Quantum Chemical Studies of Asymmetric Reactions:
Historical Aspects and Recent Examples

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Asymmetric catalysis is essential for the synthesis of chiral compounds such as pharmaceuticals, agrochemicals, fragrances, and flavors. For rational improvement of asymmetric reactions, detailed mechanistic insights are required. The usefulness of quantum mechanical (QM) studies for understanding the stereocontrol of asymmetric reactions was first demonstrated around 40 years ago, with impressive developments since then: from single-point Hartree-Fock/STO-3G calculations on small organic molecules (1970s), to the first full reaction pathway involving a metal-complex (1980s), to the beginning of the density functional theory (DFT)-area, albeit typically involving truncated models (1990s), to current state-of-the-art calculations reporting free energies of complete organometallic systems, including solvent and dispersion corrections. The combined studies show that the stereocontrol in asymmetric reactions largely is exerted by non-bonding interactions, including CH/π attraction and repulsive forces. The ability to rationalize experimental results opens up for the possibility to predict enantioselectivities or to design novel catalysts on basis of *in silico* results.

Introduction

Chirality is a fundamental property of most biologically relevant molecules. The stereoisomers of a given chiral compound exhibit different 3-dimensional structures and can be expected to elicit different biological responses. Many pharmaceuticals, e.g. L-DOPA,[1] are distributed in an enantiopure form, because the possible stereoisomers have no or non-beneficial effects. The ability to form enantiopure compounds is the ultimate goal of asymmetric catalysis. To this end, chiral organic or transition metal-based catalysts are employed, which through selective interactions with the substrate are able to favor formation of one of the product stereoisomers.

Asymmetric reactions are rarely completely selective, and the product is typically obtained enantioenriched but not enantiopure. Rational attempts to improve the *enantiomeric excess* (ee) in asymmetric reactions requires detailed insights into the mechanism and the selectivity-determining factors. Yet, such details are often unknown. Computational chemistry is a valuable tool in this context, allowing for the optimization of diastereomeric transition state structures (TSs) and analysis of the interactions between catalyst and substrate. QM methods have been employed to study asymmetric reactions for around 40 years, from some of the first single-point Hartree-Fock (HF)-based studies on truncated models,[2] to current DFT studies on complete catalyst models and full reaction pathways.[3] Recent progress in the description of dispersion interactions through parameterization of the functional or through inclusion of an empirical dispersion correction in both geometry optimizations and energy calculations have further improved the validity of DFT-based investigations of asymmetric reactions (for a review on dispersion in DFT, see [4]).

This review deals with historical perspectives on asymmetric catalysis and QM studies

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thereof, combined with recent examples. Initially, we briefly discuss asymmetric catalysis in general, highlighting the contributions of selected scientists to the discovery of chirality and the development of asymmetric synthesis and asymmetric catalysis involving chiral metal complexes. This is followed by a more detailed discussion of some of the pioneer studies in the field of quantum chemistry, which were the first to demonstrate that QM calculations can be employed to explain reaction mechanisms and the origin of stereoselectivities. The asymmetric reactions discussed include nucleophilic addition, amine-catalyzed aldol reactions, osmium-catalyzed dihydroxylation, rhodium-catalyzed hydrogenation, and ruthenium-catalyzed transfer hydrogenation. Recent examples of QM investigations of iridium-catalyzed asymmetric hydrogenation of alkenes are employed to describe the current state-of-the art in the field as well as to discuss various challenges a computational chemist might encounter. Finally, the potential to employ QM calculations not only to rationalize results, but also to predict the outcome of yet unknown reactions or to design new catalysts is briefly discussed.

2. Historical aspects of asymmetric reactions

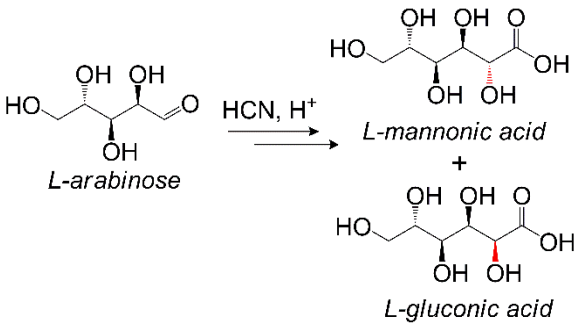
2.1 Chirality

The discovery of chirality is tightly linked to the discovery of optical rotation. In the early 1800s, work by François Arago (1786-1853) and Jean Baptiste Biot (1774-1862) showed that if plane-polarized light passes through quartz crystals, the light is rotated about the direction of the travel.[5] Biot also observed this type of optical activity for certain organic liquids such as distilled oils of turpentine and lemon.[5] By performing experiments in the gas phase, he concluded that the optical activity is an inherent property of isolated molecules. Louis Pasteur (1822-1895) showed in 1848 that sodium ammonium tartrate crystals prepared from an optically inactive salt could be separated into two forms, which in solution rotated polarized light in opposite directions.[6] He concluded that the two forms are made up of molecules that are mirror images of each other. In 1874, Jacobus H. van't Hoff (1852-1911) and Joseph A. Le Bel (1847-1930) independently proposed the tetrahedrally coordinated carbon atom.[7] With four different substituents coordinated, a chiral molecule is formed, implying that distinct stereoisomers of the same molecular formula are possible. In order to define chirality, one might say that a chiral molecule cannot be superimposed onto its mirror image, or that it does not possess an *improper* rotation axes.

2.2 Asymmetric synthesis

Asymmetric synthesis is defined by IUPAC as: *A chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts.*[8] Hermann Emil L. Fischer (1852-1919), who devised the Fischer projection, might have been the first to perform an asymmetric synthesis, reported in 1890. Fischer employed a synthetic

protocol invented by Heinrich Kiliani (1855-1945) to elongate L-arabinose with one carbon atom.[9] The products (obtained as crystalline phenyl-hydrazides) indicated that in the reaction unequal amounts of L-gluconic and L-mannoic acids had been formed, which constitute epimers (their configuration differs only at the newly formed carbon centre, Scheme 1).[9,10] Fischer wrote in a separate article: "*The simultaneous formation of two stereoisomeric products from the addition of prussic acid to aldehyde, which was observed here for the first time, is [...] quite noteworthy.*"[11]

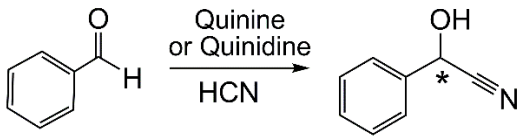


Scheme 1. In the 1-carbon elongation of L-arabinose both L-gluconic and L-mannoic acids were formed.[9]

Kagan and Gopalaiah point out that the first example of a *biocatalytic* enantioselective synthesis might have been reported by Le Bel in 1894, involving transformation of the prochiral citraconic acid or mesaconic acid by mould to the optically active citramalic acid.[12]

In 1904, Willy Marckwald (1864-1942) reported decarboxylation of the brucine salt of methylethylmalonic acid.[13] The chiral product, methylethylacetic acid, showed a small optical rotation.

In 1913, Georg Bredig (1868-1944) and P. S. Fiske reported an asymmetric synthesis using the prochiral substrate benzaldehyde combined with HCN, which, employing the chiral alkaloids quinine or quinidine as catalysts, were converted into optically active mandelonitrile (Scheme 2).[14] According to Kagan and Gopalaiah, this constituted the "*first well established non-enzymatic enantioselective synthesis involving a prochiral substrate*".[12]



Scheme 2. First well established non-enzymatic stereoselective synthesis from a prochiral substrate.[12,14]

It needs to be remembered that chirality is not restricted to organic compounds. Alfred Werner (1886-1919) and coworkers in his laboratory showed in 1911 that also inorganic complexes can be chiral. This was proven through resolution of different cobalt compounds into enantiomers, for example $[CoX(NH_3)(en)_2]^{2+}$ (en = ethylenediamine, X = Cl or Br).[15,16] In 1914, Werner extended this work to resolving the carbon-free tetranuclear complex $[Co_4(NH_3)_{12}(OH)_6]^{6+}$,[17] providing the ultimate proof that chirality is not dependent on the presence of carbon.

2.3 Metal-catalyzed asymmetric synthesis

Ager and coworkers indicate that the first homogenous metal-based hydrogenation catalysts were reported in 1938 by Melvin Calvin (1911-1997, known for the Calvin-cycle) and involved achiral copper complexes in quinoline solution.[1,18,19] The Cu complexes were able to activate H_2 and to reduce *p*-benzoquinone.[19]

The 1960s can be considered the beginning of the area of *asymmetric* metal-based catalysis. The achiral hydrogenation catalyst by Wilkinson ($[RhCl(PPh_3)_3]$ (Figure 1A) was used as a scaffold to develop chiral phosphine-based complexes. William Knowles (1917-2012) and coworkers reported some of the first efforts in this direction in 1968, incorporating a stereogenic phosphorous or carbon center in the phosphine ligand, with the former providing the better results.[20] These early attempts resulted in modest ee's of 1 to 15 % for hydrogenation of α-phenyl-acrylic and itaconic acid (note that the ee gives the *excess* of a certain enantiomer, see also definition in Figure 2).[20] The chiral (-)-methyl-propyl-phenyl-phosphine ligand was not enantiopure, but had 69% optical purity,[20]

which can be assumed to have reduced the ee of the hydrogenation reactions somewhat (a racemic catalyst mixture would yield a racemic product mixture). This highlights an interesting dilemma: the goal of asymmetric catalysis is to produce enantiopure products, but its implementation is dependent on already possessing such an enantiopure compound in form of the chiral catalyst. Despite the low ee's obtained by Knowles and Sabacky, they were fully aware of the potential of asymmetric catalytic reactions and concluded their 1968 study with the following words: "*The inherent generality of this method offers almost unlimited opportunities for matching substrates with catalysts in a rational manner and we are hopeful that our current effort will result in real progress towards complete stereospecificity*".[20]

In 1971, Henri B. Kagan reported the DIOP ligand (2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(di-phenyl-phosphino)butane, Figure 1B), which in rhodium-based hydrogenations gave ee's of up to 71%.[21] DIOP is historically significant because it was the first C2-symmetric diphosphine ligand.

Knowles reported in 1975 the DIPAMP ligand (1,2-bis((2-methoxyphenyl)(phenyl)phosphino)-ethane, Figure 1C), which in the reduction of α-acylamidoacrylic provided up to 96% ee.[22] The DIPAMP ligand was later employed in the first asymmetric hydrogenation reaction on industrial scale for enantioselective synthesis of L-DOPA; a drug against Parkinson's disease.[1]

Contemporary with Knowles, Ryōji Noyori reported in 1968 copper-based cylopropanation reactions, also giving low ee's of ~6%.[23] Later, he developed the BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) ligand, which in the first report from 1980 gave up to 100% ee in the rhodium-catalyzed hydrogenation of α-(acylamino)acrylic acid derivatives.[24] BINAP does not have a stereogenic centre but has axial chirality (Figure 1C). BINAP is used in various asymmetric hydrogenations, in particular of ketones.[25] Its impact is reflected in the close to 700 citations the 1980 paper has received, combined with close to 1000 citations for a BINAP overview article from 1990[26] (Web of Science, Jan. 2015).

