**Topic: Catalytic C-H functionalization**

1. **Introduction, definitions**

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| The term “C-H functionalization” describes the transformation of a C-H bond (of whatever kind) into a C-X bond, where X is any useful functional group.  This field of research has gained a lot of attention in the past years, and many different *catalytic* systems have been developed and studied. |
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| Suggested Reading:  Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006,** *62* (11), 2439-2463.  Crabtree, R.H. “The organometallic chemistry of the transition metals”, 5th Ed., Wiley, 2009.  Crabtree, R. H. *J. Chem. Soc. Dalton Trans.* **2001,** (17), 2437-2450. |
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| Definitions:  **- “C-H Activation”**  The replacement of a C-H bond by a C-M bond, where M is a transition metal. “Activation” in this sense means the replacement of a relatively unreactive C-H bond with a C-M bond, which can much more easily functionalized. A *C-H activation* followed by a reaction from C-M to C-X is therefore a key part of a *C-H functionalization*.    Shilov, A. E.; Shul'pin, G. B. *Chemical Reviews* **1997,** *97* (8), 2879-2932.  **- “C-H Functionalization”**  A general term describing the transformation of a C-H bond into a C-X bond. This expression is not very well defined (which leads to problems) and most general. In the following, this term is used for a *C-H activation* followed by a transformation to a C-X bond. In this way, a *C-H functionalization* has to run via an intermediate C-M bond (M = transition metal) as described for a *C-H activation*.    Kakiuchi, F.; Chatani, N. *Advanced Synthesis & Catalysis* **2003,** *345* (9-10), 1077-1101.  Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chemical Reviews* **2002,** *102* (5), 1731-1769.  Note: A *Friedel-Crafts* alkylation or acylation is therefore not a *C-H activation* (or *C-H functionalization*), as it is defined by an electrophilic aromatic substitution mechanism, even though the products obtained are similar in the sense that a C-H bond has been transformed to a C-C bond. (The terminolgy “*C-H functionalization*” does not specifically exclude these reactions types, which showcases the problems associated with the expression “*C-H functionalization*”).  **- “C-H Oxidation”**  A very general term denoting the replacement of a C-H bond by any C-X bond where X is more electronegative than H. Therefore, almost all of the *C-H* *functionalizations* discussed below are also C-H *oxidations.*  Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006,** *62* (11), 2439-2463.  **- “C-H Oxygenation, Amination, Halogenation, Borylation, etc.”**  The replacement of a C-H bond through *C-H activation* (i.e. intermediate C-M species) to a C-O, C-N, C-Hal, C-B bond. *C-H oxygenation* should be used instead of *C-H oxidation* as this definition is much more narrow and descriptive.  Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006,** *62* (11), 2439-2463.  **- “C-H Insertion”**  The reaction of a electron-deficient species such as a carbene or a nitrene or a corresponding (metal)-carbenoid or –nitrenoid that inserts between the C and the H atom of a C-H bond.    Doyle, M.P., Duffy, R., Ratnikov, M., Zhou, L. *Chem. Rev.* **2010**, *110*, 704-724 |

1.1 Bond Strengths

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| Some selected bond strengths.   |  |  |  |  | | --- | --- | --- | --- | | **Bond** | **Bond Strenth (in kcal/mol)** | **Bond** | **Bond Strenth (in kcal/mol)** | | CMethyl-H | 105 | C-C (in ethane) | 90 | | CIsopropyl-H | 99 | C-O (in MeOH) | 92 | | Ctertbutyl-H | 97 | C-N (in MeNH2) | 85 | | Callyl-H | 89 | C-F (MeF) | 115 | | Cphenyl-H | 113 | C-Cl (MeCl) | 84 | | HCC-H (ethyne) | 133 | C-Br (MeBr) | 72 | |  |  | C-I (MeI) | 58 | |
| Blanksby, S.J., Ellison, G.B. *Acc. Chem. Res.* **2003**, *36*, 255-263. |
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1.2 Problems and Challenges associated with C-H functionalization

