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The Historical Development of Asymmetric Hydrogenation

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1.1 Introduction

How did chemists gain the current levels of knowledge and expertise for controlling molecular chirality through hydrogenation or otherwise? The desirability of asymmetric synthesis was recognized in the 1880s by Emil Fischer and others, but practical solutions only arose more than 80 years later. The key reasons are explored here. This brief review has five main Sections 1.2–1.6, covering first the development of ideas underpinning our understanding of asymmetry, then the initial applications to asymmetric synthesis, and also the development of asymmetric heterogeneous hydrogenation of alkenes. The final sections on asymmetric homogeneous hydrogenation of alkenes are limited to work published in or before the early 1980s, in advance of extensive developments, and thus excluding the important inputs of iridium catalysts and more recently early transition metals.

1.2 Early Work on the Recognition of Molecular Asymmetry

Chemistry was an emerging science by the beginning of the nineteenth century with many opportunities for fundamental discovery. At that time scientists crossed disciplines easily; optics and mineralogy played important roles because of the ready accessibility and verifiable purity of solid substances. Malus had invented the first polarimeter in 1808, enabling measurement of both the sense and magnitude of rotation of plane-polarized light [4]. Following this, work by Arago and others on the interaction of polarized light with minerals intensified in the following decade [5]. Haüy had earlier concluded that each type of crystal has a fundamental primitive, nucleus or "integrant molecule" of a particular shape, that could not be broken further without destroying both the physical and chemical nature of the crystal. He had accidentally dropped and shattered a crystal of calcite that enabled him to make the deduction [6]. Biot observed the striking phenomenon that samples of plane sections

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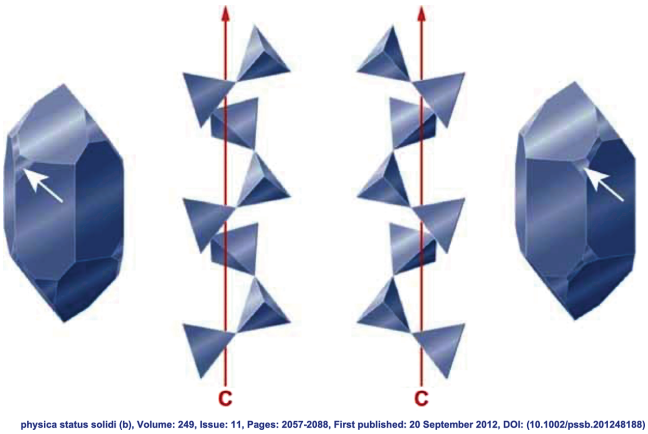


Figure 1.1 α-quartz crystals with object and mirror image hemihedral faces; inner part shows packing of sub-units. Created by K-H Ernst and reproduced with permission of Wiley-VCH.

of rock crystal (α-quartz) rotated the plane of plane-polarized light. Furthermore, some quartz crystals rotated polarized light to the right, and others to the left. The observations obtained by Biot for liquids in his designed polarimeter showed that diverse natural substances, either as liquids or in solution, showed the same phenomenon of optical activity with consistent rotations to the left or to the right for a given substance, which he quantified through Biot's Law. The vapor of oil of turpentine also demonstrated optical activity. By contrast, water, alcohol, and sulfuric acid were inactive [7, 8]. Biot deduced that the response to polarized light was a property exhibited by the individual molecules of the analyte, making a link to Haüy's proposal. The English scientist Herschel was aware of this work and was able to correlate the direction of rotation for α-quartz crystals with the structure of the crystal. He made it clear that the mirror-image pair differed by virtue of the hemihedral faces that were themselves object and mirror image (Figure 1.1) [1, 2]. Well over a 100 years then elapsed before the absolute configuration of an α-quartz crystal was determined by De Vries DeVries, using Bijvoet's recently developed anomalous dispersion method. The laevorotatory form is on the left of Figure 1.1a [3].

This laid the groundwork for explaining a puzzling observation. Cream of Tartar is a crystalline product isolated as a by-product from winemaking and was widely used in baking and otherwise. It was known to be the dipotassium salt of tartaric acid and showed an optical rotation as expected. A winemaker in the Vosges had isolated a second crystalline product at the same stage of production, and the ensuing isolated acid (racemic acid) had similar properties to tartaric acid but lacked optical activity. This became interesting to the prominent Swedish chemist Berzelius in the late 1820s [9]. He characterized his "paratartaric acid" thoroughly. It was identical to tartaric acid in analytical composition, had the same chemical composition and the same physical properties, and same distinct melting points. His student Mitscherlich [10], by then working in Berlin, discovered that an aqueous solution of paratartaric acid was "indifferent" to polarized light in contrast to the known optical activity of tartaric acid and its salts in solution, although his isolated crystal was

active. From the crystal structures of the acids and their sodium ammonium double salts, he concluded that: "the nature and number of atoms, their arrangement and their distance from one another are the same in both bodies." This sparked Pasteur's interest, as he himself acknowledged; he repeated the crystallization of both sodium ammonium salts. Both sets of crystals were hemihedral with a key proviso: the hemihedral faces of the tartrate crystals all had the same sense, while those of paratartaric acid lay either to the left or to the right. Pasteur was able to separate the right-handed from the left-handed crystals on a 5-g scale and examine them separately in solution by polarimetry. Both were optically active but in near equal and opposite directions! This Eureka moment needed rechecking under the critical gaze of his mentor and senior colleague Biot. With that test successfully achieved, his reputation was then secured in 1848 when 26 years old. Later on, he extended this seminal sequence of experiments by resolving paratartaric acid into its enantiomers with the alkaloids quinidine or cinchonidine (CD) [11–13].

All this was carried out without a proper understanding of the molecular structure at the atomic level. The first insights into that came many years later, with the publications of Van't-Hoff and Le Bel in late 1874 [14–16]. Prior to that aliphatic organic compounds were typically drawn (and presumably visualized) as a linear formula string or in-plane with dotted connections (e.g. typical Berichte papers, 1874). Van't Hoff's publication solved the existing problem of isomerism in saturated organic compounds at a stroke – "The theory is brought into accord with the facts if we consider the affinities of the carbon atom directed toward the corners of a tetrahedron of which the carbon atom itself occupies the center." He also explained the existence of enantiomers in the case when a carbon atom had affinities to four different substituent groups. Van't Hoff had claimed to be inspired by the work of Wislicenus on lactic acid, $CH_3\mathbf{C}HOHCO_2H$, stereoisomerism [11]. Le Bel made similar conclusions and was specifically concerned with explaining the link between tetravalent carbon and optical activity. These analyses proved to be the foundation stone of modern organic chemistry.

