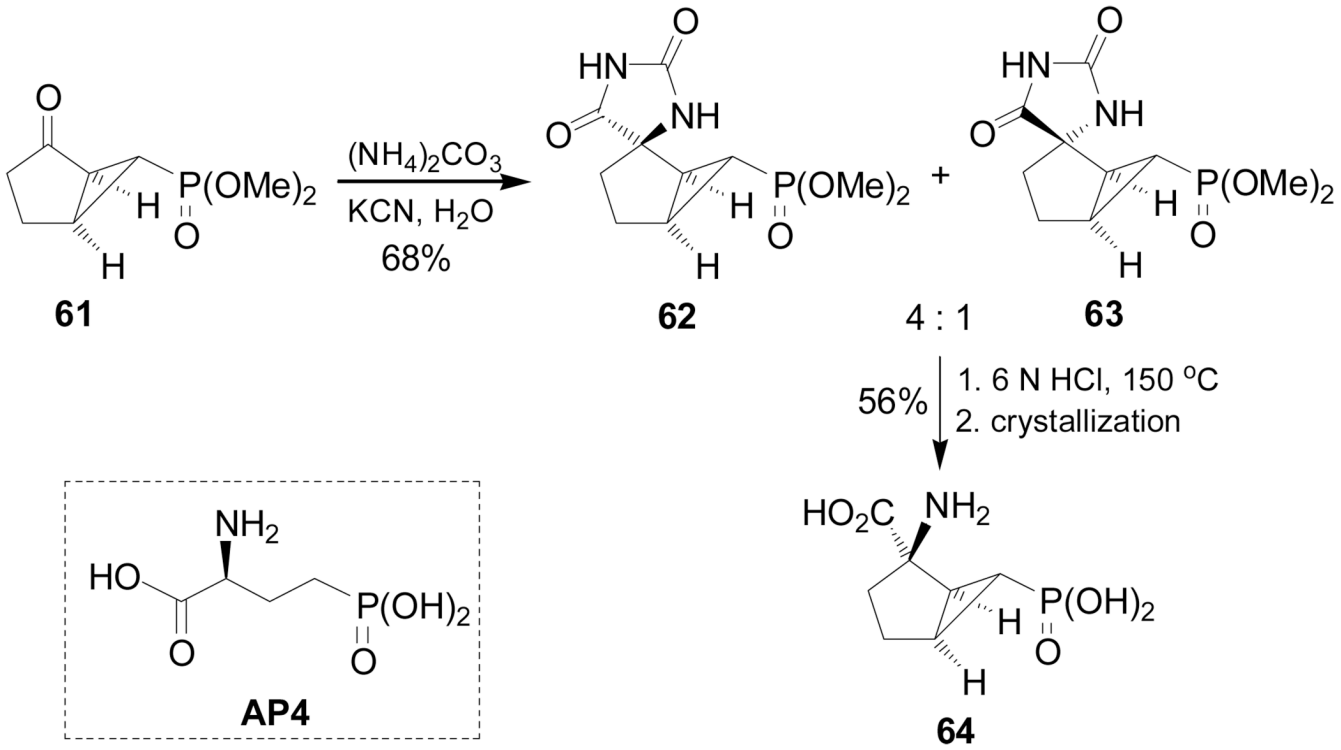
Scheme 10.



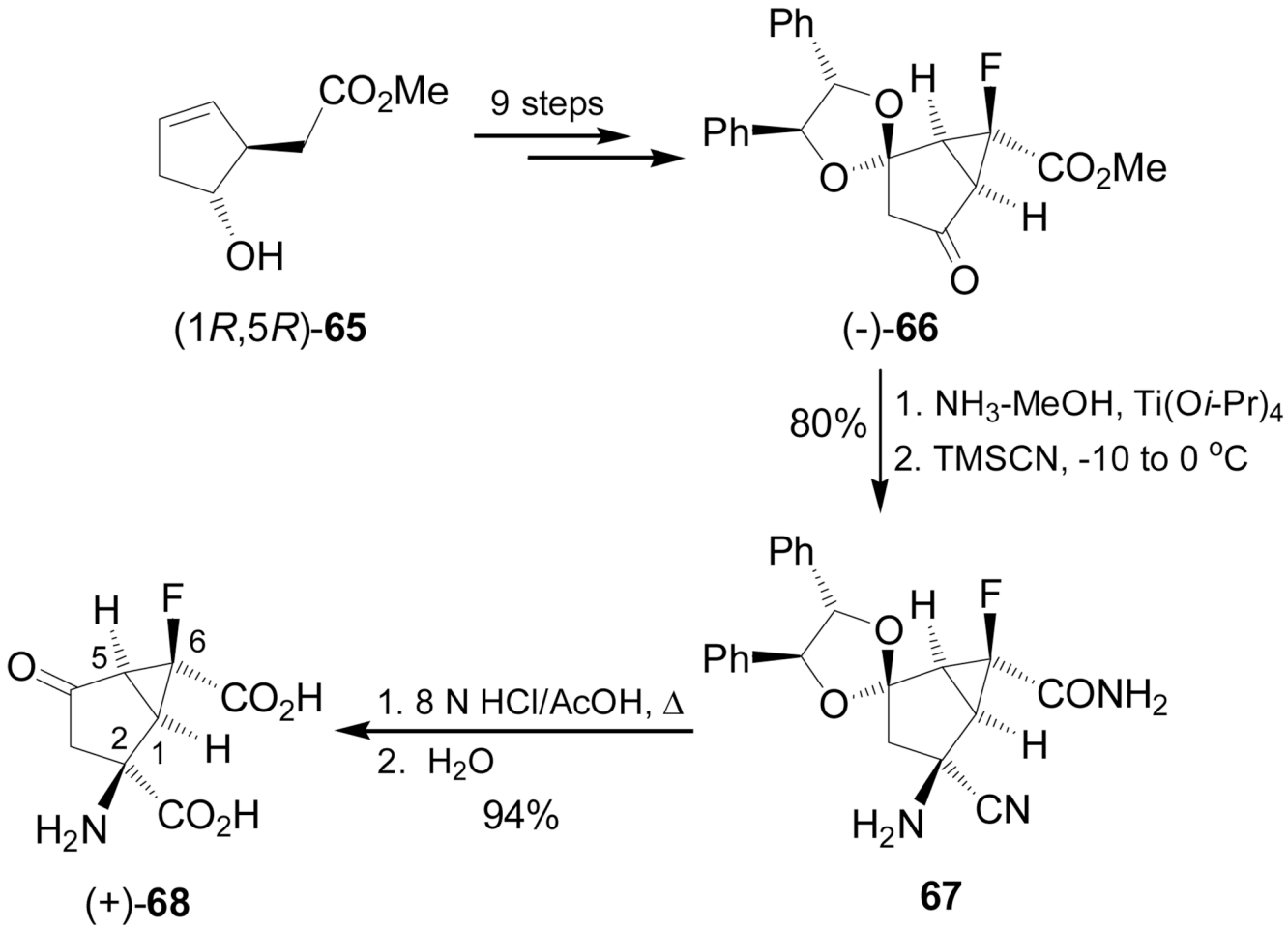
Scheme 11.



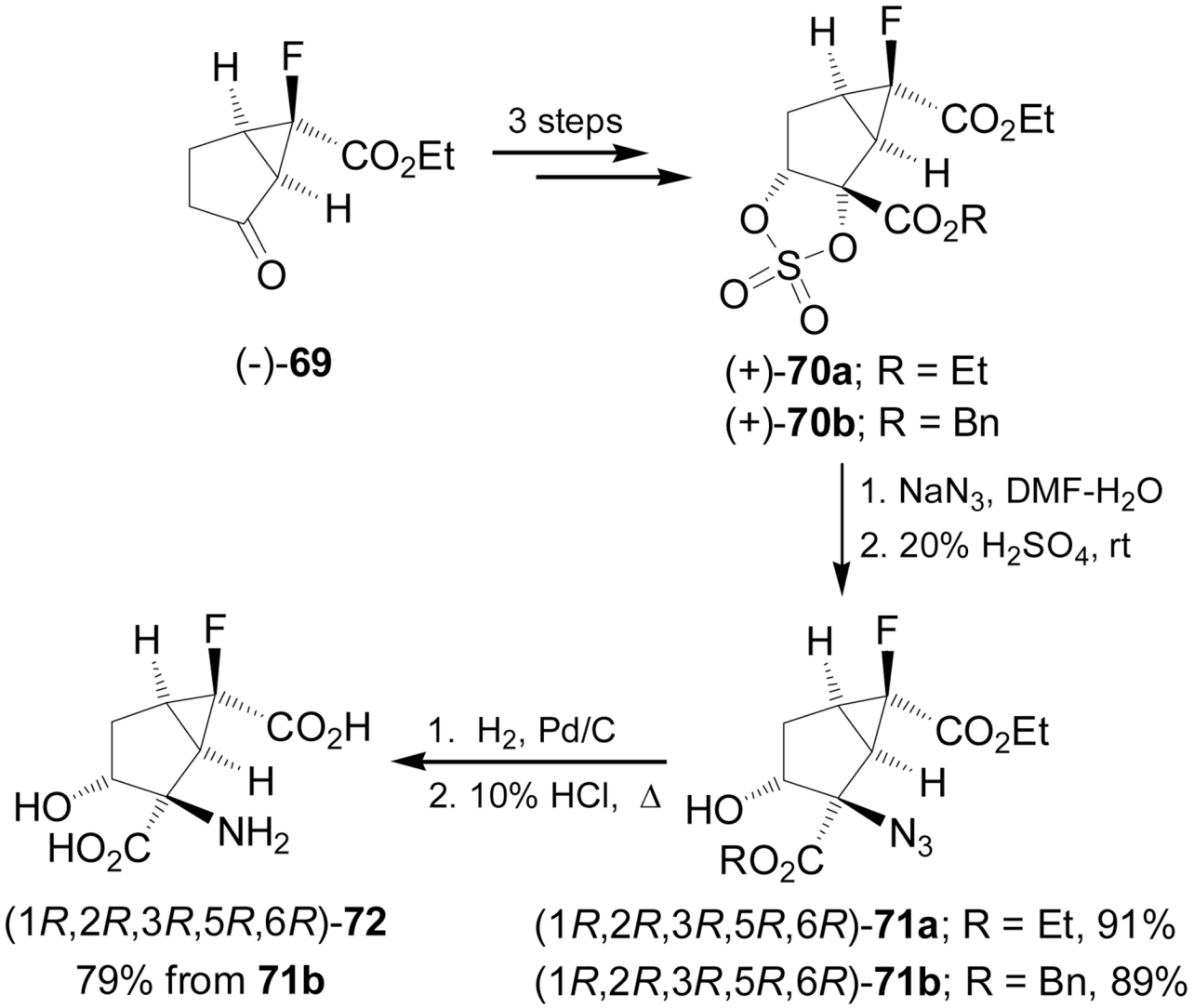
Scheme 12.



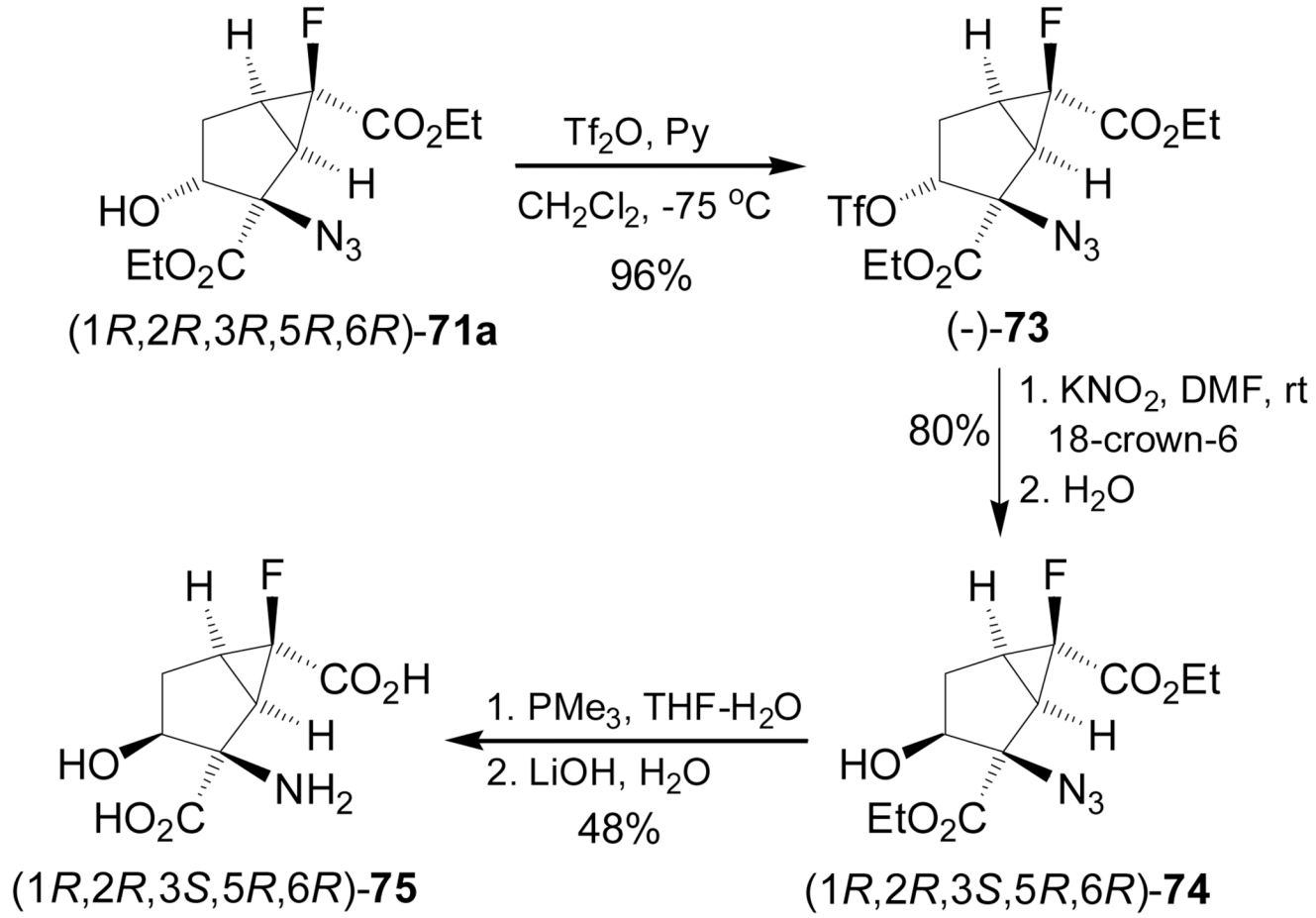
Scheme 13.



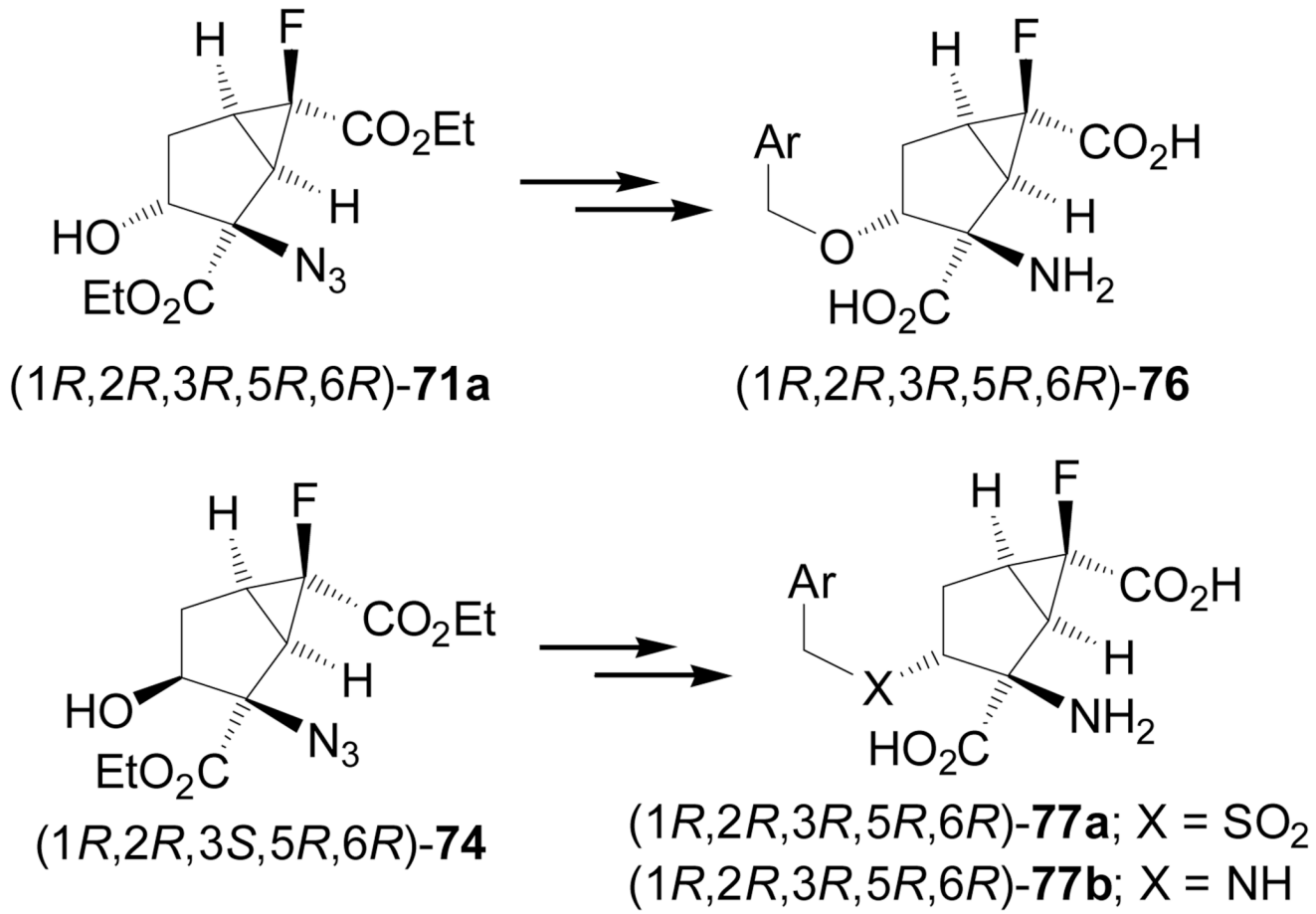
Scheme 14.



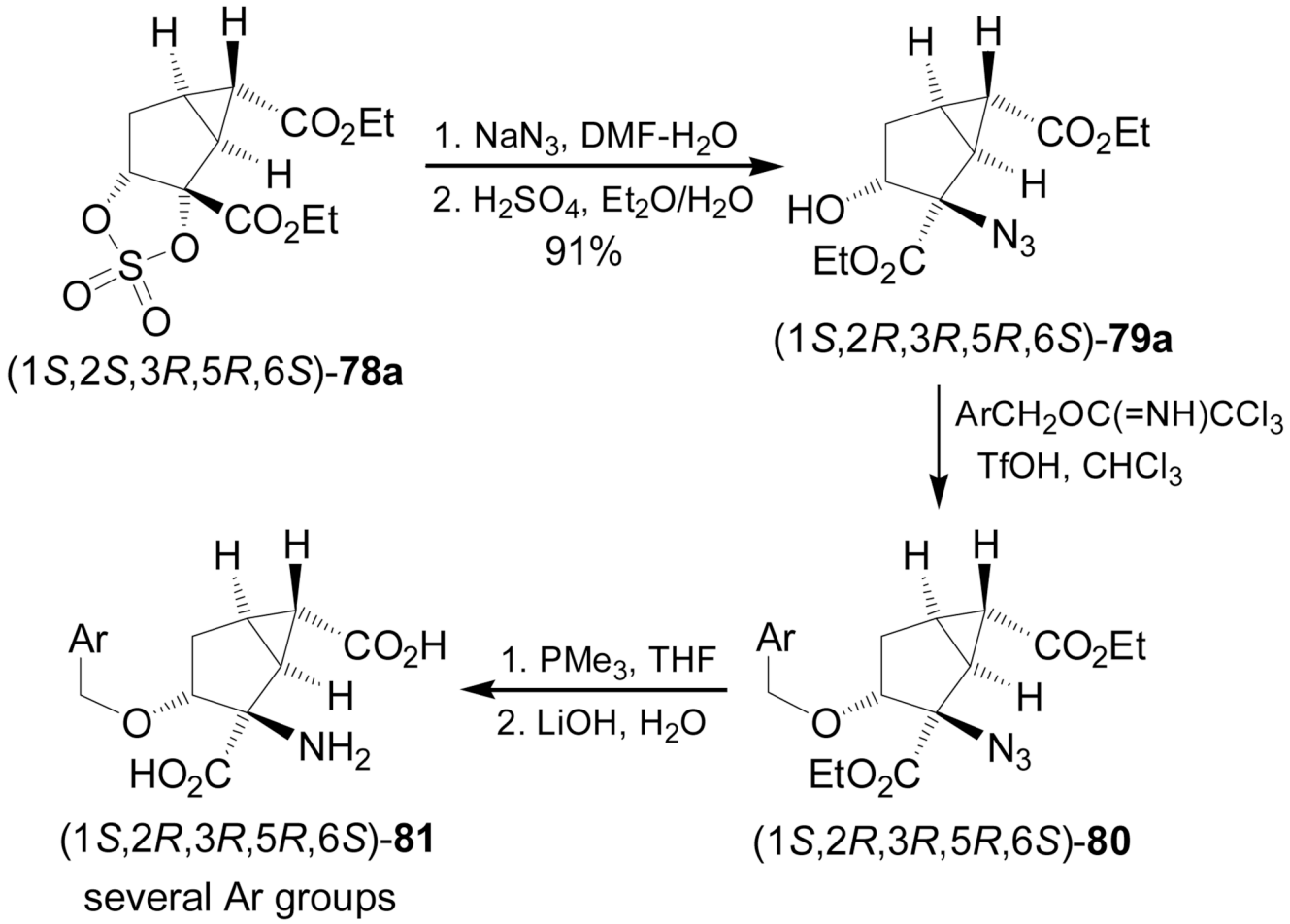
Scheme 15.



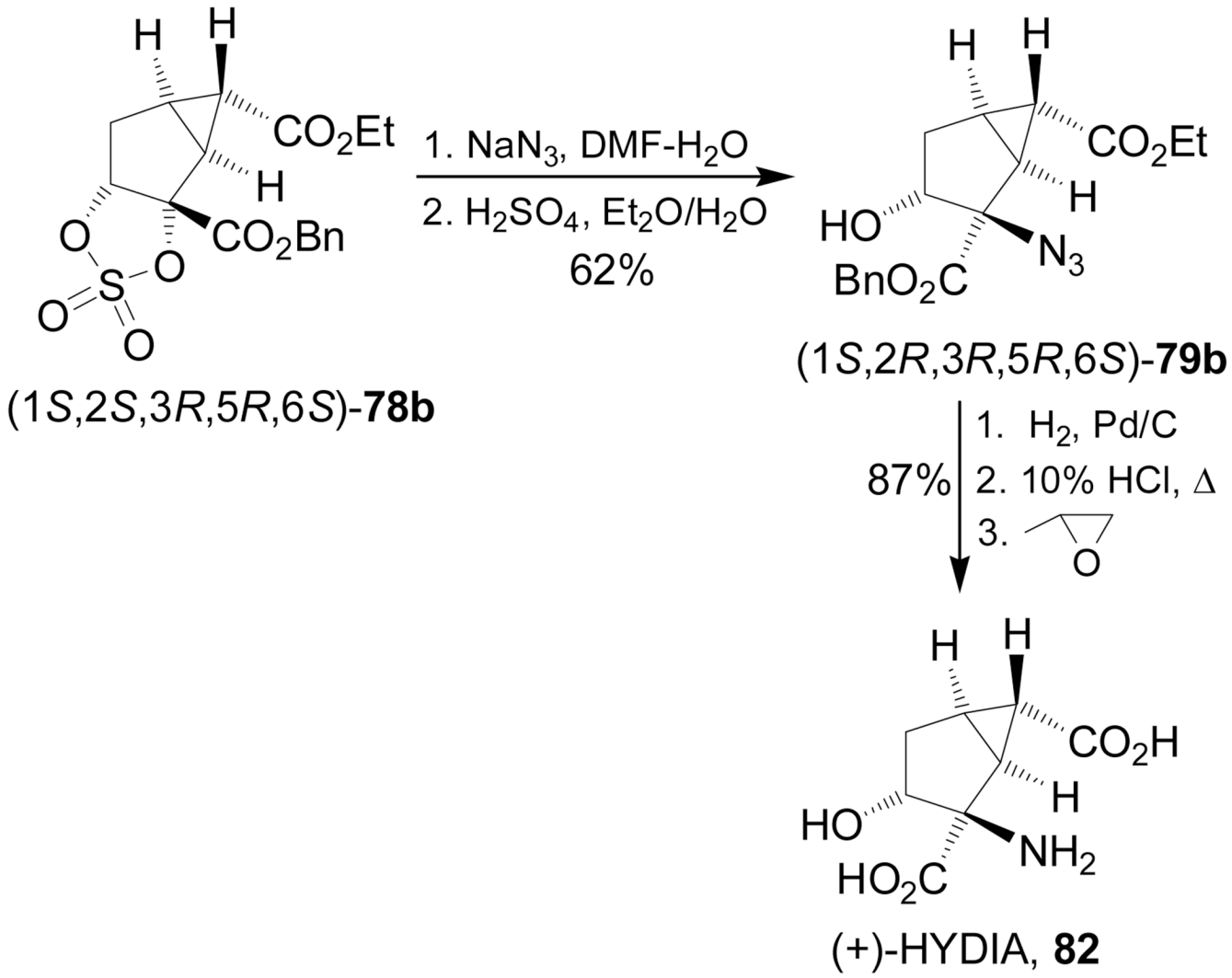
Scheme 16.



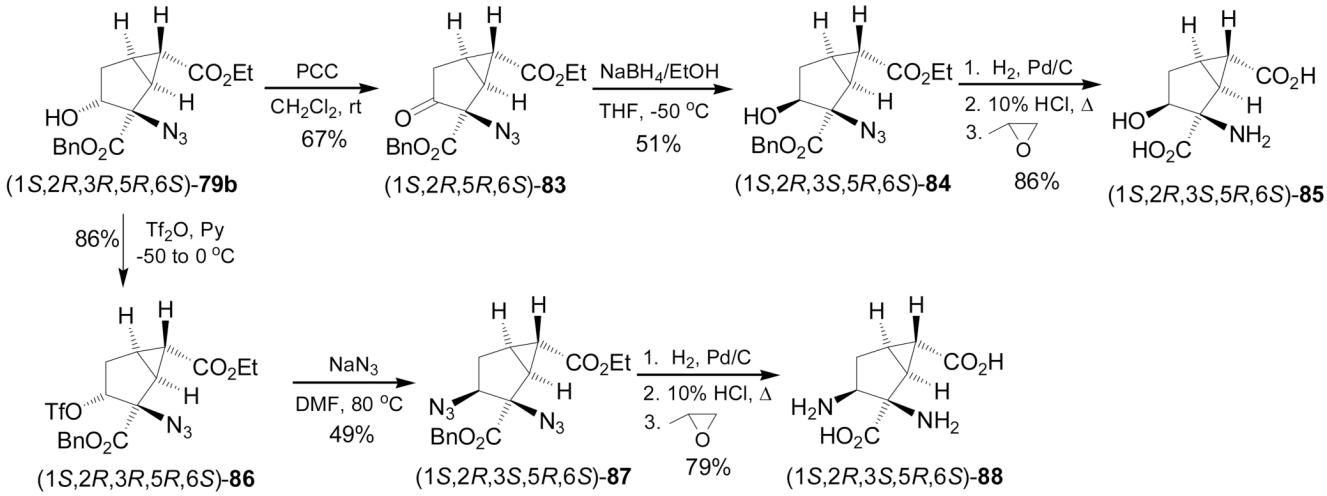
Scheme 17.



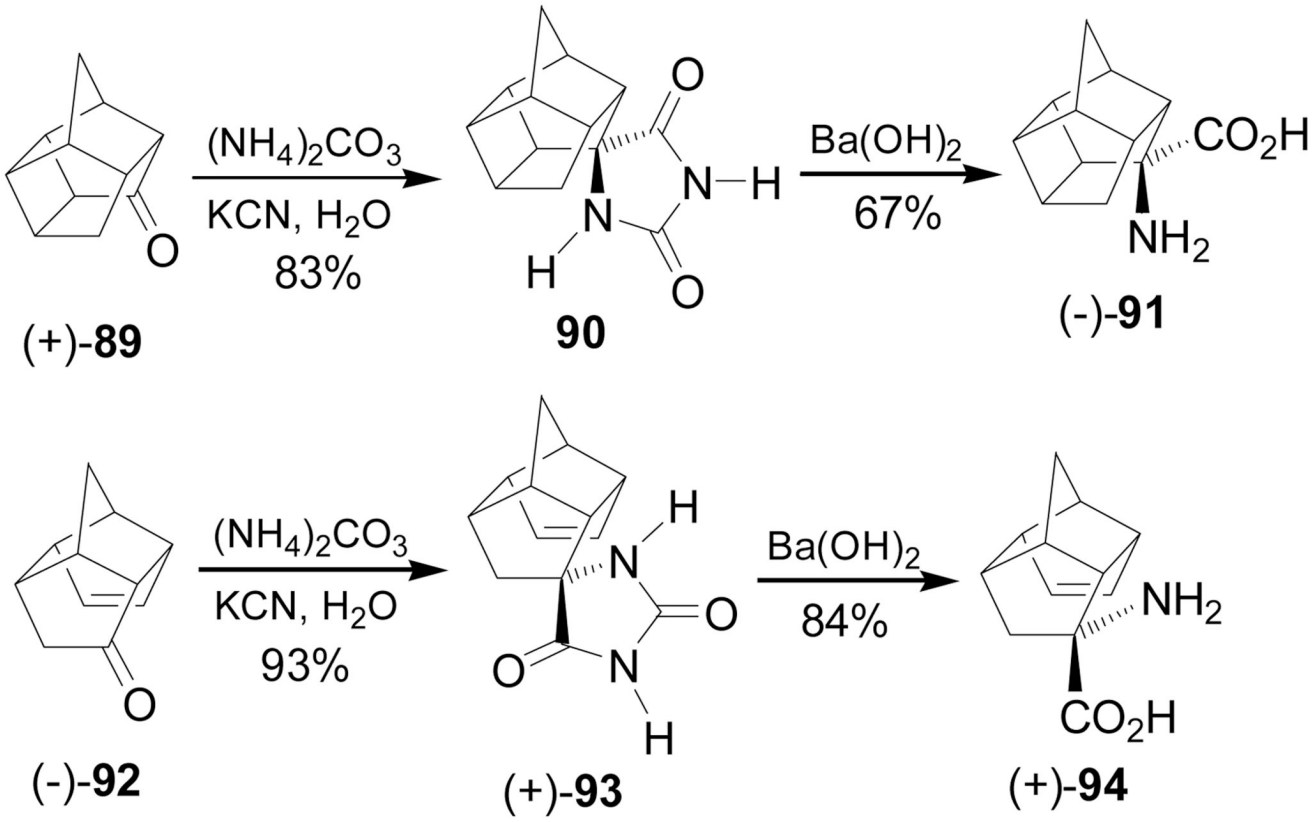
Scheme 18.



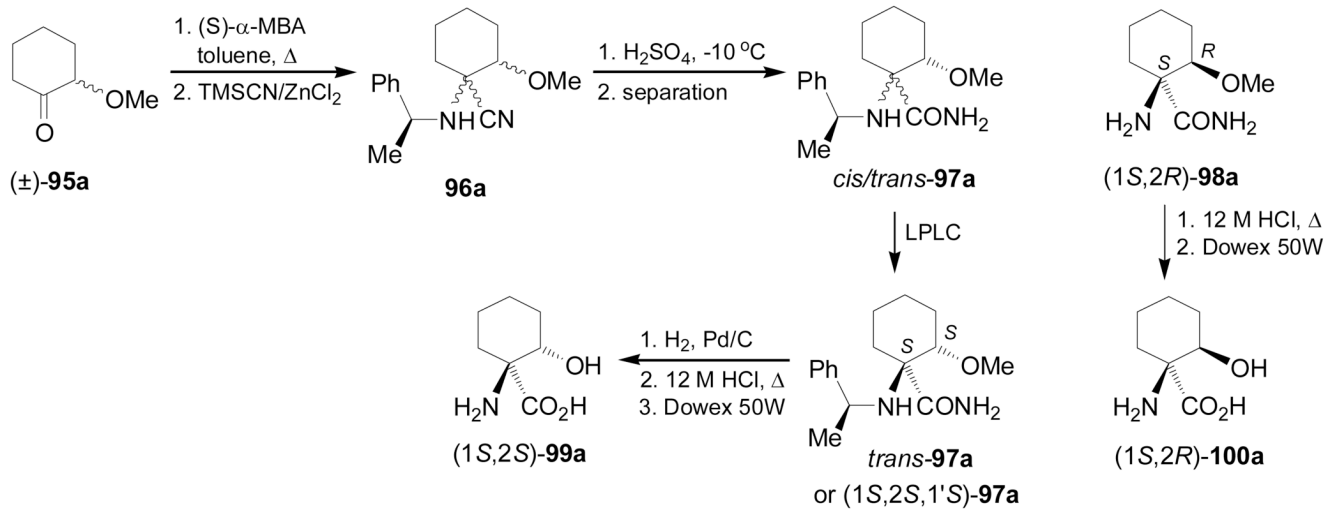
Scheme 19.



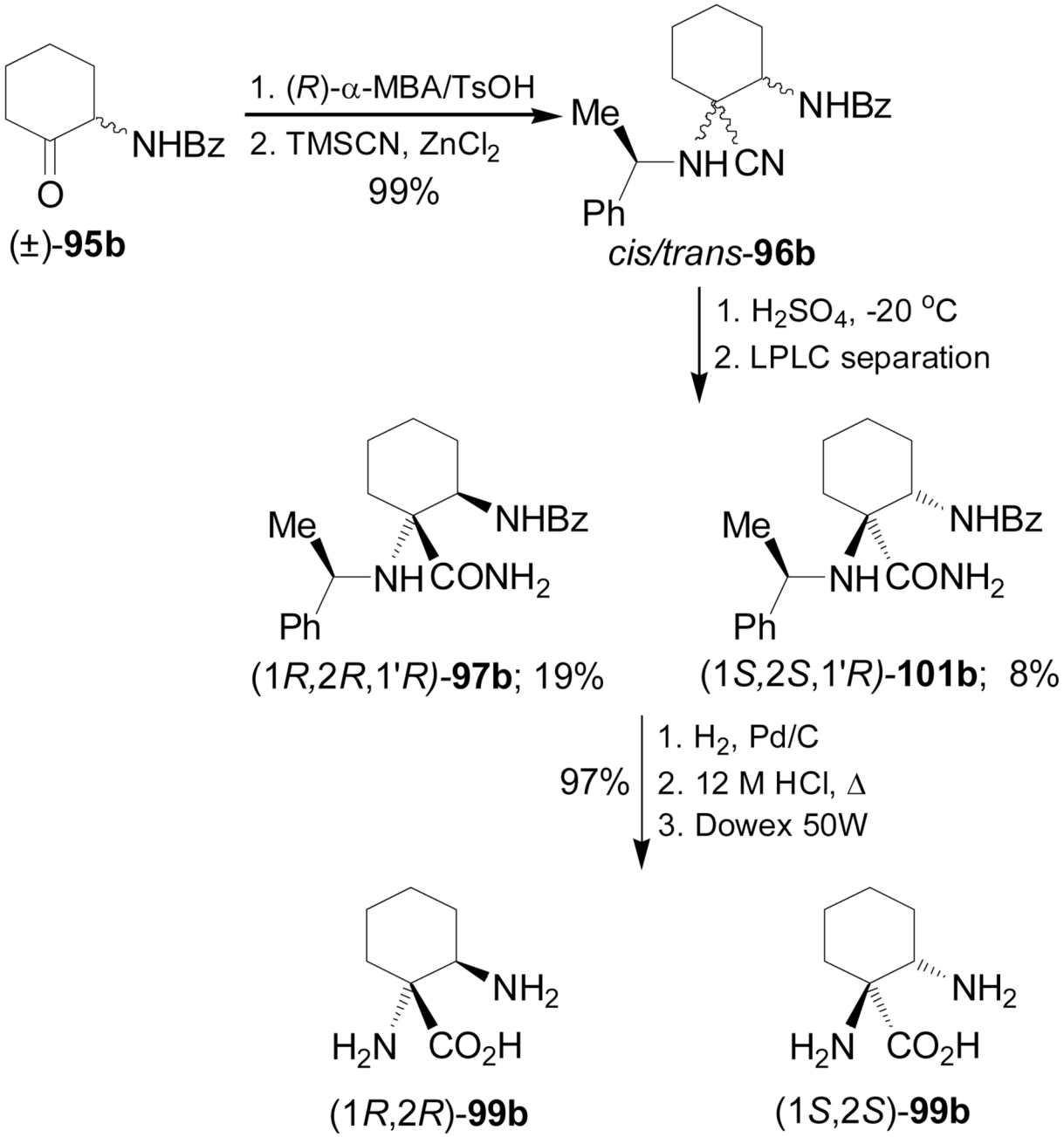
Scheme 20.



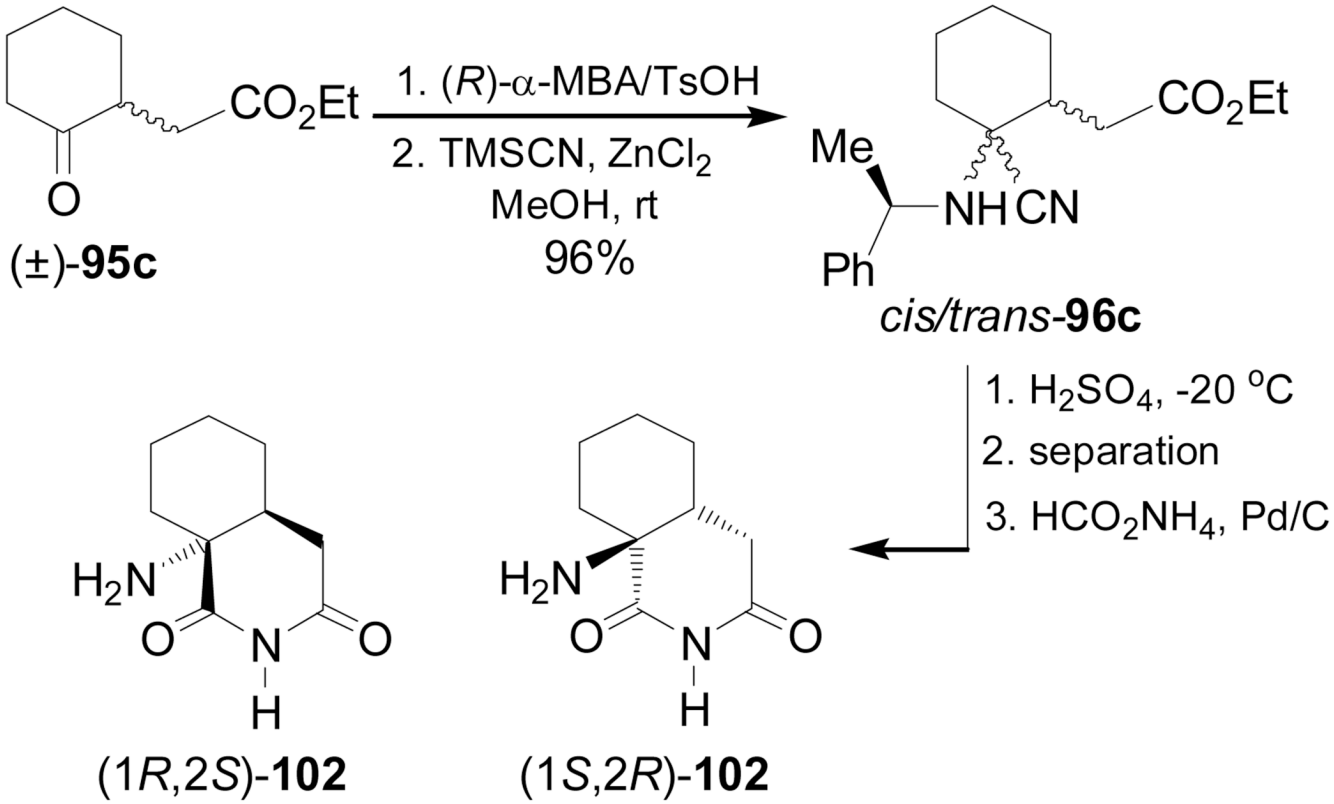
Scheme 21.



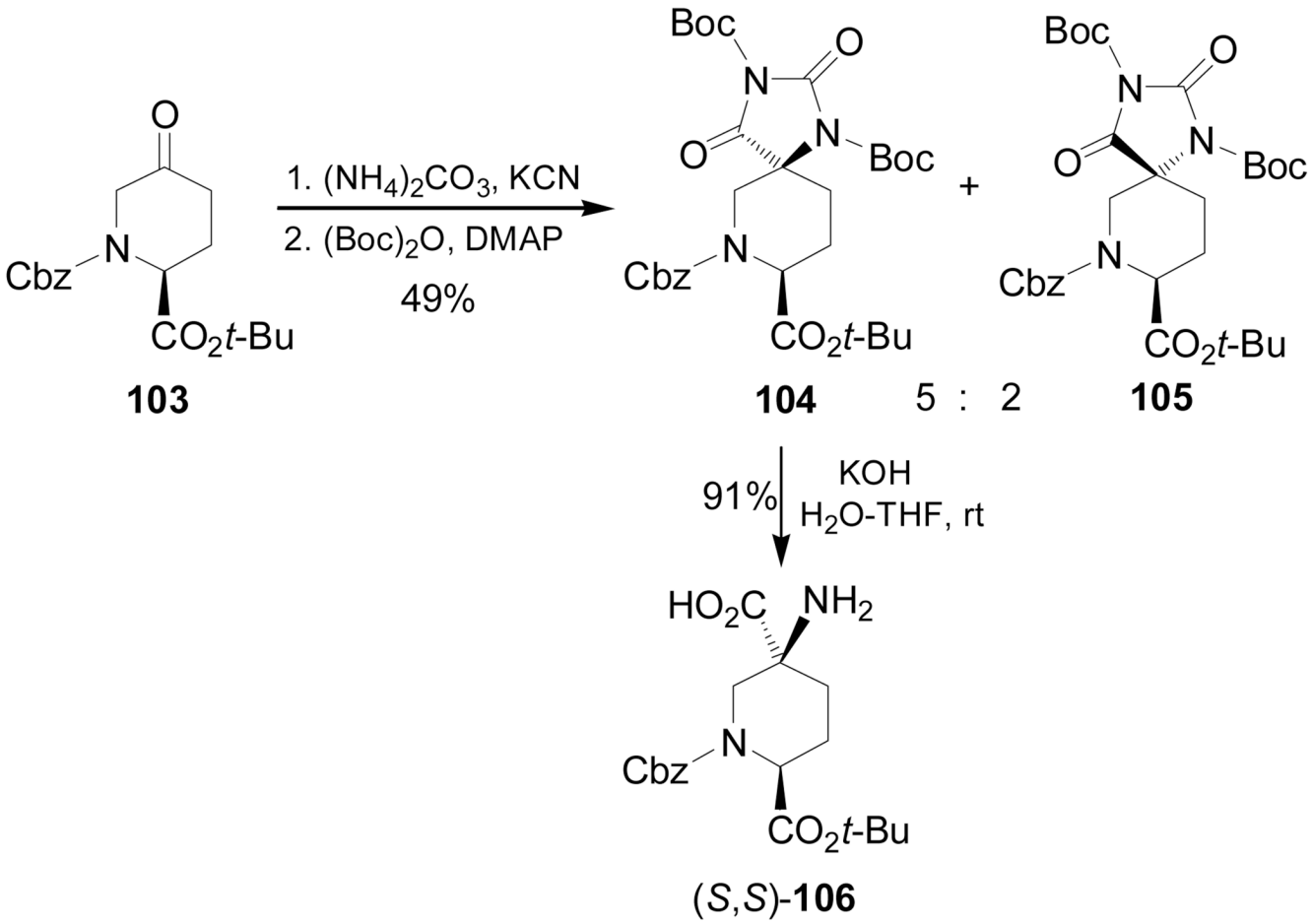
Scheme 22.



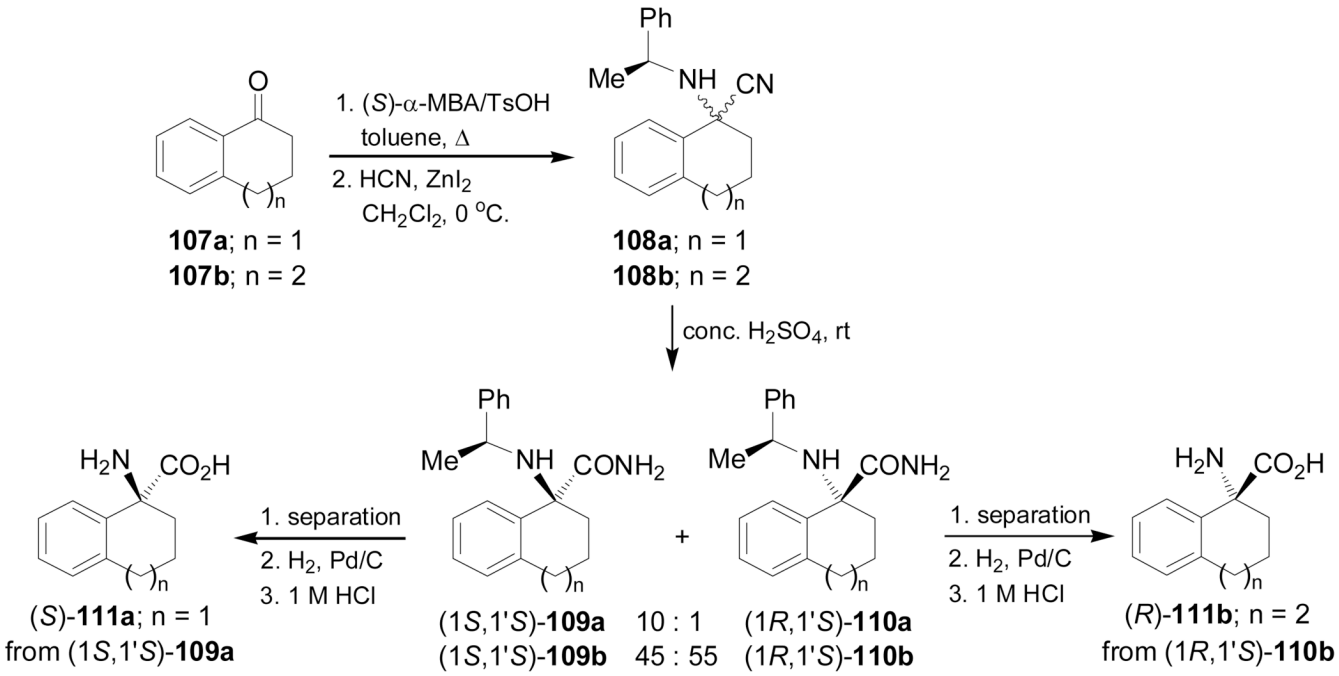
Scheme 23.



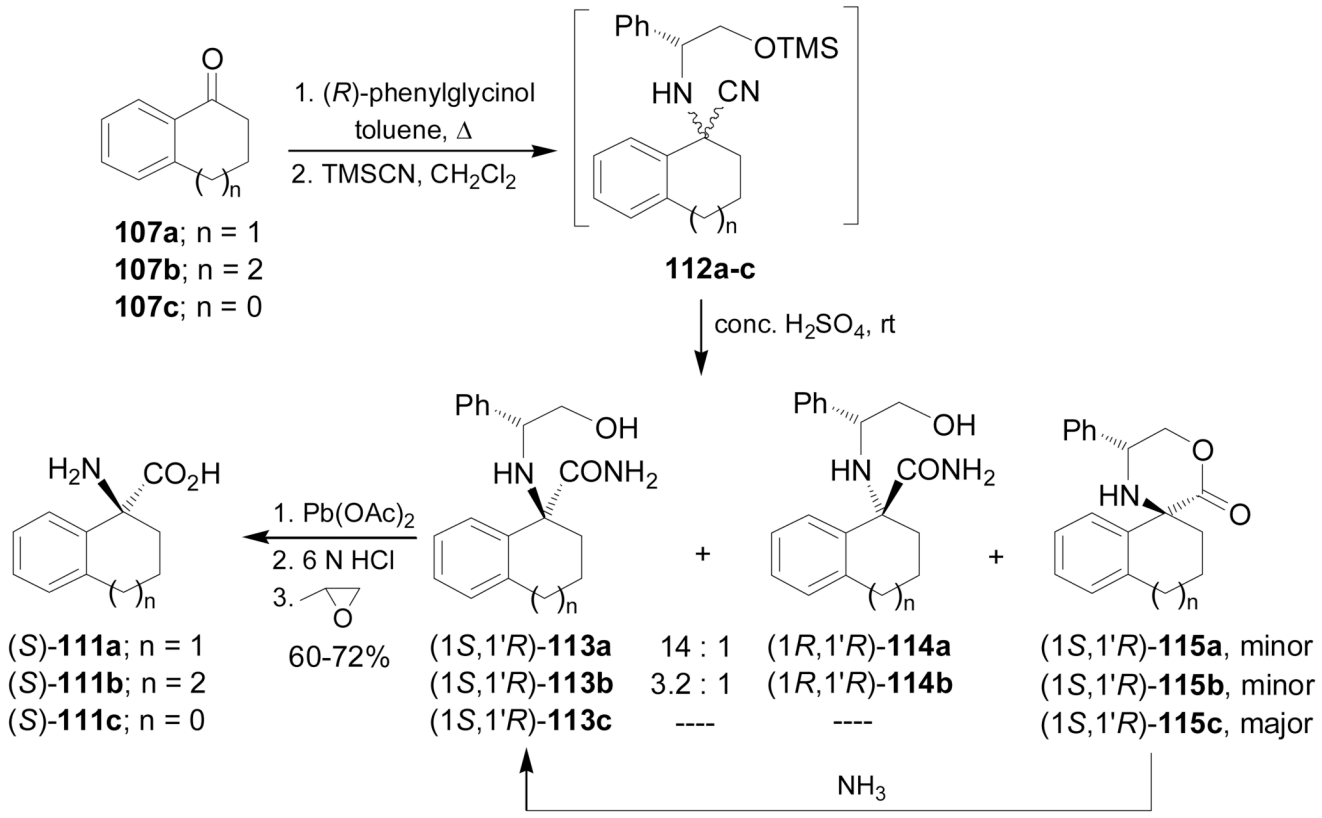
Scheme 24.



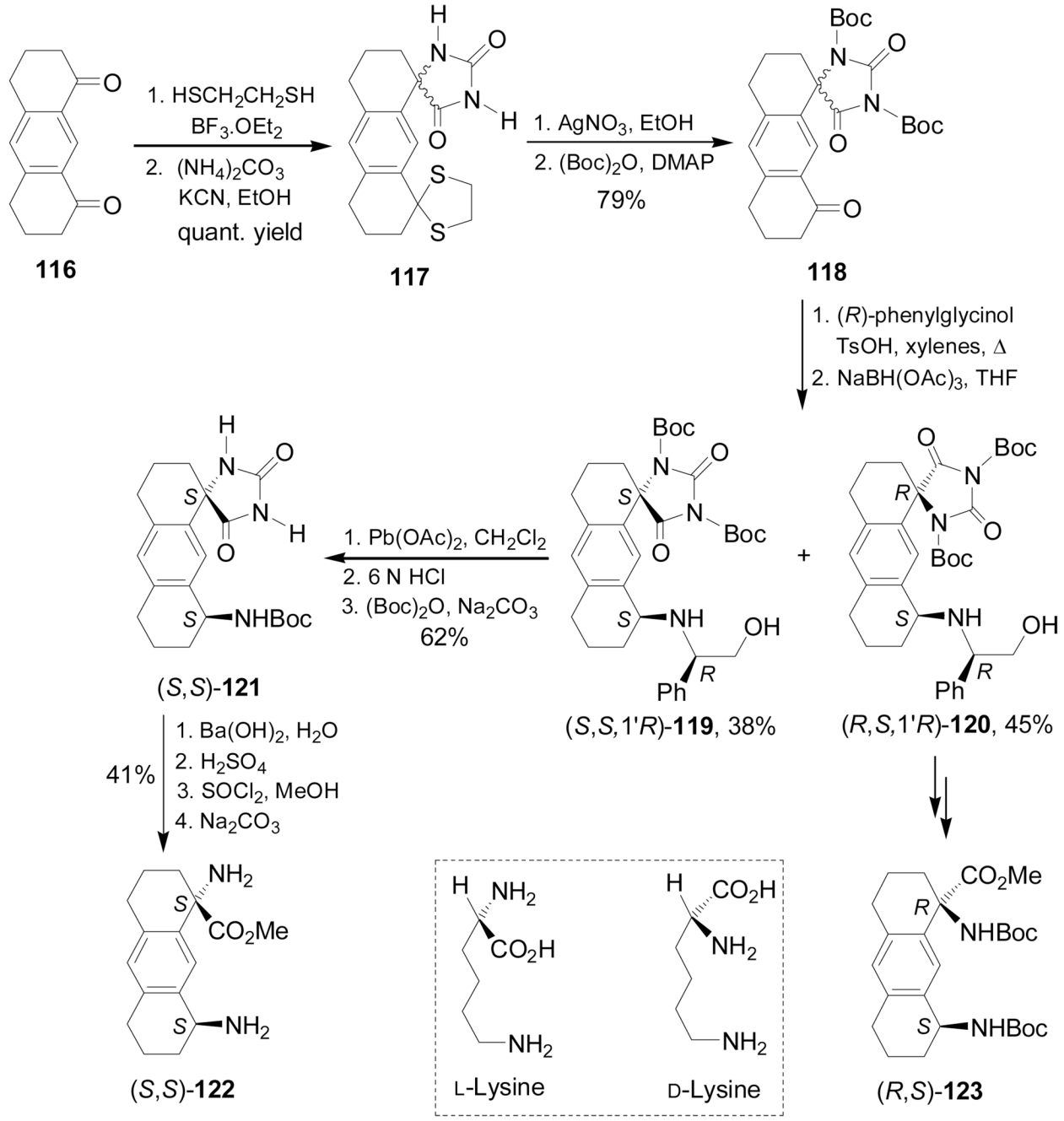
Scheme 25.



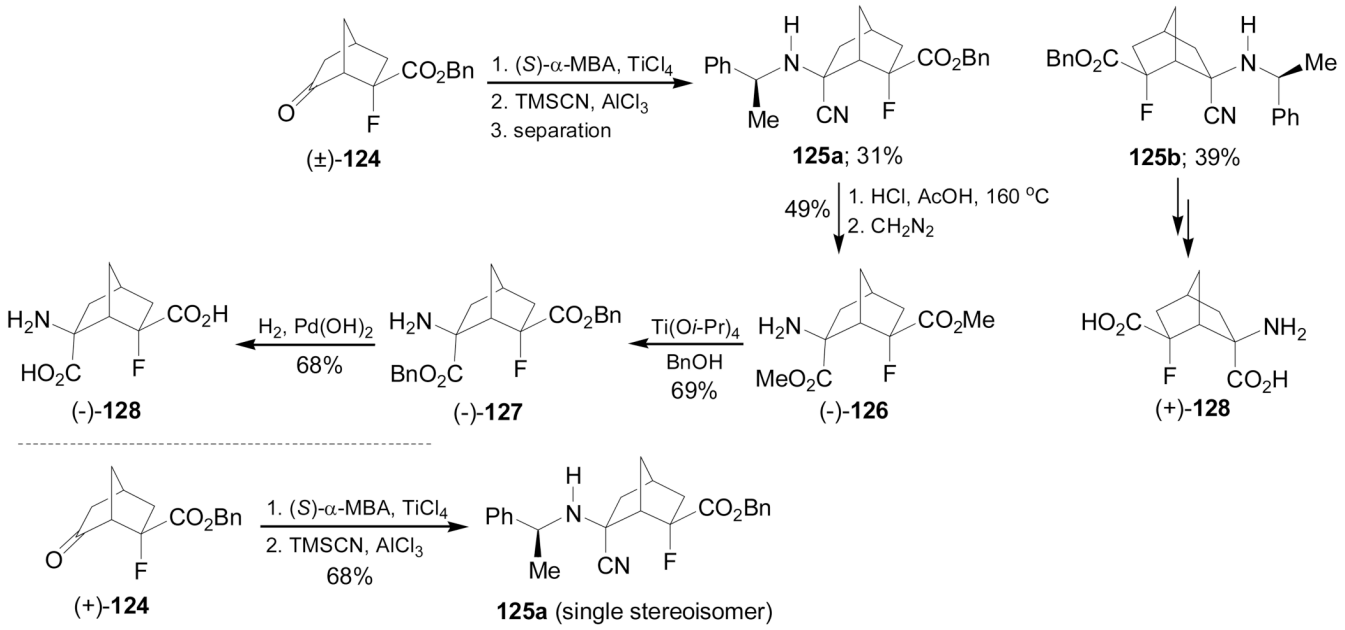
Scheme 26.



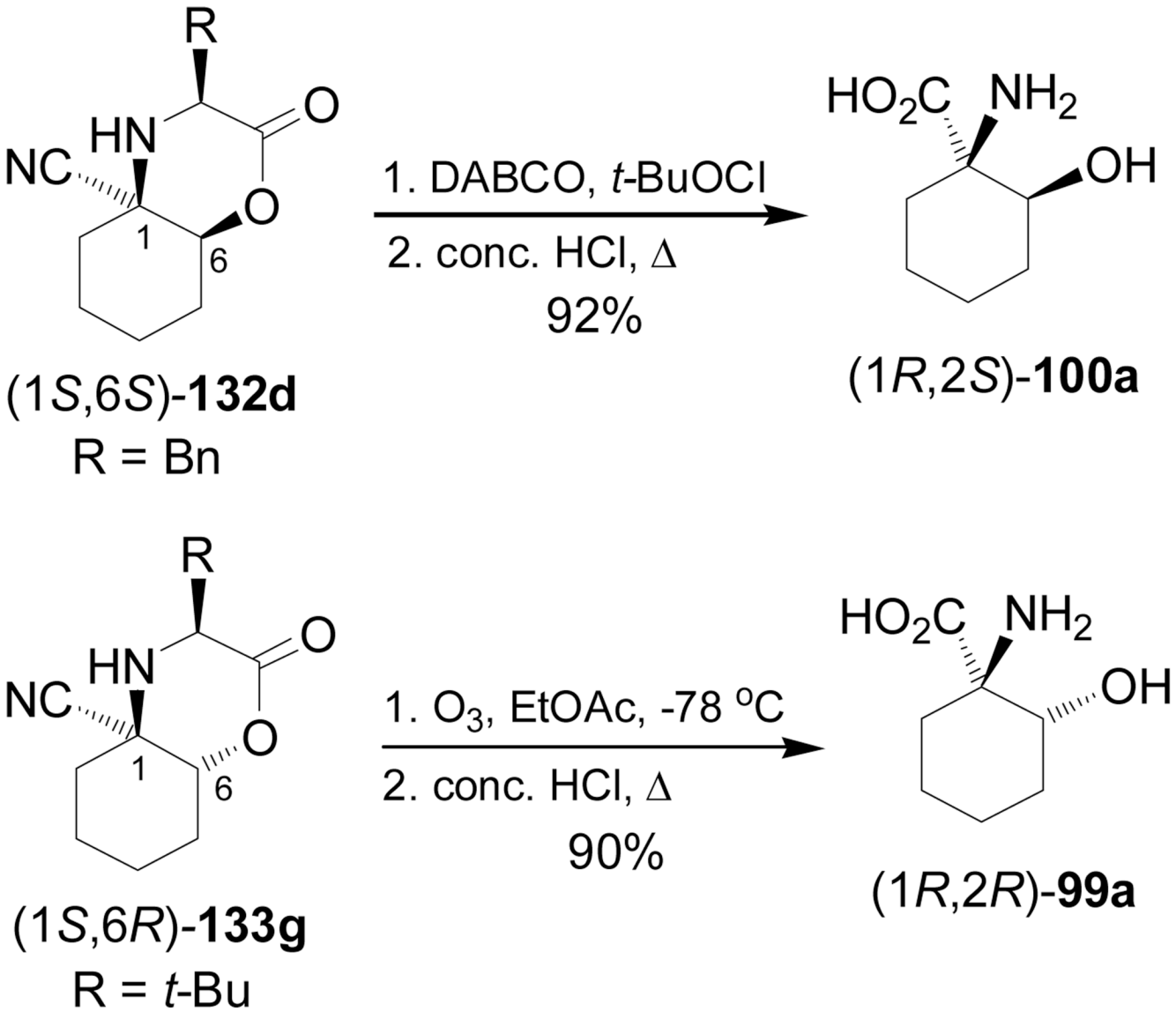
Scheme 27.



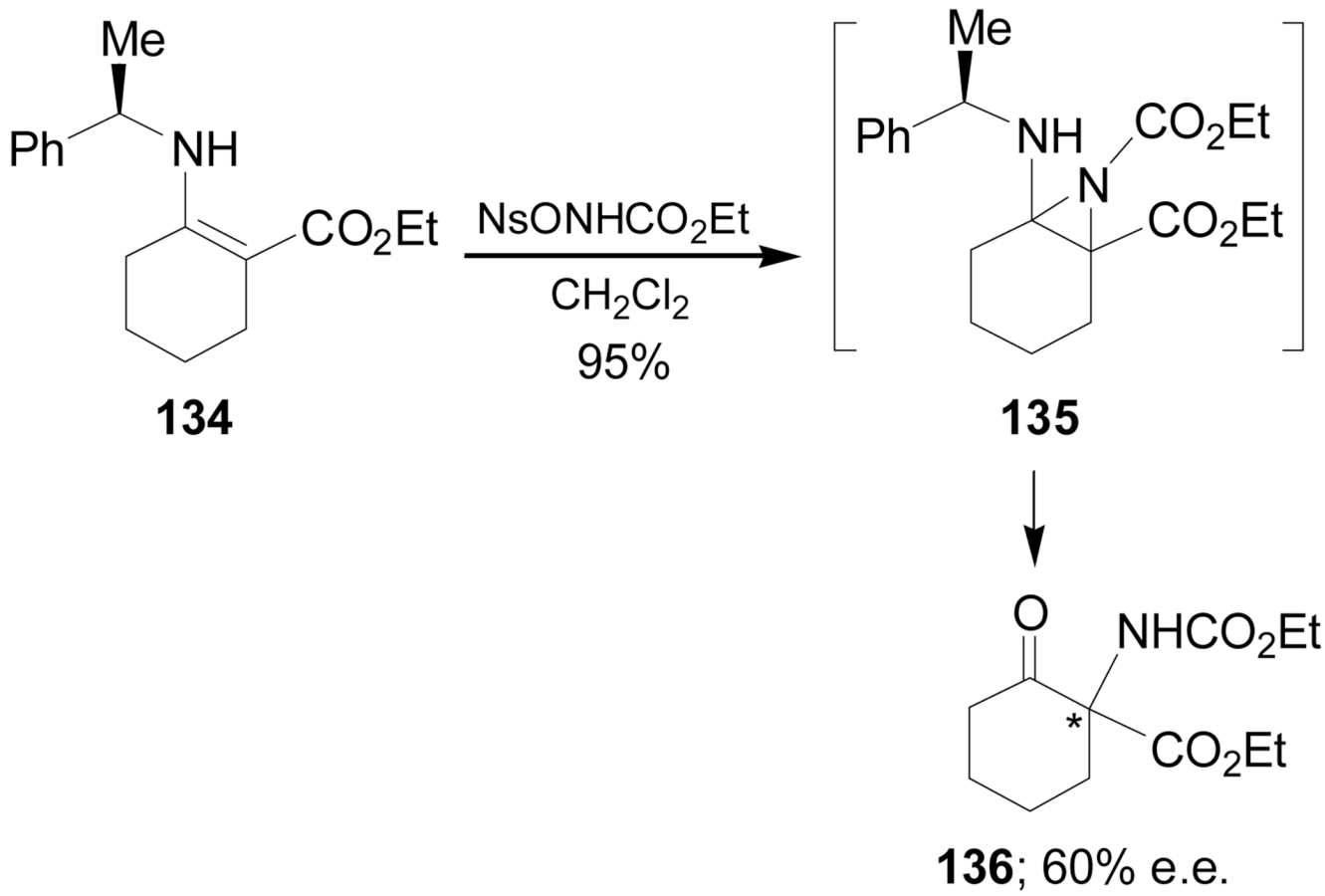
Scheme 28.



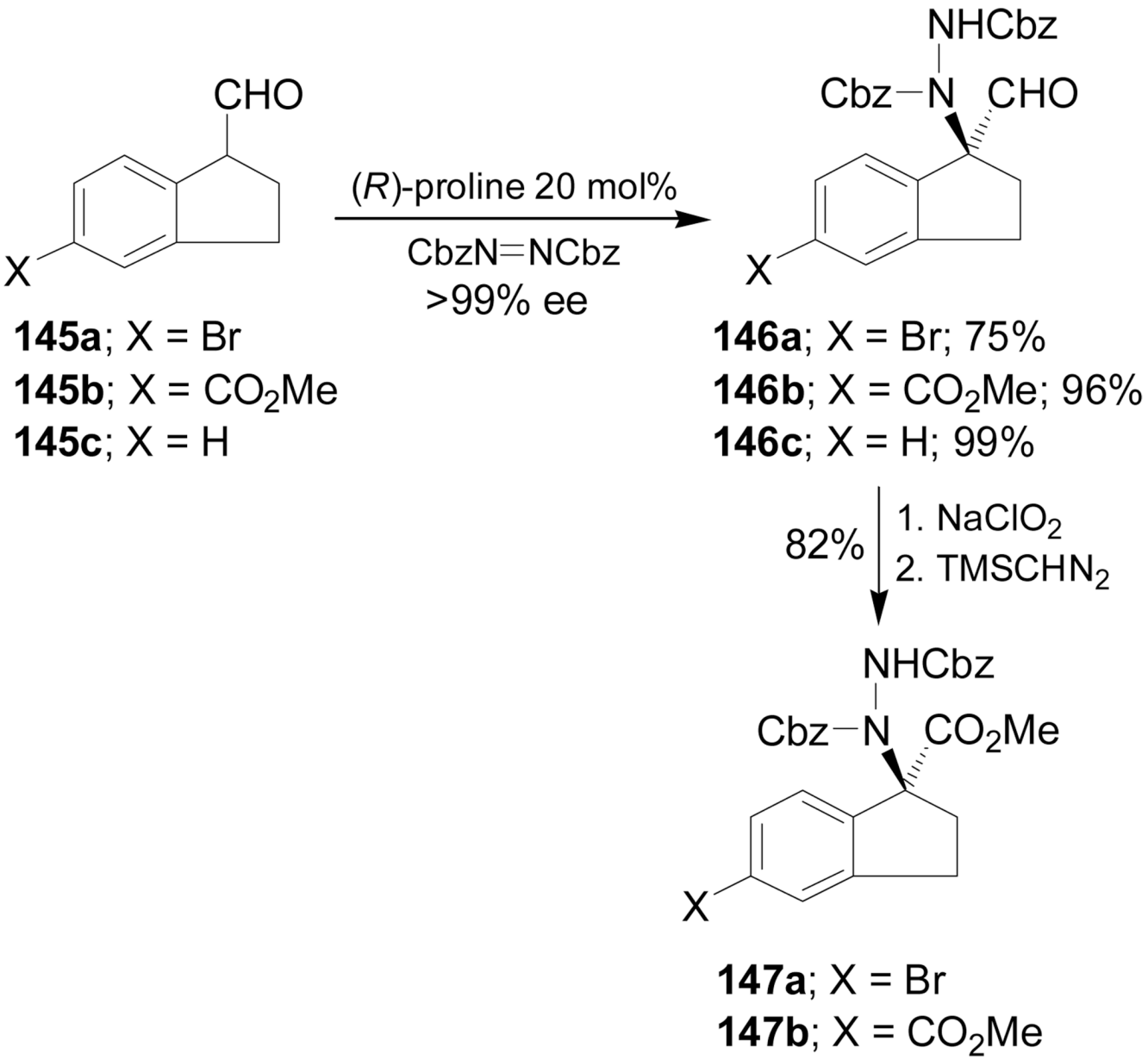
Scheme 29.



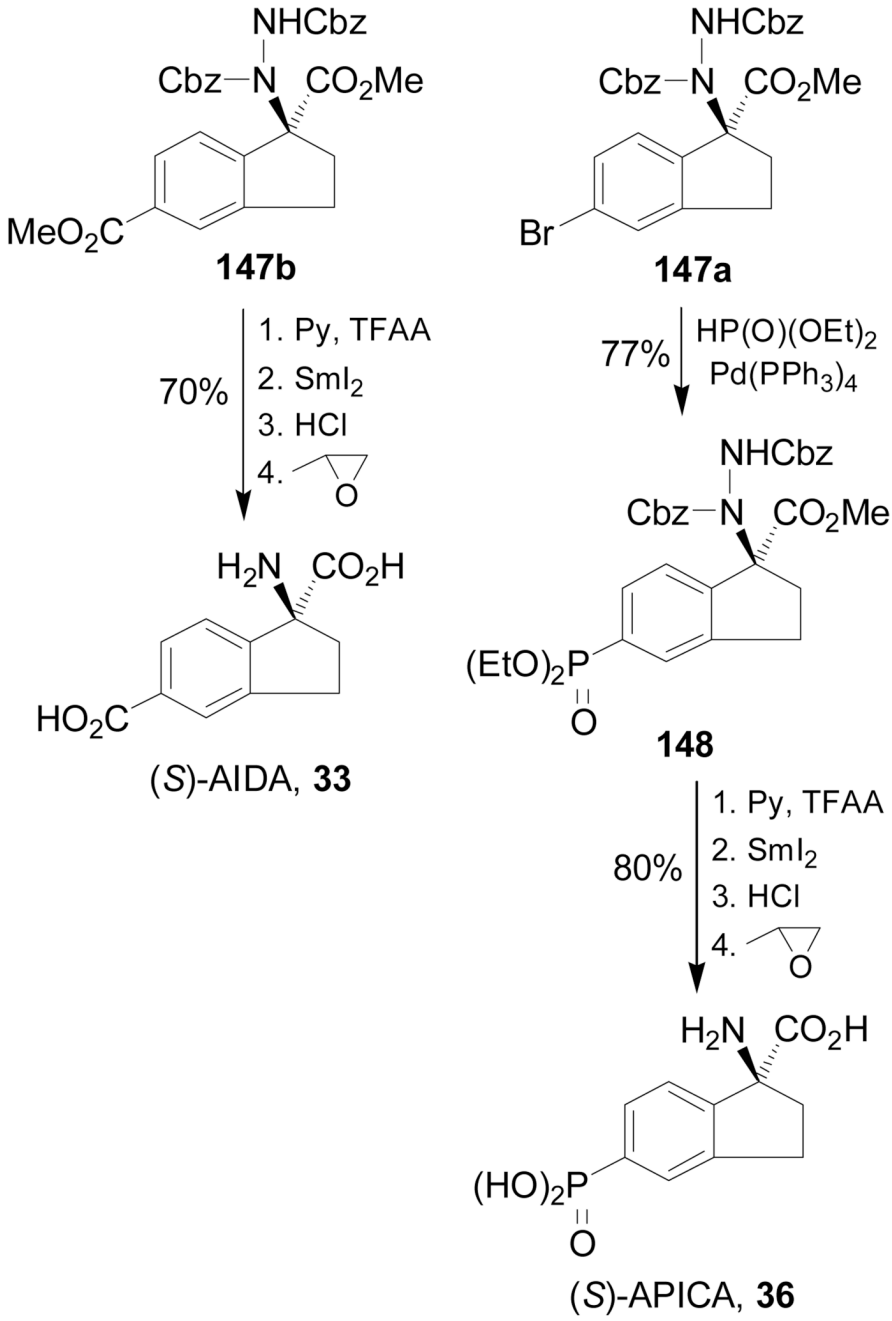
Scheme 30.