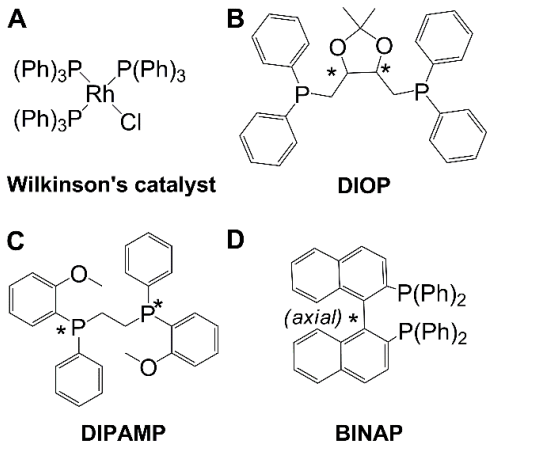


Figure 1. Wilkinson's catalyst and historically relevant chiral *P,P*-ligands for hydrogenation reactions.

By now, asymmetric transition metal-catalyzed hydrogenations are widely employed in the generation of a variety of chiral chemicals, including pharmaceuticals, agricultural compounds, fragrances, and flavor molecules.[1,27]

As asymmetric reductions, also asymmetric oxidations have found widespread applications. Several of these were developed by Barry K. Sharpless and coworkers during the 1970s and 1980s, including asymmetric epoxidation, oxyamination, and dihydroxylation.[28,29,30] The oxidation of alkenes with OsO_4 was well-known at the time (according to Strassner,[31] it was first reported by Francis C. Phillips in 1894[32]), but an asymmetric version was first reported by Sharpless, with good initial ee's of up to 90%.[30]

QM studies have played a vital role in elucidating the mechanistic details of several of the here mentioned asymmetric reactions. Selected examples are discussed in detail below, including metal-catalyzed hydrogenations (involving rhodium, ruthenium, or iridium) and osmium-catalyzed dihydroxylations (section 3).

3. Historical perspective on QM studies of asymmetric reactions

This section presents selected examples of theoretical studies of asymmetric reactions reported during the last four decades. These are meant to provide the reader with insights into

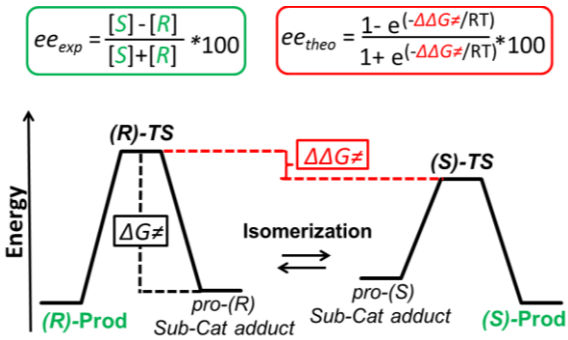


Figure 2. Illustration of relevant concepts in asymmetric catalysis. ee_{exp} = ee calculated from experimentally determined product concentrations, ee_{theo}= ee calculated from computed $\Delta\Delta G^{\neq}$. Sub-Cat adduct = diastereomeric substrate-catalyst adducts.

the methods available at the time, and the conclusions that were drawn (see also a conceptually related review from 2007 by Balcells and Maseras[33]). Some concepts relevant to the discussion can be reviewed in Figure 2.

3.1 Asymmetric induction in nucleophilic addition (1970s and early 1980s)

One of the first reports on the utilization of QM calculations to rationalize the stereochemical outcome of a reaction was published by Nguyên Trong Anh and Odile Eisenstein in 1977 (but see also earlier studies by the same authors[34,35]).[2] This study investigated asymmetric induction occurring in nucleophilic additions to chiral carbonyl compounds (Figure 3A). The factors influencing the selectivity in this type of reactions was a very debated problem in the 1950s to 1970s, with a number of different models developed by e.g. Cram, Cornforth, Karabatsos, and Felkin (for a detailed review see also [36]).[37,38,39,40] Anh and Eisenstein evaluated the different proposals employing QM models of 11 to 16 atoms with 2-chloropropanal or 2-methylbutanal as carbonyl compound and a hydride as nucleophile. 24 conformers were created, corresponding to 12 rotamers of the carbonyl compound (rotating the C-C bond by increments of 30°), with the hydride positioned 1.5 Å from the carbonyl *si* or *re* face, without geometry optimization of the model. Electronic energy calculations were performed with the first version of the Gaussian software, GAUSSIAN70, employing the Hartree-Fock (HF) method and the STO-3G basis set.[2,41] Anh and Eisenstein identified Felkin's suggestion as the energetically preferred model for explaining the selectivity in this type of reactions, and they additionally proposed significant improvements, leading to the Felkin-Anh model (Figure 3B).[2,42] A key element is the TS conformation, with the nucleophile attacking *anti* to L and with an Nu^-…C=O angle of around 103°.[36] Hyperconjugation between the $\sigma^*_{C\text{-}L}$ orbital and the π and π* orbitals on C=O allows for electron delocalization towards L.[36]

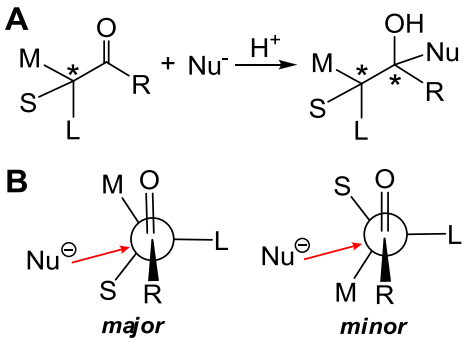


Figure 3. A) Nucleophilic addition reactions studied by Anh and Eisenstein.[2] **B)** Felkin-Anh model for explaining the stereoselectivity (S = small, M = medium, L = large or EWG, adapted from [36]).

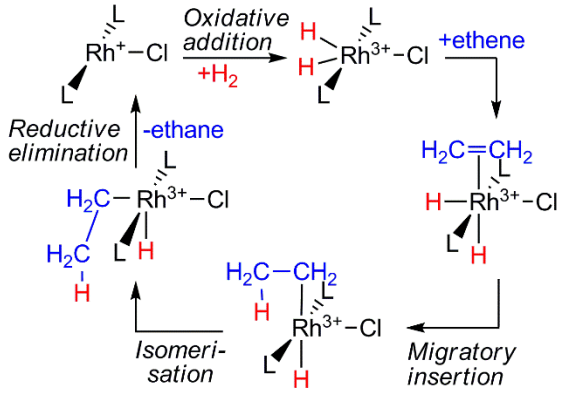
In a perspective from 2000 Kendall N. Houk points out that Anh and Eisenstein's study "*demonstrated the power of quantum mechanical calculations to solve important problems on real organic systems*".[42] Its impact is further reflected in the close to 700 citations the study has received by now (Web of Science, Jan. 2015). The simplicity of the employed computational protocol also conveys a different message to the current generation of computational chemists: indeed, chemical insight can be obtained already with small QM models and does not necessarily require expensive free energy calculations including dispersion, solvent, basis set, and counterpoise corrections, validated at three levels of theory.

During the early 1980s, calculations by Houk and coworkers further validated the usefulness of QM approaches for studying stereoselective reactions. A variety of organic addition reactions were analyzed, as summarized in an overview article from 1986.[43] QM calculations were performed with GAUSSIAN80 and GAUSSIAN82 and the 3-21G basis set on symmetric models of around 10 atoms. However, this approach did not allow computations on larger models required to explain selective effects. These were instead evaluated using a force field approach (MM2), with parameters obtained from the QM results added for atoms involved in breaking or forming bonds. Preferred TS conformations and angles of attack were identified for a large set of stereoselective nucleophilic and electrophilic addition and cycloaddition reactions.[43]

3.2 Rhodium-catalyzed alkene hydrogenation (1980s)

QM calculations of organometallic reactions became feasible during the 1980s, with the first full reaction cycle reported for rhodium-catalyzed alkene hydrogenation. A historic perspective on computational studies of Rh-catalyzed hydrogenations has been given by Wiest and co-workers.[44] In 1980, Dedieu reported LCAO-MO-SCF (self-consistent field-linear combination of atomic orbitals-molecular orbital) calculations on a model of Wilkinson's catalyst (Figure 1A).[45] However, only intermediates of a hydrogenation reaction were analyzed and these were constrained to idealized geometries. Conclusions depending on relative energies thus could not be made.[45]

In 1986, Morokuma and coworkers noted: "*It is only in the last few years that for elementary reactions of organotransition-metal compounds the transition-state geometry can be optimized [...]. Despite such success, a study of an entire cycle of a catalytic process, consisting of several elementary reactions, has been a challenge to theoreticians*."[46] They then proceeded to report the first *ab initio* study of a full reaction cycle, describing the hydrogenation



Scheme 3. Mechanism for ethene hydrogenation with Wilkinson's catalyst as proposed by Morokuma,[47] on basis of earlier proposals by Halpern.[48] L = PH_3 in calculations. Figure adapted from [44].

of alkenes mediated by Wilkinson's catalyst.[46,47] HF calculations were performed with GAUSSIAN80 and GAUSSIAN82. Due to computational limitations, a model complex was employed in which the phenyl groups on phosphorus were replaced with hydrogen and the alkene was reduced to ethene, although the authors point out that this complex and substrate are known to be inactive in experiments.[47] Nonetheless, the general electronic factors influencing the reaction pathway were probably fairly well represented also with this model. The reported calculations included optimized TS structures and supported the proposed mechanism by Halpern,[48] with some slight modifications (Scheme 3). QM studies of *asymmetric* Rh-catalyzed hydrogenations were published later and are discussed below (section 3.4).

3.3 Asymmetric osmium-catalyzed dihydroxylation (1990s)

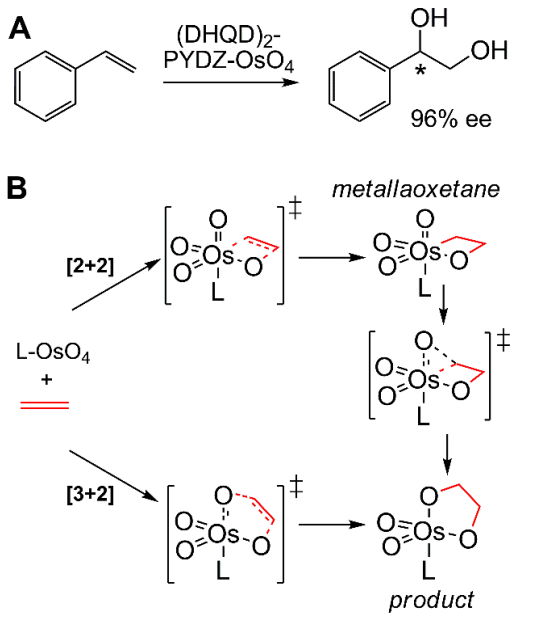
DFT became important in the field of asymmetric catalysis in the 1990s. Originally, DFT was primarily a method employed in solid-state physics. Tom Ziegler notes in his review about 'approximate DFT' from 1991 that "*molecular calculations based on DFT did not emerge before the late 1960's*".[49] Fan and Ziegler published in 1990 the first DFT-optimized transition state structures, which were obtained for small isomerization reactions of the type

RCN → CNR and HN-NH(*trans*) → HN-NH(*cis*).[50] Calculations were performed at the Hartree-Fock-Slater density functional level (HFS). The barrier for CH_3NC → CH_3CN isomerization was in good agreement with experiment and much more accurate than the HF results.[50] Ziegler and coworkers had already applied HFS to C-H activation by different Ir, Rh, Ru, and Os complexes,[51] but the reaction profiles were obtained through linear-transit calculations and TSs were not optimized explicitly. Irrespectively, the latter study was able to reproduce many experimentally observed trends in bond strength and ability for C-H activation.

