- Réactions de fonctionnalisation C-H et chimie médicinale

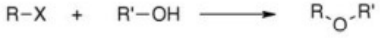
Réactions robustes de la chimie médicinale

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

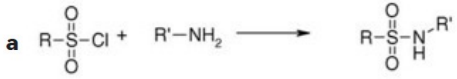
- Broad availability of starting materials and reagents
- Broad functional group tolerance including polar functionalities
- Time for delivery of the target compounds is reasonably short

(c) Ether formation (Williamson synthesis / Mitsunobu reaction)



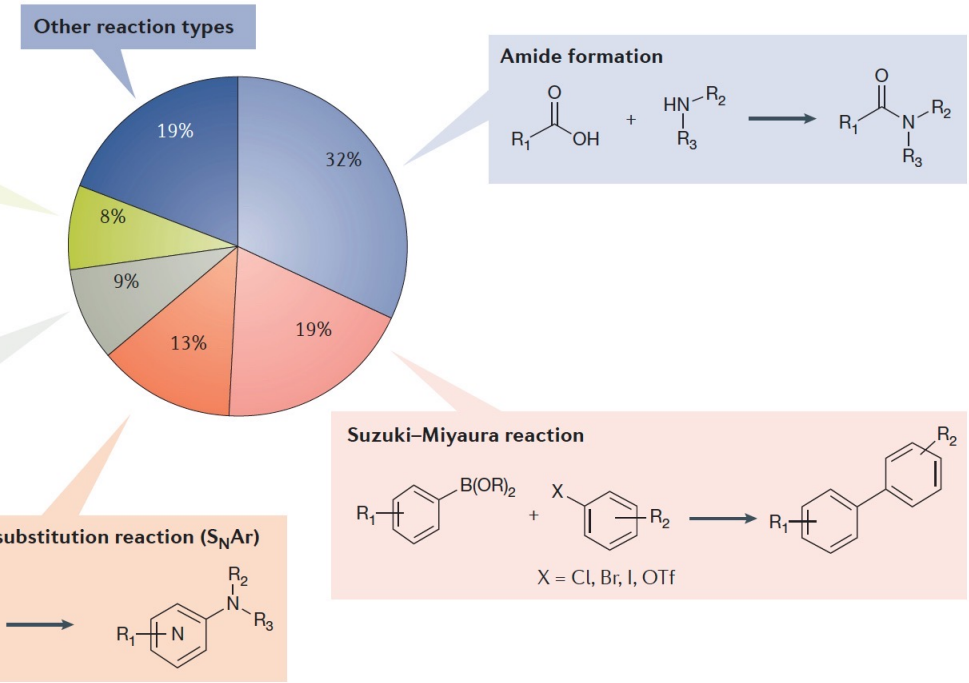
X = Leaving Group, e.g. Br, I

(e) Sulphonamide formation



(j) Wittig reaction

R' may be H



- Réactions de fonctionnalisation C-H et chimie médicinale

Late-stage functionalization

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.

Tactic 2: Methylation

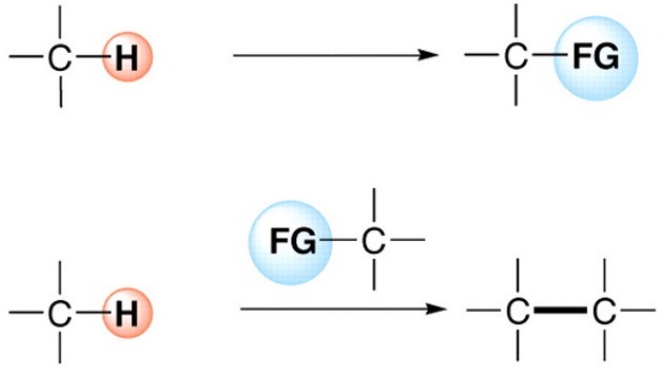
Strategic methylation can produce compounds with pronounced improvements in activity, safety and DMPK properties.
New late stage methylation methods with regio- or stereochemical control could have great utility for this purpose.

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.

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.



✓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.

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

> *New retrosynthetic strategies*

> *Structural core diversification*

- Réactions de fonctionnalisation C-H et chimie médicinale

Réactions de fonctionnalisation C-H: 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.

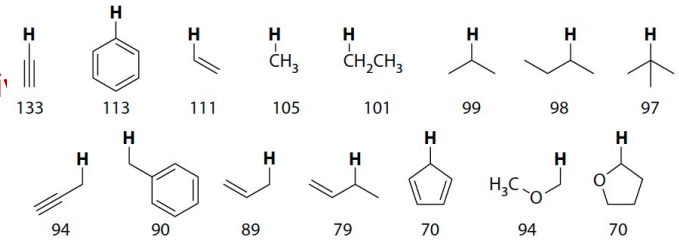
Bond	Bond Dissociation Energy kcal/mol (kJ/mol)
C—H	99 (413)
C—C	83 (347)
C—N	73 (305)
C—O	86 (358)
C—Cl	81 (339)

Alkanes > not strongly nucleophilic.

> not highly electrophilic or sensitive to light.

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

BDEs of C—H Bonds (kcal mol^{-1})



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

- 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

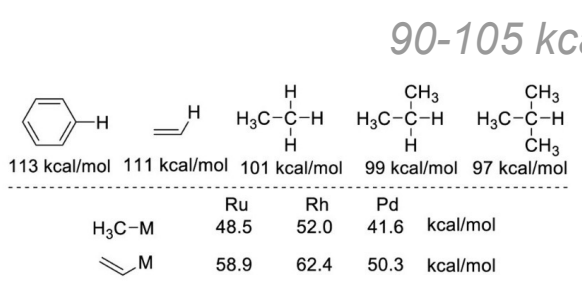
5. the introduction of a C-X bond might change the reactivity of a whole molecule.

- Réactions de fonctionnalisation C-H et chimie médicinale

Réactions de fonctionnalisation C-H: terminologie

"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.

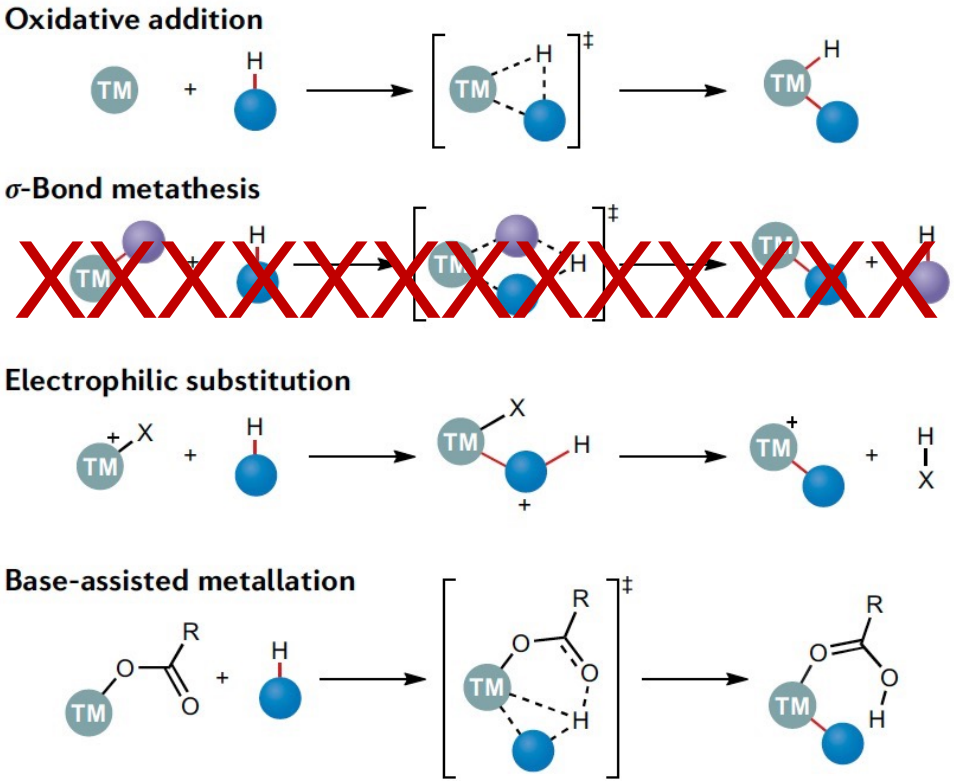
- Réactions de fonctionnalisation C-H et chimie médicinale

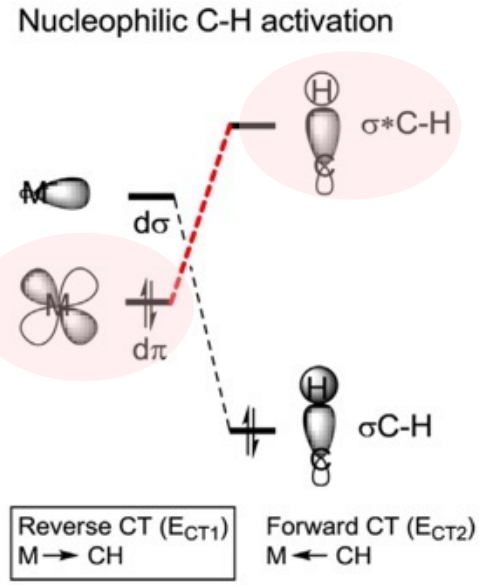
Réactions de fonctionnalisation C-H : activation C-H

C-H Activation by Oxidative Addition

- Mécanismes

> 4 General mechanisms



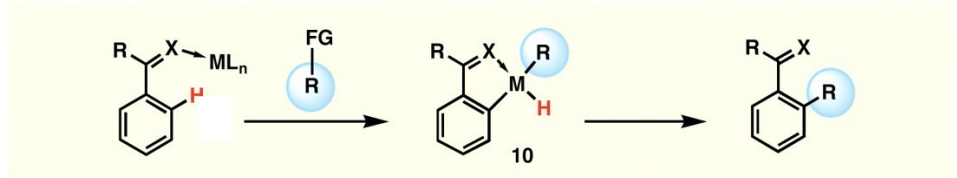


Oxidative addition favored :
low valent electron rich transition metals Rh(I), Ir(I), Ru(0)
(d^8 low-valent 2nd & 3rd raw late TM complexes)

posses high-energy dπ and dσ orbitals

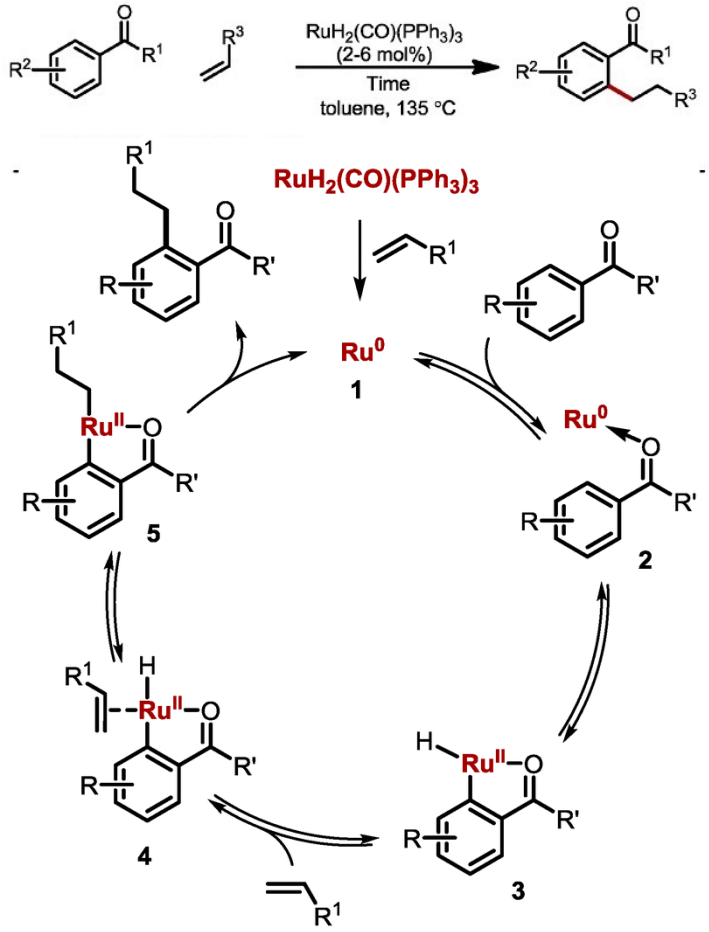
- Réactions de fonctionnalisation C-H et chimie médicinale

