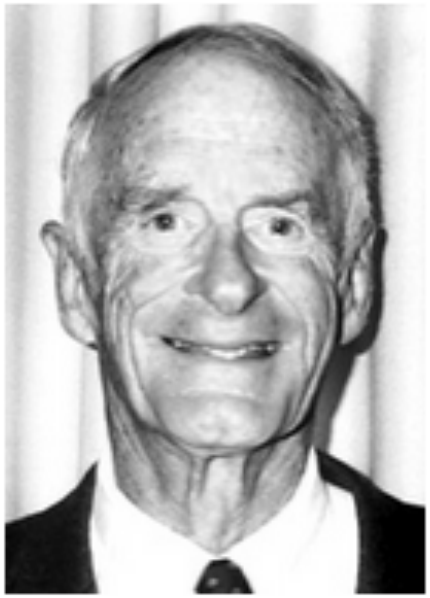
The Nobel Prize in Chemistry 2001



William S. Knowles
Prize share: 1/4

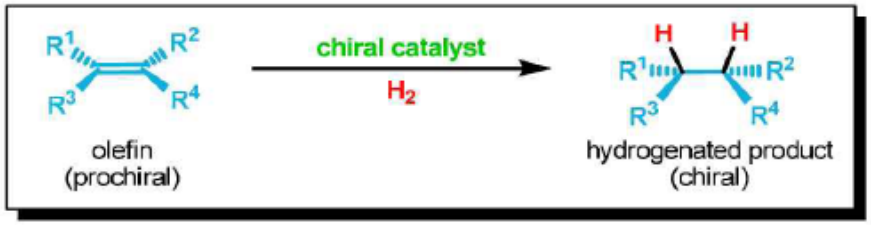
Ryoji Noyori
Prize share: 1/4

K. Barry Sharpless
Prize share: 1/2

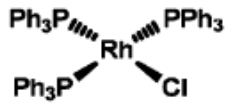
The Nobel Prize in Chemistry 2001 was divided, one half jointly to William S. Knowles and Ryoji Noyori *"for their work on chirally catalysed hydrogenation reactions"* and the other half to K. Barry Sharpless *"for his work on chirally catalysed oxidation reactions"*.

ENANTIOSELECTIVE ADDITION OF H_2 TO C=C

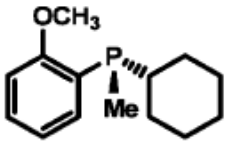
Background: Enantioselective Homogeneous Hydrogenation



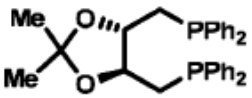
The discovery by G. Wilkinson that the solution of the rhodium complex 1, catalyzes the reduction of unhindered alkenes by H_2 gas at 1 atmosphere pressure[1] paved the way for W.S. Knowles[2] and co-workers to show that the use of the chiral monodentate phosphorous ligand (*S*)-CAMP (2) resulted in good enantioselectivity in the Wilkinson hydrogenation of dehydroamino acids. Studies by H. Kagan[3] revealed that C_2-symmetric bidentate phosphine ligands such as 3 gave comparable results.



Wilkinson's cat. (1966)
1

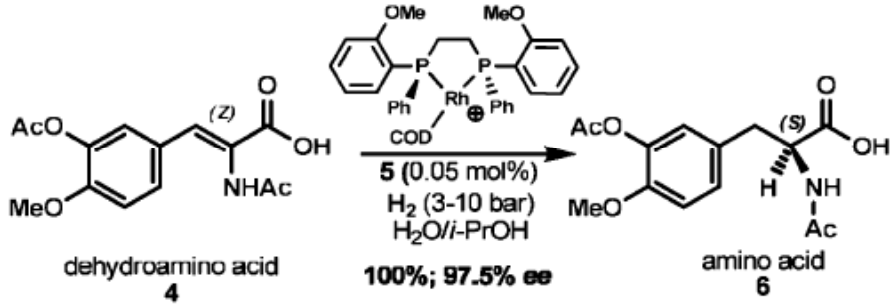


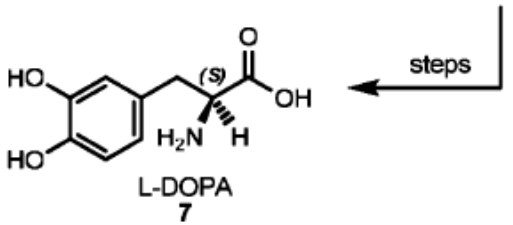
(*S*)-CAMP (1972)
2



(*S,S*)-DIOP (1971)
3

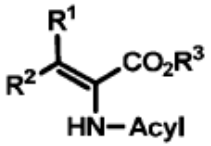
An even more effective bidentate phosphine ligand-Rh complex, (*S,S*)-DIPAMP-Rh (5), that was developed by Knowles was used in the commercial production at Monsanto of L-DOPA 7, an anti-Parkinson's drug.[4]



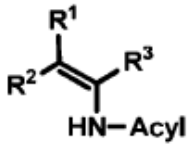


This section is organized according to the type of unsaturated substrate and the transition metal (Rh, Ru, Ir, etc.) used for reduction by H_2.

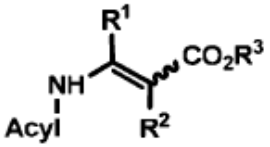
Most Common Substrate Types



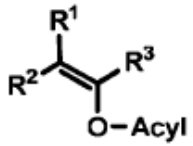
α-dehydroamino acid derivatives
8



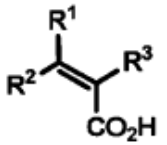
enamides
9



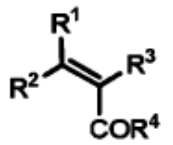
β-acylamino acrylates
10



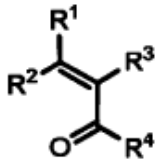
enol esters
11



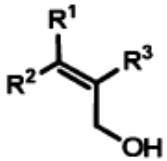
α,β-unsaturated carboxylic acids
12



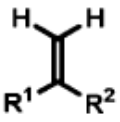
α,β-unsaturated esters and amides
13



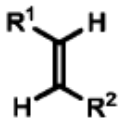
α,β-unsaturated ketones
14



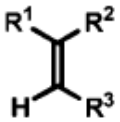
unsaturated alcohols
15



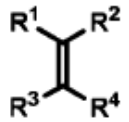
1,1-disubstituted alkenes
16



1,2-disubstituted alkenes
17



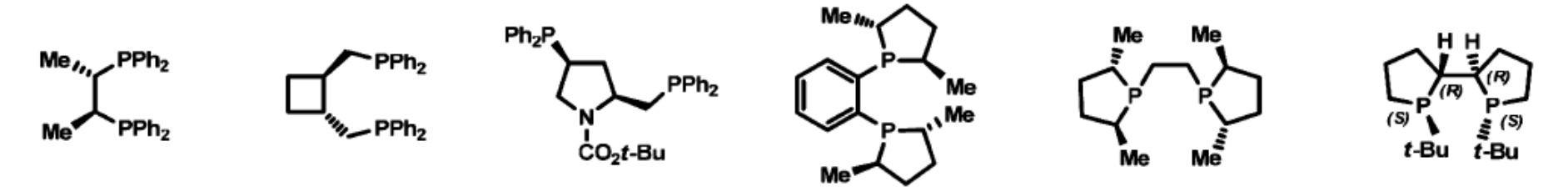
trisubstituted alkenes
18



tetrasubstituted alkenes
19

Figure 1

Representative Chiral Bidentate Phosphorus Ligands[5]

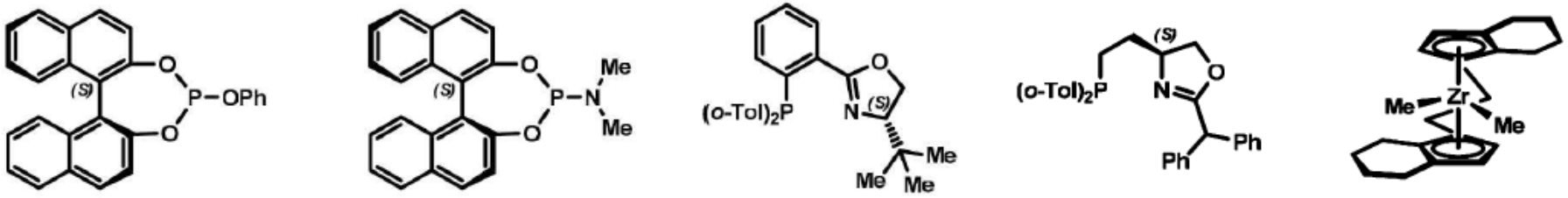


(*S,S*)-ChiraPhos **20** | (*R,R*)-CBD **21** | (*S,S*)-BPPM **22** | (*S,S*)-Me-DuPhos **23** | (*S,S*)-Me-BPE **24** | (*S,S,R,R*)-TangPhos **25**

(*S*)-BINAP **26** | (*S*)-H_8-BINAP **27** | (*S*)-BIPHEMP **28** | (*S*)-SEGPHOS **29** | (*R*)-(*S*)-JosiPhos **30** | (*S*)-[2,2]-PHANEPHOS **31**

Figure 2

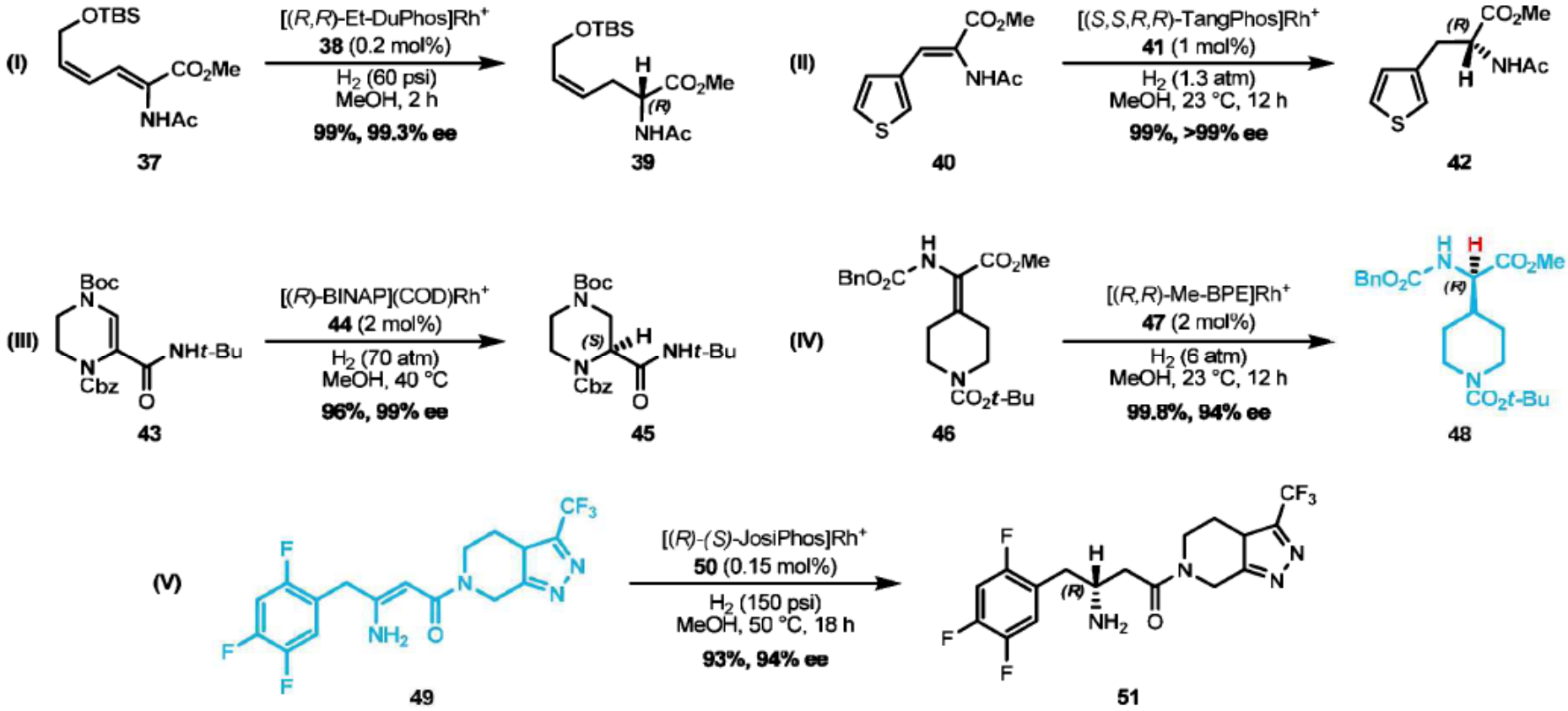
Chiral Monodentate Phosphorus, P,N and Non-Phosphorus Ligands[6]



