σ-Chelation-directed C–H functionalizations using Pd(II) and Cu(II) catalysts: regioselectivity, stereoselectivity and catalytic turnover

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Recent progress in σ-chelation directed C–H functionalization from the authors' group is described to illustrate the challenges and opportunities in the development of synthetically-useful catalytic reactions involving C–H activation as the key step. Emphasis is placed on strategies for developing catalysis under mild conditions and controlling regio- and stereoselectivity.

Introduction

Since the initial discovery of σ-chelation directed C–H cleavage,[1] often referred to as cyclometallation, continuous efforts have been invested in making this stoichiometric process synthetically useful.[2] Although σ-chelation has been widely used as a control element in asymmetric catalysis,[3] attempts to achieve catalytic turnover in directed C–H functionalizations have met with limited success due to the thermodynamic stability of the cyclometallated complexes and the limited choice of directing groups.[4] Pioneering work in achieving catalytic sp^2 C–H activation/C–C bond forming reactions by Murai[5] and Fujiwara[6] provided the early inspiration for chemists to tackle this challenge (Scheme 1), although Fujiwara's catalytic system does not require the use of a directing

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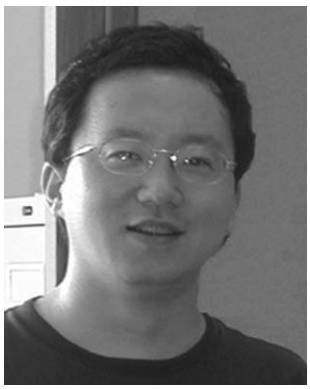
Jin-Quan Yu

Ramesh Giri



Xiao Chen

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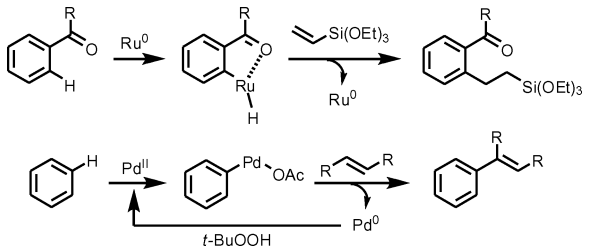
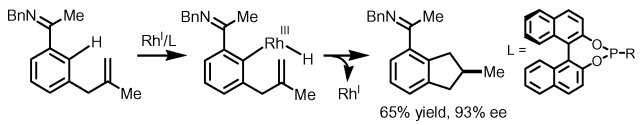


Scheme 1 Early examples of catalytic C–H activation/C–C bond forming reactions.

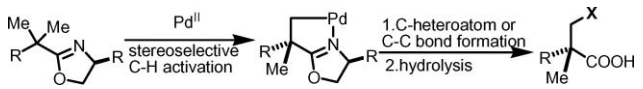
group. Recently, remarkable progress has been made in catalytic C–H activation using other approaches,[7] which will not be discussed in this short essay.

A number of significant developments involving Ru^{II}/Ru^{0} or Rh^{III}/Rh^{I} catalysis were achieved subsequently (Scheme 2).[8] Remarkably, the combination of aryl C–H cleavage and subsequent enantioselective hydrorhodation onto a double bond illustrates the potential applications of C–H activation reactions in asymmetric catalysis.[8e]



Scheme 2 A combination of directed C–H activation and enantioselective hydrorodation.

In light of the tremendous potential of aryl- and alkyl-Pd complexes in developing C–heteroatom and C–C bond forming reactions,[9] we initiated a research program to develop Pd-catalyzed C–H activation reactions using chiral oxazolines as directing groups for carboxylic acids.



Scheme 3 Early research plan for diastereoselective C–H functionalization.

