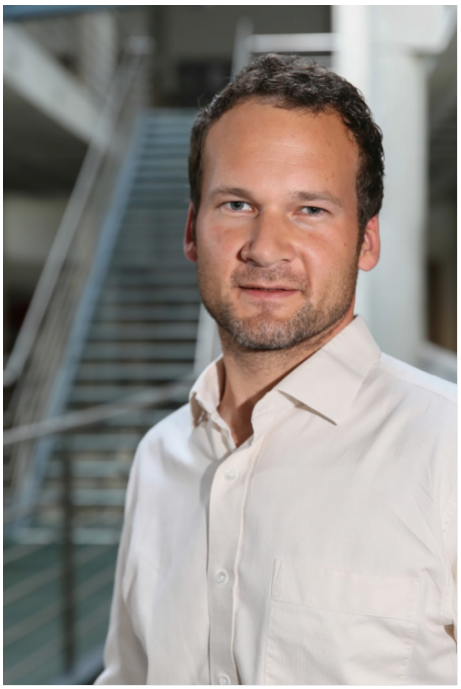
Asymmetric Metal-Catalyzed Carbon-Hydrogen Bond Functionalizations



Prof. Nicolai Cramer

SWISS FEDERAL INSTITUTE OF TECHNOLOGY, EPFL

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Abstract

My group is developing new catalysts and catalytic processes that selectively activate and asymmetrically functionalize carbon-hydrogen bonds. In general, catalysis is a critical process and 90 % of all chemical products have contact with a catalyst during their manufacture. In the subfield of asymmetric catalysis, we use chiral metal complexes to control syntheses in such a way that they become enantioselective. This allows producing only one version of two molecules that are a mirror image of each other. The demand for such molecules is high as for example two enantiomers of the same drug often have different or even adverse modes of action. Carbon-hydrogen bonds are very widespread and almost every molecule contains several of these bonds. The reactivity of these bonds is extremely low and it is difficult to make use of them in syntheses. However, their functionalization provides enormous benefits, because the spectrum of raw materials is much wider and process is more efficient compared to existing synthetic methods. We have succeeded in achieving the required reactivity and selectivity by using tailor-made rhodium and palladium complexes. These new catalysts enable access to a wide and diverse range of molecular building blocks with important biological applications.

Introduction

Catalysis is a critical process and 90 % of all chemical products have contact with at least one catalyst during their manufacture. Catalytic processes generate more than $ 1 trillion in products worldwide. Major areas of catalysis comprise energy processing, bulk chemicals, fine chemicals, food and food processing and environment. Our research is situated on catalysis for high value fine chemicals.

C-H Activation

Often, the synthesis of a specific product needs a multi-step synthetic sequence from available and affordable starting materials. The capacity of a reaction to take place is largely determined by functional groups that as well define the specific position at which reaction takes place. Before the actual reaction can proceed, the initial functional groups often need to be chemically converted into more competent ones (Figure 1). By and large, this approach is well mastered, predictable and has been refined by generations of chemists over the past century. However, there is a high interest in cutting down the number of steps of longer synthesis routes. Each chemical step adds to the costs of the final product in terms of time, produced waste and consumed energy. An attractive complementary strategy to achieve this goal is the direct functionalization of carbon-hydrogen bonds. These are ubiquitous in almost any starting material. Their selective reaction would not only allow accessing a broader range of feedstock but as well allow significantly shortening the amount of

steps of synthetic routes. However, despite of undeniable advantages, this type of catalysis is not general as numerous chemical problems need still to be solved. Mainly, these are the very poor reactivity of C-H bonds and the selectivity in the reaction.

