Chimie Médicinale : *introduction et principes généraux*

Réactions de fonctionnalisation C-H et chimie médicinale

- Introduction
  1. Catalytic C-H Functionalization Reactions vs. Functional Group Transformations
  2. Catalytic C-H Functionalization Reactions: challenges & general mechanisms

- Catalytic C-H Functionalization by C-H Activation (*inner-sphere mechanism*)
  1. Mechanistic considerations
  2. Heteroatom-directed C-H Functionalization
  3. Oxidative addition-directed C-H Functionalization

- Catalytic C-H Functionalization by C-H Insertion (*outer-sphere mechanism*)
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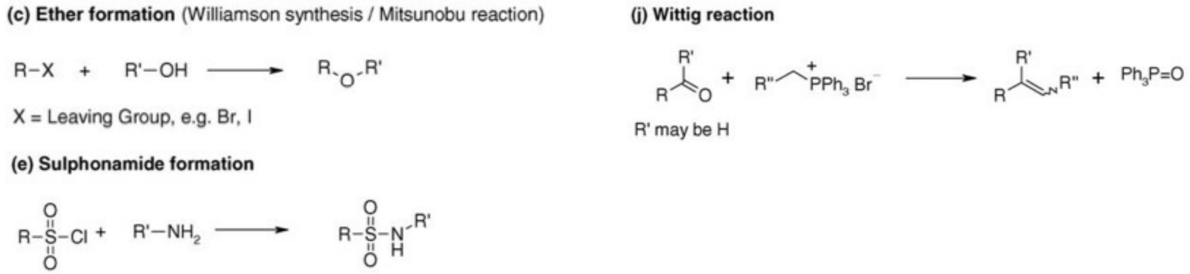
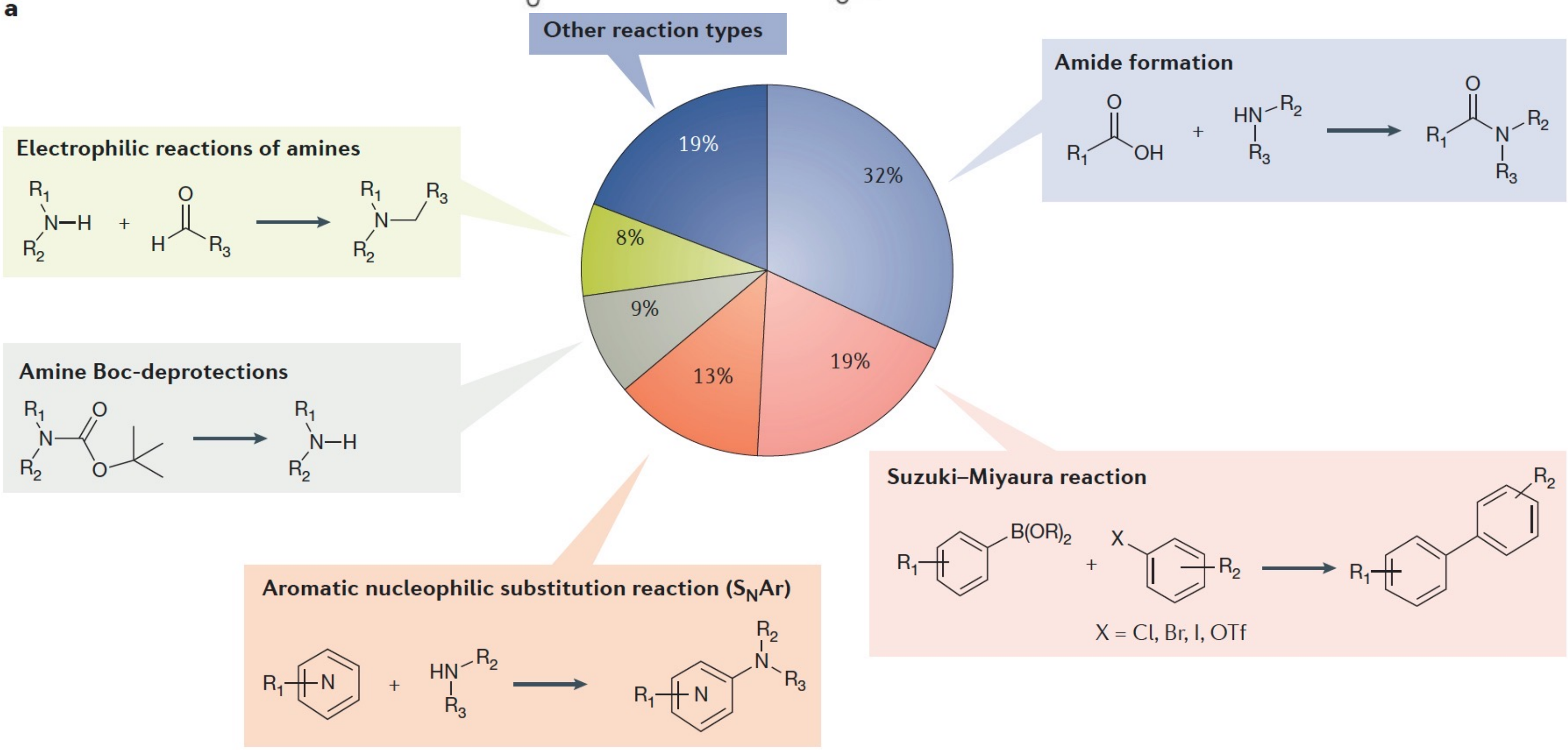
- Catalytic C-H Functionalization using radicals
  1. Historical reactions and mechanistic considerations
  2. Hydrogen Atom Transfer (HAT)
  3. Minisci-type Reaction

- Application of catalytic C-H functionalization
  Total synthesis & Late-stage functionalization of natural products and drugs

• Medicinal chemistry programmes are based on a limited number of reactions

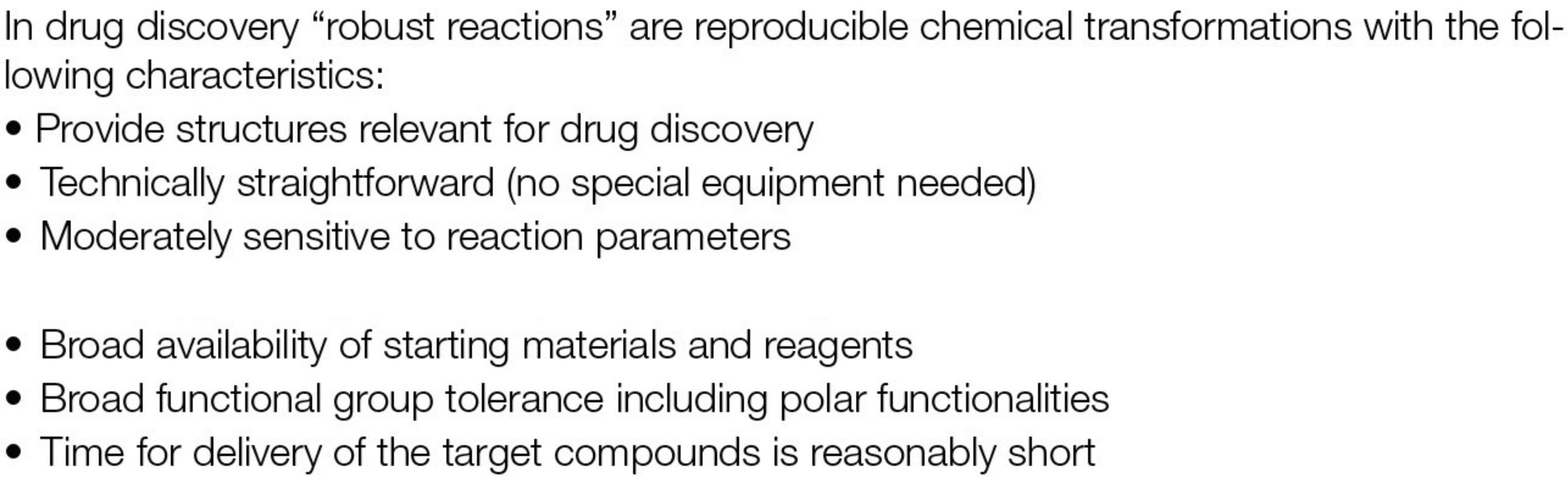
Figure 1 | **Common chemical reactions in drug discovery and development. a** | The uptake of new chemical reactions is slow, and a few have consistently dominated the past decades. The percentages of the five most frequently used reaction types (amide formation, Suzuki–Miyaura reaction, aromatic nucleophilic substitutions, amine Boc-deprotection and electrophilic reactions with amines) along with all other reaction types to produce compounds in drug discovery programmes are given





> J. Boström *et al.*, **Expanding the medicinal chemistry synthetic toolbox**, *Nat. Rev. Drug Discov.* **2018**, *17*, 709

- Pourquoi un nombre limité de reactions ? Parce qu'elles sont robustes



In drug discovery "robust reactions" are reproducible chemical transformations with the following characteristics:

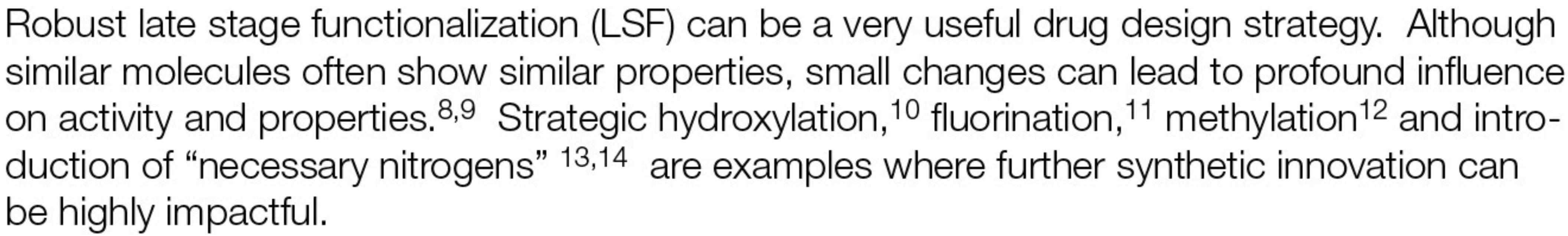
- Provide structures relevant for drug discovery
- Technically straightforward (no special equipment needed)
- Moderately sensitive to reaction parameters

- Broad availability of starting materials and reagents
- Broad functional group tolerance including polar functionalities
- Time for delivery of the target compounds is reasonably short

- BUT
  > The use of a limited set of reactions in most medicinal chemistry efforts potentially compromises the quality of drug candidates, for example because the functional group tolerance of the reactions limits the scope of SAR studies.
  > Focusing only on robust reactions may undermine the creativity of chemists.

> J. Boström *et al.*, **Expanding the medicinal chemistry synthetic toolbox**, *Nat. Rev. Drug Discov.* **2018**, *17*, 709

- Vers le développement de nouvelles stratégies pour un accès optimal à la diversité moléculaire



Robust late stage functionalization (LSF) can be a very useful drug design strategy. Although similar molecules often show similar properties, small changes can lead to profound influence on activity and properties.[8,9] Strategic hydroxylation,[10] fluorination,[11] methylation[12] and introduction of “necessary nitrogens” [13,14] are examples where further synthetic innovation can be highly impactful.

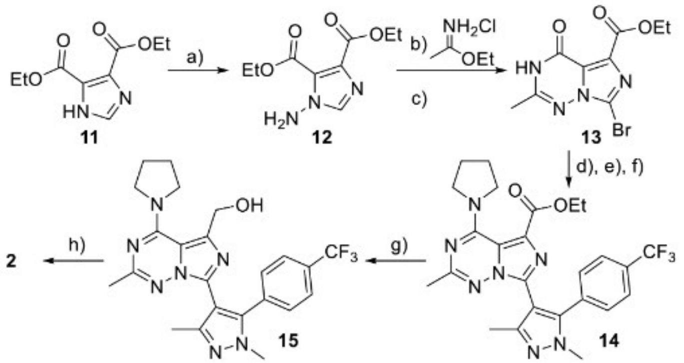
> J. Boström *et al.*, **Expanding the medicinal chemistry synthetic toolbox**, *Nat. Rev. Drug Discov.* **2018**, *17*, 709

• Vers le développement de nouvelles stratégies pour un accès optimal à la diversité moléculaire

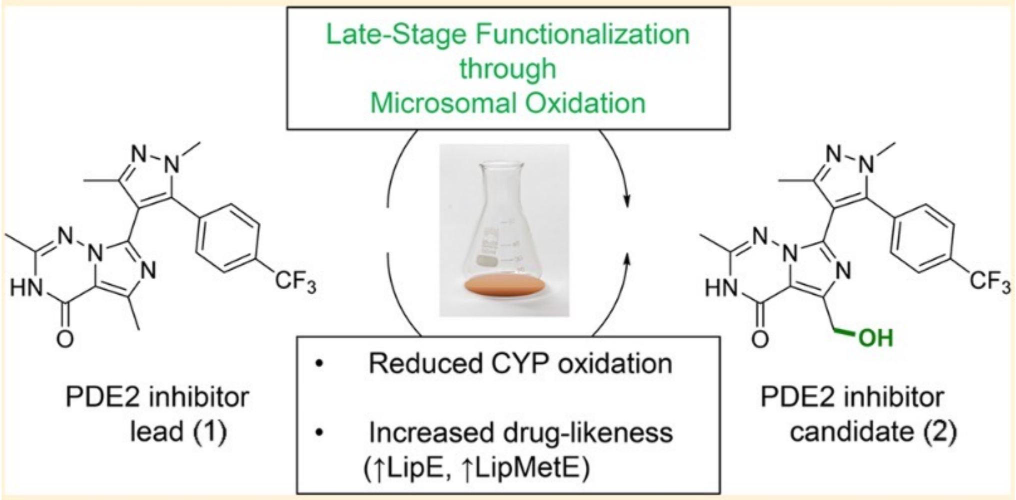
Tactic 1: Hydroxylation

Hydroxylation can for example provide improved activity, selectivity, solubility and lipophilicity. Reduction in lipophilicity can improve metabolic clearance, although increased rates of Phase II metabolism (e.g. glucuronidation) can occur. Quite a few chemical and biochemical and hydroxylation methods are emerging.

Scheme 4. Synthesis of Candidate 2, Leveraging the Symmetry of Diester–Imidazole 11[a]



[a]Reagents and conditions: (a) K_2CO_3, H_2O/EtOH, H_2NOSO_3H, 0–25 °C, 78%; (b) DIPEA, 2-Me-THF, reflux; (c) NBS, HOAc/MeCN, 70 °C, 48%, 2 steps; (d) 1,2,4-triazole, $POCl_3$, NEt_3, CH_2Cl_2; (e) pyrrolidine, NEt_3, CH_2Cl_2, 25 °C, 86%, 2 steps; (f) **10**, Pd(dppf)Cl_2·CH_2Cl_2, Na_2CO_3, dioxane/H_2O, 110 °C, 91%; (g) $LiBH_4$, THF, 50 °C, 98%; (h) 1 M HCl, THF, reflux, 92%.



Late-Stage Functionalization
through
Microsomal Oxidation

PDE2 inhibitor
lead (1)

- Reduced CYP oxidation
- Increased drug-likeness (↑LipE, ↑LipMetE)

PDE2 inhibitor
candidate (2)

PDE2 IC_{50}	0.6 nM
LipMetE	1.9
LipE	5.9

PDE2 IC_{50}	0.4 nM
LipMetE	2.4
LipE	7.4

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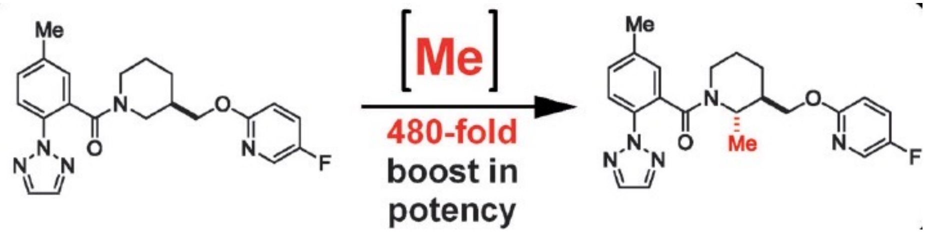
- Vers le développement de nouvelles stratégies pour un accès optimal à la diversité moléculaire

Tactic 2: Methylation

Strategic methylation can produce compounds with pronounced improvements in activity, safety and DMPK properties. New late stage methylation methods with regio- or stereochemical control could have great utility for this purpose.



Tactic 3: Fluorination

Aromatic fluorination is a common strategy to reduce metabolic liabilities and improve biological activity. The fluorine can serve to blocks C-H "hot-spots" susceptible to P450 oxidation. Aliphatic fluorines can reduce lipophilicity, modulate the pKa of ionisable centers and add conformational rigidity to structures.

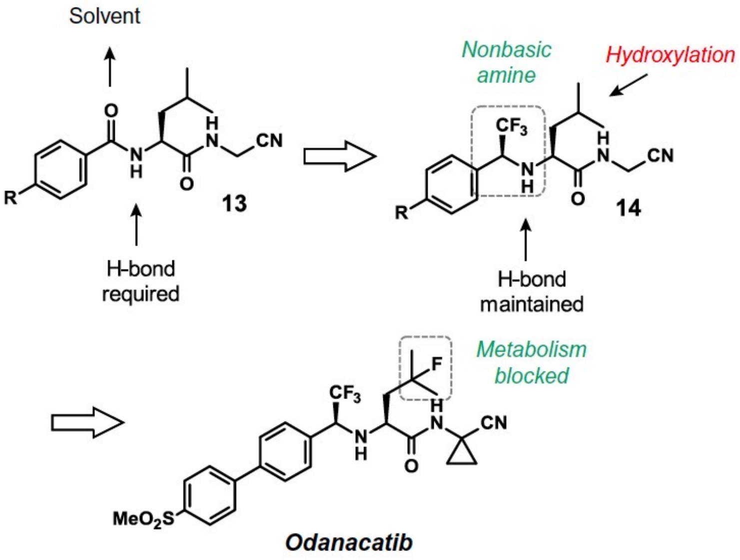


Figure 13 Use of nonbasic amine as amide isostere in the discovery of odanacatib. A second fluorine blocks the oxidation of the isopropyl group to improve pharmacokinetics.

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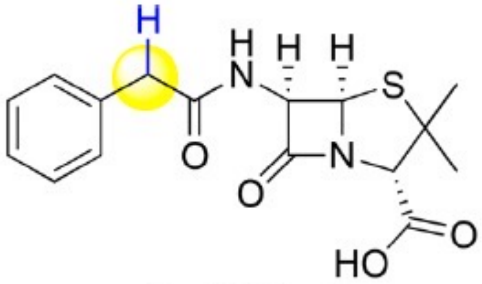
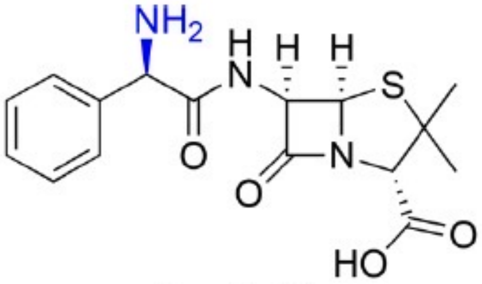
Tactic 4: Necessary nitrogens

The ubiquity of nitrogen heterocycles in drug molecules reflects their importance in molecular recognition and property modulation.[5] New methods compatible with the presence of aromatic nitrogens in intermediates, enables the production of diverse and functionalized hydrophilic compounds.



Penicillin G

Gram positive activity



Ampicillin

Gram positive and negative activity

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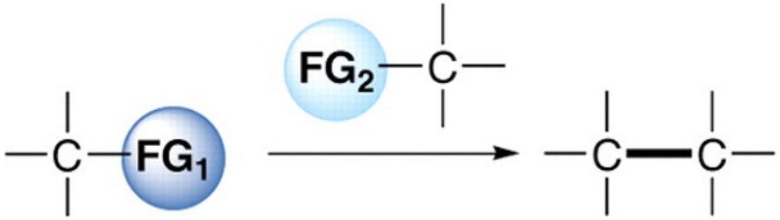
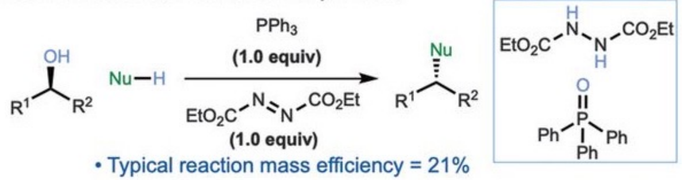
• Traditional approaches by Functional Group Transformations

- ✗ Atom and step economy
- ✗ Amounts of waste
- ✗ Selectivity
- ✗ FG tolerance

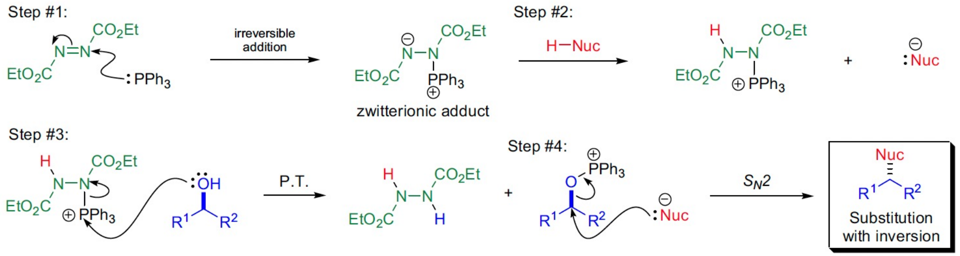


- ✗ Atom and step economy
- ✗ Amounts of waste
- ✓ Selectivity
- ✓ FG tolerance

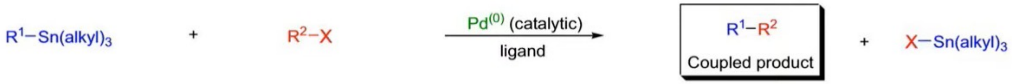
The 1967 Mitsunobu inversion protocol



• Typical reaction mass efficiency = 21%



Stille "C – C" Cross coupling reaction



$$R^1\text{–Sn(alkyl)}_3 + R^2\text{–X} \xrightarrow[\text{ligand}]{\text{Pd}^{(0)}\text{ (catalytic)}} \boxed{\begin{matrix} R^1\text{–}R^2 \\ \text{Coupled product} \end{matrix}} + \text{X–Sn(alkyl)}_3$$

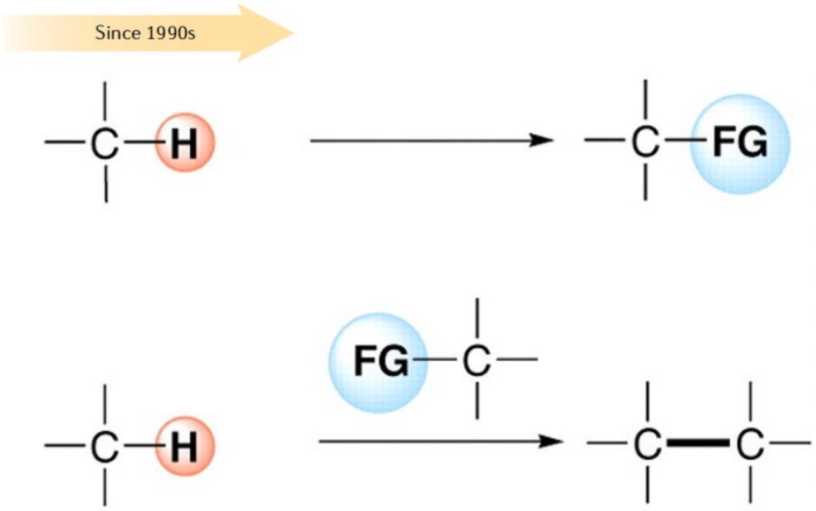
R^1 = allyl, alkenyl, aryl; R^2 = alkenyl, aryl, acyl; X = Cl, Br, I, OTf, $OPO(OR)_2$

- **Discovery :- in 1978 john Kenneth stille**

1) tolerate a wide variety of functional groups;
2) Are not sensitive to moisture or oxygen unlike other reactive organometallic compounds;
3) Are easily prepared, isolated, and stored. The main disadvantages are their toxicity and the difficulty to remove the traces of tin by-products from the reaction mixture.
4) Organotin reagent contains bulky group that's why reaction undergoes very slow and therefore it requires optimization.

> Redox-neutral organocatalytic Mitsunobu reactions, *Science* **2019**, *365*, 910-914

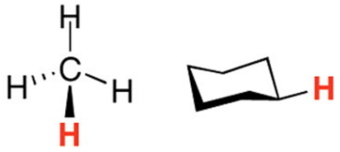
• Synthesis using Catalytic C-H Functionalization Reactions



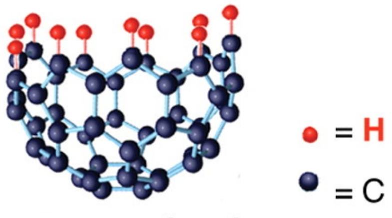
✓Atom and step economy
✓Amounts of waste
✓Selectivity
✓FG tolerance

> *An infinite choice of starting materials*

C–H bonds are found in nearly all organic compounds.



Simple hydrocarbons



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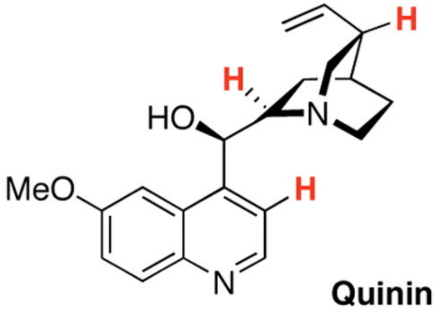
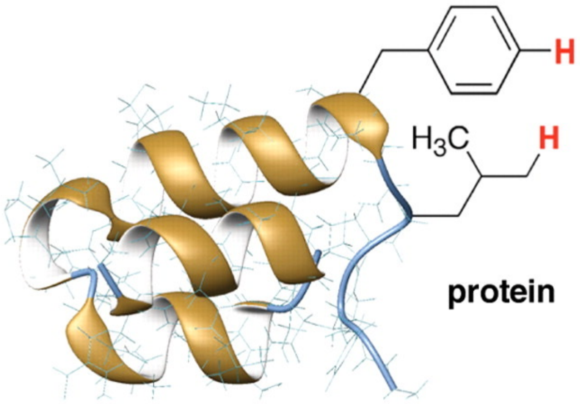
Polyarene materials



Quinine

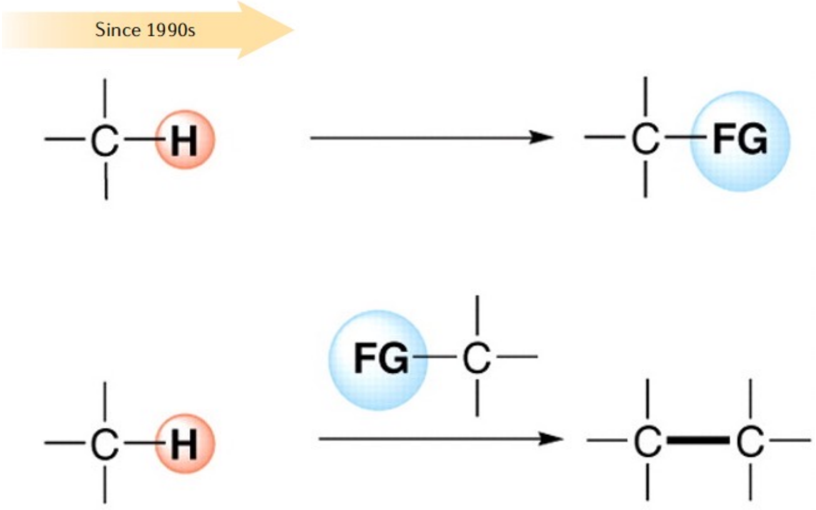
Pharmaceuticals and biological probes



Bio- and synthetic polymers

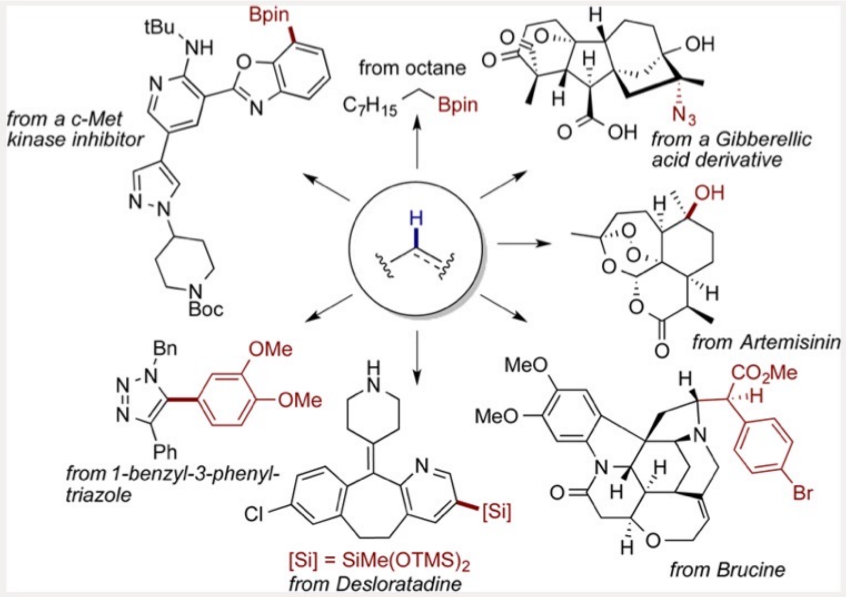
> D. Sames *et al.*, C-H Bond Functionalization in Complex Organic Synthesis, *Science* 2006, *312*, 67

- Synthesis using Catalytic C-H Functionalization Reactions



✓Atom and step economy
✓Amounts of waste
✓Selectivity
✓FG tolerance

> *C-C, C-O, C-N, C-B, C-Si Bond Forming Reactions*



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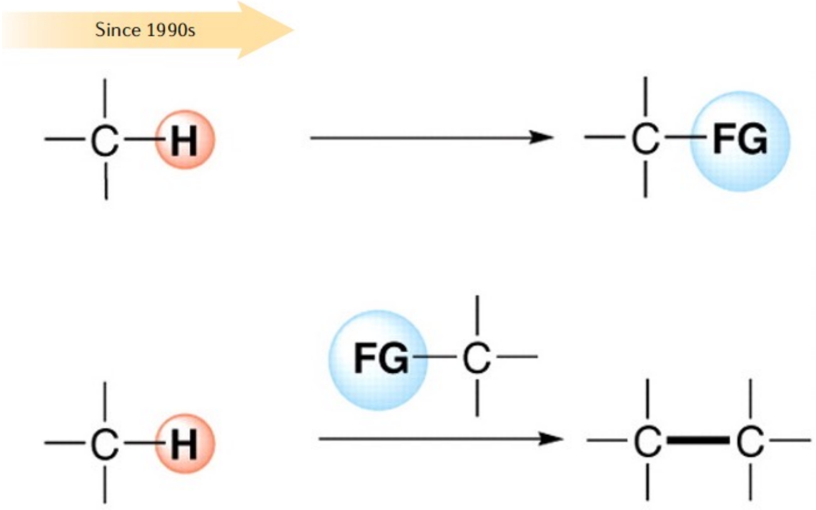

✓Atom and step economy
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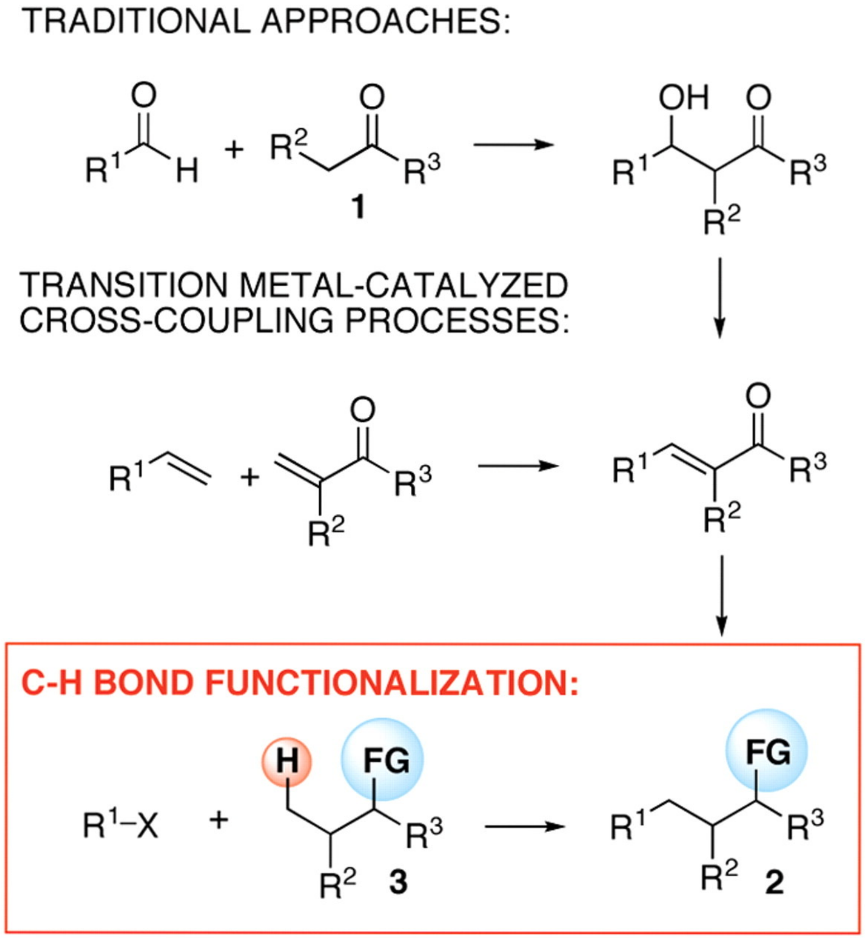
✓Selectivity
✓FG tolerance

> *New retrosynthetic strategies*



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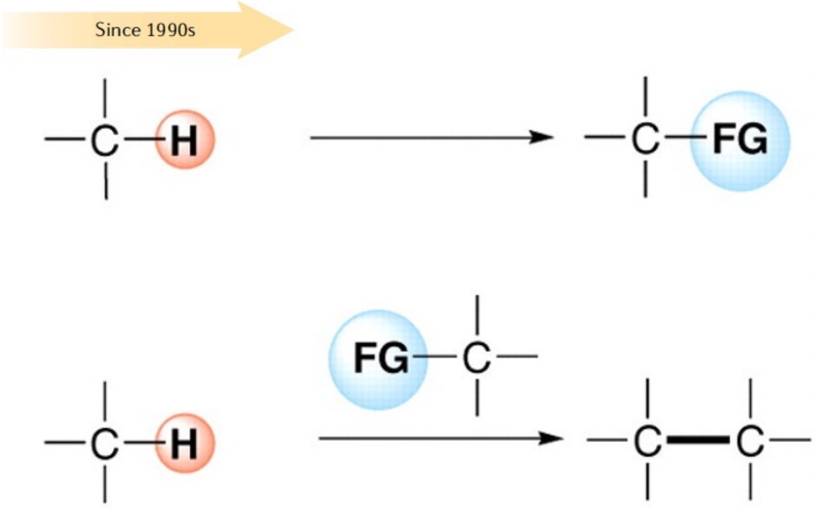
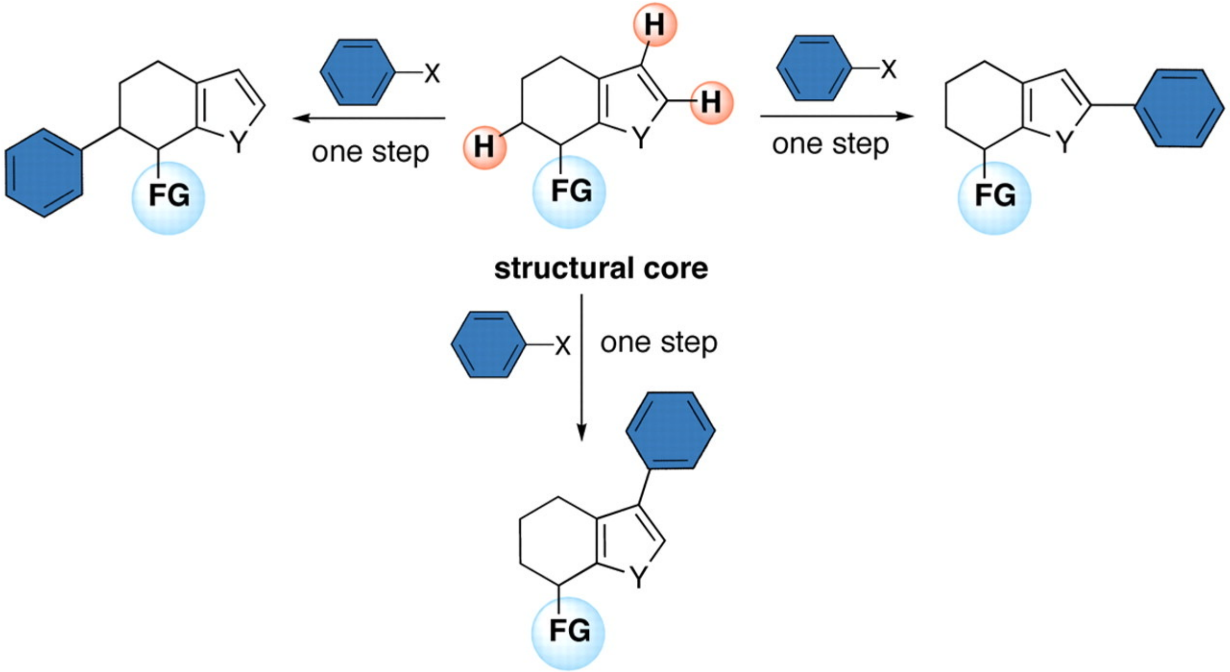


- ✓Atom and step economy
- ✓Amounts of waste
- ✓Selectivity
- ✓FG tolerance

> *Structural core diversification*



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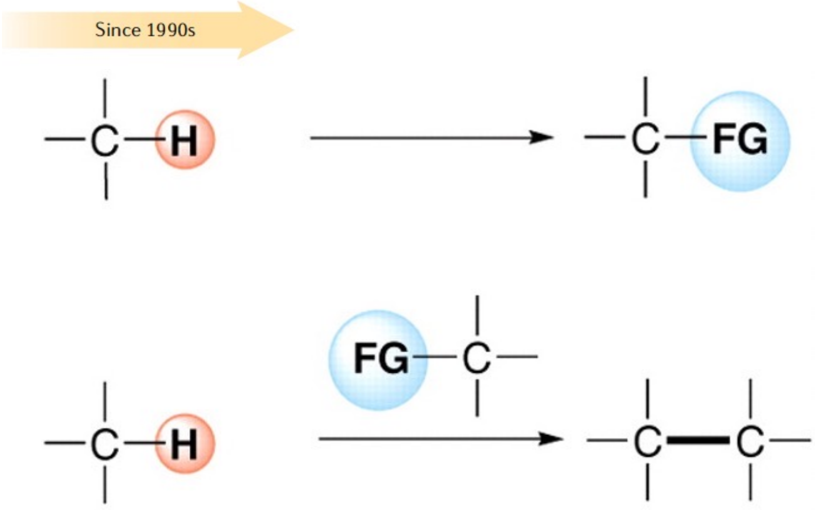
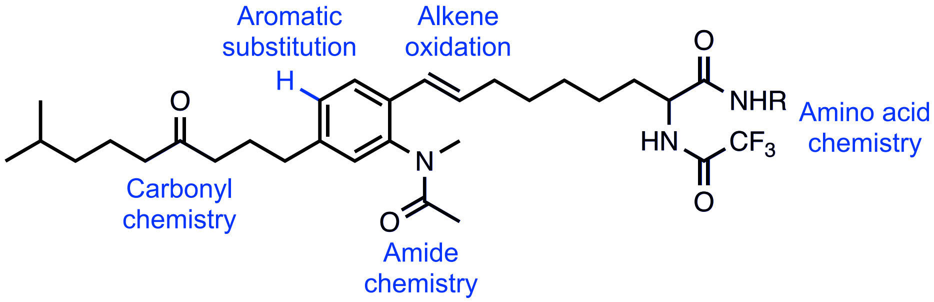
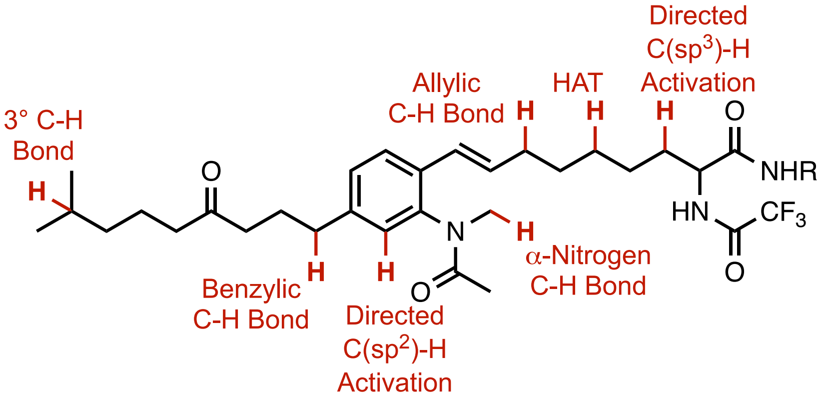


- ✓Atom and step economy
- ✓Amounts of waste
- ✓Selectivity
- ✓FG tolerance

What kind of reactions can you expect?

