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Teaching Enantioselectivity to C–H Bond Functionalizations: Initial Steps of a Rather Long Shot

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Werner Prize winner 2012

Abstract: The direct functionalization of non-activated C–H bonds, especially in an enantioselective manner, requires metal catalysts equipped with ligands with specifically designed properties. Examples for asymmetric C(sp^2)–H and C(sp^3)–H functionalizations using palladium- and rhodium catalysts are shown. This work was rewarded by the 2012 Werner Prize of the Swiss Chemical Society.

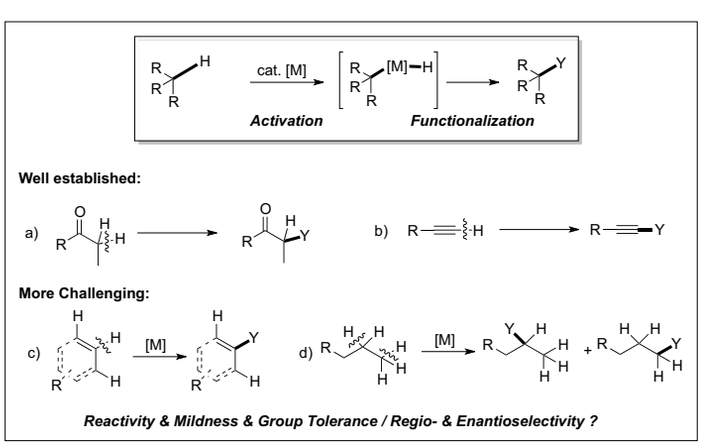
Keywords: Asymmetric catalysis · C–H Activation · Ligands · Palladium · Rhodium

Nicolai Cramer obtained his PhD from the University of Stuttgart, Germany in 2005 with Prof. Sabine Laschat. After a postdoctoral stint with Prof. Barry M. Trost at Stanford, he started his independent career as Habilitant at the chair of Prof. Erick M. Carreira at ETH Zurich in 2007. At the end of 2010, he took up his current position as Assistant Professor at the EPFL. His research interests encompass asymmetric catalysis, C–H and C–C bond activations and synthesis of bioactive natural products.

1. Introduction

Alfred Werner, one of the giants of inorganic chemistry, developed the fundamental basis for modern coordination chemistry. He was also the first to achieve the optical resolution of chiral inorganic complexes. This makes me feel even more privileged as a Werner-prize awardee, as we are often confronted by and still rely on these concepts. I chose to work in the field of catalysis not only because it is of tremendous importance for the future shape of chemistry, but mainly because I simply enjoy this incredible moment to see a nice coordination complex becoming an active catalyst. It is this transformation of simply being to function that caught me.

One of the great beauties of transition-metal catalysis is the enormous influence that ancillary ligands have on the reaction course and how even seemingly small changes dramatically alter the course of a reaction. With the right choice of ligand, almost any given overall transformation can be orchestrated from the same few elementary steps. Although the search and development for *this* ligand with the right properties can be a discouraging search for the needle in a haystack, the ability to manipulate reactivity captured my fascination for this field. It became an important research pillar of my laboratory[1–10] complementing our interest in the synthesis of bioactive natural products.[11–13] This ligand quest is driven by the need to access target molecules in a more efficient way and at the same time following the underlying principles of sustainable chemistry. One particular tactic towards this goal is the conversion of a C–H group, the typical 'non-functionality' into a valuable carbon–carbon or carbon–hetero atom bond. This is routinely done for more or less activated and predisposed C–H positions (usually the ones having a higher acidity) within the standard arsenal of organic chemistry (Scheme 1). In contrast, the direct functionalization of unactivated C–H bonds is much less established and one struggles with harsh conditions that are not very functional-group compatible, selectiv-



Scheme 1. Expanding the range of addressable C–H bonds with tailored metal complexes.