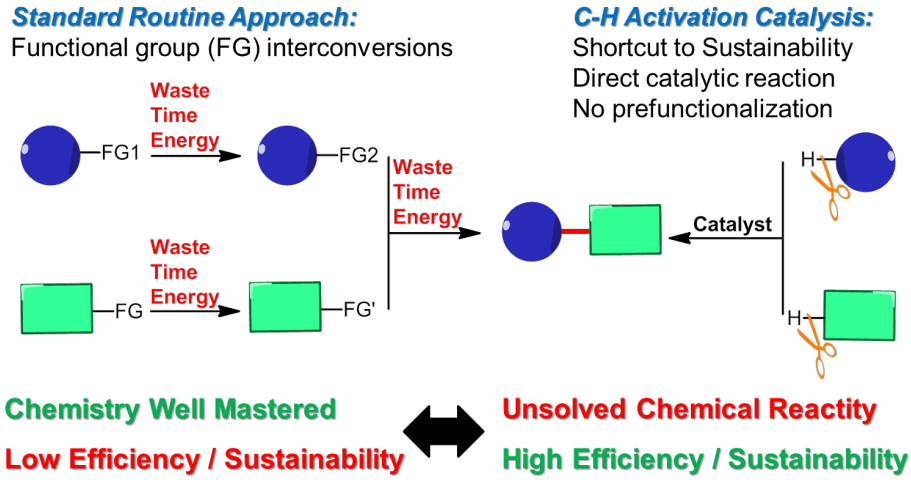

Figure 1: *Classical and C-H activation approach in chemical synthesis.*

For example, by current synthetic means it is not possible to selectively and completely convert a simple hydrocarbon starting material into the shown oxidized product (Figure 2). On the other hand, taxadiene, a more complex starting material, constituting as well only of carbon and hydrogen atoms, is enzymatically converted by nature to the famous anti-cancer drug Taxol.[1] The transformation is truly impressive and its level of complexity will probably be unparalleled by synthetic chemists in any near future. On the other hand, it is highly optimized and works exclusively on this one single substrate and nothing else. The big advantage of designed synthetic catalysts is their broader substrate tolerance. While they might struggle to be perfect on a single starting material, they are generally more robust to digest well a broader range of diverse starting materials. This renders them to practical chemical tools.

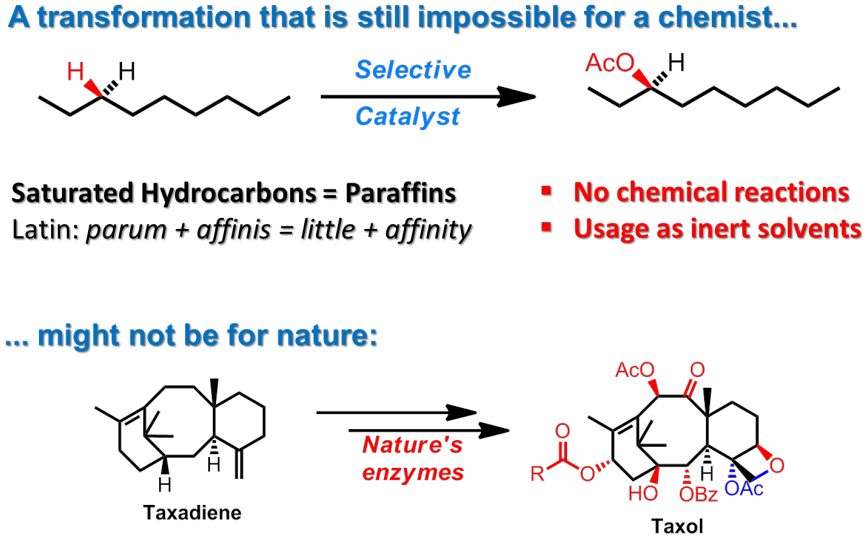

Figure 2: *Example of C-H oxidations: impossible for chemist, but possible for nature.*