monophosphite **32** | (*S*)-MonoPhos **33** | (*S*)-PHOX **34** | (*S*)-JM-Phos **35** | zirconocene **36**

Figure 3

Enantioselective Hydrogenation of α- and β-Dehydroamino Acid Derivatives[5a,14]

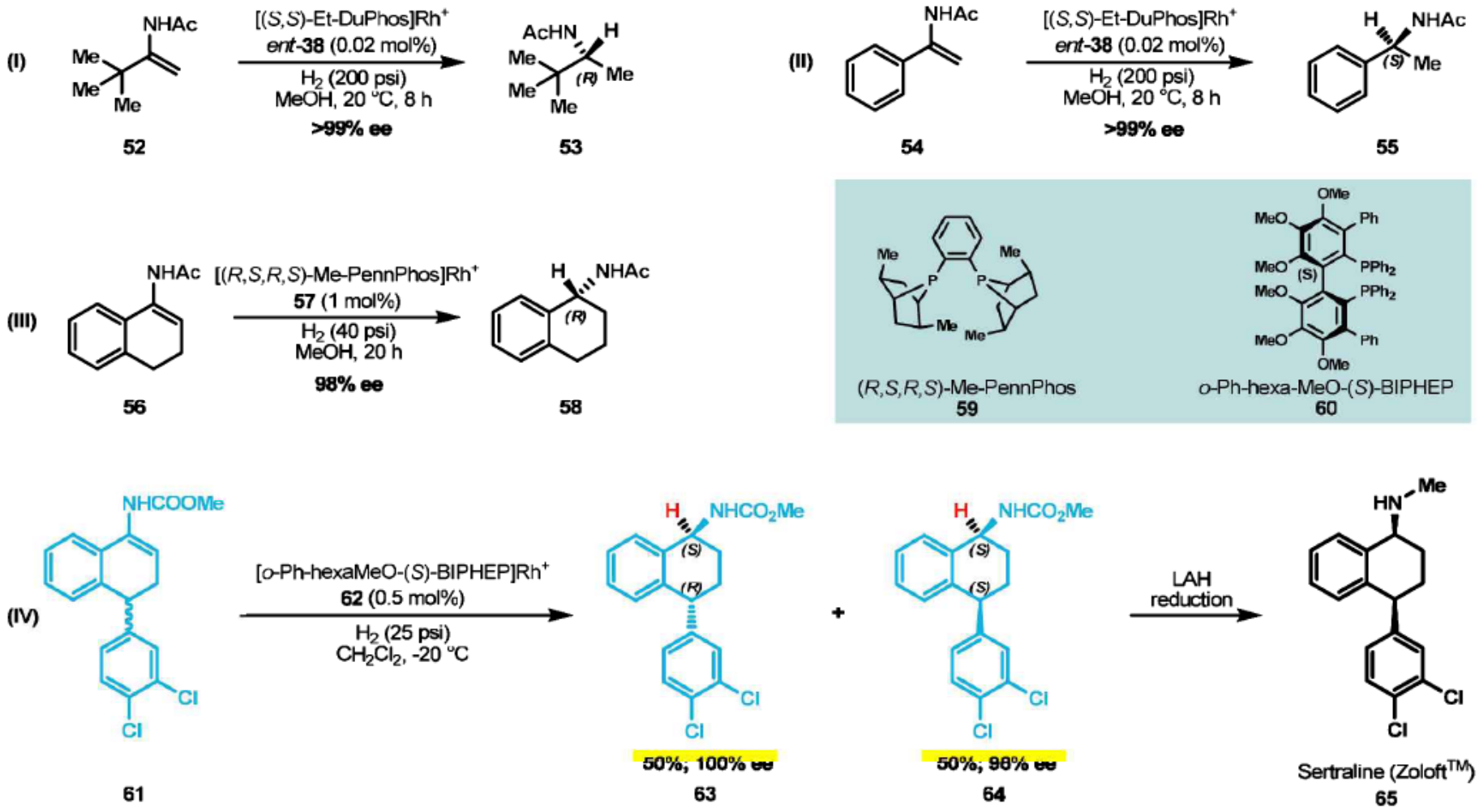


Reference Key for Equations: (I)[15];(II)[16]; (III)[17]

Scheme 1

Reference Key for Equations: (IV)[18]; (V)[19]

Enantioselective Hydrogenation of Enamides[5a,5c,5e]

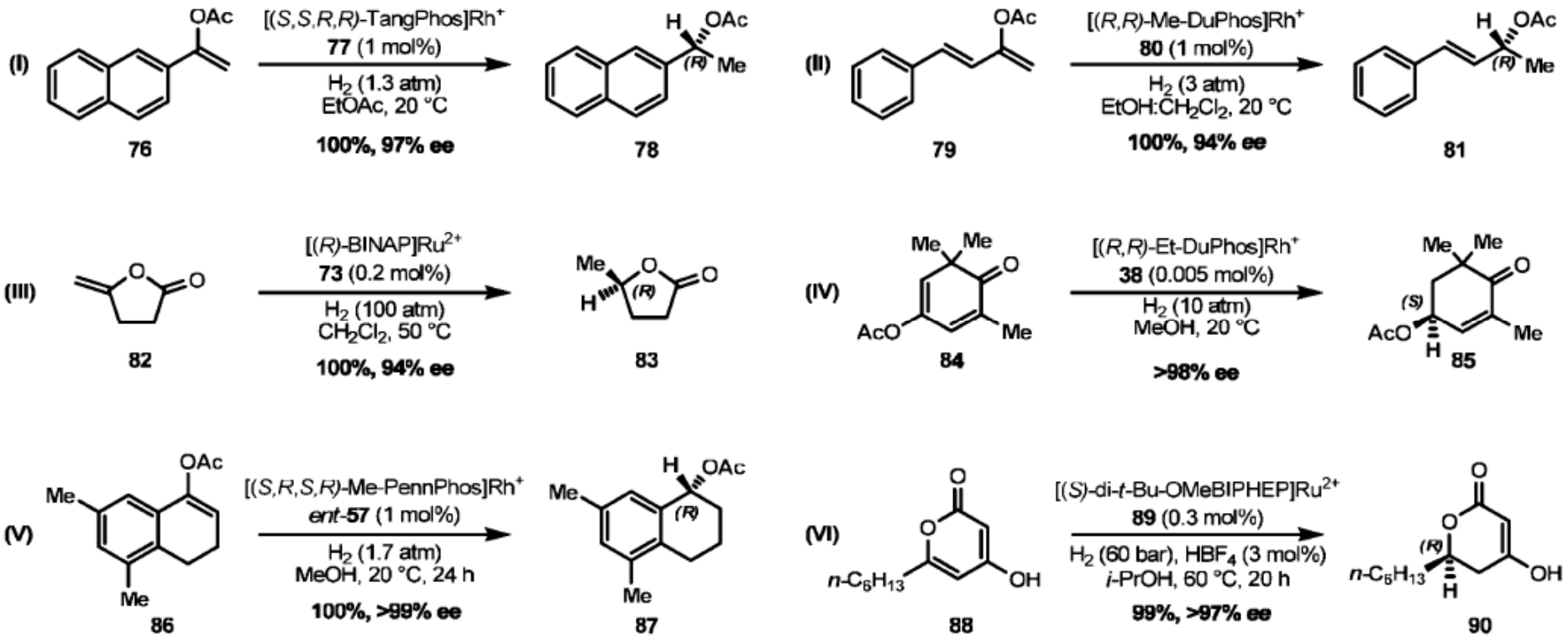


Reference Key for Equations: (I)[22]; (II)[22]

Scheme 2

Reference Key for Equations: (III)[23]; (IV)[24]

Enantioselective Hydrogenation of Enol Esters[5a,5c,5e]