The problem of visualizing representations with multiple stereocenters was first solved by Emil Fischer's in-plane notation for sugars, compared with more modern representations in Figure 1.2, [17]. He had determined the relative configurations by chemical means. In order to specify the then unknown absolute configurations, the penultimate carbon in the chain of the dextrorotatory isomer was written with OH to the right, with the aldehyde (or equivalent group) placed at the top of the chain. His guess at the absolute configuration was proved correct, much later, through

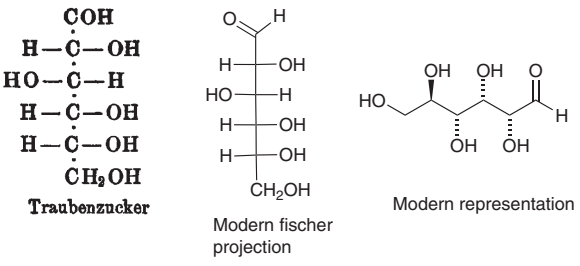


Figure 1.2 Fischer's representation of the open-chain form of glucose and its modern variants. Source: Based on Lichtenthaler [17].

stereochemical correlation with Bijvoet's X-ray analysis of the sodium *rubidium* salt of tartaric acid, using zirconium Kα radiation that specifically excited Rb [18].

1.3 Origins and Early Development of Asymmetric Synthesis [19]

The contrast between optical activity in Nature and its absence in synthesized organic compounds led to the suggestion of a "vital force" that intervened to create natural chirality. This provided a challenge to several late nineteenth century organic chemists, with Emil Fischer prominent. He first suggested that chlorophyll was responsible for the conversion of CO_2 into single enantiomers of sugars by plants. Although this was not correct, it made a link between chirality and asymmetric synthesis. He discovered how to convert hexoses into their higher homologues by successive Kiliani hydrocyanation, nitrile hydrolysis to give a lactone, and Na amalgam reduction. He observed significant excesses of one diastereomer of product, formally an asymmetric induction, but he was aware of the possibility of the interconversion of isomers in the course of a multistage reaction, however. To avert this he studied the hydrocyanation of the tetraacetyl salicylaldehyde glucoside, helicin, the glucose moiety acting as a chiral auxiliary. The ensuing cyanohydrin was hydrolyzed and oxidized to the corresponding carboxylic acid with concurrent glycoside cleavage, Figure 1.3a. The product exhibited a very small rotation that implied some asymmetric induction had occurred but insufficient to make a secure claim of success [20]. It then remained for Marckwald to provide a more robust example in the decarboxylation of methylethylmalonic acid in the presence of 1 equiv of the alkaloid brucine (Figure 1.3b). After workup and complete removal of brucine, the monoacid had an optical rotation equivalent to 10% excess of one enantiomer [21]. The observation was carefully repeated and confirmed by Erlenmeyer and Landsberger [22]. From then on it was accepted that purely chemical asymmetric syntheses could be attained. But how could this be achieved in practice? The test of a synthetic method lies in its application, and by that criterion asymmetric synthesis remained a self-contained field for the next 60 years. Asymmetric synthesis played only a marginal part in the many impressive total syntheses that were achieved in that period. To reach an asymmetric target, the chirality tended to come from a natural source [23].

Some of the reasons for the slow development of practical and efficient asymmetric syntheses are easy to understand. The first half of the twentieth century experienced two major wars, with inevitable disruption of the progression of basic science. The early examples of asymmetric synthesis were based on empirical observation and carried out at a time before the theories that underpin experimental design – the nature of the chemical bond, electronic theory, and the process of bond making and bond breaking – were properly described. The development of organic reaction mechanisms coincided with an increased appreciation of organic stereochemistry and structure, and so by the 1950s serious attempts to build a rational foundation for asymmetric synthesis were in place. One of the most conspicuous of these was the extensive systematic study of asymmetric induction

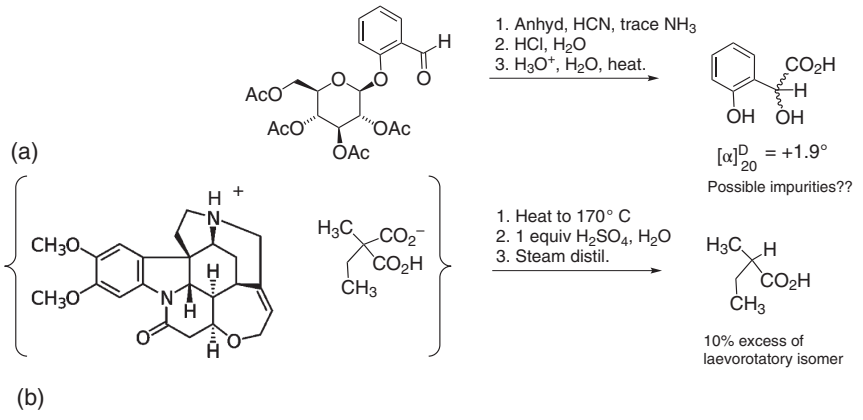


Figure 1.3 Early attempts at asymmetric synthesis: (a) Source: Based on McKenzie [20]. (b) Source: Marckwald [21] and Erlenmeyer et al. [22].

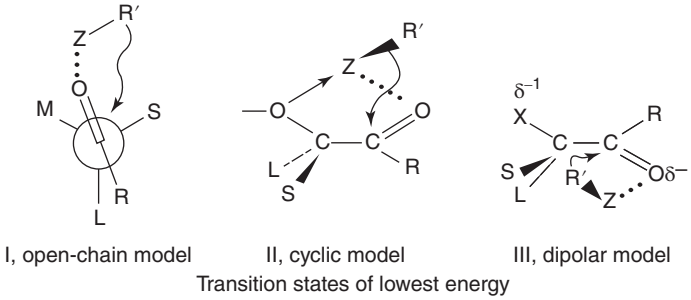


Figure 1.4 Cram's original model for 1,2-asymmetric induction. Source: Reprinted with permission from Cram and Wilson [24]. © 1963 American Chemical Society.

by Cram and coworkers. He was largely concerned with the relative configuration of diastereomers, generated through addition of nucleophilic reagents to ketones, but also recognized base-catalyzed interconversion when control reactions with pure enantiomers were performed [25, 26]. The sequence of papers led to the original Cram model for 1,2-asymmetric induction, later modified and refined [24] (Figure 1.4).

The contemporary work of Prelog was likewise directed to a precise understanding and extending of asymmetric synthesis. His analyses of mechanism and stereochemistry provided models for later workers. Bredig and Minaeff had discovered alkaloid-catalyzed aldehyde hydrocyanations, probably the first genuine example of asymmetric catalysis [28]. Prelog revisited this to elucidate the mechanism and was able to construct models that could explain the ≥25% ee involved in the cinchona alkaloid-catalyzed hydrocyanation of cinnamaldehyde [27, 29] (Figure 1.5).