C-H Activation by Oxidative Addition

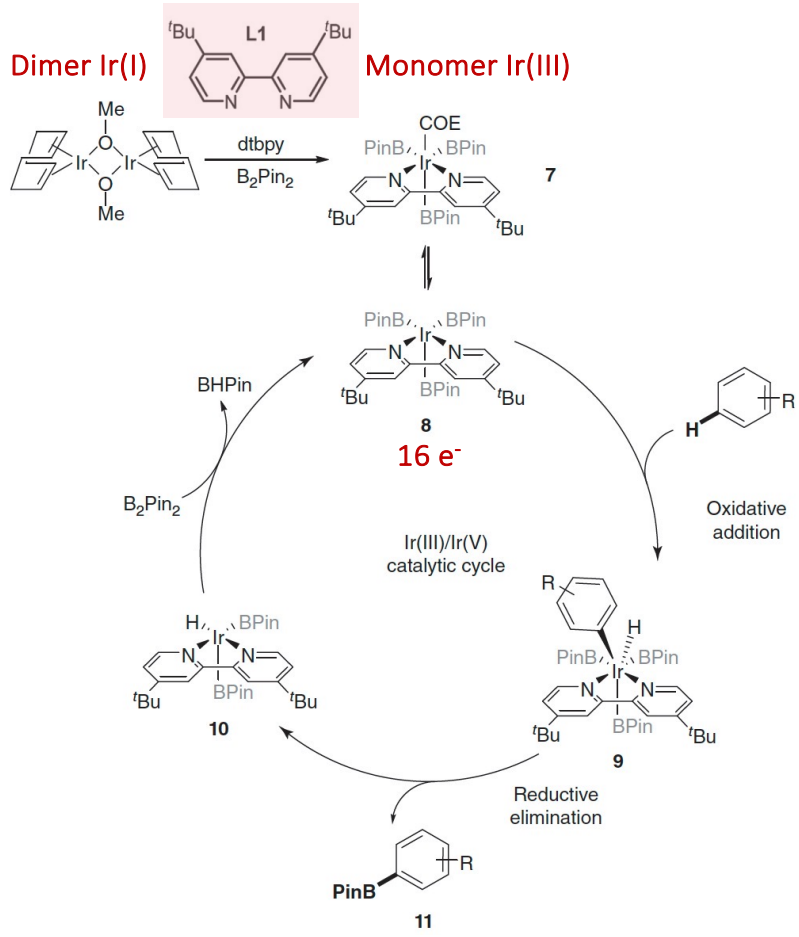


Prototypical example: Reaction de Murai

Ruthenium-catalyzed *ortho*-alkylation of aromatic ketones



Iridium-catalyzed borylation > Steric control

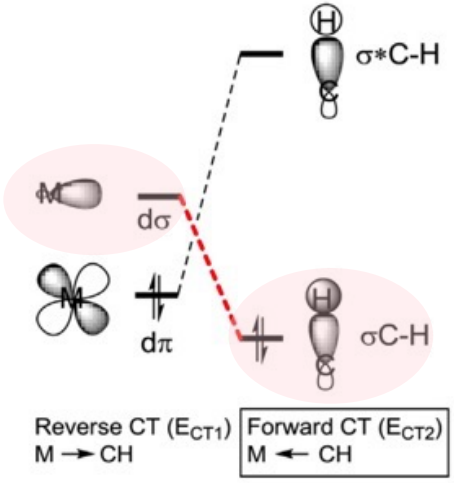


- Réactions de fonctionnalisation C-H et chimie médicinale

C-H Activation by Electrophilic Substitution

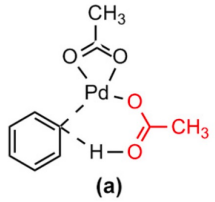
- Mécanismes

Electrophilic C-H activation

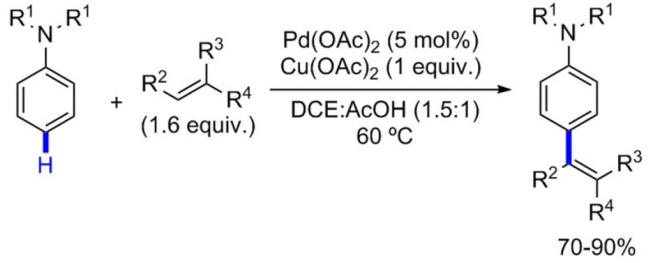


Electrophilic substitution favored :
Electron poor, late transition metals in high oxidation states, such as Pd(II), Pt(II)

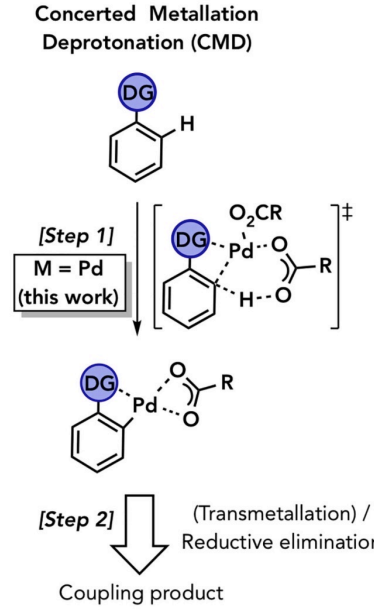
the electronic properties of the arene play a fundamental role
Works better with electron-rich arenes
Often analogous to Friedel-Crafts mechanism

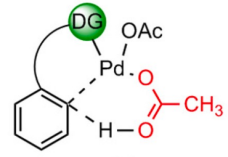


Selective para-alkenylation of anilines



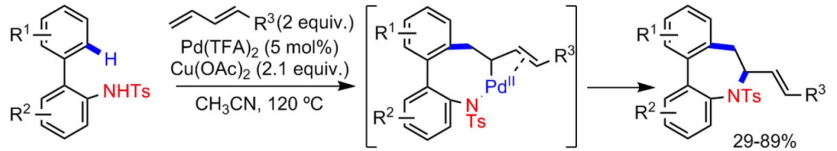
C-H Activation by Concerted Metalated Deprotonation





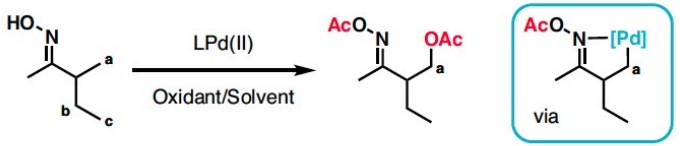
- internal base C–H deprotonation via six-membered TS
- little charge buildup during TS, donating ligands tolerate
- relative basicity of C–H bond and internal base critical
- often preceded by agostic complex formation

(D) ***Tosylamide as remote directing group***



- Réactions de fonctionnalisation C-H et chimie médicinale

Activation C-H: Groupements directeurs



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

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

Selectivity Guidelines:

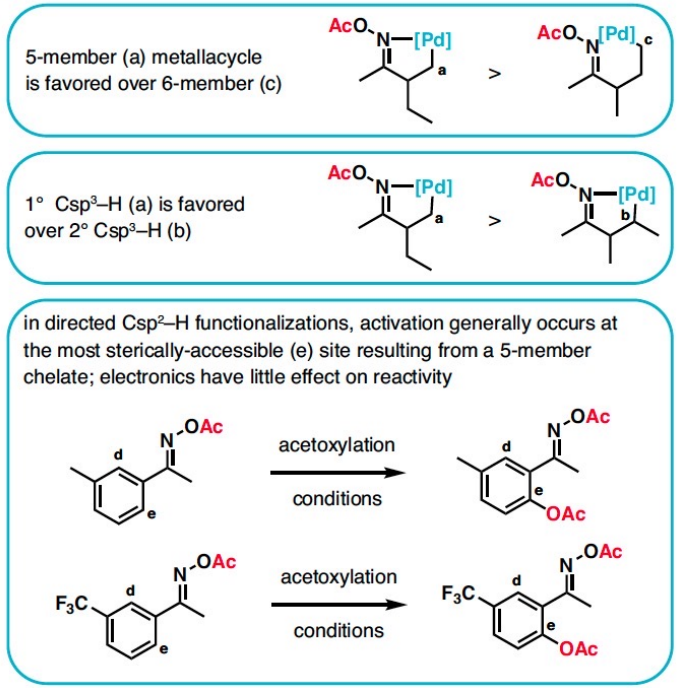
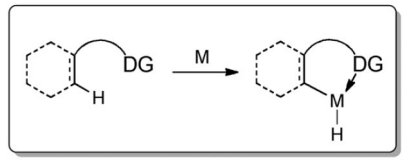
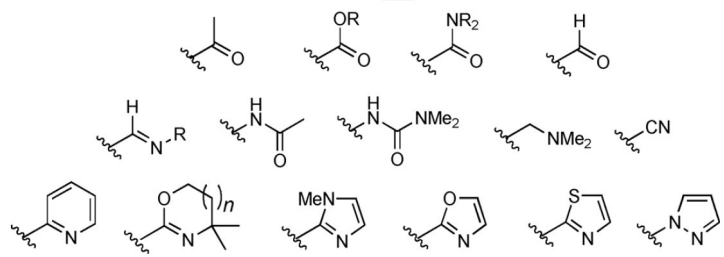


Figure 6. Directed Organometallic C–H Functionalization Selectivity Demonstrated with Acetoxylation[1]

- Native coordinating group



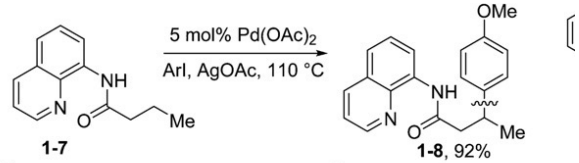
DG



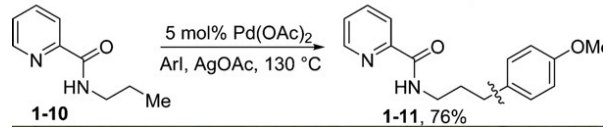
Scheme 4. Some important chemical functions that act as a monodentate directing group.

- Bidentate Directing group

8-AMINOQUINOLINE



2-PICOLINAMIDE

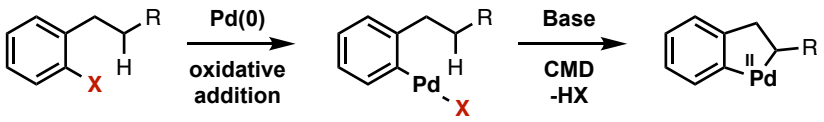


- Réactions de fonctionnalisation C-H et chimie médicinale

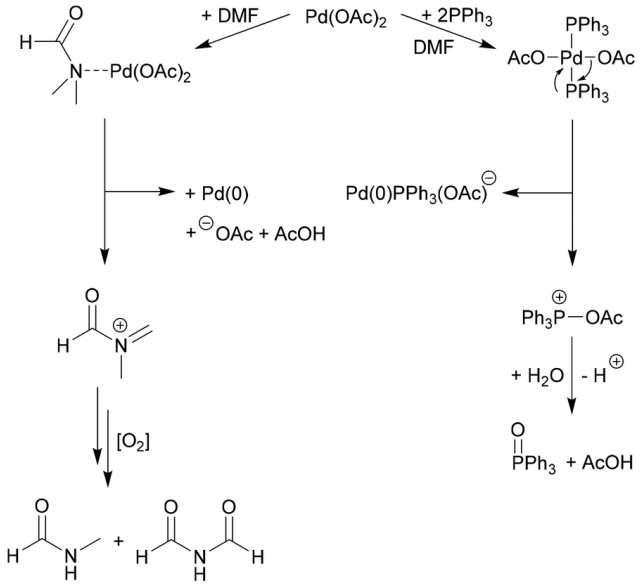
Activation C-H: Groupements directeurs

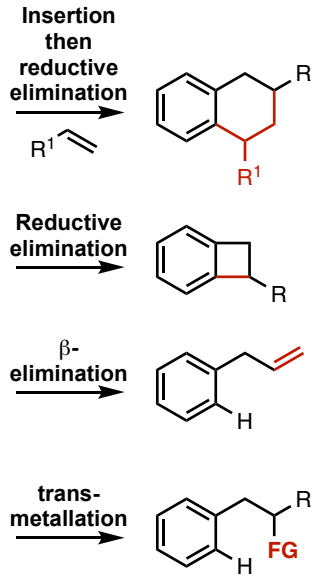
- Aryl/vinyl halides as Directing groups

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

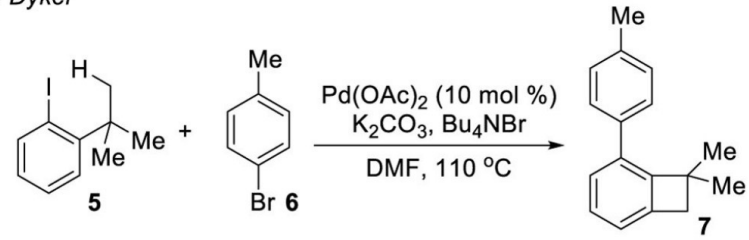


> The Halogen can be considered as a traceless DG

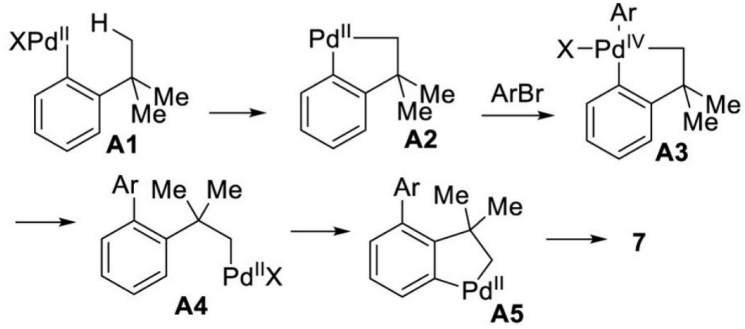




▪ *Dyker*



> Oxidative addition

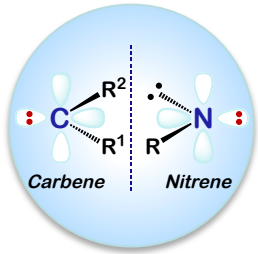


- Réactions de fonctionnalisation C-H et chimie médicinale

Réactions de fonctionnalisation C-H : insertion C-H

- Carbène-Nitrène

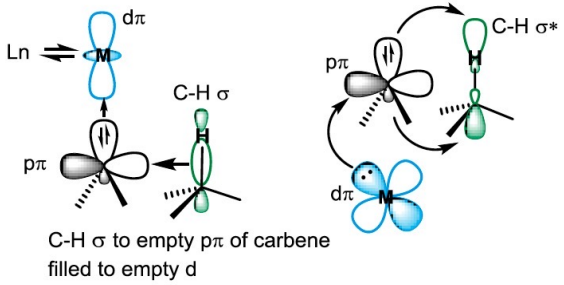
Neutral, divalent carbon species containing 6 valence electrons



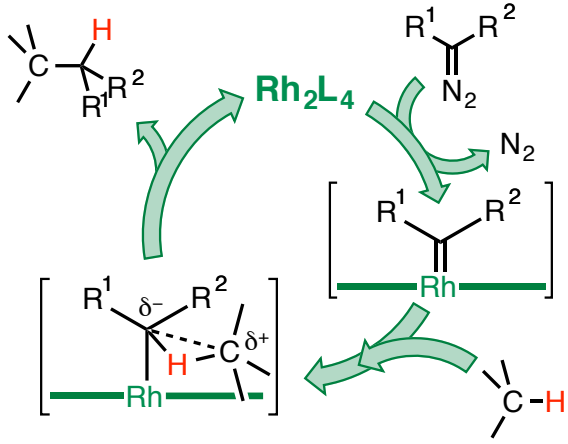
Neutral, monovalent nitrogen species containing 6 valence electrons

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.