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| **- Reactivity:** Most of the C-H bonds are stronger than the corresponding C-X bonds (see table in section 1.1), therefore a C-H functionalization is thermodynamically unfavoured.  *Possible solution(s):* Use of transition metal catalysts to lower the activation barrier  **- Chemoselectivity**: Once the desired C-X bond is formed, this bond itself has a lower bond strength than the C-H bond before, and over-reactions such as catalyst inhibition can occur. Secondly, the introduction of a C-X bond might change the reactivity of a whole molecule (for example by changing the electron density of an aromatic system), it is important to suppress overreaction.  *Possible solutions:* Running the reaction to low conversion, employ excess of substrate over oxidant, carry out intra- vs intermolecular reactions, use deactivating functional groups, catalyst design.  **- Regioselectivity**: In most molecules, more than one C-H bond of a certain type, and more than one type of C-H bond exist. Therefore, a catalyst should exert high selectivity towards one particular type of C-H bond.  *Possible solutions*: Use weak or activated C-H bonds (allylic, benzlic), use coordinating (directing) groups, try to achieve intramolecular reactions via 5- or 6-membered transition states, catalyst design.  - **Stereoselectivity**: The conversion of a C-H bond to a C-X bond can create a stereogenic center. In this case, the selective installation of a desired stereoisomer represents another challenge.  *Possible solutions*: Development of chiral catalysts. |
| Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006,** *62* (11), 2439-2463. |
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1.3 Advantages of C-H functionalization reactions

- The starting materials are cheap and easily accessible

- Reactions are very atom economical

- no further functional group transformations are required (compare to cross coupling reactions, where functionalities of both coupling partners have to be installed)

- Reactions are cost effective

1. **Historical background** 
   1. Seminal work on stoichiometric *C-H activation*

In the following are some early examples of C-M-bond forming reactions, i.e. *C-H activation* reactions.

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| The first reported C-H activation was the reaction of azobenzene with nickelocene. |
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| Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963,** *85* (10), 1544-1545. |
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| C-H activation of naphthalene with Ru complexes. |
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| Chatt, J.; Davidson, J. M. *J. Chem. Soc.* **1965**, 843-855. |
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| Intramolecular C-H activation with Pt complexes leading to cyclometallated compounds. |
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| Cheney, A.J.; Mann, B.E.; Shaw, L.; Slade, R.M. *J. Chem. Soc. Chem. Commun.* **1970**, 1175-1176.  Ibers, J.A.; DiCosimo, R.; Whitesides, G.M. *Organometallics* **1982**, 13-20.  Foley, R.; DiCosimo, R.; Whitesides, G.M. *J. Am. Chem. Soc.* **1980**, 6713-6725. |
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| Alkane dehydrogenation represents a special case of C-H activations. In this example by Crabtree, the cyclopentadienyl ligand (Cp) can be made from cyclpentane by C-H activation. It is vital to add a hydrogen scavenger (in this case dimethylbutene) for the reactions to occur. The initial step was proposed to be a oxidative addition of a C-H bond of cyclpentane. |
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| Crabtree, R. H.; Mihelcic, J. M.; Quirk, J. M. *J. Am. Chem. Soc.* **1979,** *101* (26), 7738-7740. |
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* 1. Seminal work on catalytic *C-H functionalization*

These are some early examples where catalytic C-H to C-C bond transformations have been achieved, therefore, they are all examples of *C-H functionalization*. (For a historical overview, see: Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002,** *35* (10), 826-834.)

