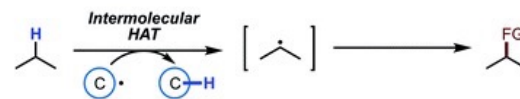
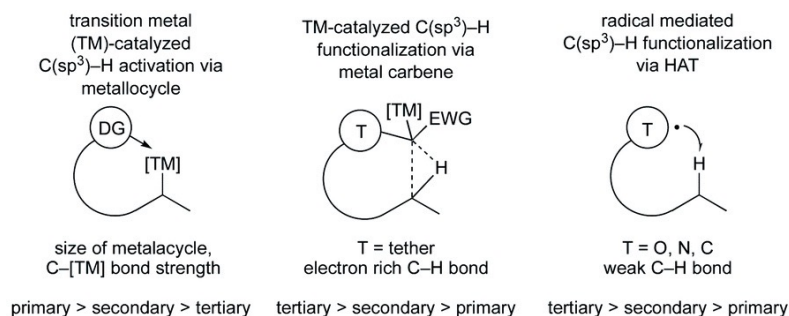


Réactions de fonctionnalisation C-H et chimie médicinale

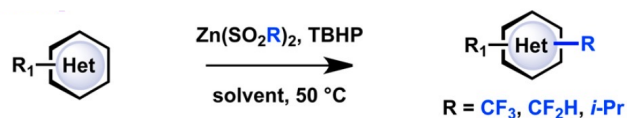
- **Introduction**
 1. *Catalytic C-H Functionalization Reactions vs. Functional Group Transformations*
 2. *Catalytic C-H Functionalization Reactions: challenges & general mechanisms*
- **Catalytic C-H Functionalization by C-H Activation (*inner-sphere mechanism*)**
 1. *Mechanistic considerations*
 2. *Heteroatom-directed C-H Functionalization*
 3. *Oxidative addition-directed C-H Functionalization*
 4. *Unsaturation-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. *Intramolecular reactions*
 3. *Intermolecular reactions*
- **The issue of regioselectivity**
 1. *Tuning the regioselective functionalization of C(sp²)-H bond*
 2. *Tuning the regioselective functionalization of C(sp³)-H bond*
- **Application of catalytic C-H functionalization**

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

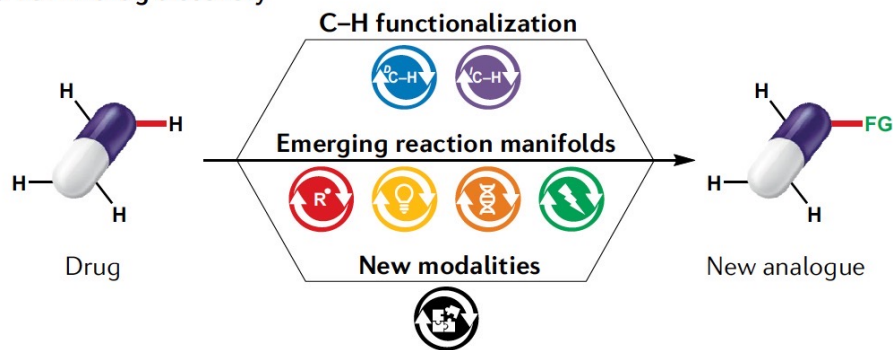
• Opportunities provided by C-H Functionalization reactions



B. Predictable, regioselective radical functionalization of heterocycles



b LSF in drug discovery

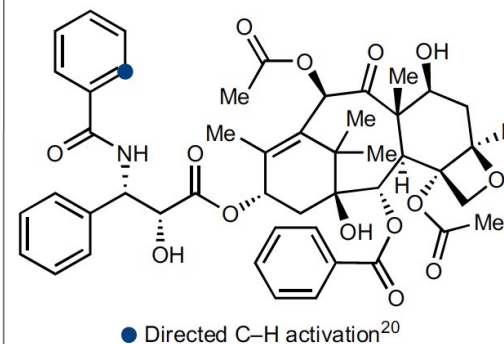


Requirements

- Structurally complex molecules
- FG tolerance
- High chemoselectivity and site selectivity
- No specific group pre-introduction
- Small substituents installation

Opportunities

- SAR exploration
- Metabolite production
- Chemical biology tool
- Physicochemical properties alteration
- Handle for further bioconjugation



Paclitaxel (99)
9 C(sp²)-H
20 C(sp³)-H

• The rise of Late-Stage C-H Functionalization

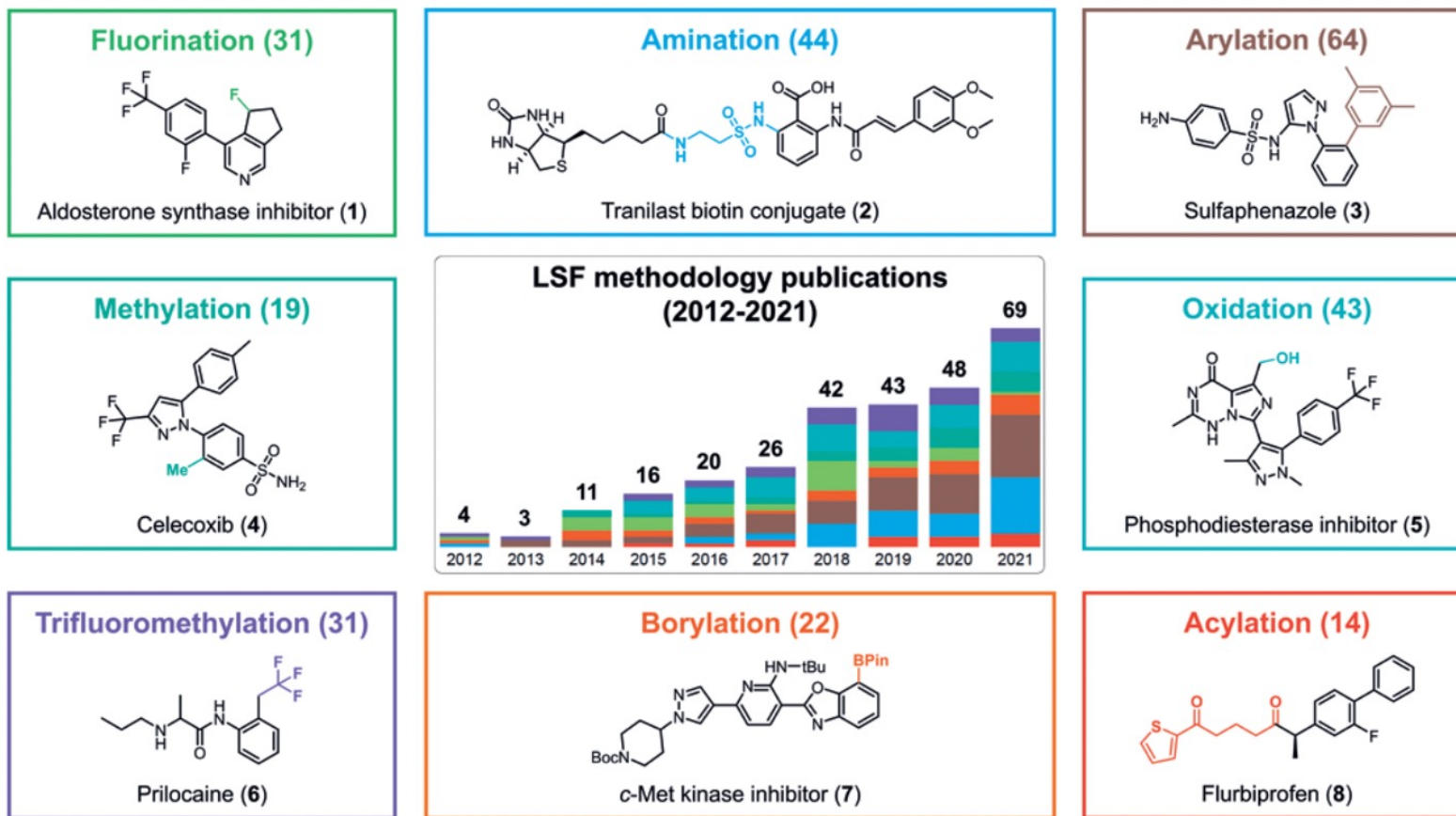
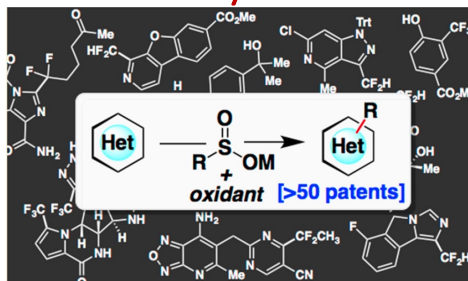


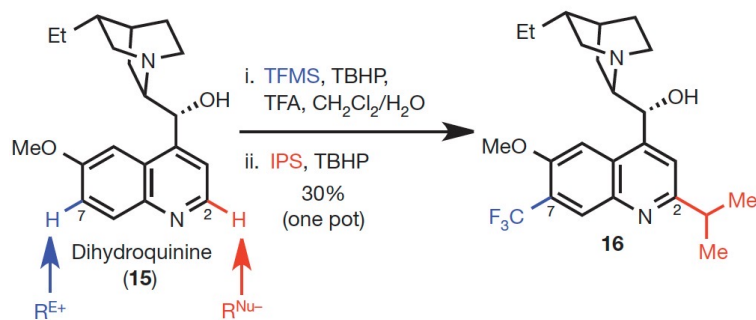
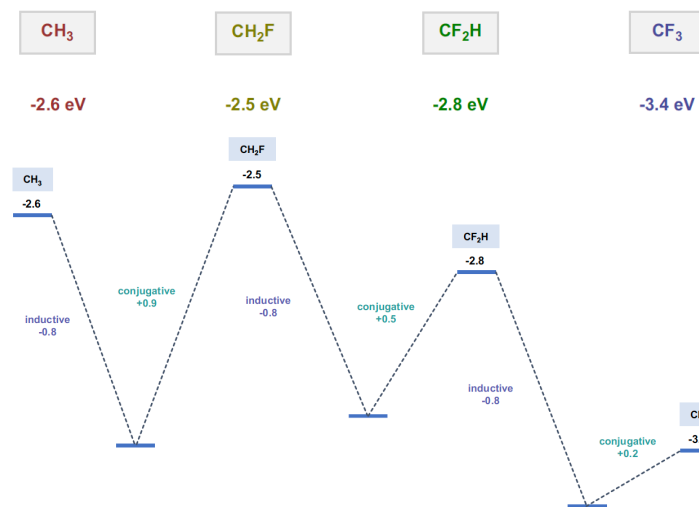
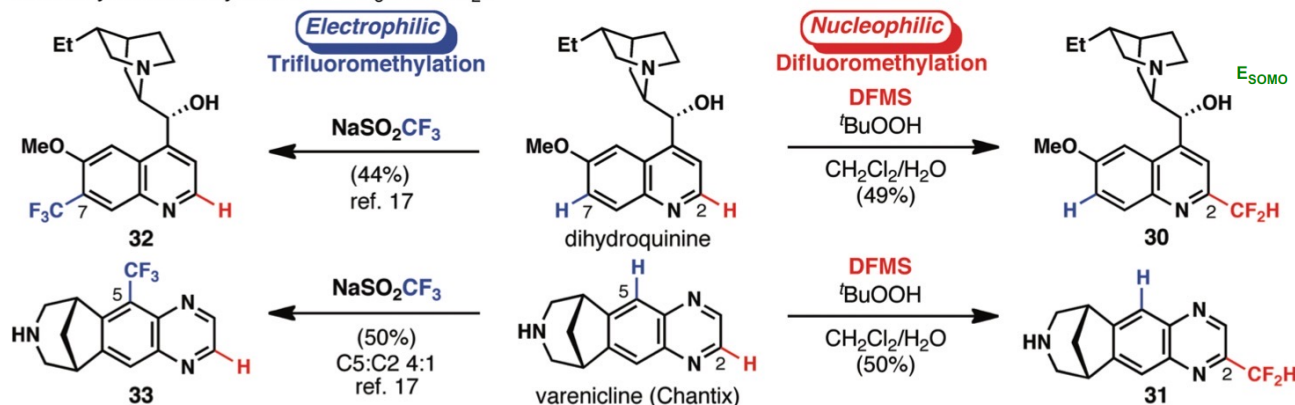
Fig. 2. Increase in publications of the most common LSF methodologies from 2012 to 2021 (center). Selected applications of LSF fluorination, amination, arylation, methylation, oxidation, trifluoromethylation, borylation and acylation found in literature. The number in brackets next to the methodology name states the publication count as of 2021.^[7]

• Late-stage functionalization using radical chemistry

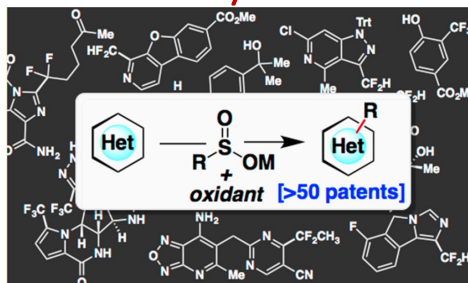
> Sulfinates and fluorine



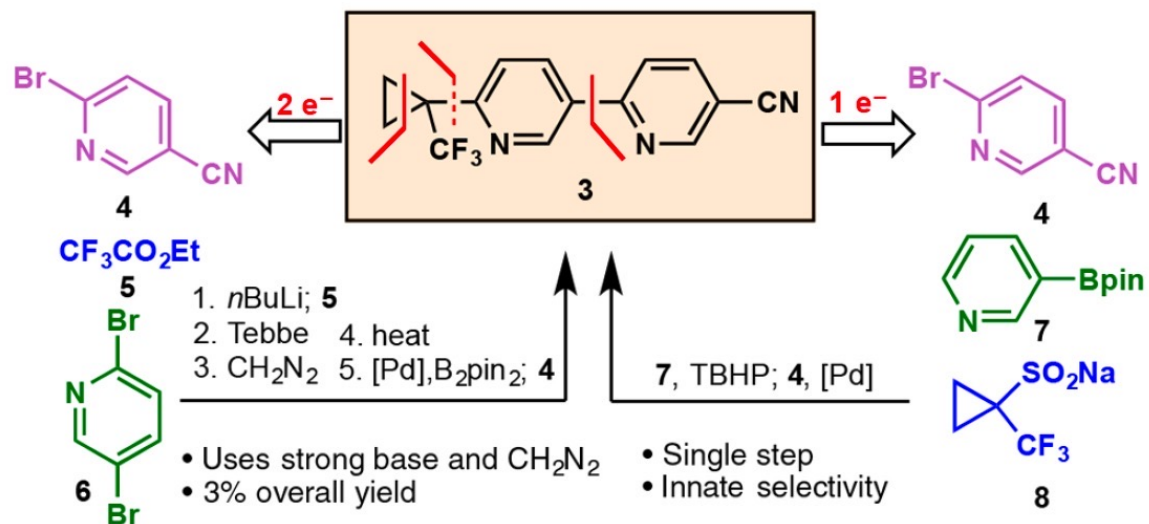
Reactivity of fluoroalkyl radicals: $\cdot\text{CF}_3$ and $\cdot\text{CF}_2\text{H}$