> *Conventional Functional-Group Based Reactivity*





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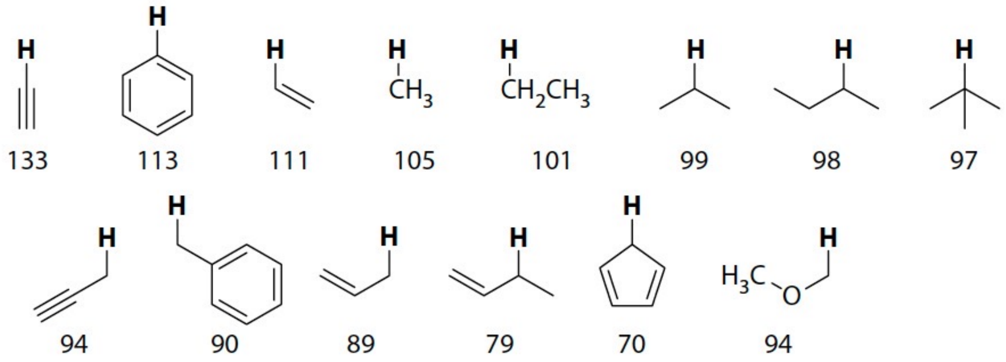
- Challenges: **Reactivity**

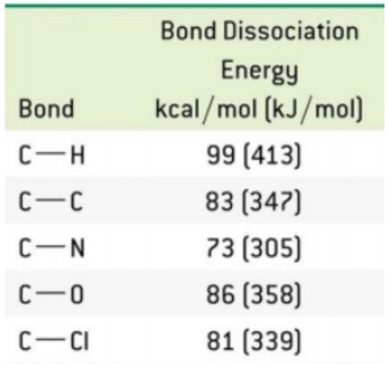
High enthalpic stability of C-H bonds : Most of them are stronger than the corresponding C-X bonds

> Therefore a C-H functionalization is thermodynamically unfavored.

BDEs of C—H Bonds (kcal mol^{-1})



Source: Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255–263.



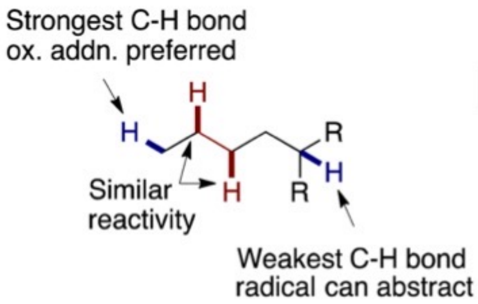
Bond	Bond Dissociation Energy kcal/mol (kJ/mol)
C—H	99 (413)
C—C	83 (347)
C—N	73 (305)
C—O	86 (358)
C—Cl	81 (339)

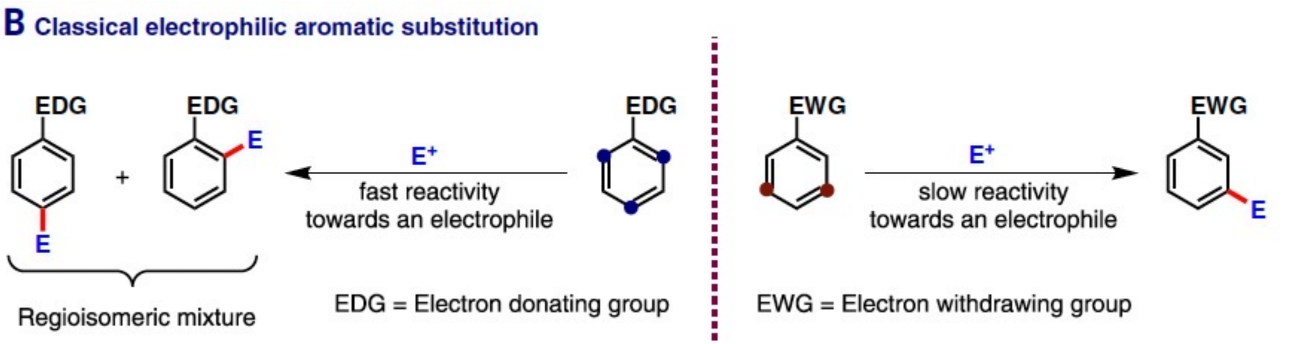
Alkanes do not possess high-energy electrons in p or π orbitals > not strongly nucleophilic.
They also lack empty, low-lying π* orbitals > not highly electrophilic or sensitive to light.

> The challenge in C-H functionalization is also attributable to a high kinetic barrier to reactivity

Challenges: **Selectivity**

1. 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.





2. Once the desired C-X bond is formed (for example, a C(sp^3)-OH bond), this bond itself has a lower bond strength than the C-H bond before, and over-reactions (such as alcohol oxidation to a carbonyl group) can occur.

3. Selectivity for a reaction at an unactivated C-H bond in the presence of C-H bonds that are weaker or more acidic due to a functional group

4. Control of the mono-functionalization

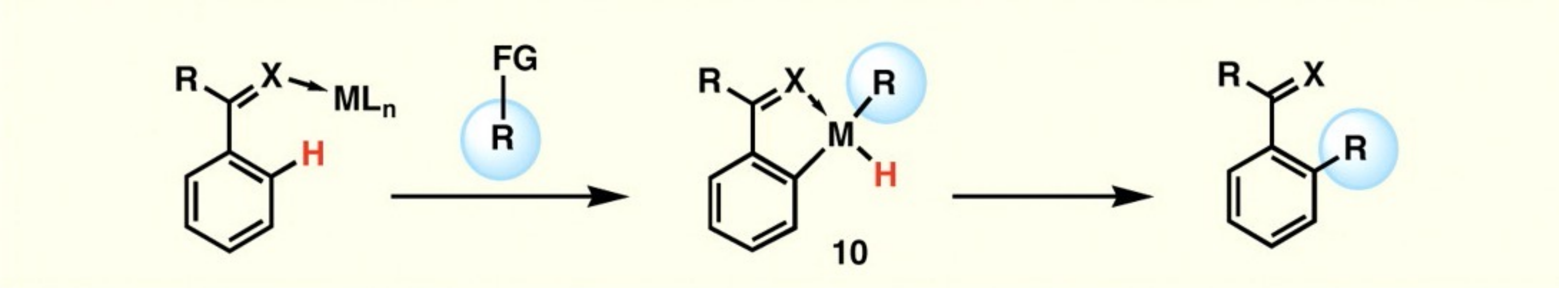
5. the introduction of a C-X bond might change the reactivity of a whole molecule.

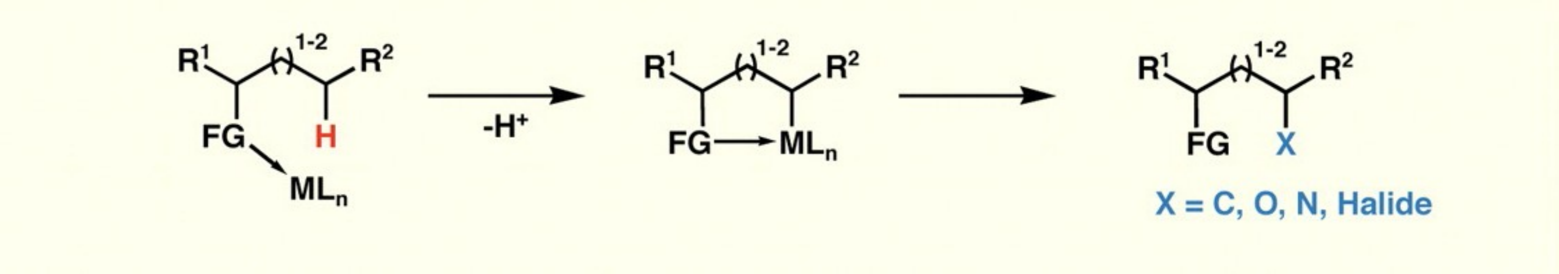
• General mechanisms: **Catalytic C-H Activation**

•**Formation of an organometallic intermediate:** *Inner sphere mechanism*

Directed reactivity

The transition metal catalyst coordinates to a Lewis basic functional group on the molecule, which brings the catalyst into proximity of a specific C-H bond. In addition to the control of the regioselectivity, this interaction lowers the energy barrier of the cleavage of this C-H bond, thereby increasing the rate of the reaction. The formation of 5-membered metallacycles is generally favored.
The resulting alkyl metal intermediate can be trapped with a reactive partner to form a C-X bond





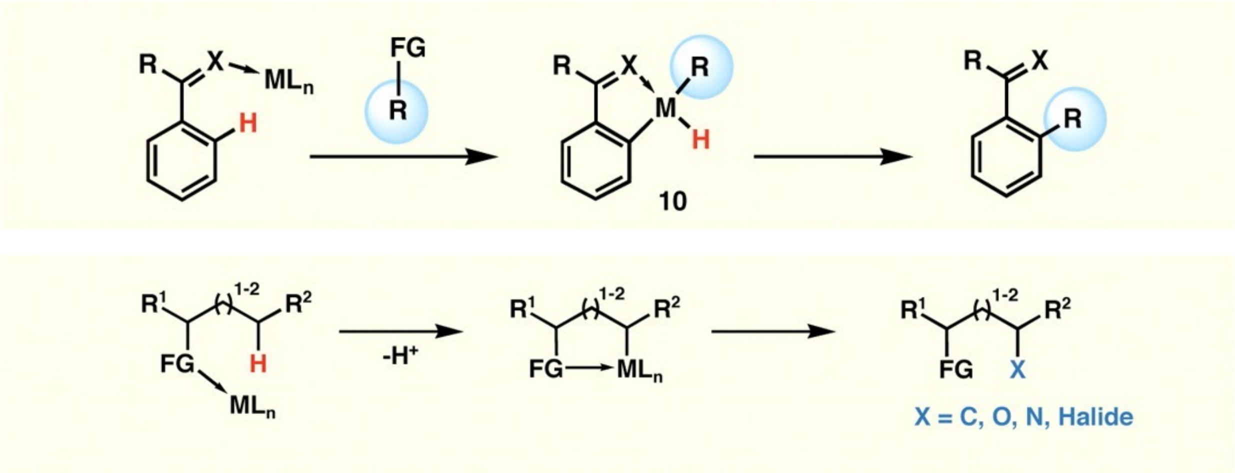
X = C, O, N, Halide

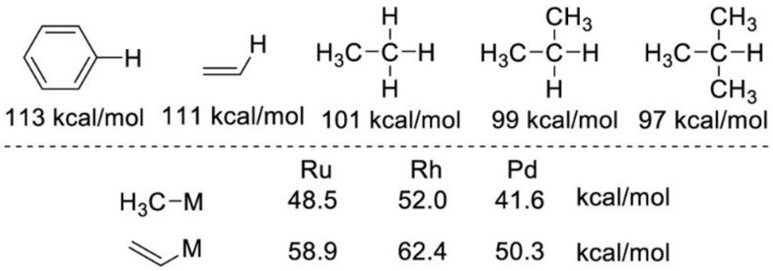
> D. Sames *et al.*, **C-H Bond Functionalization in Complex Organic Synthesis**, *Science* **2006**, *312*, 67

- General mechanisms: **Catalytic C-H Activation**

- **Formation of an organometallic intermediate:** *Inner sphere mechanism*

Directed reactivity





Since C(sp^2)-H bonds are, in general, stronger than C(sp^3)-H bonds, it might appear that the activation of C(sp^3)-H bonds would be less challenging. While this is true in reactions that proceed via homolytic bond cleavage, it is not true for metal-catalyzed C-H bond activation as we must consider the relative strengths of M-C bonds generated. In general, a metal-C(sp^3) bond is weaker than a metal-C(sp^2) bond.

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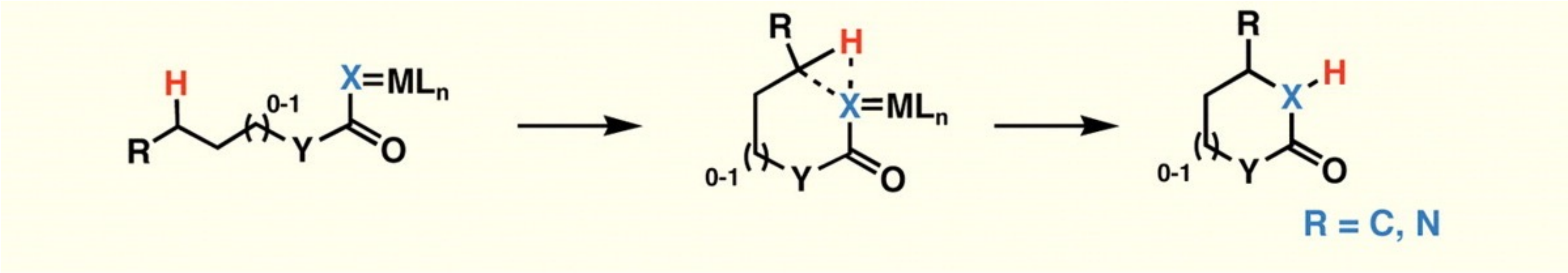
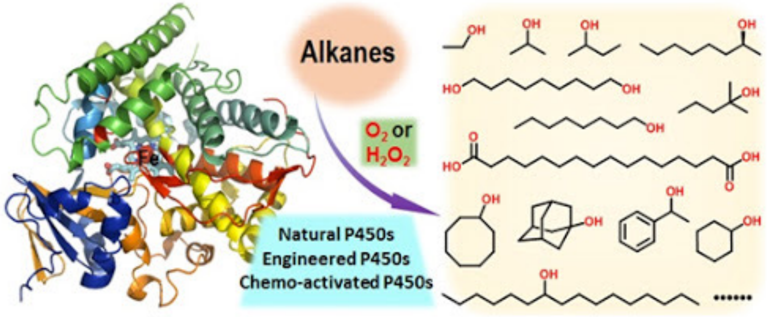
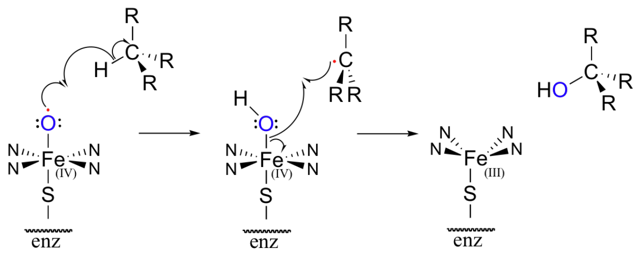
- General mechanisms: **Catalytic C-H Insertion**

- **Formation of metal-bound carbene or nitrene:** *Outer sphere mechanism*

Reminiscent of C-H oxidation mediated by cytochrome







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General mechanisms: **Terminology**

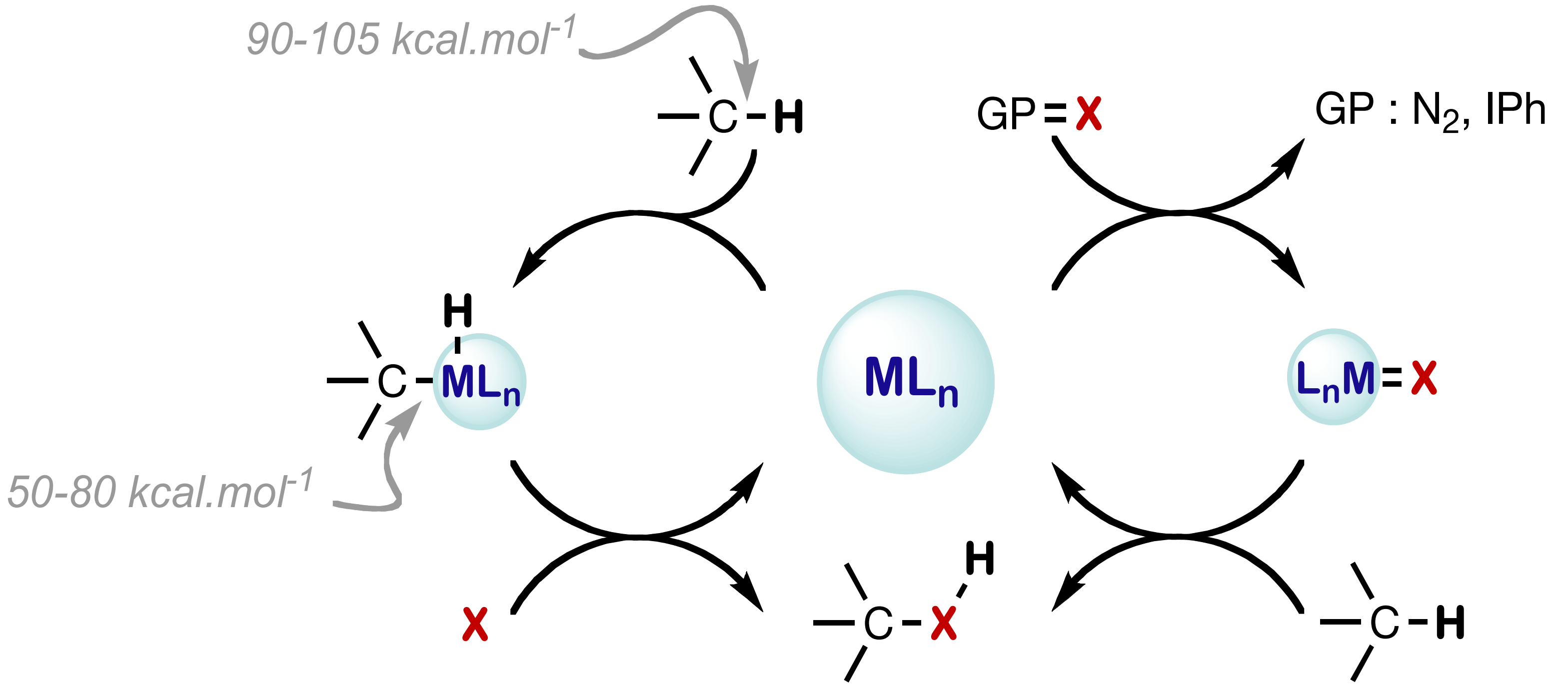
C-H Activation / C-H Insertion / C-H Functionalization

"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.

"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.

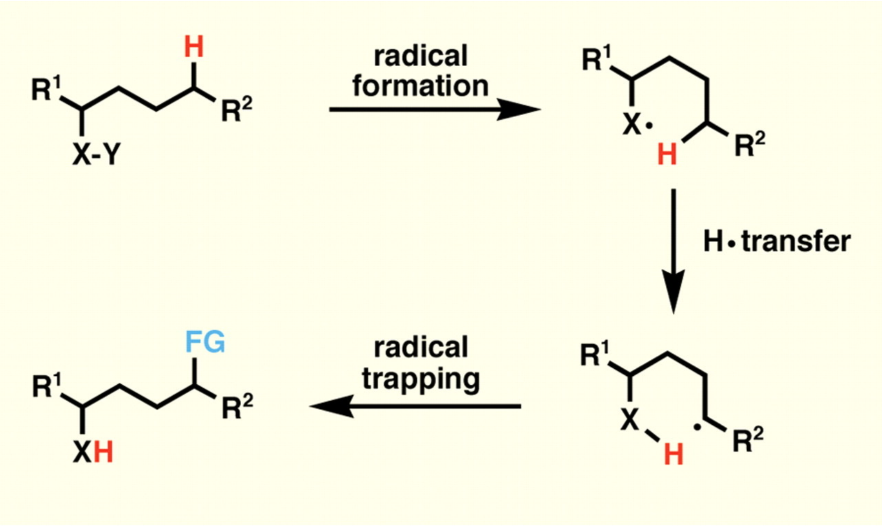


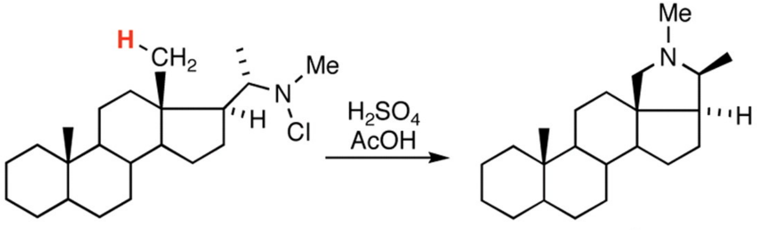
"C-H Functionalization"

A general term describing the **transformation of a C-H bond into a C-X bond**. This expression is not very well defined and most general. In the following, this term is used for a C-H activation followed by a transformation to a C-X bond. A C-H activation followed by a reaction from C-M to C-X is therefore a key part of a C-H functionalization.

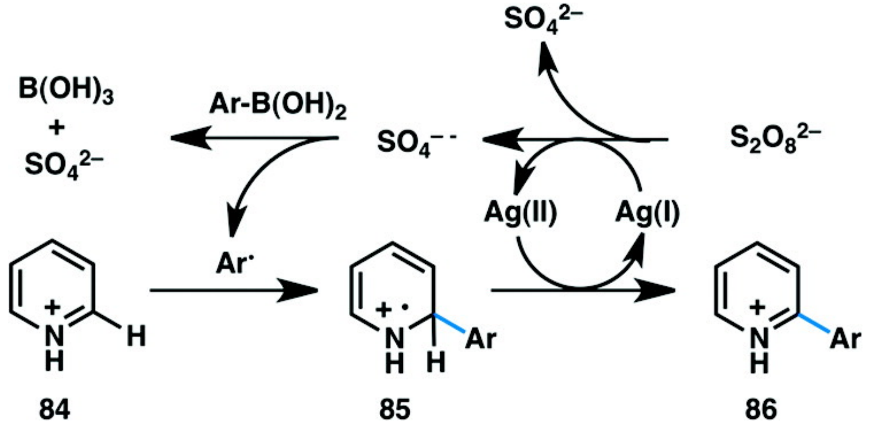
• General mechanisms: **Radical processes**

•Hydrogen Atom Transfer & Radical Addition





Conanine



> D. Sames *et al.*, **C-H Bond Functionalization in Complex Organic Synthesis**, *Science* **2006**, *312*, 67

Réactions de fonctionnalisation C-H et chimie médicinale

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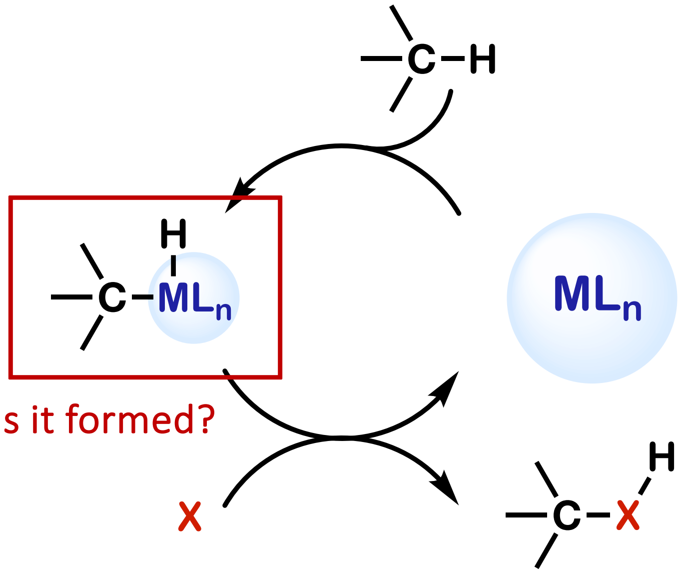
- The elementary step of C-H Activation

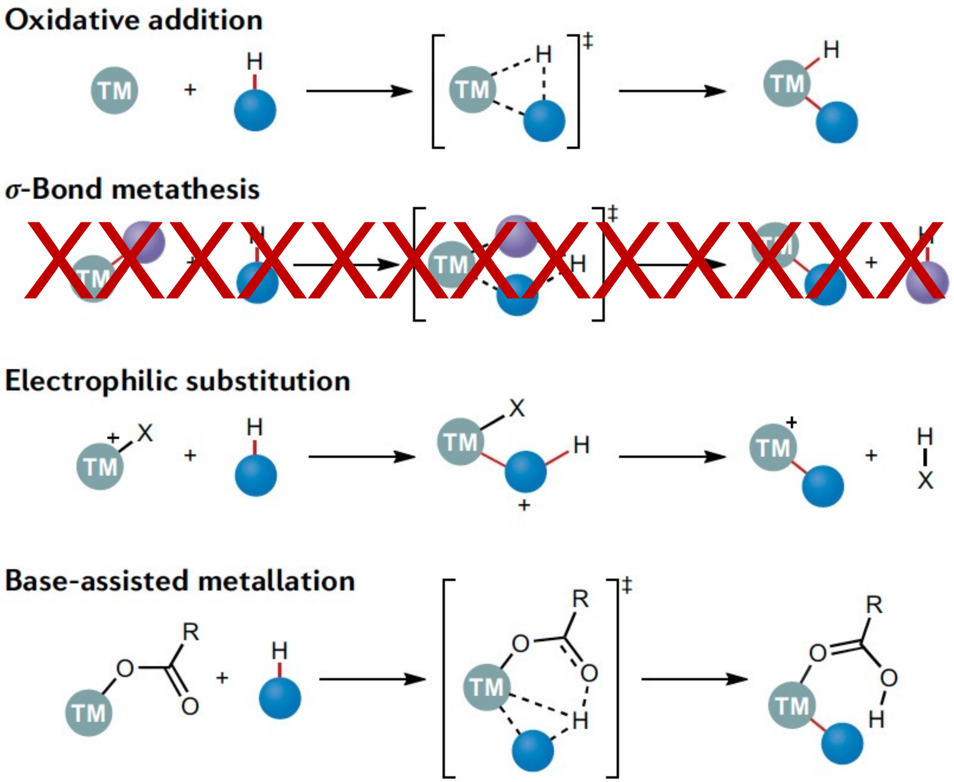
C-H Activation

"Inner-Sphere" mechanism



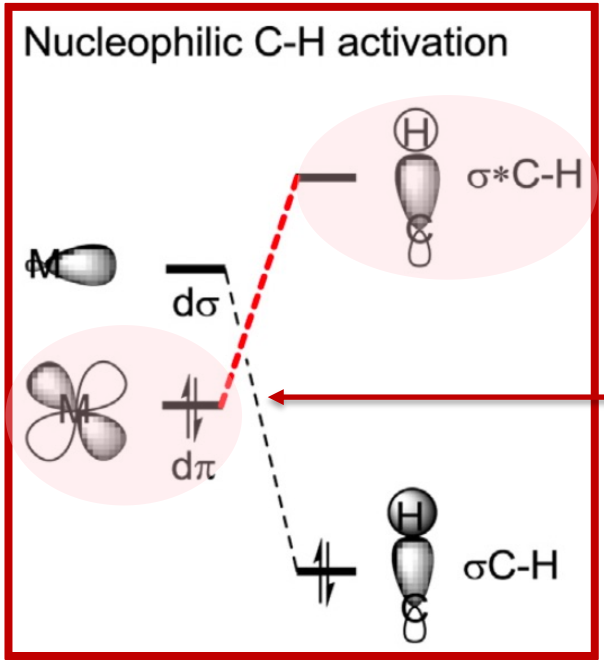
> How is it formed?

> 4 General mechanisms



> G. Poli, **Metal-catalyzed C-H Bond Activation/Functionalization: the Fundamentals**, *J. Mol. Catalysis A: Chemical* **2017**, *426*, 275

- *C-H Activation by* **Oxidative Addition**



Interaction from a metal-based occupied dπ orbital to the σ* orbital of the coordinated C-H bond (reverse CT)

Oxidative addition favored :
low valent electron rich transition metals (d^8 low-valent 2^{nd} & 3rd raw late TM complexes)

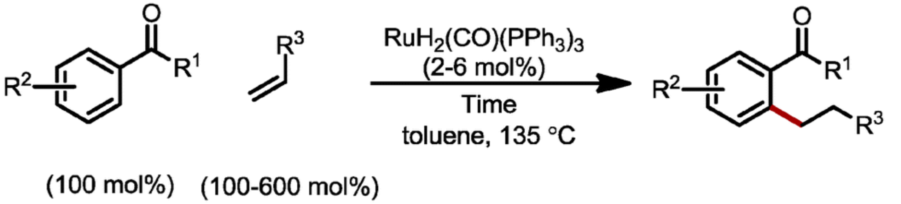
posses high-energy dπ and dσ orbitals

> G. Poli, **Metal-catalyzed C-H Bond Activation/Functionalization: the Fundamentals**, *J. Mol. Catalysis A: Chemical* **2017**, *426*, 275

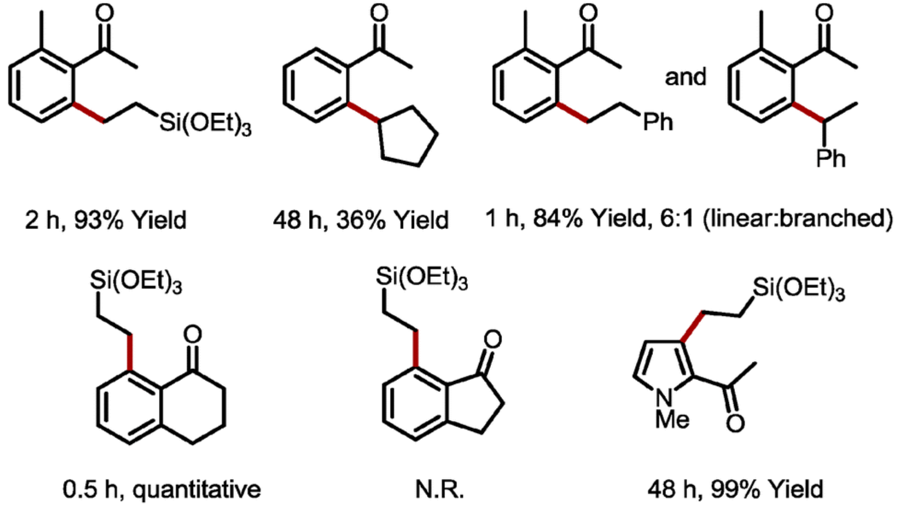
- *C-H Activation by* **Oxidative Addition**

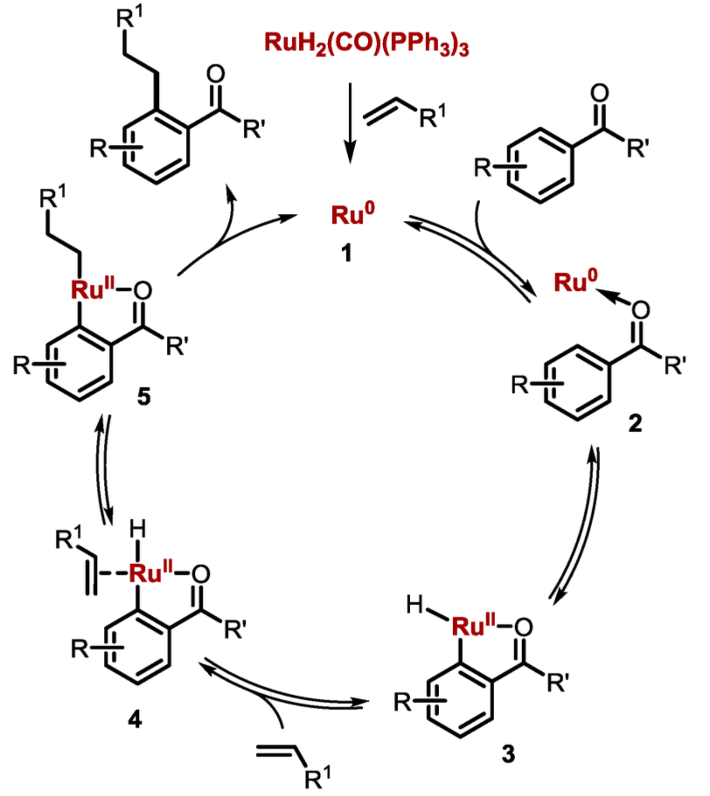
Prototypical example: Reaction de Murai

Ruthenium-catalyzed *ortho*-alkylation of aromatic ketones



Selected examples:

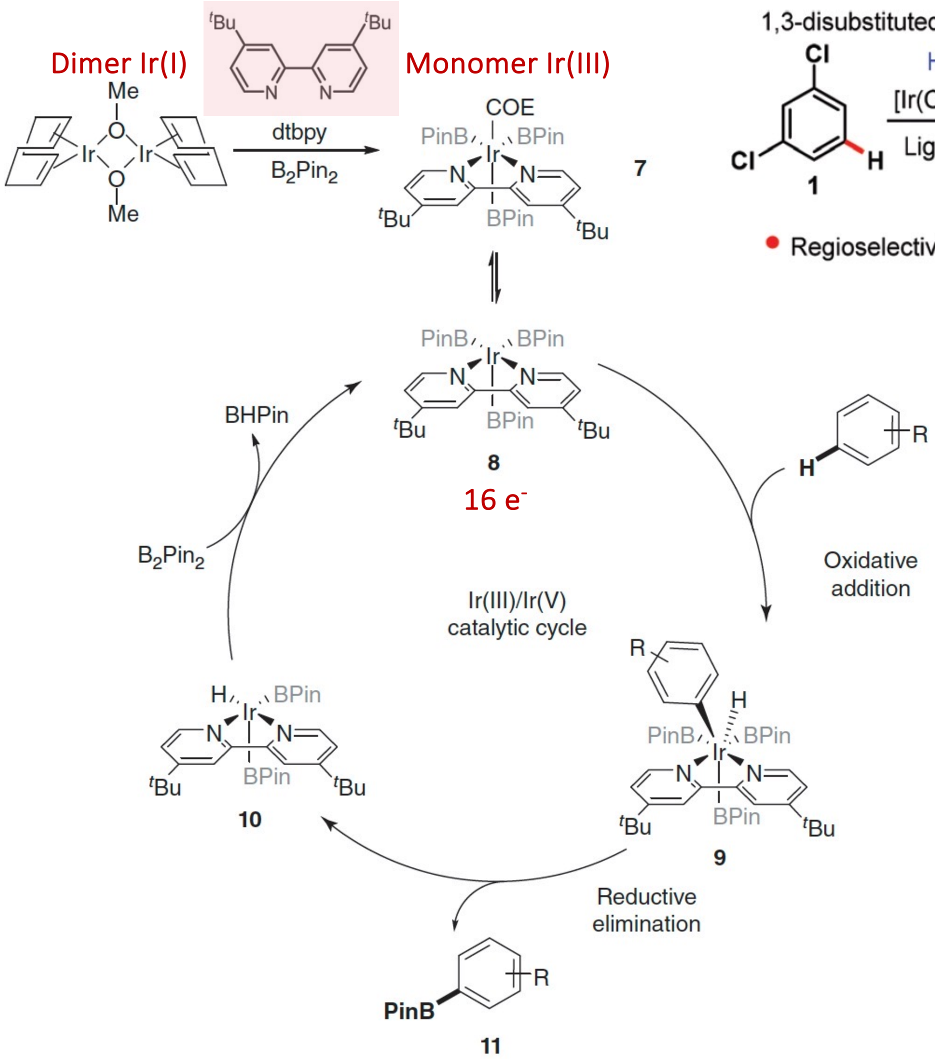




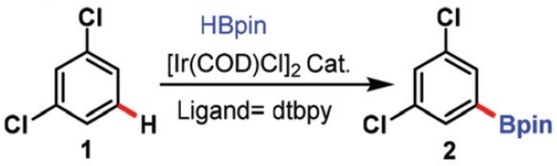
> S. Murai *et al.*, **Efficient catalytic addition of aromatic C-H bonds to olefins**, *Nature* **1993**, *366*, 529

• *C-H Activation by* Oxidative Addition

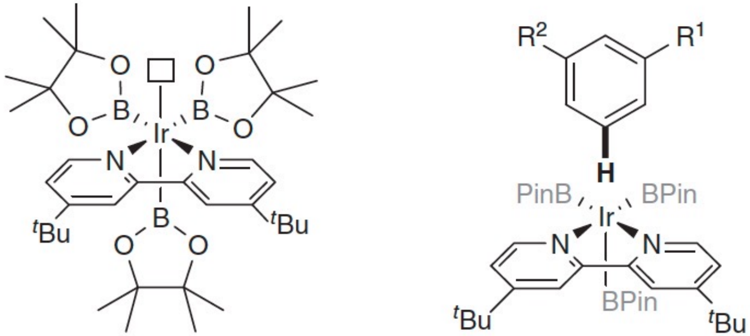
> Steric control



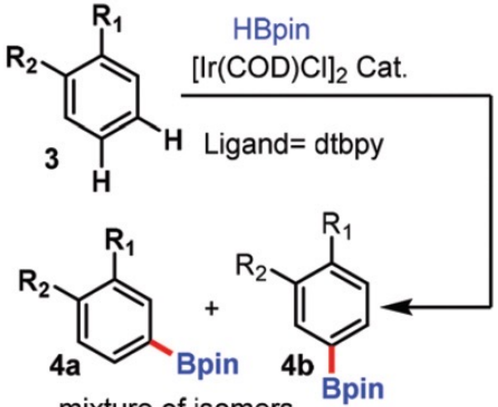
1,3-disubstituted arenes



● Regioselectivity controled by steric effects



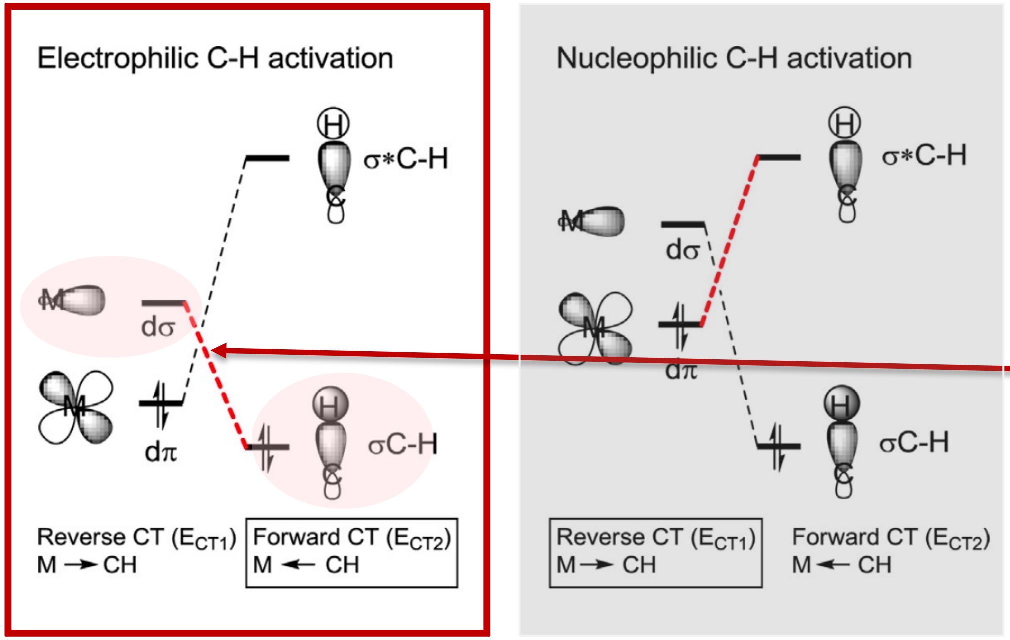
1,2-disubstituted arenes



mixture of isomers

> D. Maiti *et al.*, **Arene diversification through distal C(sp^2)-H functionalization**, *Science* **2021**, *372*, 701

- *C-H Activation by* Electrophilic Substitution

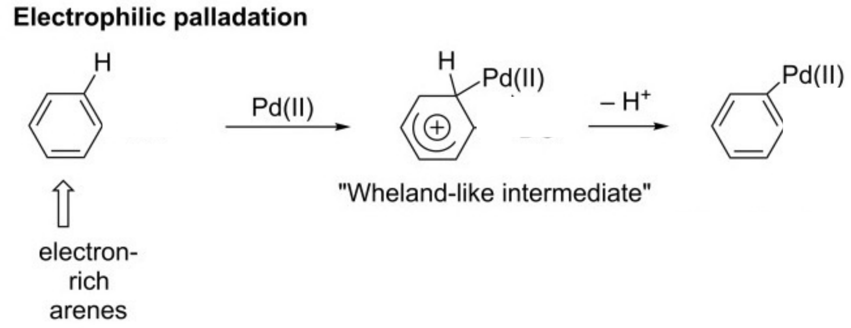


Interaction from the filled σ(C-H) bond to an empty metal-based dσ orbital (forward CT)

Electrophilic substitution favored :
Electron poor, late transition metals in high oxidation states, such as Pd(II), Pt(II), Rh(III), Ir(III) and Ru(II) > Lewis acidic metals

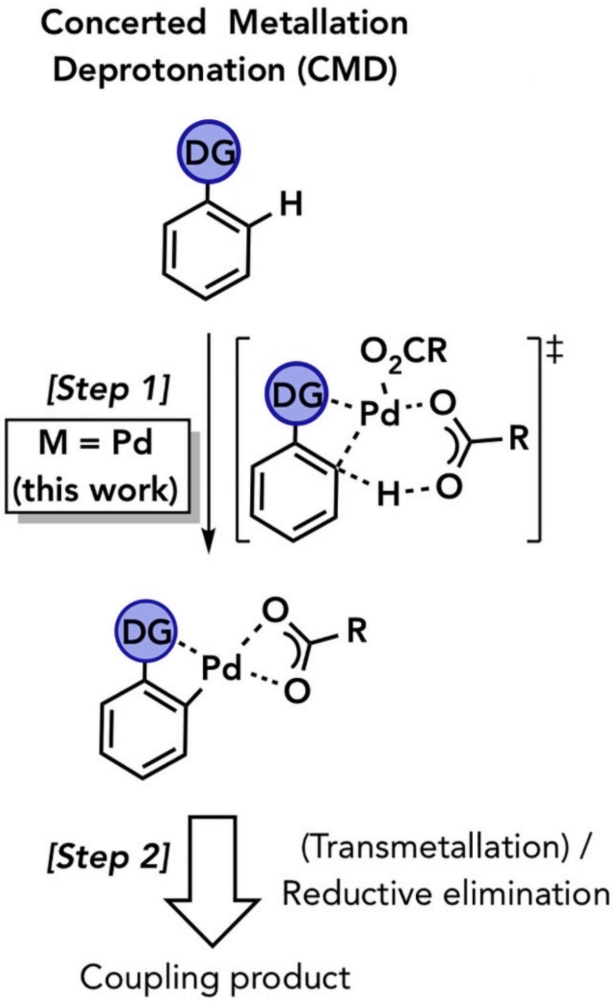
possess low-energy dπ and d**σ** electrons

the electronic properties of the arene play a fundamental role
Works better with electron-rich arenes
Often analogous to Friedel-Crafts mechanism

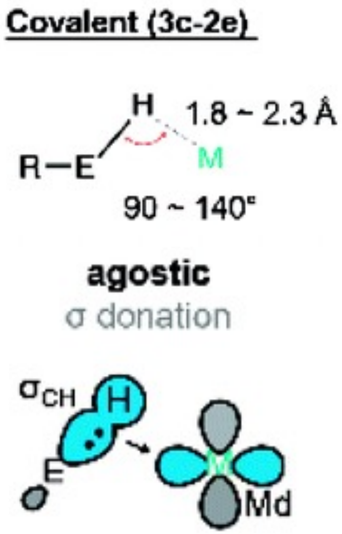


> G. Poli, **Metal-catalyzed C-H Bond Activation/Functionalization: the Fundamentals**, *J. Mol. Catalysis A: Chemical* **2017**, *426*, 275

- *C-H Activation by* Concerted Metalated Deprotonation



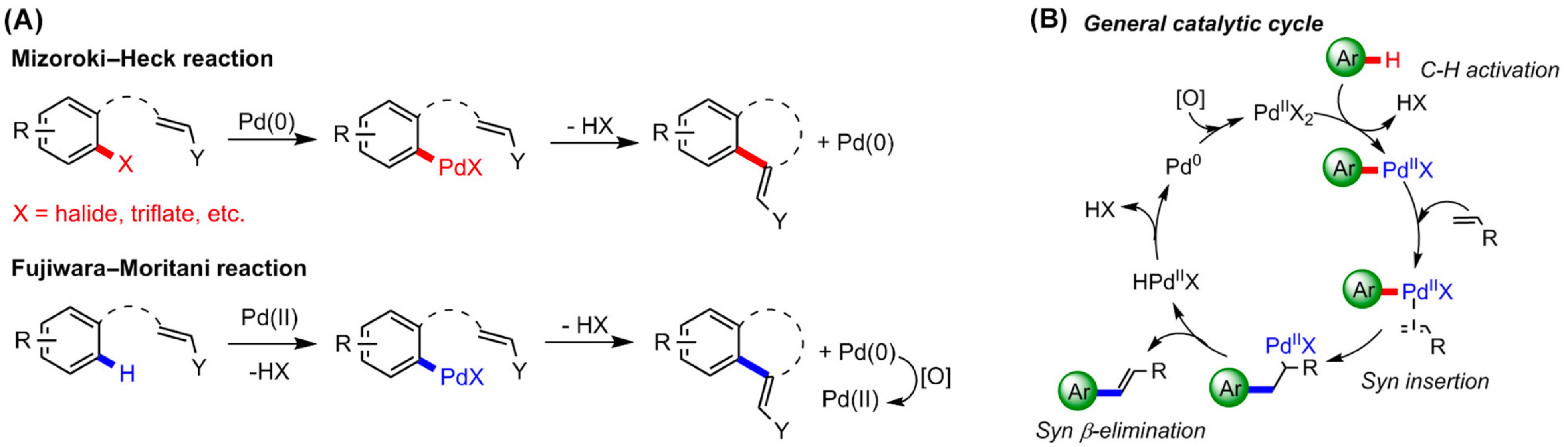
- internal base C–H deprotonation via six-membered TS
- little charge buildup during TS, donating ligands tolerate
- relative basicity of C–H bond and internal base critical
- often preceded by agostic complex formation

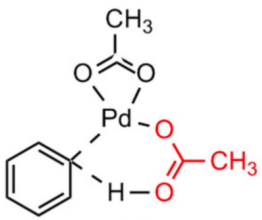


AGOSTIC INTERACTION:
It most commonly refers to a C-H bond on a ligand that undergoes an interaction with the metal complex. This interaction closely resembles the transition state of an oxidative addition or reductive elimination reaction.

> G. Poli, **Metal-catalyzed C-H Bond Activation/Functionalization: the Fundamentals**, *J. Mol. Catalysis A: Chemical* **2017**, *426*, 275

• The Fujiwara-Moritani reaction : *electrophilic substitution*

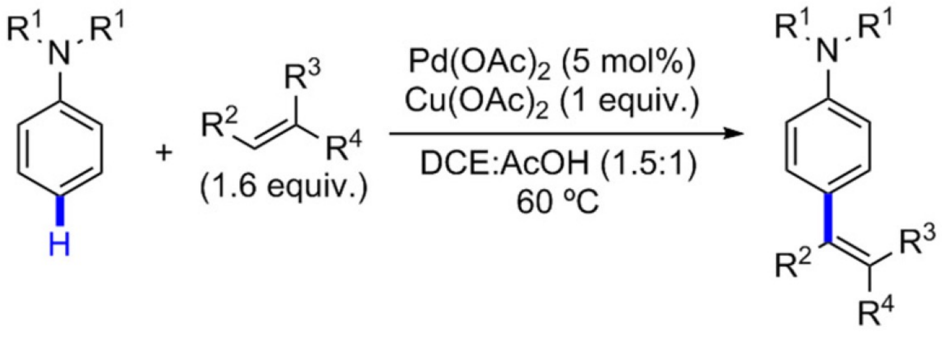




(a)

Pd(OAc)$_2$
No directing group
No ligand

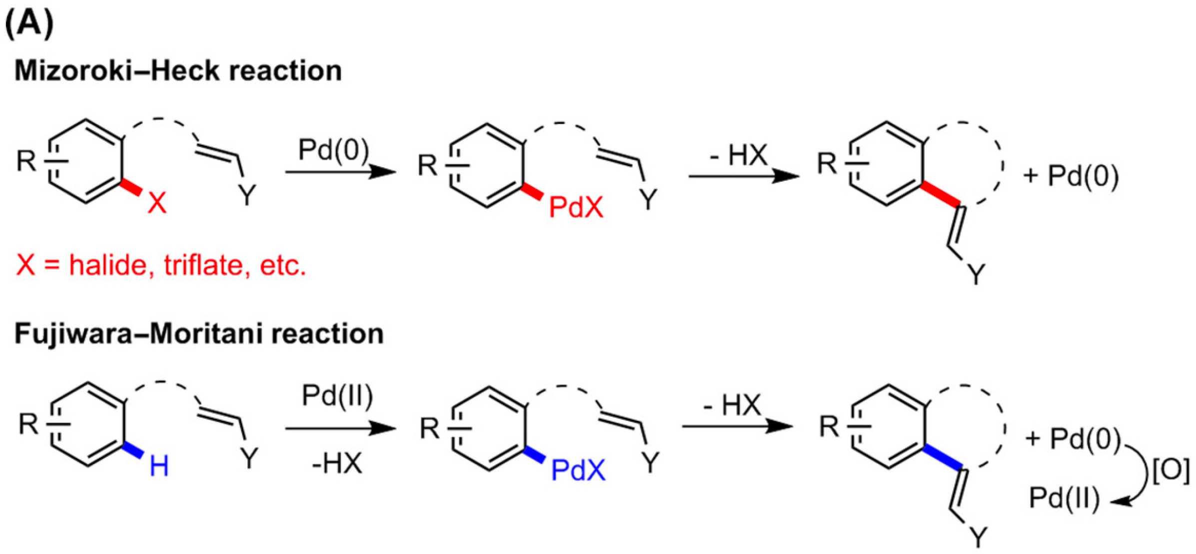
Selective para-alkenylation of anilines

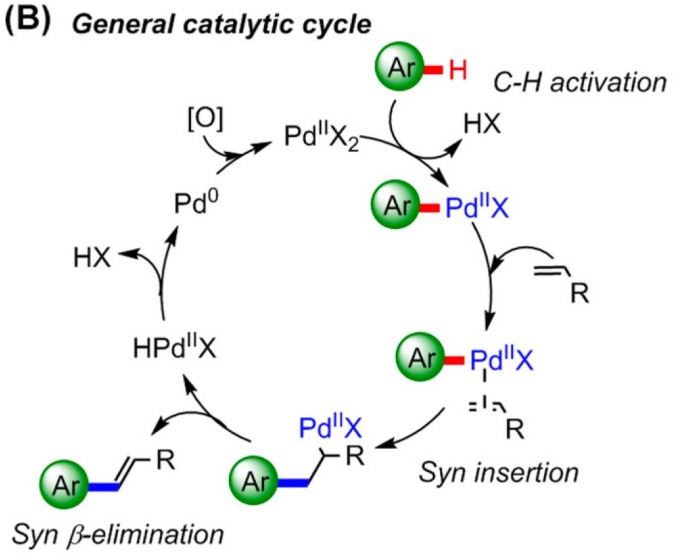


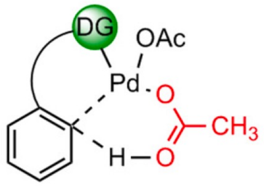
70-90%

\> Pd-catalyzed oxidative arene C-H alkenylation reactions, *Trends in Chemistry* 2022, *4*, 495

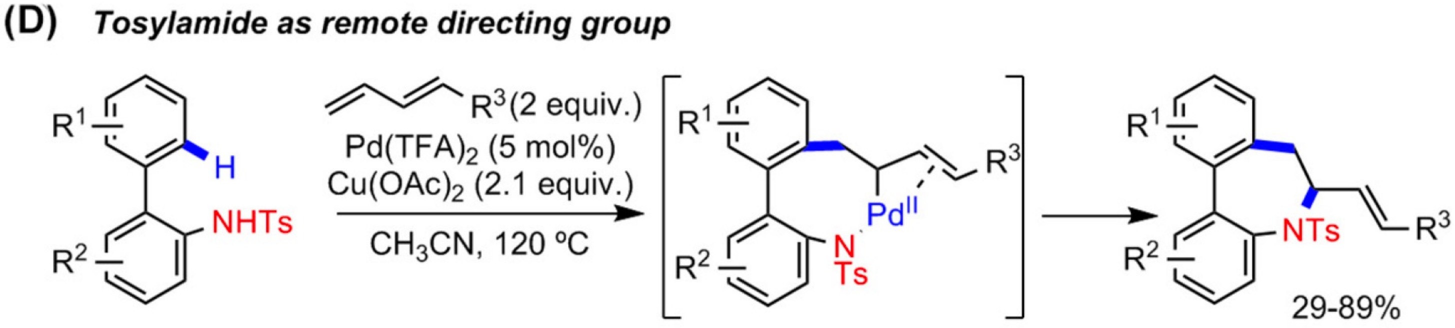
• The Fujiwara-Moritani reaction : *concerted metalated deprotonation*







(b)
$Pd(OAc)_2$
Directing group
No ligand



> Pd-catalyzed oxidative arene C-H alkenylation reactions, *Trends in Chemistry* **2022**, *4*, 495

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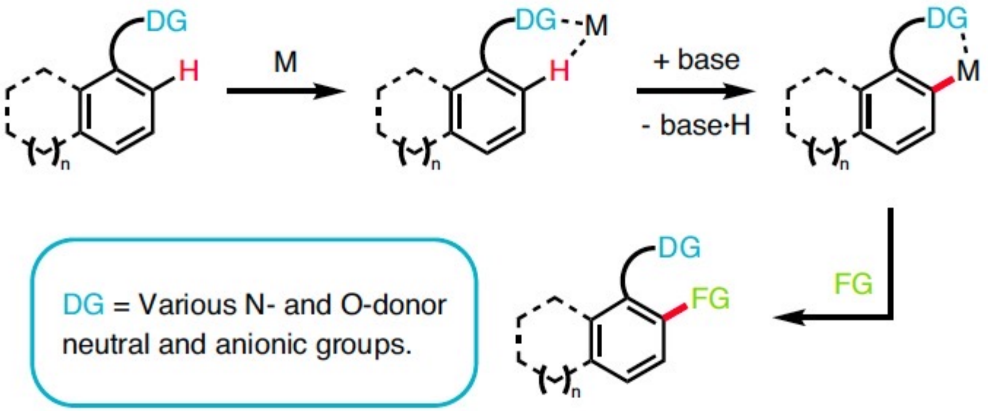
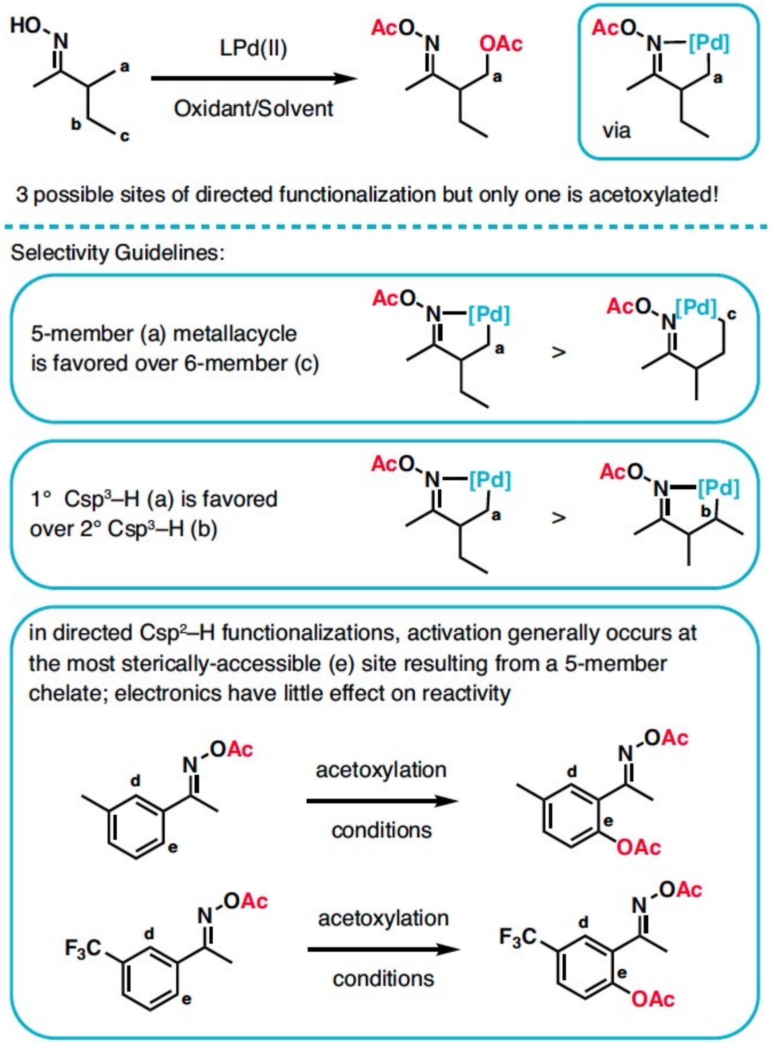
General strategy to control the site-selectivity in C-H Activation

> Temporary covalency can be achieved by **reversible coordination** between a **catalyst having a Lewis acidic metal center and substrate containing a Lewis basic FG**



DG = Various N- and O-donor neutral and anionic groups.

Figure 4. General Strategy for Directed C–H Functionalization



3 possible sites of directed functionalization but only one is acetoxylated!

Selectivity Guidelines:

5-member (a) metallacycle is favored over 6-member (c)

1° Csp^3–H (a) is favored over 2° Csp^3–H (b)

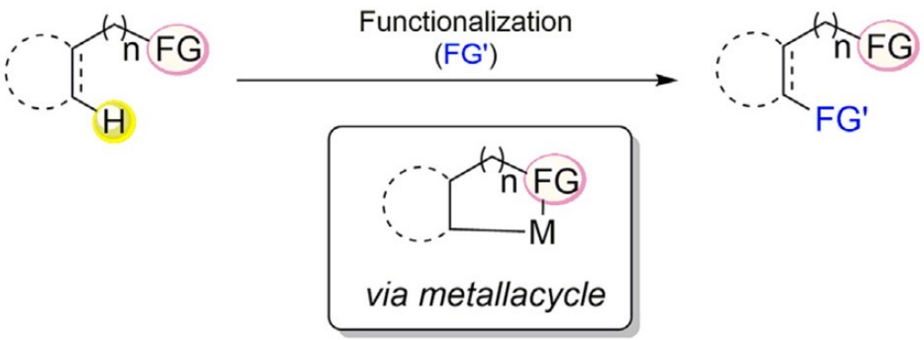
in directed Csp^2–H functionalizations, activation generally occurs at the most sterically-accessible (e) site resulting from a 5-member chelate; electronics have little effect on reactivity

Figure 6. Directed Organometallic C–H Functionalization Selectivity Demonstrated with Acetoxylation[1]

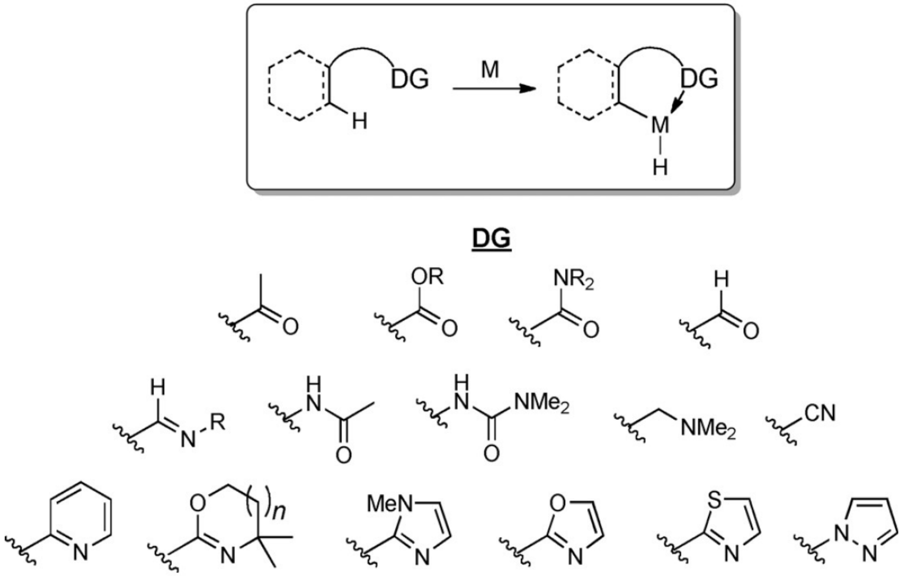
> N. Chatani *et al.*, **Strategic evolution in Metal-catalyzed directed C-H Bond Activation**, *Coord. Chem. Rev.* **2021**, *431*, 213683

- Nature of Directing groups for C-H Activation

> "Native" coordinating FG
(*already present in the molecule*)



> Mono-dentate DG



Some important chemical functions that act as a monodentate directing group.

> N. Chatani *et al.*, **Strategic evolution in Metal-catalyzed directed C-H Bond Activation**, *Coord. Chem. Rev.* **2021**, *431*, 213683

Mono-Dentate DG: Carbonyl derivatives

> Limitations

- Functional group directed monodentate C−H bond functionalization : arylation, vinylation, oxidation, etc. with many TM catalysts
- A large variety of catalytic reactions involving C(sp^2)-H bonds of arenes, heteroarenes, and alkenes have been developed

BUT

- Unexpected reactions occurred in some cases because of the weak coordination of a directing functional group to a metal.
- Directed functionalization of unactivated C(sp^3)-H bonds continues to be highly challenging

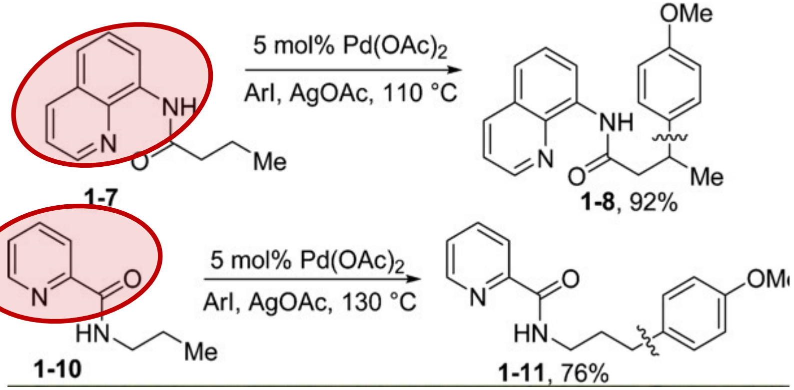
N,N-Bi-Dentate DGs

> Requirements for their design

- Cyclometalations are more facile if a stronger directing group is used or bidentate coordination of the metal is possible
- A removable directing group is required in order to increase the synthetic applicability of C−H bond functionalization reactions
- Since the arylations likely proceed through high-valent palladium complexes, an anionic auxiliary would help in stabilizing high-energy palladium(III) or -(IV) species

8-AMINOQUINOLINE

2-PICOLINAMIDE



> N. Chatani *et al.*, **Bidentate Directing Groups**, *Chem. Rev.* **2020**, *120*, 1788

- *N,N*-Bi-Dentate DGs

> 8-Aminoquinoline: functionalization of carboxylic acids

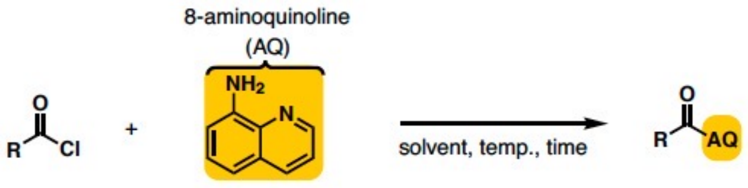
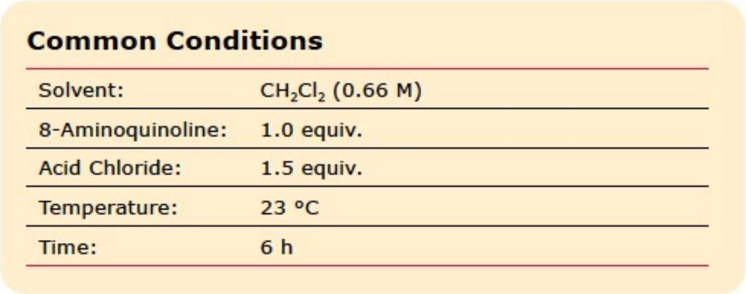
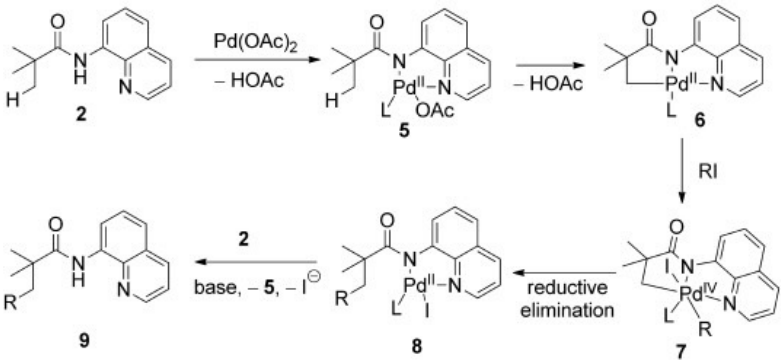


Figure 15. 8-Aminoquinoline Directing Group Installation



Common Conditions

Solvent:	CH_2Cl_2 (0.66 M)
8-Aminoquinoline:	1.0 equiv.
Acid Chloride:	1.5 equiv.
Temperature:	23 °C
Time:	6 h



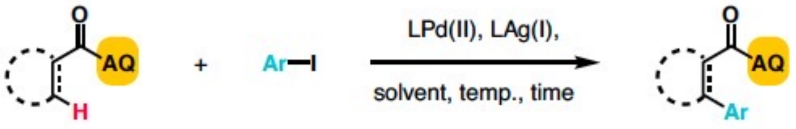
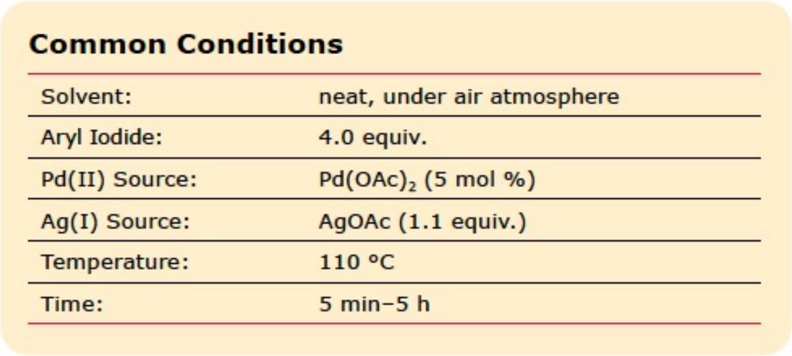


Figure 16. 8-Aminoquinoline as Directing Group in C–H Arylation



Common Conditions

Solvent:	neat, under air atmosphere
Aryl Iodide:	4.0 equiv.
Pd(II) Source:	$Pd(OAc)_2$ (5 mol %)
Ag(I) Source:	AgOAc (1.1 equiv.)
Temperature:	110 °C
Time:	5 min–5 h

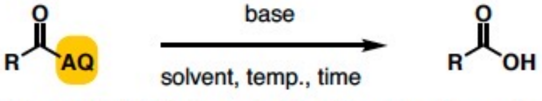
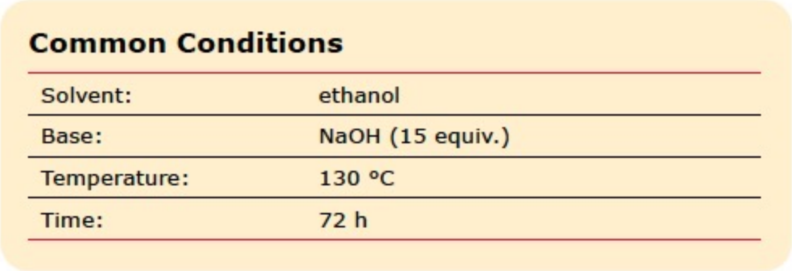