All the early work suffers from a significant handicap in that polarimetry was the only rigorous tool available for estimation of enantiomeric purity – essentially so throughout the period covered by this article. If specific rotations were small, or the product was difficult to purify completely, this placed severe demands on accuracy. The optical yields quoted in the present text are taken directly from

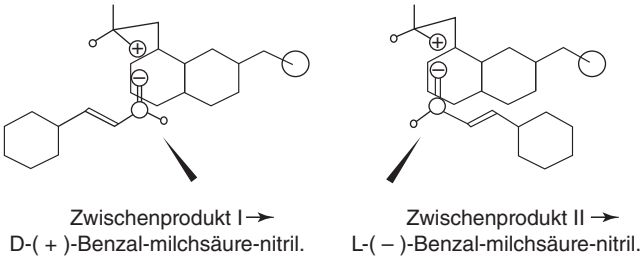


Figure 1.5 Prelog's 1954 models for alkaloid-catalyzed enantioselective HCN addition to cinnamaldehyde. Source: Reprinted with permission from Prelog and Wilhelm. © 1954, John Wiley & Sons [27].

the original literature references and may suffer from these shortcomings. The advent of chiral chromatography and NMR techniques changed perspectives and facilitated the upsurge in activity in asymmetric synthesis from the mid-late1970s onward. Enantiomer separation by gas chromatograph (GC) with chiral columns was demonstrated in Gilav's 1966 publication [30] but did not enter widespread use until commercially prepared columns were accessible several years later. Chiral HPLC, currently (2019) the most widely used technique, was developed a decade later and its convenience and accuracy prevailed [31]. Increasing use of NMR made it the primary tool for characterization of organic compounds by the mid-1960s. The invention of chiral derivatizing agents, notably Mosher's acid, allowed measurement of enantiomer excess by NMR [32]. Chiral europium shift reagents enabling direct NMR determination on a reaction product followed soon afterward [32]. These advances were critical in moving asymmetric catalysis, including hydrogenation, to a central role in synthesis. Catalytic reactions need careful optimization and without access to rapid analytical techniques that would have been a strong deterrent.

It makes a useful exercise to make comparisons of the first discoveries in asymmetric hydrogenation (1968–1972) with the contemporary state of the art in asymmetric synthesis [33]. The examples selected are intended to illustrate the breadth of effort in and shortly before that time, rather than provide a comprehensive survey.

Hydroboration of Alkenes afforded the first opportunity for a practical and general laboratory asymmetric synthesis from 1961 onward. The principle is simple in that the chiral entity lies in a natural product-derived enantiomerically enriched borohydride, and after hydroboration of the desired alkene, the borane reagent is removed stoichiometrically by oxidation [34, 35]. After further developments, a versatile synthesis of secondary alcohols derived from *cis*- or cyclic alkenes with 48–91% optical yield became available (Figure 1.6).

Asymmetric Diels–Alder Reactions are potentially of two types in that one reactant may bear an auxiliary resolved chiral group leading to asymmetric induction,

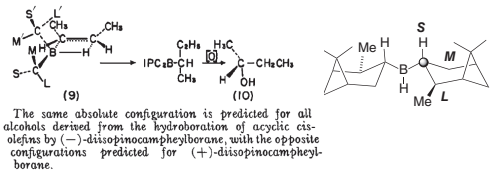


Figure 1.6 H. C. Brown's model for the asymmetric hydroboration of alkenes. Source: Based on Brown and Zweifel [34].

or alternatively the cycloaddition reaction may be driven by asymmetric catalysis, normally through chiral Lewis acid attachment to a basic group in the dienophile side chain. Early work was exclusively in the former category [36]. Walborsky's 1963 paper gave interesting insights; very low optical yields were obtained in the reaction of dimenthyl fumarate with simple dienes unless an achiral Lewis acid catalyst ($TiCl_4$ and $SnCl_4$) was present to activate the dienophile when values up to 78% could be obtained [37]. Further work by Farmer and by Sauer extended these results with varied reactants and Lewis acids [38, 39].

Asymmetric Ketone Reductions. Stereospecific NADH-promoted reductions of carbonyl compounds play a central role in metabolism and had challenged synthetic imitation. The challenge was met through Corey's need for a diastereomerically pure single secondary alcohol intermediate in his prostaglandin synthesis. He achieved this through preparing an enantiomerically pure borohydride reagent from limonene with careful optimization. Further improvement effected through precise changes to the adjacent ester group gave 92 : 8 selectivity in the desired step [40, 41] (Figure 1.7).

Asymmetric Additions to Ketenes. In a series of papers beginning in 1960, Pracejus made a robust kinetic and mechanistic study of a simple asymmetric reaction – the catalytic addition of nucleophiles to prostereogenic ketenes RR′C=C=O [42]. Addition of MeOH was effectively catalyzed by alkaloid bases, but only acetylquinidine gave optical yields ≥50%, and that only at temperatures below −80 °C, with an optimum of 74% at below −100 °C; Figure 1.8.

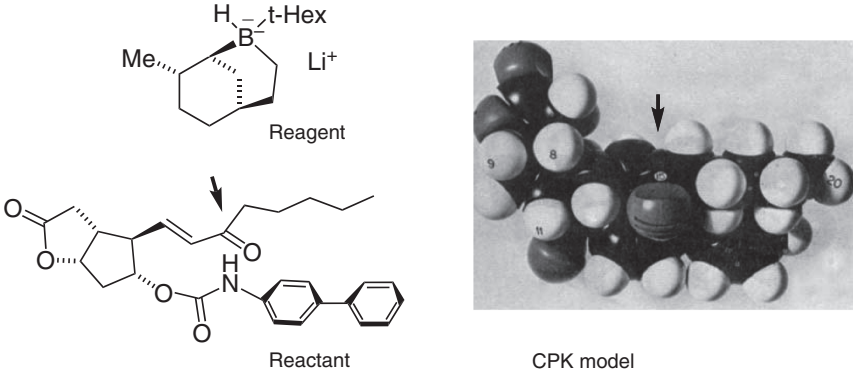


Figure 1.7 Chiral borohydride reduction of a prostaglandin precursor: CPK model. Source: Corey et al. [40], with permission from the American Chemical Society.

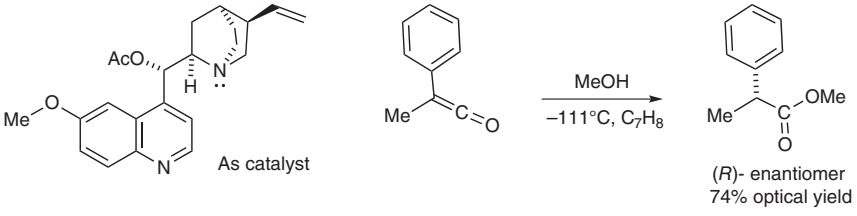


Figure 1.8 Catalytic asymmetric synthesis of α-chiral esters according to Pracejus.

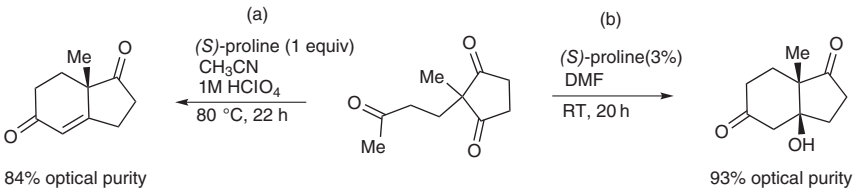


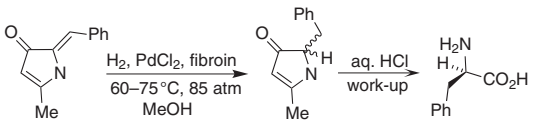
Figure 1.9 Early examples of the asymmetric aldol reaction: (a) Source: Based on Eder et al. [43]. (b) Source: Based on Hajos and Parrish [44].