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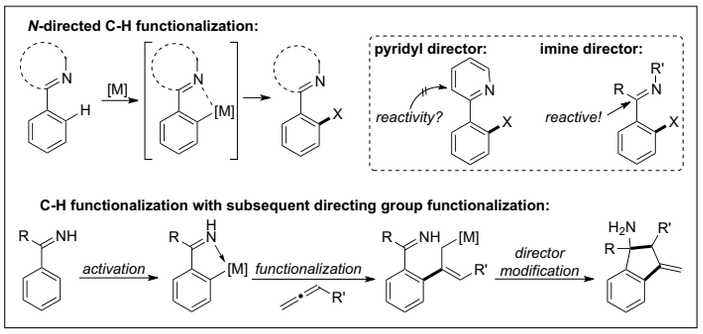
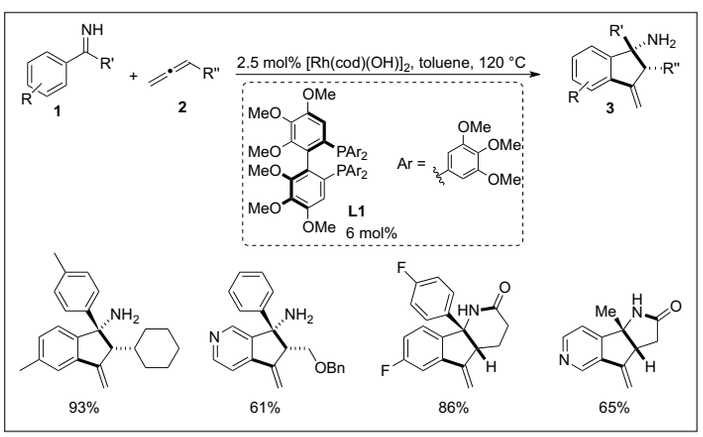
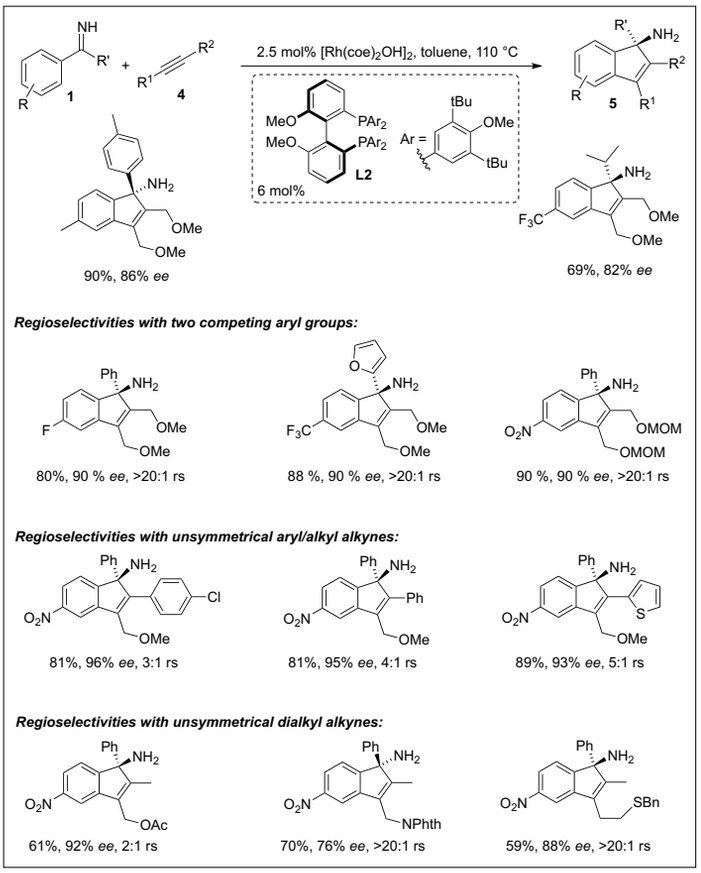


Scheme 2. The imine directing group is amenable to follow-up modifications.



Scheme 3. Imine-directed C–H functionalization: Reaction with terminal allenes.



Scheme 4. Control of the different selectivities at the imine-directed C–H functionalization.

ity issues and high catalyst loadings. This distinction between activated/unactivated C–H bonds is rather vague and sometimes different criteria are applied. We prefer a more pragmatic target-based differentiation into the addressable and non-addressable category. At the end, this is what makes the difference for the practitioners.

Generally, the potential benefits of such functionalizations are appealing: shorter step-count of a synthesis, orthogonal strategies and conversion of previously not suitable unfunctionalized compounds into amenable starting materials. Although general solutions of this complex topic seem to be a very long shot, my group has embarked on several projects that aim to shift previously non-addressable C–H groups towards the addressable pool. Herein, I describe two representative recent examples of our efforts in this area.