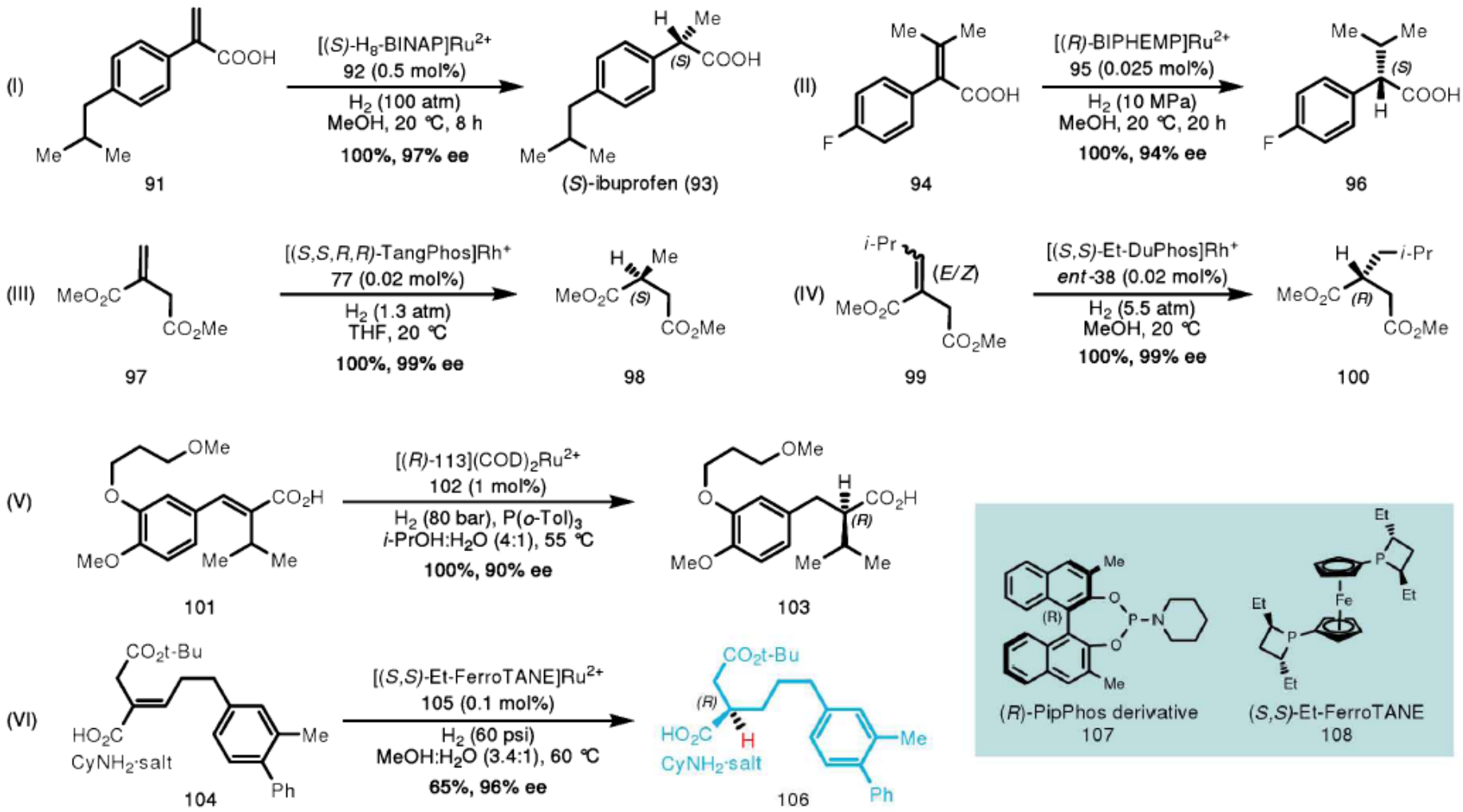


Reference Key for Equations: (I)[27]; (II)[28]; (III)[29]

Scheme 4

Reference Key for Equations: (IV)[5c]; (V)[30]; (VI)[31]

Enantioselective Hydrogenation of α,β-Unsaturated Carboxylic Acids and Derivatives[5a,5e]

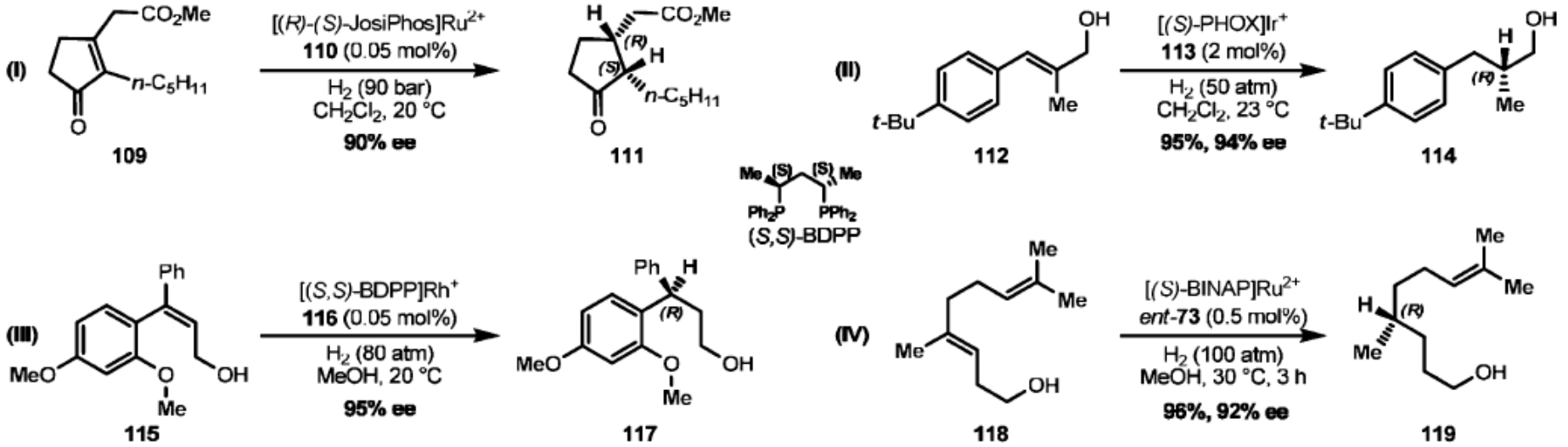


Reference Key for Equations: (I)[32]; (II)[33]; (III)[27]

Scheme 5

Reference Key for Equations: (IV)[34]; (V)[13c]; (VI)[35]

Enantioselective Hydrogenation of Unsaturated Ketones and Alcohols[5a,5e]

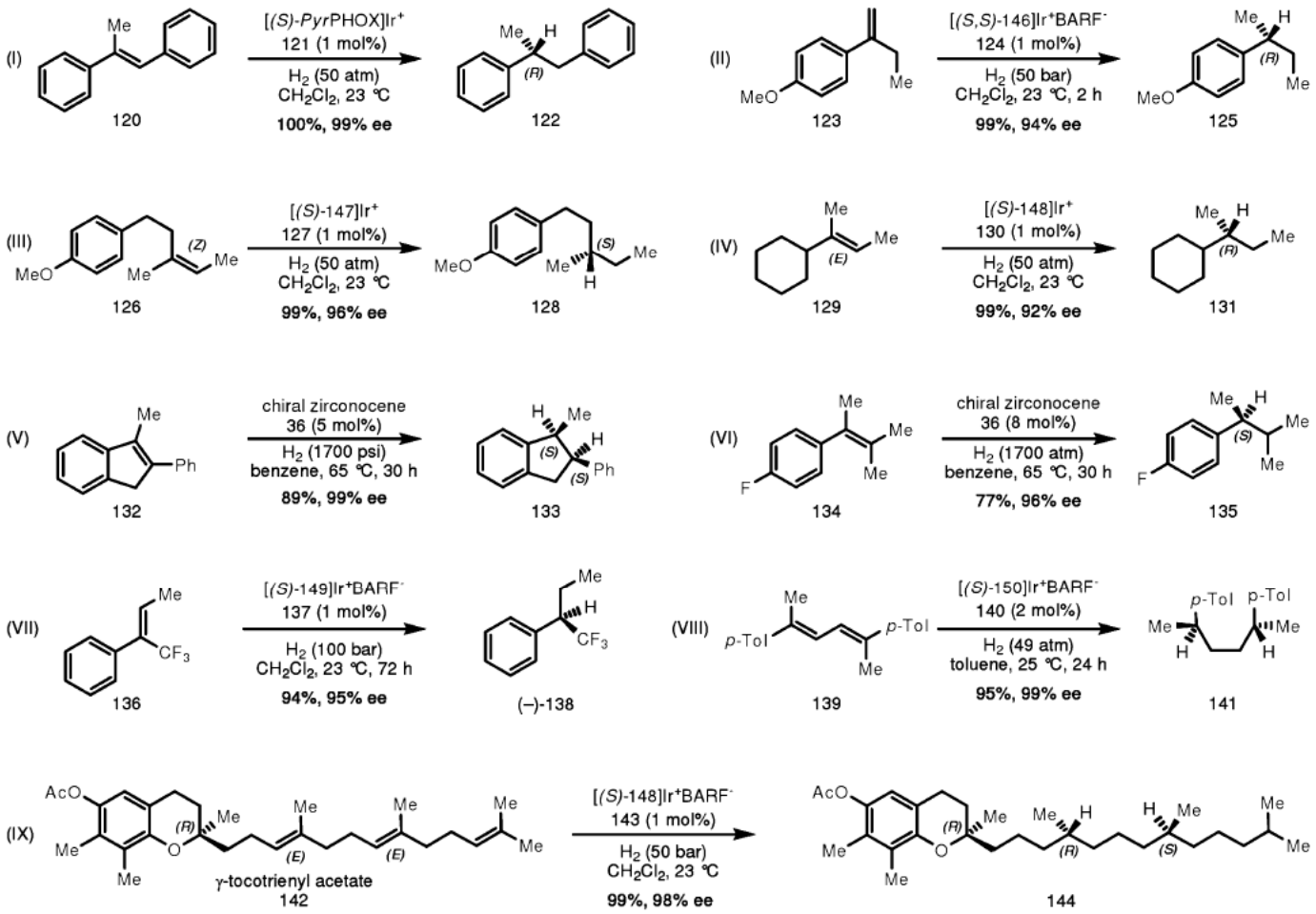


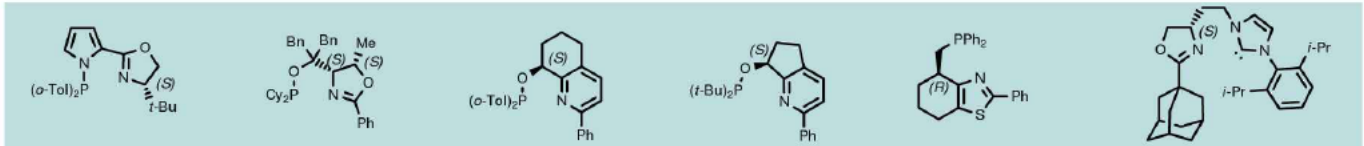
Reference Key for Equations: (I)[36,21b]; (II)[37]

Scheme 6

Reference Key for Equation: (III)[38]; (IV)[39]

Enantioselective Hydrogenation of Monodentate Olefins[8,40]





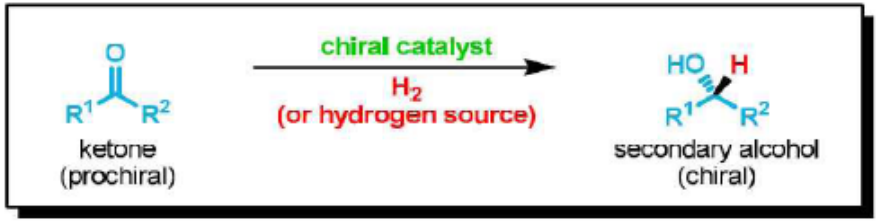
(*S*)-PyrPHOX 145 | (*S,S*)-oxazoline-phosphinite 146 | (*S*)-pyridine-phosphinite 147 | (*S*)-pyridine-phosphinite 148 | *N,P*-(*S*)-thiazole-based ligand 149 | *C,N*-type imidazolylidene ligand 150

Reference Key for Equations: (I)[41]; (II)[42]; (III)[41]; (IV)[43]; (V)[44]