Catalytic Asymmetric Aldol Condensations. The Robinson–Michael addition reaction was a standard method for preparing ring-fused cyclohexenones; the ring-closure reaction generates a new asymmetric center, and it was utilized in the preparation of the CD ring moiety in steroids. In 1971, two patents were published within weeks from separate pharmaceutical companies that demonstrated a practical method for the catalytic asymmetric synthesis of indenones (i.e. ring CD of steroids) and octalindiones in high enantiomer excess, with a simple amino acid as catalyst, preferably proline [45, 46] (Figure 1.9). The follow-up papers appeared in 1971 and 1974 [43, 44]; hence, the procedure is often called the Hajos–Parrish–Eder–Sauer–Wiechert reaction to acknowledge the dual discovery; the first two authors were based at Hoffman la Roche (New Jersey) and the other three at Schering (Berlin). Of all these early results in asymmetric synthesis, this has had the most lasting impact through the much later development of the acyclic asymmetric aldol reaction – and the (re)birth of organocatalysis [47].

1.4 Early Developments in the Asymmetric Heterogeneous Hydrogenation of Alkenes

Catalytic hydrogenation was known in the late nineteenth century. James Boyce (USA) converted plant oils into reduced edible oils for commercial use by hydrogenation over a nickel catalyst, but it was his French contemporary Paul Sabatier who undertook a systematic study of the reaction, introducing the general use of hydrogenation into organic synthesis. He demonstrated that finely divided metals could catalyze the hydrogenation of double, triple, and aromatic bonds [48].

When a C=C double bond is unsymmetrically disubstituted either at one or both termini, hydrogenation gives rise to enantiomers, depending on the face of H_2 addition, with the potential for catalytic control. This was recognized far earlier than any practical realization of asymmetric synthesis. So how could an asymmetric heterogeneous hydrogenation catalyst be created? Klabunovskii's approach involved depositing metals on single-handed α-quartz powder. The hydrogenation of ethyl 2-phenylcinnamate proceeded at 135 °C to a product that had a defined but very low optical rotation [50, 51]. Asymmetric hydrogenation reactions of higher selectivity were carried out by Akabori. He demonstrated that $PdCl_2$, deposited on silk fibroin and prereduced, catalyzed an imine–amine hydrogenation to a phenylalanine precursor in c. 25% optical yield. A similar approach was used with an alkene precursor



Optical yield (D)-phenylalanine, %	
Silk fibroin	36
Acetylated silk fibroin, wild	32
Acetylated silk fibroin, cultured	66

Figure 1.10 Asymmetric alkene reduction effected by chirality transfer from a metal supported on a natural protein. Source: Data from Izumi et al [53], and see also Izumi's 1971 review [54].

of phenylalanine, giving the desired product in 36% optical yield. This was claimed to be the first synthetic asymmetric catalyst, albeit using the natural chirality of fibroin. By employing acetylated fibroin from cultivated silkworms, an optical yield of 66% was achieved [52–54] (Figure 1.10). The current successful examples of heterogeneous asymmetric hydrogenation, arising from Orito's work on Pt/cinchona catalysts, continue the emphasis on C=N and C=O asymmetric reductions but with less encouraging results for C=C reductions [49].

Asymmetric induction in the heterogeneous hydrogenation of chiral alkenes where a stereogenic center is in proximity to the alkene had been observed in several distinct cases using unmodified metal catalysts. A very early example due to Bergmann and Tietzmann showed that enantiomerically enriched phenylalanine was formed on hydrogenation, and then hydrolysis, of the mixed diketopiperazine from (L)-proline and dehydrophenylalanine; the specific rotation of the crude product indicates high diastereoselectivity arising from asymmetric induction. Remarkably, the reversed product configuration was observed for hydrogenation of the ring-opened amination product from the bicyclic substrate [55] (Figure 1.11). In subsequent publications, Schmidt and coworkers endorsed and refined the basic

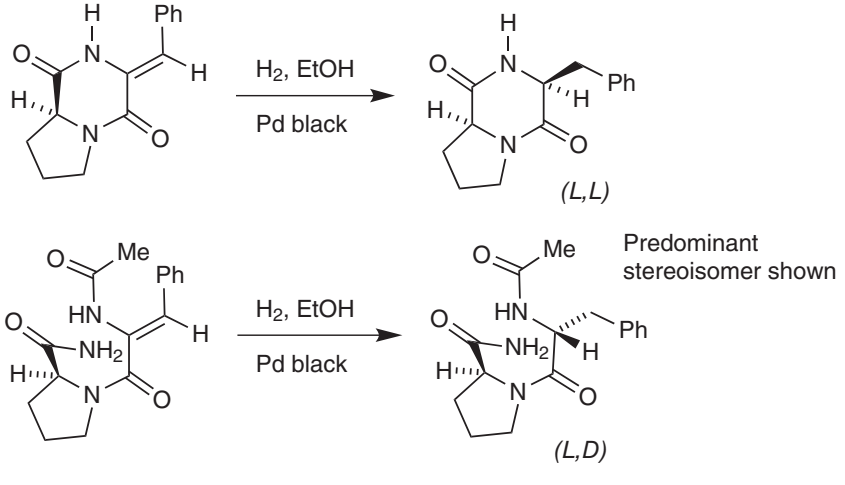


Figure 1.11 Hydrogenation of prolyl-dehydrophenylalanines according to Bergman and Tietzmann.

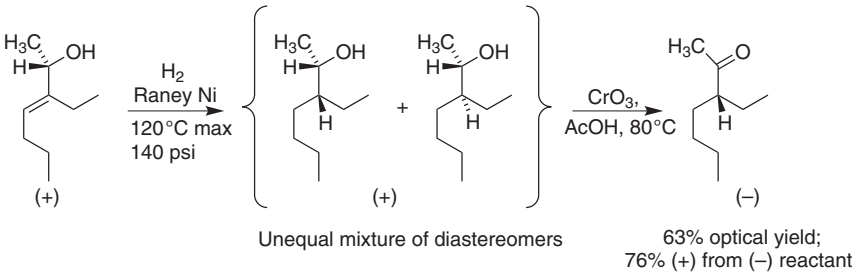


Figure 1.12 Asymmetric induction in hydrogenation; the (*R*–) configurational correlation was defined in later work by Mori et al. [58].

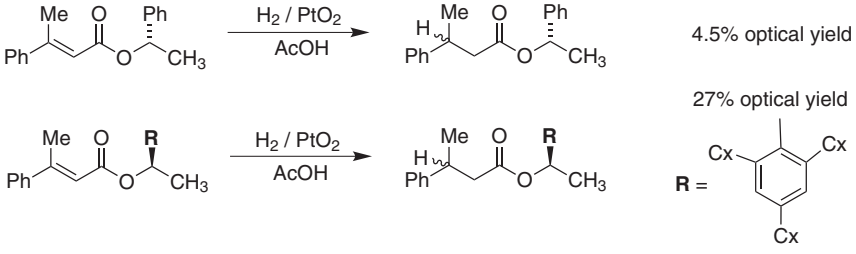


Figure 1.13 Hydrogenation of enantiomerically pure β-methylcinnamic acid esters. Source: Based on Arcus et al. [60].

elements of this work; proline was shown to be a necessary component for high diastereoselectivity [56, 57].