One of the first DFT-based investigations of a metal-catalyzed asymmetric reaction is a study from 1994 by Sharpless and coworkers on osmium-catalyzed dihydroxylation of alkenes (note that earlier theoretical studies on this system exist, starting from extended Hückel calculations by Jørgensen and Hoffmann in 1986[52]).[53] The asymmetric Os-catalyzed alkene dihydroxylation was developed in the 1980s by Sharpless,[30] who also was involved in mechanistic studies using computational methods.[53,54,55] Scheme 4 shows an example of Os-{DHQD}$_2$PYDZ catalyzed dihydroxylation ({DHQD}$_2$PYDZ = bis(dihydroquinidine)-3,6-pyridazine). The mechanism of this reaction was controversial for a while, with two pathways considered plausible: a stepwise [2+2] mechanism (involving a metallaoxetane intermediate) or a concerted [3+2] pathway (Scheme 4B, see also reviews [31,56] on this reaction).

In 1993, Norrby, Sharpless and coworkers used the UniChem DGauss 1.1.1 program and the Becke-Perdew non-local correction to study the putative metallaoxetane intermediate of the [2+2] pathway, but as the computational power did not allow calculations on osmium, ruthenium models were employed instead.[53] Transition states were not optimized, partially because it was considered to be non-feasible but also because "*little is known about the reliability of the DFT method in transition-state calculations for organometallic complexes*".[53]

The reported energies were enthalpies (probably approximated from electronic



Scheme 4. A) Example of Os-catalyzed alkene dihydroxylation,[57] **B)** Mechanistic proposals (L = ligand. Adapted from [31,56]).

energies), whereas entropies were explicitly stated to be beyond the computational capabilities. The calculations indicated that formation of a metallaoxetane is possible and that its geometry fit with empirical (mnemonic) models used to explain the stereoselectivity in these reactions.[53] However, DFT calculations performed a few years later by different groups on osmium models concluded that the [3+2] pathway is strongly favoured.[55,58,59,60]

Maseras and coworkers reported in 1999 a QM/MM (MM = molecular mechanics) study on the stereocontrol of Os-catalyzed dihydroxylation, assuming a [3+2] mechanism (modified GAUSSIAN92, B3LYP/LANL2DZ[Ir],6-31G*[O],6-31G[N,C,H], MM3[92]).[61] The full {DHQD}$_2$PYDZ ligand was employed and styrene as substrate, with a computed ee of 99 % (*R*), in good agreement with experiment (96 % (*R*)).[57] It was concluded that stacking interactions between aromatic rings are the main factor determining the selectivity (Figure 4). It can be noted that the contribution of favourable non-bonding interactions to the stereocontrol of asymmetric reactions is increasingly being recognized (*vide infra*, see also [62] for a recent review).

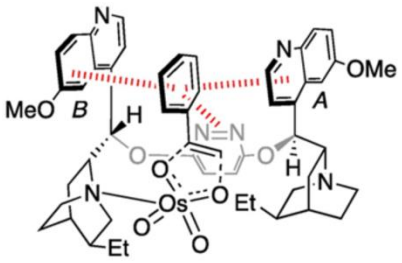


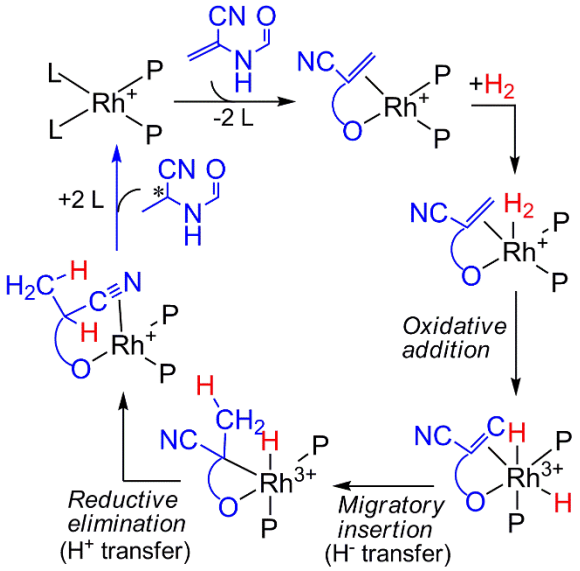
Figure 4. Stacking interactions proposed to determine the stereoselectivity in Os-(DHQD)$_2$PYDZ-catalyzed styrene dihydroxylation.[61] Reproduced with permission from {E. H. Krenske, K. N. Houk, *Acc. Chem. Res.*, **2013**, *46,* 979-989}. Copyright 2013 American Chemical Society.

3.4 Asymmetric rhodium-catalyzed enamide hydrogenation (1990s and early 2000)

Around the beginning of the new millennium, the use of DFT methods to study asymmetric reactions increased significantly and several seminal studies were published. Some of the first DFT investigations of asymmetric metal-catalyzed hydrogenation reactions concerned Rh-catalyzed hydrogenation of enamides, which was investigated computationally by Clark R. Landis and coworkers (~120 citations for the most cited of these by Jan. 2015, Web of Science).[63,64,65] Initially, a small achiral model of the catalyst was studied with GAUSSIAN94 at the B3LYP/LANL2DZ level in order to evaluate different mechanistic hypotheses.[63] This study, published in 1999, determined a preferred reaction cycle involving H_2 coordination, oxidative addition, turn-over limiting alkene migratory insertion (i.e. hydride transfer to the substrate), and reductive elimination (i.e. proton transfer forming the final product, Scheme 5).[63]

Subsequently, the stereocontrol of [Rh-(*R*,*R*)-Me-DuPHOS]$^+$-mediated hydrogenation of prochiral enamides was investigated using an ONIOM approach involving B3LYP, HF, and MM layers (DuPHOS = 1,2-bis(2,5-dimethyl-phospholan-1-yl)benzene, ONIOM = our own n-layered integrated molecular orbital and molecular mechanics; developed by Morokuma and coworkers[66]).[64,67] Earlier studies on the selectivity of Rh-catalyzed enamide hydrogenation had been performed at the MM level only.[68,69,70] The ONIOM study, reported in 2000, was performed with GAUSSIAN98 and included full models of the catalyst and a model enamide (62 atoms in total, Figure 5).[64] Free energies were reported, including zero-point vibrational energy (ZPVE), thermal enthalpy corrections, and entropy. Landis and coworkers wrote: "*Two recent developments make the computations reported in this paper possible: the demonstration that hybrid density functionals efficiently model the quantum mechanics (QM) of organotransition metal complexes [...] and the rise of easily implemented QM/MM hybrid methods*."[64]

The results by Landis and coworkers were able to rationalize an intriguing phenomenon, repeatedly observed in asymmetric catalysis (e.g. in rhodium[71,72,73,74,75,76] and iridium systems[77]): coordination of the substrate to the catalyst leads to formation of diastereomeric catalyst-substrate adducts (Figure 5A), of which the less abundant (*minor*) isomer leads to formation of the *major* product enantiomer. This is sometimes referred to as the anti-lock-and-key principle or major/minor concept,[76] and is in contrast to situations where the major product enantiomer originates from the major



Scheme 5. Mechanism for enamide hydrogenation with *P,P*-rhodium catalysts (adapted from [44,63]).

adduct (referred to as lock-and-key catalysis,[76] as it is somewhat reminiscent of the enzymatic lock-and-key concept by Fischer[78]). In the calculations by Landis and coworkers, the major isomer (with pro-(*S)* coordination mode of the substrate) is 3.6 kcal/mol lower in energy than the minor pro-(*R)* isomer, indicating a ratio of 500(*S*):1(*R*).[64,67] However, the hydrogenation barrier is much lower for the minor pro-(*R*)-isomer ($\Delta\Delta G^{\neq}_{S\text{-}R}$ = 4.4 kcal/mol), rationalizing the formation of the (*R*)-product in experiments.[67]

It is also worth noting that these calculations indicated that the rate-limiting step in this system is not substrate migratory insertion (as observed for the small achiral model), but the addition of H_2.[64] The lower barrier of the minor isomer was ascribed to the fact that the molecular distortions required for H_2 addition are sterically less demanding than for the major isomer (Figure 5C).[67] For the latter, distortions of the double bond geometry and placement of the nitrile in a hindered quadrant are required, whereas the minor isomer only has to distort slightly.[67] Note that the results are substrate-dependent, and a change from electron-withdrawing substituents to alkyl groups leads to a reversal in enantioselectivity.[65] This illustrates that insights into selectivity-determining factors are highly system specific, which for example implies that for a given system, full molecular models should be employed in calculations. This conclusion might appear frustrating to some (the organic chemist might prefer to be able to rationalize and predict the selectivity of any

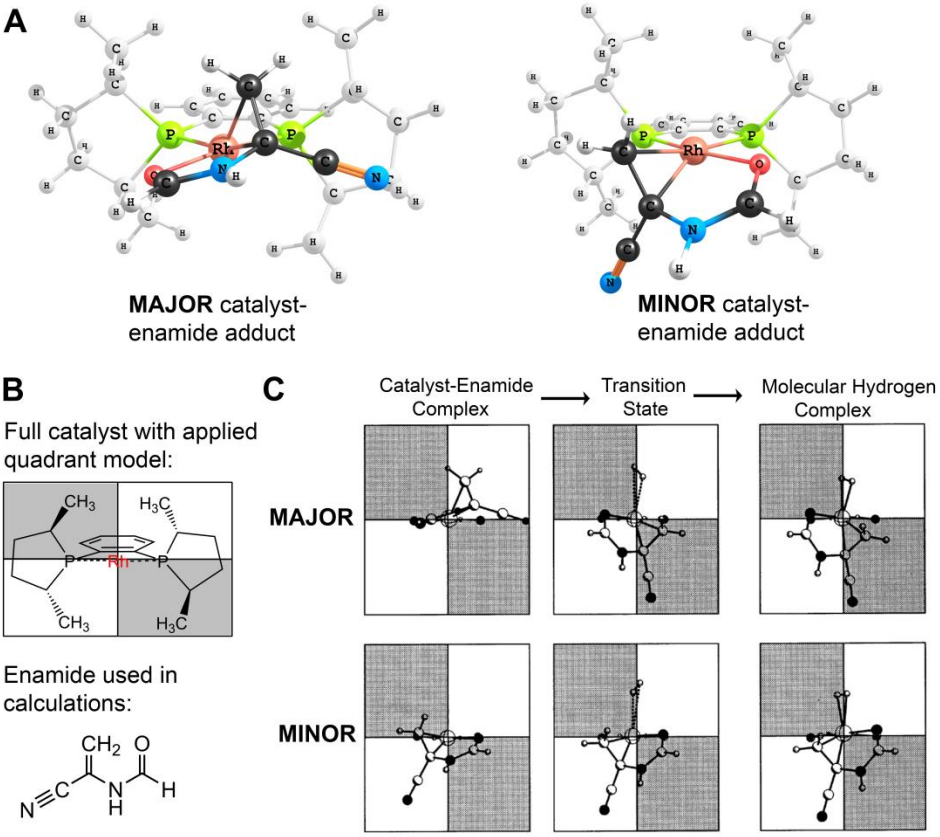


Figure 5. A) Major and minor (*R*,*R*)-Me-DuPHOS-enamide complexes (ligand atoms in grey, drawn from geometries reported in [67]), **B)** Enamide and full (*R*,*R*)-Me-DuPHOS catalyst employed in calculations, including quadrant model applied in C (gray shadings = hindered quadrants, adapted from [67]). **C)** Schematic illustration of conformational distortions required for H_2 addition to the major and minor complex. Majority of atoms omitted for clarity. Drawing corresponds to original figure by Landis (Copyright (2000) Wiley. Reproduced with permission from [C. R. Landis; S. Feldgus, *Ang. Chem. Int. Edition* **2000**, *39*, 2863–2866, Wiley]).

