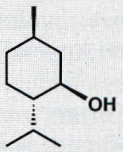


1: menthol

22

Takasago (1984)

Menthol

22.1 Introduction

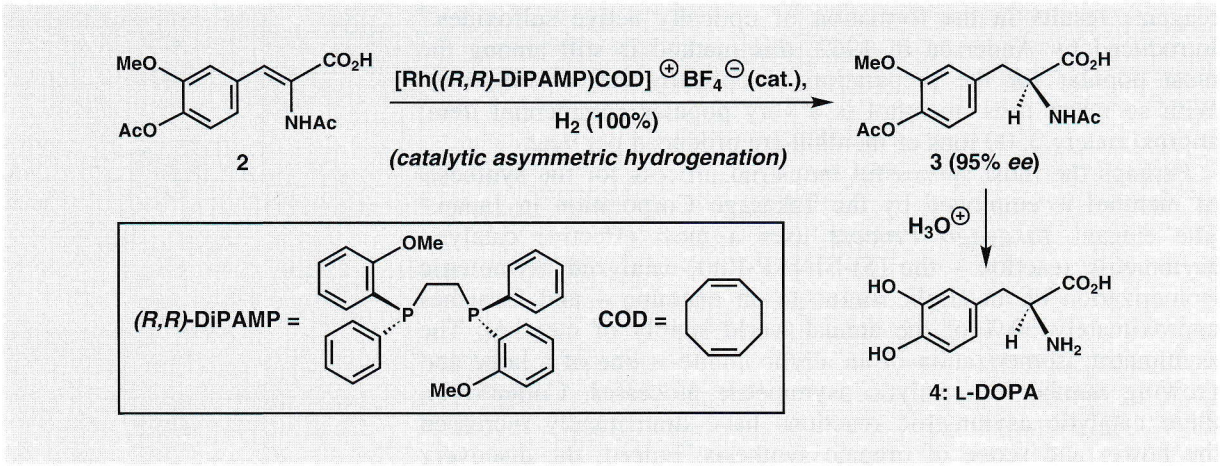
Menthol (**1**), a major constituent of peppermint and other mint oils, is a widely utilized terpene, finding use in confectionery, perfumery, liqueurs, cough drops, cigarettes, toothpaste, and nasal inhalers. In organic synthesis, this naturally occurring substance is a convenient source of chirality, serving as a chiral auxiliary for several asymmetric reactions.[1] Menthol can also be used to esterify racemic carboxylic acids;[2] after separation of the resulting diastereomeric mixture of menthol esters, a simple ester hydrolysis step can provide both enantiomers of the carboxylic acid in enantiomerically pure form. In another important process, reaction of diastereomerically pure sulfinate esters of menthol with organometallic reagents results in the formation of optically active sulfoxides.[3] Introduced by Andersen in 1962, this method is still among the most popular for the preparation of optically active sulfoxides. With so many uses, menthol is a very popular commercial item; approximately 3500 tons of menthol are produced per year.

Perhaps the most successful industrial process for the synthesis of menthol is employed by the Takasago Corporation in Japan.[4] The elegant *Takasago Process* uses a most effective catalytic asymmetric reaction – the (*S*)-BINAP-Rh(I)-catalyzed asymmetric isomerization of an allylic amine to an enamine – and furnishes approximately 30% of the annual world supply of menthol. The asymmetric isomerization of an allylic amine is one of a large and growing number of catalytic asymmetric processes. Collectively, these catalytic asymmetric reactions have dramatically increased the power and scope of organic synthesis. Indeed, the discovery that certain chiral transition metal catalysts can dictate the stereo-

chemical course of fundamental reactions such as hydrogenations, isomerizations, epoxidations, dihydroxylations, cyclopropanations, and aziridinations of alkenes, carbonyl reductions, carbonyl additions, aldol condensations, and pericyclic reactions has revolutionalized organic synthesis (see Schemes A1–A18 in the Appendix to this chapter for representative examples and references).[5–55]

In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral. In recent years, synthetic chemists have developed numerous catalytic asymmetric reaction processes that transform prochiral substrates into chiral products with impressive margins of enantioselectivity, feats that were once the exclusive domain of enzymes.[56] These developments have had an enormous impact on academic and industrial organic synthesis. In the pharmaceutical industry, where there is a great emphasis on the production of enantiomerically pure compounds, effective catalytic asymmetric reactions are particularly valuable because one molecule of an enantiomerically pure catalyst can, in principle, direct the stereoselective formation of millions of chiral product molecules. Such reactions are thus highly productive and economical, and, when applicable, they make the wasteful practice of racemate resolution obsolete.

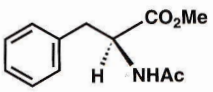
An early success story in the field of catalytic asymmetric synthesis is the *Monsanto Process* for the commercial synthesis of L-DOPA (**4**) (see Scheme 1), a rare amino acid that is effective in the treatment of Parkinson's disease.[57] The *Monsanto Process*, the first commercialized catalytic asymmetric synthesis employing a chiral transition metal complex, was introduced by W. S. Knowles and coworkers and has been in operation since 1974. This large-scale process for the synthesis of L-DOPA (**4**) is based on catalytic asymmetric hydrogenation, and its development can be



Scheme 1: The Monsanto synthesis of L-DOPA (**4**) using catalytic asymmetric hydrogenation.

traced to Wilkinson's pioneering discovery of the homogeneous hydrogenation catalyst, tris(triphenylphosphine)rhodium chloride [$(Ph_3P)_3RhCl$], in 1966.[58] Wilkinson's catalyst is a soluble transition metal complex that catalyzes the hydrogenation of unhindered olefins with rates that compare favorably to those obtained with the familiar heterogeneous catalysts. Soon after this important discovery, several groups, including the Monsanto group, demonstrated that replacement of the achiral triphenylphosphine ligands of Wilkinson's catalyst with chiral phosphines afforded optically active hydrogenation catalysts that could effect enantioselective olefin hydrogenations, albeit with rather low enantiomeric excesses. Nonetheless, during the course of this work, Knowles and coworkers at Monsanto discovered that a cationic rhodium complex bearing DiPAMP (see Scheme 1), a chelating diphosphine with two chiral phosphorus atoms, can catalyze highly enantioselective hydrogenations of enamides such as **2**. Enamides are, in fact, exceptional substrates for catalytic asymmetric hydrogenation. In the key step of the synthesis of L-DOPA by Monsanto, enamide **2** is hydrogenated in the presence of a catalytic amount of [Rh((*R,R*)-DiPAMP)COD]$^+BF_4^-$ affording protected amino acid **3** in quantitative yield and in 95% *ee*. A simple acid-catalyzed hydrolysis step completes the synthesis of L-DOPA (**4**).

The spectacular success of the commercial L-DOPA synthesis by Monsanto has significantly contributed to the explosive growth of research aimed at the development and application of other catalytic asymmetric reactions in ensuing years. Since the introduction of the *Monsanto Process* in the early seventies, several other commercial syntheses based on powerful catalytic asymmetric reactions have emerged as a result of a productive interplay between academic and industrial research. For example, the acetamide of (*S*)-phenylalanine methyl ester (**6**) (see Scheme 2) is available in bulk by a two-step reaction sequence that features a Rh-catalyzed enantioselective hydrogenation of enamide **5**. The key asymmetric hydrogenation step is conducted in ethanol at a substrate:catalyst ratio of 15000:1. Although the enantiomeric excess for the hydrogenation step is only 83%, a simple recrystallization of amino ester **6** raises the enantiomeric purity to 97%. The acetamide of (*S*)-phenylalanine methyl ester (**6**) is a key intermediate in the commercial synthesis of the non-nutritive sweetener aspartame (**7**) by Anic and Enichem.[4b,5r]



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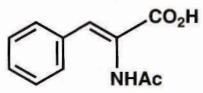

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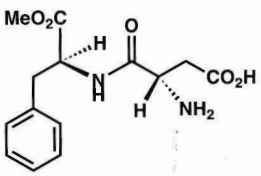
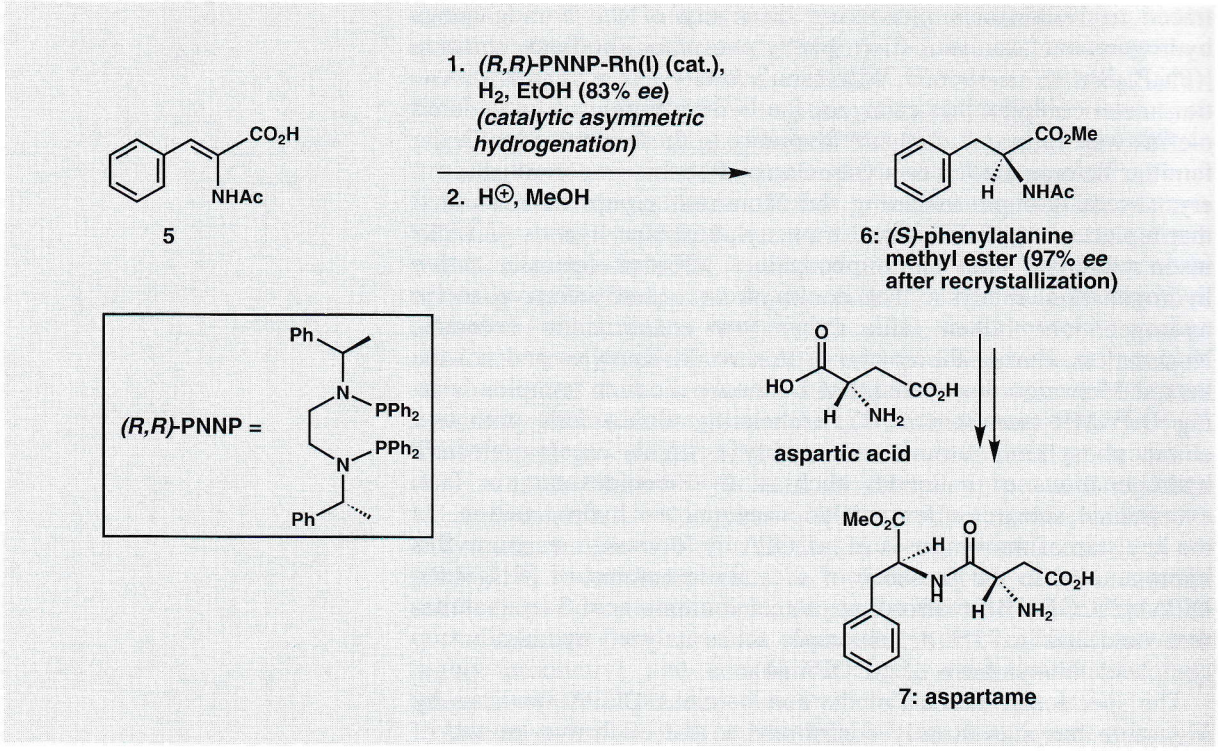


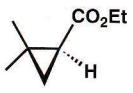
7: aspartame

The emergence of the powerful Sharpless asymmetric epoxidation (SAE) reaction in the 1980s has stimulated major advances in both academic and industrial organic synthesis.[14] Through the action of an enantiomerically pure titanium/tartrate complex, a myriad of achiral and chiral allylic alcohols can be epoxidized with exceptional stereoselectivities (see Chapter 19 for a more detailed discussion). Interest in the SAE as a tool for industrial organic synthesis grew substantially after Sharpless *et al.* discovered that the asymmetric epoxidation process can be conducted with catalytic amounts of the enantiomerically pure titanium/tartrate complex simply by adding molecular sieves to the epoxidation reaction mix-



Scheme 2. Anic and Enichem's commercial synthesis of aspartame (**7**) using catalytic asymmetric hydrogenation.

ture.[59] Using this practical and reproducible catalytic variant, the ARCO chemical company developed an industrial process for ton-scale productions of (*S*)- and (*R*)-glycidol (see **8** and **9**, Scheme 3) and (*S*)- and (*R*)-methylglycidol (see **10** and **11**, Scheme 3). These low molecular weight epoxy alcohols are versatile building blocks for the syntheses of a number of chiral molecules.[60] It has been reported[4b] that the commercial production of optically active glycidols in this manner is more viable financially than the competitive route to glycidols based on the porcine pancreatic lipase catalyzed hydrolysis of glycidyl butyrate.[61] In another successful industrial application of the SAE, the J.T. Baker Company adapted Sharpless's synthesis of (7*R*,8*S*)-disparlure (**15**)[62] (see **12** → **13** → **14** → **15**, Scheme 4), the pheromone of the gypsy moth, to the commercial production of this valuable compound.



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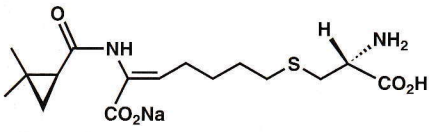
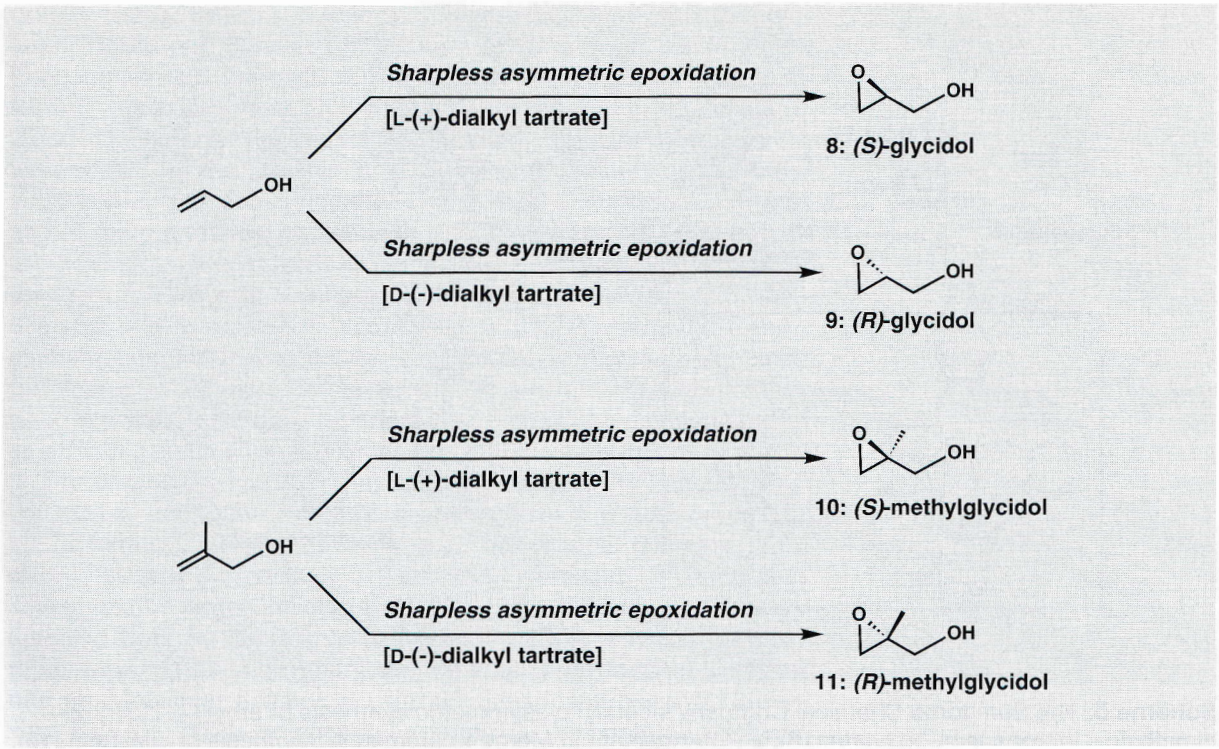
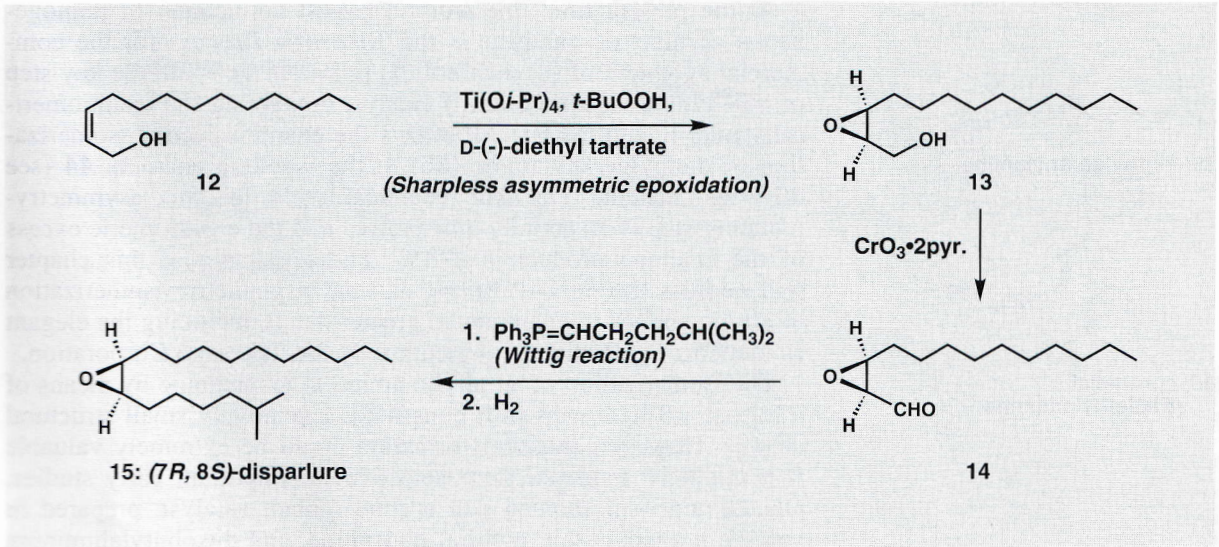


