Ru- and Rh-Catalyzed Asymmetric Hydrogenations: Recent Surprises from an Old Reaction

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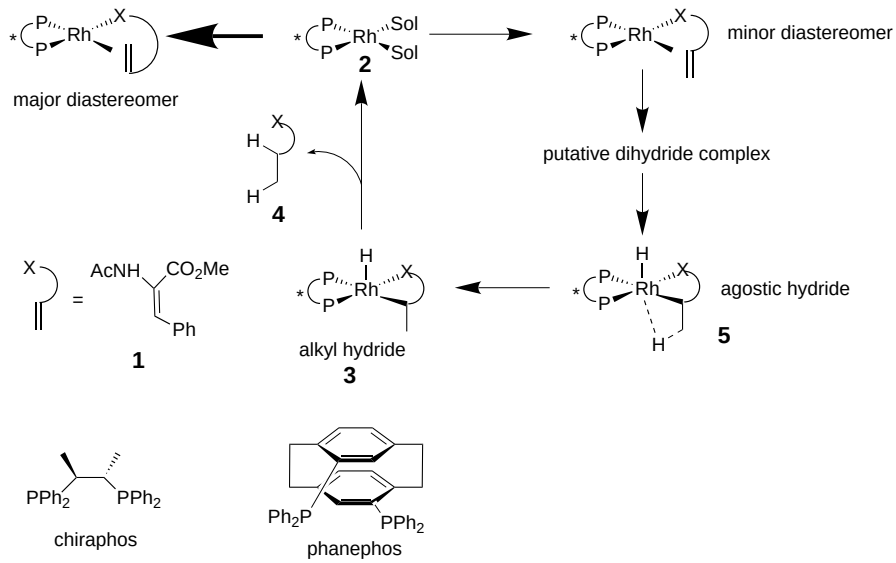
There is an increasing demand for efficiently prepared, enantiomerically pure building blocks, for example as intermediates in the production of pharmaceuticals.[1] Asymmetric catalysis holds the promise of efficiently setting up chirality and has turned into one of the most important fields at the interface between organic synthesis and organometallic chemistry.[2]

Although amazing progress has been made in the last few decades, there is still a clear need for more selective and active catalysts. The use of combinatorial and high through-put techniques has become fashionable lately, but combinatorial methods cannot be a substitute for understanding the reason behind the success or failure of a given catalyst system.[3] Ultimately, detailed mechanistic studies have to be undertaken, not only to satisfy scientific curiosity, but also to provide the understanding that is essential for the field to move ahead.[4]



Scheme 1. The classical mechanism for the hydrogenation of [Rh(bisphosphane)]$^+$. Sol = solvent.

Recently, a number of spectacular results have been published on the mechanism of Rh- and Ru-catalyzed asymmetric hydrogenations. While the classic studies of Rh-catalyzed reactions are now taught as textbook examples for the elegant elucidation of mechanisms, the field is clearly not free from surprises.[5] These unexpected results come from the groups of Brown and Bargon[6b, 7] as well as Gridnev and Imamoto.[8] A common feature of these groups is the extensive use of NMR techniques, demonstrating the extreme power of this tool.

The Rh-catalyzed hydrogenation of dehydroamino acids leading to enantiomerically pure α-amino acids is considered to be a thoroughly understood reaction based on work carried out in the research groups of Halpern and Brown.[6] However, the most recent results clearly show that we are still far from a clear understanding.

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The mechanism elucidated for the asymmetric reduction of the standard dehydroacetamide substrate methyl (*Z*)-α-acetamidocinnamate (**1**, Scheme 1) using the chiraphos–rhodium catalyst **2** was clearly shown to proceed by binding of the enamide substrate to the cationic Rh–bisphosphane complex.[6] Both the minor and the major diastereomer have been characterized by various techniques. While it could be demonstrated that the minor diastereomer reacts more rapidly with H_2, the reason for this increased reactivity is not understood. Furthermore, the expected dihydride complex has never been observed with the bisphosphane complexes examined, although the analogous compound for the prototypical Wilkinson catalyst [$(Ph_3P)_3RhCl$] is well-characterized. The first intermediate that can be observed is the alkyl monohydride **3**, which then releases the product **4** and the regenerated active catalyst. While numerous attempts have been made to find experimental evidence for the key step of the hydrogenation, which must clearly be the addition of hydrogen to the catalyst, there is little data on species appearing before the alkyl hydride. It is at this point that the groups of Bargon and Brown can combine hydrogenation using para-hydrogen with use of a new ligand (phanephos) which permits reactions at very low temperatures.[7] With this