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

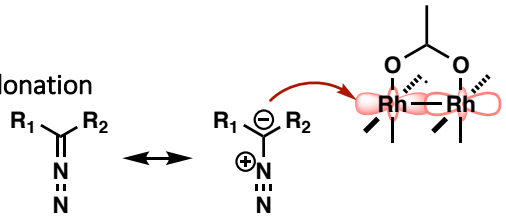


> Stereochemical probe

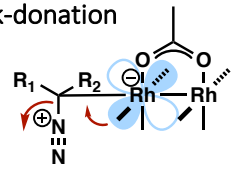


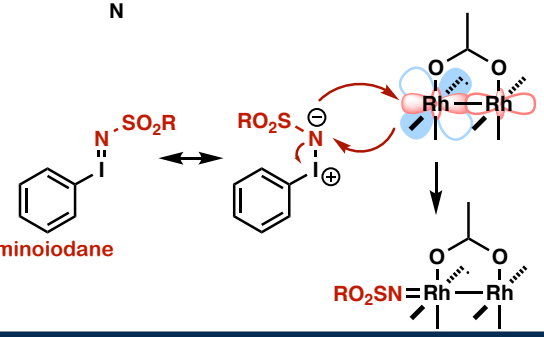
> Concerted
> Asynchronous
> Transition State

> σ-donation



> π-back-donation

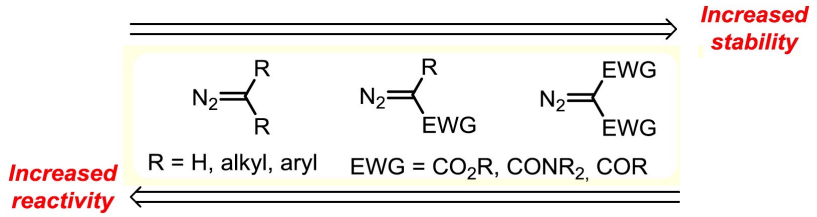




- Réactions de fonctionnalisation C-H et chimie médicinale

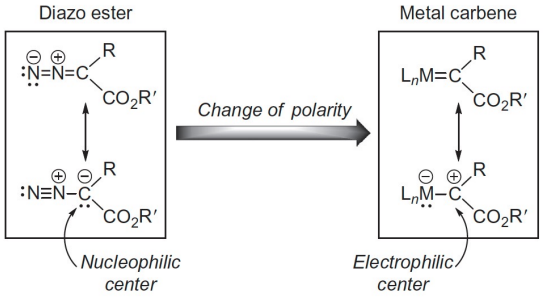
Insertion C-H de carbènes

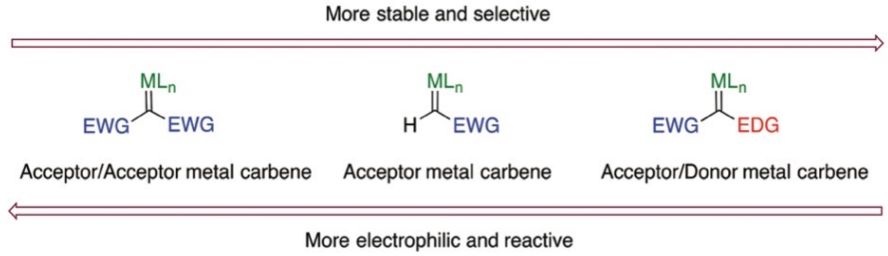
- Reactivity



> R = EDG or Electron-Donating Group

> 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*

> The starting diazos are often unstable
Recent studies have demonstrated their utility in intramolecular reactions

> Suitable for intramolecular reactions
Issue in intermolecular processes: dimerization

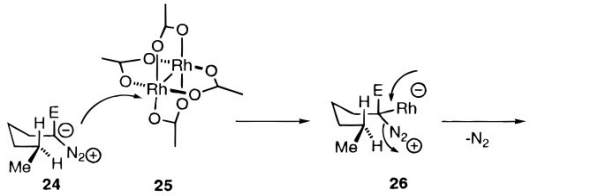
> Suitable for intermolecular reactions
The donor group has a stabilizing effect, reducing the electrophilicity of the carbene. Its lifetime is increased, thus the selectivity is improved

- Réactions de fonctionnalisation C-H et chimie médicinale

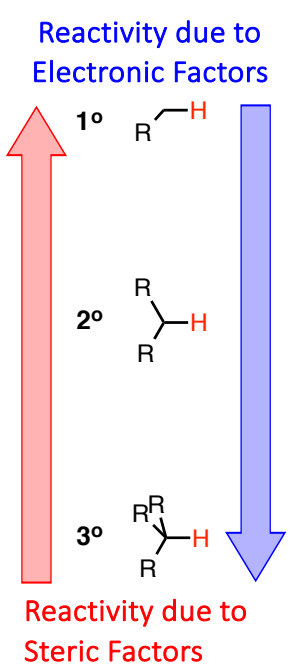
Insertion C-H de carbènes

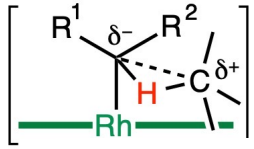
- Selectivity

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



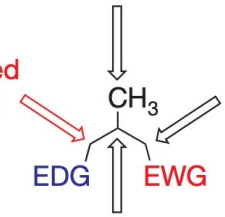
> The selectivity is controlled by a combination of STERIC and ELECTRONIC factors (Intra- and Inter-molecular reactions)





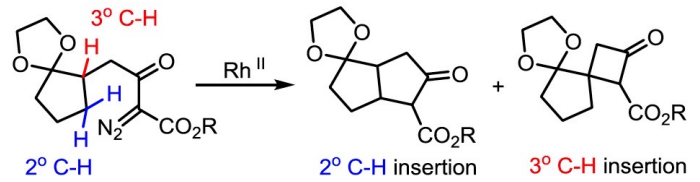
1° C–H sterically favoured
electronically disfavoured

2° C–H sterically favoured
electronically favoured



2° C–H sterically favoured
electronically disfavoured

3° C–H sterically disfavoured
electronically favoured



Note:
acam: acetamide
TPA: triphenylacetate
Piv: pivalate ^{t}Bu$_3$CO$_2$H
BzO: benzoic acid
TPA: OCOCPh$_3$

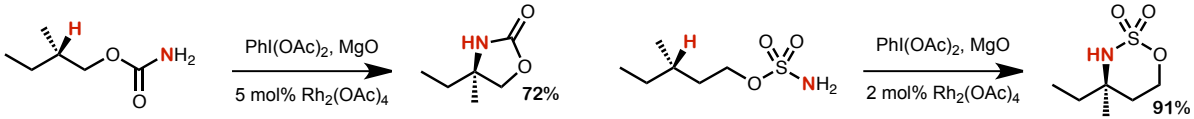
Catalyst	Ratio.
$[Rh_2(OAc)_4]$	37 : 63
$[Rh_2(TFA)_4]$	56 : 44
$[Rh_2(acam)_4]$	14 : 86
$[Rh_2(Piv)_4]$	37 : 63
$[Rh_2(OBz)_4]$	54 : 46
$[Rh_2(OCOCHPh_2)_4]$	64 : 36
$[Rh_2(OCOCMePh_2)_4]$	82 : 18
$[Rh_2(TPA)_4]$	96 : 4

bulkier — less hindered C-H favored

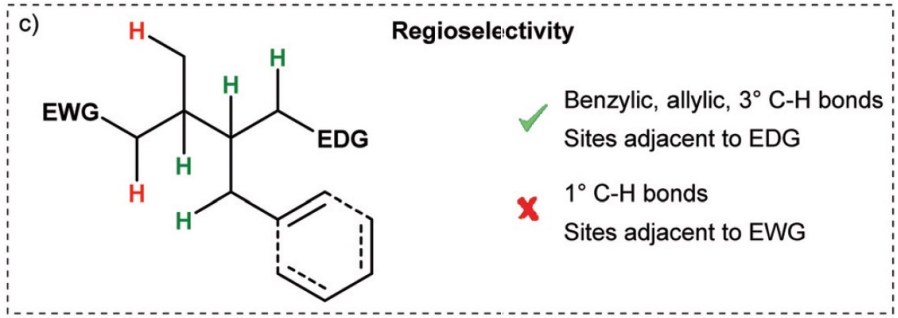
Angew. Chem. Int. Ed. **1994**, *33*, 1797

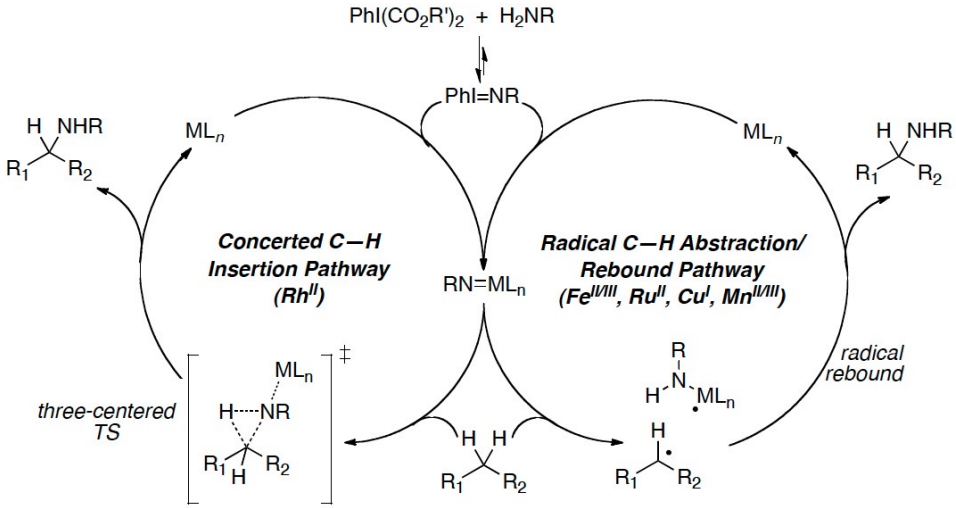
- Réactions de fonctionnalisation C-H et chimie médicinale

Insertion C-H de nitrènes



As in the case of carbenes
> The selectivity is controlled by a combination of STERIC and ELECTRONIC factors + BDE



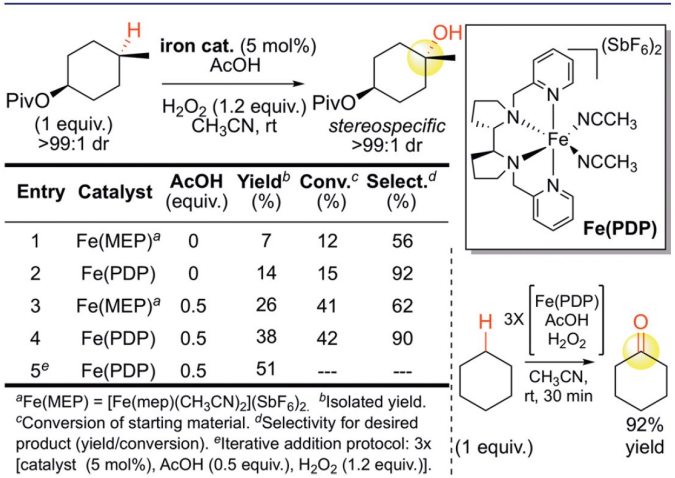


Concerted asynchronous insertion:
-examples: Rh
-turnover-limiting step is normally formation of iminoiodane
-three-centered transition state
-reactivity trends are dictated by the electron density of the reacting site (e.g. more electron-rich C-H bonds, such as 3°, are more reactive)

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)

- Réactions de fonctionnalisation C-H et chimie médicinale

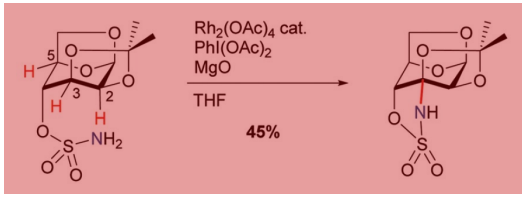
Oxydation de liaisons C-H

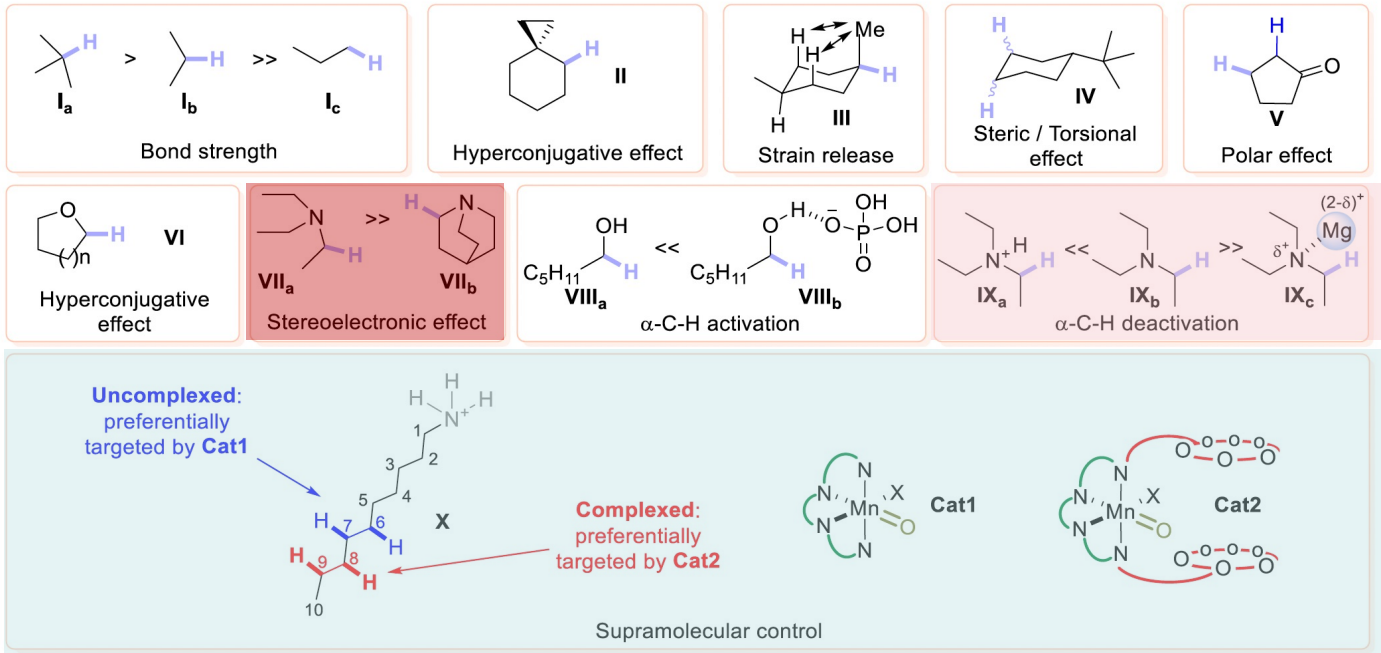


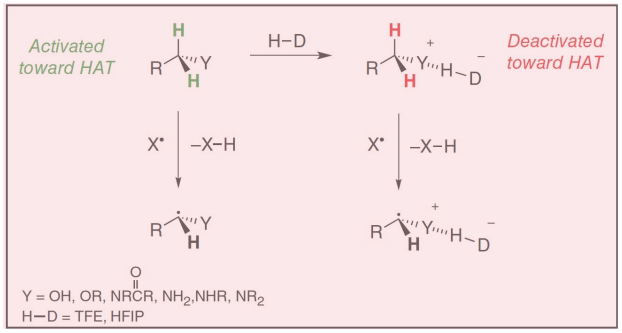
Entry	Catalyst	AcOH (equiv.)	Yield[b] (%)	Conv.[c] (%)	Select.[d] (%)
1	Fe(MEP)[a]	0	7	12	56
2	Fe(PDP)	0	14	15	92
3	Fe(MEP)[a]	0.5	26	41	62
4	Fe(PDP)	0.5	38	42	90
5[e]	Fe(PDP)	0.5	51	---	---

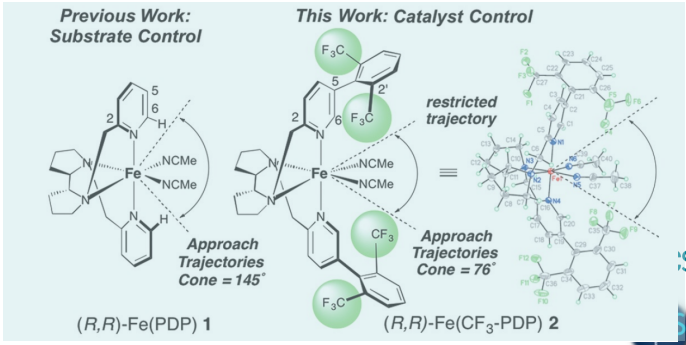
[a]Fe(MEP) = $[Fe(mep)(CH_3CN)_2](SbF_6)_2$. [b]Isolated yield. [c]Conversion of starting material. [d]Selectivity for desired product (yield/conversion). [e]Iterative addition protocol: 3x [catalyst (5 mol%), AcOH (0.5 equiv.), H_2O_2 (1.2 equiv.)].

