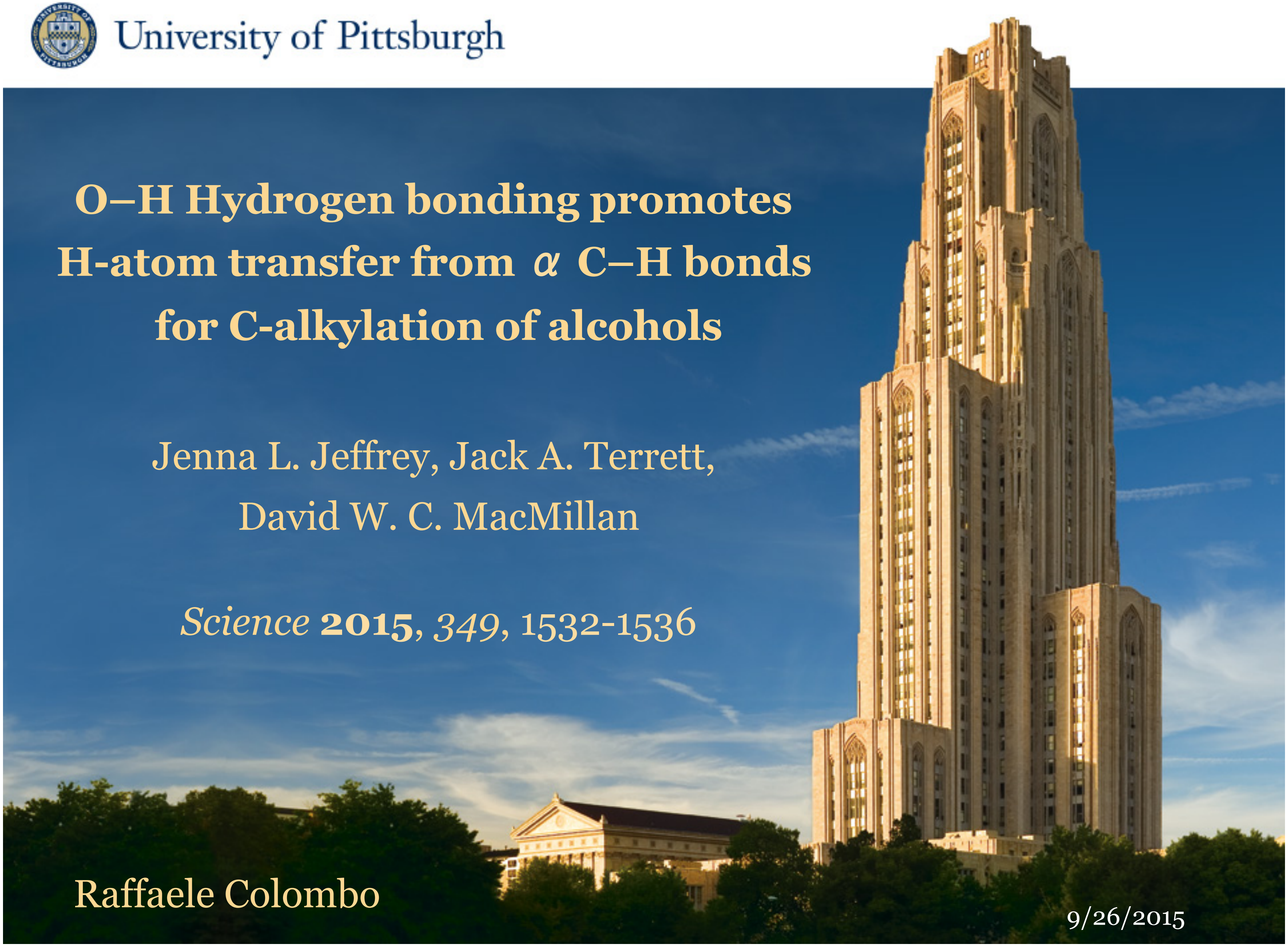
University of Pittsburgh



O–H Hydrogen bonding promotes H-atom transfer from α C–H bonds for C-alkylation of alcohols

Jenna L. Jeffrey, Jack A. Terrett,
David W. C. MacMillan

Science **2015**, *349*, 1532-1536

Raffaele Colombo

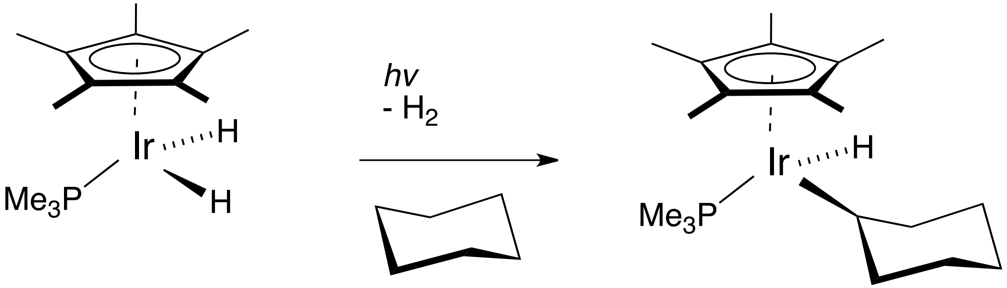
9/26/2015

C-H activation

- "C-H activation" refers to reactions involving the cleavage of an **unreactive C-H bond** of alkanes, arenes, or alkyl chains by transition metal complexes

- The intermolecular catalytic **functionalization** of **C(sp3)–H** bonds in a **selective manner** represents a longstanding **challenge**

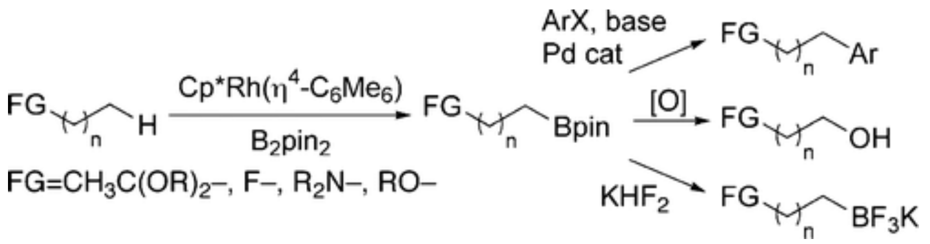
Early studies by Bergman:

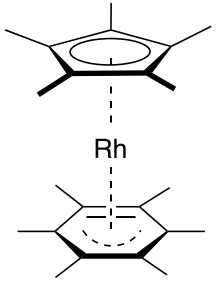


Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352-354.

C(sp3)-H activation

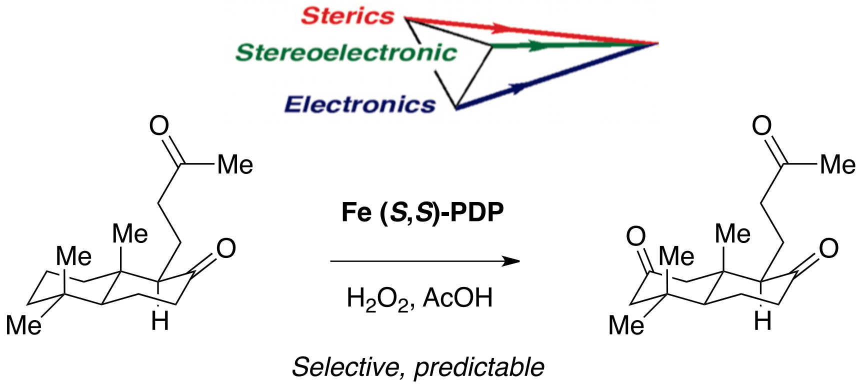
- **Hartwig**: rhodium-catalyzed borylation of terminal methyl groups

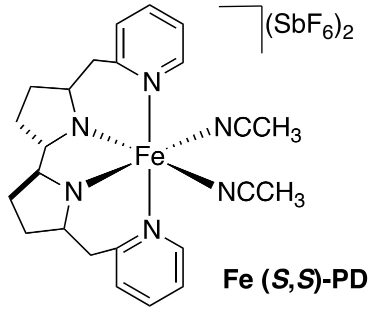




$Cp^*Rh(\eta^4-C_6Me_6)$

- **White**: iron-catalyzed oxidation of 2° and 3° aliphatic C–H bonds





Fe (*S*,*S*)-PDP

- **Importance of catalyst structure for site selectivity!**

Hydrogen abstraction

- The rate of hydrogen abstraction from a C–H bond depends on:
  - **- the C–H bond dissociation enthalpy (BDE)**
  - **- polar effects in the transition state**

In 1987, Roberts discovered that certain **electrophilic radicals** (*e.g., t-butoxyl*) preferentially abstract hydrogen from **electron-rich bonds**, while **nucleophilic radicals** (*e.g., amine-boryl*) selectively cleave **electron-deficient C–H bonds**.

$$Bu^tO^\bullet + Me_3N\rightarrow BH_2Hex^t \longrightarrow Bu^tOH + Me_3N\rightarrow \dot{B}HHex^t$$