In the following discussion, we will first briefly introduce our rationale for the design of several types of directing groups. Special attention is paid to regio- and stereoselectivity in the C–H cleavage step. The practicality of the directing groups from the viewpoint of synthetic chemistry is also a major concern. Second, the development of three different types of catalysis involving Pd(II) is presented. A Cu(II) catalyzed C–H functionalization process is also described. A major goal in this context is to allow the use of mild conditions and cheap oxidants in C–H activation reactions. We wish to point out that a number of other groups have made significant progress in the development of Pd-catalyzed C–H functionalization reactions using directing groups,[10,11] which have been reviewed recently by Sanford[10a] and Daugulis.[10b]

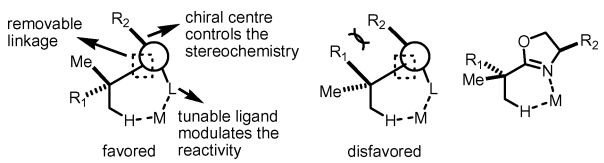
Directing groups

General considerations

σ-Chelation directed C–H cleavage process usually involves a nitrogen atom containing functional group as the directing group. An excellent review by Chantani describes recently-developed directing groups for the activation of sp^3 C–H bonds.[12] In our efforts toward the development of directing groups, we have aimed to address a number of specific challenges in this field: 1. controlling the stereoselectivity in the C–H cleavage step; 2. activating remote C–H bonds *via* seven- and eight-membered cyclometallation processes that were not possible previously; and 3. enhancing the efficiency of directed C–H activation reactions by either carrying out sequential C–H activation processes using a single directing group or identifying a synthetically useful protecting group as a directing group. C–H Activation directed by these groups is successfully exploited to develop a wide range of C–halogen, C–heteroatom and C–C bond forming reactions, as described in the following section.

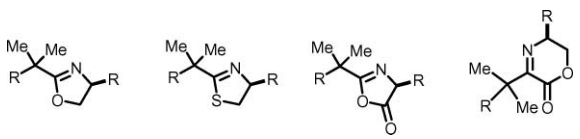
Stereoselectivity

Our first goal was to find a combination of a removable chiral directing group and a metal centre that would form reactive complexes and result in stereoselective C–H cleavage. It is well established that σ-chelation assisted C–H activation takes place through a cyclic transition state. We, therefore, reasoned that the use of a cyclic chiral directing group could be advantageous in controlling the stereochemistry *via* a steric repulsion model (Scheme 4).



Scheme 4 Control of stereoselectivity in C–H activation.

Since we are particularly interested in selective β- and γ-functionalization of carboxylic acids, the chiral oxazoline auxiliaries established by Meyers[13] for asymmetric α-alkylation appeared to be especially promising among a number of possible cyclic chiral directing groups (Scheme 5). In addition, Murai has reported oxazoline directed C–H activation of aryl C–H bonds using a Ru^{0} catalyst.[14]



Scheme 5 Cyclic chiral directing groups for carboxylic acids.

However, our initial efforts to use chiral oxazoline **1**, prepared from the relatively cheap chiral aminoalcohol valinol, to direct C–H activation proved unsuccessful (Scheme 6).

While the cause remains to be elucidated, we speculated on the basis of crystallographic studies[15] that the methine C–H bond is positioned on top of the Pd centre and may have interfered with

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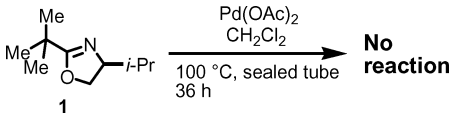
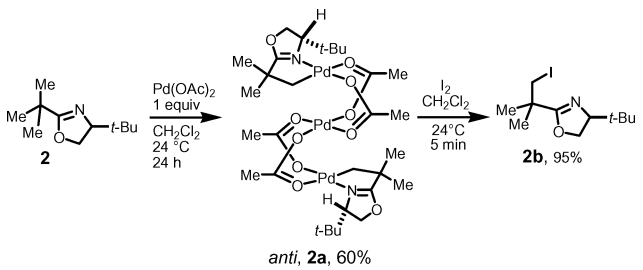


Scheme 6 Unreactive oxazoline.