system on basis of simple quadrant models), but it also illustrates why theoretical methods have become so important to fully understand asymmetric systems: only computations are able to provide a detailed picture of the involved transition states, allowing for the identification of the attractive and repulsive forces that govern the stereocontrol. Also Landis and coworkers warn from generalizing the reported results to other systems, as the reaction steps might be very dependent on the nature of the catalyst ligands.[64] They further emphasize that "*our computations concern model systems in the gas phase and in the absence of counterions. [...] we are not able to estimate equilibrium constants, association barriers, or dissociation barriers [...] The computational model has accuracy limitations, also".*[64] The accuracy was estimated to 1-2 kcal/mol for relative and 3-4 kcal/mol for absolute energies, although a justification for these values was not given.[64] Interestingly, in 2007, Wiest and coworkers revisited the system studied by Landis employing DFT calculations only (B3LYP/LACVP**, Jaguar 5.5) and confirmed the mechanistic details, although somewhat different energies were obtained.[79]

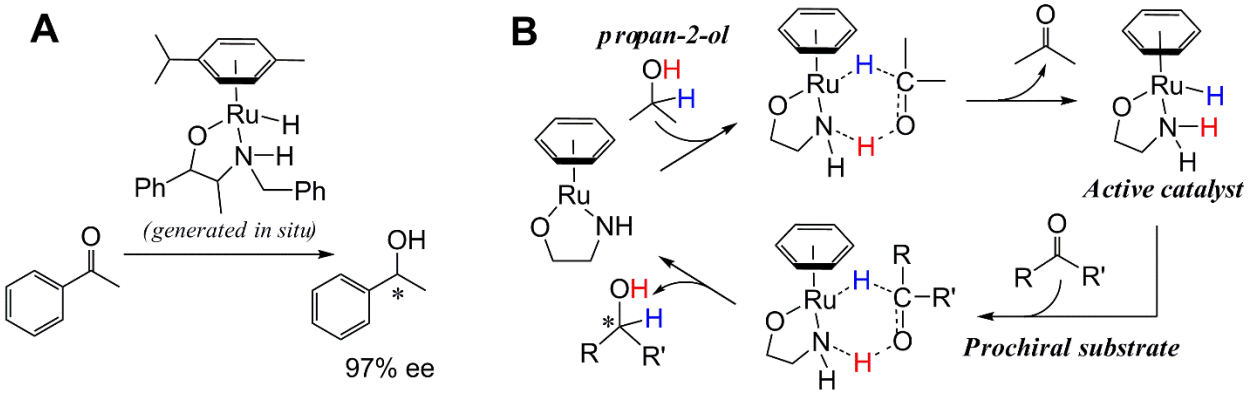
3.5 Asymmetric ruthenium-amino-alcohol-catalyzed transfer hydrogenation of ketones (1990s and early 2000)

Contemporary with Landis' investigations on rhodium systems, various groups also turned their attention to ruthenium-catalyzed transfer hydrogenations. For ruthenium, an entirely different and novel hydrogenation mechanism was proposed, alongside with unexpected selectivity-determining interactions (*vide infra*).

The asymmetric Ru-amino-alcohol-catalyzed transfer hydrogenation of ketones was originally reported by Noyori and coworkers,[80] but several other groups followed with efforts in this direction.[81,82] In transfer hydrogenations, the hydrogen necessary to reduce the substrate does not originate from molecular H_2, but from organic molecules such as propan-2-ol. With chiral elements incorporated into the amino-alcohol ligand, ee's of up to 97% could be achieved (Scheme 6A).[82] Two essentially simultaneous QM studies of ruthenium-catalyzed hydrogenations were reported: Andersson and coworkers (1999, ~250 citations)[83] and Petra *et al.* (2000, ~140 citations).[84] Subsequently, in 2001, Noyori and coworkers proposed selectivity-determining interactions for this system on basis of QM calculations (~230 citations by Jan. 2015, Web of Science).[85]

Andersson and coworkers reported GAUSSIAN98 calculations employing B3PW91/LANL2DZ (triple-ζ basis and SDD[Ru] for final electronic energies).[83] The QM model employed in the mechanistic studies was somewhat truncated compared to the experimental system (Figure 6, middle). ZPVEs were computed, alongside PCM (polarizable continuum model) single point corrections for some structures to estimate the effect of the bulk solvent (modeled as a homogeneous continuum) on the reaction energies. It can be noted that PCM methods had been around for some time at this point (first reported by Tomasi in 1981,[86] for reviews see [87,88]), but the PCM code was first available in GAUSSIAN from 1998 (prior other solvation methods were available, see e.g. [87]).

Andersson and coworkers conclude that Ru-amino-alcohol-catalyzed ketone reduction occurs through a concerted mechanism (Scheme 6B), originally proposed by Noyori and coworkers.[89,90] In the first step, propan-2-ol transfers a proton to the nitrogen ligand and a hydride to ruthenium, generating acetone and the active catalyst species. The formed acetone is then replaced by the prochiral ketone substrate, and in the second step, the proton (from the ligand) and hydride (from the metal) are transferred to the substrate. Both steps can be described by the same cyclic 6-membered TS (Scheme 6). For this reaction, Noyori and coworkers coined the term *metal-ligand bifunctional mechanism*.[89] Note that the reaction occurs in the *outer sphere*, i.e. the substrate does not coordinate to the metal during the hydrogenation step. It is thus especially



Scheme 6. A) Example of Ru-amino-alcohol-catalyzed asymmetric transfer hydrogenation of acetophenone,[81] **B)** Proposed mechanism, employing propan-2-ol as hydrogen donor (adapted from [83], mechanism originally by Noyori and coworkers[89]). Substituents on the catalyst are omitted for clarity.

intriguing to elucidate how high selectivities can be obtained in such a reaction. Interestingly, by now a variety of transition metal-catalyzed hydrogenation reactions have been proposed to occur though outer sphere mechanisms (for recent reviews on this topic see e.g. Eisenstein and Crabtree[91] or Hopmann and Bayer[92]).

In order to obtain insight into the stereo-control of Ru-amino-alcohol-catalyzed transfer hydrogenation of ketones, Andersson and co-workers performed calculations on acetophenone and chiral amino-alcohols, employing the same computational protocol as above.[83] (*R*)- and (*S*)-alcohol forming TS structures were optimized, but the geometries were not shown in the paper and no conclusions were made about the selectivity-determining interactions. $\Delta\Delta E^{\neq}$ values were reported, from which it was concluded that the gas phase calculations did not capture the selectivity-determining effects and that inclusion of PCM corrections was essential.[83] However, for the single case where experiment and theory were compared, it does appear as if the gas phase $\Delta\Delta E^{\neq}_{R\text{-}S}$ value (2.2 kcal/mol) fits better with the experimental ee (77% *(S)*) than the PCM corrected value (3.2 kcal/mol).[83]

Petra *et al.* reported a combined experimental and theoretical study of Ru-amino-alcohol-catalyzed transfer hydrogenation in 2000.[83] Calculations were performed with ADF (1999) and GAUSSIAN98 (Rev. A5, B3LYP and B3PW91, LANL2DZ) on a QM model containing benzene as arene, NH_3 as amine, and OH as alcohol ligands (Figure 6, right). The substrate was the smallest possible 'ketone',

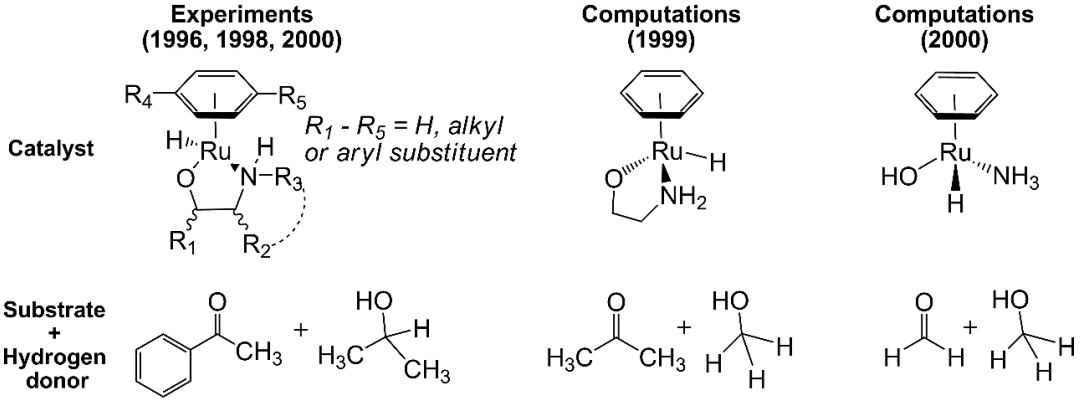


Figure 6. Ruthenium-amino-alcohol-catalyzed transfer hydrogenation of ketones. Experimental systems (1996[80], 1998[82], 2000[84]) versus computational models used in mechanistic studies (1999,[83] 2000[84]).

formaldehyde. Vacuum electronic energies were reported. Petra *et al.* first investigated the reaction mechanism and reported a cycle similar to the one shown in Scheme 6 (at the time, Andersson's study[83] was not yet published).[84] They then attempted to rationalize the selectivity, but noted that "*[a]symmetric catalysis is a challenge to theoretical investigations because it is sensitive to energy differences of less than 1 kcal mol*$^{-1}$".[84] This is particularly problematic when the estimated accuracy of the computed results is proposed to lie within a few kcal/mol.[84] The preferred conformation of a chiral amino-alcohol-ruthenium complex was determined, followed by addition of acetophenone to the model. It was concluded that acetophenone is sterically hindered from approaching the catalyst from the *si*-face, but not from the *re*-face, which is given as an explanation for the experimental selectivity. However, no TS structures were optimized.