19: cilastatin (MK-0791)

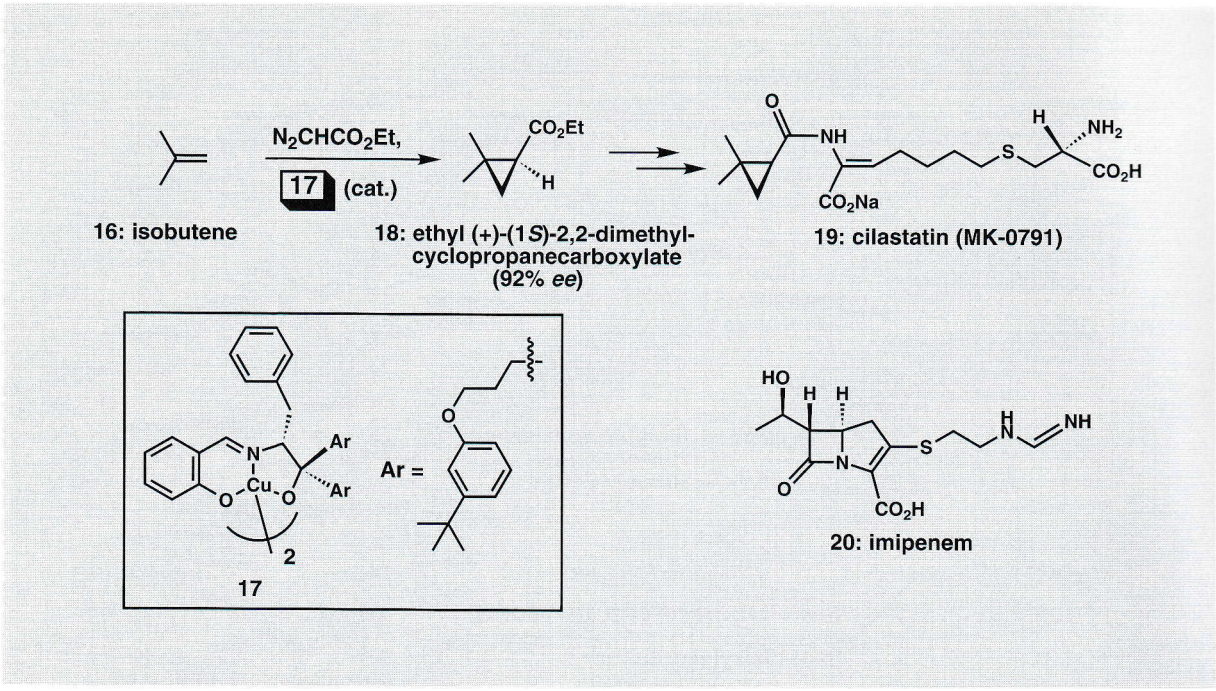
The catalytic asymmetric cyclopropanation of an alkene, a reaction which was studied as early as 1966 by Nozaki and Noyori,[63] is used in a commercial synthesis of ethyl (+)-(1*S*)-2,2-dimethylcyclopropanecarboxylate (**18**) by the Sumitomo Chemical Company (see Scheme 5).[64] In Aratani's *Sumitomo Process*, ethyl diazoacetate is decomposed in the presence of isobutene (**16**) and a catalytic amount of the dimeric chiral copper complex **17**. Compound **18**, produced in 92% *ee*, is a key intermediate in Merck's commercial synthesis of cilastatin (**19**). The latter compound is a reversible



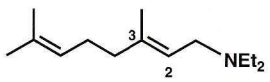
Scheme 3. The ARCO Chemical Company's commercial synthesis of the glycidols using the Sharpless asymmetric epoxidation reaction.



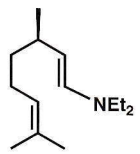
Scheme 4. The Sharpless asymmetric epoxidation in the J. T. Baker Company's commercial synthesis of (7*R*,8*S*)-disparlure (**15**).



Scheme 5. The Sumitomo Chemical Company's catalytic asymmetric synthesis of ethyl (+)-(1*S*)-2,2-dimethylcyclopropanecarboxylate (**18**), an intermediate in Merck's commercial synthesis of cilastatin (**19**).



35: diethylgeranylamine



44: citronellal *(E)*-diethylenamine

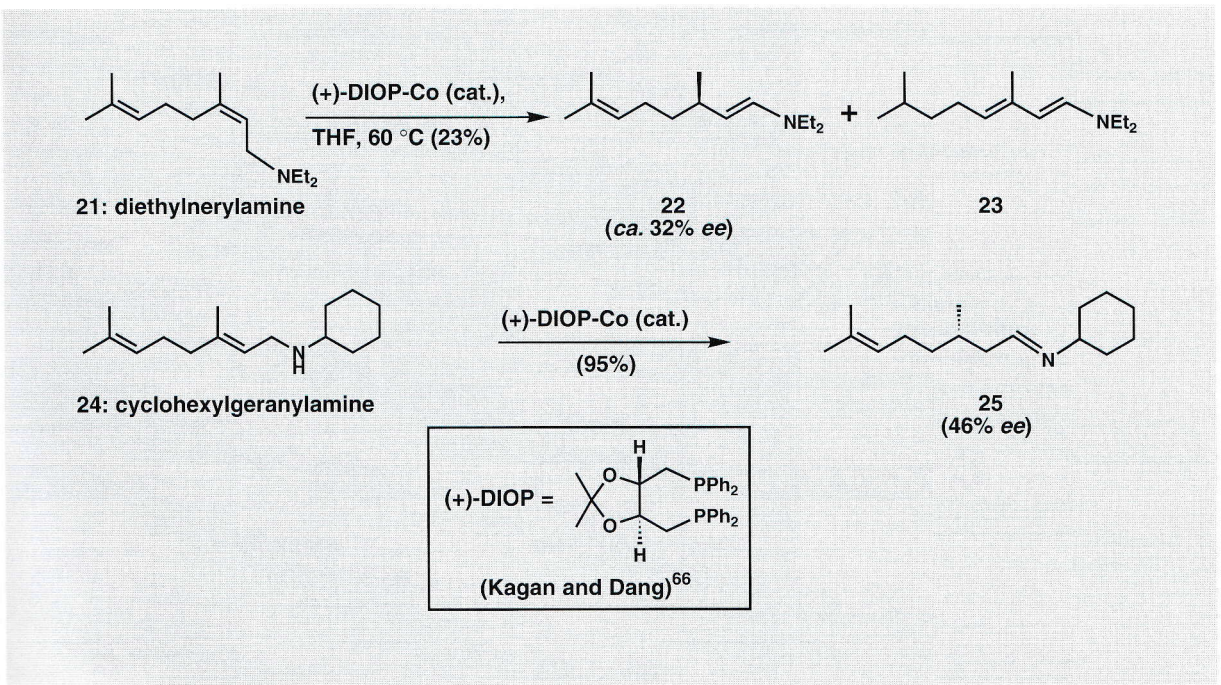
inhibitor of the renal enzyme dehydropeptidase I and serves as an *in vivo* stabilizer of the β-lactam antibiotic, imipenem (**20**, Scheme 5); a combination of cilastatin (**19**) and imipenem (**20**) is a successful pharmaceutical marketed by Merck.

At the present time, the world's largest application of homogeneous asymmetric catalysis is the *Takasago Process* for the commercial synthesis of (–)-menthol (**1**) (*vide infra*).[4,5d] In the key step of this synthesis, a rhodium(I) catalyst containing the enantiomerically pure ligand (*S*)-BINAP effects the enantioselective isomerization of diethylgeranylamine (**35**) to the isomeric enamine **44** (see **35** → **44**, Scheme 12). The chemical yield for this asymmetry-inducing step is essentially quantitative and the enantiomeric excess of the enamine product is ≥98 %. The remainder of this chapter will address the BINAP-Rh(I)-catalyzed asymmetric isomerization of allylic amines to enamines in greater detail, including the elegant asymmetric synthesis of (–)-menthol by the Takasago Corporation.

The isomerization of an allylic amine to an enamine by means of a formal 1,3-hydrogen shift constitutes a relatively small structural change. However, this transformation could be extremely valuable if it could be rendered stereoselective. In important early studies, Otsuka and Tani showed that a chiral cobalt catalyst, prepared *in situ* from a Co(II) salt, a chiral phosphine, and diisobutylaluminum hydride (Dibal-H), can bring about the conversion of certain prochiral olefins to chiral, isomeric olefins by double bond migra-

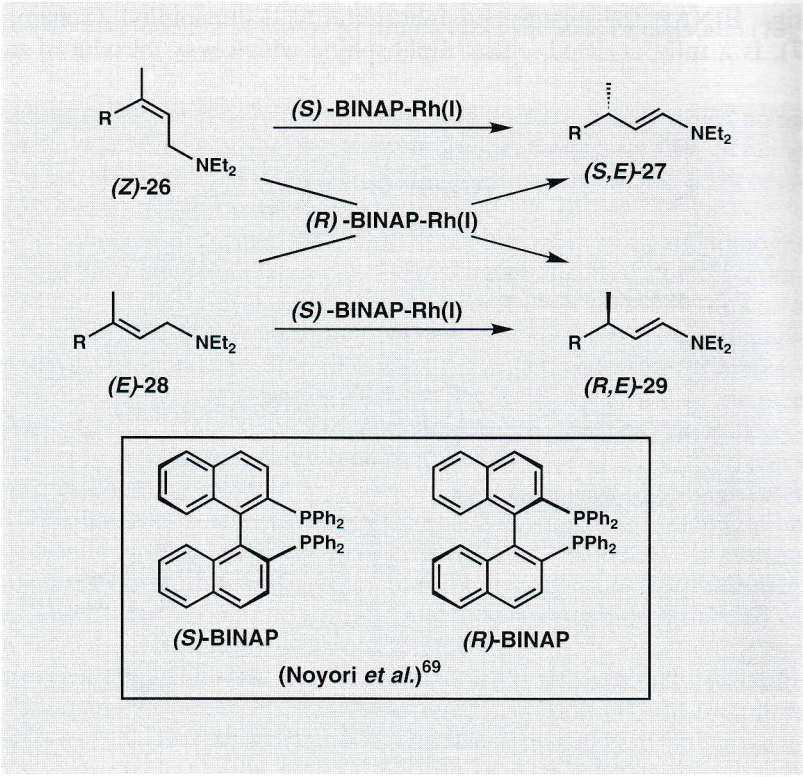
tion.[65] Using Kagan's historically significant C_2-symmetric (+)-DIOP ligand (see Scheme 6),[66] Otsuka *et al.* prepared a (+)-DIOP–Co complex and demonstrated its ability to catalyze an enantioselective isomerization of diethylnerylamine (**21**) to the (*R*)-enamine **22** in *ca.* 32 % *ee* but in only 23 % yield. This transformation is undermined by the production of significant amounts of the undesired conjugated dienamine **23**. Under milder reaction conditions and in the presence of the same (+)-DIOP–Co catalyst, the secondary amine, cyclohexylgeranylamine (**24**) undergoes conversion to the (*S*)-imine **25** with an improved 46 % *ee* and in 95 % yield. Incidentally, when secondary amines are used, the initially formed enamine tautomerizes to the more stable imine. Although the enantioselectivities of these two processes are too low to be of practical use, they represented an important first step in the development of an efficient asymmetric allylic amine isomerization process.

The disclosure, in 1982, that cationic, enantiopure BINAP–Rh(I) complexes can induce highly enantioselective isomerizations of allylic amines in THF or acetone, at or below room temperature, to afford optically active enamines in >95 % yield and >95 % *ee*, thus constituted a major breakthrough.[67,68] This important discovery emerged from an impressive collaborative effort between chemists representing Osaka University, the Takasago Corporation, the Institute for Molecular Science at Okazaki, Japan, and Nagoya University. BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (Scheme 7), is a fully arylated, chiral diphosphine which was introduced in



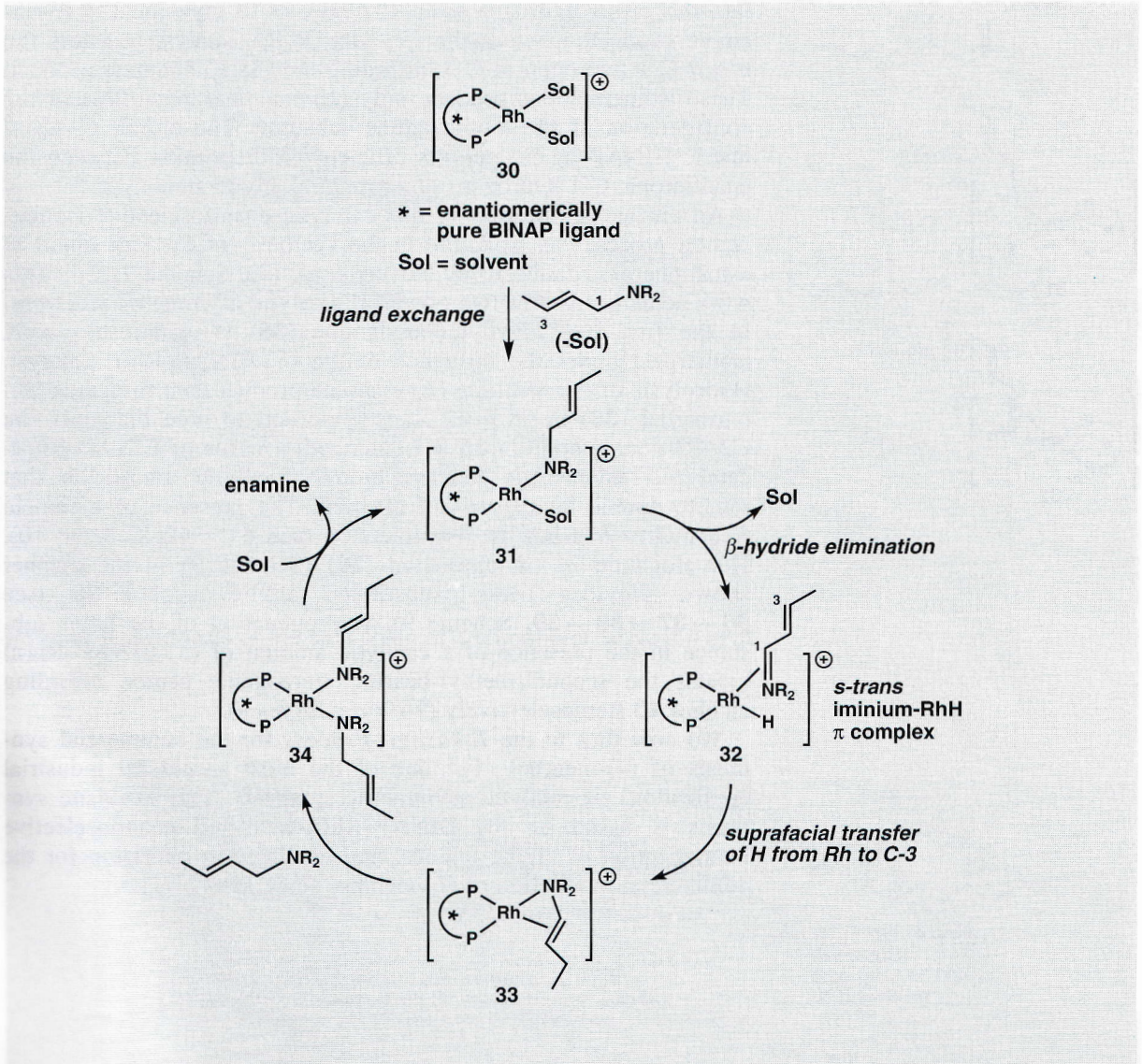
Scheme 6. Otsuka and Tani's (+)-DIOP–Co-catalyzed asymmetric isomerization of diethylnerylamine (**21**) and cyclohexylgeranylamine (**24**).