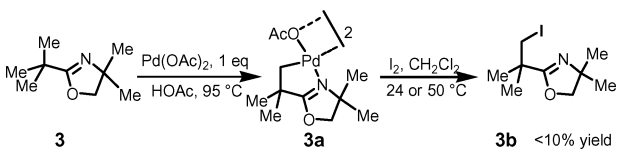
C–H activation. This speculation led us to replace this methine C–H bond with a methyl group as shown in oxazoline **2** prepared from *tert*-lucinol. This minor alteration resulted in facile cleavage of the sp^3 C–H bonds at room temperature to give a trinuclear Pd-alkyl complex **2a** (Scheme 7).



Scheme 7 Room temperature sp^3 C–H cleavage directed by oxazolines.

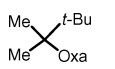
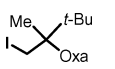
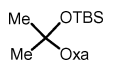
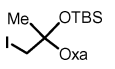
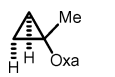
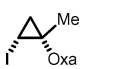
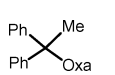
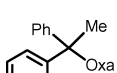
Complex **2a** reacts with I_2 instantly to give the iodinated product **2b**. A detailed study of this stoichiometric iodination reaction led us to discover catalytic conditions and will be described in the next section. Good to excellent diastereoselectivity was obtained with selected prochiral substrates (Table 1).[16]

It should be pointed out that the dimeric cyclopalladated complex prepared using a literature procedure[17] (reflux in HOAc) exhibits poor reactivity with I_2 (Scheme 8).



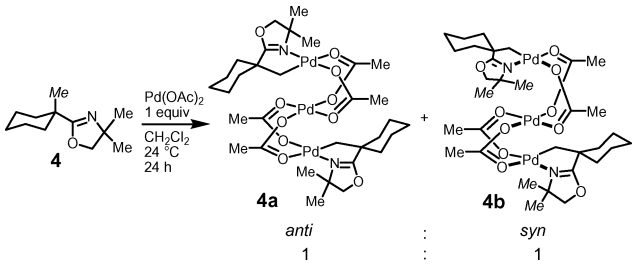
Scheme 8 Reactivity of dimeric cyclopalladated complex.

Table 1 Diastereoselective iodination of sp^2 and sp^3 C–H bonds

Entry	Substrate[b]	Product	Yield (%)	dr
1			83[c]	91 : 9
2			62[d]	93 : 7
3			65[e]	99 : 1
4			98[f]	99 : 1

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), I_2 (1 equiv.), $PhI(OAc)_2$ (1 equiv.), CH_2Cl_2. [b] Oxa = 4-(*S*)-*tert*-butyloxazoline-2-. [c] 24 °C, 30 h. [d] 50 °C, 48 h. [e] 24 °C, 96 h. [f] 24 °C, 13 h.

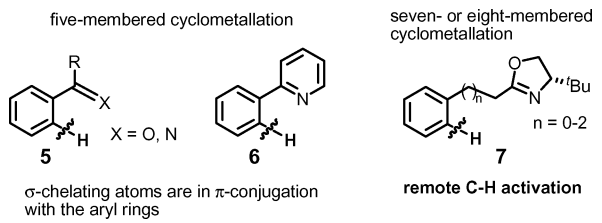
Furthermore, the presence of the chiral centre on the oxazoline has a dramatic influence on the structure of the trinuclear complexes. The reaction of the chiral oxazoline **2** with $Pd(OAc)_2$ gives the isomer **2a** only in which the top and the bottom oxazolines are in an *anti*-relationship. In contrast, non-chiral oxazoline **4** reacts with $Pd(OAc)_2$ to give a mixture of *anti*- and *syn*-trinuclear Pd-alkyl complexes **4a** and **4b** in 1 : 1 ratio (Scheme 9). Future work will concentrate on the establishment of a stereomodel for the diastereoselective iodination reaction.