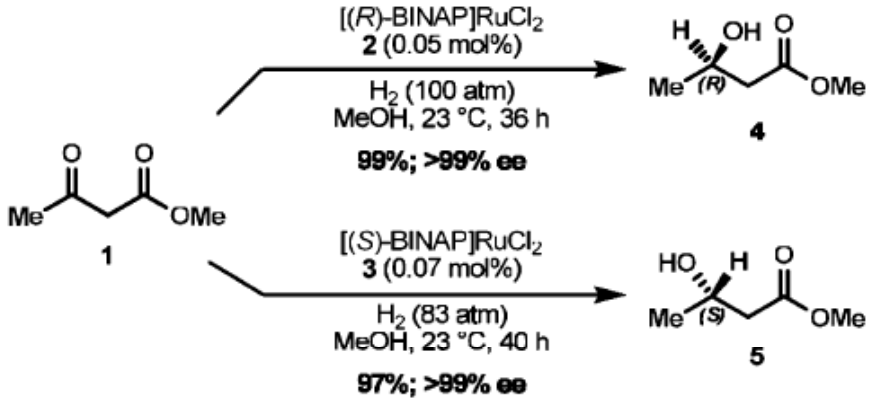
Scheme 7

Reference Key for Equation: (VI)[44]; (VII)[45]; (VIII)[46]; (IX)[43]

Background: Highly Enantioselective Homogeneous Hydrogenation of Ketones



The first transition metal-catalyzed highly enantioselective homogeneous hydrogenation of functionalized ketones to form enantiopure secondary alcohols was reported by R. Noyori et al. in the late 1980s.[1] Using either (*R*)- or (*S*)-BINAP-Ru(II) complexes (2 or 3), β-keto esters such as 1 were converted to the corresponding (*R*)- or (*S*)-β-hydroxy esters (4 or 5) in high yield and enantiomeric purity. Catalysts 2 and 3 were also highly effective for the enantioselective hydrogenation of a wide variety of α- and β-functionalized ketones (e.g., α-amino ketones and β-hydroxy ketones).[2] Later it was discovered that Ru-catalysts having both chiral bisphosphine and chiral diamine ligands catalyzed the enantioselective reduction of unfunctionalized ketones (e.g., dialkyl ketones, aryl-alkyl ketones).[3]



It was also demonstrated that hydrogen donors, such as small ethanol, 2-propanol and triethylammonium formate, can replace hydrogen gas (H_2) as the hydrogen source in the enantioselective reduction of ketones, a process called *asymmetric transfer hydrogenation*.[4] A significant advantage of this version is that it does not require the use of pressurized reaction vessels.

Common Ketonic Substrates

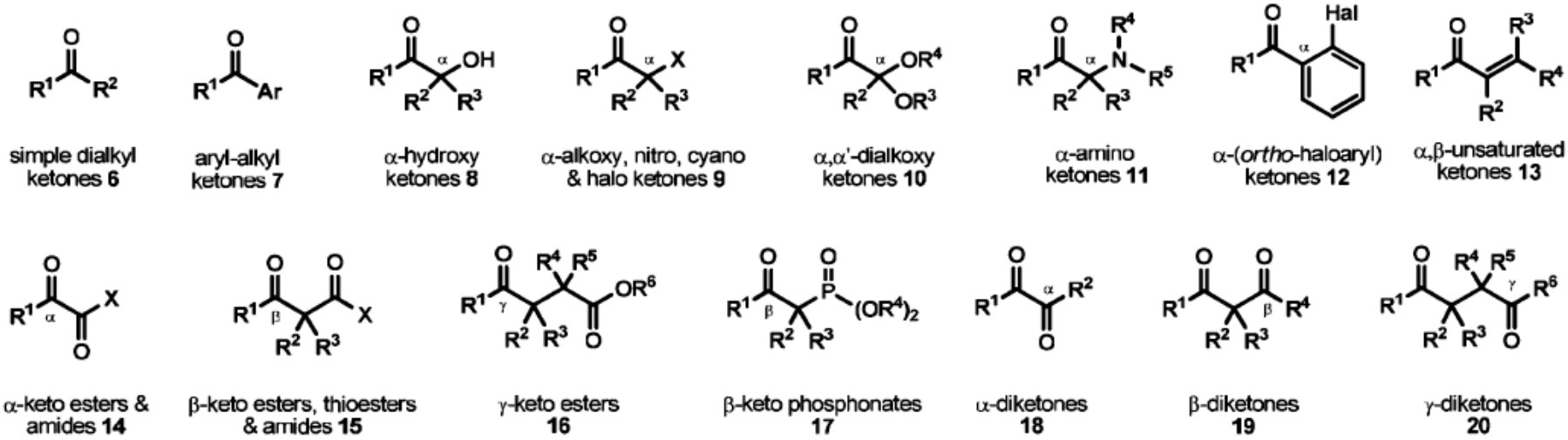
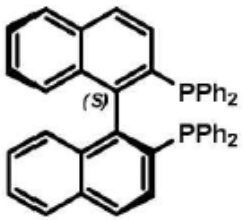
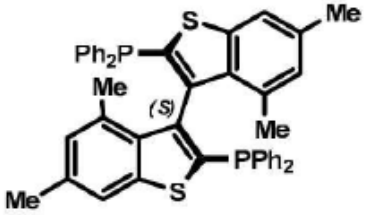


Figure 1

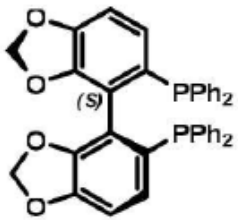
Some Bisphosphine Ligands



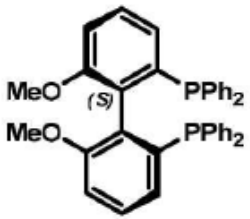
(*S*)-BINAP
21



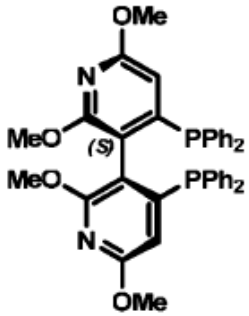
(*S*)-TetraMe-BITIANP
22



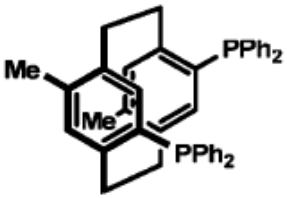
(*S*)-SEGPHOS
23



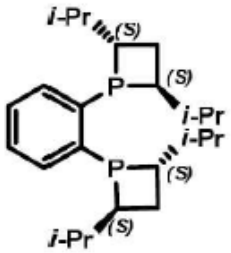
(*S*)-MeO-BIPHEMP
24



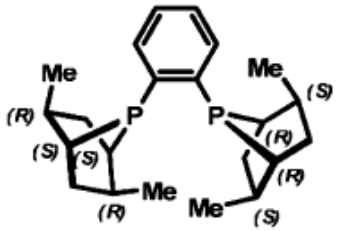
(*S*)-P-Phos
25



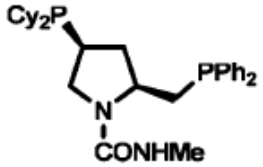
(*S*)-[2,2]-ParaPhos
26



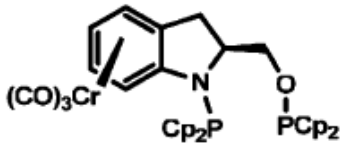
(*S*)-*i*-PrCnrPHOS
27



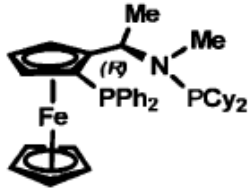
(*R,S,R,S*)-Me-PennPhos
28



(*S,S*)-MCCPM
29



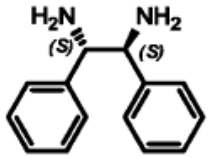
(*S,2S*)-Cr(CO)$_3$-Cp,Cp-IndoNOP
30



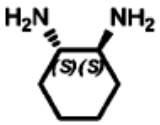
(*R*)-(*R*)-BoPhoz
31

Figure 2

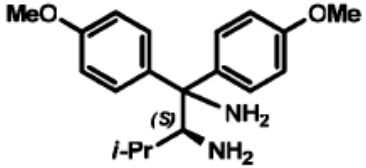
Chiral 1,2- and 1,4-Diamine Ancillary Ligands



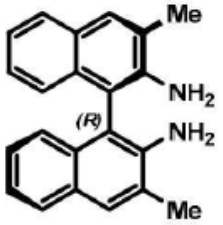
(*S,S*)-DPEN
32



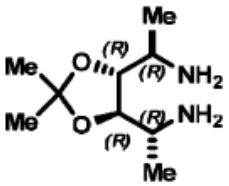
(*S,S*)-DACH
33



(*S*)-DAIPEN
34



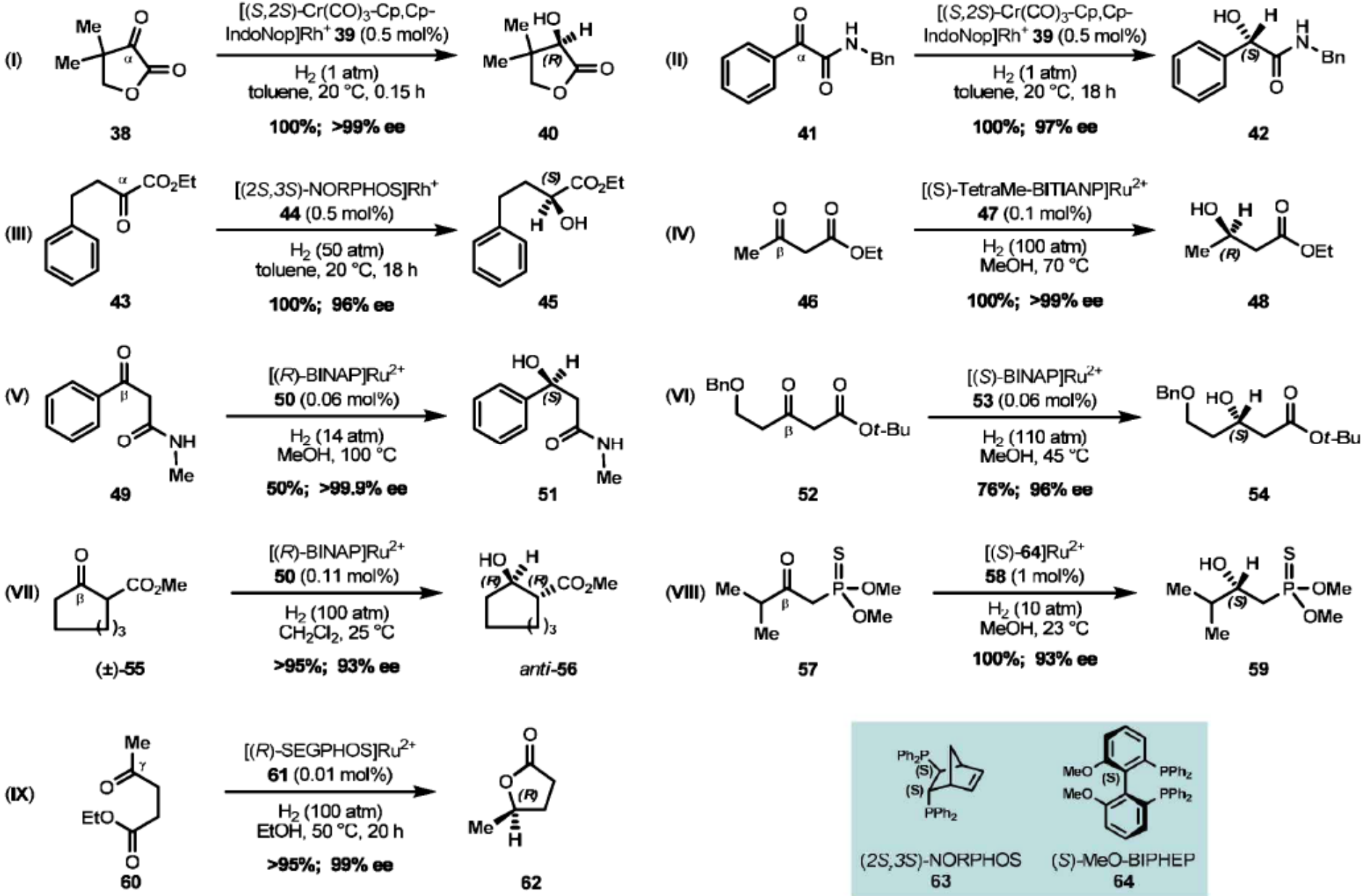
(*R*)-DM-DABN
35



(*R*)-IPHAN
36

Figure 3

Enantioselective Hydrogenation of α-, β- and γ-Keto Acid Derivatives[3g,3k,3l]