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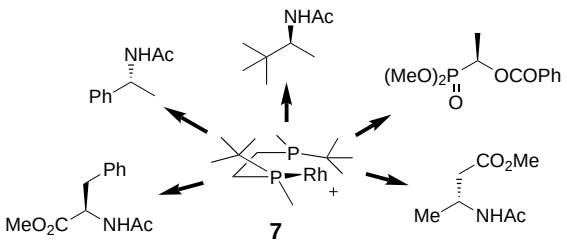
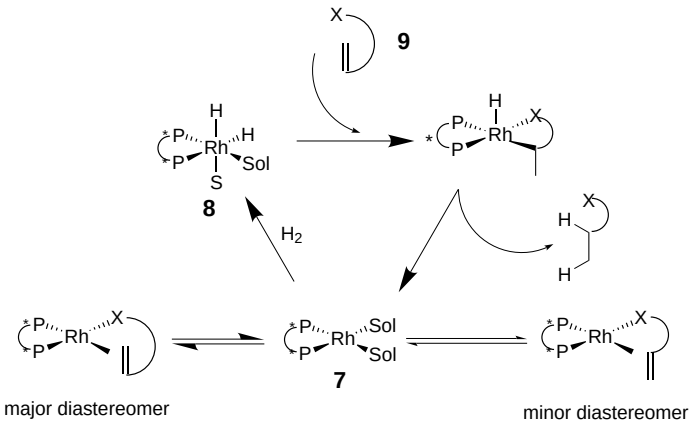
system it becomes possible to identify an agostically bound hydride **5**—that is, a species that could be imagined as lying on the pathway from the dihydrogen complex to the alkyl hydride—and to glimpse for the first time at the initial steps of this reaction. This work thus nicely adds a new facet to our understanding of the classical hydrogenation mechanism.

Recently, the group of Gridnev and Imamoto introduced the electron-rich bisphosphane ligand *t*Bu-BisP* (**6**), which is chiral at P.[8] This ligand adds to the small number of bisphosphane ligands with chirality at P, as opposed to the common attachment of a PPh_2 group onto a chiral backbone. The Gridnev/Imamoto group has demonstrated that the *t*Bu-BisP* – rhodium catalyst **7** (see Scheme 2) can reduce not only α-acetamidoacrylates, but also enamides, (*E*)-β-(acylamino)-acrylates, and protected α,β-unsaturated α-acyloxyphosphonates with high enantioselectivity and reactivity.[8] Thus the catalyst affords a useful entry to the synthesis of enantiomerically highly enriched α-amino acids, amines, β-amino acids, and α-acyloxyphosphonate (Scheme 2).



Scheme 2. Various products obtained with the *t*Bu-BisP* – rhodium catalyst **7** from Gridnev and Imamoto.

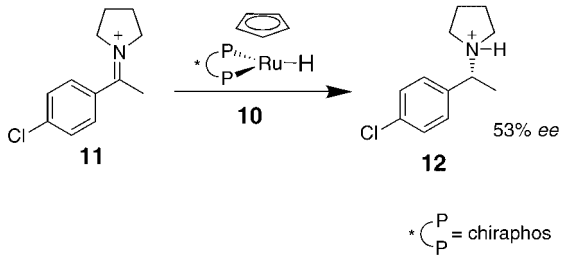
While ligand **6** is clearly an important addition to the repertoire of bisphosphane ligands, the mechanistic work of the inventors is especially notable and surprising.[8] By using their *t*Bu-BisP* ligand, the Gridnev/Imamoto group was able to show that the Rh-catalyzed hydrogenation with this electron-rich system can proceed by an entirely different mechanism (Scheme 3): As expected, the catalyst binds to the substrate, but the authors provide conclusive data that the anticipated oxidative addition of H_2 to this substrate – catalyst complex is not the major pathway. Indeed, the catalytic cycle involves the initial formation of a Rh – hydride species by oxidative addition of hydrogen to the catalyst! Complexation of substrate **9** to the Rh – hydride species **8** initiates the highly enantioselective hydrogenation. It is remarkable how the change from the traditionally used bisphosphane ligands with PPh_2 groups to a trialkylphosphane such as *t*Bu-BisP* induces a fundamental change in the mechanism of the hydrogenation.



Scheme 3. The hydride mechanism of the Gridnev/Imamoto catalyst **7**. Sol = solvent.