1980 by Noyori and his colleagues at Nagoya University.[69] BINAP is a very effective chelating diphosphine chiral ligand for numerous transition metals and is available in both (*R*) and (*S*) enantiomeric forms. In the BINAP–Rh(I)-catalyzed asymmetric isomerization of allylic amines, there is an interesting correlation between the chirality of the BINAP ligand, the configuration of the starting allylic amine (i.e. *E* or *Z*), and the configuration at C-3 in the (*E*)-enamine product (see Scheme 7). For example, in the presence of the (*S*)-BINAP–Rh(I) catalyst, stereochemically pure samples of (*Z*)-allylic amine **26** and (*E*)-allylic amine **28** are isomerized to enantiomeric (*E*)-enamines; with the (*S*)-BINAP–Rh(I) catalyst, (*Z*)-allylic amine **26** is smoothly isomerized to (*S,E*)-enamine **27**, while the stereoisomeric (*E*)-allylic amine **28** is isomerized to (*R,E*)-enamine **29**. If one had access to a particular allylic amine stereoisomer, it would still be possible to obtain, at will, either enamine enantiomer simply by choosing the appropriate BINAP–Rh(I) complex. To obtain excellent enantioselectivities, it is therefore imperative that enantiomerically pure BINAP and configurationally uniform allylic amines be employed. The BINAP–Rh(I)-catalyzed asymmetric isomerization of an allylic amine is a *stereospecific* process, since there is a relationship between starting materials and product stereochemistries.

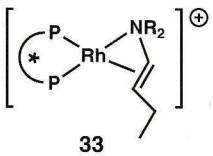


Scheme 7. Stereochemical outcome of BINAP–Rh(I)-catalyzed asymmetric isomerization of allylic amines.

The general picture illustrated in Scheme 7 indicates that an enantiopure BINAP–Rh(I) complex can efficiently recognize the enantiotopic hydrogens at C-1 or the enantiofaces of the $\Delta^{2,3}$ double bond. The mechanism of the BINAP–Rh(I)-catalyzed asymmetric isomerization of an allylic amine is shown in Scheme 8.[65,68c,70] This reaction commences with a simple ligand exchange between the bis-solvent complex **30** and the allylic amine substrate, generating the nitrogen-coordinated Rh^+ complex **31**. Loss of a solvent molecule from the square-planar complex **31** initiates a β-hydride elimination reaction to give the transient imi-



Scheme 8. Catalytic cycle for the BINAP–Rh(I)-catalyzed asymmetric isomerization of allylic amines.



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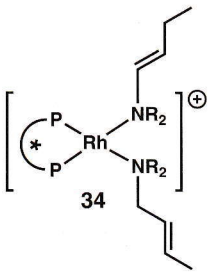

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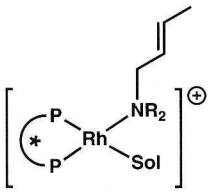

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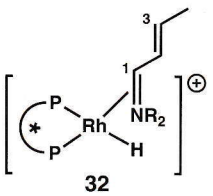

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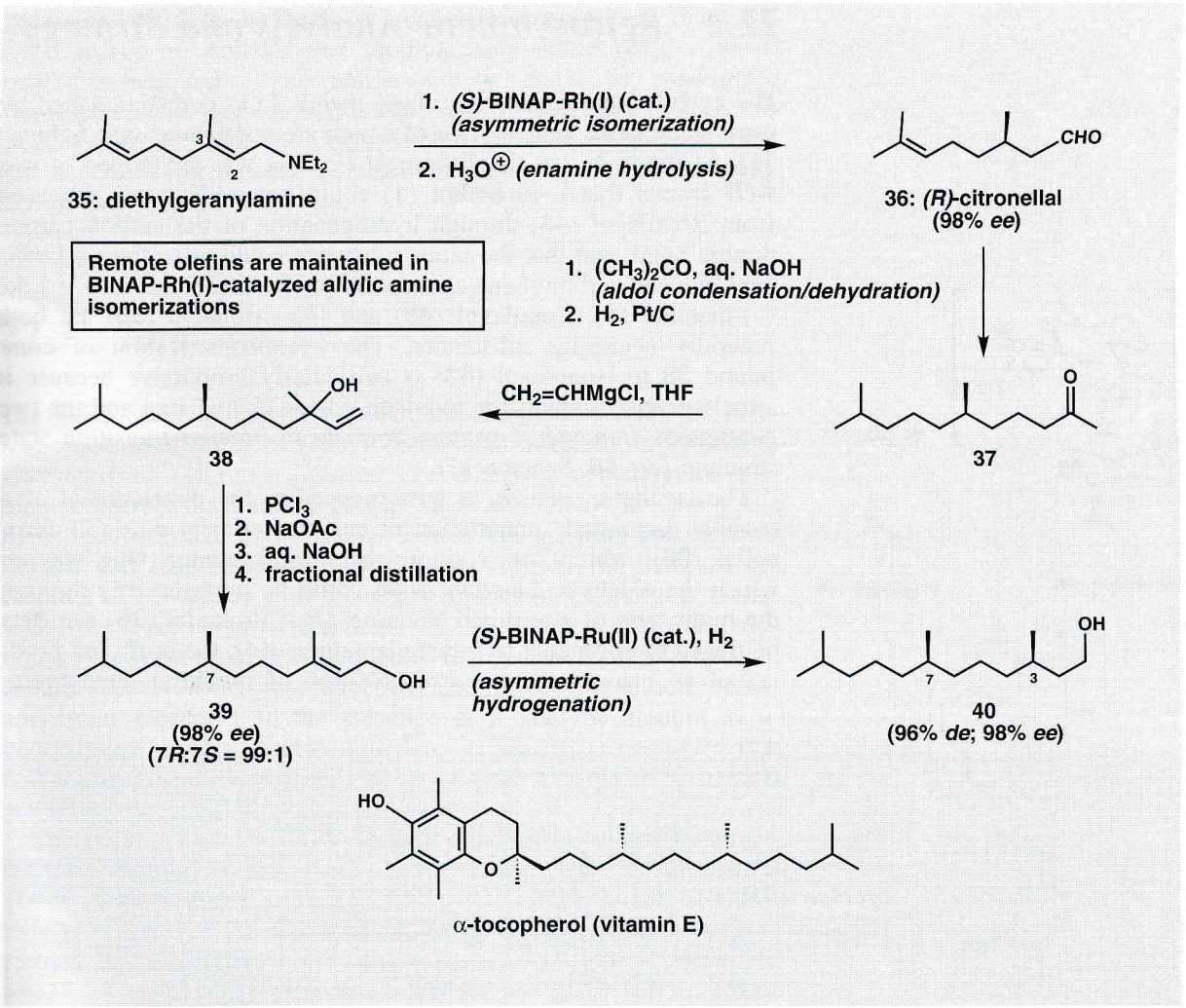
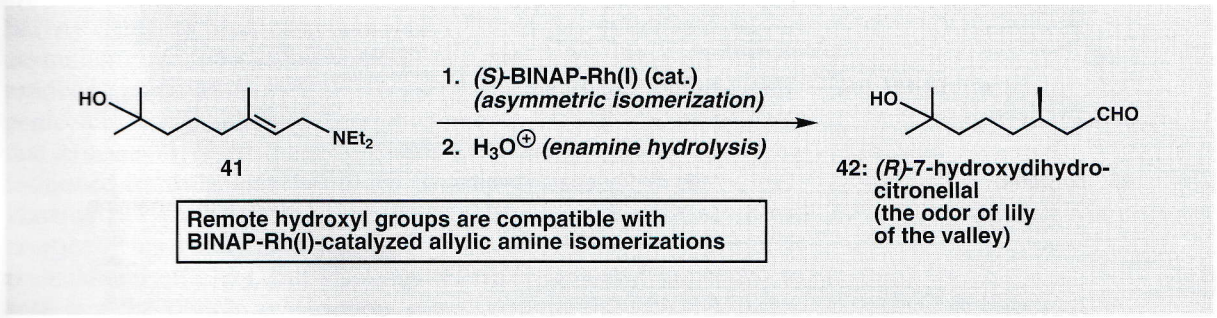
nium–RhH π complex **32**. A suprafacial delivery of the hydrogen atom from Rh to C-3 via an *s-trans* conformer then gives the η^3-enamine complex **33.** The aza–allyl type complex **33** can be isolated and characterized by NMR spectroscopy, and functions as the chain-carrying species; isolated **33** catalyzes the isomerization of the allylic amine substrate. The replacement of the enamine product in **33** with a new molecule of substrate is the rate-determining step and presumably occurs via the mixed substrate–product complex **34**. Liberation of the enamine product from the mixed-ligand complex **34** produces the reactive 14-electron species **31** and thence iminium–RhH complex **32** through *β*-hydride elimination, thereby completing the catalytic cycle. The (*S*)-BINAP–Rh catalyst transfers the *pro-S* hydrogen from C-1 to C-3 to give the (3*R*,*E*)-enamine product, whereas the (*R*)-BINAP–Rh catalyst transfers the *pro-R* C-1 hydrogen to C-3, affording the (3*S*,*E*)-enamine product. These isomerizations produce only (*E*)-enamines regardless of the configuration of the allylic amine substrate. The chiral, C_2-symmetric BINAP ligand permits efficient differentiation between the enantiotopic C-1 hydrogens of a prochiral allylic amine.

An elegant application of this catalytic enantioselective isomerization process can be found in the synthesis of the side chain of *α*-tocopherol (vitamin E) by Noyori *et al.* (see Scheme 9).[10,71] This work actually features two powerful catalytic asymmetric reactions. In the first step, diethylgeranylamine (**35**) is enantioselectively isomerized under the influence of the (*S*)-BINAP–Rh(I) catalyst. Hydrolysis of the resulting (*E*)-enamine product then furnishes (*R*)-citronellal (**36**) in 98 % *ee*. It is important to note that only the C2–C3 double bond in **35** is isomerized; a virtue of BINAP–Rh(I)-catalyzed asymmetric isomerizations of allylic amines is that remote double bonds are not affected. The presence of a remote free hydroxyl group is also tolerated (see **41** → **42**, Scheme 10). Homologation of (*R*)-citronellal (**36**) (Scheme 9) in the manner shown provides *trans*-trisubstituted allylic alcohol **39** (see **36** → **37** → **38** → **39**, Scheme 9). Hydrogenation of the latter substance in the presence of a catalytic amount of (*S*)-BINAP–Ru(II) creates the second methyl-bearing stereogenic center, affording alcohol **40** stereoselectively (96 % *de*; 98 % *ee*).

We now turn to the *Takasago Process* for the commercial synthesis of (–)-menthol (**1**),[4] one of the most successful industrial applications of catalytic asymmetric synthesis. This exquisite synthesis is based on the BINAP–Rh(I)-catalyzed enantioselective isomerization of allylic amines, and has been in operation for the commercial production of (–)-menthol since 1984.

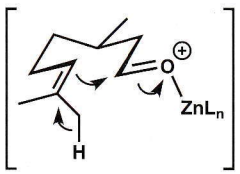


Scheme 9. Synthesis of the side chain of α-tocopherol by Noyori *et al.*



Scheme 10. Catalytic asymmetric synthesis of (*R*)-7-hydroxydihydrocitronellal (**42**).

22.2 Retrosynthetic Analysis and Strategy



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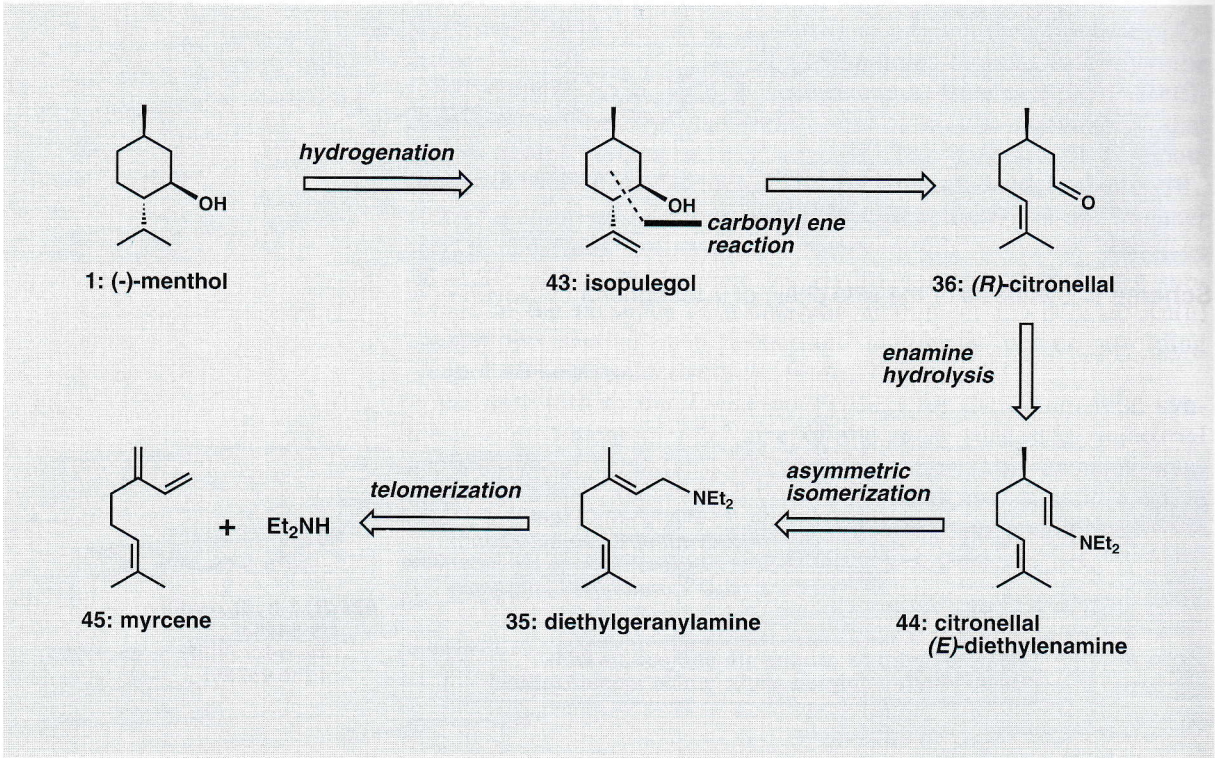
The cyclohexane framework of (–)-menthol (**1**) is distinguished by three stereogenic centers, two of which are contiguous (see Scheme 11). At the time that the *Takasago Process* was developed, it was well known that (–)-menthol (**1**) could be produced in one step from isopulegol (**43**) through hydrogenation of the carbon–carbon double bond, and that the latter substance could arise from a Lewis acid induced carbonyl ene cyclization of (*R*)-citronellal (**36**).[72] Like (–)-menthol (**1**), isopulegol (**43**) and (*R*)-citronellal (**36**) are both naturally occurring substances. The cycloisomerization of compound **36** to isopulegol (**43**) is particularly productive because it simultaneously creates the requisite six-membered ring and the two contiguous stereogenic centers through an ordered transition state structure (see **48**, Scheme 12).