Figure 12. Discovery of Fe(PDP) catalysis for preparative aliphatic C–H oxidations. Table from ref 11. Reproduced with permission from AAAS.





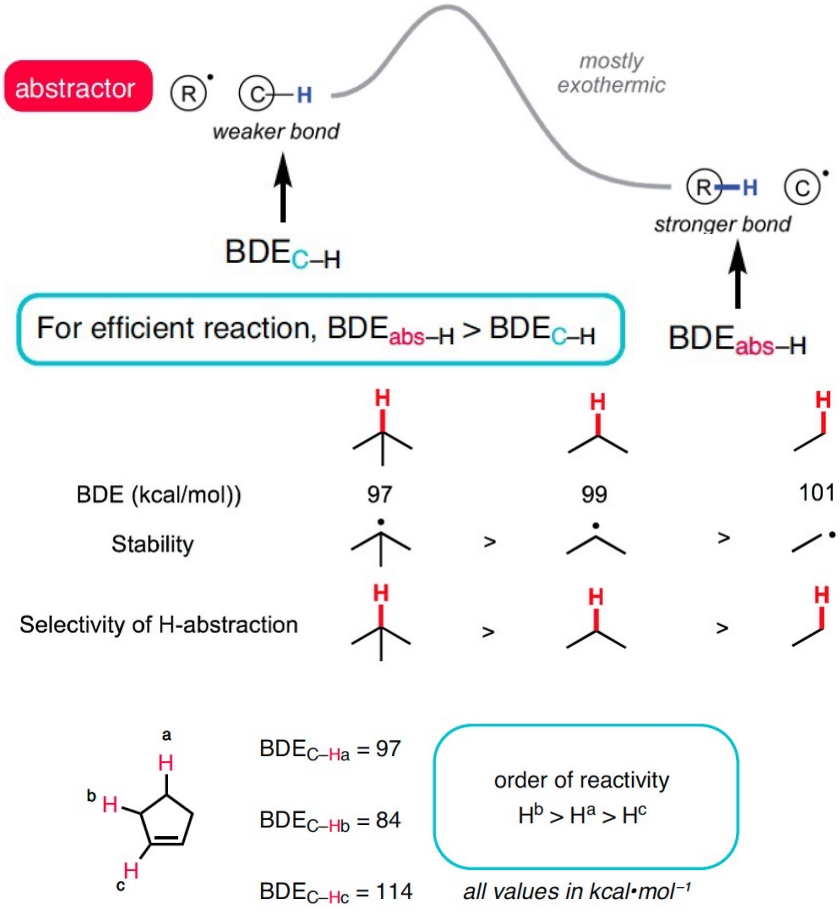


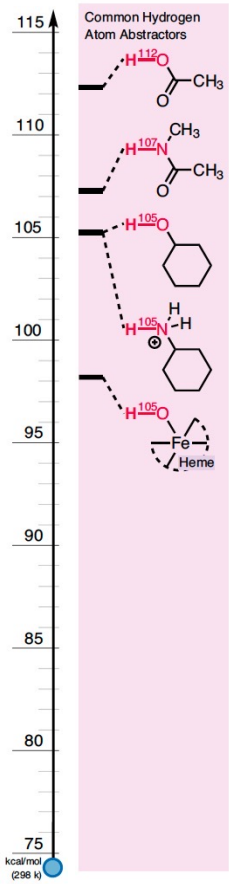


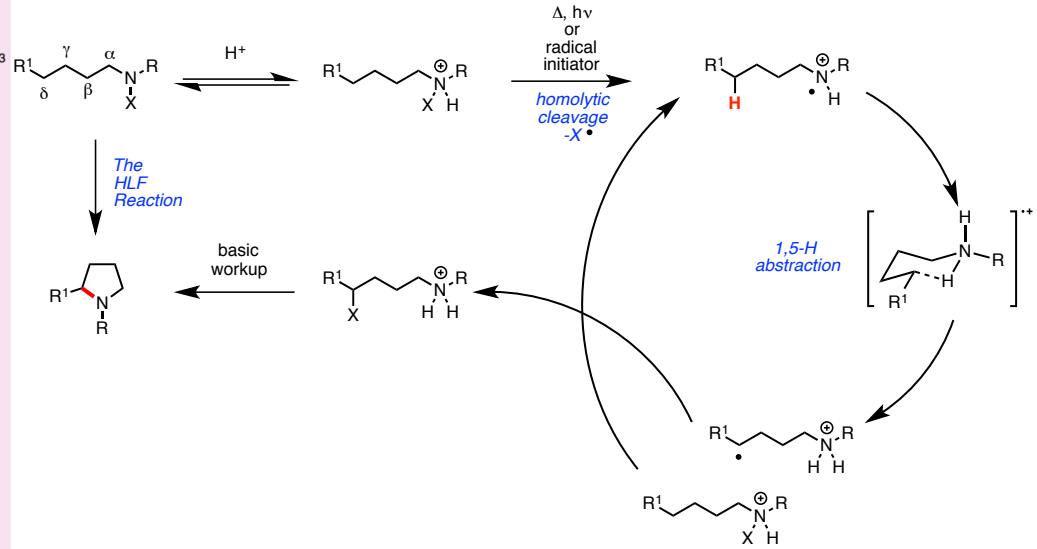
- Réactions de fonctionnalisation C-H et chimie médicinale

Réactions de fonctionnalisation C-H : HAT : transfert d'atome d'hydrogène

- *BDE: Thermodynamic factor*







- Réactions de fonctionnalisation C-H et chimie médicinale

HAT : transfert d'atome d'hydrogène

- *Polarity: kinetic factor*

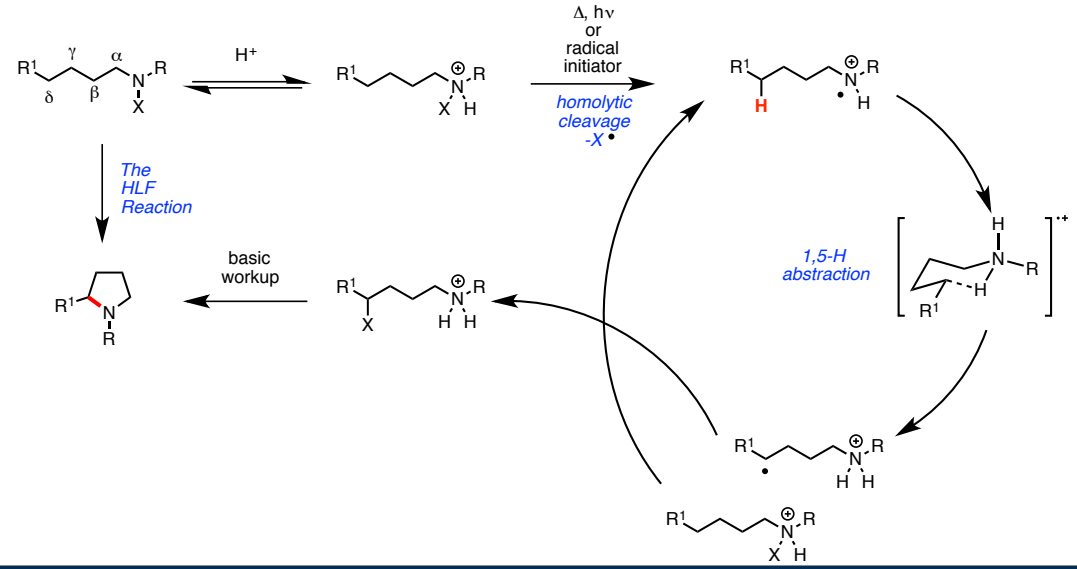
A qualitative approach to determining the "philicity" of a radical

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

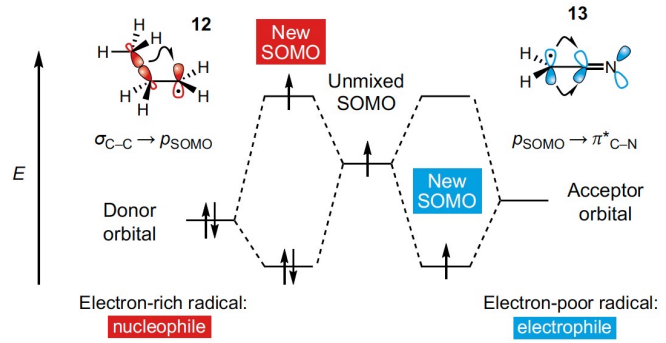
$A^{\oplus}$ ⟵ (- e^-, *nucleophilic radicals*) $A^{\bullet}$ ⟶ (+ e^-, *electrophilic radicals*) $A^{\ominus}$

Nucleophilic radicals abstract
δ+ 'protic' hydrogen atoms

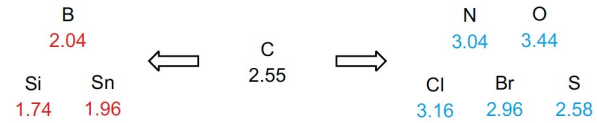
Electrophilic radicals abstract
δ− 'hydridic' hydrogen atoms



Stabilization of alkyl radicals by adjacent groups



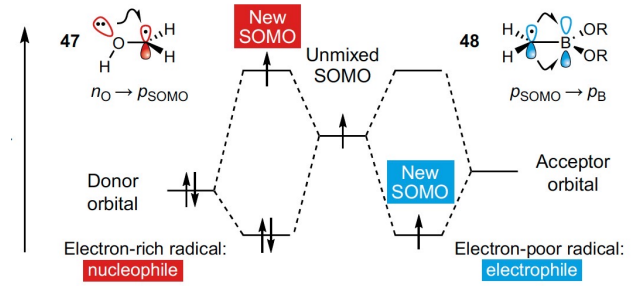
Heteroatom-centred radicals: electronegativity (χ_P) relative to carbon



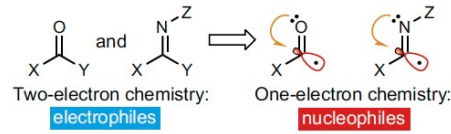
Atom is less electronegative than C: typically **nucleophilic**

Atom is more electronegative than C: typically **electrophilic**

π-Bonding characteristics determine effect of heteroatom substitution



Acyl and imidoyl radicals: nucleophilic

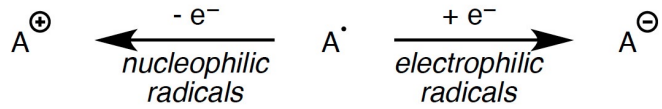


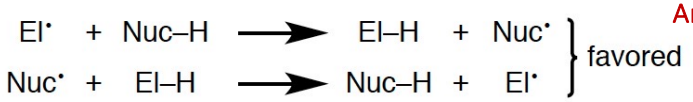
Umpolung:
traditional reactivity pattern reversed within one-electron manifold

- Réactions de fonctionnalisation C-H et chimie médicinale

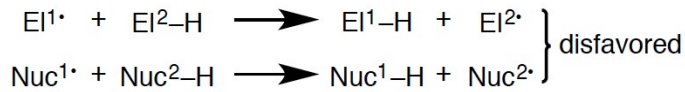
HAT : transfert d'atome d'hydrogène

Polarity: kinetic factor

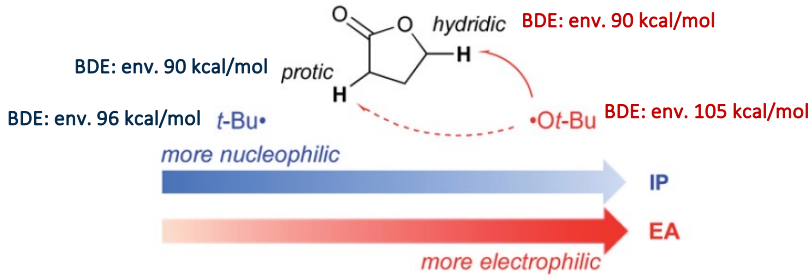


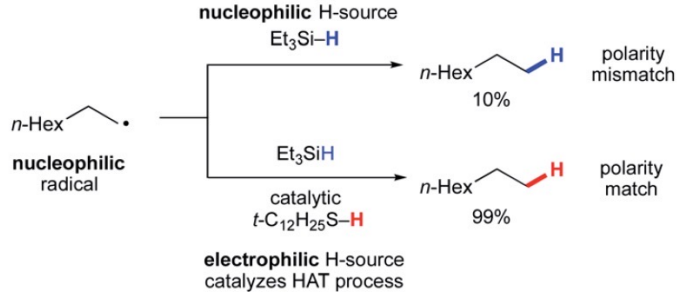


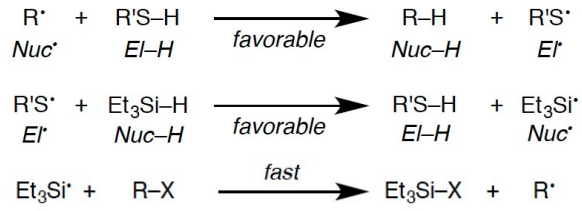
An ELECTROPHILIC radical will react via a HAT to generate a NUCLEOPHILIC radical