In a sequence of studies with simple acyclic reactants, Arcus and coworkers discovered very early examples of alkene hydrogenation directed by a hydroxyl group. He resolved his allylic alcohol reactant (Figure 1.12) and hydrogenated each hand separately to produce an unequal mixture of diastereomers. The level of stereoselectivity was revealed by oxidation of the secondary alcohol while retaining the new asymmetric center created in the hydrogenation reaction [59, 60].

Prelog systematically investigated steric effects on diastereoselectivity in hydrogenation, varying the bulk of the substituents at the stereogenic center remote from the alkene, in the further examples shown in Figure 1.13 [61].

In summary and despite much interesting work, there was little prospect of a synthetically useful heterogeneous asymmetric catalyst *for alkene reduction* by the early 1970s [62].

1.5 The Development of Rhodium Asymmetric Homogeneous Hydrogenation of Alkenes

Initial Work. After 1945, the practical use of metal catalysts was extensively explored. One of the first major applications in industry was the hydroformylation of terminal

alkenes based on Roelen's pioneering work [63]. It was realized that hydroformylation of alkenes using $HCo(CO)_4$, the preferred homogeneous catalyst, could be accompanied by hydrogenation of the product aldehyde as a side reaction, and sometimes hydrogenation of the reacting alkene was observed (e.g. with dienes) [64]. There was an early demonstration of alkene hydrogenation as the preferred reaction pathway; high-temperature reaction of methyl acrylate with CO/H_2 with $Fe(CO)_5$ as catalyst in benzene leads to predominant reduction to methyl propionate as the main product at low CO pressure [65]. Halpern then achieved homogeneous hydrogenation under ambient conditions. In aqueous 3 M HCl, the coordination complex $(NH_4)_2RuCl_6$ catalyzes the hydrogenation of simple unsaturated acids, and an alkene–Ru complex may be observed spectroscopically [66]. At about that time, the catalytic hydrogenation of alkenes by added tributylborane under forcing conditions was demonstrated [67].

Rhodium–Phosphine Hydrogenation Catalysts. In the following years, many further examples of homogeneous hydrogenation were recorded, although none held the promise of a general synthetic method. This goal was realized with the introduction by Wilkinson and coworkers of the low oxidation state PPh_3 complexes of rhodium and ruthenium that are simply prepared and bench stable. They showed that $ClRh(PPh_3)_3$ is a general homogeneous catalyst for alkene reduction, allowing extensive physicochemical studies [68–70], while $HRu(PPh_3)_3Cl$ is a selective catalyst for hydrogenation of terminal alkenes [71, 72]. The efficacy of "Wilkinson's catalyst" for a range of homogeneous alkene hydrogenations brought rhodium catalysis into the mainstream of organic chemistry. The advantages in selectivity over heterogeneous processes were manifestly demonstrated by selective monohydrogenation of dienes [73], selective deuteration [74], and face-selective hydrogenations in steroidal cycloalkenes [75] (Figure 1.14). Horner made a detailed study of reactivity with *in situ* generated P_3RhCl complexes and demonstrated that electron-releasing aryl groups enhanced reactivity. This work suggested that the catalytically active species was the dihydrido complex ClH_2RhPS, where S was a labile solvent molecule displaceable by the alkene [76].

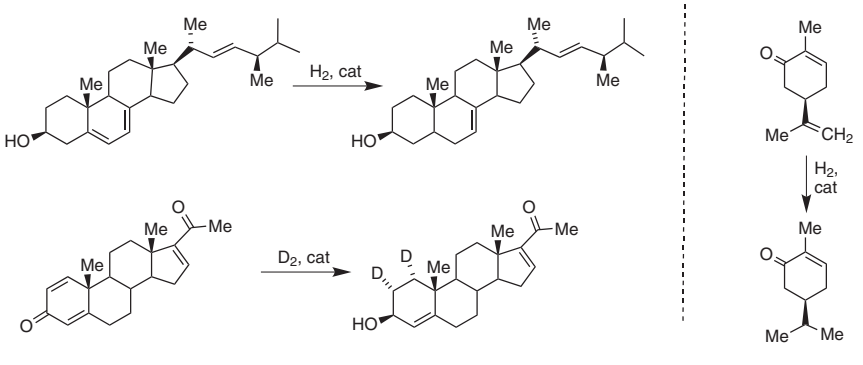


Figure 1.14 Early examples of selectivity in homogeneous hydrogenation with Wilkinson's catalyst.

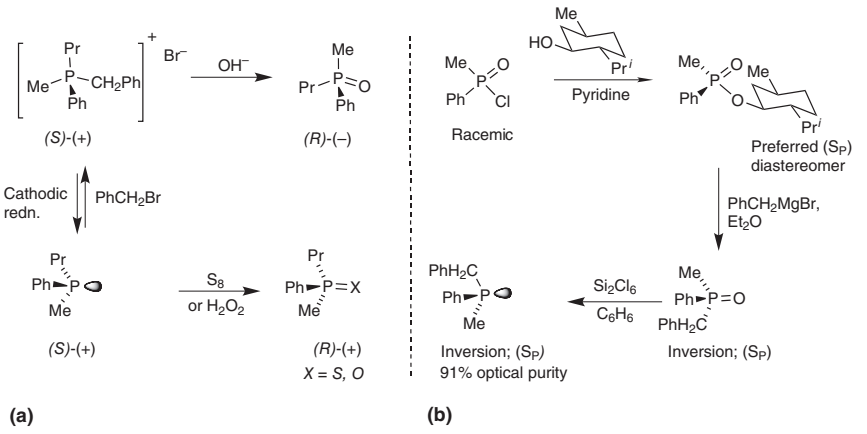


Figure 1.15 (a) Enantiomerically pure phosphines; (a) Horner's stereochemical correlation set; (b) Mislow's method for asymmetric synthesis of tertiary phosphines.

Phosphorus chirality . By the early 1960s it was known that enantiomerically pure benzylphosphonium salts underwent a stereospecific transformation to the corresponding phosphine oxide in aqueous base through debenzylation. Horner extended this chemistry, showing that electrochemical reduction of resolved phosphonium salts led to fragmentation of the most labile substituent with stereospecific formation of the phosphine, typically through loss of a benzyl group. The phosphines produced racemized with half-lives of a few hours at 130 °C [77, 78]. The absolute configuration of (*S*)-(+)-MePrPhP was established by the chemical correlation with the benzylphosphonium salt of the established absolute configuration [79]. In a later work, the direct reduction of phosphine oxides to the corresponding phosphines using $HSiCl_3$ was shown to occur with only a small loss of enantiomeric purity [80]. Mislow's work was initially directed to quantifying the slow pyramidal inversion in compounds of third-row elements, especially compounds of sulfur and phosphorus [81]. This enabled the development of a versatile synthesis of enantiomerically pure phosphine oxides using menthol as chiral auxiliary [82, 83]. Furthermore, he improved Horner's silane reduction procedure, using Si_2Cl_6 in place of $HSiCl_3$ [84]. These advances laid the groundwork for the rapid utilization of phosphine ligands in asymmetric hydrogenation (Figure 1.15).

