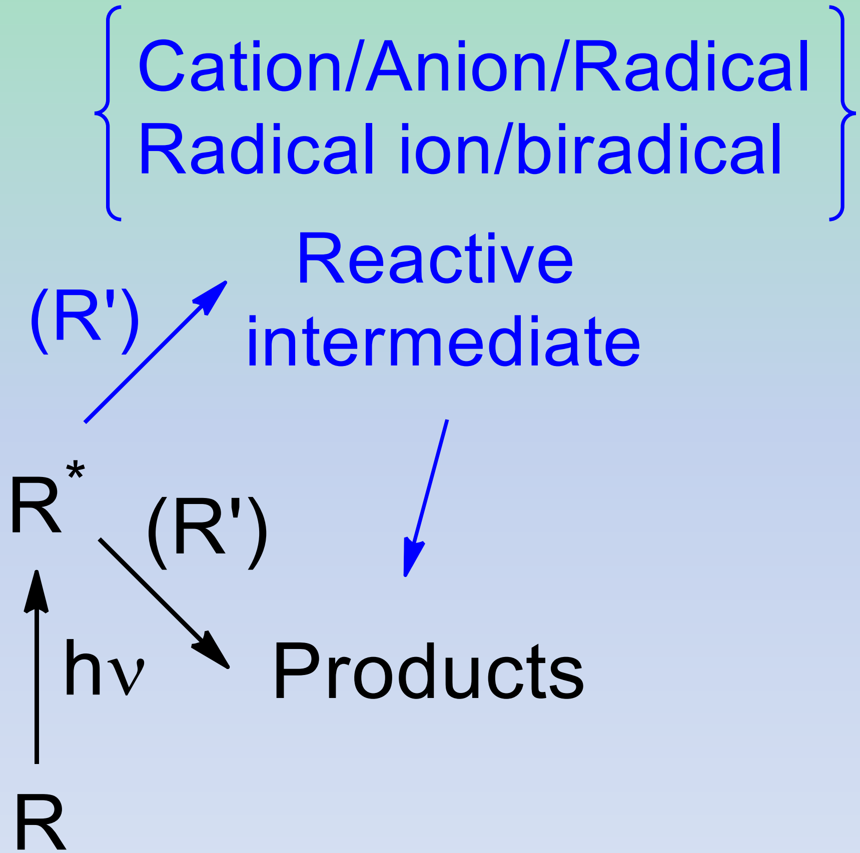
Photocatalyzed hydrogen atom transfer (HAT) reactions for selective $C(sp^3)$-H / $C(sp^2)$-H functionalization

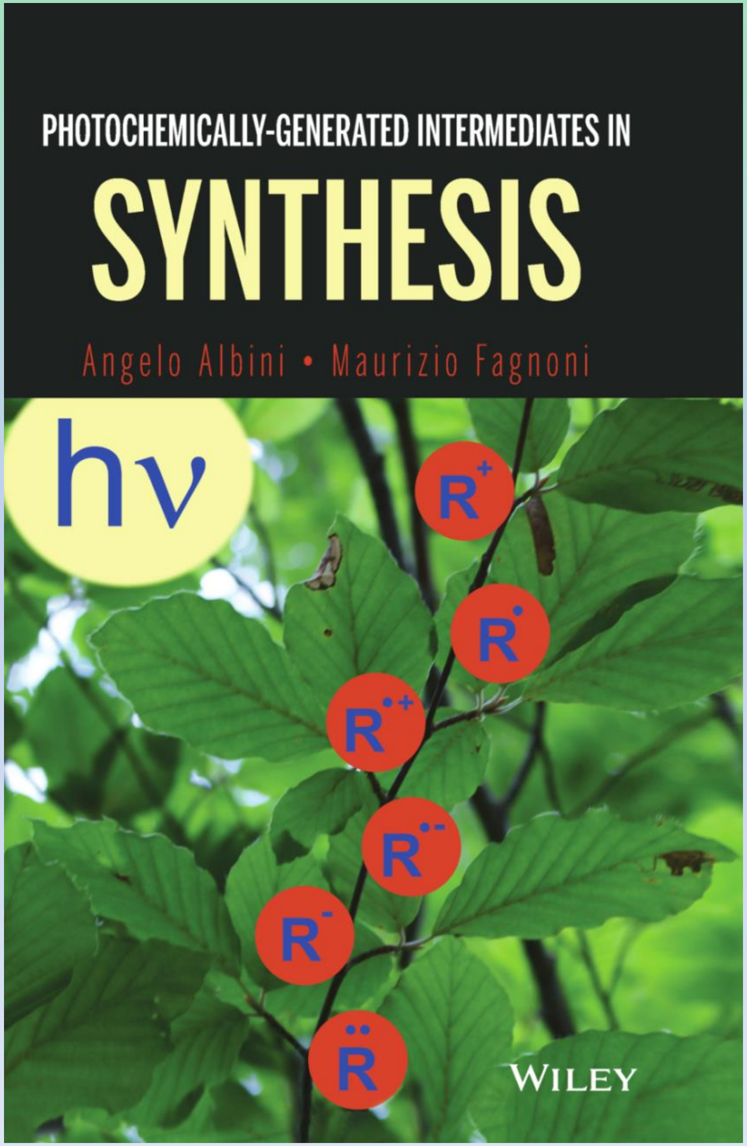
PhotoGreen Lab, Department of Chemistry,
University of Pavia, viale Taramelli 12, 27100 Pavia

website: www.unipv.it/photogreenlab

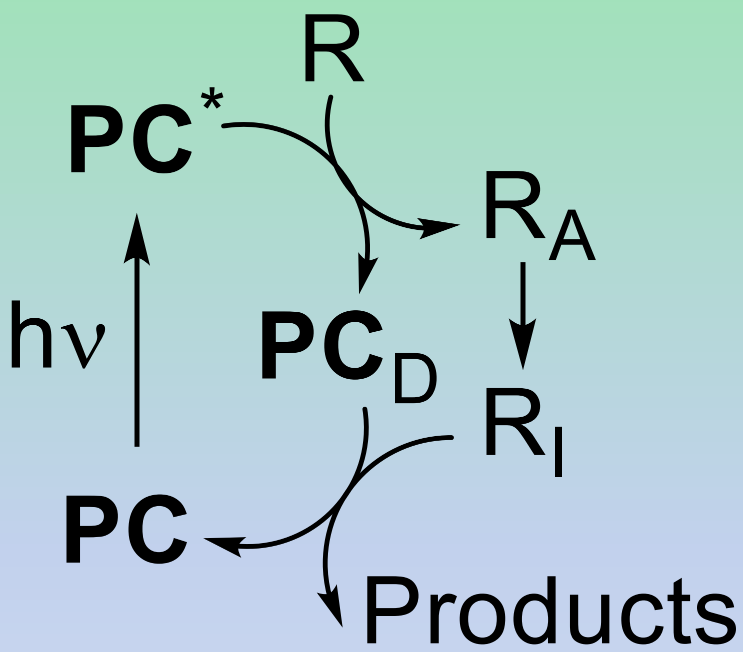
Photogeneration of reactive intermediates



Chem. Rev. **2016**, *116*, 9850



PHOTOCATALYSIS in organic synthesis



1) The PC is the absorbing species (R is transparent to the radiation used)

2) The PC is active ONLY In the excited state. NO reaction in the dark !

3) A chemical reaction between The PC and one reagent occurs

4) The PC is regenerated at the end of the reaction

5) No R* is involved in the reaction

Photocatalyst (PC) IUPAC definition: Catalyst able to produce, upon absorption of light, chemical transformations of the reaction partners. The excited state of the photocatalyst repeatedly interacts with the reaction partners forming reaction intermediates and regenerates itself after each cycle of such interactions.

Tetrahedron 66 (2010) 1028

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journal homepage: www.elsevier.com/locate/tet

ELSEVIER

Insight: Green chemistry: the key to our future

Ryoji Noyori

Department of Chemistry and Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

Ryoji Noyori

Furthermore, in order to enhance the power of chemical synthesis by removing current thermodynamic restrictions, I strongly recommend that our young generation develop
1- a **“photo-synthetic” catalyst** that facilitates a thermally unachievable, energetically uphill reaction
2- a ‘single-step cascade synthesis’ using multiple components.