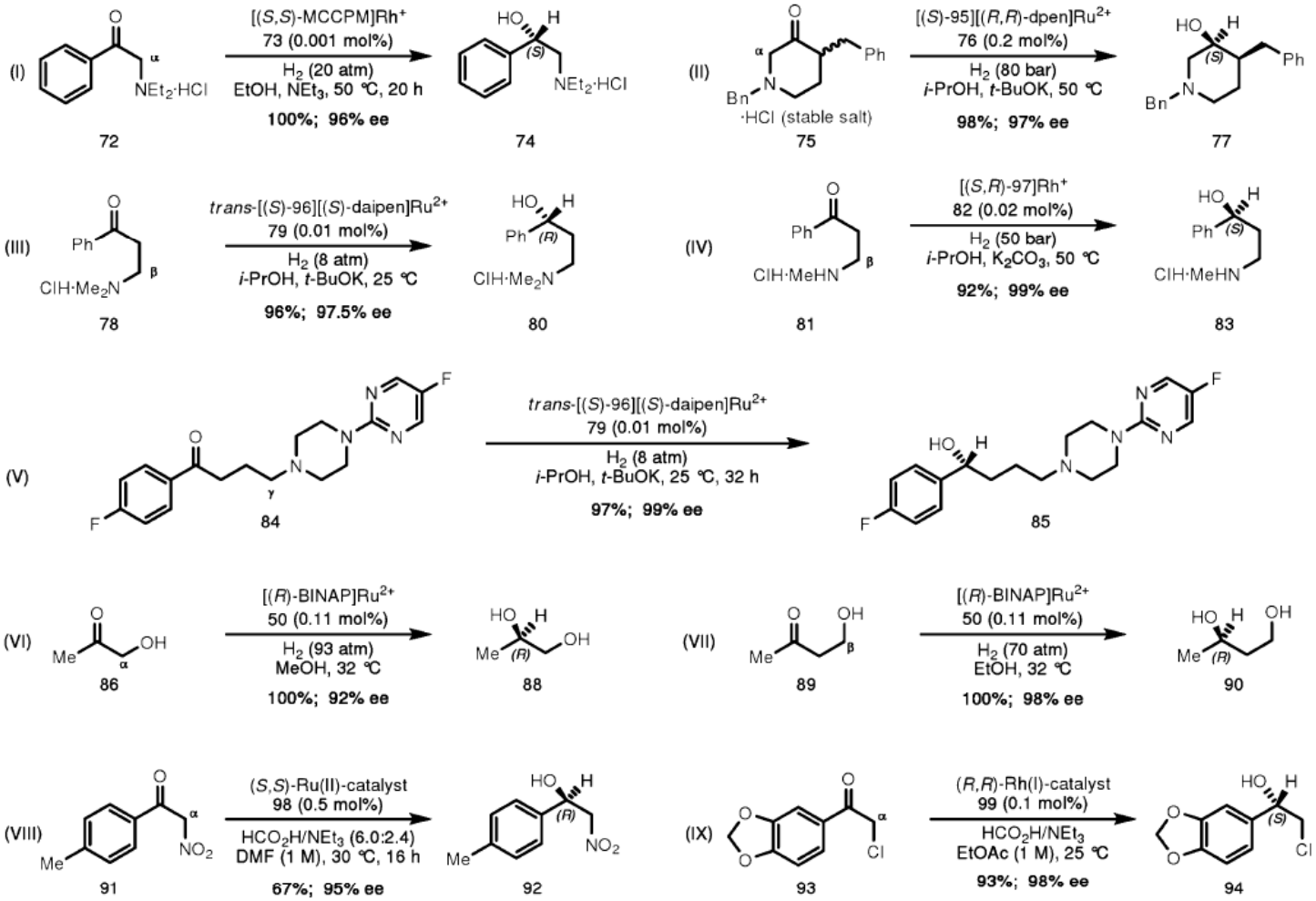


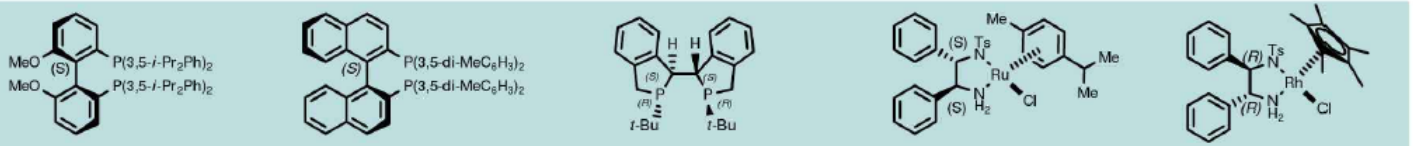
Reference Key for Equations: (I)[5]; (II)[5]; (III)[6]; (IV)[7]; (V)[8]

Scheme 1

Reference Key for Equations: (VI)[9]; (VII)[10]; (VIII)[11]; (IX)[12]

Enantioselective Hydrogenation of α-, β- and γ-Functionalized Ketones



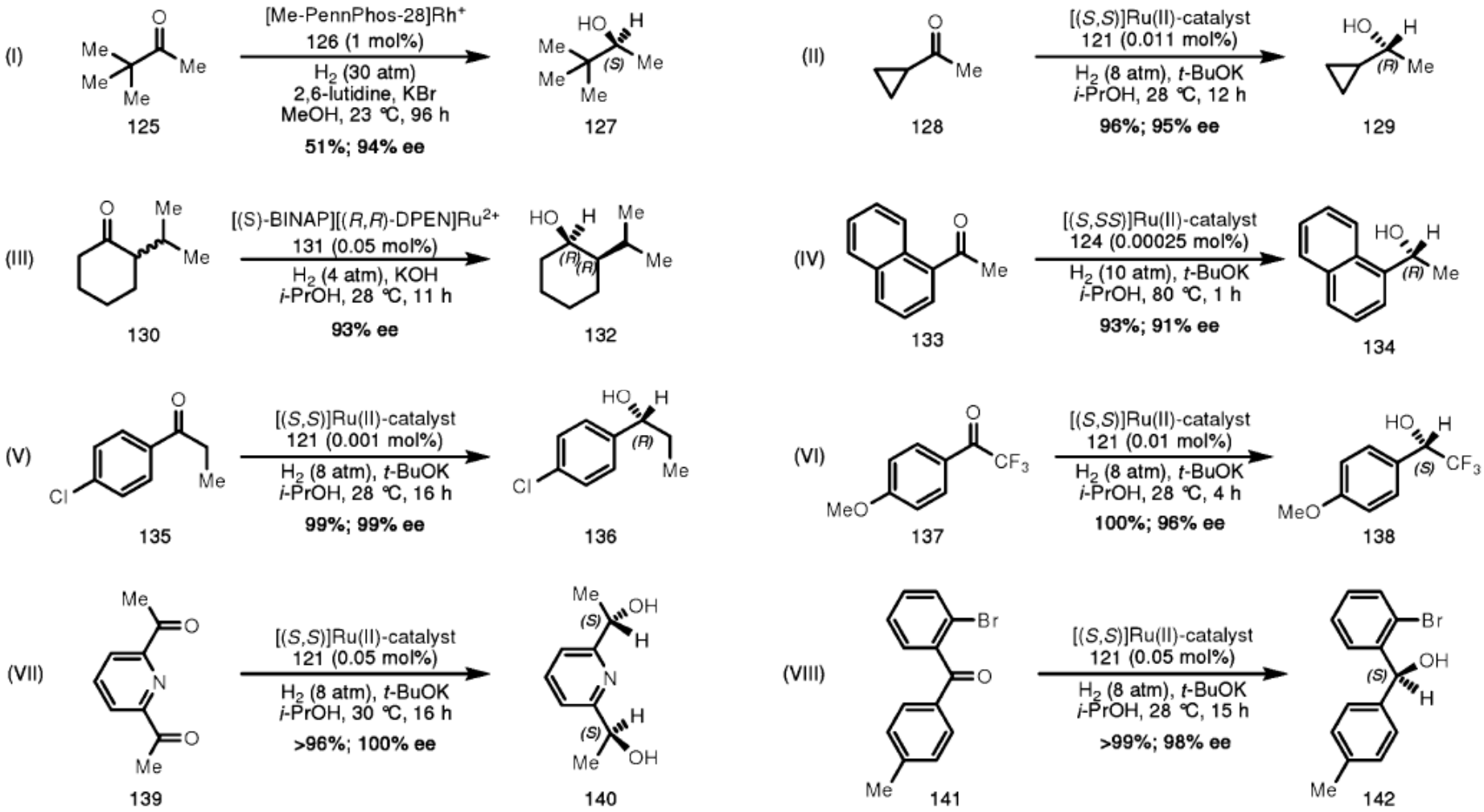


Reference Key for Equations (I)[15]; (II)[16]; (III)[17]; (IV)[18]; (V)[17]

Scheme 3

Reference Key for Equations: (VI)[1]; (VII)[1]; (VIII)[19]; (IX)[20]

Enantioselective Hydrogenation of Simple Ketones[3b,3g,3k,4e]



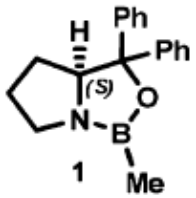
Reference Key for Equations (I)[27]; (II)[23]; (III)[28]; (IV)[3a]

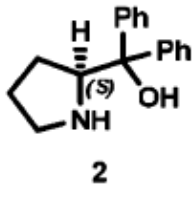
Scheme 5

Reference Key for Equations: (V)[23]; (VI)[23]; (VII)[29]; (VIII)[30]