Figure 17. 8-Aminoquinoline Directing Group Removal



Common Conditions

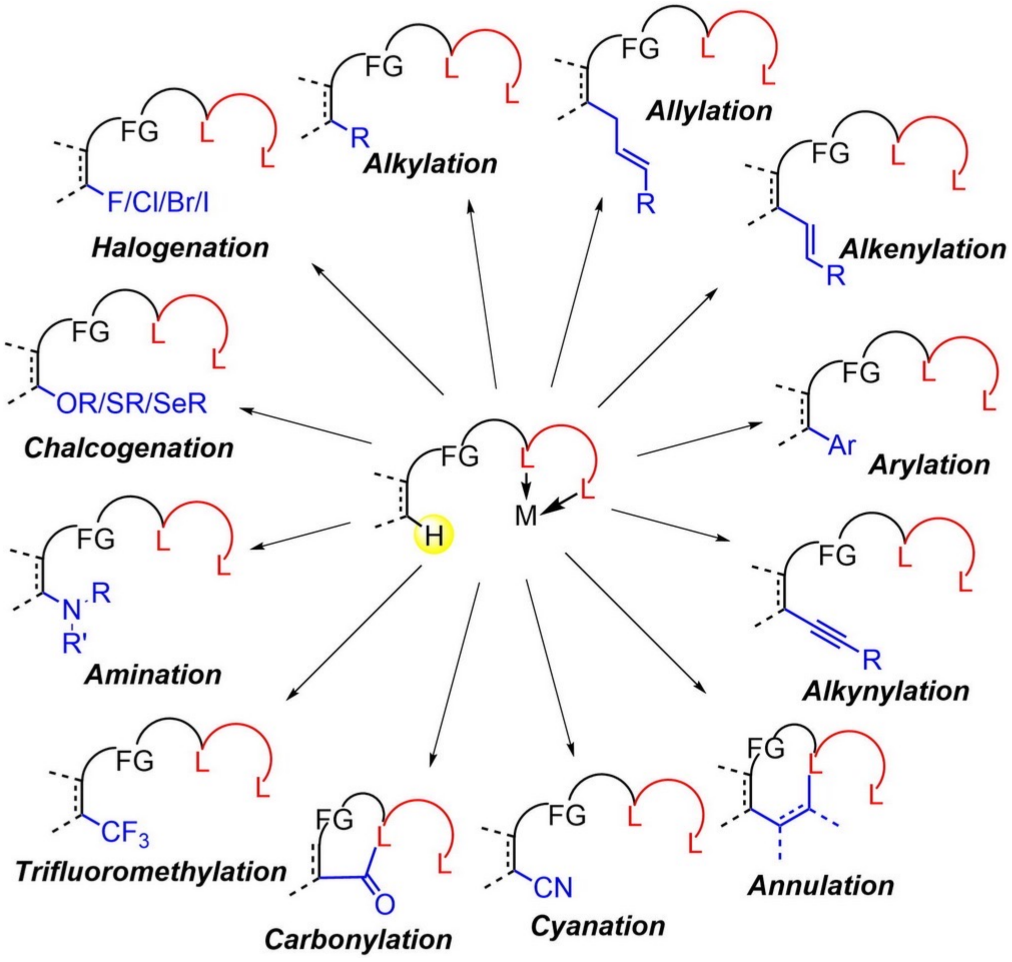
Solvent:	ethanol
Base:	NaOH (15 equiv.)
Temperature:	130 °C
Time:	72 h

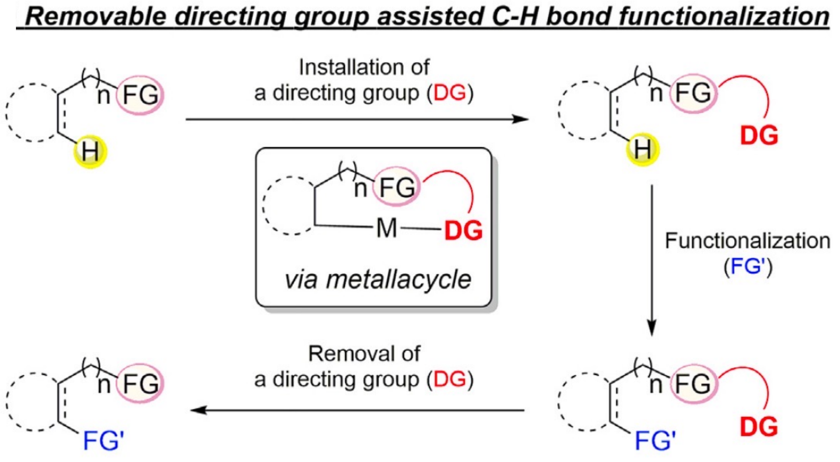
> N. Chatani *et al.*, **Bidentate Directing Groups**, *Chem. Rev.* **2020**, *120*, 1788

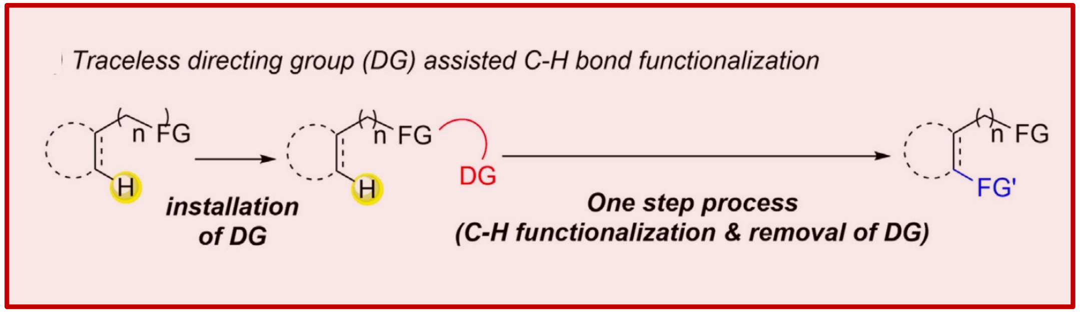
- *N,N*-Bi-Dentate DGs

> A rich chemistry

> BUT not really step-economical




Removable directing group assisted C-H bond functionalization


Traceless directing group (DG) assisted C-H bond functionalization

> N. Chatani *et al.*, **Strategic evolution in Metal-catalyzed directed C-H Bond Activation**, *Coord. Chem. Rev.* **2021**, *431*, 213683

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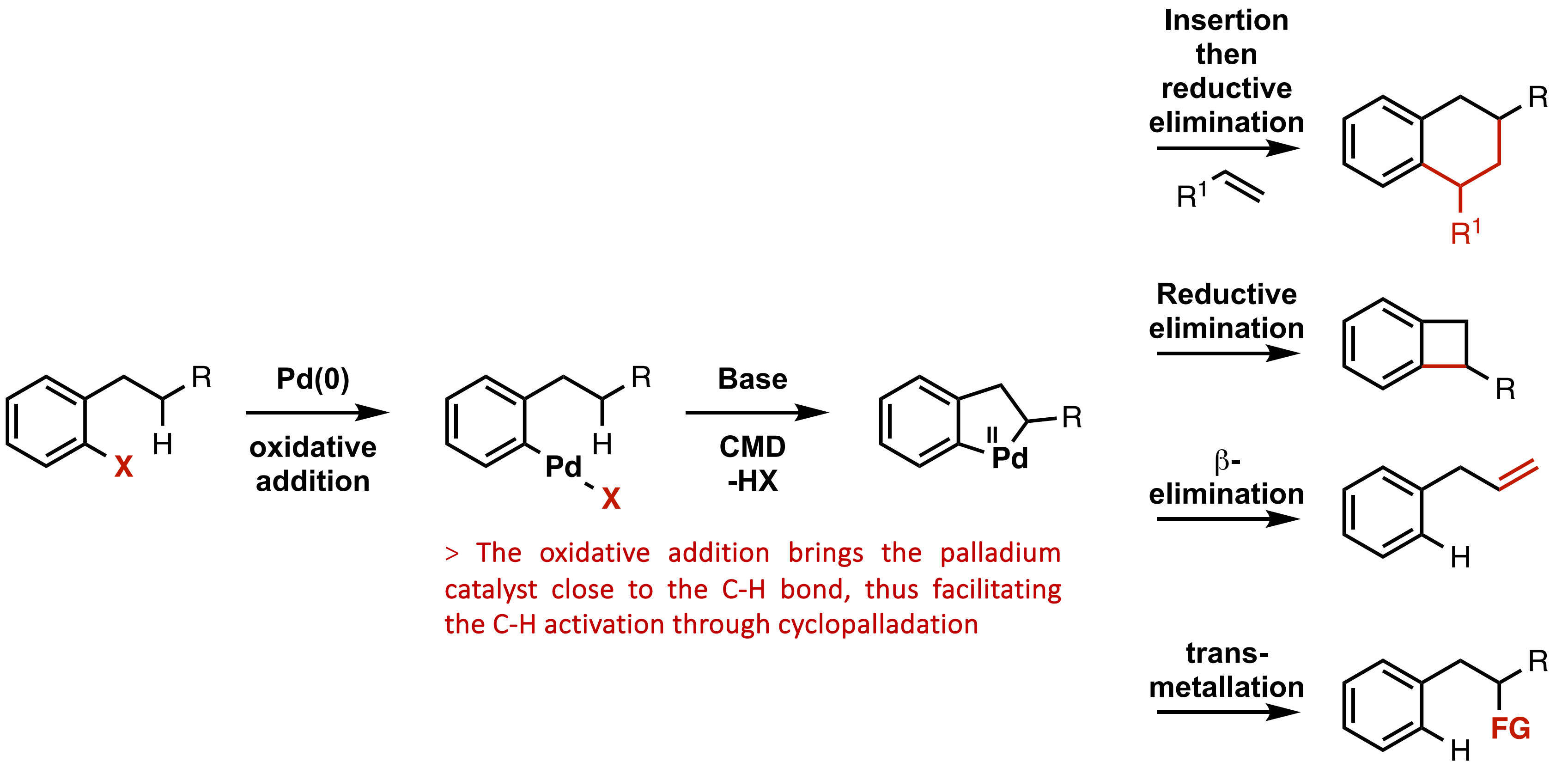
• What about aryl/vinyl halides as DG

> The **oxidative addition of a C-X bond** to a transition-metal complex gives rise to an **organometallic intermediate** that can behave similarly to the previous coordination complexes and, therefore, undergo intramolecular CH activation in the same way, generally via a base-mediated proton abstraction



> The oxidative addition brings the palladium catalyst close to the C-H bond, thus facilitating the C-H activation through cyclopalladation

> The Halogen can be considered as a traceless DG

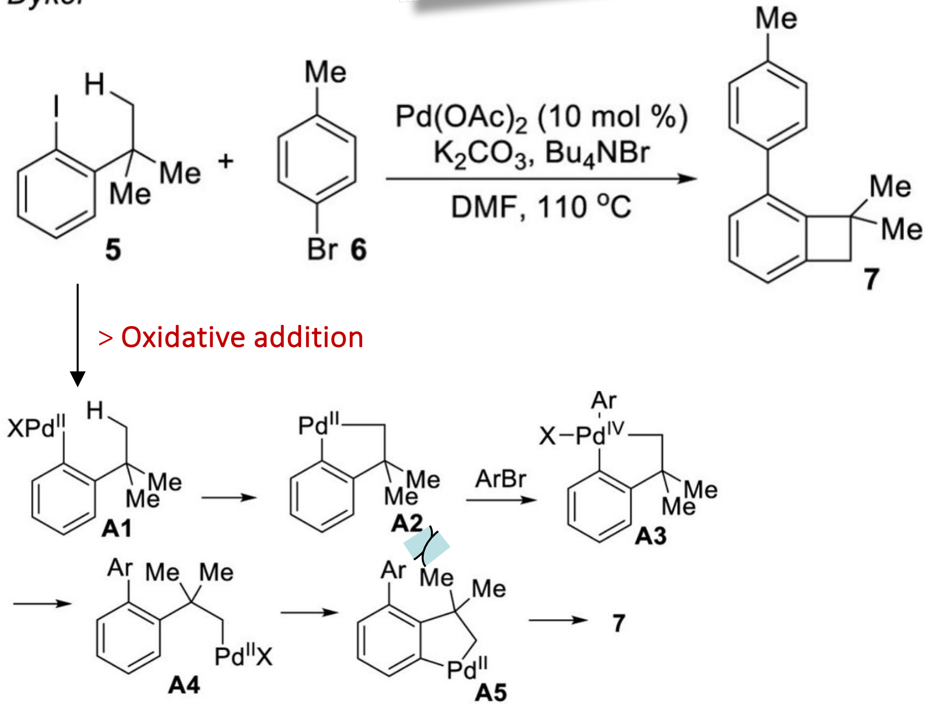
> O. Baudoin *et al.*, Functionalization of organic molecules by TM-catalyzed C(sp^3)-H activation, *Chem. Eur. J.* **2010**, *16*, 2654

- Aryl halides as DG

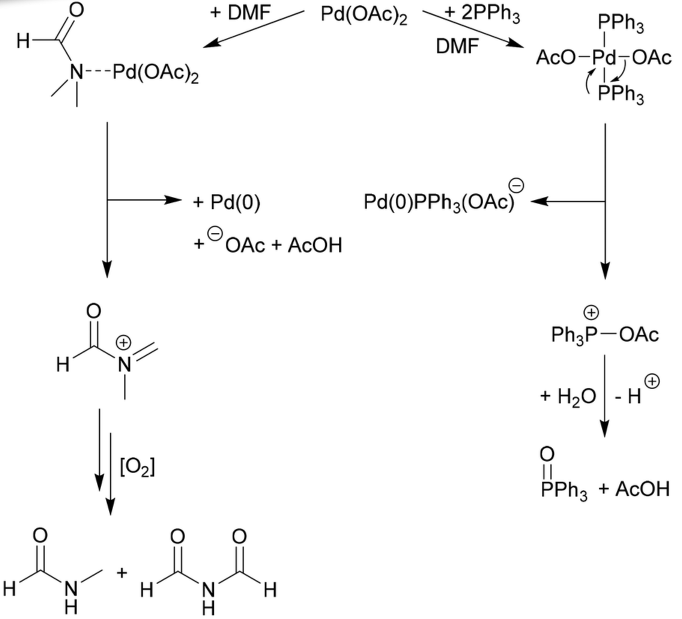
> Historical background

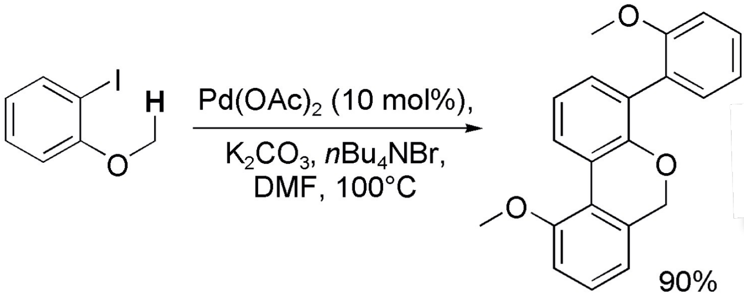
- *Dyker*

Which mechanism for the C-H activation step?



How a Pd(II) complex can be engaged in an initial step of oxidative addition?





How can you explain the formation of this polycycle?

> O. Baudoin *et al.*, Functionalization of organic molecules by TM-catalyzed C(sp^3)-H activation, *Chem. Eur. J.* 2010, *16*, 2654

Réactions de fonctionnalisation C-H et chimie médicinale

- Introduction
  1. Catalytic C-H Functionalization Reactions vs. Functional Group Transformations
  2. Catalytic C-H Functionalization Reactions: challenges & general mechanisms

- Catalytic C-H Functionalization by C-H Activation (*inner-sphere mechanism*)
  1. Mechanistic considerations
  2. Heteroatom-directed C-H Functionalization
  3. Oxidative addition-directed C-H Functionalization

- Catalytic C-H Functionalization by C-H Insertion (*outer-sphere mechanism*)
  1. Mechanistic considerations
  2. Carbene chemistry
  3. Nitrene chemistry
  4. C-H oxidation

- Catalytic C-H Functionalization using radicals
  1. Historical reactions and mechanistic considerations
  2. Hydrogen Atom Transfer (HAT)
  3. Minisci-type Reaction

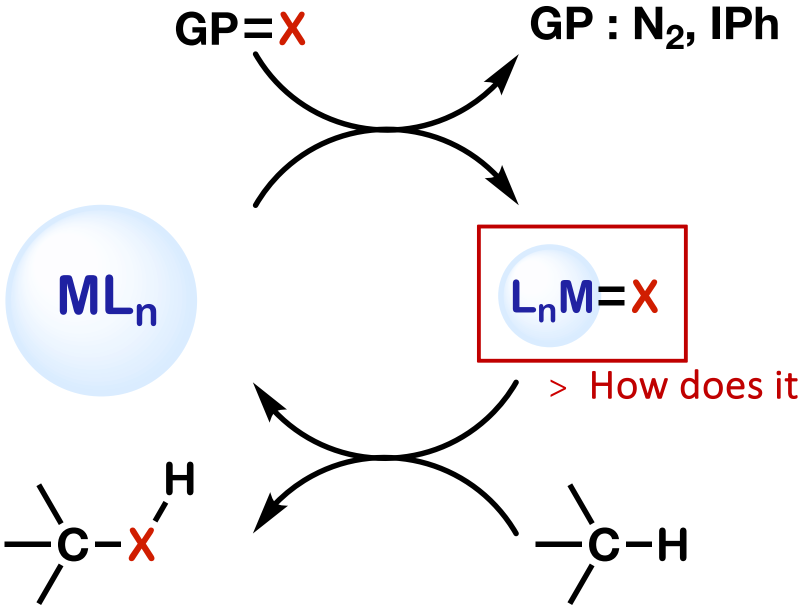
- Application of catalytic C-H functionalization
  Total synthesis & Late-stage functionalization of natural products and drugs

- The elementary step of C-H Insertion

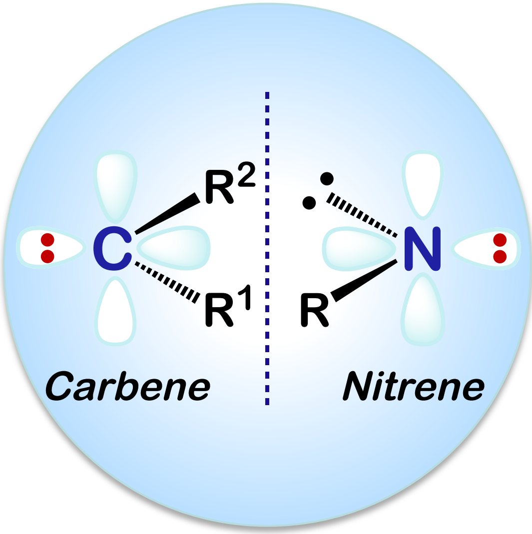
C-H Insertion

"Outer-Sphere" mechanism

> 1st step: *An electrophilic TM promotes the irreversible extrusion of a leaving group to generate a **M=X** species*



> How does it react?

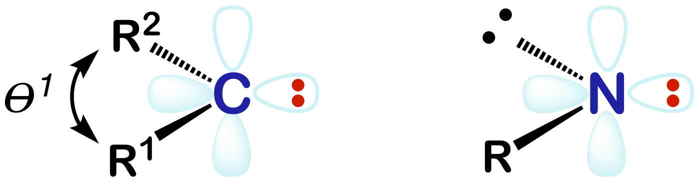


> 2nd step: *Metal mediated insertion of **X** into a C-H bond*

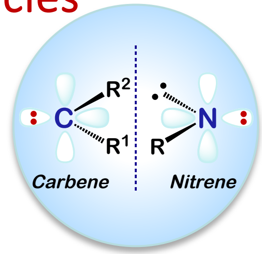
> H. M. L. Davies *et al.*, Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion, *Nature* **2008**, *451*, 417

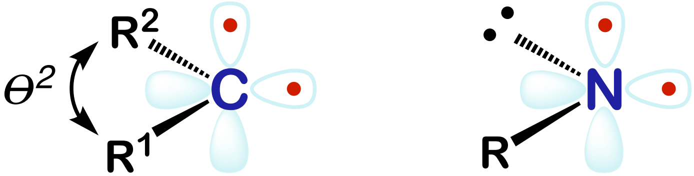
• General background on carbene/nitrene species

> Electronic configuration



Singlet state **Singlet state**



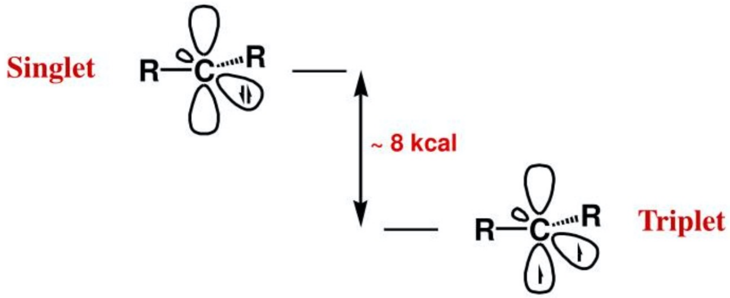


Triplet state **Triplet state**

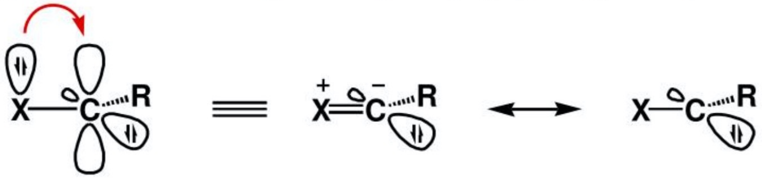
> unshared electron pair (σ orbital) and empty p orbital
> Ambiphilic: paired electrons = Nu : empty orbital = E
> *many R & R' groups can stabilize singlet carbene (more than triplet carbene).*
> *Typical angle* θ^1 *(calculated) : 100-110 °*

> 2 electron shared with p orbital and σ orbital
> resembles biradical
> *Typical angle* θ^2 *(calculated) : 130-150 °*

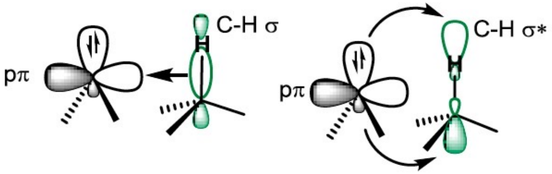
- **Triplet more stable than singlet (R=H, alkyl)**



- **Unless, added stabilization possible (X=O, N, S, halogen etc.)**

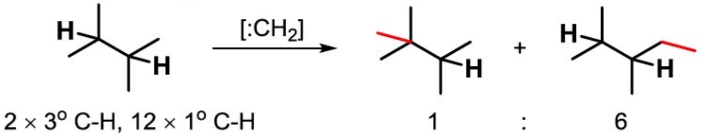


b. For a free carbene interacting with a C-H bond:



The frontier orbitals of carbene carbon center and the C-H bond were both 2p or 2p-hybridized orbitals, which matched perfectly with each other at energy level. Besides, their frontier orbitals were also symetrically matched, offering them possibility to get a very good overlap.

Free carbenes: **great** reactivity but **poor** selectivity.



> H. M. L. Davies *et al.*, Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion, *Nature* 2008, *451*, 417

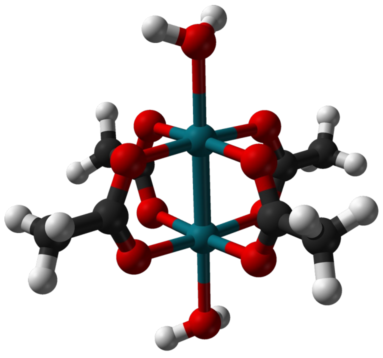
General background on METAL-carbene/nitrene species

> Dirhodium(II)-Carbene/Nitrene complexes

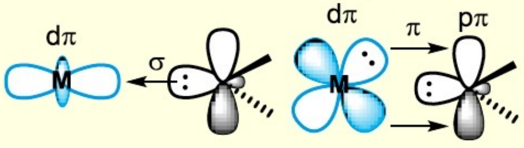
Based on their unique molecular and electronic structure, Rh(II) dimers have proven the most effective for catalysis of C-H insertion reactions

Rhodium complexes are Lewis acidic and bind additional ligands at **two open axial sites**. Binding of a second ligand after addition of a first to an axial site is less favorable and **catalysis is thought to occur only at a single Rh center**. The second Rh center acts as an electron reservoir.

> … with two molecules of water bound to the apical positions

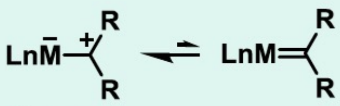


Fischer carbene complex



- Formed by a singlet free carbene and a late TM with a low oxidation state (a low energy d orbital).
- Electrophilic carbene

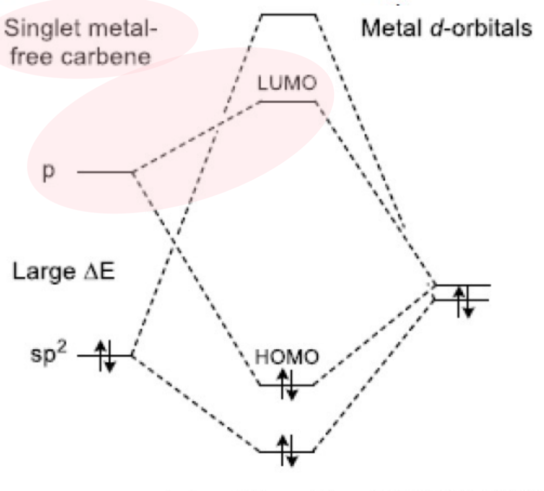
Fischer carbene complex



favored

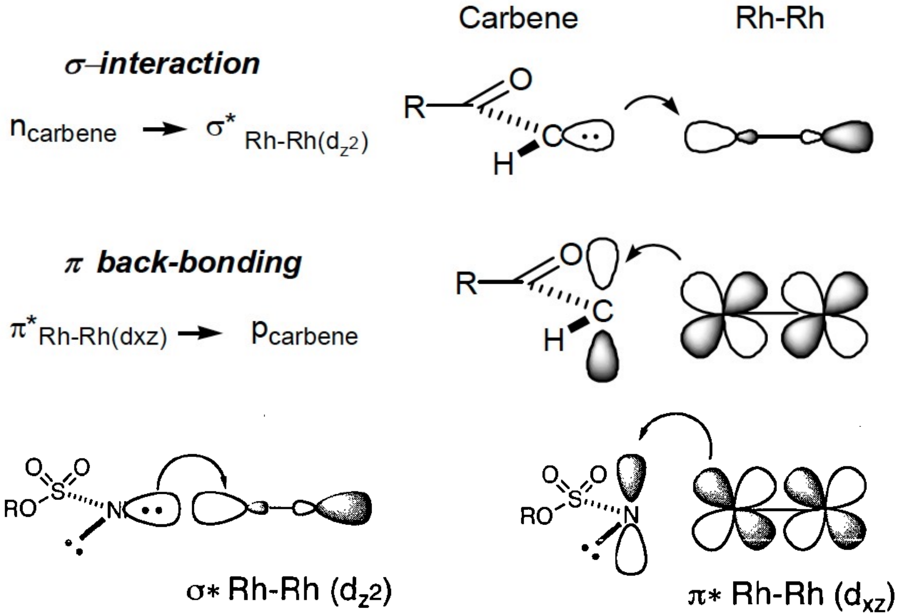
$\Delta E \approx 8 - 10$ kcal/mol

In Fischer carbene, LUMO is closer in energy to carbene, so the carbon center of the carbene is more electrophilic than the metal.



J. Am. Chem. Soc. **1984**, *106*, 1576

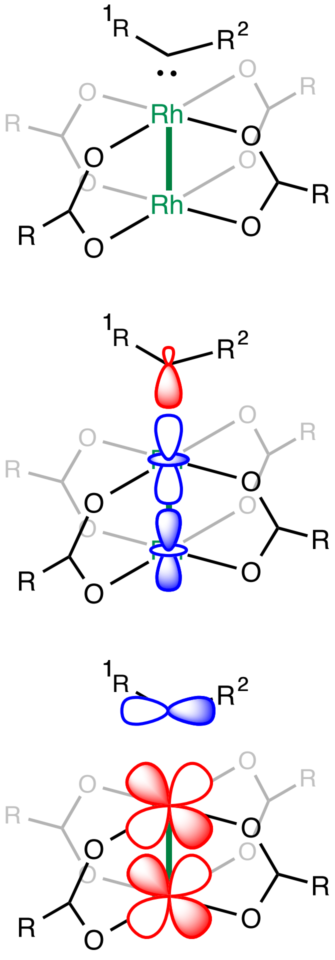
Diazo Decomposition:

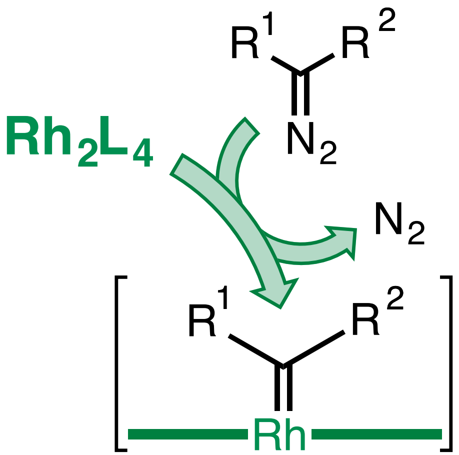


> H. M. L. Davies *et al.*, Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion, *Nature* **2008**, *451*, 417

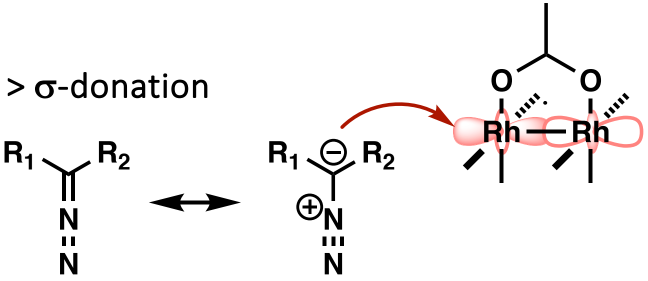
General background on METAL-carbene/nitrene species

> Mechanism of Rhodium(II)-catalyzed C-H insertion

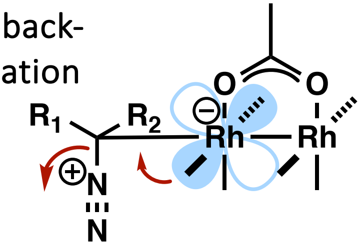


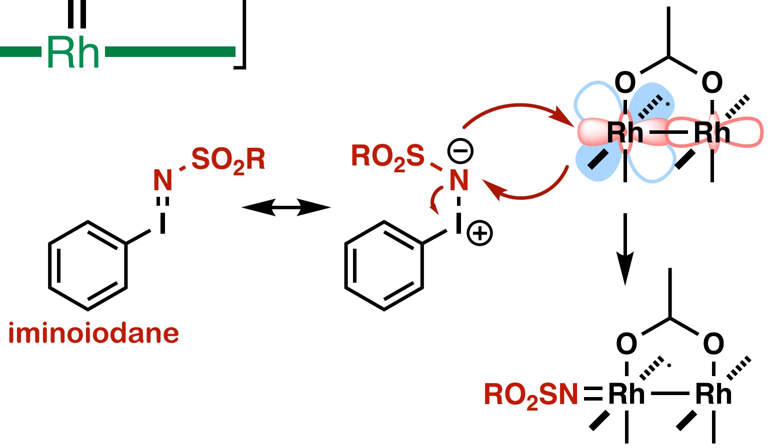


> σ-donation



> π-back-donation



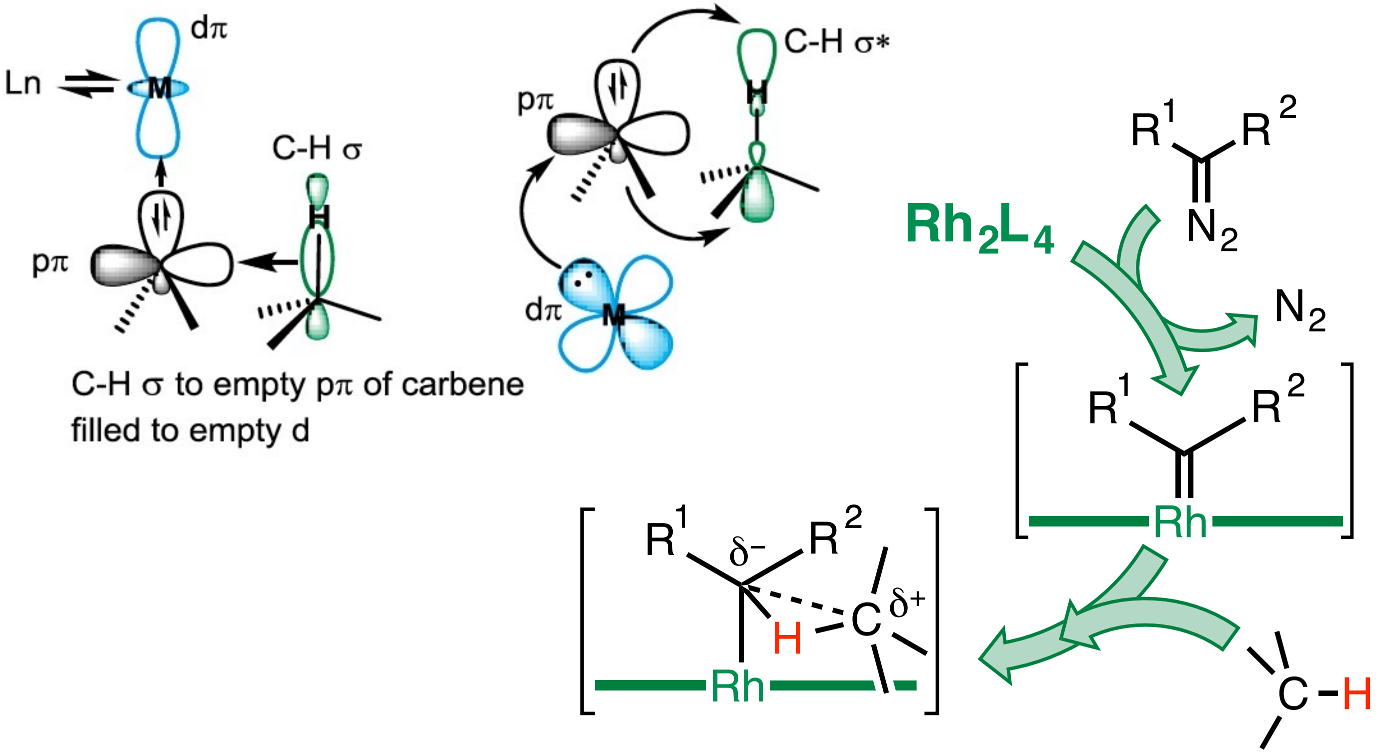


> H. M. L. Davies *et al.*, Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion, *Nature* 2008, *451*, 417

• General background on METAL-carbene/nitrene species

> Mechanism of Rhodium(II)-catalyzed C-H insertion

For a TM carbene interacting with a C-H bond:



C-H σ to empty pπ of carbene
filled to empty d

> Concerted
3-centers 2-electrons
Transition State

> H. M. L. Davies *et al.*, Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion, *Nature* 2008, *451*, 417

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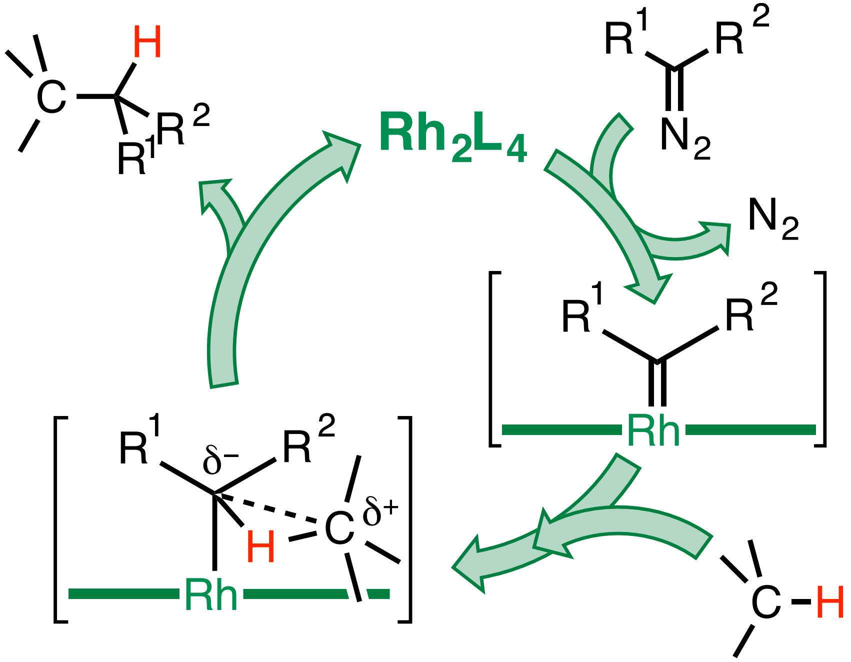
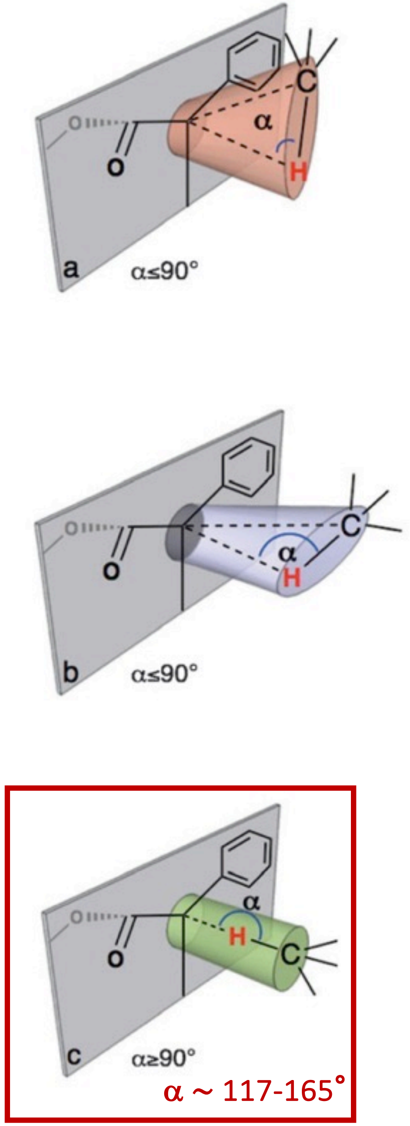
> Mechanism of Rhodium(II)-catalyzed C-H insertion



> Concerted Asynchronous Transition State



α ~ 117-165°

Shown here is a scheme that shows the 3 possible conformations of the key step in this reaction, **the approach of the substrate to the carbenoid**. Computational chemistry has been used to deduce the angle of attack. Based on the significant **hydride character** shown in the calculations **transition state C was found to be the most favorable**.