First Rh-catalyzed asymmetric hydrogenations: Catalytic asymmetric hydrogenation began in 1968. A prior insight was given by Horner's comment in a paper on the effect of phosphorus ligands on alkene isomerization vs. hydrogenation: "*Aliphatische und grossvolumige Substituenten verlangsamen die Hydrierung. Diese Fakten müssen bei der von uns geplanten* ***stereospezifischen Hydrierung mit optisch aktiven tertiären Phosphinen*** *berücksichtigt werden."* [76]. Shortly thereafter, however, Knowles published the first experimental demonstration using an optically impure tertiary phosphine prepared according to Mislow's procedure. The Rh(III) complex hydrogenated unsaturated carboxylic acids at 60 °C in up to 15% optical purity [85] (Figure 1.16). The paper ended on a prophetic note "*The inherent generality of this method offers almost unlimited opportunities for matching*

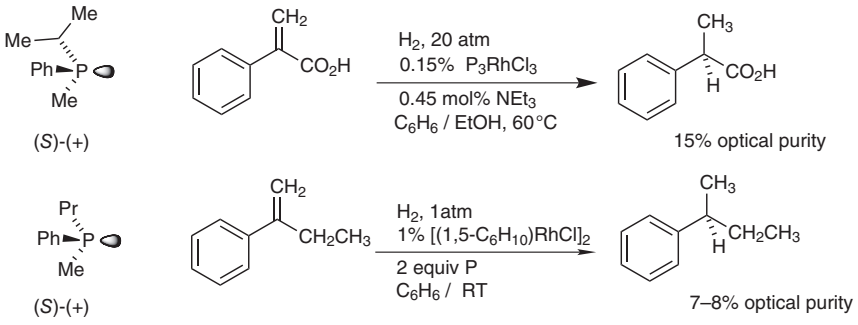


Figure 1.16 Asymmetric hydrogenations presented in the original Horner and Knowles papers.

substrates with catalysts in a rational manner and we are hopeful that our current effort will result in real progress towards complete stereospecificity." His emphasis on the need for catalyst optimization in asymmetric catalysis has later been proved to be correct. Possibly this publication forced Horner's hand, since it was quickly followed by their asymmetric synthesis of 2-phenylbutane in 7–8% optical yield through a similar asymmetric hydrogenation [86]. These papers were not widely publicized at the time; perhaps, the untapped potential had not yet been widely recognized.

Taking a distinct approach, McQuillin showed that a partially reduced Rh(III) complex incorporating an enantiomerically pure formamide catalyzed the hydrogenation of an unsaturated ester with up to 60% optical purity [88]. Crabtree indicated that the application of homogeneity tests to hydrogenations with this type of catalyst indicated that the catalytic species was colloidal or nanoparticulate rather than homogeneous. This was assumed to apply to McQuillin's work, although the homogeneity of his actual catalytic system was not specifically tested [89]. Morrison's contribution offered comparable levels of selectivity. He reasoned that chirality in the organic backbone of a tertiary phosphine might be easier to achieve than chirality at phosphorus. The synthesis of neomenthyldiphenyl phosphine involved difficult purification but was rewarded by the hydrogenation of a series of unsaturated acids including both α- and β-cinnamic acids in up to 61% optical yield, albeit under fairly forcing conditions [87] (Figure 1.17).

In a lecture published in late 1970, Knowles's work was extended to other enantiomerically enriched dialkylphenylphosphines, but optical yields ≤30% were obtained. But from the question session at the end of the lecture: *"**DR. ATKINSON**: I have another question based on the phosphorous rhodium bonds, a preferred conformation, that, of course, would not be the only conformation. Did you consider the possibility of using a bi-phosphine, optically active? **DR. KNOWLES**: We've considered that very strongly. The main problem is that of synthetically making it*" [91]. That consideration became reality with Kagan's first paper on asymmetric hydrogenation in early 1971. Using tartaric acid as the chiral scaffold, the ensuing DIOP ligand was the first effective chelating biphosphine for asymmetric catalysis. The favored reactants were dehydroamino acids, and optical yields of up to 72% were obtained

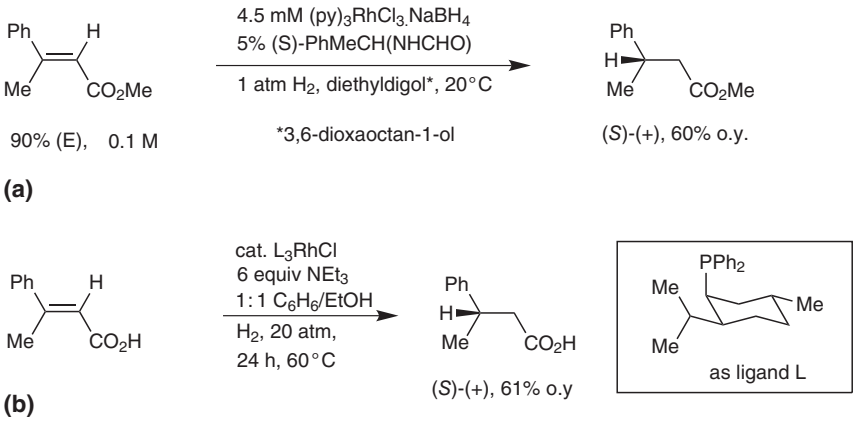


Figure 1.17 (a) McQuillin's chiral amide-catalyzed asymmetric hydrogenation. (b) Morrison's application of the NMDPP ligand in asymmetric hydrogenation. Source: Based on Morrison et al. [87].

under gentle conditions [92, 93]. This was improved to 80%, for the synthesis of *N*-acetyltyrosine, in the ensuing full paper [94]. In a later work with DIOP rhodium catalysts, building on the development of cationic dialkene bisphosphine complexes by Schrock and Osborn to provide the precursor [95], enantiomer excesses up to 92% were recorded with a simple enamide [90] (Figure 1.18). First Knowles, and then Kagan, had filed patents on asymmetric hydrogenation with 1970 priority dates, recognizing the potential for commercial as well as academic applications [96, 97].

Practical catalytic asymmetric hydrogenation. A further paper from Knowles and the Monsanto group revealed that the amino-acid L-Dopa, the standard treatment for alleviation of the symptoms of Parkinson's disease, was accessible to synthesis by asymmetric hydrogenation [98]. Their initial breakthrough came using (*R*)-(o-anisyl)PPhMe, (*R*)-PAMP, previously prepared by Mislow [84], that enabled hydrogenation of the protected (L)-Dopa precursor in 58% optical yield, starting with ligand of c. 95% optical purity. From that point, systematic optimization through ligand synthesis provided their preferred ligand (o-anisyl)PCxMe ((*R*)-CAMP) and gave the desired product with up to 90% optical purity. There is a strong positive nonlinear effect favoring (*R*,R**) over (*R,S*) for the bis-phosphine rhodium solvate intermediate derived from (*R*)-PAMP observed by NMR in solution, and in this case the effect could have diminished any contribution from (*S*)-impurity [99] (Figure 1.19).