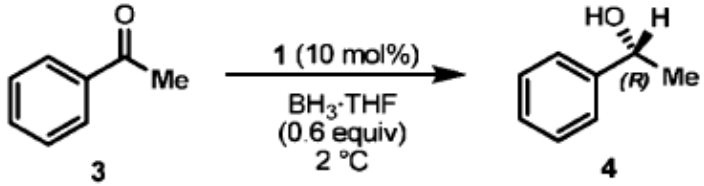
Background: Catalytic Enantioselective Reduction of Prochiral Ketones by Boranes

Chiral B-substituted oxazaborolidines such as 1, derived from diphenylprolinol (2, 1,1-diphenylpyrrolidinomethanol), are very useful as catalysts for the enantioselective synthesis of chiral secondary alcohols from ketones using various boranes as the stoichiometric reductant.[1]

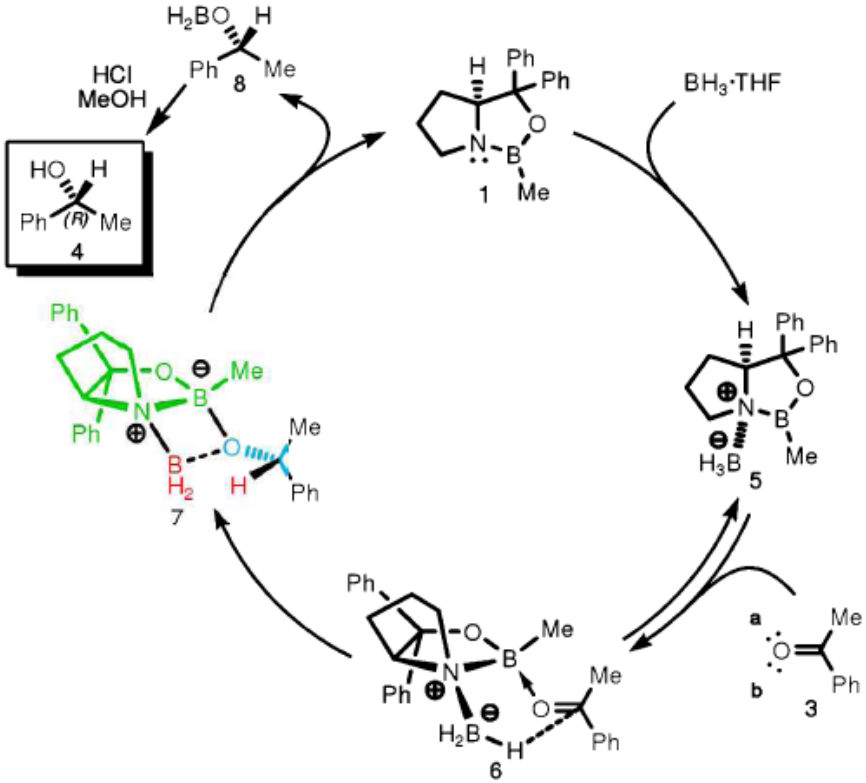

1


2

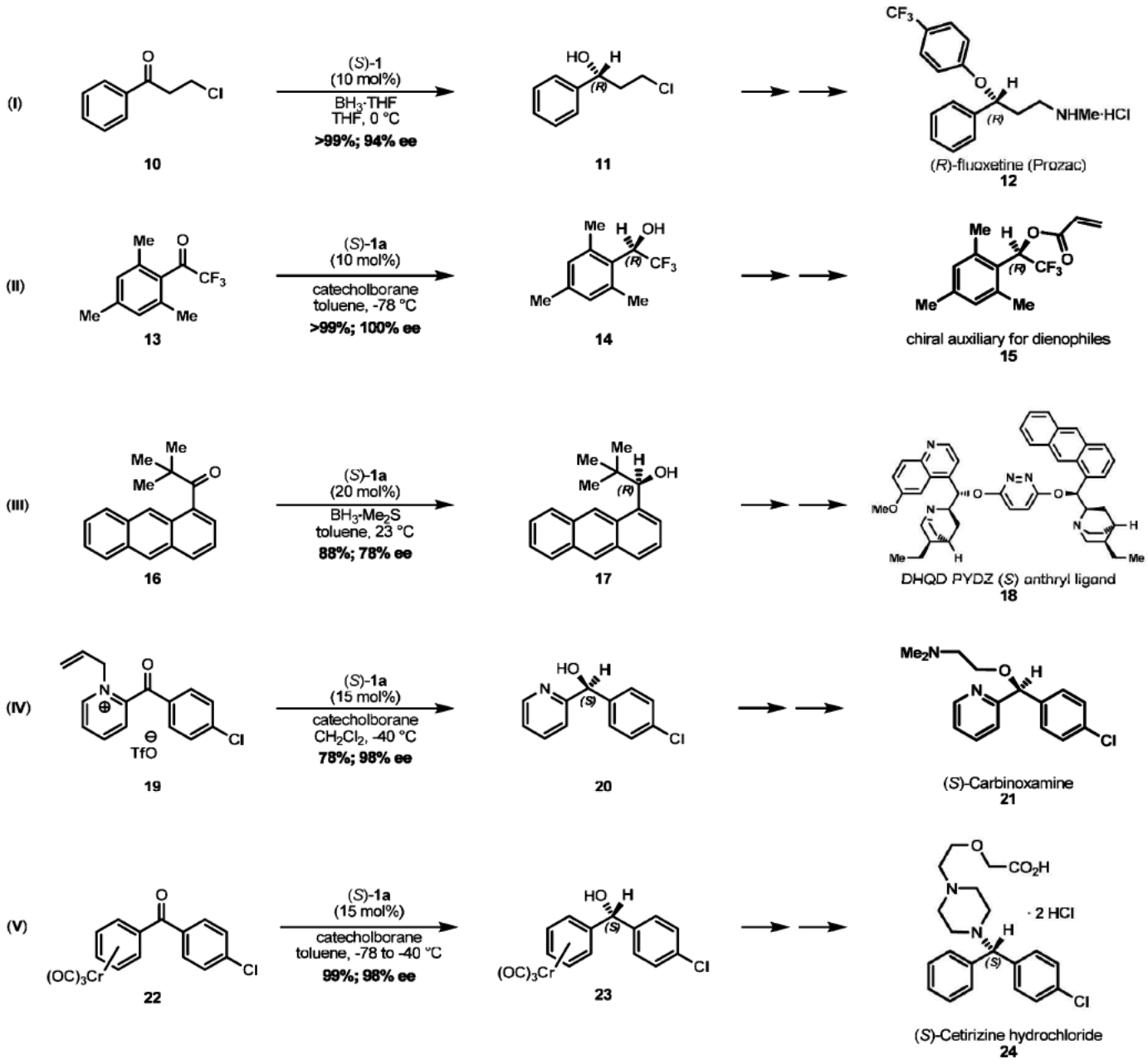
The reduction of acetophenone (3) by the borane-tetrahydrofuran complex (BH_3·THF, 0.6 equiv) in the presence of 10 mol% of 1 in THF at 2 °C to form (*R*)-1-phenylethanol (4) in 99% yield and 96.5% enantiomeric purity represents a simple and typical example of the general method.[2]



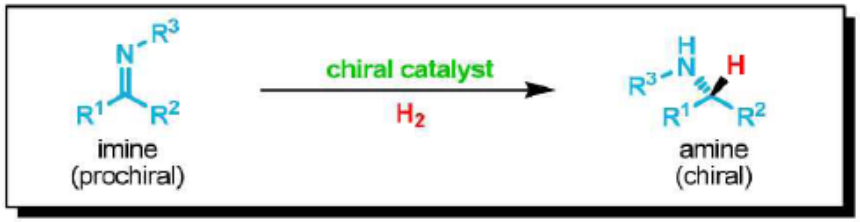
3 4


Scheme 1

Enantioselective Reduction of Prochiral Ketones by the CBS Method



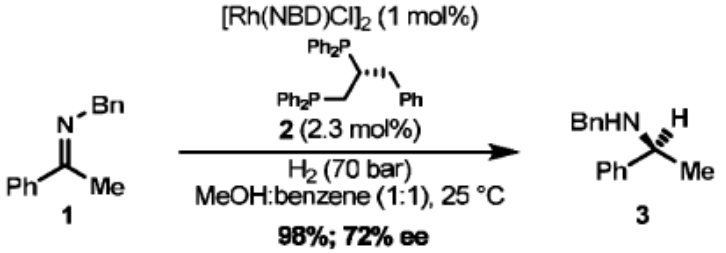
Background: Highly Enantioselective Homogeneous Hydrogenation of Imines



The enantioselective catalytic hydrogenation of imines to chiral amines provides a route to many useful intermediates, pharmaceuticals and agrochemicals.[1] There are fewer effective catalysts for this transformation than for the enantioselective reduction of C=O because of the following problems: (a) stronger coordination of the transition metal to the unshared electron than to the C=N π-bond resulting in low catalytic activity/turnover; (b) frequent problems in preparing pure (*E*) and (*Z*) imines; (c) hydrolytic instability of the imine substrate and (d) requirement for H_2 at elevated pressure.

An early and modestly enantioselective catalytic reduction of an imine by hydrosilylation, using a chiral Rh(I) complex was reported by H. Kagan in 1973.[2]

Subsequent to Kagan's report, a large number of Ru-, Ir- and Rh-chiral bisphosphine complexes have been examined for imine hydrogenation. Various additives (e.g., TBAI, KI, I_2) have been found to influence enantioselectivity.[1b]



An effective catalytic homogeneous hydrogenation of imines (e.g., 1→3) was demonstrated by Markó et al.[3] However, it was not until the late 1990s that highly effective chiral catalysts emerged for this transformation using either hydrogen gas or various hydrogen donors such as 2-propanol or triethylammonium formate.[1k,1n,1p]

Common Imine Substrates

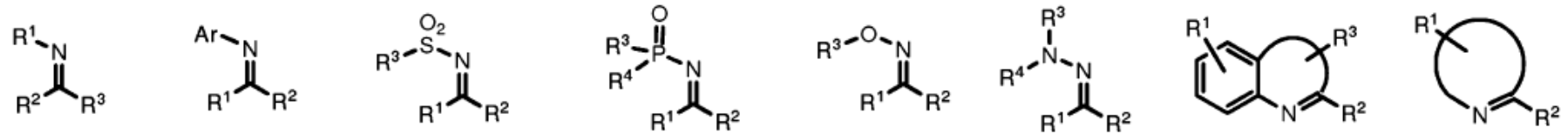
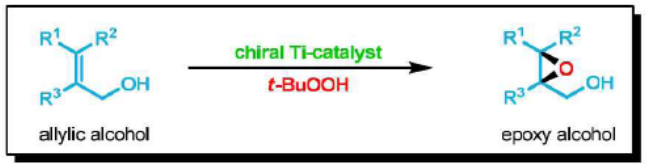