Nobel Prize in Chemistry in 2001

"for its work on chirally catalysed hydrogenation reactions"

Type of Photocatalysts

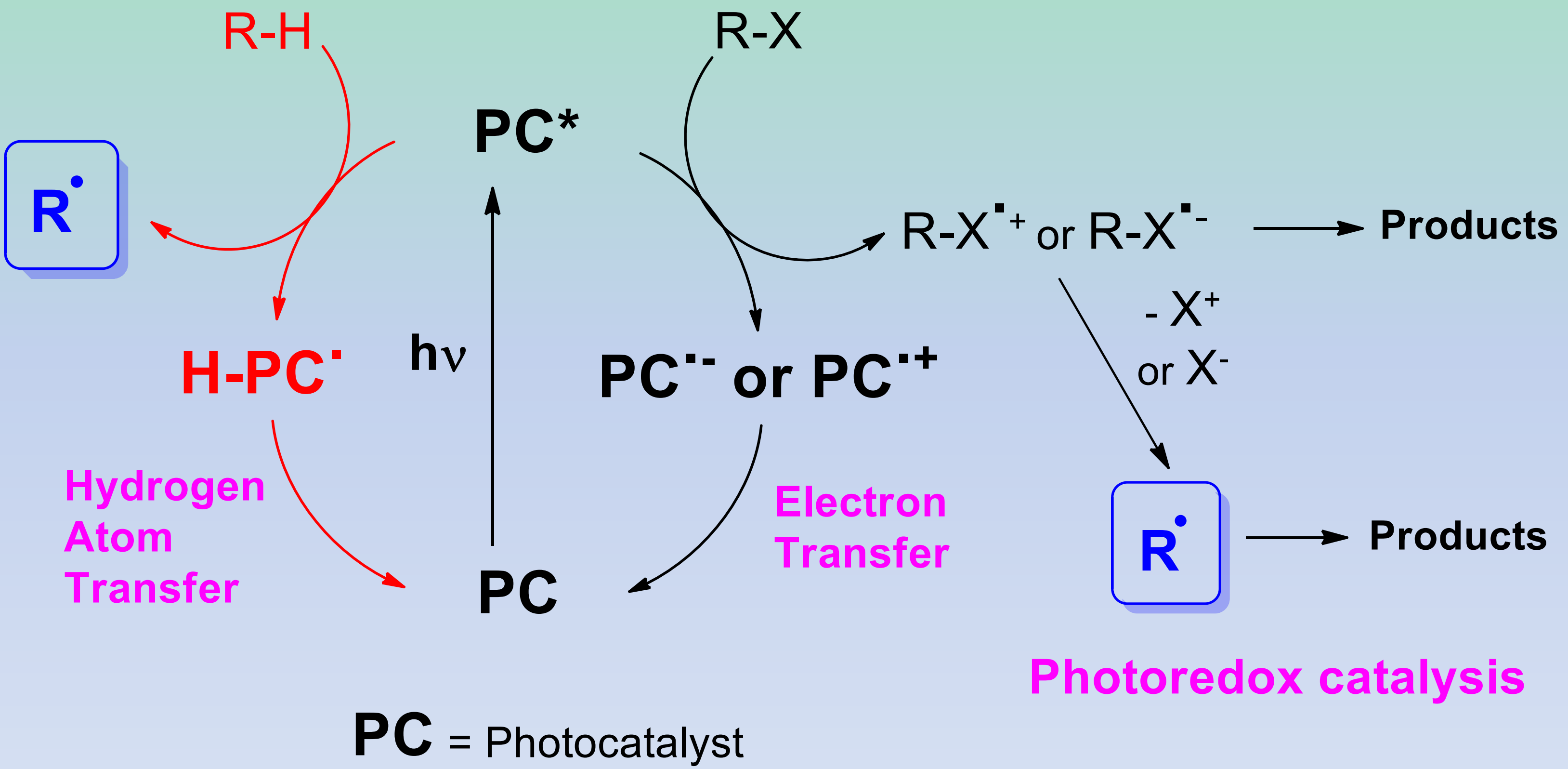
- **Metal oxides: TiO_2**
- **Polyoxometalates (Tetrabutylammonium decatungstate, $(Bu_4N)_4W_{10}O_{32}$)**
- **Organic Molecules (PhotoOrganoCatalysts = POC): Benzophenone, dyes**
- **Metal complexes ($Ru^{II}(bpy)_3^{2+}$, *fac*-$Ir^{III}(ppy)_3$)**

Mode of action

- **Electron transfer**
- **Atom transfer**

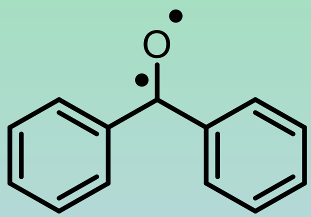
Chem. Rev. **2007**, 107, 2725

Mode of action of a Photocatalyst

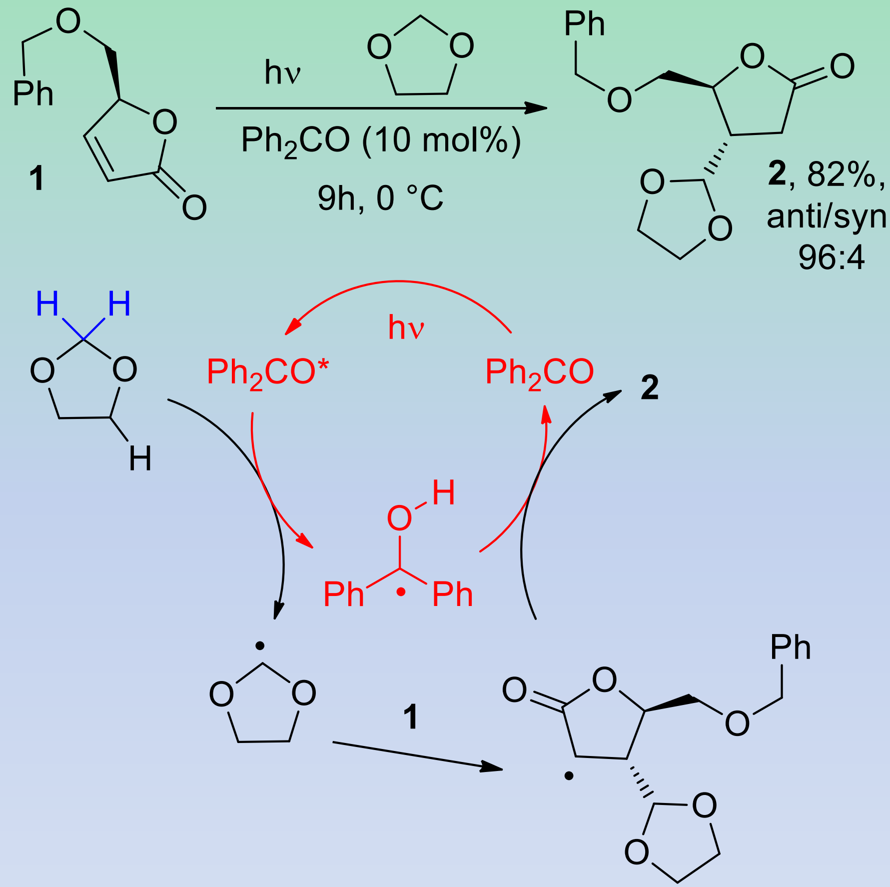


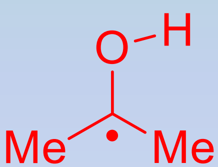
HAT reactions: the problem of the photocatalyst