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| Zirconocene complexes were found to catalyze the alkylation of pyridine under relatively mild conditions. |
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| Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989,** *111* (2), 778-779. |
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| Ru-catalyzed acylation of pyridine. Note that the reaction only occurred in the presence of a CO atmosphere, no direct C-H functionalization with the olefin was observed. |
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| Moore, E. J.; Pretzer, W. R.; O’Connell, T. J.; Harris, J.; Labounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992,** *114,* 5888-5890. |
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| The first example of a direct C-H olefin coupling (Murai reaction). Very high yields and regioselectivties could be achieved through this first usage of a *directing group* to make use of chelation control in the intermediate Ru complex. Note that the coupling partners chosen lack the ability to facilitate a beta-hydride elimination reaction. |
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| Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993,** *366* (6455), 529-531. |
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| First examples of catalytic activation and functionalization of C-H bonds at sp3 centers. For the reaction to occur, aromatic iodides had to be employed. In the absence of I, the C-H functionalization was not observed. The second example with the activation of the tert-butyl groups demonstrates that the presence of a heteroatom as directing group is not required. |
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| Dyker, G. *Angew. Chem. Int. Ed.* **1992,** *31* (8), 1023-1025.  Dyker, G. *Angew. Chem. Int. Ed.* **1994,** *33* (1), 103-105. |
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| The Shilov system: Catalytic homogeneous alkane oxidation with Pt(II) complexes. This catalyst has been found to facilitate H/D exchange in alkanes as well as chlorination and oxygenation. The catalyst prefers terminal CH3 carbons of alkane chains (even over allylic and benzylic position), suggesting that the reaction does not run via a radical or electrophilic mechanism, but an organometallic C-H activation mechanism.  As terminal oxidant, Pt(IV) complexes are used (for alternatives, see below). |
| The mechanism is believed to run via an intial interaction of the Pt(II) complex to give an alkane complex. This is then converted to a Pt-alkyl complex (whose existence has been shown for alkyl=Me), however, it is not known whether this step runs via a direct oxidative addition followed by deprotonation or, alternatively, via direct deprotonation of the Pt-alkane complex. The Pt(II) complex is then oxidized to a Pt(IV) complex by the terminal oxidant [PtCl6]2. After loss of one chloro-ligand, the resulting complex can be seen as an alkyl fragment bearing a terminal PtCl4 leaving group. Nucleophilic attack by a chloride ion (or, alternatively, water) results in the chlorinated or hydroxylated product, respectively. |
| Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997,** *97* (8), 2879-2932.  Suggested reading: Crabtree, R. H. *J. Chem. Soc. Dalton Trans.* **2001,** (17), 2437-2450. |
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| In order to circumvent the use of Pt(IV) complexes, Pt-diazine complexes have been developed as catalysts for methane oxidation, employing H2SO4 as the terminal oxidant. The product of this reaction is is MeSO3H, in which the SO3-group is believed to prevent the product from overoxidation. It is remarkable that the catalytic Pt complexes are stable under the reaction conditions. |
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| Periana, R.A.; Taube, D.J.; Gamble, S.; Taube,H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560-564 |
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1. **Mechanistic Considerations**

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| In general, the different mechanisms for C-H activation are divided into two classes: *Inner sphere* (or organometallic) mechanisms and *outer sphere* (or coordination) mechanisms. The differences lie in the way the metal catalysts interact with the C-H bond to be activated.  Note: These mechanisms are just dealing with the different ways for *C-H activation*, the follow-up mechanisms leading to *C-H functionalization* can be very different and do not necessarily depend on which C-H activation pathway has been taken. For an overview of some possible C-H functionalization mechanisms, see section 4.1.1.  *- Inner sphere (organometallic) mechanism*  This mechanism involves two discrete steps, namely the cleavage of a C-H bond first, leading to a metal-alkyl or metal aryl (C-M) species. Secondly, this intermediate undergoes functionalization towards M-X. The formation of the organometallic C-M species is the defining factor of this mechanism. This C-M species governs all follow-up reaction with respect to regio- and stereoselectivity.  Generally, inner sphere mechanism have a tendency to prefer less hindered C-H bonds, since they avoid radical or electrophilic steps. Since organometallic species are generally oxidation-labile, reactions via inner sphere mechanisms normally employ no or very weak oxidants.    *- Outer sphere (coordination) mechanism*  This mechanism involves a activated ligand of the metal complex, which is directly involved in the C-H activation/C-H functionalization reaction. The general steps are: 1. Formation of a high oxidation state metal complex with and activated ligand X (generally oxo-, nitrene or carbine species). This M-X complex then undergoes a reaction with the C-H bond to be functionalized. This reaction can run via a direct insertion mechanism or H-abstraction (radical rebound). These secondary reactions already comprise the C-H functionalization reaction. In contrast to the inner sphere mechanisms, no distinct organometallic species has to be present and that the substrate to be functionalized does not directly interact with the metal catalyst (instead, it reacts with the activated ligand).  Note: In practice, direct insertion and radical rebound steps are hard to distinguish.  Generally, and in contrast to inner sphere mechanisms, outer sphere mechanisms comprise some radical or cationic character at the C to be activated, therefore leading to a higher selectivity towards weaker C-H bonds (tertiary, allylic, benzylic or alpha to heteroatoms). |
| Crabtree, R. H. *J. Chem. Soc. Dalton Trans.* **2001,** (17), 2437-2450.  Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006,** *62* (11), 2439-2463. |

1. **C-C bond formation**
   1. Sp2 C-H functionalization

C-C Bond forming processes via sp2-sp2 coupling are among the most studied C-H functionalizations. 3 distinct strategies can be used to overcome the inherent lack of regioselectivity of these reactions:

- Take advantage of the intrinsic reactivity of the substrate (in particular for heterocycles)

- Use of intramolecular reactions

- Use of directing groups able to coordinate the metal (nowadays, much attention is focused on “removable” directing groups).