This was almost but not quite good enough to provide the basis of a commercial process. Further synthesis, surely guided by Kagan's effective use of a chelating biphosphine [93], led to the oxidative dimerization of the P-oxide of (*R*)-CAMP, followed by stereospecific reduction to give (*R,R*)-DIPAMP [100, 101]. In this "double asymmetric induction" dimerization, the 95% enantiomeric purity of the monophosphine is amplified to c. 99% [102]. This synthesis formed the basis of the Monsanto (L)-DOPA process used therapeutically for over 30 years [103] (Figure 1.20). The

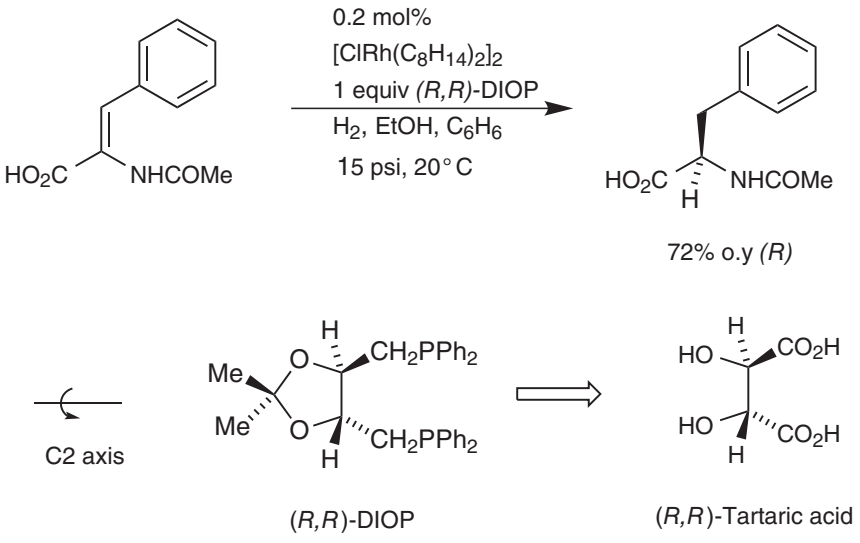


Figure 1.18 (*R,R*)-DIOP, derived from natural tartaric acid, forms an efficient and stereoselective rhodium catalyst for asymmetric hydrogenation. Source: Based on Sinou and Kagan [90].

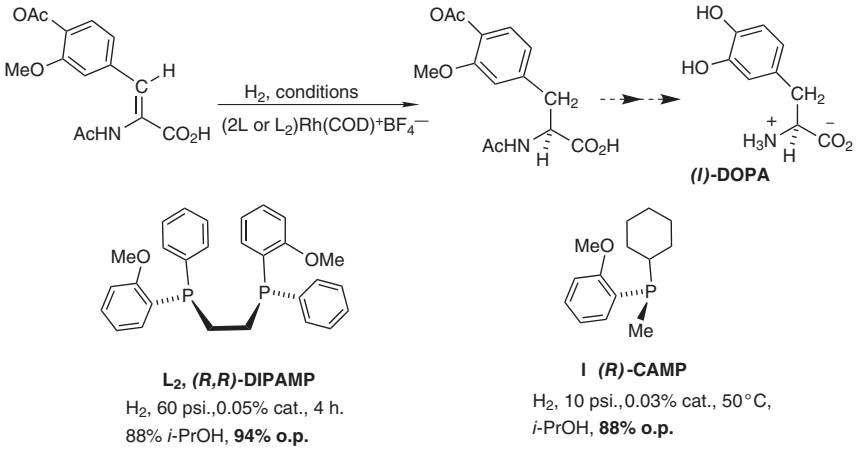


Figure 1.19 The asymmetric hydrogenation of an L-DOPA precursor; comparison of the bidentate (*R,R*)-DIPAMP and monodentate (*R*)-CAMP ligands.

Knowles and Kagan papers in particular led to an upsurge of interest in broadening the scope of asymmetric hydrogenation and in asymmetric catalysis more generally. In 2001, William Knowles shared a Nobel Prize with Ryoji Noyori (Ru in asymmetric hydrogenation and transfer hydrogenation, 1985 onward) and Barry Sharpless (Ti in asymmetric epoxidation, 1980 onward). The powerful influence of the early catalytic asymmetric hydrogenations on the direction of organic chemical research thereafter

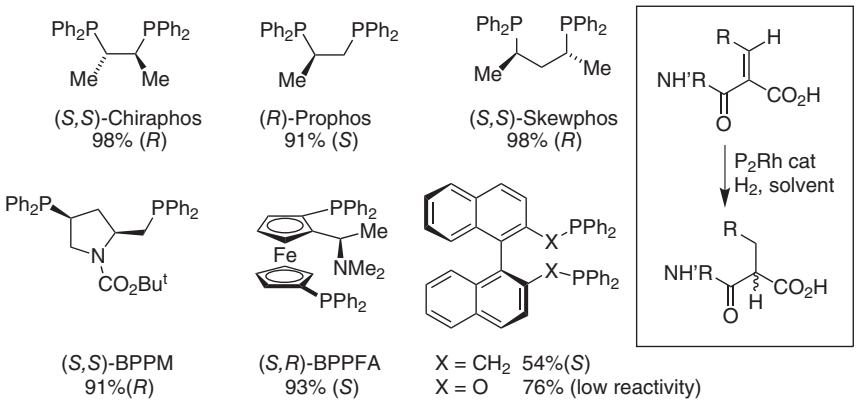


Figure 1.20 The efficiency of early examples of chelating biphosphines in asymmetric hydrogenation. Optical yield data is the highest value obtained with that ligand.

is abundantly clear. Contemporary organic chemistry widely engages catalytic reactions, and the rapid development of asymmetric rhodium hydrogenation up to 1975 should be regarded as a true "paradigm shift" [104].

With these early results, rhodium asymmetric hydrogenation opened up new challenges, both to extend the scope and to broaden the basis of ligand design. The second of these provided a purely synthetic challenge that was widely adopted, following the principles first demonstrated by Kagan: a moderately rigid scaffold, supporting two phenylphosphino or arylphosphino groups that could chelate to rhodium. An initial success was achieved by Bosnich using scaffolds based on enantiomerically pure analogues of diphenylphosphino-ethane or diphenylphosphino-propane [105]. 4-Hydroxyproline [106], or a 1,2-disubstituted ferrocene [107], provided alternative approaches. The potential of a biaryl ligand with asymmetry based on hindered rotation between atropisomers was recognized; both Kumada and Hayashi, and Grubbs, used a binaphthyl scaffold with spacers to the phosphine links, but only moderate enantiomer excesses were achieved in asymmetric hydrogenation [108, 109] (Figure 1.20). Early reviews could point to the broadening interest in the field, and also note the limitation to functional alkenes capable of chelation to rhodium in catalysis [110].