Chirality and Asymmetric Catalysis

A particular class of molecules possesses a chiral carbon atom (highlighted in blue, Figure 3). This feature makes the molecule to behave like a pair of hands. To the same extent as left and the right hand are not superimposable and are mirror images to each other, these molecules exist in two forms, so-called (*R*)- and (*S*)-enantiomer. While both enantiomers have in many aspects identical (physical and chemical) properties, they behave differently in the interaction with other chiral molecules. For instance, enantiomeric molecules may have completely different biological activities. For example, the (*R*)-isomer of olean is the active sex pheromone of the olive fruit fly. The opposite enantiomer (*S*)-olean is only active on females.[2] The importance of the proper chirality on drugs becomes immediately apparent with the Contergan tragedy. The active intergradient, Thalidomid, was used as racemic mixture, the equal amount of (*S*)-Thalidomid and (*R*)-Thalidomid. Whereas the (*R*)-Thalidomid carries the desired sedating effect, (*S*)-Thalidomid is responsible for its infamous teratogenic effect.[3] Since then, the importance of the manufacture of enantiopure material is widely recognized. To achieve this, two approaches can be pursued. The first one is an unselective racemic synthesis followed by a physical separation of both enantiomers. While this strategy is simpler on the synthesis stage, it results in a loss of 50% of the material as the wrong enantiomer is lost and disposed. The second strategy involves the selective synthesis leading to only the desired enantiomer and is termed asymmetric catalysis. This is more demanding as specific and efficient chiral catalyst need to be developed. A good part of our research is focused on the design of such chiral catalysts.

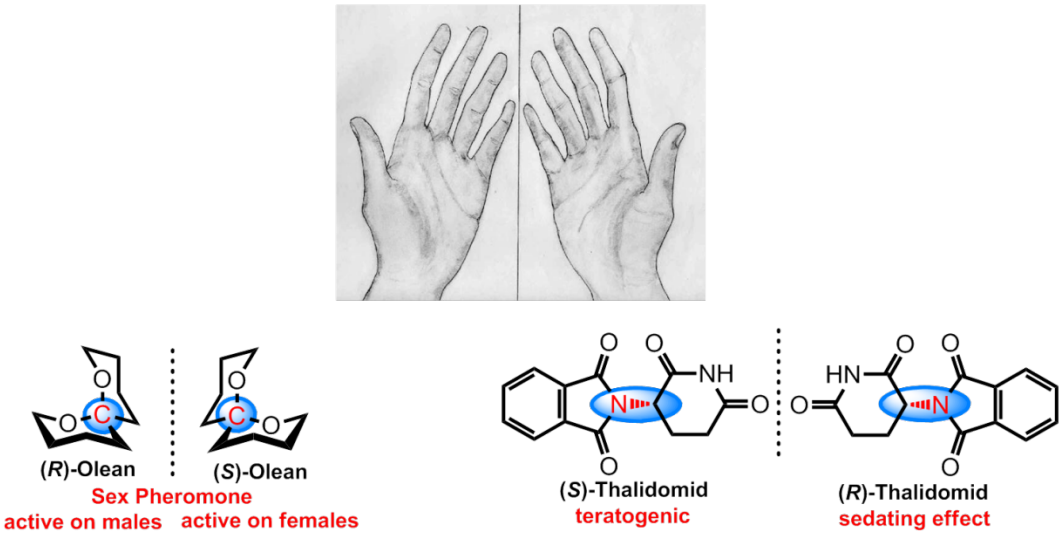

Figure 3: *Chirality (handiness) in molecules: Huge impact on biological activity.*

Aims

A central aim of my research is to invent sophisticated tools to provide application oriented researchers in chemistry better tools to reach their target molecules in a more efficient, faster and sustainable way. We focus on new and efficient catalytic transformations. These should convert a cheap and abundant starting material with a carbon-hydrogen bond into a product of significantly higher value, which can be an increased molecular complexity or a compound that exhibits desirable biological or pharmaceutical properties (Figure 4). To achieve this goal, we investigate metal catalysts, abbreviated as simple "[M]". Boiled down the essential, we seek to answer the question: "*What can [M] be"* to be optimally suited for a specific and new chemical transformation. Chemically [M] stands for a transition-metal complex which is composed of the catalytically active metal ion (e.g. rhodium, palladium, iridium, ruthenium, nickel, copper, iron) and attached organic ligands. These ligands are largely modulating the properties of the catalyst. They are decisive on their activity and stability and most importantly guide the selectivity of the catalyst.