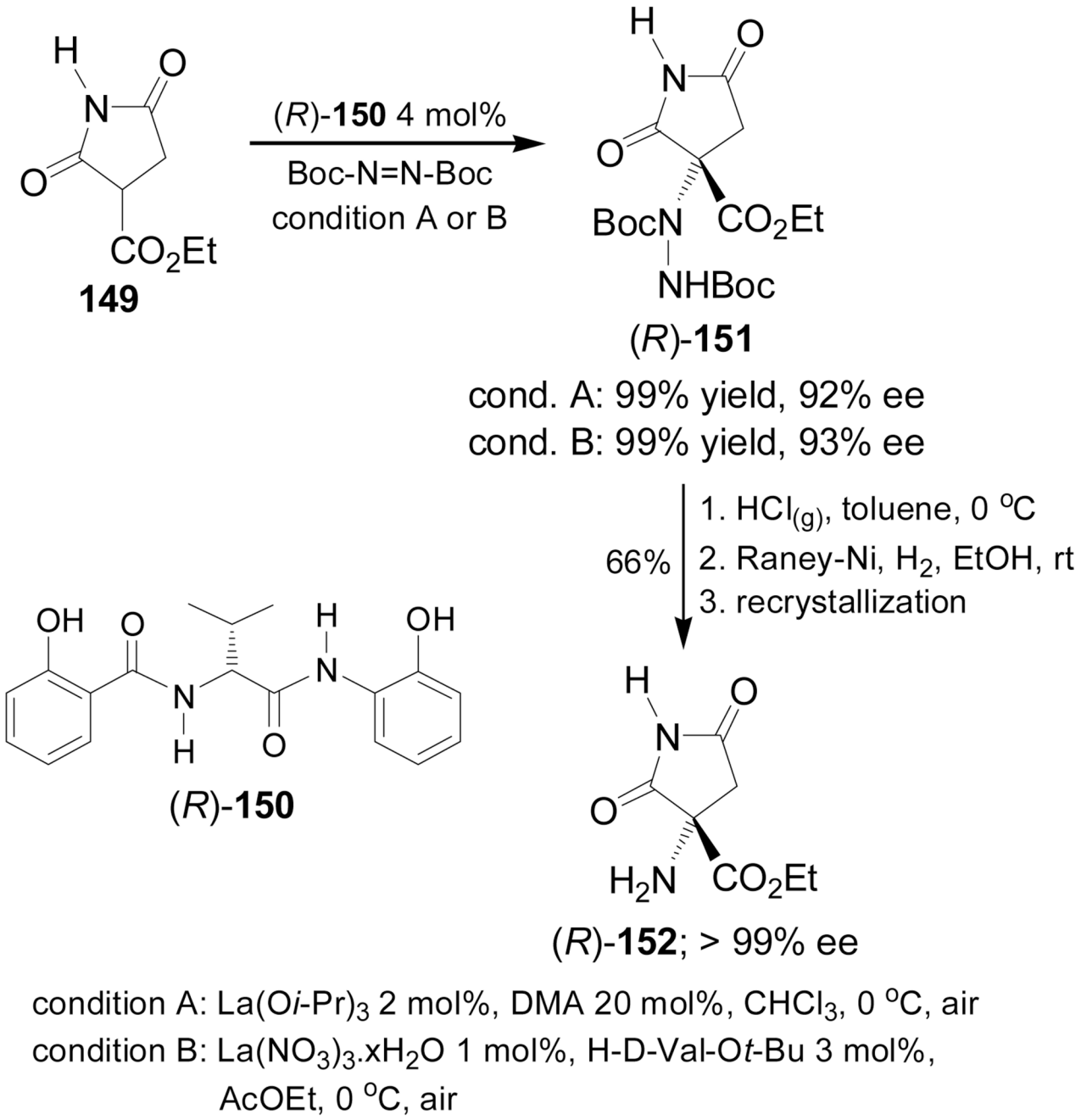
Scheme 31.



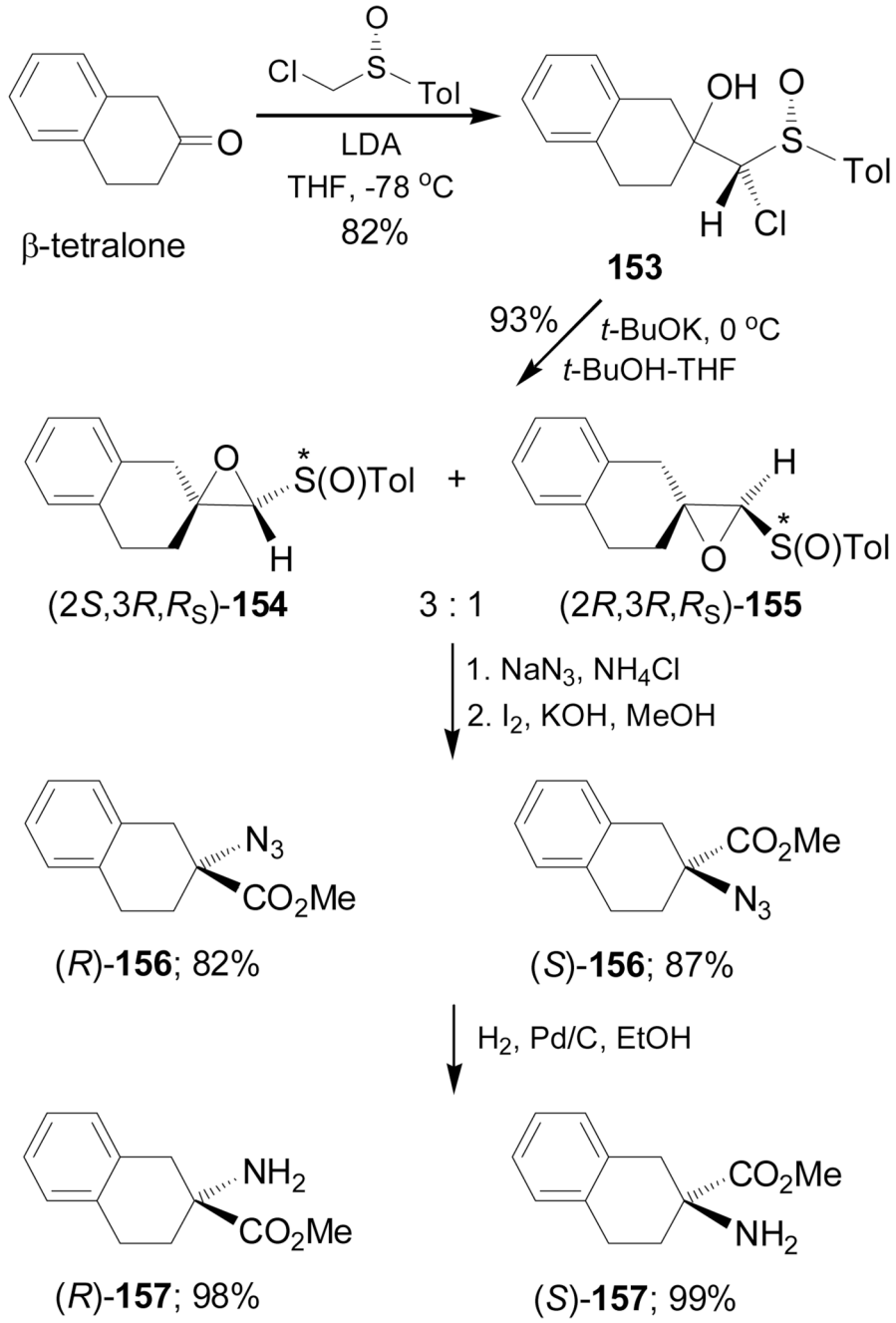
Scheme 32.



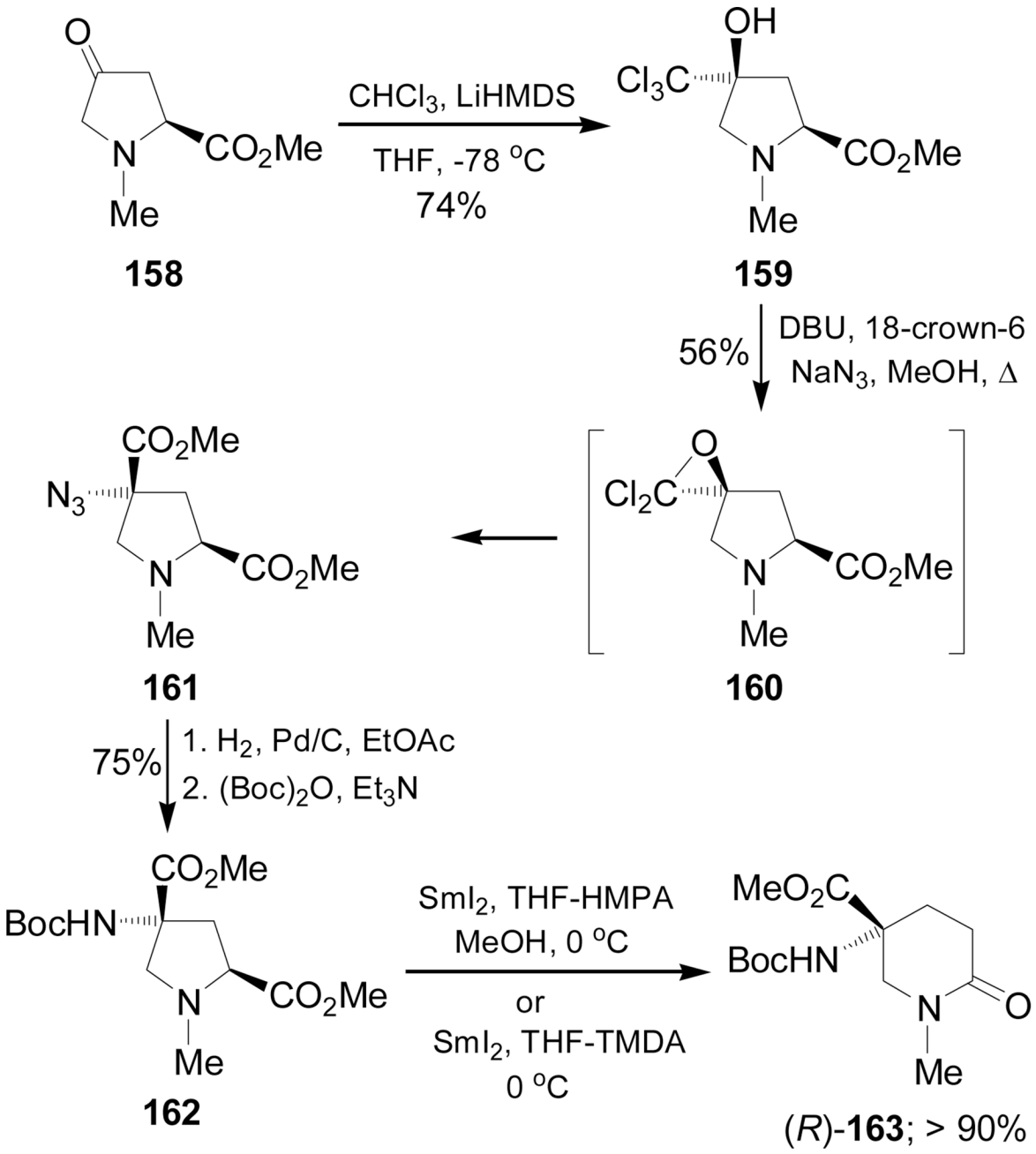
Scheme 33.



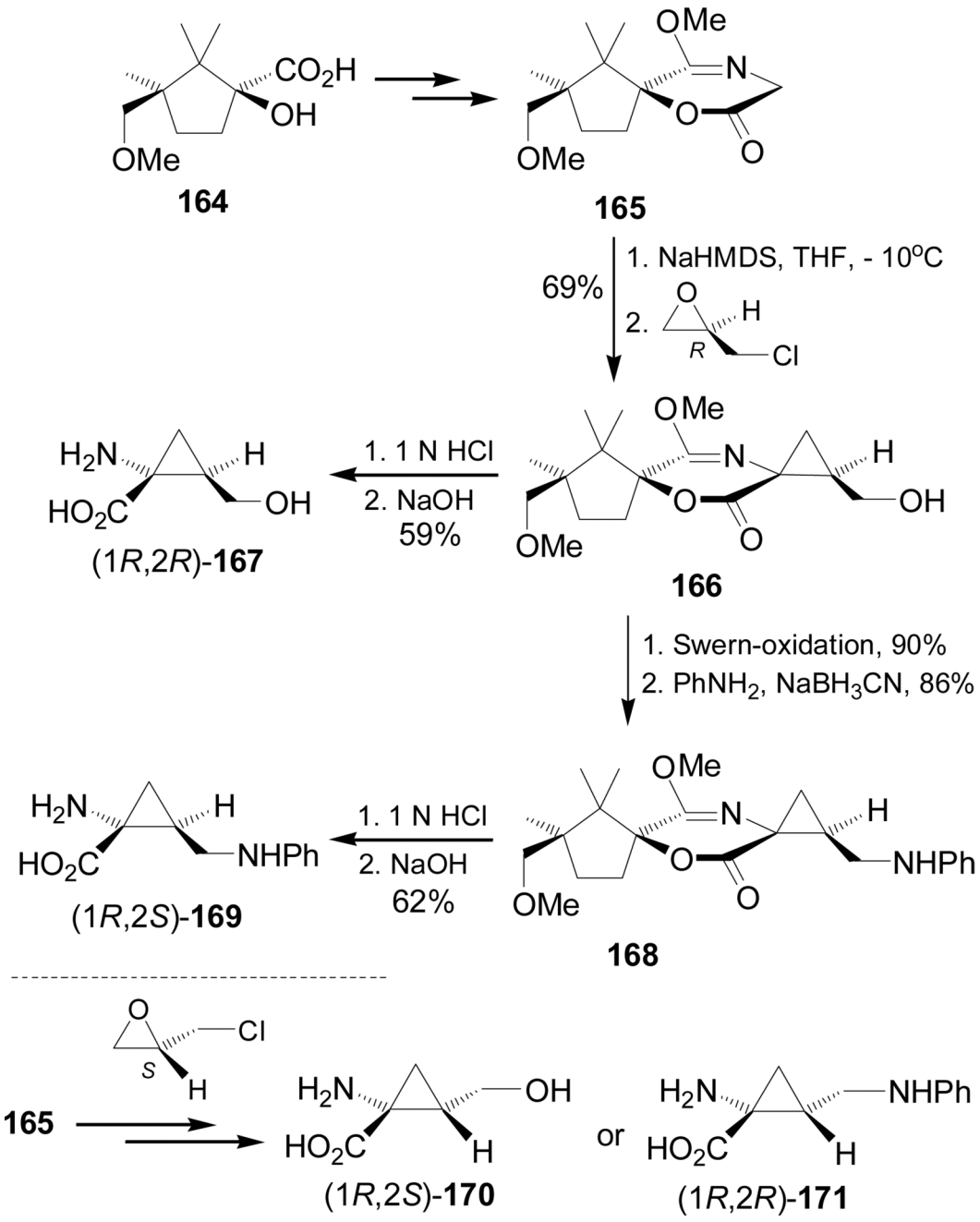
Scheme 34.



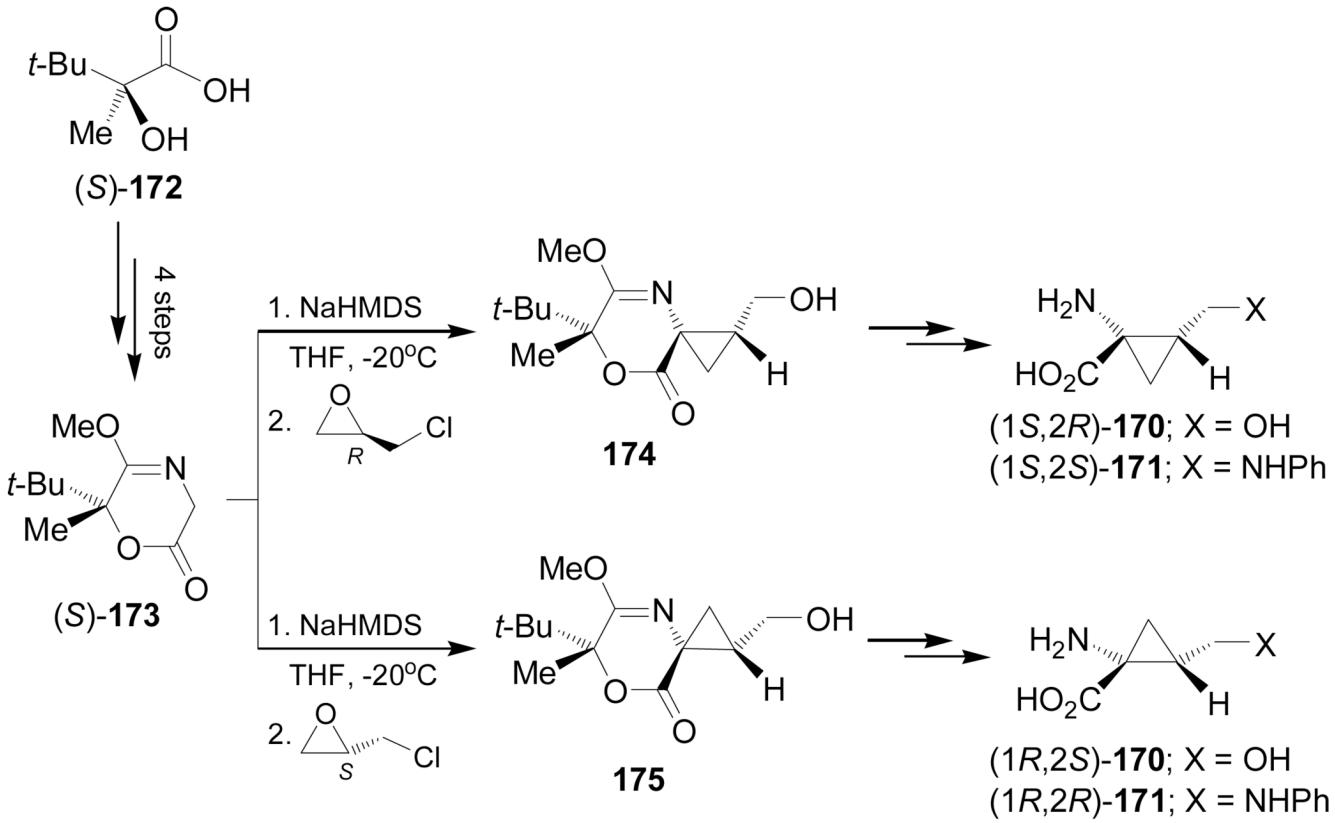
Scheme 35.



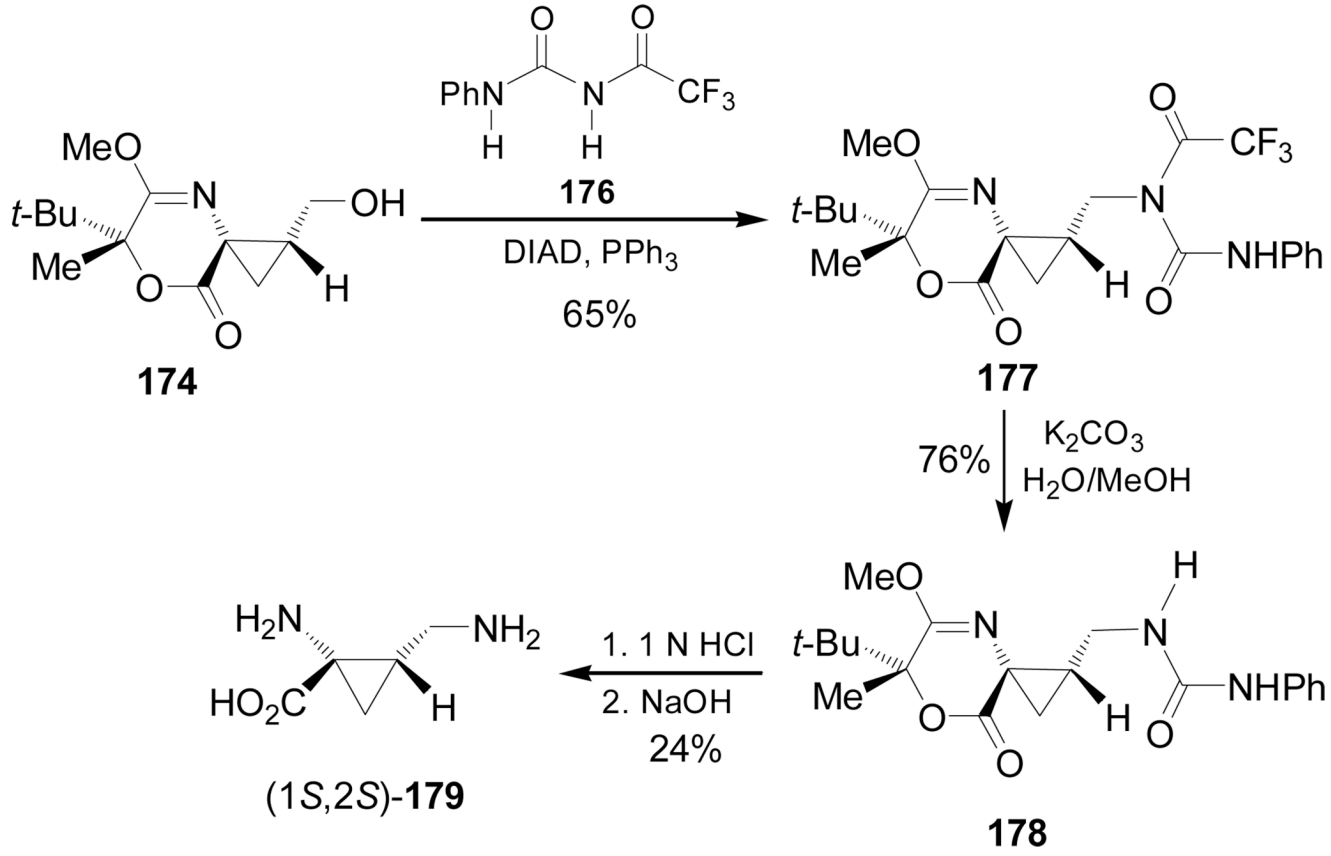
Scheme 36.



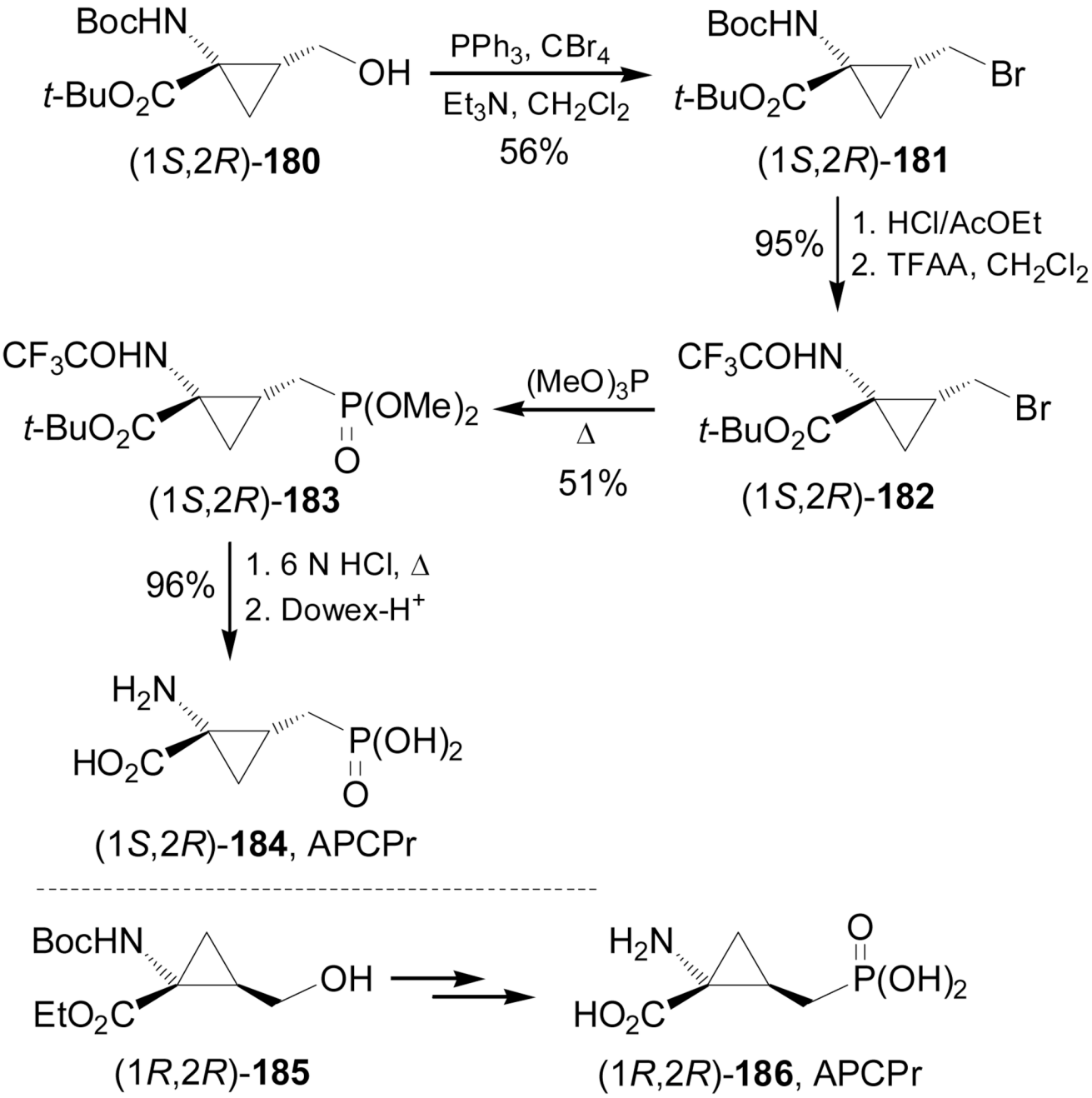
Scheme 37.



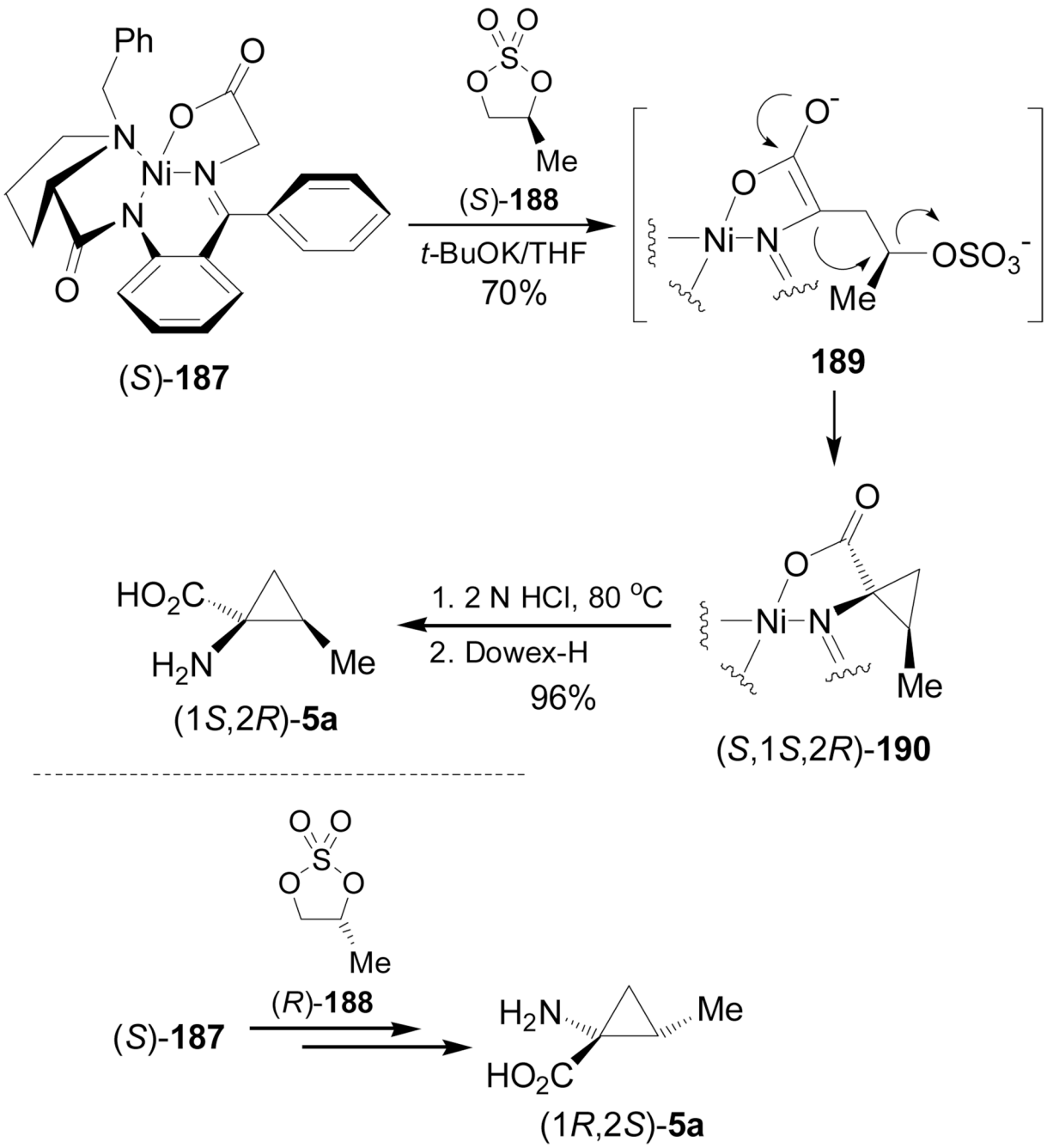
Scheme 38.



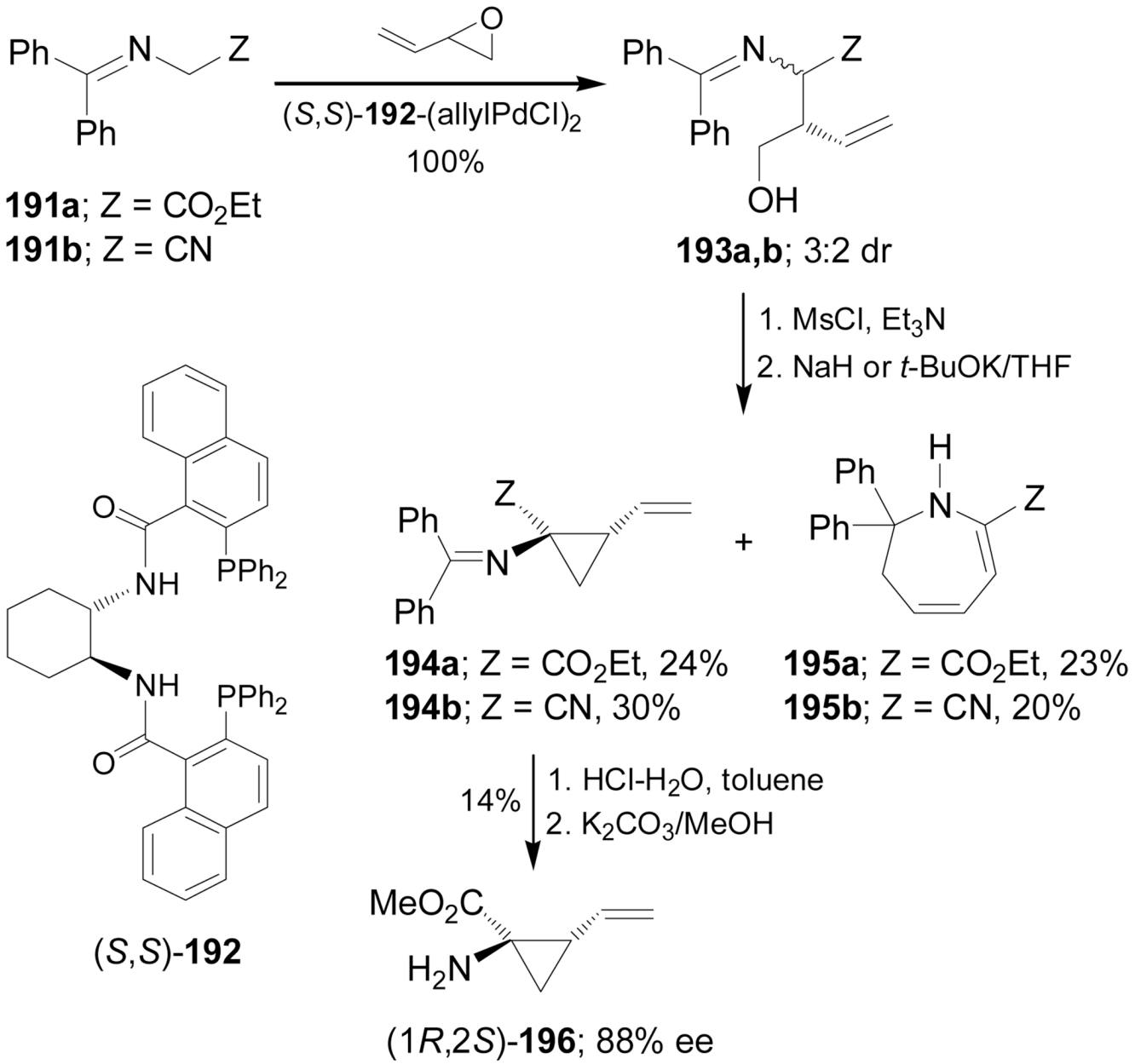
Scheme 39.



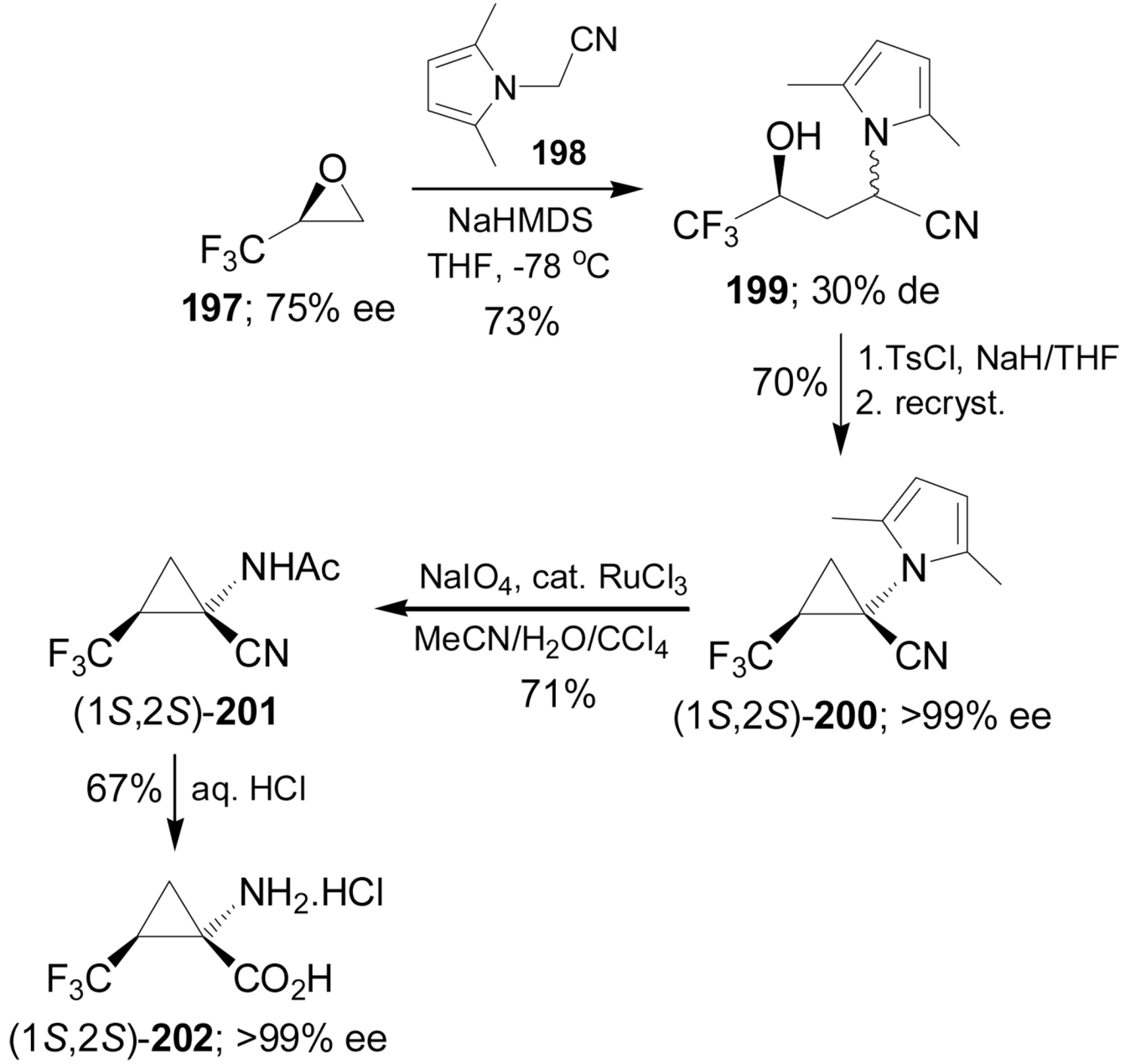
Scheme 40.



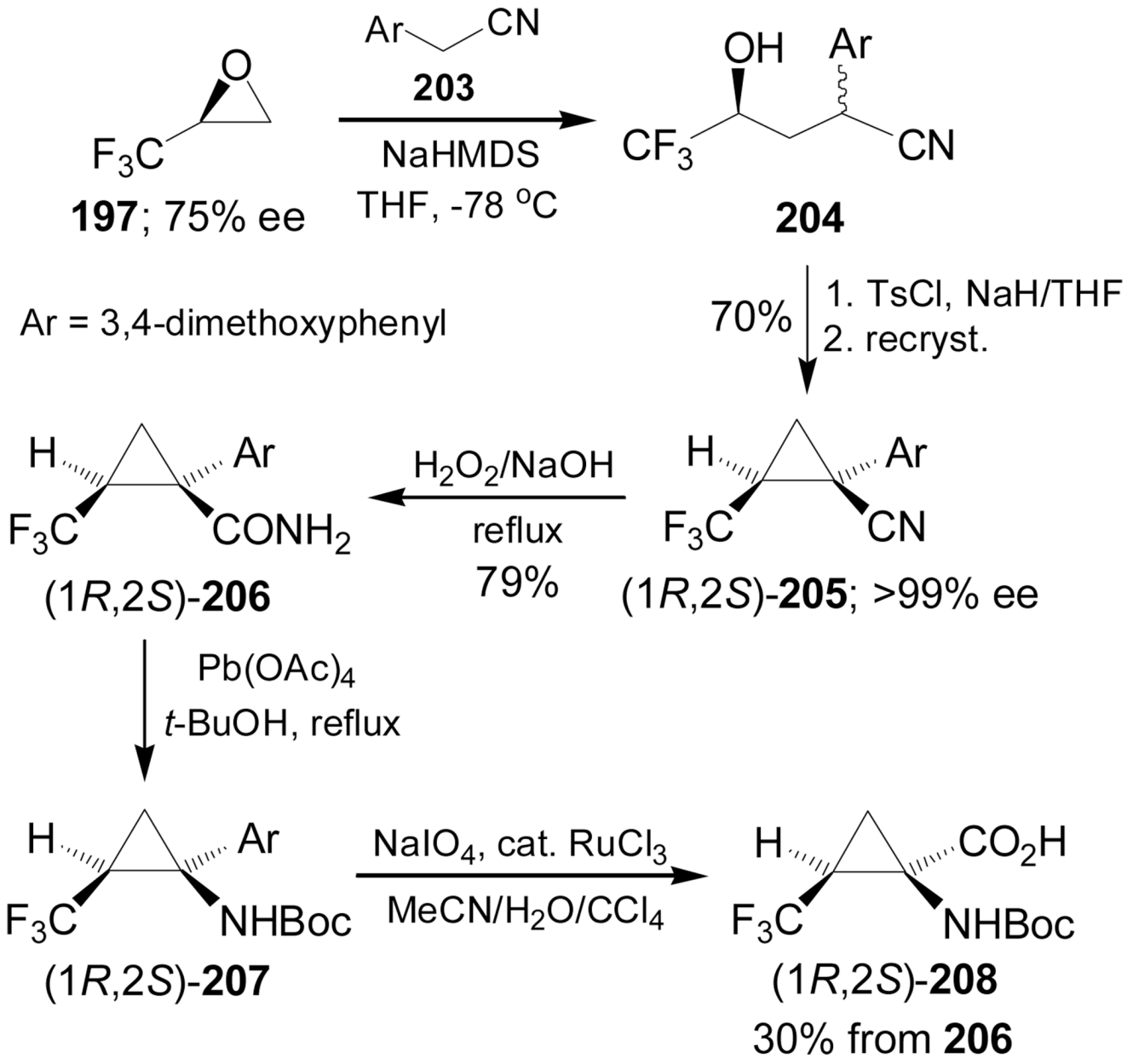
Scheme 41.



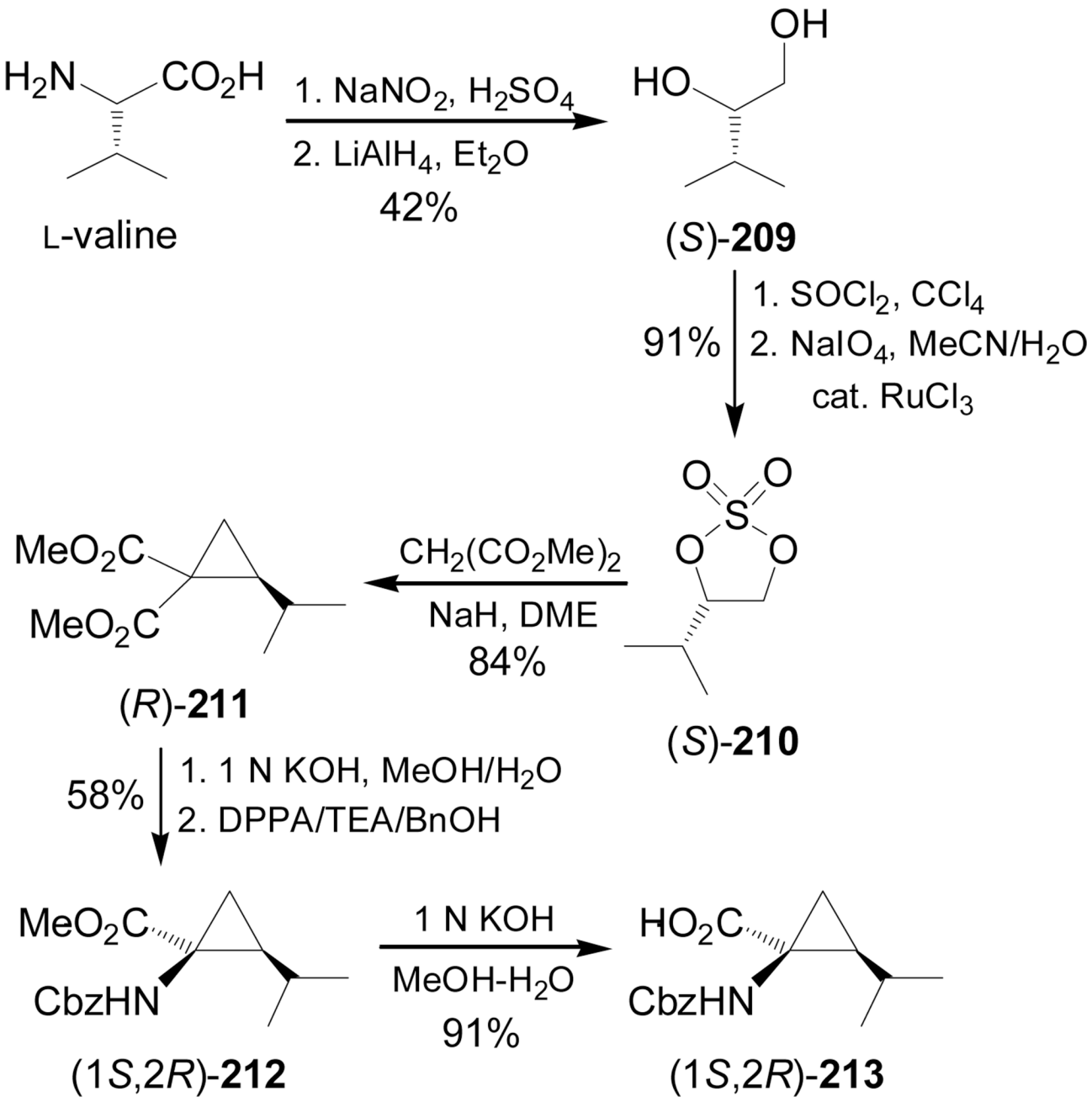
Scheme 42.



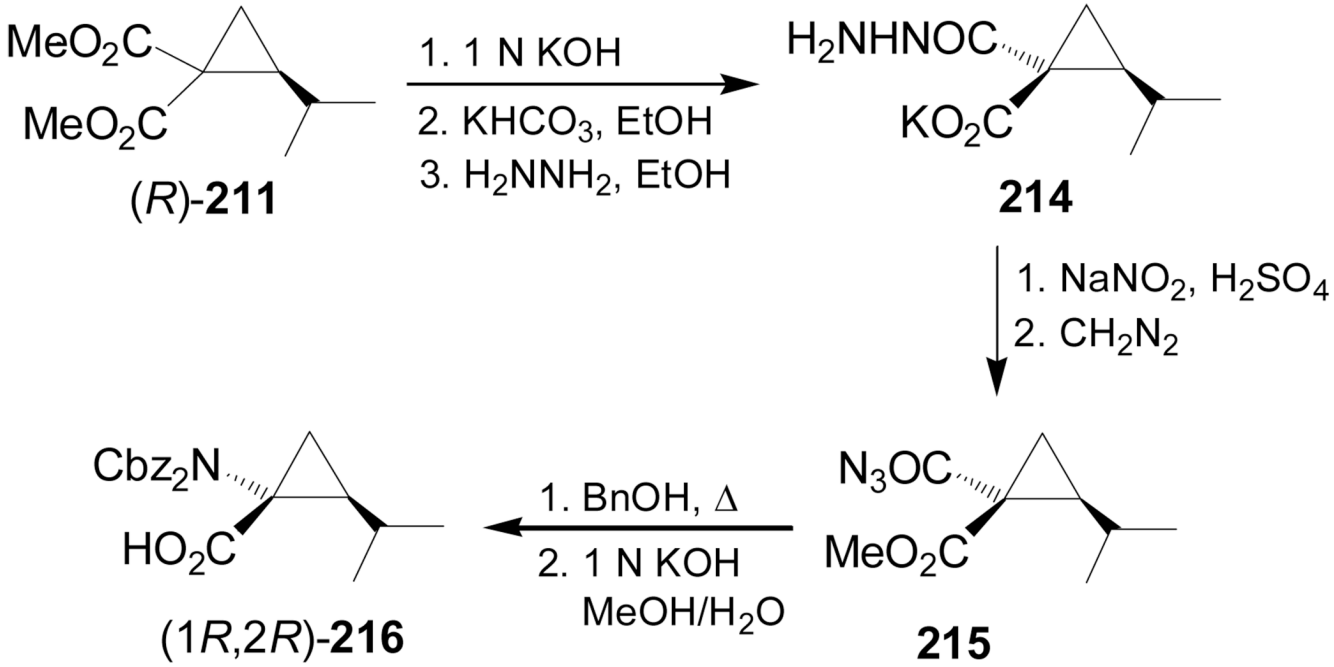
Scheme 43.



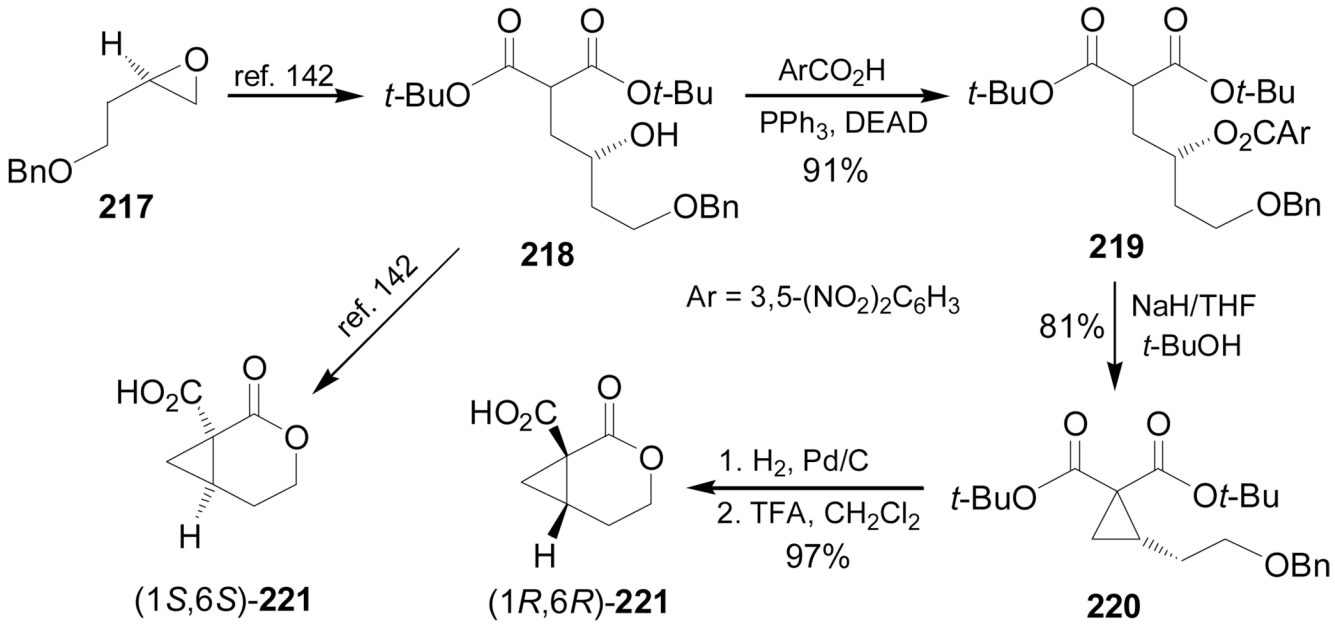
Scheme 44.



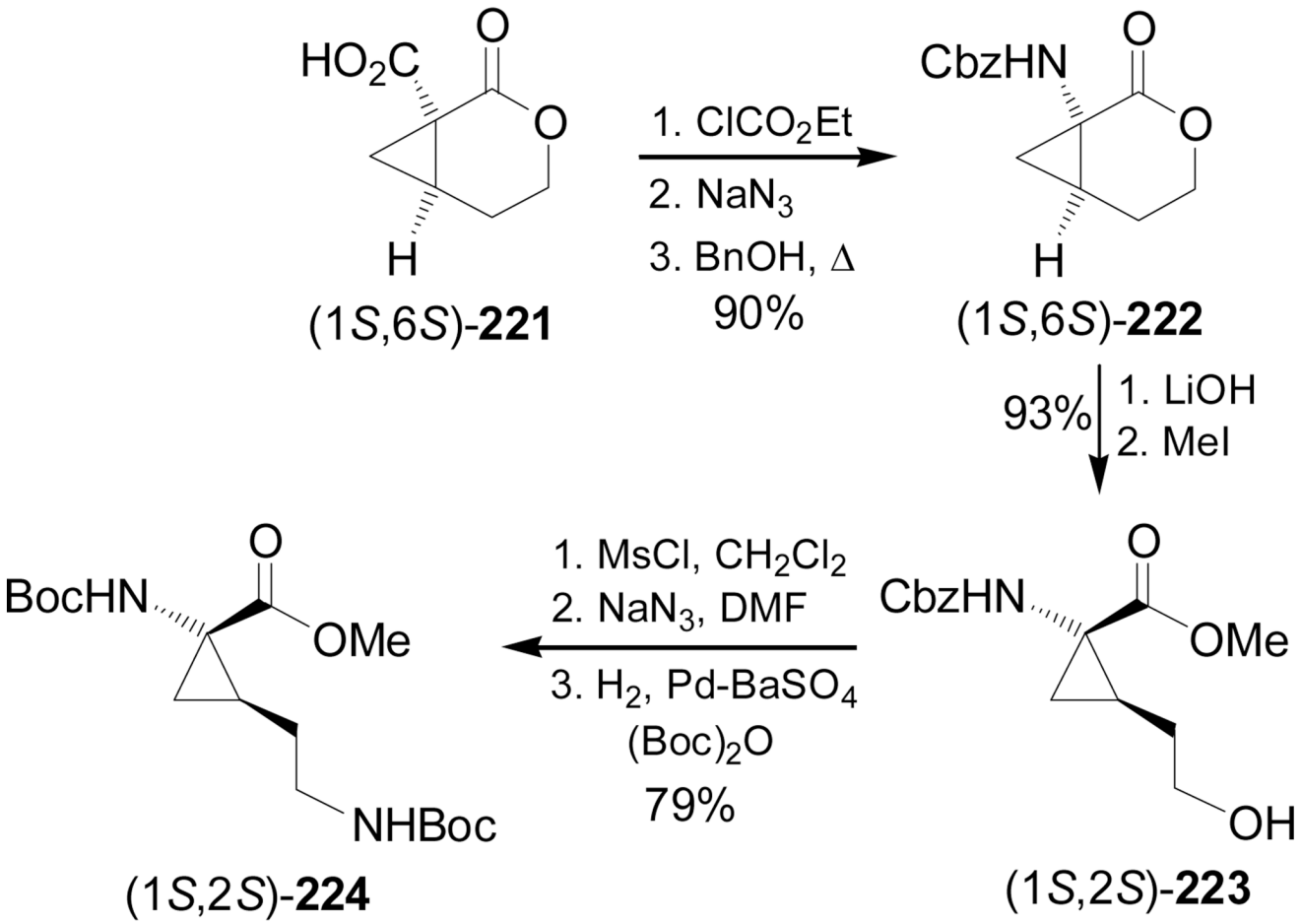
Scheme 45.



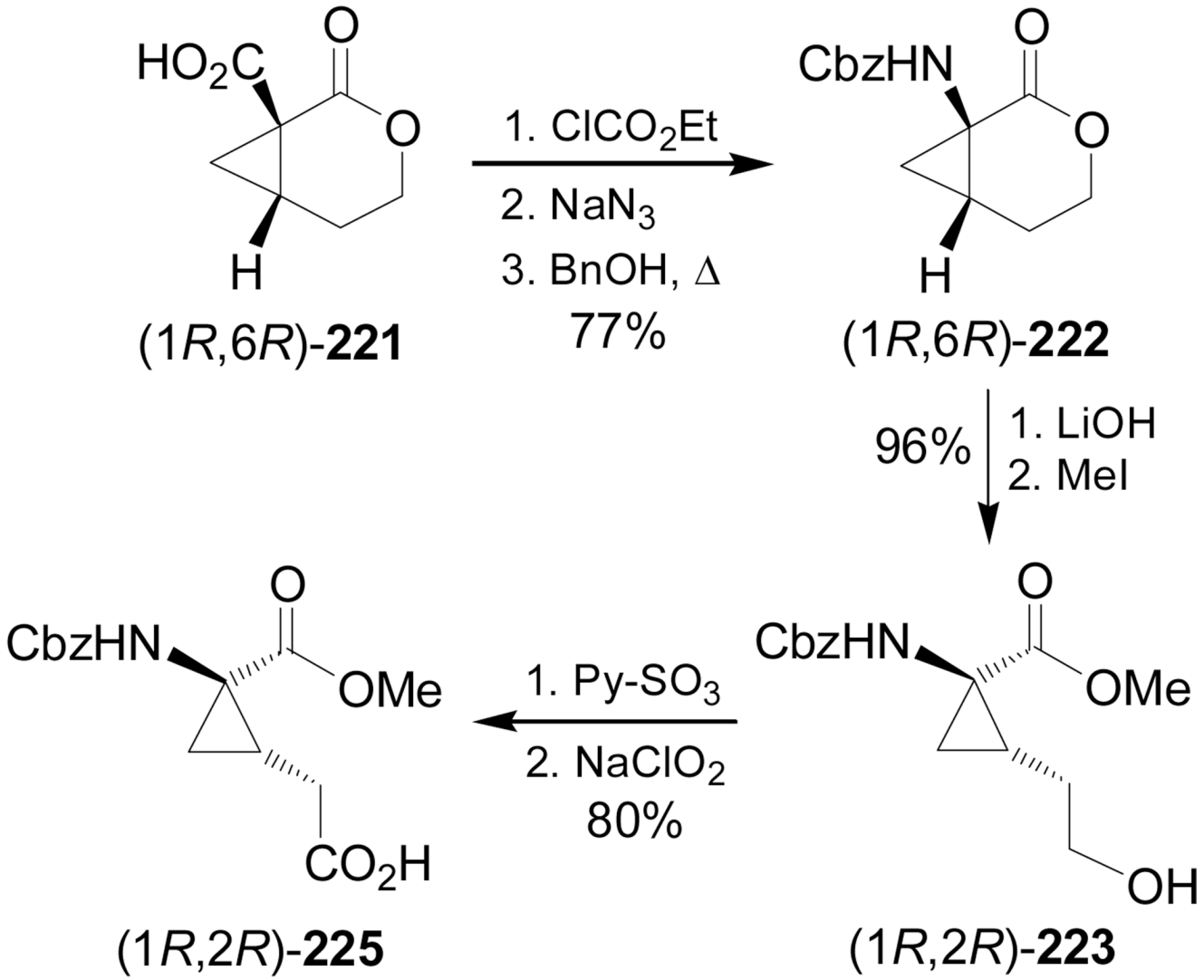
Scheme 46.



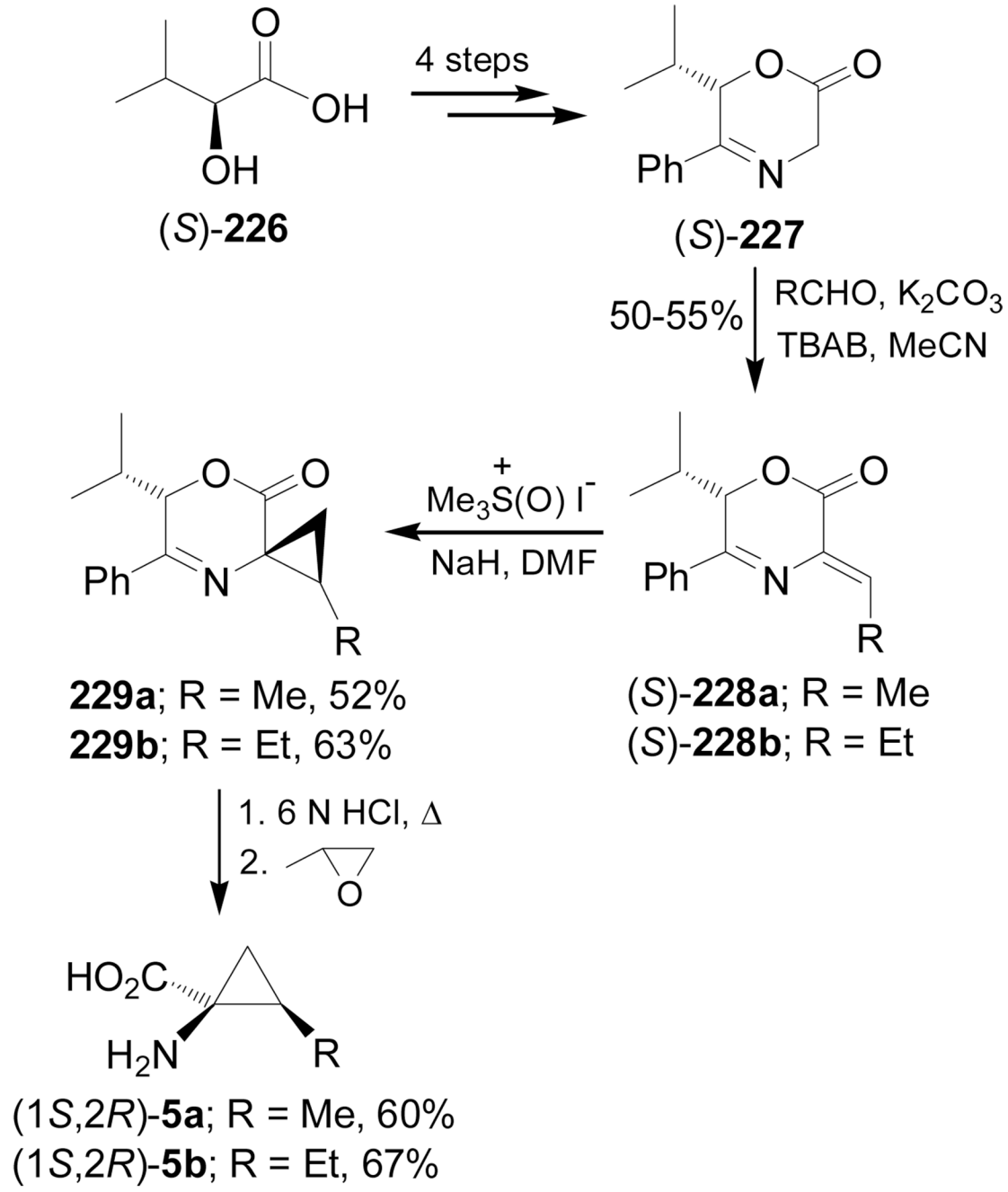
Scheme 47.



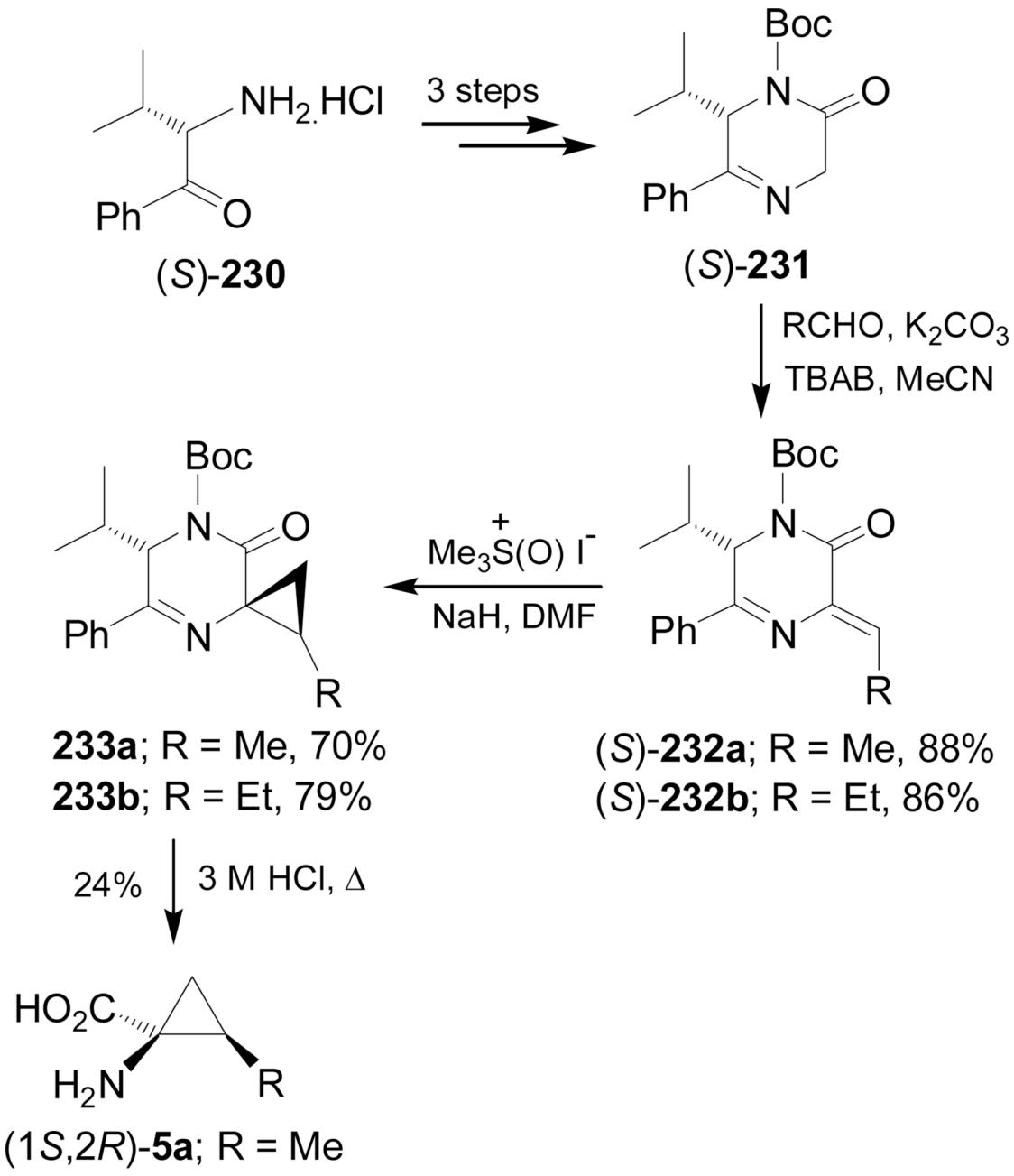
Scheme 48.



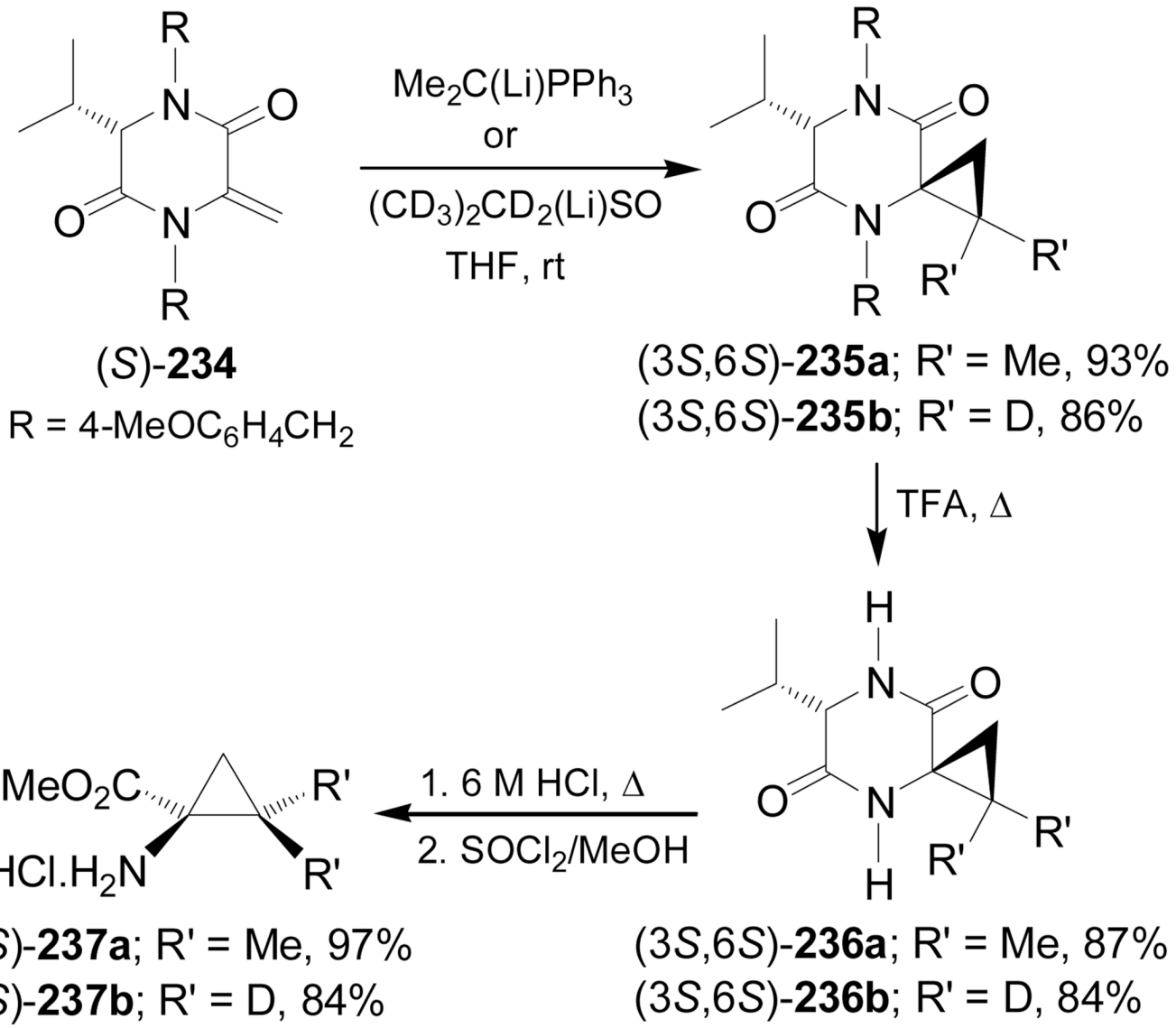
Scheme 49.



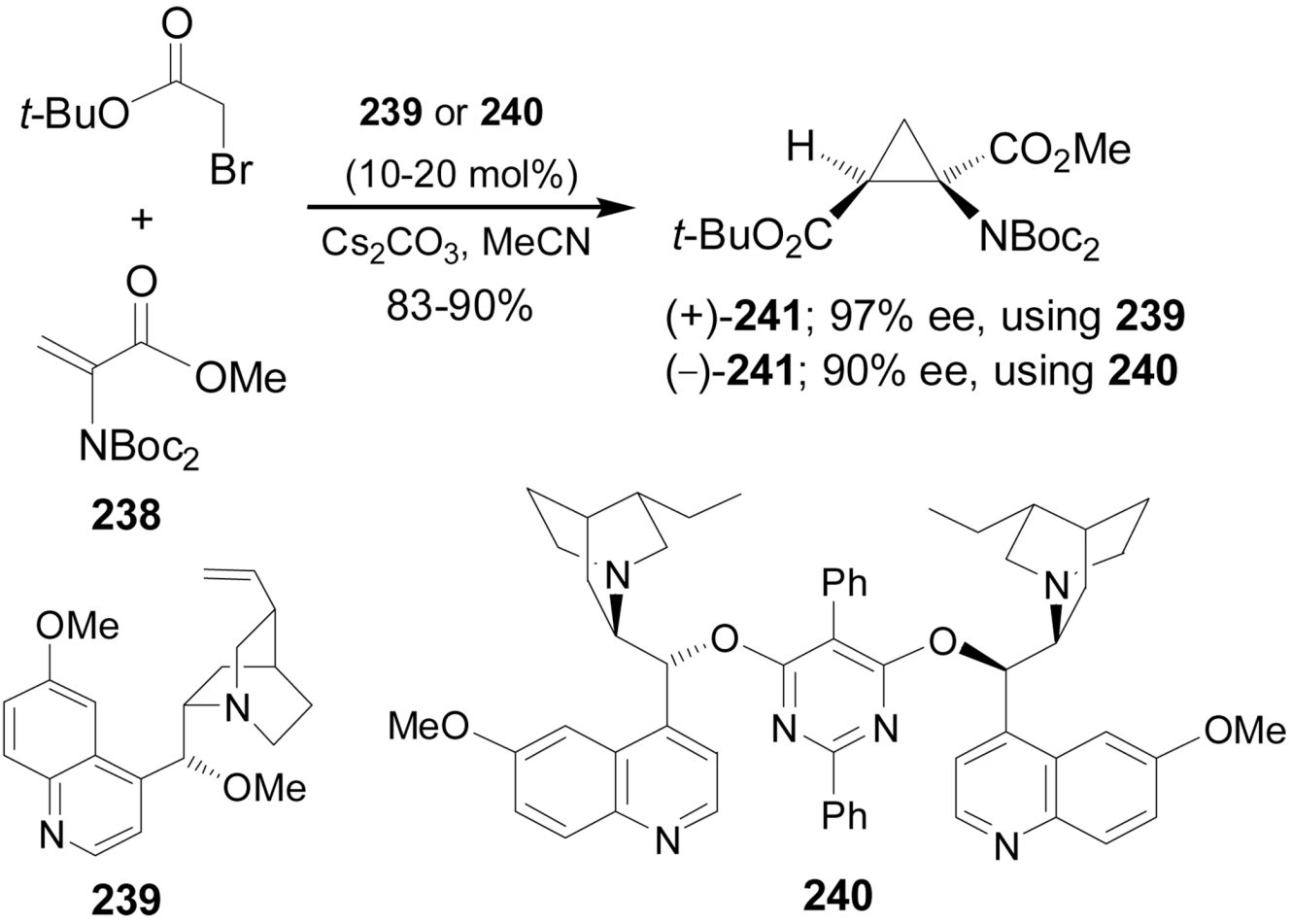
Scheme 50.