The synthetic problem is now reduced to the development of a feasible, large-scale preparation of enantiomerically pure (*R*)-citronellal (**36**), which has a single stereogenic center. One way in which the aldehyde function in **36** could be introduced is through the hydrolysis of a terminal enamine. (*R*)-Citronellal (**36**) can thus be traced to citronellal (*E*)-diethylenamine (**44**), the projected product of an enantioselective isomerization of prochiral diethylgera-

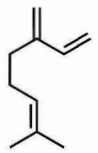


Scheme 11. Retrosynthetic analysis of menthol (**1**).

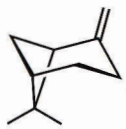
nylamine (**35**). On the basis of some known chemistry, there was good reason to believe that diethylgeranylamine (**35**), with its *trans*-trisubstituted allylic amine moiety, could be constructed stereoselectively from myrcene (**45**) and diethylamine. Using this elegant plan, the Takasago Corporation developed a highly practical and economically feasible commercial process based on catalytic asymmetric synthesis.

22.3 *Total Synthesis*

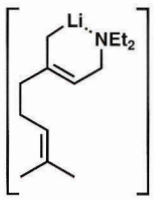
The Takasago synthesis of (–)-menthol commences with the thermal cracking of *β*-pinene (**46**), a constituent of cheap turpentine, to give myrcene (**45**) (see Scheme 12). Although a conjugated 1,3-diene construct may, at first glance, seem an unlikely precursor to a *trans*-trisubstituted allylic amine, it was known from the work of Takabe and his colleagues[73] that *n*-butyllithium can catalyze the reaction of 1,3-dienes with secondary amines to give allylic amines with very good stereoselectivities. In the chemical literature, this type of addition process is frequently referred to as *telomerization*. In the case at hand, myrcene (**45**) and diethylamine join regio- and stereoselectively in the presence of a catalytic amount of *n*-butyllithium to give diethylgeranylamine (**35**). It is presumed that this addition reaction proceeds by way of the *N*-chelated intermediate **47**.



45: myrcene

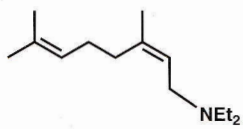


46: β-pinene

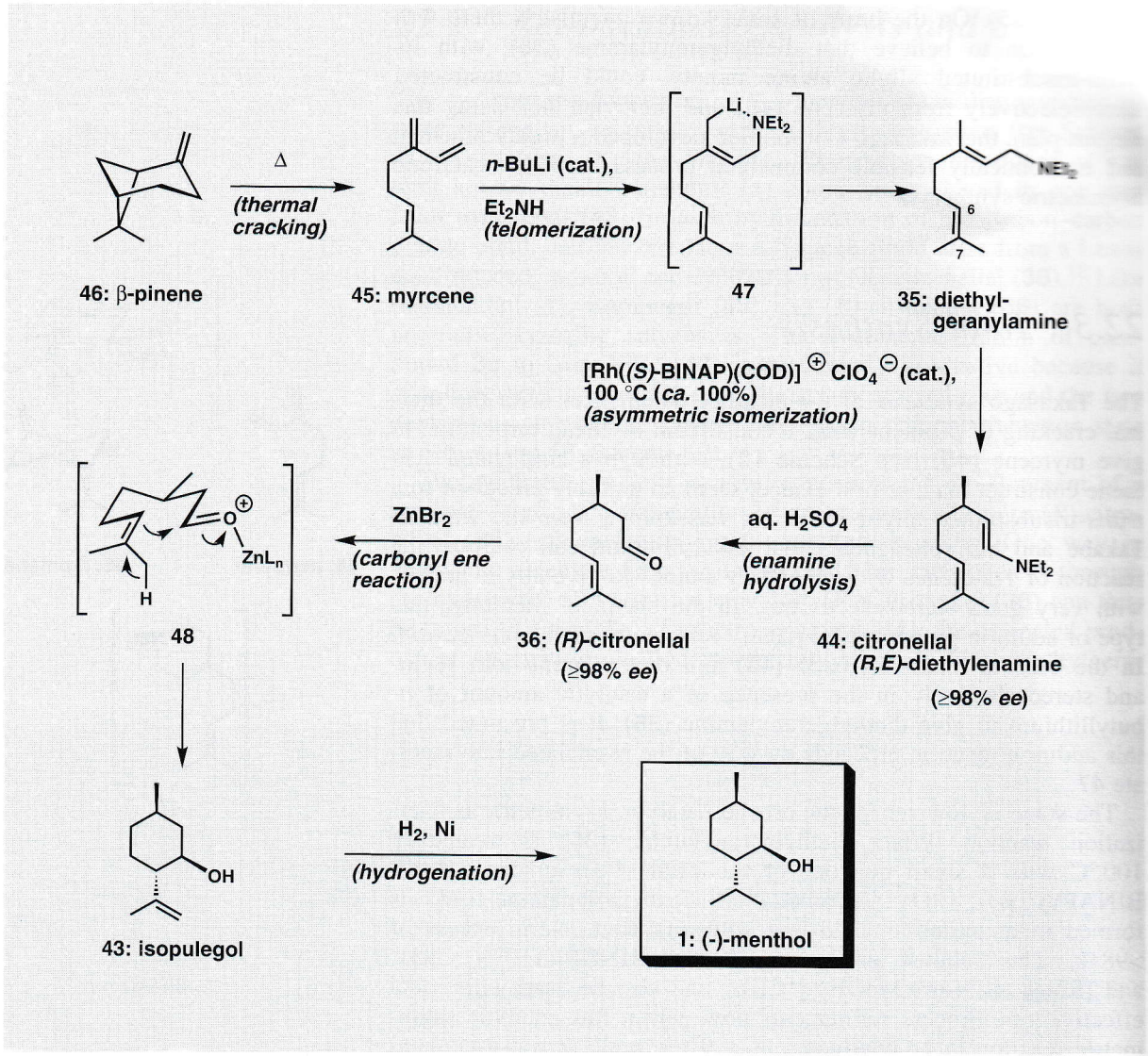


47

The stage is now set for the crucial catalytic asymmetric isomerization reaction. When diethylgeranylamine (**35**) is treated at 100 °C with a small quantity of the catalyst presursor, [Rh((*S*)-BINAP)(COD)]$^+$ClO$_4^-$, citronellal (*R,E*)-diethylenamine (**44**) is formed in quantitative yield and with an enantiomeric excess of >98 %. The catalyst precursors, [Rh((*S*)-BINAP)(THF)$_2$]$^+$ClO$_4^-$ and [Rh((*S*)-BINAP)(MeOH)$_2$]$^+$ClO$_4^-$ can also be used with equal effectiveness. Process refinements now permit this catalytic asymmetric reaction to be conducted on a 9 ton scale at substrate:catalyst ratios of 8000:1 to 10000:1. The enantiomerically enriched (nearly enantiomerically pure) enamine product can be distilled directly from the reaction mixture at low pressure, and the (*S*)-BINAP–Rh(I) catalyst can be recycled. Using this effective catalytic asymmetric reaction as the central step, the Takasago Corporation produces approximately 1500 tons of (–)-menthol and other terpenic substances annually. From Scheme 7, it should be recognized that citronellal (*R,E*)-diethylenamine (**44**) could just as easily be fashioned from the stereoisomeric (*Z*)-allylic amine [i. e. diethylnerylamine (**21**)] by switching to the enantiomeric (*R*)-BINAP–Rh(I) catalyst. This catalytic asymmetric process is thus not only economical and efficient, but also very flexible. It is also important to note that the remote $\Delta^{6,7}$ double bond is impervious to the asymmetric isomerization reaction.



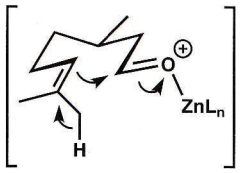
21: diethylnerylamine



Scheme 12. The Takasago process for the asymmetric synthesis of (–)-menthol (**1**).

With compound **44** in hand, the completion of the synthesis only requires three straightforward operations. As expected, enamine **44** can be converted to (*R*)-citronellal (**36**) by the action of mild aqueous acid. It is of interest that (*R*)-citronellal (**36**), produced in this manner, is of a much higher enantiomeric purity (i.e. 98–99 % *ee*) than the same substance obtained from its natural source! Indeed, the enantiomeric purity of natural (*R*)-citronellal is at best 80 %. On the basis of well-established precedent,[72] it was anticipated all along that the methyl-bearing C-3 stereocenter in citronellal would guide the stereochemical course of a carbonyl ene cyclization[74] to give the isomeric isopulegol molecule (**43**). Gratifyingly, treatment of (*R*)-citronellal (**36**) with either $ZnCl_2$ or $ZnBr_2$, both active

Lewis acids, results in the formation of isopulegol (**43**) with greater than 98 % diastereoselectivity; isopulegol (**43**), wherein all of the ring substituents are equatorially oriented, arises naturally from a chairlike transition state structure in which the C-3 methyl group, the coordinated C-1 aldehyde carbonyl, and the $\Delta^{6,7}$ double bond are all equatorial (see **48**). A low-temperature crystallization raises the chemical and enantiomeric purity of isopulegol (**43**) close to 100 %. Finally, hydrogenation of the double bond in **43** completes the synthesis of (–)-menthol (**1**).



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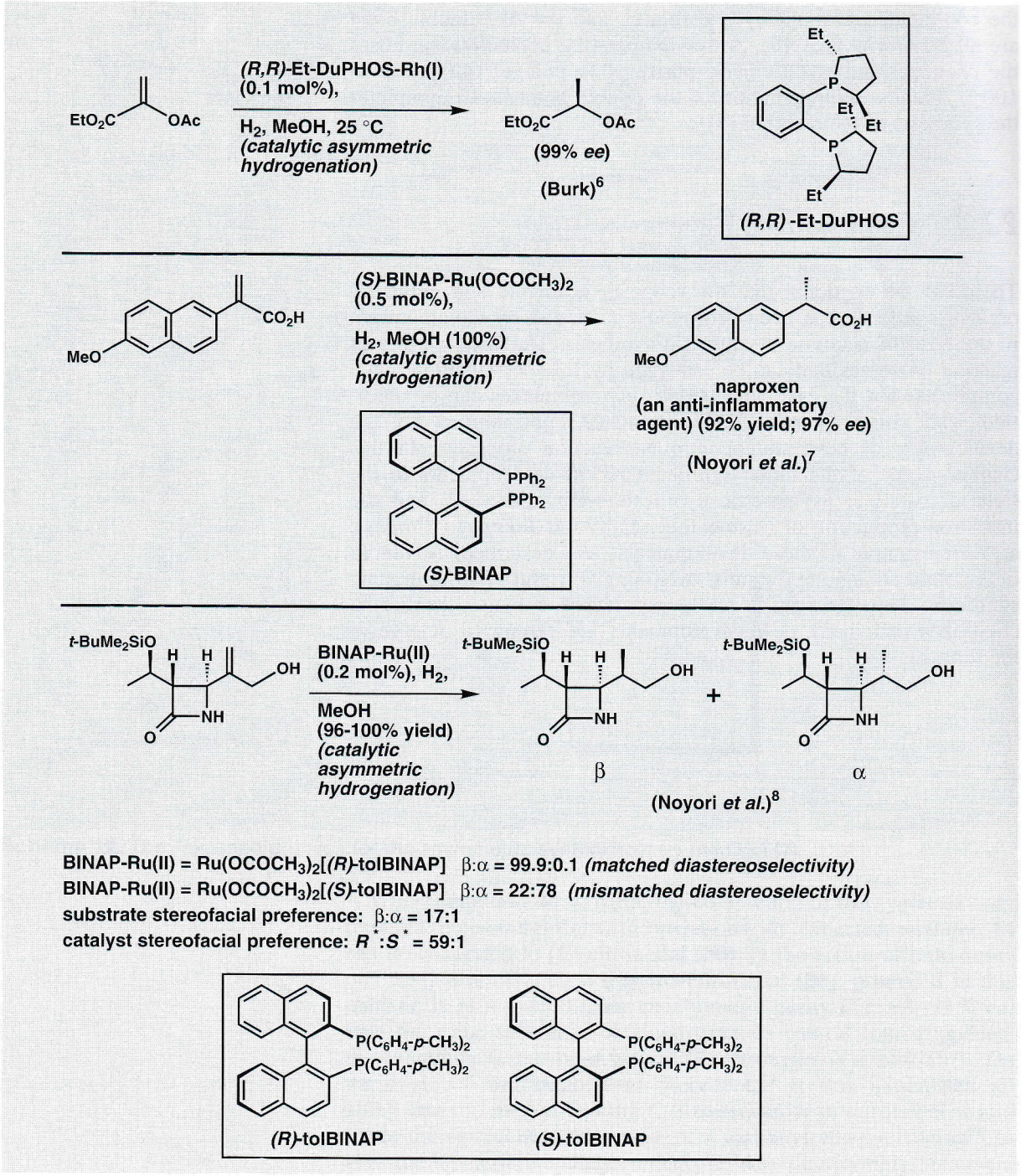
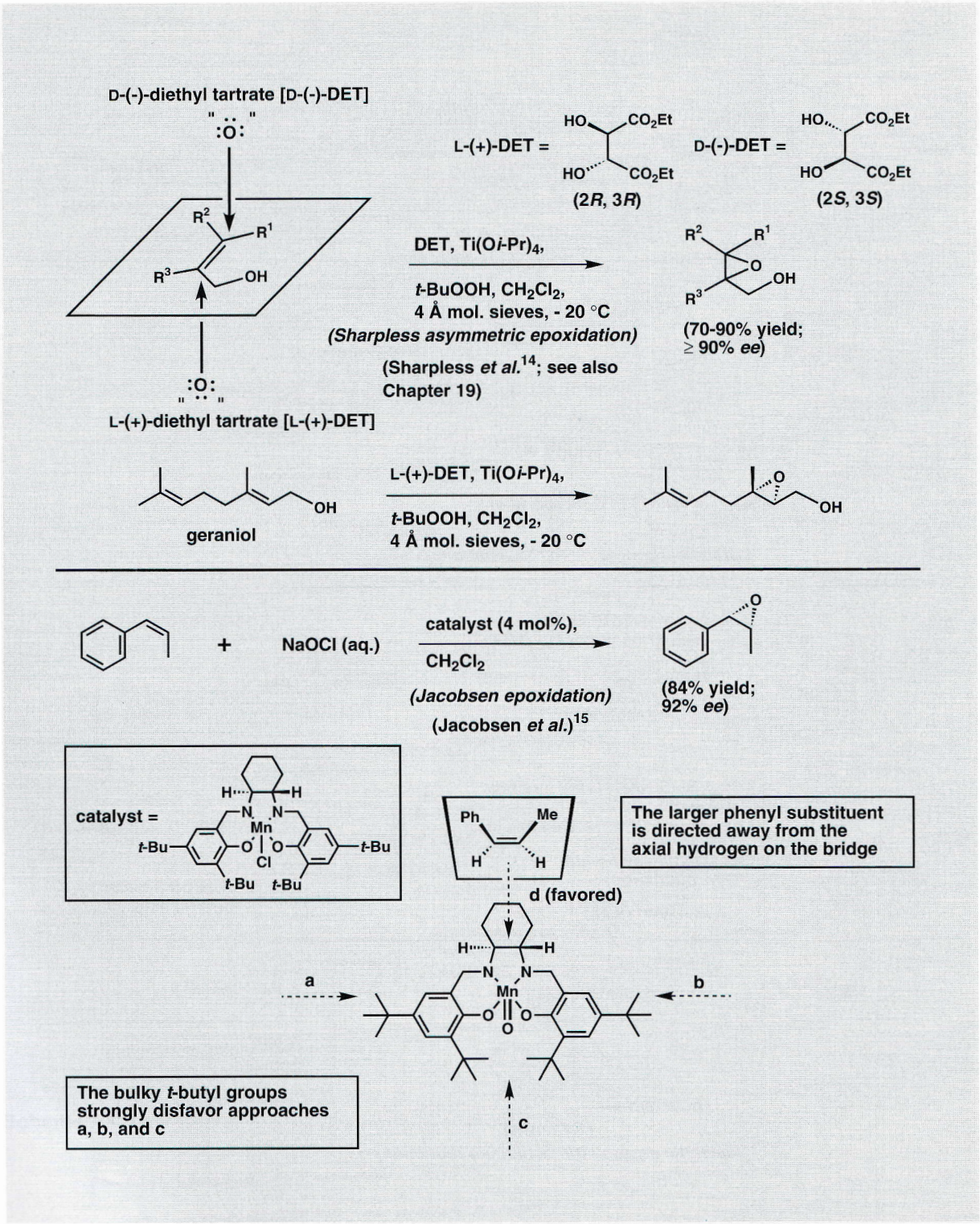
22.4 Conclusion

There can be no doubt that the scope of academic and industrial organic synthesis has been profoundly extended by developments in the field of catalytic asymmetric synthesis. The wide variety of reaction processes that can be catalyzed by soluble transition metal complexes, and the ease with which such complexes can be modified with chiral ligands creates manifold opportunities for the development of new, stereocontrolled reaction processes. In this chapter, some of the most significant recent developments in the field of catalytic asymmetric synthesis were addressed; and the industrial production of (–)-menthol (**1**) by the *Takasago Process*, a prime example of these developments, was described. Advances in this field are among the most exciting and useful in all of organic synthesis. This field is currently considered a major frontier in chemistry, and many new developments are certain to emerge in the future.