In 2001, Noyori and coworkers reported B3LYP/LANL2DZ (GAUSSIAN98) calculations of a full chiral Ru-amino-alcohol-catalyst with acetophenone.[85] On basis of optimized TS structures it was concluded that the stereoselectivity is influenced by the catalyst conformation but also by an attractive CH/π interaction between a C-H on the ruthenium arene ligand and the aryl substituent of the substrate (Figure 7, left).[85] This was an important proposal, because it was in contrast to a view that non-bonded repulsive effects (sterics) typically mediate the stereocontrol (with some exceptions, as the stacking interactions identified in Os-catalyzed dihydroxylation,[61] section 3.3). Attractive CH/π interactions have by now been identified as selectivity-determining interactions in various metal-based asymmetric systems (section 4.2.2),[3,62,93,94] and appear equally important also for organocatalyzed reactions.[95]

Later studies by Meijer and coworkers in 2007 (DFT-based molecular dynamics)[96,97] and by Dub and Ikariya in 2013 (DFT/M06)[98] on Ru-catalyzed transfer hydrogenation evaluated the effect of including either implicit or explicit solvent in the calculations. These studies reached a noteworthy conclusion: although the six-membered pericyclic TS is favoured in the gas-phase, in solvent, the mechanism is likely step-wise, involving first enantiodetermining hydride transfer and then a proton transfer from the ligand or possibly a solvent molecule.[96,98] However, attractive CH/π interactions were still considered to be a main factor governing the stereoselectivity.[98]

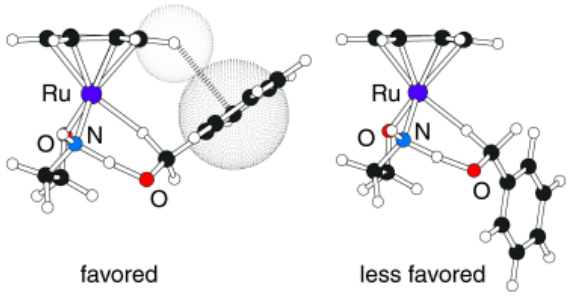
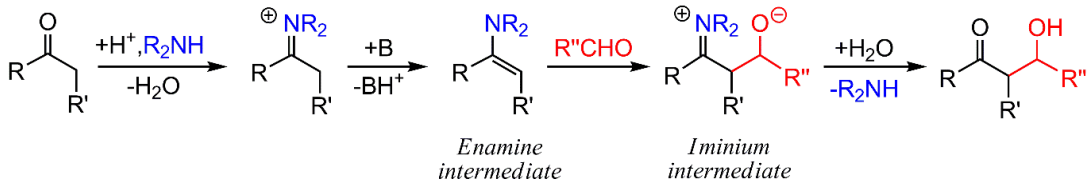


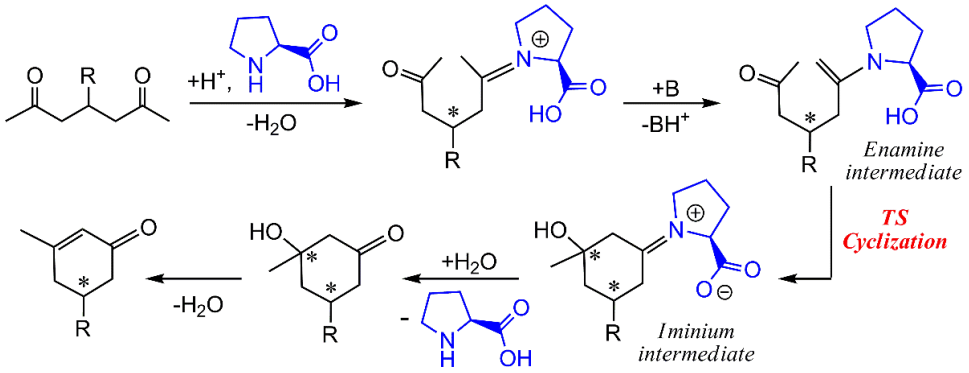
Figure 7. Attractive CH/π interaction (left) in Ru-amino-alcohol-catalyzed transfer hydrogenation of aryl ketones (figure by Noyori and coworkers[85]: Copyright (2001) WILEY-VCH Verlag GmbH. Reproduced with permission from [M. Yamakawa, I. Yamada, R. Noyori, *Angew. Chem. Int. Ed.* **2001**, *40*, 2818-2821]).

3.6 Asymmetric amine-catalyzed aldol reactions (beyond 2000)

Shortly after Houk highlighted the seminal work by Anh and Eisenstein on asymmetric induction,[42] he and coworkers published in 2001-2004 a series of equally seminal work on amine-catalyzed aldol reactions.[99,100,101,102] These papers constitute some of the most cited DFT-based studies of stereoselective reaction mechanisms (with ~370 citations for the most cited paper by Jan. 2015). The first study reported mechanistic details of inter- and intramolecular aldol reactions catalyzed by amines.[99] The calculations were performed with GAUSSIAN98 at the B3LYP/6-31G* level in the gas phase, with PCM solvation energies added as single point corrections. Final energies were ZPVE-corrected electronic energies (corresponding to enthalpies). All reactions were assumed to proceed through an enamine intermediate (Scheme 7), in analogy to known enzymatic mechanisms. An analysis of the facial



Scheme 7. Amine-catalyzed intermolecular aldol reaction (amine in blue, adapted from [99]).



Scheme 8. Proline-catalyzed intramolecular aldol reaction, for which the cyclization TS was studied theoretically (adapted from [100]). According to Houk,[102] this type of mechanism was first proposed by Jung in 1976.[103]

stereoselectivity with chiral aldehydes gave results in full agreement with the Felkin-Anh model (section 3.1, Figure 3).

Subsequently, the stereocontrol of proline-catalyzed intramolecular aldol reactions was studied, assuming an enamine mechanism (Scheme 8).[100] Calculations were performed with GAUSSIAN98 at the B3LYP/6-31G* level, with ZPVE-corrected energies reported. The identified selectivity-determining factors appear to be *i*) the geometry of the cyclization TS (involving concerted proton transfer and C-C bond formation), with the preferred (*R,S*)-structure allowing for a more planar geometry around the nitrogen of the forming iminium intermediate and *ii*) favorable electrostatic interactions between the proline methylidene groups (next to nitrogen) and the forming alkoxide, with the (*R,S*)-structure showing a stronger CH...O interaction (Figure 8).[100] Planarity is important because optimal orbital overlap between the C=C double bond and the nitrogen lone-pair is required, alongside maximum sp^2 hybridization of the nitrogen.[104] The computed $\Delta\Delta H^{\neq}$ value was 1.0 kcal/mol, which agreed reasonably well with the 42% ee observed in experiment.[100]

In a later DFT study from 2004, Clemente and Houk compared a variety of proposed reaction mechanisms and confirmed that the enamine pathway is preferred.[102] Pihko and coworkers have noted that alongside experimental results, the theoretical work by the Houk group provided key contributions to making the enamine mechanism "*widely accepted in the context of one of its oldest examples, the intramolecular aldol reaction. In retrospect, the simplicity of the enamine catalysis concept looks obvious, but as we all know, only in hindsight do we all have perfect vision*." [104]

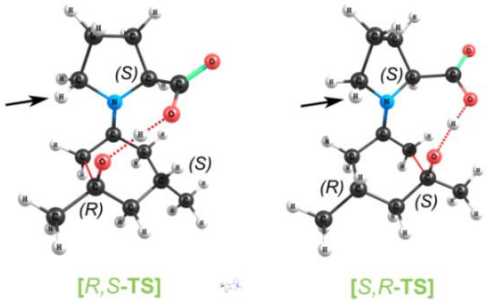


Figure 8. Diastereomeric TS structures for the cyclization step in the proline-catalyzed intramolecular aldol reaction of 4-methylheptane-2,6-dione.[100] Red lines indicate breaking/forming bonds, arrows indicate the C-H providing electrostatic stabilization of the forming alkoxide.

Interestingly, in 2014, Rzepa and coworkers published a DFT study revisiting the intermolecular aldol reaction, employing "*a variety of computational techniques that have been introduced or improved since the original study*."[105] Overall, the Rzepa study supports the earlier results by Houk and coworkers, including the contribution of the C-H…O interaction to the stereocontrol.

Contemporary example: Asymmetric iridium-catalyzed hydrogenation

DFT studies have been essential in determining the mechanistic details of asymmetric hydrogenation reactions, e.g. rhodium-catalyzed enamide hydrogenations (section 3.4), ruthenium-catalyzed transfer hydrogenation of ketones (section 3.5), and iridium-catalyzed imine and alkene hydrogenations (*vide infra*).[64,67,94,106] Here we will briefly discuss iridium-catalyzed asymmetric hydrogenation of alkenes and, in some more detail, QM studies thereof.

4.1 Historical perspective on iridium hydrogenation catalysts

Iridium holds a prominent role among hydrogenation catalysts. This stems from the fact that iridium complexes are able to hydrogenate challenging substrates such as tri- and tetra-substituted alkenes and non-functionalized alkenes and imines.[92,107,108,109,110,111,112] However, the potential of iridium as hydrogenation catalyst was initially not realized.

Crabtree has given an excellent account on the early days of iridium catalysis.[113] Although Vaska and coworkers had shown in the 1960s that iridium complexes such as $[IrCl(CO)(PPh_3)_2]$ could undergo oxidative addition reactions with for example molecular hydrogen,[114] the resulting dihydrides were so stable that they showed little catalytic activity (for a more detailed discussion see [115]).[113] Also the iridium analogues of the well-known neutral Wilkinson's catalyst

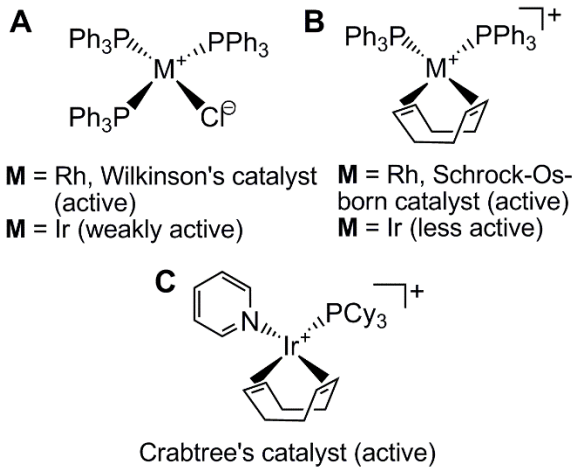


Figure 9. Early examples of achiral Rh-based hydrogenation catalysts and iridium-derivatives thereof.

or the cationic 1,5-cyclooctadiene (cod)-coordinated Schrock-Osborn type catalysts such as $[Rh(cod)(PPh_3)_2]^+$ gave less hydrogenation activity than the rhodium variants (Figure 9).[116,117] However, in the mid-1970s work by Crabtree and Morris in the laboratory of Felkin in Paris established that Ir-analogues of Schrock-Osborn type catalysts worked well in non-coordinating solvents such as dichloromethane.[113,118,119] Interestingly, dichloromethane is still the preferred solvent of choice for many iridium hydrogena-