Aromatic ketones as Photocatalysts



^{3}**BP (nπ*)**

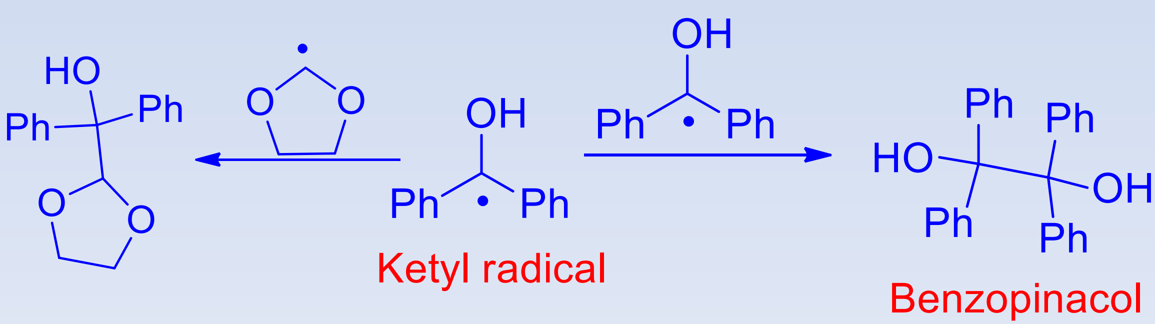




BDE O-H
ca. 16 kcal mol^{-1}

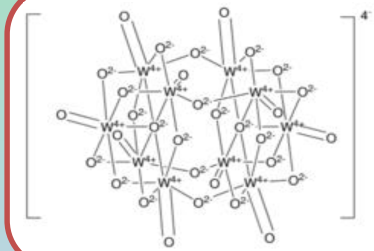
Synlett **2014**, *25*, 2819

Competitive pathways:



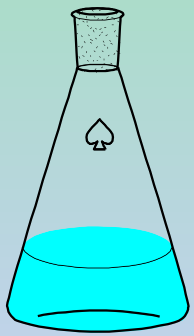
J. Org. Chem. **2004**, *69*, 7822

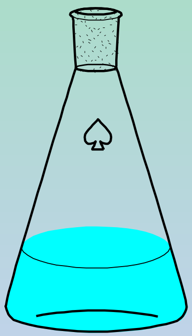
Preparation of $(Bu_4N)_4W_{10}O_{32}$, (TBADT)



SIGMA-ALDRICH

250 mg = 110.00 €





Na_2WO_4 x 2 H_2O

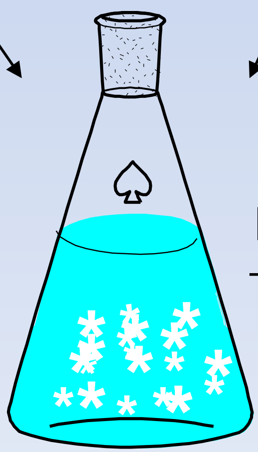
pH = 2, 90 °C

Bu_4NBr

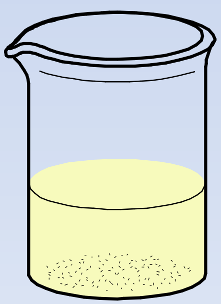
pH = 2, 90 °C

Easy preparation

MIX



FILTRATION



Suspension in CH_2Cl_2

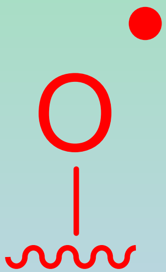
FILTRATION

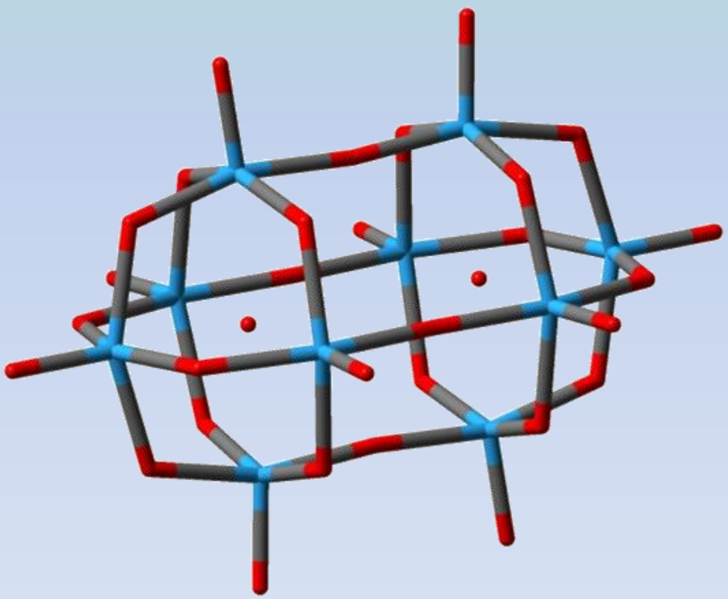
Photocatalyzed Hydrogen Atom Transfer (HAT)

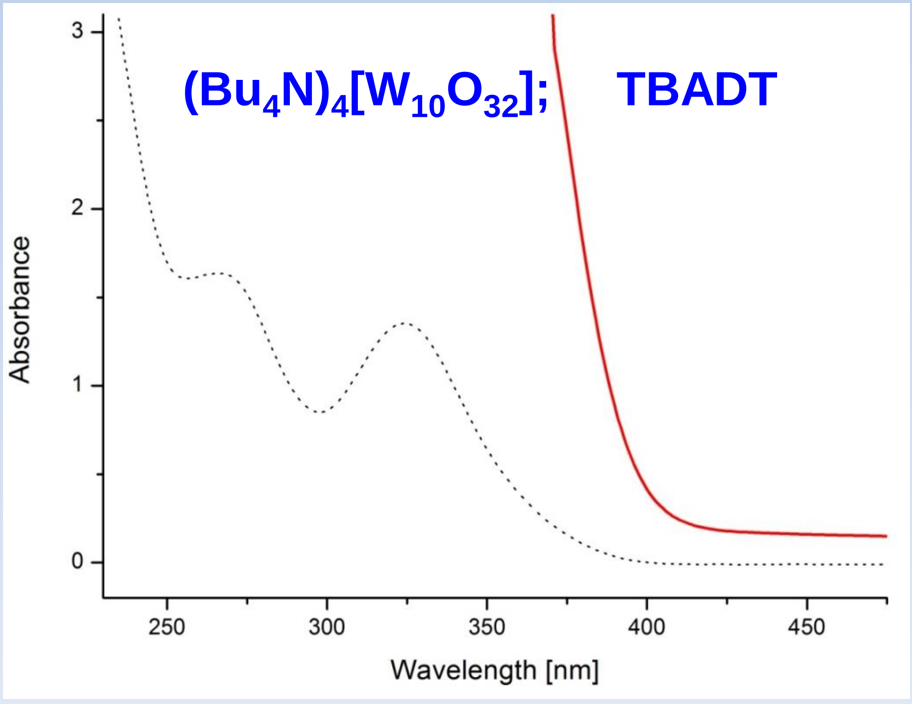
$[W_{10}O_{32}]^{4-}$: *an unknown player behaving like an oxyl radical*

$$[W_{10}O_{32}]^{4-} \xrightarrow{h\nu} [W_{10}O_{32}]^{4-\,*} \longrightarrow \textbf{wO}$$

LMCT



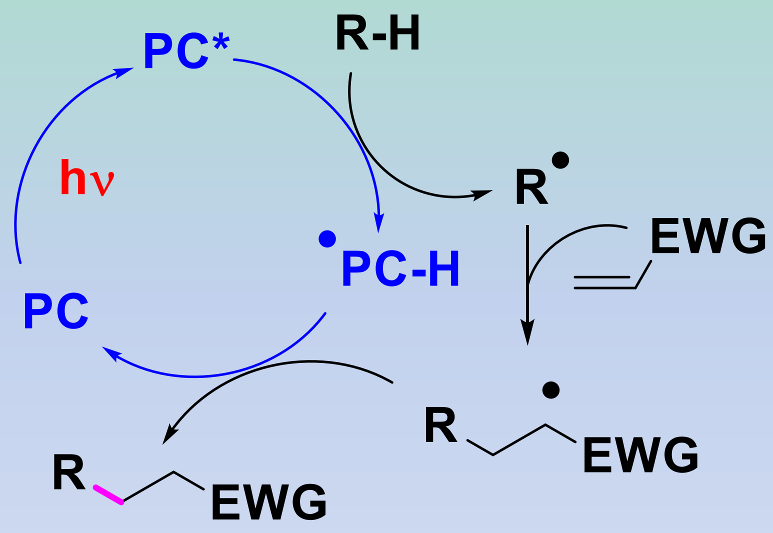




Chem. Soc. Rev. **2009**, *38*, 2609;
Acc. Chem. Res. **2016**, 49, 2232;
ACS Catal. **2016**, *6*, 7174

Applications in Organic Synthesis

C-C Bond Formation via Conjugate Radical Addition



PC = (*n*-$Bu_4N)_4$ $[W_{10}O_{32}]$

Atom economy = 100% !