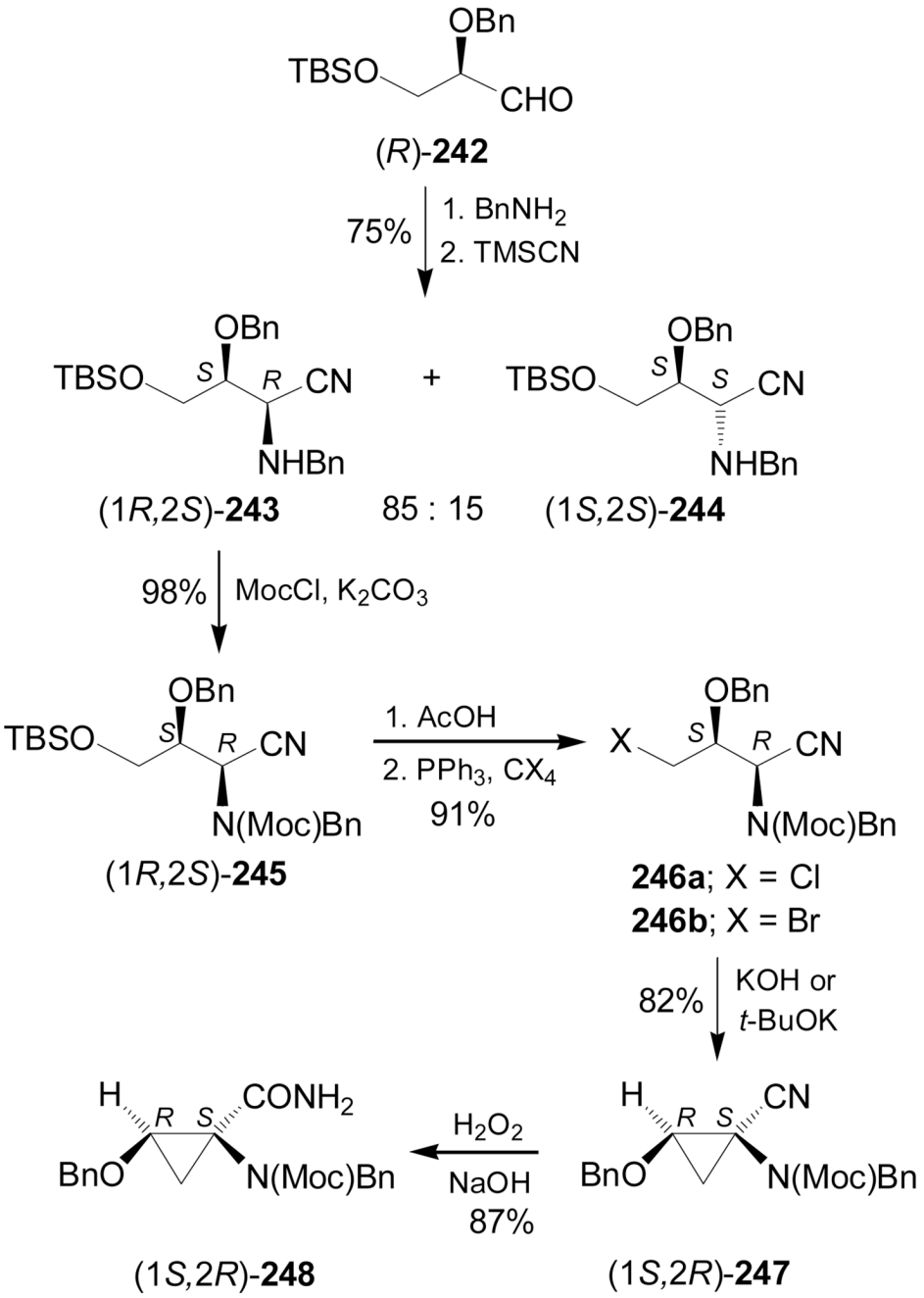
Scheme 51.



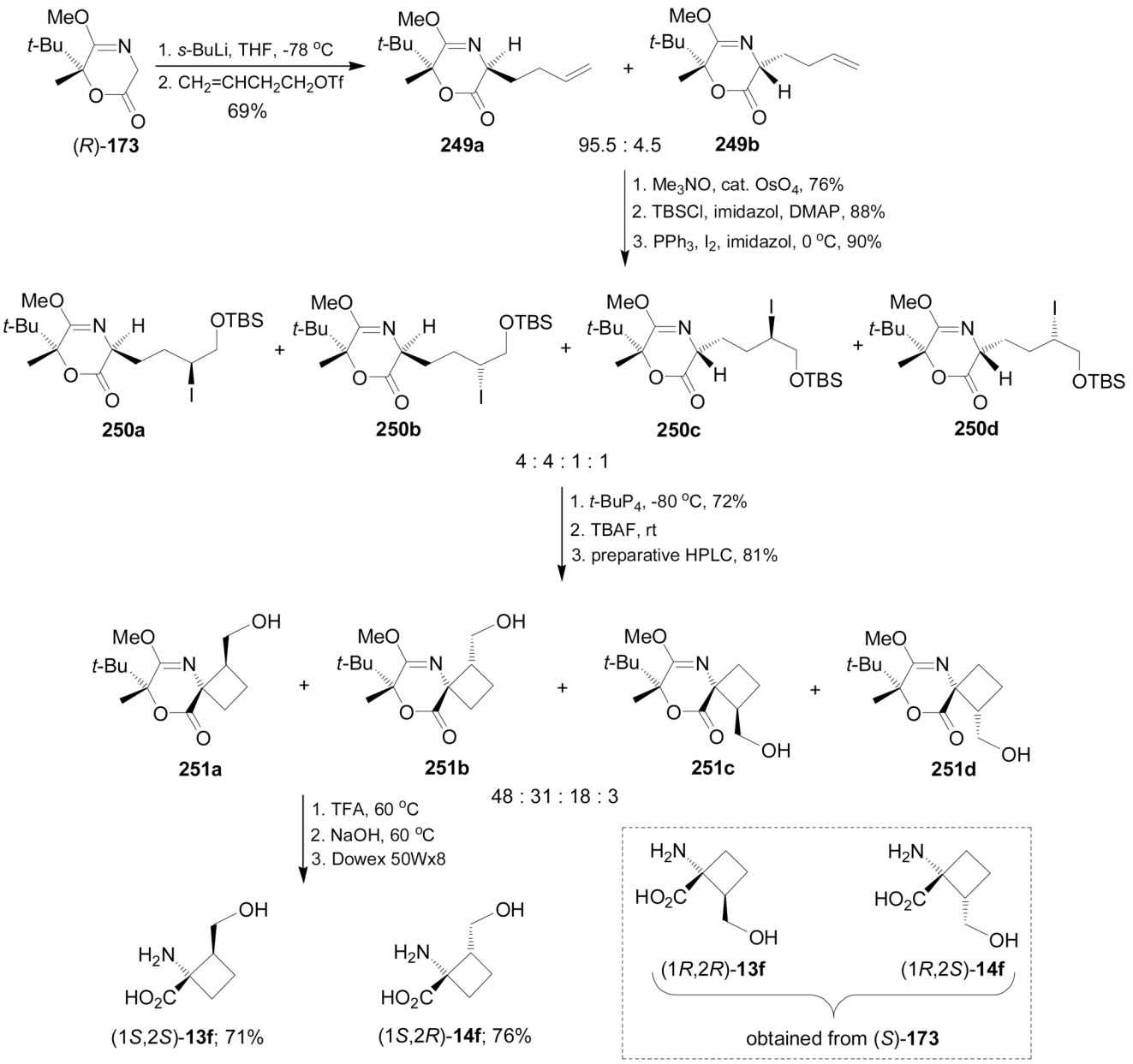
Scheme 52.



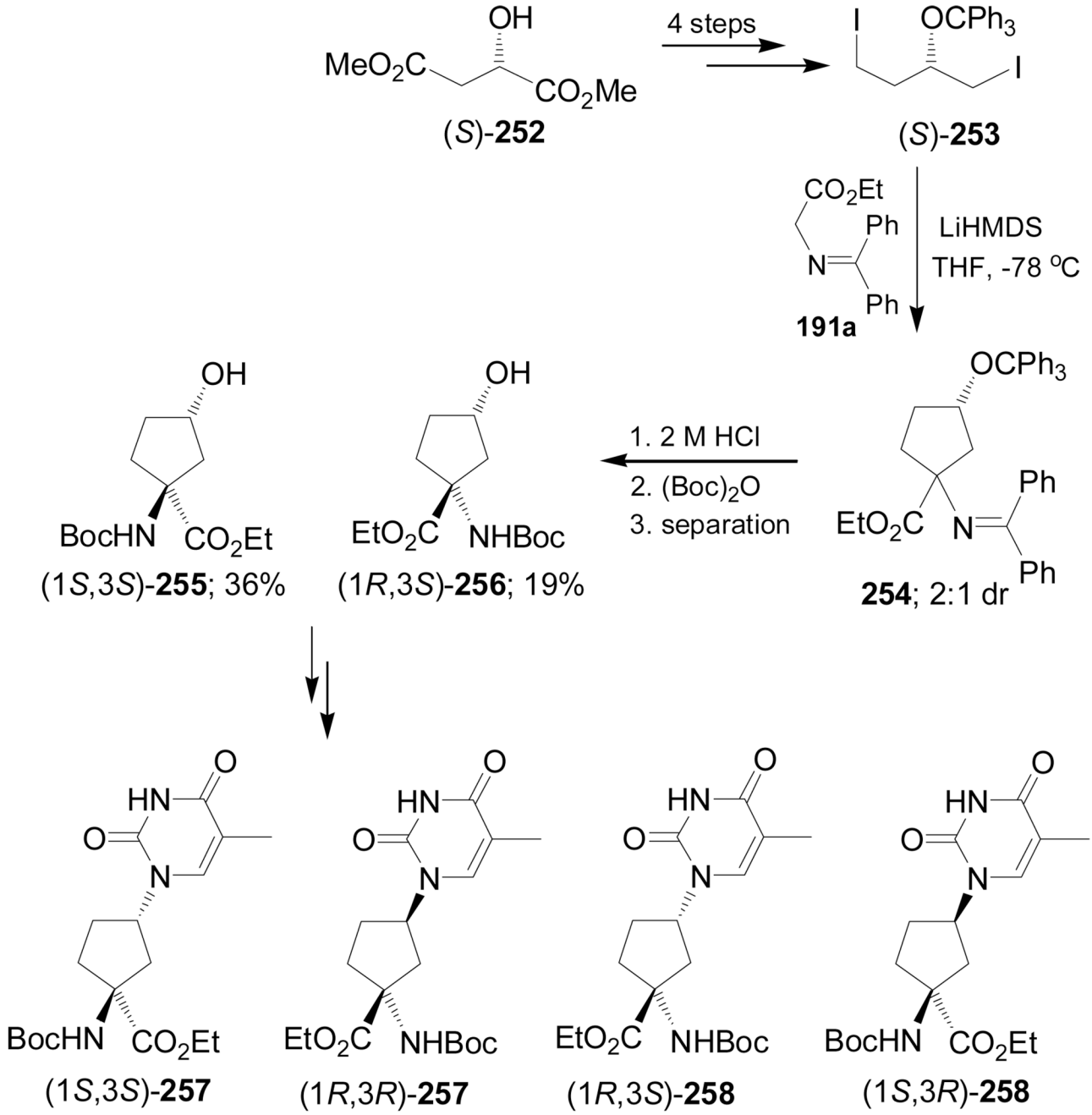
Scheme 53.



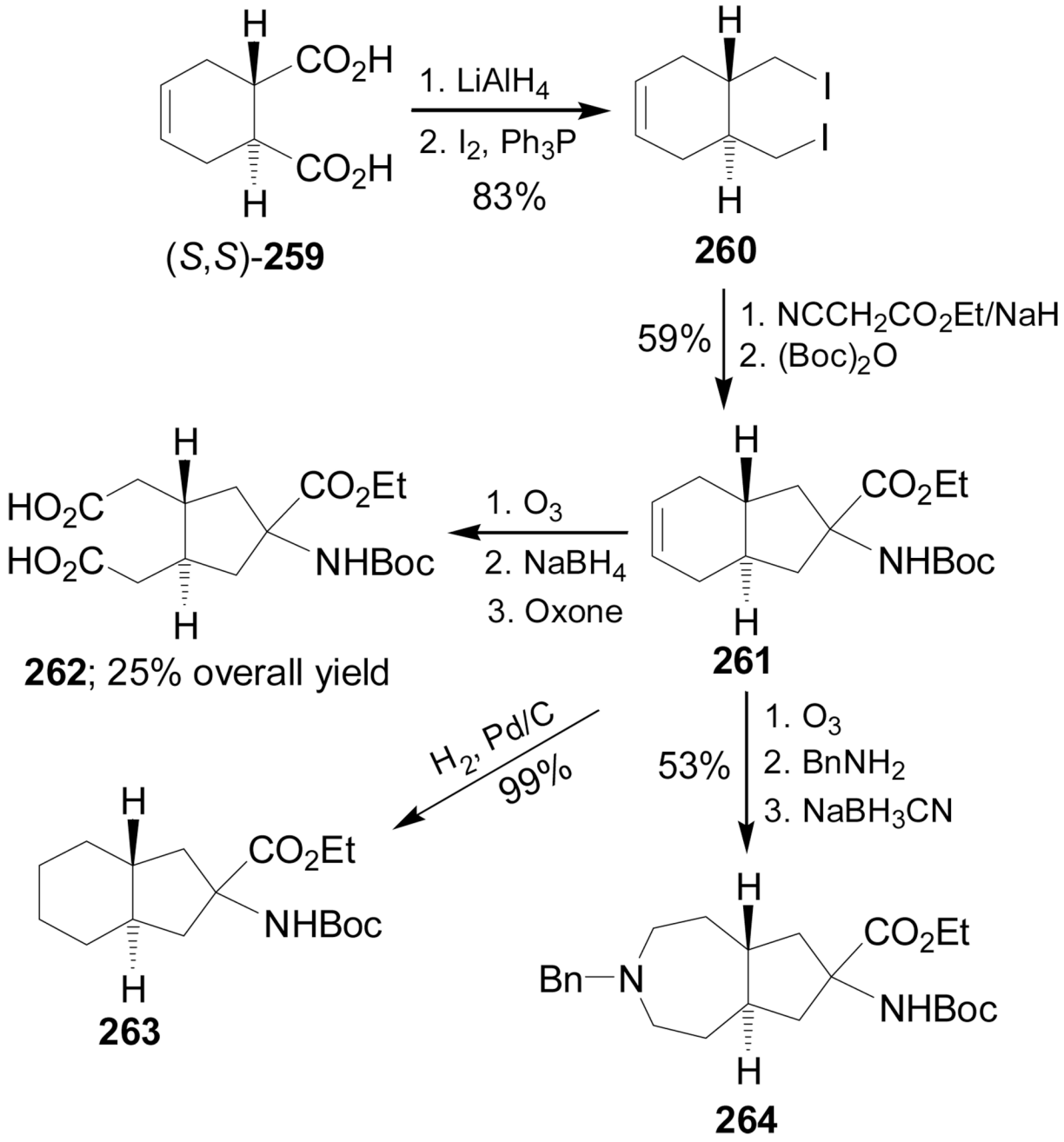
Scheme 54.



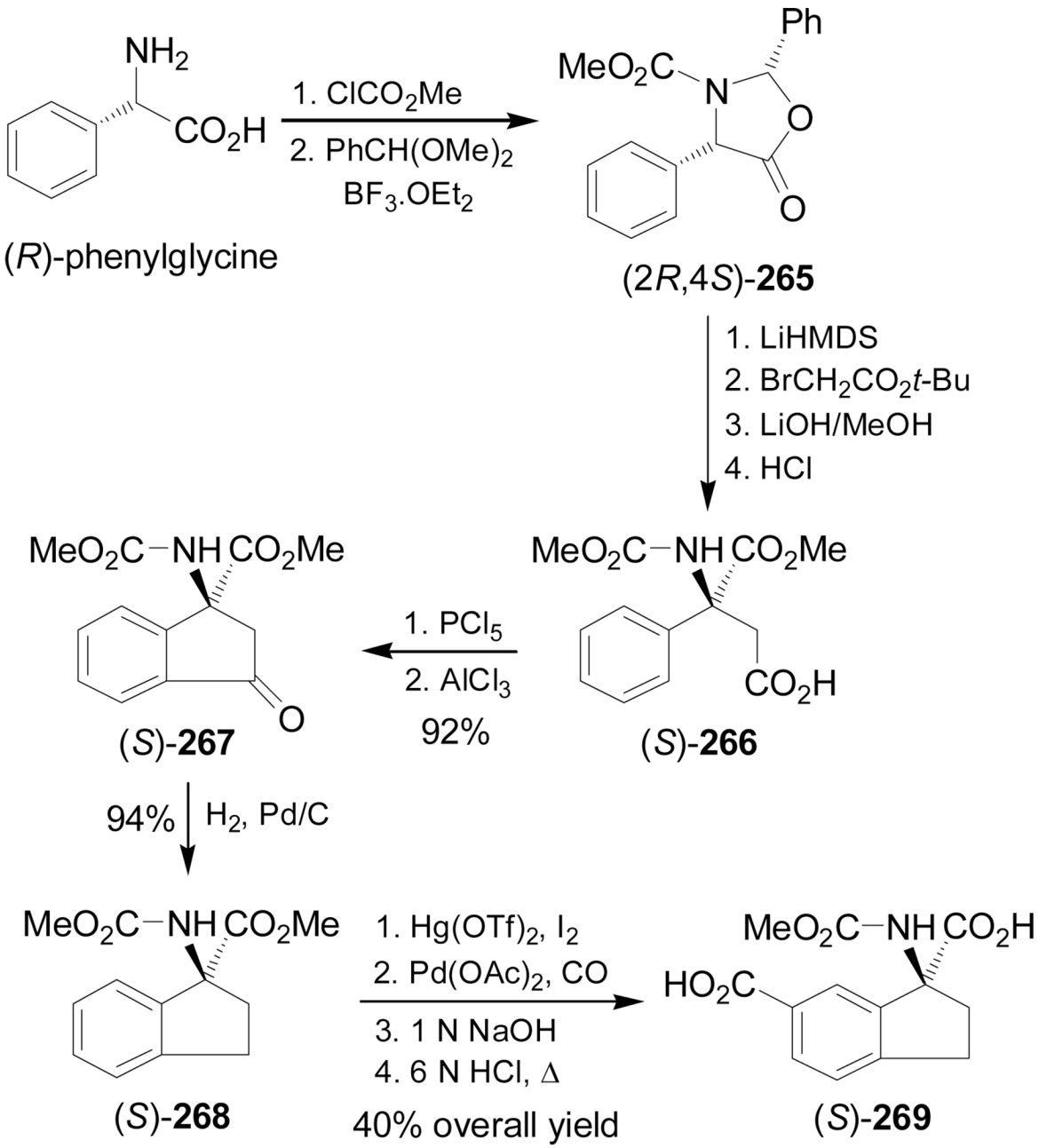
Scheme 55.



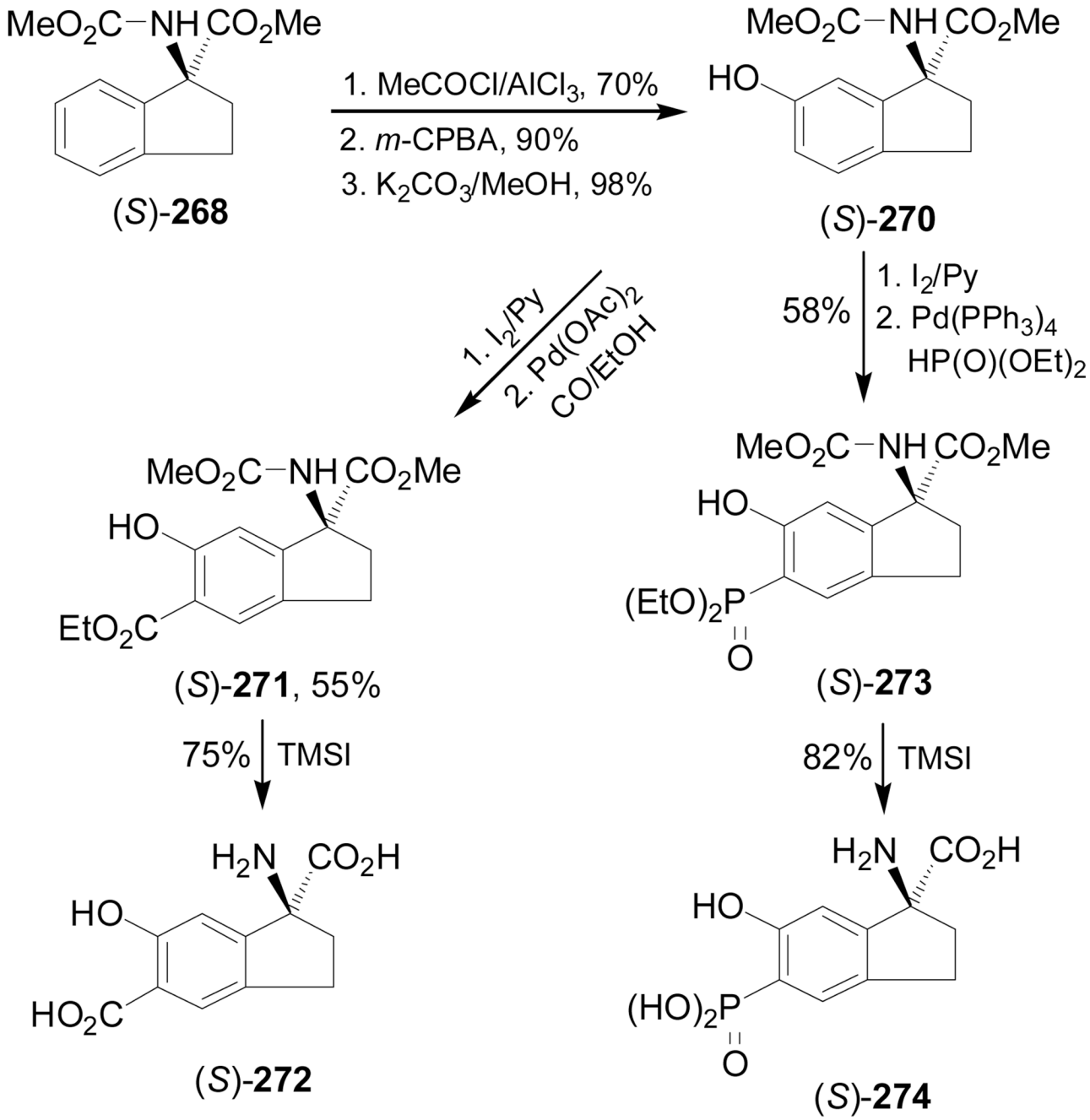
Scheme 56.



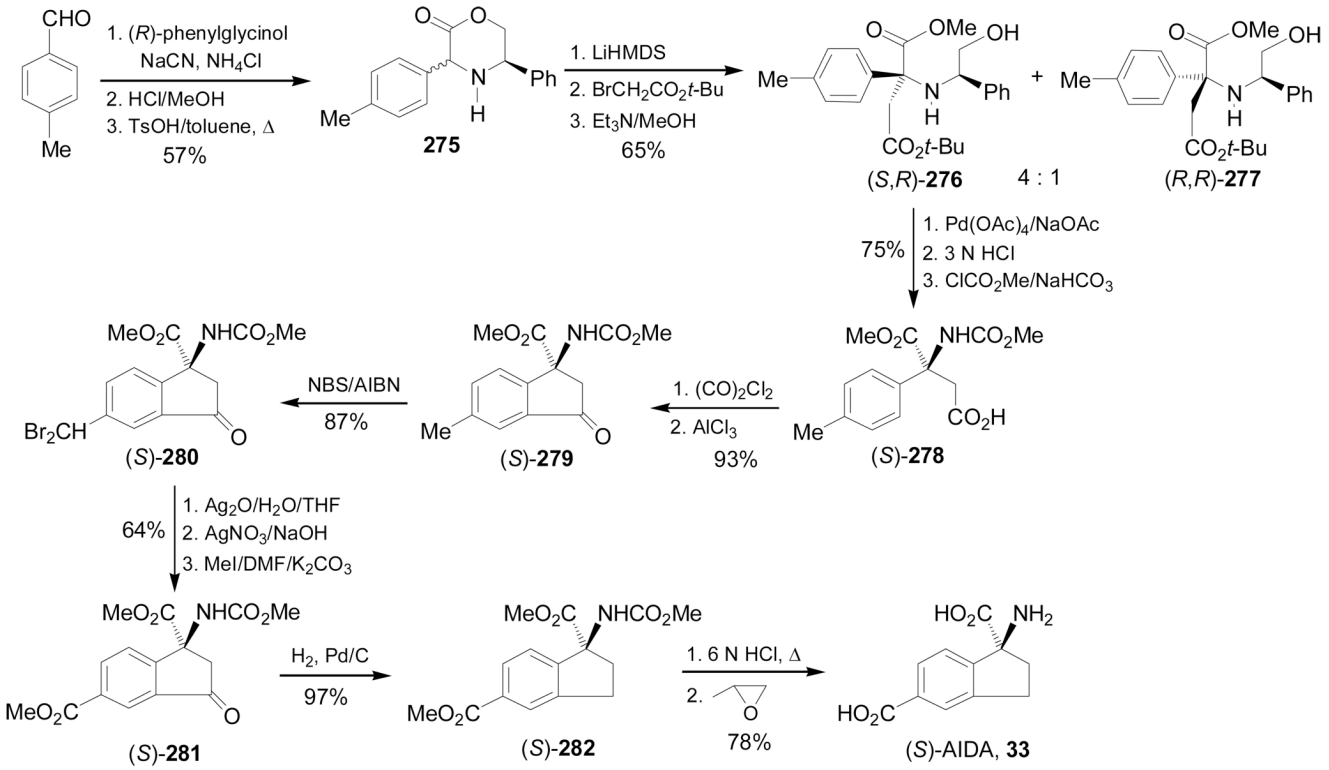
Scheme 57.



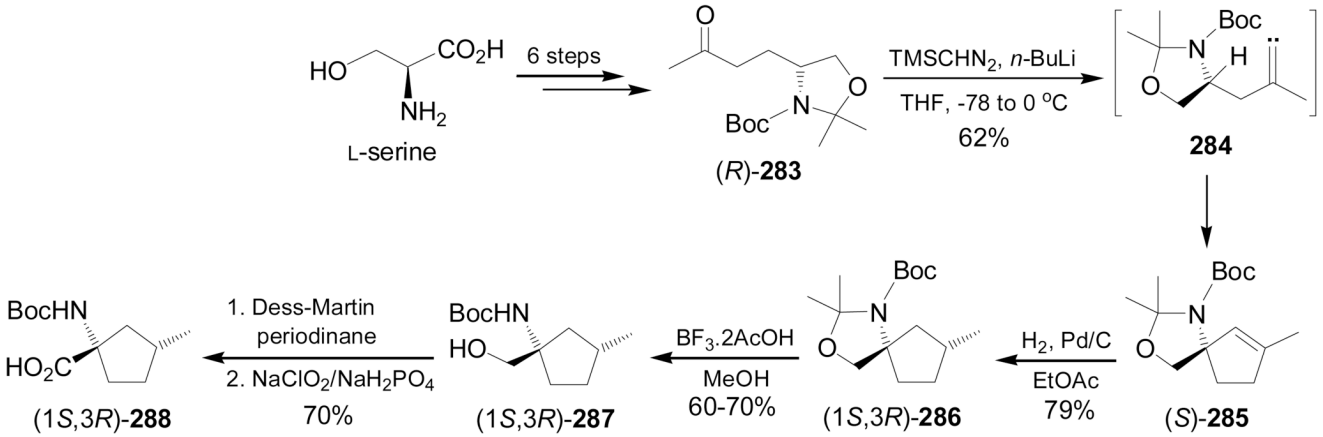
Scheme 58.



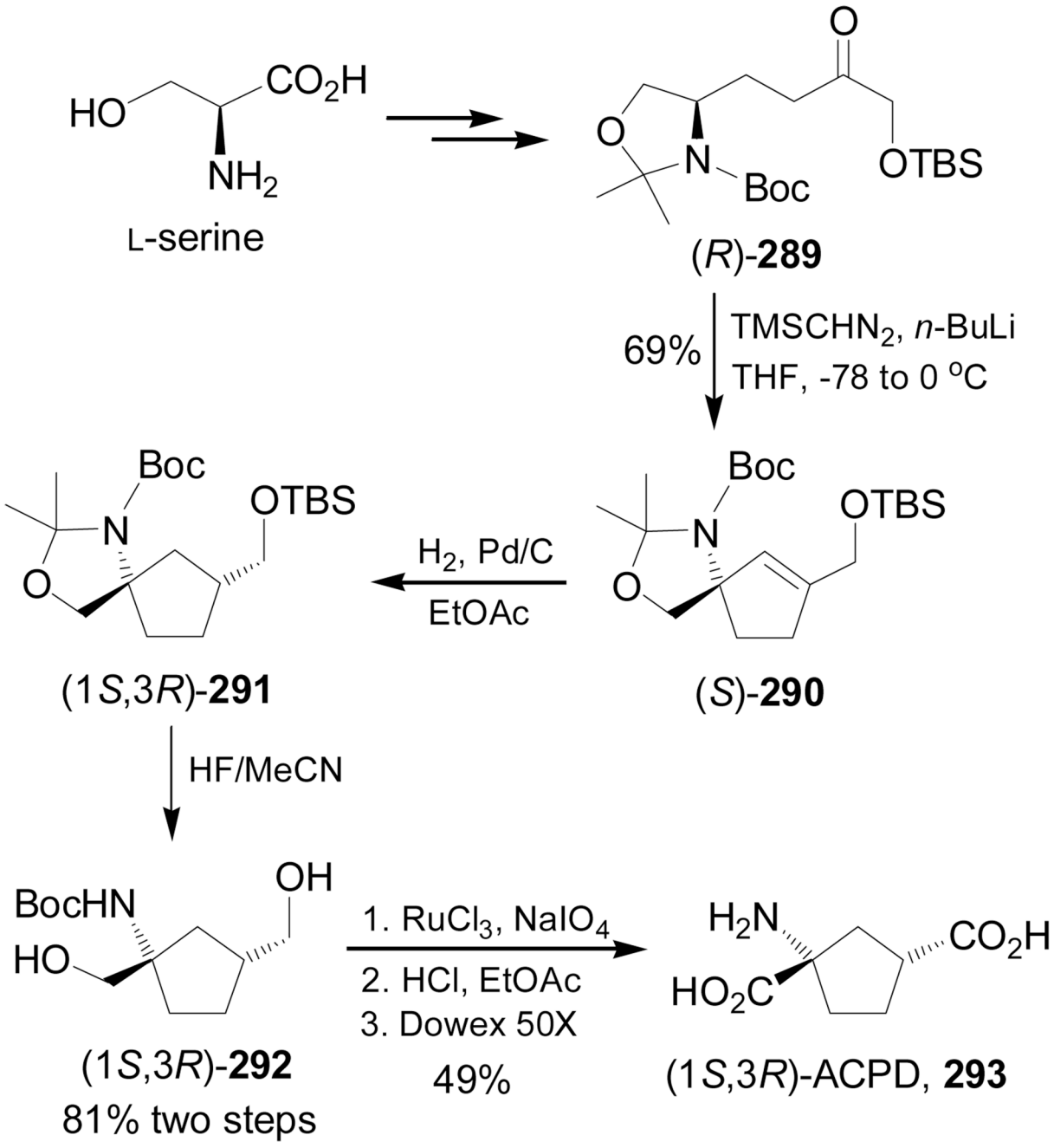
Scheme 59.



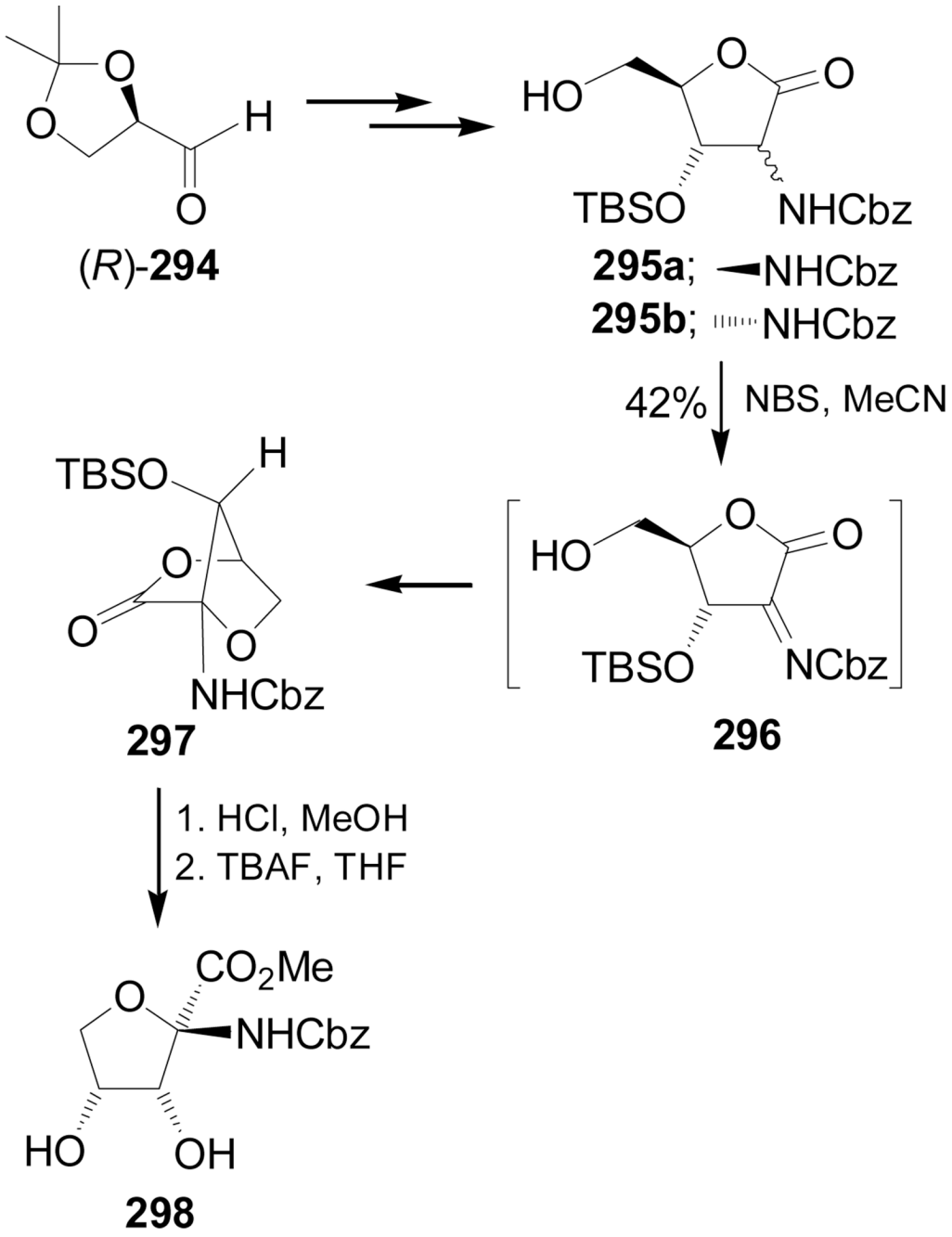
Scheme 60.



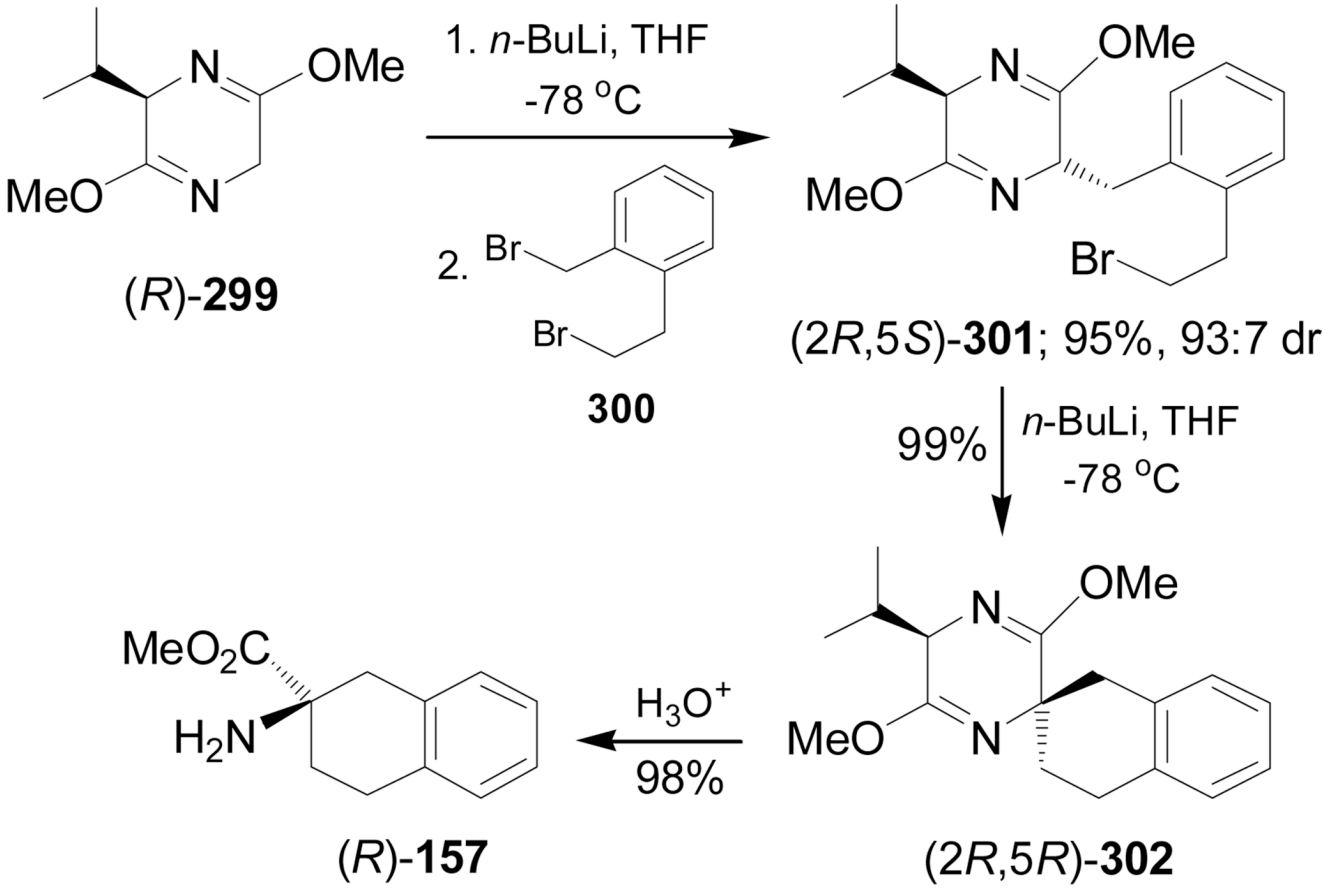
Scheme 61.



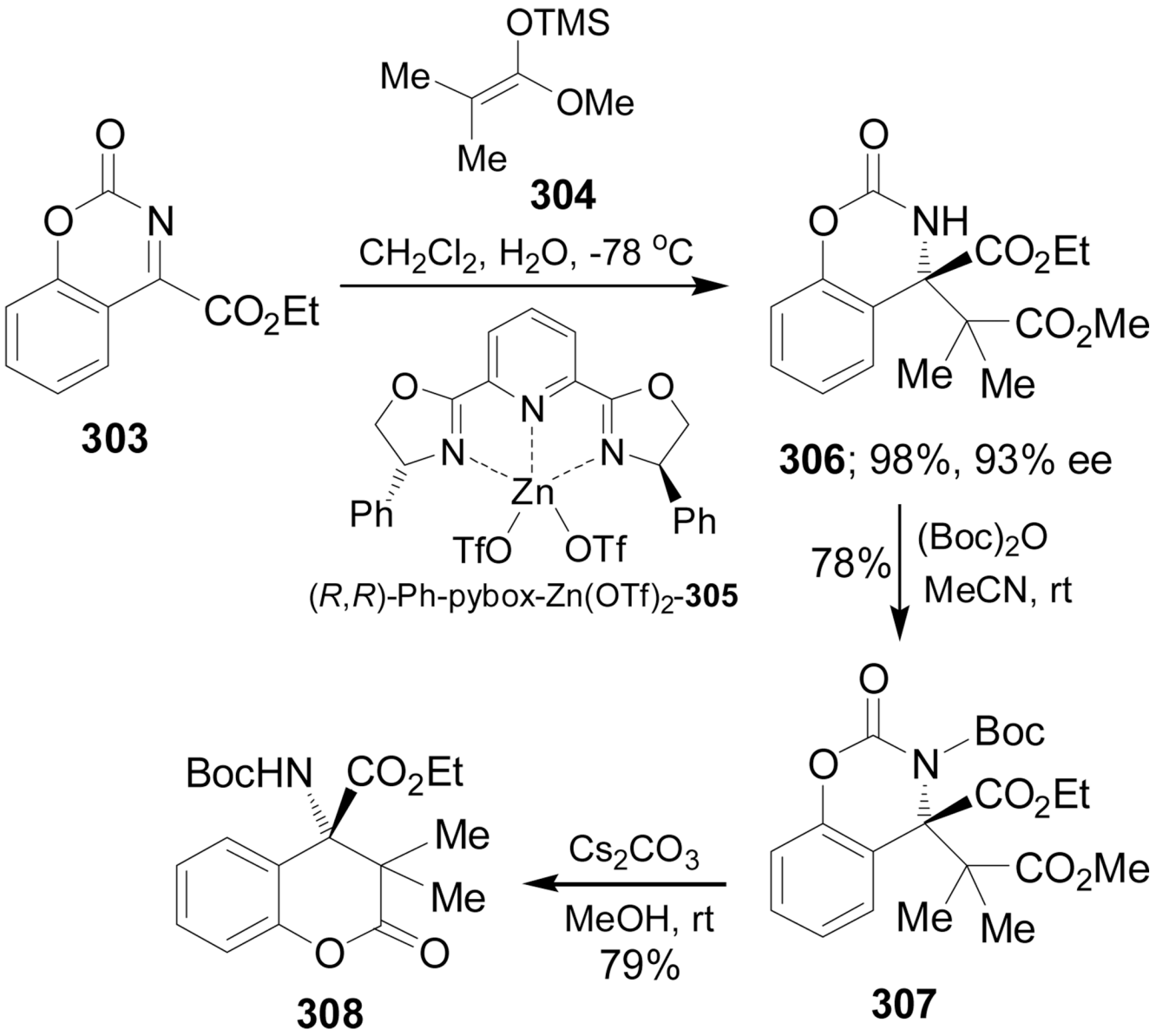
Scheme 62.



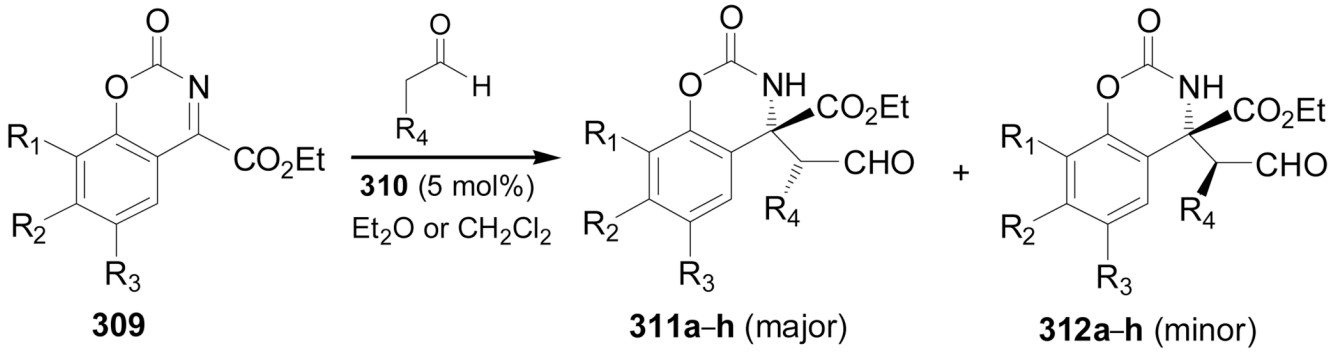
Scheme 63.

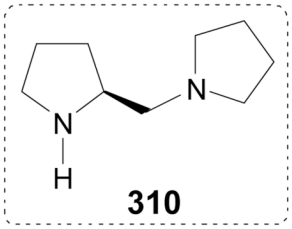


Scheme 64.



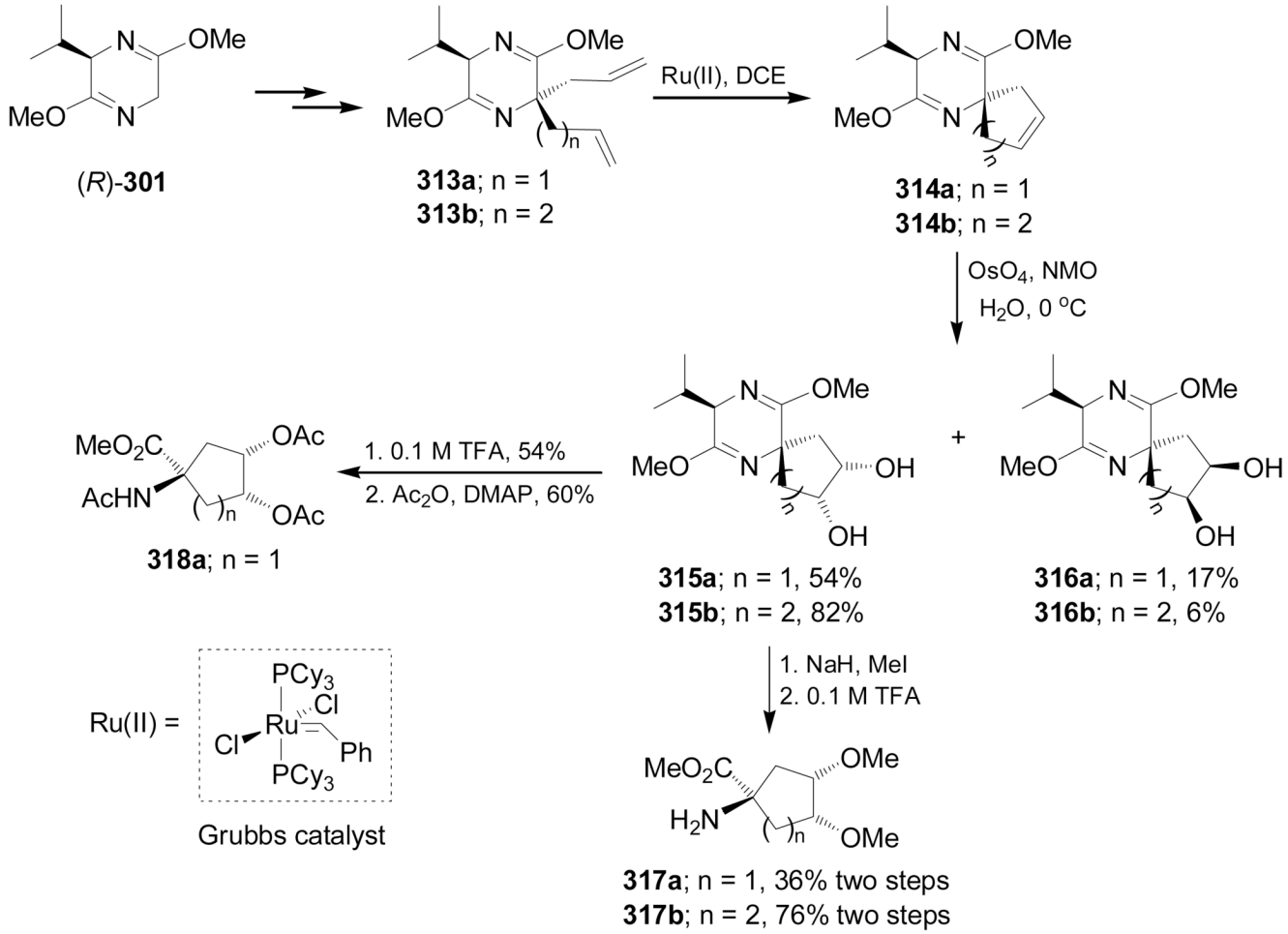
Scheme 65.



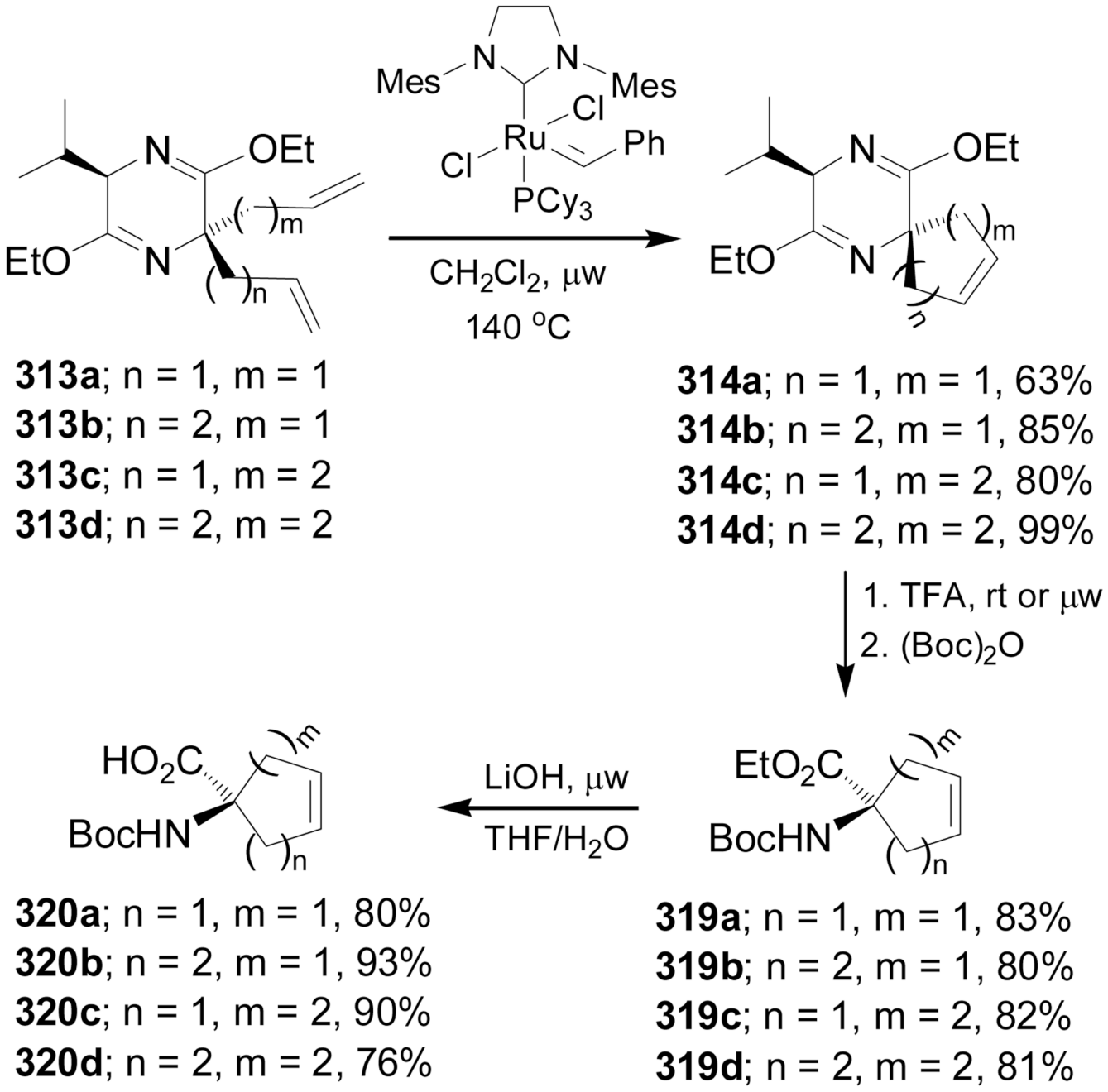


a; $R_1 = R_2 = R_3 = H$, $R_4 = i$-Pr, 99%, >20:1
b; $R_1 = R_2 = H$, $R_3 = Me$, $R_4 = i$-Pr, 98%, 6:1
c; $R_1 = R_2 = H$, $R_3 = OMe$, $R_4 = i$-Pr, 95%, 9:1
d; $R_1 = R_2 = H$, $R_3 = F$, $R_4 = i$-Pr, 97%, 19:1
e; $R_1 = H$, $R_2 = OMe$, $R_3 = H$, $R_4 = i$-Pr, 90%, >20:1
f; $R_1 = R_2 = -C_4H_4-$, $R_3 = H$, $R_4 = i$-Pr, 93%, >20:1
g; $R_1 = R_2 = R_3 = H$, $R_4 = Me$, 72%, 5:1
h; $R_1 = R_2 = R_3 = H$, $R_4 = allyl$, 82%, 4:1

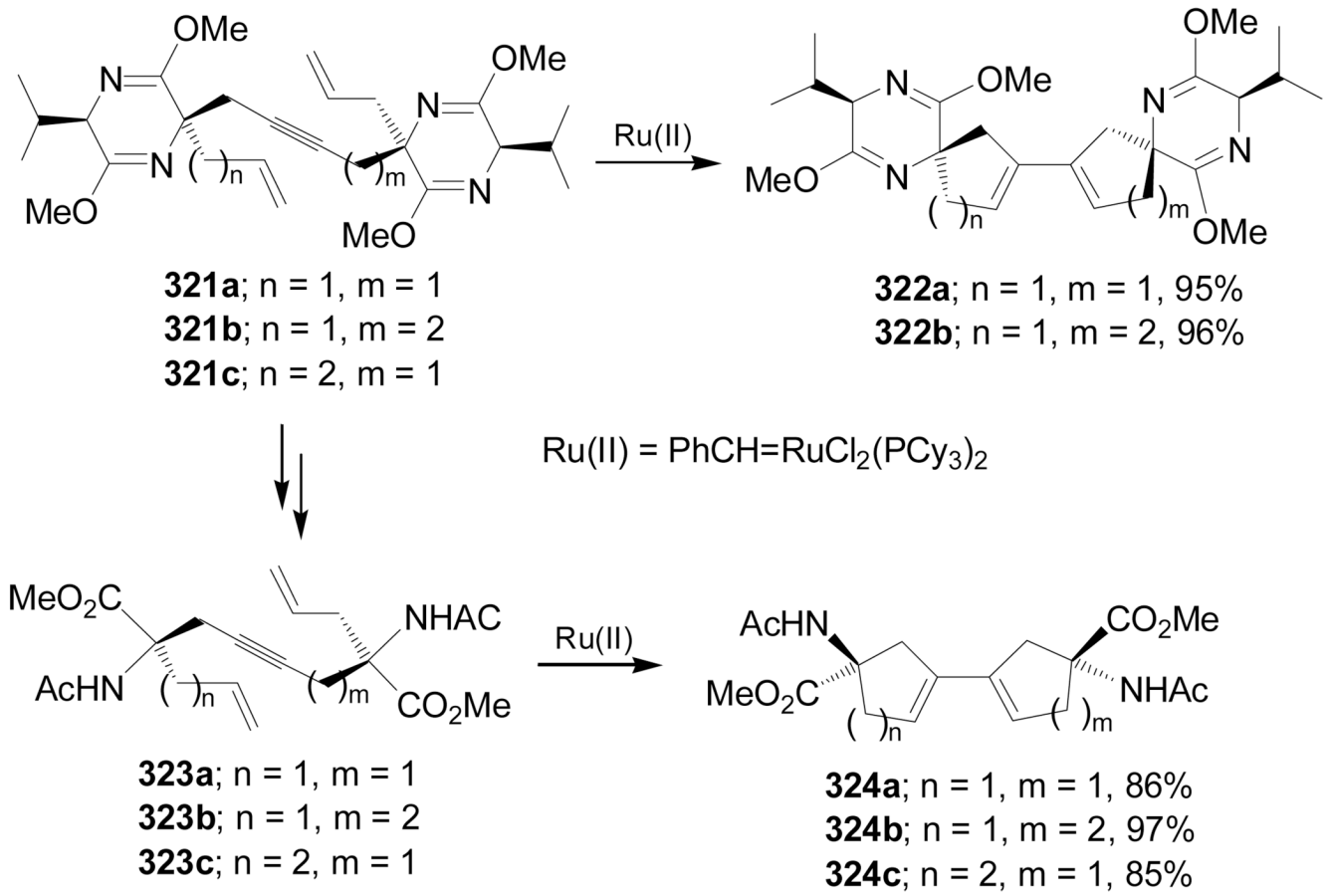
Scheme 66.



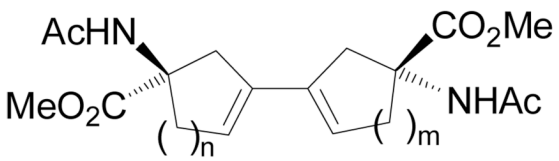
Scheme 67.



Scheme 68.

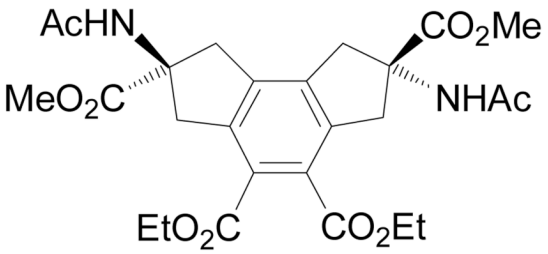


Scheme 69.

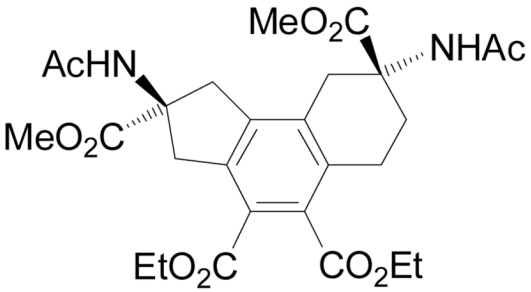


324a; n = 1, m = 1
324b; n = 1, m = 2
324d; n = 2, m = 2

1. DEAD
2. MnO_2

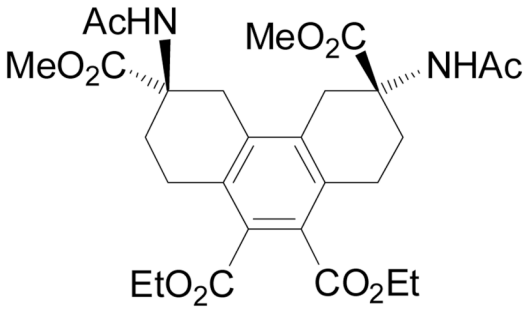


(2*S*,7*S*)-**325a**; 57% two steps



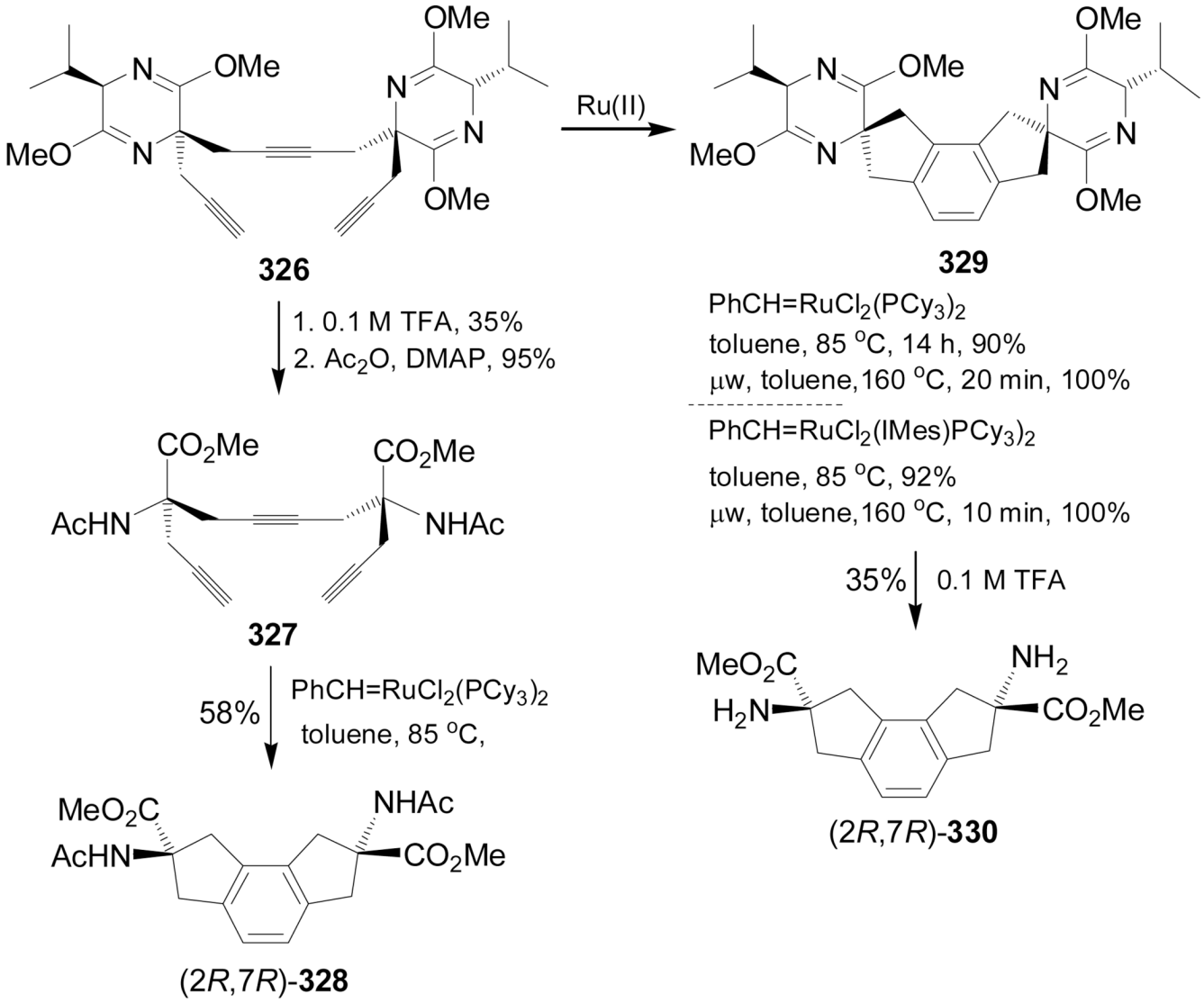
(2*R*,8*S*)-**325b**; 65% two steps

DEAD = $EtO_2C{\equiv}CO_2Et$

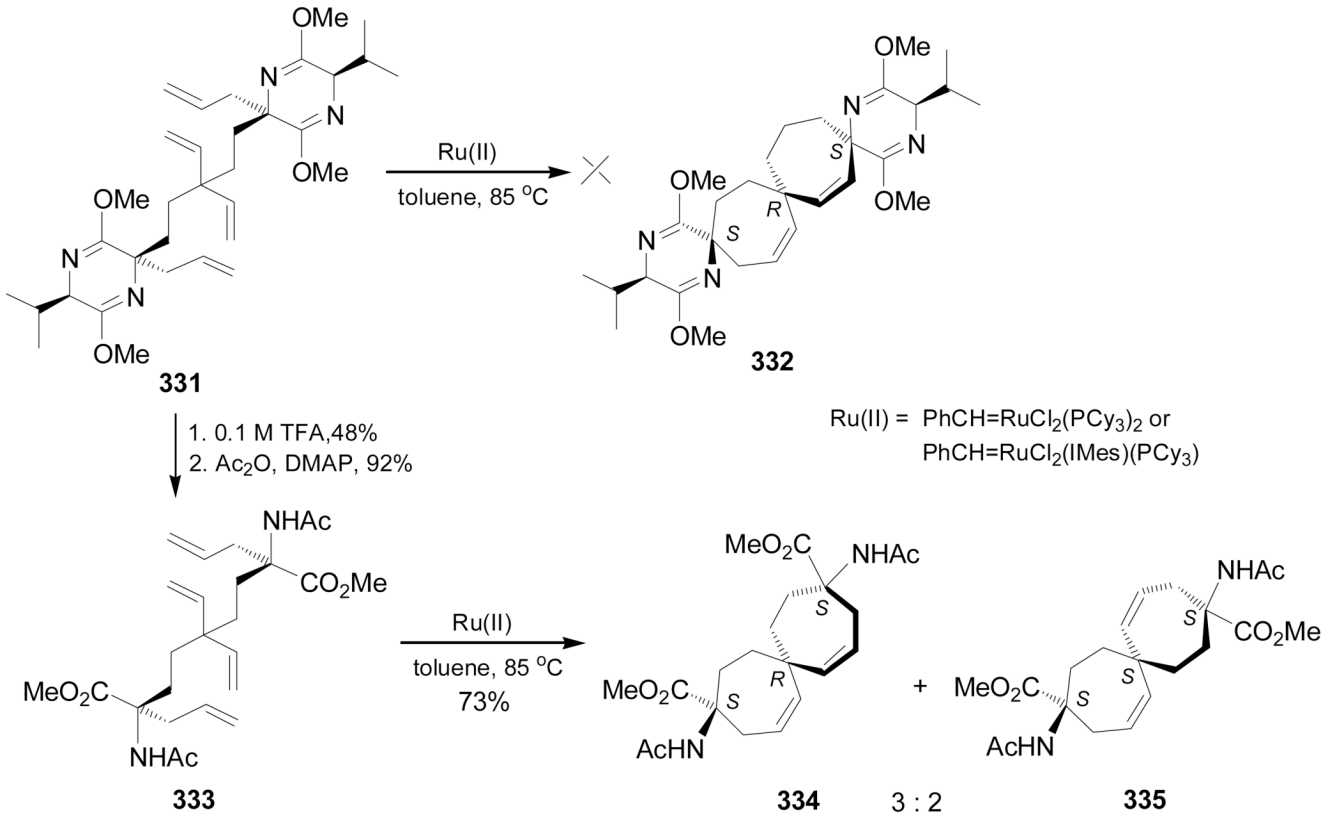


(2*R*,9*R*)-**325d**; 60% two steps

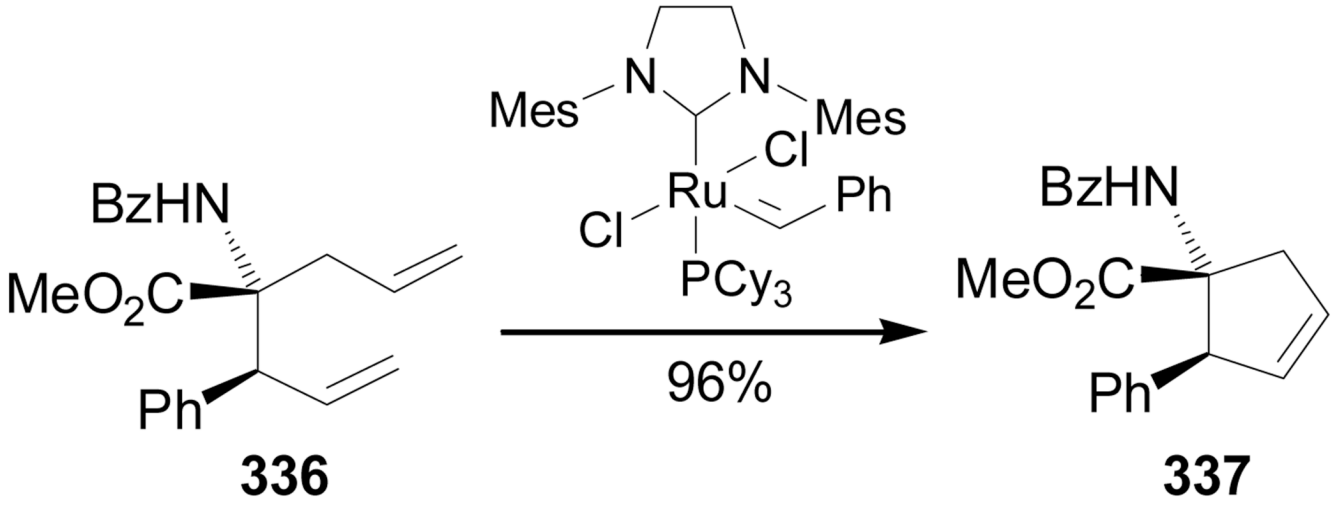
Scheme 70.



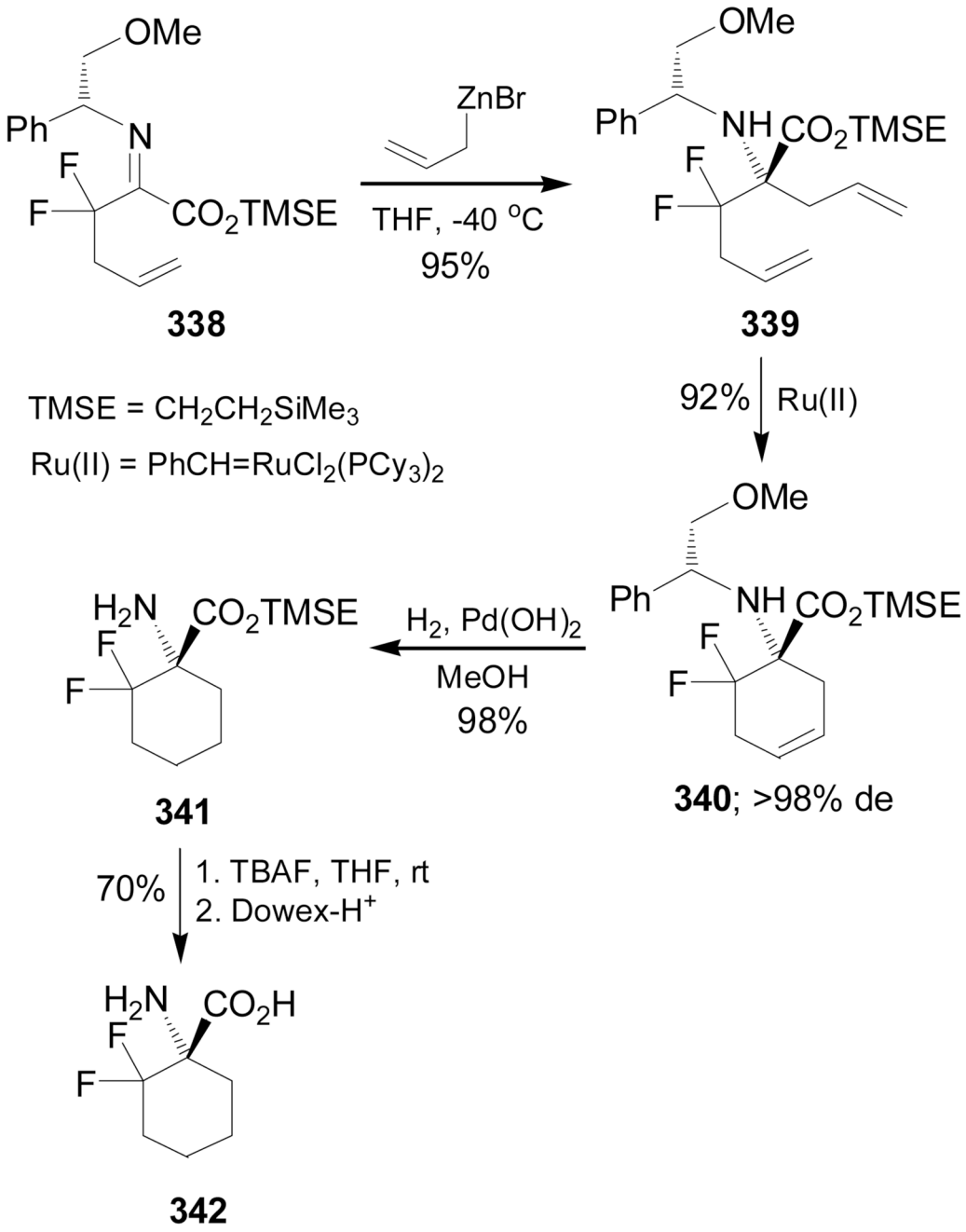
Scheme 71.