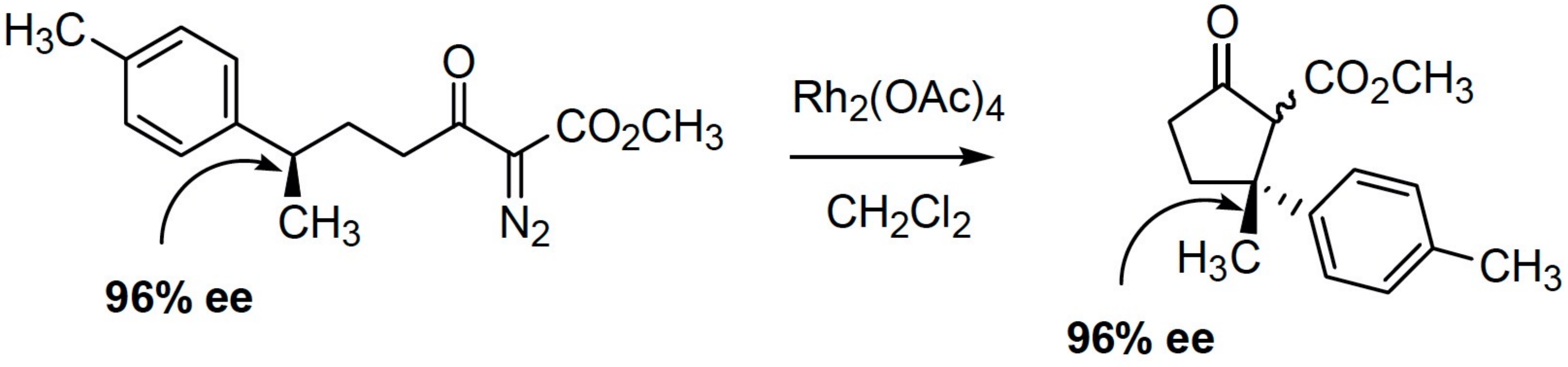
> H. M. L. Davies *et al.*, Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion, *Nature* 2008, *451*, 417

- General background on METAL-carbene/nitrene species

> Mechanism of Rhodium(II)-catalyzed C-H insertion: concerted pathway and test experiments

> Stereochemical probe

Evidence for a singlet carbenoid species: 3-centered, 2-electron transition state.
C-H Insertion is **Stereospecific**



Taber *J. Am. Chem. Soc*, **1985,** *107*, 196

> H. M. L. Davies *et al.*, Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion, *Nature* 2008, *451*, 417

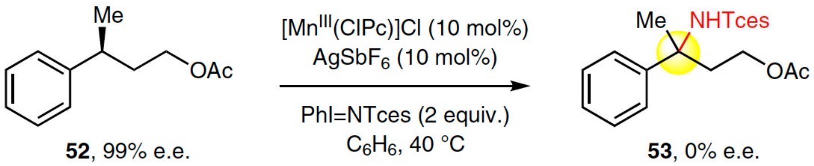
- Catalytic C-H Functionalization by C-H Insertion

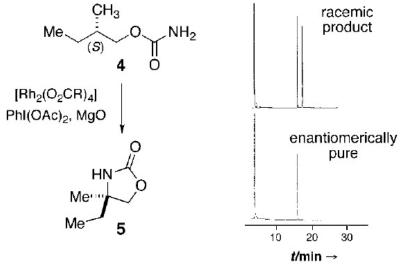
1. Mechanistic considerations

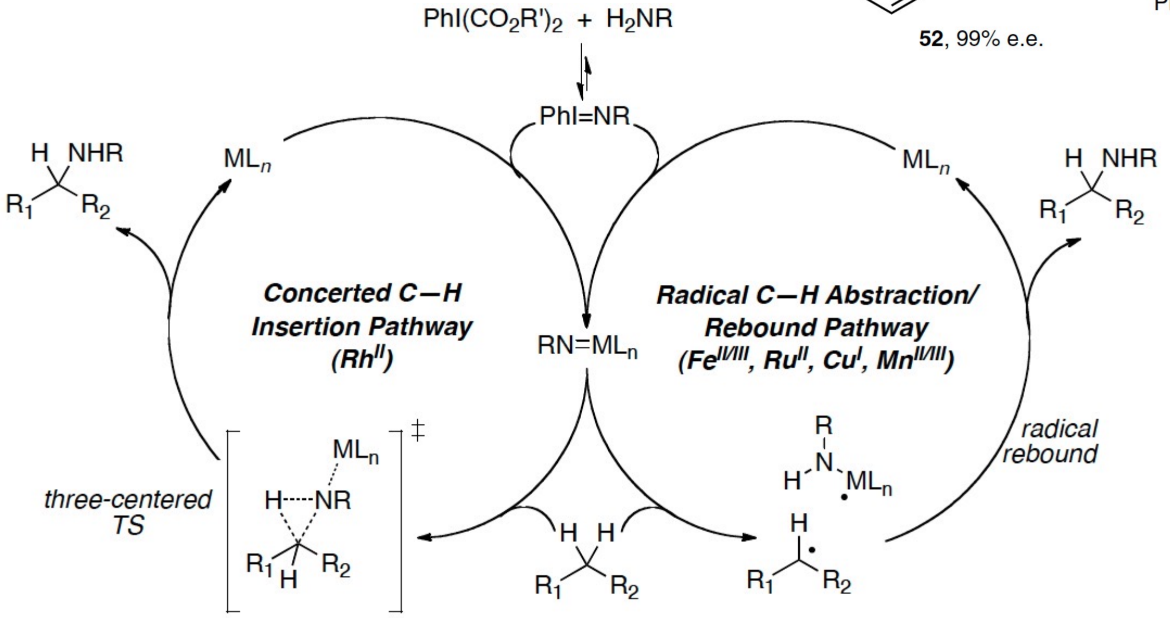
• General background on METAL-carbene/nitrene species

> Mechanism of Rhodium(II)-catalyzed C-H insertion of nitrene

> A more complicated picture







Concerted asynchronous insertion:
-examples: Rh
-turnover-limiting step is normally formation of iminoiodane
-three-centered transition state
-reactivity trends are dictated by the electron density of the reacting site (e.g. more electron-rich C-H bonds, such as 3°, are more reactive)

Radical C-H abstraction/rebound:
-examples: Fe, Mn, Cu, Ru, Ag, Co
-turnover-limiting step is normally C-H abstraction
-carbon-centered radical intermediate; lifetime of intermediate can be tuned by changing metal and ligand environment around metal center
-reactivity trends are dictated by the BDE of the reacting site (lower BDE = more reactive)

> H. M. L. Davies *et al.*, Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion, *Nature* 2008, *451*, 417

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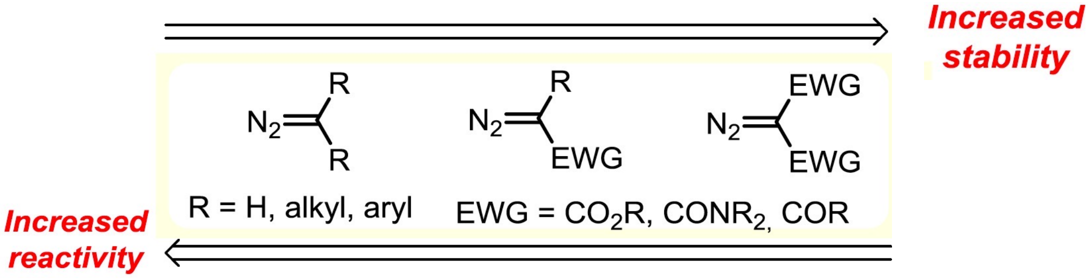
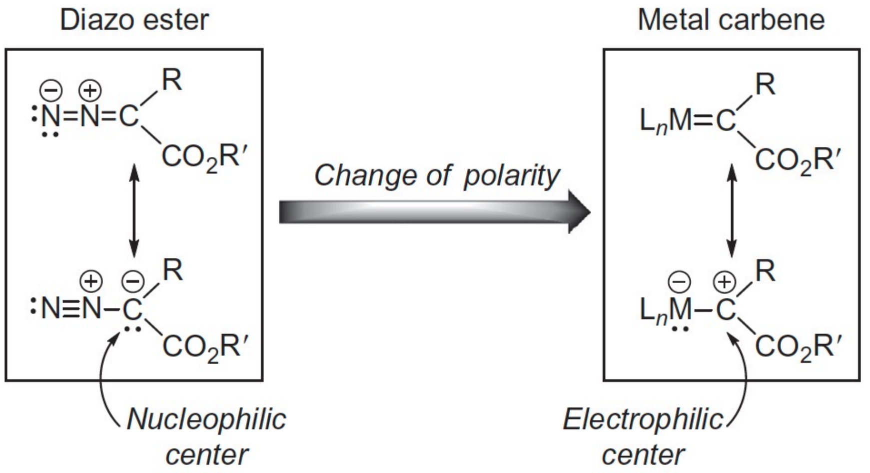
  - *Total synthesis & Late-stage functionalization of natural products and drugs*

General trends in catalytic carbene C-H insertion

> Diazo *vs.* Carbene





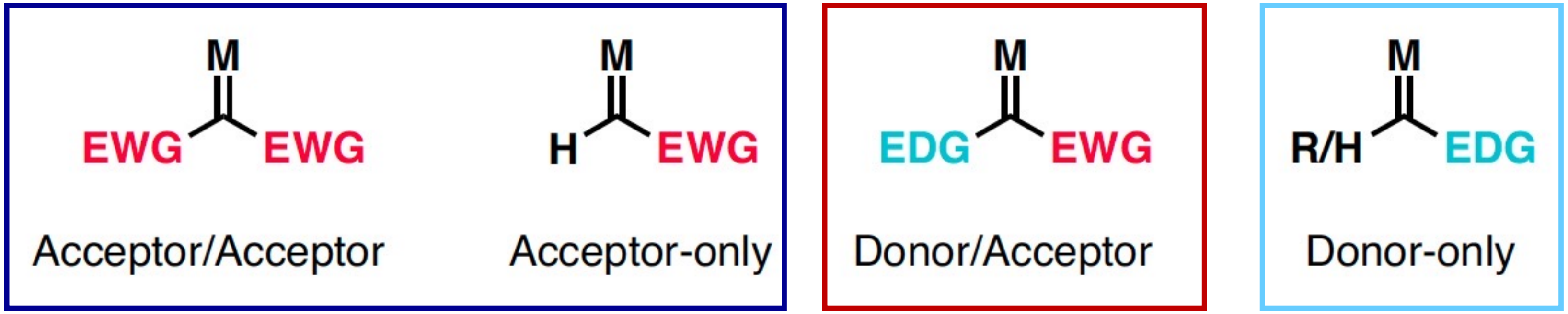
> A COMPLETE REVERSAL IN THE REACTIVITY SCALE!!!

EWG = CO_2R, COR, $CONR_2$, CN, $PO(OR)_2$, CF_3
EDG = vinyl, aryl, heteroaryl
M = Pd, Rh, Ru, Cu, Ag, Fe, *etc*

> HML Davies, **Guiding principles for intermolecular C-H functionalization with rhodium carbenes**, *Chem. Soc. Rev.* **2011**, *40*, 1857

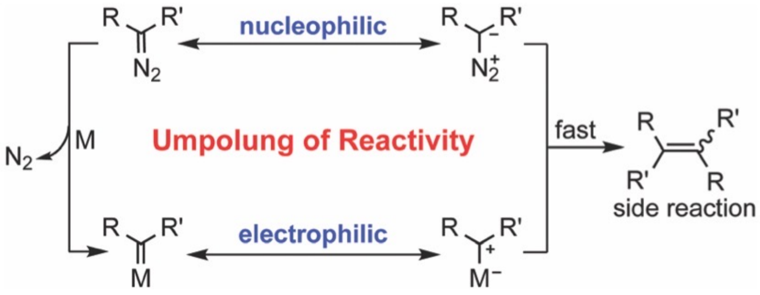
General trends in catalytic carbene C-H insertion

> Reactivity of metal-carbenes



> Suitable for intramolecular reactions

Issue in intermolecular processes: dimerization



Scheme 2 Homo-dimerization of diazo precursors.

> Suitable for intermolecular reactions

The donor group has a stabilizing effect, reducing the electrophilicity of the carbene. Its lifetime is increased, thus the selectivity is improved

> The starting diazos are often unstable

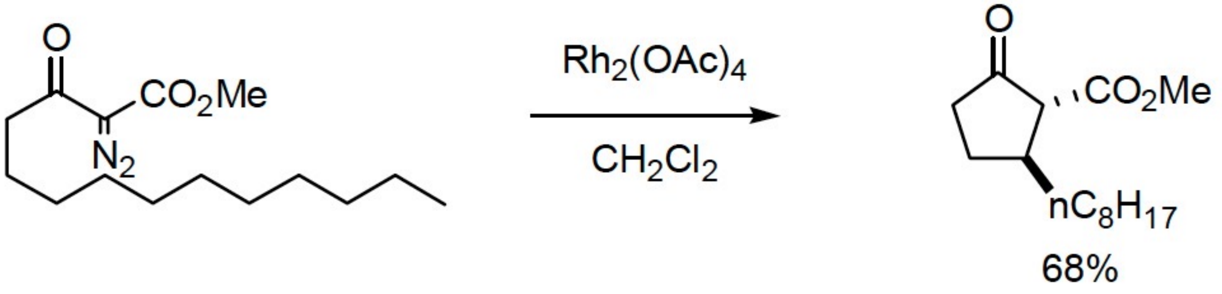
Recent studies have demonstrated their utility in intramolecular reactions

> HML Davies, **Guiding principles for intermolecular C-H functionalization with rhodium carbenes**, *Chem. Soc. Rev.* **2011**, *40*, 1857

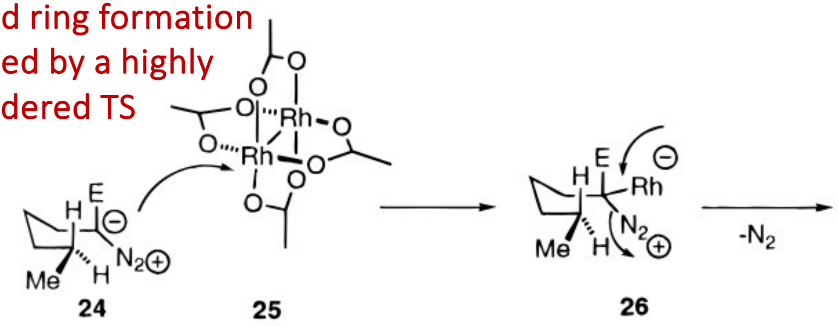
General trends in catalytic carbene C-H insertion

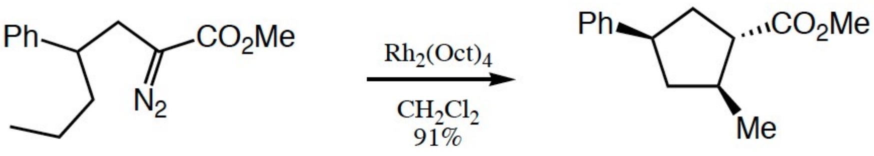
> Site-selectivity (*or regioselectivity*) issue: substrate parameters

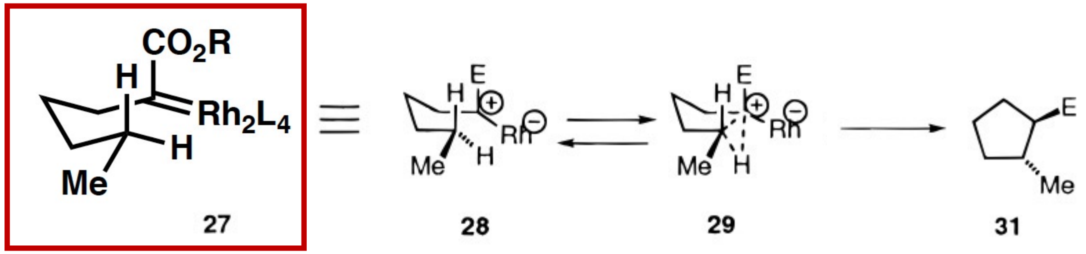
- intramolecular C-H insertion > intermolecular C-H insertion
- 5-membered ring formation > other size ring formation

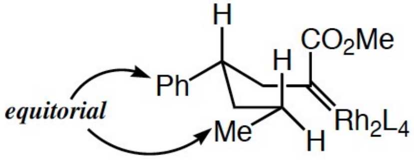


> High selectivity for 5-membered ring formation explained by a highly ordered TS









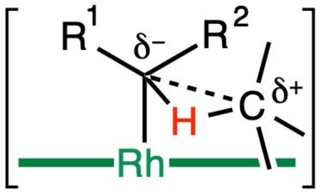
> HML Davies, **Guiding principles for intermolecular C-H functionalization with rhodium carbenes**, *Chem. Soc. Rev.* **2011**, *40*, 1857

- General trends in catalytic carbene C-H insertion

> Site-selectivity (*or regioselectivity*) issue: substrate parameters

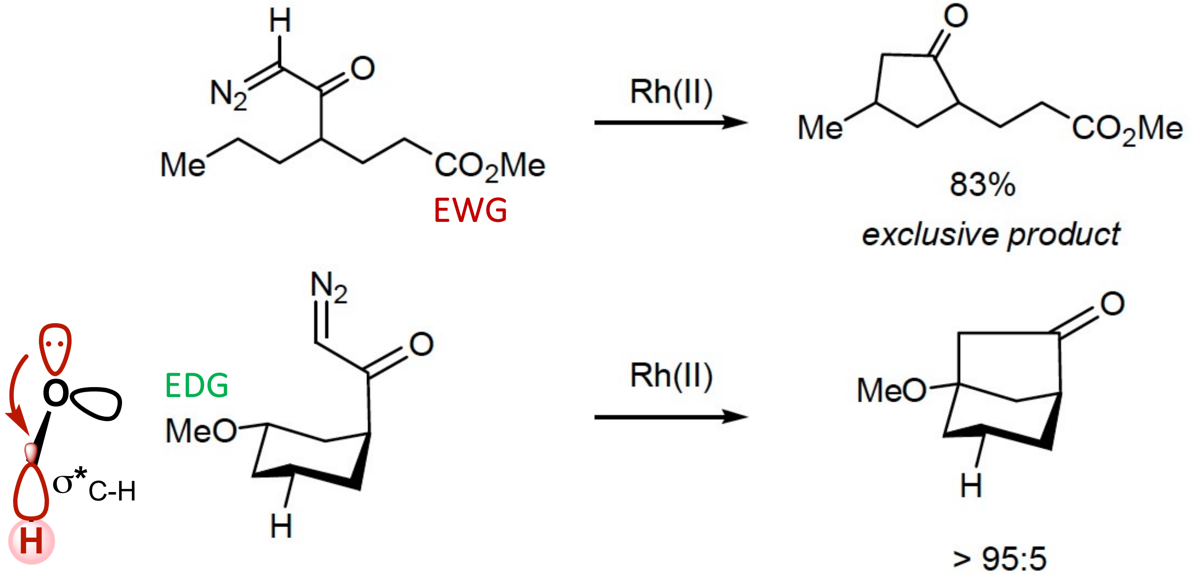
> The selectivity is controlled by a combination of STERIC and ELECTRONIC factors

> Going back to the mechanism: reactions will be favored at sites that stabilize the build-up of positive charge



EDG > Stabilizing effect

EWG > Destabilizing effect



Stork *Tet. Lett.* **1988**, *29*, 2283

> HML Davies, **Guiding principles for intermolecular C-H functionalization with rhodium carbenes**, *Chem. Soc. Rev.* **2011**, *40*, 1857

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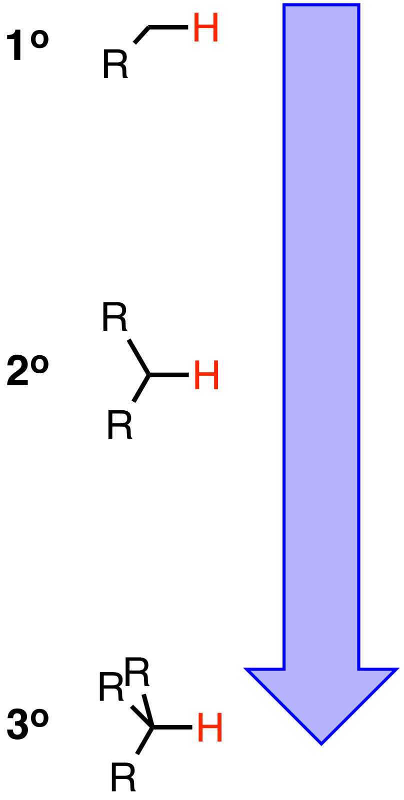
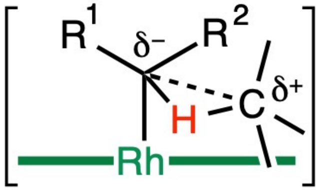
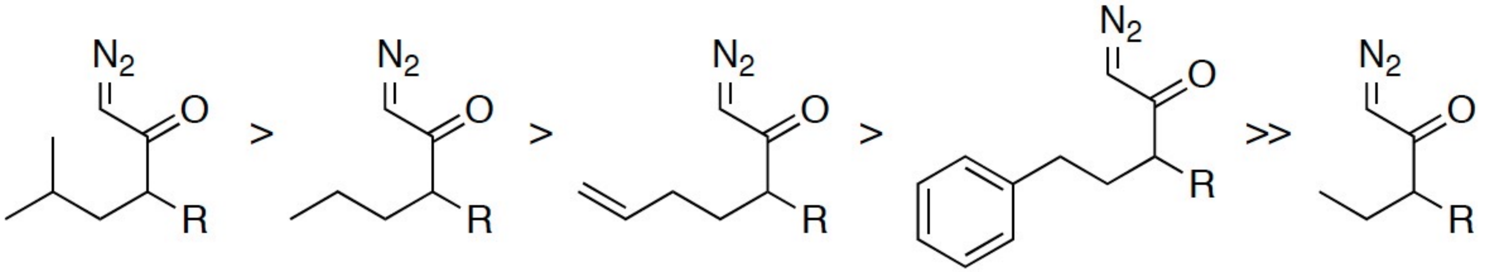
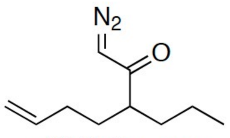
Reactivity due to Electronic Factors







Taber, *JACS* **1986**, *108*, 7686.



2°/allylic = 3:1

Unusual result:
researchers since have found that allylic and benzylic C-H bonds are actually highly reactive

> HML Davies, **Guiding principles for intermolecular C-H functionalization with rhodium carbenes**, *Chem. Soc. Rev.* **2011**, *40*, 1857

• General trends in catalytic carbene C-H insertion

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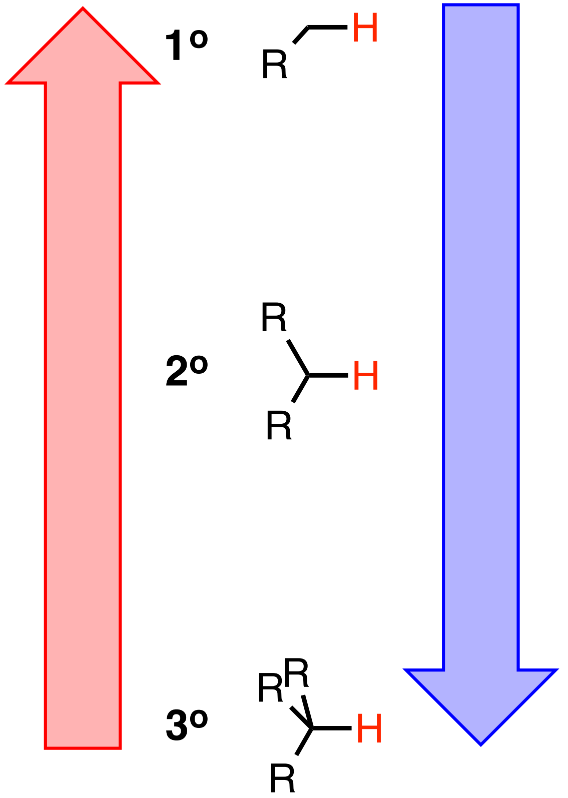
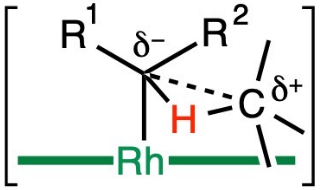
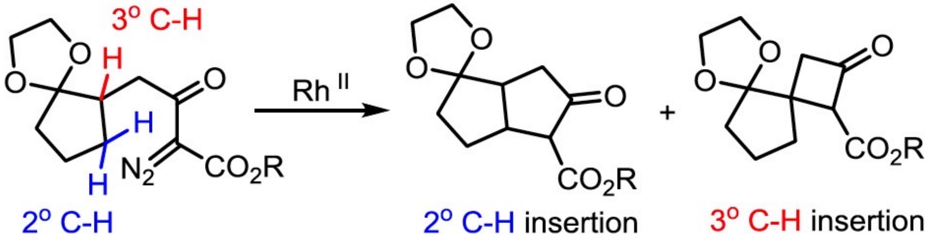


Reactivity due to Electronic Factors

Reactivity due to Steric Factors





Note:
acam: acetamide
TPA: triphenylacetate
Piv: pivalate ${}^tBu_3CO_2H$
BzO: benzoic acid
TPA: $OCOCPh_3$

Catalyst	**Ratio.**
$[Rh_2(OAc)_4]$	37 : 63
$[Rh_2(TFA)_4]$	56 : 44
$[Rh_2(acam)_4]$	14 : 86
$[Rh_2(Piv)_4]$	37 : 63
$[Rh_2(OBz)_4]$	54 : 46
$[Rh_2(OCOCHPh_2)_4]$	64 : 36
$[Rh_2(OCOCMePh_2)_4]$	82 : 18
$[Rh_2(TPA)_4]$	96 : 4

↓ bulkier

↓ less hindered C-H favored

Angew. Chem. Int. Ed. **1994**, *33*, 1797

> HML Davies, **Guiding principles for intermolecular C-H functionalization with rhodium carbenes**, *Chem. Soc. Rev.* **2011**, *40*, 1857

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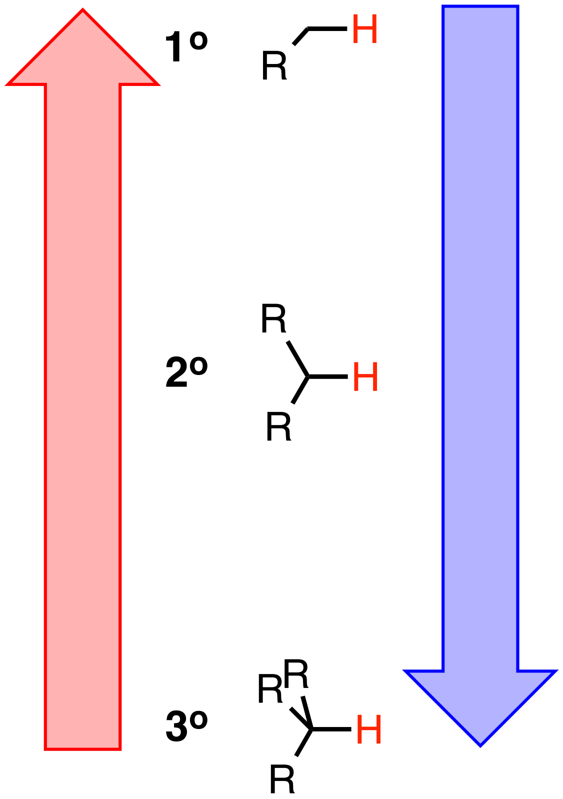
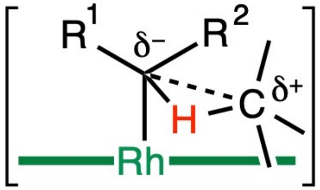
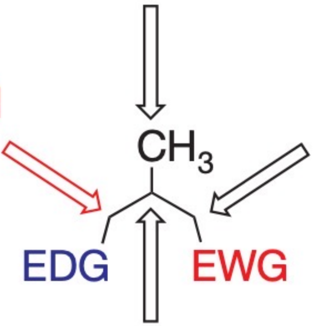


Reactivity due to Steric Factors





1° C–H sterically favoured
electronically disfavoured

2° C–H sterically favoured
electronically favoured

2° C–H sterically favoured
electronically disfavoured

3° C–H sterically disfavoured
electronically favoured

> HML Davies, **Guiding principles for intermolecular C-H functionalization with rhodium carbenes**, *Chem. Soc. Rev.* **2011**, *40*, 1857

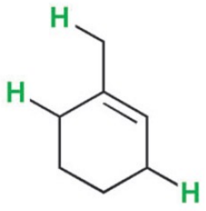
General trends in catalytic carbene C-H insertion

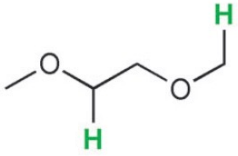
> Site-selectivity (*or regioselectivity*) issue: substrate parameters

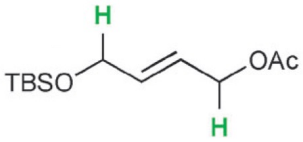
> The selectivity is controlled by a combination of STERIC and ELECTRONIC factors

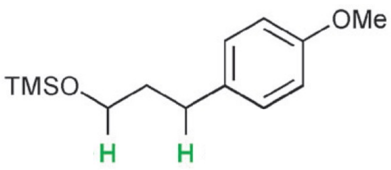
Can you predict then rationalize the site-selectivity in these examples?

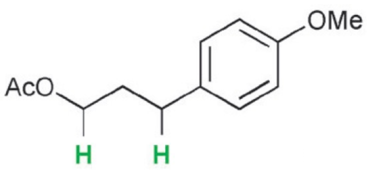
> INTERMOLECULAR Carbene C-H Insertions











> HML Davies, **Guiding principles for intermolecular C-H functionalization with rhodium carbenes**, *Chem. Soc. Rev.* **2011**, *40*, 1857

Réactions de fonctionnalisation C-H et chimie médicinale

- Introduction
  1. Catalytic C-H Functionalization Reactions vs. Functional Group Transformations
  2. Catalytic C-H Functionalization Reactions: challenges & general mechanisms

- Catalytic C-H Functionalization by C-H Activation (*inner-sphere mechanism*)
  1. Mechanistic considerations
  2. Heteroatom-directed C-H Functionalization
  3. Oxidative addition-directed C-H Functionalization

- Catalytic C-H Functionalization by C-H Insertion (*outer-sphere mechanism*)
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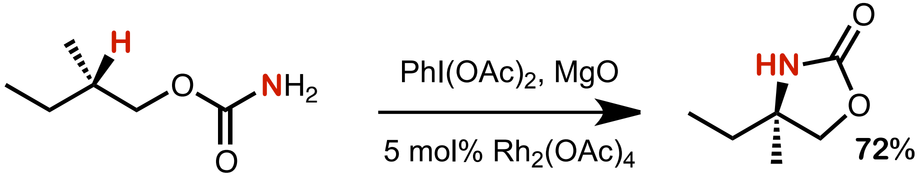
  2. Carbene chemistry
  3. Nitrene chemistry
  4. C-H oxidation

- Catalytic C-H Functionalization using radicals
  1. Historical reactions and mechanistic considerations
  2. Hydrogen Atom Transfer (HAT)
  3. Minisci-type Reaction

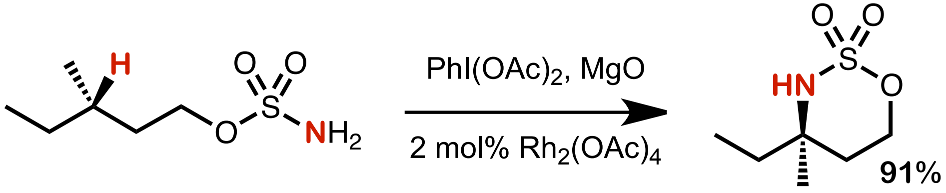
- Application of catalytic C-H functionalization
  Total synthesis & Late-stage functionalization of natural products and drugs

Catalytic C(sp^3)-H amination mediated by iodine(III) oxidants

> Seminal papers

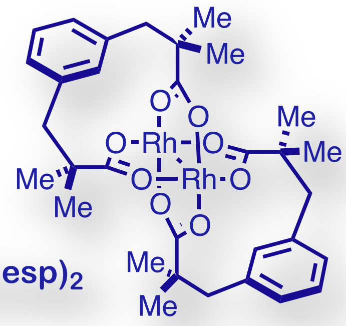


J. Du Bois *et al. Angew. Chem. Int. Ed.* **2001**, *40*, 598



J. Am. Chem. Soc. **2001**, *123*, 6935.

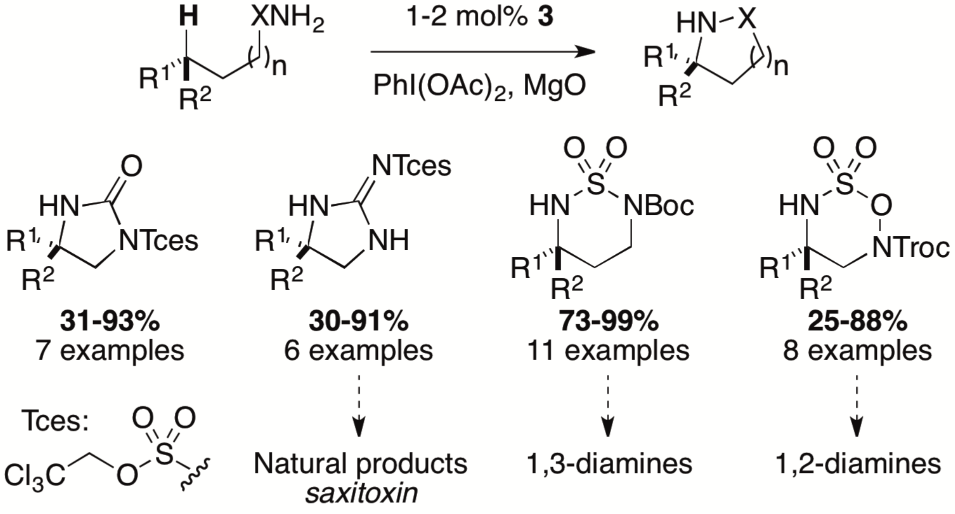
The chelate effect of the bridging tetradentate dicarboxylate ligand ***esp*** *increase the stability of the Rh complex*



$Rh_2(esp)_2$

J. Am. Chem. Soc. **2004**, *126*, 15378

> General trend in intramolecular reactions: 5 *vs.* 6-membered rings



31-93%
7 examples

30-91%
6 examples

73-99%
11 examples

25-88%
8 examples

Natural products
saxitoxin

1,3-diamines

1,2-diamines

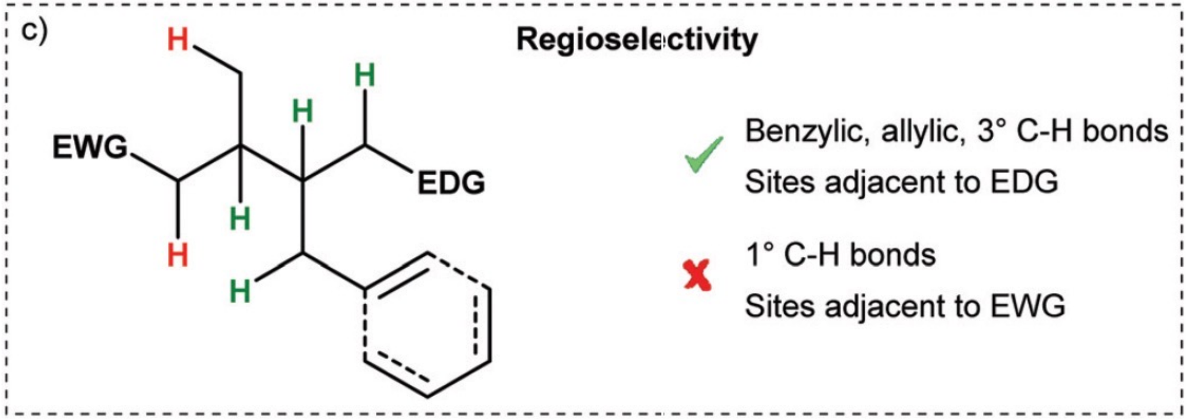
> P. Dauban *et al.*, **Dirhodium(II)-catalyzed C(sp^3)-H amination using iodine(III) oxidants**, *Adv. Organomet. Chem.* **2015**, *64*, 77-118

- Catalytic C(sp^3)-H amination mediated by iodine(III) oxidants

> Site-selectivity (*or regioselectivity*) issue: substrate parameters

As in the case of carbenes

> The selectivity is controlled by a combination of STERIC and ELECTRONIC factors



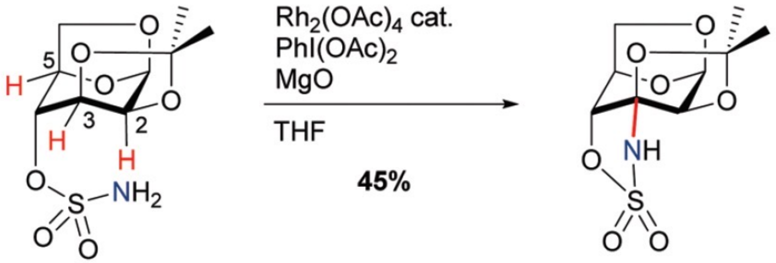
Regioselectivity

✓ Benzylic, allylic, 3° C-H bonds
Sites adjacent to EDG

✗ 1° C-H bonds
Sites adjacent to EWG

Impact of conformational and stereoelectronic factor

Can you guess which C-H bond will react?