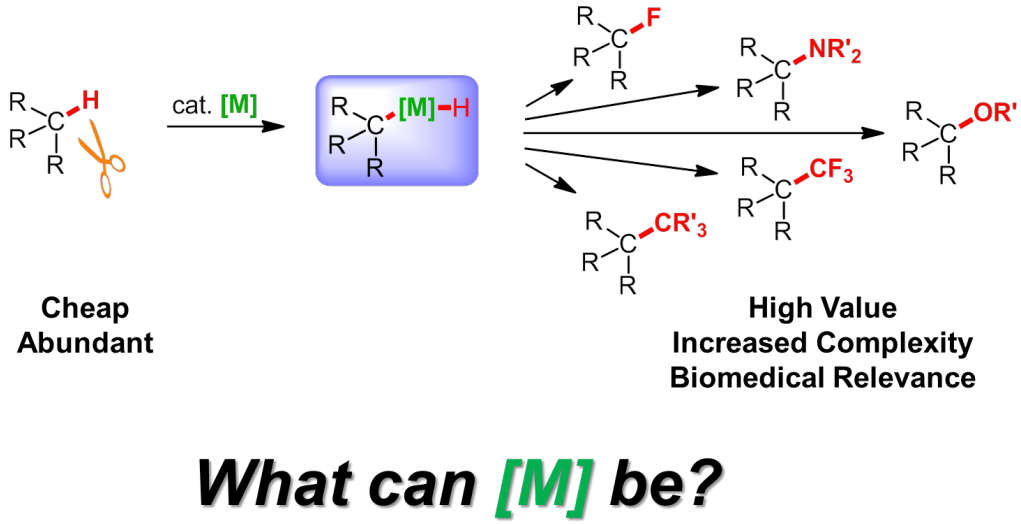

Figure 4: *The quest of efficient metal-catalyst, a central focus of our research efforts.*

Results

Generally, a decisive starting point for the development of suitable catalysts for an envisioned reaction is a decent hypothesis of its reaction mechanism and the individual steps of the catalytic cycle. This allows identifying the problematic portions. The journey from the idea to the bottled catalyst is then an long iterative process and consists of a mixture between simulation, educated guessing, parallel screening and a portion of luck. For instance, we become in 2009 interested in palladium-catalyzed carbon-hydrogen bond functionalizations for ring-closing reactions. Those reactions are highly useful to access versatile building blocks in a complementary fashion. To

realize a general process we selected first one specific model system to learn as much as possible of the reaction (Figure 5). This starting material possesses four similar carbon-hydrogen bonds (red) that can react. But only one specific of them would lead to the desired product enantiomer. The key question is how to teach the catalyst to pick the correct one! The answer to this question lays at the highlighted intermediate which is directly linked to the selectivity determining step. From there on, an exhaustive screening and matching of the passive and active ligand let to the discovery of a powerful catalyst.[4]

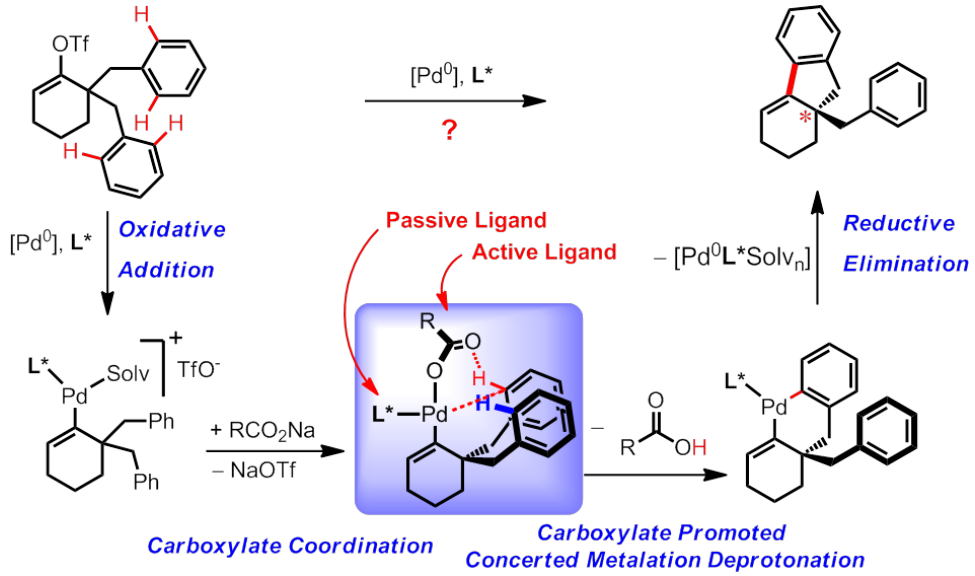

Figure 5: *Palladium-catalyzed asymmetric C-H functionalization. Knowledge of the catalytic cycle leads to efficient ligand and catalyst discovery.*