Figure 1

ENANTIOSELECTIVE EPOXIDATION OF C=C

Katsuki-Sharpless Epoxidation



In 1980, T. Katsuki and K.B. Sharpless made the surprising discovery that allylic alcohols undergo enantioselective epoxidation in the presence of $Ti(Oi\text{-}Pr)_4$, diethyl tartrate (1) or diisopropyl tartrate (2) and *tert*-butylhydroperoxide (3) (Figure 1).[1] Later, they reported that the inclusion of 4 Å molecular sieves allows the use of *substoichiomeric* amounts of $Ti(Oi\text{-}Pr)_4$ and tartrate ester when dry *t*-BuOOH is used. This process (Katsuki-Sharpless epoxidation) is now one of the most widely used catalytic asymmetric oxidations in organic synthesis.[2] The 2,3-epoxy alcohols produced by it are valuable chiral building blocks and have been used extensively in the preparation of pharmaceutical intermediates and in the synthesis of many complex natural products.[3]

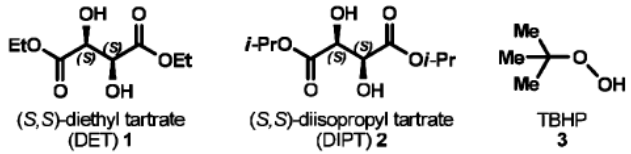


Figure 1

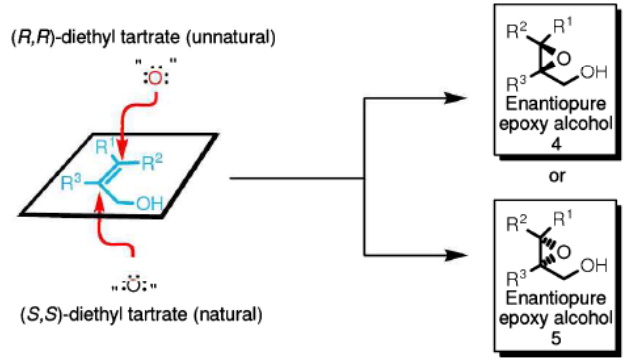


Figure 2

Allylic alcohols are the most favorable substrates and presence of the hydroxyl group is essential. The reaction proceeds enantioselectively with virtually any substitution pattern on C=C. The stereochemistry is reagent-controlled and either enantiomeric 2,3-epoxy alcohol (4 or 5) can be obtained by use of the appropriate tartrate ester (*S,S* or *R,R*). The enantiofacial selectivity of the reaction may be predicted using the diagram shown in Figure 2.

The Katsuki-Sharpless epoxidation has also been applied to the kinetic resolution of racemic secondary allylic alcohols and to the desymmetrization of meso bis-allylic alcohols.[4] Labile epoxides have been utilized for further transformation without isolation.[5] There are also examples of successful enantioselective epoxidation with homoallylic, bis-homoallylic and tris-homoallylic alcohols.[6]

The detailed mechanism remains uncertain despite experimental[7] and theoretical [8] studies. Two pathways have been proposed, one via the dimeric structure (B, Figure 3) and the other involving a zwitterionic titanium species (A, Figure 3).[8a]

In contrast to the Katsuki-Sharpless epoxidation, which must be carried out under anhydrous conditions because the reaction is inhibited by water, there is a water-tolerant catalytic system for the enantioselective epoxidation of allylic alcohols based on vanadium complexes of type C.[9]

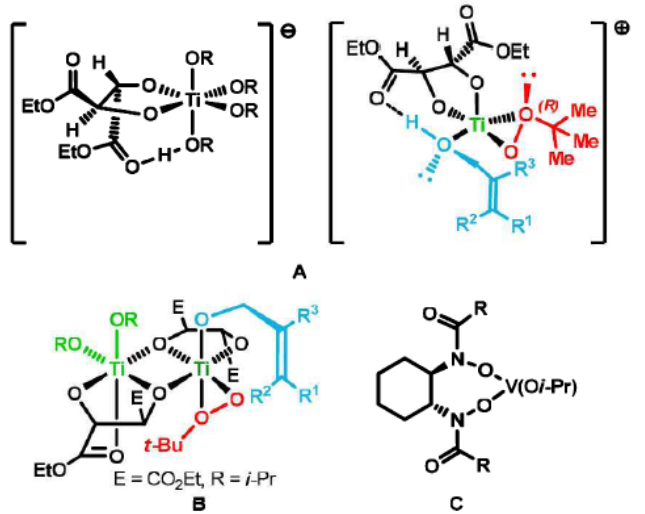
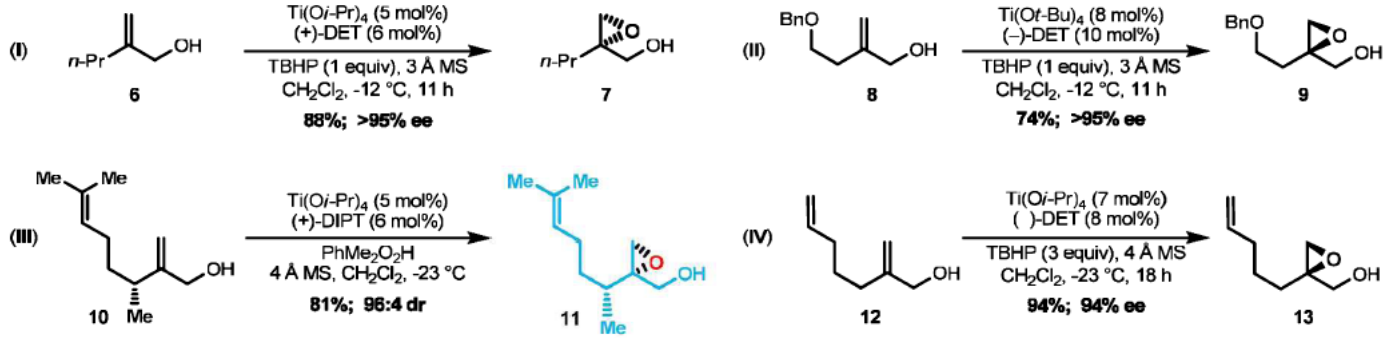


Figure 3

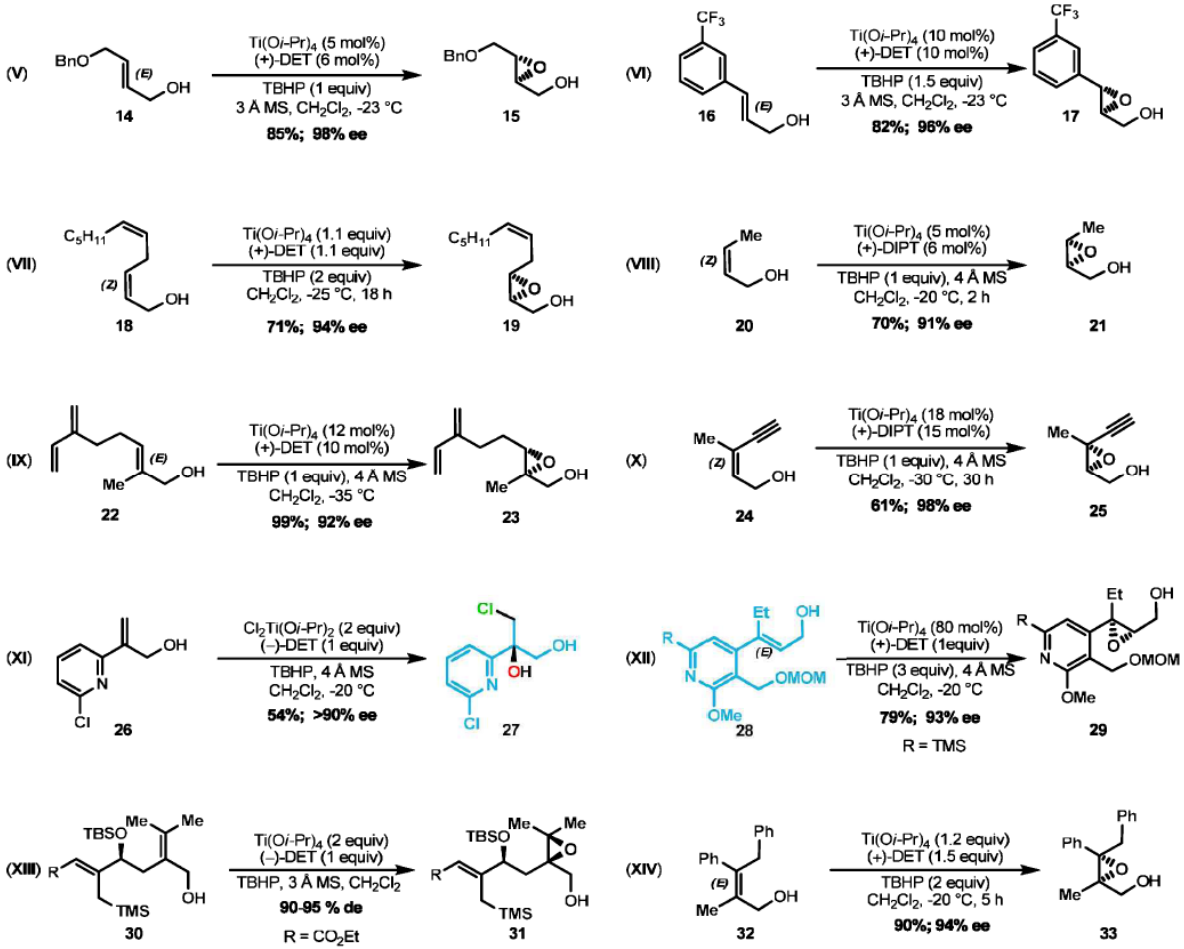
Asymmetric Epoxidation of Structurally Diverse Allylic Alcohols



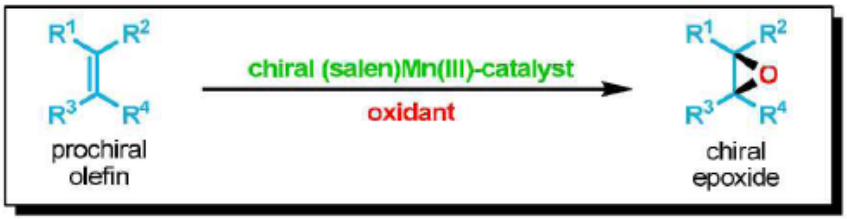
Reference Key for Equations: (I)[10]; (II)[11]

Scheme 1

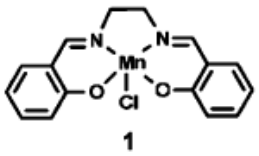
Reference Key for Equations: (III)[12]; (IV)[13]



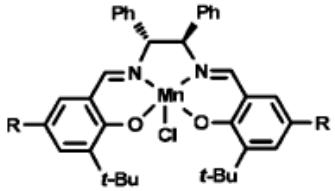
Jacobsen (salen)Mn(III)-Catalyzed Oxidation of Unfunctionalized Olefins