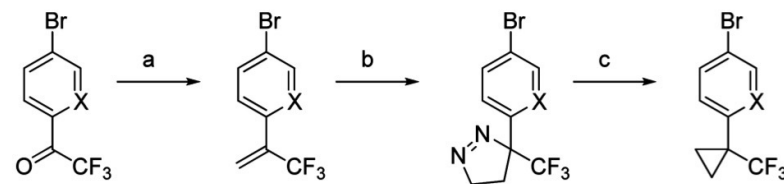
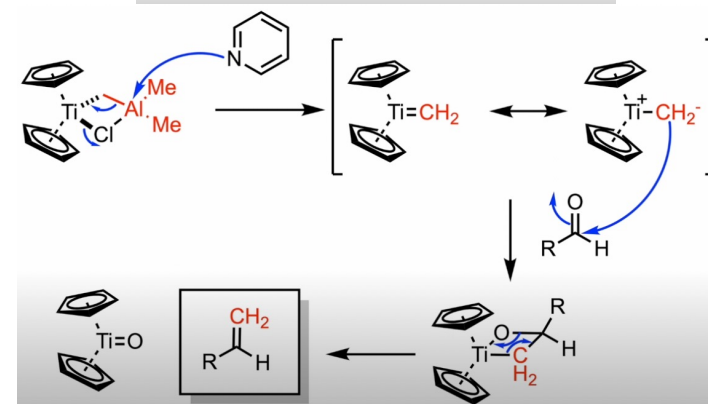
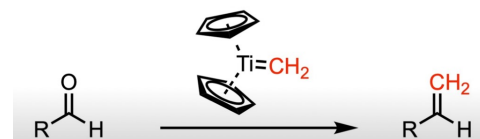
• Late-stage functionalization using radical chemistry



> Sulfinates and retrosynthesis



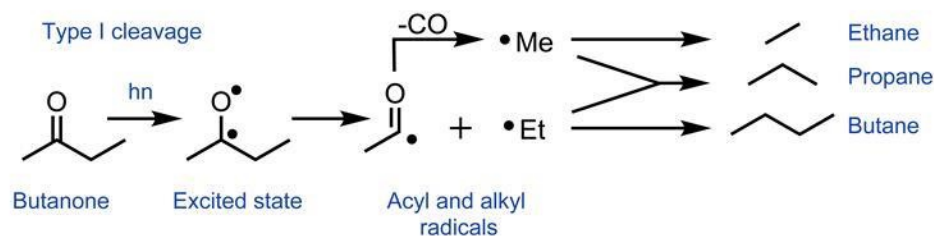
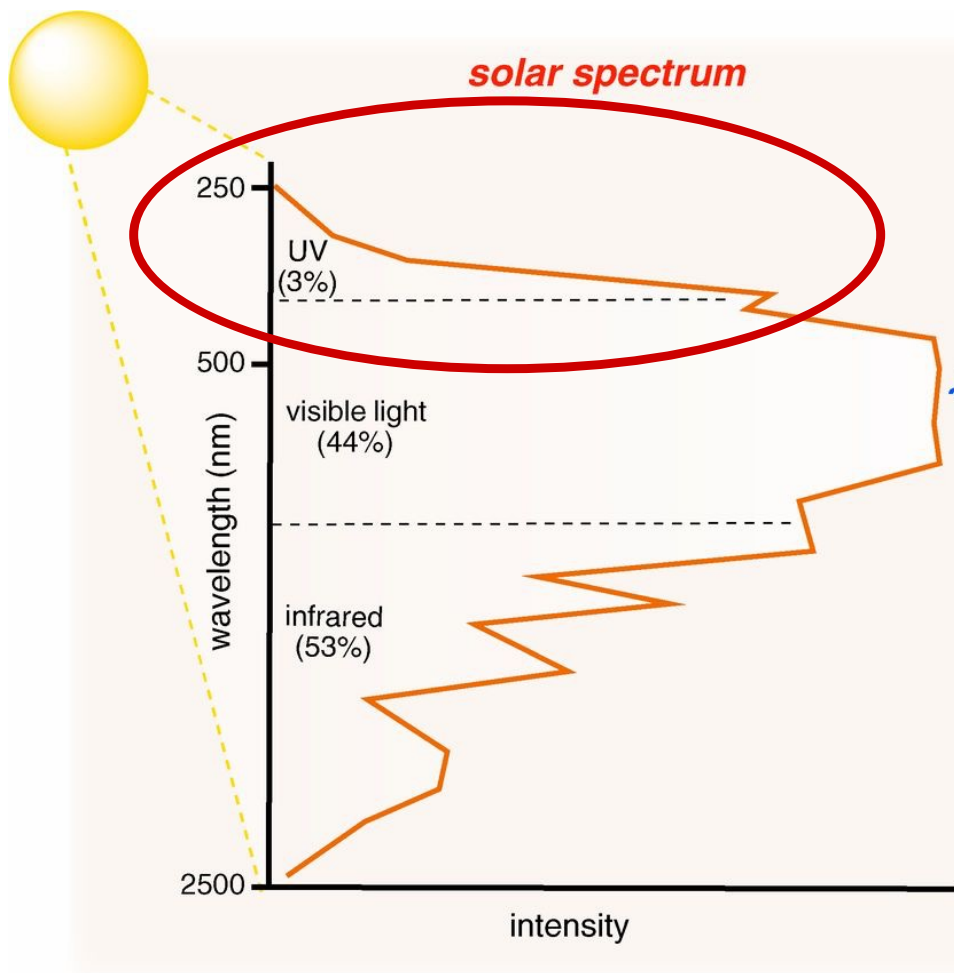
Tebbe Olefination



^aReagents and conditions: (a) X = CH, MsCl, 18-crown-6, KF, DMF, 100 °C;¹⁷ X = N: Tebbe reagent;¹⁸ (b) CH₂N₂;¹⁹ (c) Xylenes reflux¹⁹.

Solar synthesis

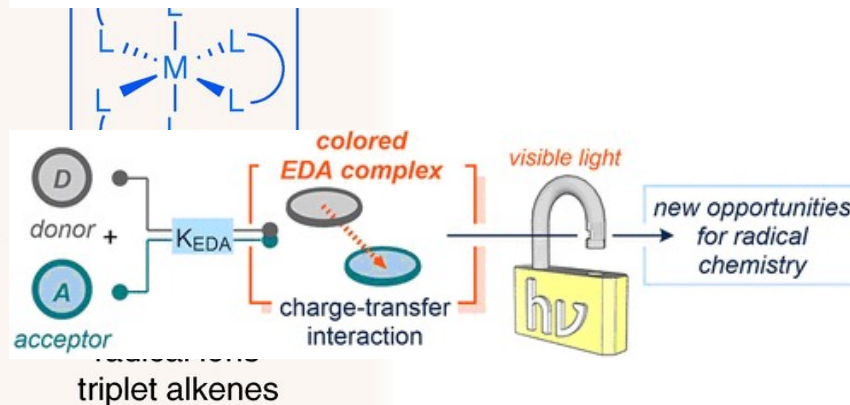
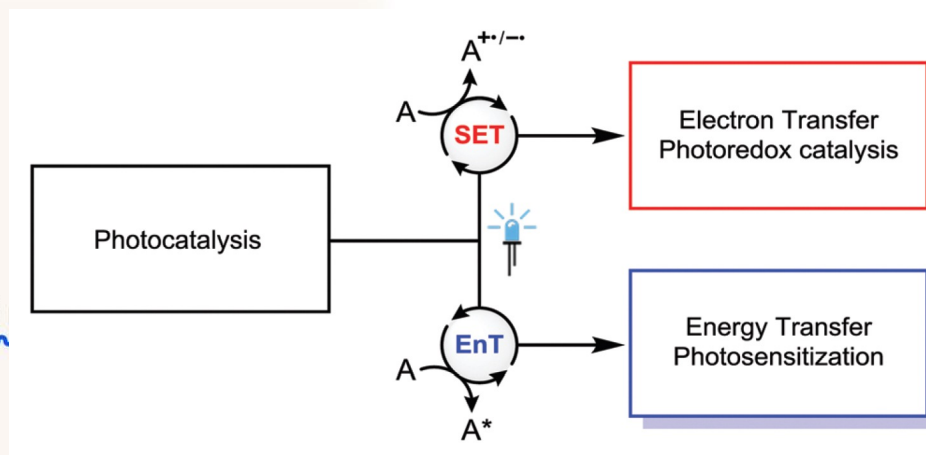
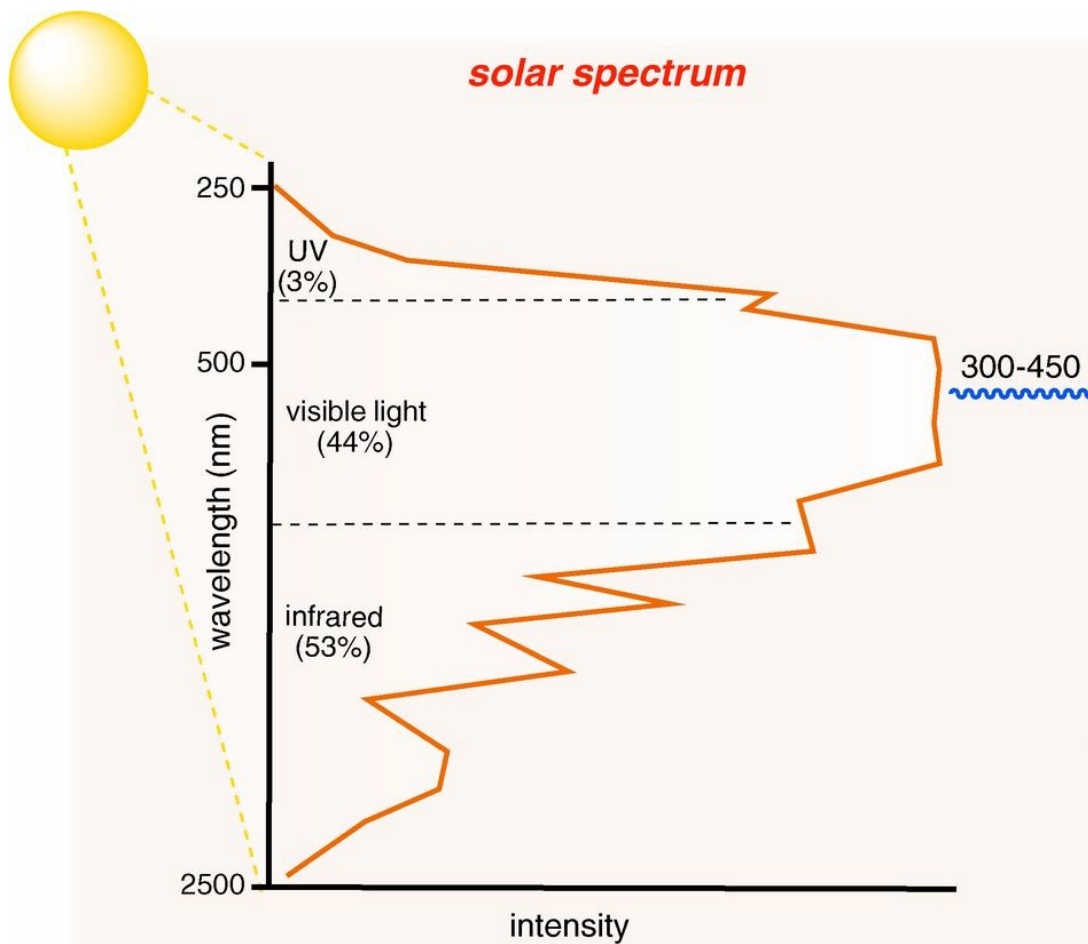
> Photochemical reactions: Norrish-Type



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

Solar synthesis

> Visible Light PhotoCatalysis

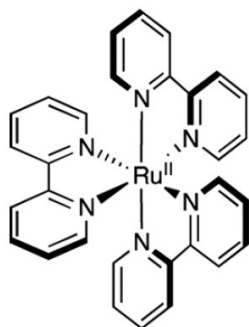


• Application of catalytic C-H Functionalization

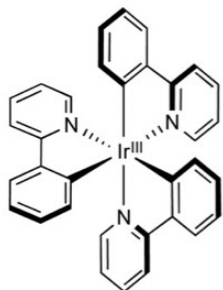
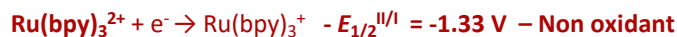
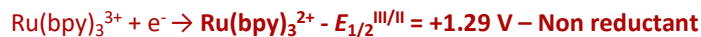
Total synthesis & Late-stage functionalization of natural products and drugs

• Use of visible light

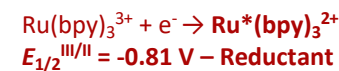
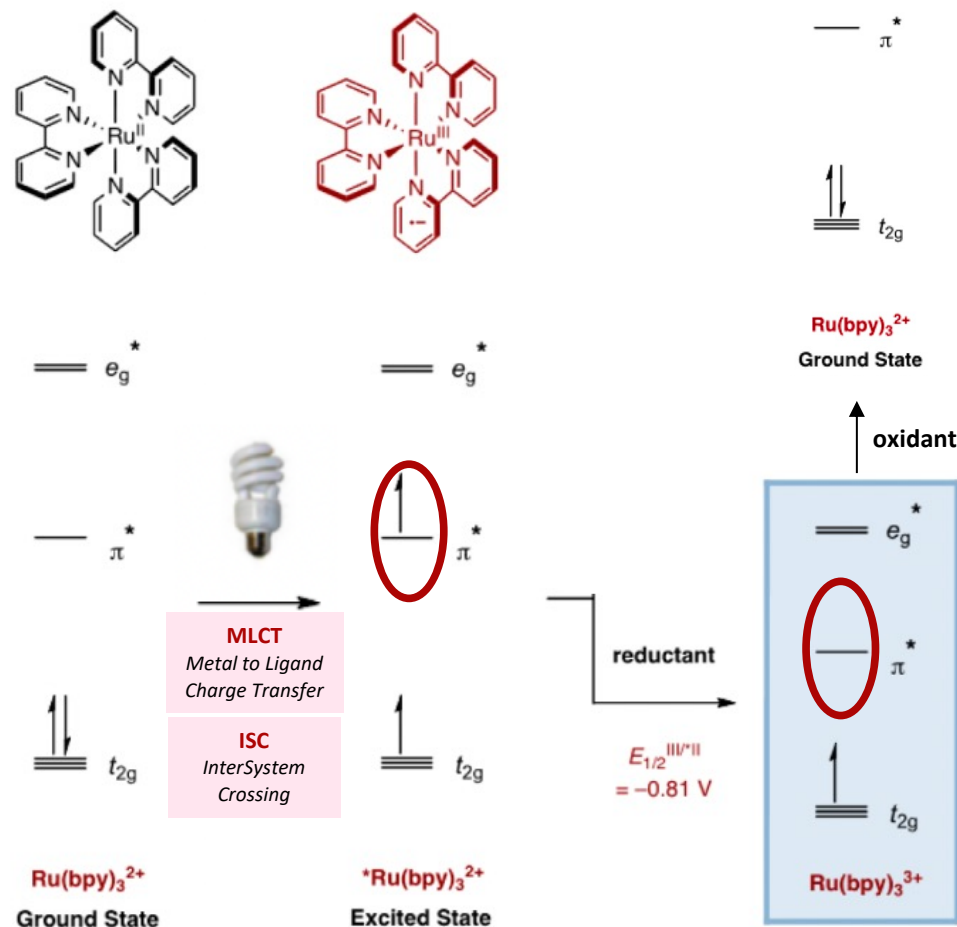
> Visible Light Photoredox Catalysis