R-H

Aldehydes

Ethers (Acetals)

Cycloalkanones

Nitriles

Alkanes

How we can perform selective C-H activation ?

Acc. Chem. Res. **2016**, 49, 2232

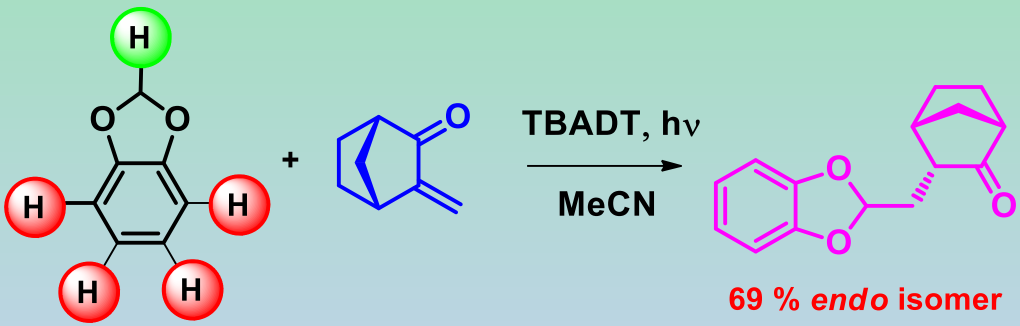
BDE of selected C-H bonds

a rough guide

C–H bond	Dissociation energy, kJ mol^{-1}
CH_3–H (methyl)	439
$MeCH_2$–H (primary)	423
Me_2CH–H (secondary)	410
Me_3C–H (tertiary)	397
HC≡C–H (alkynyl)	544
H_2C=CH–H (vinyl)	431
Ph–H (phenyl)	464
H_2C=CH_2CH_2–H (allyl)	364
$PhCH_2$–H (benzyl)	372
RC(=O)–H (acyl)	364
EtOCHMe–H	385
N≡CCH_2–H	360
$MeCOCH_2$–H	385

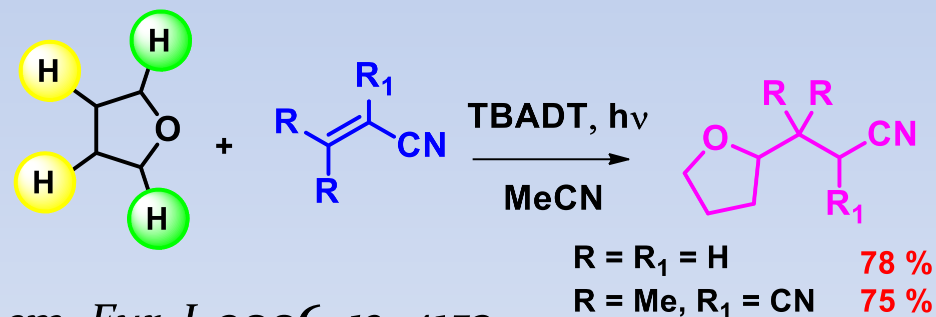
C-H Activation in oxygenated derivatives

HAT for the generation of α-oxy radicals

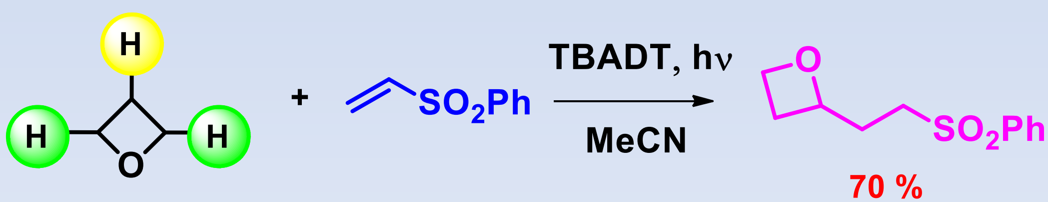


Chem. Eur. J. **2011**, *17*, 572

BDE (THF) = 92.1 kcal mol $^{-1}$



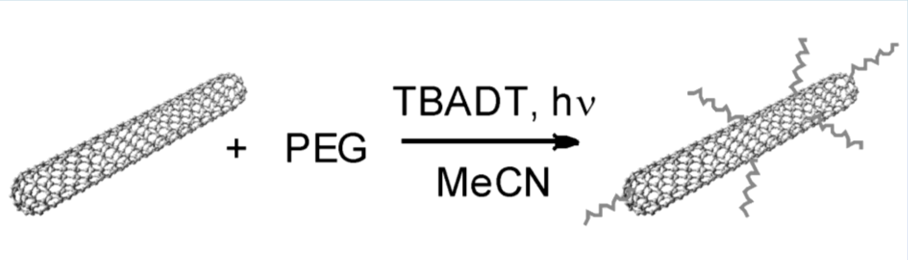
Chem. Eur. J. **2006**, *12*, 4153



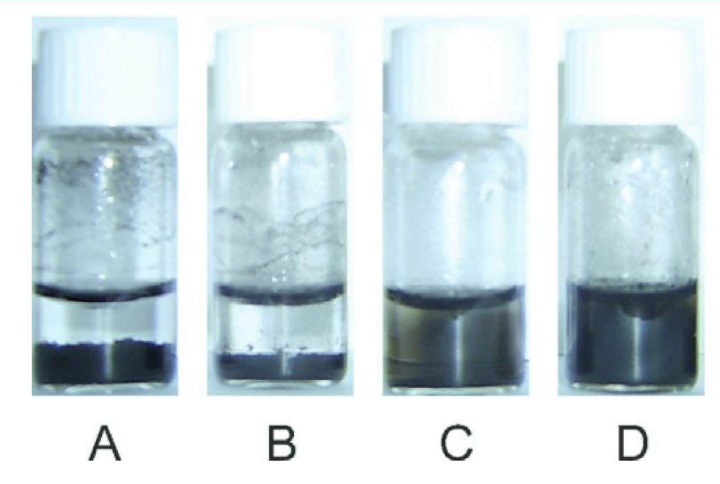
Adv. Synth. Catal., **2014**, *356*, 2781

C-H Activation in oxygenated derivatives

HAT for the generation of α-oxy radicals

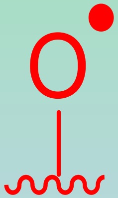


ChemPlusChem **2012**, *77*, 210

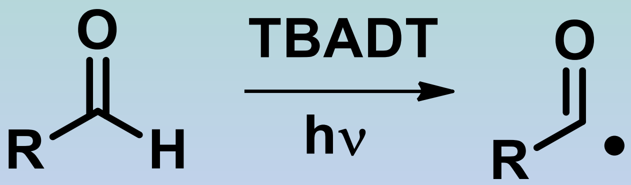


Samples of suspended A) pristine SWCNTs in water, B) pristine SWCNTs in water/PEG 400 (9/1 v/v), C/D) functionalized SWCNTs in water after four days standing.