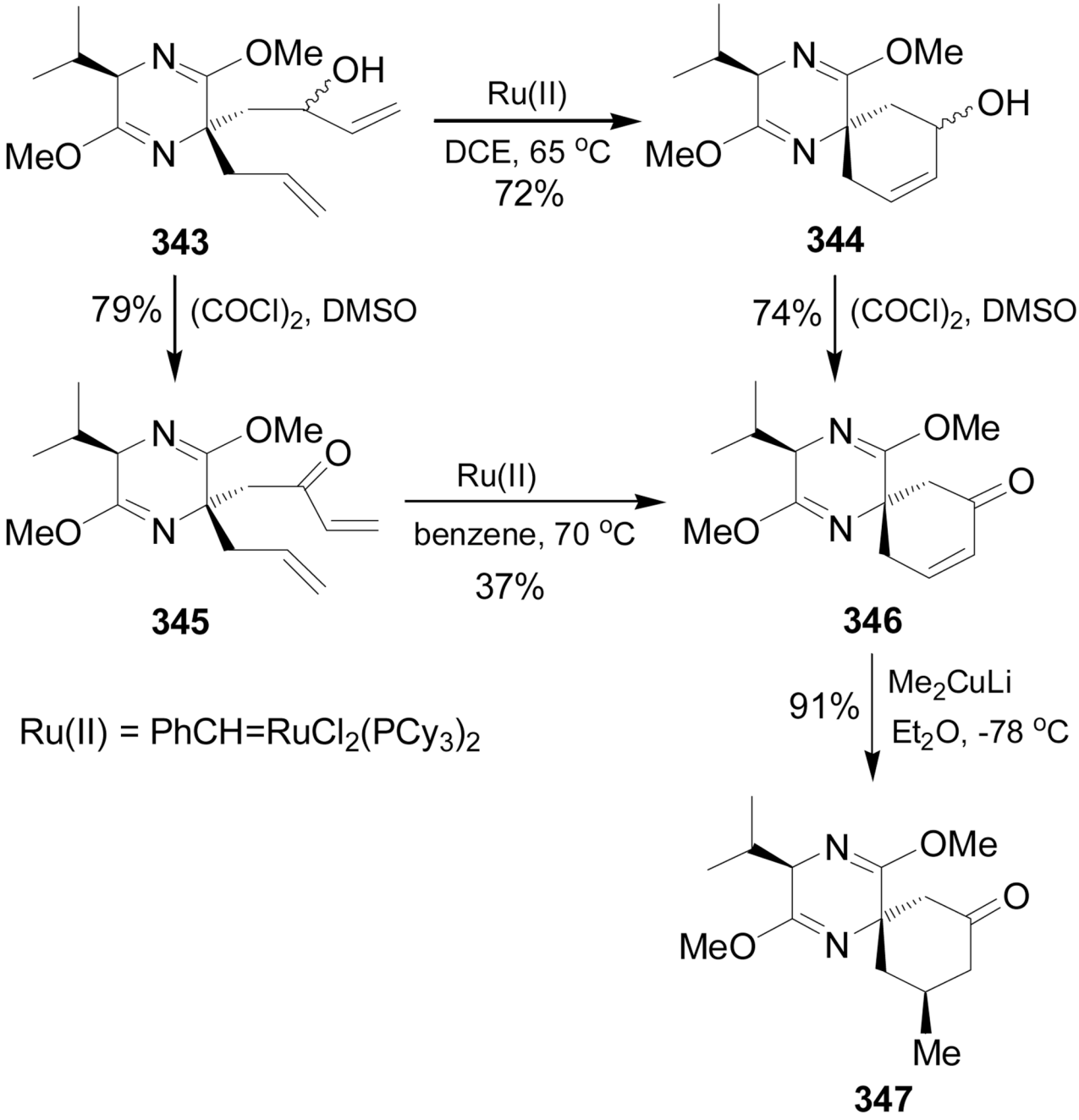
Scheme 72.



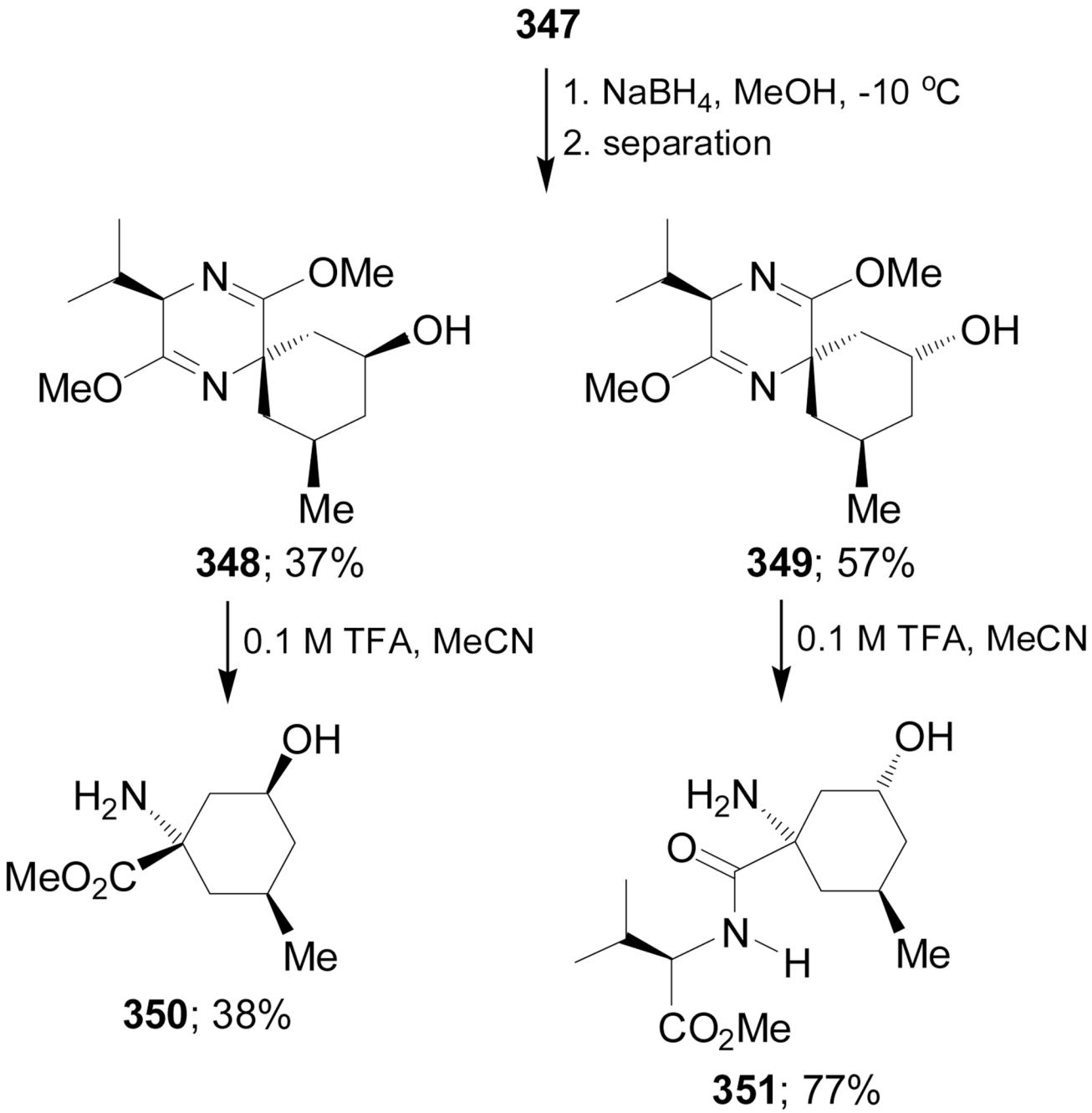
Scheme 73.



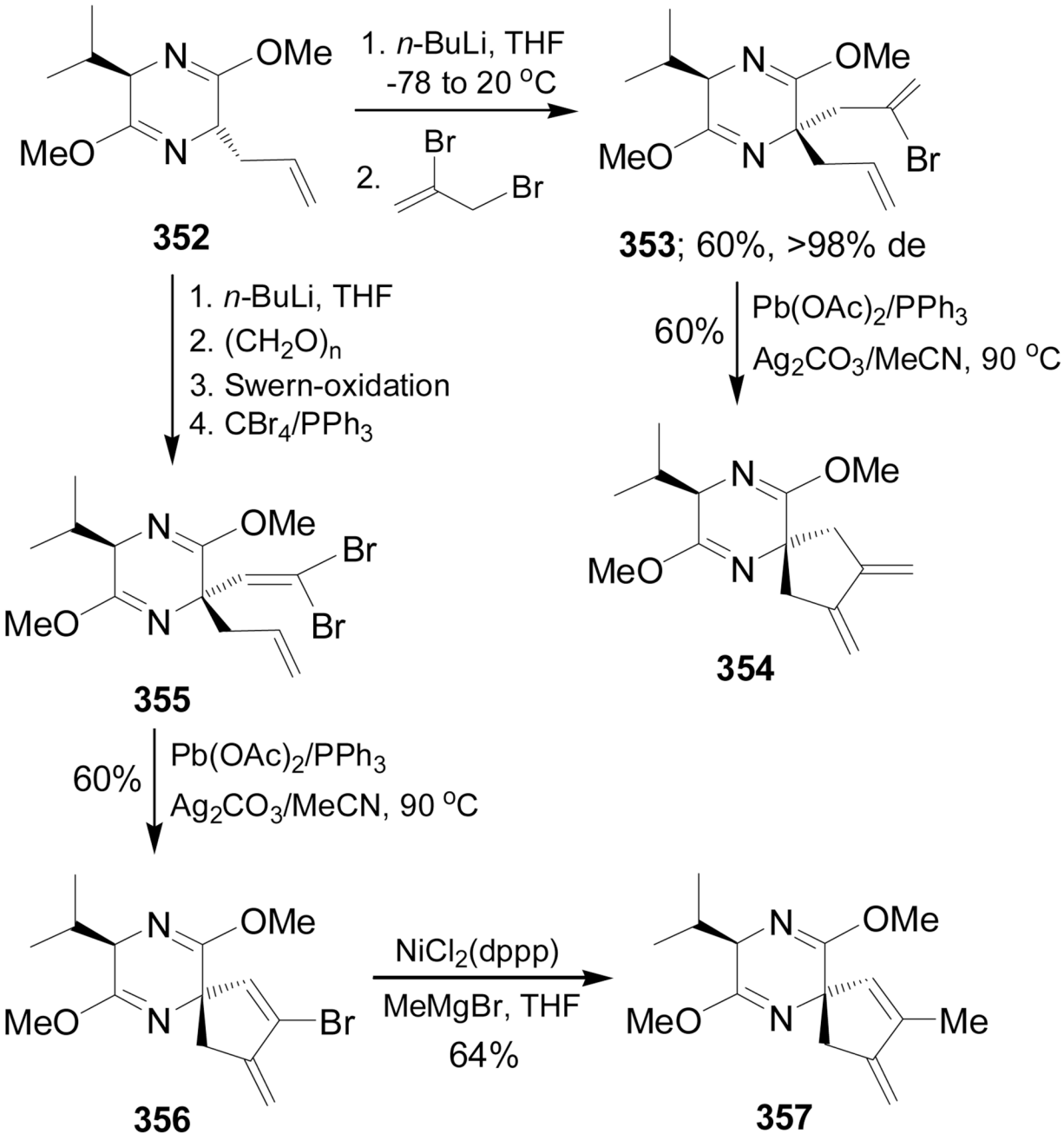
Scheme 74.



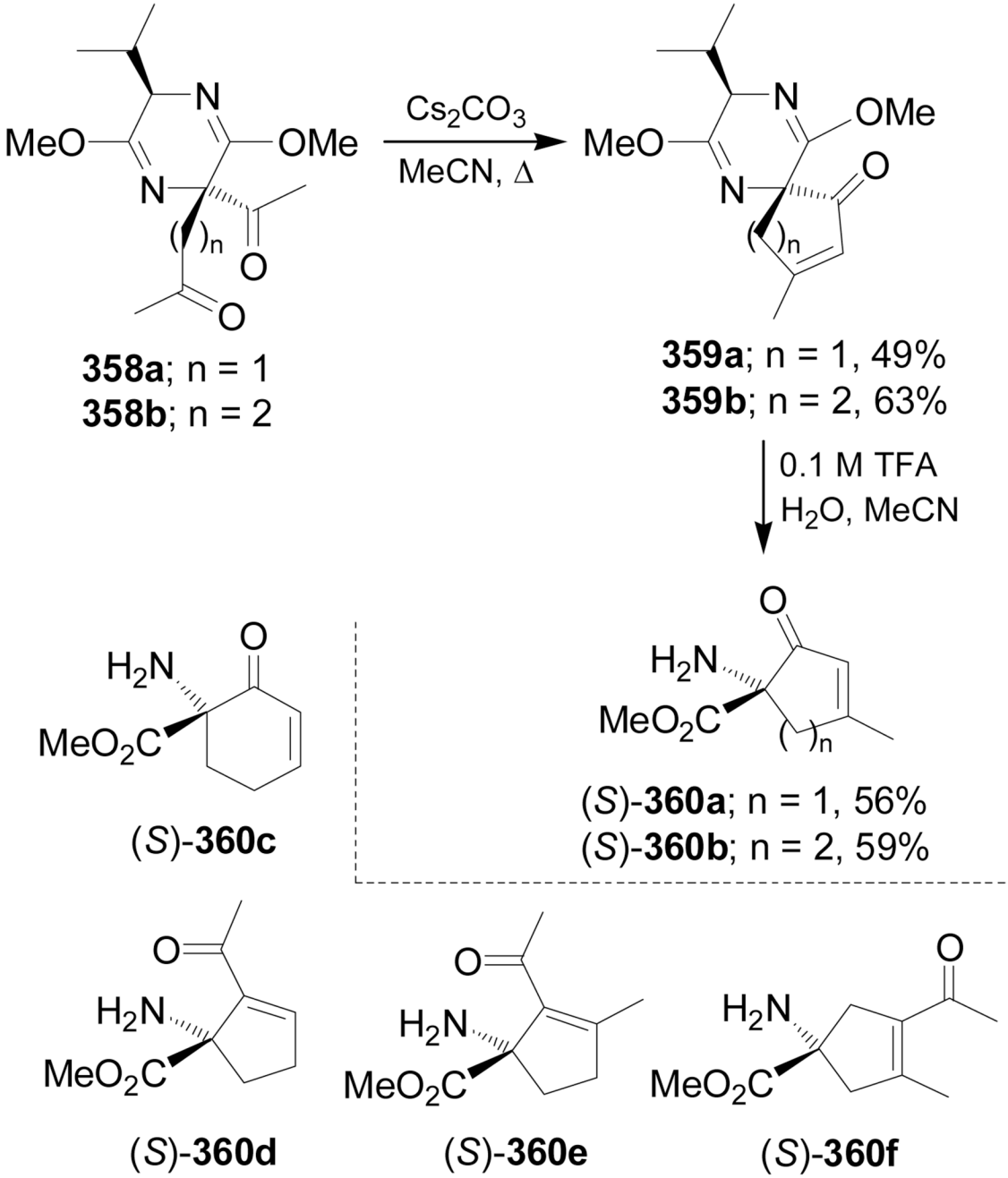
Scheme 75.



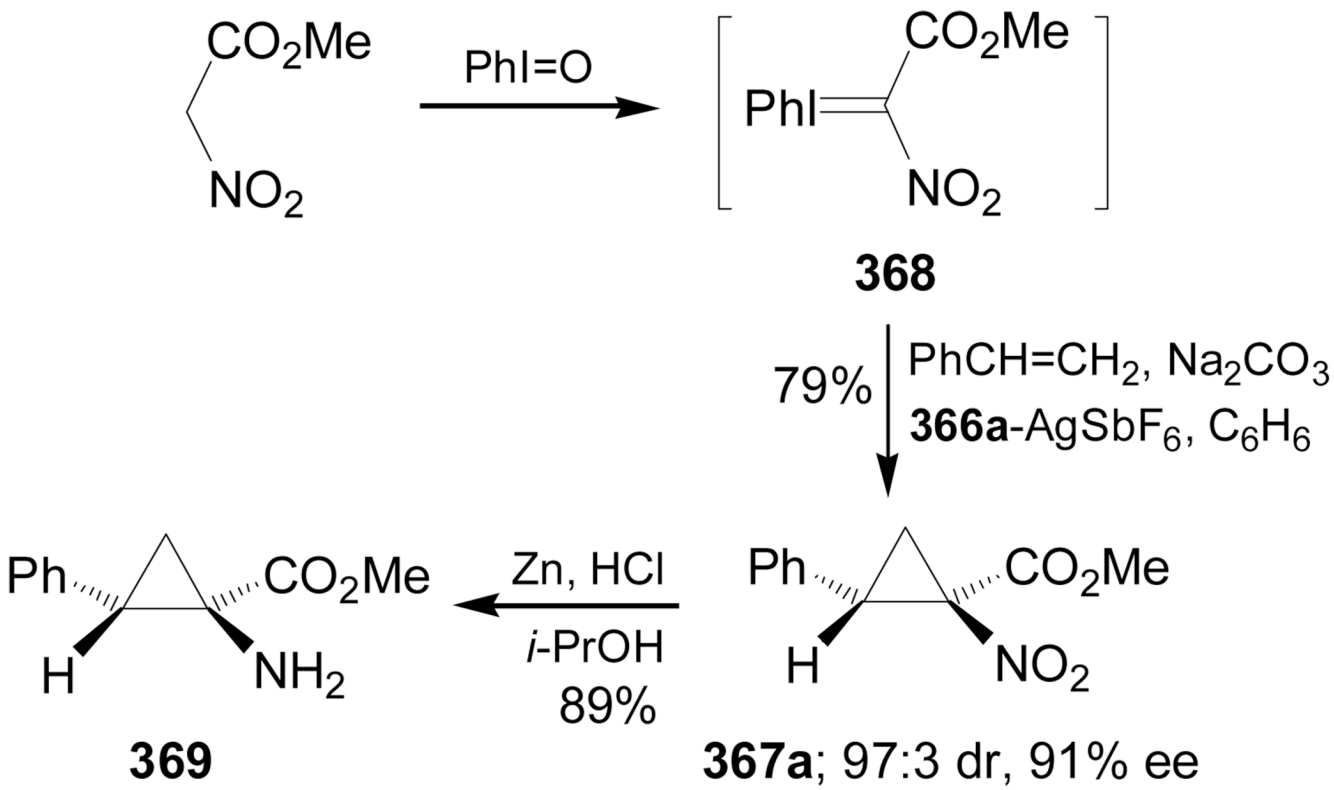
Scheme 76.



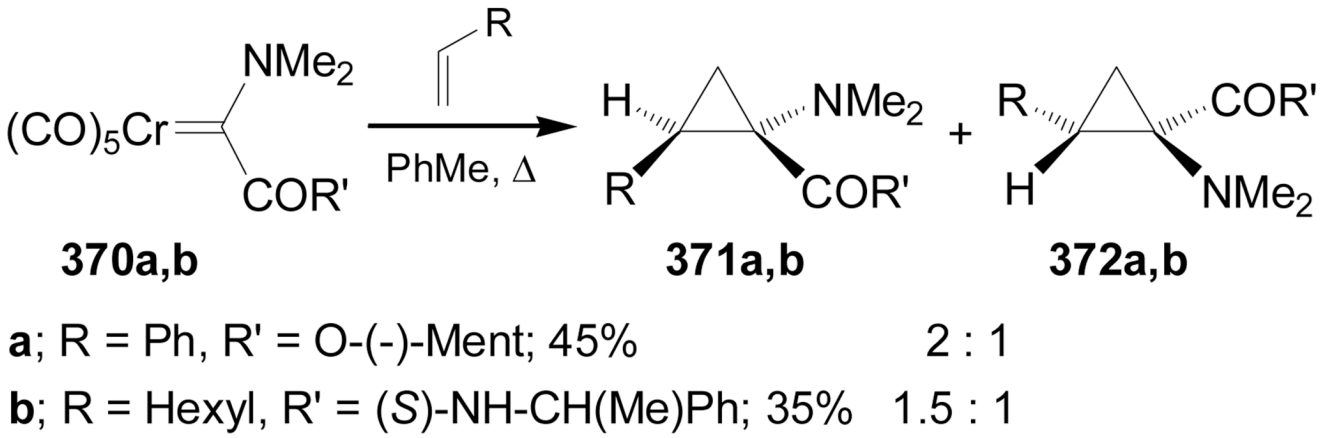
Scheme 77.



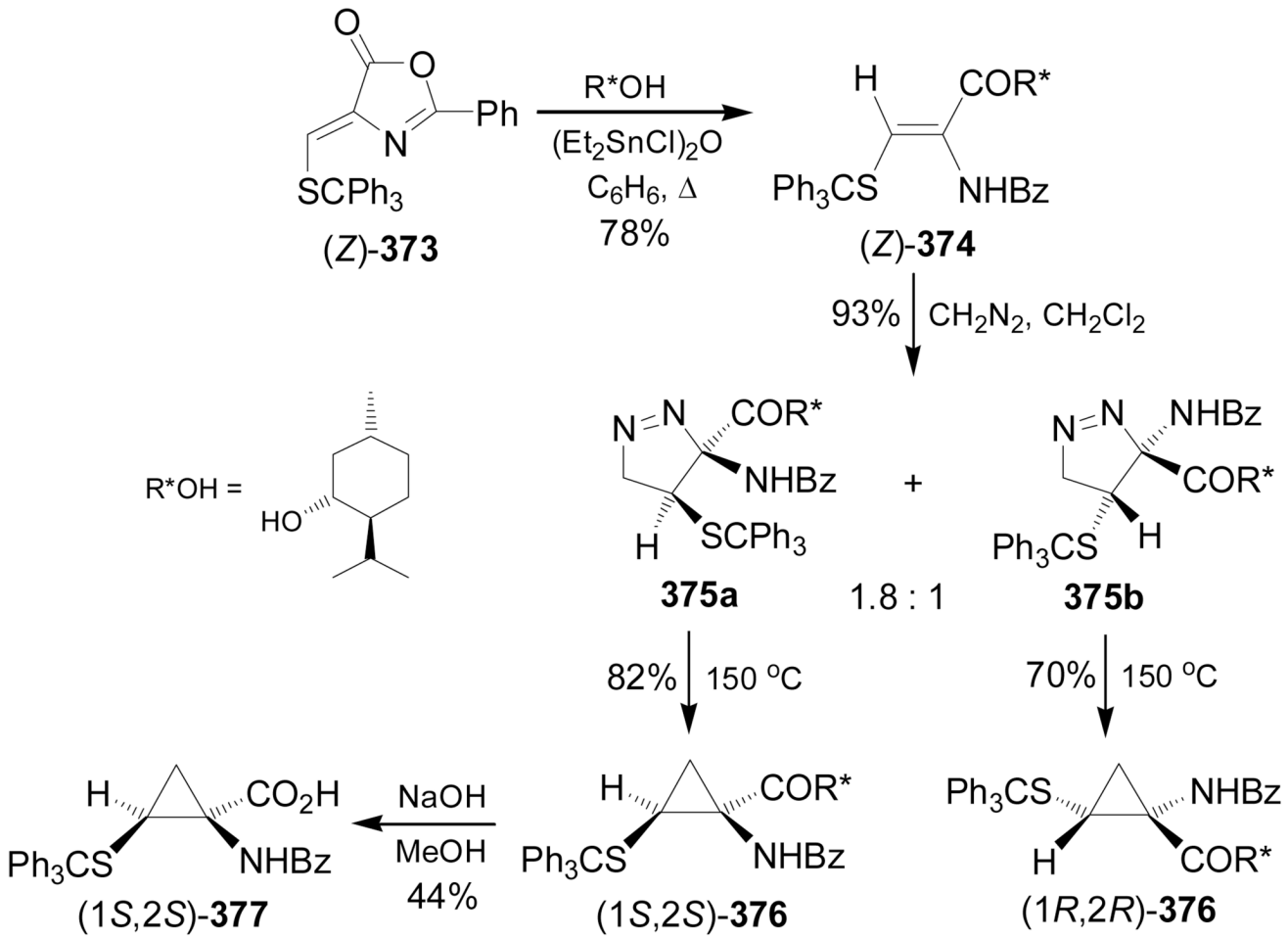
Scheme 78.



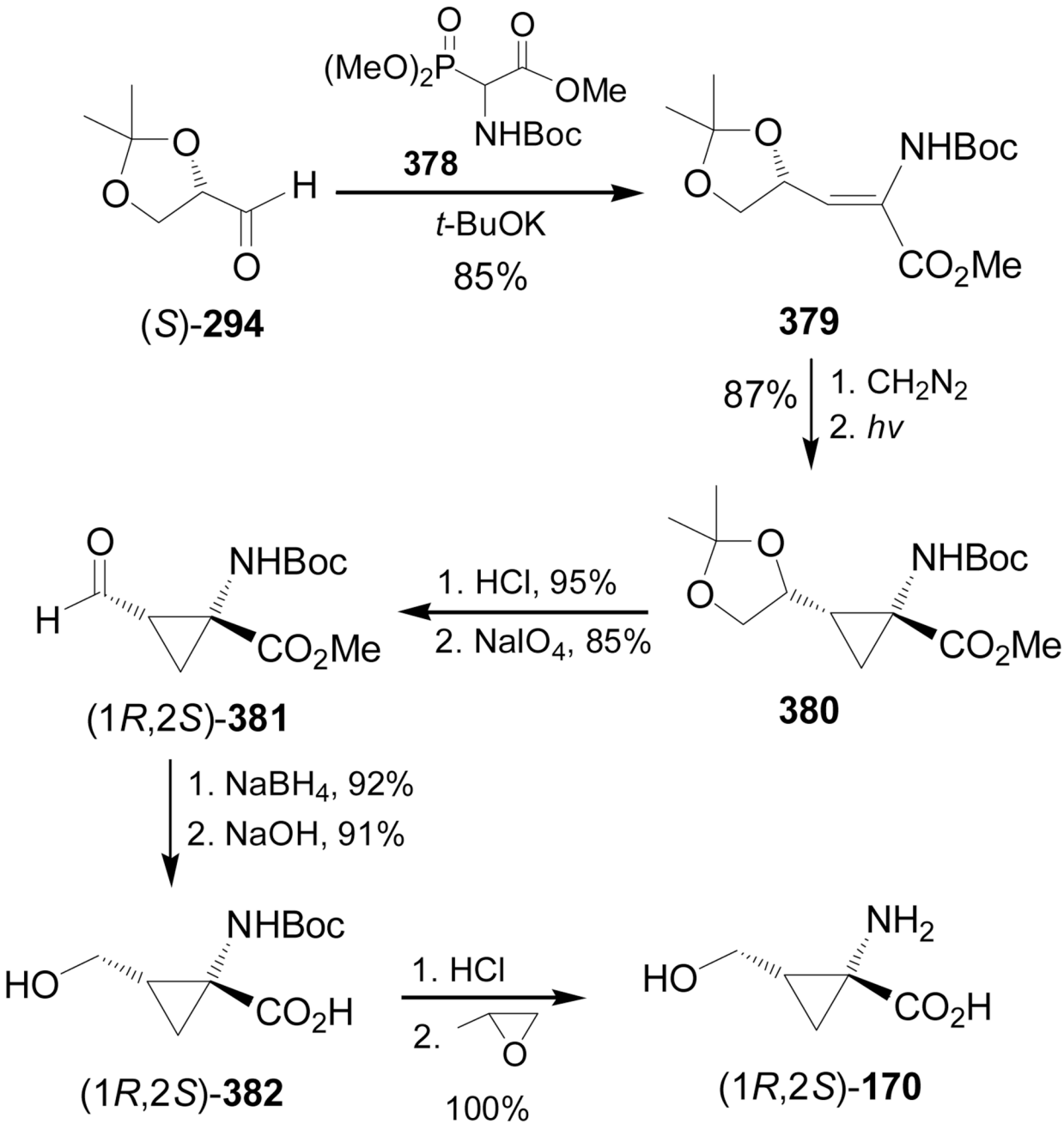
Scheme 79.



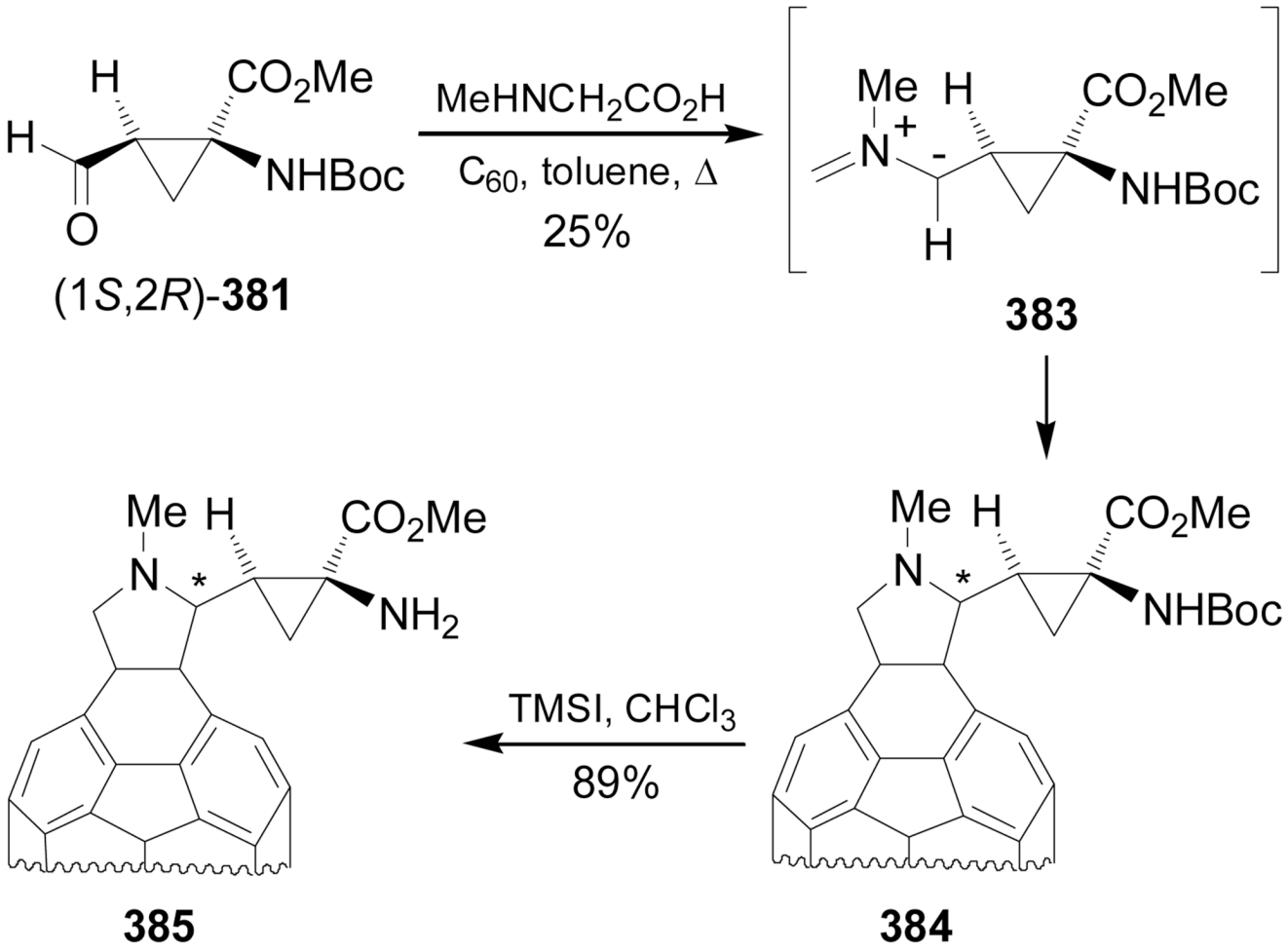
Scheme 80.



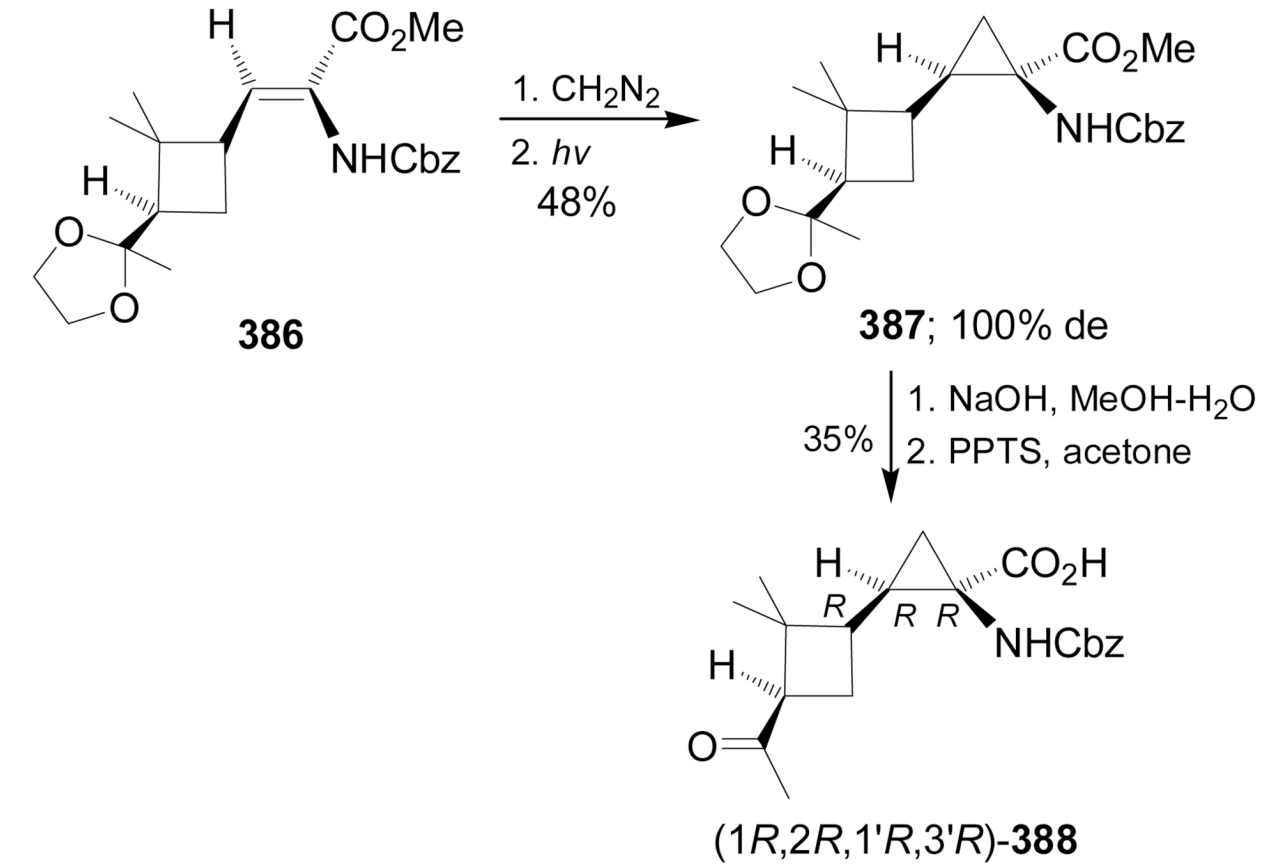
Scheme 81.

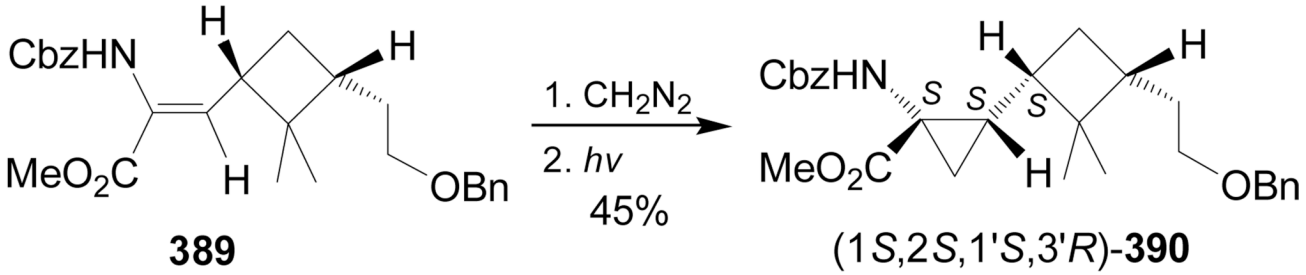


Scheme 82.

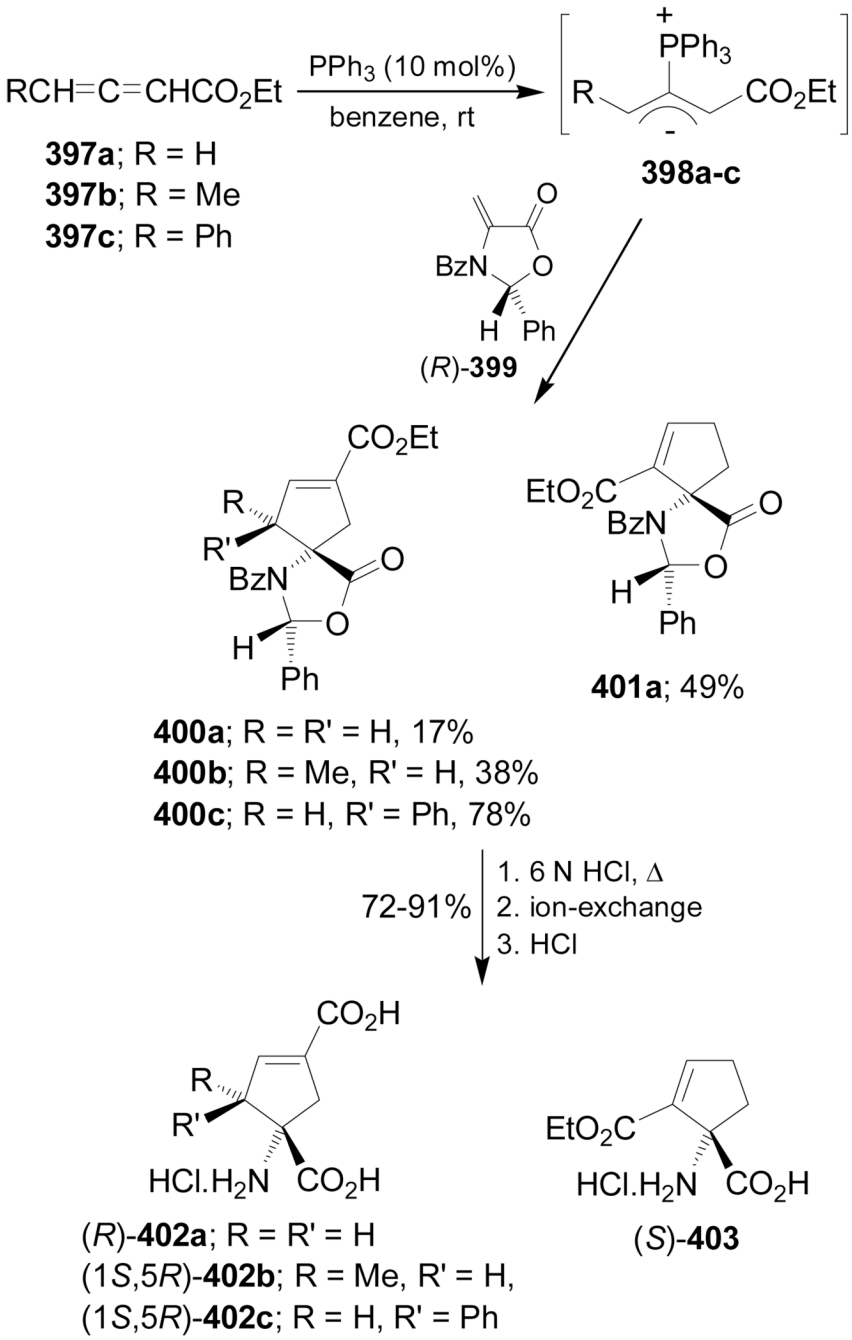


Scheme 83.

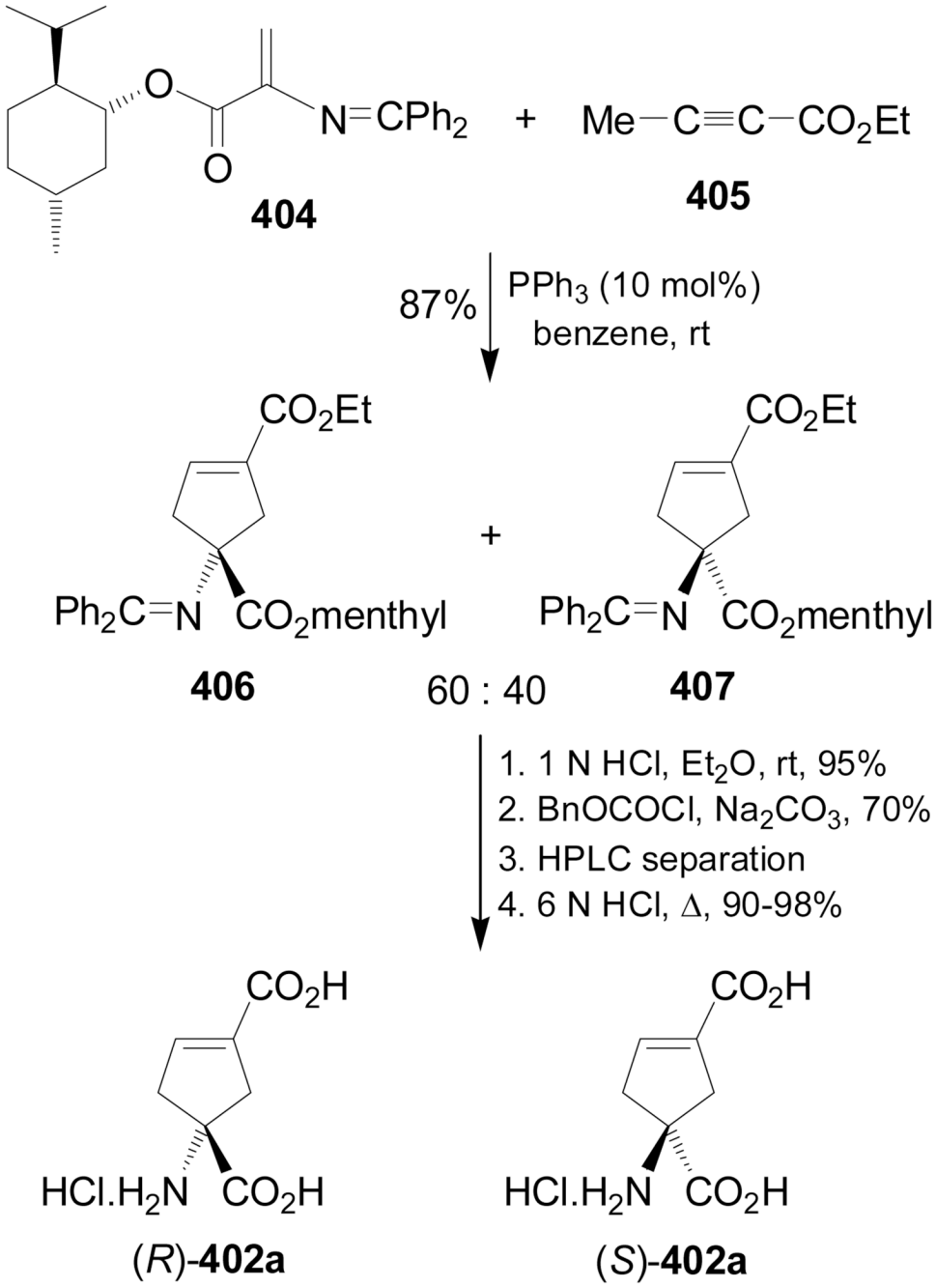




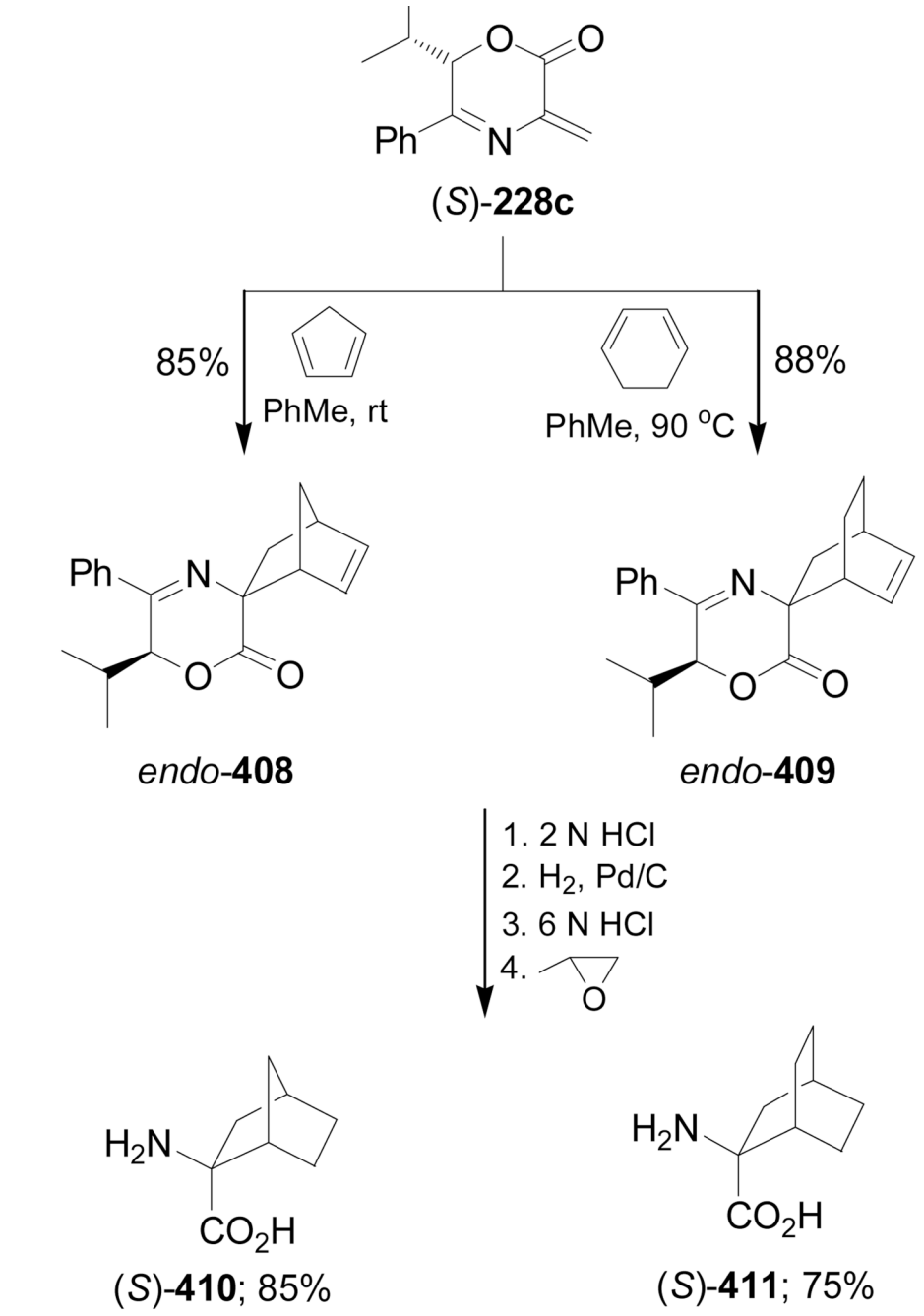
Scheme 84.



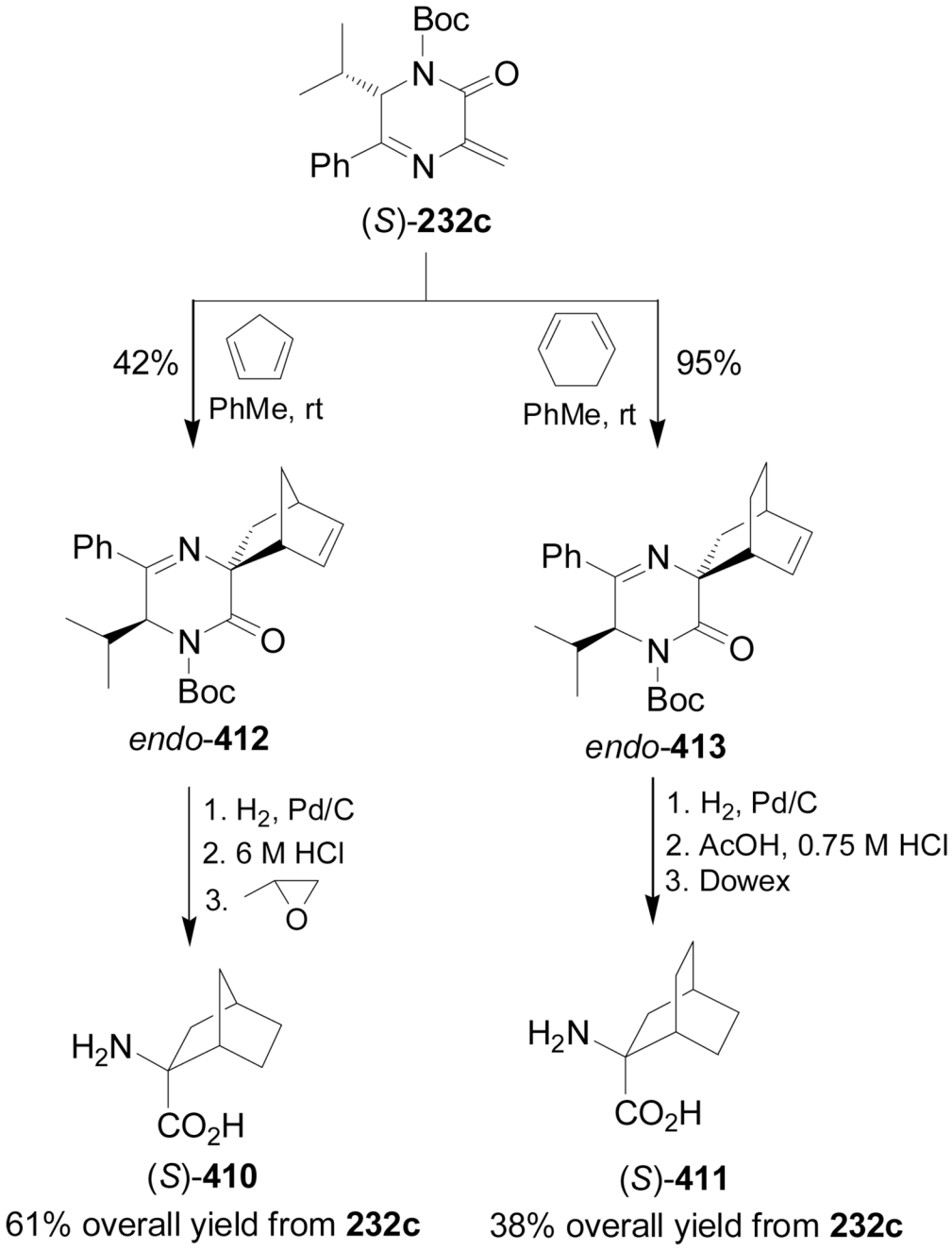
Scheme 85.



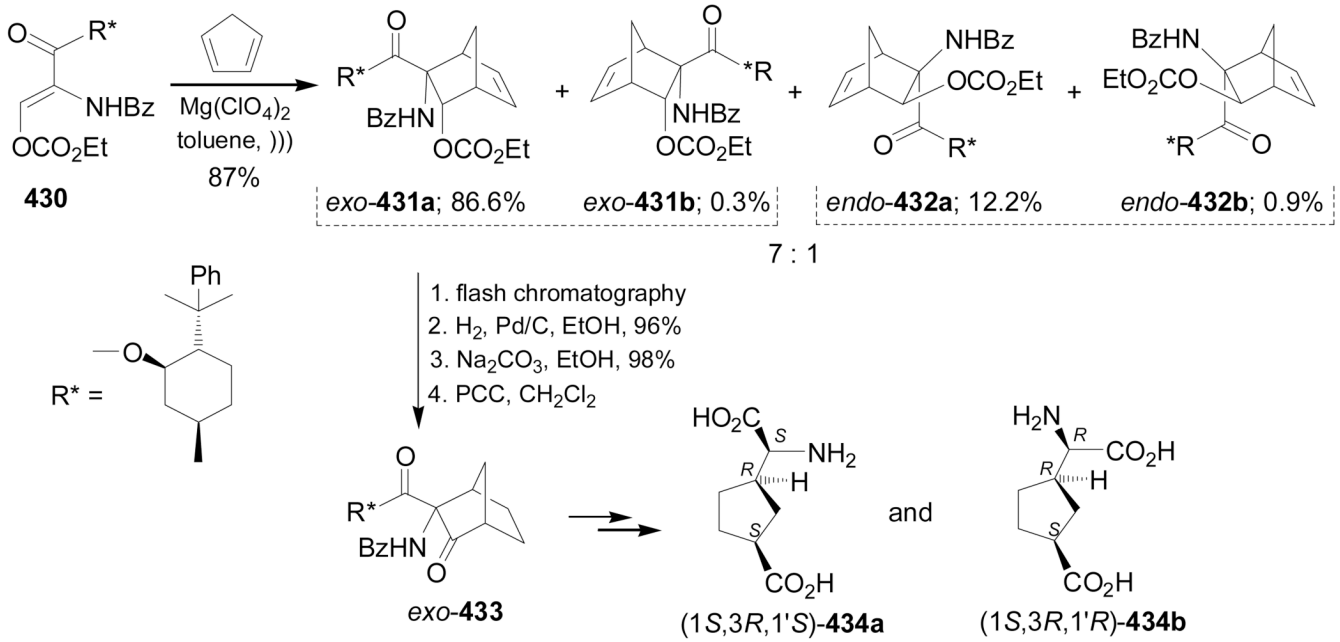
Scheme 86.



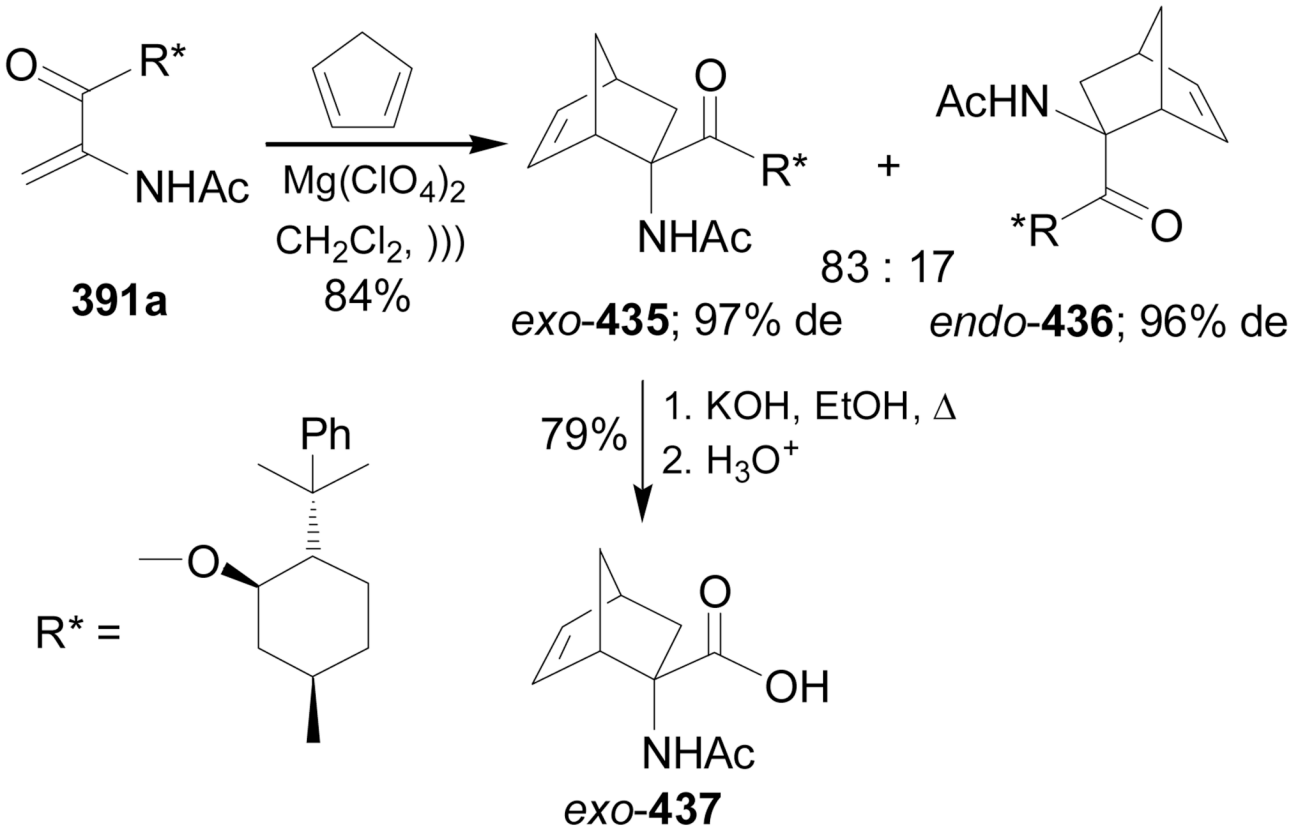
Scheme 87.



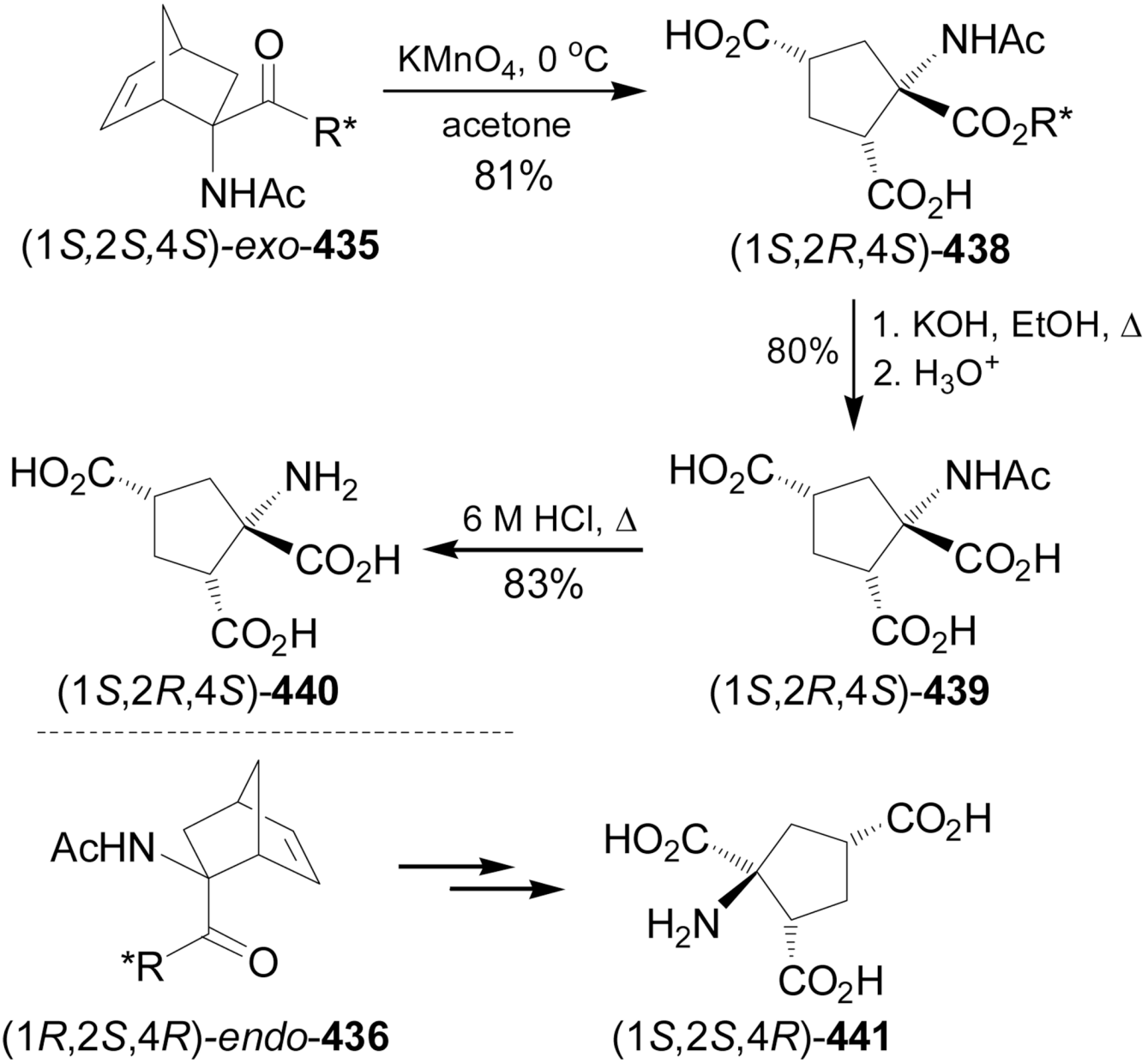
Scheme 88.



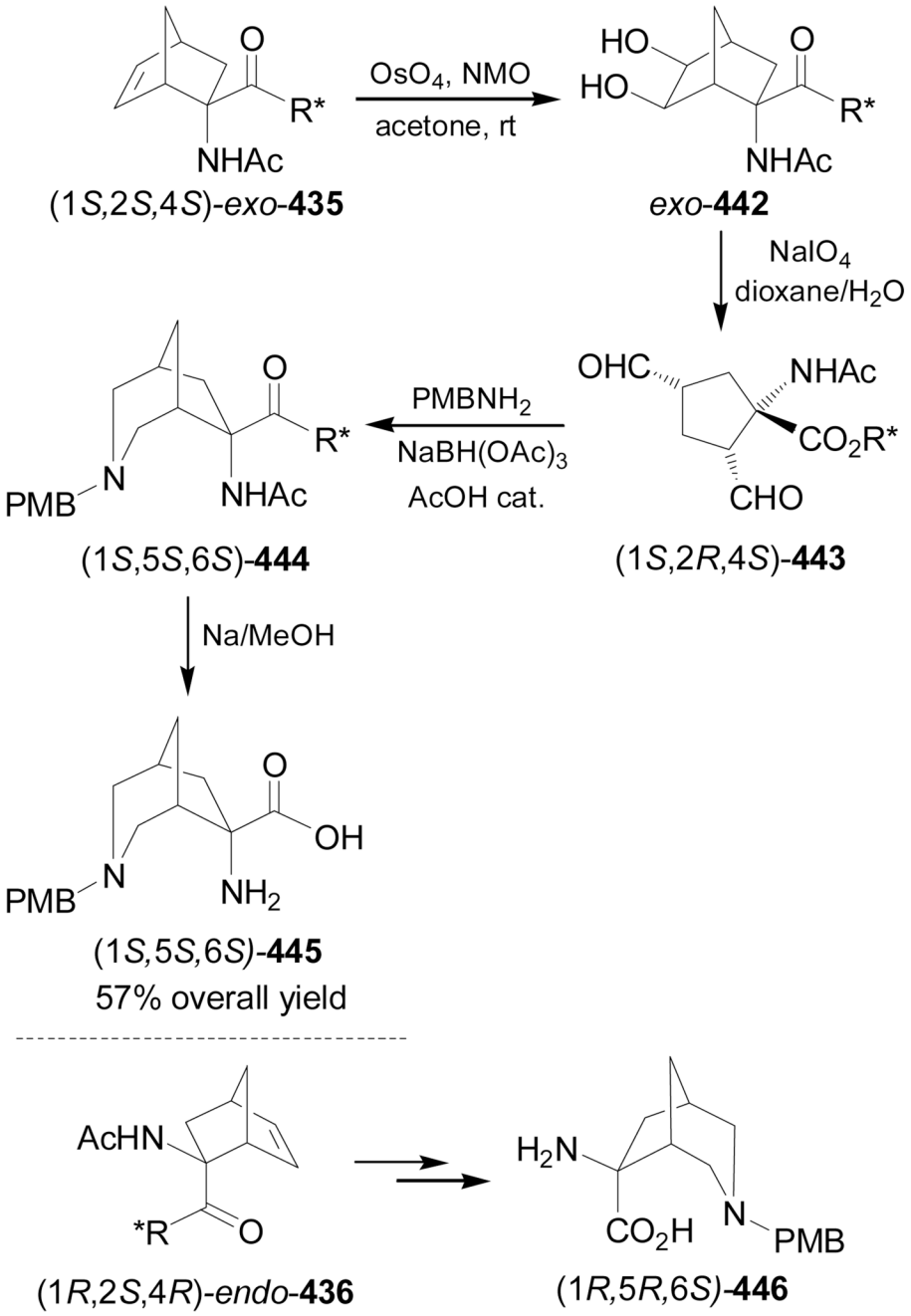
Scheme 89.



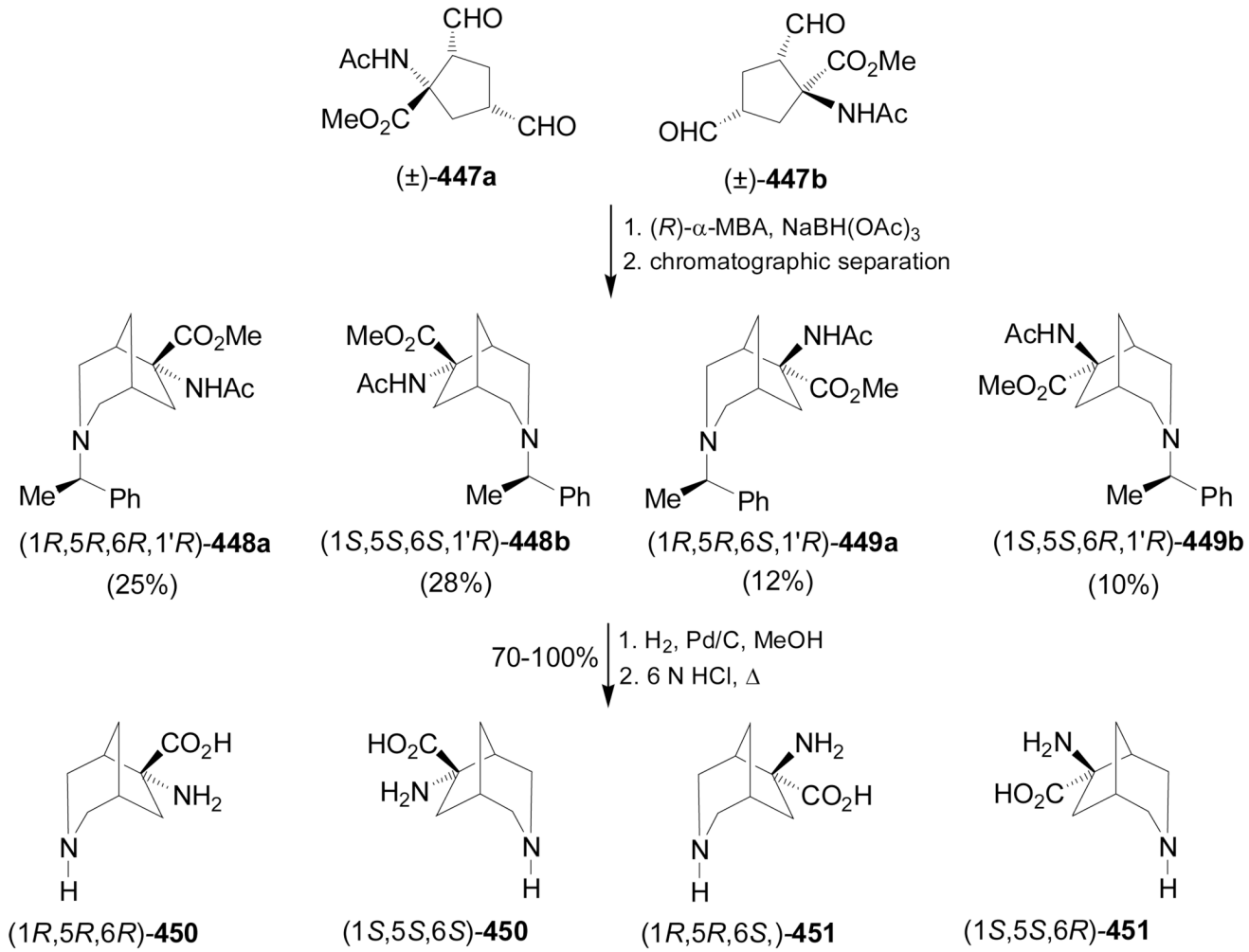
Scheme 90.



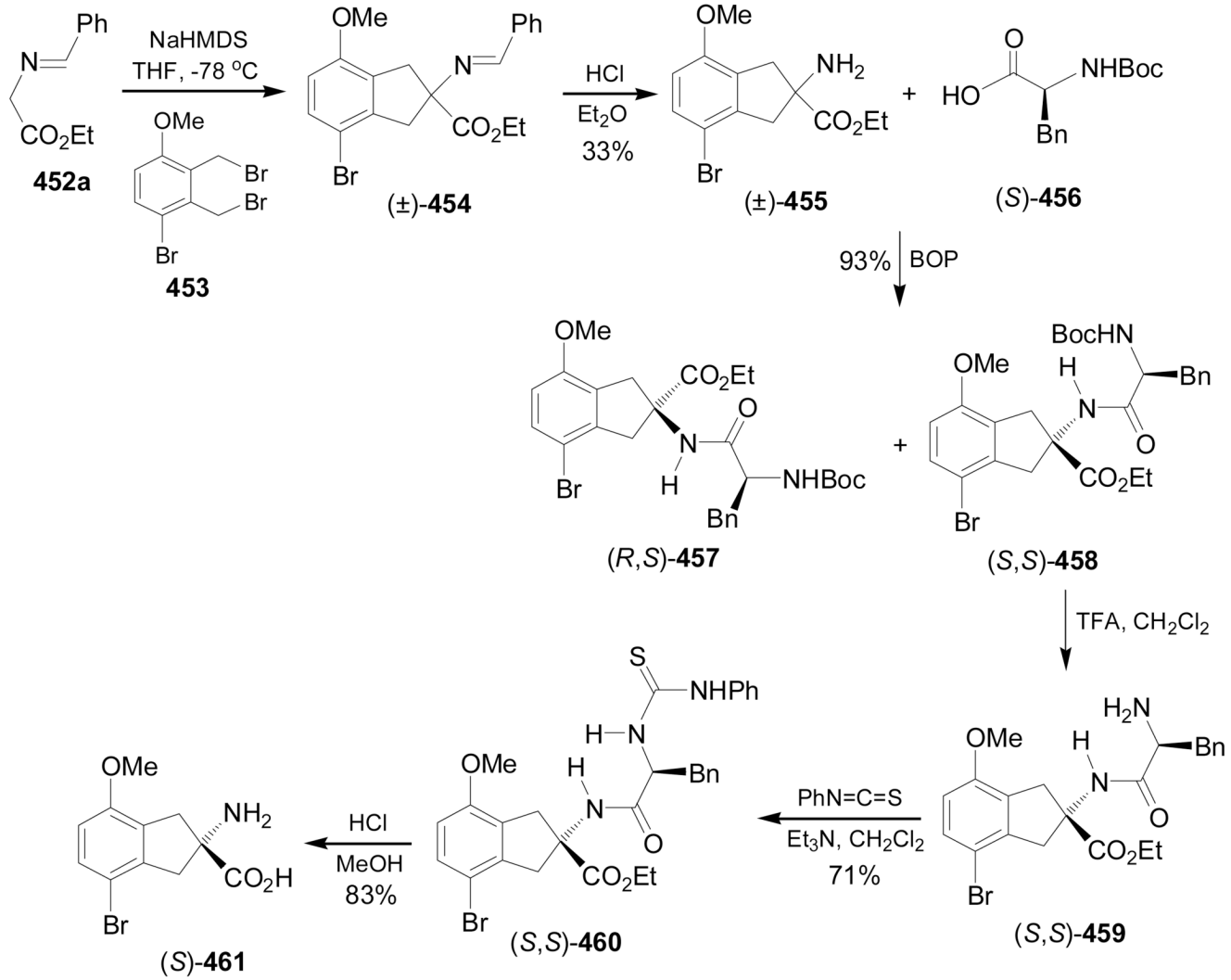
Scheme 91.