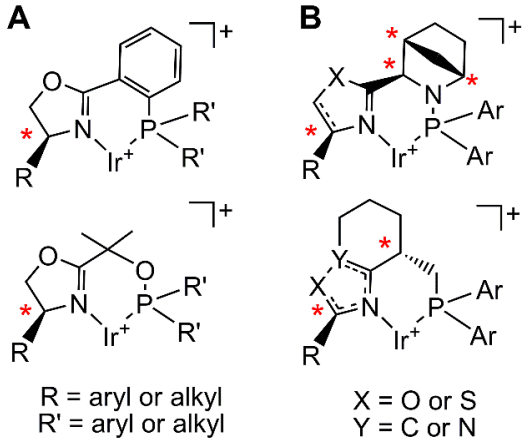


Figure 10. Examples of chiral *P,N*-iridium hydrogenation catalysts. **A)** PHOX complexes reported by Pfaltz and coworkers (only two of many skeleton variants shown).[107,111] **B)** Generalized representation of catalysts by Andersson and coworkers (adapted from [112]). Asterisks mark stereogenic centres.

tion reactions.[107] The cationic complex that later became known as Crabtree's catalyst is $[Ir(cod)(PCy_3)(C_5H_5N)]^+$ (Figure 9C), which has a phosphine and a pyridine ligand.[119] This complex constitutes the achiral precursor of a large variety of chiral *P,N* catalysts now employed in asymmetric Ir-mediated hydrogenation reactions. Well-known members of this group are the phosphinooxazoline (PHOX)-type catalysts by Pfaltz and coworkers,[107,110] and related complexes by Andersson and coworkers (Figure 10, see also a recent review by Andersson [111]). These complexes have a broad substrate scope and are able to achieve high enantioselectivities (*ee*'s up to >99%) for example for hydrogenation of unfunctionalized tri- and tetrasubstituted aryl and alkyl alkenes, terminal alkenes, cyclic alkenes, allylic alcohols, and vinylboronates.[111,120]

4.2 QM studies of asymmetric iridium-catalyzed alkene hydrogenation

The dramatic improvement of computational protocols in the field of QM-studies of asymmetric reactions during the 1970s to 2000 is apparent from section 3. The following discussion will focus on recent quantum chemical applications to enantioselective iridium catalysts, illustrating early DFT studies on truncated models (2004), but also very recent computations (2014) including dispersion-corrected DFT calculations on full molecular models and complete diastereomeric reaction pathways.

4.2.1 Mechanistic aspects

The mechanism for alkene hydrogenation with *P,N*-iridium complexes is still somewhat debated, although the majority of studies agree that it involves an Ir(III)/Ir(V) cycle.[94,3,106,121,122,123] This mechanism was first proposed on basis of DFT studies by Brandt *et al.* in 2004.[106] The initial study involved B3LYP/LANL2DZ (GAUSSIAN98) calculations on a highly truncated QM model (Figure 11). Electronic energies without ZPVE were reported (with some exceptions).

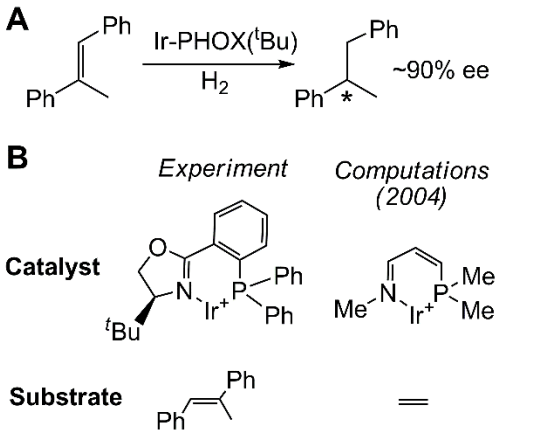
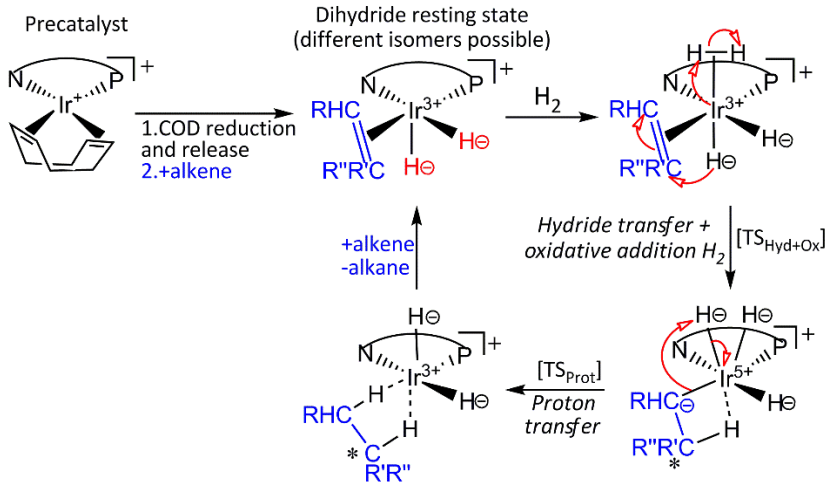


Figure 11. A) Example of Ir-PHOX mediated alkene hydrogenation,[106] **B)** Comparison of the QM model employed by Brandt *et al*. (right) and the experimental system.[106]

In the mechanism by Brandt *et al.*, the active species is an alkene-coordinated Ir(III) complex with two hydrides and one H_2 ligand (Scheme 9). Sequential hydride transfer (migratory insertion, concomitant with H_2 oxidative addition) and proton transfer (reductive elimination) provide the alkane product. The mechanism proposed by Brandt *et al.* involves formation of an Ir(V) intermediate, which was a novel proposal, and which is still not fully accepted by the community. Due to the smallness of the computational model, the Ir(III)/Ir(V) mechanism was considered controversial for several years. Roseblade and Pfaltz write in 2007: "*Since an extremely truncated model for the ligand and substrate (ethylene) was used, which neglected the severe steric interactions present in the actual catalysts, it seems dangerous to rule out an IrI–IrIII cycle*."[120] Later DFT studies by us (2011) on a full Ir-PHOX catalyst and substrate supported the Ir(III)/Ir(V) mechanism,[94] but pointed out that the energy differences to alternative mechanistic possibilities is small. The calculations were performed employing GAUSSIAN09, B3LYP, triple-ζ basis set except on Ir(LANL2DZ), and PCM single-point corrections to the Gibbs free energies. Also Grimme empirical dispersion corrections were computed for some structures. These are gradually becoming standard in



Scheme 9. Currently accepted Ir(III)/Ir(V) mechanism for *P,N*-iridium-mediated alkene hydrogenation. Based on the original proposal by Brandt *et al.* for a truncated model[106] and our calculations on a full asymmetric catalyst system.[94] Formal charges are indicated to clearly illustrate the electron flow and iridium oxidation states.

the field, with the first version, D1, reported in 2004,[124] followed by D2,[125] D3,[126] and D3BJ,[127] with the latter three being available for various functionals in GAUSSIAN09 from Rev. D. Empirical dispersion corrections improve some of the deficiencies of conventional DFT in describing dispersion interactions and their inclusion appears to yield better results for a variety of properties, in particular non-bonding interactions and binding energies.[128,129] They might also be crucial for the accurate description of enantioselectivities.[3,123,130] Such corrections are often included to the energy only, but also dispersion-corrected geometries can be obtained. An alternative approach to DFT-D is the use of parameterized functionals, e.g. the Truhlar functionals (see [131] and references therein). Calculations by us in 2014, including IEFPCM (integral equation formalism PCM) and D2 dispersion corrections also in the geometry optimizations of all species again provided the same mechanistic picture for Ir-PHOX-mediated alkene hydrogenation, with a preference for the Ir(III)/Ir(V) mechanism over other alternatives.[3]

Neese and coworkers revisited this system in 2014 with a full Ir-PHOX model and ethene as substrate, employing DFT optimized structures alongside single-point energies obtained with a higher level *ab initio* code [DLPNO-CCSD(T) = domain-based local pair natural orbital-coupled cluster single double (triples correction)] and again confirmed the Ir(III)/Ir(V) mechanism.[123] The study by Neese also highlighted the importance of empirical dispersion corrections for accurate DFT descriptions of stereoselectivities.

It might be noted that the QM studies predicting an Ir(III)/Ir(V) mechanism all involve bidentate *P,N* ligands and unfunctionalized alkene substrates (sometimes only ethene[121]). Some conflicting experimental and theoretical studies exist,[132,133,134] e.g. for hydrogenation of exocyclic α,β-unsaturated carbonyl compounds with a related Ir-BiphPhox complex, an Ir(I)/Ir(III) mechanism has been proposed on basis of DFT calculations (GAUSSIAN09, B3LYP/PCM).[133] However, computations on the Ir(III)/Ir(V) mechanism failed.[133] Also for a complex with mono-dentate ligands, $[IrH_2(NCMe)_3(P^iPr_3)]^+$, it has been proposed on basis of DFT studies that H_2 coordination occurs after migratory insertion (slightly truncated QM model, GAUSSIAN09, B3LYP-D3/PCM).[134] Although no Ir(V) intermediates were optimized, the final proton transfer TS was proposed to have Ir(V) character.

4.2.2 Selectivity-determining interactions

Brandt *et al.* proposed selectivity-determining interactions in Ir-PHOX-mediated alkene hydro-

genation in 2004.[106] B3LYP/LACVP calculations were performed with Jaguar (Version 4.0) on a full catalyst (IrPHOX with ^{t}Bu as substituent at the stereogenic centre) and (*E*)-1,2-diphenylpropene as substrate. The calculations indicated that the oxazoline substituent (^{t}Bu) serves to recognize the least substituted position of the alkene substrate (Figure 12A). In addition, it was proposed that van der Waals (dispersion) interactions between a substrate phenyl and the oxazoline ring would be relevant, but this could not be confirmed in calculations, as B3LYP is not able to describe the proposed stacking interactions. Note that only a single TS structure was reported in this study, and other diastereomeric conformations were not evaluated.[106]

A full analysis of different diastereomeric pathways was reported by us in 2011 for essentially the same catalyst, but with ^{i}Pr as substituent at the stereogenic centre (GAUSSIAN2009, B3LYP, triple-ζ basis set except on Ir[LANL2DZ], PCM and D2 single-point corrections to free energies).[3] 8 diastereomeric TS structures were reported, with the preferred geometry corresponding to the arrangement proposed by Brandt *et al.*.[3,106] Later calculations by us on the same catalyst studied by Brandt, including IEFPCM and Grimme empirical dispersion corrections in the geometry optimizations, support non-bonding interactions between substrate and oxazoline.[136] However, these appear to be of CH/π character between a hydrogen on the oxazoline ring and a substrate phenyl (Figure 12B). We performed a related analysis for a different Ir-PHOX catalyst in 2014, again employing full models and computations of all diastereomeric pathways (GAUSSIAN09, B3LYP-D2/IEFPCM).[3] The latter study identified two strong CH/π interactions involved in the enantiodiscrimination (Figure 12C). The $\Delta\Delta G^{\neq}_{R\text{-}S}$ value computed with B3LYP-D2 was 2.6 kcal/mol, corresponding to an ee of 98% (*S*), in good agreement with experiment (94% (*S*)[77]).[3]

4.2.3 Computational challenges

QM studies of asymmetric systems face a number of challenges, of which a few selected ones will be discussed in the following, mainly employing iridium-based systems as examples.