Radical philicity and selectivity of HAT:







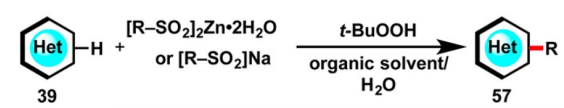
BDE (C-H) > BDE (S-H) > BDE (Si-H)

- Chimie médicinale : Développement en chimie organique

Réactions de fonctionnalisation C-H : la réaction de Minisci

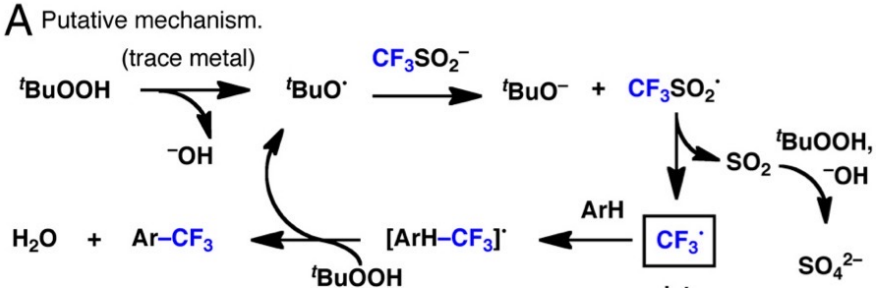
- Alkyl sulfinates

B. Development of zinc sulfinate toolbox for drug discovery.

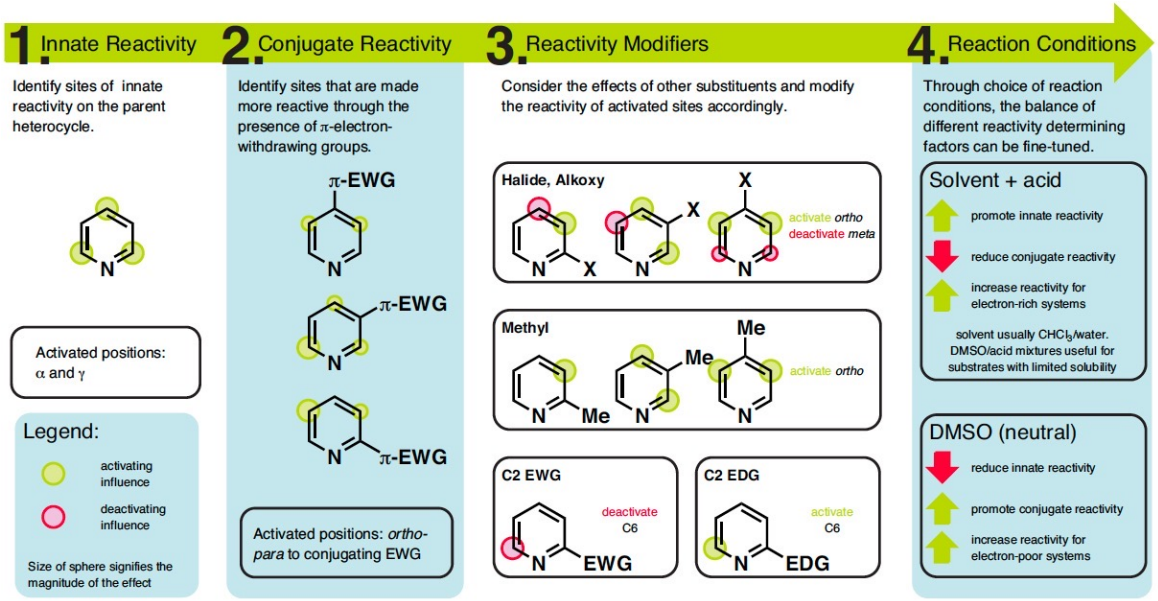


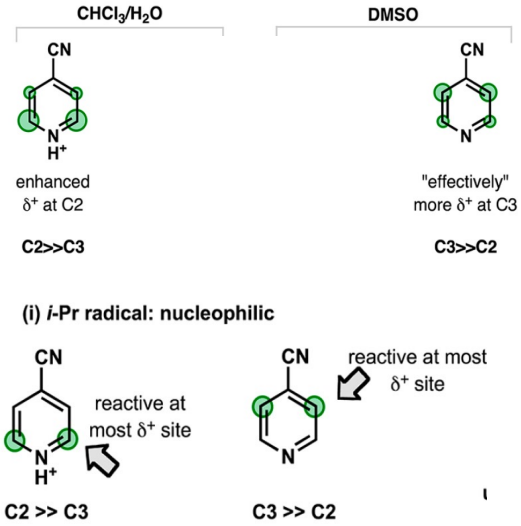
R group	Acronym of zinc sulfinate reagent	Sigma–Aldrich catalog number
CF_3	TFMS	771406
CF_2H	DFMS	767840
CH_2Cl	MCMS	791105
CH_2SO_2Ph	PSMS	792187
CF_2CH_3 (Na salt)	DFES-Na	745405
CH_2CF_3	TFES	745499
CH_2CH_2Cl	MCES	790788
$CH_2CH_2CH_3$	NPS	791040
$CH(CH_3)_2$	IPS	745480
CH_2Ph	BNS	790796

A Putative mechanism.



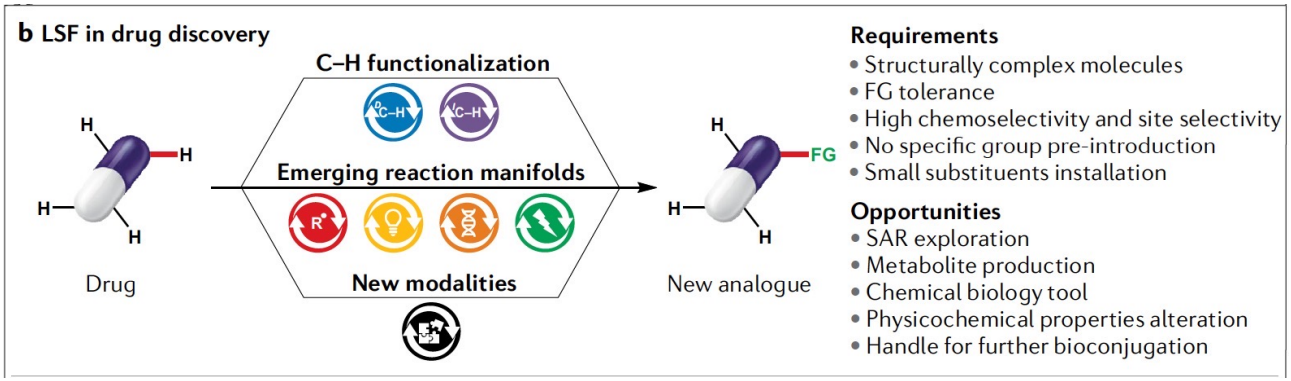
> Alkyl sulfinates: *generally nucleophilic so will react with electrophilic π-systems at their more electron-deficient sites*

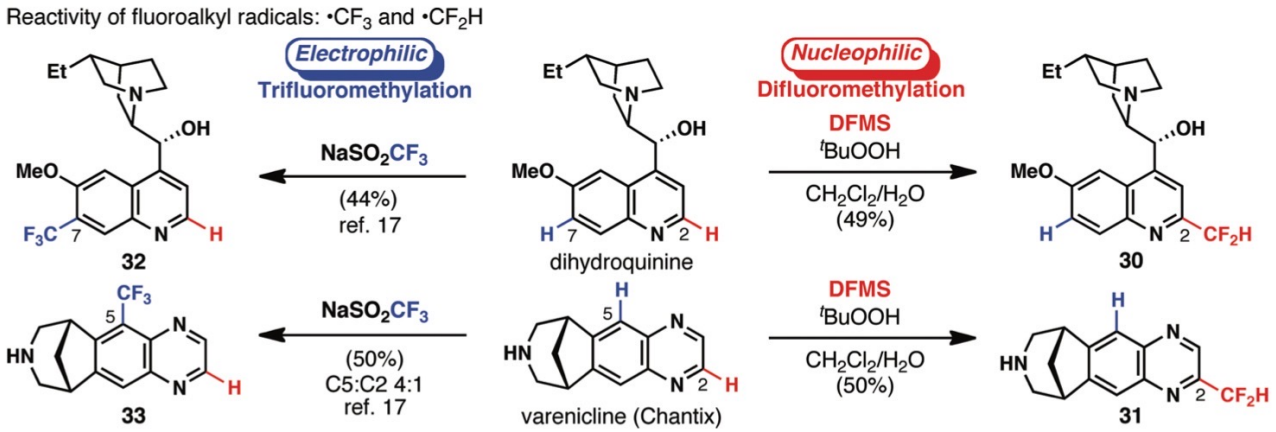


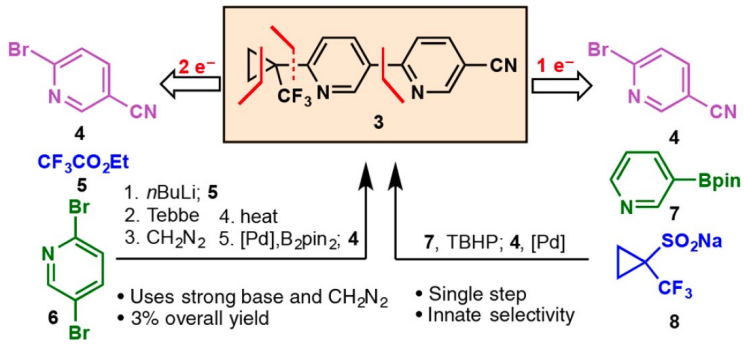


- Chimie médicinale : Développement en chimie organique

Réactions de fonctionnalisation C-H : Applications de la réaction de Minisci







- Chimie médicinale : Développement en chimie organique

Réactions de fonctionnalisation C-H : fluoration et méthylation

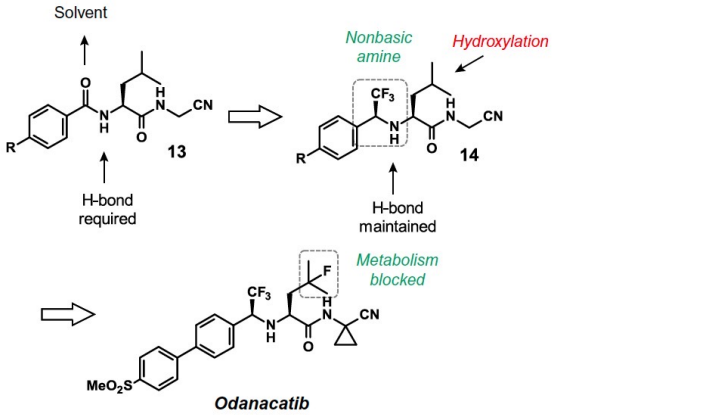
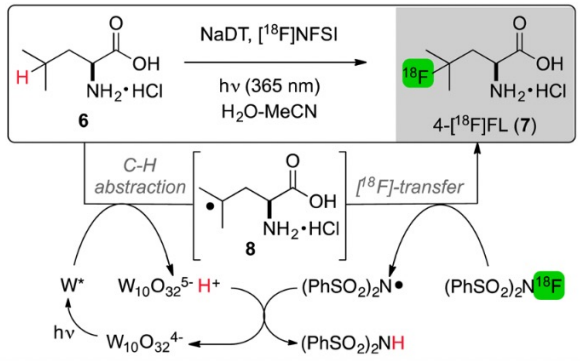
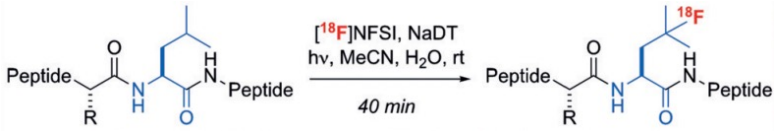
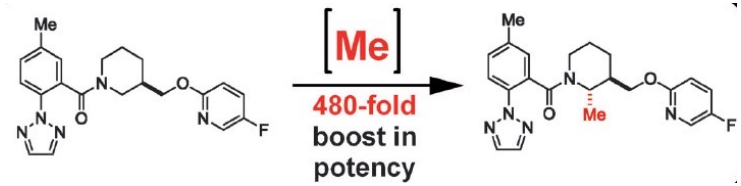


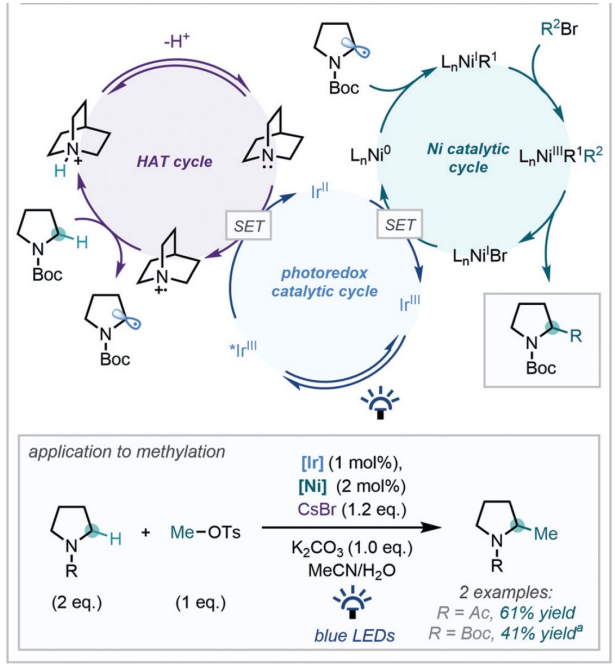
Figure 13 Use of nonbasic amine as amide isostere in the discovery of odanacatib. A second fluorine blocks the oxidation of the isopropyl group to improve pharmacokinetics.