2. Imines as Reaction-participating Directing Groups

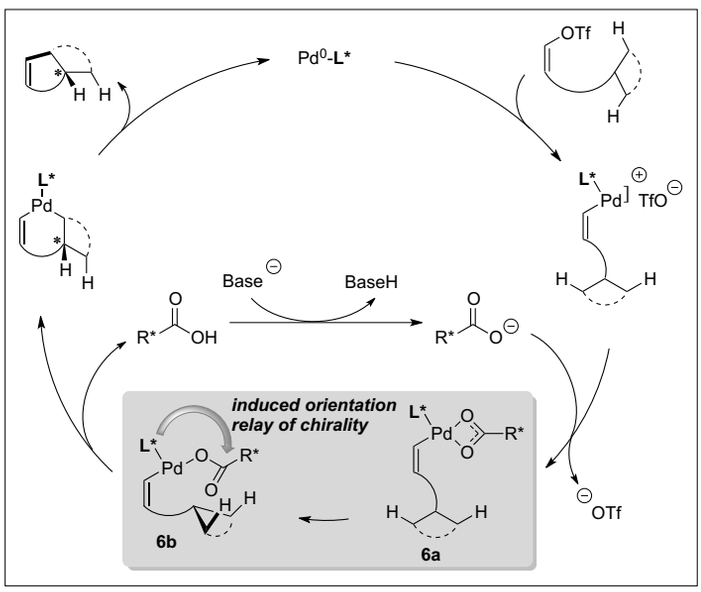
2-Pyridyl-substituted aromatics have been used extensively as a strong directing group for all kinds of *ortho* C–H bond functionalizations.[14] Although it represents an excellent test substrate to explore new methodology, it is poorly interconvertible thus limiting severely its synthetic applicability. Therefore, the development of second generation directing groups that are commonly used functional groups, fall off after the reaction (traceless directing groups), or are being transformed during the course of the reaction once their initial directing purpose is fulfilled, is a key objective. For the latter group, we have envisaged unprotected aryl ketimines. These are readily available and still possess a nitrogen lone pair appropriate for the *ortho*-metalation. In contrast to the pyridine group, they are reactive, *e.g.* straight forward hydrolysis to ketones, and more importantly, can be converted to free primary amines by the addition of carbon nucleophiles (Scheme 2). Optimally, their dual role as directing group and as electrophilic imine can be exploited in one single cascade transformation. To showcase this principle, we envisioned a reaction with a terminal allene thus creating an intermediary allyl metal species which displays the anticipated imine allylation reactivity. The general hurdle for such sequential reaction is the individual steps which might all have different or even contradicting requirements for an optimal catalyst/ligand. Often, this leaves only a narrow window of reactivity and complicates the search for a set of functional ligands. These characteristics held true for the allene imine formal [3+2]-cycloaddition. We found that the electron-rich TriMeOBiphep (**L1**) which has in total 18 methoxy groups is the best overall performing ligand, identified from a large library (Scheme 3).[15] The reward for the exhaustive screening was a highly selective reaction, providing single isomers of amines **3**. A wide range of imines, including aryl alkyl imines and functionalized terminal allenes are well tolerated for this process. As shown, even congested free primary amines are readily accessible or can be directly trapped as lactam with this procedure.[16]

In further studies, we were able extend the process to internal alkynes **4** instead of allenes providing access to amines **5** (Scheme 4).[17] For this substrate class, the sterically demanding DTBM-MeOBiphep (**L2**) was optimally suited. It not only controls the enantioselectivity, but also the yield and the regioselectivity of the C–H metalation step. Good enantioselectivities were observed for simple combinations of symmetrically substituted alkynes and imines. The selectivity determining factors for the cyclometalation were tested with two different competing aryl groups. As general rule, kinetic C–H bond acidity is the decisive factor and the relatively electron poorer aryl group is preferentially attacked. Common substituents such as nitro, trifluoromethyl, or chlorine groups provide good to exclusive regioselectivi-

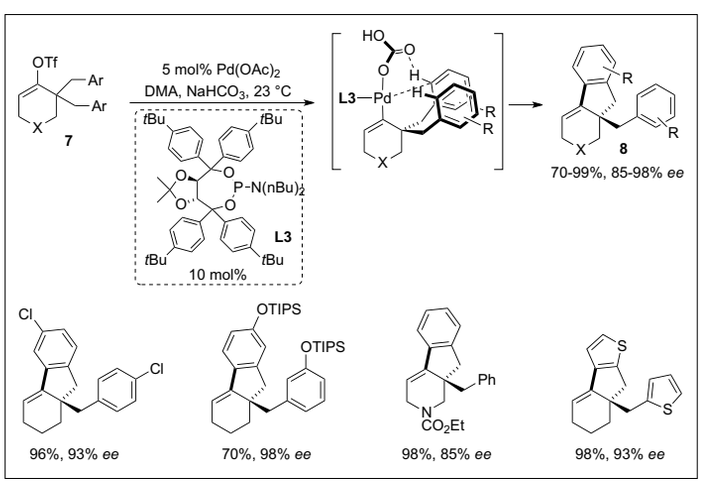
ties. On the alkyne acceptor side, selectivity rules for regioselective incorporations of unsymmetrically substituted alkynes are less obvious to derive. For aryl alkyl substituted alkynes, an intrinsic selectivity was observed with an increase in electron-richness of the aryl group. For internal alkynes with two different alkyl substituents, notoriously problematic for regioselective insertions, we found that Lewis-basic hetero atoms at a distance of three to four atoms from the alkyne moiety can fulfill the role of secondary directing groups. For instance, phthalimido, thioether or thio acetal groups are strongly directing and provide products as single regioisomers.