Scheme 9 Formation of *syn*- and *anti*-trinuclear Pd–alkyl complexes from a nonchiral oxazoline.

Regioselectivity: remote C–H activation

Directed C–H activation reactions are largely limited to five- and six-membered cyclometallation processes.[1] Although six-membered cyclometallation in a stoichiometric manner has been observed, the catalytic version has not been realized. DFT calculations of Ru-catalyzed C–H activation of aryl C–H bonds in **5** and **6** provided a possible explanation for the requirement of a σ-chelating heteroatom in conjugation with the aryl rings (Scheme 10).[18] The development of non-π-conjugated chelation assisted catalytic C–H activation reactions remains a significant challenge.[19]



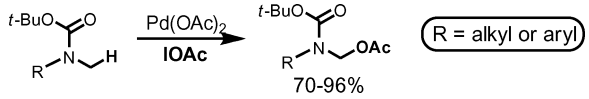
Scheme 10 Remote C–H activation.

We are delighted to find that sterically bulky oxazoline in **7** was able to direct the activation of remote C–H bonds *via* six-,[16] seven- and eight-membered cyclopalladation (Scheme 10).[20] Encouraged by this finding, we are currently developing new directing groups to activate remote sp^3 C–H bonds. These developments upon further elaboration will greatly expand the scope and utility of directed C–H activation reactions.

Practicality and efficiency of directing groups

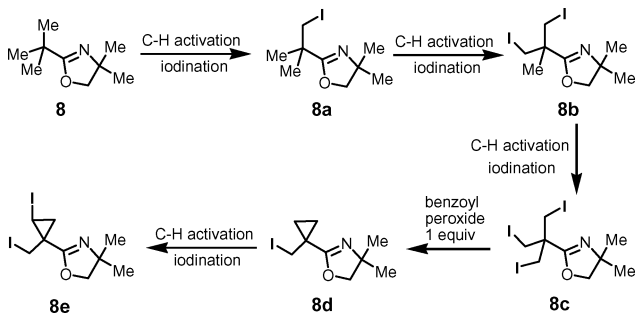
From a practical viewpoint, the installation and removal of the directing groups is an inherent drawback. It is, therefore, imperative to give due consideration to the minimization of this disadvantage in the process of development of directing groups. We think that the following two criteria of a directing group are highly

desirable: 1. ease of installation and removal; and 2. convenience for further transformations. We have recently demonstrated that one of the most commonly used protecting groups, Boc, can direct the activation of sp^3 C–H bonds adjacent to nitrogen atoms (Scheme 11).[21] Prior to this success, the activation of C–H bonds adjacent to nitrogen atom was only achieved by using pyridine as a directing group.[22] The use of IOAc as a novel oxidant is the key to the development of this reaction. Either $PhI(OAc)_2$ or I_2 alone is not reactive under the same reaction conditions. The details of the catalysis will be discussed in the next section.



Scheme 11 Use of protecting groups as directing groups.

The efficiency of directed C–H activation can also be enhanced by carrying out sequential C–H activation reactions as illustrated in Scheme 12. We have demonstrated that multi-step C–H activation assisted by one directing group allows novel transformations which convert *gem*-dimethyl groups into cyclopropyl groups.[23]



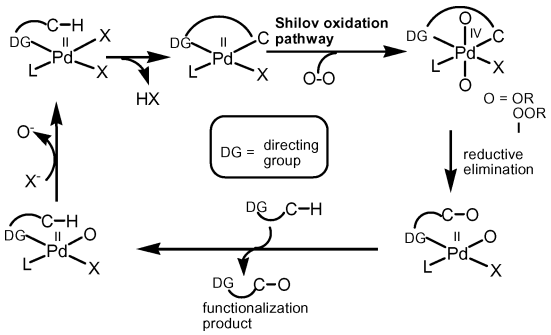
Scheme 12 Sequential C–H functionalizations.