Having established the proof of principle of two synergistically working ligands to effect the carbon-hydrogen bond activation, we investigated the applicability of the discovered reaction. In particular, we focused on the activation of a range of different C-H bonds ranging from saturated C(sp^3)-H[5, 6] to cyclopropane C-H[7, 8] and C(sp^2)-H[9] bonds of pharmaceutically important ring systems (Figure 6). With a broader set of matching pairs of the passive ligand (A) and the active ligand (B), all these can be efficiently and highly selectively functionalized. Noteworthy, these catalysts overcome the difficult hurdle of the ring-size limitation. Whereas it is highly challenging to obtain ring-sizes greater than five by C-H activation, our catalysts allow access to five-, six- and seven-membered rings as illustrated for indolines, dihydroquinolones and benzazepinones. All obtained products feature a nitrogen atom in the built ring system, making them typical scaffolds for medicinal chemistry.

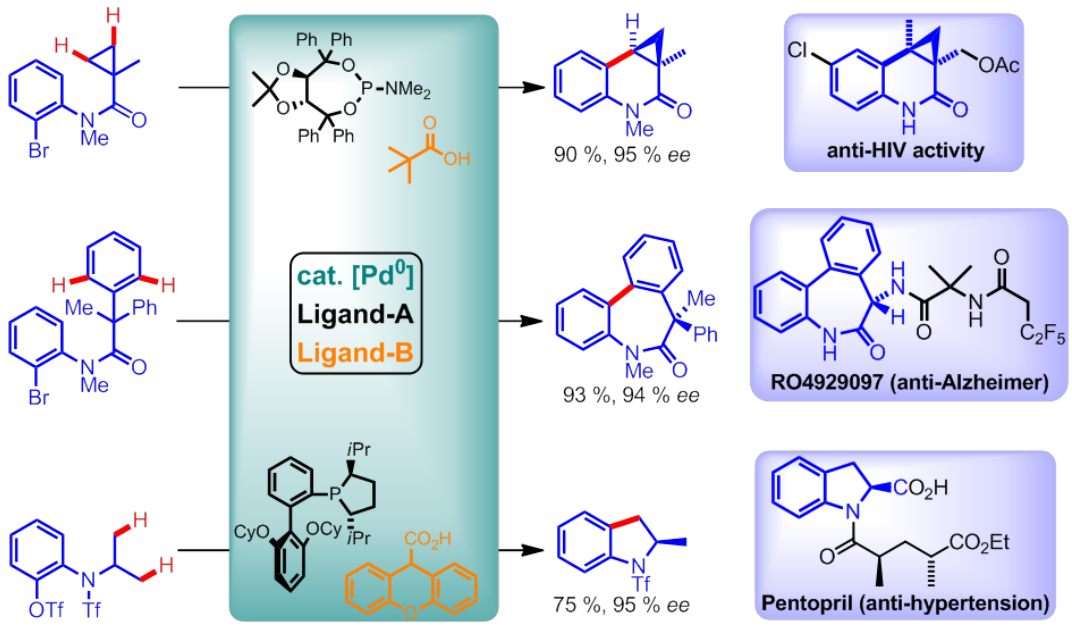

Figure 6: *Application of our asymmetric palladium-catalyzed C-H functionalization technology for the synthesis of relevant nitrogen-containing ring scaffolds.*

Another outstanding ligand for many kinds of metal complexes is the so-called cyclopendienyl anion. Since its discovery over 60 years ago,[10] it is heavily used on a wide variety of catalytically active metal complexes. Despite its great utility, rendering the cyclopentadienyl ligand chiral for applications in asymmetric catalysis has been a been a long-standing challenge (Figure 7). Creation of a successful ligand design has an immense potential to be applicable for a wide range of desirable transformations. In this respect, we embarked on the challenge to lend handiness to the cyclopentadienyl ligand.