> P. Dauban *et al.*, Dirhodium(II)-catalyzed C(sp^3)-H amination using iodine(III) oxidants, *Adv. Organomet. Chem.* **2015**, *64*, 77-118

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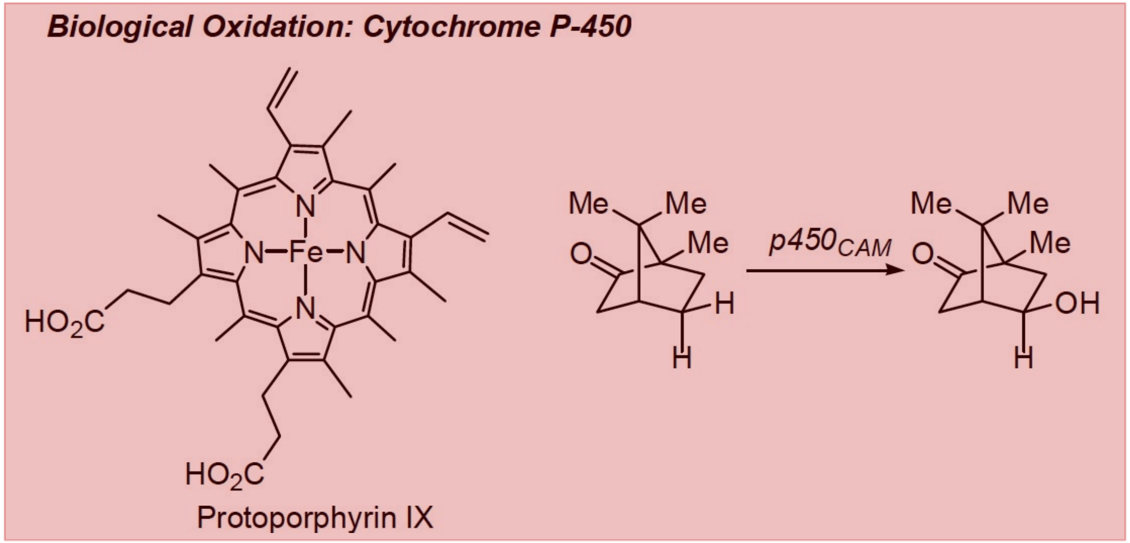
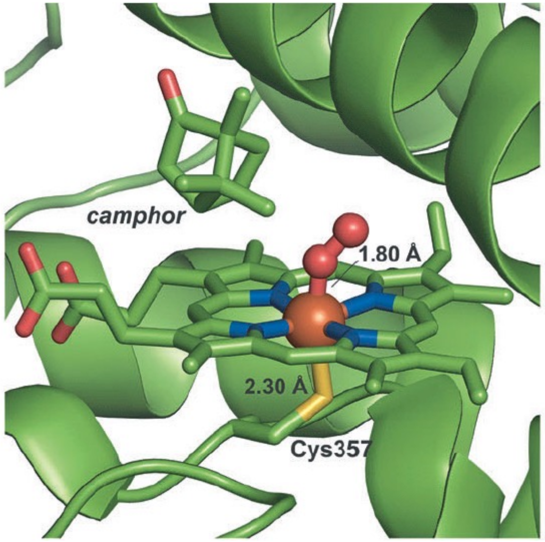
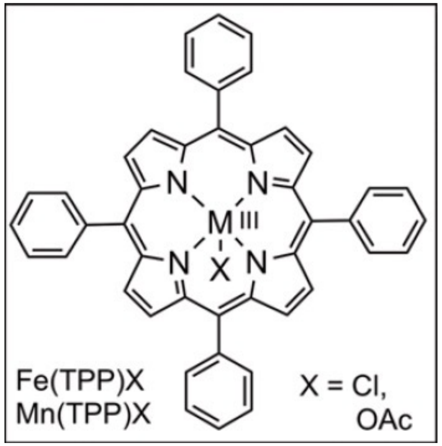
C-H Oxidation in Nature

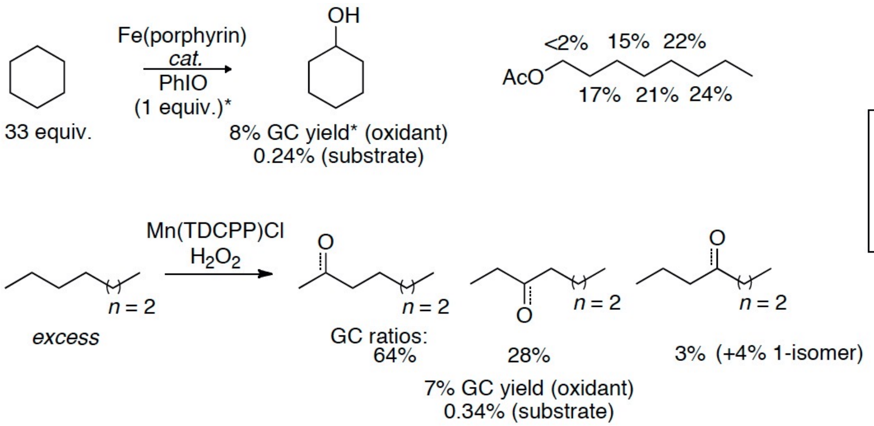
> Taking inspiration from Cytochrome P450



Biological Oxidation: Cytochrome P-450







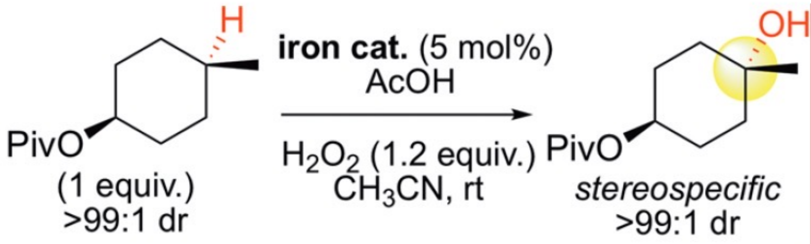
Early examples of non-enzymatic aliphatic C-H oxidations used large excesses of substrates, with low yields and poor selectivities when multiple sites of C-H oxidation were possible

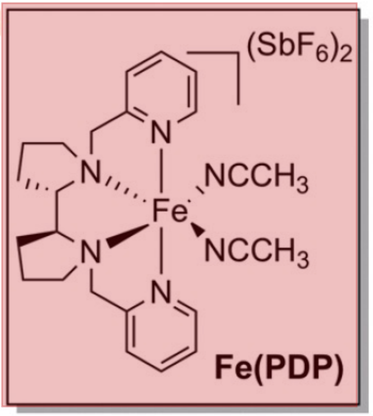
Groves *JACS* **1979**, *101*, 1032.
Mansuy *JACS* **1988**, *110*, 8462.

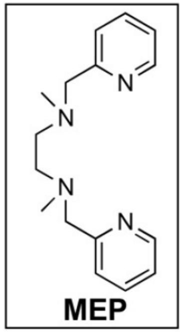
> I. G. Denisov *et al*, **Structure and chemistry of Cytochrome P450**, *Chem. Rev.* **2005**, *105*, 2253-2277

C-H Oxidation in the Laboratory

> Increasing the σ-donation of the amine ligands and rigidification + key role of AcOH additive







Entry	Catalyst	AcOH (equiv.)	Yield[b] (%)	Conv.[c] (%)	Select.[d] (%)
1	Fe(MEP)[a]	0	7	12	56
2	Fe(PDP)	0	14	15	92
3	Fe(MEP)[a]	0.5	26	41	62
4	Fe(PDP)	0.5	38	42	90
5[e]	Fe(PDP)	0.5	51	---	---

[a] Fe(MEP) = $[Fe(mep)(CH_3CN)_2](SbF_6)_2$. [b] Isolated yield. [c] Conversion of starting material. [d] Selectivity for desired product (yield/conversion). [e] Iterative addition protocol: 3x [catalyst (5 mol%), AcOH (0.5 equiv.), H_2O_2 (1.2 equiv.)].

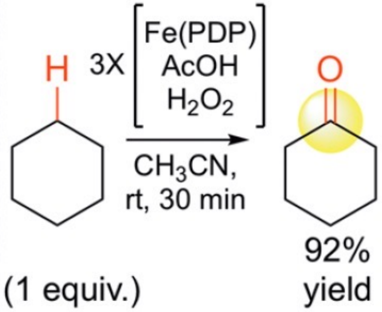
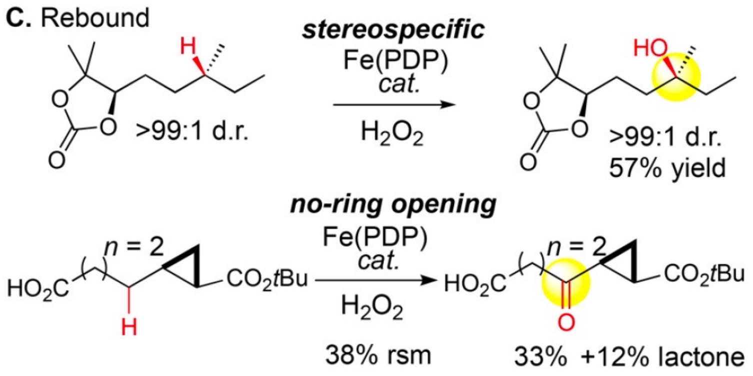


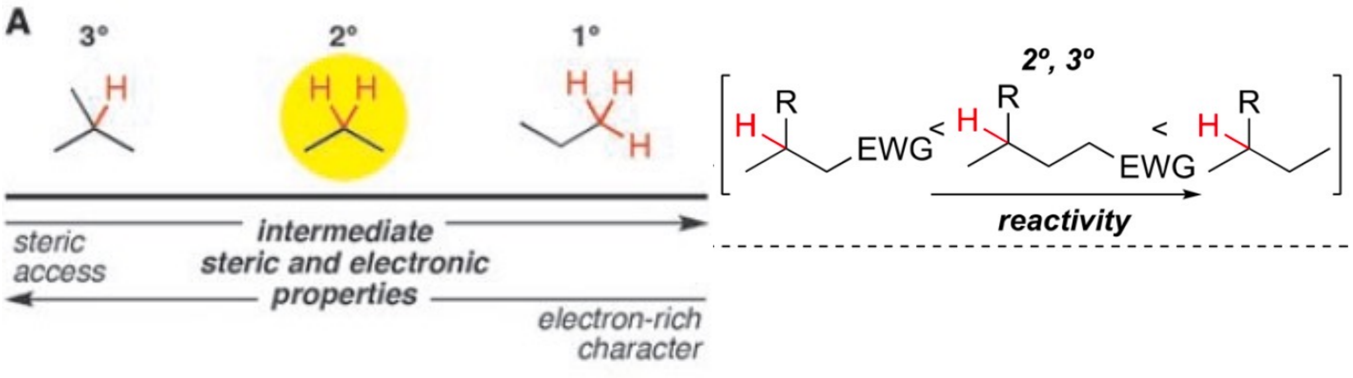
Figure 12. Discovery of Fe(PDP) catalysis for preparative aliphatic C–H oxidations.

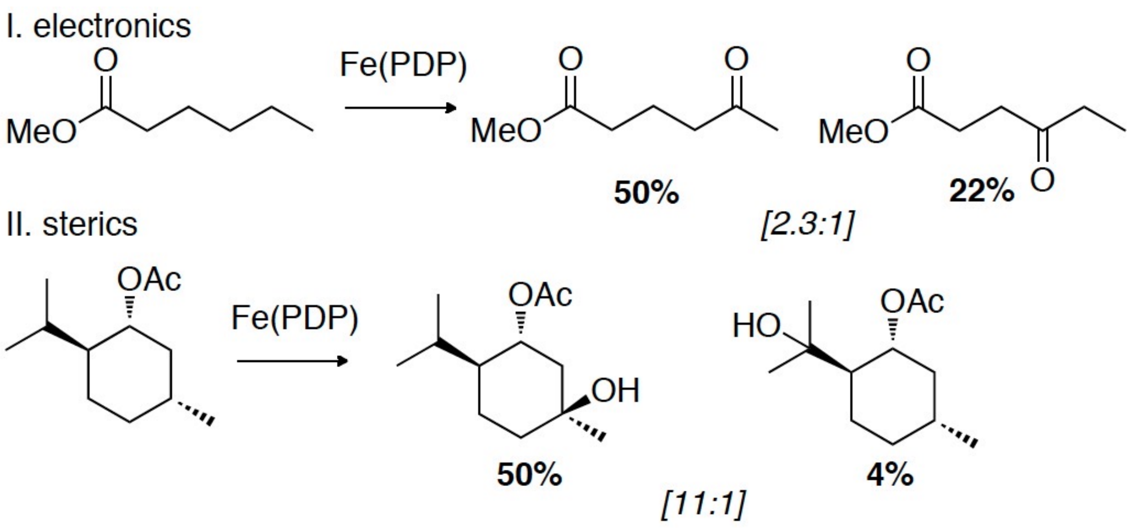


> M. C. White *et al*, **Aliphatic C-H oxidations for late-stage functionalization**, *J. Am. Chem. Soc.* **2018**, *140*, 13988-14009

C-H Oxidation in the Laboratory

> Site-selectivity (*or regioselectivity*) issue



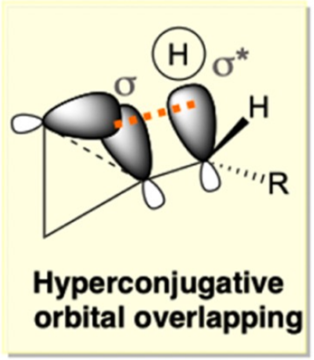


> M. C. White *et al*, **Aliphatic C-H oxidations for late-stage functionalization**, *J. Am. Chem. Soc.* **2018**, *140*, 13988-14009

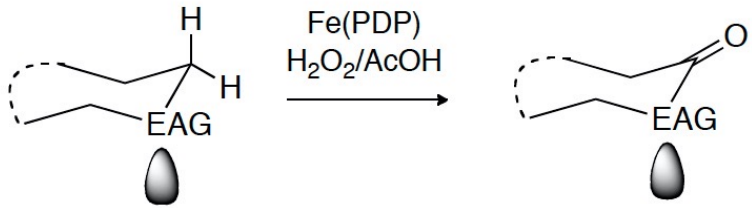
C-H Oxidation in the Laboratory

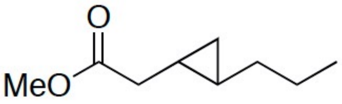
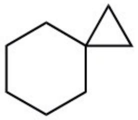
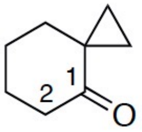
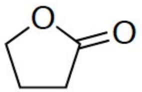
> Site-selectivity (*or regioselectivity*) issue

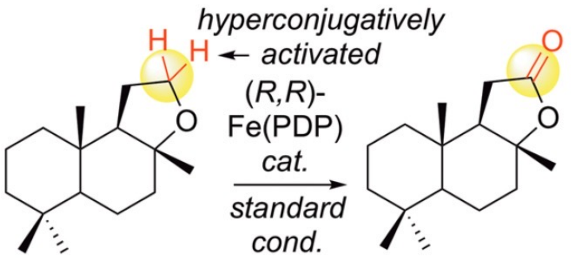
Hyperconjugative Activation
Groups such as cyclopropanes and oxygen, have lone pairs that are arranged in space so as to hyperconjugatively activate the adjacent C-H bond, increasing selectivity for that position (*note that these groups are generally inductively withdrawing!*)



Hyperconjugative orbital overlapping



Substrate	**Major Product**	**Isolated % Yield (rsm)**
		62% (17%) [C5:C6 = 6:1]
		52% (15%) [C1:C2 = 5:1]
		41% (---)



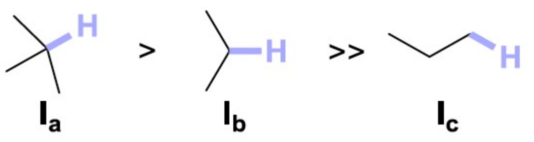
(-)-ambroxide

(+)-sclareolide
80% yield
(isolated)

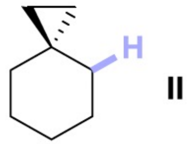
> M. C. White *et al*, **Aliphatic C-H oxidations for late-stage functionalization**, *J. Am. Chem. Soc.* **2018**, *140*, 13988-14009

C-H Oxidation in the Laboratory

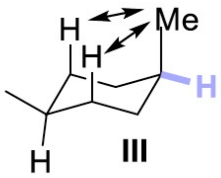
> Factors affecting C–H bond cleavage



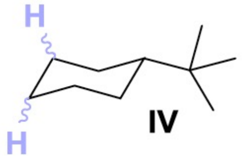
Bond strength



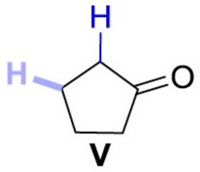
Hyperconjugative effect



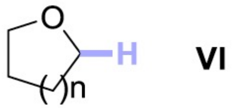
Strain release



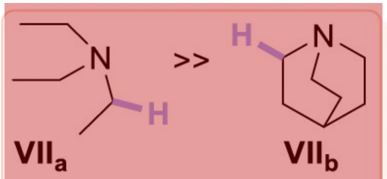
Steric / Torsional effect



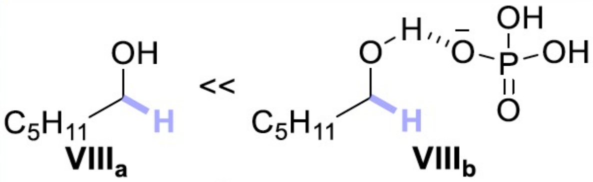
Polar effect



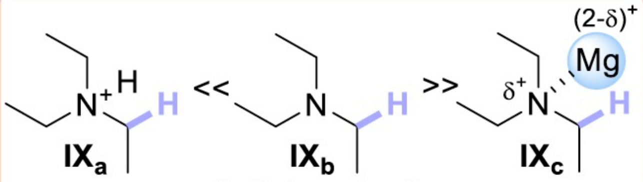
Hyperconjugative effect



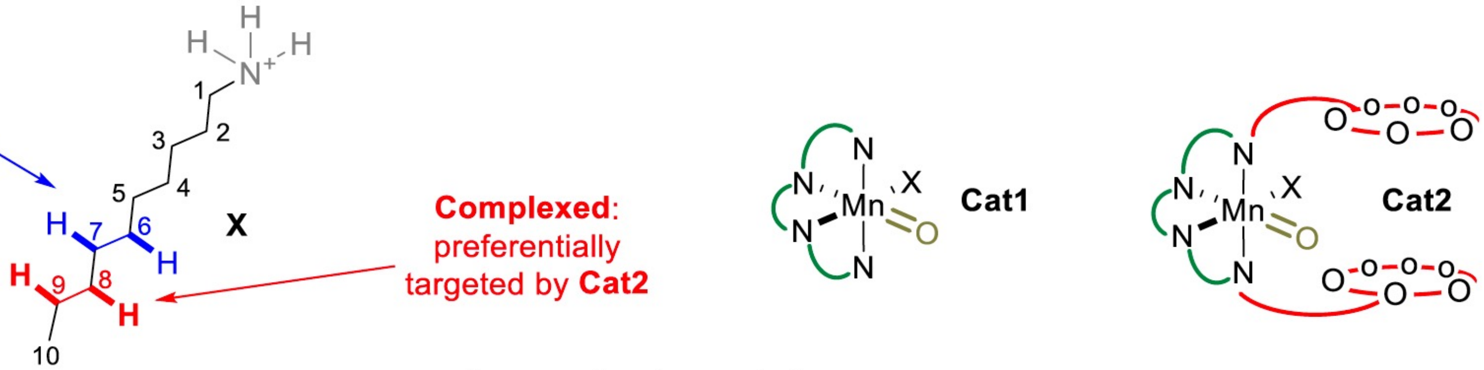
Stereoelectronic effect



α-C-H activation



α-C-H deactivation



Uncomplexed: preferentially targeted by **Cat1**

Complexed: preferentially targeted by **Cat2**

Supramolecular control

> M. Fagnoni *et al.*, **Direct Photocatalyzed Hydrogen Atom Transfer (HAT) for Aliphatic C–H Bonds Elaboration**, *Chem. Rev.* **2022**, *122*, 1875

- C-H Oxidation in the Laboratory

> Stereoelectronic effects

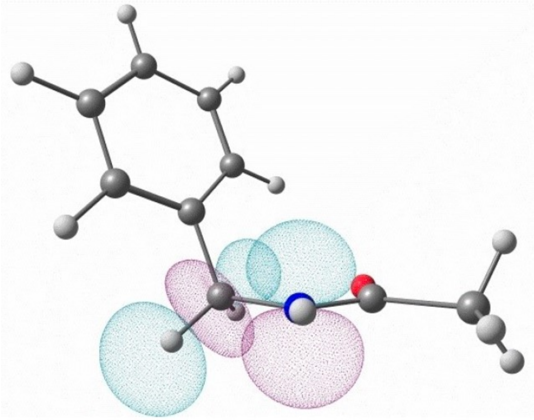
$$t\mathrm{BuO{-}O}t\mathrm{Bu} \xrightarrow{h\nu} 2\ t\mathrm{BuO}^\bullet$$

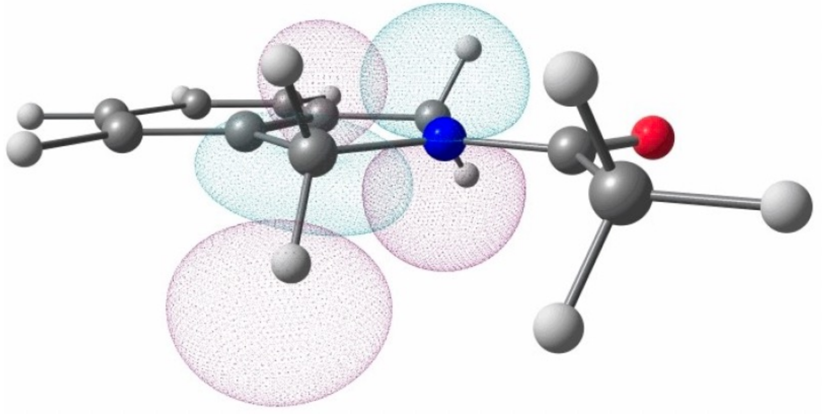
DTBP

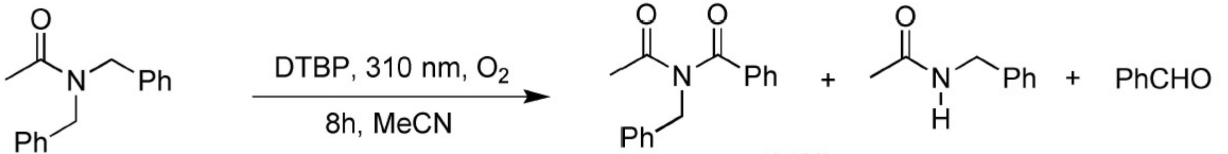
$$t\mathrm{BuO}^\bullet + \mathrm{R{-}H} \longrightarrow t\mathrm{BuOH} + \mathrm{R}^\bullet$$

$$\mathrm{R}^\bullet + \mathrm{O_2} \longrightarrow \mathrm{R{-}O{-}O}^\bullet$$

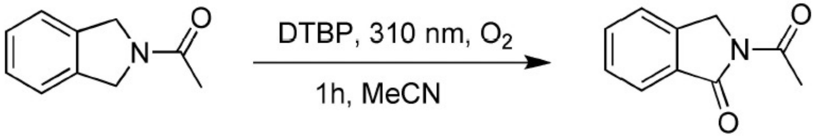
$$\mathrm{R{-}O{-}O}^\bullet \rightrightarrows \text{oxidation products}$$



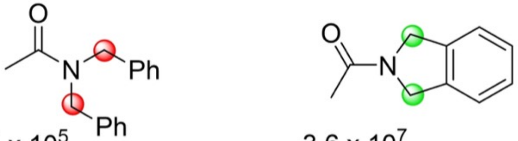




S4 (28% conv.) **P4a** (21%) **P4b** (3%) **P4c** (3%)



S6 (>99% conv.) **P6a** (92%)



2.1×10^5

3.6×10^7

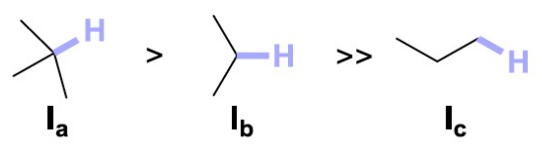
lack of benzylic activation

benzylic activation enforced by stereoelectronics effects

> Activation & deactivation of benzylic C–H bonds guided by stereoelectronic effects in HAT, *Eur. J. Org. Chem.* **2023**, *26*, e202300419

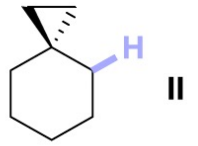
C-H Oxidation in the Laboratory

> Factors affecting C–H bond cleavage



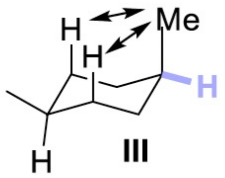
I_a I_b I_c

Bond strength



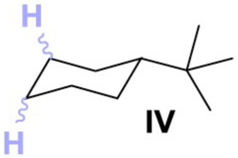
II

Hyperconjugative effect



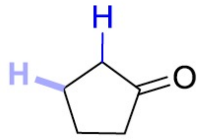
III

Strain release



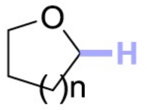
IV

Steric / Torsional effect



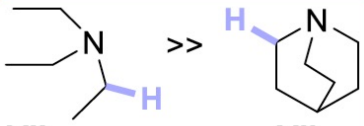
V

Polar effect



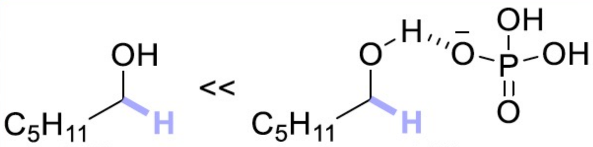
VI

Hyperconjugative effect



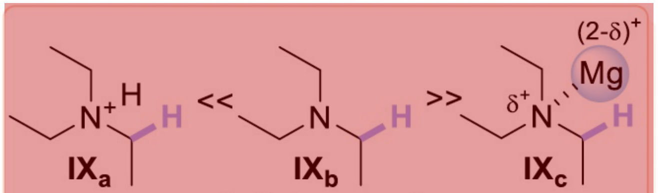
VII_a VII_b

Stereoelectronic effect



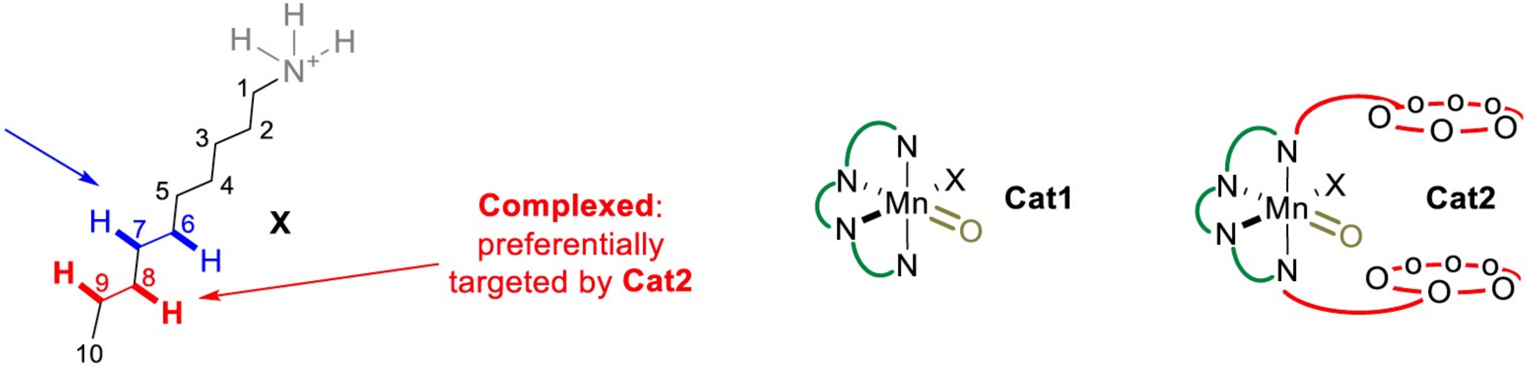
$VIII_a$ $VIII_b$

α-C-H activation



IX_a IX_b IX_c

α-C-H deactivation



Uncomplexed: preferentially targeted by **Cat1**

X

Complexed: preferentially targeted by **Cat2**

Cat1

Cat2

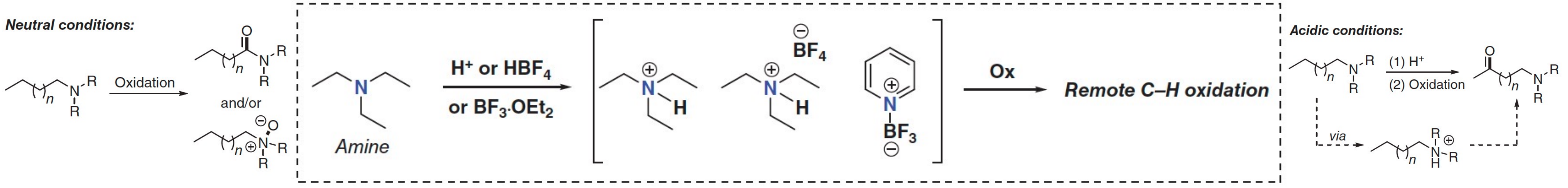
Supramolecular control

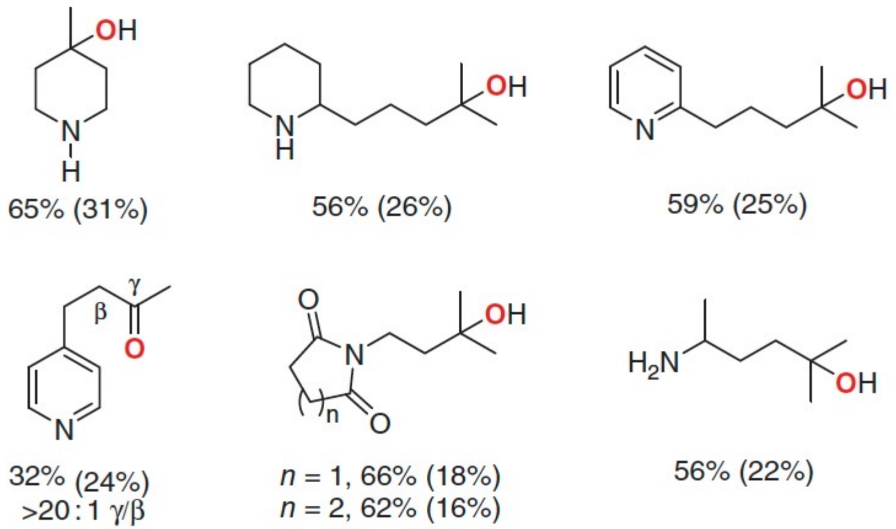
> M. Fagnoni *et al.*, Direct Photocatalyzed Hydrogen Atom Transfer (HAT) for Aliphatic C–H Bonds Elaboration, *Chem. Rev.* **2022**, *122*, 1875

- # C-H Oxidation in the Laboratory

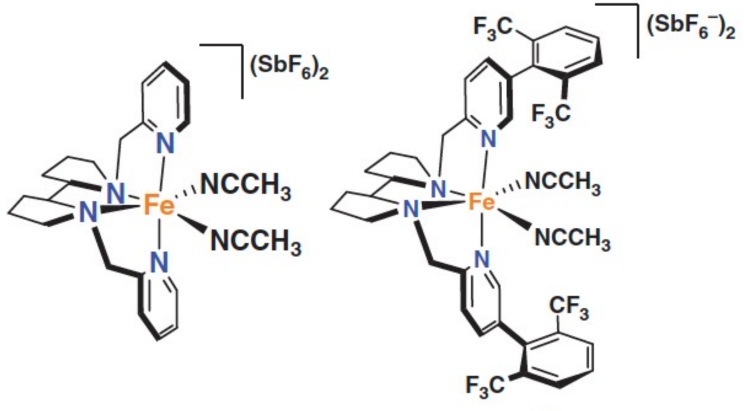
> Remote oxidation by reversal of polarity: the case of amine

Oxidation of C—H bonds in amine containing substrate has traditionally represented a challenging problem for several reasons.
In first place, amine oxidation is often easier than C–H oxidation.
In addition, amines readily bind to metal centers, causing the deactivation of metal catalysts





(1) HBF_4 or $BF_3{\cdot}OEt_2$
(2) Fe cat/H_2O_2/AcOH

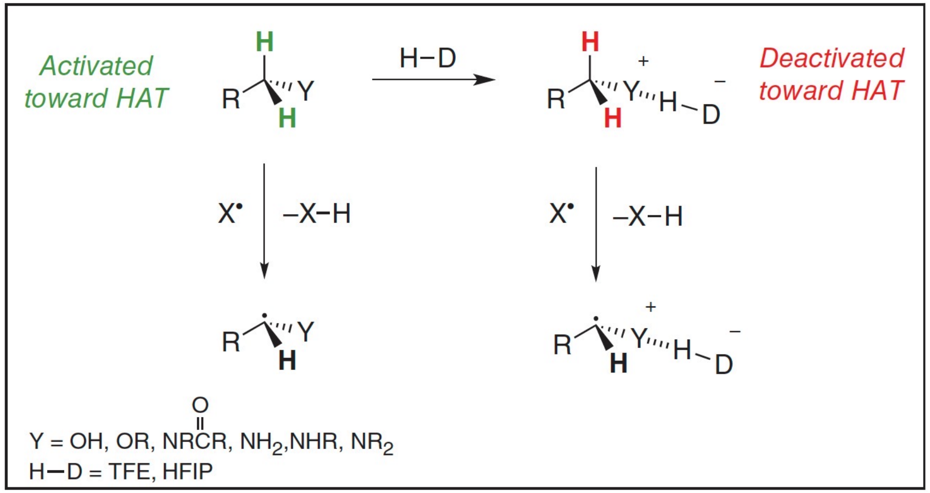


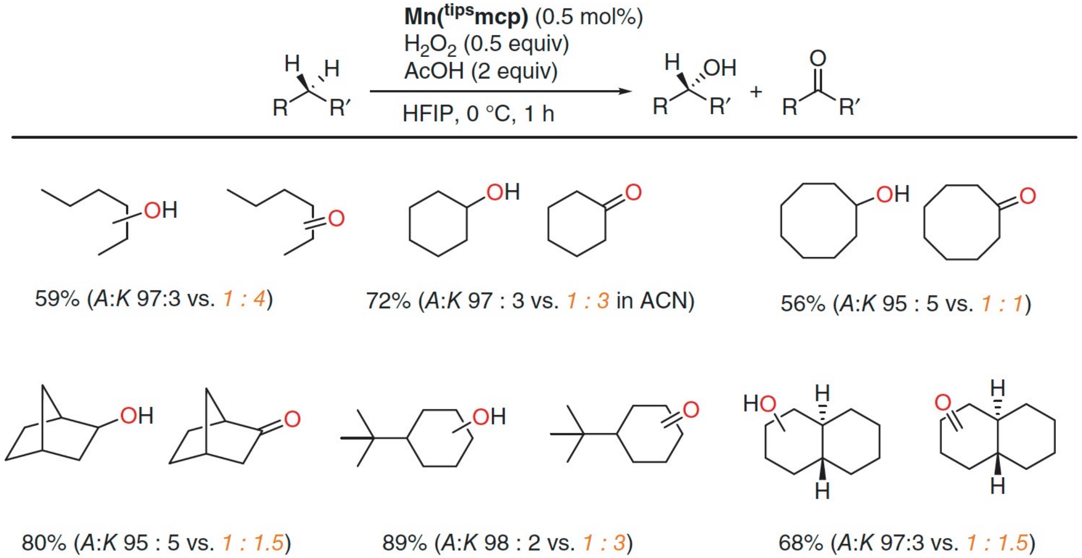
(*S*,*S*)-Fe(pdp) **(*S*,*S*)-Fe(^{CF_3}pdp)**

> M. C. White *et al*., Aliphatic C-H oxidations for late-stage functionalization, *J. Am. Chem. Soc.* **2018**, *140*, 13988

C-H Oxidation in the Laboratory

> Remote oxidation by reversal of polarity: How to stop the C-H oxidation at the alcohol level?