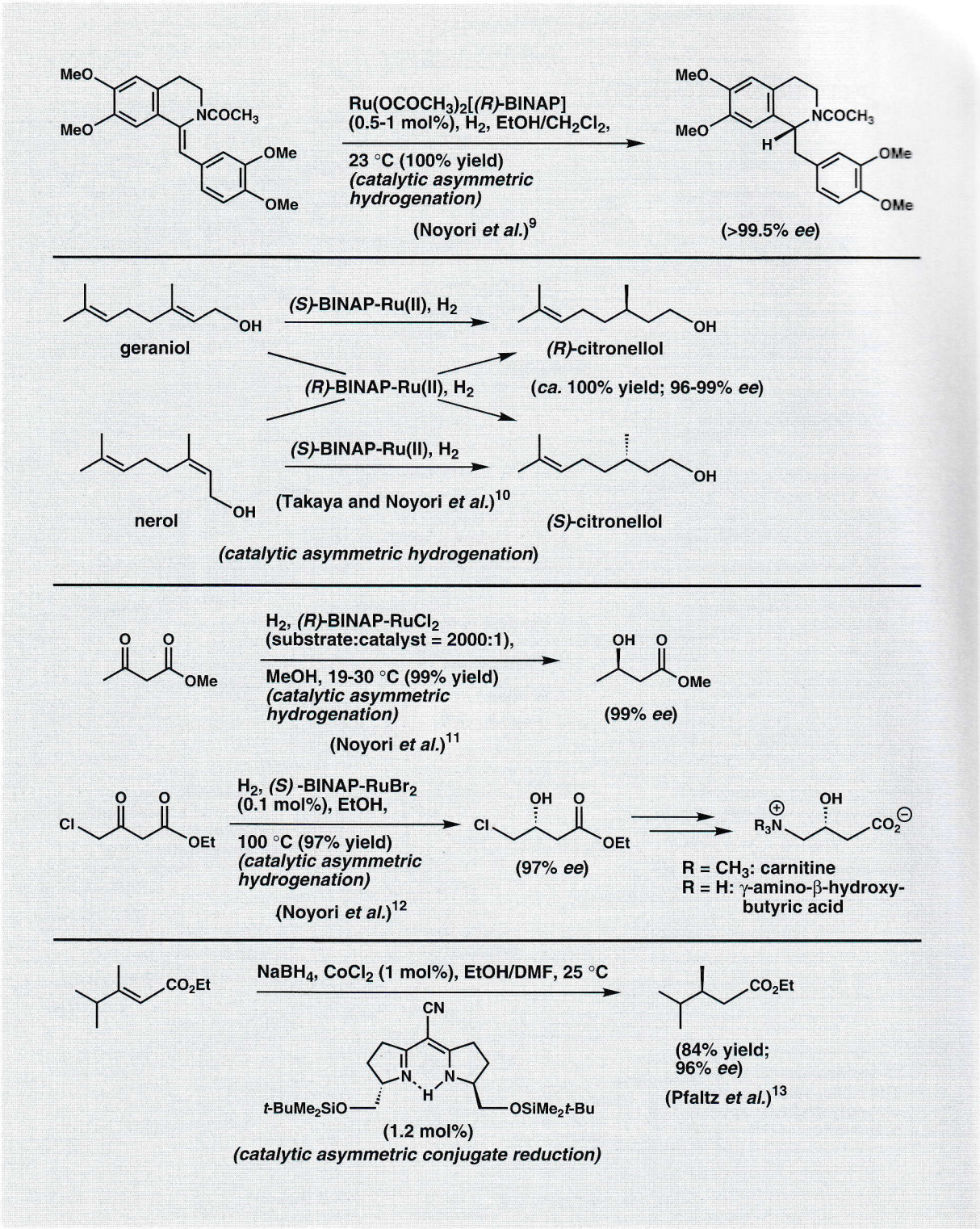
22.5 *Appendix: Catalytic Asymmetric Reactions, an Overview*



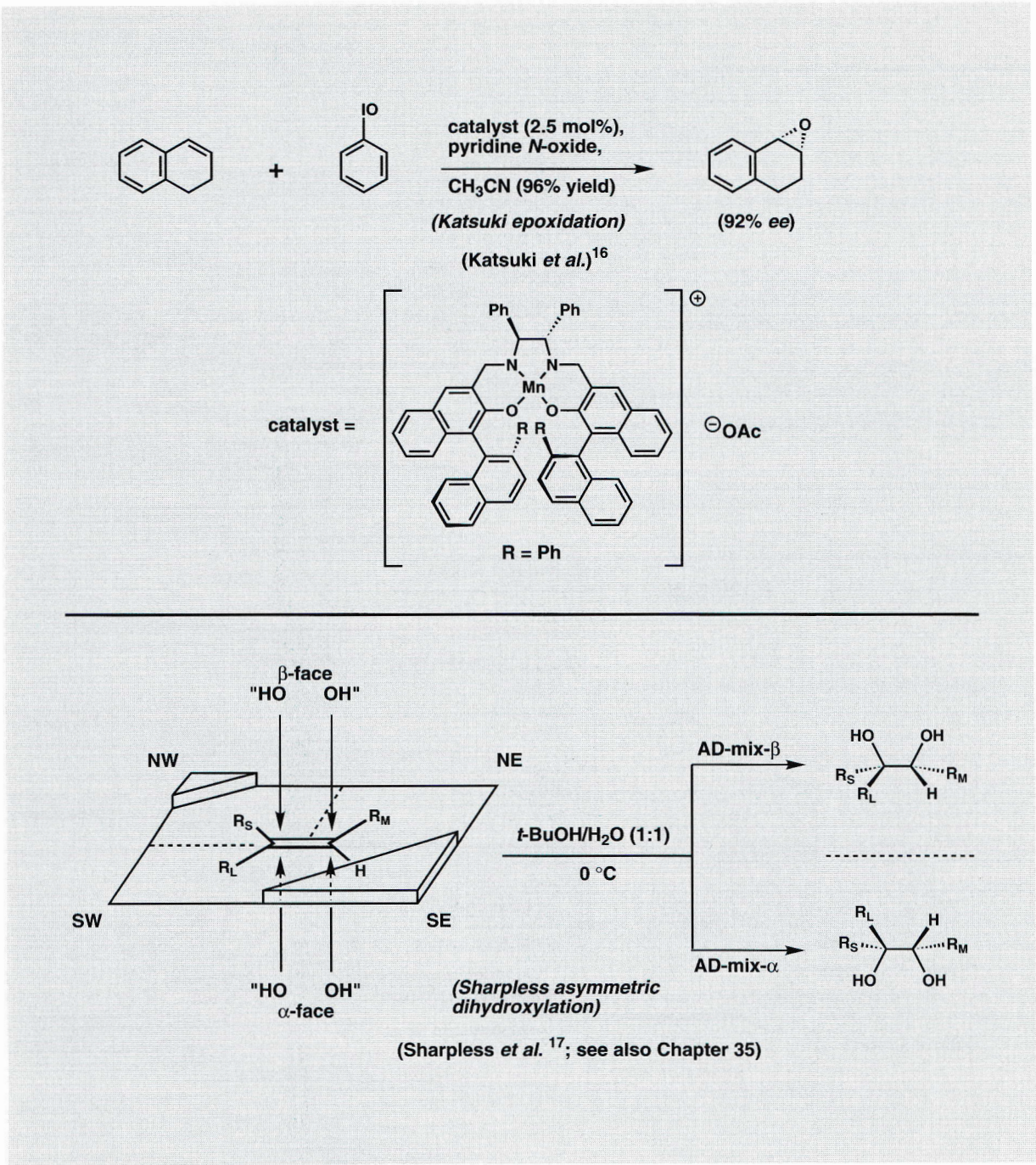
Scheme A1. Representative catalytic asymmetric reactions (references on scheme).



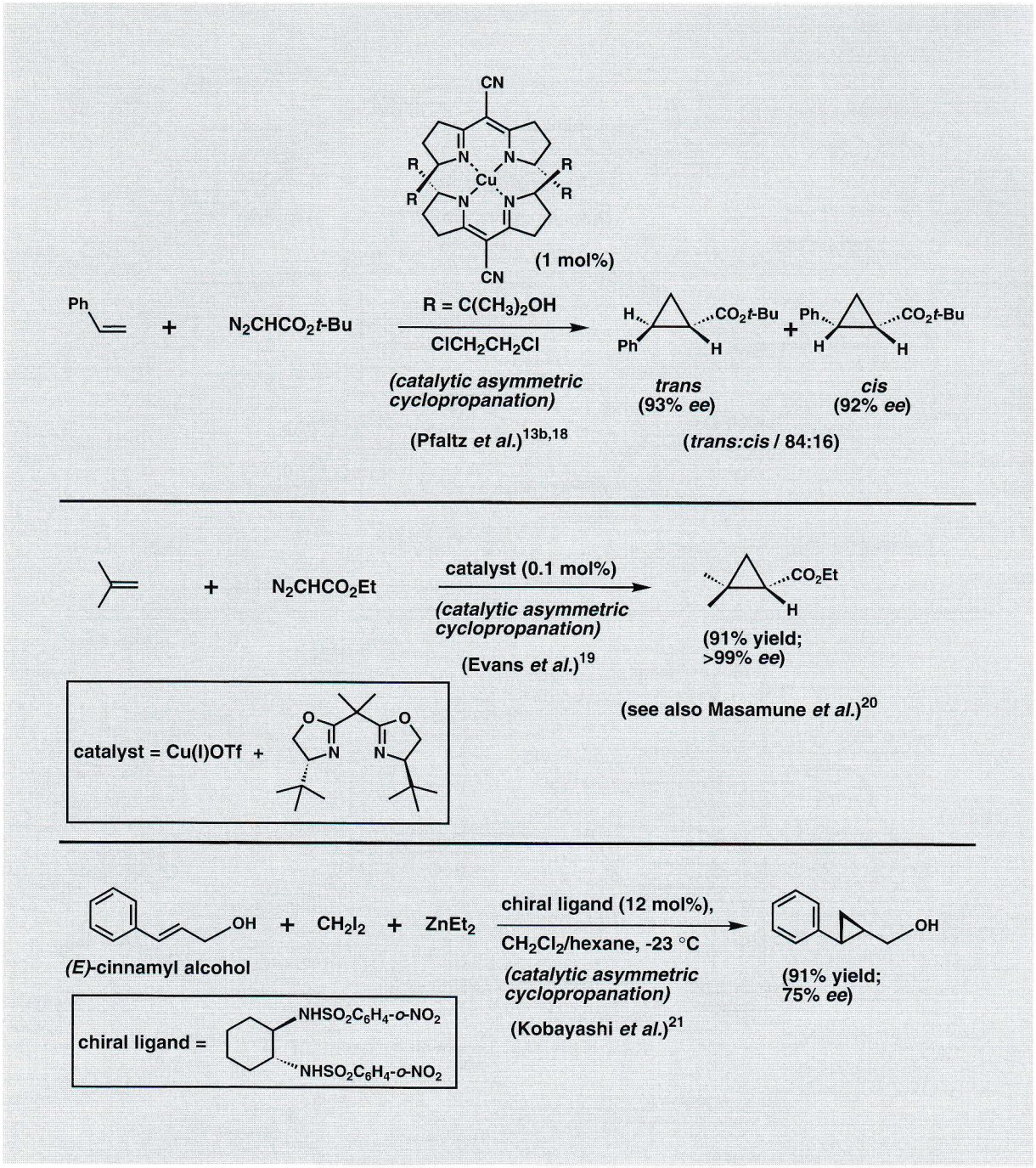
Scheme A2. Representative catalytic asymmetric reactions.



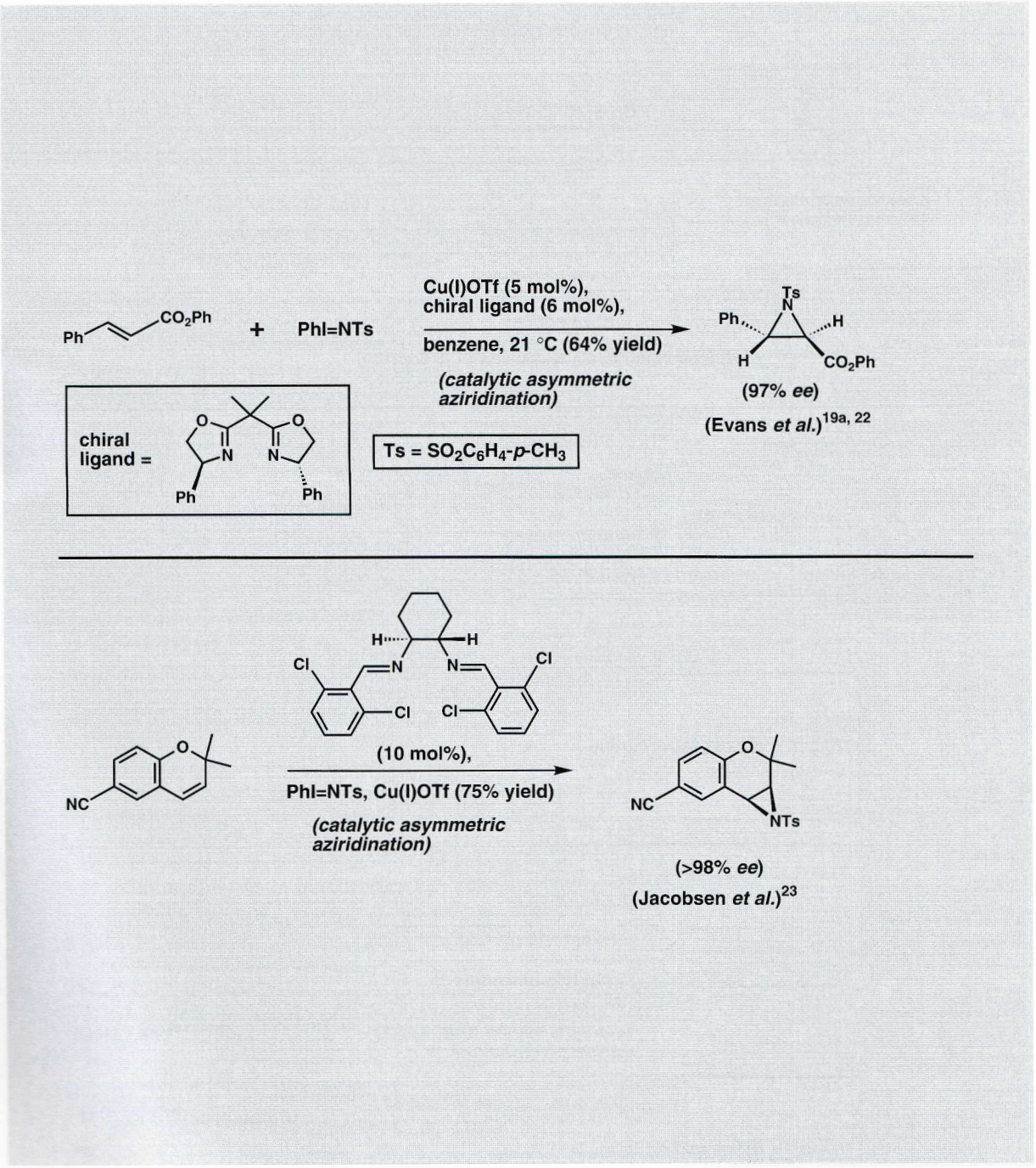
Scheme A3. Representative catalytic asymmetric reactions.