Ru(bpy)₃²⁺

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

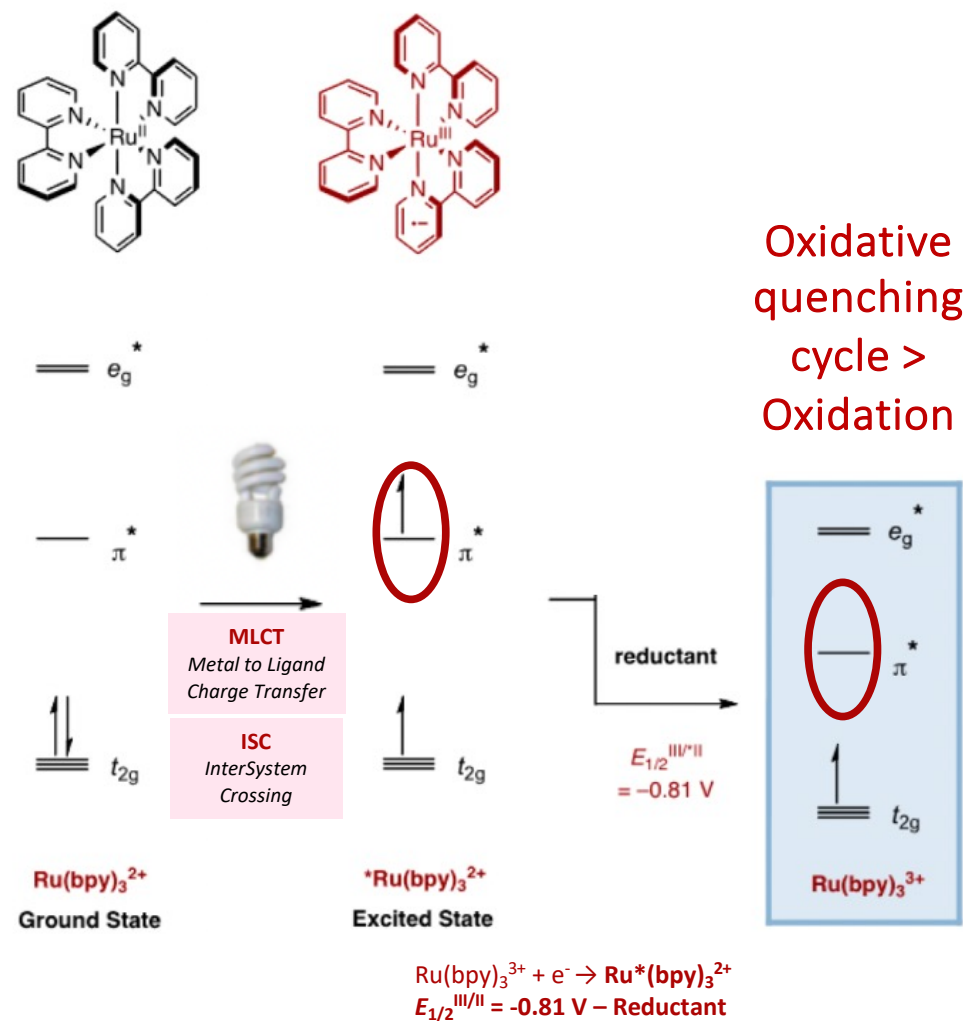
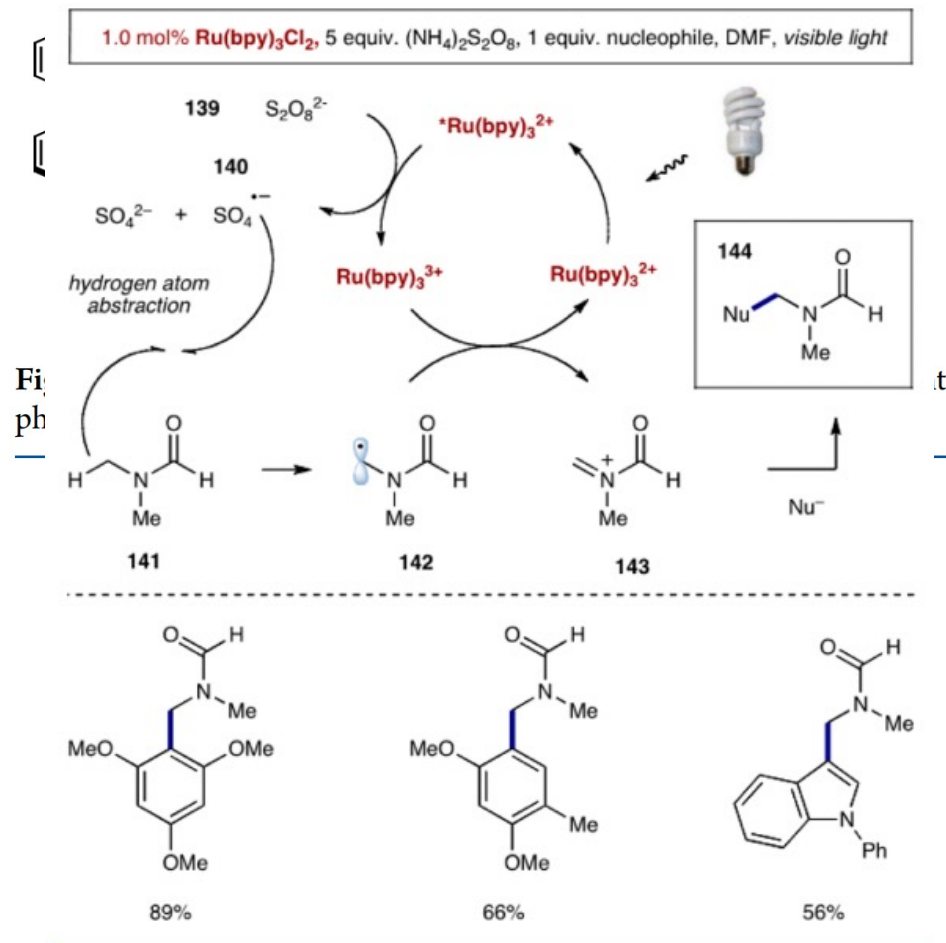

Ir(ppy)₃

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



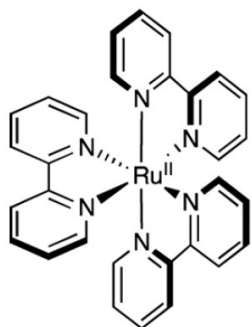
• Use of visible light

> Visible Light Photoredox Catalysis

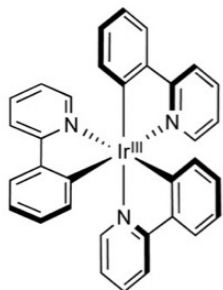
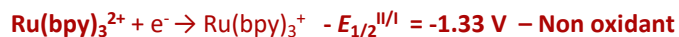
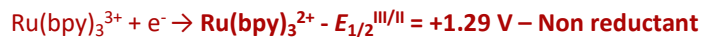
 Scheme 32. α -Arylation of Amides via Hydrogen Atom Abstraction


• Use of visible light

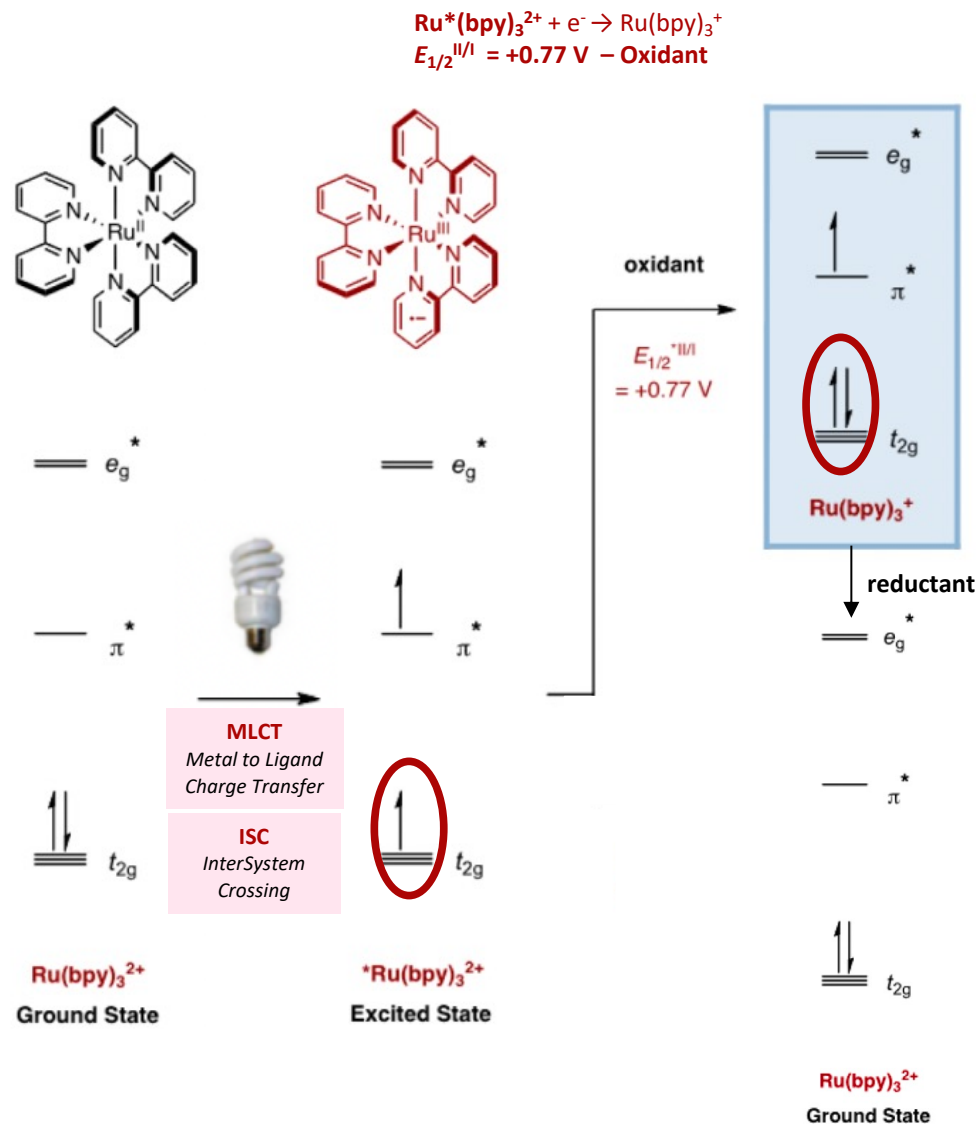
> Visible Light Photoredox Catalysis


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

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


 $\text{Ir}(\text{ppy})_3$

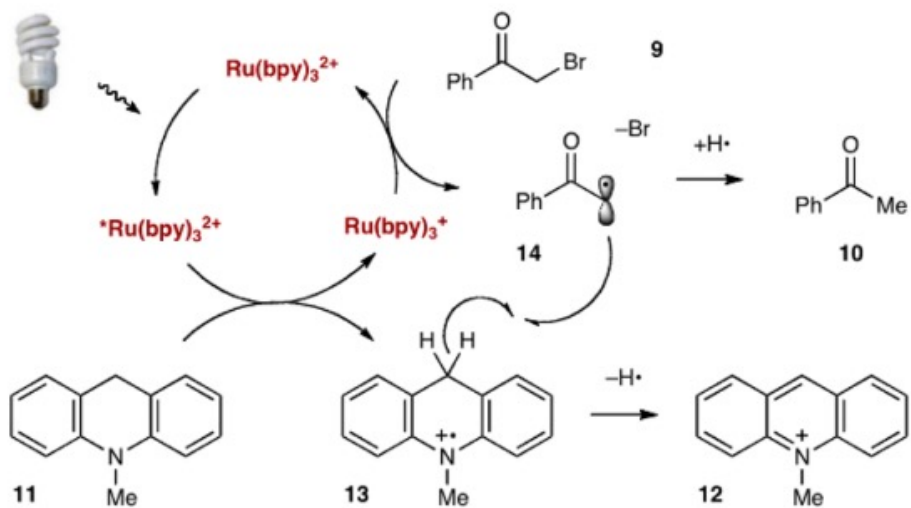
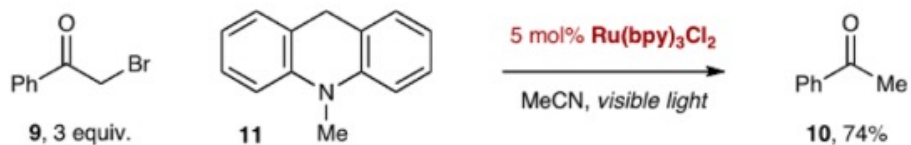
- Max absorption at 375 nm (visible light)
- Long-lived excited state ($\tau = 1.9$ μs)
- Single-electron transfer catalyst
- Effective oxidant and reductant
- Triplet energy of 56 kcal mol⁻¹



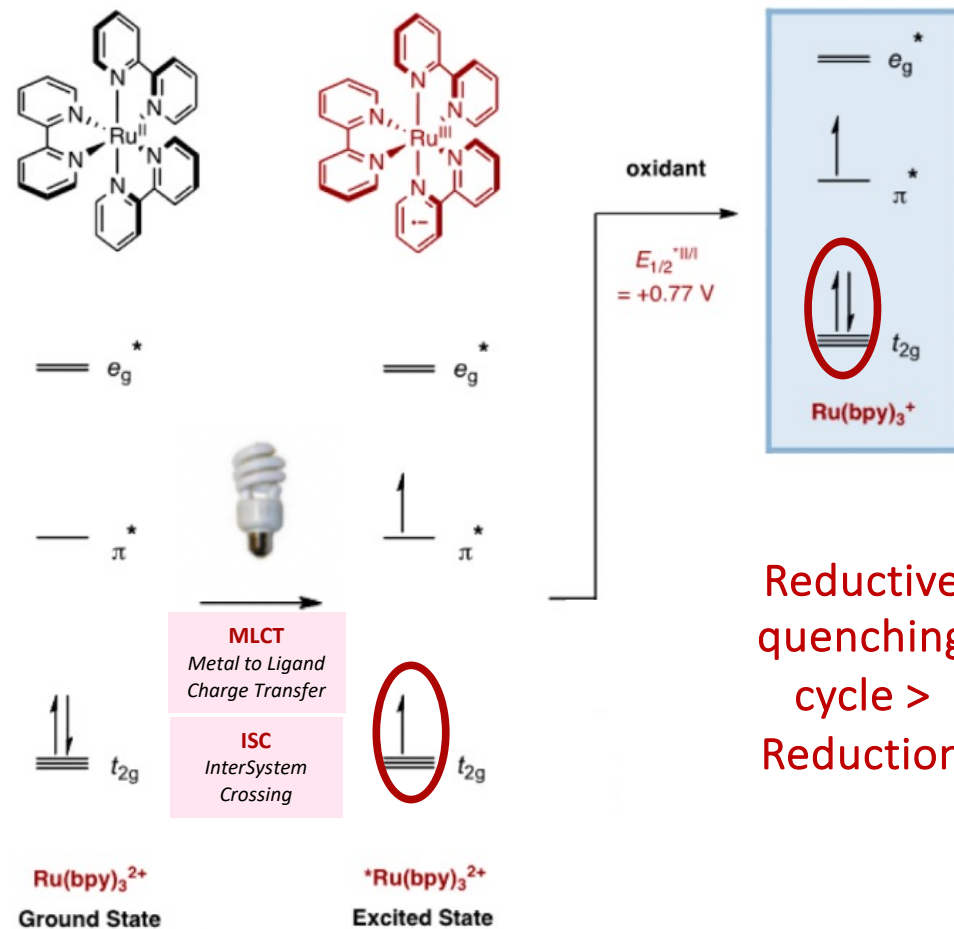
• Use of visible light

> Visible Light Photoredox Catalysis

Scheme 4. Reductive Dehalogenation of Phenacyl Bromides



- Effective oxidant and reductant
- Triplet energy of 56 kcal mol⁻¹



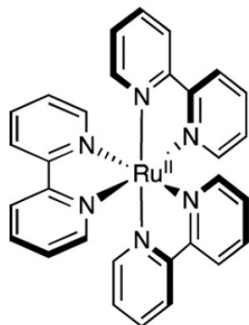
Reductive quenching cycle > Reduction

• Application of catalytic C-H Functionalization

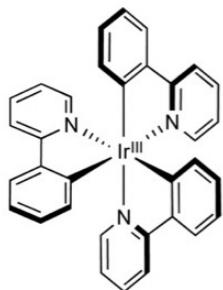
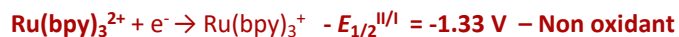
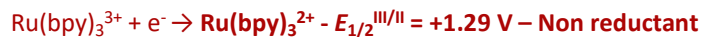
Total synthesis & Late-stage functionalization of natural products and drugs