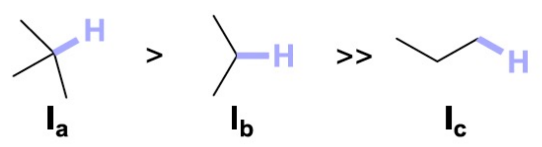


Scheme 13.14 Catalytic hydroxylation of methylenes in HFIP. Values in italics (orange) indicate the alcohol/ketone ratio observed when the reaction is conducted in acetonitrile.

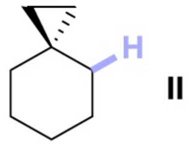
> M. C. White *et al.*, **Aliphatic C-H oxidations for late-stage functionalization**, *J. Am. Chem. Soc.* **2018**, *140*, 13988

- # C-H Oxidation in the Laboratory

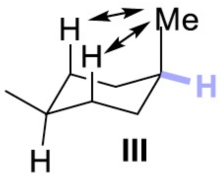
> Factors affecting C–H bond cleavage


I_a > I_b >> I_c

Bond strength

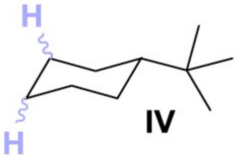

II

Hyperconjugative effect



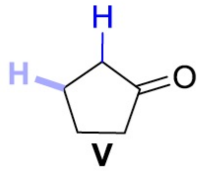
III

Strain release



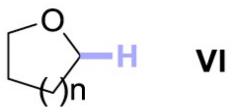
IV

Steric / Torsional effect



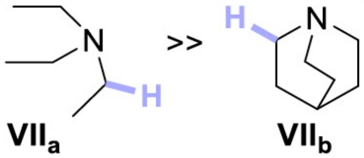
V

Polar effect

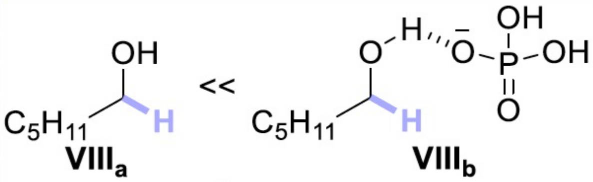


VI

Hyperconjugative effect

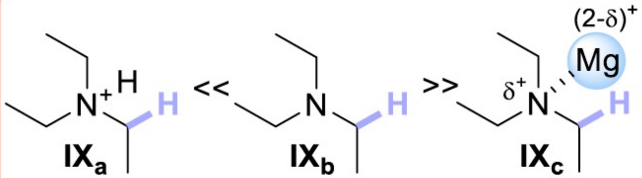

VII_a >> VII_b

Stereoelectronic effect



$VIII_a$ << $VIII_b$

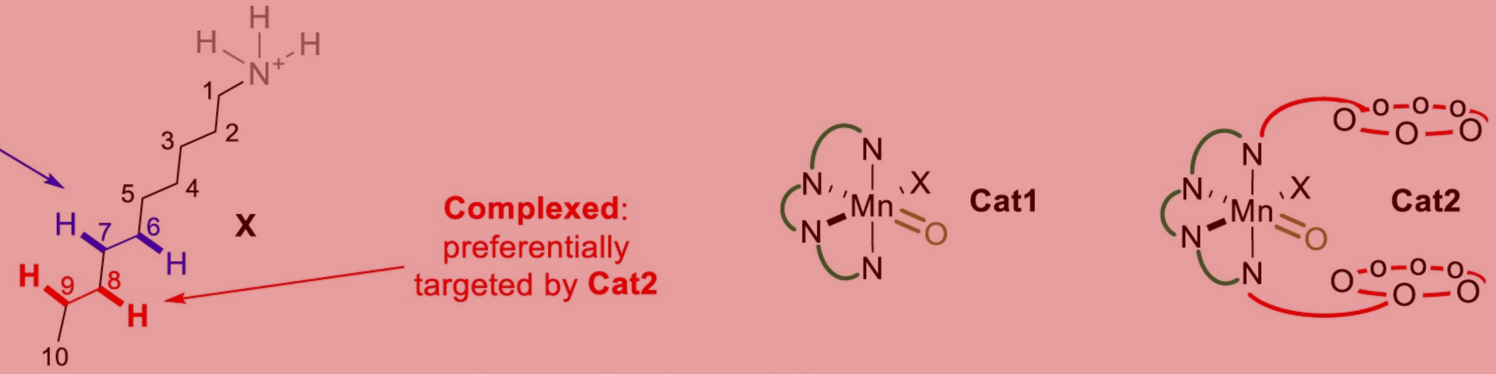
α-C-H activation



IX_a IX_b IX_c

α-C-H deactivation

Uncomplexed: preferentially targeted by **Cat1**



X

Complexed: preferentially targeted by **Cat2**

Cat1

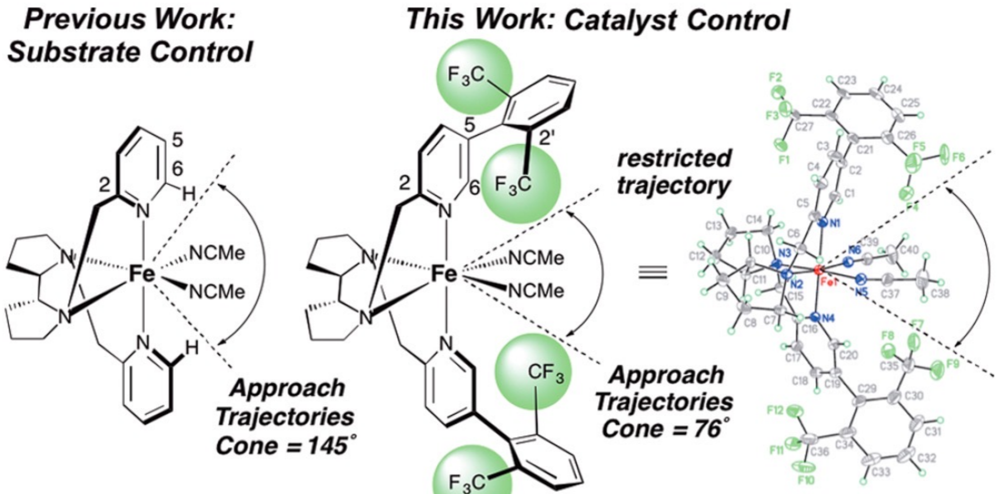
Cat2

Supramolecular control

> M. Fagnoni *et al.*, Direct Photocatalyzed Hydrogen Atom Transfer (HAT) for Aliphatic C–H Bonds Elaboration, *Chem. Rev.* 2022, *122*, 1875

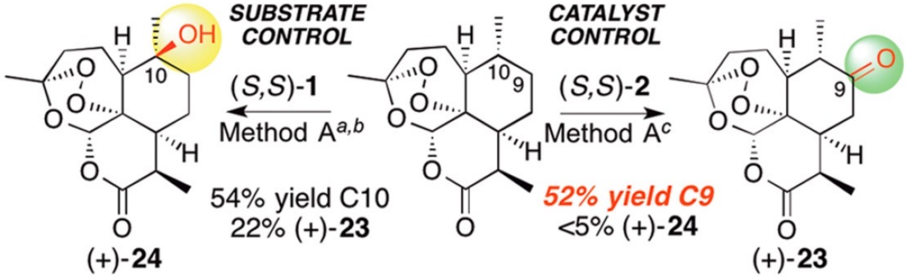
- C-H Oxidation in the Laboratory

> Steric effects:
From Substrate-controlled to Catalyst-controlled C-H oxidation



(R,R)-Fe(PDP) **1**

(R,R)-Fe(CF_3-PDP) **2**



Sites (a:b)	Calc'd Ratio	Observed Ratio
C9:C10	1:1.3	1:2

(+)-artemisinin **22**

Sites (a:b)	Calc'd Ratio	Observed Ratio
C9:C10	17:1	11:1

> M. C. White *et al.*, **Aliphatic C-H oxidations for late-stage functionalization**, *J. Am. Chem. Soc.* **2018**, *140*, 13988

Réactions de fonctionnalisation C-H et chimie médicinale

- Introduction
  1. Catalytic C-H Functionalization Reactions vs. Functional Group Transformations
  2. Catalytic C-H Functionalization Reactions: challenges & general mechanisms

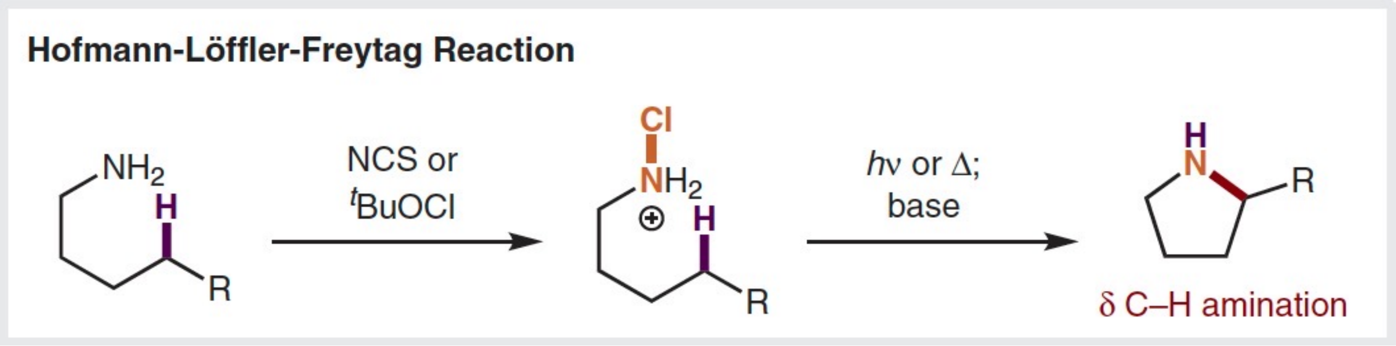
- Catalytic C-H Functionalization by C-H Activation (*inner-sphere mechanism*)
  1. Mechanistic considerations
  2. Heteroatom-directed C-H Functionalization
  3. Oxidative addition-directed C-H Functionalization

- Catalytic C-H Functionalization by C-H Insertion (*outer-sphere mechanism*)
  1. Mechanistic considerations
  2. Carbene chemistry
  3. Nitrene chemistry
  4. C-H oxidation

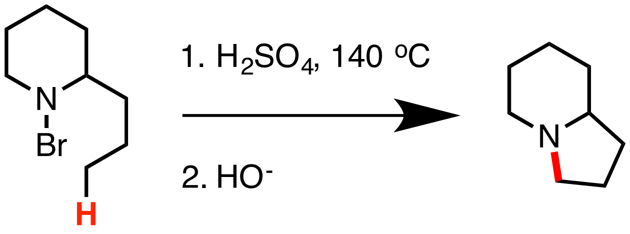
- Catalytic C-H Functionalization using radicals
  1. Historical reactions and mechanistic considerations
  2. Hydrogen Atom Transfer (HAT)
  3. Minisci-type Reaction

- Application of catalytic C-H functionalization
  Total synthesis & Late-stage functionalization of natural products and drugs

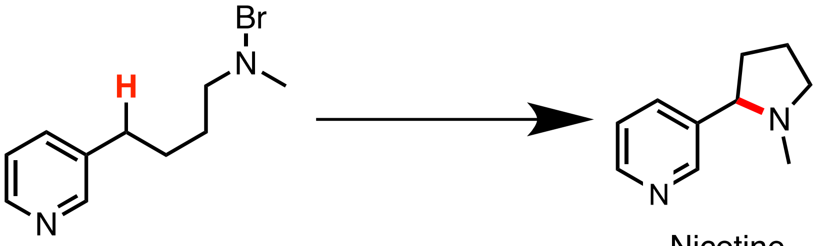
- The Hoffman-Löffler-Freytag Reaction (1883)



> Initial Discovery



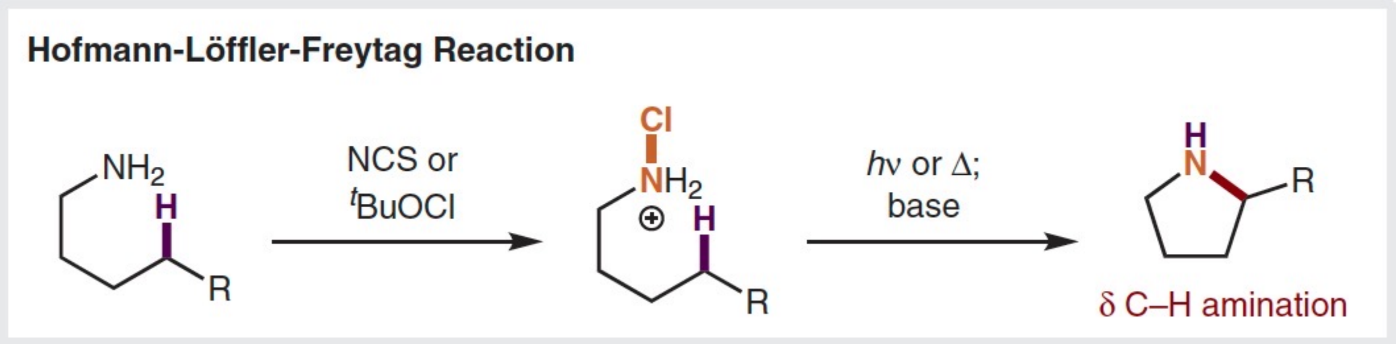
> First Application:



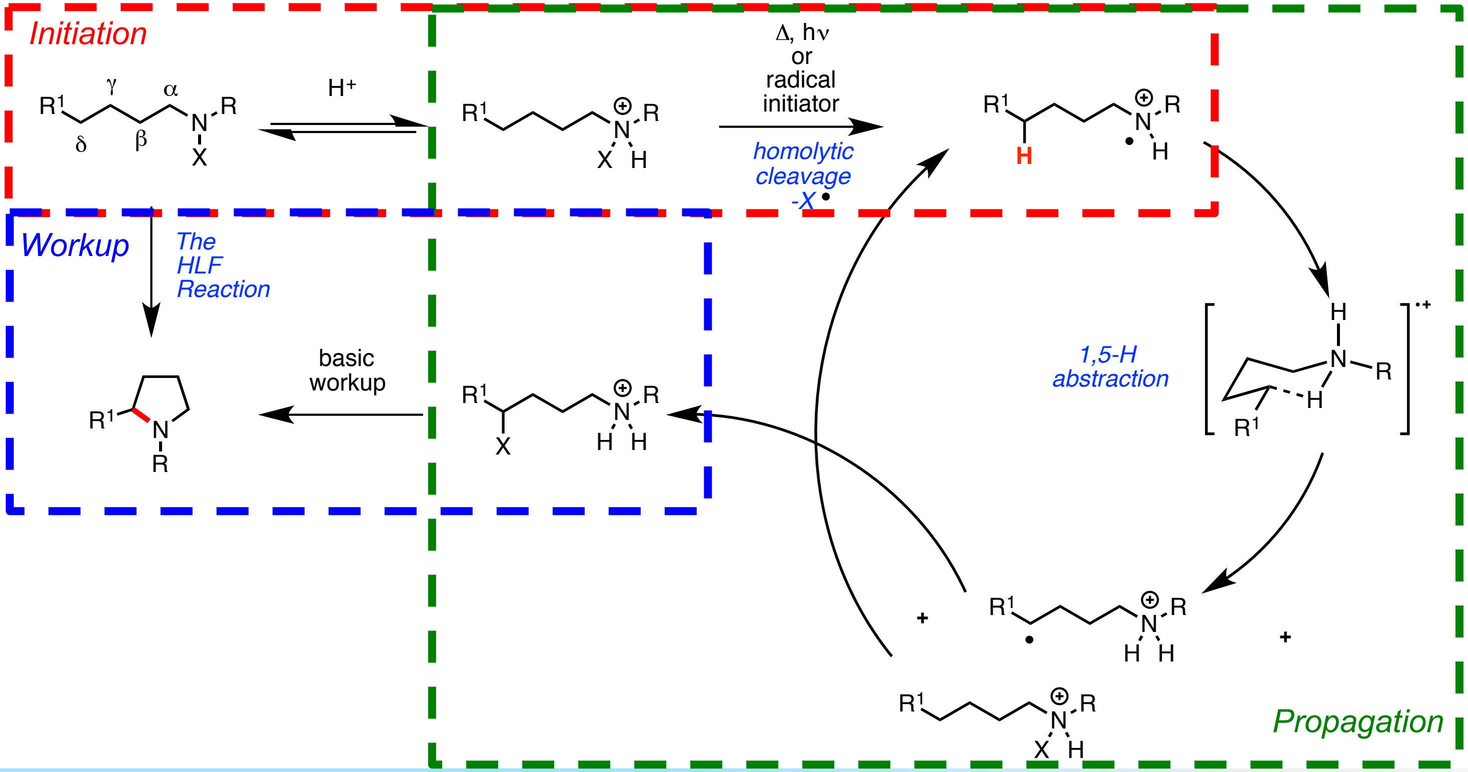
Nicotine

> D. Nagib *et al.*, **Remote C-H Functionalization via Selective Hydrogen Atom Transfer**, *Synthesis* **2018**, *50*, 1569

• The Hoffman-Löffler-Freytag Reaction (1883)

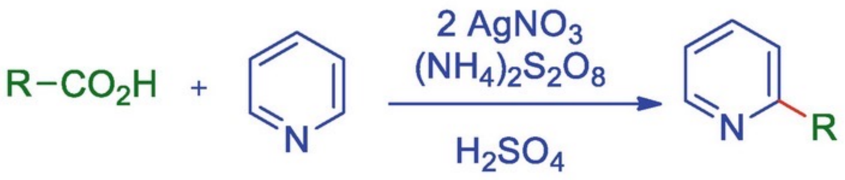


> Mechanism



> D. Nagib *et al*., **Remote C-H Functionalization via Selective Hydrogen Atom Transfer**, *Synthesis* **2018**, *50*, 1569

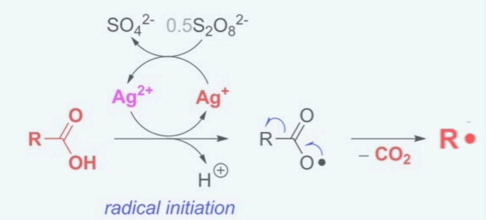
The Minisci Reaction (1968)

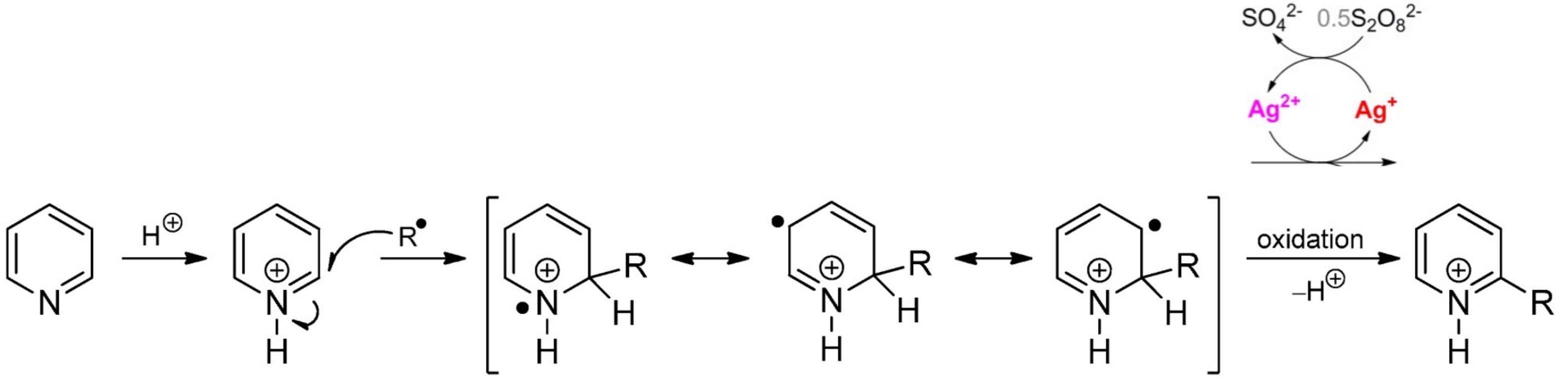


> Mechanism

$$2Ag^{\oplus} + S_2O_8^{2\ominus} \longrightarrow 2Ag^{2\oplus} + 2SO_4^{2\ominus}$$

$$R\text{-}COOH + Ag^{2\oplus} \longrightarrow R^{\bullet} + CO_2 + H^{\oplus} + Ag^{\oplus}$$





> R. J. Phipps *et al.*, **Recent advances in Minisci-type reactions**, *Angew. Chem. Int. Ed* **2019**, *58*, 13666

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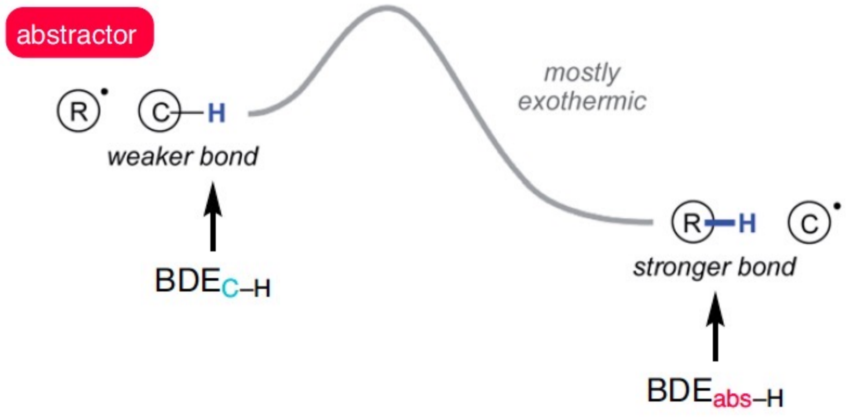
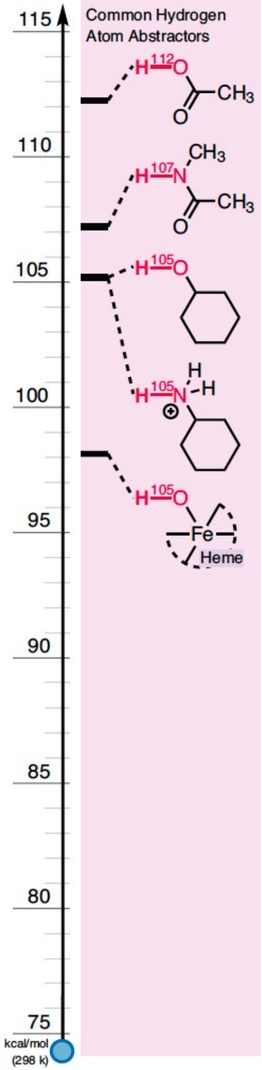
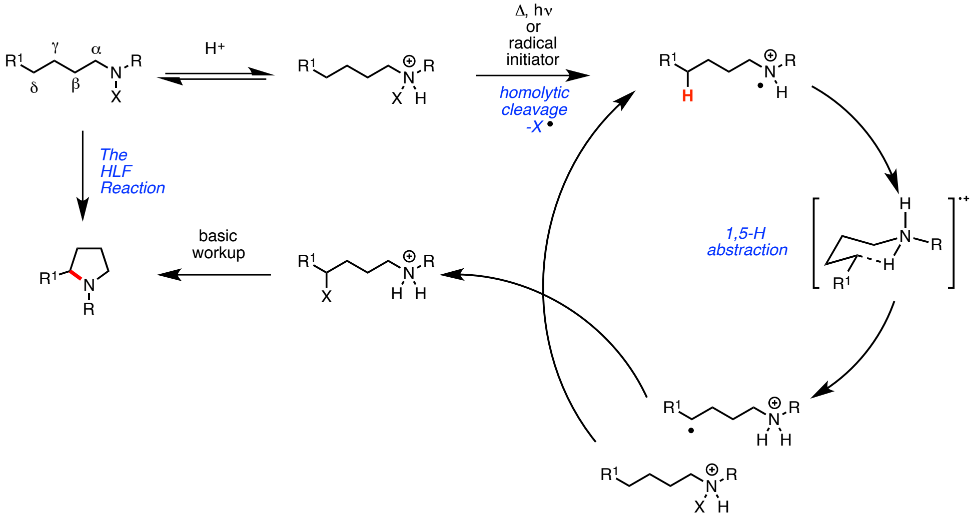
• Guiding factors in radical chemistry

> Bond Dissociation Energy (BDE) and H-Abstractor







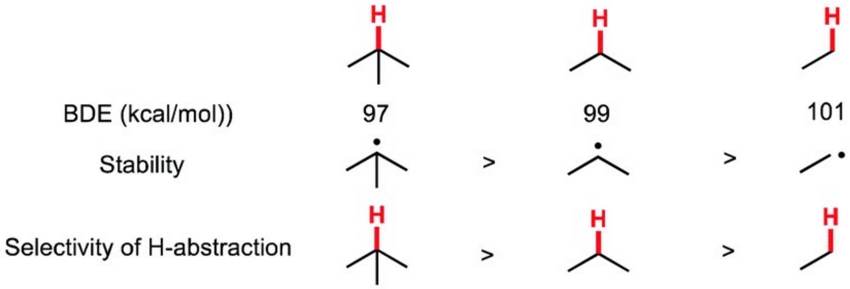
For efficient reaction, BDE$_{abs-H}$ > BDE$_{C-H}$

BDE: Thermodynamic factor

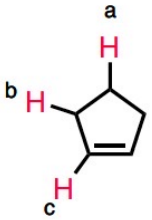
> D. Nagib *et al*., **Remote C-H Functionalization via Selective Hydrogen Atom Transfer**, *Synthesis* **2018**, *50*, 1569

• Guiding factors in radical chemistry

> Bond Dissociation Energy (BDE) and selectivity



In the absence of directing or polar effects



$BDE_{C-Ha} = 97$

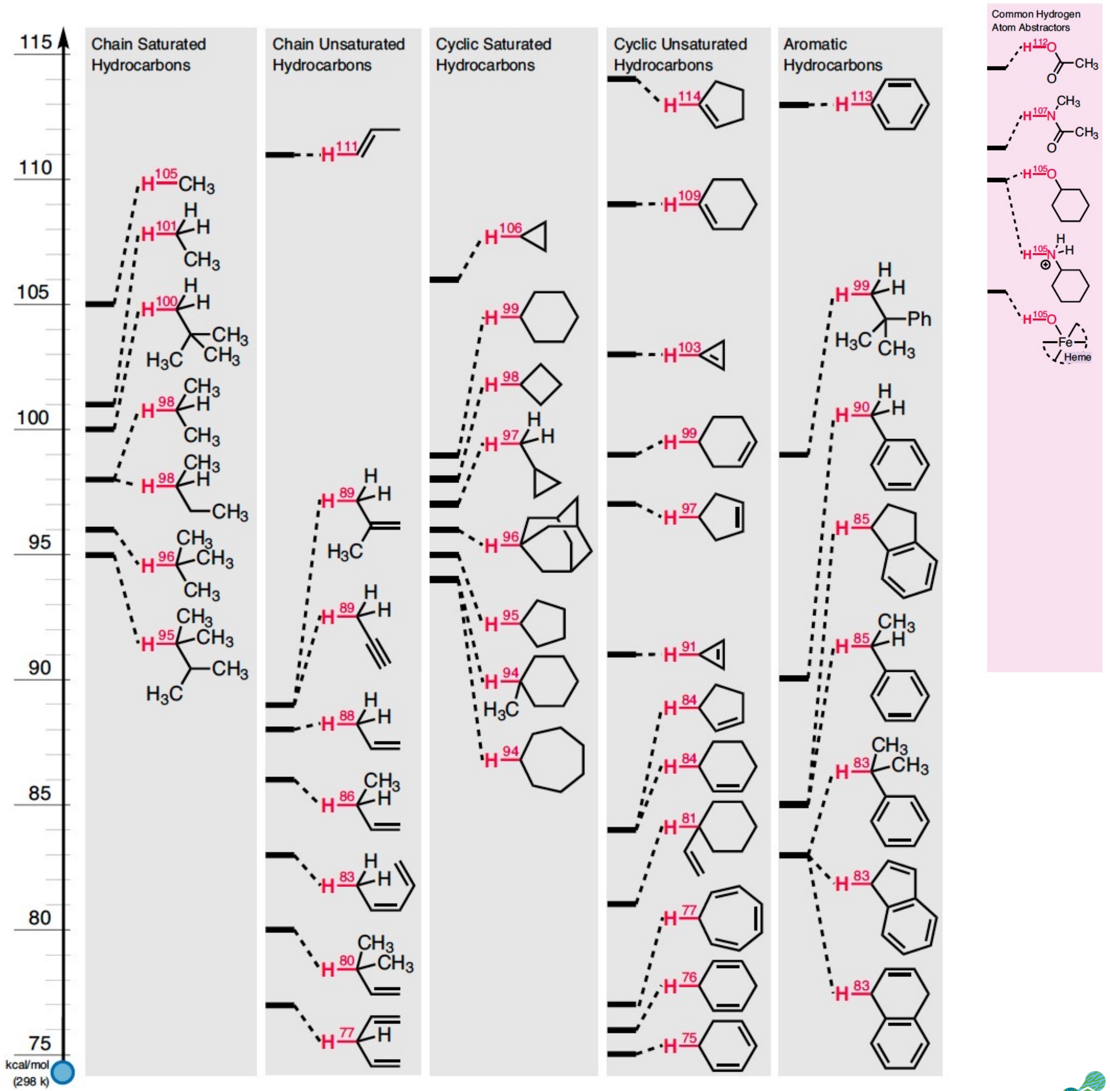
$BDE_{C-Hb} = 84$

$BDE_{C-Hc} = 114$

order of reactivity

$H^b > H^a > H^c$

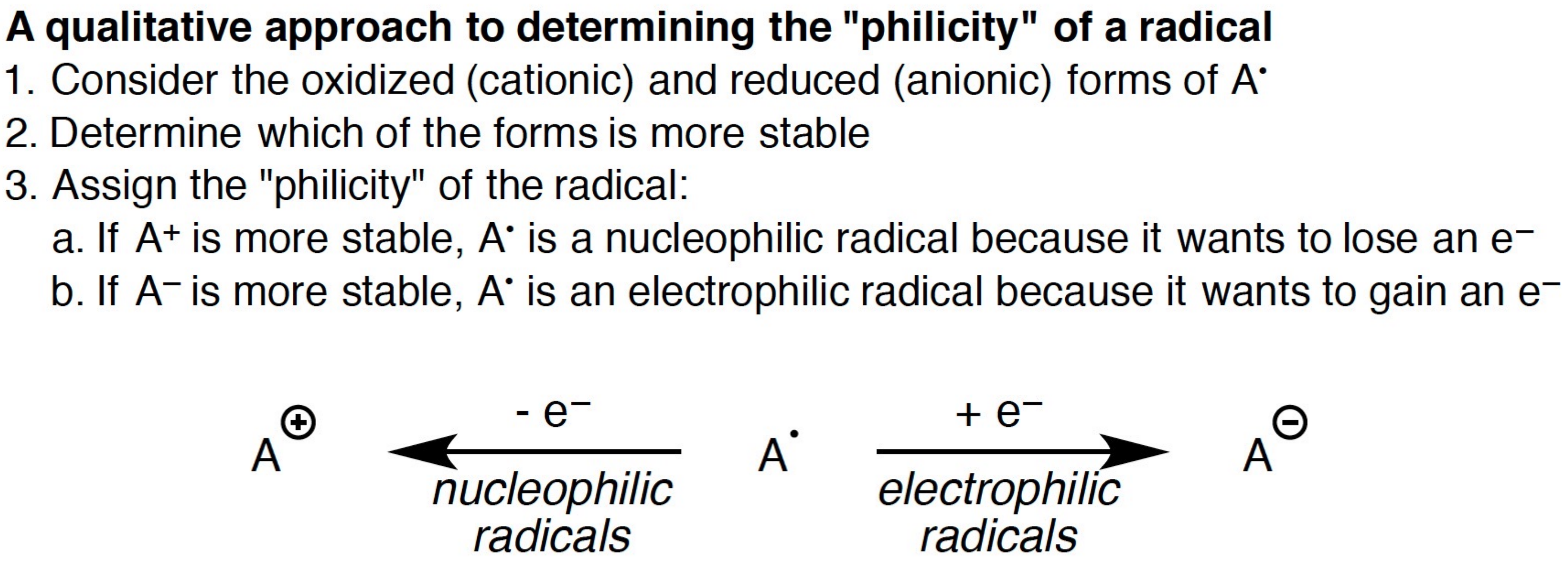
all values in kcal•mol⁻¹



> D. Nagib *et al.*, **Remote C-H Functionalization via Selective Hydrogen Atom Transfer**, *Synthesis* **2018**, *50*, 1569

Guiding factors in radical chemistry

> Radical polarity ou philicity Despite being uncharged species, radicals can have a nucleophilic or electrophilic character



A qualitative approach to determining the "philicity" of a radical

1. Consider the oxidized (cationic) and reduced (anionic) forms of A$^\bullet$
2. Determine which of the forms is more stable
3. Assign the "philicity" of the radical:
   a. If A$^+$ is more stable, A$^\bullet$ is a nucleophilic radical because it wants to lose an e$^-$
   b. If A$^-$ is more stable, A$^\bullet$ is an electrophilic radical because it wants to gain an e$^-$

$$A^{\oplus} \xleftarrow[\text{nucleophilic radicals}]{-\ e^-} A^{\bullet} \xrightarrow[\text{electrophilic radicals}]{+\ e^-} A^{\ominus}$$

Nucleophilic radicals abstract δ+ ‘protic’ hydrogen atoms

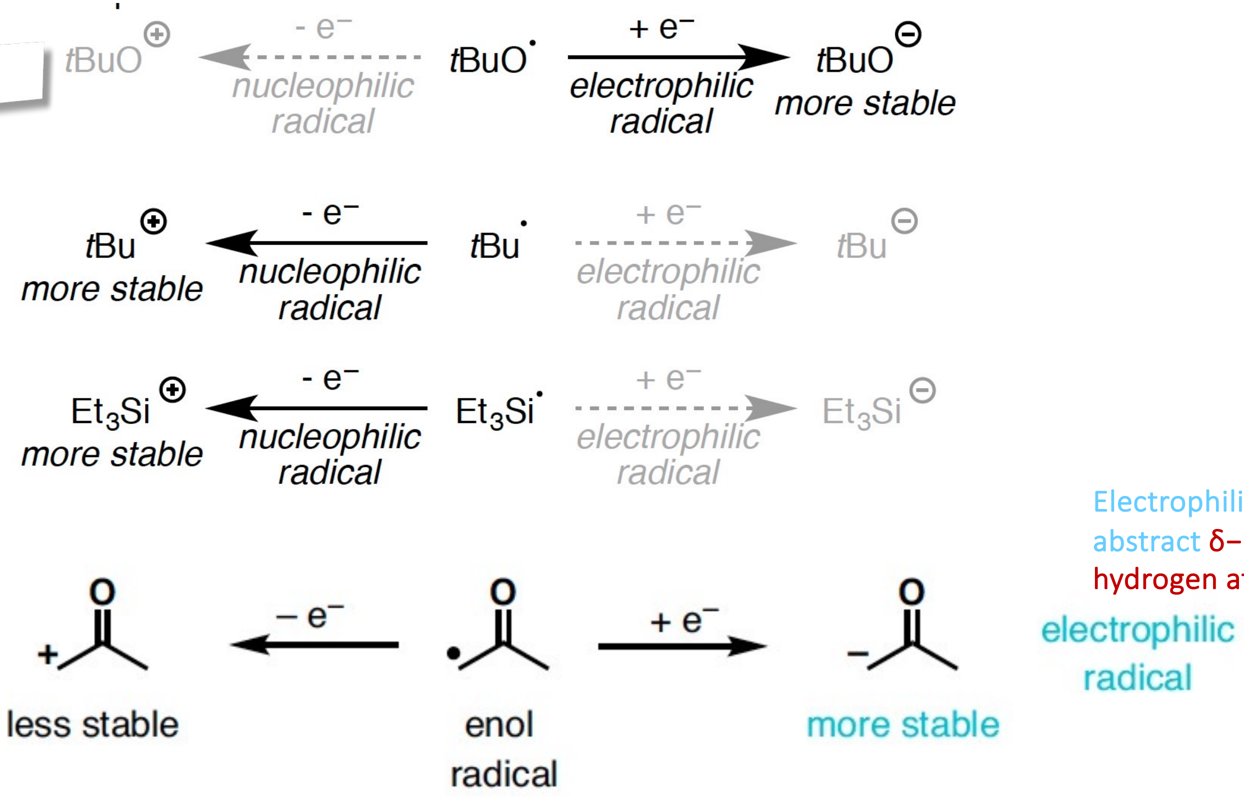
Electrophilic radicals abstract δ– ‘hydridic’ hydrogen atoms

> E. R. Welin *et al.*, Radical philicity and its role in selective organic transformations, *Nat. Rev. Chem.* 2021, *5*, 486

Guiding factors in radical chemistry

> Radical polarity ou philicity Despite being uncharged species, radicals can have a nucleophilic or electrophilic character

Nucleophilic or electrophilic?