4.2.3.1 Conformations

A particular challenge in QM descriptions of asymmetric systems is the generation of conformations. The catalyst might have floppy groups (like ethyls), allowing for many different conformations. This is particularly important when small energy differences, such as those between diastereomeric TSs, are involved. Houk and coworkers noted in 2004 that a "*thorough consideration of all the possible transition states is needed in order to make those predictions, and this becomes tedious as the size and flexibility of the system increases.*"[135] There is no shortcut available, the conformational space has to be mapped adequately to allow for any proper conclusions. Also Gusev recently pointed

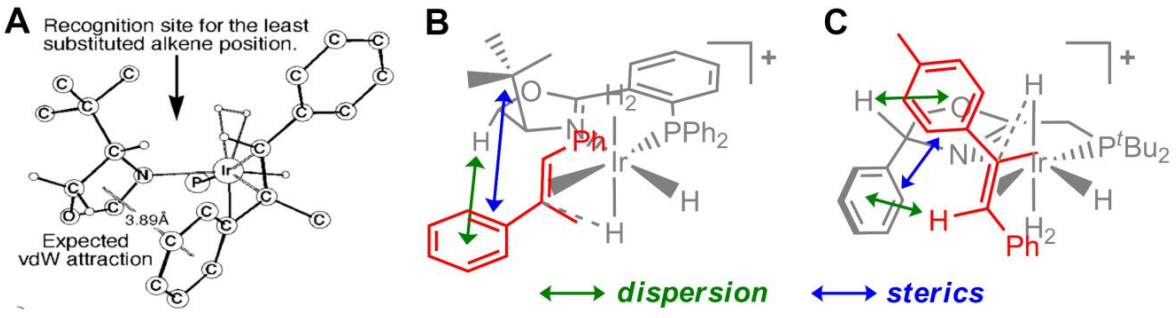


Figure 12. Selectivity-determining interactions in Ir-PHOX-mediated alkene hydrogenation. **A)** Original figure by Brandt *et al.:* Copyright (2003) WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Reproduced with permission from [P. Brandt, C. Hedberg, P. G. Andersson, *Chem. Eur. J.* **2003**, *9*, 339-347]. **B)** Model for catalyst in A) based on B3LYP-D3 calculations,[136] **C)** Related Ir-PHOX system, showing CH/π interactions between substrate and catalyst.[3]

this out and identified several cases in the literature, where incorrect ground state conformations had been employed for a Ru-phosphine complex.[137]

In order to map the conformational space, the computational chemist might employ manual labour and intuition, or use more automated force-field based methods to generate random conformations. For example, Jensen and co-workers report the use of the SCAN program implemented in Tinker and the MM3 force field for conformational searches of organometallic complexes.[138]

Semi-automated approaches for TS searches have also been reported, as e.g. illustrated by the recently reported Automated Alkylation Reaction Optimizer for N-oxides (AARON) by Wheeler and coworkers.[139] In order to investigate the stereoselectivity of 18 chiral bipyridine N,N'-dioxide catalysts for allylation of benzaldehyde, a text-based interface with GAUSSIAN09 was written that automatically located the relevant 820 TS structures. However, note that this approach was based on detailed pre-knowledge about the reaction pathway and expected transition states, as the initial TS structures were constructed by mapping the 18 catalysts onto the already known TS structures for a related catalyst.[139]

4.2.3.2 Non-Curtin Hammet conditions

In studies of asymmetric reactions, the ee is normally evaluated through computation of the energy difference between diastereomeric TSs ($\Delta\Delta G^{\neq}$) and can be computed as given in Figure 2.[33] When applying this strategy, it is implicitly assumed that only the TS barriers are of relevance and that the ee is independent of the energies of intermediates, such as diastereomeric substrate-catalyst adducts. This is based on the assumption that isomerization between intermediates is fast, much faster than e.g. the hydrogenation step in asymmetric hydrogenations. However, there might be conditions, where this assumption is not valid.

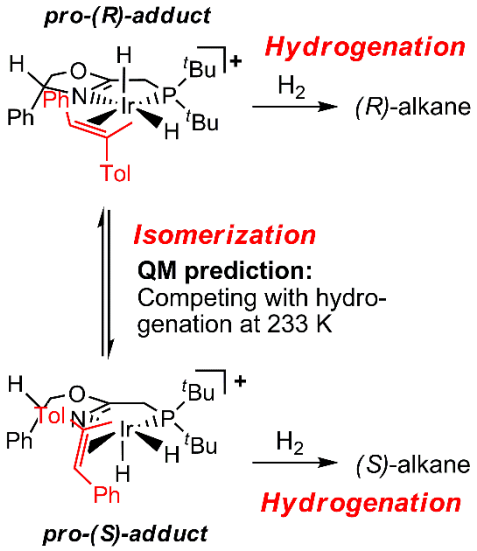


Figure 13. Diastereomeric alkene-catalyst adducts in Ir-PHOX-mediated hydrogenation (as identified by NMR[77] and supported by our calculations[3]). The computed barrier for isomerization between adducts approaches that of hydrogenation at 233 K.[3]

We have recently proposed that the barrier for isomerization between diastereomeric iridium-PHOX-alkene adducts becomes close to the hydrogenation barriers at 233 K, which implies that the ee becomes dependent on the barrier for isomerization (Figure 13).[3] Numerical modelling of the reaction kinetics on basis of the QM barriers for isomerization and hydrogenation support this hypothesis.[3] Therefore, for a given system one should evaluate how diastereomeric intermediates isomerize and if such isomerization steps can affect the selectivity.

4.2.3.3 Competing reaction pathways

A given catalyst might be able to catalyze different chemical reactions, alongside the desired conversion, complicating the computational analysis. Competing reactions might for example involve isomerization of the starting material. In cobalt-bis(imino)pyridine-catalyzed hydrogenation reactions, the hydrogenation of an exocyclic alkene occurs concomitantly with isomerization of the substrate to the more stable endocyclic alkene.[140,141] QM calculations by us indicate that the catalyst efficiently

catalyzes the isomerization of the substrate.[141] Surprisingly, in calculations, the endocyclic and exocyclic alkene isomers are hydrogenated with similar enantioselectivities, i.e. the isomerization of the starting material does not have a direct effect on the ee.[141] However, in general it can be assumed that different isomers of a given substrate, such as E/Z isomers of double bonds, internal and external alkenes, or imine and enamine tautomers (Figure 14), are converted with different selectivities. Therefore, for any asymmetric reaction it is advisable to evaluate if an isomerization of the starting material might occur, what the barrier for the isomerization is (is it competing with the desired catalytic step?), and how conversion of the isomer (if formed) might affect the selectivity.

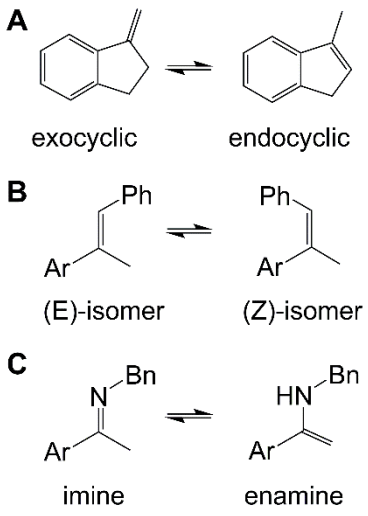


Figure 14. Examples of substrate isomerizations occurring in metal-catalyzed reactions. Isomerization between **A**) endo- and exocyclic alkenes,[140] **B**) (*E*)- and (*Z*)-alkenes,[77] **C**) imines and enamines.[142]

Fortunately, in many cases, although substrate isomers might be formed, they might not be converted. For example, in rhodium-phosphine catalyzed hydrogenation of imines, it has been shown that the enamine tautomer of the starting material is formed, but labeling studies indicate that it is not the species being hydrogenated.[142] In this case it should be sufficient to study the ee on basis of the imine form only. For Ir-PHOX mediated hydrogenation of an (*E*)-alkene, a small amount of the (*Z*)-isomer of the starting material was detected after work-up.[77] However, QM calculations of the cost of formation of the (*Z)*-isomer indicate that it should not be formed in significant amounts under hydrogenation conditions, and calculations on the (*E)*-isomer are considered sufficient to rationalize the experimental ee.[3]

4.2.3.4 Dependence on DFT functional

The current state of the art in the field of QM-based studies on asymmetric catalysis is DFT, which provides a reasonable trade-off between speed and accuracy (for a review on the performance of DFT see e.g. [131]). With the computational power available today, DFT allows for quantum chemical studies involving full molecular models of the catalyst and substrate. An obvious question one might ask is: how dependent are the computed results on the choice of DFT functional? The answer is: it depends on the property studied.

A small benchmark analysis by us on alkene hydrogenation with an iridium-PHOX catalyst shows that absolute hydrogenation barriers are remarkably similar with different DFT functionals, irrespectively if pure functionals (without HF exchange) or hybrid functionals are used, and if empirical dispersion corrections are included or not (Table 1).[3] Unfortunately, no experimental value is known for this system in order to evaluate how good the agreement with computation is.

Table 1 shows that computed $\Delta\Delta G^{\neq}$ values vary somewhat for the different functionals. However, despite the variation of 1.3 kcal/mol for $\Delta\Delta G^{\neq}$, the variation in predicted ee is only 2.1 %, from 97.6 to 99.7 % (Table 1). This is due to the exponential relationship between the $\Delta\Delta G^{\neq}$ and the ee (Figure 2). The computed values show that the best results are obtained through inclusion of empirical dispersion, either through parameterization (as in the M06 family of functionals[131]) or as an add-on to the DFT functional (such as Grimme empirical dispersion corrections D2[125] or D3,[126] but surprisingly not

D3BJ[127]). Neese and coworkers have reported similar results.[123] As discussed above (section 4.2.2), the selectivity in these systems appears to be determined by non-bonding dispersion-type forces such as CH/π interactions. This might explain why dispersion-corrected functionals provide better results.

It can be emphasized here that the dependence on the DFT functional for the reproduction of small experimental ee's can be expected to be much larger, as these typically involve energy differences of less than 1 kcal/mol (e.g. the $\Delta\Delta G^{\neq}$ difference between 25% ee and 70% ee is 0.7 kcal/mol at 298 K). This accuracy cannot be expected from currently employed DFT methods, although one might assume that favourable cancellation of errors implies that the absolute error for $\Delta\Delta G^{\neq}$ values in general should be less than for absolute barriers (i.e. $\Delta G^{\neq}$ values).