• Use of visible light

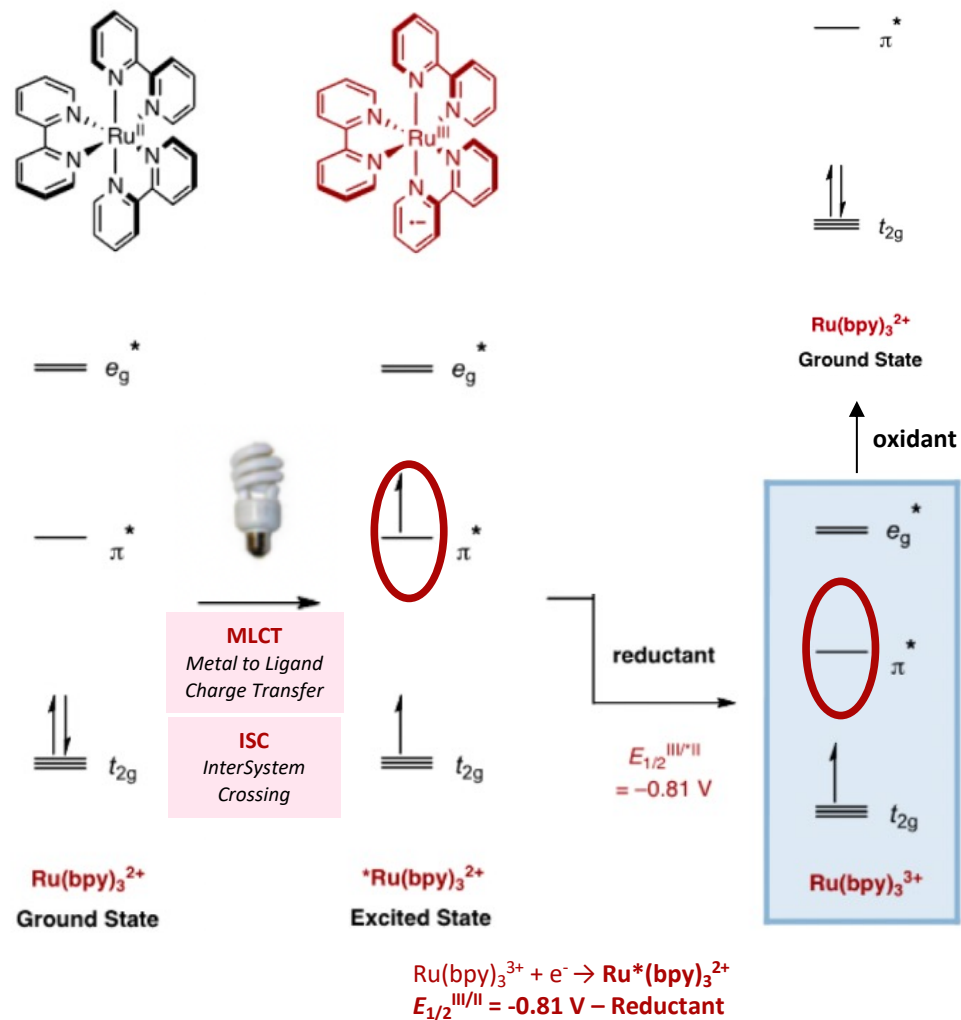
> Visible Light Photoredox Catalysis


Ru(bpy)₃²⁺

- Absorption at 452 nm (visible light)
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- Single electron transfer (SET) catalyst
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Ir(ppy)₃

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

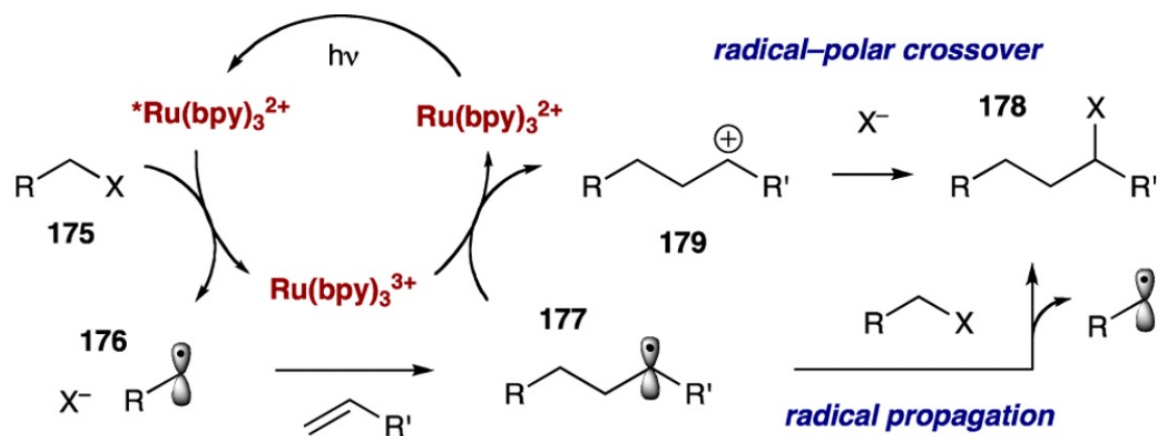

 > D. W.C. MacMillan *et al.*, Visible Light Photoredox Catalysis with TM Complexes, *Chem. Rev.* 2013, 113, 5322-5363

• Use of visible light

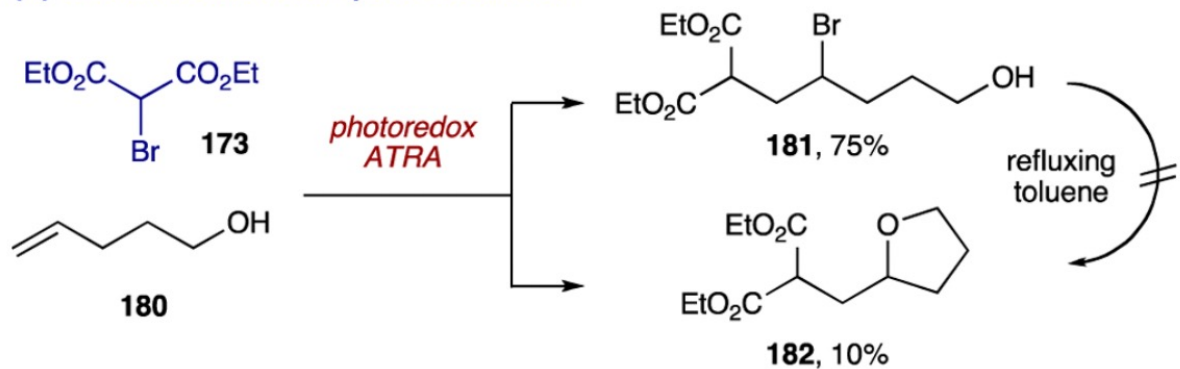
> Visible Light Photoredox Catalysis

REDOX NEUTRAL REACTIONS

Scheme 39. Mechanism of the Photoredox ATRA



(A) Evidence for radical-polar crossover

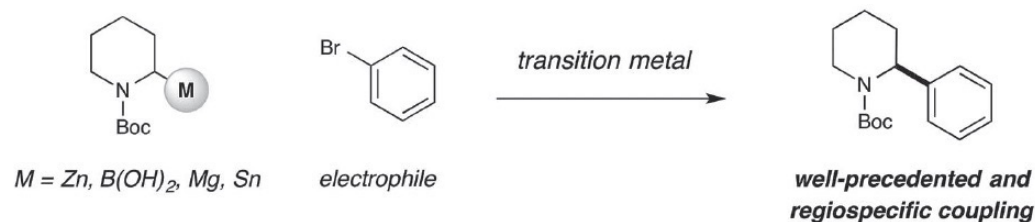


- Application of catalytic C-H Functionalization
Total synthesis & Late-stage functionalization of natural products and drugs

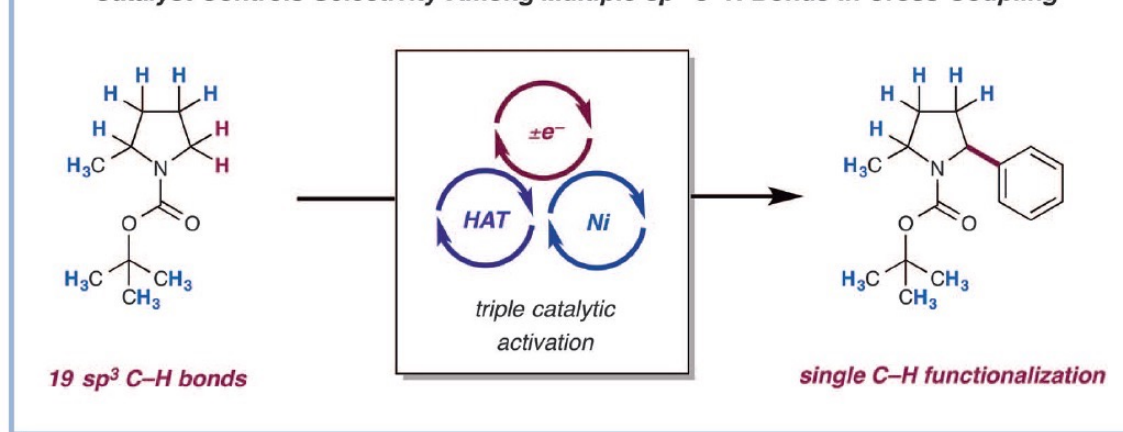
- Intermolecular HAT

- > Metallophotoredox catalysis

Traditional Cross-Coupling Regioselectivity Controlled by Nucleophile Pre-Activation



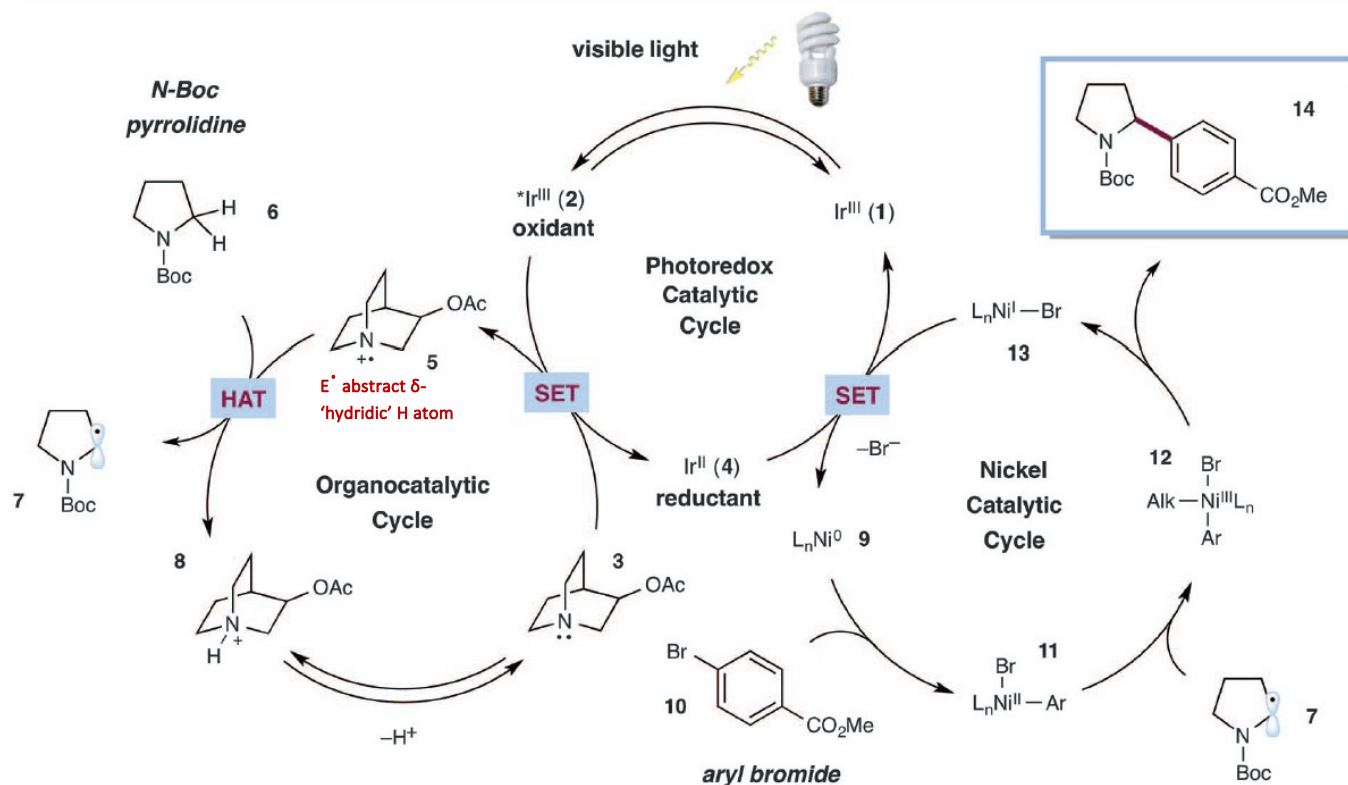
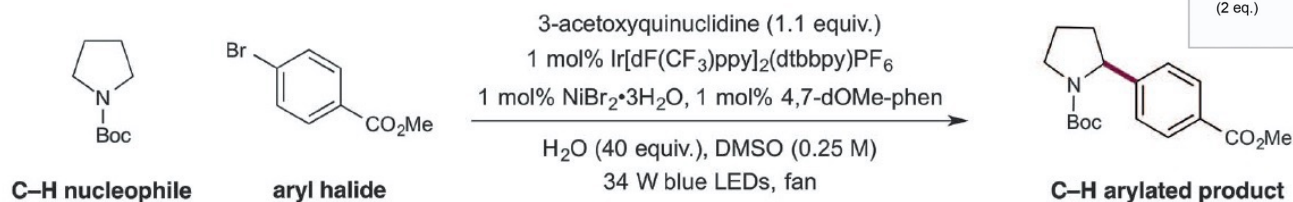
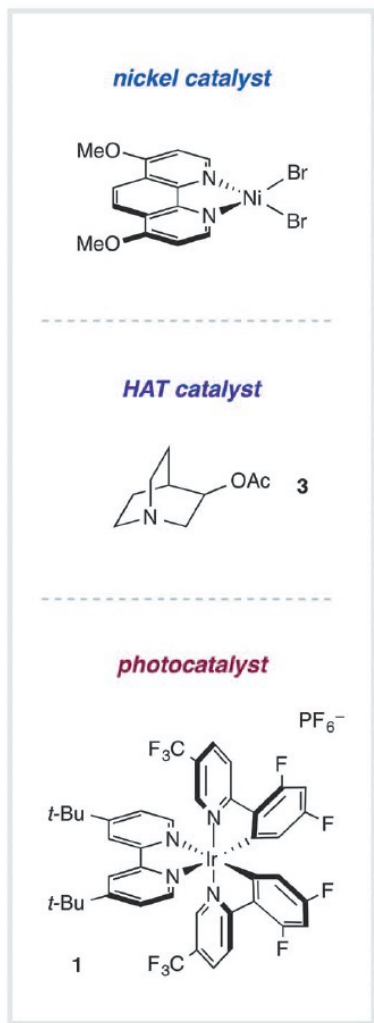
Catalyst Controls Selectivity Among Multiple sp^3 C-H Bonds in Cross-Coupling