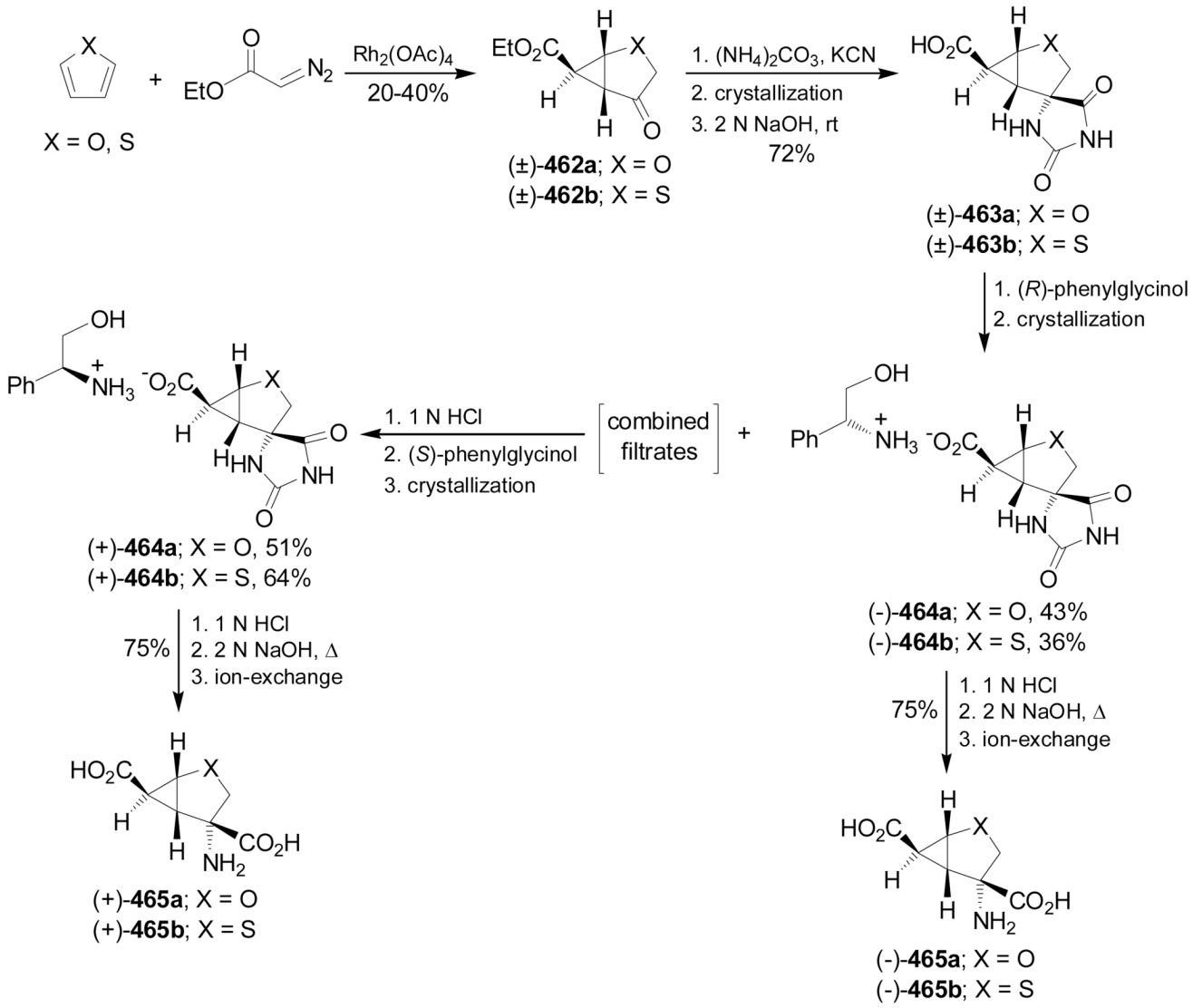
Scheme 92.



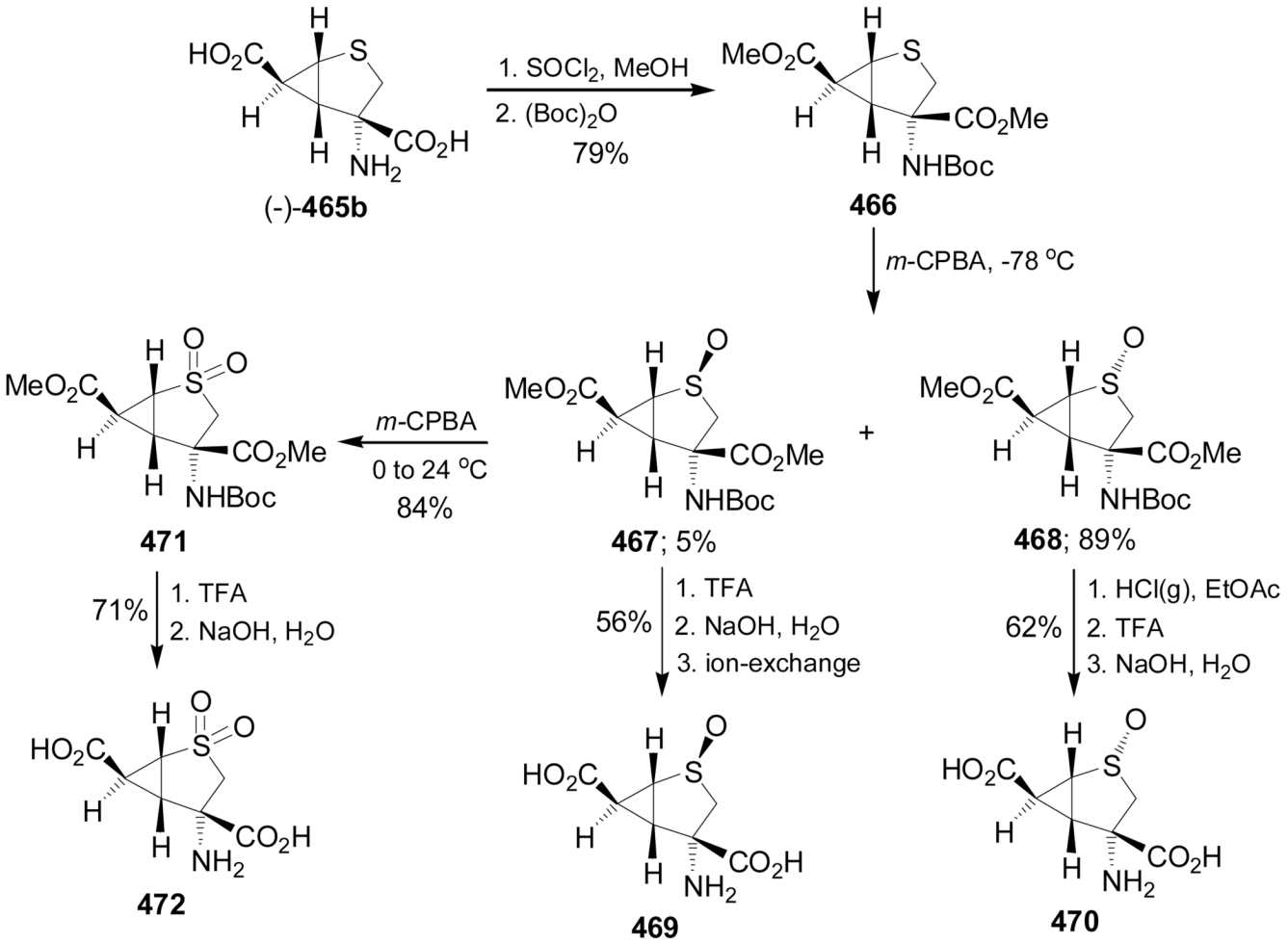
Scheme 93.



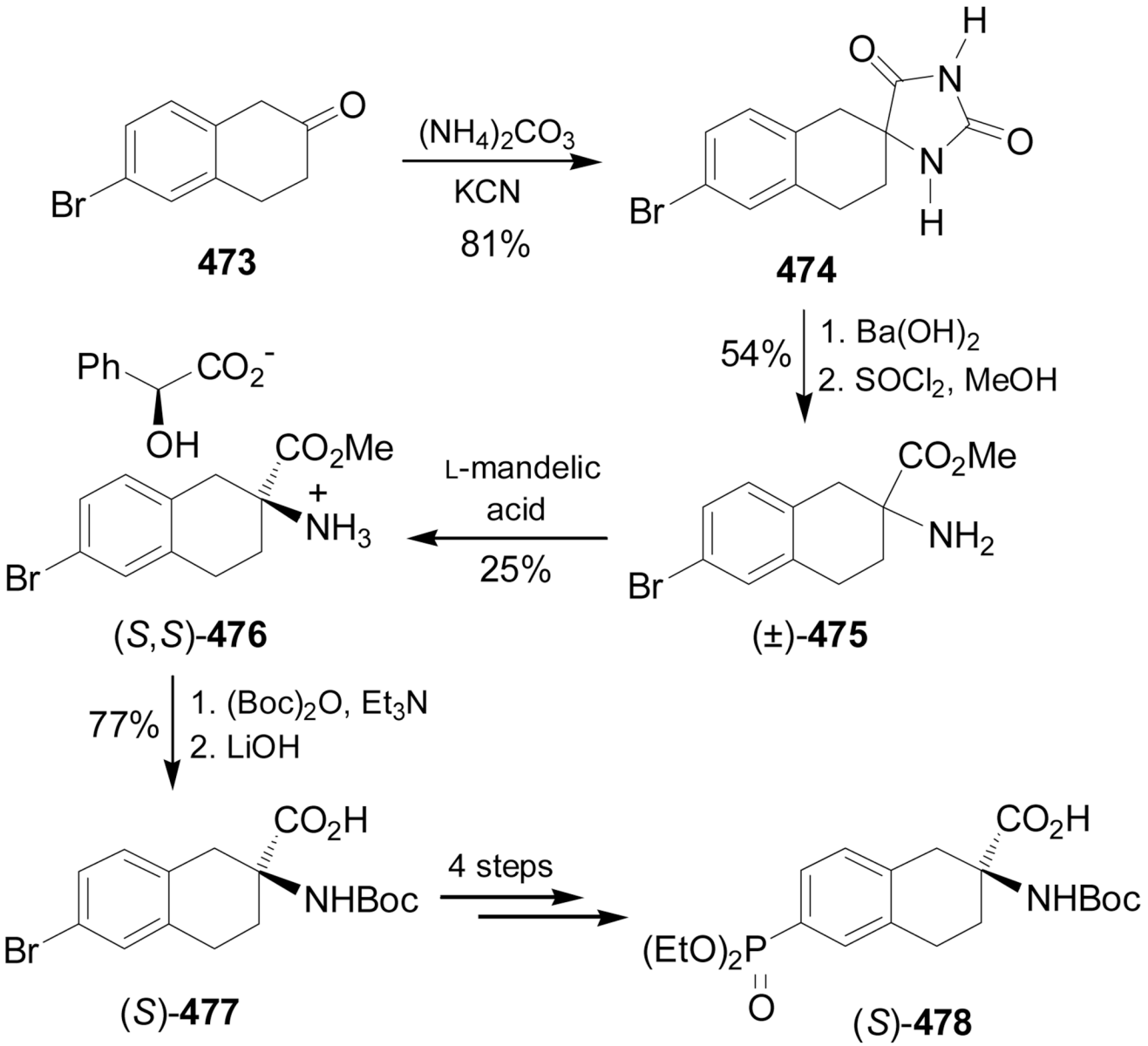
Scheme 94.



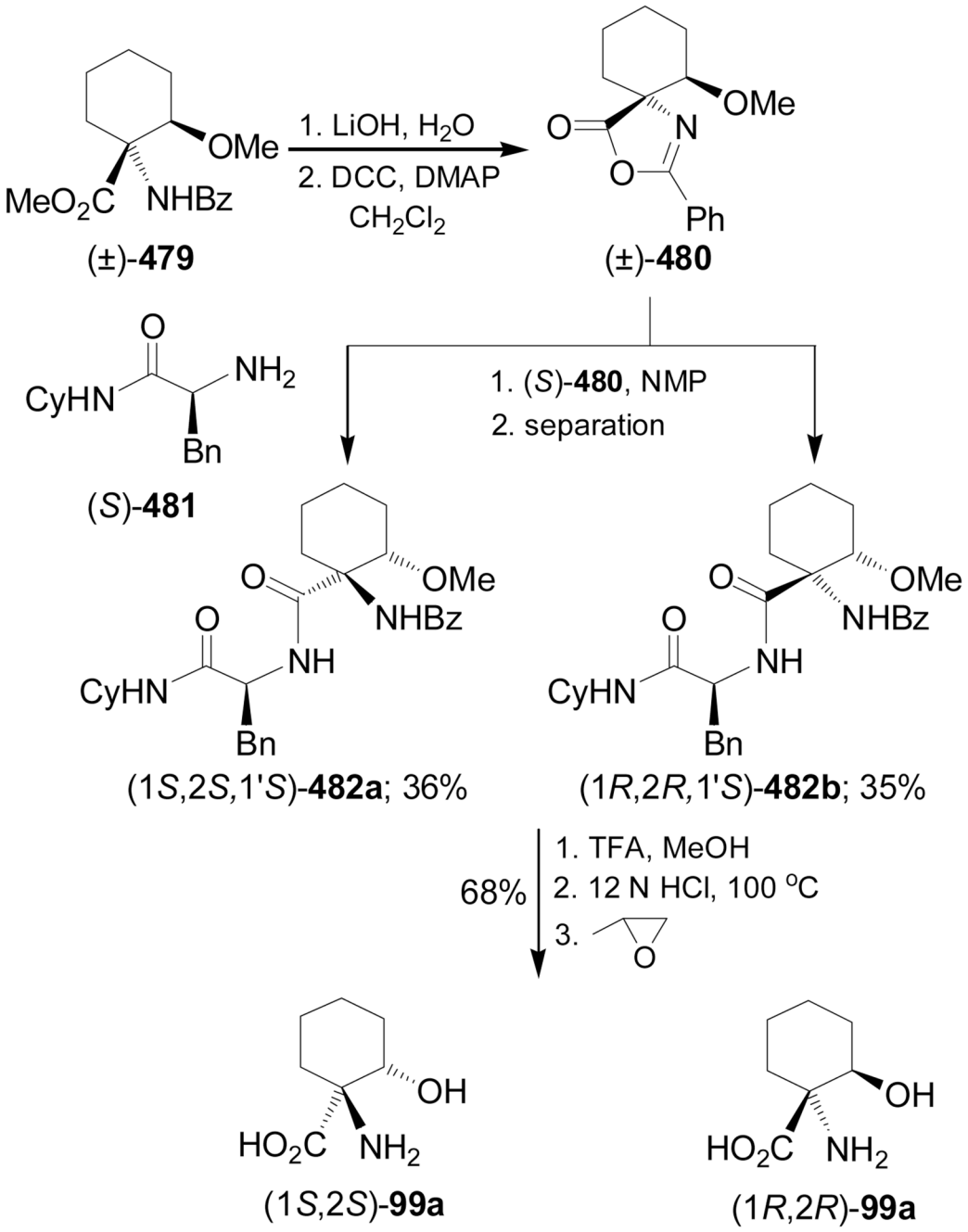
Scheme 95.



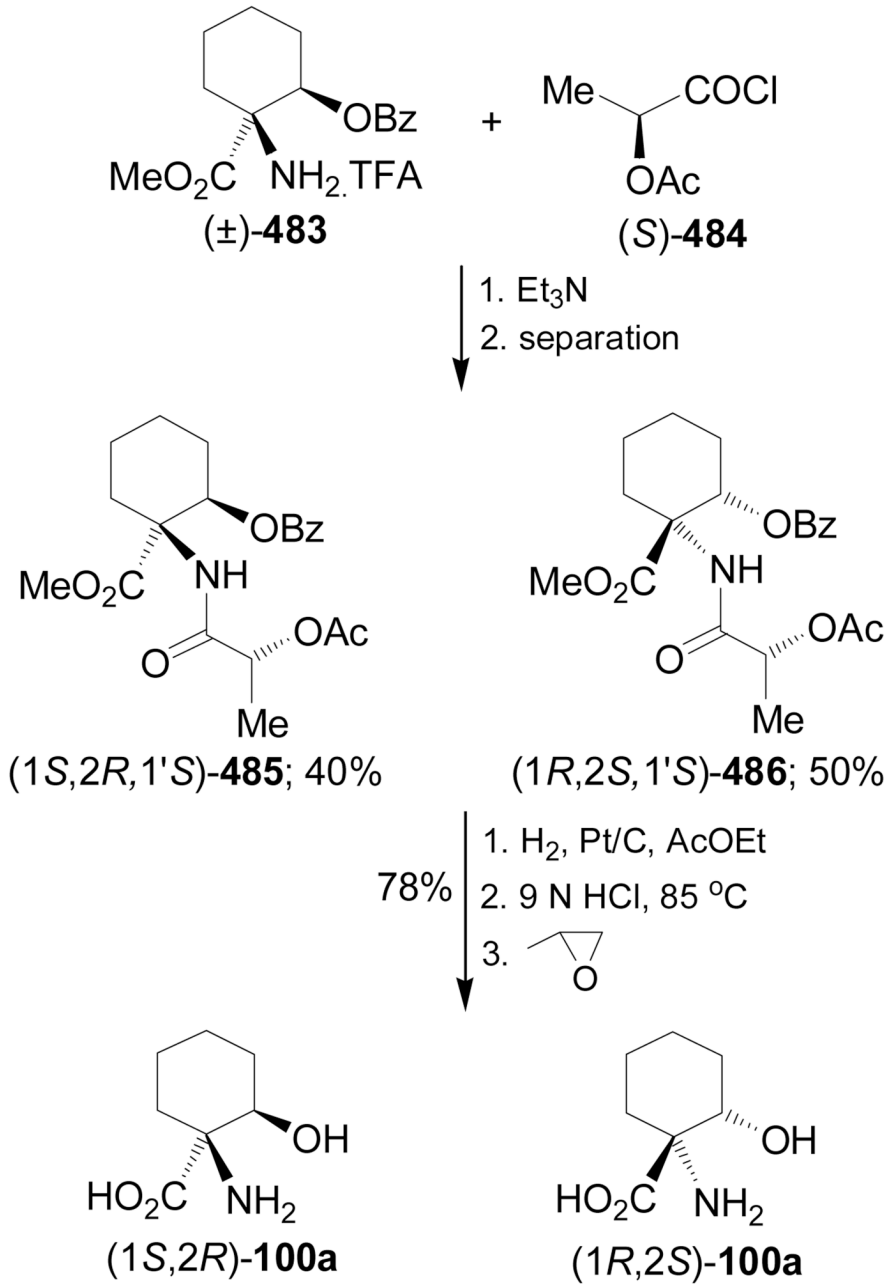
Scheme 96.



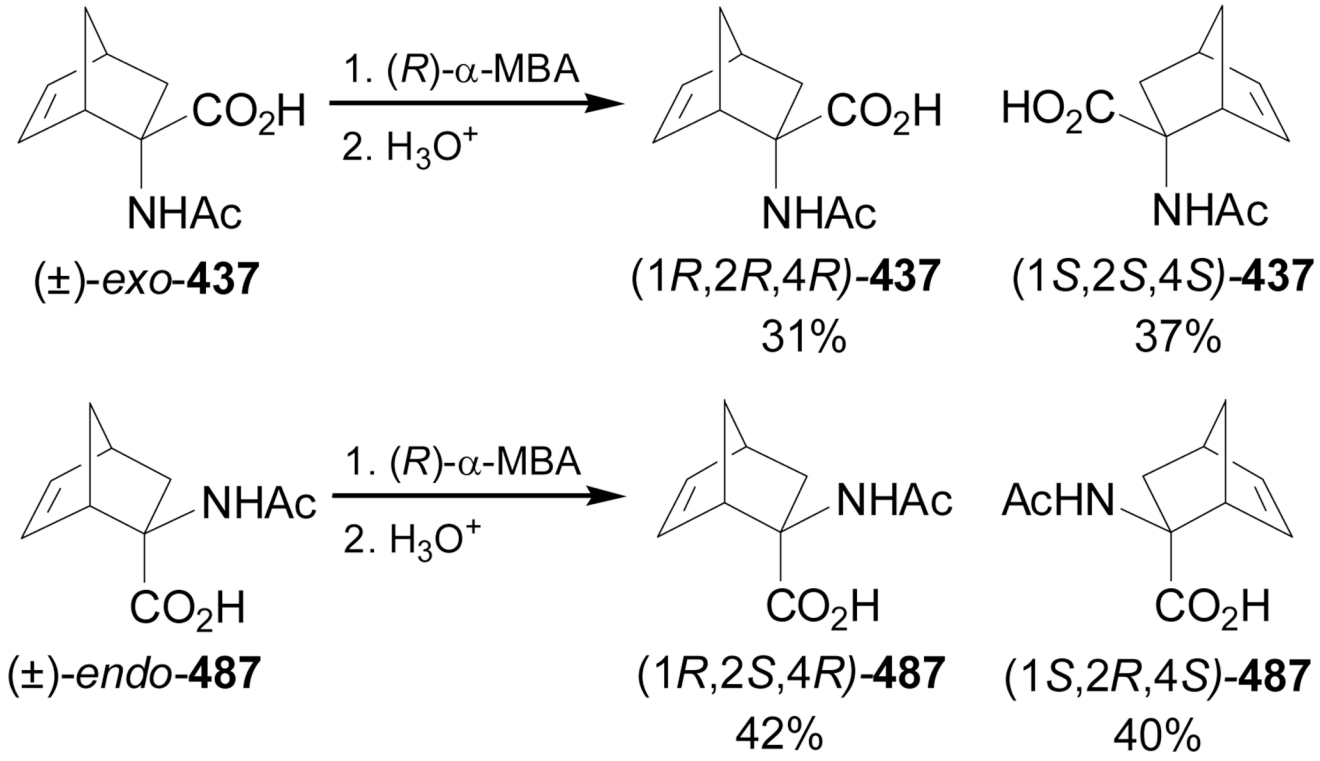
Scheme 97.



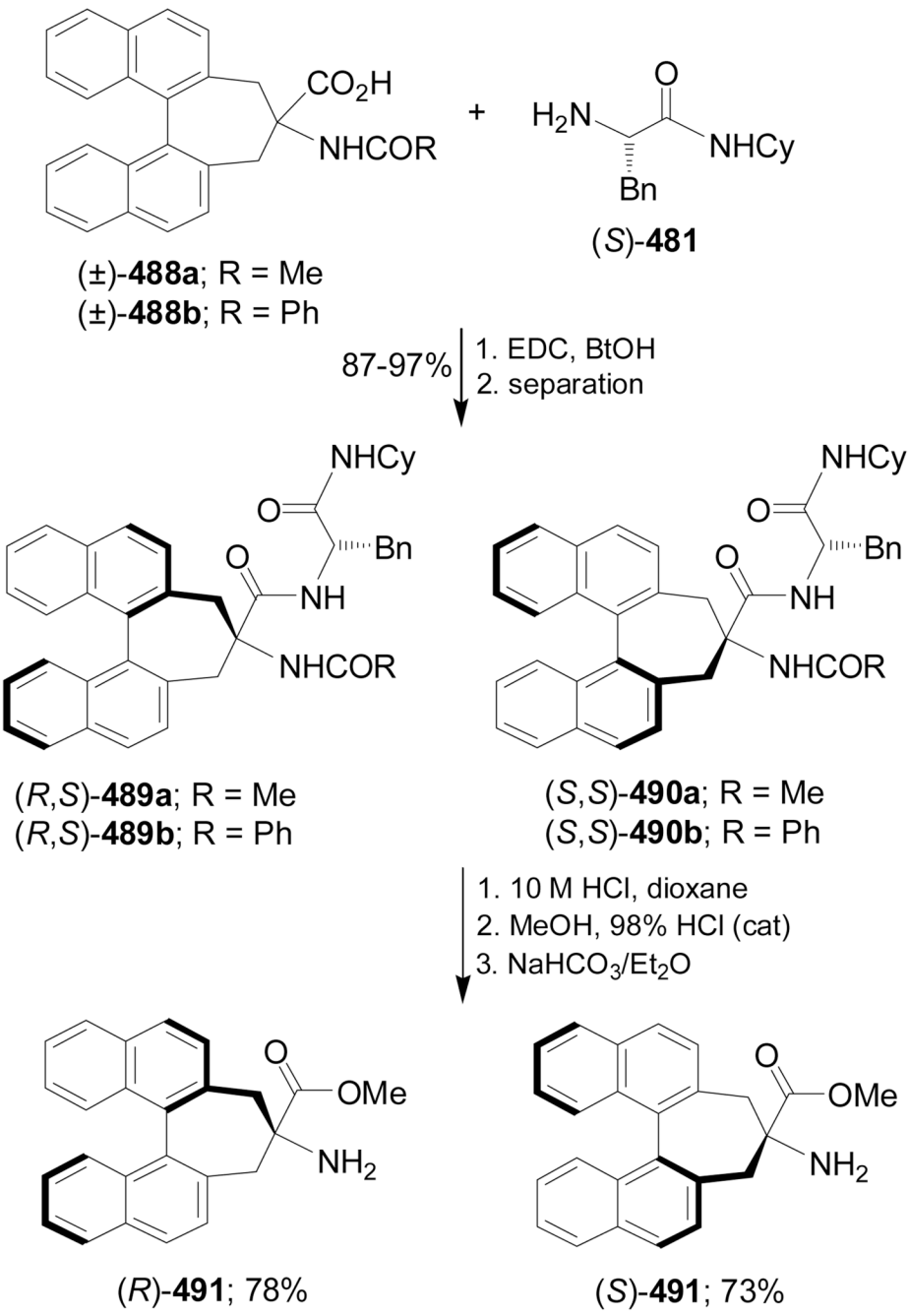
Scheme 98.



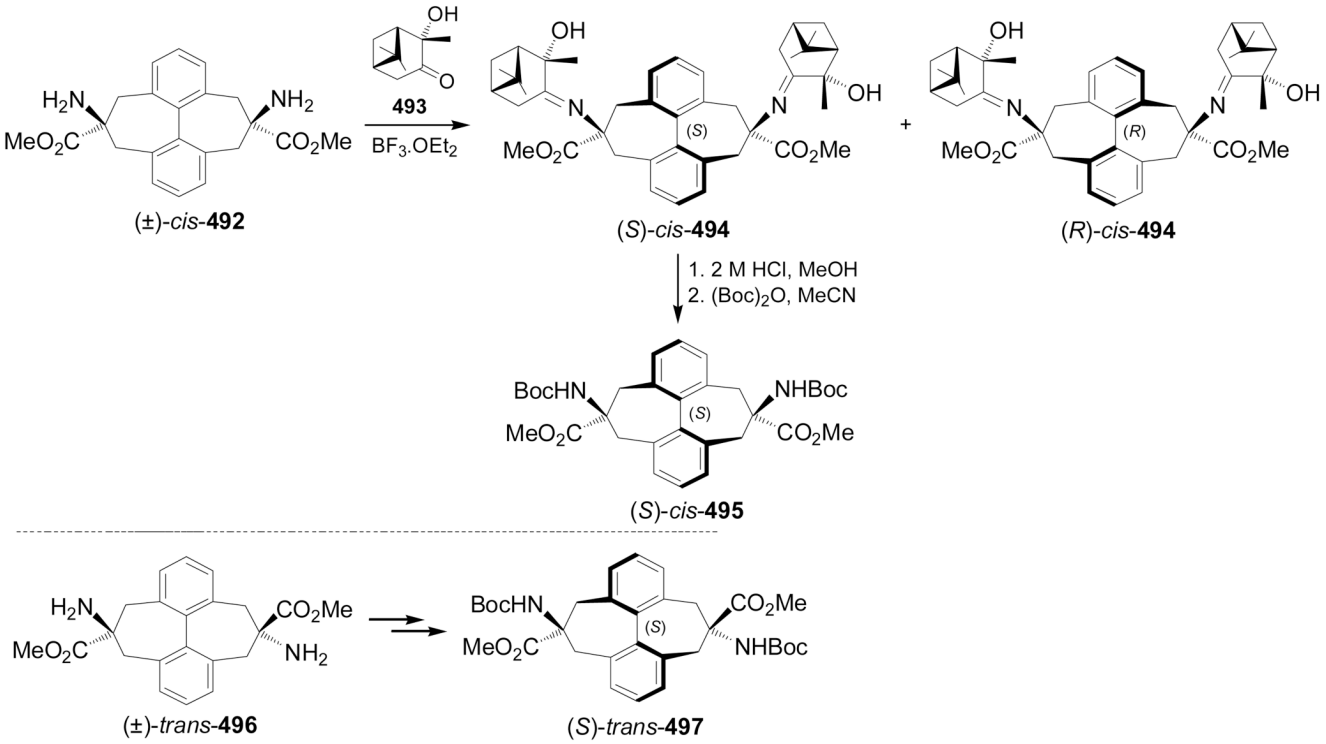
Scheme 99.



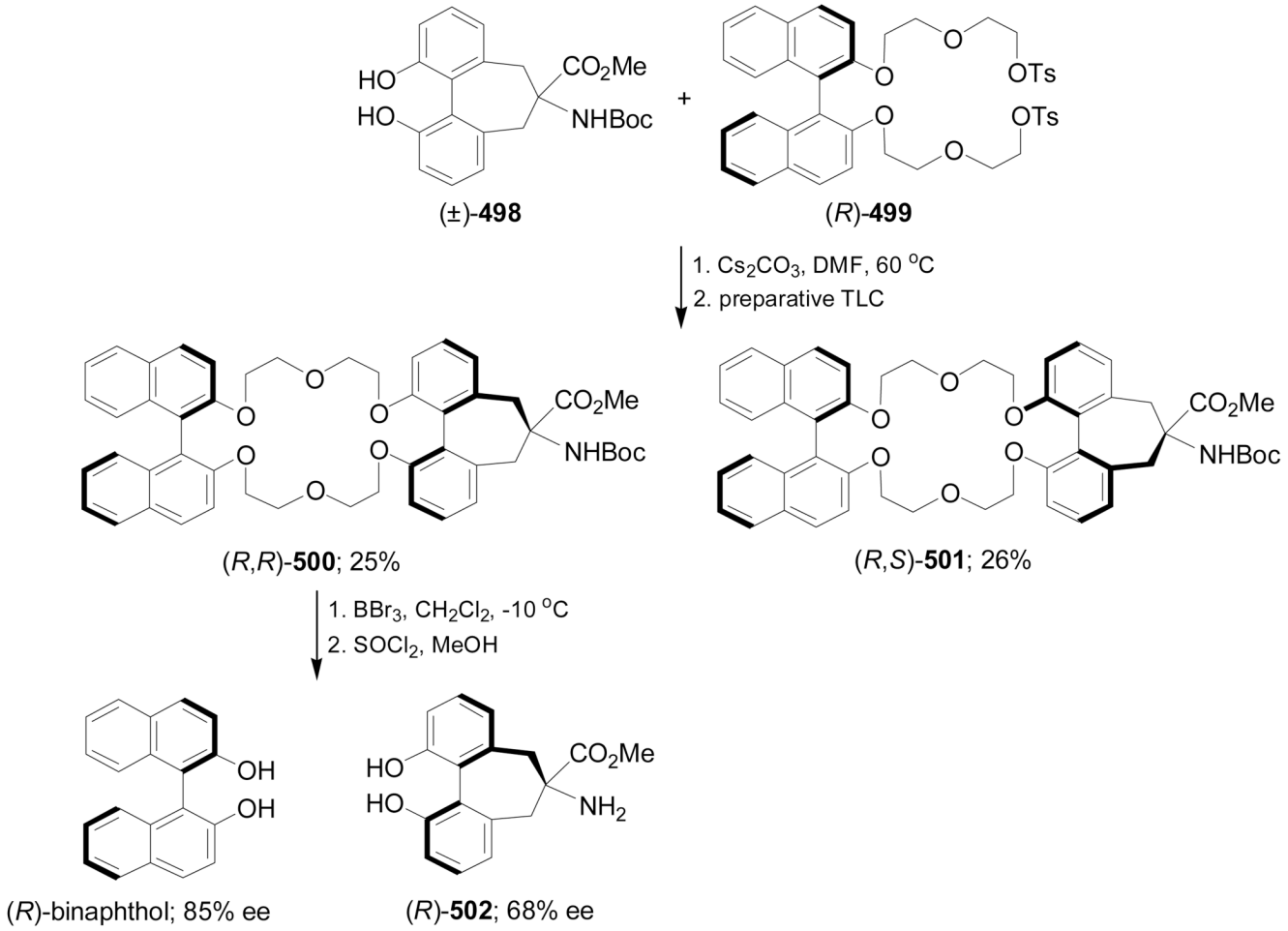
Scheme 100.



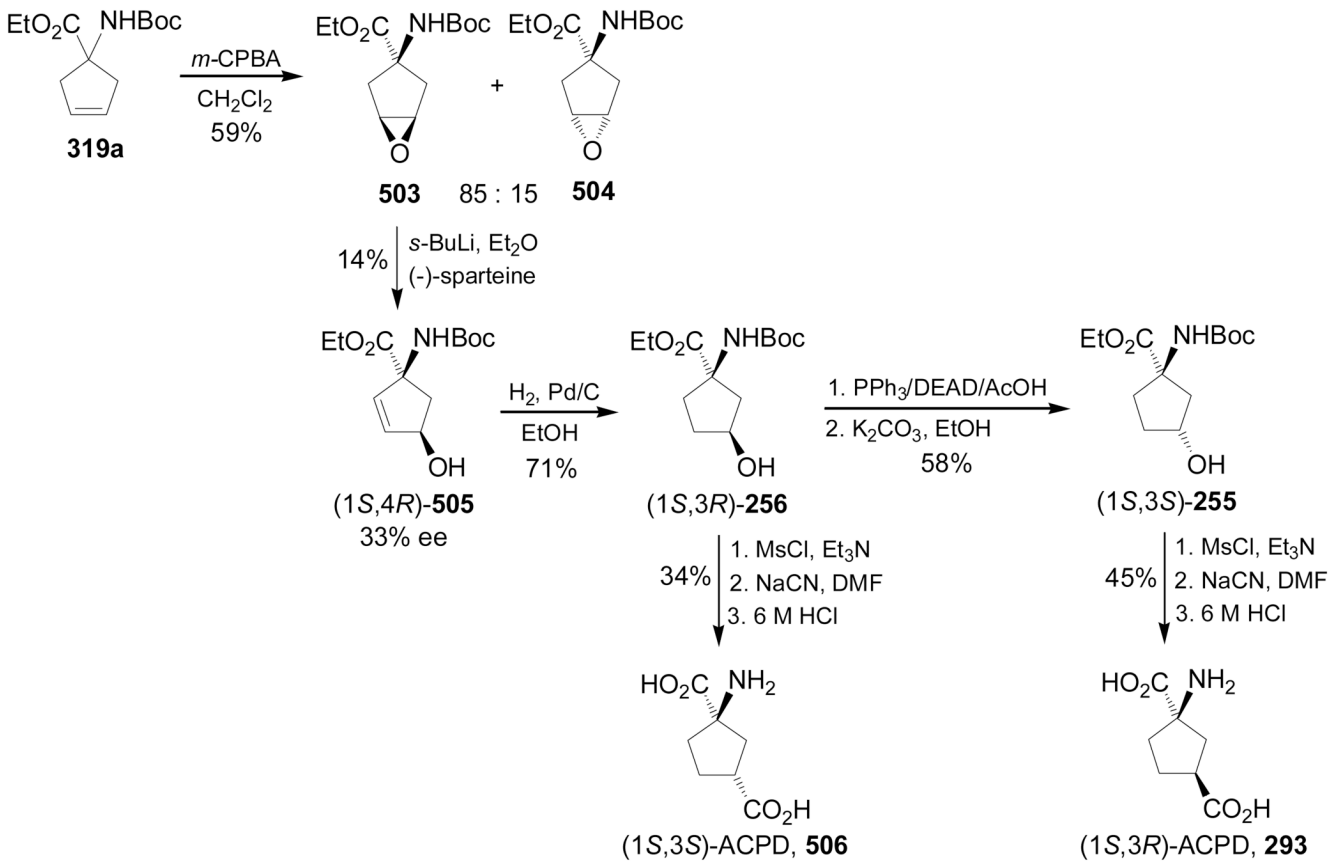
Scheme 101.



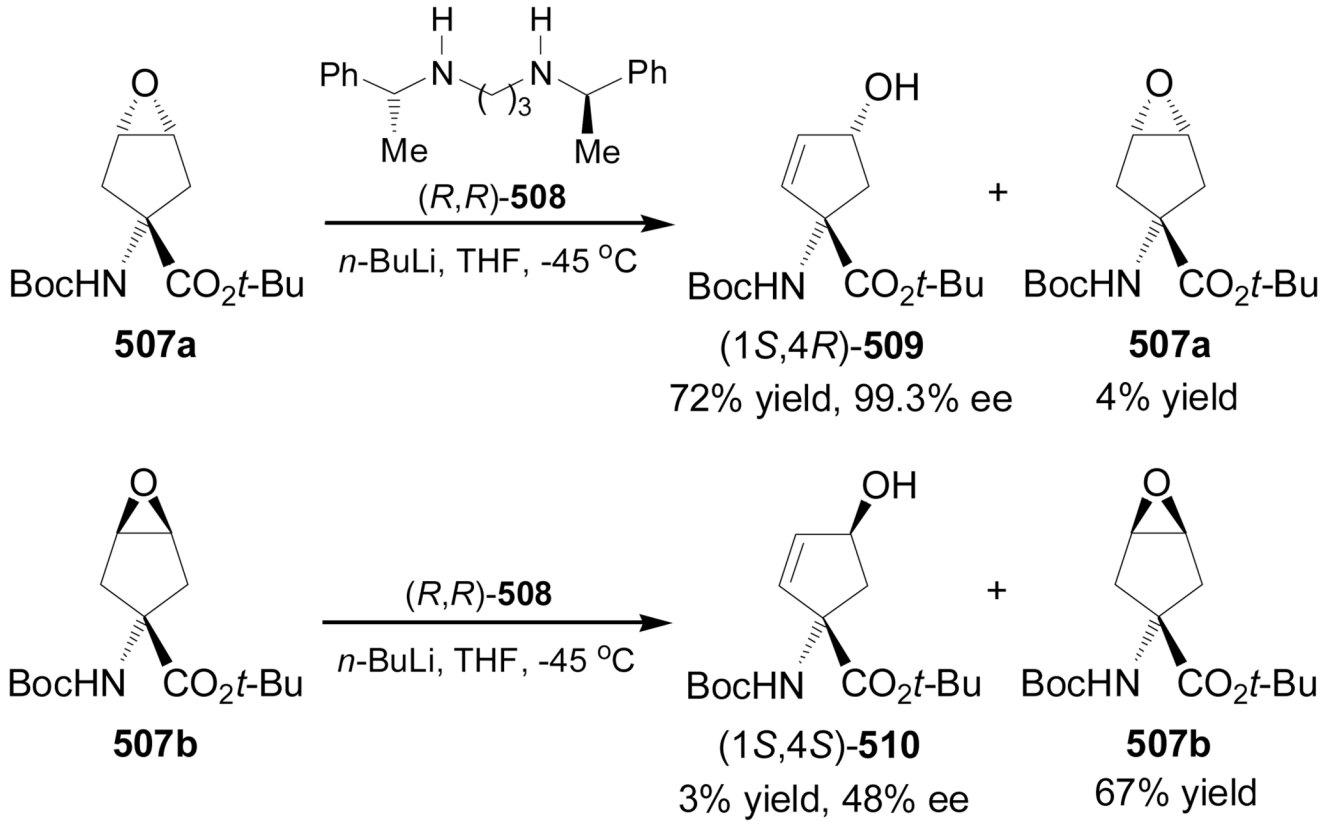
Scheme 102.



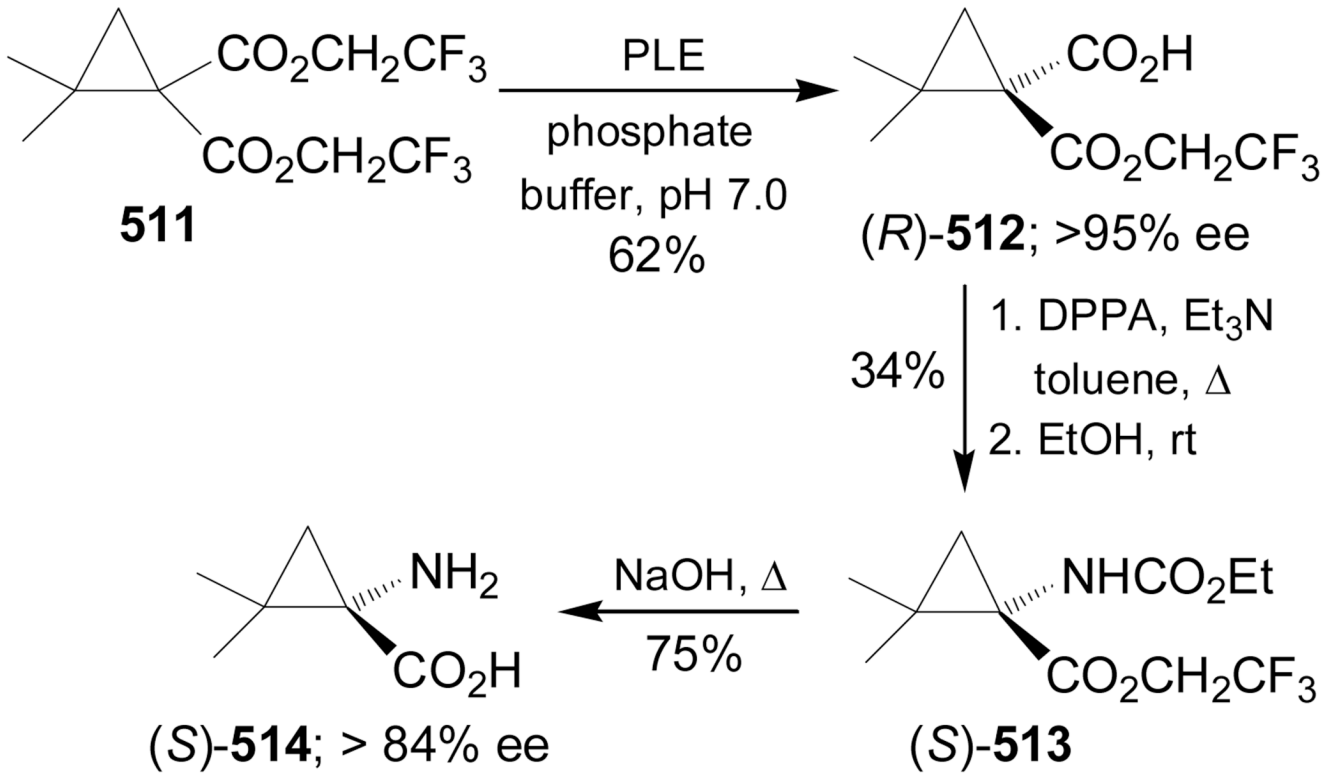
Scheme 103.



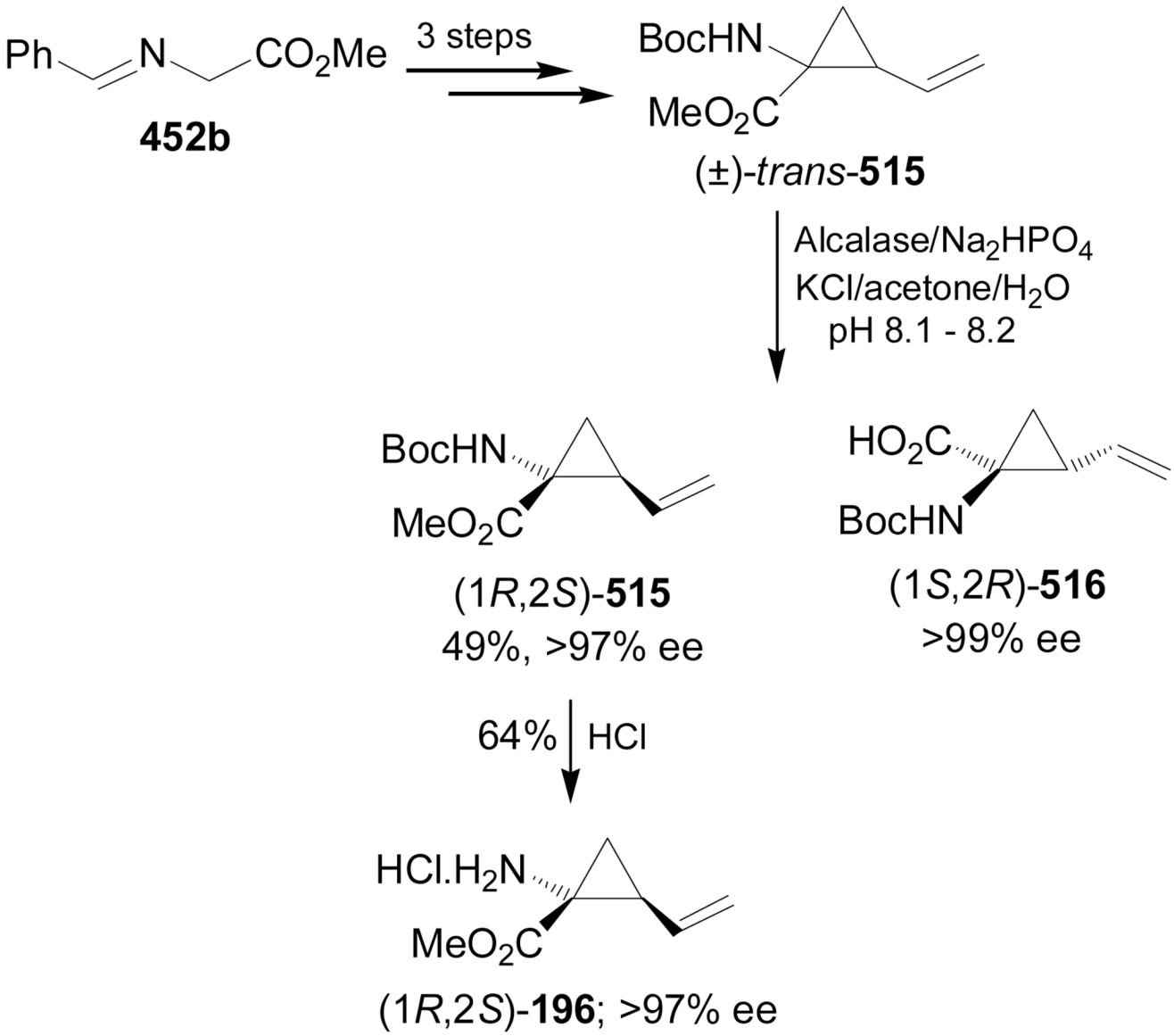
Scheme 104.



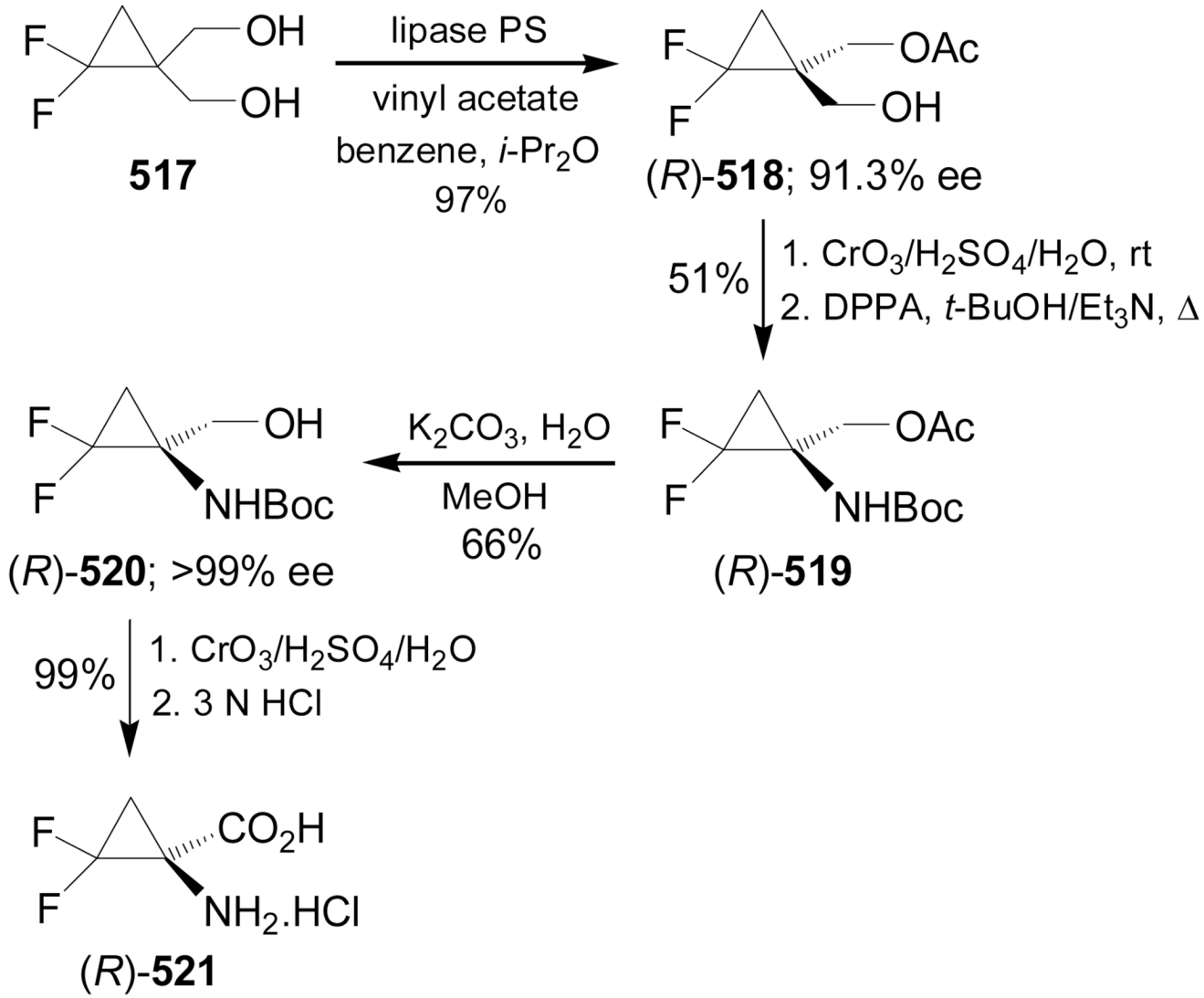
Scheme 105.



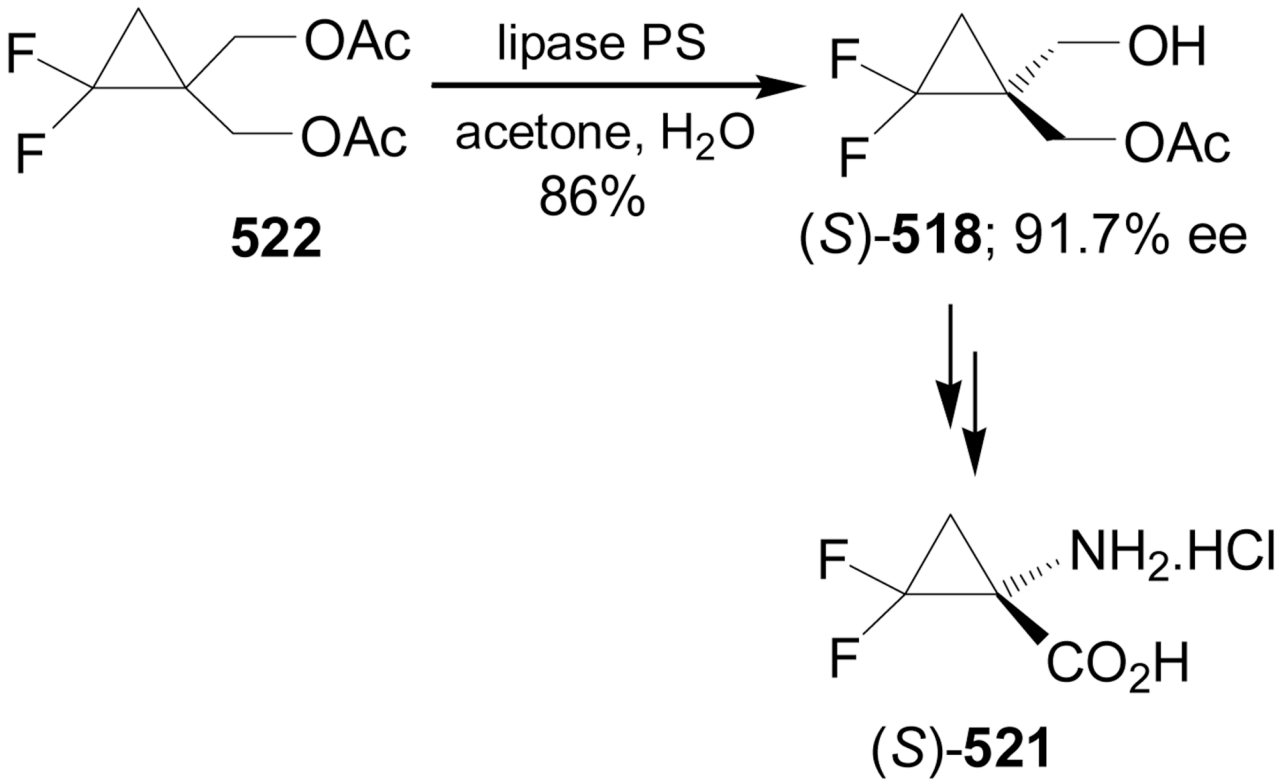
Scheme 106.



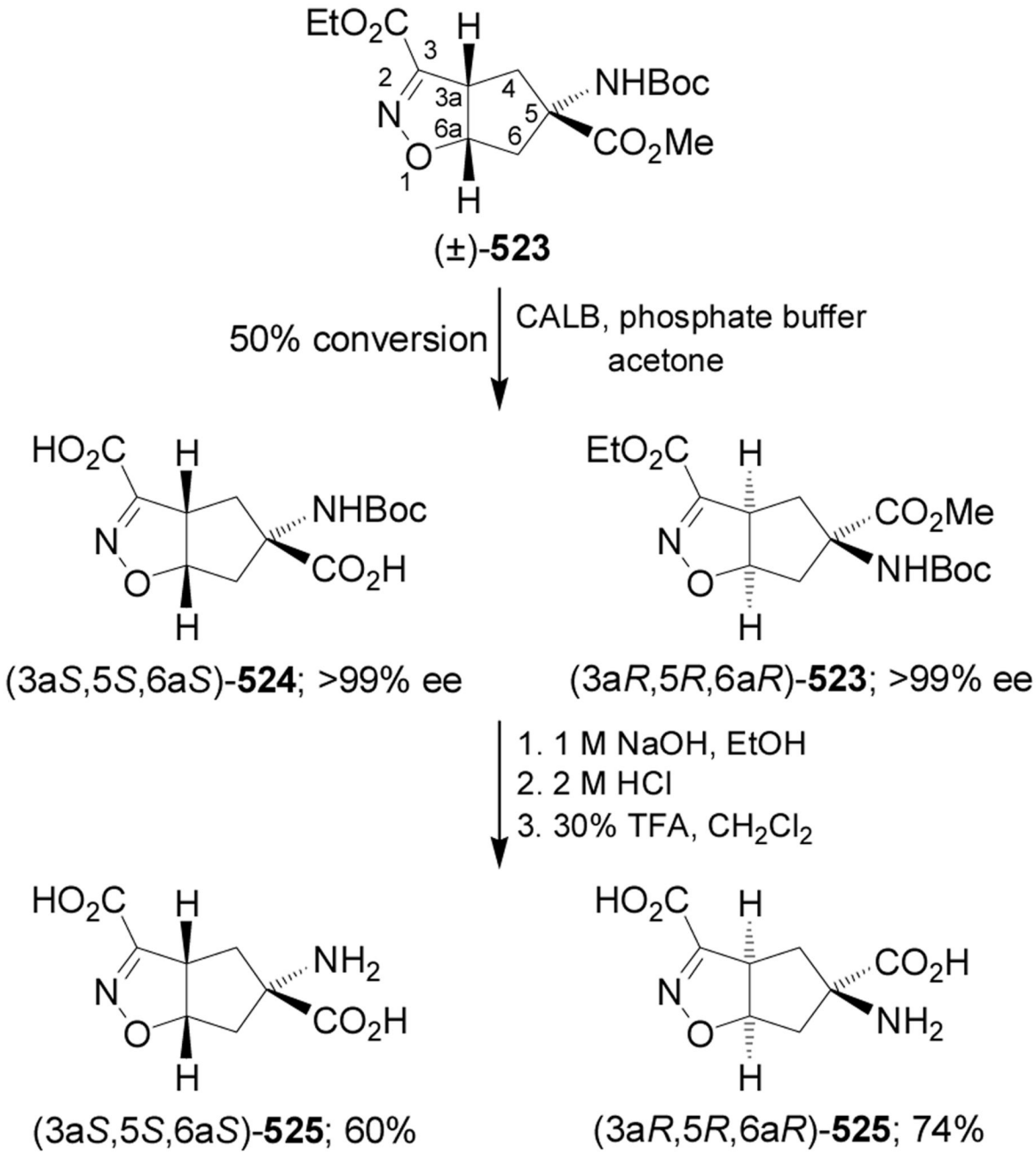
Scheme 107.



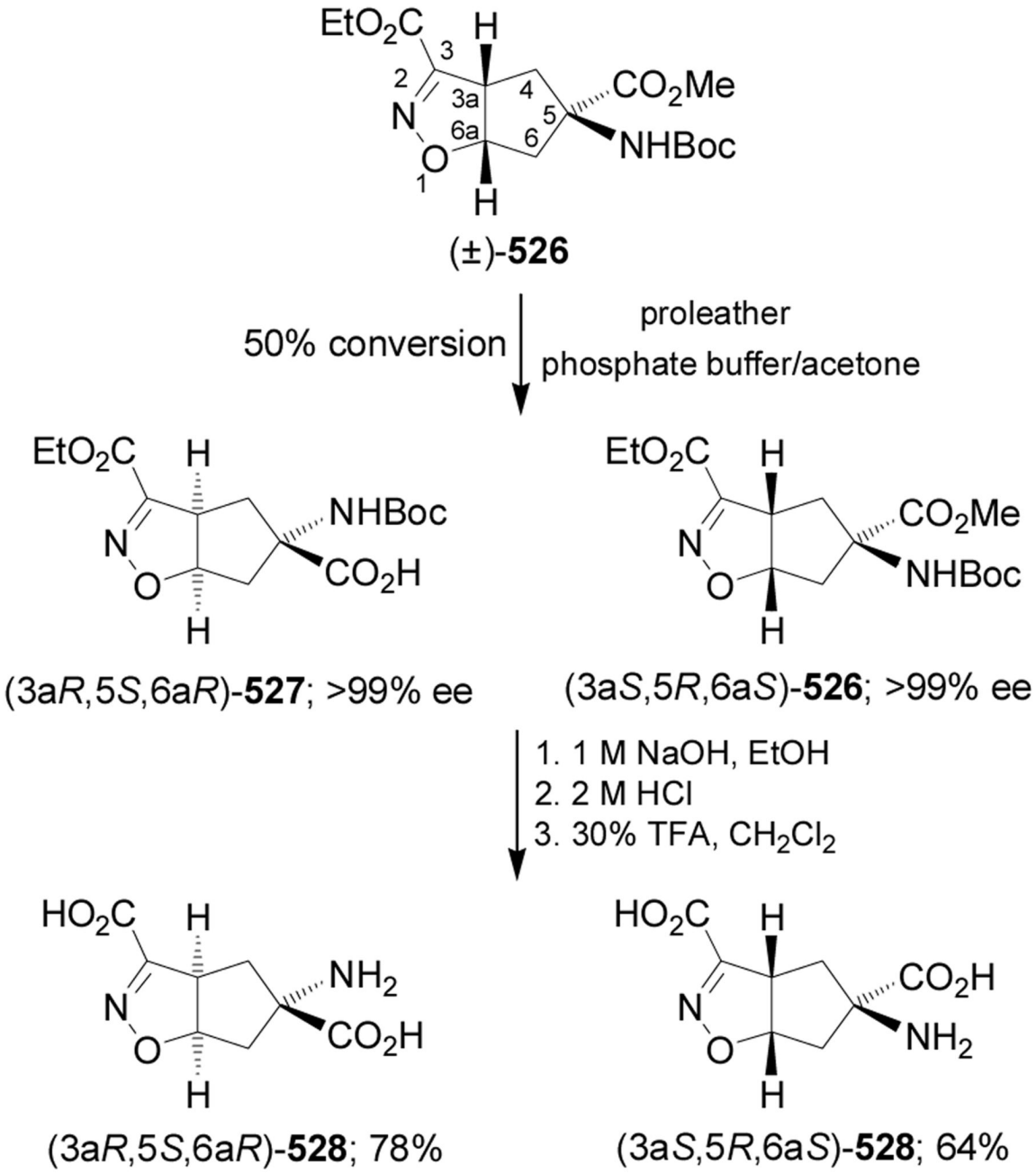
Scheme 108.



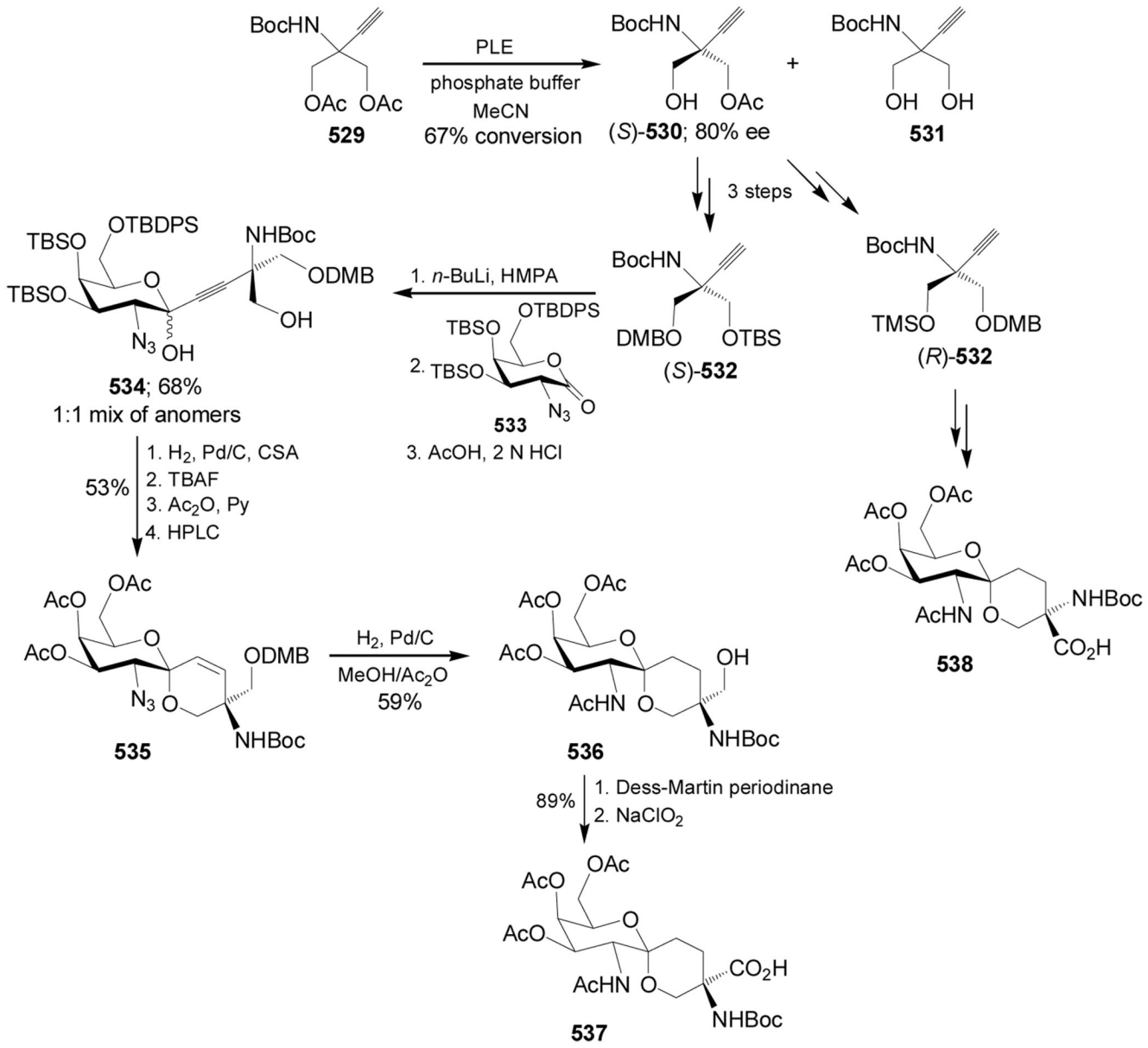
Scheme 109.



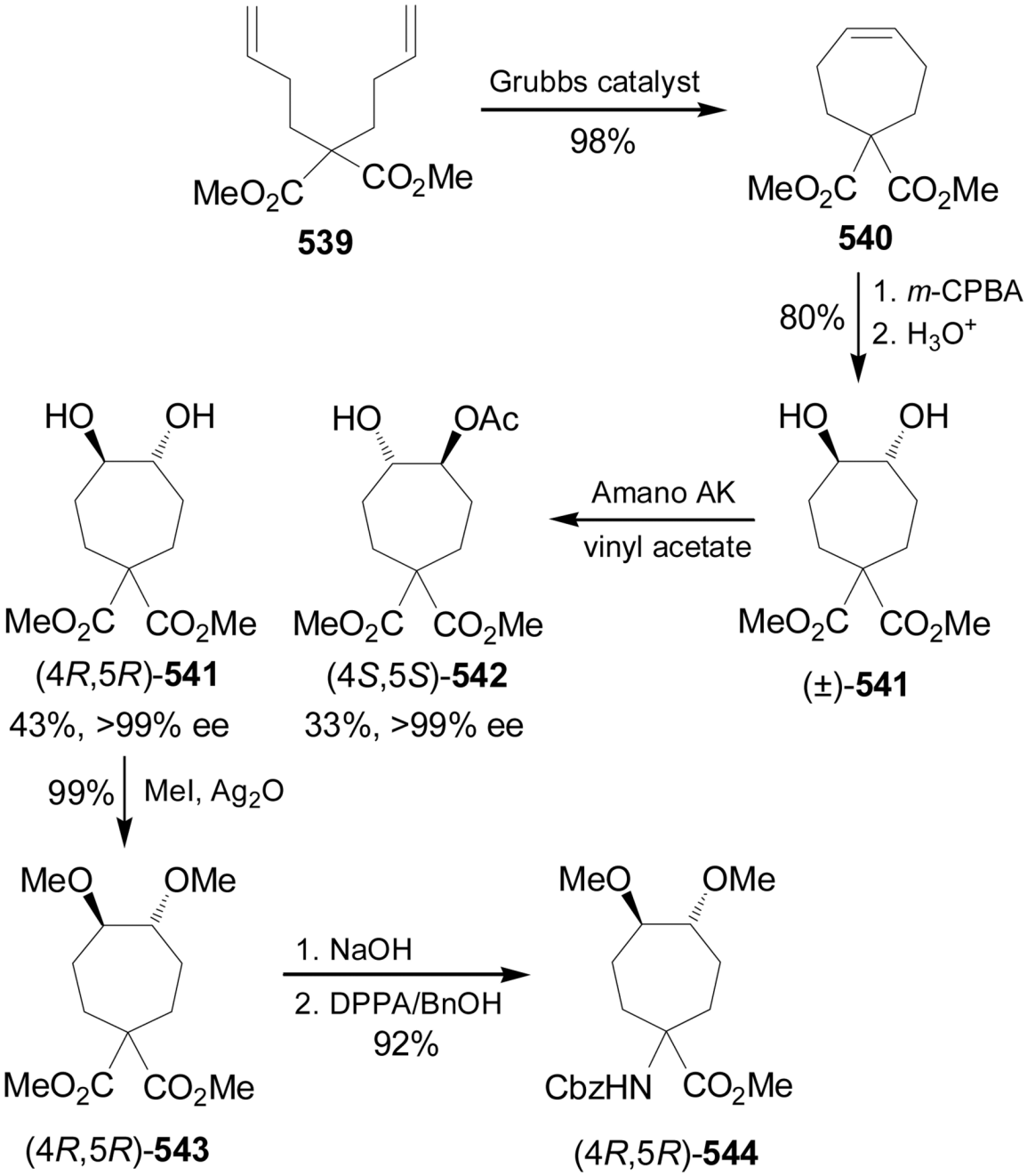
Scheme 110.



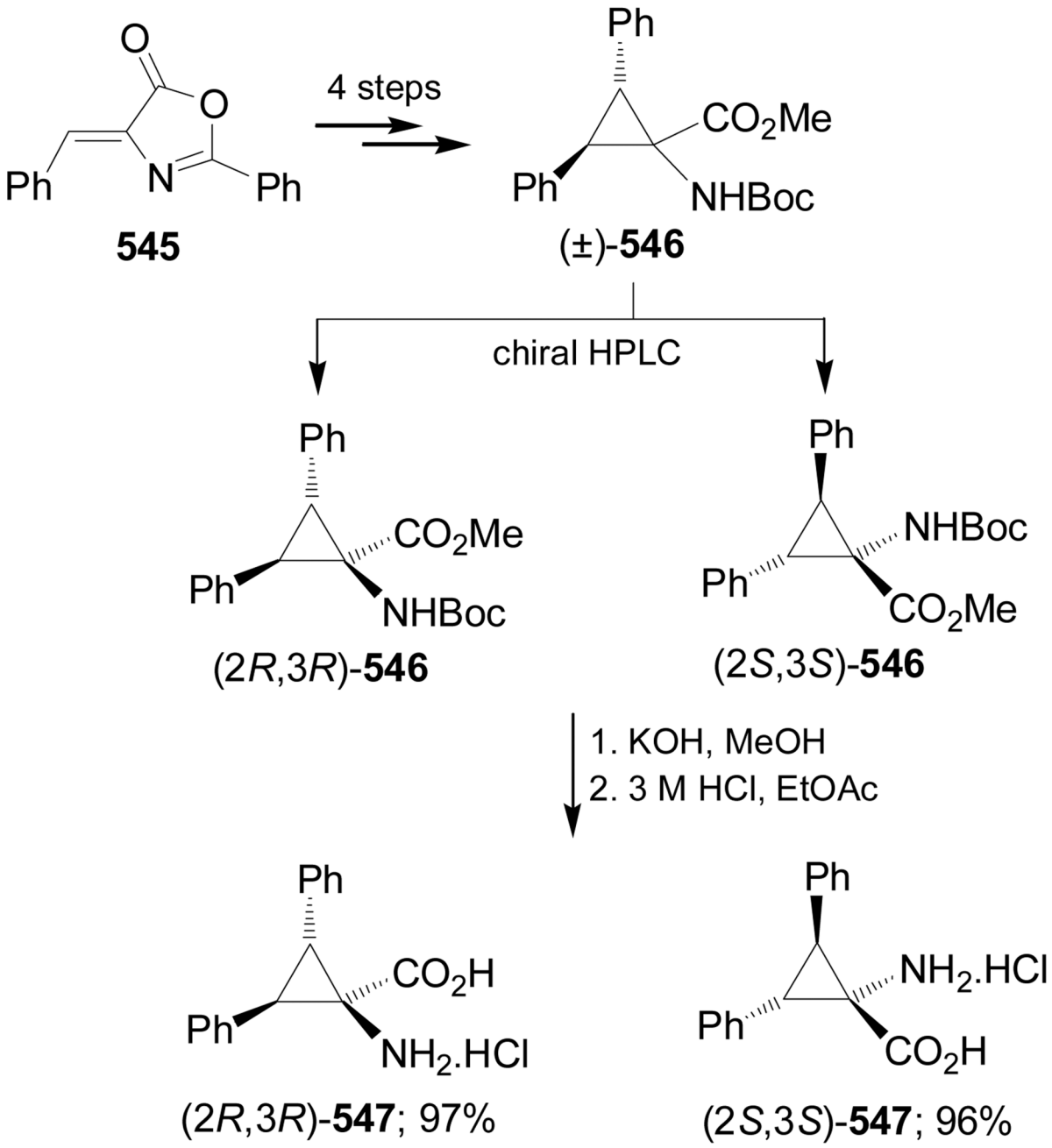
Scheme 111.