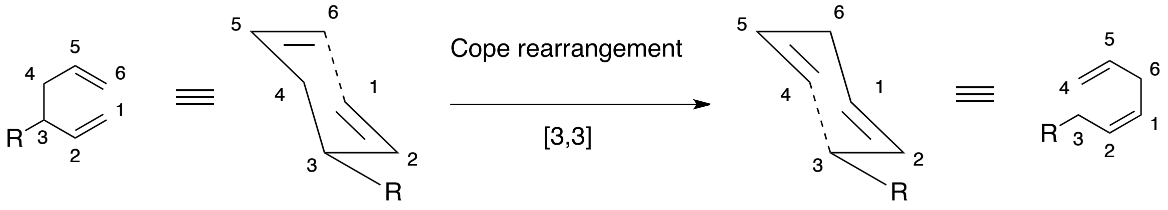
$$Me_3N\rightarrow \dot{B}HHex^t + MeCN \longrightarrow Me_3N\rightarrow BH_2Hex^t + {}^\bullet CH_2CN$$

$$Hex^t = Me_2CHCMe_2$$

For examples and theory of polarity-reversal catalysis of hydrogen-atom abstraction reactions see: *Chem. Soc. Rev.* **1999**, *28*, 25–35

Oxy-anionic substituent effect

- An **alkoxide** functionality **accelerates** sigmatropic processes wherein a bond to the carbon bearing the alkoxy group is broken.



R = H k (s^{-1}) = 1.6 10^{-14}
R = OH k (s^{-1}) = 1.0 10^{-12}
R = $O^- K^+$ k (s^{-1}) = 1.6 10^{8}

- An alkoxide **enhances homolitic hydrogen atom abstractions** by highly electrophilic perfluoro **radicals**.

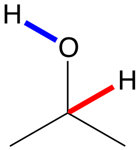
$$R_1R_2CHOX \xrightarrow{Na^+\ {}^-O_3SCF_2CF_2OCF_2CF_2^{\bullet}} R_1R_2\dot{C}\,OX$$

$CF_3CH_2O^-\ Na^+$	k (M^{-1} s^{-1}) = 77000	$k_{rel} = 960$
CF_3CH_2OH	k (M^{-1} s^{-1}) = 80	
$(CF_3)_2CHO^-\ Na^+$	k (M^{-1} s^{-1}) = 108000	$k_{rel} = 280$
$(CF_3)CHOH$	k (M^{-1} s^{-1}) = 390	

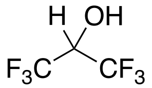
Evans et al. *J. Am. Chem. Soc.* **1979**, *101*, 1994–1997.
William R. Dolbier, Jr. et al. *Org. Biomol. Chem.* **2004**, 2, 2083–2086

Effect of H-bond on Cα-H bond

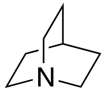
H-Bonding in alcohols is reflected in the **Cα-H bond** strength



The strength of **Cα-H bond** is reflected in the one-bond **^{13}C-^{1}H coupling constant ($^{1}J_{CH}$).**

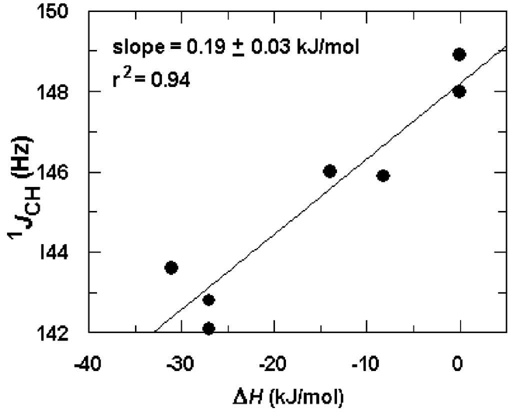


HFIP



quinuclidine

solvent	$^{1}J_{CH}$ (±0.1 Hz)	pK_a[a]	ΔH[b] ((± 2 kJ/mol)
toluene	148.0		
chloroform	148.9		
dimethylaniline	145.9	5.1	−8.2
N-methylmorpholine	146.0	7.4	−14
N,*N*-diisopropyl-ethylamine	142.1	10.7	−27
triethylamine	142.8	10.8	−27
quinuclidine	143.6	11.0	−31

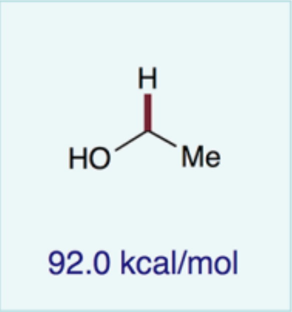


Hexafluoroisopropanpl (HFIP) solutions (1 M) in the tertiary amine solvents or an equimolar HFIP/amine solution in $CHCl_3$

Enthalpy of H-bond formation measured by Isothermal Titration Calorimetry

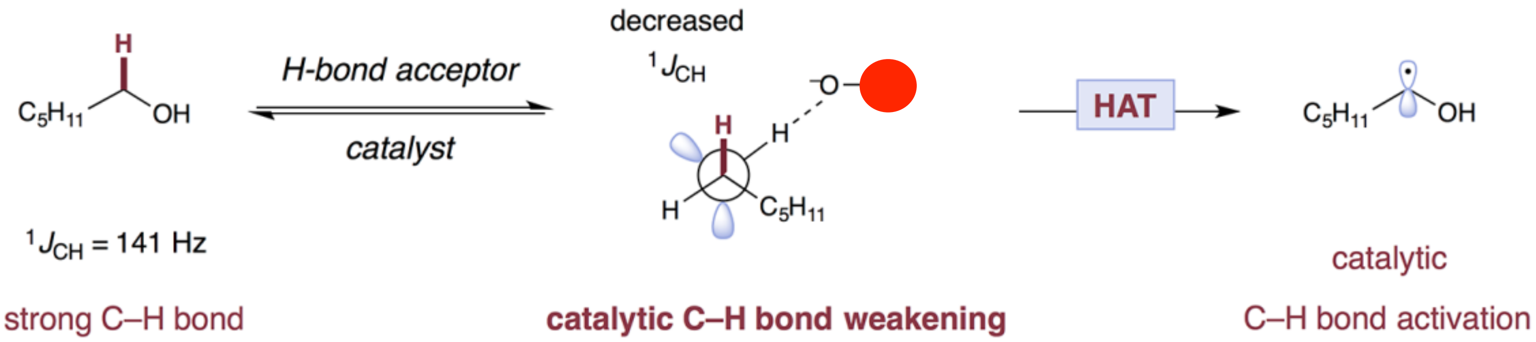
V. E. Anderson et al. *J. Am. Chem. Soc.* **2000**, *122*, 11660–11669; *J. Org. Chem.* **2006**, *71*, 2878–2880

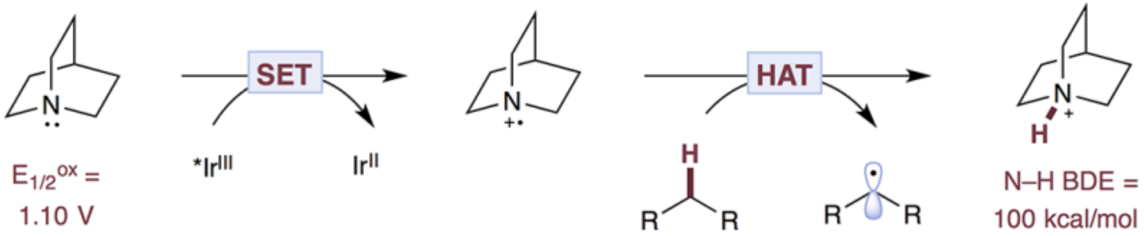
This work



Is it possible to achieve **efficient** and **selective activation** of alcohol Cα–H bonds by catalytic complexation with a suitable **hydrogen-bond acceptor?**

Proton-coupled C–H bond activation of strong α-C–H bonds:

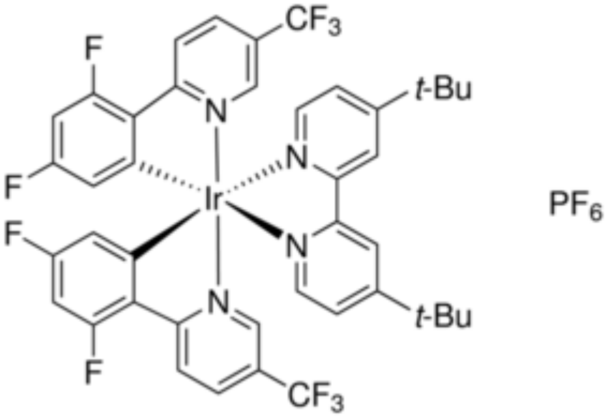




Three catalyst system

Photocatalyst

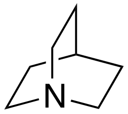
1 mol%



Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$

HAT catalyst

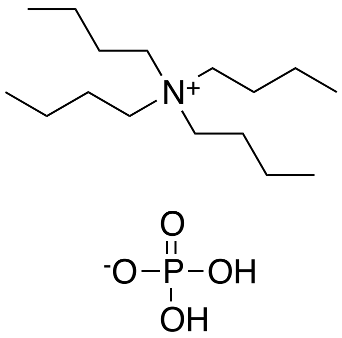
10 mol%



quinuclidine

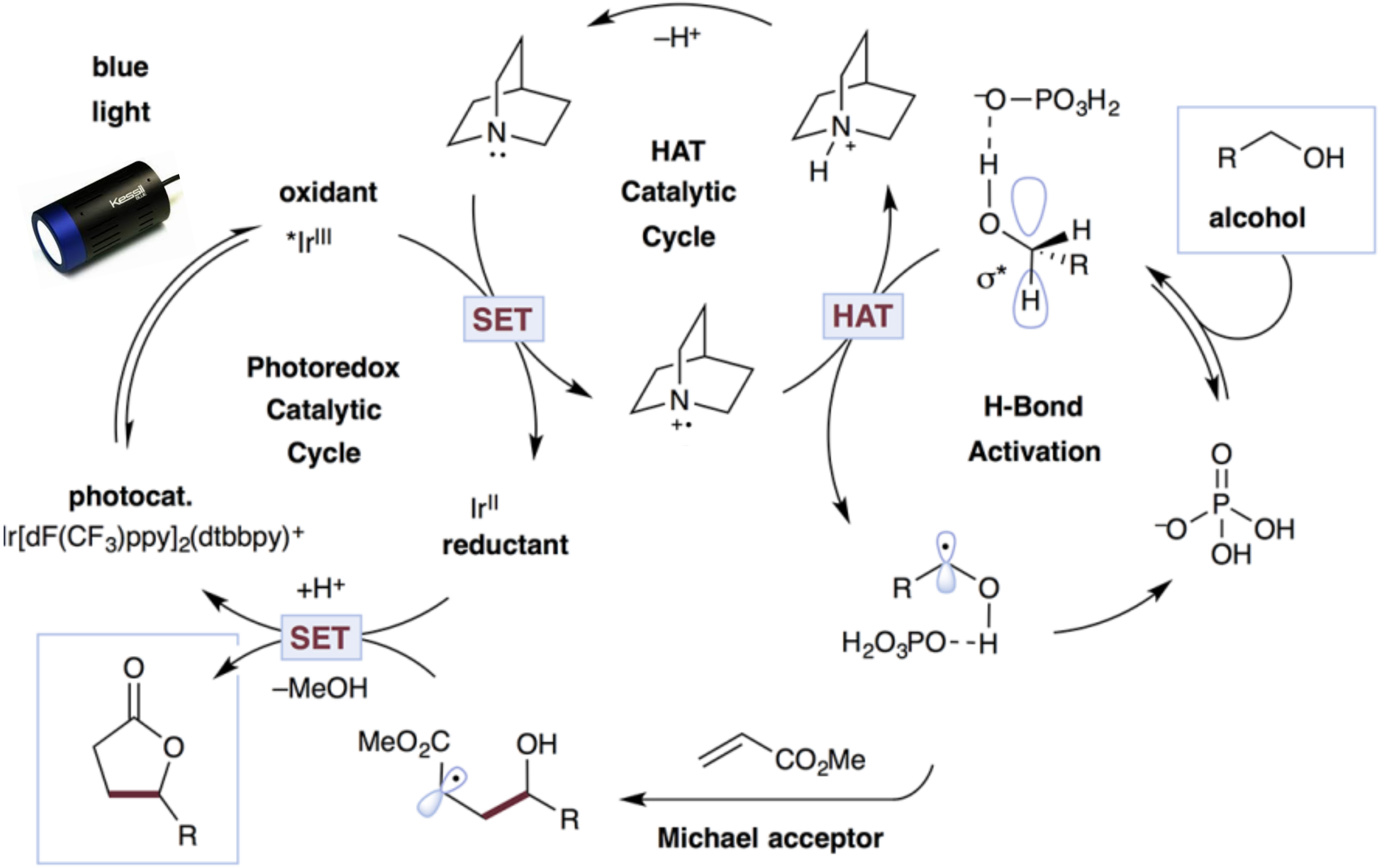
H-bond acceptor catalyst

25 mol%

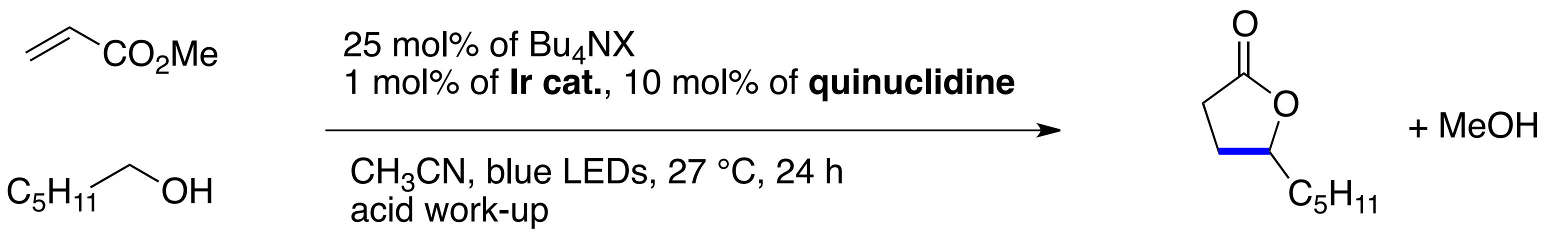


TBAP

Three catalyst system



Preliminary results



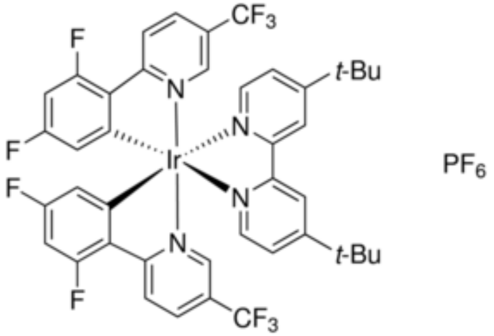
25 mol% of Bu_4NX
1 mol% of **Ir cat.**, 10 mol% of **quinuclidine**

CH_3CN, blue LEDs, 27 °C, 24 h
acid work-up

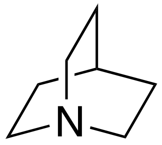
1-Hexanol

catalyst (Bu_4NX)	relative rate$_{init}$	yield lactone
–	1.0	67%
Bu_4NBF_4	1.0	71%
$Bu_4NPO_4H_2$	1.8	84%
$Bu_4N(PhO)_2PO_2$	2.5	76%
$Bu_4NCO_2CF_3$	2.6	75%