Catalysis

The importance of developing new approaches to close the catalytic cycle of C–H activation reactions can not be overemphasized. A number of approaches have been employed in our laboratory. The choice of a particular catalysis depends on the specific reaction of interest. Successful examples selected from our laboratory will be used to demonstrate the principle, advantages and disadvantages of each type of catalysis.

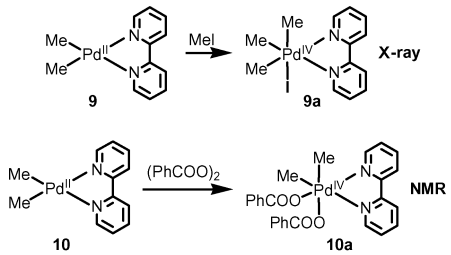
Pd^{II}/Pd^{IV} Catalysis

Shilov Pt^{II}/Pt^{IV} catalysis has been a major subject of study owing to its potential to afford catalytic turnover in C–H activation reactions.[24] Although remarkable progress has been made in methane oxidation using this catalysis,[7a] few examples of Pt^{II}-catalyzed directed C–H activation reactions appeared in the literature.[25] On the other hand, stoichiometric cyclopalladation of C–H bonds by Pd^{II} salts are most widespread.[1] If Pd^{II}/Pd^{IV} catalysis operates in a similar fashion to Pt^{II}/Pt^{IV} cycle, Pd^{II}-catalyzed C–H functionalizations with a broad substrate scope can be realized (Scheme 13). The success of this approach will open up a great opportunity to make C–heteroatom and C–C bonds directly from unactivated C–H bonds.



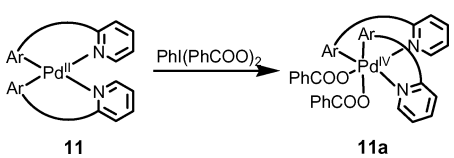
Scheme 13 Pd^{II}/Pd^{IV} Catalysis for C–H functionalizations.

Fortunately, the feasibility of the key step, oxidation of Pd^{II} to Pd^{IV}, was beautifully established by Canty *via* rigorous experimentation. The first crystal structure of Pd^{IV} complex **9a** was obtained by oxidizing Pd^{II} complex **9** with MeI in 1986 (Scheme 14).[26] Remarkably, Canty was also able to oxidize Pd^{II} complex **10** to Pd^{IV} complex **10a** using a commonly used peroxide oxidant $(PhCO)_2O_2$.[27]



Scheme 14 Oxidation of Pd^{II} to Pd^{IV} by dichalcogenides.

Prior to these remarkable mechanistic discoveries, Tremont had used MeI as the oxidant to methylate aryl C–H bonds in the presence of stoichometric amount of $Pd(OAc)_2$, which is important for further developments in this field.[28a] The use of aryl halides as oxidants by Miura in Pd-catalyzed *ortho*-arylation of phenols and amides is also a significant advance.[28b,c] In general, dichalcogenide types of oxidants or analogues can effectively oxidize Pd^{II} to Pd^{IV}, which lays the foundation for some of the Pd-catalyzed C–H functionalizations that appeared recently. New mechanistic evidence continues to accumulate in support of Pd^{II}/Pd^{IV} catalysis,[10,16] among which the isolation of a Pd^{IV} complex **11a** structurally similar to **10a** provides an additional physical evidence for Pd^{II}/Pd^{IV} catalysis (Scheme 15).[29]



Scheme 15 Oxidation of Pd^{II} to Pd^{IV} by iodobenzene dibenzoate.