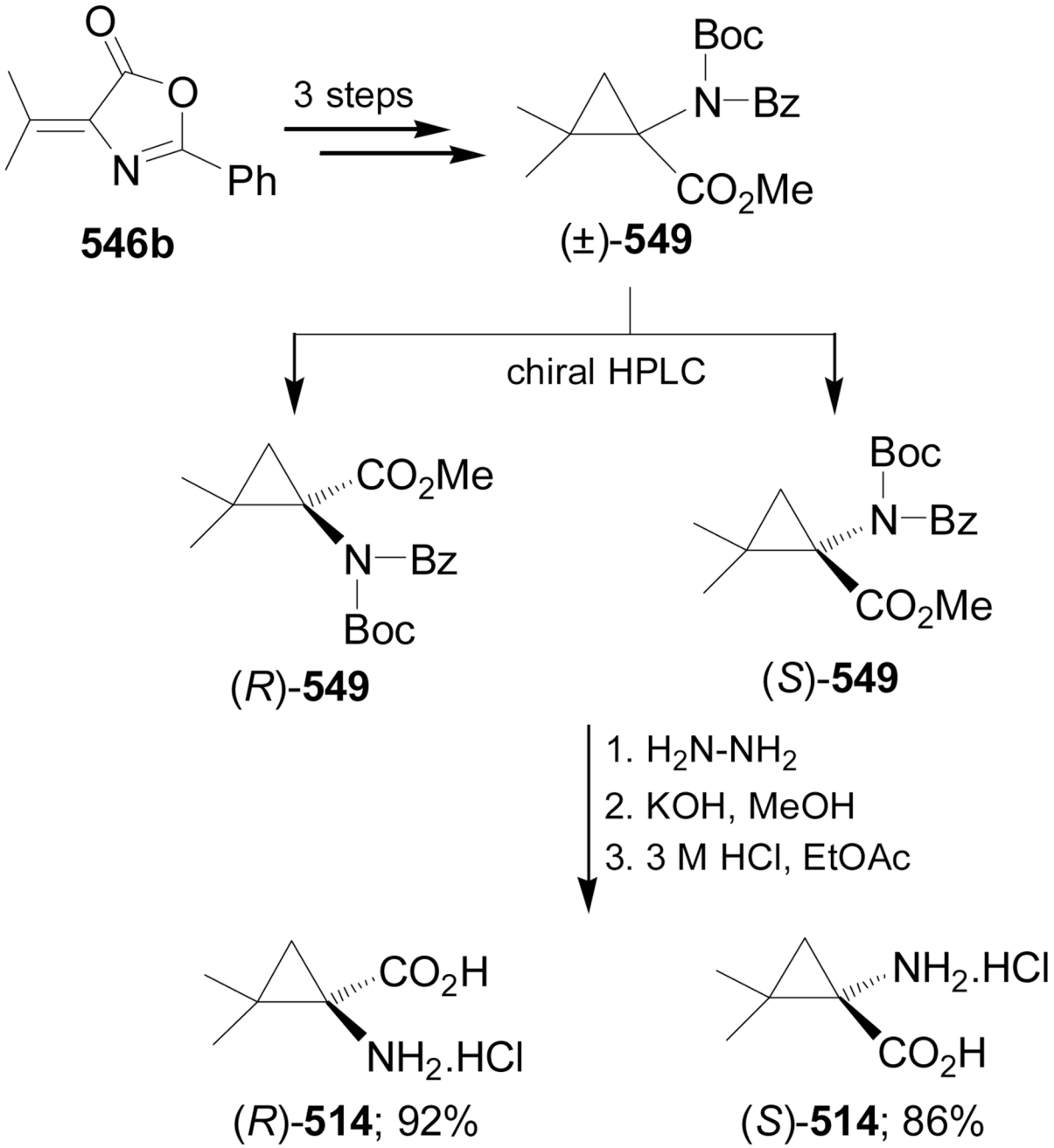
Scheme 112.



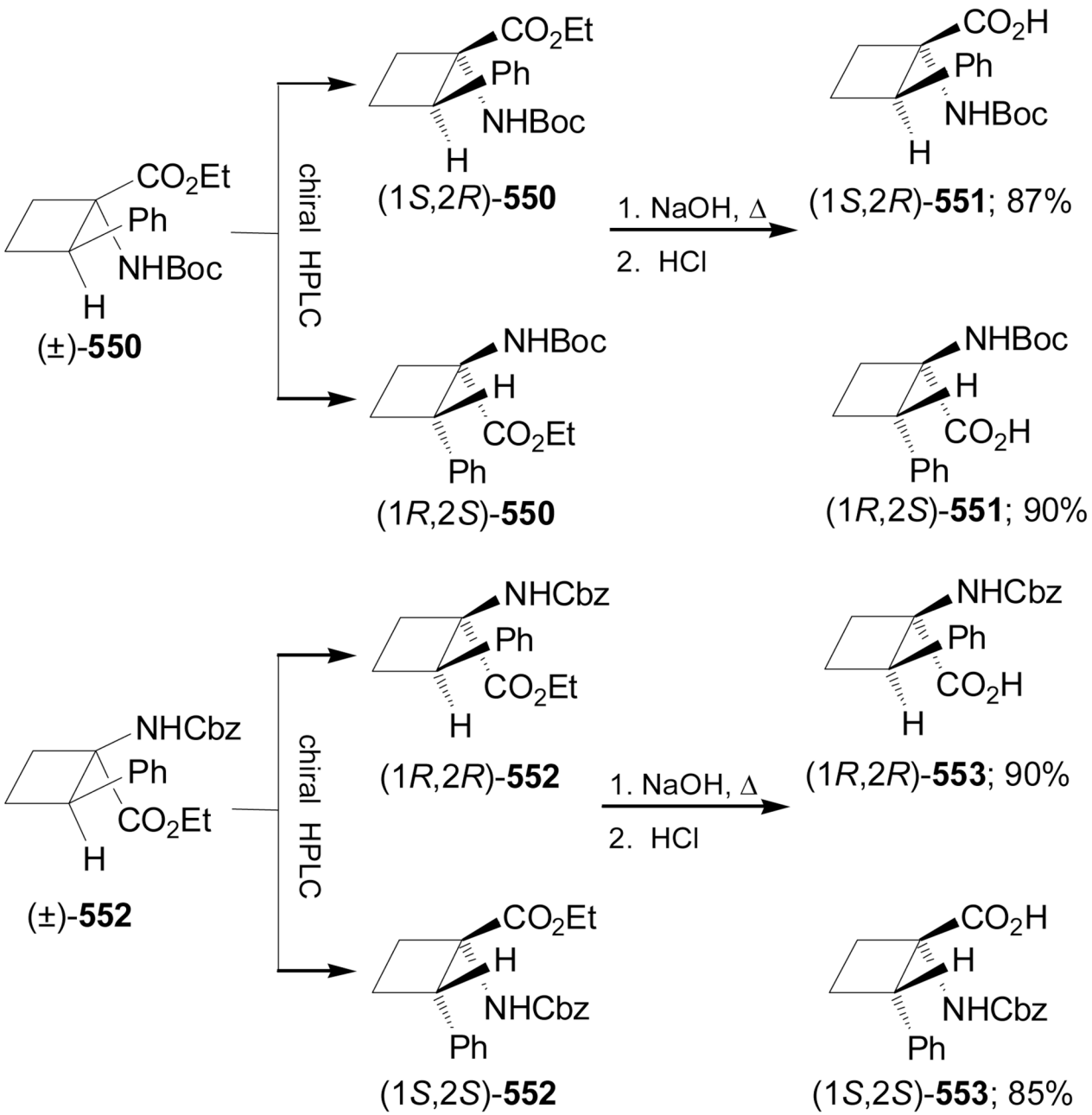
Scheme 113.



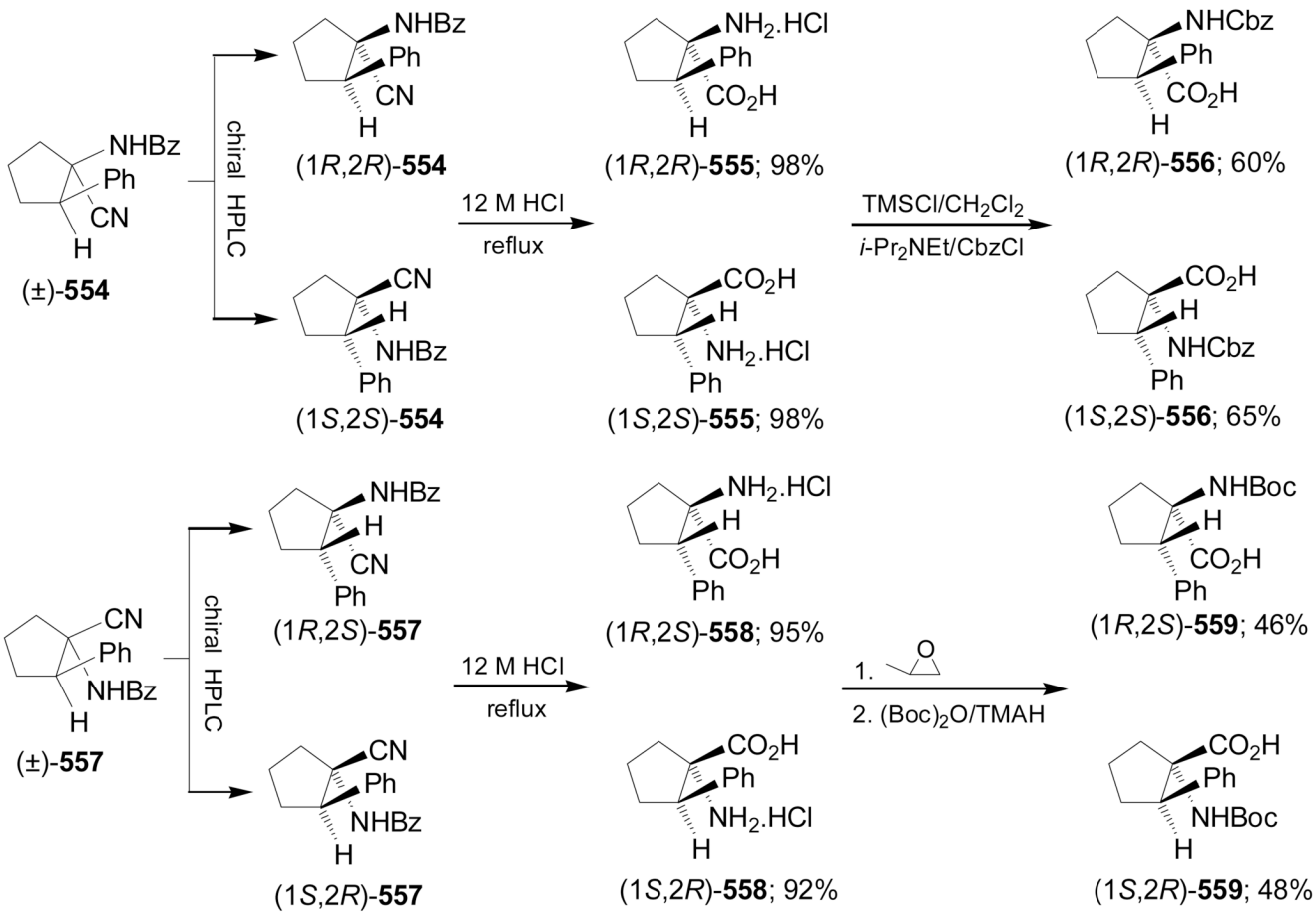
Scheme 114.



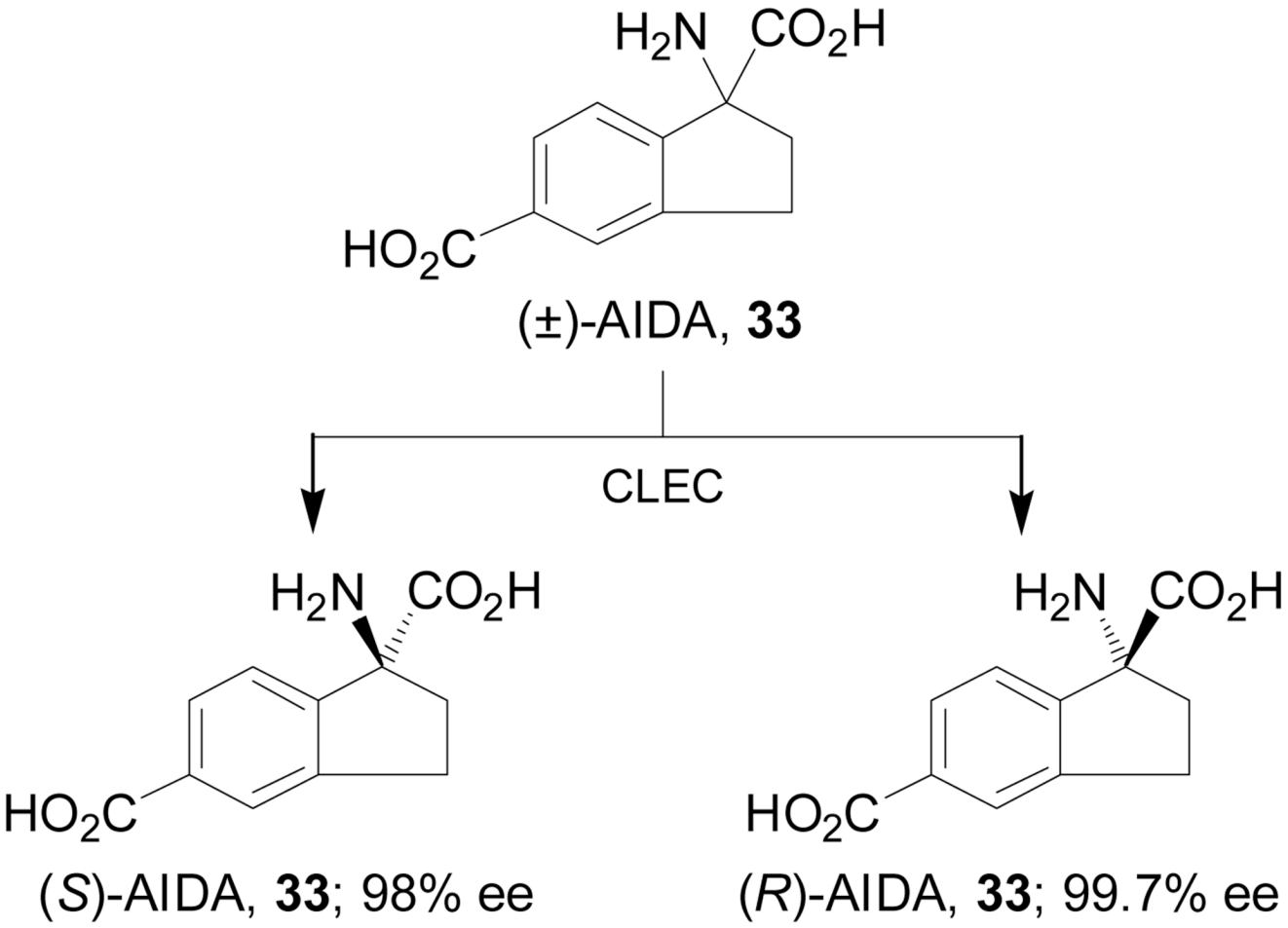
Scheme 115.



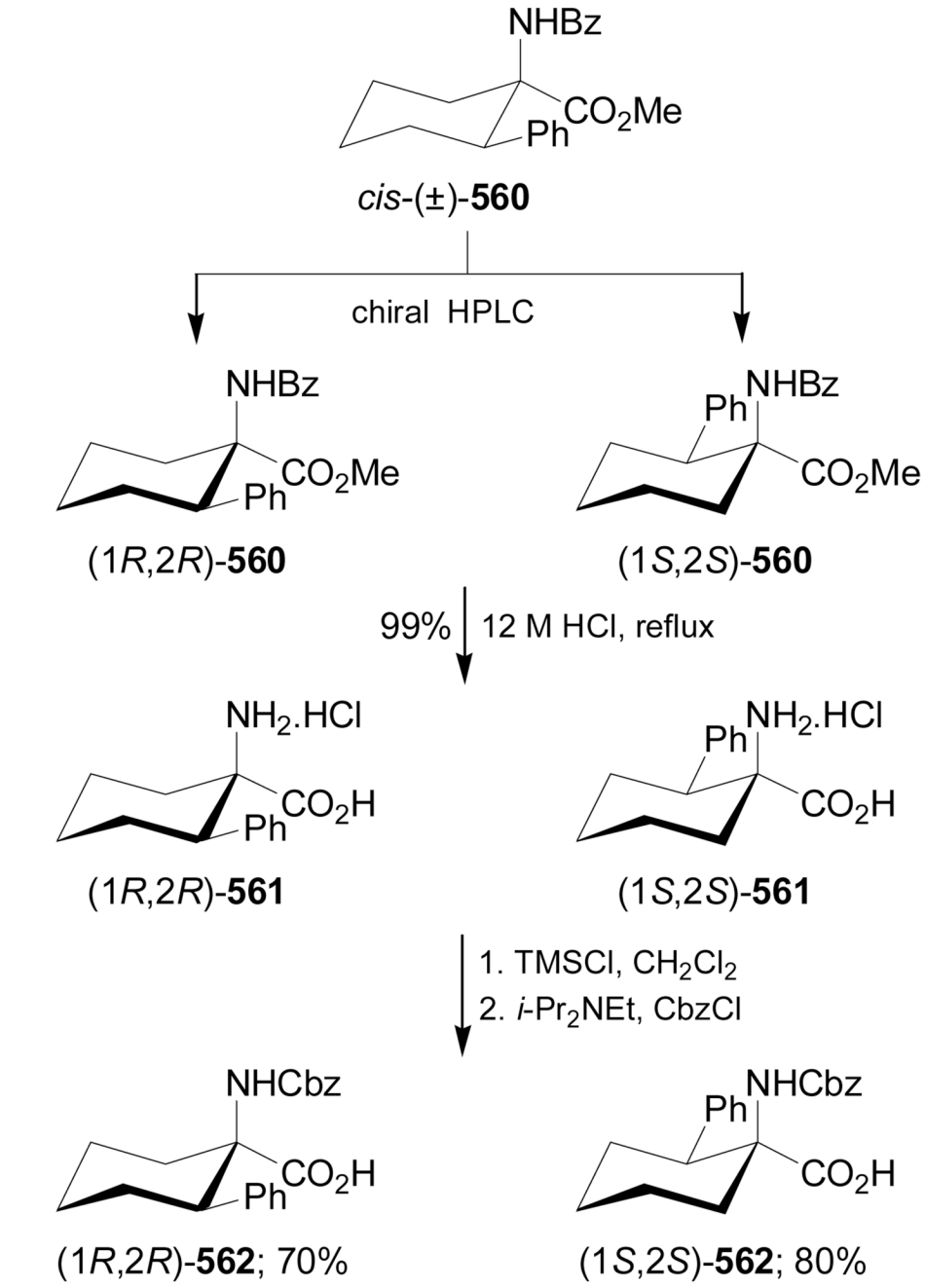
Scheme 116.



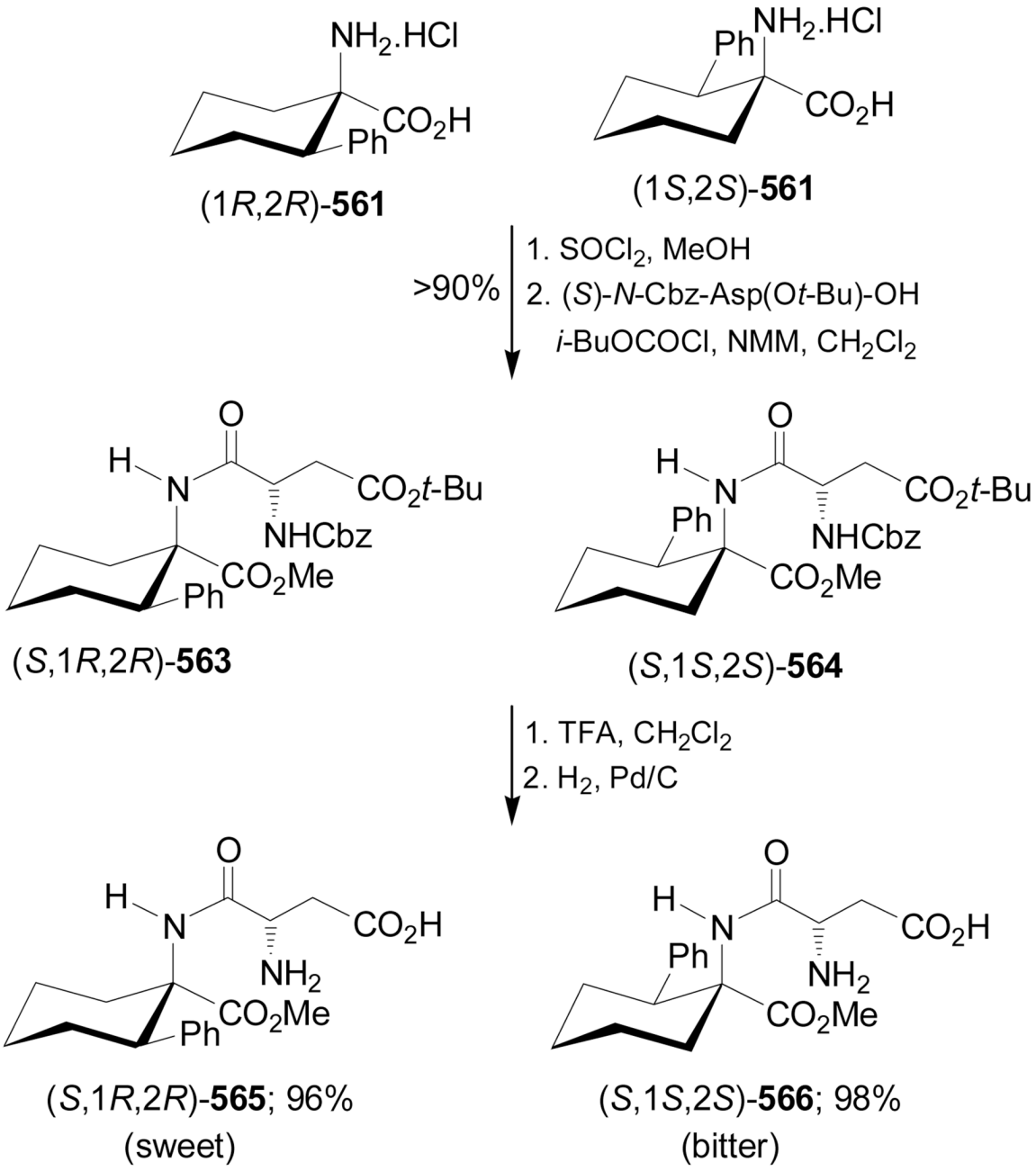
Scheme 117.



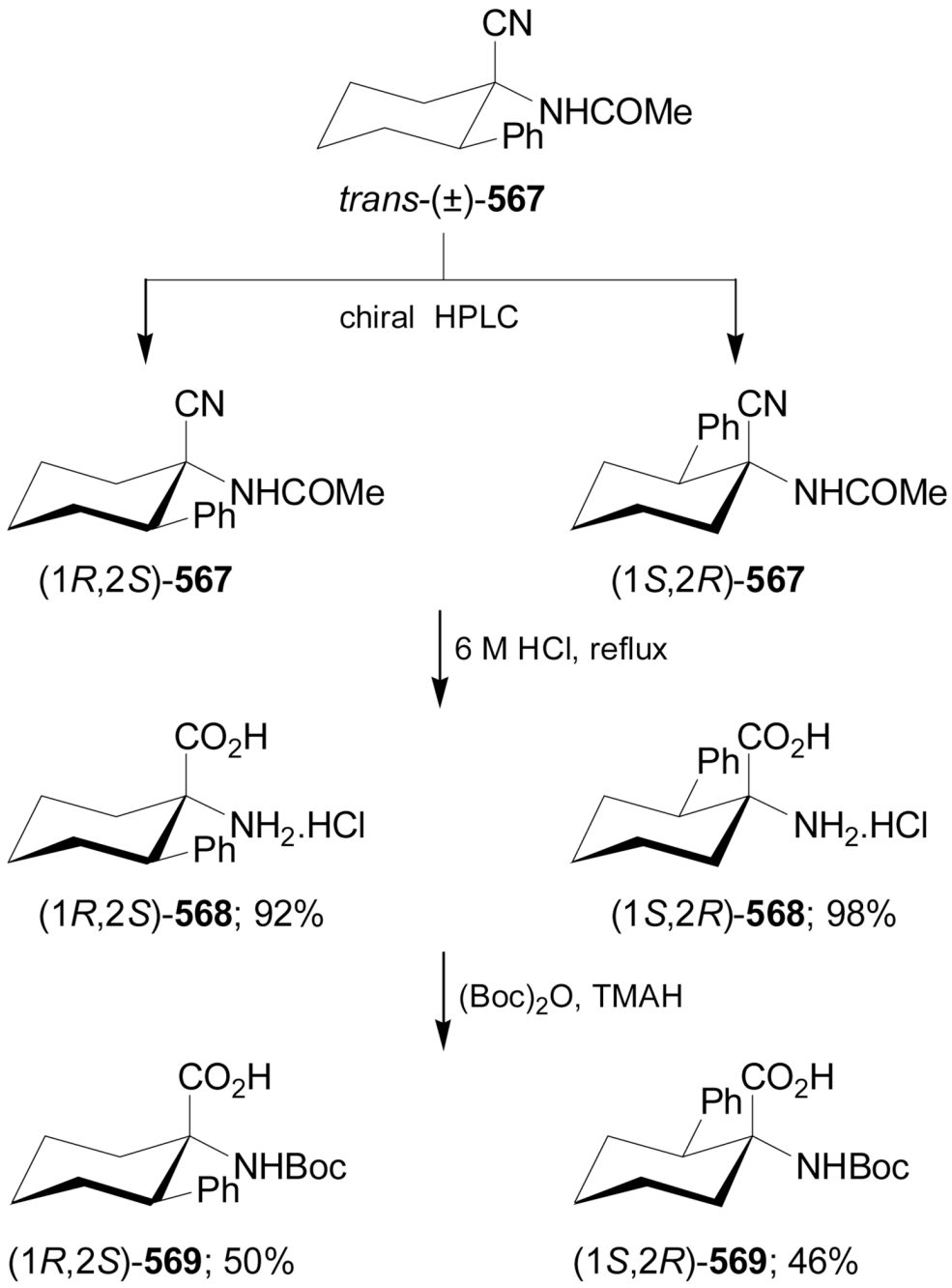
Scheme 118.



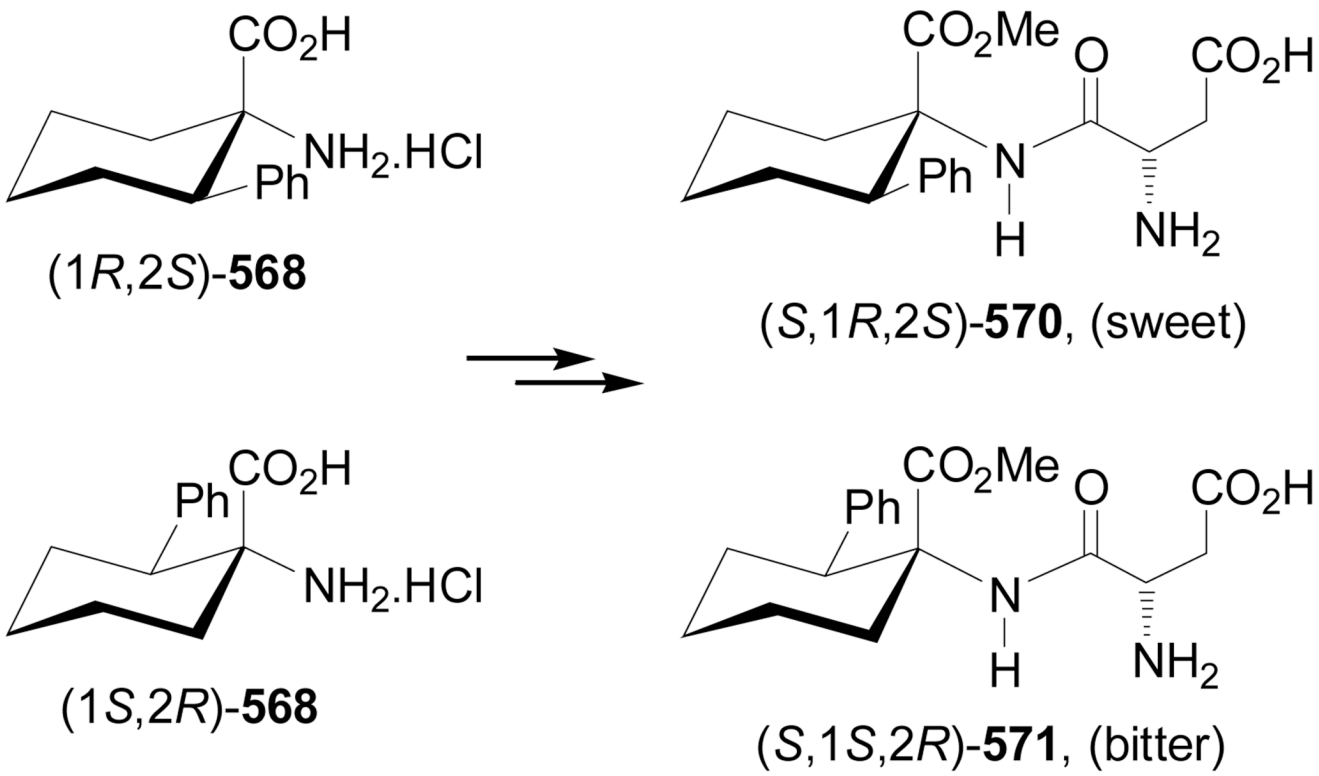
Scheme 119.



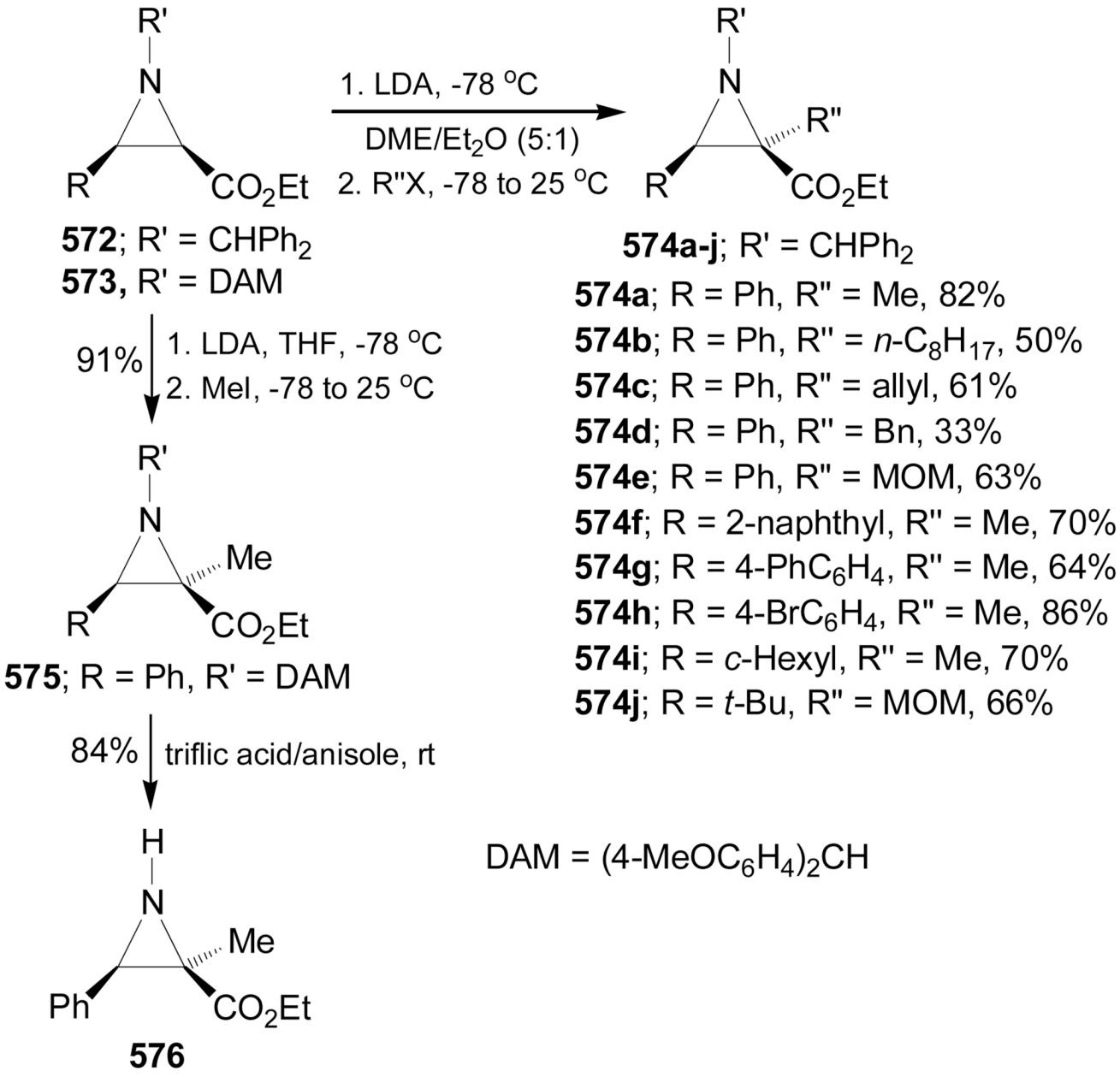
Scheme 120.



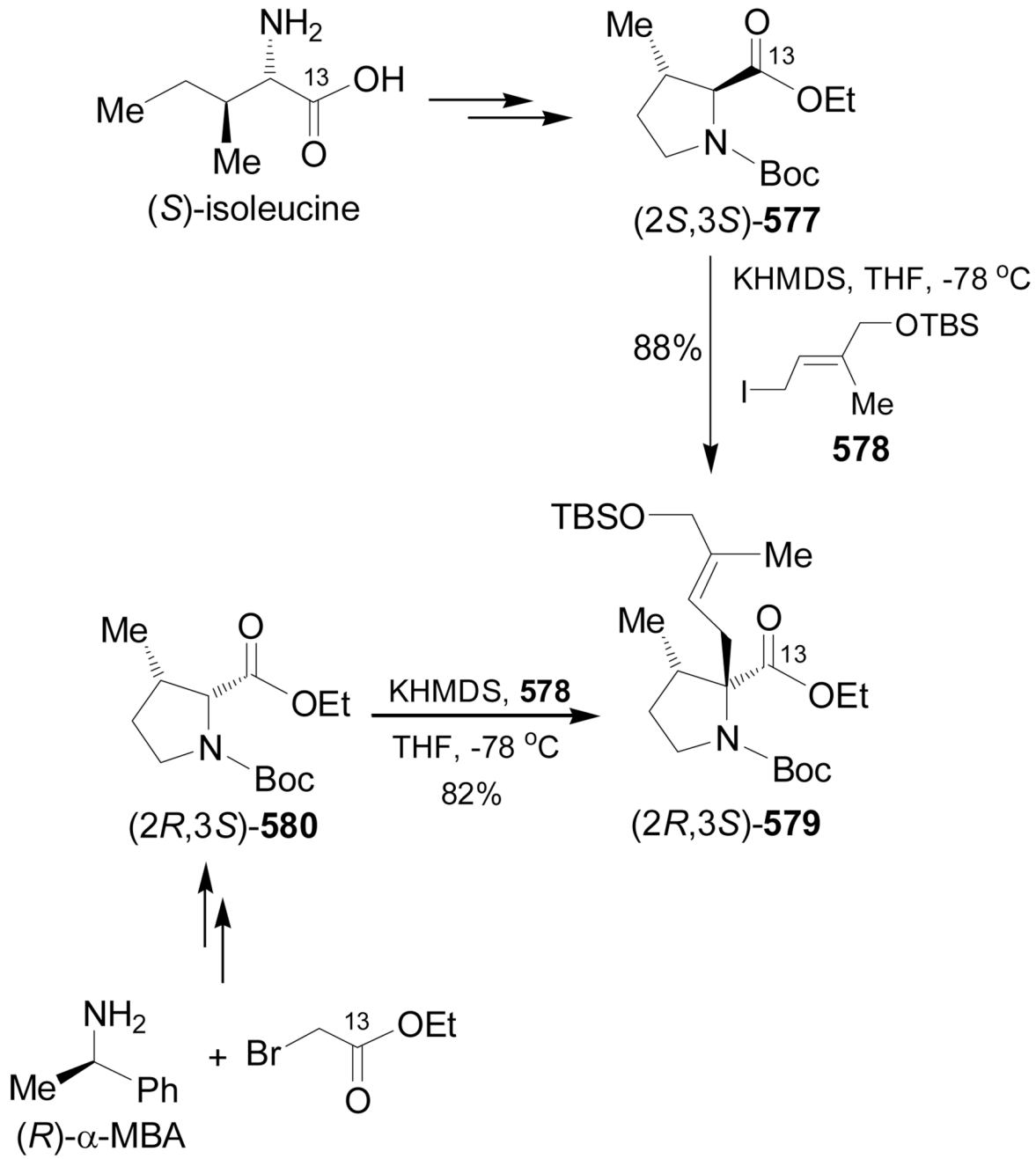
Scheme 121.



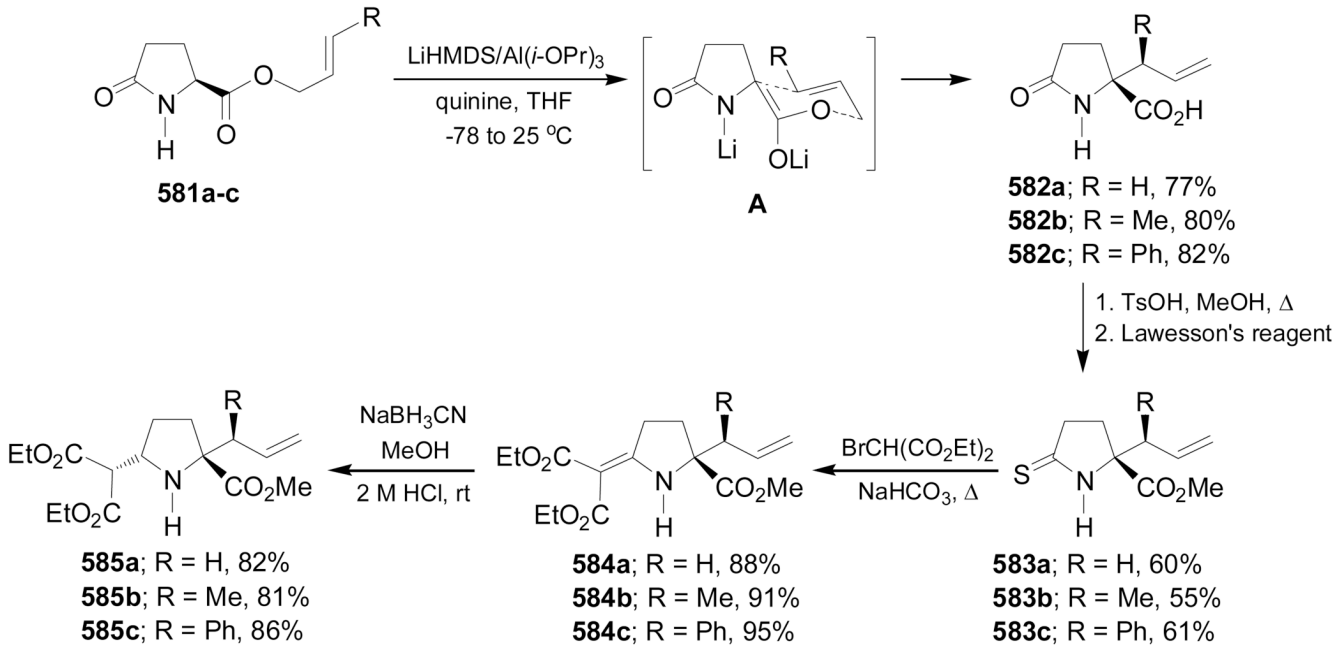
Scheme 122.



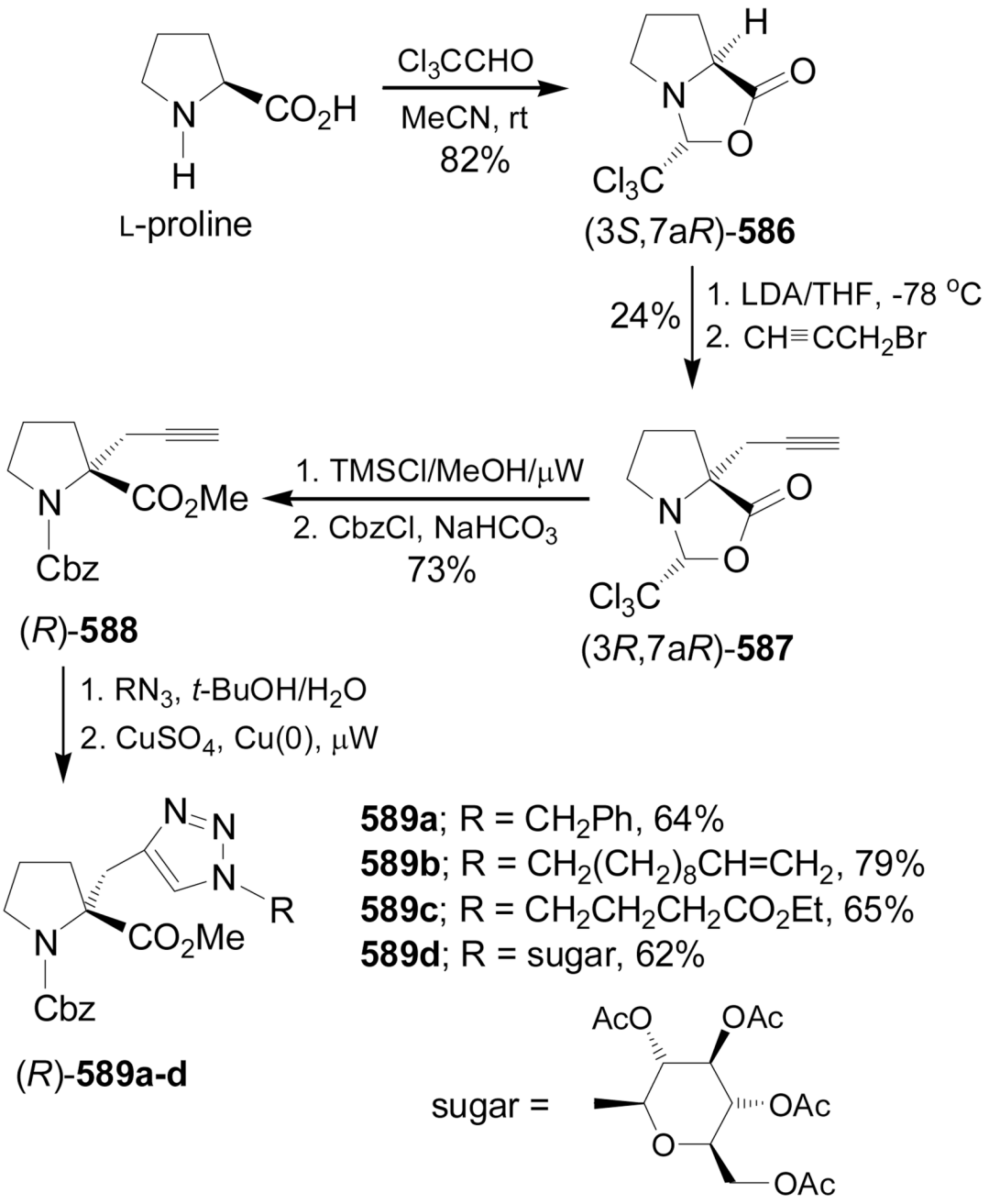
Scheme 123.



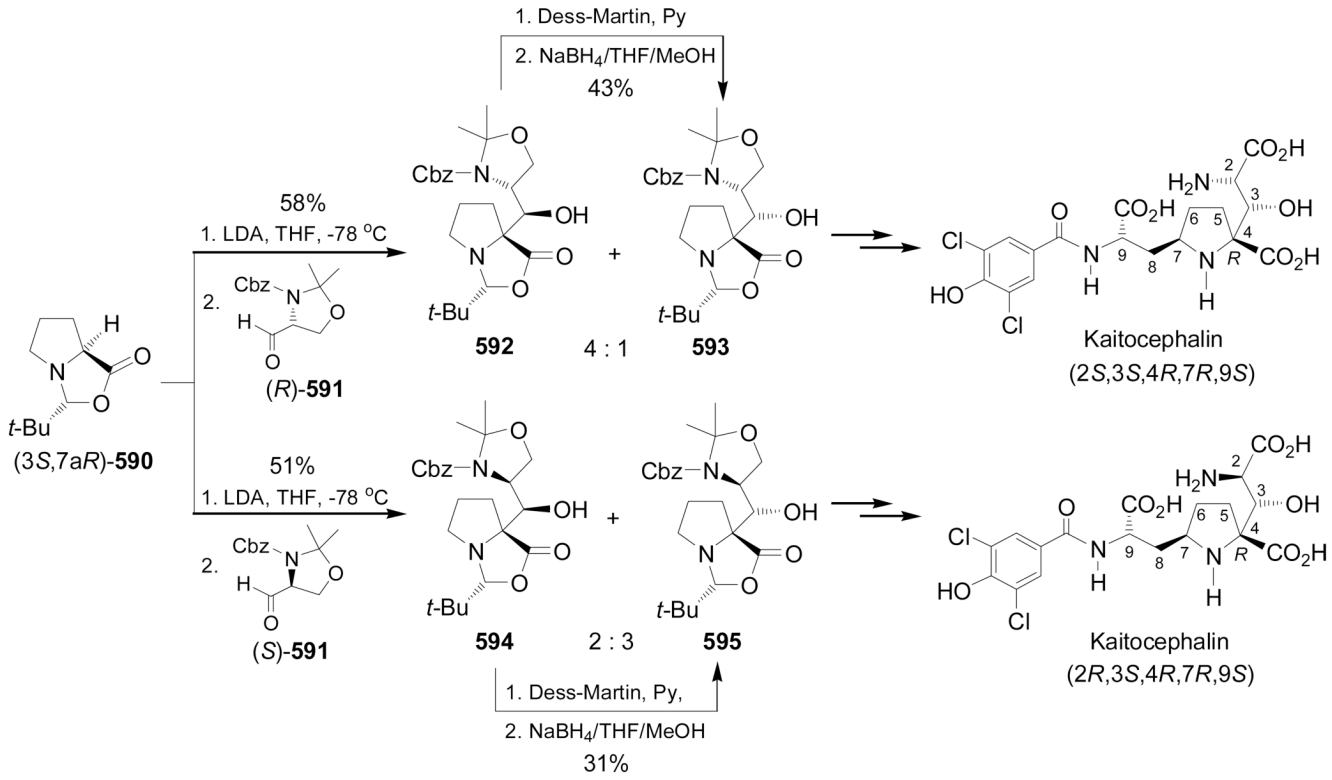
Scheme 124.



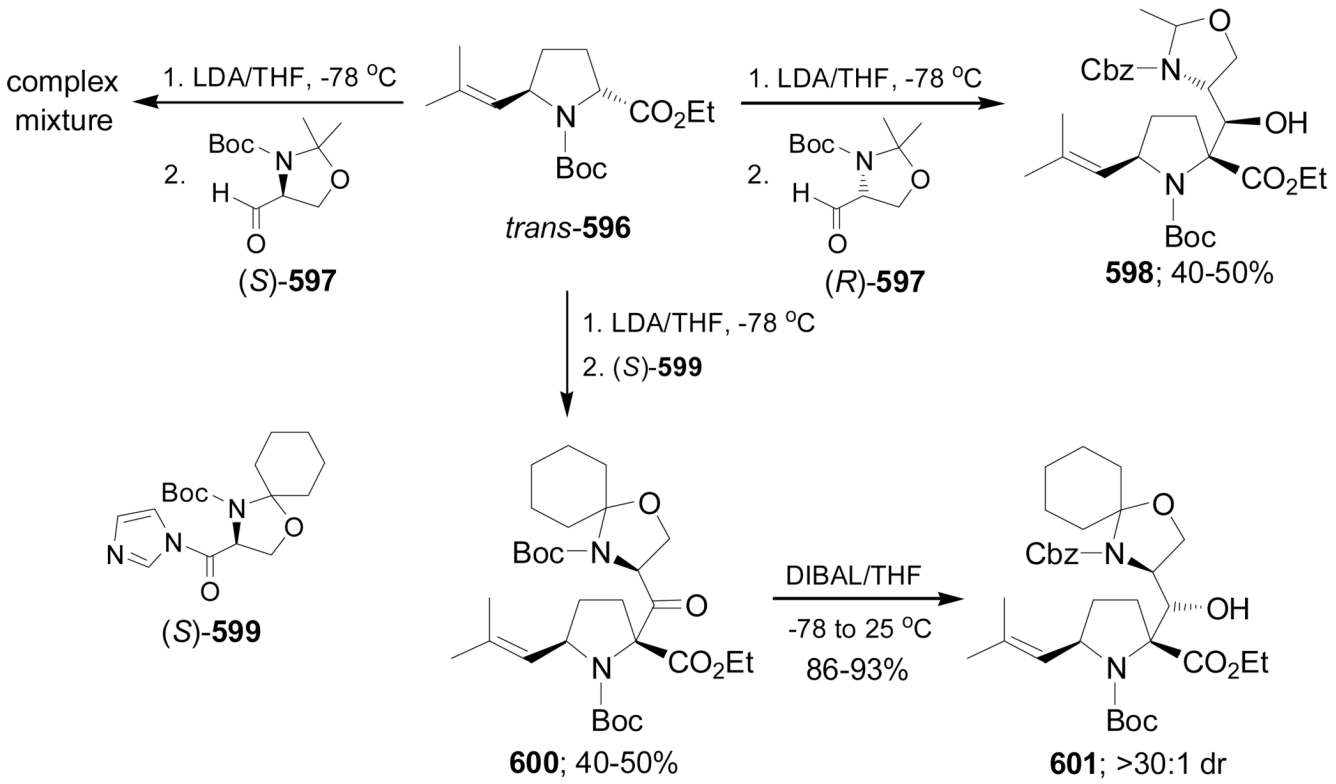
Scheme 125.



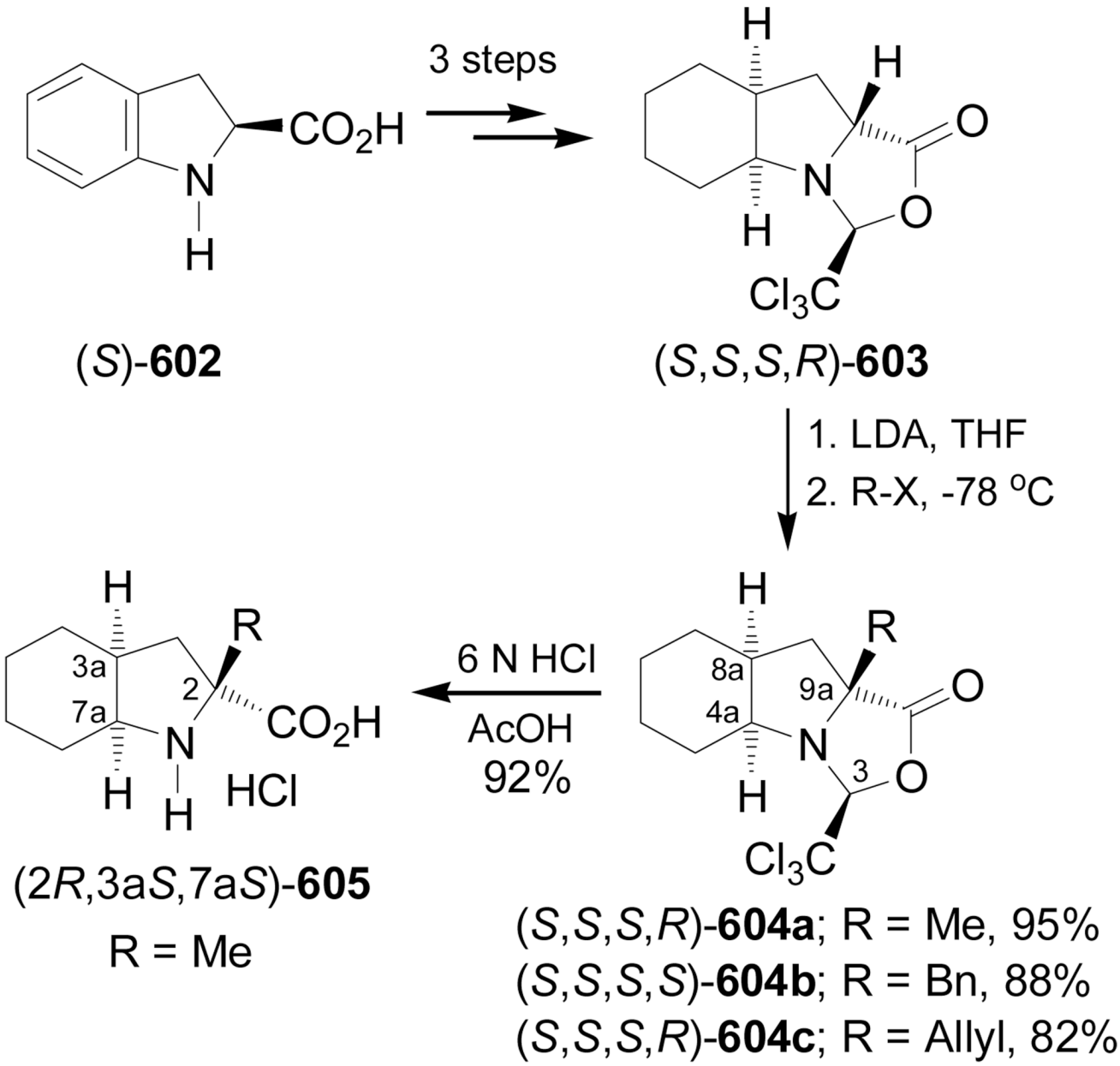
Scheme 126.



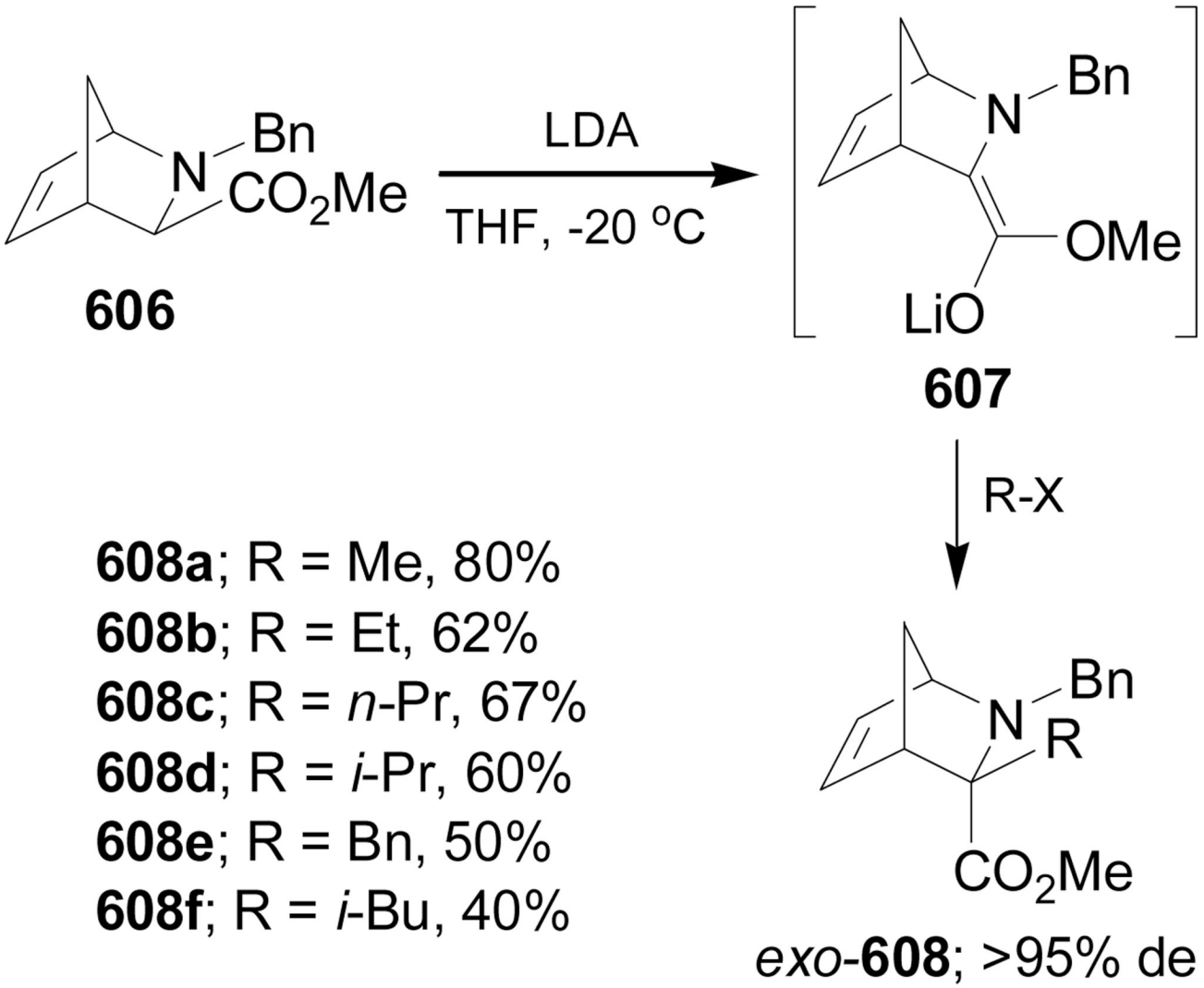
Scheme 127.



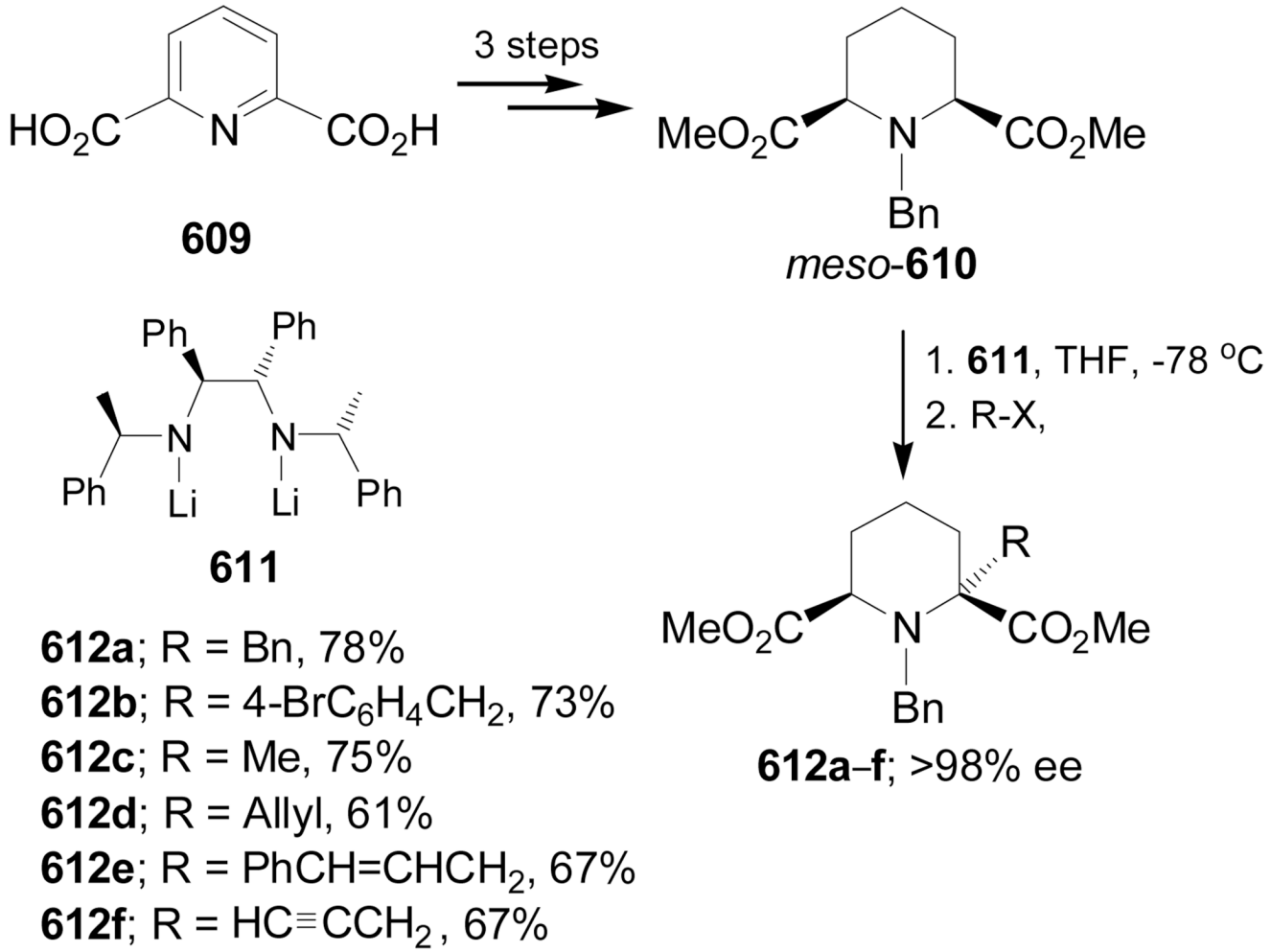
Scheme 128.



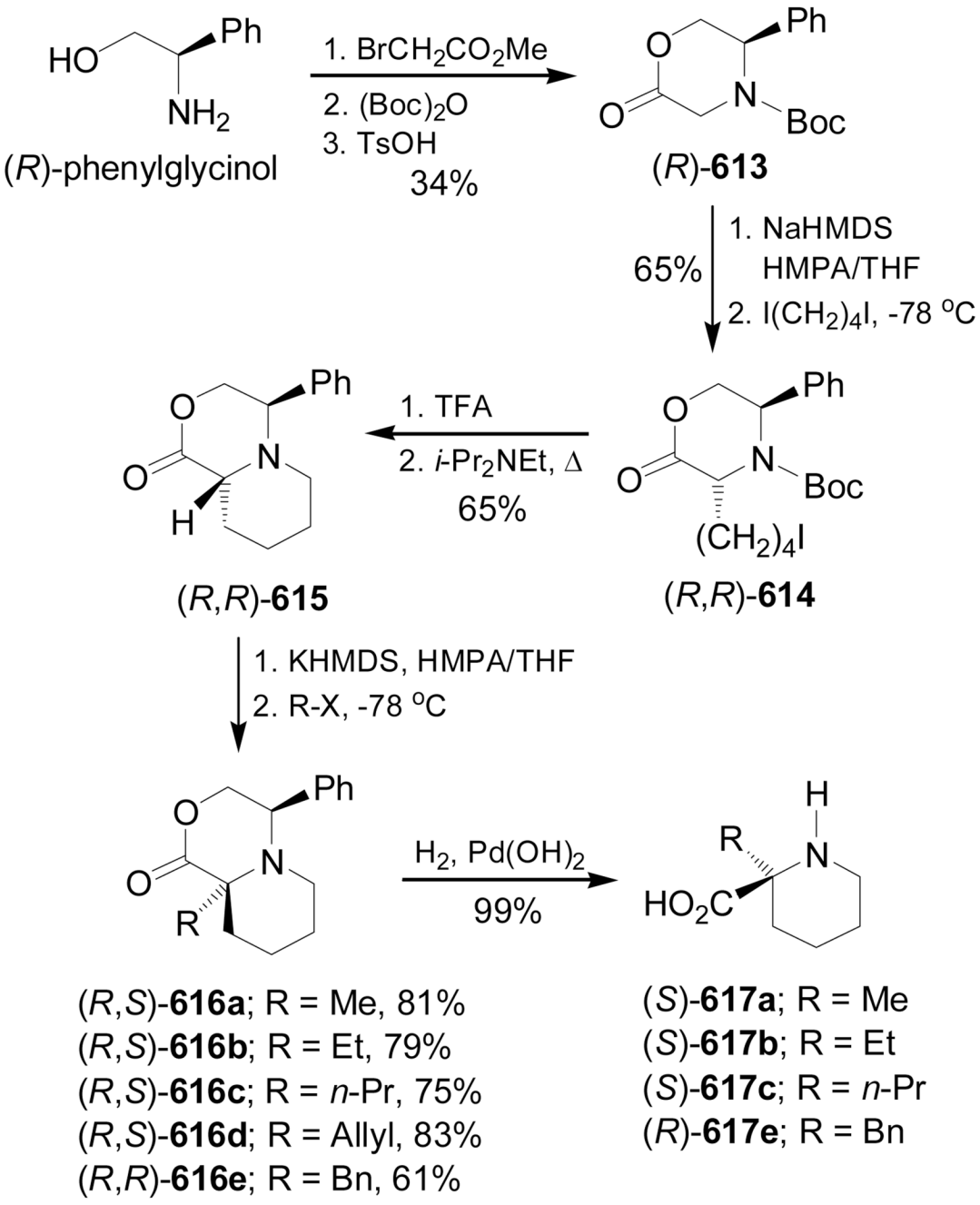
Scheme 129.



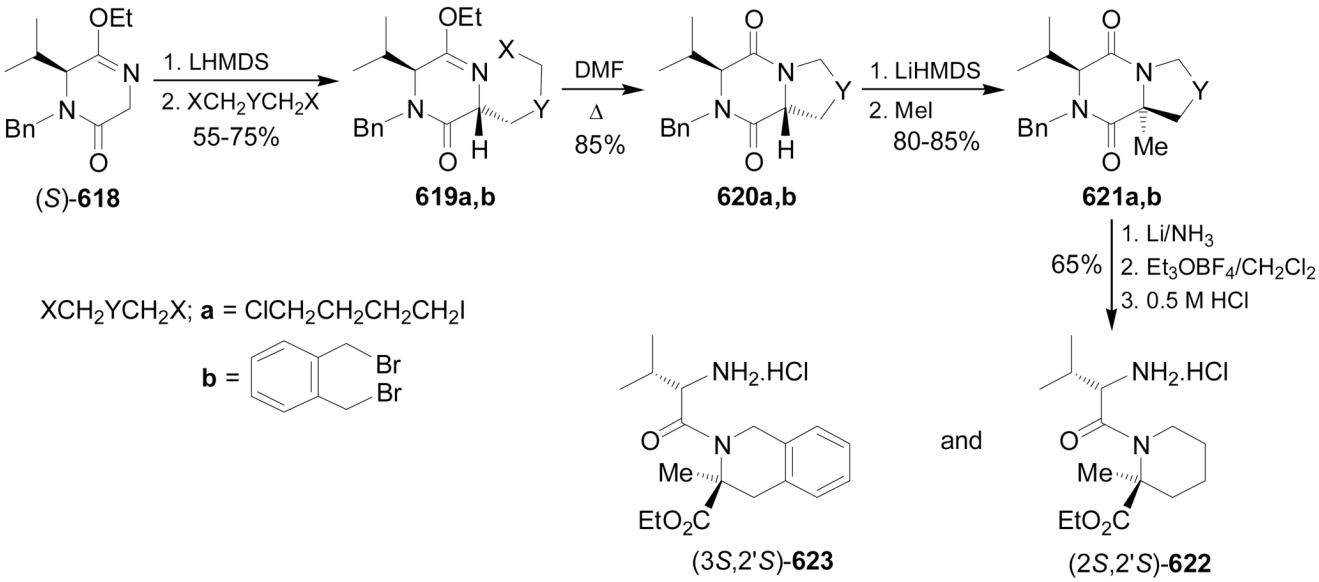
Scheme 130.



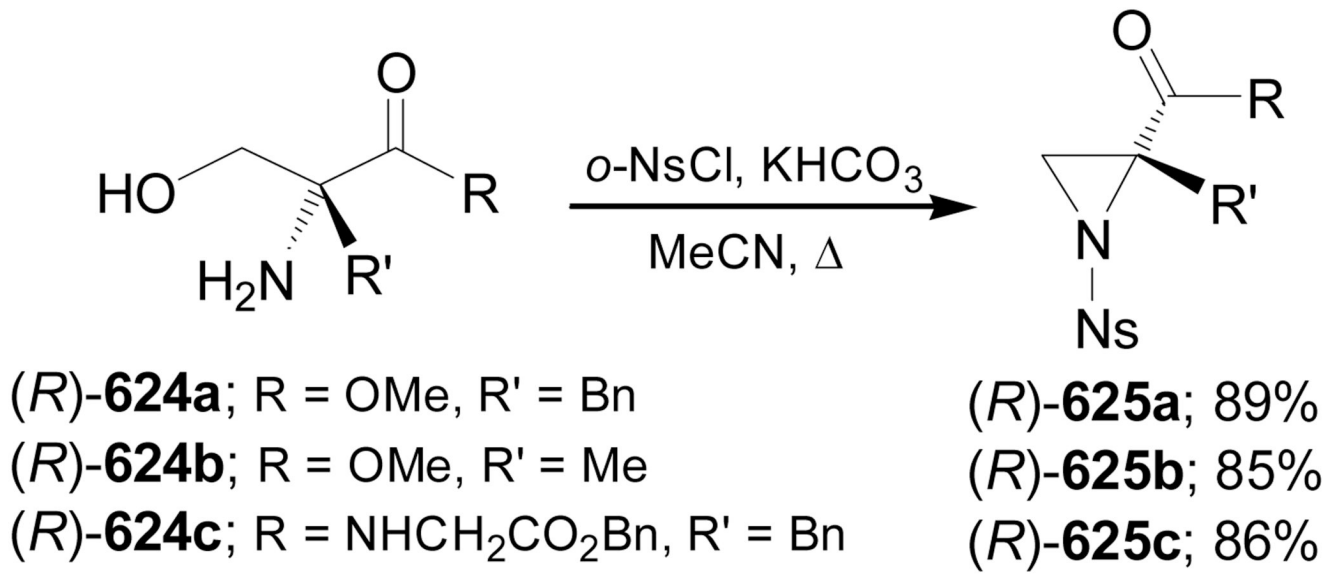
Scheme 131.



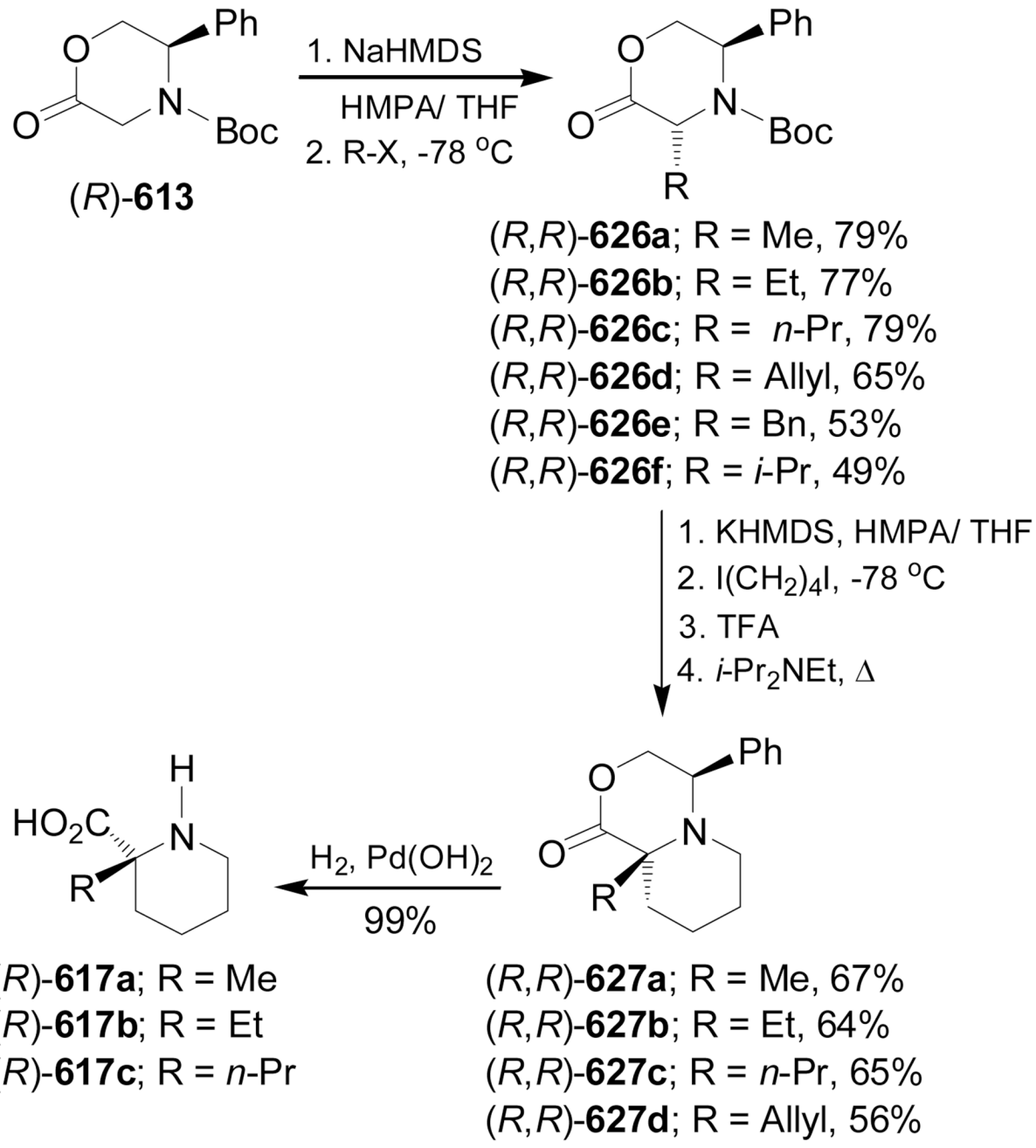
Scheme 132.