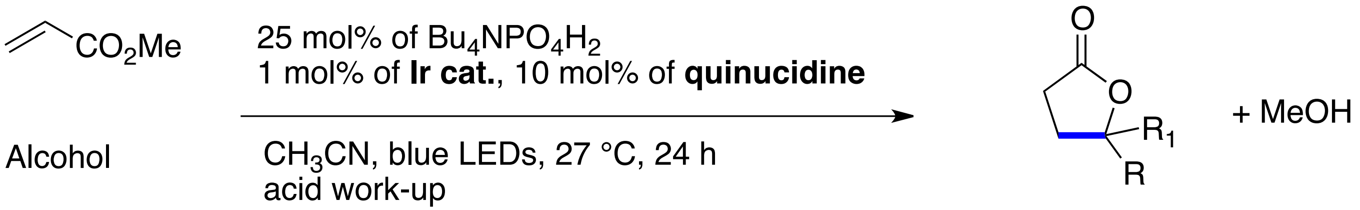
Ir cat. =



quinuclidine =



Reaction scope

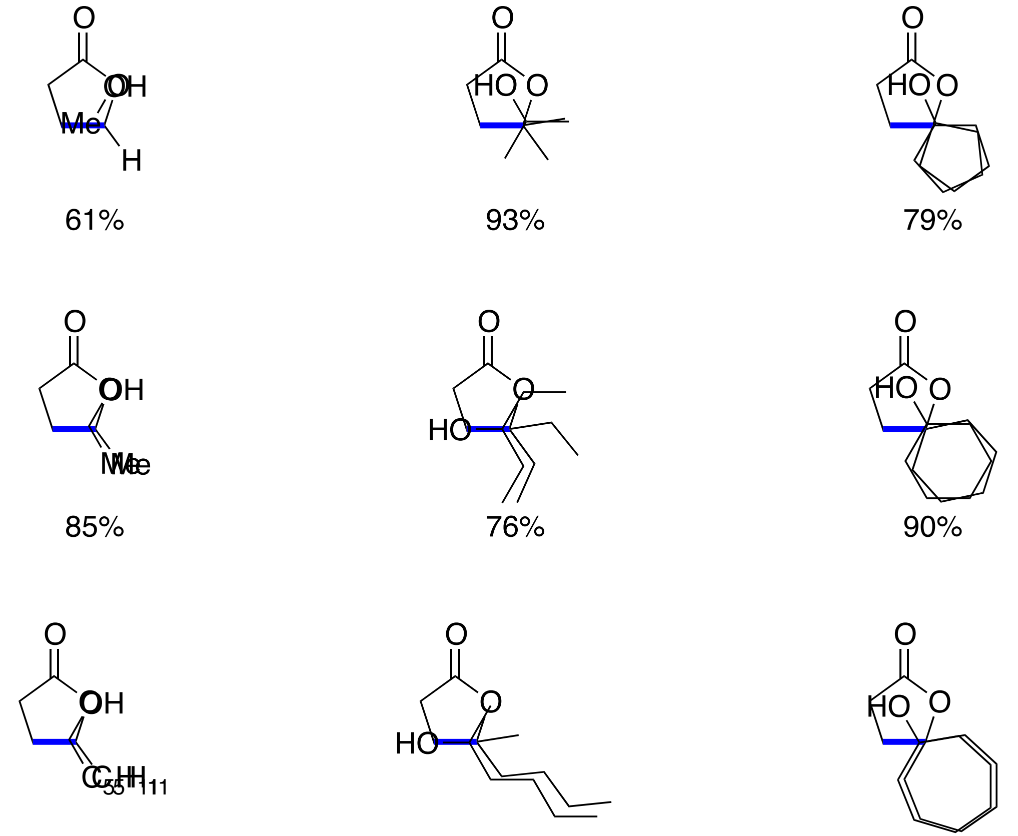


Alcohol

25 mol% of $Bu_4NPO_4H_2$
1 mol% of **Ir cat.**, 10 mol% of **quinucidine**

CH_3CN, blue LEDs, 27 °C, 24 h
acid work-up

+ MeOH

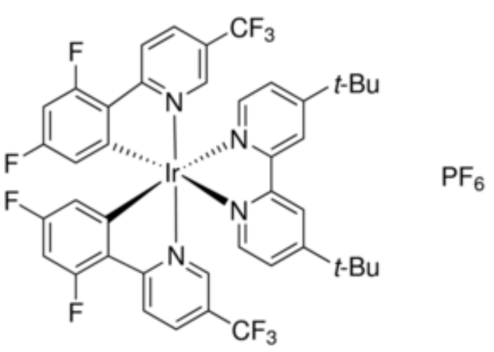


61% 93% 79%

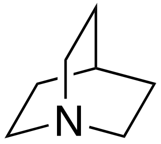
85% 76% 90%

84% 80% 90%

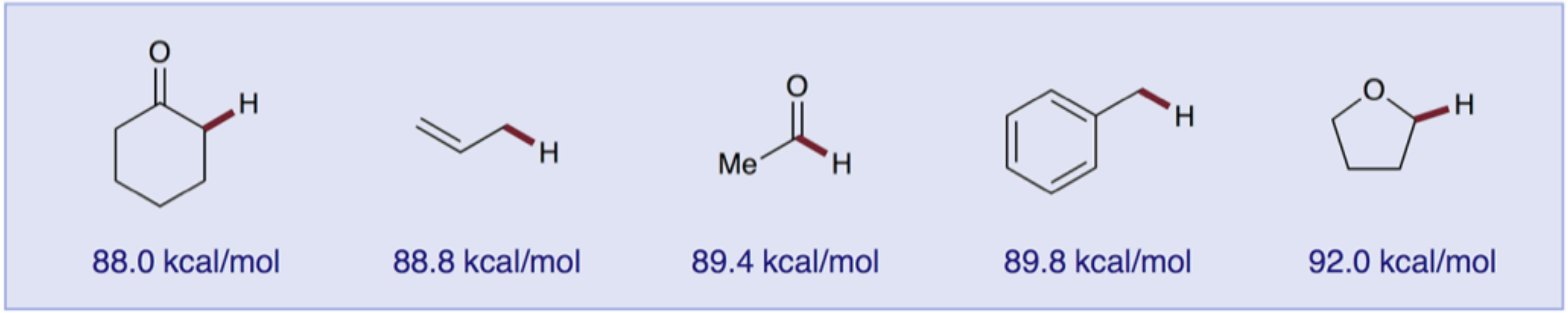
Ir cat. =

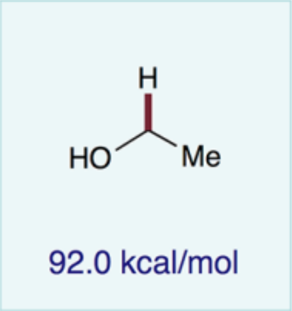


quiniclidine =

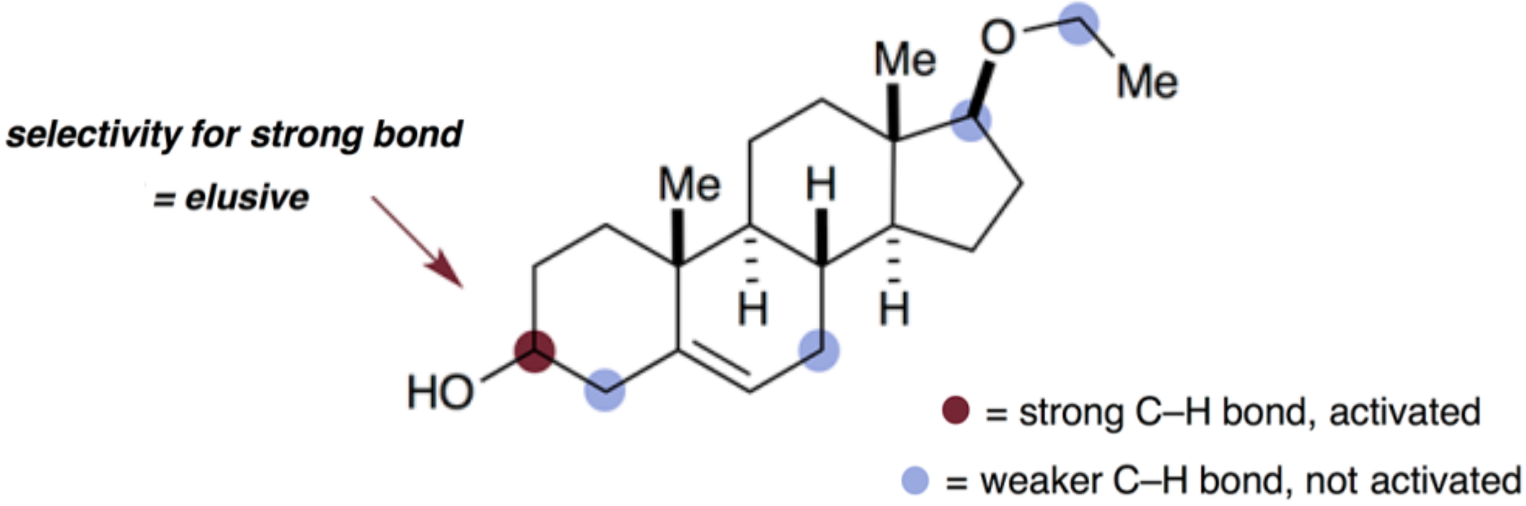


Selectivity in C-H activation

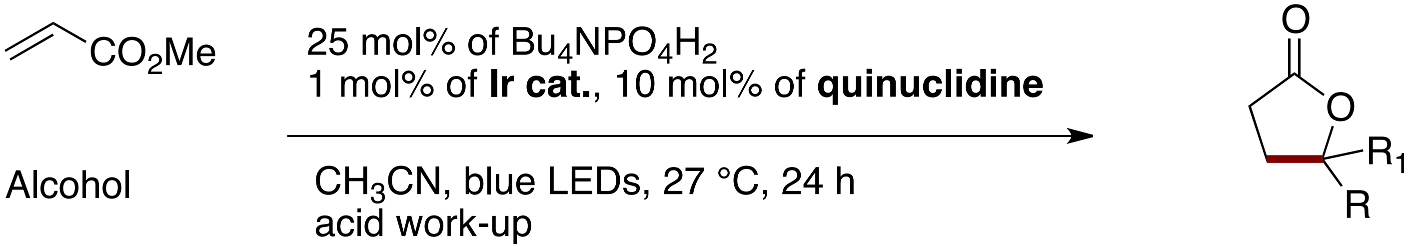




Can **strong C-H** bonds be **activated** in the presence of **weaker C-H** bonds?