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

Intermolecular HAT

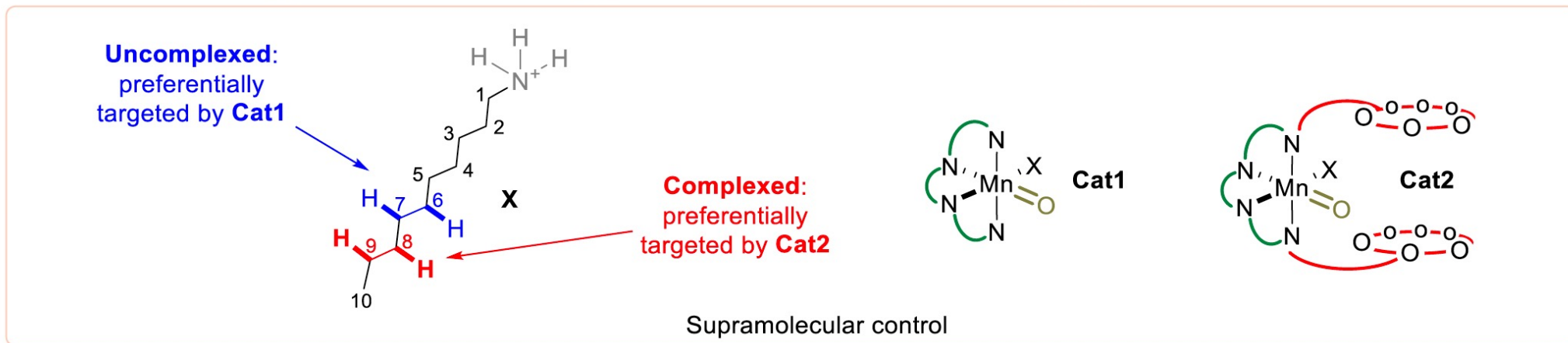
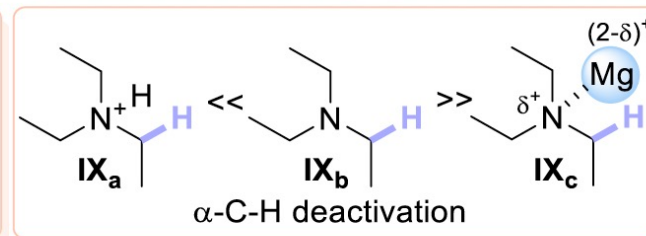
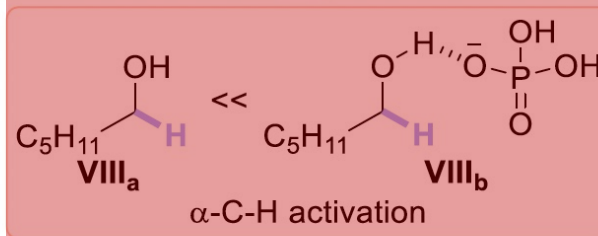
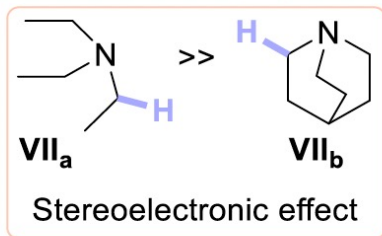
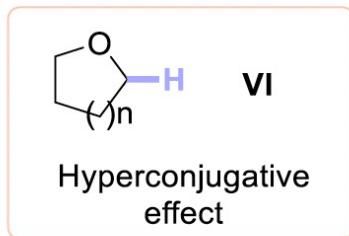
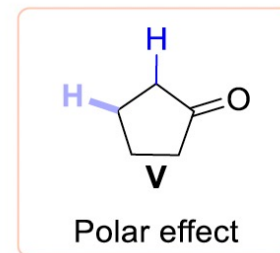
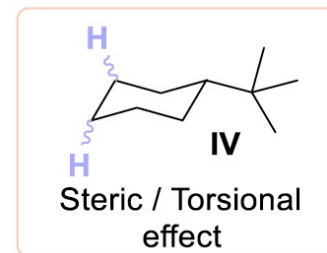
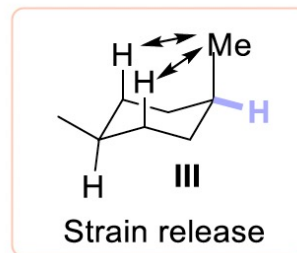
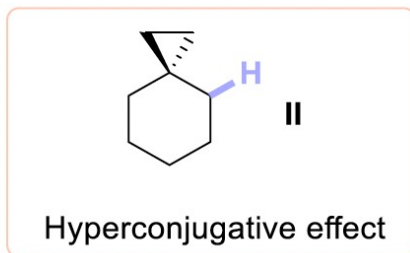
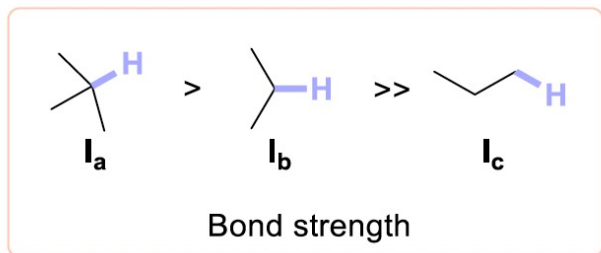
> Metallophotoredox catalysis



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

• C-H Oxidation in the Laboratory

> Factors affecting C-H bond cleavage

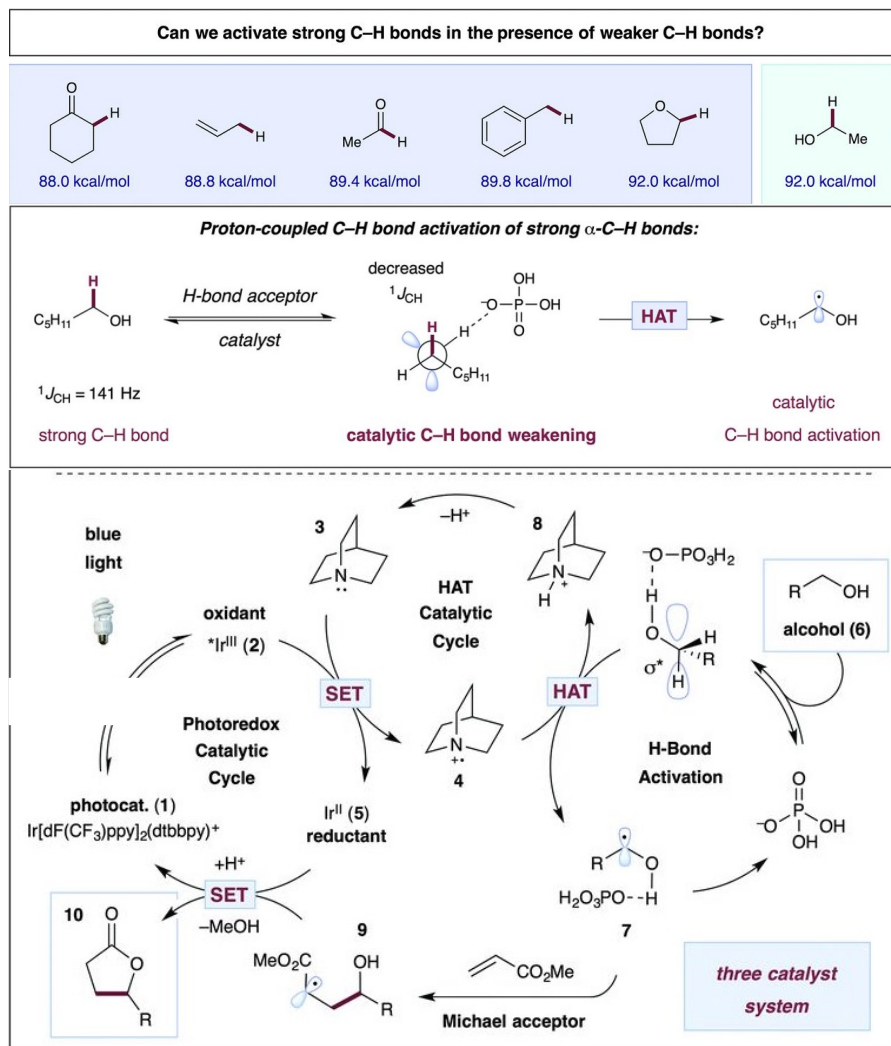


• Application of catalytic C-H Functionalization

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

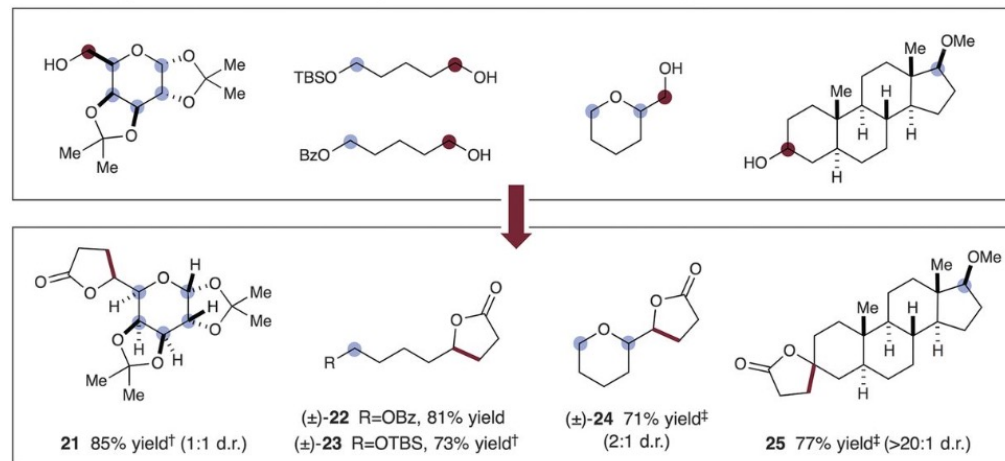
• C-H Oxidation in the Laboratory

> Activation of alcohol

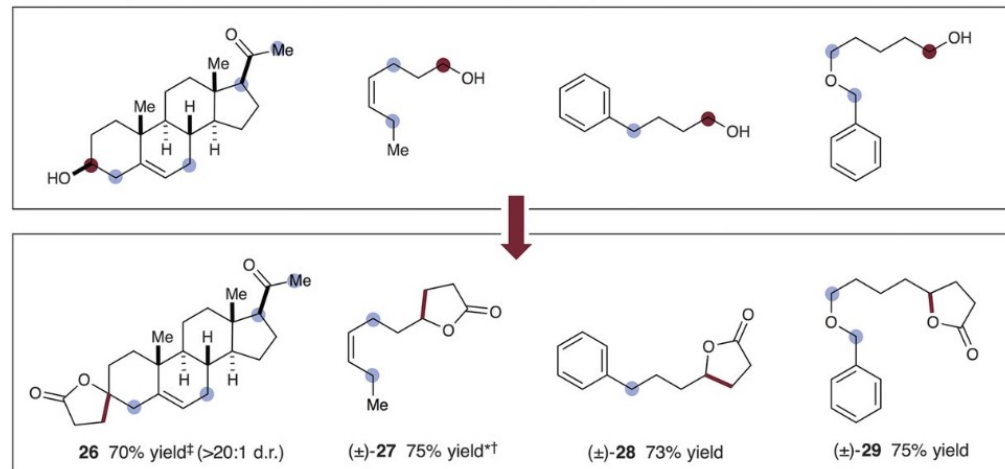


Selective alkylation of alcohol C-H in the presence of ether C-H

(● = strong C-H ● = weaker C-H)