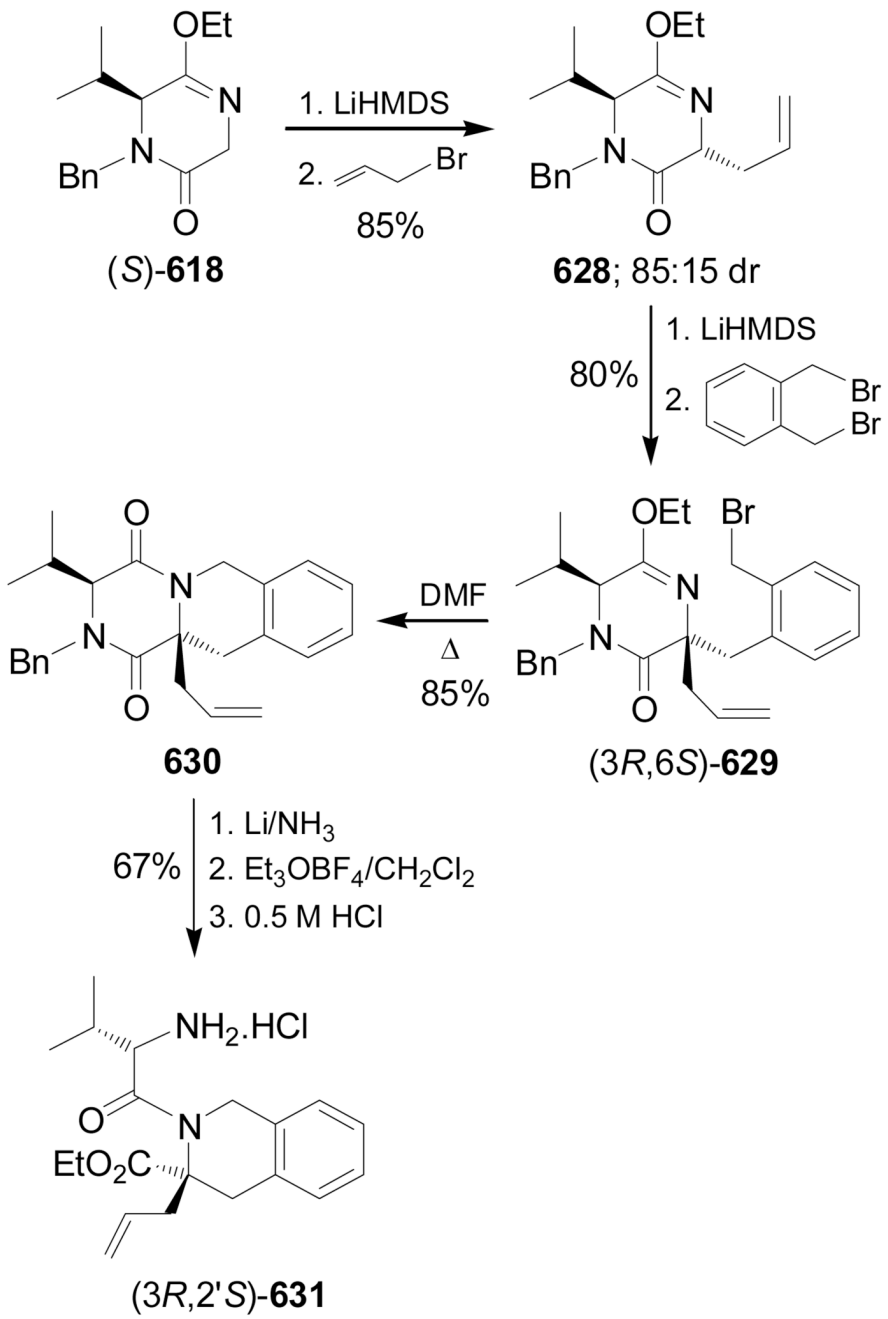
Scheme 133.



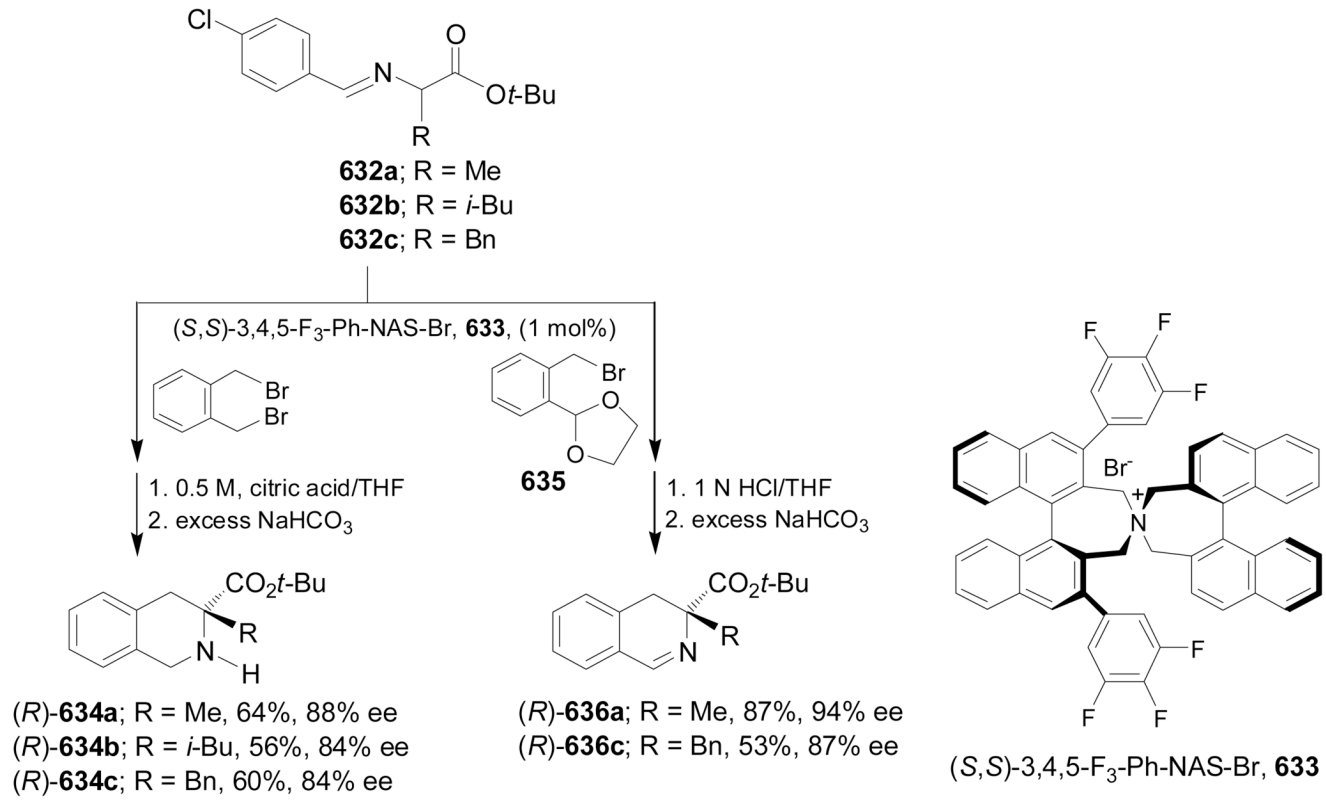
Scheme 134.



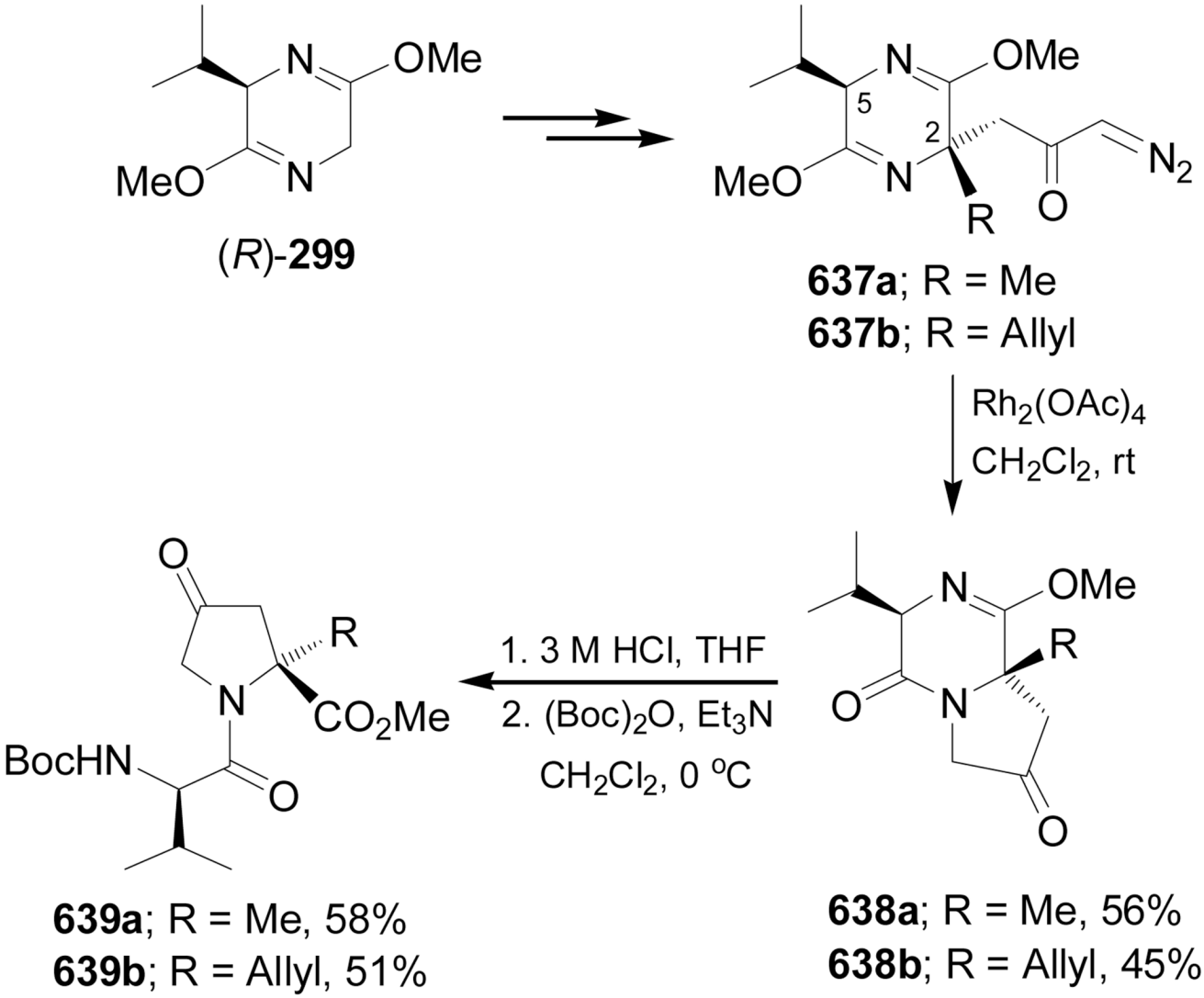
Scheme 135.



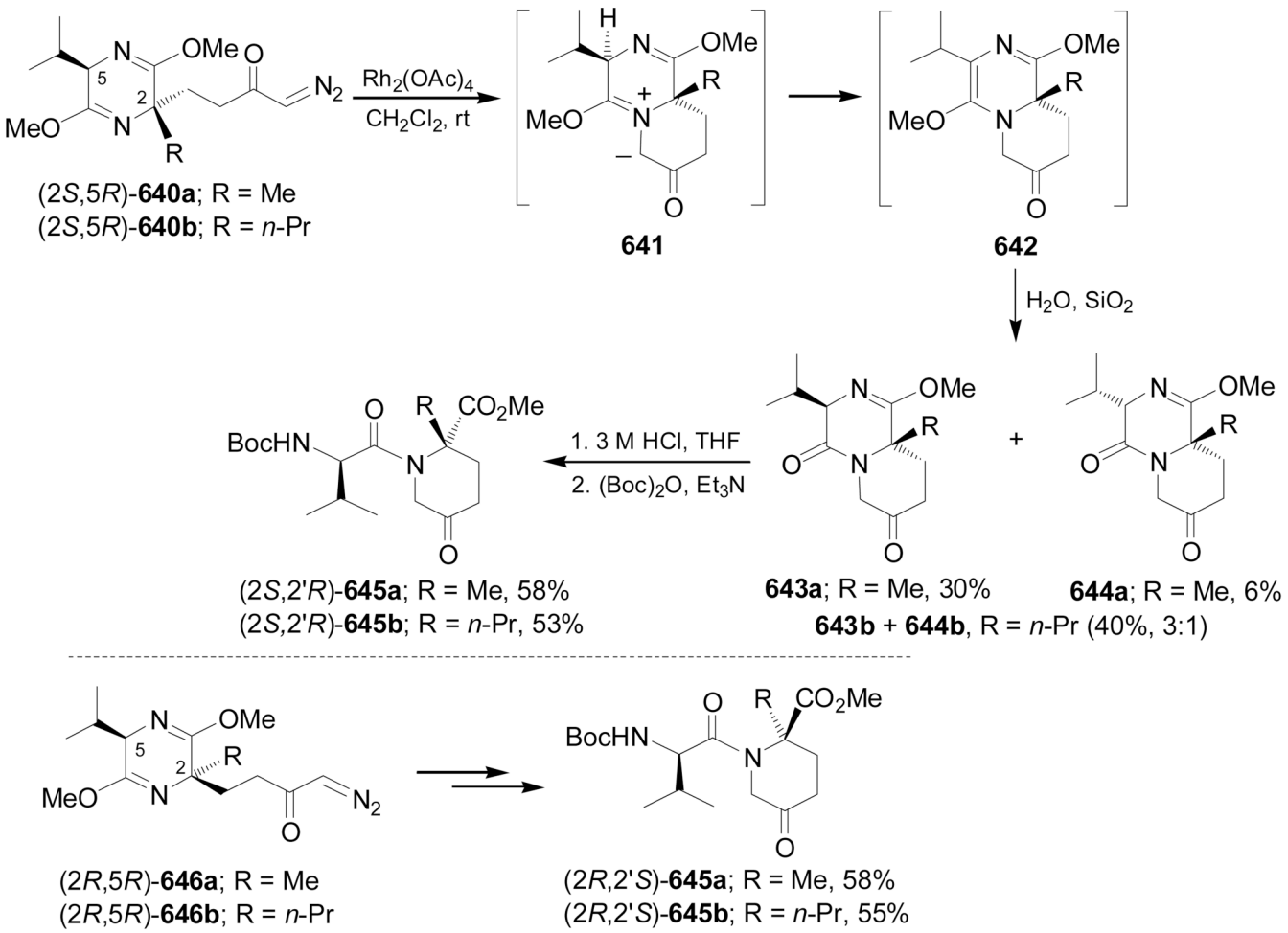
Scheme 136.



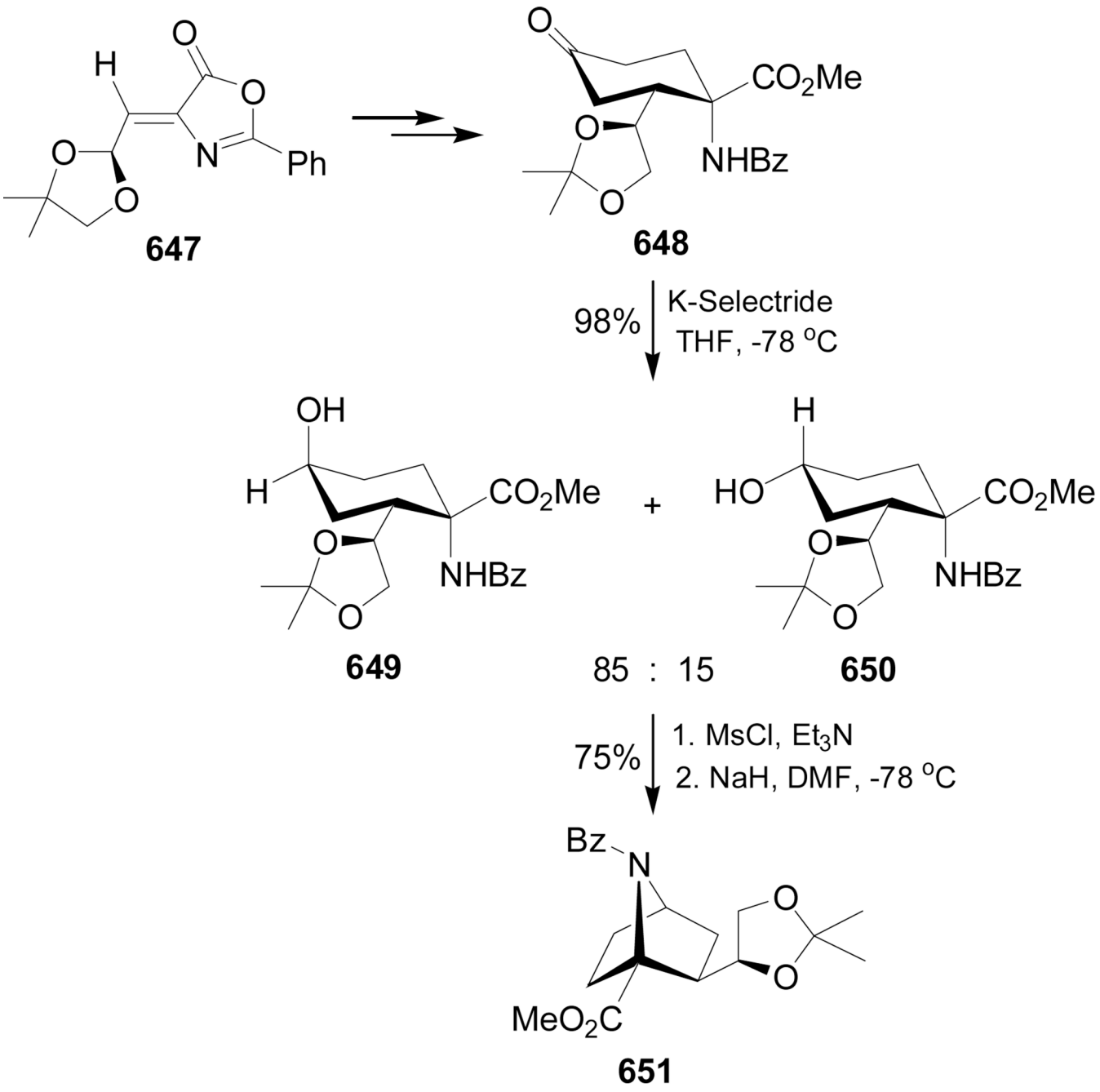
Scheme 137.



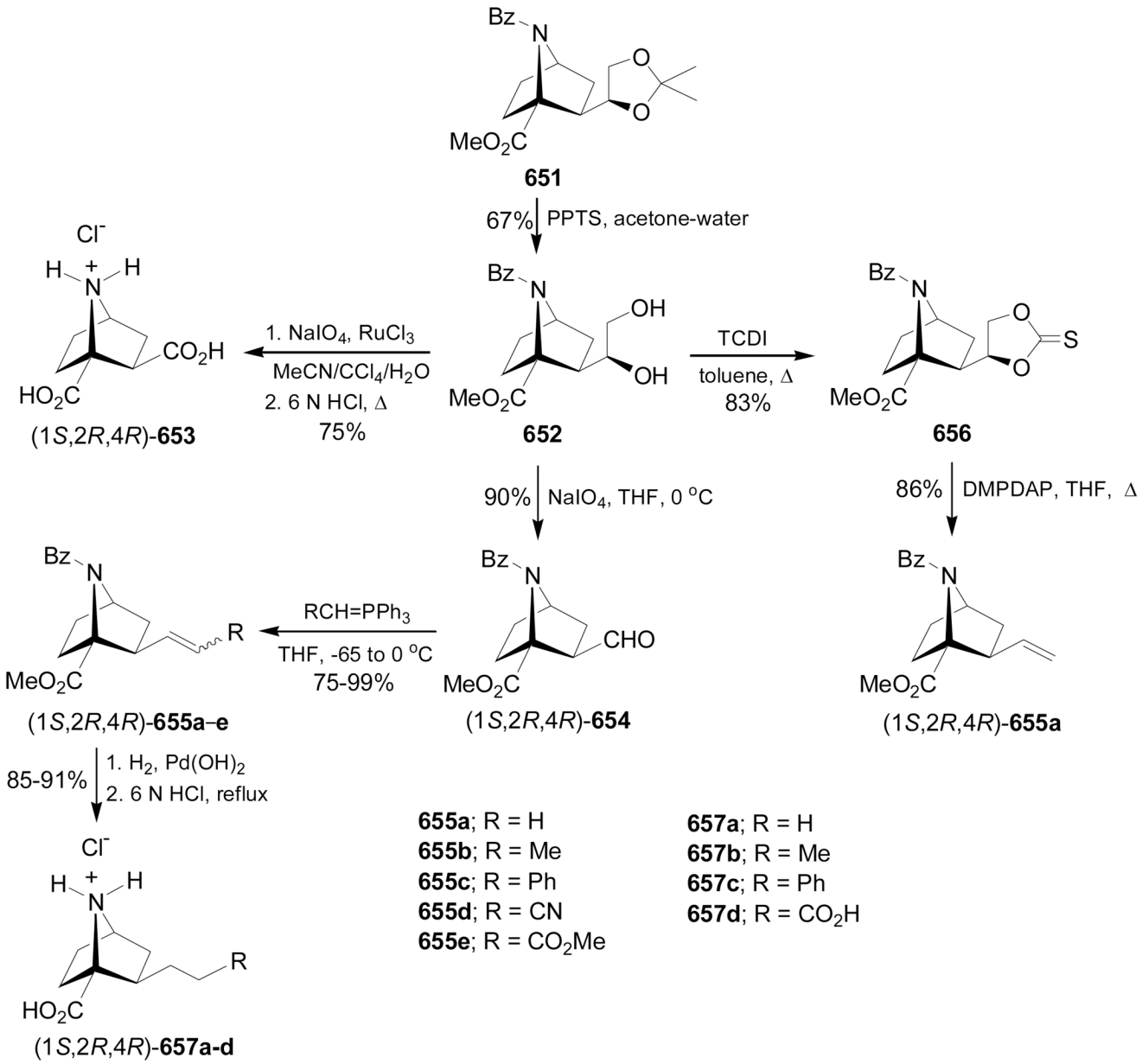
Scheme 138.



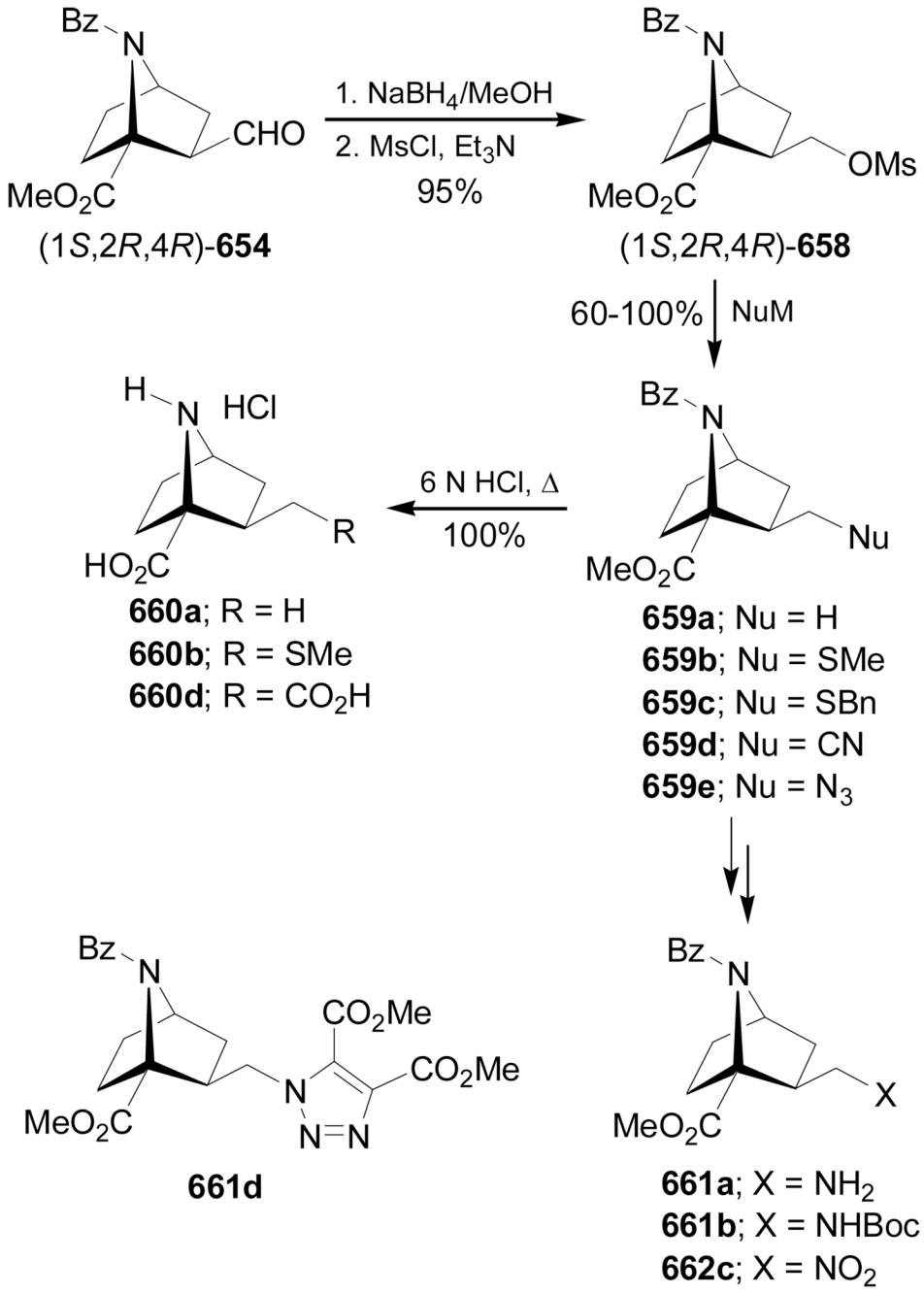
Scheme 139.



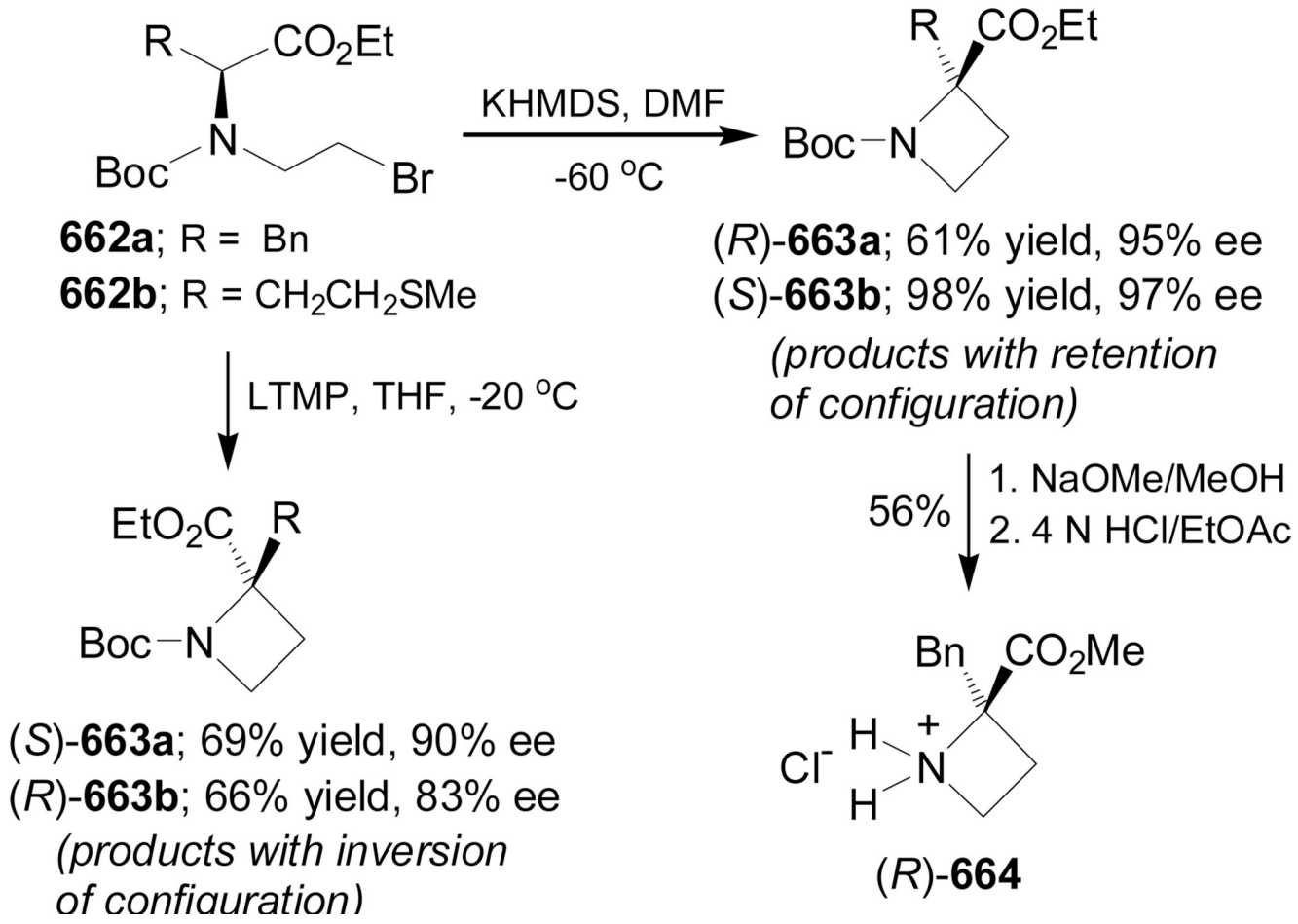
Scheme 140.



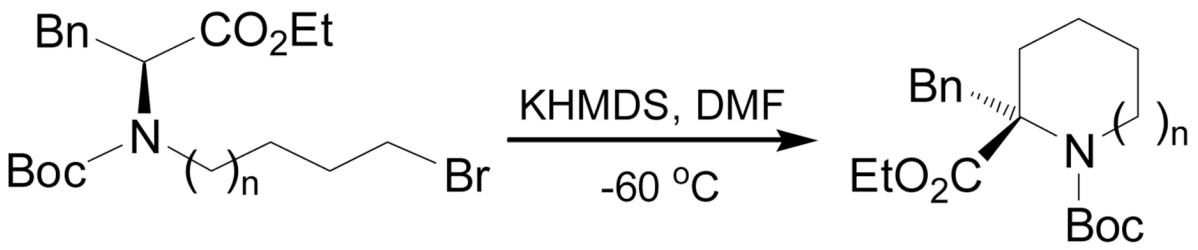
Scheme 141.



Scheme 142.



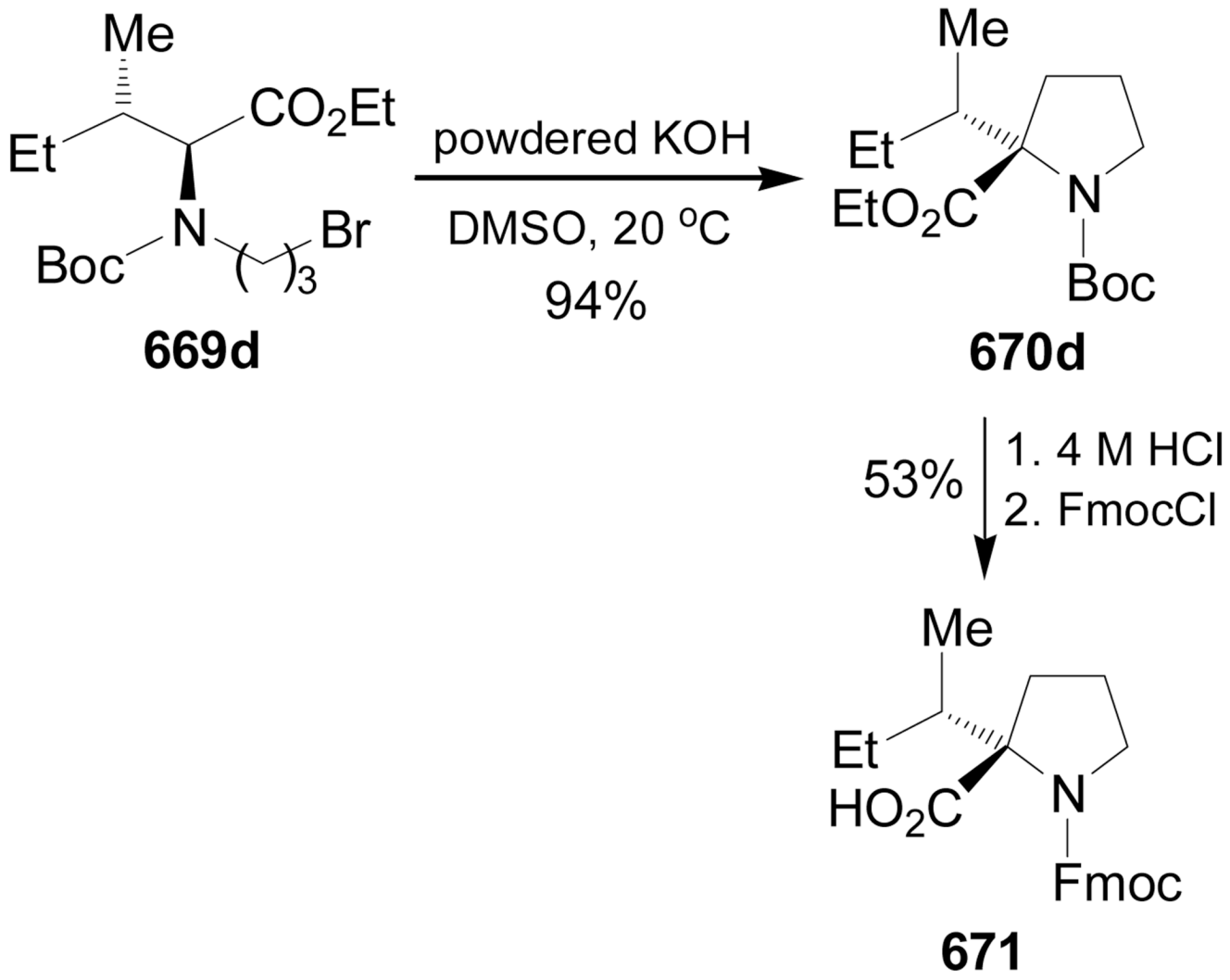
Scheme 143.



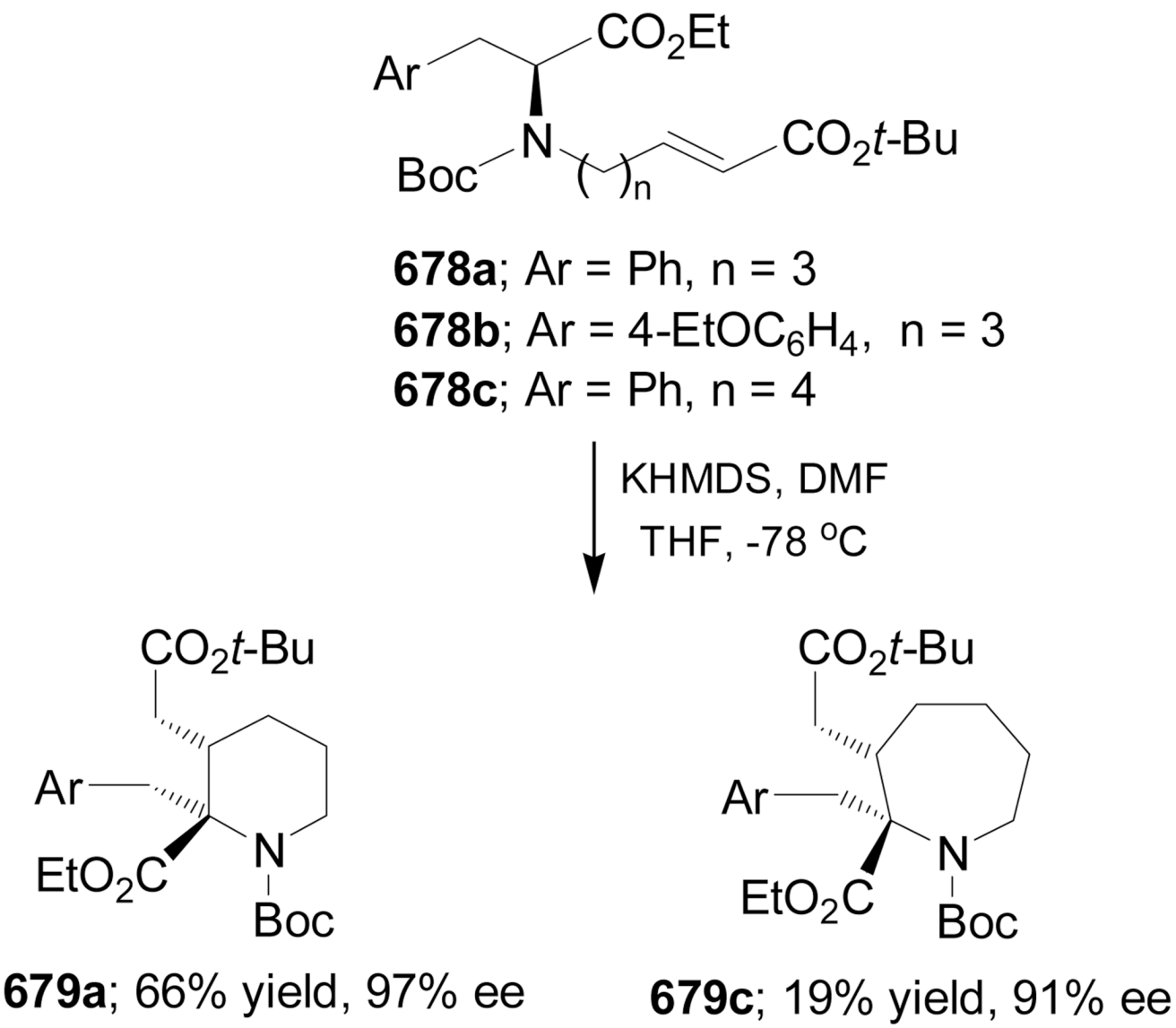
665; n = 1
666; n = 2

667; n = 1, 84% yield, 97% ee
668; n = 2, 31% yield, 83% ee

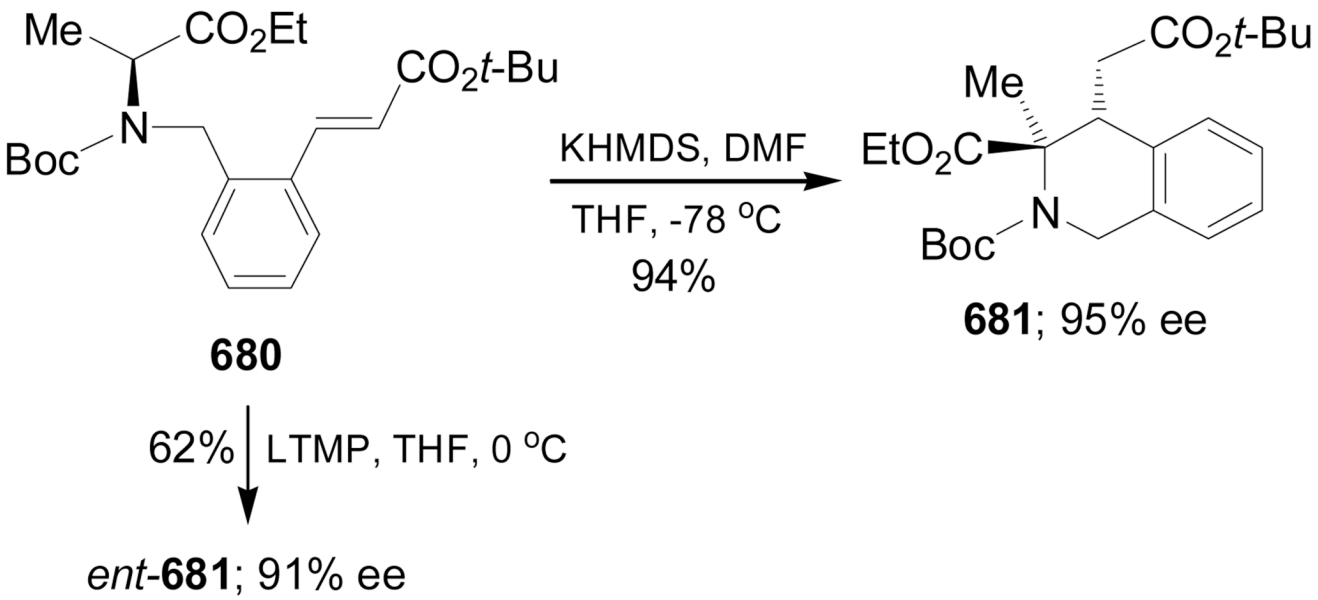
Scheme 144.



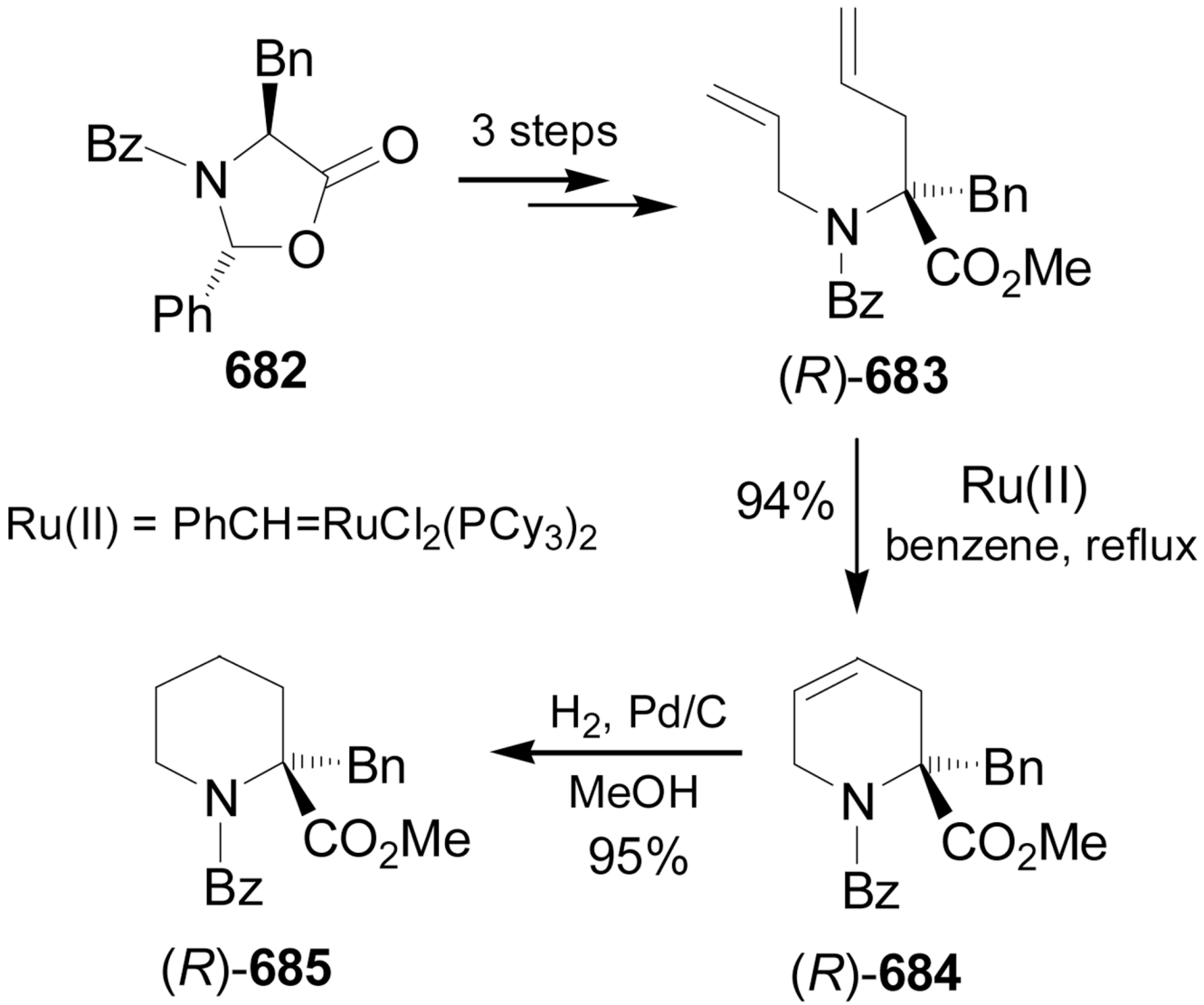
Scheme 145.



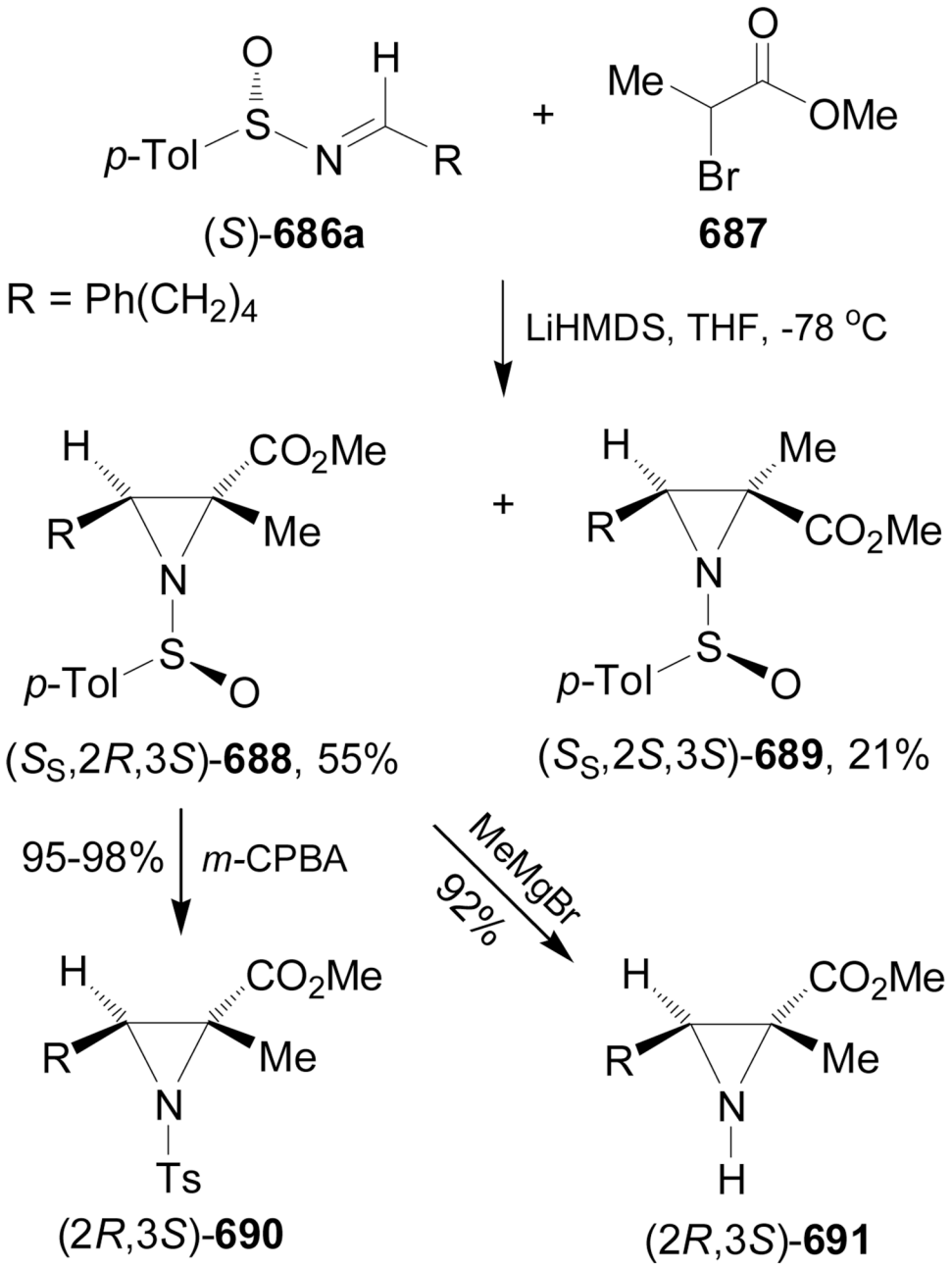
Scheme 146.



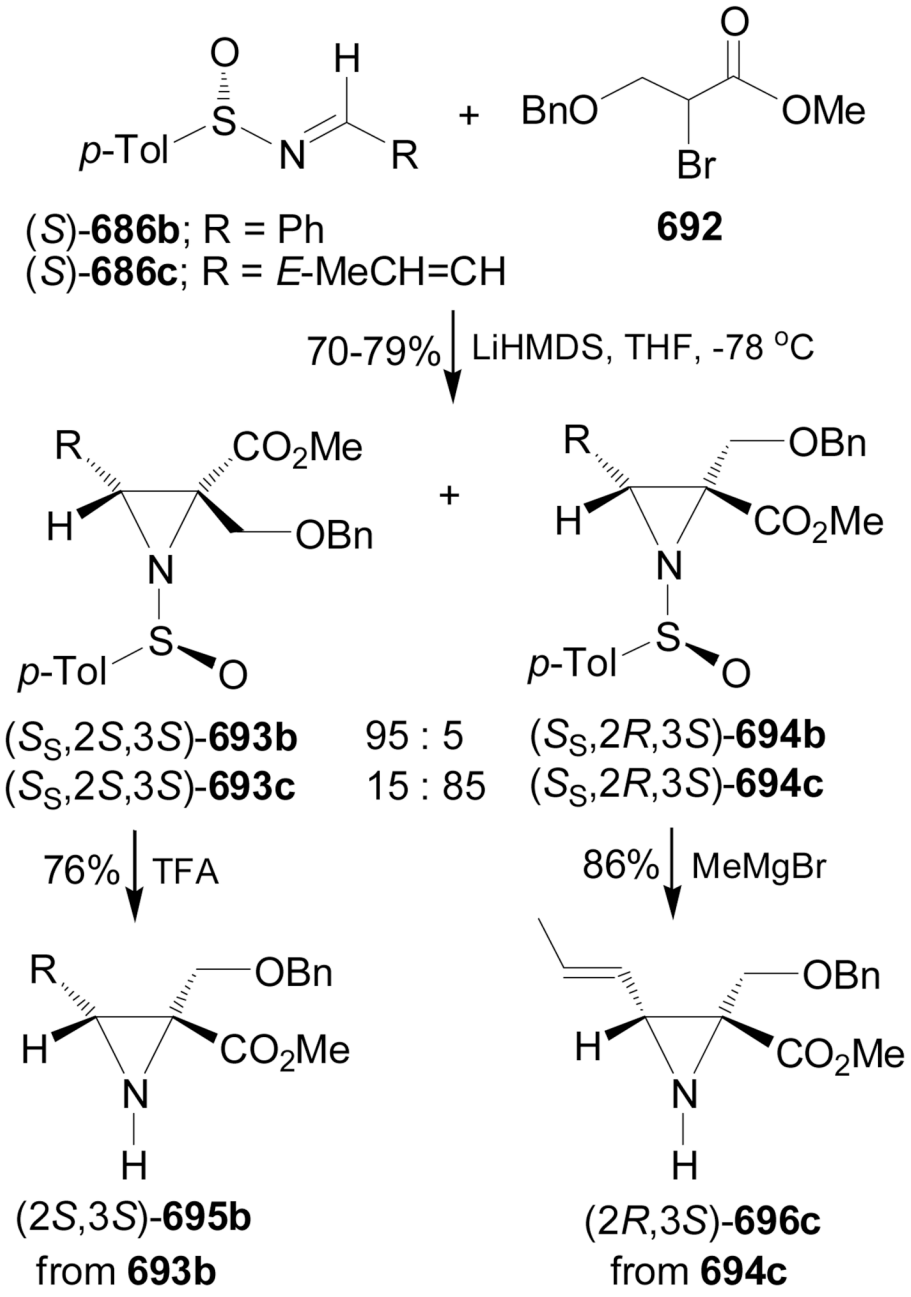
Scheme 147.



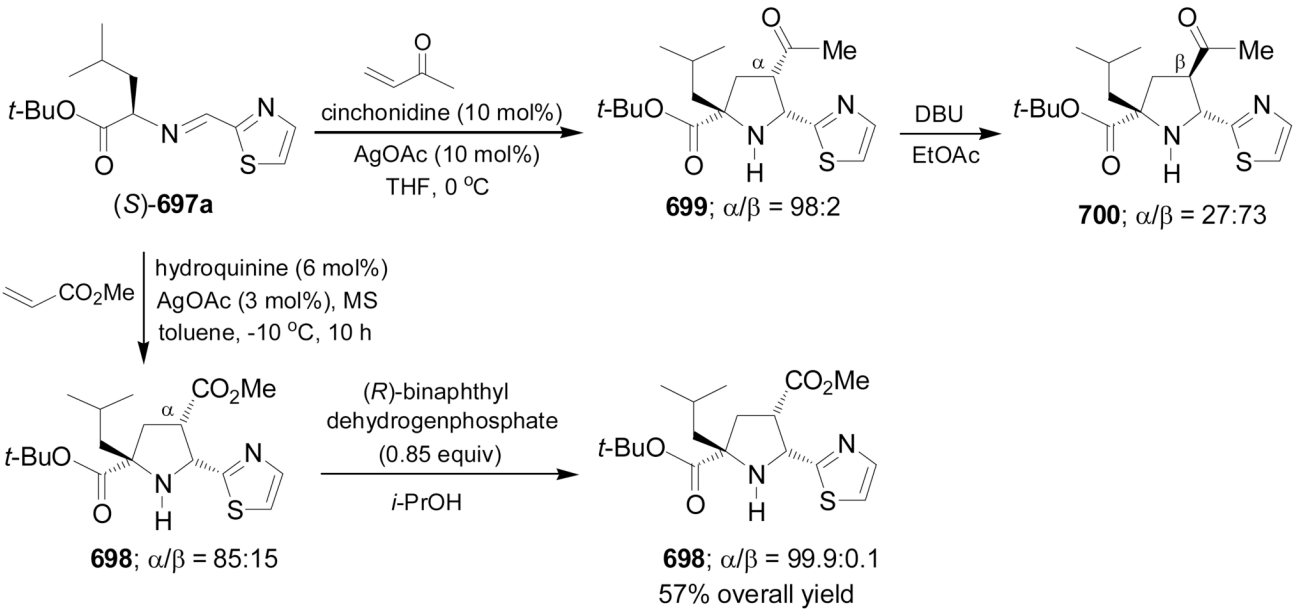
Scheme 148.



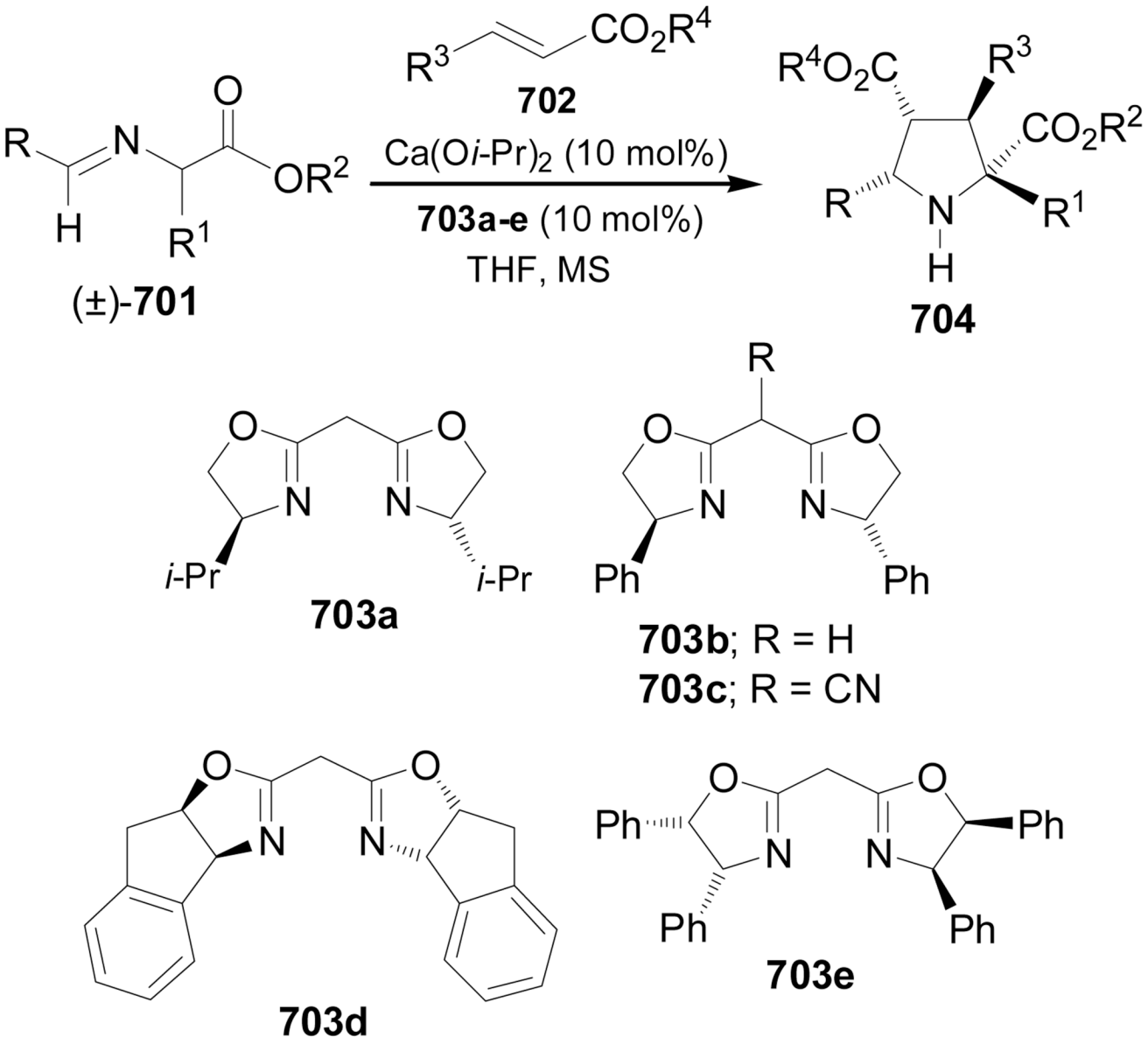
Scheme 149.



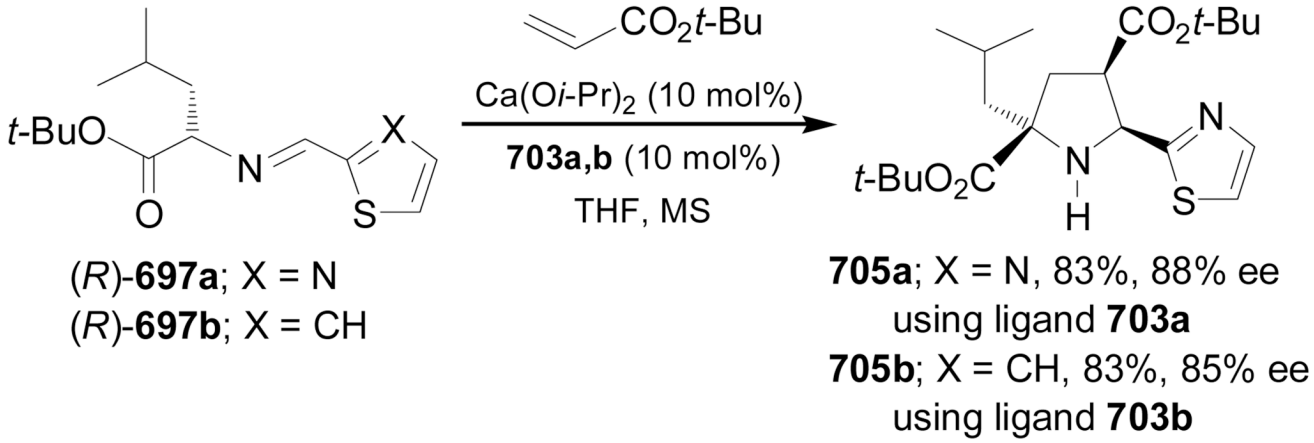
Scheme 150.



Scheme 151.



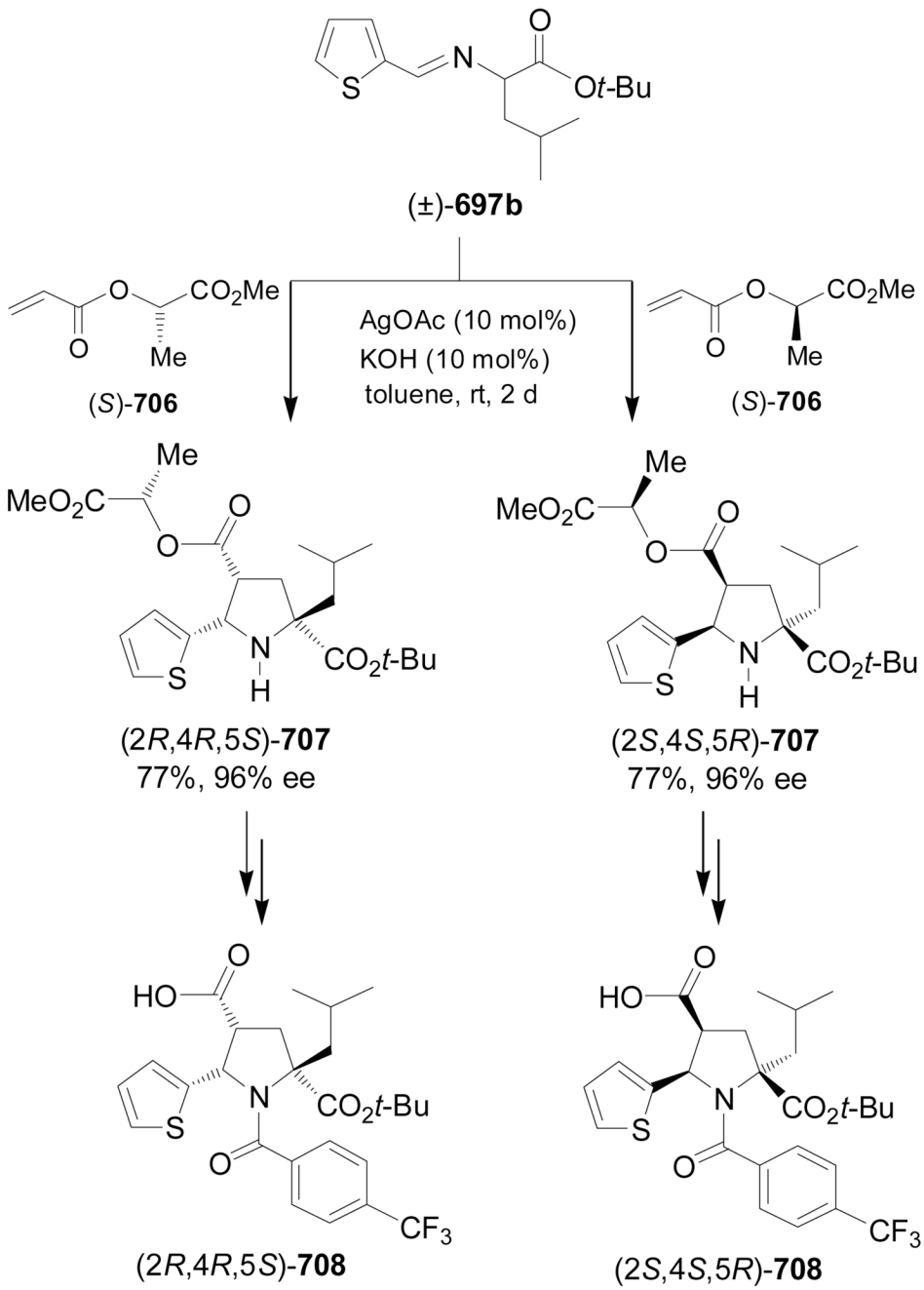
Scheme 152.



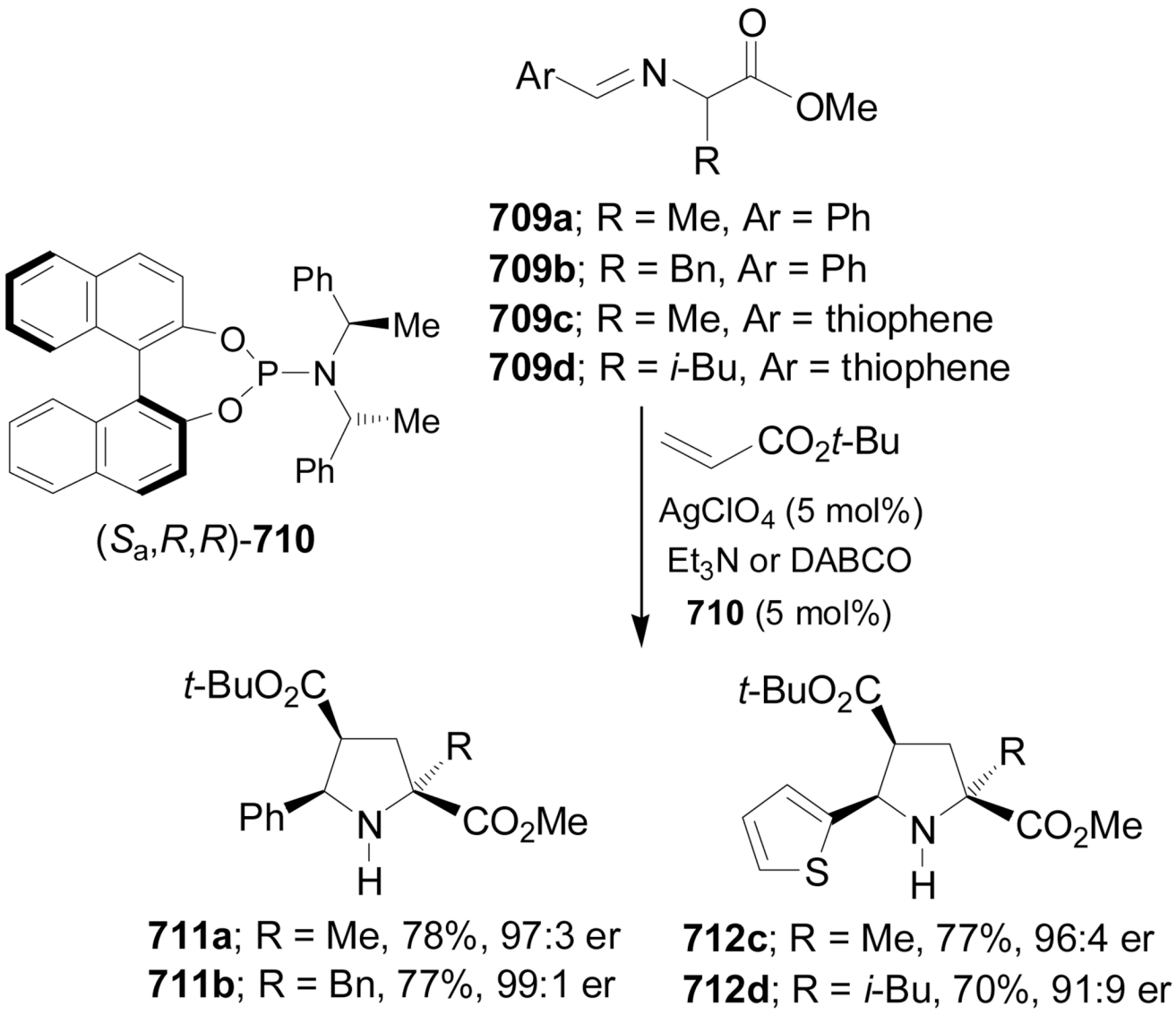
(*R*)-**697a**; X = N
(*R*)-**697b**; X = CH

705a; X = N, 83%, 88% ee using ligand **703a**
705b; X = CH, 83%, 85% ee using ligand **703b**

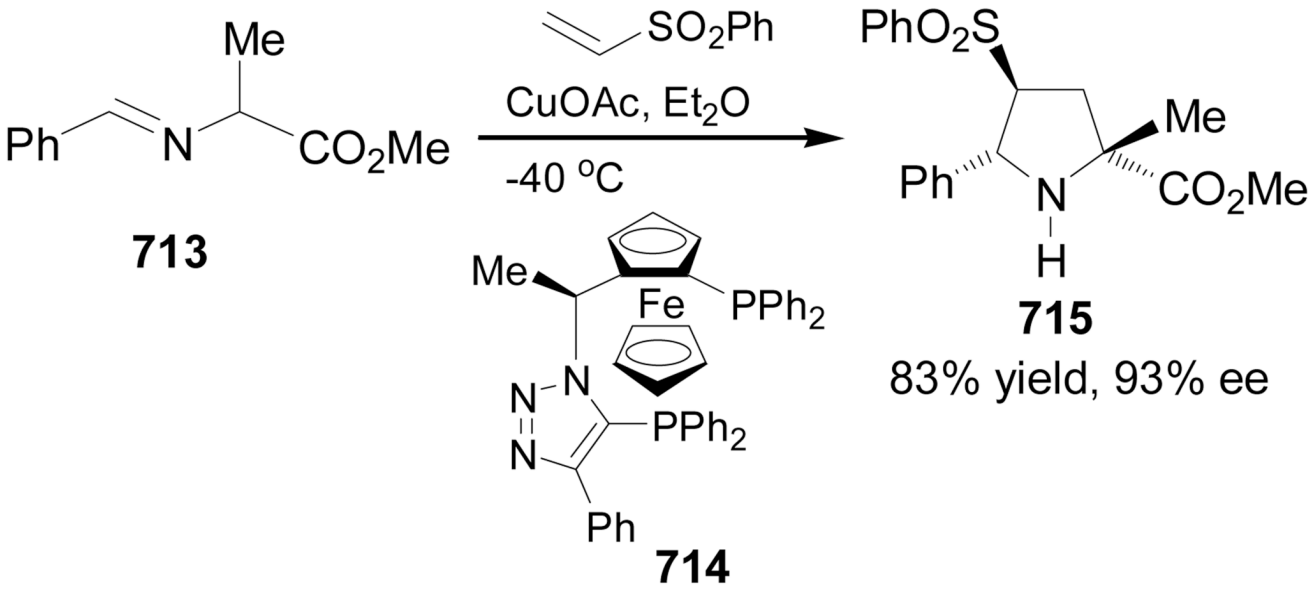
Scheme 153.



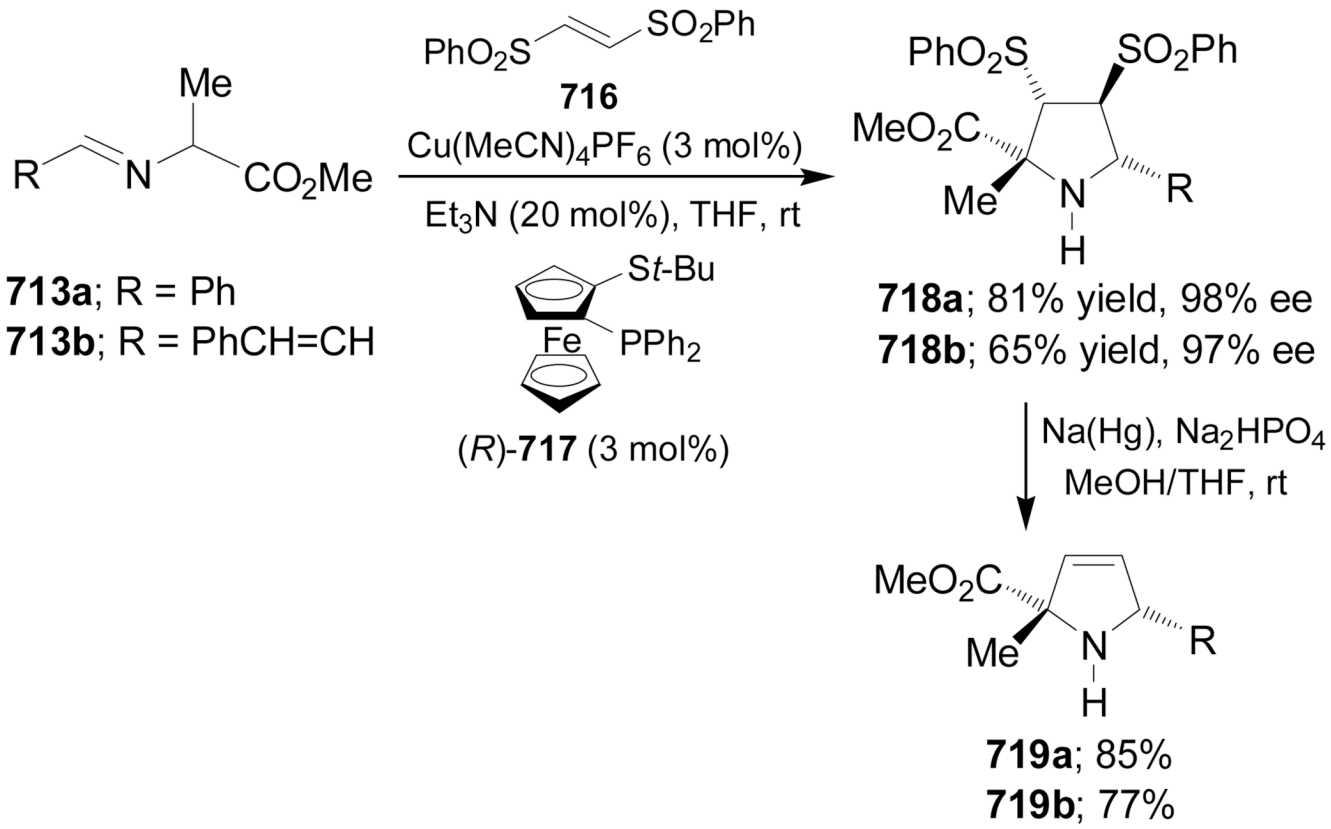
Scheme 154.