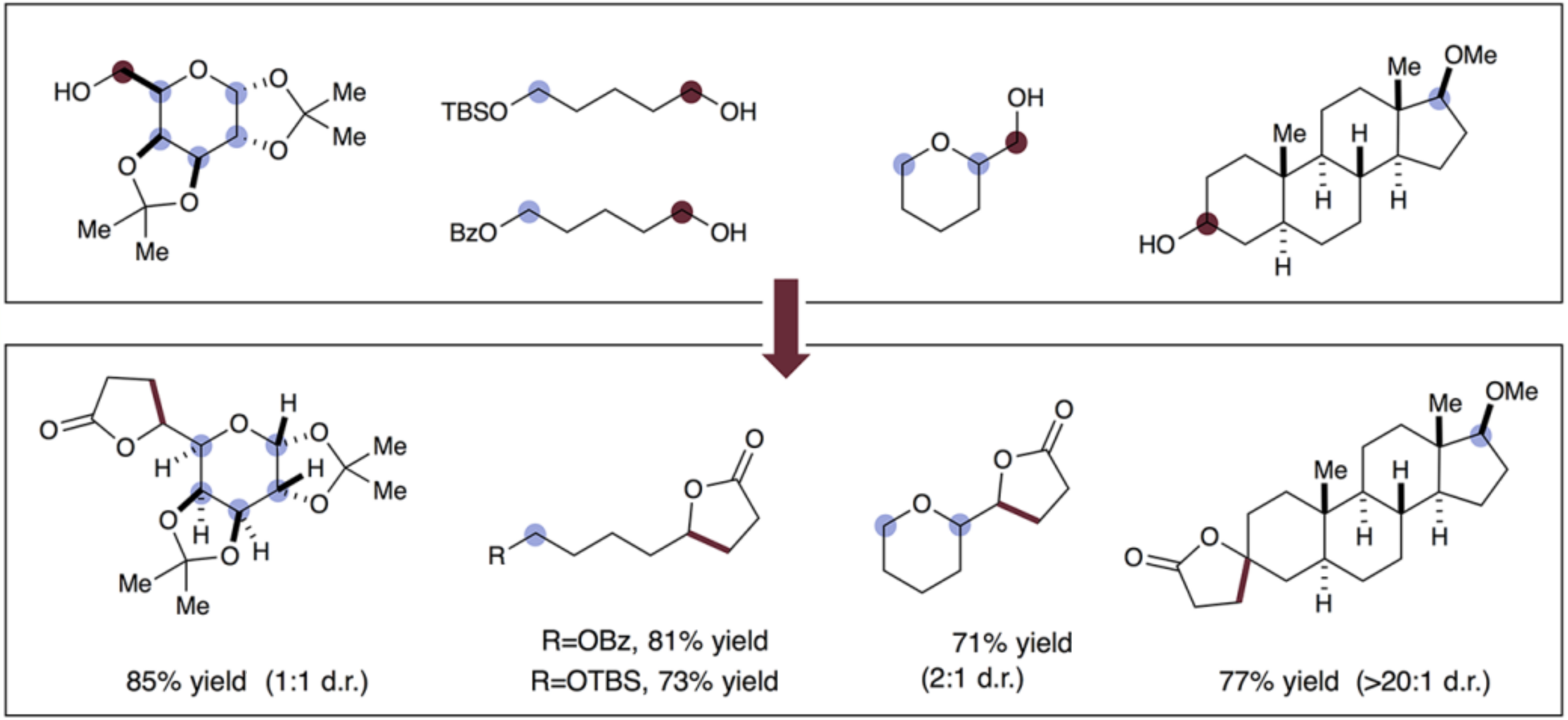
Selectivity in C-H activation



Alcohol

25 mol% of $Bu_4NPO_4H_2$
1 mol% of **Ir cat.**, 10 mol% of **quinuclidine**

CH_3CN, blue LEDs, 27 °C, 24 h
acid work-up



85% yield (1:1 d.r.)

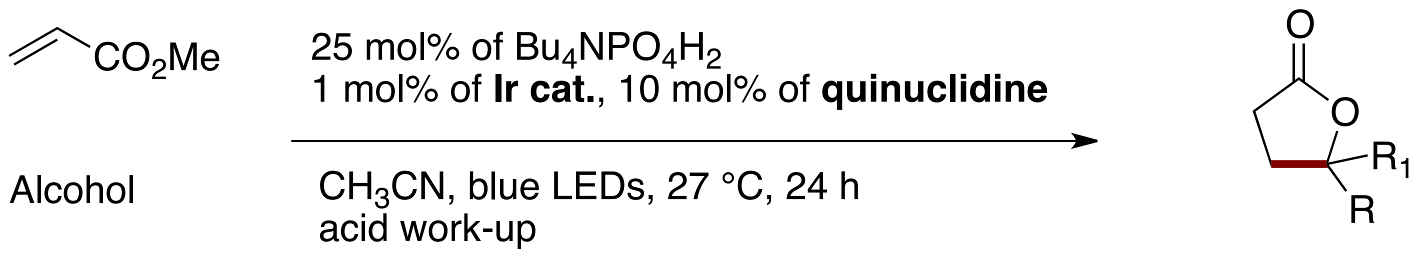
R=OBz, 81% yield
R=OTBS, 73% yield

71% yield
(2:1 d.r.)

77% yield (>20:1 d.r.)

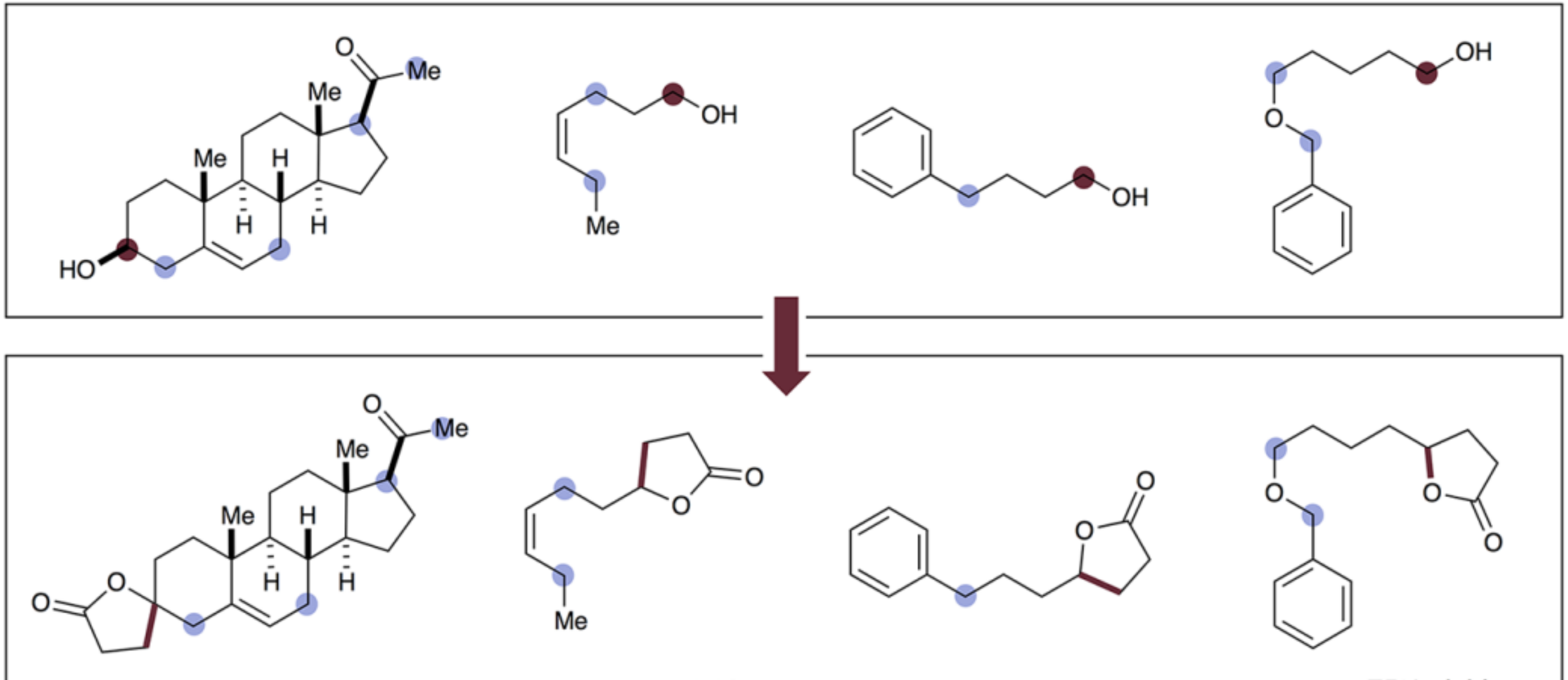
(● = strong C–H ● = weaker C–H)

Selectivity in C-H activation



25 mol% of $Bu_4NPO_4H_2$
1 mol% of **Ir cat.**, 10 mol% of **quinuclidine**

CH_3CN, blue LEDs, 27 °C, 24 h
acid work-up



70% yield (>20:1 d.r.)