Rhodium – bisphosphane catalysts set the benchmark for a number of asymmetric hydrogenations, but the versatility of Ru – bisphosphane catalysts for a wide number of substrates coupled with the markedly lower price of Ru compared to Rh make the Ru-based hydrogenations very attractive. The work of the Noyori group has provided the practical and mechanistic understanding that makes these Ru-based systems probably the most useful family of catalysts for the efficient generation of chirality.[9]

Despite the detailed mechanistic explanation worked out by the Noyori group for a number of these reactions, the mechanism of the "standard" hydrogenation using the bisphosphane – Ru complex is still poorly understood. Additional progress in this area is highly appreciated, and in this context a recent publication by Norton and Magee is important, even though it deals with both a special catalyst and substrate.[10] The Norton group used the bisphosphane – Ru hydride **10** for the hydrogenation of iminium ion **11** (Scheme 4). They showed that the reaction proceeds by an ionic mechanism to give the enantiomerically enriched amine. From a purely practical point of view the obtained enantiomeric excesses show some room for improvement, but more importantly the demonstration of a purely ionic mechanism in the hydrogenation of the iminium ion adds another interesting facet to the myriad of proven mechanisms of Rh- and Ru-based asymmetric hydrogenations.[11]



Scheme 4. Ionic mechanism for the hydrogenation of iminium ion **11** with with the Ru – hydride complex **10**.

The catalyst system used by Norton and Magee[10] adds to the small number of structurally defined bisphosphane – Ru catalyst systems. That the search for these structures is more than a mere academic exercise has been amply proven by the beautiful work from the collaborators at Firmenich in Switzerland and the University of Alberta.[12] Their work allows access to a number of highly active and well-defined catalysts of the type [Ru(bisphosphane)(H)(solvent)$_3$](BF$_4$) (**13**, Scheme 5). To this end [Ru(1,2:5,6-η-cod)(η^6-cot)] (**15**) is allowed to react with the monoprotio salt of Me-DuPHOS

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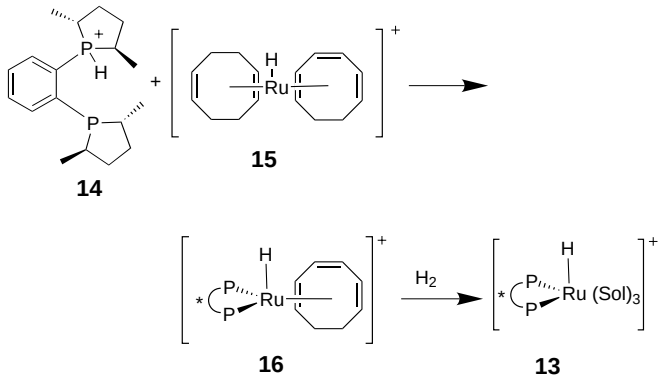
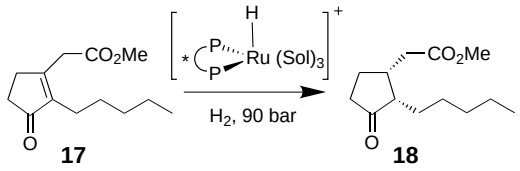


Scheme 5. Preparation of the Firmenich/Alberta Ru–hydride catalyst **13**. Sol = solvent.

(**14**) to give the catalyst precursor [Ru(Me-DuPHOS)(H)(η^6-cot)]$^+$ (**16**) (cod = cycloocta-1,5-diene, cot = cycloocta-1,3,5,7-tetraene). Subsequent hydrogenation leads to the active catalyst species **13**. Complex **13** has demonstrated its utility in the highly enantioselective hydrogenation of the difficult to reduce vinylogous β-oxoester **17**, which leads directly to **18**, a commercially important perfume component (Scheme 6).



Scheme 6. Application of the Firmenich/Alberta Ru–hydride catalyst **13** in the hydrogenation of **17**. Sol = solvent.

Just as in the work of the Norton group, the Firmenich/Alberta group prepared and used a Ru–hydride complex. However, while the Norton catalyst is stabilized by the cyclopentadienyl ligand, [Ru(bisphosphane)(H)(solvent)$_3$]$^+$ (**13**) used by Firmenich is reminesicent of the complex [Rh(bisphosphane)(H)(H)(solvent)$_2$]$^+$ (**8**) identified by Gridnev and Imamoto for the right neighbor of Ru in the periodic table. In terms of practicality the Firmenich/Alberta procedure has the advantage of allowing the straightforward synthesis of Ru–bisphosphane complexes with a number of different bisphosphane ligands. This allows the facile screening of ligands for a given hydrogenation substrate with well-defined catalyst systems, a clear prerequisite for understanding the reaction in question.

In summary, recent developments have shown the danger of assuming that the classical mechanism of Rh-catalyzed hydrogenation is valid for all bisphosphane ligands and metal combinations. Furthermore, we now know that the field is not safe from surprises, such as the discovery of a purely ionic reaction mechanism. Stepping back from the individual results, the wide range of observed mechanisms cannot be astonishing: A short look at the complexity of mechanisms for a simple aliphatic nucleophilic substitution would have demonstrated that one cannot expect to describe the far more complex asymmetric hydrogenations—with widely different metals, ligands, and substrates—by a single mechanism. While simple and all-encompassing explanations may have some appeal, mechanistic diversity is also an opportunity to be explored and exploited.

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