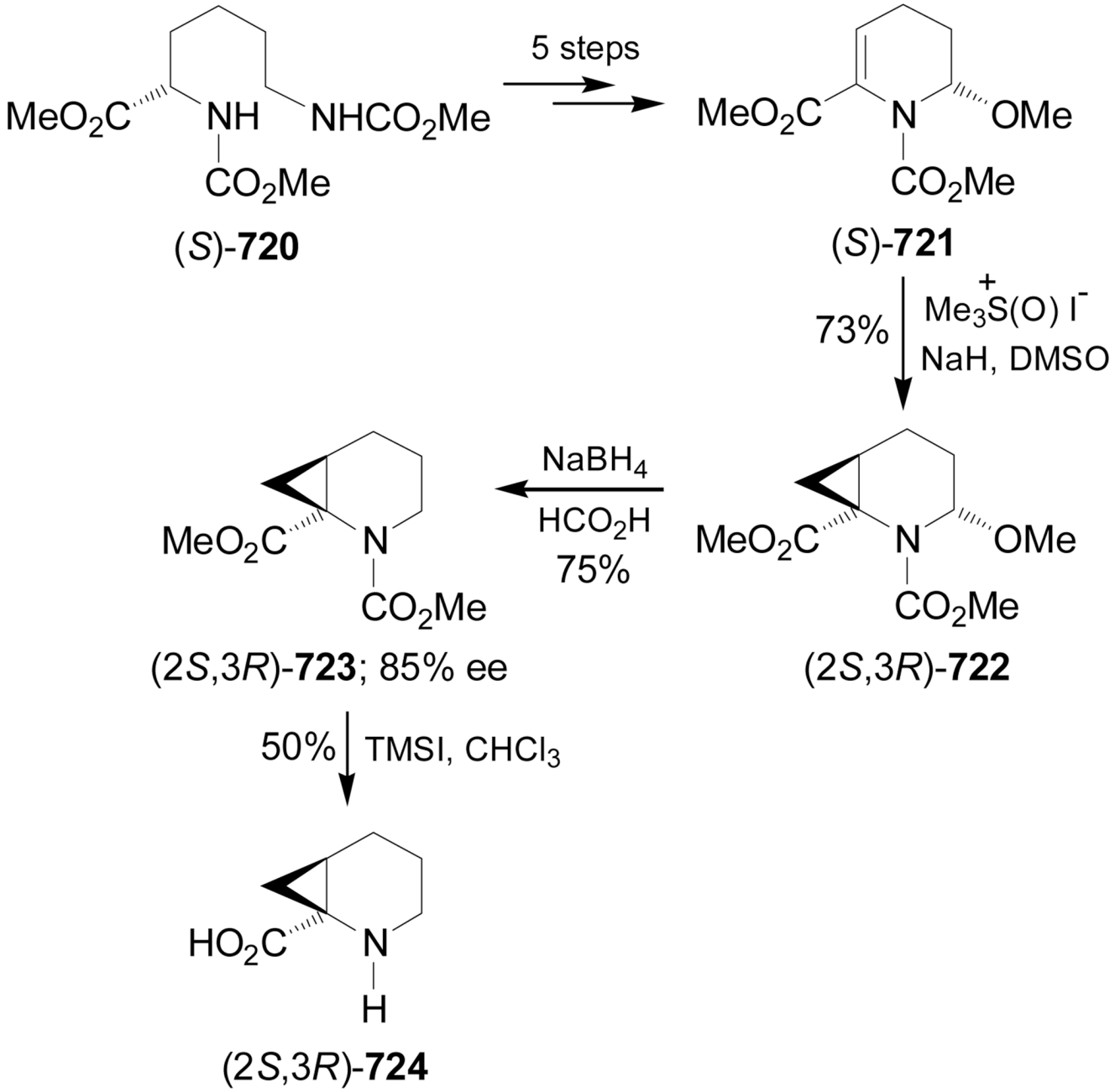
Scheme 155.



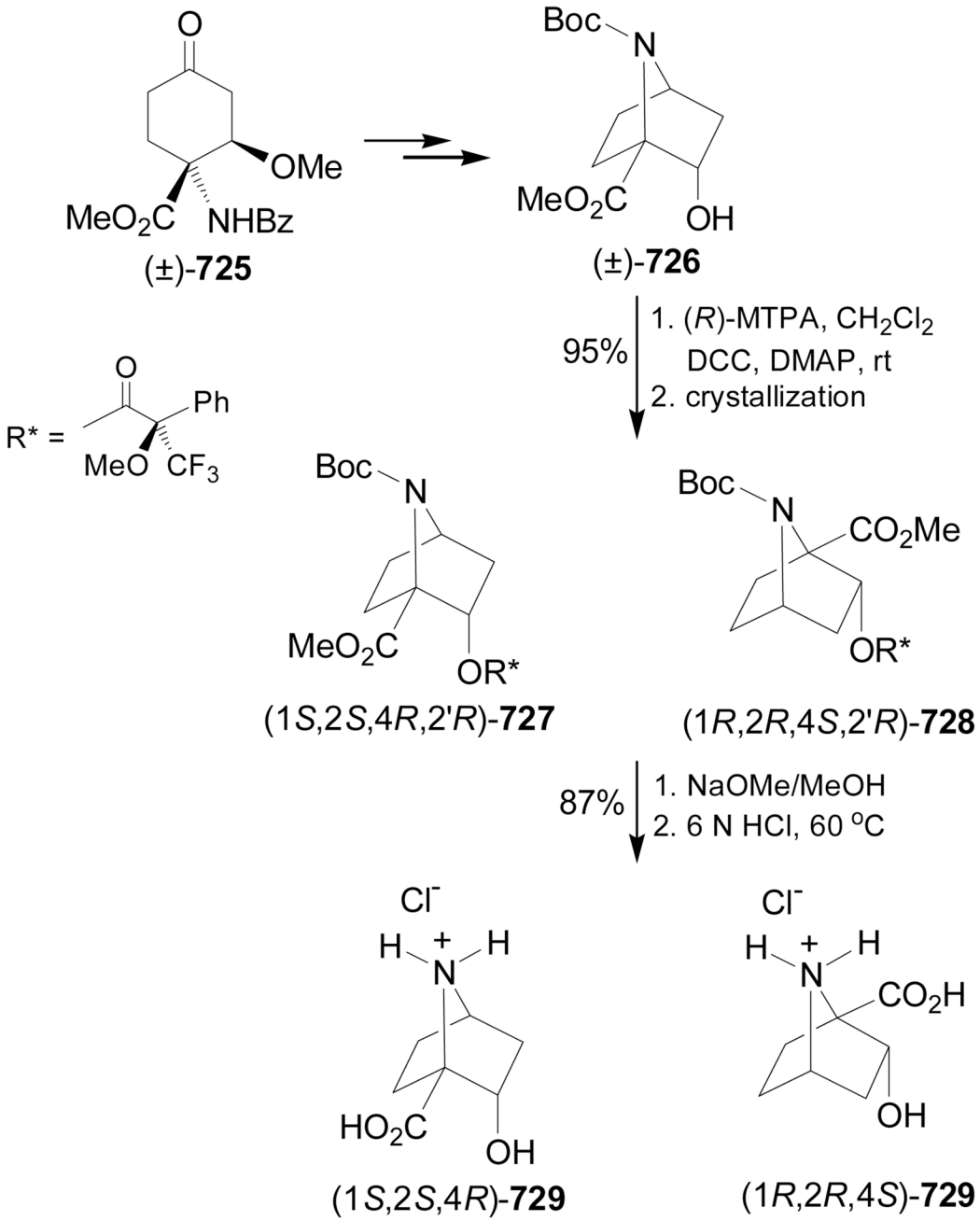
Scheme 156.



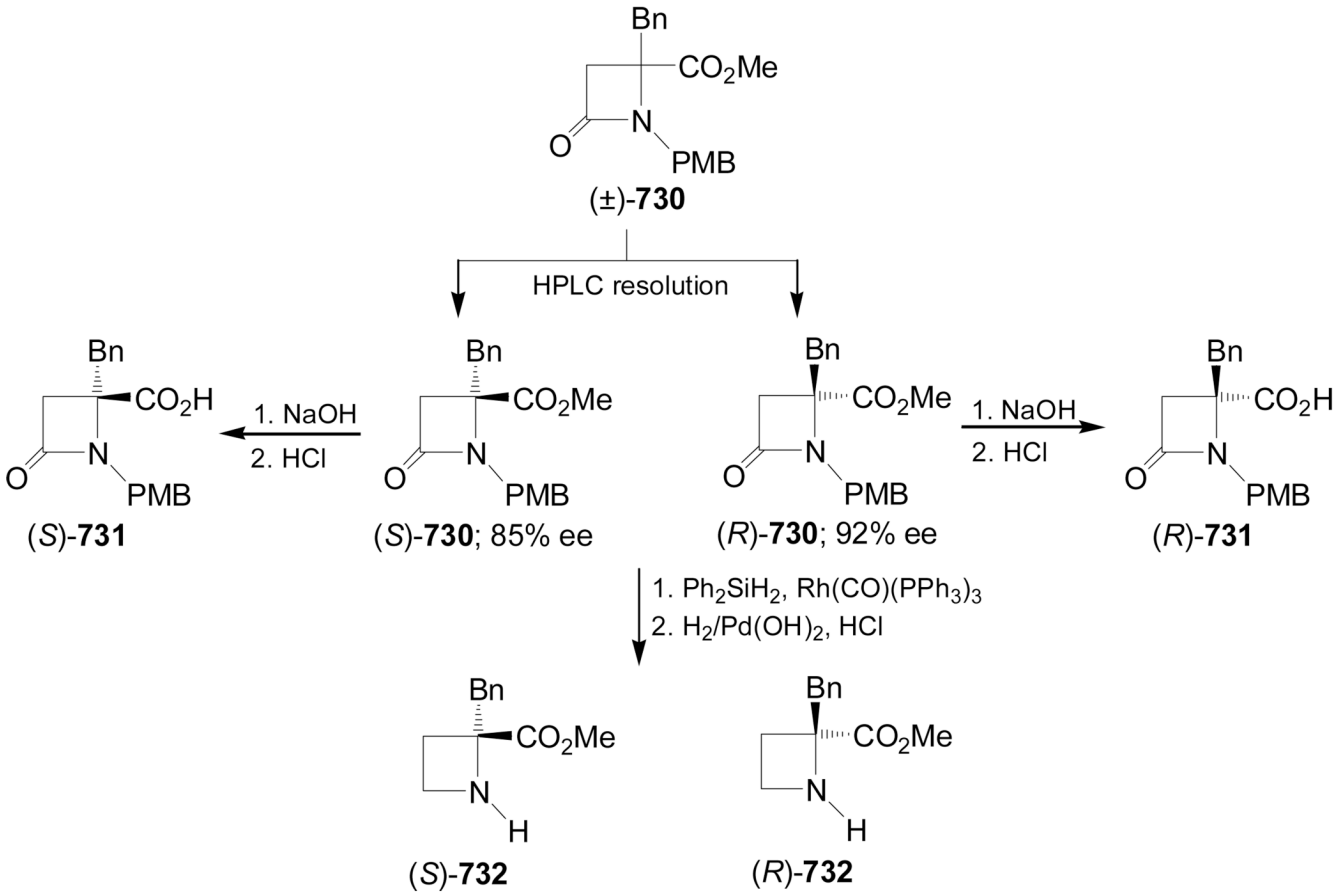
Scheme 157.



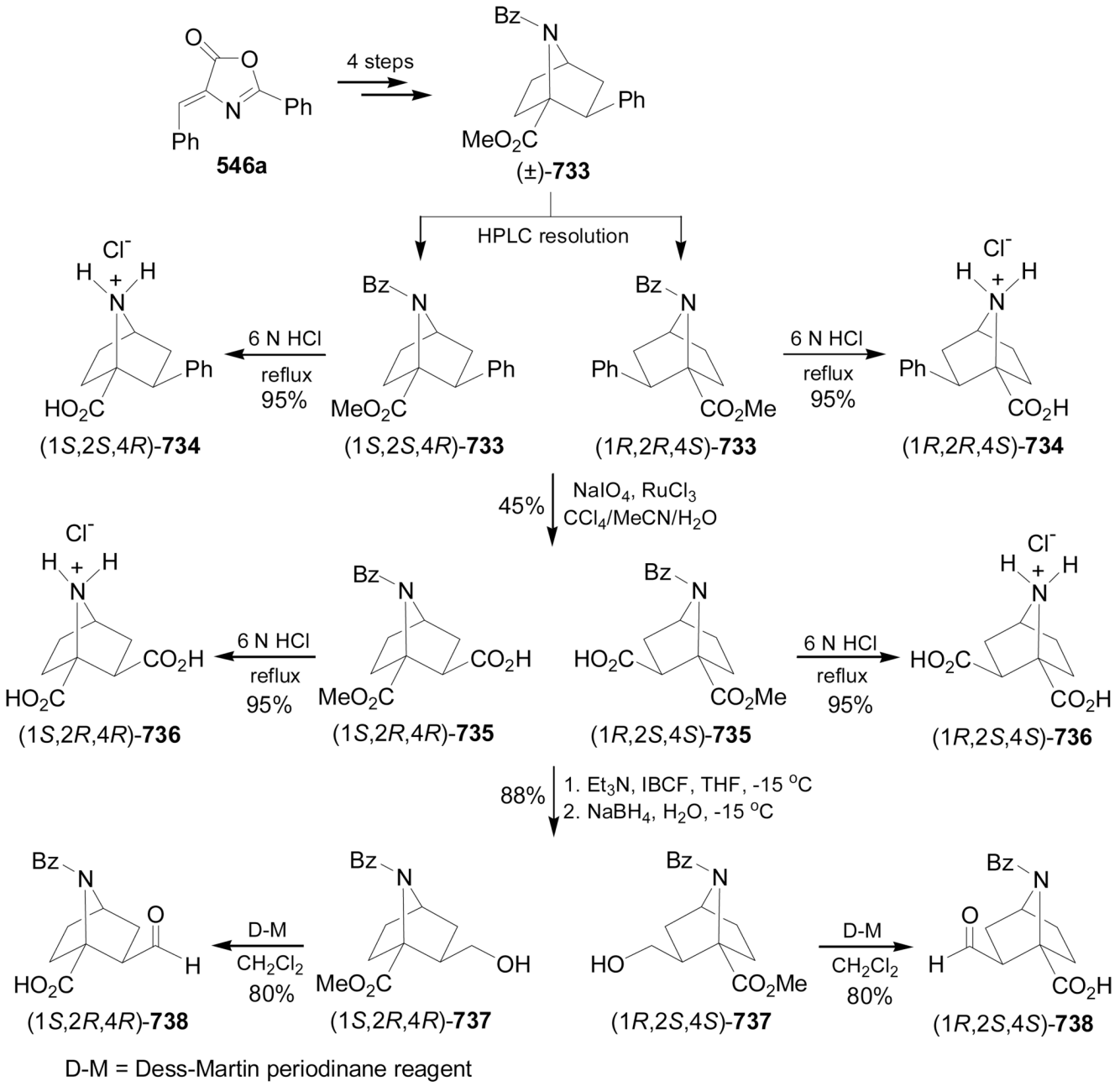
Scheme 158.



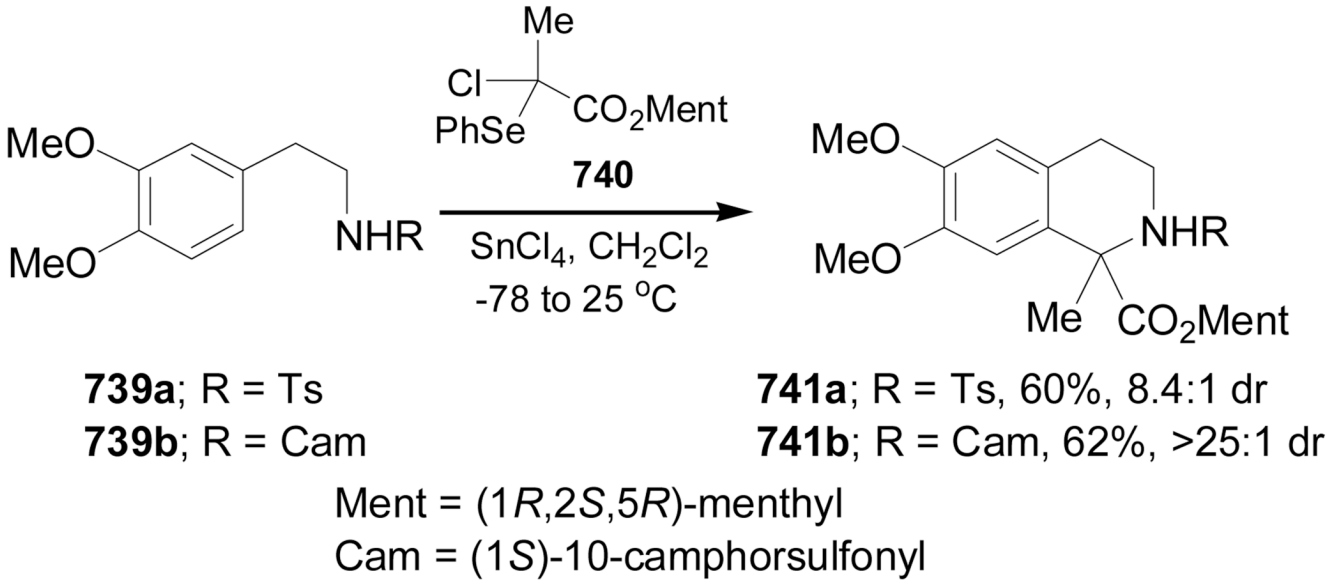
Scheme 159.



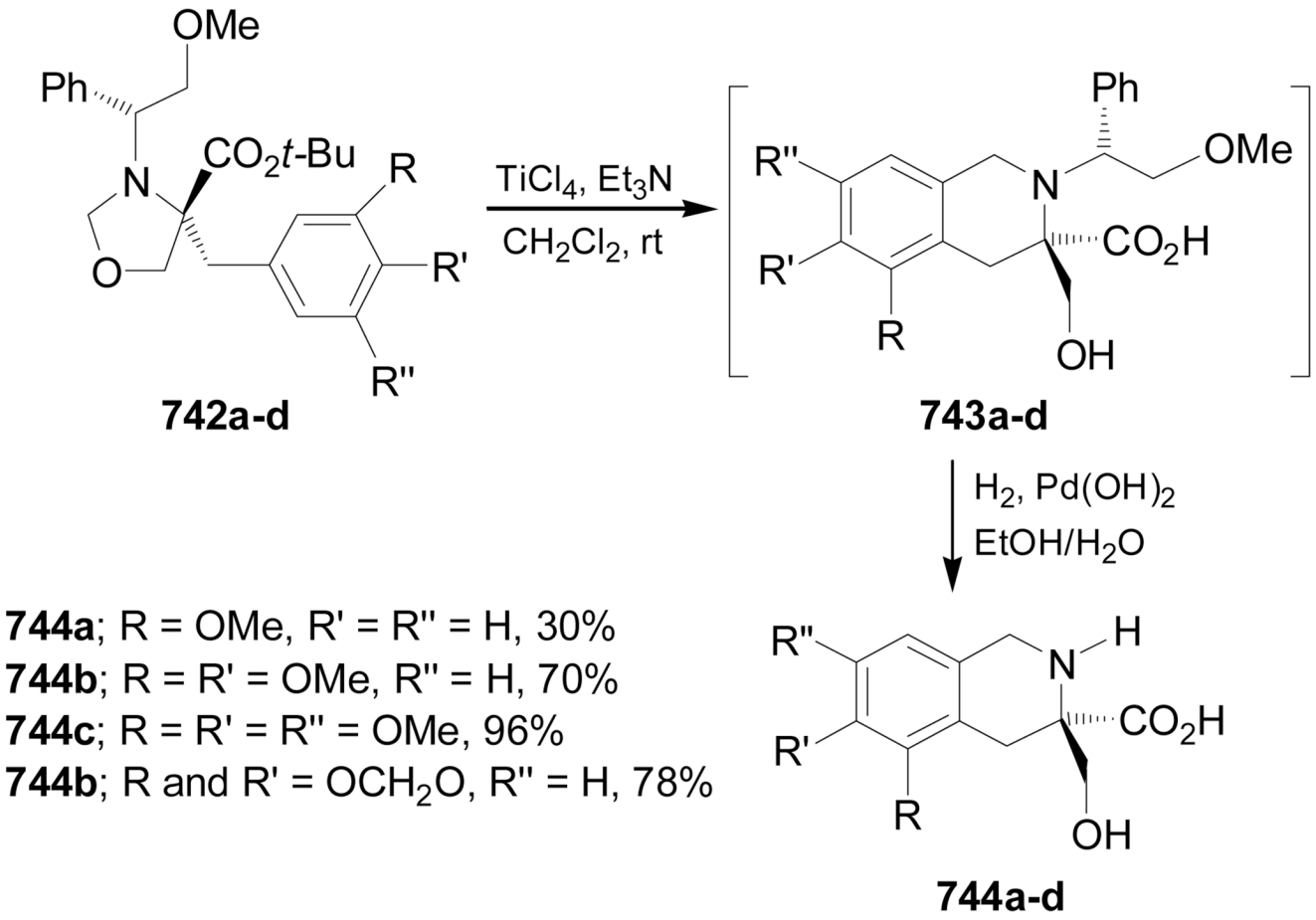
Scheme 160.



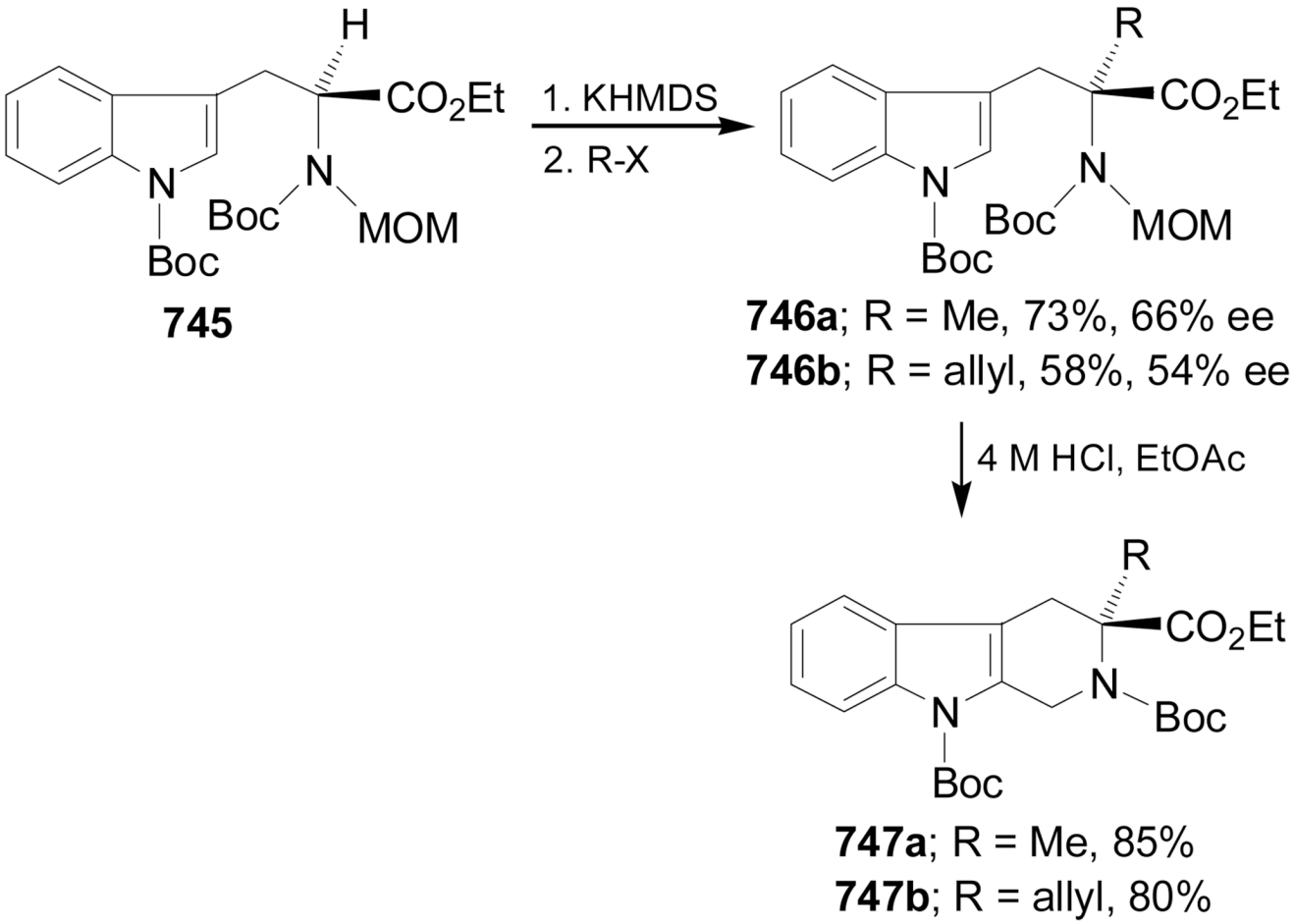
Scheme 161.



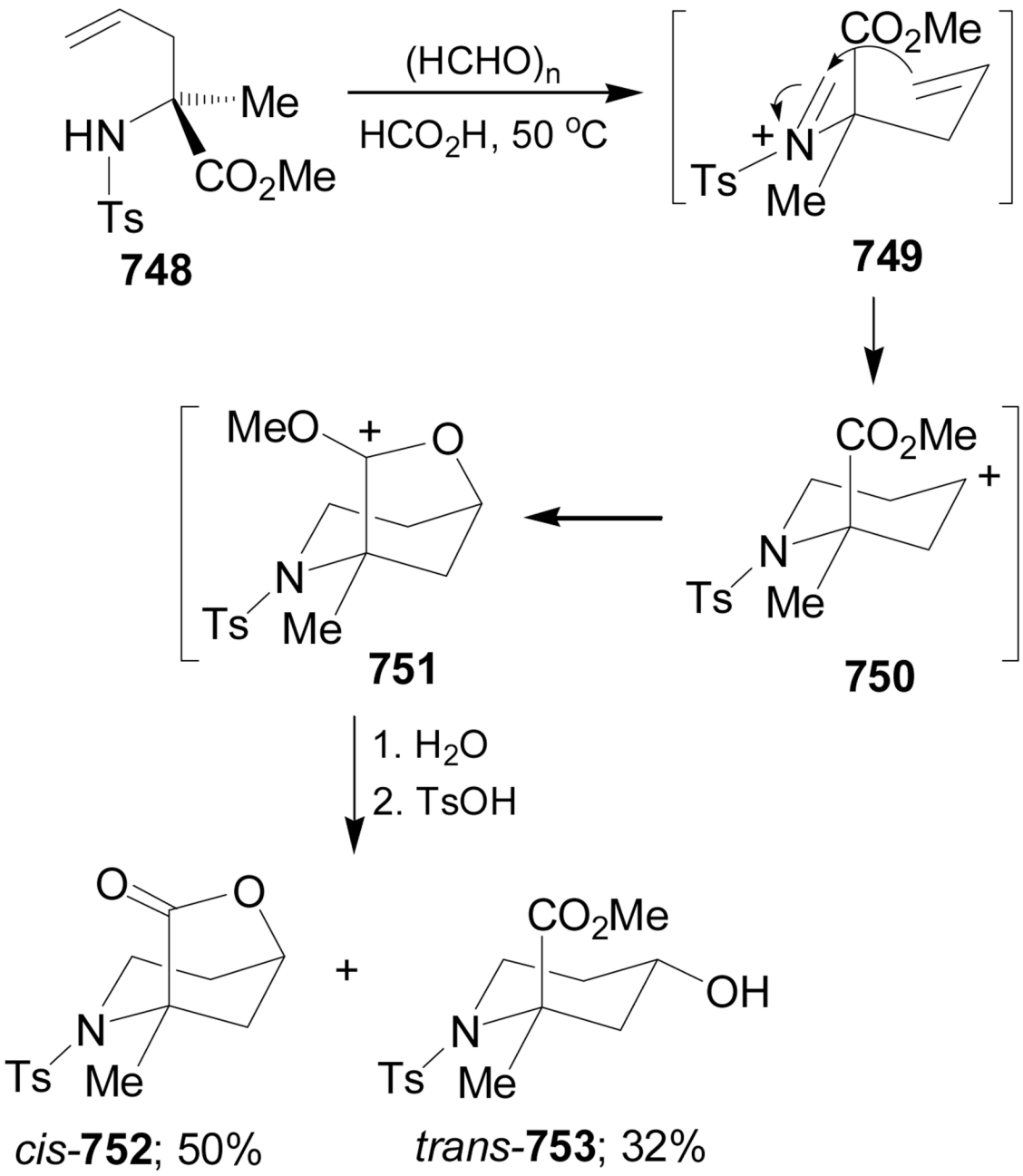
Scheme 162.



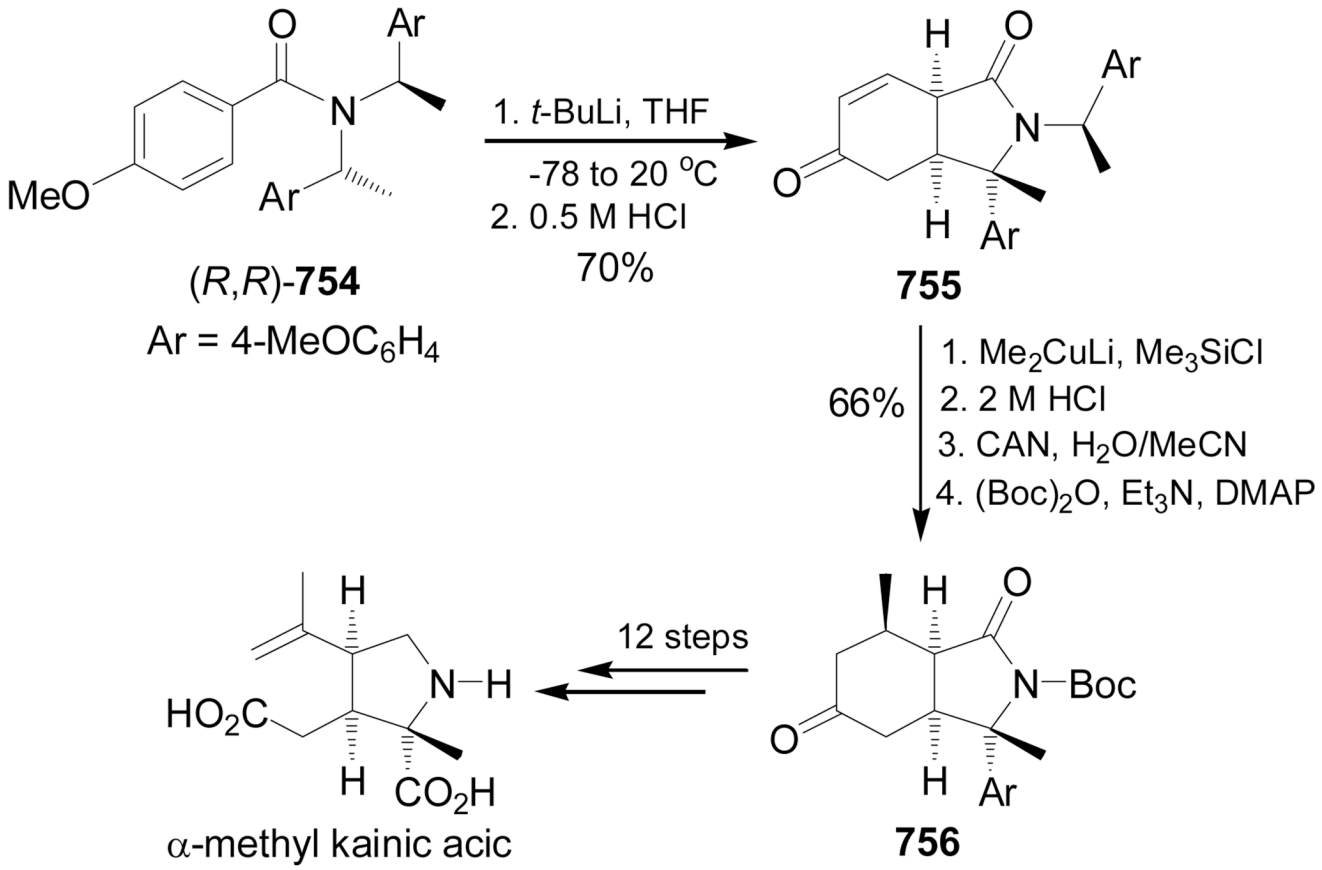
Scheme 163.



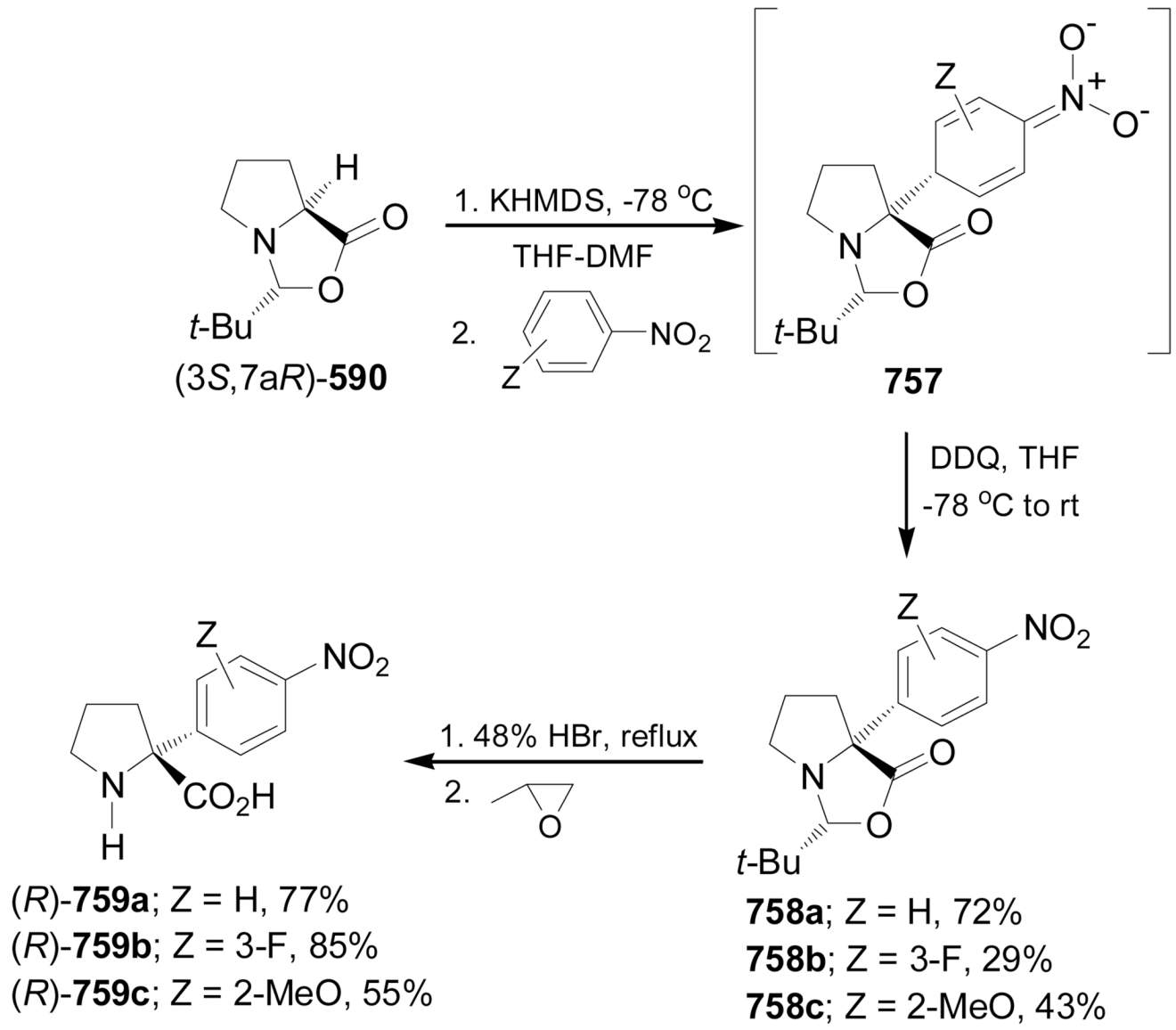
Scheme 164.



Scheme 165.



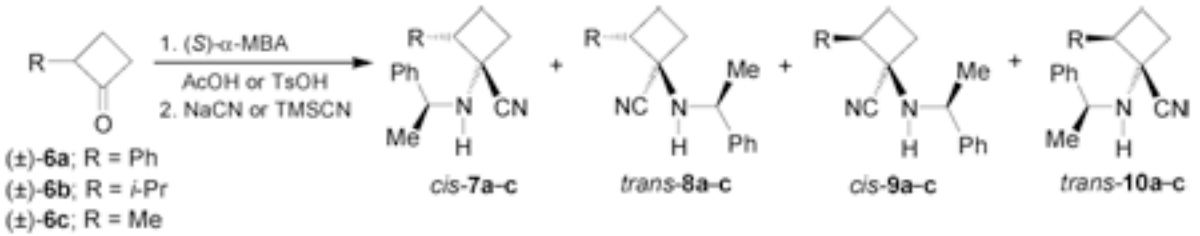
Scheme 166.



Scheme 167.

Table 1

Preparation of α-amino nitriles from the ketones (±)-**6a–c**.



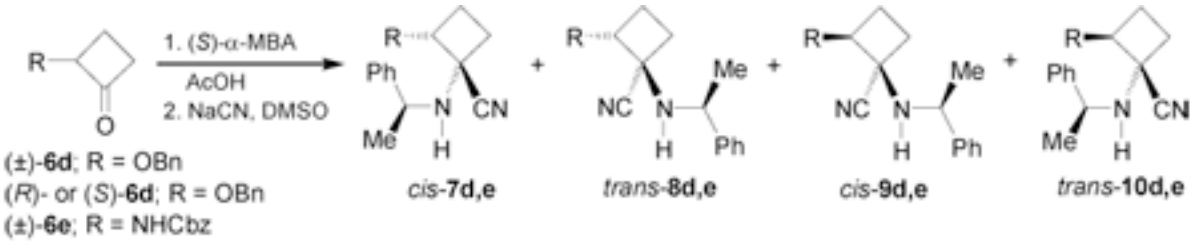
Entry	Conditions	R	Yield (%)	Diastereoisomeric ratio			
				7	8	9	10
1	NaCN, DMSO, 55–60 °C	**a** = Ph[a]	54	51	<2.5	45	<1.5
2	NaCN, MeOH, 55–60 °C	**a** = Ph	43	52	2.5	44	<1.5
3	NaCN, DMSO, 55–60 °C	**b** = *i*-Pr	46	56	1.0	42	<1
4	NaCN, MeOH, 55–60 °C	**b** = *i*-Pr	42	54	<1.0	44	<1
5	TMSCN, MeOH, $ZnCl_2$, 0 °C	**c** = Me[b]	--	6	46	11	37
6	TMSCN, hexane, $ZnCl_2$, −10 °C	**c** = Me[b]	--	11	15	33	41

[a] Similar results were obtained using (*R*)-phenylglycinol and (*R*)-MOMBA.

[b] The chiral amine was (*R*).

Table 2

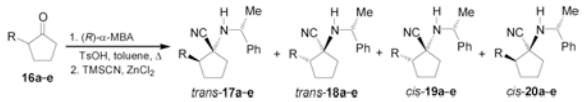
Asymmetric Strecker reaction of ketones **6d,e**.



Entry	Ketone	Conditions			Diastereoisomeric ratio			
		Time	Temperature (°C)	Yield (%)	7d,e	8d,e	9d,e	10d,e
1	(±)-**6d**	4 h	20	52	35	15	35	15
2	(±)-**6d**	4 days	50	54	10	40	10	40
3	(*R*)-**6d**	4 h	20	55	75	13	6	6
4	(*R*)-**6d**	4 days	50	54	28	60	2	10
5	(*S*)-**6d**	5 h	20	55	5.8	2.5	72.5	19.2
6	(±)-**6e**	3 days	50	90	--	45	--	55

Table 3

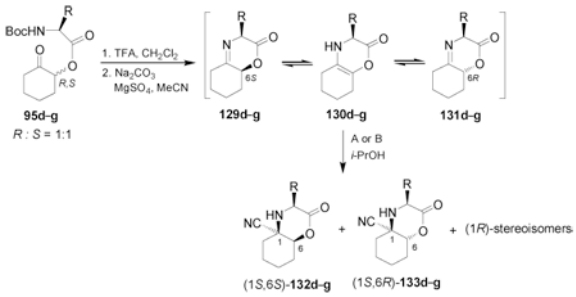
Asymmetric Strecker reaction of the ketones (±)-**16a–e**.



				Diastereoisomeric ratio			
Entry	**R**	**Conditions**	**Yield (%)**	**17**	**18**	**19**	**20**
1	**a** = OMe	MeOH, 20 °C, 12 h	98	41	22	29	8
2	**a** = OMe	Hexane, −10 °C, 18 h	98	10	0	61	29
3	**b** = Me	MeOH, 25 °C, 24 h	100	55	24	16	5
4	**b** = Me	MeOH, −10 °C, 3 h	100	45	30	21	4
5	**b** = Me	Hexane, −10 °C, 3 h	100	43	5	47	5
6	**c** = Et	MeOH, 25 °C, 24 h	98	57	23	14	6
7	**c** = Et	MeOH, −10 °C, 3 h	98	45	21	28	6
8	**c** = Et	Hexane, −10 °C, 3 h	82	39	5	45	11
9	**d** = *i*-Pr	MeOH, 25 °C, 24 h	86	44	23	28	5
10	**d** = *i*-Pr	MeOH, −10 °C, 3 h	92	37	4	47	12
11	**d** = *i*-Pr	Hexane, −10 °C, 3 h	84	12	4	57	27
12	**e** = *t*-Bu	MeOH, 25 °C, 24 h	74	61	23	14	2
13	**e** = *t*-Bu	MeOH, −10 °C, 3 h	36	26	0	59	15
14	**e** = *t*-Bu	Hexane, −10 °C, 3 h	37	5	1	66	28

Table 4

Formation of α-amino nitriles (1*S*,6*S*)-**132d–g** and (1*S*,6*R*)-**133d–g** from **95d–g**.

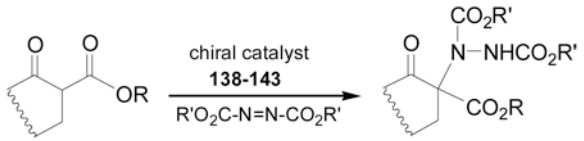


Entry	R	Ratio of 129131	Ratio of 132 : 133 : A: NaCN/TFA	(1*R*)-isomers (Yield %) B: TMSCN/$ZnCl_2$
1	**d** = Bn	50 : 50	66 : 34 : ND (96)	41 : 59 : ND (89)
2	**e** = Indm[a]	50 : 50	77 : 23 : ND (56)	33 : 67: ND (48)
3	**f** = *i*-Bu	50 : 50	39 : 42 : 19 (86)	18 : 71 : 11 (73)
4	**g** = *t*-Bu	20 : 80	16 : 82 : 02 (88)	05 : 90 : 05 (80)

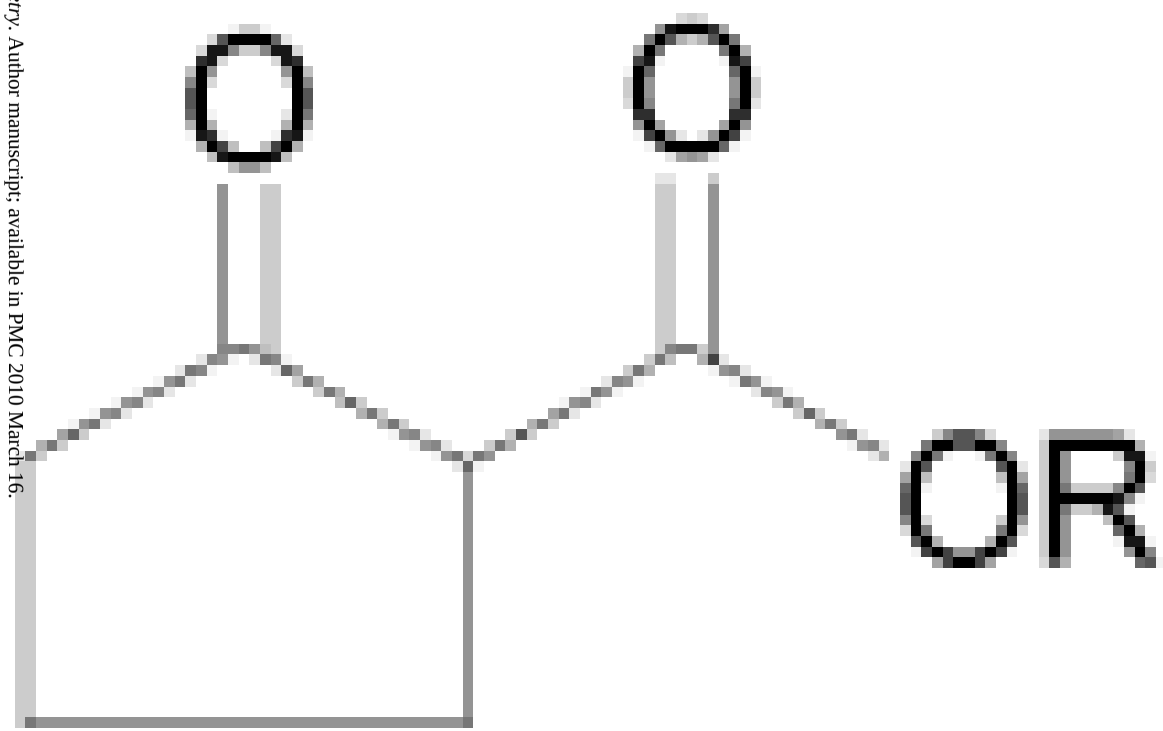
[a]Indm = 2-indolylmethyl fragment. ND = (1*R*)-isomers were not detected by ^{1}H NMR.

Table 5

Enantioselective hydrazination of **137** in the presence of chiral catalysts **138–143**.

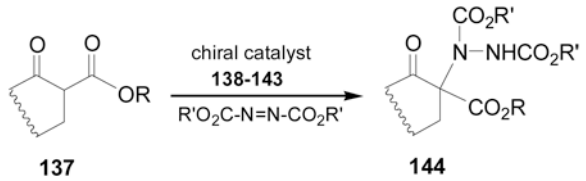


137 **144**

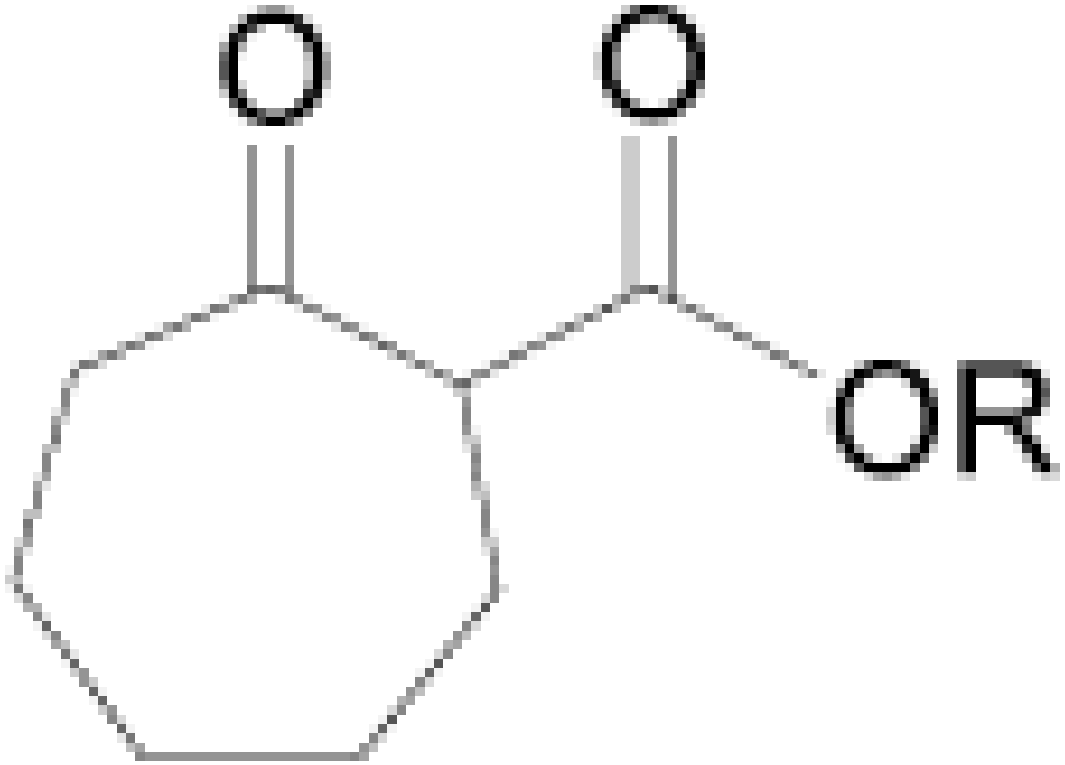
Substrate	R	R’	Catalyst	Yield (%)	ee (%), (Config)	Ref.
	*t*-Bu	*t*-Bu	**138**	99	89 (*S*)	112
	i-Pr	*t*-Bu	**139**	98	91 (*S*)	113
	Et	Bn	**140**	95	90 (*R*)	114
	Et	*t*-Bu	**141**	99	97 (*R*)	115
	Et	Bn	**142**	73	93 (*R*)	116
	t-Bu	*t*-Bu	**143**	81	95 (*R*)	117

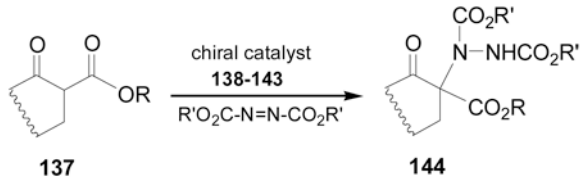
137 **144**

Substrate	R	R'	Catalyst	Yield (%)	ee (%), (Config)	Ref.
	Et	*t*-Bu	**138**	86	83 (*S*)	112
	Me	*t*-Bu	**139**	52	87 (*S*)	113
	Et	Bn	**140**	92	84 (*R*)	114
	Et	*t*-Bu	**141**	99	98 (*R*)	115

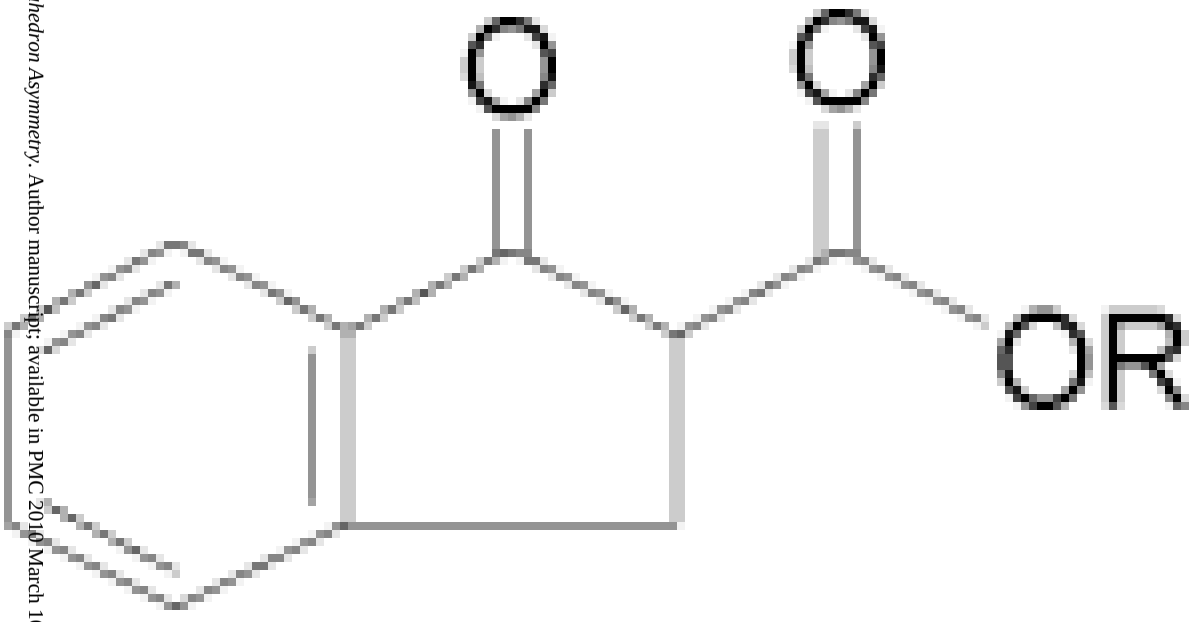


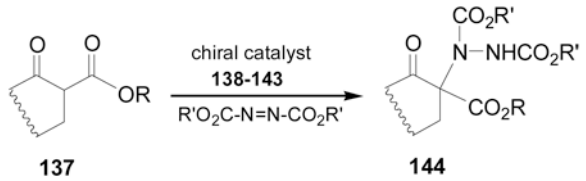
137 144

Substrate	R	R’	Catalyst	Yield (%)	ee (%), (Config)	Ref.
	*t*-Bu	*t*-Bu	**139**	90	90 (*S*)	113



137 144

Substrate	R	R’	Catalyst	Yield (%)	ee (%), (Config)	Ref.
	*t*-Bu	*t*-Bu	**139**	93	90 (*S*)	113
	Et	Bn	**142**	94	99 (*S*)	116



137 144

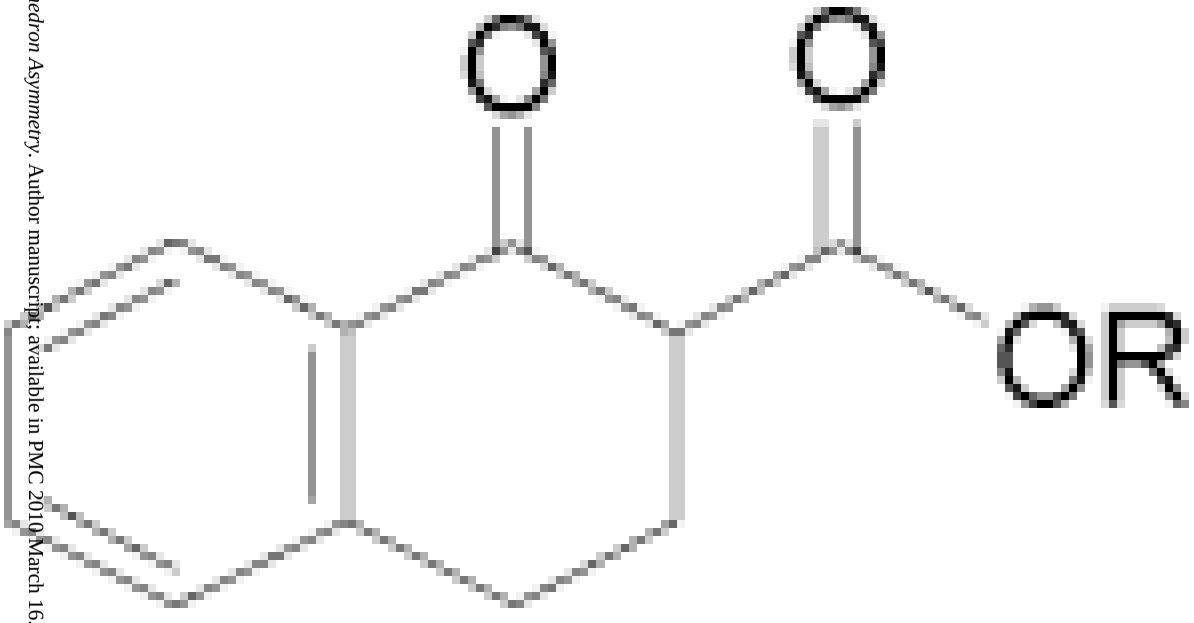
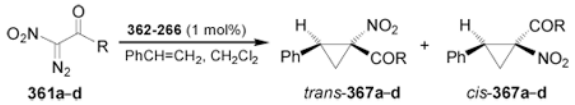
Substrate	R	R’	Catalyst	Yield (%)	ee (%), (Config)	Ref.
	Me	*t*-Bu	**139**	99	87 (*S*)	113
	Et	*t*-Bu	**141**	99	97 (*R*)	115
	Me	*t*-Bu	**142**	56	95 (*S*)	116

Table 6

Asymmetric cyclopropanation of styrene with α-nitro-α-diazocarbonyl compounds **361a–d**.



361a–d *trans*-**367a–d** *cis*-**367a–d**

Substrate	Catalyst	Aditive	Yield (%)	Ratio (*trans:cis*)	% ee (*trans*)	% ee (*cis*)
361a; R = OMe	**362**	--	75	86 : 14	28	13
361b; R = OEt	**362**	--	72	83 : 17	30	0
361c; R = O*t*-Bu	**362**	--	68	68 : 32	41	6
361d; R = Ph	**362**	--	64	39 : 61	31	13
361b; R = OEt	**363**	--	71	75 : 25	13	16
361b; R = OEt	**364**	--	76	86 : 14	33	0
361b; R = OEt	**365a**	--	89	89 : 11	2	17
361b; R = OEt	**365b**	--	74	79 : 21	8	10
361a; R = OMe[a]	**366a**	$(BzO)_2$	27	90 : 10	nd	nd
361a; R = OMe[a]	**366a**	EDA (20%)	55	90 : 10	72	51
361a; R = OMe[a]	**366a**	EDA (10%)	52	90 : 10	66	49
361a; R = OMe[b]	**366a**	$PhNHNH_2$	39	90 : 10	70	49
361a; R = OMe[a]	**366b**	EDA (10%)	16	95 : 05	68	nd
361a; R = OMe[a]	**366c**	EDA (10%)	7	95 : 05	63	nd

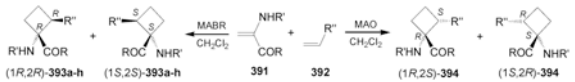
[a] in the presence of 5 mol% of $Cu(MeCN)_4PF_6$.

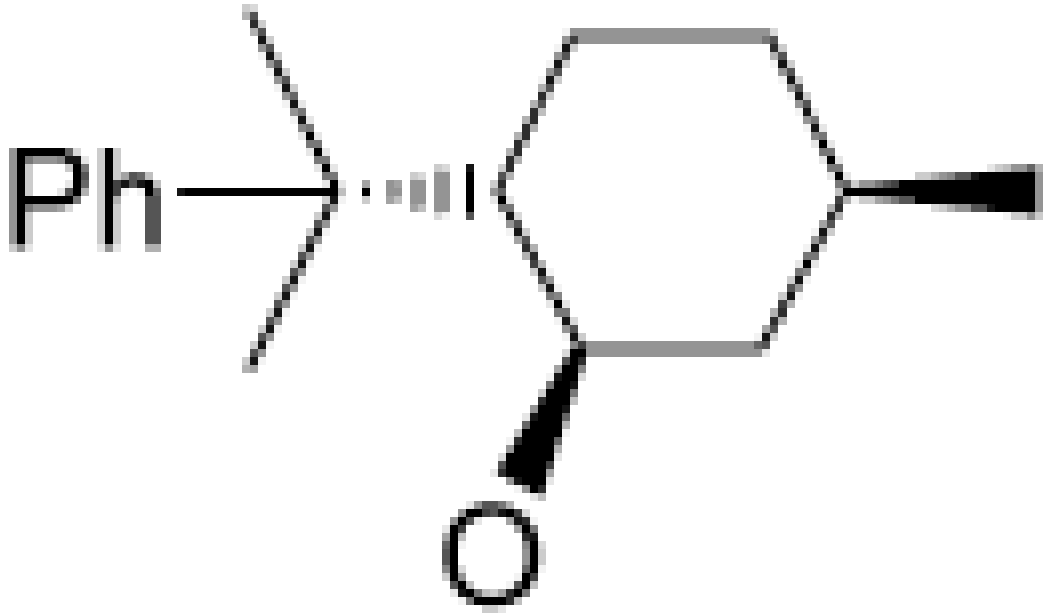
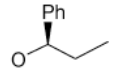
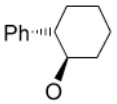
[b] $Cu(II)OTf_2$ was used as the copper source

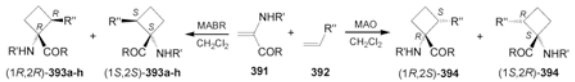
R'	R''	Yield (%)	(1*R*,2*R*) : (1*S*,2*S*)
COMe	OEt	13	15 : 85

R'	R''	Yield (%)	(1R,2R) : (1S,2S)
COMe	OEt	30	40 : 60

COMe	45	>98 : 02



R'	R''	Yield (%)	(1*R*,2*R*) : (1*S*,2*S*)
COMe		70	76 : 24
COMe		55	60 : 40
$COCF_3$		18	>98 : 02



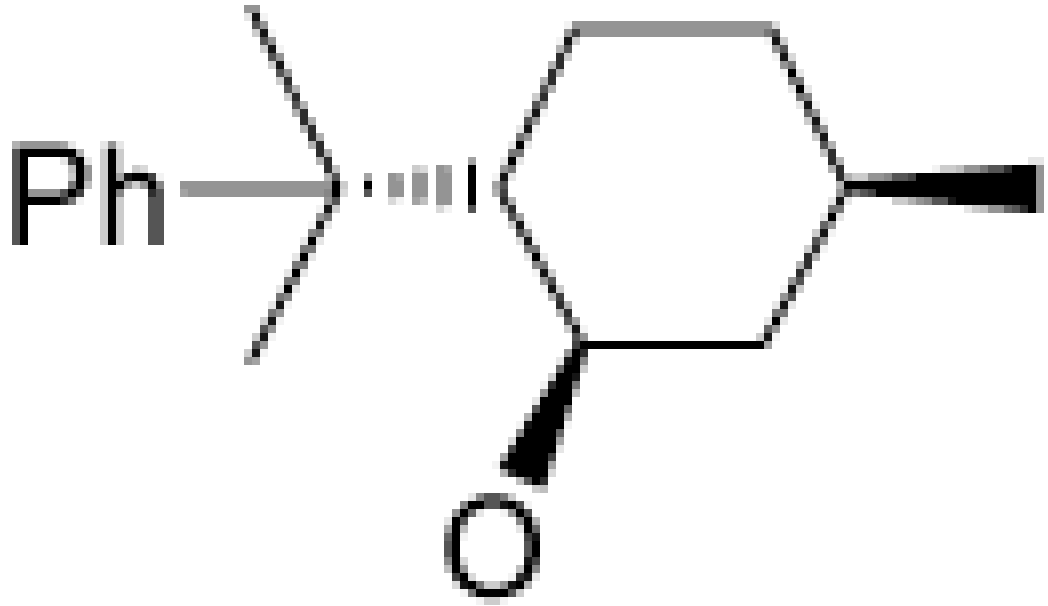
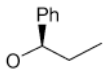
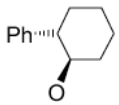
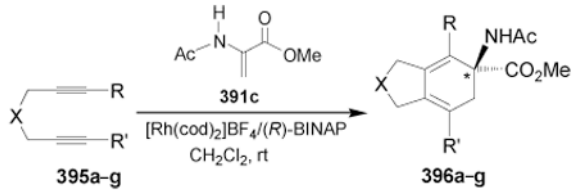
R’	R’’	Yield (%)	(1*R*,2*R*) : (1*S*,2*S*)
$COCF_3$		56	80 : 20
$COCF_3$		30	60 : 40
COMe		62	02 : 98[a]

Table 8

Rh(I)/(*R*)-BINAP-catalyzed enantioselective [2+2+2] cycloaddtion of **395a–g** with **391c**.



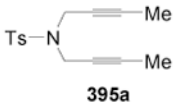
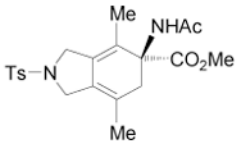
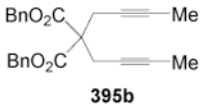
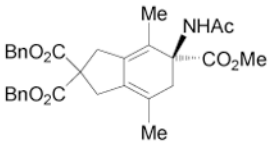
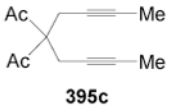
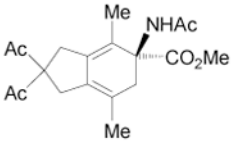
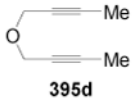
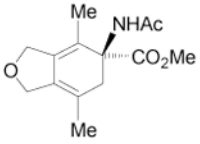
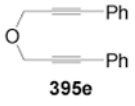
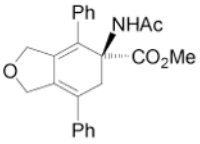
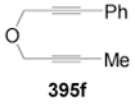
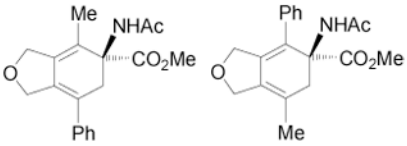
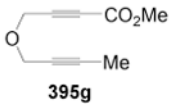
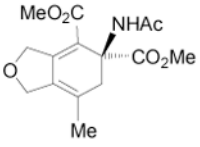
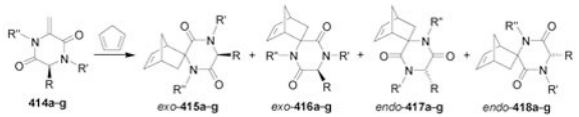
Sustrate	Product, % yield (% ee)
 **395a**	 **396a**; 95% (96% ee)
 **395b**	 **396b**; 90% (93% ee)
 **395c**	 **396c**; 91% (98% ee)
 **395d**	 **396d**; 68% (99% ee)
 **395e**	 **396e**; 84% (99% ee)
 **395f**	 **396f**; 53% (99% ee) **396f'**; 20% (99% ee)
 **395g**	 **396g**; 67% (99% ee)

Table 9

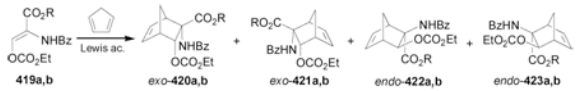
Diels-Alder cycloaddition of **414a–g** with cyclopentadiene.



dienophile	R	R'	R"	Yield (%)	415 : 416 : 417 : 418
414a	Me	Ac	H	60	10 : 17 : 1 : 1
414b	Me	Ac	Ac	50	trace : 1.2 : trace : 1
414c	Me	Me	H	<10	not determined
414d	*i*-Pr	Ac	H	60	12 : 1.4 : 1 : 0
414e	*i*-Pr	Ac	Ac	trace	not determined
414f	4-$AcOC_6H_4CH_2$	Ac	H	60	7 : 1 : 1 : 0
414g	4-$AcOC_6H_4CH_2$	Ac	Ac	trace	not determined

Table 10

Asymmetric Diels-Alder cycloaddition of **419a,b** with cyclopentadiene.

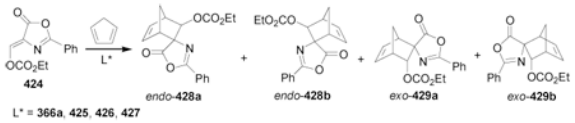


419a,b *exo*-**420a,b** *exo*-**421a,b** *endo*-**422a,b** *endo*-**423a,b**

	R	Conditions	Yield (%)	*exo : endo*	420 : 421 (de)	422 : 423 (de)
419a	(−)-menthyl	$EtAlCl_2$,)))	36	70 : 30	23 : 77 (54)	87 : 13 (74)
419b	(+)-menthyl	$Mg(ClO_4)_2$, Δ	50	77 : 23	90 : 10 (80)	07 : 93 (86)
419a	(−)-menthyl	$Mg(ClO_4)_2$, Δ	50	77 : 23	10 : 90 (80)	93 : 07 (86)
419b	(+)-menthyl	$Mg(ClO_4)_2$,)))	90	78 : 22	89 : 11 (78)	07 : 93 (86)
419a	(−)-menthyl	$Mg(ClO_4)_2$,)))	90	77 : 23	10 : 90 (80)	92 : 08 (84)

Table 11

Enantioselective Diels-Alder cycloaddition of **424** with cyclopentadiene.

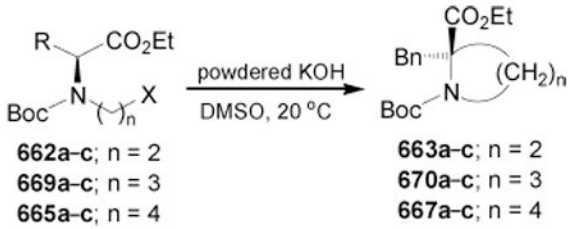


Conditions	*t* (h)	*exo: endo*	*endo* ratio	*exo* ratio
366a-$Mg(ClO_4)_2$	48	75 : 25	43 : 57	50 : 50
366a-$Ce(OTf)_4.H_2O$[a]	75	70 : 30	50 : 50	50 : 50
425-$Mg(ClO_4)_2$	100	70 : 30	50 : 50	50 : 50
425-$Ce(OTf)_4.H_2O$[a]	150	75 : 25	50 : 50	50 : 50
426-$Mg(ClO_4)_2$	24	80 : 20	47 : 53	43 : 57
427-$Mg(ClO_4)_2$	24	75 : 25	56 : 44	66 : 34
427-$Ce(OTf)_4.H_2O$[a]	200	75 : 25	50 : 50	50 : 50

[a] In the presence of molecular sieves.

Table 12

Asymmetric cyclization of α-amino acids derivatives with KOH/DMSO at 20 °C.

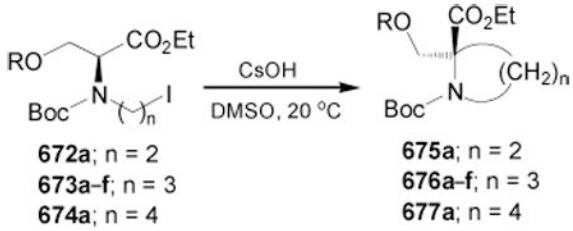


entry	R	X	product	Yield (%)	ee (%)
1	**a** = Bn	Br	**663a**; n = 2	82	99 (*R*)
2	**b** = $MeSCH_2CH_2$	Br	**663b**; n = 2	85	99 (*S*)
3	**c** = *i*-Pr	Br	**663c**; n = 2	79	99 [a]
4	**a** = Bn	Br	**670a**; n = 3	91	99 (*S*)
5	**b** = $MeSCH_2CH_2$	Br	**670b**; n = 3	91	98 (*S*)
6	**c** = *i*-Pr	Br	**670c**; n = 3	94	98 [a]
7	**a** = Bn	Br	**667a**; n = 4	73	90 [a]
8	**b** = $MeSCH_2CH_2$	Br	**667b**; n = 4	86	88 [a]
9	**c** = *i*-Pr	Br	**667c**; n = 4	74	94 [a]
10	**a** = Bn	I	**667a**; n = 4	97	97 [a]
11	**b** = $MeSCH_2CH_2$	I	**667b**; n = 4	89	97 [a]
12	**c** = *i*-Pr	I	**667c**; n = 4	90	98 [a]

[a]The configuration was not reported.

Table 13

Asymmetric cyclization of serine derivatives.



672a; n = 2
673a–f; n = 3
674a; n = 4

675a; n = 2
676a–f; n = 3
677a; n = 4

entry	substrate	product	Yield (%)	ee (%)
1	**672a**; R = *t*-Bu	**675a**; n = 2	74	92 [a]
2	**673a**; R = Bn	**676a**; n = 3	84	86 (*S*)
3	**673b**; R = Me	**676b**; n = 3	75	82 (*S*)
4	**673c**; R = MOM	**676c**; n = 3	72	82 (*S*)
5	**673d**; R = TBDPS	**676d**; n = 3	13	88 (*S*)
6	**673e**; R = PMB	**676e**; n = 3	88	92 (*S*)
7	**673f**; R = *t*-Bu	**676f**; n = 3	89	93 (*S*)
8	**674a**; R = *t*-Bu	**677a**; n = 4	77	94 [a]

[a] The configuration was not reported.