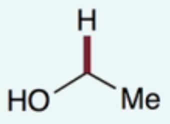
75% yield

73% yield

75% yield

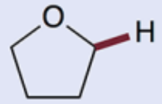
(● = strong C–H ● = weaker C–H)

Selectivity in C-H activation

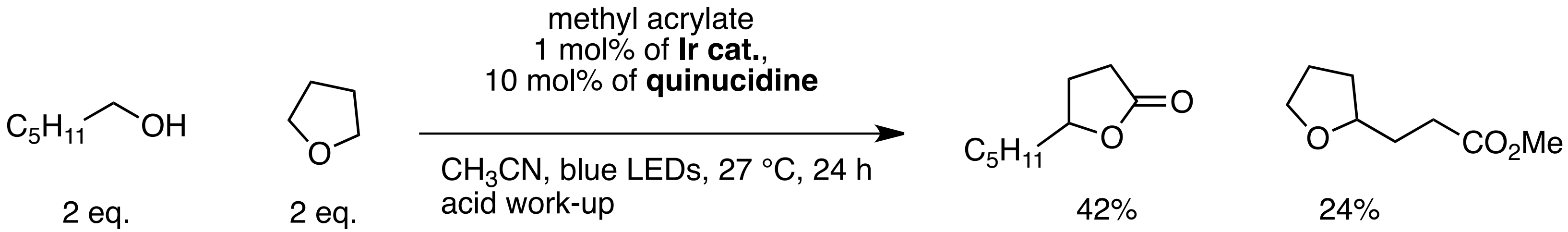


92.0 kcal/mol

VS



92.0 kcal/mol



2 eq. | 2 eq.

methyl acrylate
1 mol% of **Ir cat.**,
10 mol% of **quinucidine**

CH_3CN, blue LEDs, 27 °C, 24 h
acid work-up

42% | 24%

with $BuNPO_4H_2$ (25 mol%) 75% 1%

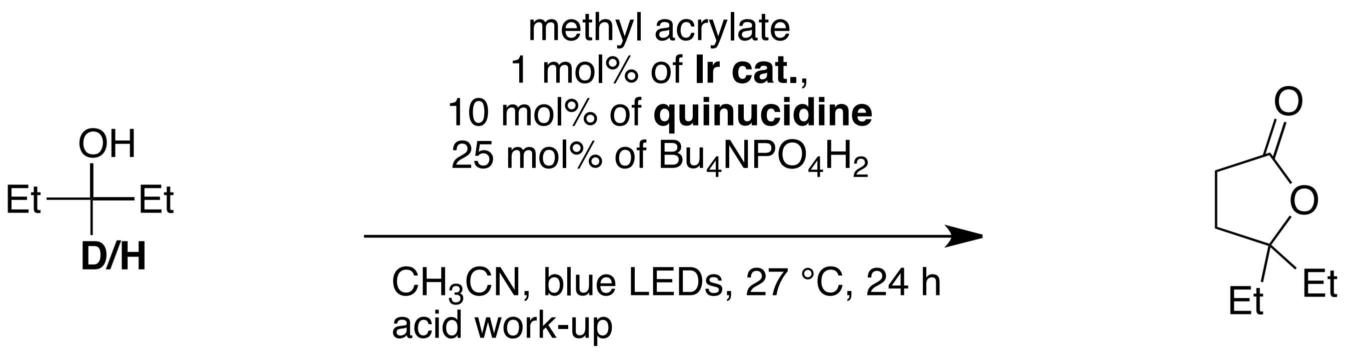
NMR experiments

^{13}C-NMR in $CDCl_3$

	Chemical shift of C1 (ppm)	$^1J_{CH}$ (Hz)
1-hexanol	63.1	141.1
1-hexanol / quinicidine 1:1	62.7	140.4
1-hexanol / TBAP 1:1	62.6	140.3

Both **quinuclidine** and **TBAP** can induce **bond weakening** of the C1–H of 1-hexanol via hydrogen bonding

Kinetic isotope effect



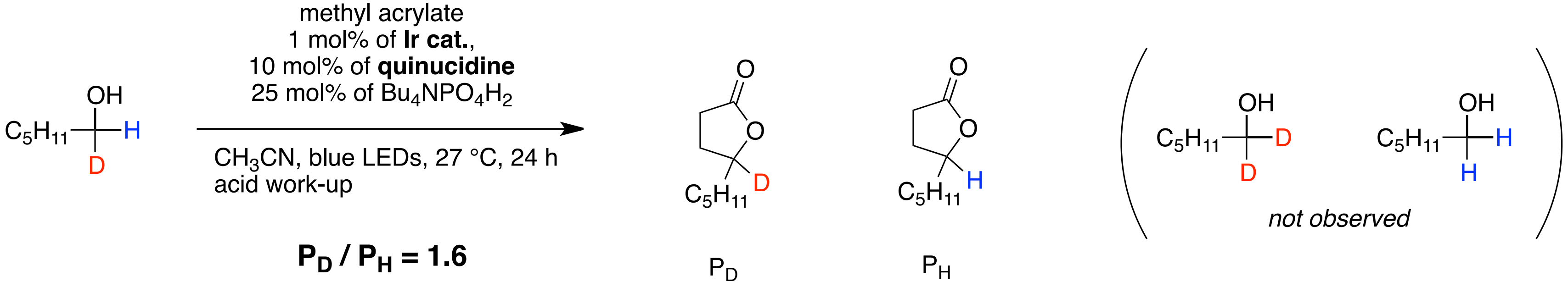
methyl acrylate
1 mol% of **Ir cat.**,
10 mol% of **quinucidine**
25 mol% of $Bu_4NPO_4H_2$

CH_3CN, blue LEDs, 27 °C, 24 h
acid work-up

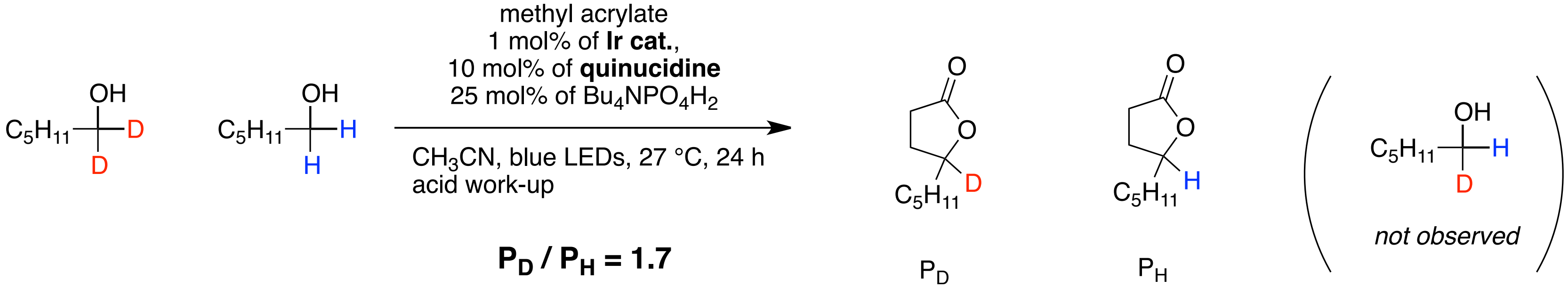
KIE = k_H / k_D = 1

C–H/D abstraction from the alcohol **does not occur during** the turnover-limiting transition state (**TLTS**)

Kinetic isotope effect



P_D / P_H = 1.6

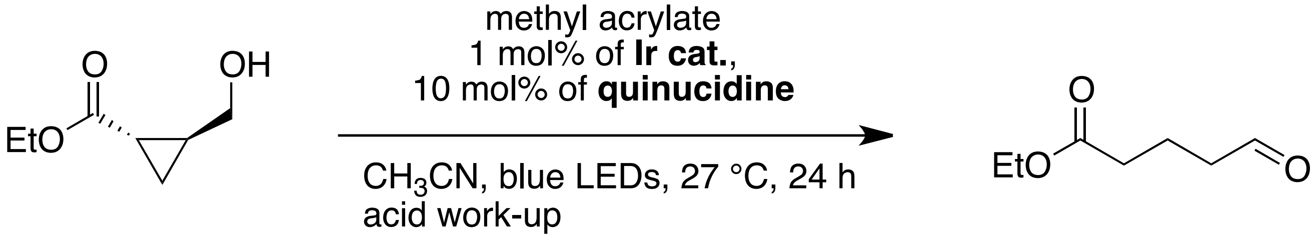


P_D / P_H = 1.7

Irreversible C-H abstraction prior to the turnover-limiting transition state

Dual role of **TBAP** in both **accelerating** the **C–H abstraction** from alcohols and **enhancing the rate of addition** of the resulting radical to Michael acceptors

Cyclopropyl radical clock



methyl acrylate
1 mol% of **Ir cat.**,
10 mol% of **quinucidine**

CH_3CN, blue LEDs, 27 °C, 24 h
acid work-up

catalysis	k_{rel}
none	1
with 25 mol% of $Bu_4NPO_4H_2$	9

C–H abstraction from the alcohol to generate the radical is rate-limiting (rate constant for cyclopropyl rearrangement on similar sistems = 5×10^{10} to 8×10^{10} s^{-1} at 25 °C).