3. Enantioselective Palladium-catalyzed C–H Functionalization

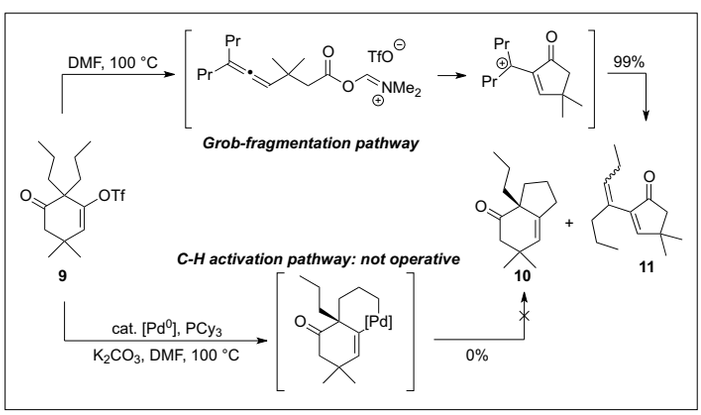
The so-called CMD-pathway (concerted-metalation-deprotonation)[18] is a common mechanism that has been shown to be operative for an increasing number of C–H functionalization mainly with ruthenium, rhodium and palladium catalysts. With respect to the reactions illustrated here involving a palladium(II)-intermediate prior to the C–H activation step, an analysis of the key intermediate reveals the important challenge for catalysis (Scheme 5). As an open coordination side on the metal is mandatory for the C–H activation (**6b**), a potentially suitable catalyst calls therefore strictly for a monodentate (phosphine) ligand in combination with a carboxylic acid playing the role of an active temporary ligand. It is still much more difficult for a monodentate ligand compared to its chelating bidentate congeners to ensure an efficient control of chiral space for any reaction. Additionally, simultaneous association of two phosphine ligands, which would shut down the catalytic process, must be prevented. Furthermore, as the carboxylate is bound to palladium in the enantiodetermining step of the reaction (**6b**), a chiral carboxylic acid could be used as well to exercise selectivity control. In this scenario, one could further imagine matched/mismatched effects between the phosphorous ligand and the carboxylic acid. We initially examined the differentiation of two enantiotopic aryl groups of substrates **7**, to test the general viability of our concept and to foster our understanding of the critical reaction parameters (Scheme 6). After some initial ligand screening, TADDOL-derived phosphoramidites came out as the most promising hit. Due to the highly modular nature of this ligand scaffold, we could identify ligand **L3** with a somewhat unconventional substitution pattern (greasy alkyl substituents with steric bulk far from the binding phosphorous atom) as the best performer providing product **8** in 85–98% *ee*.[19] The optimized protocol accommodates very well different steric and electronic environments on the aryl ring. Most importantly, this reaction shows an exceptional mildness unprecedented for related C–H functionalizations. Whereas generally high reaction temperatures and strong bases are required to enforce the desired reactivity, this process smoothly operates at ambient temperature under essentially neutral conditions using virtually neutral and cheap sodium bicarbonate as carboxylate derivative. After the successful initial proof of concept, we tried to raise the bar significantly: Activation and functionalization of alkyl C(sp^3)–H bonds.[20] However, our initial attempts with the closely related alkyl substrate **9** did not provide the expected carbocycle **10**, but gave instead a clean conversion to cyclopentenone **11** (Scheme 7).[21] It rapidly turned out that neither the ligand, nor the palladium catalyst and not even the base was required for the reaction to occur! Although this is not the metal-catalyzed C–H functionalization we were aiming for, the process showed



Scheme 5. Mechanistic picture of the CMD-activation pathways with Pd(0)-catalysts.



Scheme 6. Enantioselective palladium-catalyzed C(sp^2)–H functionalization.