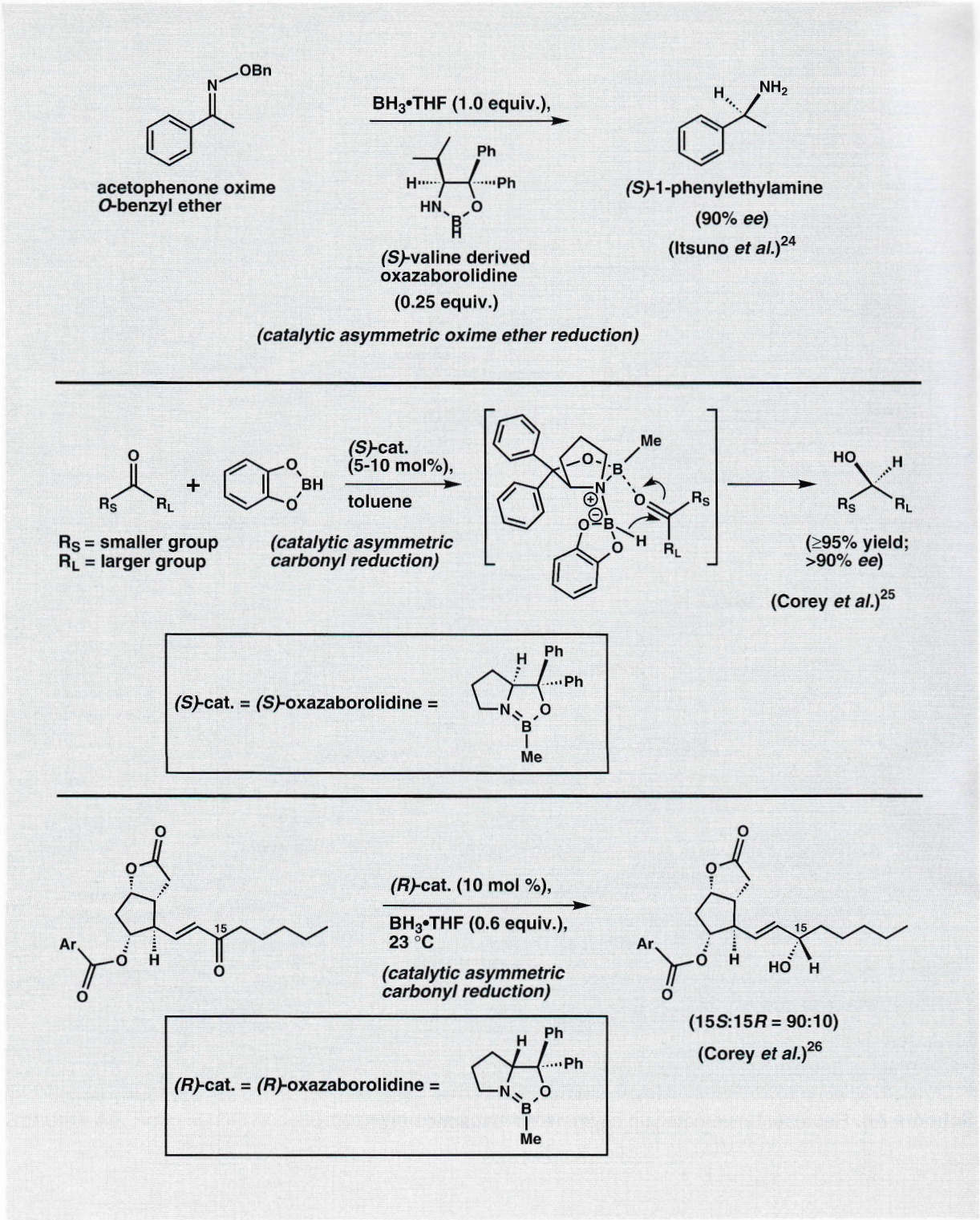
Scheme A4. Representative catalytic asymmetric reactions.



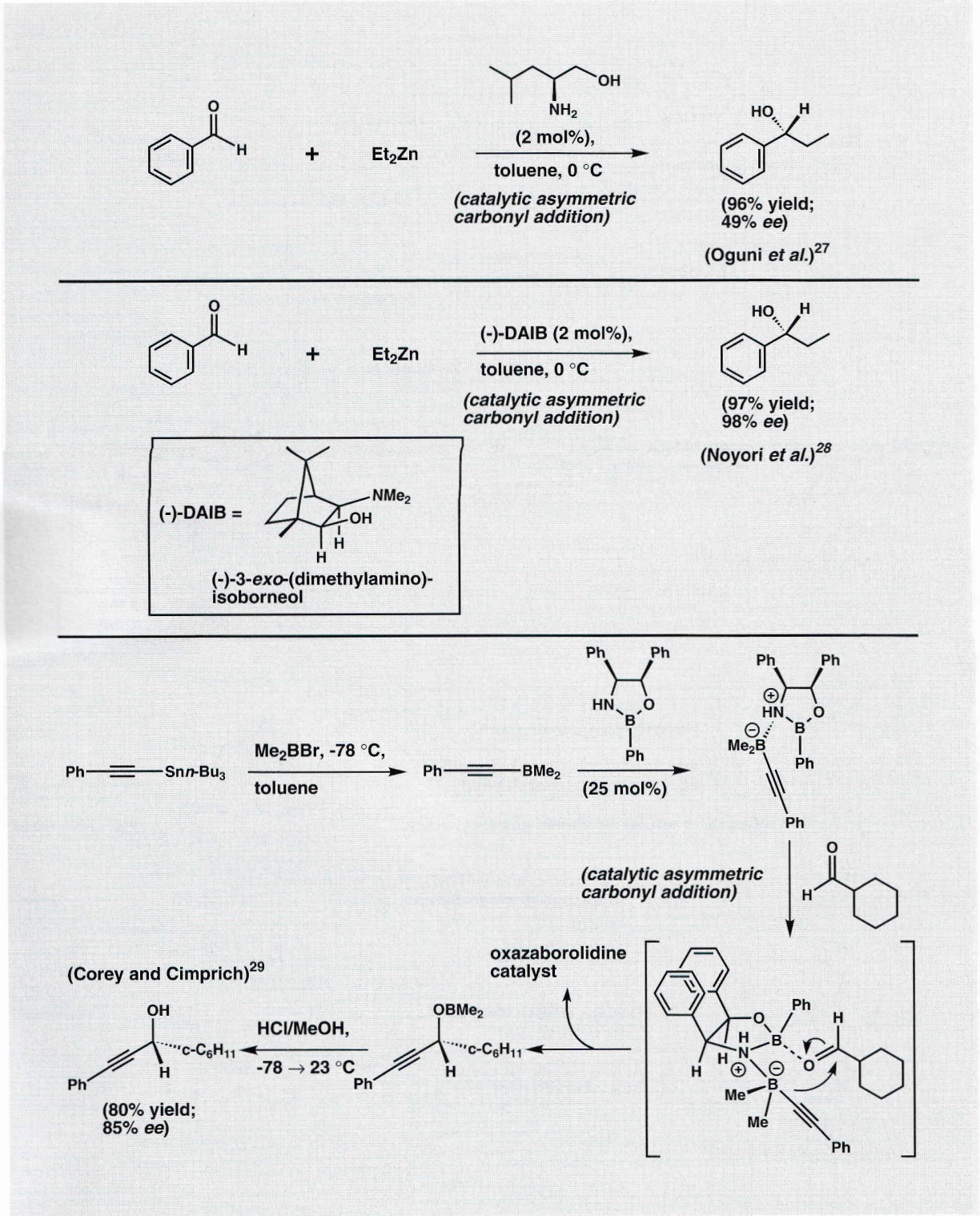
Scheme A5. Representative catalytic asymmetric reactions.



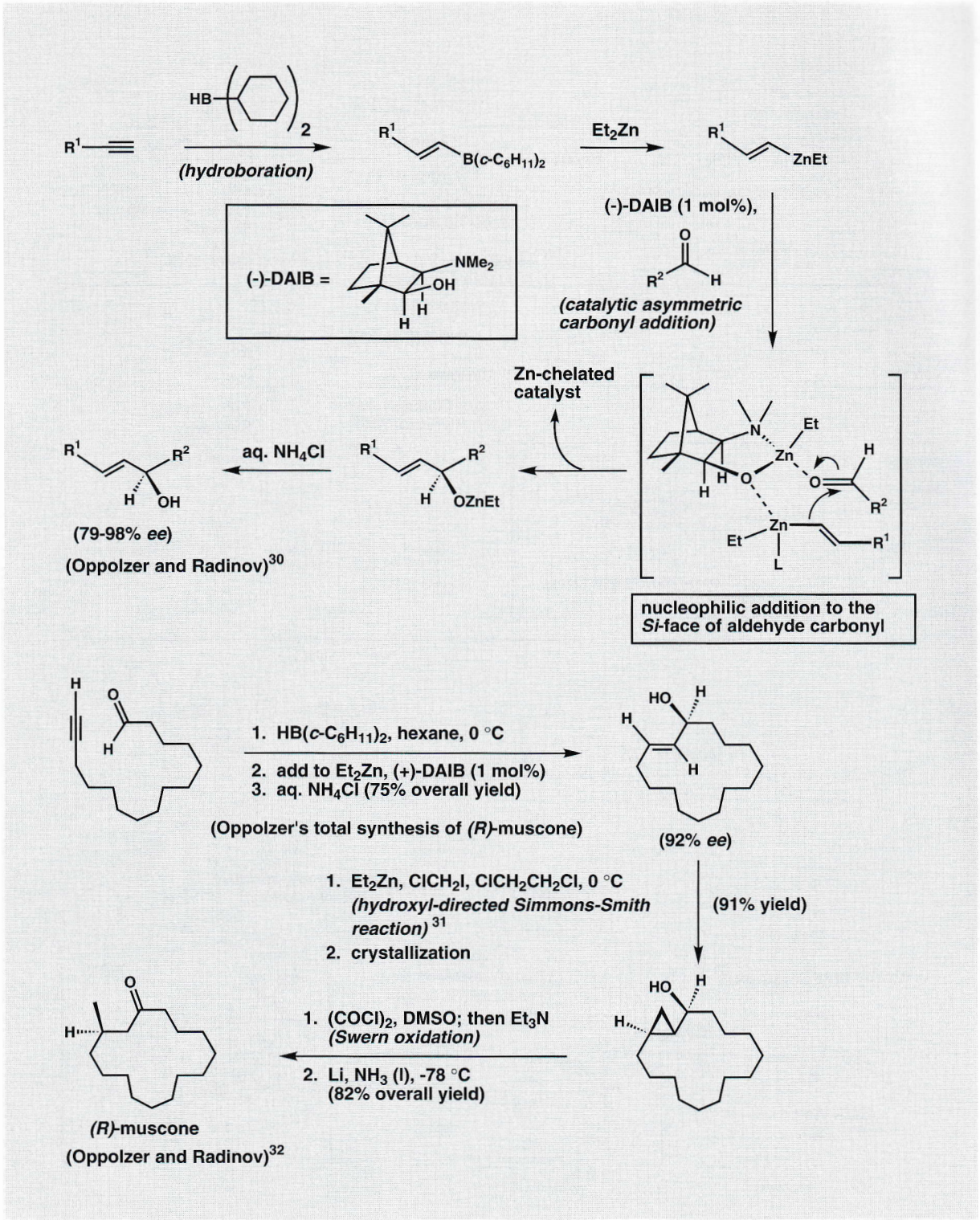
Scheme A6. Representative catalytic asymmetric reactions.



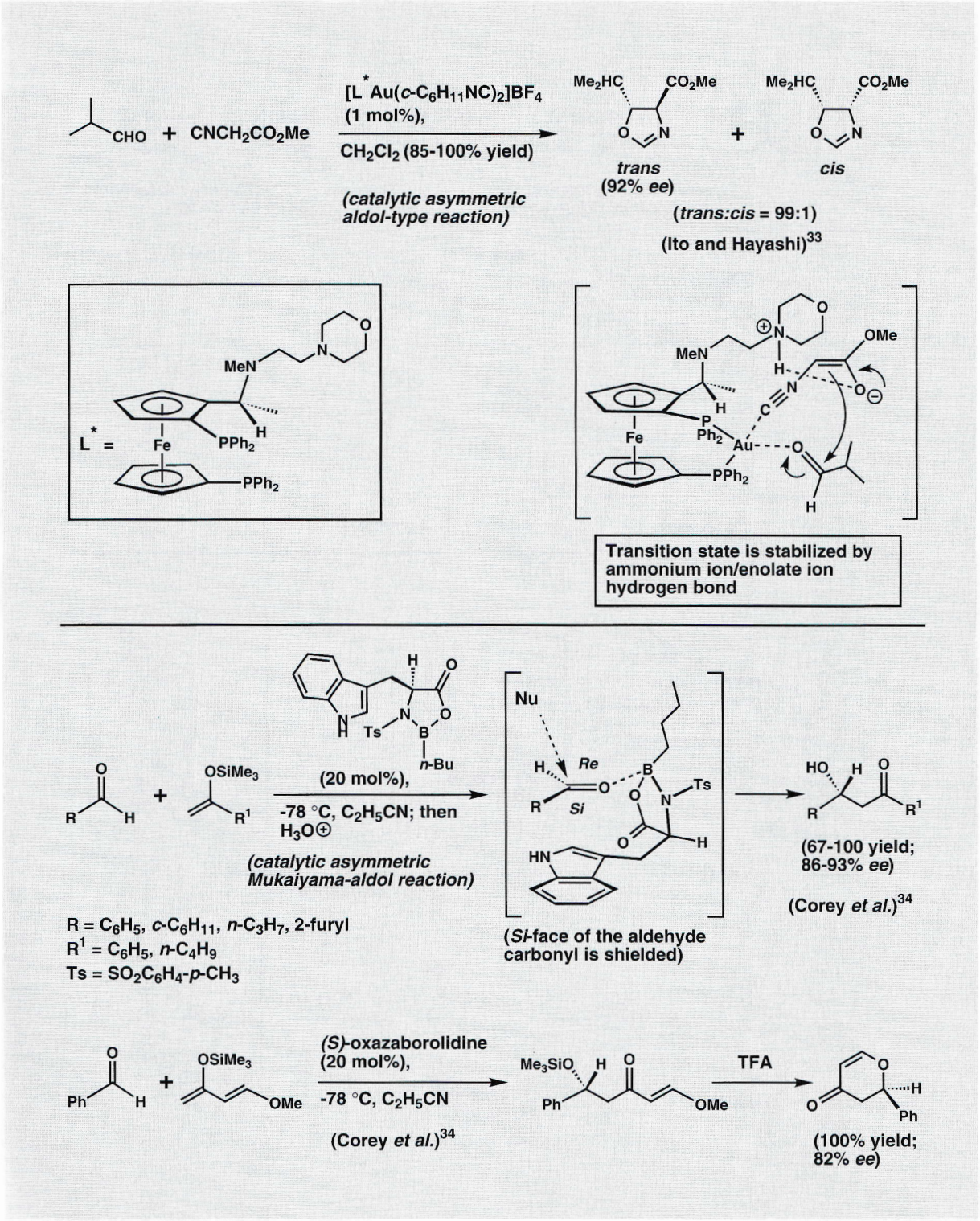
Scheme A7. Representative catalytic asymmetric reactions.