Ninefold rate enhancement was observed upon addition of 25 mol% TBAP

TBAP facilitate C-H abstraction from alcohol via hydrogen bond activation

Conclusion

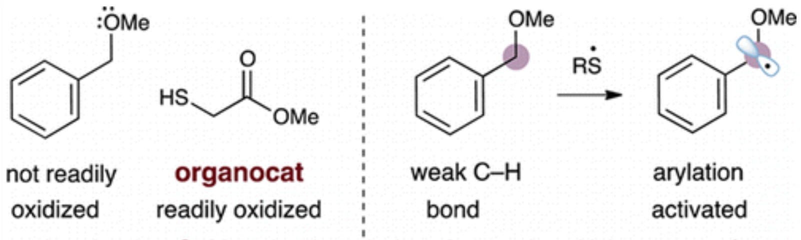
Selective α-activation of alcohol C–H bonds in the presence of allylic, benzylic, α-oxy, and α-acyl C–H groups via a photoredox protocol.

Cooperation of three distinct catalysts:
- an iridium-based photoredox catalyst
- quiniclidine as HAT catalyst
- TBAP as hydrogen-bonding catalyst

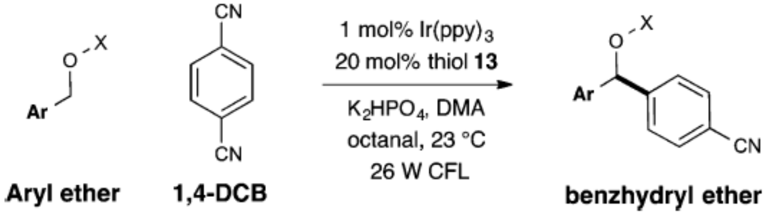
Demonstration of the **role of TBAP in facilitating the highly selective** a hydrogen atom abstraction from alcohols, on the basis of kinetic analyses, NMR structural data, and kinetic isotope effects

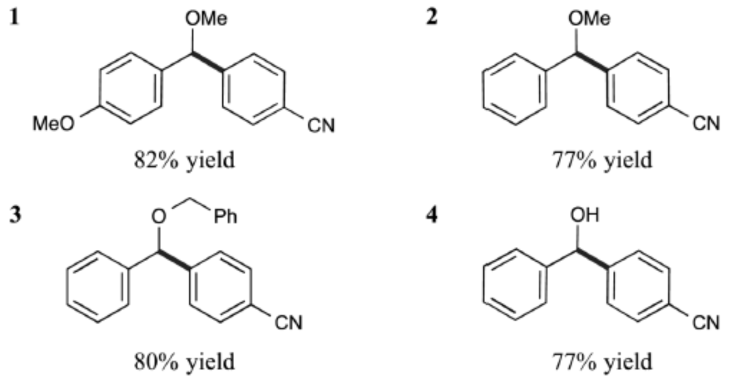
Acknowledgment

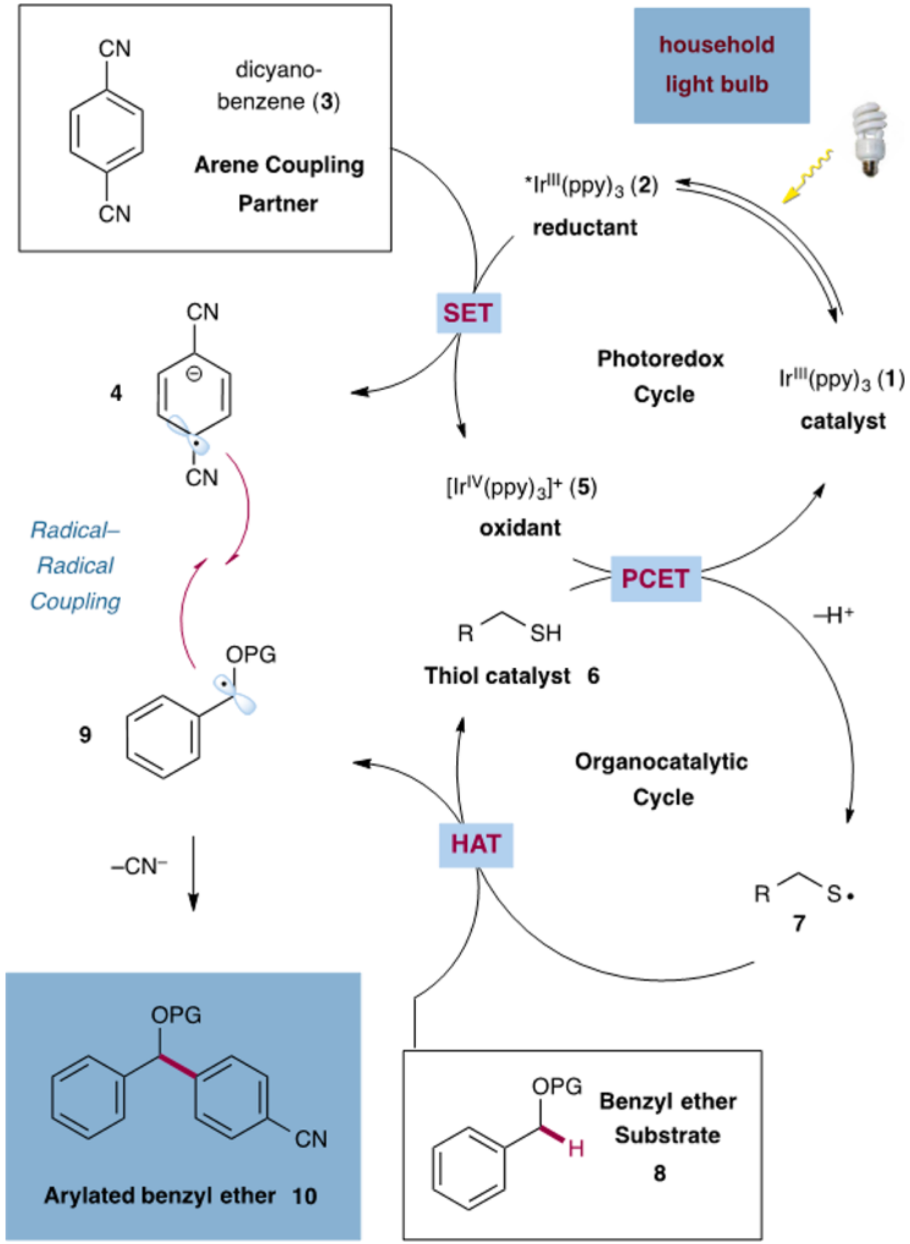
General α-Alkylation Procedure: An 8-mL glass vial equipped with a Teflon septum and magnetic stir bar was charged with Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.8 mg, 2.5 µmol, 1 mol%), quinuclidine (2.8 mg, 25 µmol, 10 mol%), and either tetra-*n*-butylammonium phosphate (21 mg, 63 µmol, 25 mol%) or tetra-*n*-butylammonium trifluoroacetate (63 µmol, 25 mol%), followed by CH$_3$CN (0.31 mL, 0.8 M), 1-hexanol (63 µL, 0.50 mmol, 2.0 equiv) and methyl acrylate (23 µL, 0.25 mmol, 1.0 equiv). The resulting solution was then sparged with N$_2$ for 3 minutes. The vial was sealed and placed approximately 3 inches away from a Kessil® LED illuminator (model H150 blue, http://www.kessil.com/horticulture/H150.php). The reaction mixture was stirred and irradiated for 24 h. The internal temperature was maintained at approximately 27 °C by an electric fan placed approximately 10 inches above the vial. Upon completion, Amberlyst® 15 (dry, 100 mg) was added to the reaction mixture in one portion. The resulting mixture was heated with stirring at 50 °C for 3 h. After cooling to room temperature, the Amberlyst® 15 beads were removed by filtration and the reaction mixture was concentrated *in vacuo*. Purification of the crude product by flash column chromatography on silica gel using the indicated solvent system afforded the desired product.