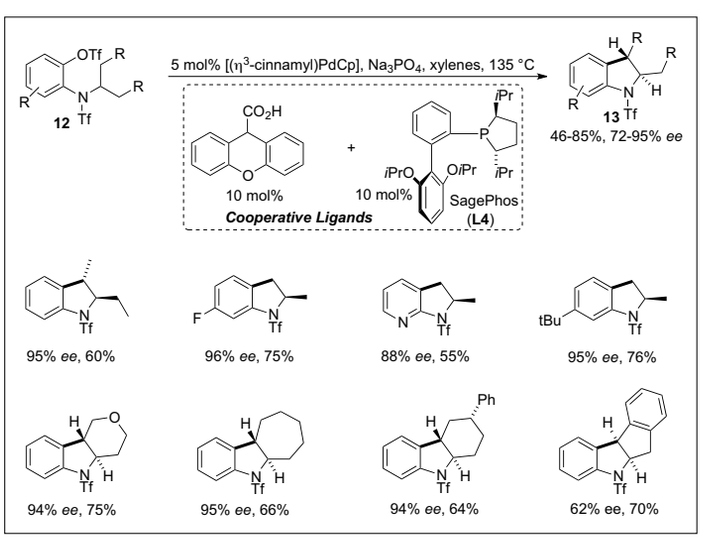
Scheme 7. Grob-fragmentation occurs instead of palladium-catalyzed C–H functionalization.

an interesting and synthetically useful solvent-induced Grob fragmentation, which was recently highlighted in CHIMIA as an SCS-Poster award account.[22]

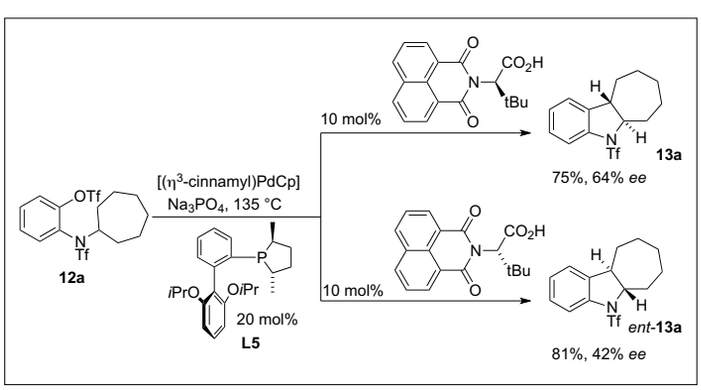
As second substrate class, we then turned our attention towards aniline derivatives **12** previously shown as viable for achiral C–H functionalization. This is an appealing substrate class which is conformationally more restricted and gives rise to the pharmacologically important indoline scaffold **13** (Scheme 8). Soon, we found that this substrate class displayed a very different demand for the phosphorous ligands and neither the previously well optimized phosphoramidite **L3** possessed the right electronic properties, nor was any other chiral phosphine well suited.[23–26] So we had to go for the hard way: Taking the beneficial properties of the sterically demanding achiral Buchwald-type phosphine ligand and the superior chiral environment of C_2-symmetric 2,5-disubstituted phospholane unit of the DuPhos-type ligand, we created the SagePhos ligand (**L4**) fulfilling the anticipated functionalization reaction.[27] Optimal results were obtained with xanthene carboxylic acid, which was picked from a large screening as best match in terms of yield and selectivity. Remarkably, enantioselectivities remain excellent even at elevated temperatures of 135 °C. The confirmation of the key role that the carboxylic acid is playing in a successful catalysis came from the enantiomeric pair of acids derived from *tert*-leucine (Scheme 9). These displayed a strong matched/mismatched effect when used in combination with the phosphine ligand **L5**. In fact, the influence of the carboxylic acid on the selectivity turned out to be stronger than that of the phosphine, reversing the sense of induction quite significantly (**13a** *vs ent*-**13a**). At the end, the observations acquired during this study have set a solid base to design better cooperative systems in the future. The scope of reactions following this pathway is very far from being exhausted and we strongly believe that there is a tremendous potential just waiting to be unlocked.

4. Summary and Outlook

In conclusion, we have reported two distinct examples of selective functionalization of unactivated C-H bonds by transition-metal catalysts equipped with specifically tailored chiral ligands. The reactions conditions can be tuned to mild and selective processes with the right ligand! As for many other transition-metal catalyzed processes, the judicious choice of the ligand proved to be once more boon and bane. With already this small set of different reaction types, a wide variety of structural space became addressable. The more the general understanding for the decisive factors of such activations matures, the more we can expect that the limits of reactivity will be pushed further down the road. On this way, we are optimistic that for all other critical reaction attributes like selectivity, mildness of the conditions and catalyst loadings better solutions will evolve. A constant will certainly remain: The challenges will not run out.



Scheme 8. Enantioselective C(sp³)-H activation to give indolines.



Scheme 9. Chiral carboxylic acids show a strong cooperative effect.

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