As described in Scheme 7, we have established mild conditions for cyclopalladation using sterically bulky oxazolines. Next, we selected I_2 as a dichalcogenide type of oxidant to functionalize the Pd–alkyl complexes. I_2 was previously shown to react with a few cyclopalladated complexes to give the iodinated product in

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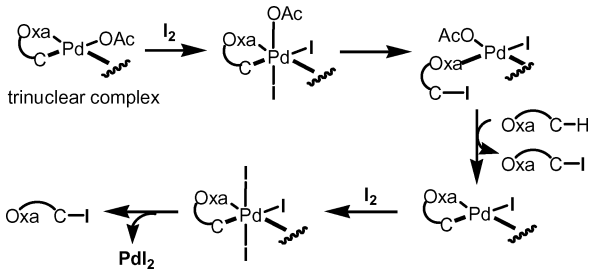
stoichiometric manner.[2] We found that the reaction of oxazoline **2** with 1 equiv. of $Pd(OAc)_2$ and 1 equiv. of I_2 gave the iodinated product **2a** in 80% yield. The precipitate from the reaction mixture was characterized to be PdI_2 (isolated as a powder in quantitative yield and characterized by powder X-ray diffraction). On the basis of this observation and Canty's redox chemistry, we proposed a catalytic cycle in which the PdI_2 needs to be converted to $Pd(OAc)_2$ to achieve the turnover (Scheme 16).



Scheme 16 Pd-catalyzed iodination.

Extensive screening of oxidants and acetate donors identified that IOAc can convert PdI_2 to $Pd(OAc)_2$ [eqn (1)]. According to literature procedures,[30] IOAc is generated by reacting I_2 with either AgOAc or $PhI(OAc)_2$ [eqn (2) and (3)].

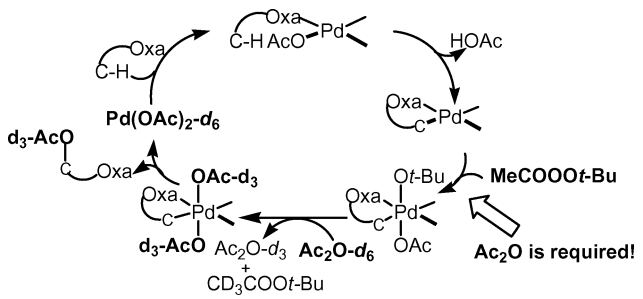
$$PdI + 2IOAC \rightarrow Pd(OAc)_2 + 2I_2 \quad (1)$$

$$AgOAc + I_2 \rightarrow AgI + IOAc \quad (2)$$

$$PhI(OAc) + I_2 \rightarrow PhI + 2\,IOAc \quad (3)$$

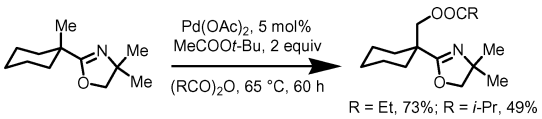
From the viewpoint of catalysis, a practical advantage of this catalytic iodination is that PdI_2 can be readily recycled and reused five times by simply decanting the reaction solution. The next challenge is to discover cheaper and environmentally friendly reagents to convert PdI_2 into $Pd(OAc)_2$ since $PhI(OAc)_2$ is not only expensive, but also produces PhI that needs to be removed by column chromatography.

Since benzoyl peroxide was shown to oxidize Pd^{II} to Pd^{IV},[27] we tested peroxide oxidants in order to oxygenate C–H bonds. Among a wide range of peroxides screened, MeCOOO*t*Bu, lauroyl peroxide and benzoyl peroxide were found to be efficient to oxygenate C–H bonds. Importantly, we discovered Ac_2O is crucial for this catalytic reaction.[31] First, Ac_2O promotes the oxidation of Pd^{II} to Pd^{IV}. Second, Ac_2O reacts with Pd^{IV}–OR species to regenerate $Pd(OAc)_2$ (Scheme 17).



Scheme 17 Catalytic cycle of C–H oxygenation using peroxide oxidants.