Some relevant directing groups



**4.1.1** Direct arylation

Formation of aryl-aryl bond is usually called ‘‘direct arylation’’. For a general review see*ACIE*, **2009**, 48, 9792-9826.



In a “classical” cross coupling, an aryl (pseudo)halide reacts with an organometallic partner

C-H activation can be used to replace one or both of the reaction partners

**4.1.1.1** Direct arylation with pseudohalides

Direct arylations with easily accessible pseudohalides, does not require oxidants and expensive organometallic reagents and had, therefore, the greatest impact on bi(hetero)aryl syntheses thus far.

Early examples:



Ames, *Tetrahedron* **1982**, *38*, 383-387

With heterocycles:



Ohta, *Chem. Pharm. Bull.* **1989**, *37*, 1477-1480

Plausible mechanisms



Evidences for different types of mechanisms have been obtained, depending on the nature of the reaction partners. While for heterocycles and electron-rich π–nucleophilic aromatics, SEAr mechanism (Friedel-Crafts type reaction) predominates; strong evidences for **Concerted Metalation Deprotonation** (CMD) have been obtained in other cases.



Fagnou, *JACS* **2008**, *130*, 10848-10849

The use of strained alkene norbornene as a temporary covalent linker, has been developed by Catellani for chemo and regio selective direct arylation of ortho-C-H bonds in aryl iodides with aryl bromides as reaction partners.



Catellani, *JACS* **2004**, *126*, 78-79

Aryl iodonium salts have also been investigated for direct arylation. In this case, a Pd(II)/Pd(IV) cycle is operating. Oxidation of the stable Pd(II) intermediate to unstable Pd(IV) enable reductive elimination.



with heterocycles:



for a review see: Sanford, *Inorg. Chem.* **2007**, *46*, 1924-1935

**4.1.1.2** Direct arylation with an organometallic partner (oxidative arylation)

Direct arylations with an organometallic partner have been less studied because they require a terminal oxidant and because organometallic partners are expensive and difficult to prepare. They were first developed by Yu, using Pd as a catalyst but can also be carried out with Cu, Rh, Ru, Fe… Organometallic partners: B(OH)2, BF3K, SnR3, ZnX…

Benzoic acids as directing groups:



Yu, *JACS* **2006**, *128*, 12634-12635

Pyridine directing groups

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Studer, *OL* **2008**, *10*, 129-131

Oxygen as terminal oxidant



Yu, *JACS* **2008**, *130*, 17676-17677

Iron as catalyst, imine DG



Nakamura, *ACIE* **2009**, *48*, 2925-2928

**4.1.1.3** Dehydrating arylation

This method his highly desirable because neither of the partners have to be pre-functionalized. Nowadays, intramolecular and homo couplings are well established. However, regioselectivity in intermolecular cross-dehydrogenative arylation reactions represents a major obstacle.

Early examples:



Itatani, *Angew. Chem. Int. Ed.* **1974**, *13*, 471-472

Sequential C-N coupling/oxidative arylation



Ohno, *Chem. Commun.* **2007**, 4516-4518

First intermolecular examples:



Fagnou, *Science* **2007**, *316*, 1172-1175

Homocoupling

Intermolecular dehydrogenative homocoupling of heteroarene is one of the most useful tools for the preparation of symmetrically substituted 1,1’-binaphtyls.



Katsuki, *JACS* **2009**, *131*, 6082-6083

**4.2**. Other couplings involving sp2 C-H activation

Alkene-arene coupling (Fujiwara Moritani reaction)

Also called oxidative Heck coupling, this reaction has been applied to a wide range of arenes and alkenes. It can be catalyzed by Pd, Ru… See section 2.2 for early examples

With (2-pyridyl)sulfonyl as removable DG



Carretero, ACIE **2009**, 48, 6511-6515.

Selective functionalization of indoles

In this case, the nature of the solvent influences the regioselectivity of the reaction. C-H activation occurs first at C3 position but under acidic conditions and with a weekly coordinating solvent, Pd can migrate at C2 (thermodynamically more stable) prior to functionalization.



Gaunt, ACIE, **2005**, *44*, 3125

With enaminone



Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230-7233

Aldehydic C-H bond functionalization

Transition metals are known to activate aldehydic C-H bonds and this type of C-H activation has been used in oxidative coupling to prepare ketones.