- rapid (50 min) ^{18}F-fluorination of *unprotected* amino acids
- aqueous, rt process, no azeotropic drying or solvent switches
- product isolated directly as suitable formulation for IV injection







- Chimie médicinale : Développement en chimie organique

Réactions de fonctionnalisation C-H : Propriétés physicochimiques (solubilité). Chemical Biology

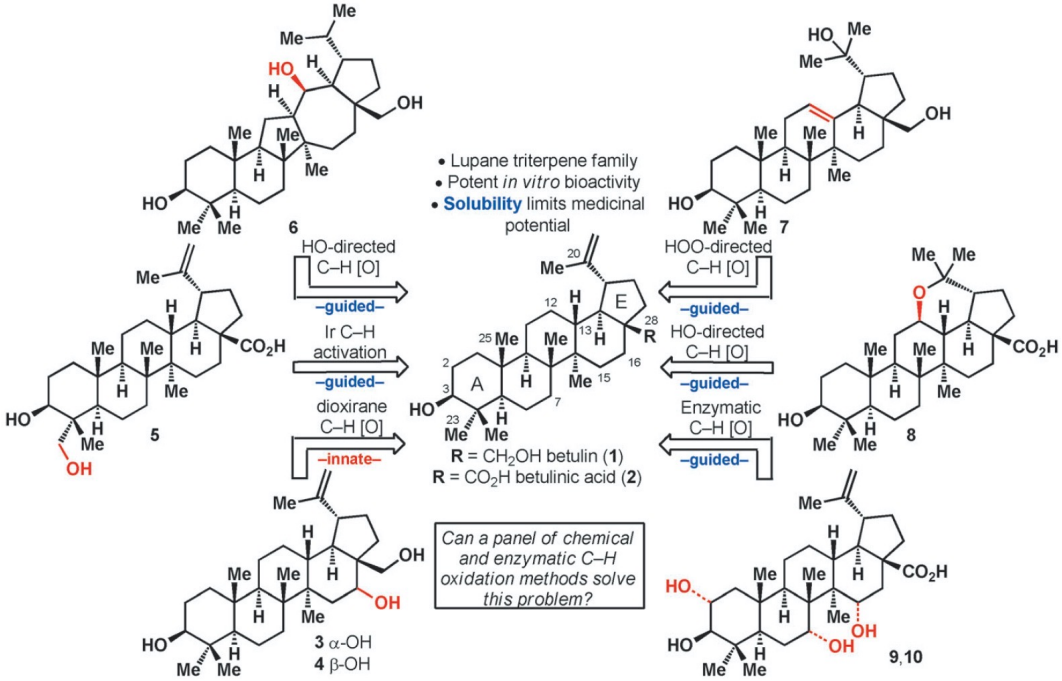
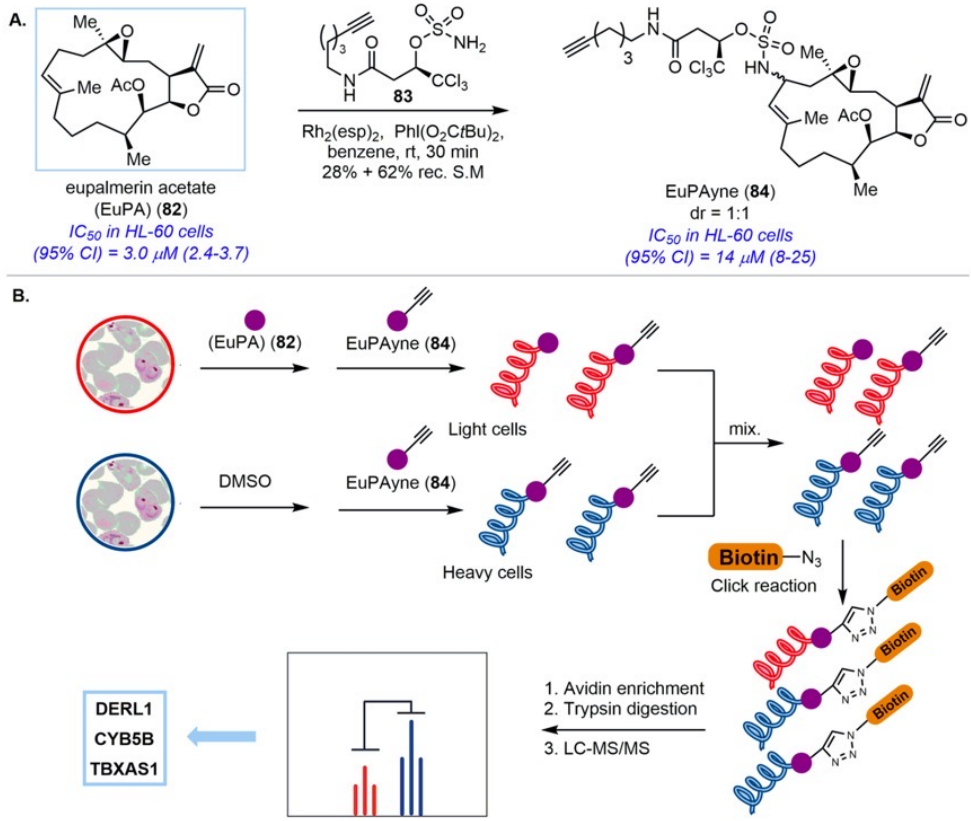


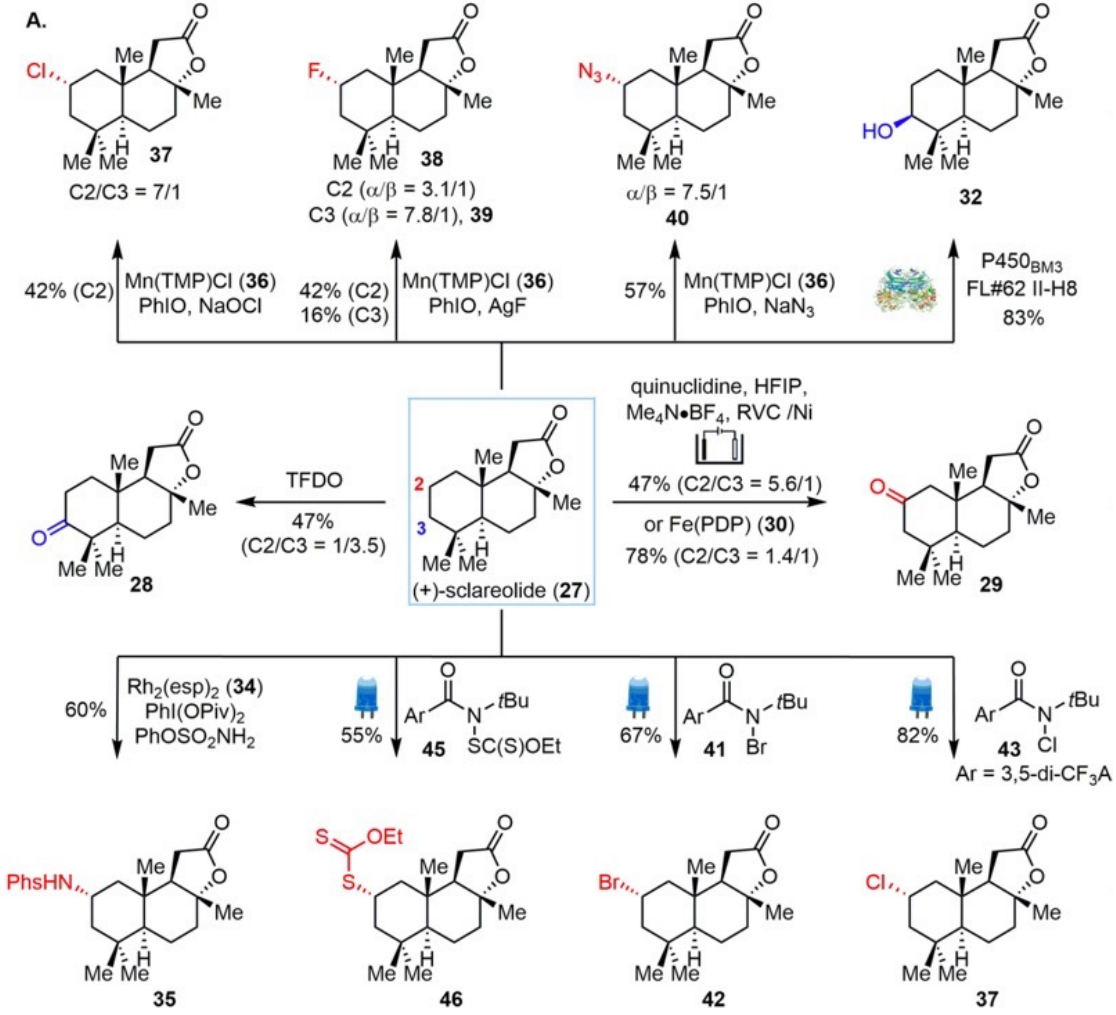
Figure 1. Diversification of the lupane core by C–H oxidation.

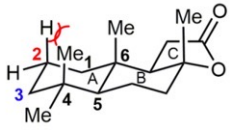
Entry	Substrate	R^1	Relative Solubility Enhancement: Assay 1 (FaSSIF)[a]
1	**3**	CH_2OH	274×
2	**4**	CH_2OH	8.00×
3	**7**	CH_2OH	121×
4	**6**	CH_2OH	no change
5	**5**	CO_2H	0.056×[c]
6	**8**	CO_2H	0.112×[c]
7	**9**	CO_2H	0.019×[c]
8	**10**	CO_2H	0.002×[c]



- Chimie médicinale : Développement en chimie organique

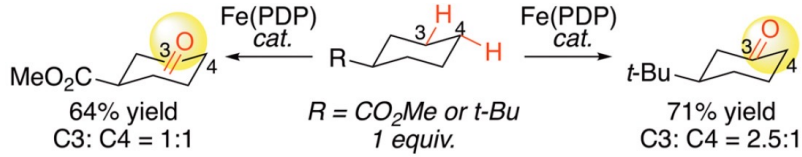
Réactions de fonctionnalisation C-H : Applications en diversité moléculaire





(+)-sclareolide (**27**)

1) CH bond nucleophilicity,
2) steric hindrance to reagent approach,
3) strain release in transition state formation.



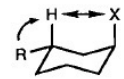
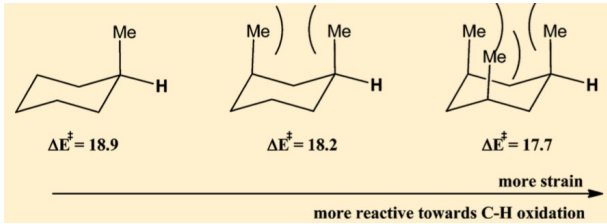


Figure 11.20. "Allinger buttressing."

(Eliel et al., 1966; Eliel and Biros, 1966). The reason has been pointed out by Allinger et al. (1967; see also Burkert and Allinger, 1982): An equatorial alkyl group buttresses the hydrogen geminal with it and thus prevents it from bending outward. If the alkyl group is at position 3 or 5 relative to an axial substituent to be studied, this "lack of give" will increase the synaxial H/X repulsion and thus increase the conformational energy of X as well as cause other changes (Fig. 11.20).



- Chimie médicinale : Développement en chimie organique

Réactions de fonctionnalisation C-H : Nouvelles rétrosynthèses et SAR en chimie médicinale

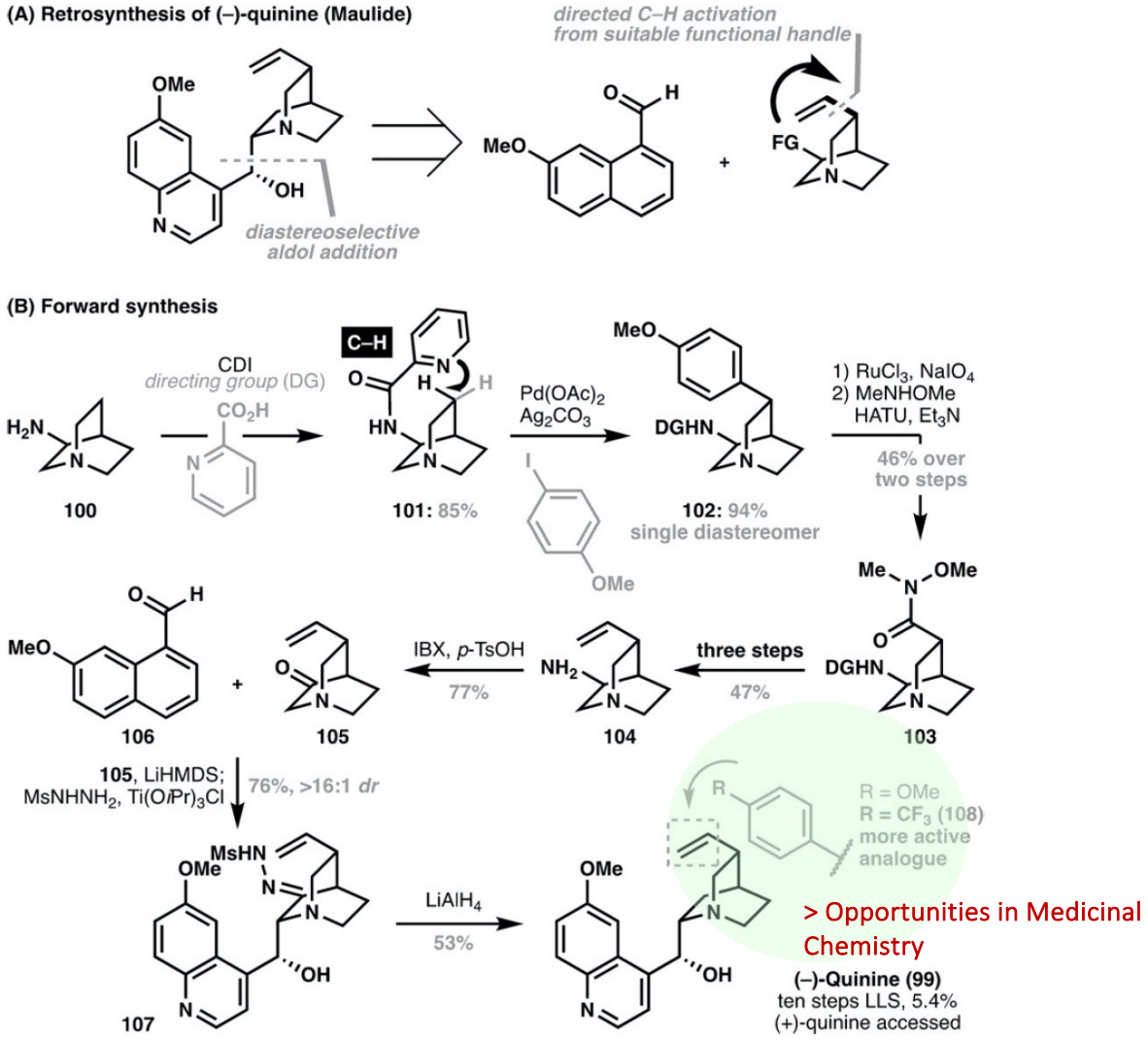
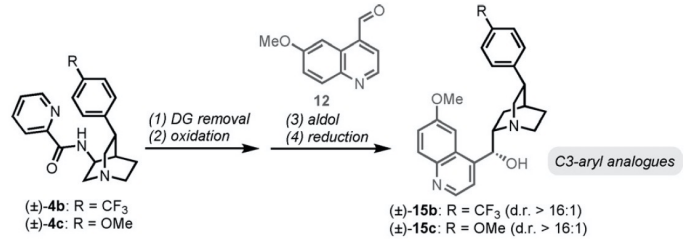


Table 1: In vivo activity of the racemic aryl analogues (±)-**15b** and (±)-**15c** and (−)-quinine hydrochloride as a reference against *P. berghei* in mice.