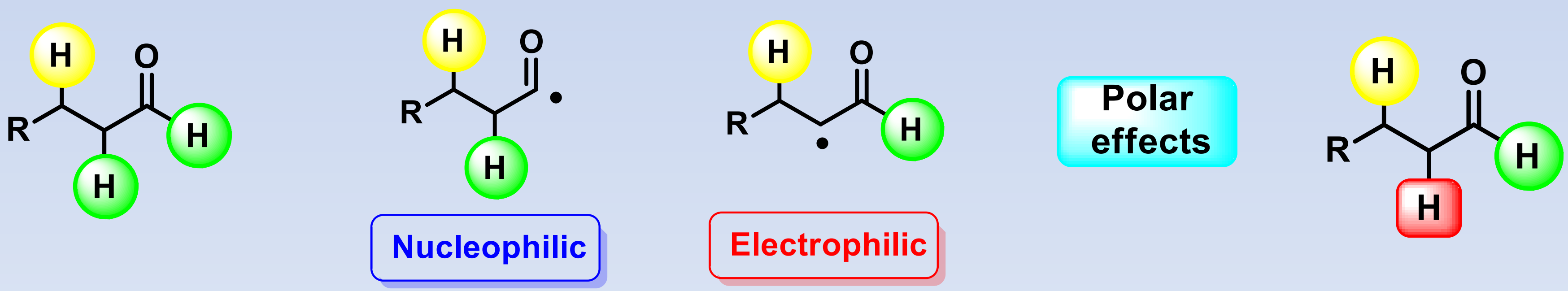
C(sp^2)-H Activation in Aldehydes



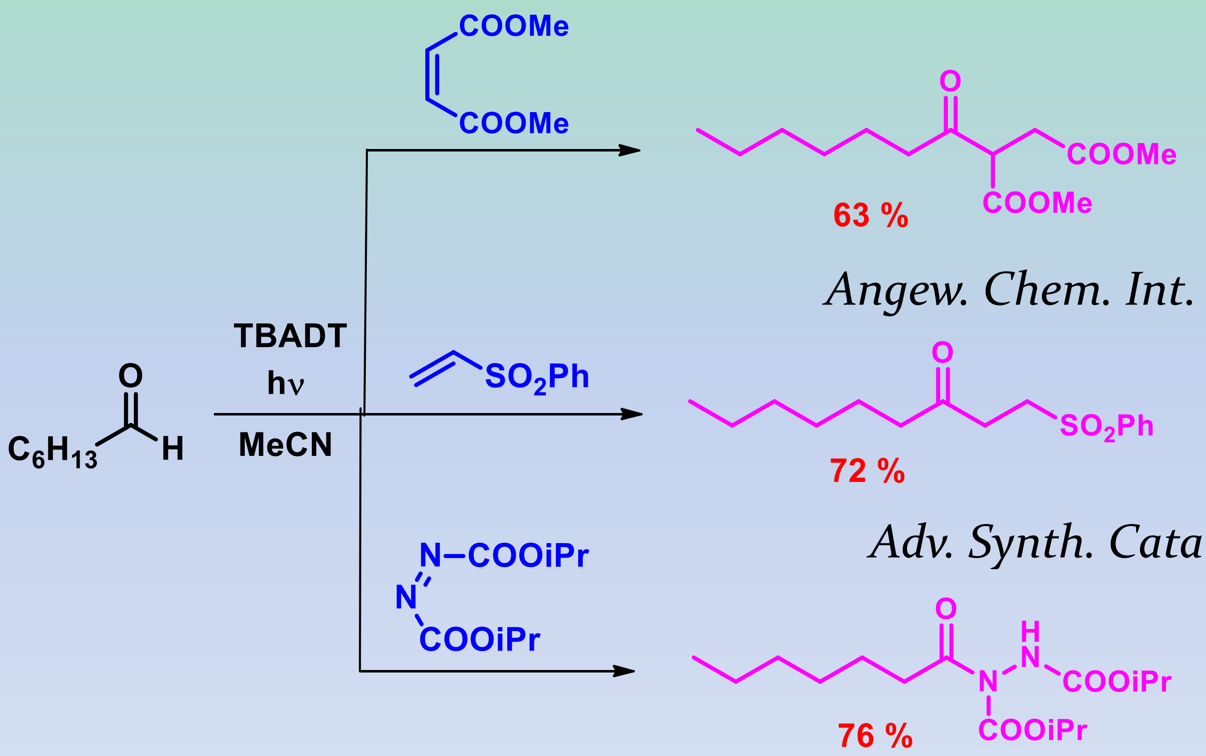
Electrophilic species



BDE = 88.7 kcal mol^{-1} for propanal



C(sp^2)-H Activation in Aldehydes



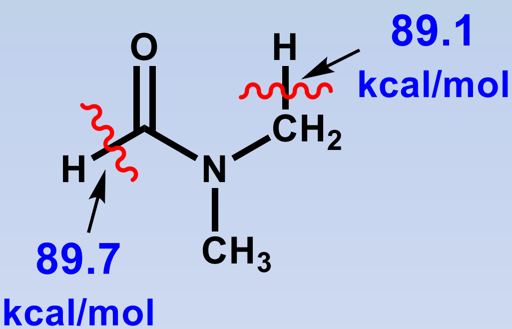
Angew. Chem. Int. Ed. **2007**, *46*, 2531