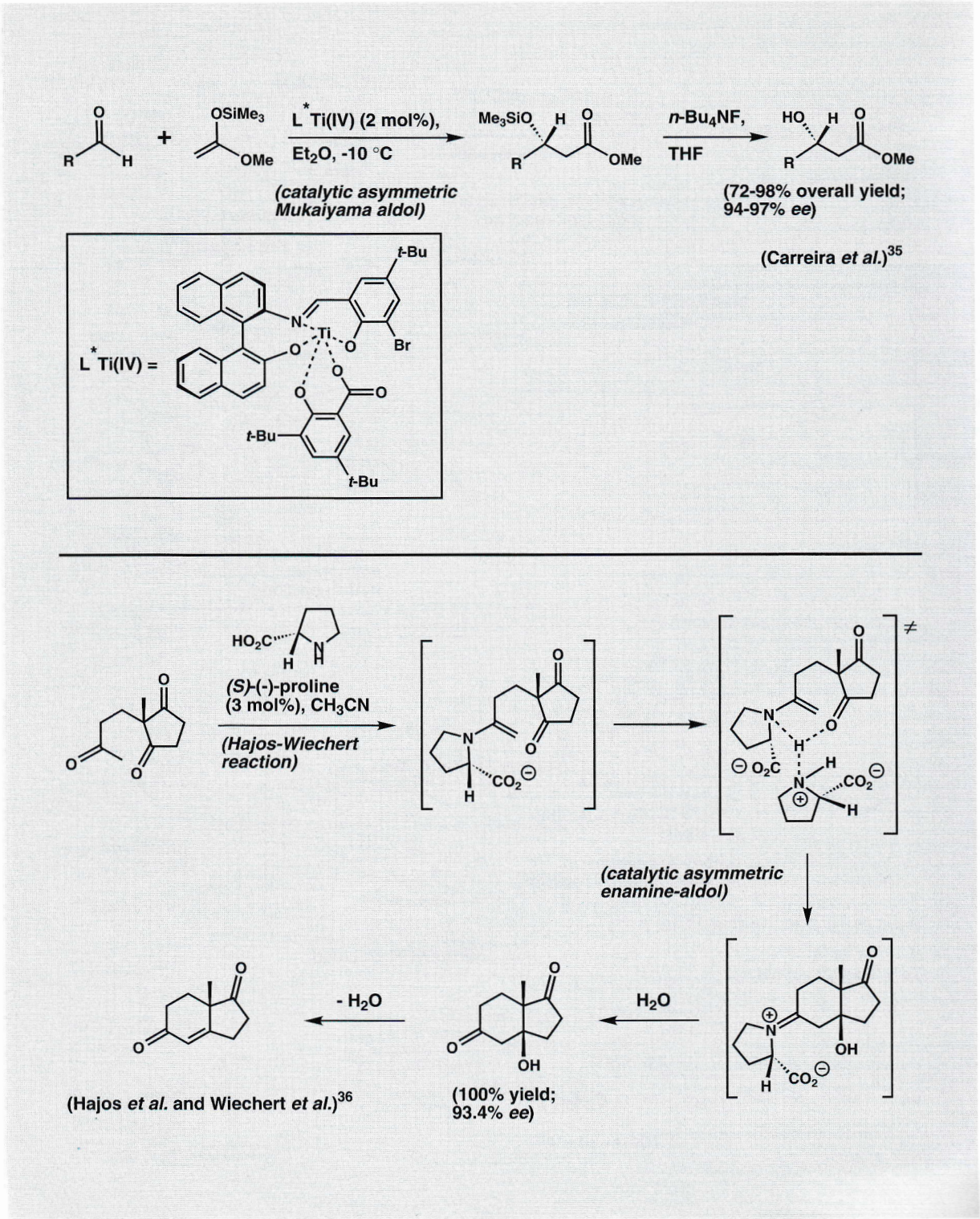
Scheme A8. Representative catalytic asymmetric reactions.



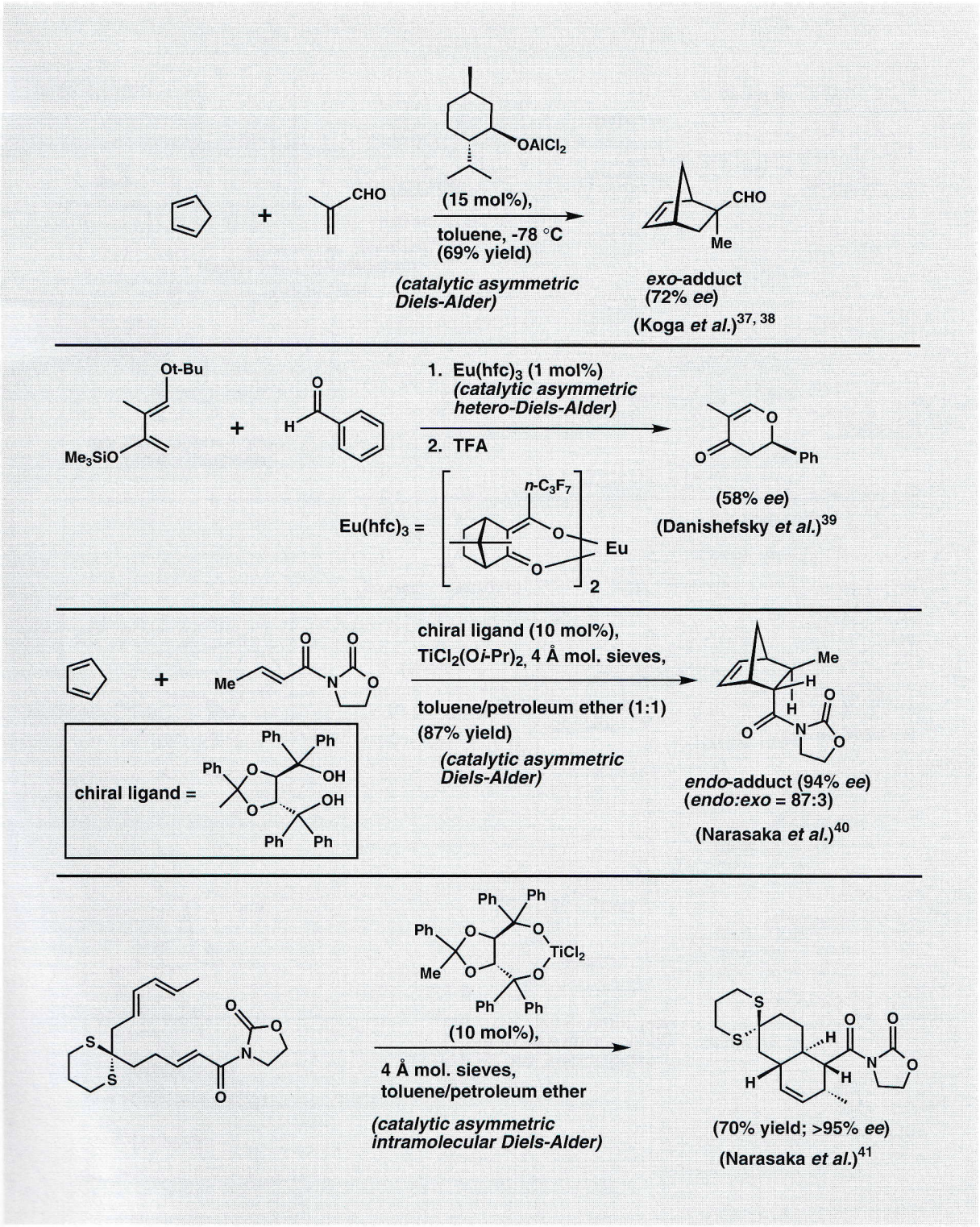
Scheme A9. Representative catalytic asymmetric reactions.



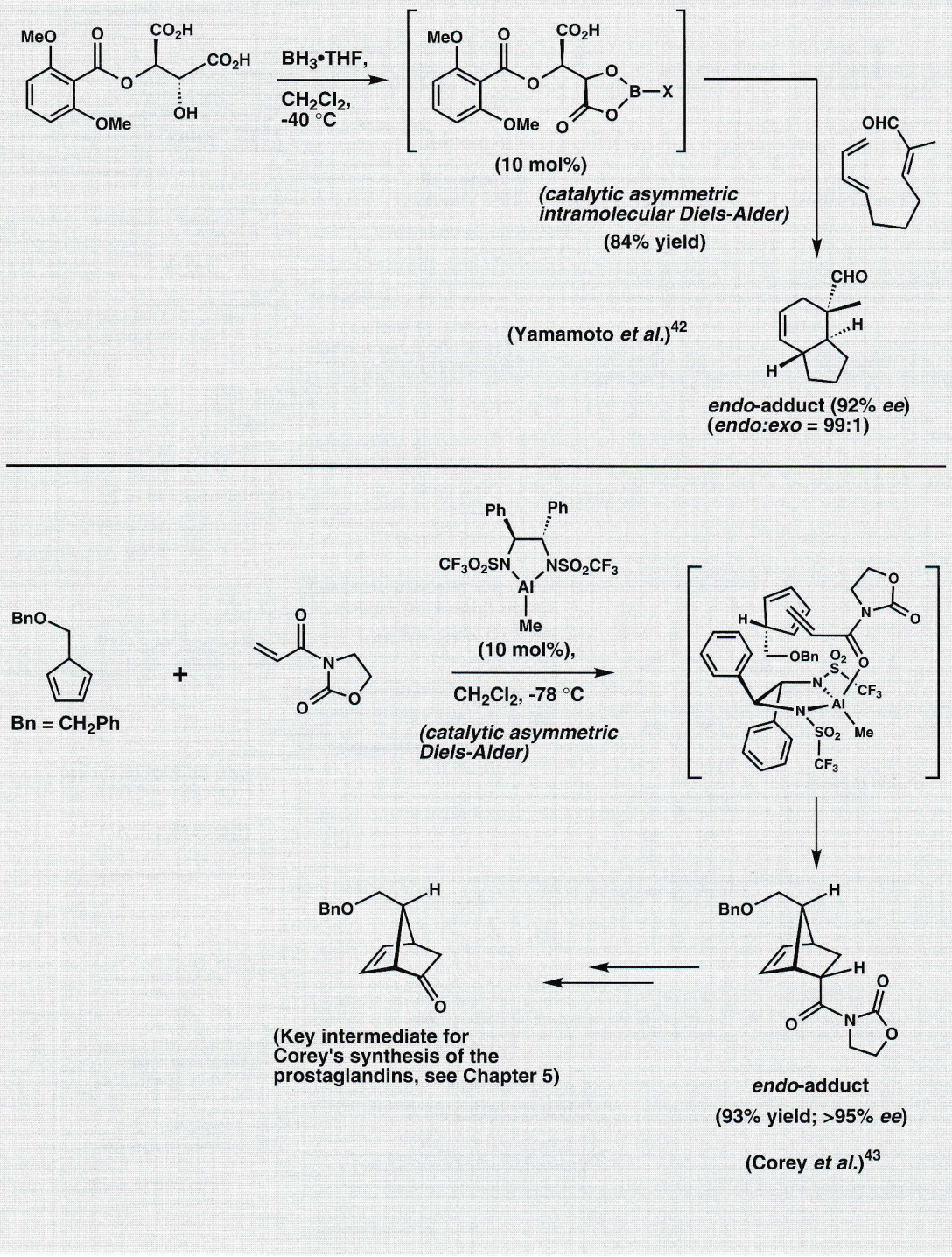
Scheme A10. Representative catalytic asymmetric reactions.



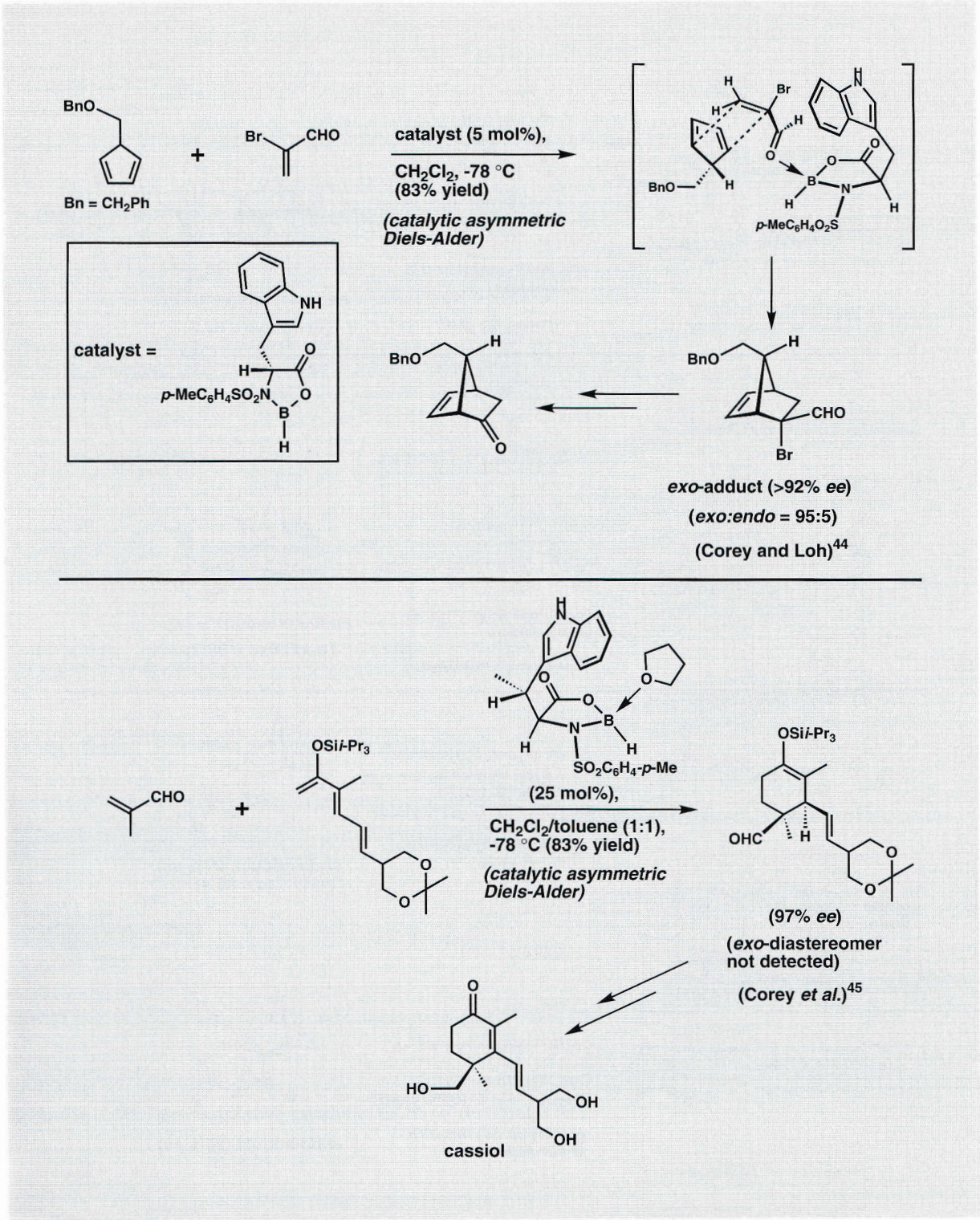
Scheme A11. Representative catalytic asymmetric reactions.