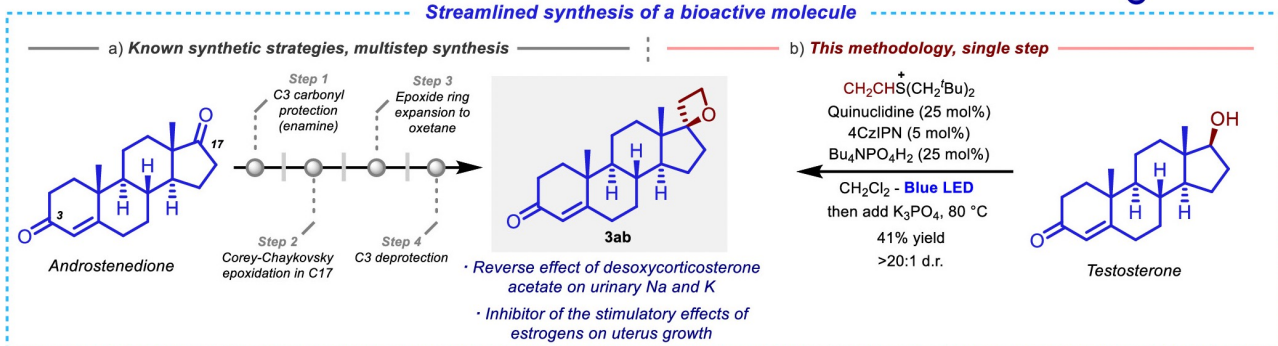
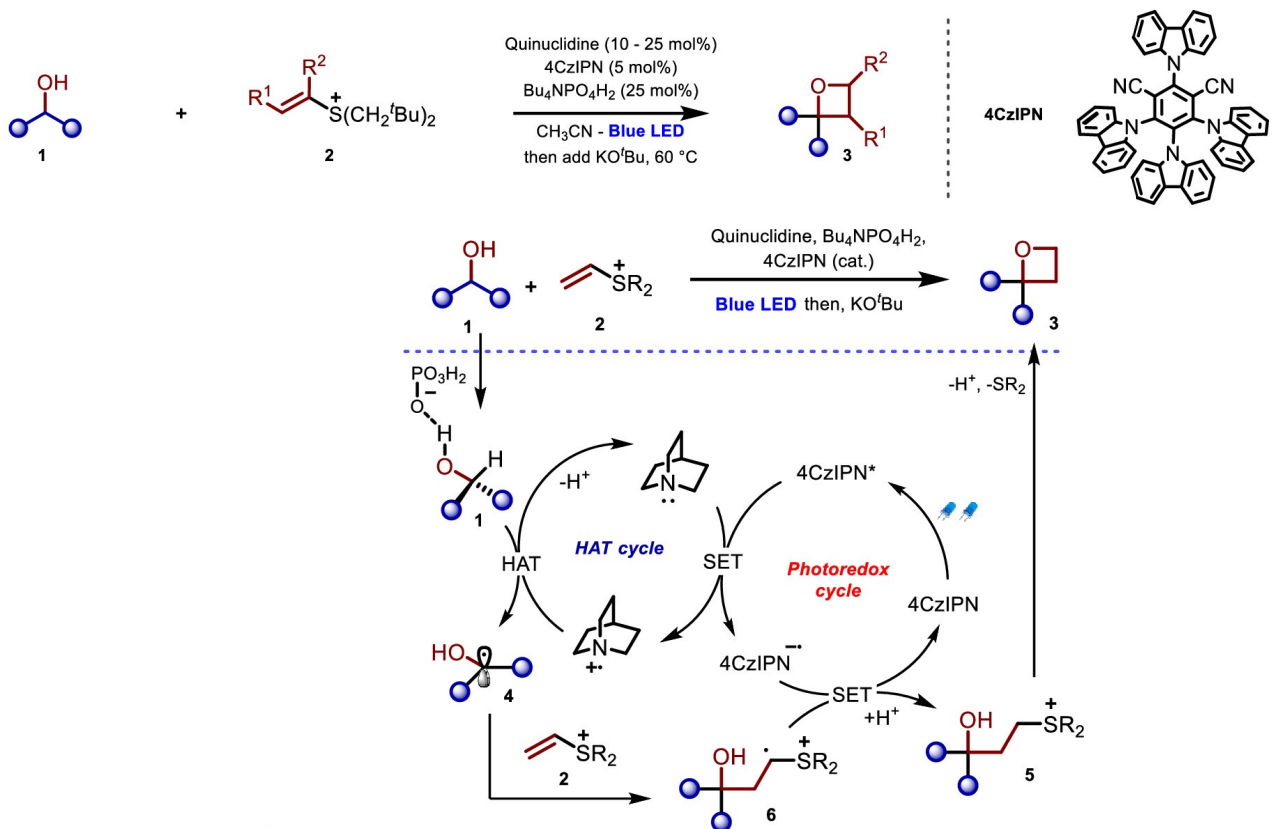
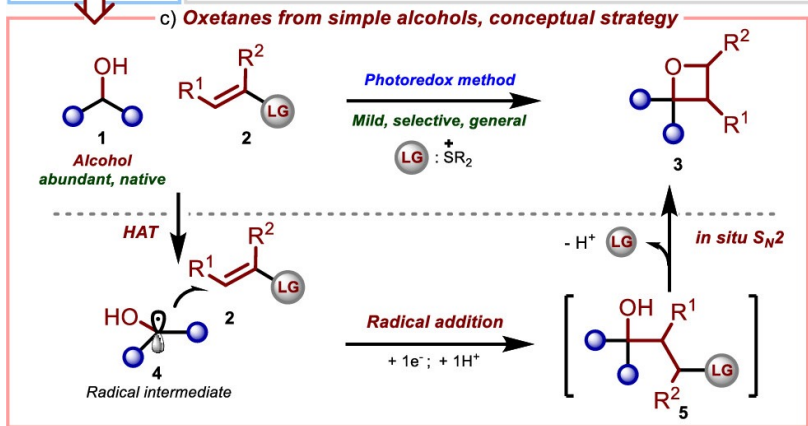
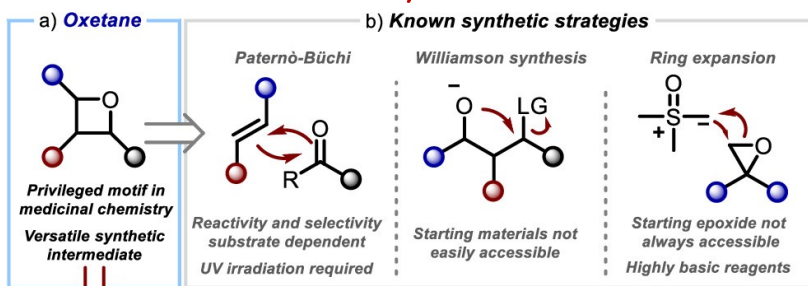


Selective alkylation of alcohol C-H in the presence of allylic, benzylic C-H (● = strong C-H ● = weaker C-H)


 > DWC McMillan *et al*, O-H hydrogen bonding promotes HAT from α C-H bonds for C-alkylation of alcohols, *Science* 2015, 349, 6255

• Introduction of oxetanes

> Back to the chemistry of Oxetanes



• Application of catalytic C-H Functionalization

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

• Late-stage fluorination of peptides

> Visible Light Photoredox Catalysis

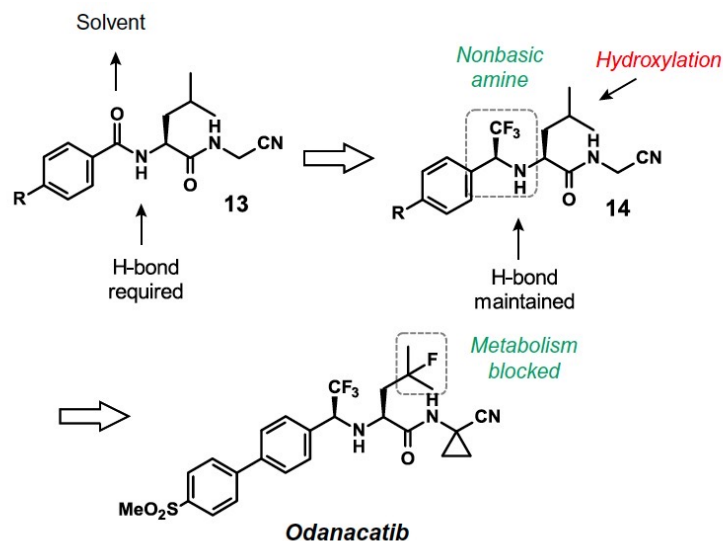
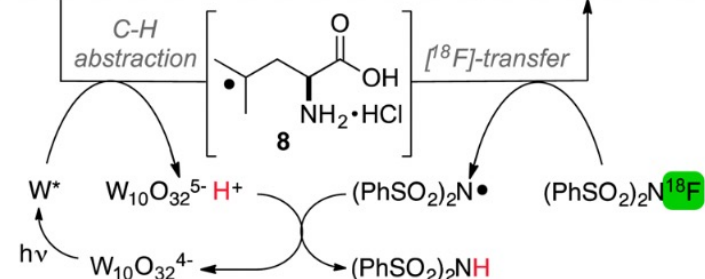
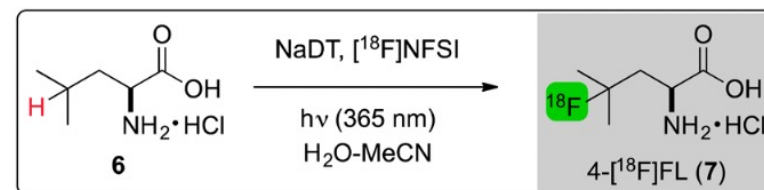
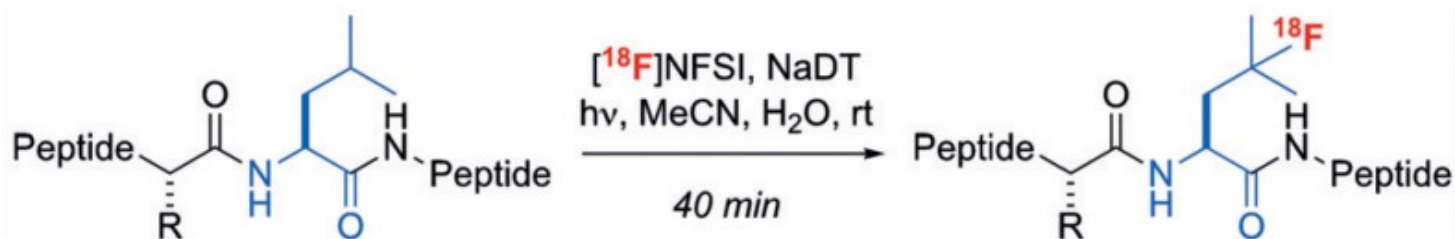
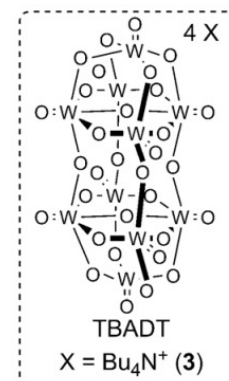


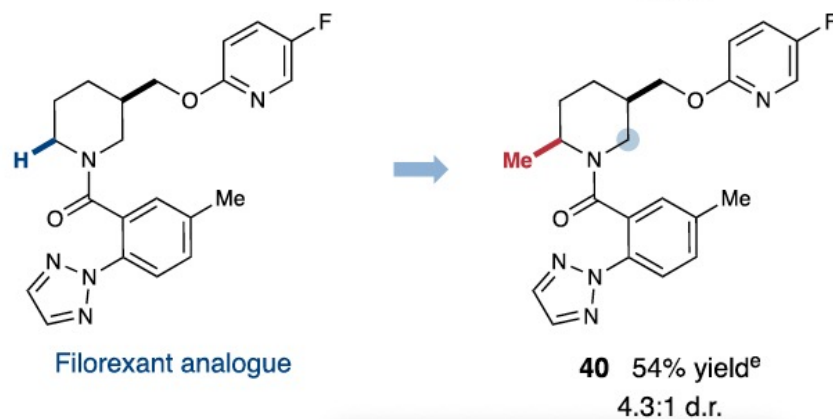
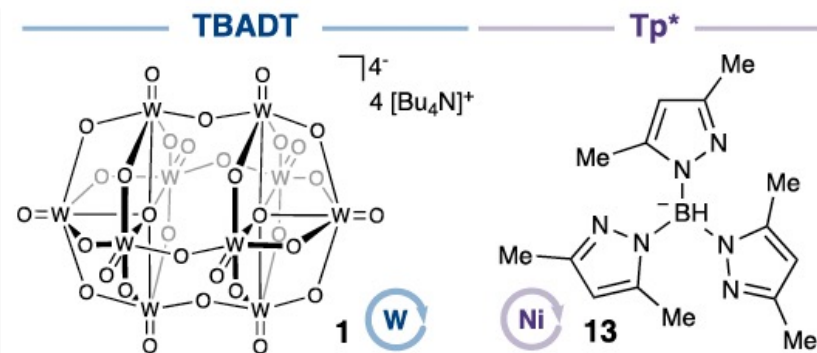
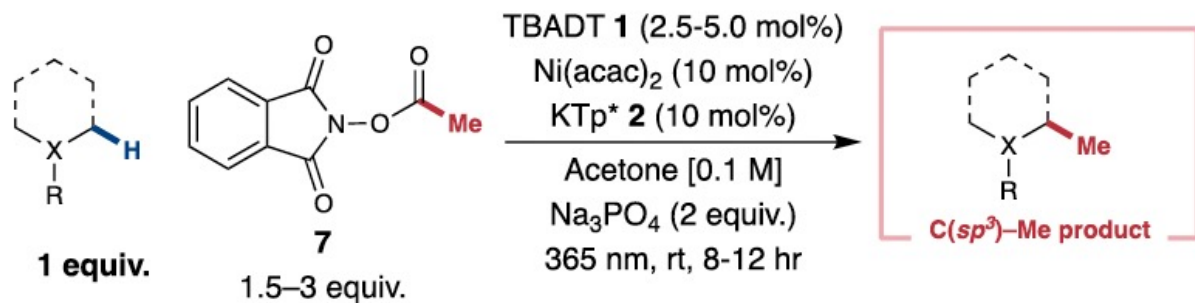
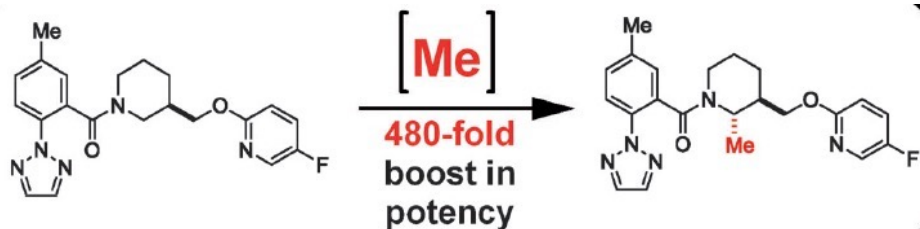
Figure 13 Use of nonbasic amine as amide isostere in the discovery of odanacatib. A second fluorine blocks the oxidation of the isopropyl group to improve pharmacokinetics.



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

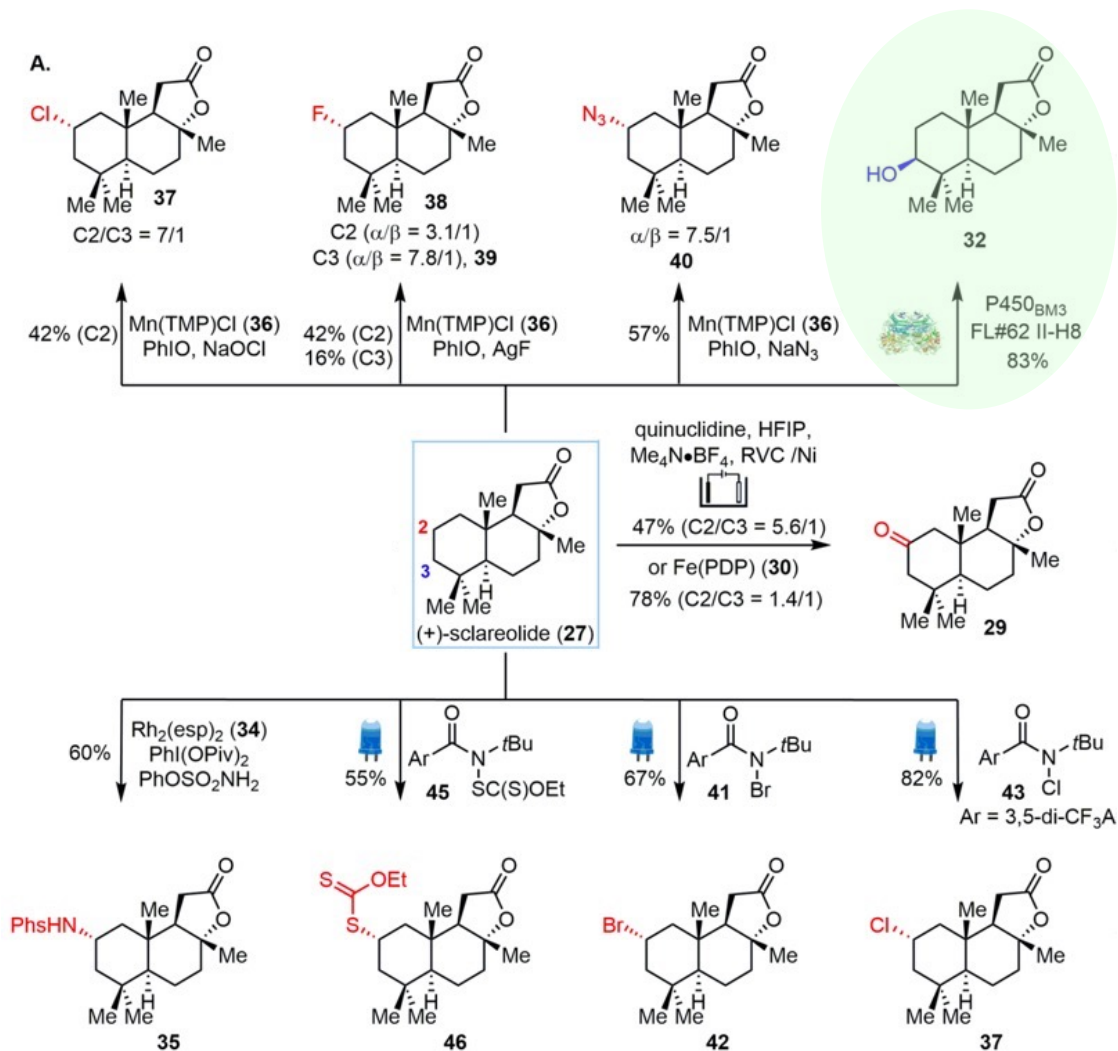


- Late-stage C-H methylation



• C-H functionalization and molecular diversity

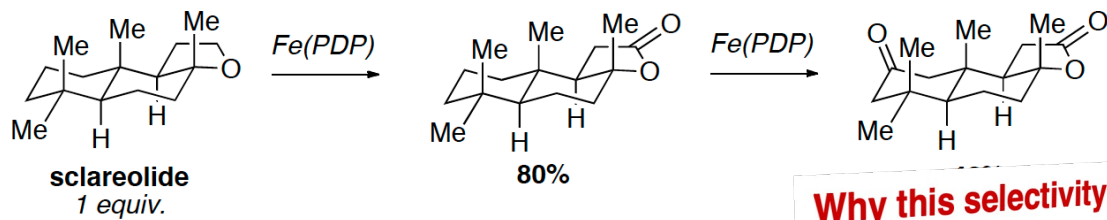
> Molecular diversity in terms of substitution (*in addition to the site-selectivity*)