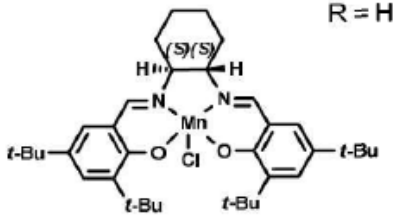
Kochi's report[1] in 1986 that the (salen)Mn(III) complex[2] 1 catalyzes the efficient epoxidation of olefins by iodosyl benzene (PhIO) led to Jacobsen's finding in 1990[3] that this reaction is fairly enantioselective (33-93% ee) if the ethylenediamine part of the ligand is replaced by (*S,S*)- or (*R,R*)-1,2-diphenyldiaminoethane, *and* if the positions *ortho* to the phenolic hydroxyl carry a bulky group, as in the (*R,R*)-complex 2 (Figure 1).[4] Further improvements included the use of the related catalyst 3, and NaOCl as the terminal oxidant.[5]



1



R = H (**2**); R = OTIPS (**3**)
R = Me (**4**)



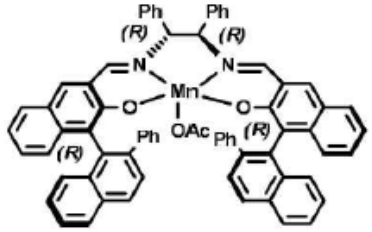
(*S,S*)-**5**

Figure 1

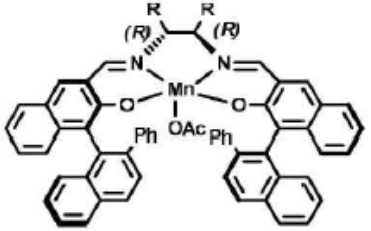
A similar catalyst system was developed by Katsuki and coworkers (Figure 2).[6] The most widely used catalysts are 3 and 5 which are commercially available (Figure 1).[7]

The Jacobsen epoxidation has been applied to the enantioselective epoxidation of mono-, di-, tri- and tetrasubstituted olefins and to unsymmetrical (*Z*)-disubstituted olefins with good results.[8] However, the epoxidation of (*E*)-disubstituted alkenes is usually only poorly enantioselective.

The Jacobsen epoxidation takes place with higher yield and enantioselectivity if the olefinic bond is conjugated with a π-system. The rate of the epoxidation, the yield and the enantioselectivity can be affected by the use of various additives, for example pyridine *N*-oxide, which may imply that a hexacoordinate oxomanganese(V) species is the effective epoxidation reagent, possibly with C_2-symmetric, canted, non-planar six-membered chelate rings.[8] The geometric details of the pre-transition state assembly and the basis of enantioselectivity have been analyzed (see page 167 for pathway).[9] Twelve examples of the Jacobsen epoxidation are shown in Schemes 1 and 2. Entries VII-X in Scheme 2 illustrate the formation of a *trans* epoxide from a *cis*-double bond. These cases show that the Jacobsen epoxidation can occur by a 2-step pathway with intervening C-C bond rotation. The 2-step process is also favored by the use of certain chiral quaternary ammonium halides.[11c]



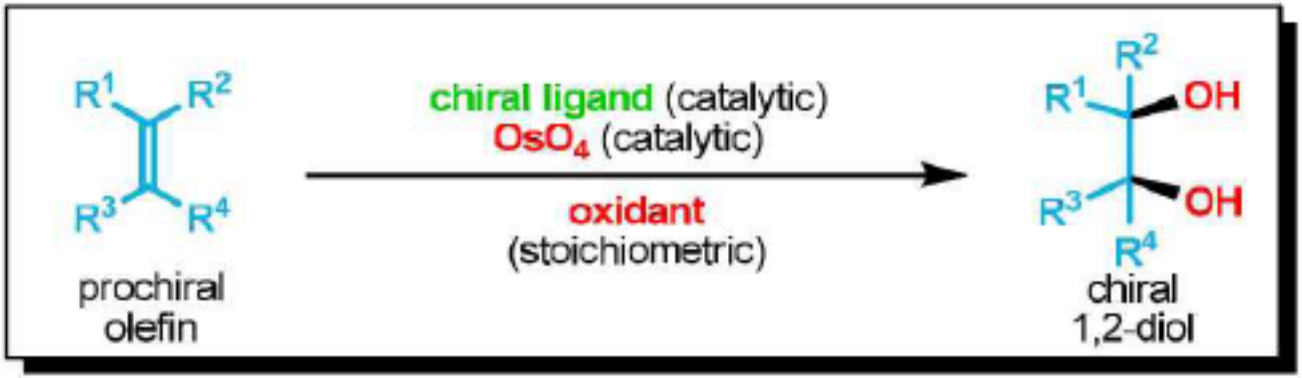
6 (all *R*)



R = 3,5-di-MeC_6H_3 (**7**)

Figure 2

Sharpless Asymmetric Dihydroxylation of Unfunctionalized Olefins



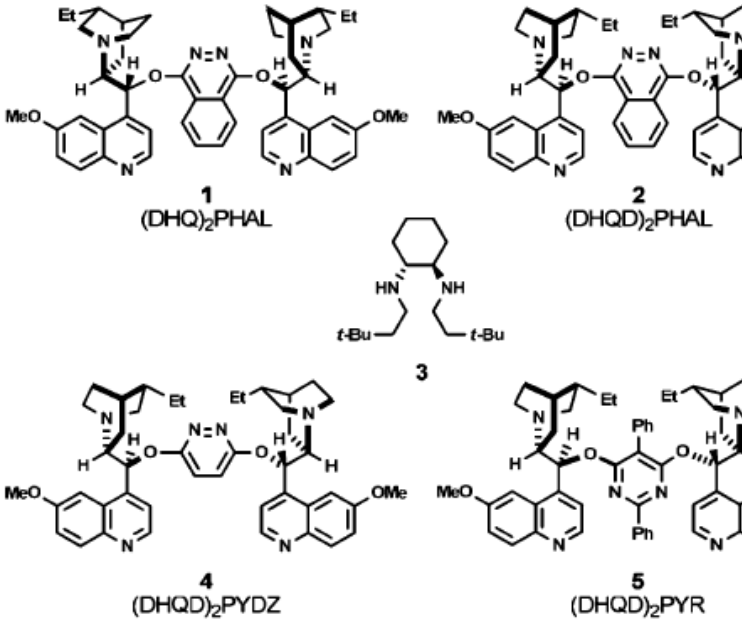
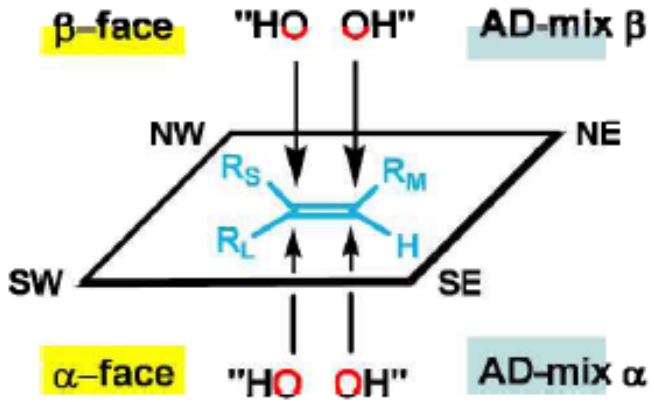


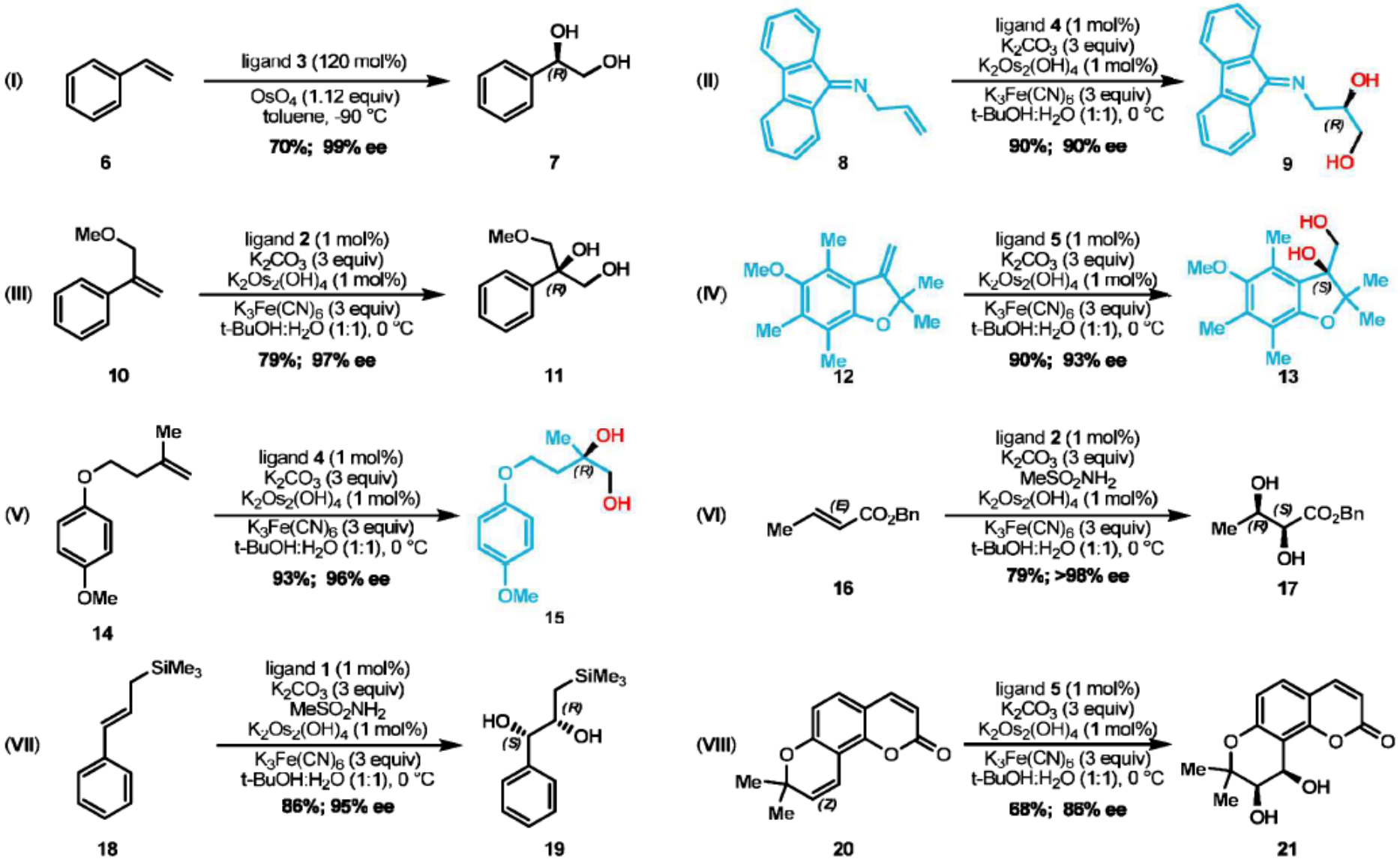
Figure 1



AD-mix α: $(DHQ)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

AD-mix β: $(DHQD)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

Asymmetric Dihydroxylation of Structurally Diverse Alkenes



Reference Key for Equations: (I)[6]; (II)[5b]; (III)[7]; (IV)[8]

Scheme 4

Reference Key for Equations: (V)[9]; (VI)[10]; (VII)[11]; (VIII)[12]