Adv. Synth. Catal. **2011**, *353*, 3295

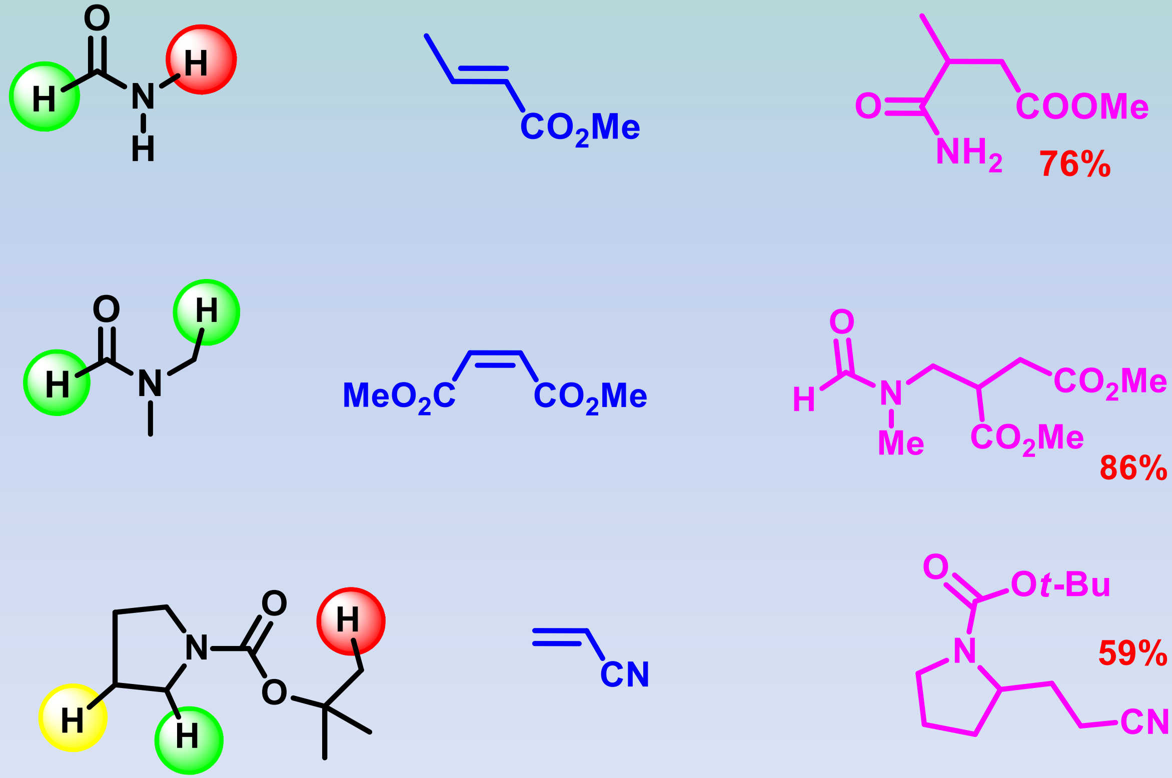
Org. Lett. **2013**, *15*, 2554

Activation of C-H bonds in Amides

Chemoselective C-H Cleavage



Amide | **Olefin** | **Product**



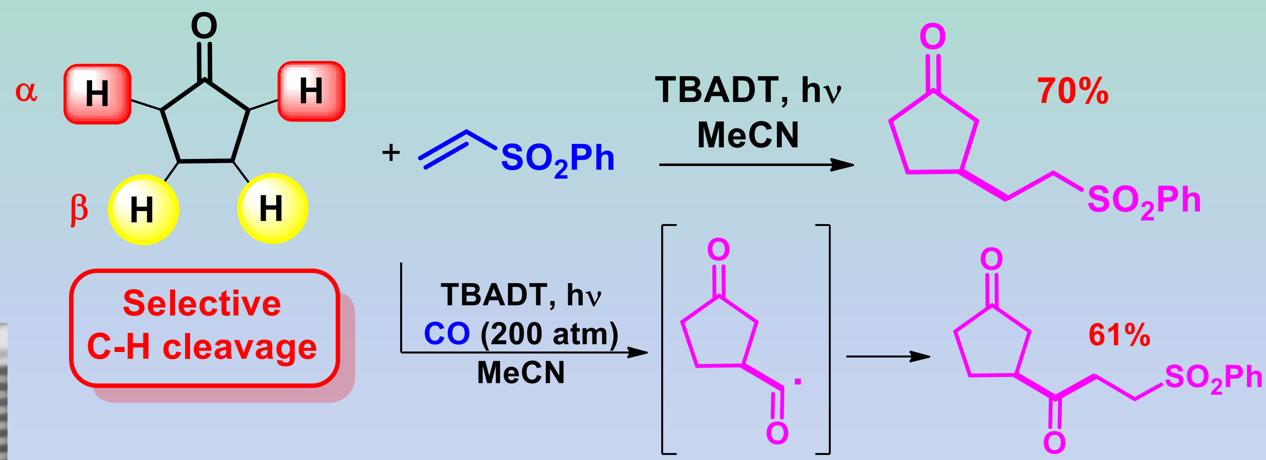
Adv. Synth. Catal. **2008**, *350*, 2209

β-Alkylation of Cyclopentanones
Exploiting polar effects in radical chemistry

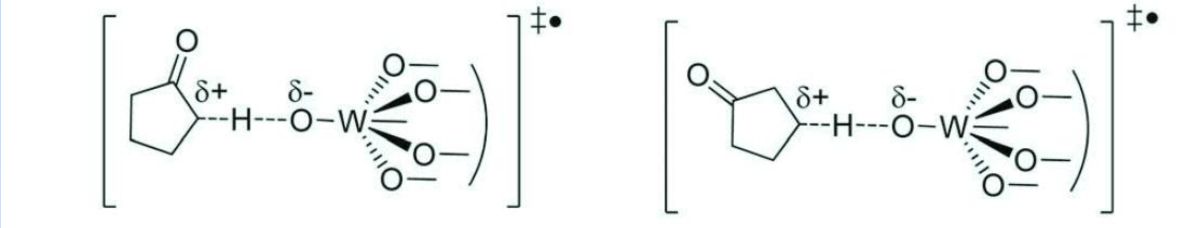
- **High Selectivity towards the abstraction of <u>Nucleophilic</u> Hydrogens:**

α C-H: 88.0 kcal mol^{-1}

β C-H: ca. 95.6 kcal mol^{-1}



Prof. *RYU*, Osaka (JPN)



TS-a: *unfavorable (Umpolung type)*   ***TS-b***: *favorable*

Chem. Sci. **2014**, 5, 2893

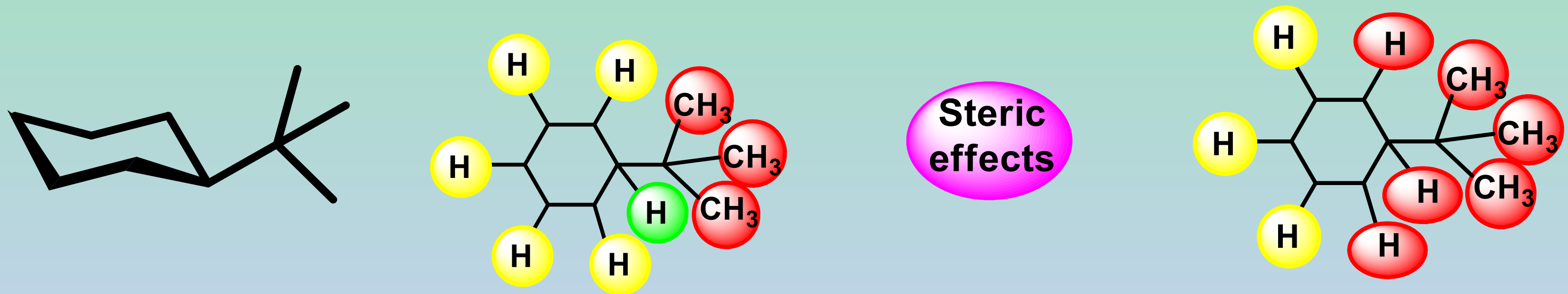
HAT in Cycloalkanes

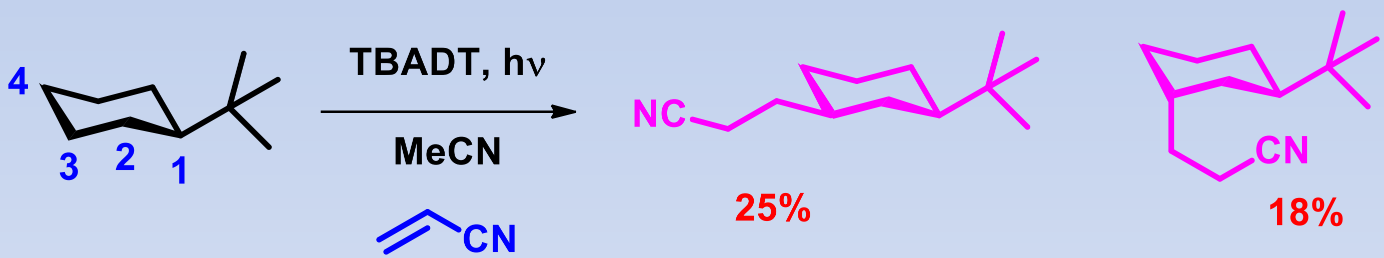
R = CN 63 %
R = COOMe 65 %

C-H: 99.5 kcal mol^{-1}

Chem. Eur. J. **2006**, *12*, 4153

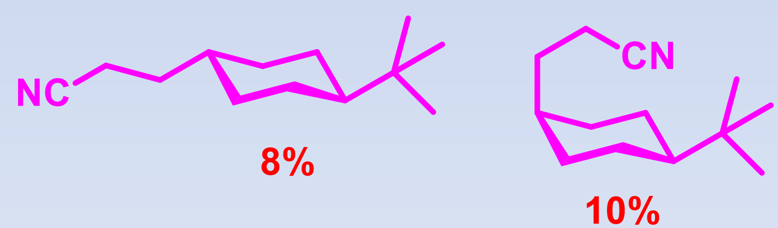
HAT in substituted Cycloalkanes





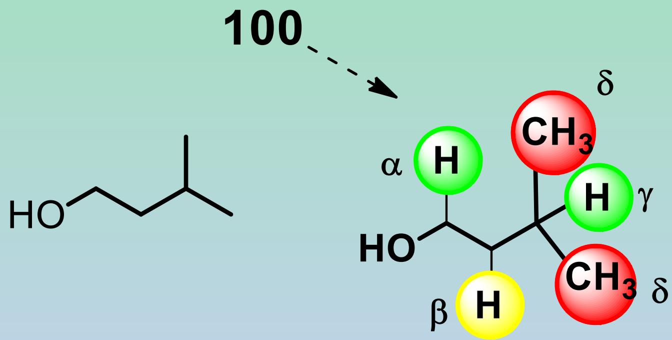
Total Yield: 61%

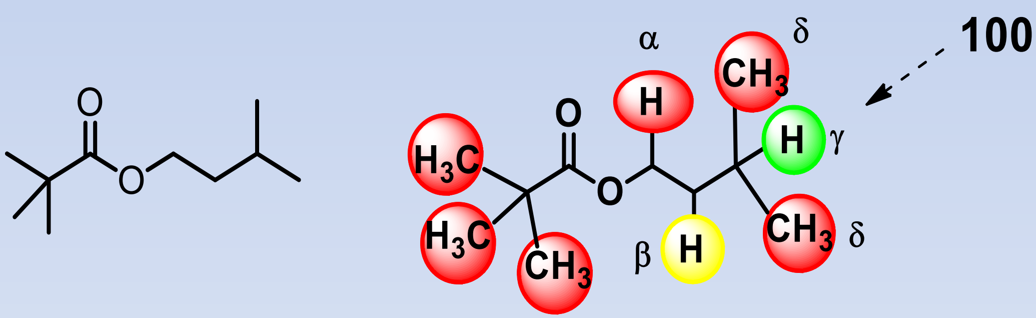
3 : 4 = 1.19
(statistically corrected)