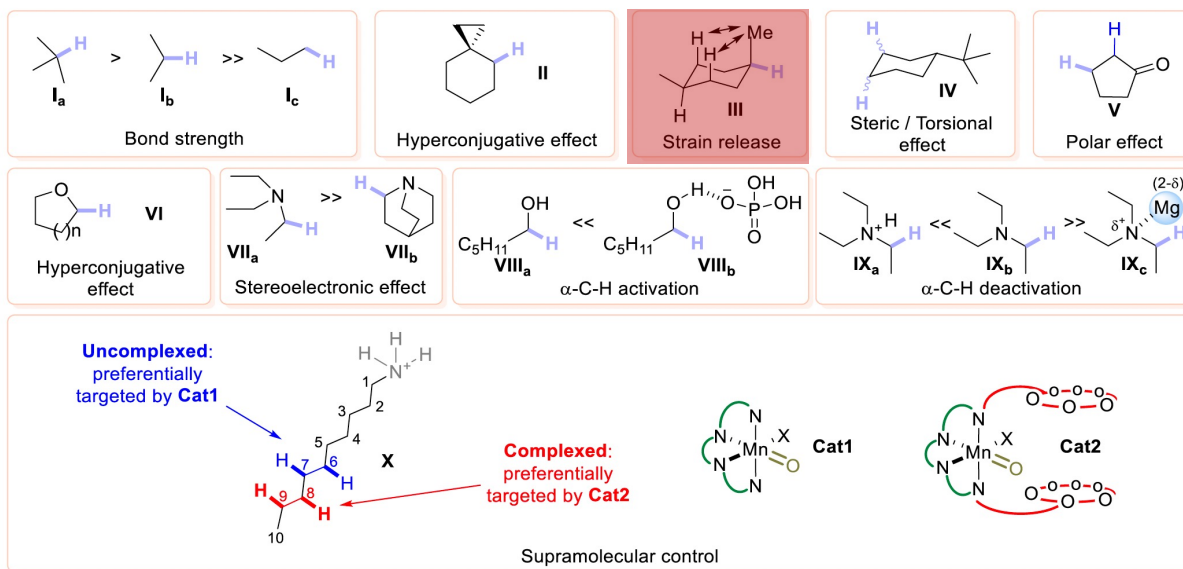
A relevant example of a catalyst-controlled reaction

• C-H functionalization and molecular diversity

> Molecular diversity in terms of substitution (*in addition to the site-selectivity*)

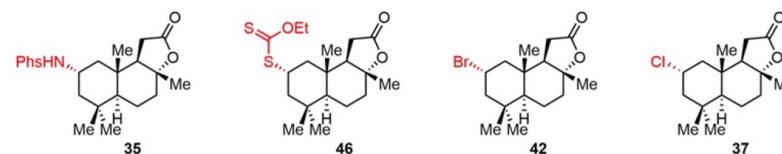
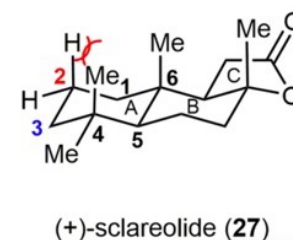
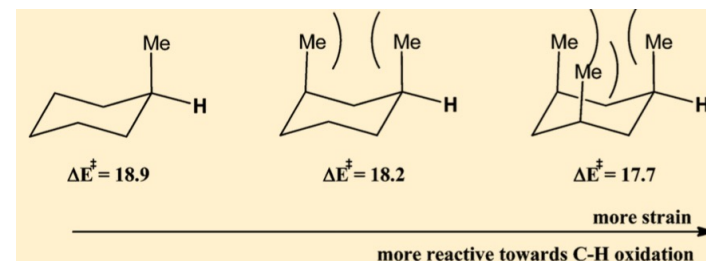


**Why this selectivity
in the substrate-
controlled reaction?**



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

equatorial C-H bonds are more reactive because of both the strain-release effect and higher steric accessibilities.



• C-H functionalization for the improvement of physical properties

> C-H Oxidation

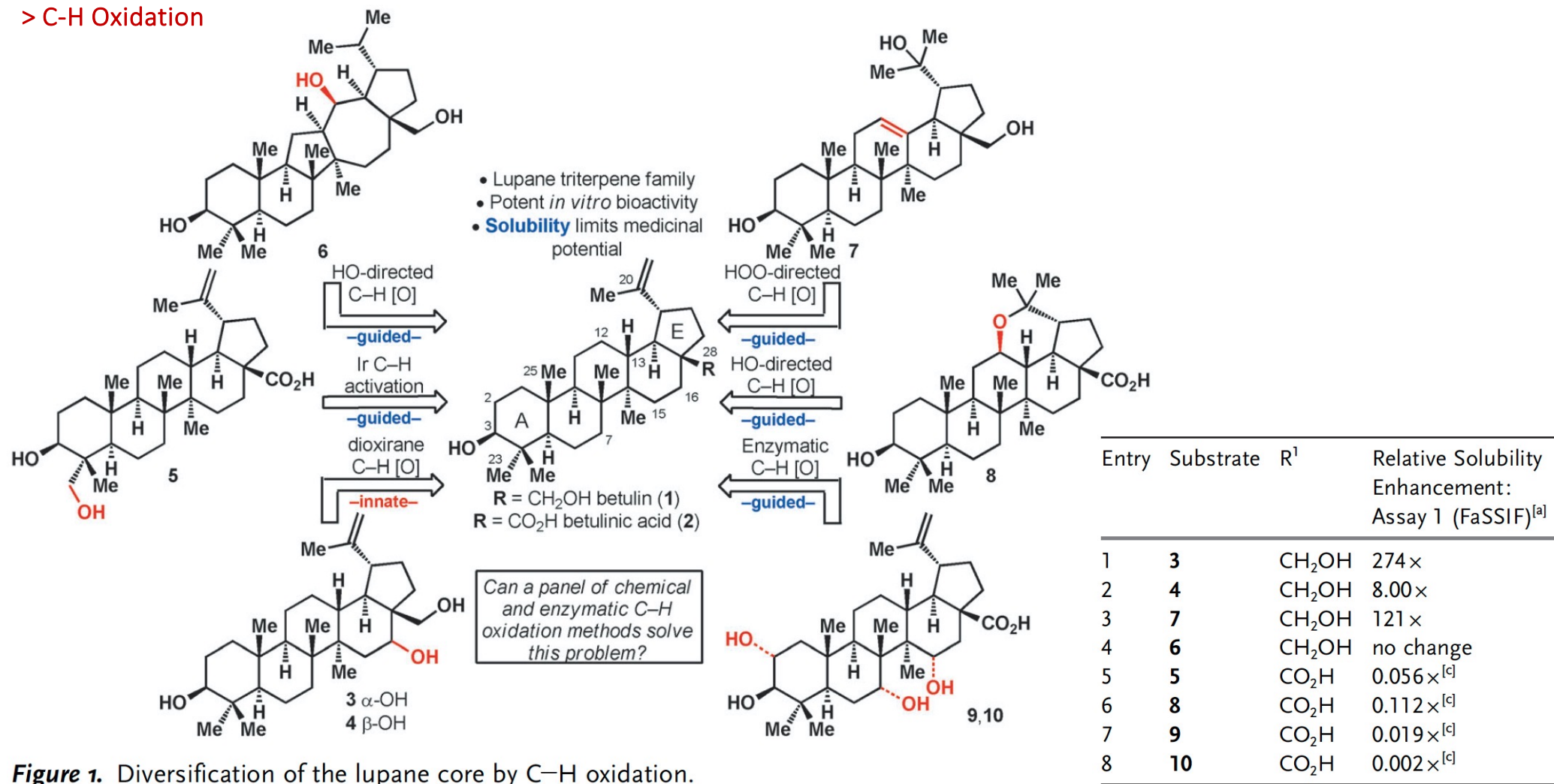


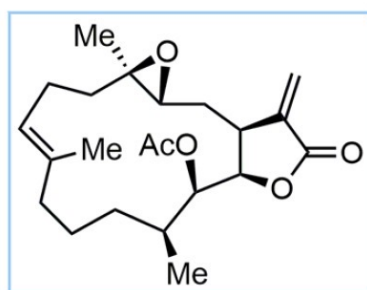
Figure 1. Diversification of the lupane core by C-H oxidation.

• C-H functionalization and chemical biology

> Identification of the biological target

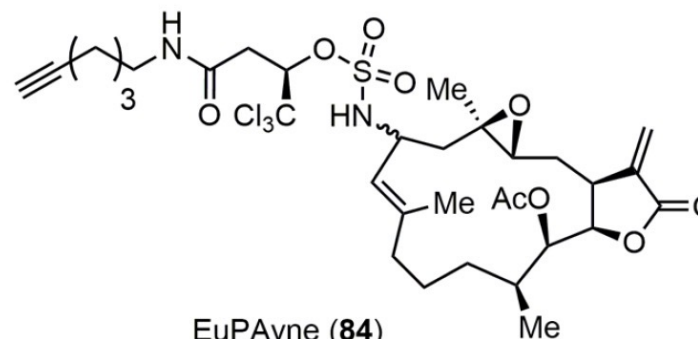
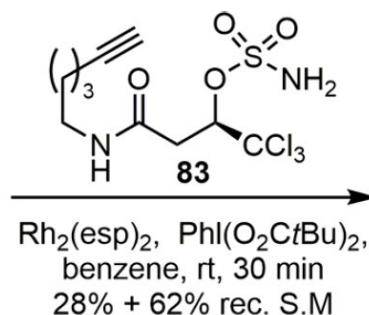
The target identification process often requires natural product-derived chemical probes, which must retain activities comparable to those of the parent compounds. Conventional functionalization of natural products mostly depends on the pre-existing reactive sites present in the native structure, which are often required for biological activity.

Synthesis of the EuPA probe via conventional chemical transformations is very challenging due to the limited number of reactive functional group handles within the EuPA skeleton.



eupalmerin acetate
(EuPA) (**82**)

*IC*₅₀ in HL-60 cells
(95% CI) = 3.0 μM (2.4-3.7)



EuPAYne (**84**)
dr = 1:1

*IC*₅₀ in HL-60 cells
(95% CI) = 14 μM (8-25)

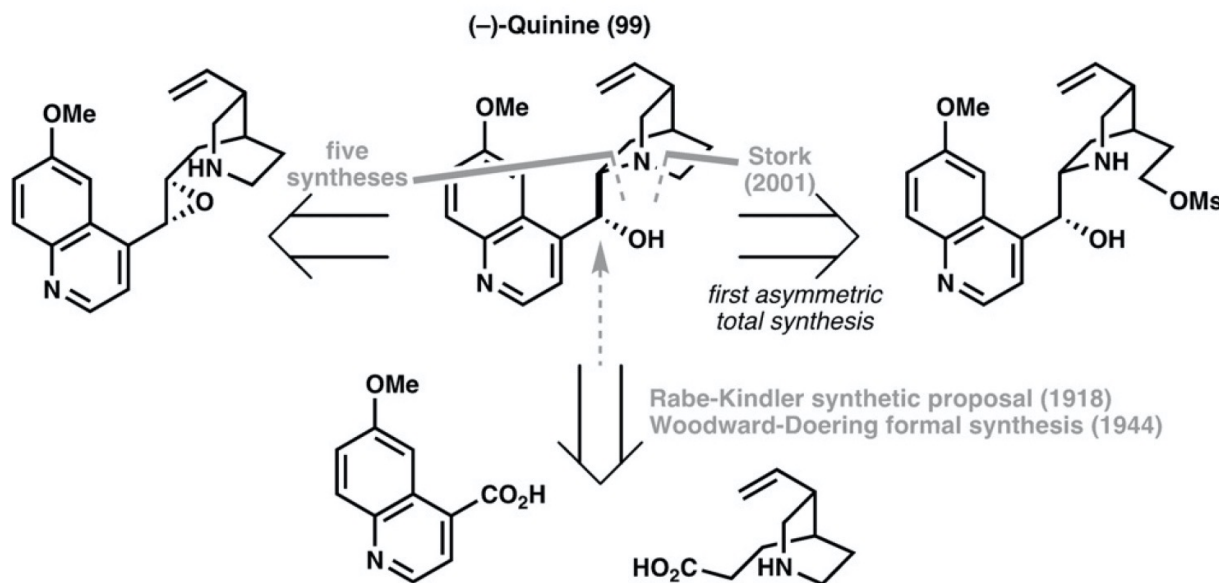
Application of Rh-catalyzed selective C-H amination to EuPA gives probe EuPAYne (**84**) in one step as a 1:1 diastereomeric mixture at the macrocyclic allylic position without affecting the bioactive enone double bond, which may form a covalent bond with nucleophilic residues of the target protein(s).