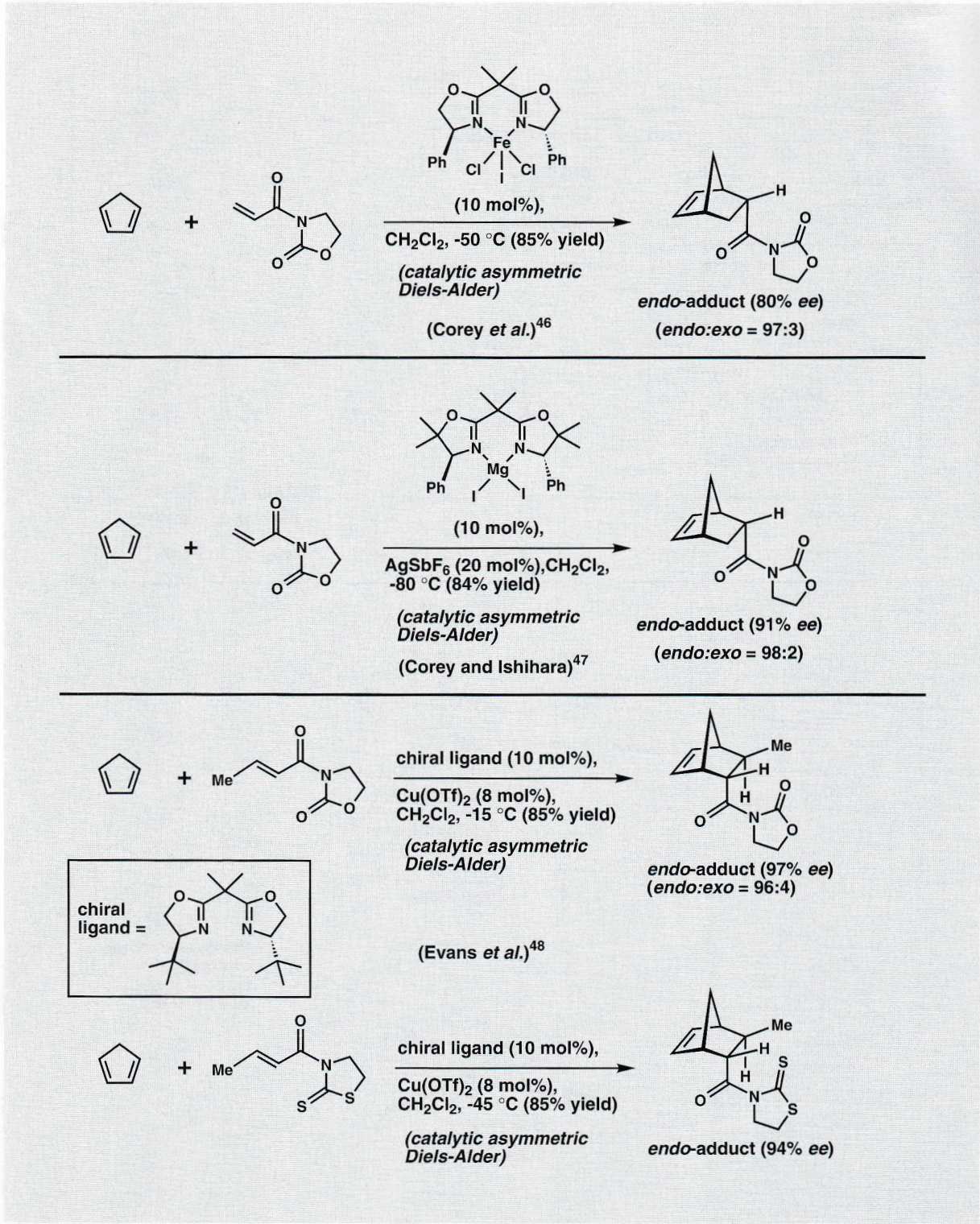
Scheme A12. Representative catalytic asymmetric reactions.



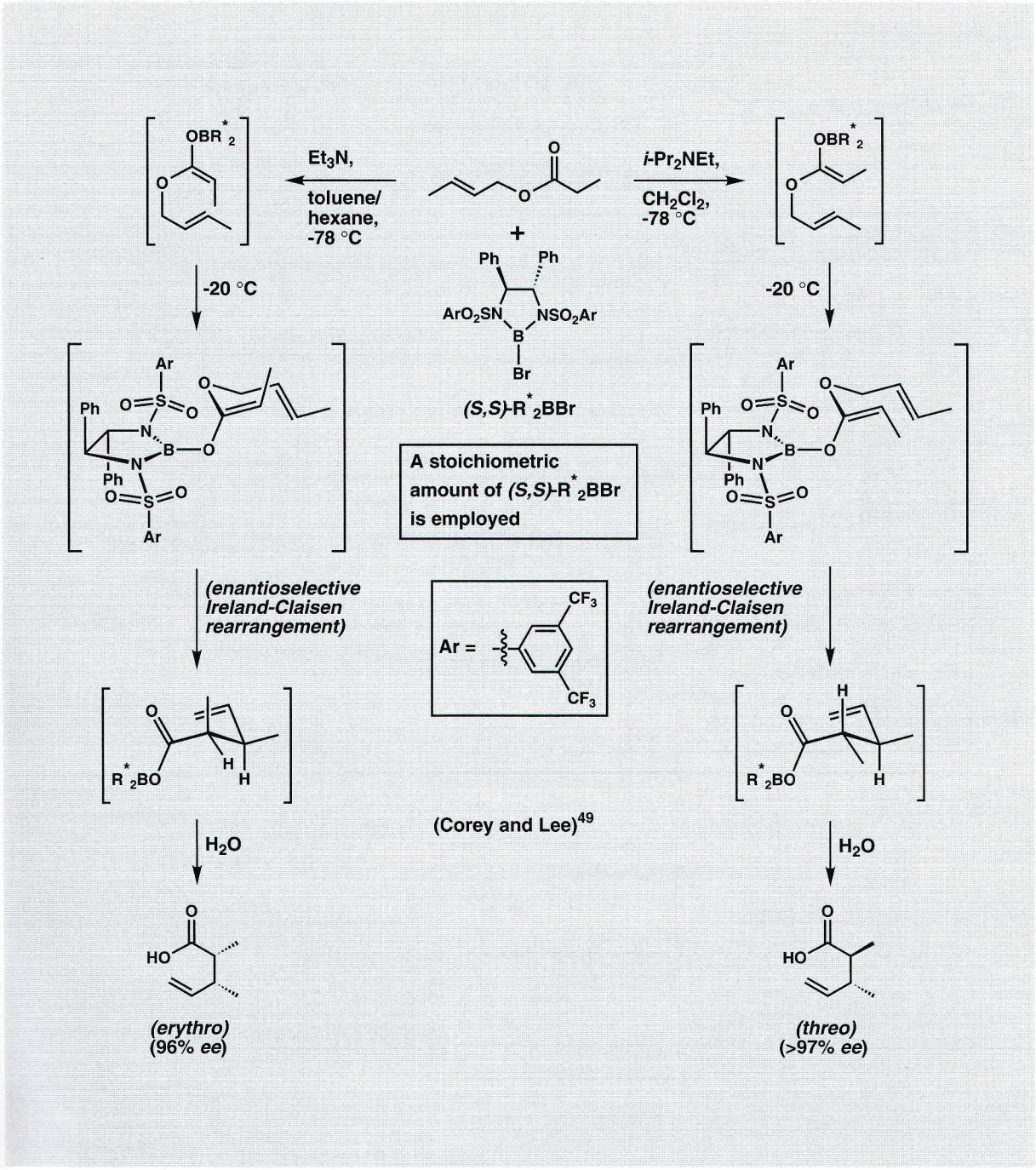
Scheme A13. Representative catalytic asymmetric reactions.



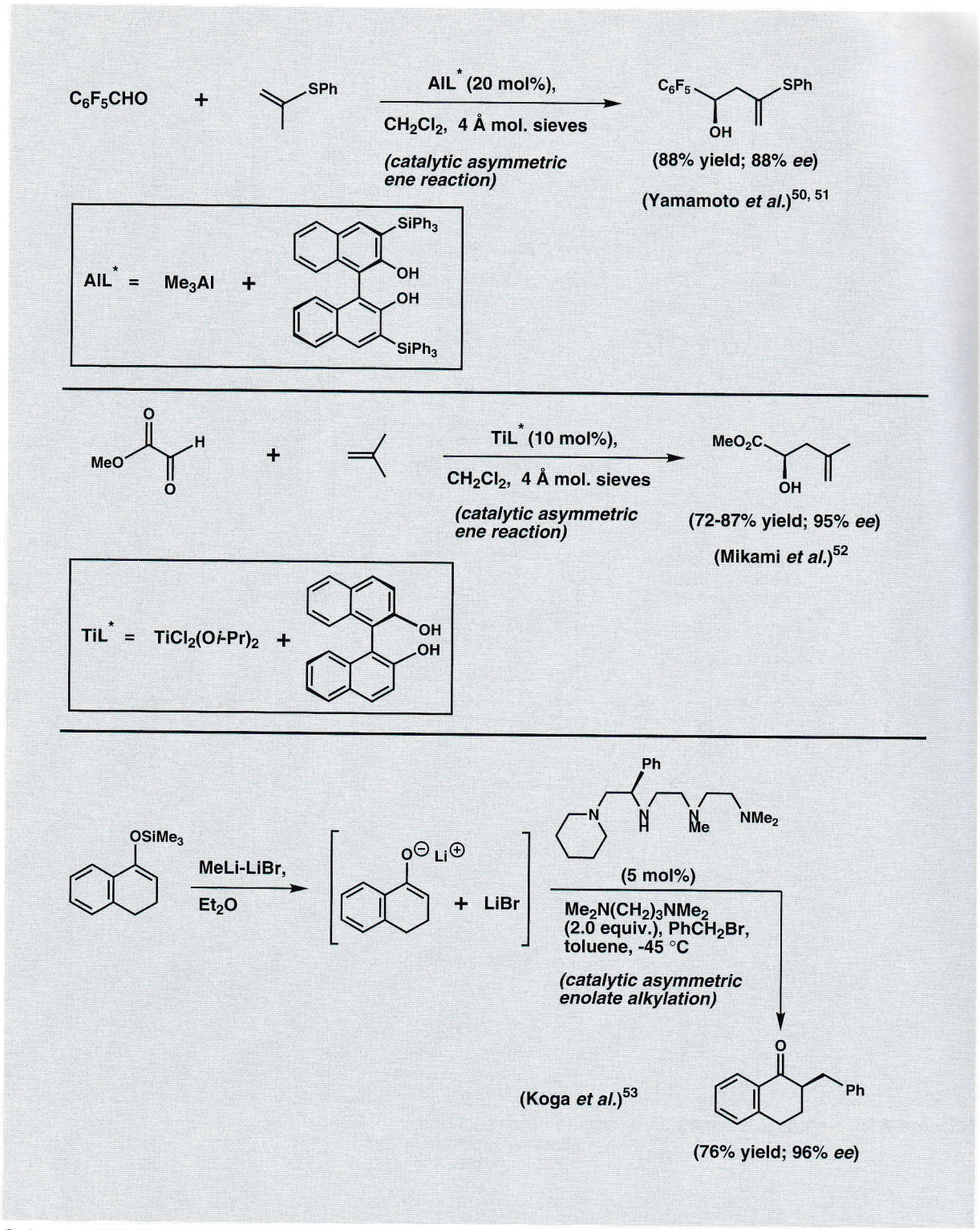
Scheme A14. Representative catalytic asymmetric reactions.



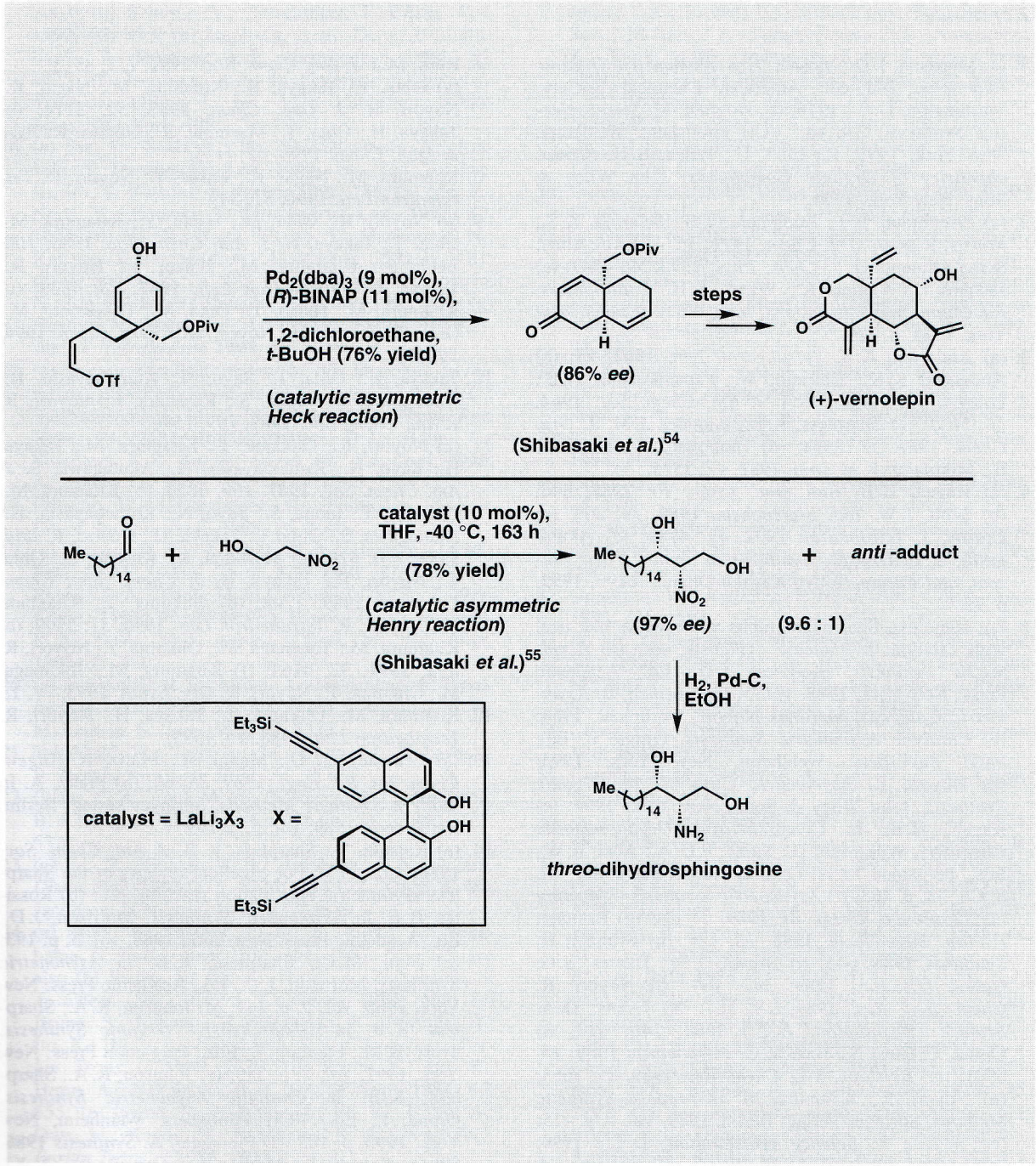
Scheme A15. Representative catalytic asymmetric reactions.



Scheme A16. Representative catalytic asymmetric reactions.



Scheme A17. Representative catalytic asymmetric reactions.



Scheme A18. Representative catalytic asymmetric reactions.

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