Nucleophilic radicals abstract δ+ 'protic' hydrogen atoms

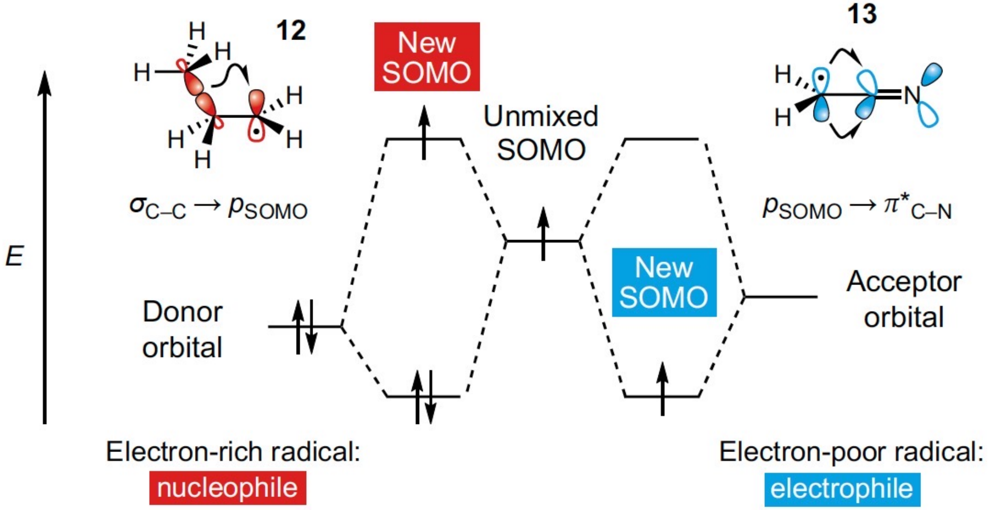
Electrophilic radicals abstract δ– 'hydridic' hydrogen atoms

> E. R. Welin *et al.*, Radical philicity and its role in selective organic transformations, *Nat. Rev. Chem.* **2021**, *5*, 486

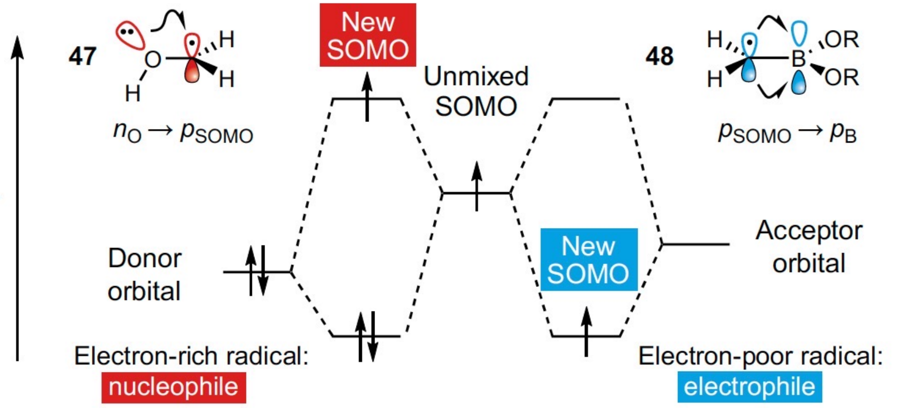
Guiding factors in radical chemistry

> Radical polarity ou philicity Despite being uncharged species, radicals can have a nucleophilic or electrophilic character

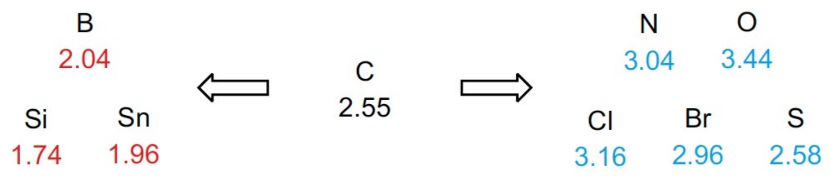
Stabilization of alkyl radicals by adjacent groups



π-Bonding characteristics determine effect of heteroatom substitution



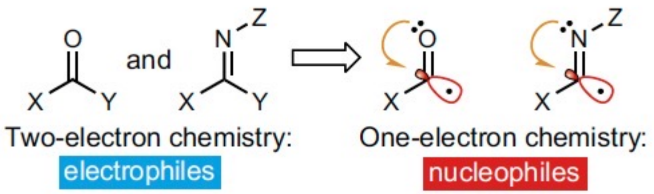
Heteroatom-centred radicals: electronegativity (χ_P) relative to carbon



Atom is less electronegative than C: typically nucleophilic

Atom is more electronegative than C: typically electrophilic

Acyl and imidoyl radicals: nucleophilic



Umpolung:
traditional reactivity pattern reversed within one-electron manifold

> E. R. Welin *et al.*, Radical philicity and its role in selective organic transformations, *Nat. Rev. Chem.* **2021**, *5*, 486

• Guiding factors in radical chemistry

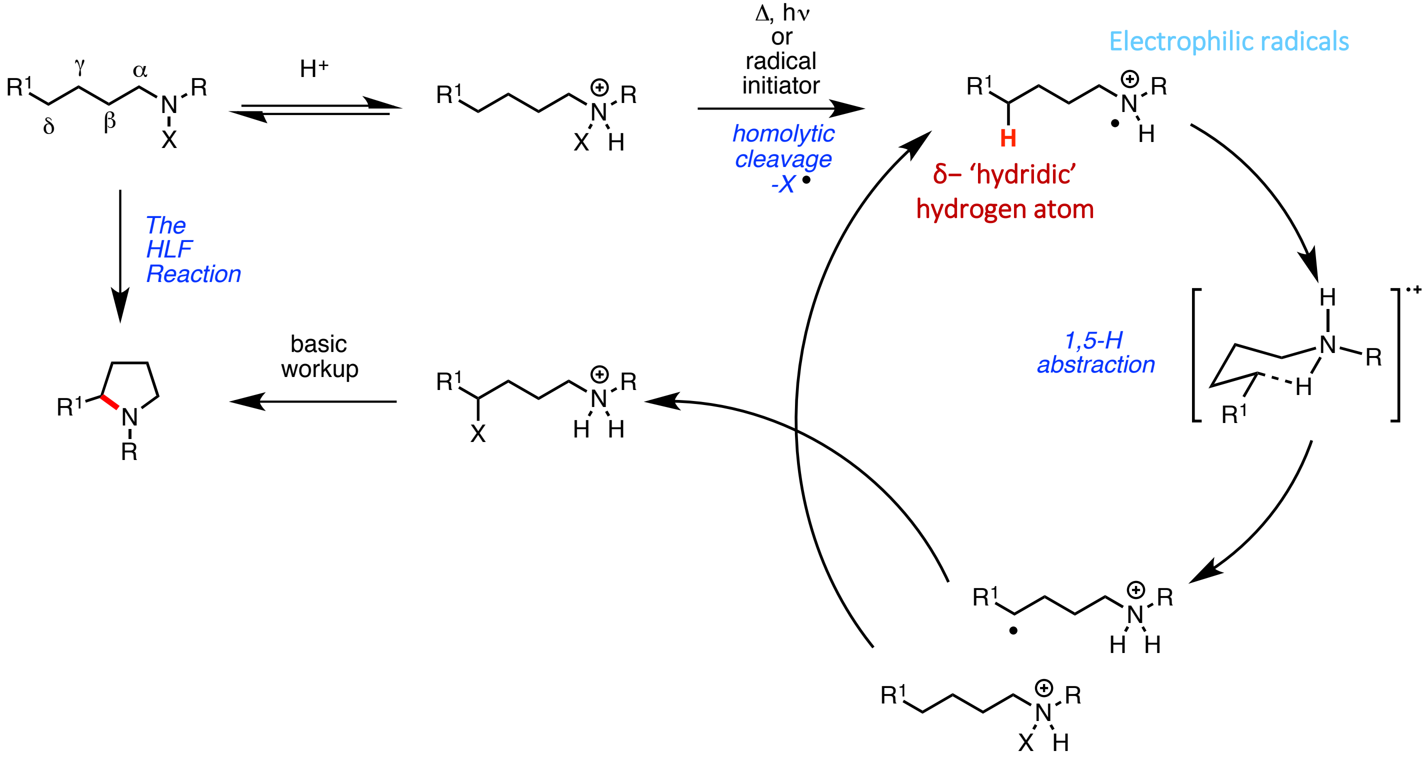
> Polarity effect in HAT reactions: matched polarity

Just like S_n2 reactions, polarities of the reactants should be matched for favorable reactivity.

Polarity: kinetic factor

$$\left.\begin{array}{l} \mathrm{El^{\bullet}} + \overset{\delta-}{\mathrm{Nuc{-}H}} \longrightarrow \mathrm{El{-}H} + \mathrm{Nuc^{\bullet}} \\ \mathrm{Nuc^{\bullet}} + \underset{\delta+}{\mathrm{El{-}H}} \longrightarrow \mathrm{Nuc{-}H} + \mathrm{El^{\bullet}} \end{array}\right\}\ \text{favored}$$

An ELECTROPHILIC radical will react via a HAT to generate a NUCLEOPHILIC radical



> E. R. Welin *et al.*, **Radical philicity and its role in selective organic transformations**, *Nat. Rev. Chem.* **2021**, *5*, 486

Guiding factors in radical chemistry

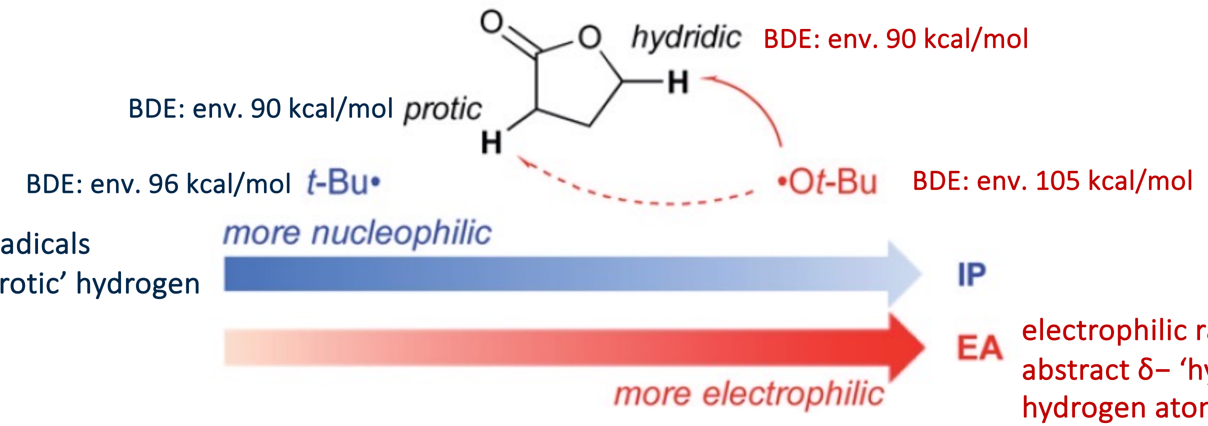
> Polarity effect in HAT reactions: matched polarity

Just like S_n2 reactions, polarities of the reactants should be matched for favorable reactivity.

$$\left.\begin{array}{l} El^{\bullet} + \overset{\delta-}{Nuc\text{–}H} \longrightarrow El\text{–}H + Nuc^{\bullet} \\ Nuc^{\bullet} + \underset{\delta+}{El\text{–}H} \longrightarrow Nuc\text{–}H + El^{\bullet} \end{array}\right\} \text{favored}$$

Can you predict the reactivity?

Radical philicity and selectivity of HAT:



Nucleophilic radicals abstract δ+ 'protic' hydrogen atoms

electrophilic radicals abstract δ– 'hydridic' hydrogen atoms

BDE: Thermodynamic factor

Polarity: kinetic factor

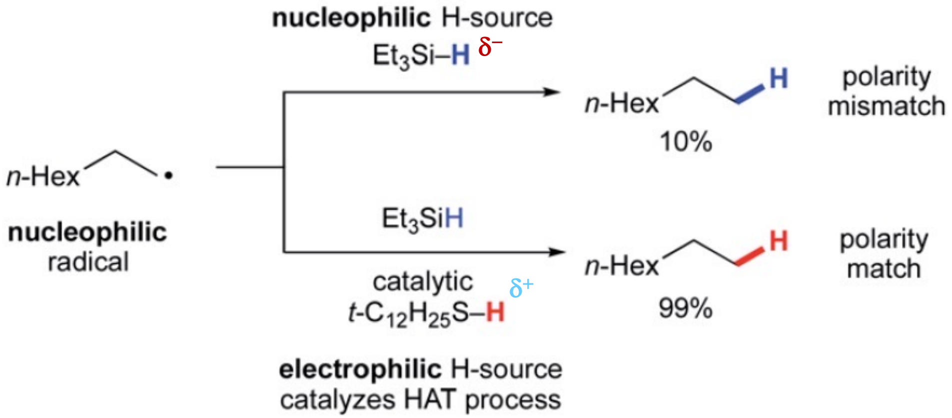
Both are favored in this case

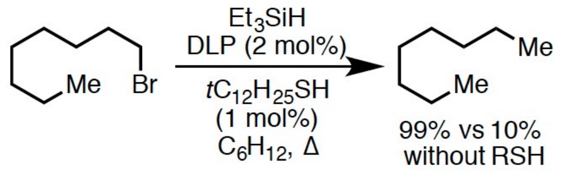
> E. R. Welin *et al.*, Radical philicity and its role in selective organic transformations, *Nat. Rev. Chem.* 2021, *5*, 486

Guiding factors in radical chemistry

> Polarity effect in HAT reactions: what happens in the case of mismatched polarity?

$$\left.\begin{array}{l} \mathrm{El^{1\bullet}} + \mathrm{El^2{-}\overset{\delta+}{H}} \longrightarrow \mathrm{El^1{-}H} + \mathrm{El^{2\bullet}} \\ \mathrm{Nuc^{1\bullet}} + \mathrm{Nuc^2{-}\underset{\delta-}{H}} \longrightarrow \mathrm{Nuc^1{-}H} + \mathrm{Nuc^{2\bullet}} \end{array}\right\} \text{disfavored}$$





$$\underset{Nuc^\bullet}{R^\bullet} + \underset{El{-}H}{R'S{-}H} \xrightarrow[\text{favorable}]{} \underset{Nuc{-}H}{R{-}H} + \underset{El^\bullet}{R'S^\bullet}$$

$$\underset{El^\bullet}{R'S^\bullet} + \underset{Nuc{-}H}{Et_3Si{-}H} \xrightarrow[\text{favorable}]{} \underset{El{-}H}{R'S{-}H} + \underset{Nuc^\bullet}{Et_3Si^\bullet}$$

$$Et_3Si^\bullet + R{-}X \xrightarrow{\text{fast}} Et_3Si{-}X + R^\bullet$$

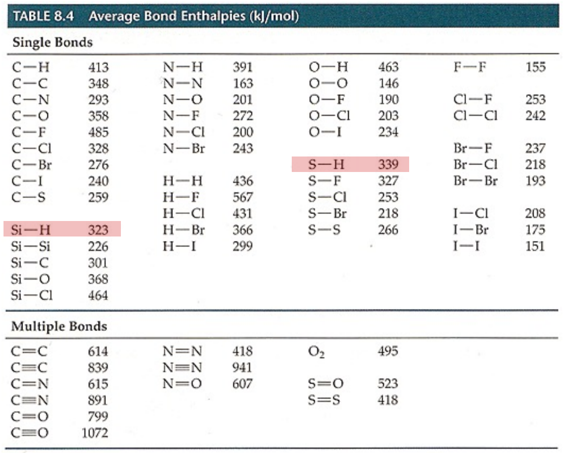
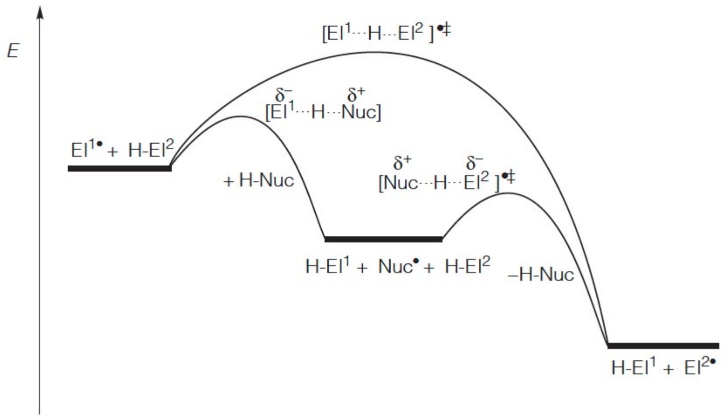


TABLE 8.4 Average Bond Enthalpies (kJ/mol)

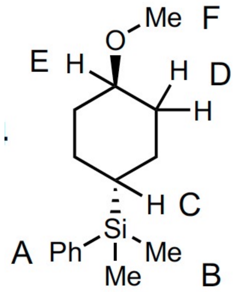
Single Bonds							
C—H	413	N—H	391	O—H	463	F—F	155
C—C	348	N—N	163	O—O	146		
C—N	293	N—O	201	O—F	190	Cl—F	253
C—O	358	N—F	272	O—Cl	203	Cl—Cl	242
C—F	485	N—Cl	200	O—I	234		
C—Cl	328	N—Br	243			Br—F	237
C—Br	276			S—H	339	Br—Cl	218
C—I	240	H—H	436	S—F	327	Br—Br	193
C—S	259	H—F	567	S—Cl	253		
		H—Cl	431	S—Br	218	I—Cl	208
Si—H	323	H—Br	366	S—S	266	I—Br	175
Si—Si	226	H—I	299			I—I	151
Si—C	301						
Si—O	368						
Si—Cl	464						
Multiple Bonds							
C=C	614	N=N	418	O_2	495		
C≡C	839	N≡N	941				
C=N	615	N=O	607	S=O	523		
C≡N	891			S=S	418		
C=O	799						
C≡O	1072						



\> E. R. Welin *et al.*, Radical philicity and its role in selective organic transformations, *Nat. Rev. Chem.* **2021**, *5*, 486

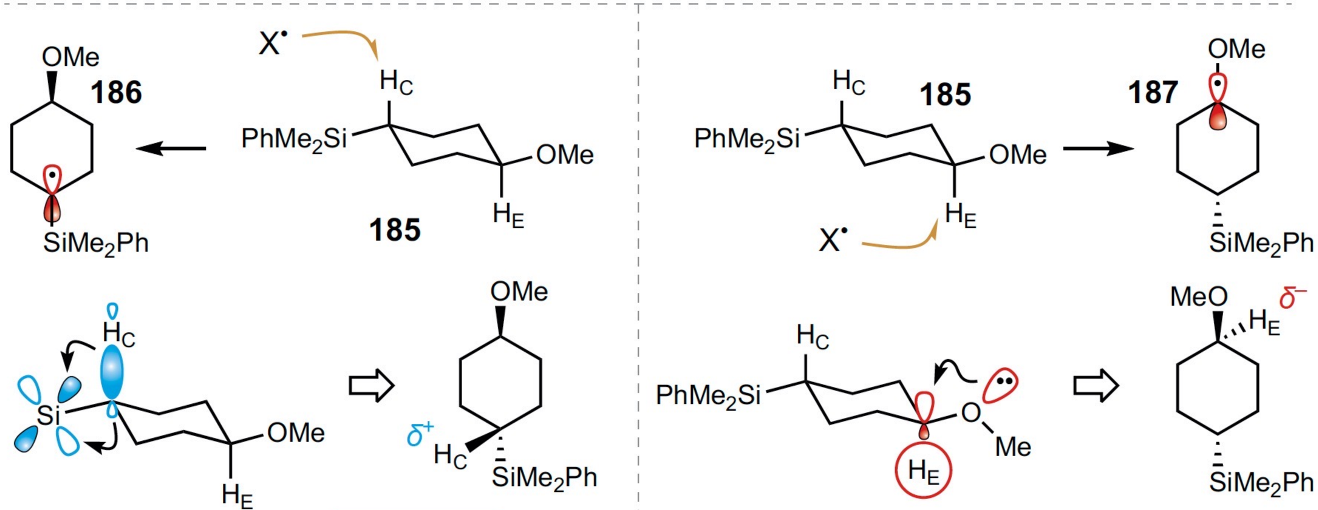
Guiding factors in radical chemistry

> At which location might radical C-H abstraction occur?



C–H bond	Expected BDE (kcal mol^{-1})
A	110–112
B	99–101
C	90–92
D	96–98
E	90–92
F	95–96

> How can we predict which radical is likely to abstract the most reactive H?



$\sigma_{C-H} \rightarrow d_{Si}$ results in δ^+ on H_C ⇨ Nucleophilic radicals will abstract H_C

$p_O \rightarrow \sigma^*_{C-H}$ results in δ^- on H_E ⇨ Electrophilic radicals will abstract H_E

> E. R. Welin *et al.*, **Radical philicity and its role in selective organic transformations**, *Nat. Rev. Chem.* **2021**, *5*, 486

Réactions de fonctionnalisation C-H et chimie médicinale

- Introduction
  1. Catalytic C-H Functionalization Reactions vs. Functional Group Transformations
  2. Catalytic C-H Functionalization Reactions: challenges & general mechanisms

- Catalytic C-H Functionalization by C-H Activation (*inner-sphere mechanism*)
  1. Mechanistic considerations
  2. Heteroatom-directed C-H Functionalization
  3. Oxidative addition-directed C-H Functionalization

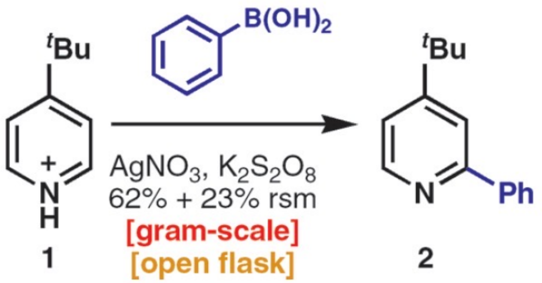
- Catalytic C-H Functionalization by C-H Insertion (*outer-sphere mechanism*)
  1. Mechanistic considerations
  2. Carbene chemistry
  3. Nitrene chemistry
  4. C-H oxidation

- Catalytic C-H Functionalization using radicals
  1. Historical reactions and mechanistic considerations
  2. Hydrogen Atom Transfer (HAT)
  3. Minisci-type Reaction

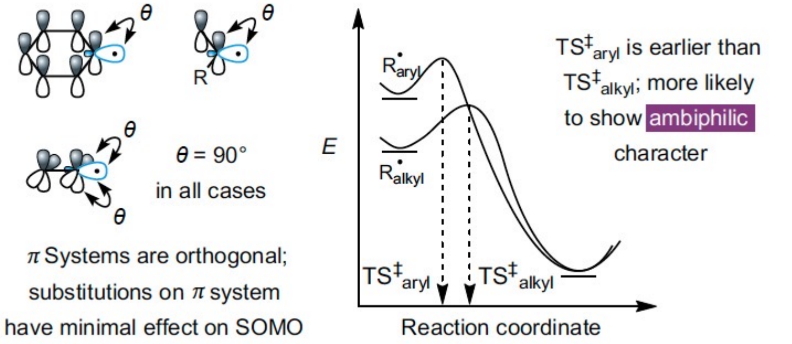
- Application of catalytic C-H functionalization
  Total synthesis & Late-stage functionalization of natural products and drugs

• Intermolecular radical C-H functionalization

> The Borono-Minisci reaction

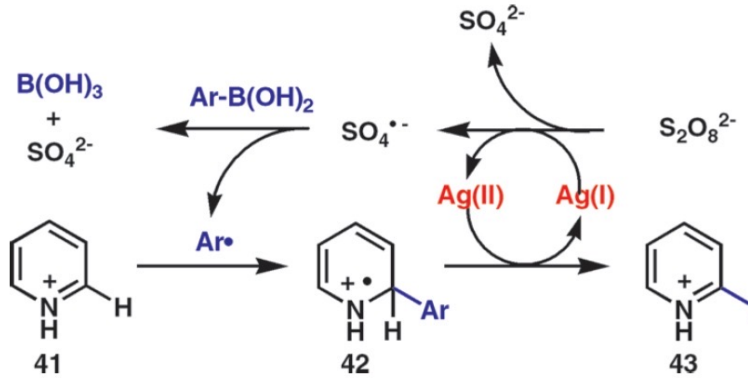


sp and sp² hybrid radicals: increased s character increases electrophilicity



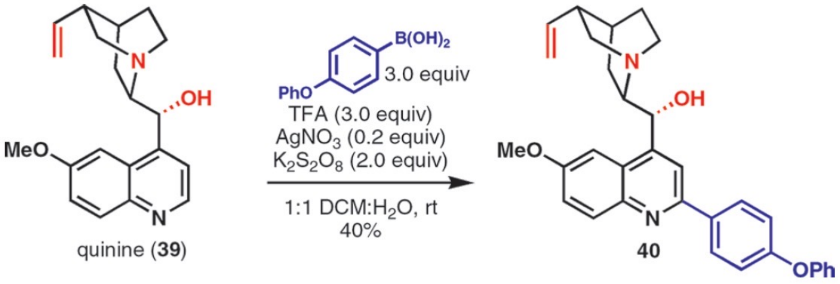
π Systems are orthogonal; substitutions on π system have minimal effect on SOMO

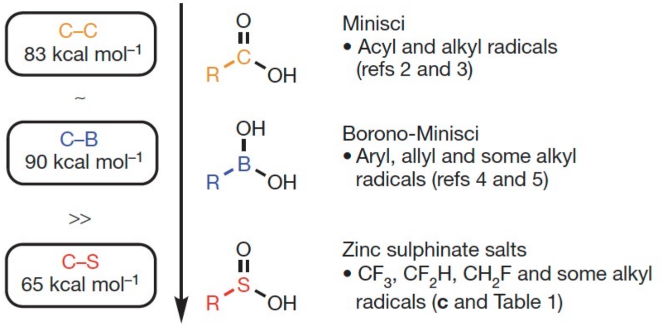
TS‡aryl is earlier than TS‡alkyl; more likely to show ambiphilic character



Ar˙ weakly nucleophilic
But pyridine highly activated by the acid

Scheme 1. Direct Arylation of Quinine^a





Minisci
- Acyl and alkyl radicals (refs 2 and 3)

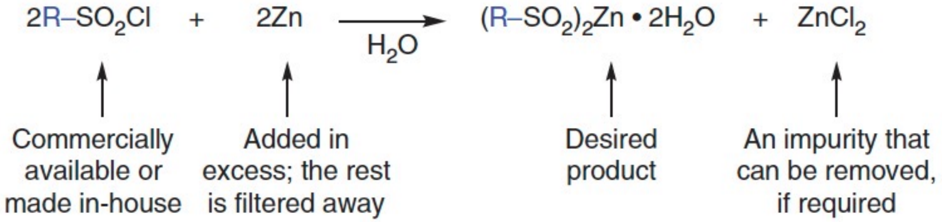
Borono-Minisci
- Aryl, allyl and some alkyl radicals (refs 4 and 5)

Zinc sulphinate salts
- CF$_3$, CF$_2$H, CH$_2$F and some alkyl radicals (**c** and Table 1)

> P. S. Baran *et al.*, Direct C-H arylation of electron-deficient heterocycles with arylboronic acids, *J. Am. Chem. Soc.* **2010**, *132*, 13194

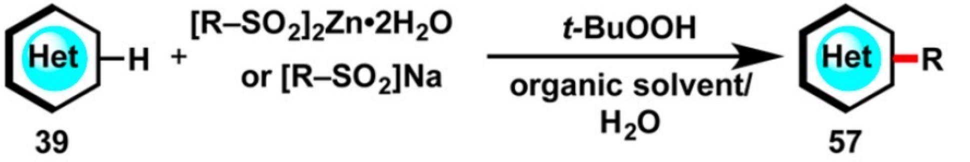
• Intermolecular radical C-H functionalization

> Alkyl sulfinates

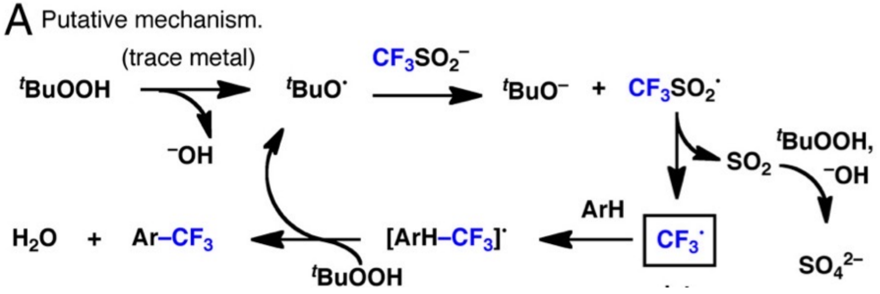


$$2R\text{–}SO_2Cl + 2Zn \xrightarrow[H_2O]{} (R\text{–}SO_2)_2Zn \bullet 2H_2O + ZnCl_2$$

B. Development of zinc sulfinate toolbox for drug discovery.



R group	Acronym of zinc sulfinate reagent	Sigma–Aldrich catalog number
CF_3	TFMS	771406
CF_2H	DFMS	767840
CH_2Cl	MCMS	791105
CH_2SO_2Ph	PSMS	792187
CF_2CH_3 (Na salt)	DFES-Na	745405
CH_2CF_3	TFES	745499
CH_2CH_2Cl	MCES	790788
$CH_2CH_2CH_3$	NPS	791040
$CH(CH_3)_2$	IPS	745480
CH_2Ph	BNS	790796

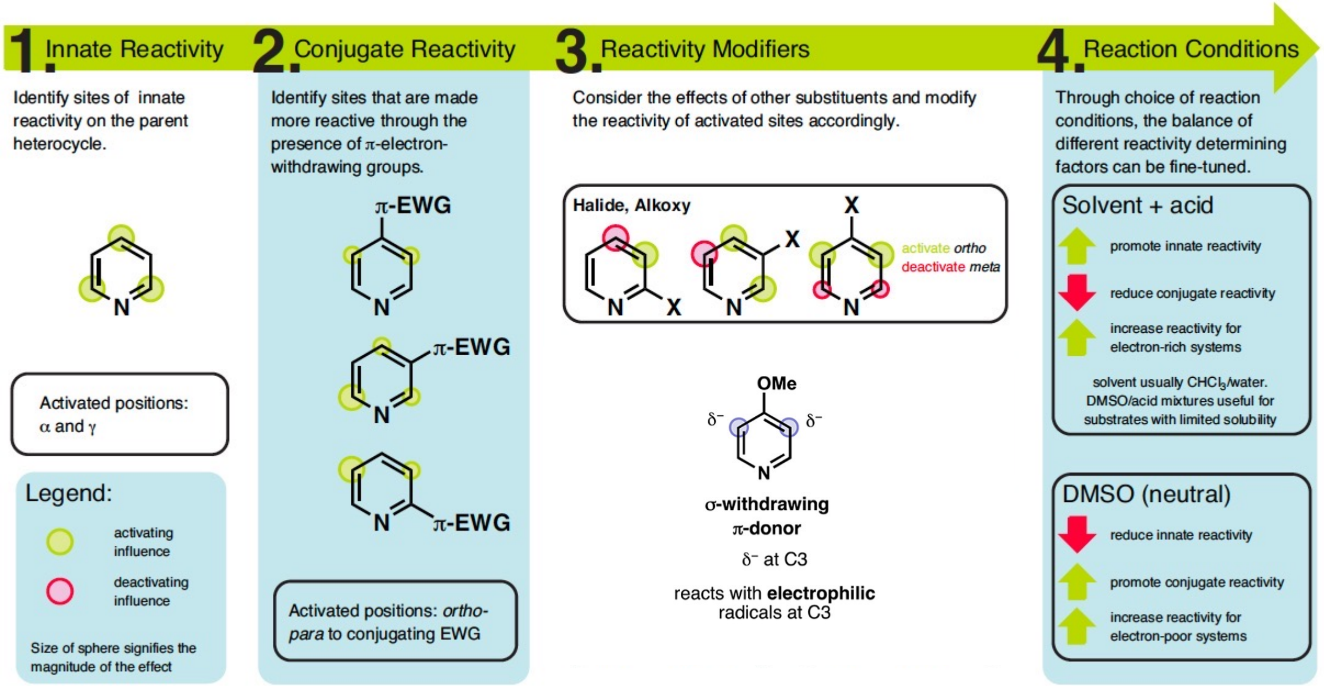


A Putative mechanism.

> P. S. Baran *et al.*, Practical and innate C-H functionalization of heterocycles, *Nature* 2012, *492*, 95

- Intermolecular radical C-H functionalization

> Alkyl sulfinates



1. Innate Reactivity

Identify sites of innate reactivity on the parent heterocycle.

Activated positions: α and γ

Legend:

- ● activating influence
- ● deactivating influence

Size of sphere signifies the magnitude of the effect

2. Conjugate Reactivity

Identify sites that are made more reactive through the presence of π-electron-withdrawing groups.

Activated positions: *ortho*-*para* to conjugating EWG

3. Reactivity Modifiers

Consider the effects of other substituents and modify the reactivity of activated sites accordingly.

Halide, Alkoxy: activate *ortho*, deactivate *meta*

σ-withdrawing π-donor

δ⁻ at C3

reacts with **electrophilic** radicals at C3

4. Reaction Conditions

Through choice of reaction conditions, the balance of different reactivity determining factors can be fine-tuned.

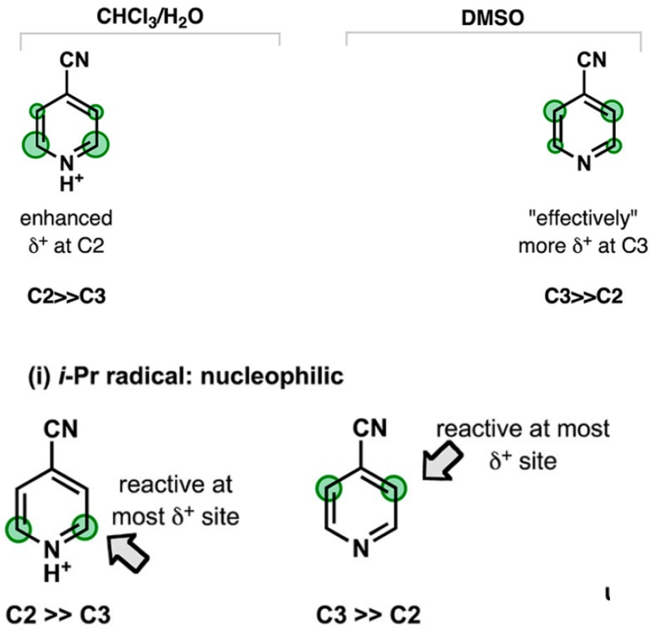
Solvent + acid

- promote innate reactivity
- reduce conjugate reactivity
- increase reactivity for electron-rich systems

solvent usually $CHCl_3$/water. DMSO/acid mixtures useful for substrates with limited solubility

DMSO (neutral)

- reduce innate reactivity
- promote conjugate reactivity
- increase reactivity for electron-poor systems



enhanced δ⁺ at C2

C2>>C3

"effectively" more δ⁺ at C3

C3>>C2

(i) *i*-Pr radical: nucleophilic

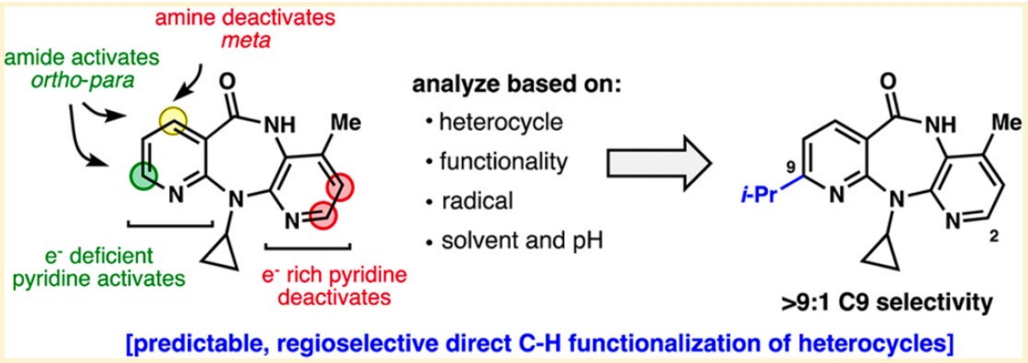
reactive at most δ⁺ site

C2 >> C3

reactive at most δ⁺ site

C3 >> C2

In DMSO



analyze based on:

- heterocycle
- functionality
- radical
- solvent and pH

>9:1 C9 selectivity

[predictable, regioselective direct C-H functionalization of heterocycles]

> PS Baran *et al.*, Radical-based regioselective C-H functionalization of electron-deficient heteroarenes, *J. Am. Chem. Soc.* **2013**, *135*, 12122