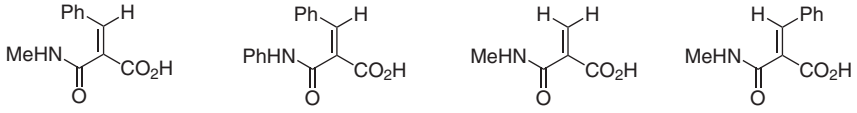
1.6 The Development of Ruthenium Asymmetric Homogeneous Hydrogenation of Alkenes

Ruthenium phosphine complexes had played a role in the development of effective homogeneous hydrogenation, which encouraged the development of asymmetric catalysts. The first success came from James's work in which the isolated complex $Ru_2Cl_4[DIOP]_3$ catalyzed the hydrogenation of *N*-acetyldehydroalanine in 60% optical yield, similar to the result when $HRh[DIOP]_2$ was employed and to the same preferred enantiomer [111, 112]. Later studies used $HRuCl[DIOP]_2$ or

carbonyl ruthenium clusters such as $H_4Ru_4(CO)_8$[DIOP] for catalysis of hydrogenation [113]. This early work had demonstrated the potential of ruthenium complexes in asymmetric hydrogenation but did not lead to practical synthetic outcomes [114]. At about the same time, Noyori's efforts were directed toward the initially difficult synthesis and resolution of BINAP (resolved enantiomers of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), as described in a retrospective review [111]. The first indication of success lay in a rhodium complex-catalyzed asymmetric synthesis of amino-acid derivatives that rivaled the optical purities achieved by Knowles or Bosnich in their best cases [115]. Optimization required fine-tuning with regard to the nature of the catalyst and lower substrate concentrations, however, and significantly higher optical yields were obtained with *N*-benzoyl enamides than with *N*-acetyl enamides. Subsequently, other research groups reported lower enantioselectivity in asymmetric hydrogenations with BINAP under standard conditions [116]. The utility of BINAP in rhodium catalysis was underscored by the demonstration of an industrially useful stereospecific alkene isomerization, however. This work linked catalyzed isoprene dimerization with fragrances related to monoterpenes [117].

Ruthenium BINAP hydrogenation chemistry was initiated by Ikariya [118]. He was able to synthesize a reactive dimeric Ru complex $Ru_2Cl_4[BINAP]_2$ directly from the corresponding cycloocta-[4, 8]-diene precursor and to show that it was a good hydrogenation catalyst for enamide substrates under mild conditions, giving the opposite enantiomer of product to BINAP–Rh hydrogenation for all (*Z*)-dehydroamino acid derivatives, albeit the same enantiomer as BINAP–Rh for the one example of an (*E*)-isomeric substrate tested; Figure 1.21.

At this stage it was far from obvious that using Ru complexes might confer any advantage over Rh in asymmetric hydrogenation. Further progress depended on the identification of a problem that had unsatisfactory solutions with existing methods. The monoterpene citronellol, existing in Nature as both (*R*)- and (*S*)-enantiomers, is commercially important for its flavor and fragrance properties. In principle, it is accessible by the asymmetric hydrogenation of geraniol or its (*Z*)-isomer nerol (Figure 1.22). Using ClRh(COD)((*R*)(+)BINAP) as catalyst at ambient temperature and elevated H_2 pressure, reaction occurred exclusively at the allylic double bond



Ru catalysis: Ru_2Cl_2[(*S*)-BINAP]$_2$, NEt_3, 2 atm. H_2, 35 °C, (EtOH, THF 1 : 1)

86% (*S*) **92% (*S*)** **76% (*S*)** **65% (*S*)**

Rh catalysis: Rh([(*S*)-BINAP](Solv)$_2$])$^+$ ClO_4^-, 3–4 atm. H_2, RT; (Solv = EtOH or THF)

84% (*R*) **96% (*R*)** **67% (*R*)** **87% (*S*)**

Figure 1.21 Comparative data for optical yields in the asymmetric hydrogenation of dehydroamino acids. Source: Data from Ikariya et al. [118].

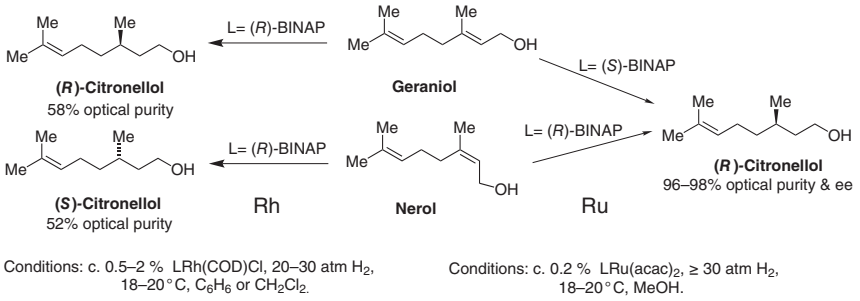


Figure 1.22 Comparison of rhodium and ruthenium BINAP catalysts in the asymmetric synthesis of citronellol.

giving (*R*)-citronellol in 58% ee (by hplc). Conversely, nerol gave the (*S*)-enantiomer in 52% ee [119]. Later work described ruthenium hydrogenation, notably using the catalyst precursor $(CH_3CO_2)_2$Ru(BINAP) or its trifluoroacetate analogue, described in patents [120]. The reaction occurred in high enantioselectivity for both geraniol and nerol under accessible reaction conditions and was further applied to both allylic and homoallylic alcohols [121].

It was clear that asymmetric hydrogenation by Ru complexes still required a chelating functional group in proximity to the reacting alkene but with wider substrate tolerance than for rhodium. A sequence of papers demonstrated that principle, further applied to unsaturated acids [122], benzomorphans and morphinans (*N*-formylenamides) [123], and isoquinoline alkaloids (*N*-acyl enamides) [124]. A major driving force for optimization of ruthenium asymmetric hydrogenation was the industrial potential, providing a parallel to rhodium catalysis for the synthesis of L-DOPA. In this particular case, Takasago Perfumery Co. synthesized citronellal from geraniol with BINAP as the Ru ligand, both for its direct use and also for application as an intermediate in Vitamin E synthesis. Their efficient BINAP–Ru-catalyzed process worked to provide 350 tons per annum of the desired product [125]. Rhodium and ruthenium asymmetric hydrogenations of prochiral alkenes continue to provide an important methodology in modern pharmaceutical process chemistry [126].

1.7 Conclusions

The original intent was to understand why there was a time lapse of nearly 70 years between identifying the aim of using synthetic chemistry to achieve effective asymmetric synthesis and its realization. Some of the key factors are clarified, especially the introduction of new methods for the measurement of enantiomer excess, that are not dependent on assaying by polarimetry. These advances were both instrumental (GC, LC, and NMR) and chemical (Mosher reagent and lanthanide shift reagents). With better methodology, the field advanced rapidly. The clearest advance came with the recognition that Wilkinson's catalyst provides a potential pathway for catalytic

asymmetric hydrogenation and the diverse approaches of Knowles and Kagan. But there are other factors in play, deserving more detailed scrutiny. Early workers had no design template for an effective asymmetric synthesis and insufficient guidance on the variations in reactant structure that are presently taken for granted in systematic optimization procedures. The "gold rush" era of asymmetric synthesis was closely linked to the timing of general advances in organic synthesis based on a better understanding of structure and mechanism, the discovery of new stoichiometric and catalytic reactions, and a better appreciation of enzymology.

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