Li, *JACS*, **2010**, *132*, 8900-8902

The proposed mechanism involves Cu insertion into the aldehydic C-H bond as the rate limiting step (kH/kD = 2.4). A Friedel-Craft mechanism as also been ruled out by complementary experiments.

* 1. Sp3 C-H functionalization

**4.2.1** Via C-H activation

Sp3 C-H activation has been less studied because C(sp3)-H bonds lack π-orbitals to interact with the metal center.

Pd(II)/Pd(0) catalysis:

Hydroxamic acids as directing groups (easily converted to esters, amides or alkanes), O2 as terminal oxidant, sp2 and sp3 boronic acids can be used.



Yu, *JACS* **2008**, *130*, 7190-7191

Pd(0)/Pd(II) catalysis:

Amides as directing group, no oxidant needed



Yu, *JACS* **2009**, *131*, 9886-9887

Recent application:

With 2-aminothioanisole as DG:



Baran, *JACS*, **2011**, ASAP

Amide substrate (Ir catalysis)

sp3 C-H activation, followed by Heck type reaction and isomerization promoted by norbornene.

 

Sames, *JACS*, **2004**, 126, 6556-6557

**4.2.2** via C-H insertion

See the definition in Section 1. Loss of nitrogen provides the driving force for the energetically unfavorable formation of the carbenoid. Even if different metals are known to form and stabilize carbenes (Ru, Ag, Cu…), rhodium and dirhodium species are the most studied to date because of their higher reactivity and versatility.

These reactions have been mostly studied in systems capable of intramolecular reactions to overcome regioselectivity issues.



Doyle, *Chirality* **2002**, *14*, 169-172

Chemoselectivity is controlled by both steric and electronic factors. The carbenoid has an electronic preference to functionalize C-H bonds in which the carbon can stabilize positive charge build-up (C-H insertion has a partial characteristic of a hydride abstraction). Bulky ligands on the metal species are used to modulate its reactivity and limit concurrent cyclopropanation on unsaturated substrates.



Davies, *JACS* **1999**, *121*, 6509-6510

A preference for insertion into tertiary over secondary C-H bonds has been observed, insertion into primary C-H bonds are scarce. Insertion occurs with retention of configuration.



Davies, *JOC* **2003**, *68*, 6126-6132

Synthetic utility of these reactions remains limited, mainly because of the difficult preparation of diazo compounds other than diazocarbonyls.

* 1. Allylic C-H activation

Formation of π-allyl intermediates can occur via a C-H activation pathway and have successfully been trapped by carbon nucleophiles to create C-C bonds.



White, JACS, **2008**, *130*, 14090-14091

1. **C-O bond formation**
   1. C-O bond formation with the aid of directing group

Nitrogen containing groups such as pyridines, amides, and oximes could control the regioselectivity in predictable manner. Sanford reported the first example of ligand-directed sp2 C-H bond oxygenation as well as sp3 C-H bond.



Sanford, *JACS* **2004**, *126*, 9542



Sanford, *OL* **2010**, *12*, 532

* 1. C-O bond formation through allylic C-H bond activation (also see 4.3)

White reported the catalytic system enable to control the product distribution (linear / branched) by using different condition. Although ees were moderate, her group also succeeded to develop enanchioselective variant with the combination of achiral Pd catalyst and chiral Cr-salen catalyst.



White, *JACS* **2004**, *126*, 1346



White, *ACIE* **2008**, *47*, 6448

* 1. C-O bond formation with Fe-based catalyst and H2O2 as oxidant

Fe-based catalyst was reported to recognize subtle differences between electronic / steric natures and existence of directing group even in complex molecules with a lot of C-H bonds, and selectively oxidize the most reactive sp3 C-H bond.



White, *Science* **2007**, *318*, 783

1. **C-N bond formation** 
   1. C-N bond formation through C-H insertion

Similar to C-H insertion of metal carbenoid into C-H bond(see 4.2.2), metal nitorenoid can insert C-H bond. Breslow investigated several catalysts for intramolecular amination and Rh2(OAc)4 showed the best reactivity.



Breslow, *JACS* **1983**, *105*, 6728

Du Bois reported Rh-catalyzed intramolecular C-H amination to form 5 and 6 membered rings, which could be transformed to 1,2- and 1,3-aminoalcohol. Use of simple carbamates and sulfamate esters as nitrene precursors instead of iodoimine made these protocols simpler.