This mechanistic understanding has allowed us to prepare various carboxylated products using the corresponding anhydrides (Scheme 18).

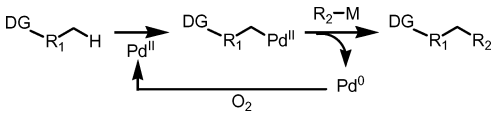


Scheme 18 Pd-Catalyzed carboxylation using carboxylic anhydrides.

Subsequently, Ac_2O in combination with peroxides or oxone was also successfully exploited by Sanford's group to oxygenate C–H bonds.[32] The next challenge is to oxidize Pd^{II} to Pd^{IV} using O_2 or air to achieve catalytic turnovers.

Pd^0/Pd^{II} catalysis

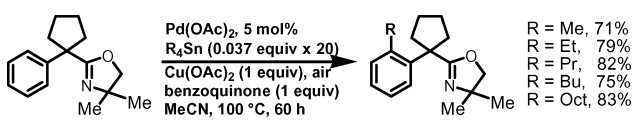
The practical advantage of C–H activation reactions involving Pd^{II}/Pd^0 catalysis is the use of O_2 or air as the oxidant in catalytic C–H activation reactions.[33] This approach proved remarkably successful in our C–H activation/C–C coupling reactions (Scheme 19).



Scheme 19 Catalysis for a C–H activation/C–C coupling sequence.

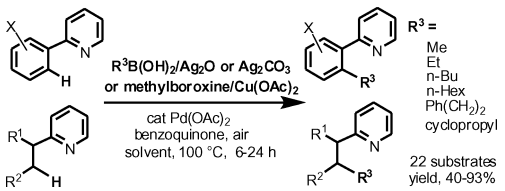
Coupling of Pd^{II}–alkyl(aryl) species with organometallic reagents has witnessed remarkable progress in recent years.[34] Various protocols to promote the oxidation of Pd^0 to Pd^{II} under mild conditions have also been developed.[35] However, the execution of the sequential steps in a catalytic cycle represents a formidable challenge for the following two reasons: 1. Pd^{II}-catalyzed homocoupling of organometallic reagents[36] is faster than C–H activation, and 2. the palladacycle formed in the C–H activation step catalyzes homocoupling of the organometallic reagents[37] if the subsequent transmetallation and reductive elimination are not sufficiently fast. Our strategy is to identify promoters for each step to overcome this thorny challenge.

The first Pd-catalyzed alkylation reaction of C–H bonds was achieved using the following two techniques: 1. batch-wise addition of tin reagents to minimize the homo-coupling, and 2. use of benzoquinone to accelerate the reductive elimination step (Scheme 20).[38]



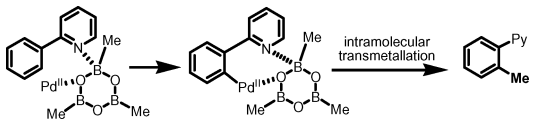
Scheme 20 Pd-Catalyzed coupling of C–H bonds with alkyltin reagents.

The batch-wise addition and the toxicity of the tin reagents are major practical disadvantages in synthetic applications. We have further established an one-pot procedure using boroxine or boronic acids as environmentally-friendly coupling reagents to achieve a practically useful C–C bond forming reaction (Scheme 21).[39] In these coupling reactions, the presence of air or O_2 was found to drastically increase the catalytic turnover.



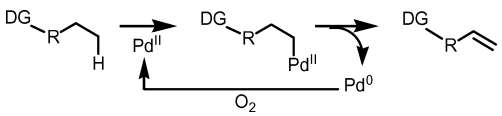
Scheme 21 Pd-Catalyzed coupling of C–H bonds with organoboron reagents.

Strikingly, we have also identified a new C–H activation pathway with methylboroxine that is distinct from the cyclopalladation pathway (Scheme 22).[39] Unlike in the pyridine-directed cyclopalladation pathway, boron coordinates with pyridine and the oxygen atom in the B–O bond directs palladium to activate the C–H bonds.