Chem. Eur. J. **2009**, *15*, 7949

Polar/steric cooperative effects

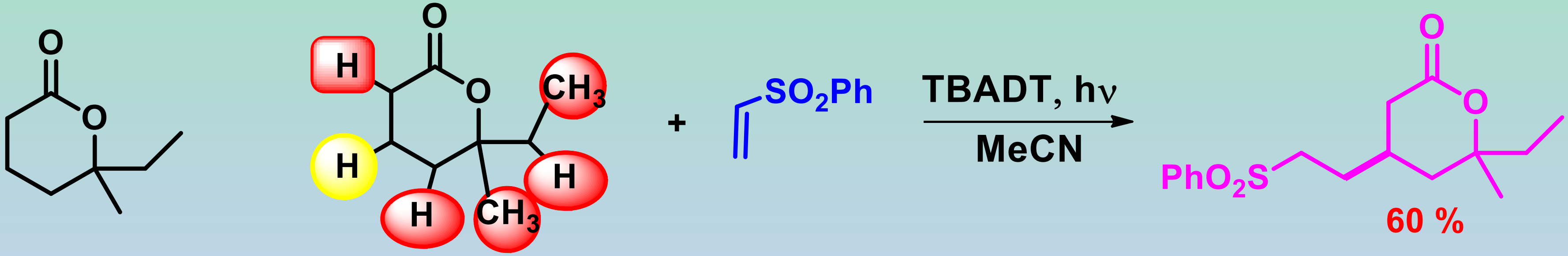


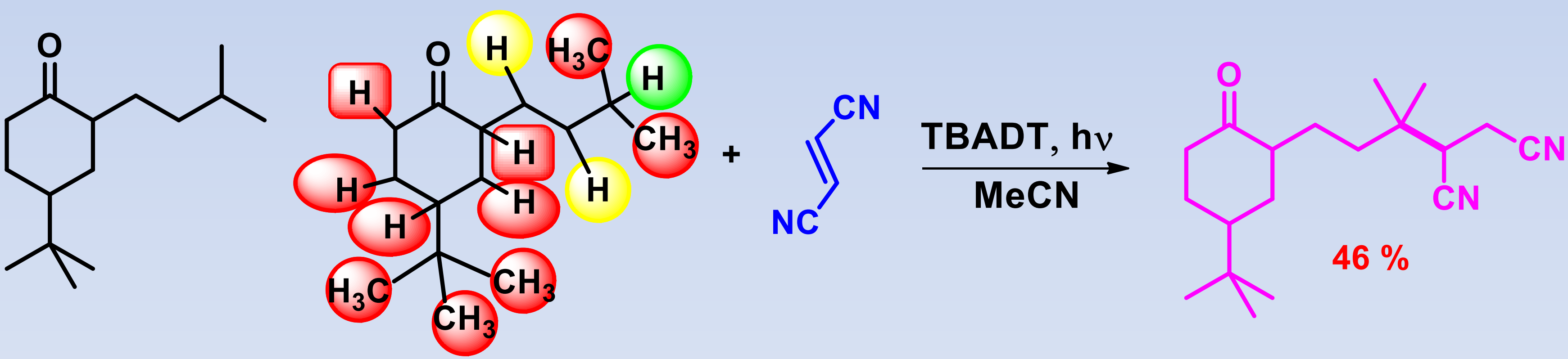


Chem. Eur. J. **2017**, *23*, 8615

ACS Catal. **2018**, *8*, 701

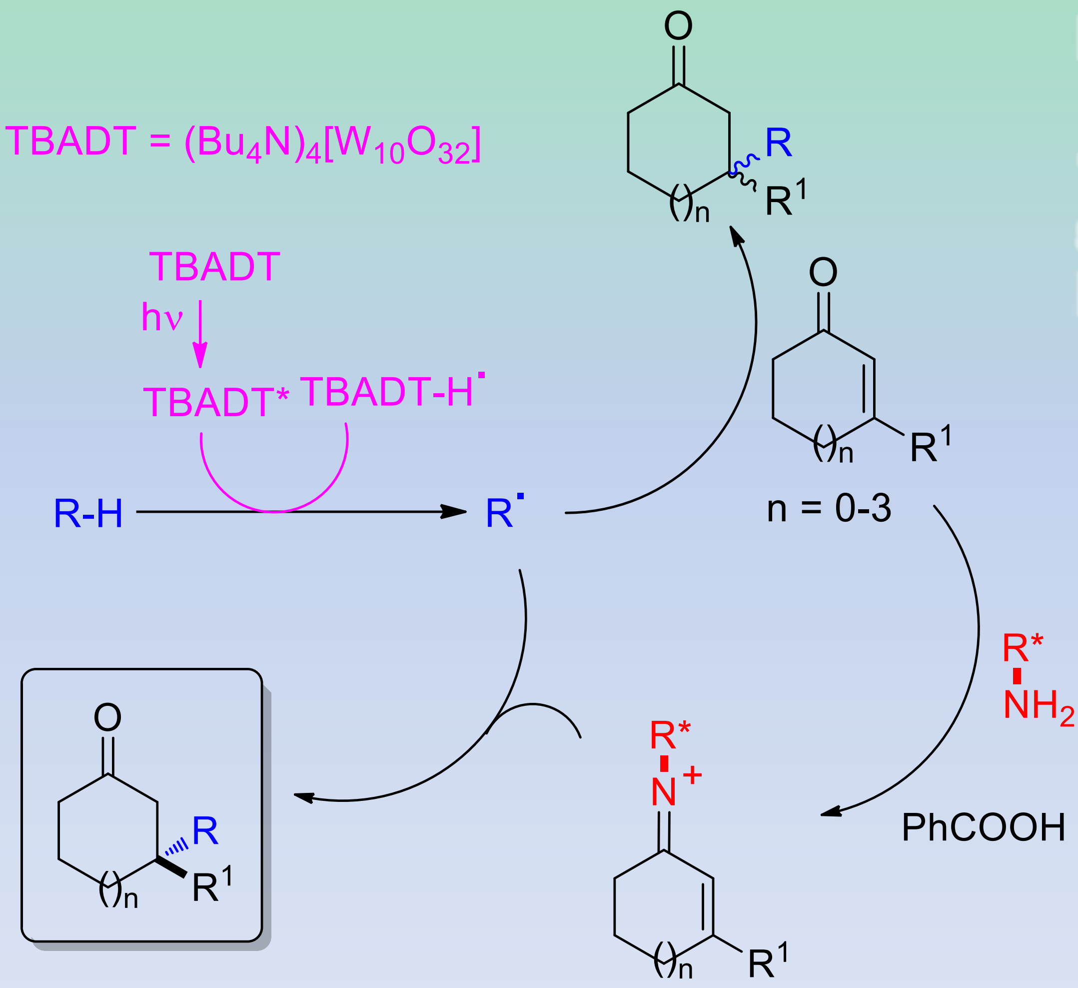
Polar/steric cooperative effects





Chem. Eur. J. **2017**, *23*, 8615

Enantioselective reactions



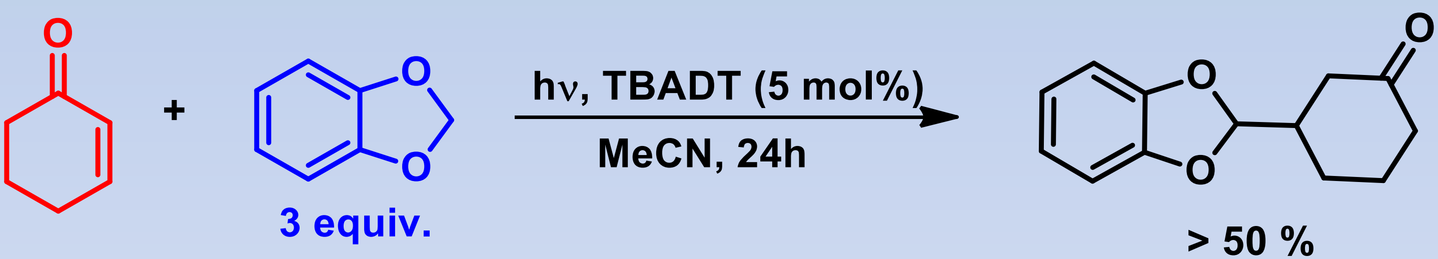