Du Bois, *ACIE* **2001**, *40*, 598



Du Bois, *JACS* **2001**, *123*, 6935

Du Bois succeeded to apply these methodologies to the total syntheses of complex natural products.



Du Bois, *JACS* **2003**, *125*, 11510



Du Bois, *JACS* **2008**, *130*, 12630

Vinyl azides were found to generate nitorene species *in situ*, and be inserted into C-H bond intramolecularly.



Driver, *JACS* **2007**, *129*, 7500

The reactivity for nitrene C-H bond insertion follows the order 3º > 2º >> 1º bond. Sp2 C-H bond also shows low reactivity. For intermolecular amination, these tendencies become challenges to control regioselectivity among many C-H bonds. Use of directing group is one of the solutions.



Che, *JACS* **2006**, *128*, 9048

Au-catalyzed C-H amination of sp2 C-H bond was reported. Although substrate scopes were narrow, this is rare example for the insertion into sp2 C-H bond in intermolecular manner.





He, *JACS* **2007**, *129*, 12058

* 1. C-N bond formation through oxidative amination

Buchwald reported intramolecular oxidative amidation to form carbazole. Acetyl group on the nitrogen was important to obtain product in high yield. Authors proposed amide-directed C-H activation mechanism.



Buchwald, *JACS* **2005**, *127*, 14560

Buchwald also reported benzimidazole formation by Cu-catalyzed oxidative amination. Authors proposed three possible mechanisms, but they didn’t get any mechanistic insights. In this system, alkyl substituted substrate showed lower reactivity.





Buchwald, *ACIE* **2008**, *47*, 1932

For intermolecular oxidative amination, similar protocols were reported by several groups. Amides, 2º-anilines, 2º-aliphatic amines, and 1º-aliphatic amines can be used in this transformation. On the other hand, scopes for arenes were limited to ones with relatively weak C-H bond.



Mori, *OL* **2009**, *11*, 1607



Duan, *JOC* **2011**, *76*, 5444



Chang, *ACIE* **2010**, *49*, 9899

Yu reported intermolecular amination with simple arenes by using *O*-Bz hydroxylamines as amine source.



Yu, *JACS* **2011**, *133*, 7652

1. **C-B bond formation** 
   1. Bond strength of C-B bond

Different from other C-H functionalization such as formations of C-O, C-N, and C-C bond, functionalization of C-H to C-B bond is thermoneutral or thermodynamically favorable process (also see 1.1).



Hartwig, *JACS* **1996**, *118*, 4648

The accessible barriers for C-H bond cleavage and C-B bond formation are attributed to the combination of the strong -donor properties of the boryl group, and the presence of an unoccupied pz-orbital on boron in a boryl complex.

* 1. Seminal work on catalytic C-H activation / boryration

Smith reported the first example of catalytic C-H activation / boryration process with Ir complex. Although this reaction was slow, benzene was used as solvent, and TON was only 3, still it is an important precedent for the feasibility of this catalytic transformation.



Smith, *JACS* **1999**, *121*, 7696

* 1. Alkane C-H bond boryration

Based on his W-mediated system and Re-catalyzed system with photo-irradiation, Hartwig reported Ir-catalyzed thermal system. Steric factor has a major influence on regioselectivity, so that terminal 1º-CH bond reacts selectively. Existence of heteroatom wouldn’t override the regioselectivity to C-H bond adjacent to heteroatoms such as oxygen and nitrogen, but inductive effect has still some influences on the selectivity.





Hartwig, *Science* **2000**, *287*, 1995

*JACS* **2004**, *126*, 15334

* 1. Aromatic C-H bond boryration

Normally the catalysts for alkane C-H boryration showed poor reactivity for aromatic substrates, probably due to unfavorable interaction of substrate with catalyst. Addition of P or N-based ligands was found to increase reactivity of catalyst for aromatic substrates, and Ir/dtbpy complex was reported as a good catalyst for a variety of aromatic substrates including heteroaromatics even at ambient temperature. Similar to aliphatic cases, steric factor is important to determine the regioselectivity. Directing group, however, could control the reaction to be *o*-selective over steric preferences.



Ishiyama, Hartwig, and Miyaura, *ACIE* **2002**, *41*, 3056



Hartwig, *JACS* **2008**, *130*, 7534

Extensive mechanistic study revealed that trisboryl complex is important intermediate in this system.



Ishiyama, Miyaura, and Hartwig, *JACS* **2005**, *127*, 14263