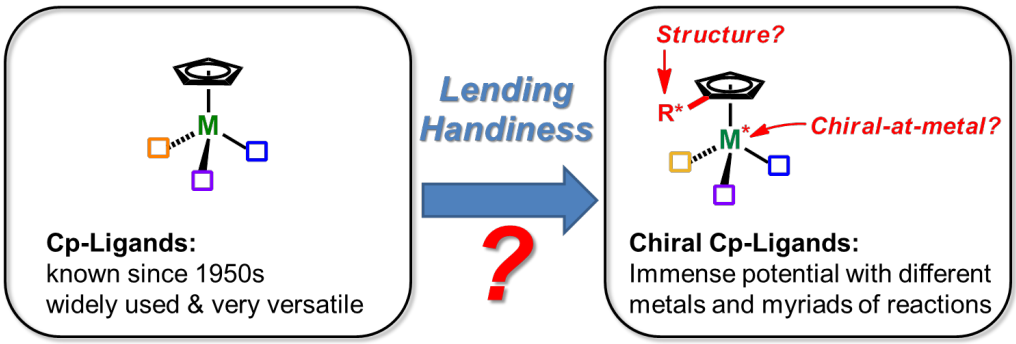

Figure 7: *Concept of lending handiness to the famous cyclopentadienyl ligand for application in asymmetric catalysis.*

After a careful design of the ligands and several failed approaches, we were able to synthesize these ligands and obtain different metal complexes. For instance, their corresponding rhodium complexes are shown in Figure 8. The X-ray crystallographic representations give detailed information on their molecular structure. A comparison as a more or less opened baseball glove with a ball allows to grasp their design principle.[11-13] The catalysis event is taking place at the ball.

Figure 8: *Representation of the chiral Cp-rhodium complexes as gloves around a baseball. The ligand is the glove, and the ball represents the transition-metal.*

In 2012, we demonstrated in a break-through application the high performance of our chiral cyclopentadienyl complexes in asymmetric C-H bond activation catalysis.[11] With the rhodium-catalyst, two simple starting materials, aryl hydroxamates and styrenes, are converted in good chemical yield and high enantioselectivity to cyclized products. The obtained chiral dihydroquinolone structure is a ubiquitous motive in a wide variety of biologically active molecules (Figure 9). Importantly, the reaction features as well attractive process aspect. It is running at ambient temperature and requires neither heating nor cooling. Moreover, it performs very well in technical grade ethanol, a green and sustainable solvent.

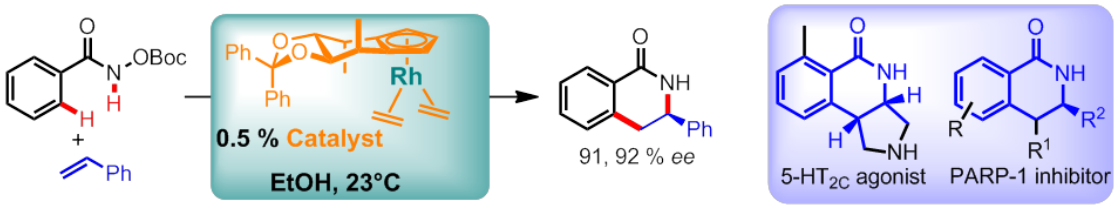

Figure 9: *Application of the chiral cyclopentadienyl complexes in C-H bond activation for the selective synthesis of biologically relevant dihydroquinolone scaffolds.*

In this short overview, I could only show two of our recent projects in metal-catalyzed bond activation. Already these provided us a lot of joy and took us far beyond our expectations that we had just a couple years ago. We are now quite certain to have only scratched the surface of what could be possible in asymmetric activation catalysis. And for future, we strongly believe that these catalysts and reaction can contribute to a more efficient and sustainable chemical production.

Acknowledgements

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