Substance	Dose [mg/kg]	Parasitemia reduction [%][a]	Survival[b] [days]
(−)-quinine hydrochloride	30	42	euthanized
	100	80	7 ± 0
(±)-**15b**[c]	30	98	8 ± 1
	100	99	21 ± 7
(±)-**15c**[c]	30	0	euthanized
	100	98	7 ± 1

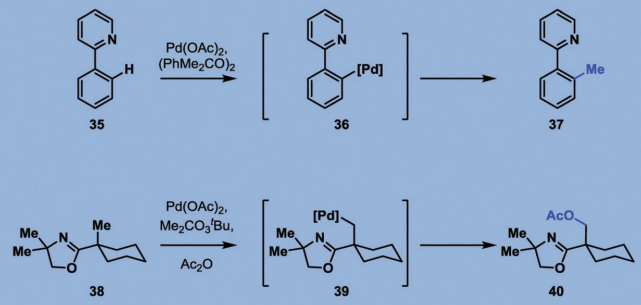
[a] Blood for parasitemia determination was collected on day 3 (72 h after infection). [b] Mean survival time in days ± standard deviation. Mice with a parasitemia reduction < 50% were euthanized on day 3 post-infection in order to prevent death, otherwise occurring on day 6. [c] Purity of > 99% determined by HPLC analysis.

- Chimie médicinale : Développement en chimie organique

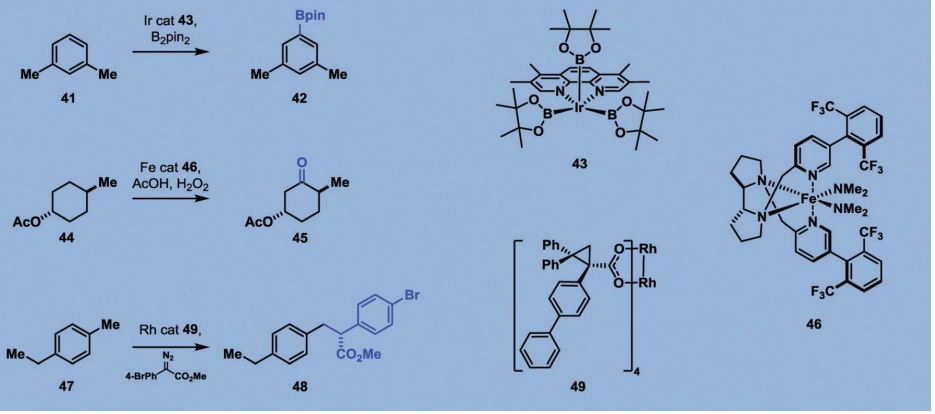
Réactions de fonctionnalisation C-H : General strategy for late-stage C-H functionalization

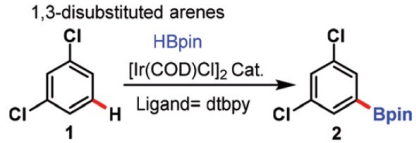
Guided Reaction Manifolds

DG ***1. Guided by directing groups.*** *Catalyst or reagent is directed to an adjacent sp^2 or sp^3 C-H bond by a chelating heterocycle or functional group on the substrate. Substitution ortho to the directing group in sp^2 systems is most common, although many sp^3 systems as well as long-range directing groups are known.*

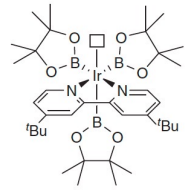


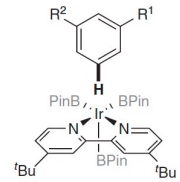
2. Guided by sterics. *Bulky catalysts drive reactivity towards sterically accessible C-H bonds. This class includes true insertion and H-abstraction reactions, as in Fig. 3, entry 1, where the substrate or catalyst are sterically encumbered.* **43**, **46** *and* **49** *are bulky catalysts that override the innate reactivity of C-H bonds in* **41**, **44** *and* **47**, *respectively.*

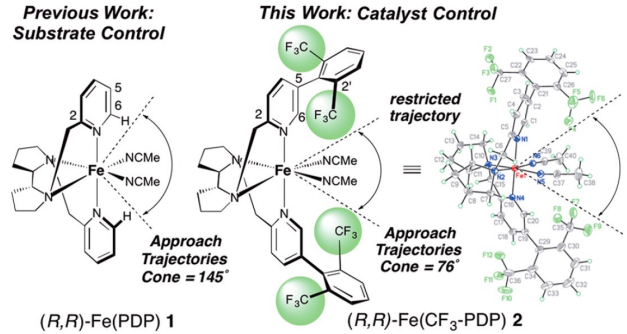




- Regioselectivity controled by steric effects





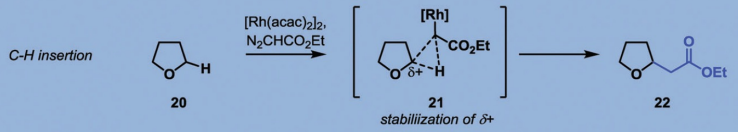


- Chimie médicinale : Développement en chimie organique

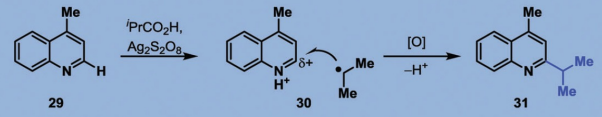
Réactions de fonctionnalisation C-H : General strategy for late-stage C-H functionalization

Innate Reaction Manifolds

C···H **1. Innate insertion or H-abstraction.** *Although mechanistically distinct, insertion into an electron-rich C-H bond or formation of a stable radical at an sp^3 center usually follows the same pattern of 3° > 2° > 1°. Reacting C-H bonds tend to be distal from electron withdrawing groups. When reagents and catalysts are large, sterics may dominate, see Fig. 4, entry 2.*

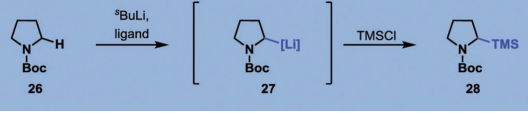


δ+ **3. Addition-elimination at innately electrophilic sp^2 carbon.** *Addition-elimination at an electropositive sp^2 carbon, typically with nucleophilic radicals, generally occurs on most electron deficient heterocycle. Selectivity can sometimes be perturbed by addition of acid.*



δ− **4. Addition-elimination at innately nucleophilic sp^2 carbon.** *Addition-elimination at an electronegative sp^2 carbon follows electrophilic aromatic substitution patterns.*

H+ **2. Deprotonation of innately acidic C-H bonds.** *Deprotonation by strong bases can occur at sp^2 or sp^3 centers. Reactivity is driven by the acidity of the C-H bond. If directing groups steer the base to the site of reaction, see Fig. 4, entry 1.*

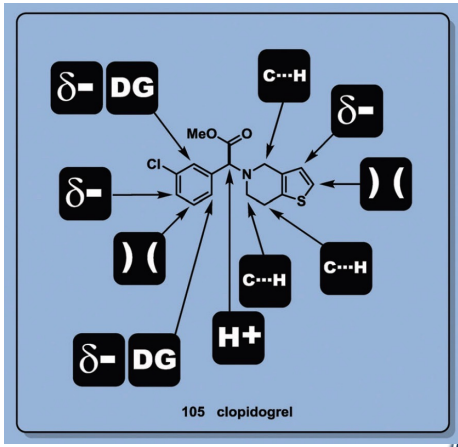


1.Identify which C-H bonds are possible candidates for C-H functionalization.

2.Match each C-H bond to a possible reaction manifold. Consider if reaction selectivity can be influenced by choice of reagent or catalyst.

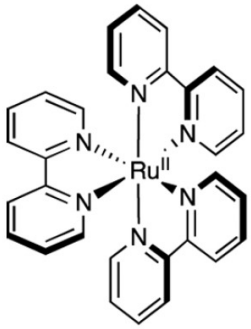
3.Identify which functional groups or building blocks can be installed using the selected reaction manifolds.

4.Confirm the proposed products have desirable physicochemical properties and if possible perform docking studies.



• Use of visible light

> Visible Light Photoredox Catalysis

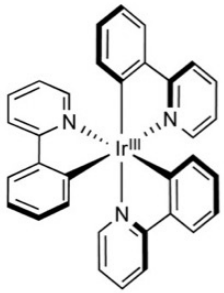


$Ru(bpy)_3^{2+}$

- Absorption at 452 nm (visible light)
- Stable, long-lived excited state (τ = 1100 ns)
- Single electron transfer (SET) catalyst
- Effective excited state oxidant and reductant

$Ru(bpy)_3^{3+} + e^- \rightarrow$ **$Ru(bpy)_3^{2+}$ - $E_{1/2}^{III/II}$ = +1.29 V – Non reductant**

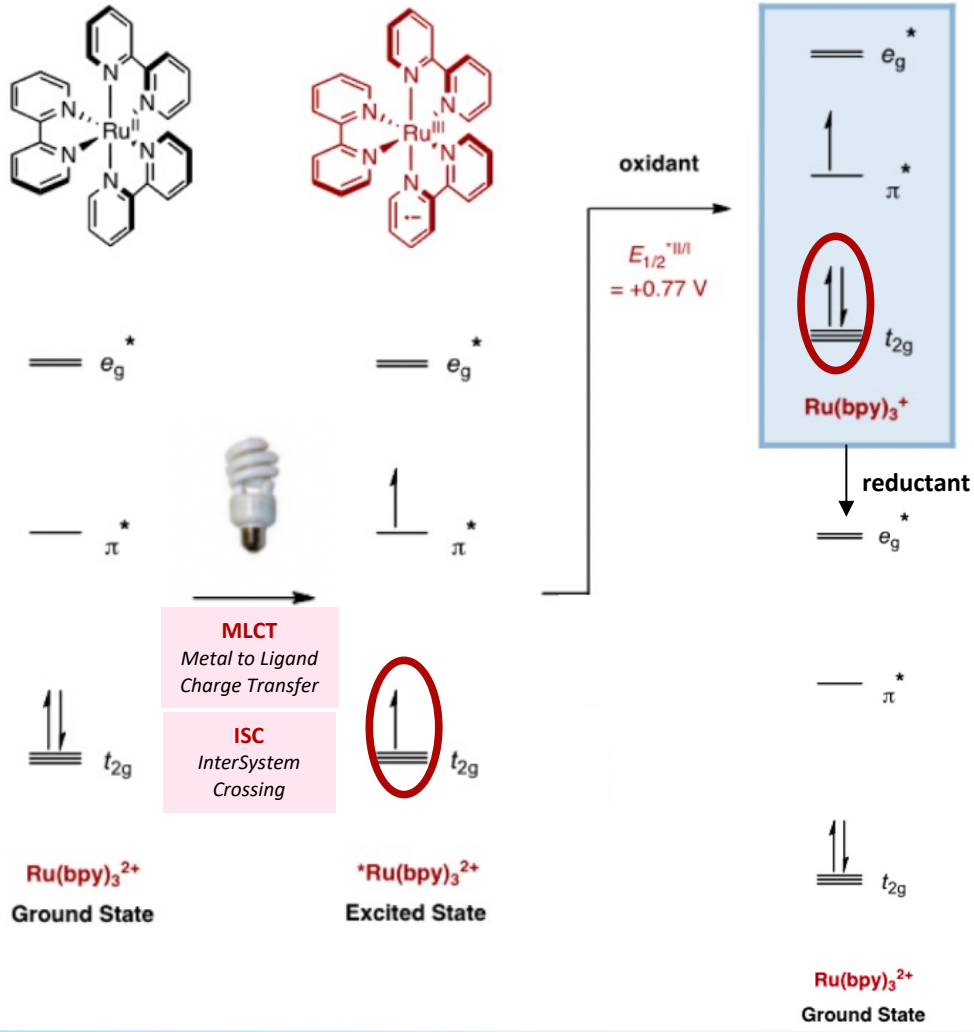
$Ru(bpy)_3^{2+} + e^- \rightarrow Ru(bpy)_3^{+}$ - $E_{1/2}^{II/I}$ = -1.33 V – Non oxidant



$Ir(ppy)_3$

- Max absorption at 375 nm (visible light)
- Long-lived excited state (τ = 1.9 µs)
- Single-electron transfer catalyst
- Effective oxidant and reductant
- Triplet energy of 56 kcal mol^{-1}

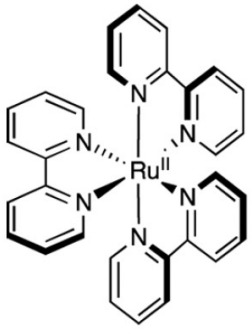
$Ru^*(bpy)_3^{2+} + e^- \rightarrow Ru(bpy)_3^{+}$
$E_{1/2}^{II/I}$ = +0.77 V – Oxidant



> D. W.C. MacMillan *et al.*, Visible Light Photoredox Catalysis with TM Complexes, *Chem. Rev.* 2013, *113*, 5322-5363