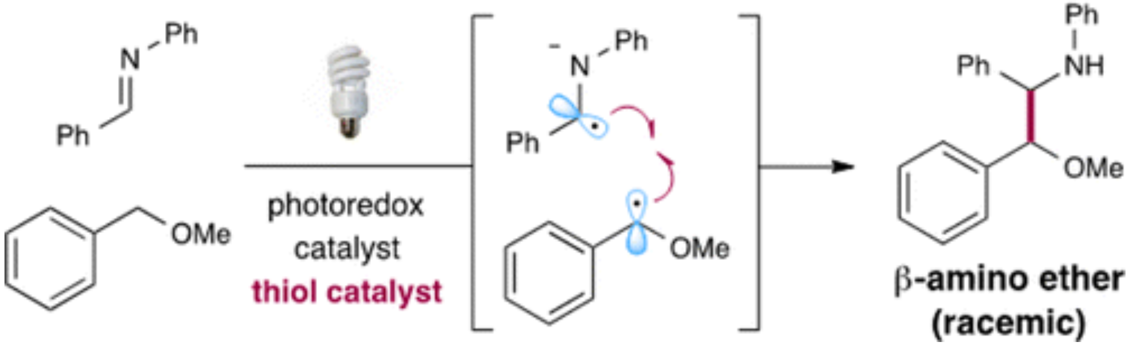
regioselective C–H activation via bond energies, H Atom transfer

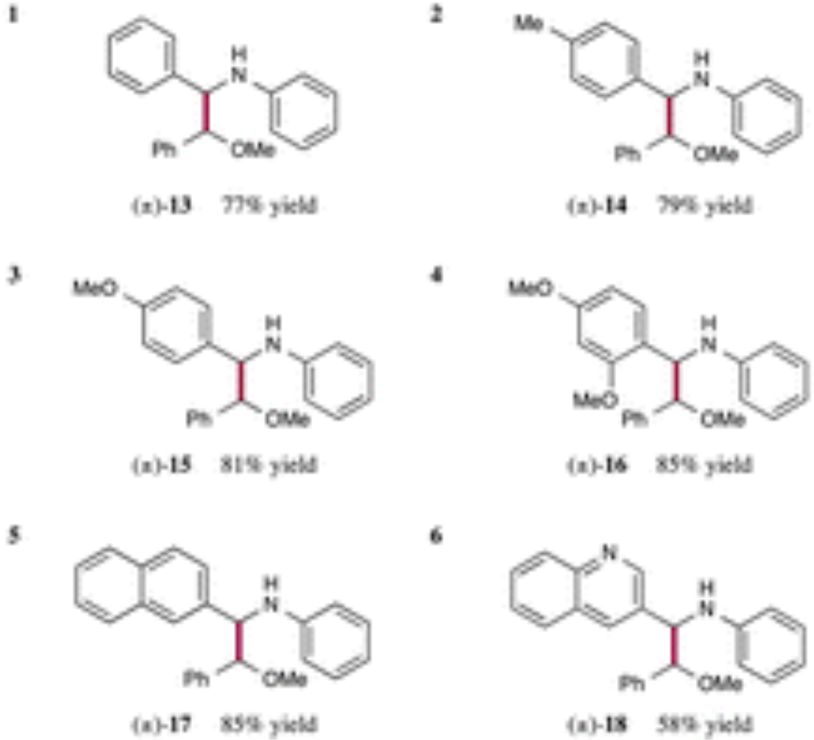


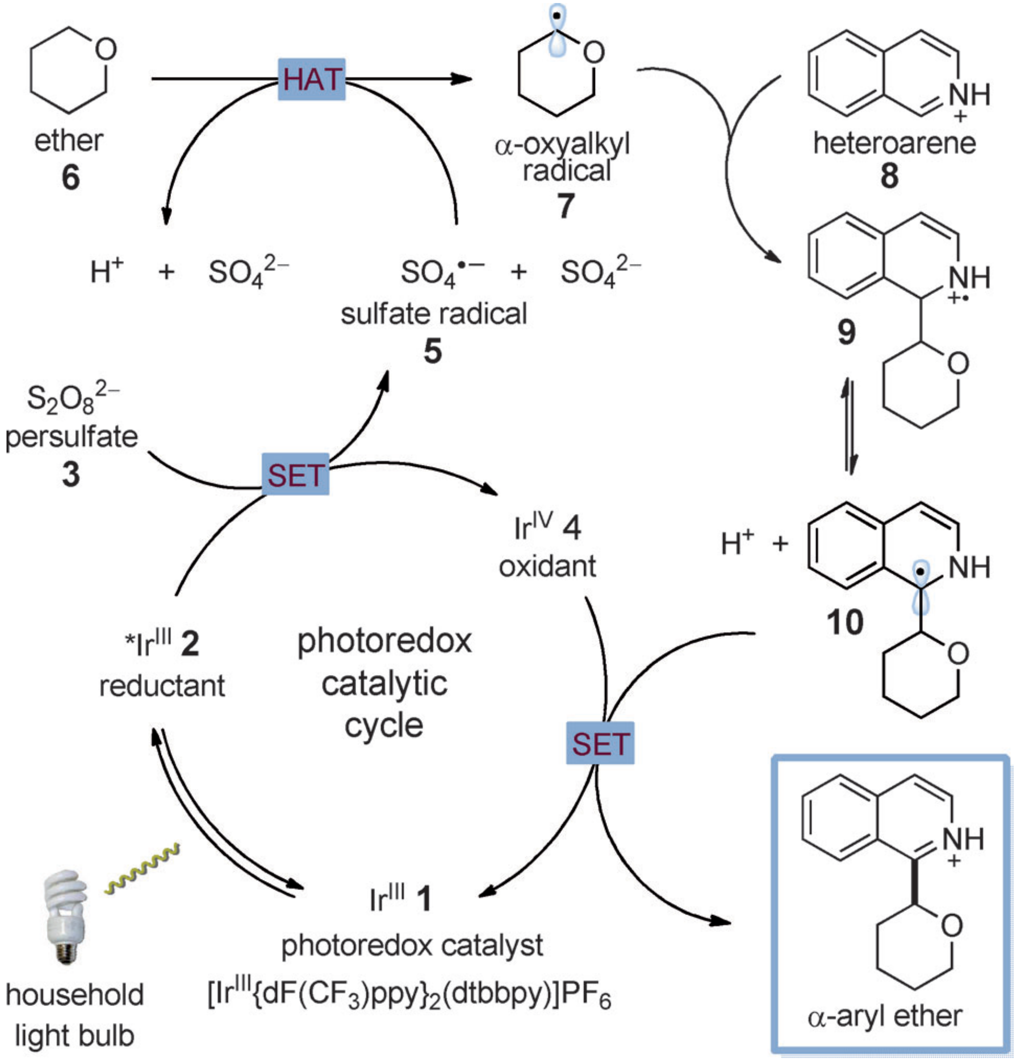




Reaction of benzylic ethers with Schiff bases







ether
6

HAT

α-oxyalkyl radical
7

heteroarene
8

H^+ + SO_4^{2-}

$SO_4^{\bullet-}$ + SO_4^{2-}
sulfate radical
5

9

$S_2O_8^{2-}$
persulfate
3

SET

Ir^{IV} **4**
oxidant

H^+ +

10

$^*Ir^{III}$ **2**
reductant

photoredox
catalytic
cycle

SET

Ir^{III} **1**
photoredox catalyst
$[Ir^{III}\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$

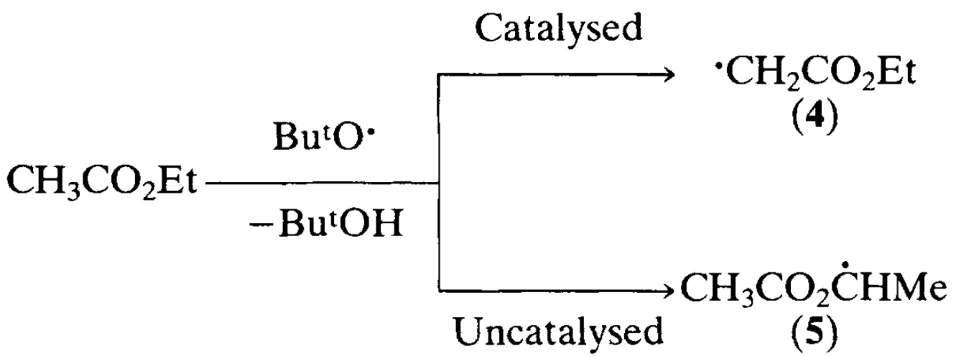
household
light bulb

α-aryl ether

$$\mathrm{Bu^tO^{\bullet} + \underset{\textbf{(2)}}{Me_3N{\rightarrow}BH_2Hex^t} \longrightarrow Bu^tOH + \underset{\textbf{(3)}}{Me_3N{\rightarrow}\dot{B}Hex^t}} \tag{7}$$

$$\mathrm{Me_3N{\rightarrow}\dot{B}HHex^t + MeCN \longrightarrow Me_3N{\rightarrow}BH_2Hex^t + {}^{\bullet}CH_2CN} \tag{8}$$

$$\mathrm{Hex^t = Me_2CHCMe_2}$$



$$\mathrm{CH_3CO_2Et \xrightarrow[-Bu^tOH]{Bu^tO^{\bullet}}}$$

Catalysed $\longrightarrow$ $\mathrm{{}^{\bullet}CH_2CO_2Et}$ **(4)**

Uncatalysed $\longrightarrow$ $\mathrm{CH_3CO_2\dot{C}HMe}$ **(5)**

$$\mathrm{RO^{\bullet} + \overset{\delta-\ \delta+}{H{-}Y} \xrightarrow{\text{fast}} ROH + Y^{\bullet}}$$

$$\mathrm{Y^{\bullet} + \overset{\delta+\ \delta-}{H{-}X} \xrightarrow{\text{fast}} HY + X^{\bullet}}$$