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COMMENTARY

Pioneering Perspectives on Asymmetric Hydrogenation†

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Asymmetric hydrogenation (AH)[1,2] has become such a mature field that present workers have almost forgotten its modest beginnings. It was all made possible by Wilkinson's discovery that triphenylphosphine/Rh complexes catalyzed hydrogenation of olefins in solution.[3] Now, we are no longer dealing with catalysis on a metal surface but with a coordination compound in molecular dispersion. Thus, one could use the power of the synthetic chemist to vary structures without limit to optimize results in a more or less rational manner. Asymmetric catalysis, using chiral ligands, presented a particularly demanding challenge, and in retrospect, it was quite surprising that simple small ligand molecules could achieve efficiencies and rates rivaling enzymes. This success in achieving asymmetric bias has even changed our terminology. We seldom say "optically active" any more, and the term "asymmetric induction", implying action at a distance, has become obsolete. Indeed, the chemist has entered the domain usually reserved for enzymes, and we have yet another instance in the annals of chemistry where the monopoly of nature has been broken.

Historically, things began in 1968 with the chiral phosphine/Rh-catalyzed AH of simple prochiral olefins, albeit with low enantioselectivity.[4] Within a relatively short period, the first efficient chiral ligand, CAMP, was discovered, giving an 80% enantiomeric excess (ee) on dehydroamino acids.[5] This modest result, fortunately coupled with easy separations, enabled the commercial production of the anti-Parkinsonian drug L-DOPA at Monsanto, where AH was the key step.[1] The field really got underway with the discovery of C_2-chiral DIOP by Dang and Kagan,[6] followed by Monsanto's improved C_2 bisphosphine DiPAMP.[1] This success generated a lot of interest, and for the next decade, a considerable number of efficient bisphosphine ligands of wildly different structures were discovered, useful only on enamide precursors of α-amino acids and closely related substrates and little else. Notably, the important α-arylacrylic acids went poorly. This is quite typical of progress in science. Once a thing is shown to work, then others come in and show it can be done in a lot of different ways.

By the early 1980s, progress in AH had seemed stalled, until the advent of BINAP.[2] This axially dis-symmetric C_2 bisphosphine ligand worked well with Rh^I but offered no advantage over other candidates. The first breakthrough came when Rh^I was replaced with Ru^{II}. Both metals gave high ee values in AH of enamides but with an opposite sense of asymmetric bias. This is due to the operation of different catalytic cycles, namely, an unsaturate/dihydride mechanism for Rh^I versus a monohydride/unsaturate pathway for Ru^{II}. This new BINAP/Ru system greatly extended the reaction scope to allow for the AH of a wide range of functionalized olefins. The list includes α-arylacrylic acids and a lot of other α,β- and β,γ-unsaturated carboxylic acids, as well as allylic and homo-allylic alcohols and many other things. Strategic application of Ru chemistry allowed extension into all kinds of ketones and many other substrates still using BINAP as the chiral ligand. None of the previous phosphines offered anything like this kind of generality. Thus, BINAP, coupled with Ru^{II} in a variety of ways, comes about as close as we are going to get to a universal ligand.[2]

In the 1990s, the discovery of DuPhos with Rh showed that fast catalysis for amino acids could be achieved at 99–100% bias.[7] Now, the near quantitative efficiency of enzymes has been accomplished. An ee of 90% only requires an energy difference comparable with the rotation barrier in ethane, but as we approach 100%, these differences become quite significant. It is truly remarkable that these small molecule catalysts, which cannot have the capability of a lock and key fit like enzymes, can achieve such high efficiency. ee values of 99% are a trivial advance for laboratory preps, but for a large scale, where separations from residual racemate are frequently inefficient, they are very important. Again, it was soon found that a lot of other structures can give the same fast rates and high ee values.

The mechanism of the AHs has been studied in detail and fairly well worked out.[8–10] However, finding efficient catalysts still remains pretty much guesswork. Notably, asymmetric catalysis is different from stoichiometric asymmetric synthesis. The shape of the catalyst is not sufficient to achieve a practical AH, which requires not only a high ee but also a high turnover number (TON) and turnover frequency (TOF). Asymmetric catalysis is four-dimensional (4D) chemistry. High efficiency can be achieved only by combining an ideal 3D structure (*x*, *y*, *z*) and suitable kinetics (*t*).[9] Although H–H bonds are readily cleaved by transition-metal complexes, the catalytic efficiency is highly dependent upon the substrate structure, the properties of the metal, the auxiliary ligand (either anionic or neutral), and the reaction parameters, such as pressure, temperature, solvent, additive, etc. It is a global endeavor that continues to offer an exciting challenge for today's chemists.

Commercial applications of asymmetric catalysis started early on at Monsanto with L-DOPA,[1] followed 10 years later with Takasago's menthol process.[2] Since then, the technology has been used for a number of small applications. An exception is the chiral herbicide, Metolachlor,

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at Novartis, which is made by Ir-catalyzed AH in multitonnage quantities.[11] For large-scale use, these soluble catalysts have presented a major problem because of their high cost and difficult separations. It appears that this problem has been solved by choosing ligand/metal systems that give very high TONs. Typically, laboratory AH preps use a TON of 2000. For a pharmaceutical process, like the L-DOPA process, a TON of 20 000 results in acceptable catalyst costs without any recovery. Larger volume products have achieved a TON approaching 1×10^6. Thus, with these very expensive catalysts, high TON is just about as important as high ee values. It turns out to be much easier not to use much catalyst in the first place rather than rely on quantitative recoveries. In the laboratory, molecular catalysis using a BINAP/diamine/Ru complex has yielded a TON of 2.4×10^6, which will beat many enzymes.[10] In industry, 4D chemistry is much more important than in laboratory preps.[11]

Maybe the greatest use of AH will turn out to be as a labor-saving device in the laboratory to prepare chiral compounds used in testing and in synthesis in the growing field of life sciences. The availability of a variety of chiral ligands in the laboratory supply houses has made the job easy. It is remarkable that since the turn of the century new efficient ligand structures continue to appear. The vast majority of work has been with chelating bisphosphines with chirality in the carbon backbone. A rigid chelating structure is very attractive to chemists, but the facts show that it is not at all necessary. Monophosphines, like CAMP, as well as bisphosphines with chirality on the phosphorus have been neglected and are only now getting a relook, despite their original success.[1]

It is not possible to predict the future of AH and the related asymmetric transfer hydrogenation (ATH).[12] Hydrogenation is a core process in chemistry. AH and ATH are widely practiced in research laboratories, especially in the pharmaceutical industry. The progress in AH has totally changed the way that we synthesize fine chemicals. In this present era of green chemistry, where environmentally benign reactions are a "must", AH with its high yields, no byproducts, and very low catalyst usage will always play an important role.

The discovery of AH in 1968[5] was the "big bang" that created this significant field.[1,2] Recalling the past 4 decades, we have seen AH grow from a single bright point of light (Rh) to a long broad line (Rh to Ru, Ir, and others). This new dedicated special issue of *Accounts of Chemical Research* covering AH and ATH as well as the more complicated hydrogen-mediated C–C coupling indicates that the field may well be at another takeoff point, forming a wide plane or even a 3D space, just as in the 1980s. The possibilities of asymmetric catalysis are limitless.

Admittedly, the early pioneers are overwhelmed and unable to keep up with all of this activity, but instead of being dismayed, they should take pride in having started something so important and useful.

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