The prediction of equilibria between two diastereomeric alkene-iridium complexes turned out to be rather functional dependent. Whereas dispersion-corrected B3LYP provided good agreement with experiment (ratios of 5:1 for B3LYP-D2 and 9:1 for B3LYP-D3, compared to 11:1 in experiments[77]), for example M062X incorrectly assigned the minor isomer as the major isomer.[3] An evaluation of B3LYP-D2 and B3LYP-D3 with respect to six known experimental quantities for iridium systems (barriers, equilibria, dissociation energies) gave errors of 0.3 to 2.5 kcal kcal/mol for B3LYP-D2, but up to 6.2 kcal/mol for B3LYP-D3.[3]

One of the most problematic properties to compute are binding and dissociation energies. Unfortunately, many reaction pathways involve steps, where ligands associate or dissociate from a metal centre. Benchmark studies show that dissociation energies can vary enormously between different DFT functionals,[3,138,143,144] up to 40 kcal/mol.[143] For binding enthalpies of a phosphine ligand to a ruthenium complex, Sieffert and Bühl report values that vary from -24.2 kcal/mol for B3LYP-D (i.e. coordination is strongly favoured) to 17.9 kcal/mol for B3LYP (i.e. coordination is strongly disfavoured).[143] For an Ir-PHOX system, values of 7.4 to 19.2 kcal/mol were obtained for dissociation of an alkene from iridium, i.e. a variation of more than 10 kcal/mol.[3] It appears that inclusion of empirical dispersion corrections provides the best results for binding and dissociation energies.[138,143] However, any conclusions on basis of binding or dissociation energies should be made with caution.

Table 1. Computed barriers for preferred pro-(*R*) and pro-(*S*) TS structures in Ir-PHOX-mediated hydrogenation of (*E*)-1-methyl-4-(1-phenylprop-1-en-2-yl)benzene (system shown in Fig. 12C).[a]

	HF[b] ex.%	Emp. Disp.[b]	TS, $\Delta G^{\neq}$ pro-(*R*)	TS, $\Delta G^{\neq}$ pro-(*S*)	$\Delta\Delta G^{\neq}$	ee, %(S)
OLYP[c]	0	No	-	-	3.9	99.7
PBE[c]	0	No	-	-	3.5	99.5
B3LYP	20	No	22.9	19.3	3.5	99.5
M06	27	Param.	22.6	19.6	3.1	99.0
M062X	54	Param.	26.0	23.4	2.6	97.6
B3LYP-D2	20	D2	22.5	19.9	2.6	97.6
B3LYP-D3	20	D3	22.4	19.6	2.8	98.3
B3LYP-D3BJ[c]	20	D3BJ	23.3	19.7	3.6	99.6
M06-D3	27	Param. + D3	22.6	19.1	3.5	99.5
Experiment					2.2[d]	94[d]

[a] GAUSSIAN09, B3LYP-D2/IEFPCM, including basis set and counterpoise corrections, for details see [3]. [b] ex. = exchange, Emp. Disp. = empirical dispersion, Param. = parameterized. [c] Unpublished results. [d] From [77]. Experimental $\Delta\Delta G^{\neq}$ value estimated from known ee value.

5. Predictions and *in silico* design of novel catalysts

If computational methods are able to rationalize the results of performed experiments, are they also able to predict the outcome of experiments not yet performed?

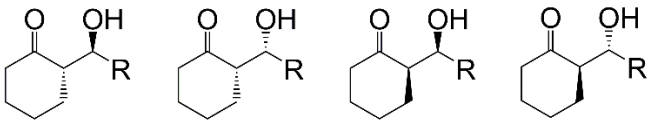
5.1 Prediction of enantioselectivities

QM studies aimed at predicting the outcome of asymmetric experiments have been reported as far back as the 1980s. In particular K. N. Houk and coworkers have done impressive work in this field and reported already in 1987 a study on electrocyclization of substituted cyclobutene.[145] TS structures were optimized with GAUSSIAN82 at the HF/321-G level (6-31G* for energies) for 3-formylcyclobutene. Based on the electronic energies, it was predicted that the (*Z*)-isomer of the product is formed, although the (*E*)-isomer is thermodynamically favoured. Experiments by the same authors confirmed the predictions.[145]

In 2003, Houk, List, and coworkers reported a related investigation: They employed B3LYP/6-31G* (GAUSSIAN98) to predict the ratio between four stereoisomeric products formed in the proline-catalyzed intermolecular aldol reaction between cyclohexanone and benzaldehyde or isobutyraldehyde and then went on to conduct the corresponding experiments.[101] From known experimental ee's for three aldol reactions the absolute errors on computed barriers were estimated. For these known reactions, the computed gas phase enthalpies were closer to the experimentally derived free energies (absolute errors of 0.44 kcal/mol) than the computed gas-phase free energies (absolute errors of 0.48 kcal/mol) or than PCM-corrected free energies (absolute errors of 0.78 kcal/mol). Therefore, for the reactions with unknown outcome, the gas phase enthalpies were employed to predict the product ratio (Figure 15). Subsequently, the results were compared to experiments. For the reaction between cyclohexanone and isobutyraldehyde very good agreement was observed (Figure 15, R = iPr). For the reaction between cyclohexanone and benzaldehyde, the predicted amounts have a rather large error bar due to the expected error on computed energies of up to 0.4 kcal/mol (50-80 % for the major product, 20-50% for the second major product), making it difficult to evaluate the accuracy of the prediction. However, the experimentally observed amounts (45-47% and 43-45%, respectively) do fall within the predicted range (Figure 15, R = Ph).

Houk and coworkers conclude in their 2003 study that: "*quantum chemical calculations of this type will soon become a common predictive tool*".[101] More than 10 years later it appears that this was a somewhat optimistic prediction. One problem in this type of calculations is the complexity of asymmetric systems. Fey and coworkers recently pointed out some of the challenges encountered: on one site the technical demands (costly computations of free energies, solvation, dispersion) and on the other site, the reaction-dependent inherent demands, such as conformers, isomers, and alternative reaction pathways.[154]

In 2009, Deeth and Brown asked, if it is possible to predict the enantioselectivity of asymmetric reactions for a defined set of catalysts and reactants.[146] It was concluded that promising developments have been reported, however, full QM calculations on for example organometallic systems can become too



R = Ph	*Theory*	50-80%	20-50%	<1%	1-4%
	Experiment	45-47%	43-45%	5-7%	3-5%
R = ^{i}Pr	*Theory*	≥99%	<1%	<1%	<1%
	Experiment	97-100%	<1%	<1%	0-3%

Figure 15. Predicted and experimental product ratios for the proline-catalyzed intermolecular aldol reaction between cyclohexanone and benzaldehyde (R = Ph) or isobutyraldehyde (R = ^{i}Pr). Data adapted from Houk and coworkers.[101] Note that predictions were made on basis of gas phase enthalpies, as these were considered to provide a more accurate estimate of the experimental free energies in solution than computed free energies.

demanding, in particular if many conformers and catalyst/substrate combinations have to be evaluated. MM methods, developed on basis of DFT-optimized parameters, are highlighted as one possibility to overcome these challenges.[146] An example is the Q2MM approach by Norrby, Wiest and coworkers, which has been applied to e.g. metal-catalyzed hydrogenation reactions.[147,148] For Ru-catalyzed ketone hydrogenation, enantioselectivities of 13 catalytic systems were predicted with a mean unsigned error of 2.7 kJ/mol.[148] However, the development of such methods requires a large investment of time and expertise, as commented upon by the authors themselves[147] and also Jover and Fey.[154] A slightly different approach is to use QM/MM methods when studying asymmetric metal-based systems (with the MM methods applied to describe the metal ligands).[33] However, such approaches can fail where ligand-induced electronic effects are important. For example, the enantioselectivity of methyl-(*N*)-acetyl-aminoacrylate hydrogenation with a phosphine-phosphinite-rhodium complex could not be described with QM/MM but only with a full QM treatment. [149]

5.2 *In silico* catalyst design

In 1988, Morokuma and coworkers wrote: "*Even a catalytic cycle of an unknown complex could be a subject of an ab initio MO study. One may some day be able to use the information obtained from such a study for a theoretical design of a new catalyst*."[47] Indeed, approaches to design new catalysts on basis of *in silico* results are ongoing, with very different computational approaches applied. Examples are QM-based calculations of a single reaction and optimizations of (diastereomeric) transition states to predict the outcome with a novel or redesigned catalyst (analogous to the examples covered in section 5.1),[3,150,151] quantitative structure–activity relationship (QSAR)-based approaches[152] or structure-based parameter-databases.[153,154]

An interesting concept proposed by Houk and coworkers in the 1990s is that of 'theozymes': here QM methods are employed to compute the TS for a given reaction *in absence* of catalytic groups, and this structure is then decorated with functional groups (such as amino acids) that can provide optimal non-covalent stabilization to the TS. The added groups form the artificial catalyst or 'theozyme'.[155] Although theozymes were largely discussed in the context of enzymatic catalysis, also organometallic catalysts should be designable in this fashion. The theozyme can be based on already known structures or be predicted completely *ad hoc*, progressing, as Houk and coworkers put it, "*towards the purest of theozymes, that which is created by theory alone in the absence of the biases imposed by structural and biochemical information or human intuition*".[155]

In 2008, Houk and Cheong summarized some of the ongoing efforts in designing small-molecule catalysts employing QM methods.[156] Several successful examples were given, such as the prediction of organocatalysts to perform *anti*-selective Mannich reactions on basis of HF/6-31G* calculations.[150] Also Jover and Fey have recently (2014) reviewed computational studies attempting to predict new catalysts.[154] Examples include for example *in silico* prediction of ruthenium-pincer complexes for carboxylation of arene C-H bonds.[151] However, in this, as in many other cases, the predicted systems await to be studied experimentally and it is therefore too early to make conclusions on the quality of the predictions made.

6. Conclusions

QM calculations have been essential in elucidating the mechanisms and selectivity-determining factors in a variety of asymmetric systems. Early calculations in the 1970s on non-catalytic asymmetric induction demonstrated the usefulness of this type of calculations, even at a single-point HF/STO-3G level.[2] One decade later, the first *ab initio* computation of a full

reaction pathway of an organometallic catalyst system was reported,[47] followed in the 1990s by the first DFT studies on asymmetric systems.[64,83,84] Initially, these involved heavily truncated models, but the beginning of the new millennium saw calculations on full systems, also including solvent (PCM) effects. The development of empirical dispersion corrections was a further significant advance,[4] providing a more accurate description of non-bonding interactions, which have turned out to be essential selectivity-determining factors in a variety of asymmetric systems.[3,62] The current state-of-the-art in this field can be considered to be DFT, with appropriate corrections (solvent and dispersion) to geometries and energies. Such calculations are now feasible also for larger organometallic systems.[3] Nonetheless, QM studies of asymmetric reactions remain somewhat challenging, requiring adequate mapping of the conformational space and considerations of isomers and alternative reaction pathways.[3,141] Although the potential to use QM calculations to make predictions about enantioselectivities was pointed out already in the 1980s,[145] the progress in this type of applications is slow, partially due to the inherent complexity of asymmetric systems but also because the quality of the *in silico* predictions cannot be assessed before they have been experimentally validated.

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