Scheme 22 Boroxine assisted C–H activation.

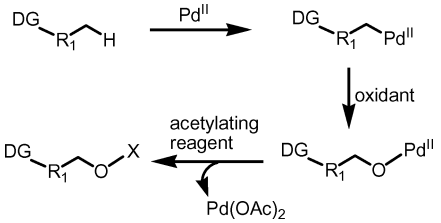
Pd^{II}/Pd^{0} catalysis can also be employed to develop catalytic C–H activation–dehydrogenation reactions (Scheme 23). We are currently exploiting this reaction pathway to develop synthetically valuable transformations.



Scheme 23 Catalyic C–H activation–dehydrogenation.

Pd^{II}/Pd^{II} catalysis

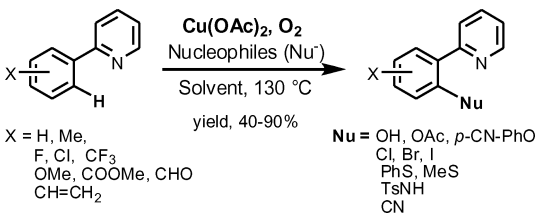
Inspired by the early observation of oxygen insertion into Pd–C bonds,[40] we envisioned that a catalytic oxygenation can also be achieved *via* Pd^{II}/Pd^{II} catalysis (Scheme 24). TBHP was shown to insert an oxygen into the Pd–C bond, however, the Ac_2O required to acetylate the Pd–alkoxy bond reacts with TBHP to give MeCOOO^{t}Bu and derails the reaction pathway to Pd^{II}/Pd^{IV} catalysis as described in Scheme 17.[31] We are currently searching for a new combination of oxidants and acetylating reagents that will furnish Pd^{II}/Pd^{II} catalysis.



Scheme 24 Pd^{II}/Pd^{II} Catalysis for C–H functionalizations.

Cu^{II}/Cu^{0} Catalysis

While Pd^{II} salts are showing great potential for the development of catalytic C–H activation reactions, the use of cheaper Cu^{II} catalysts is a significant goal. A bio-inspired approach has led us to discover a wide range of Cu-catalyzed functionalizations of aryl C–H bonds using O_2 as the terminal oxidant (Scheme 25).[41] Notably, Cu^{II}-mediated direct coupling of indoles with carbonyl compounds has been previously employed to gram-scale syntheses of hapalindole Fischer indole alkaloid families by Baran's group.[42] Recently, Chatani also reported an efficient amination of aryl C–H bonds by Cu-mediated reaction of 2-phenylpyridines with anilines.[43] We will carry out mechanistic investigations into this catalytic pathway in order to further improve the efficiency of the C–N and C–C bond forming reactions.



Scheme 25 Cu^{II}-Catalyzed diverse C–H functionalizations.

Conclusions

We have achieved stereoselective, regioselective and remote C–H functionalization processes using oxazolines as directing groups. C–H Activation directed by a weakly coordinating protecting group (*Boc*) is also developed. These processes provide new avenues for the formation of a wide range of C–heteroatom and C–C bonds. The use of peroxide–Ac_2O, IOAc or air as the oxidants for catalytic C–H activation reactions provides practically useful catalytic methods.

Each step forward in the development of directed C–H activation reactions, sometimes involving a seemingly minor alteration, is always associated with a new finding. The understanding obtained from these studies will guide researchers to ultimately achieve the three most important goals: 1. mild-condition catalysis using environmentally-friendly oxidants, 2. regioselective functionalization of simple substrates such as carboxylic acids, ketones, esters and alcohols, and 3. enantioselective activation of prochiral C–H bonds. Once these challenges are addressed, catalytic C–H activation reactions will set a vantage-ground in the realm of synthetic chemistry for years to come.

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