• C-H Functionalization and synthesis

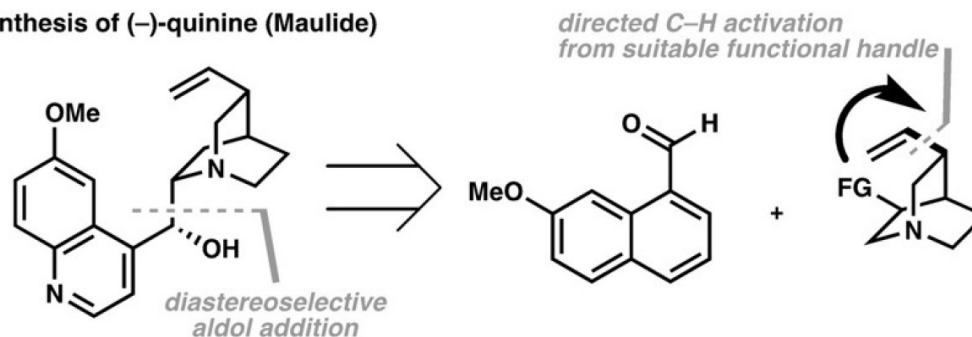
> A landmark example: Quinine

A brief summary of the history of quinine total synthesis:

C–N bond disconnection represents a key disconnection in all quinine total syntheses



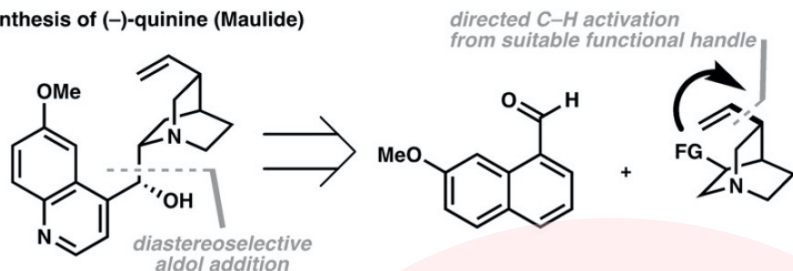
(A) Retrosynthesis of (-)-quinine (Maulide)



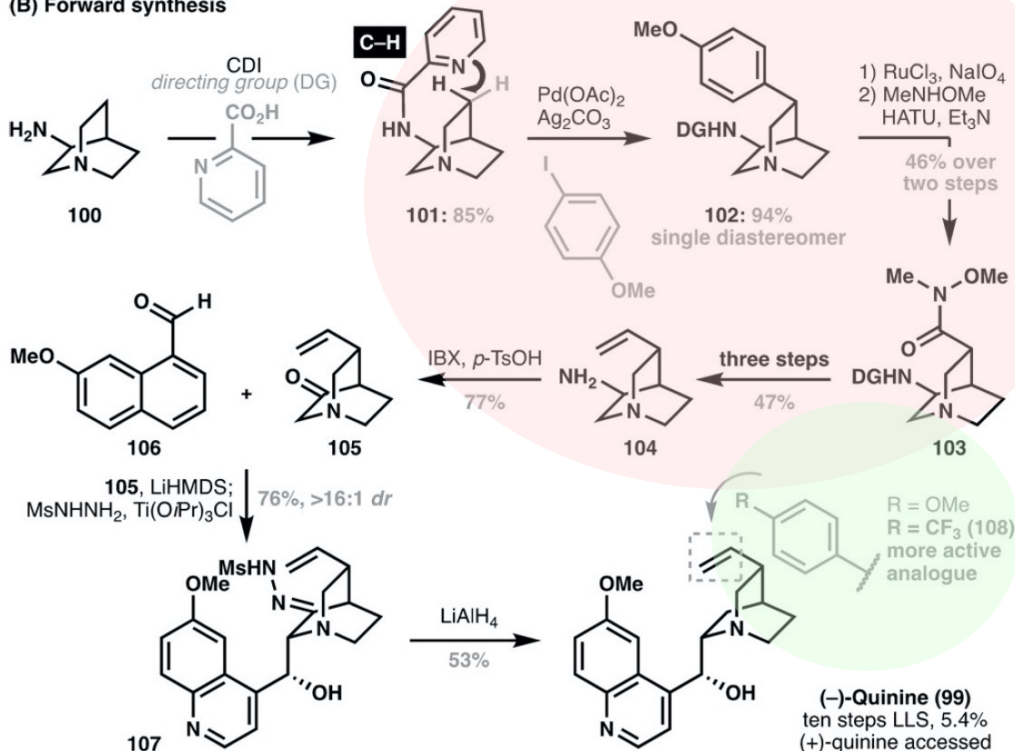
• C-H Functionalization and synthesis

> A landmark example of synthesis

(A) Retrosynthesis of (-)-quinine (Maulide)

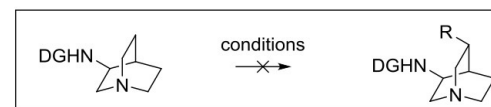


(B) Forward synthesis



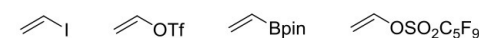
> But there is room for improvement

Summary of Failed Attempts for C-H Functionalization



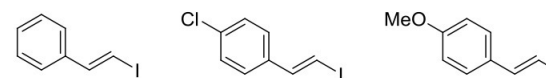
C-H Vinylation

Coupling partners investigated:



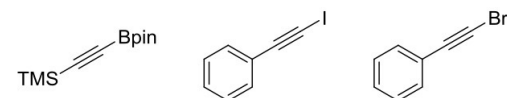
C-H Alkenylation

Coupling partners investigated:



C-H Alkynylation

Coupling partners investigated:



> Opportunities in Medicinal Chemistry

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

C-H Functionalization and synthesis

> A landmark example: opportunities

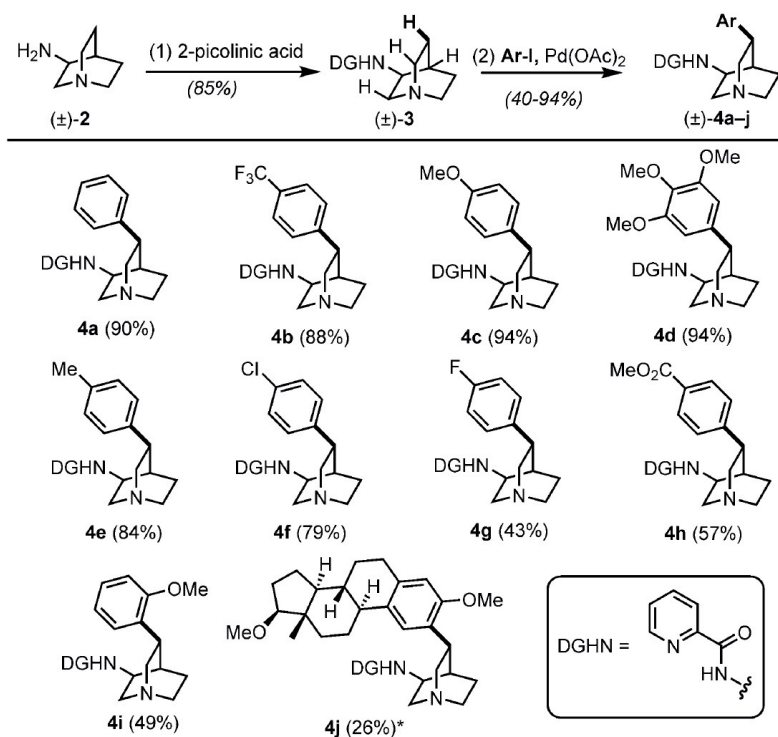
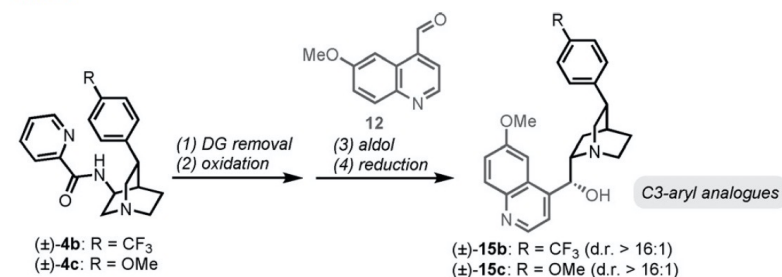


Table 1: In vivo activity of the racemic aryl analogues (**±**)-**15b** and (**±**)-**15c** and (–)-quinine hydrochloride as a reference against *P. berghei* in mice.



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

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

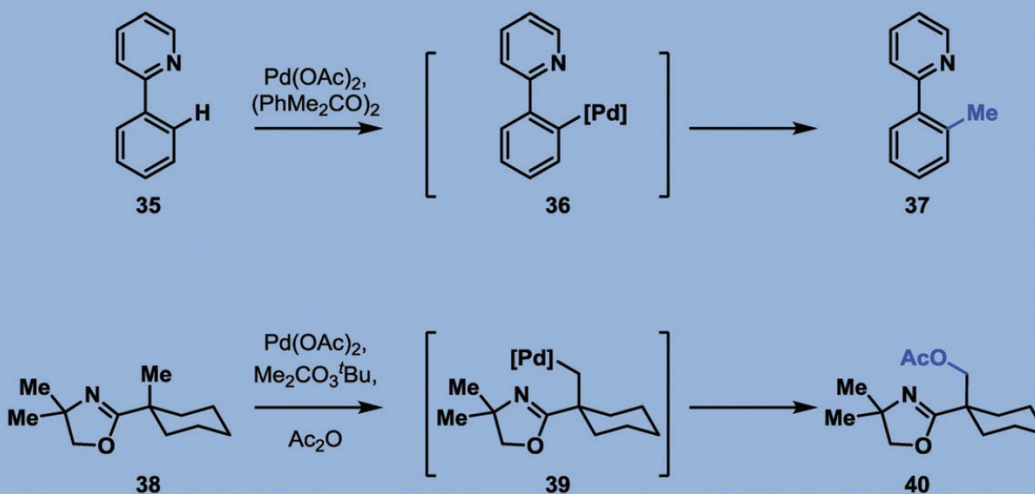
Late stage C-H Functionalization

> A general strategy

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.



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

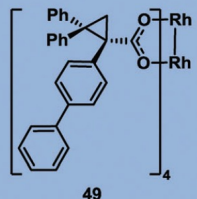
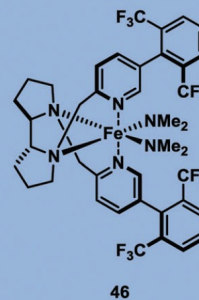
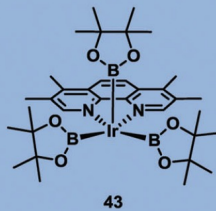
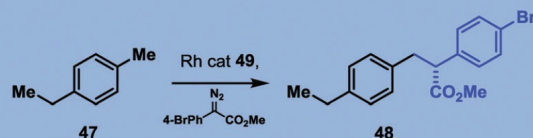
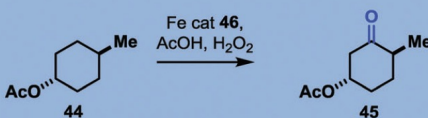
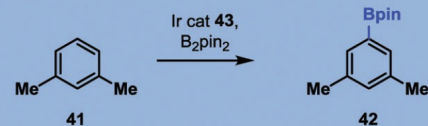
Late stage C-H Functionalization

> A general strategy

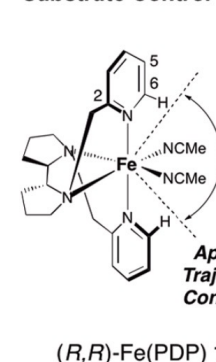
Guided Reaction Manifolds



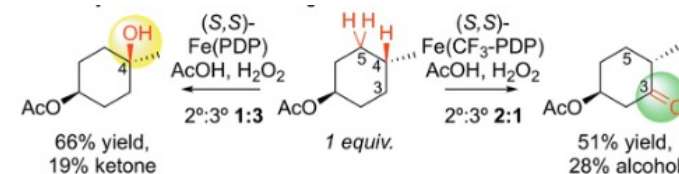
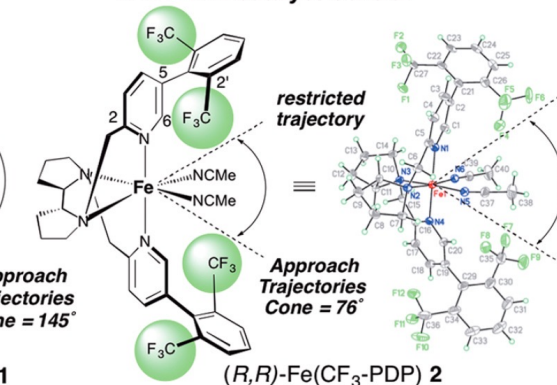
2. Guided by sterics. Bulky catalysts drive reactivity towards sterically accessible C-H bonds. This class includes true insertion and H-abstraction reactions, as in Fig. 3, entry 1, where the substrate or catalyst are sterically encumbered. **43**, **46** and **49** are bulky catalysts that override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



Previous Work:
Substrate Control



This Work: Catalyst Control



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

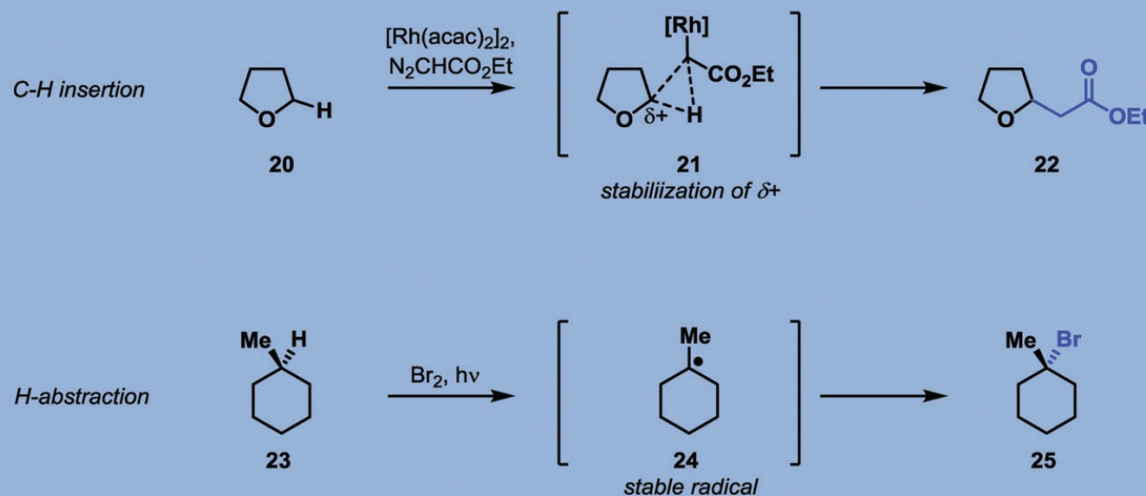
- Late stage C-H Functionalization

> A general strategy

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 $3^\circ > 2^\circ > 1^\circ$. 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.



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

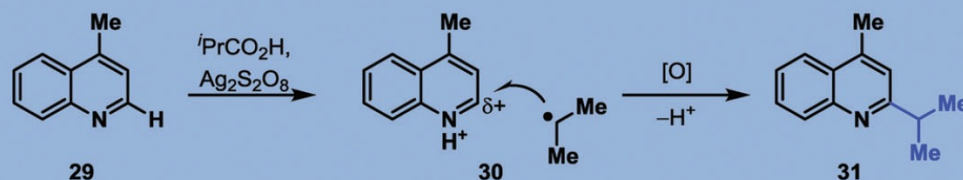
Late stage C-H Functionalization

> A general strategy

Innate Reaction Manifolds

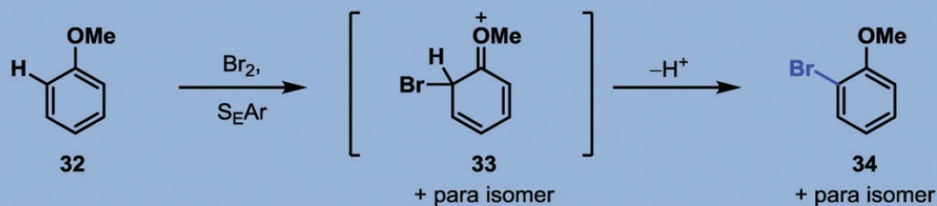
δ^+

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.



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

Late stage C-H Functionalization

> A general strategy

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.

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.