• Use of visible light

> Visible Light Photoredox Catalysis



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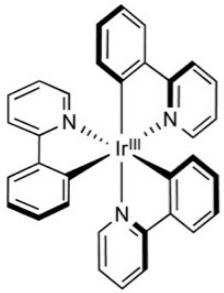

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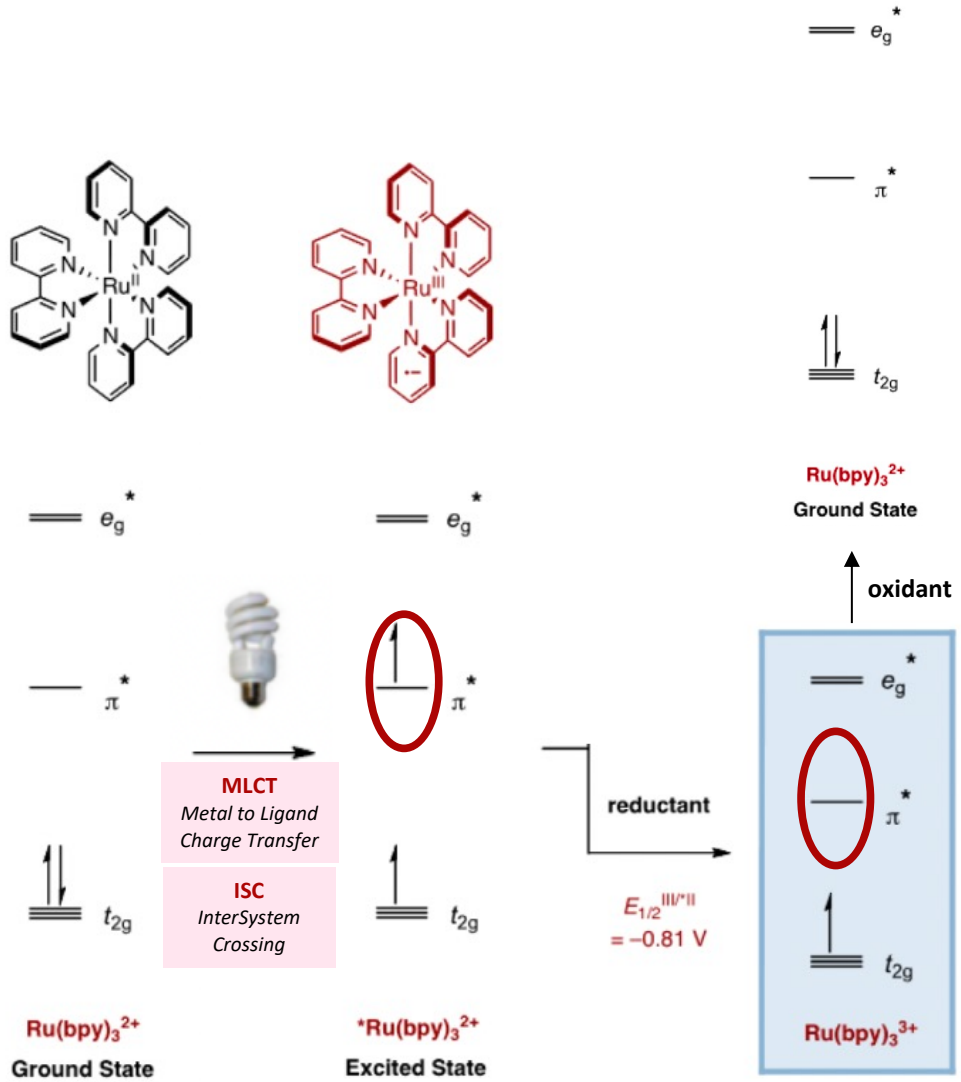


$Ru(bpy)_3^{3+} + e^- \rightarrow$ **$Ru^*(bpy)_3^{2+}$**
$E_{1/2}^{III/II}$ = -0.81 V – Reductant

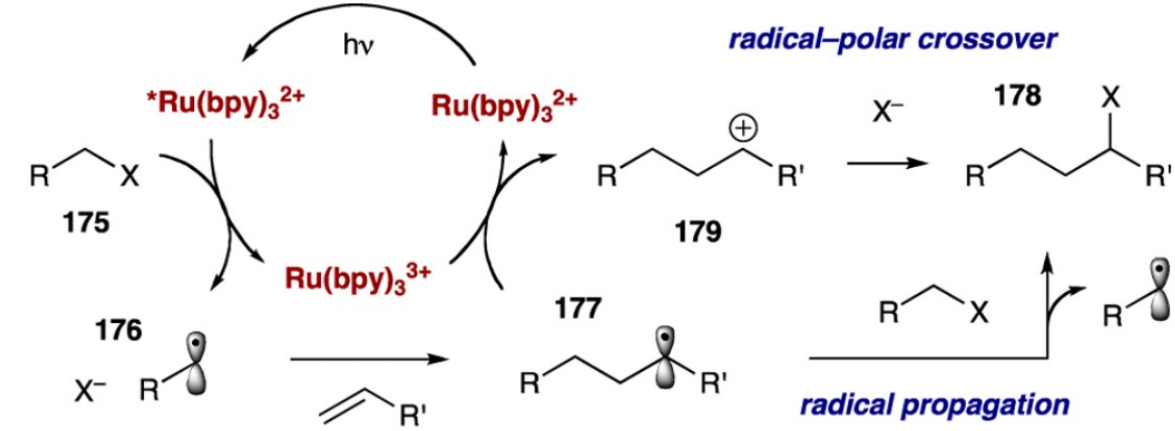
> D. W.C. MacMillan *et al.*, Visible Light Photoredox Catalysis with TM Complexes, *Chem. Rev.* **2013**, *113*, 5322-5363

- Use of visible light

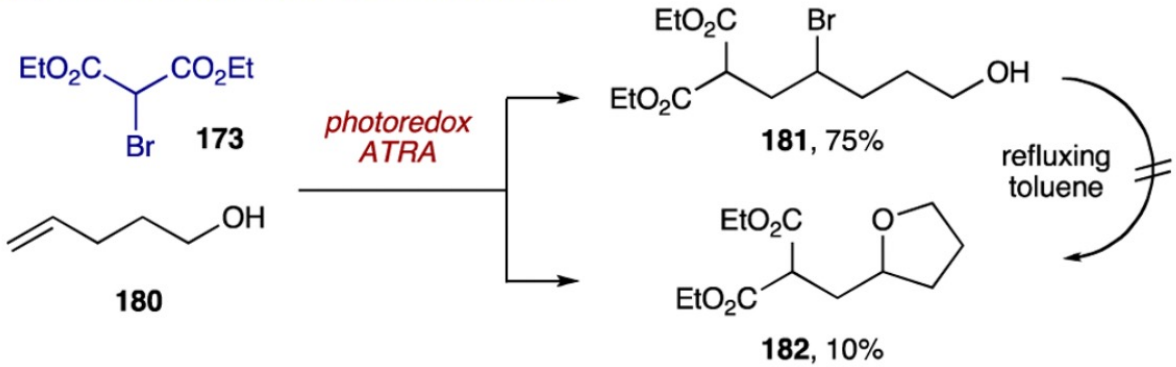
> Visible Light Photoredox Catalysis

REDOX NEUTRAL REACTIONS

Scheme 39. Mechanism of the Photoredox ATRA



(A) Evidence for radical–polar crossover

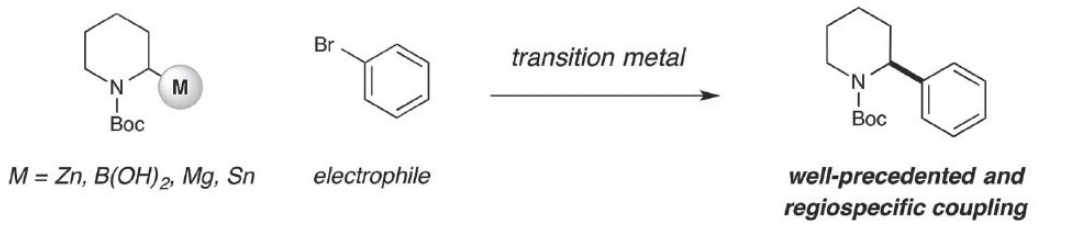


> D. W.C. MacMillan *et al.*, Visible Light Photoredox Catalysis with TM Complexes, *Chem. Rev.* 2013, *113*, 5322-5363

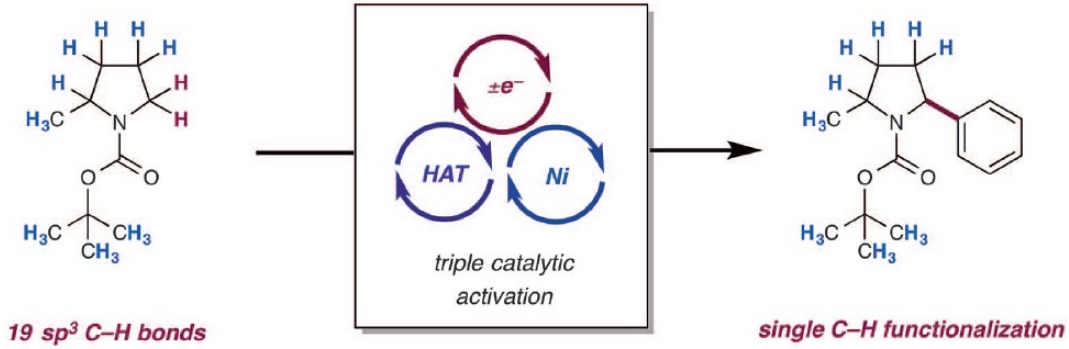
- Intermolecular HAT

> Metallophotoredox catalysis

Traditional Cross-Coupling Regioselectivity Controlled by Nucleophile Pre-Activation



Catalyst Controls Selectivity Among Multiple sp³ C–H Bonds in Cross-Coupling

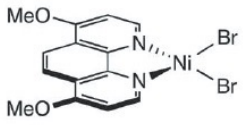


> D. W. C. MacMillan *et al.*, Native functionality in triple catalytic cross coupling, *Science* 2015, *352*, 1304

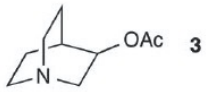
• Intermolecular HAT

> Metallophotoredox catalysis

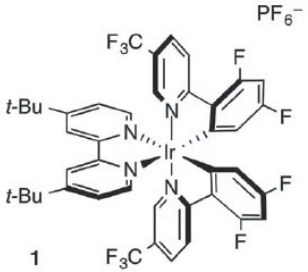
nickel catalyst

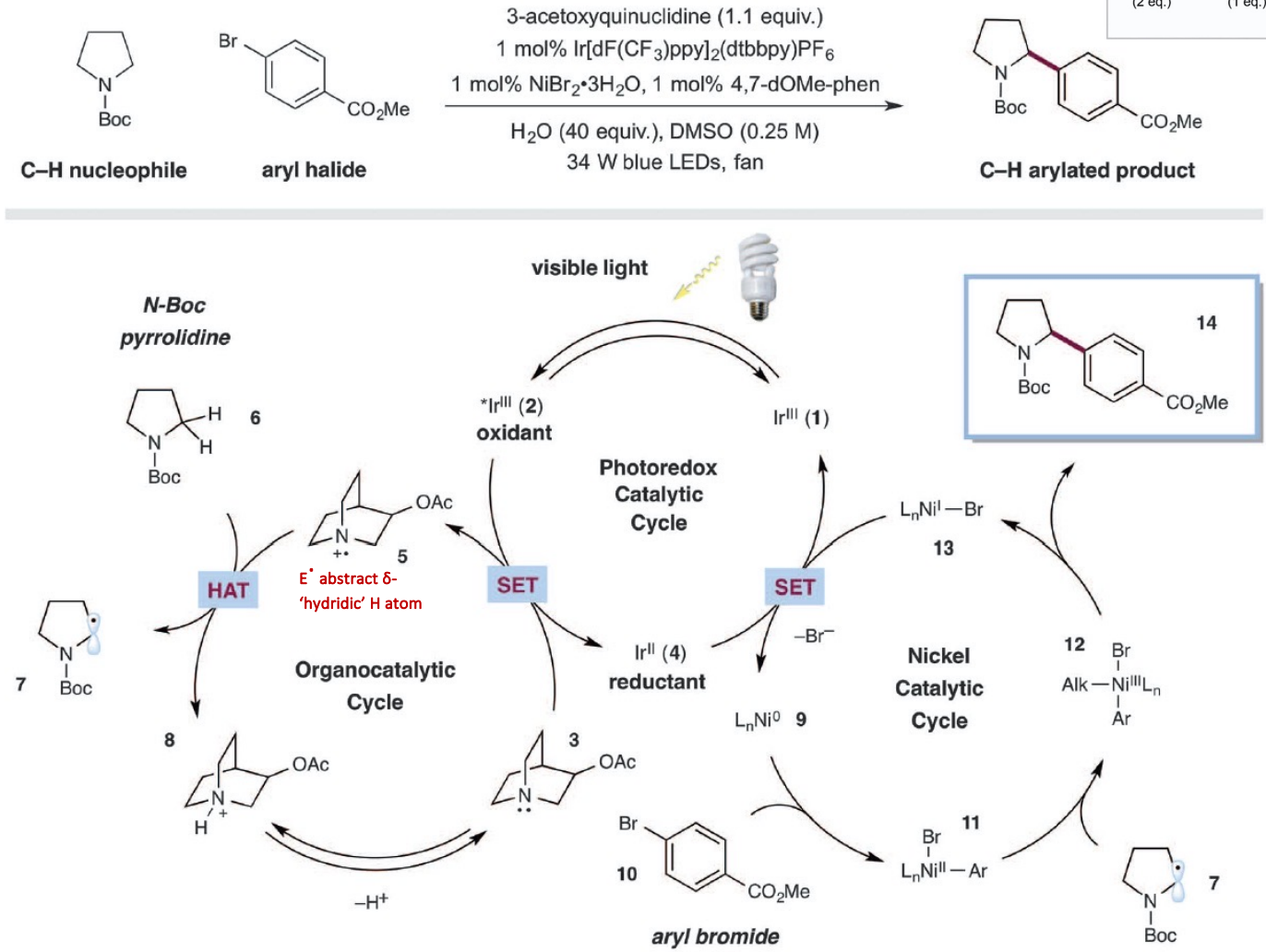


HAT catalyst



photocatalyst





> D. W. C. MacMillan *et al.*, Native functionality in triple catalytic cross coupling, *Science* **2015**, *352*, 1304