Possible drawbacks

1 The organocatalyst MUST shield one face in the resulting iminium ion

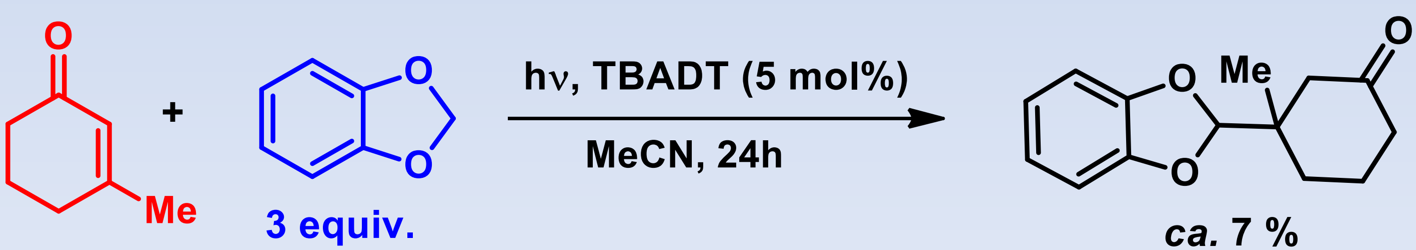
2 The starting enone and the resulting iminium ion are both electrophilic

Effect of the background reaction

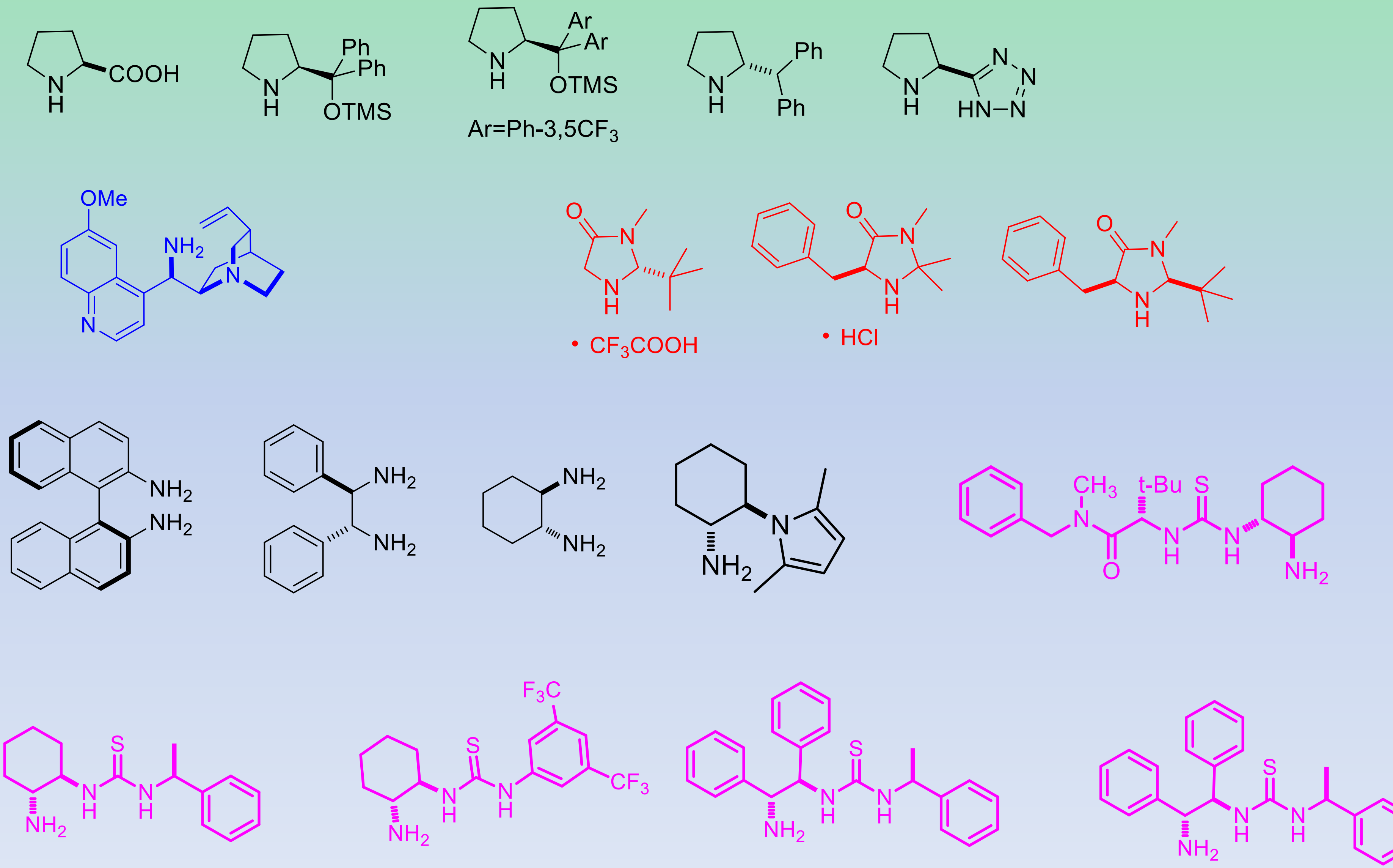
Prof. MELCHIORRE,
Tarragona (Spain)



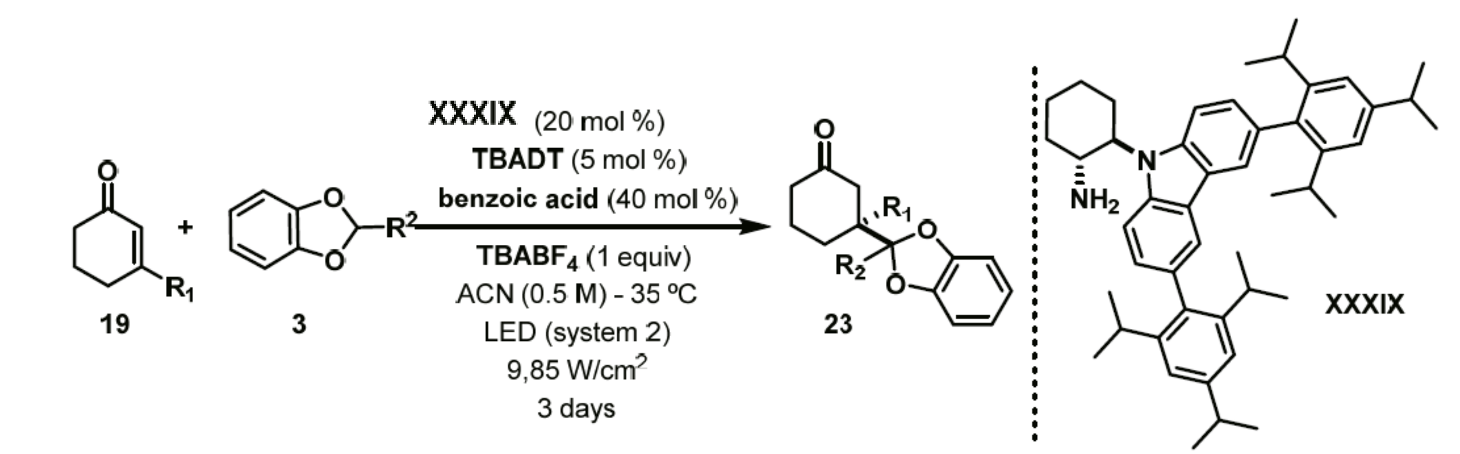
How we can lower the reactivity of the enone ?

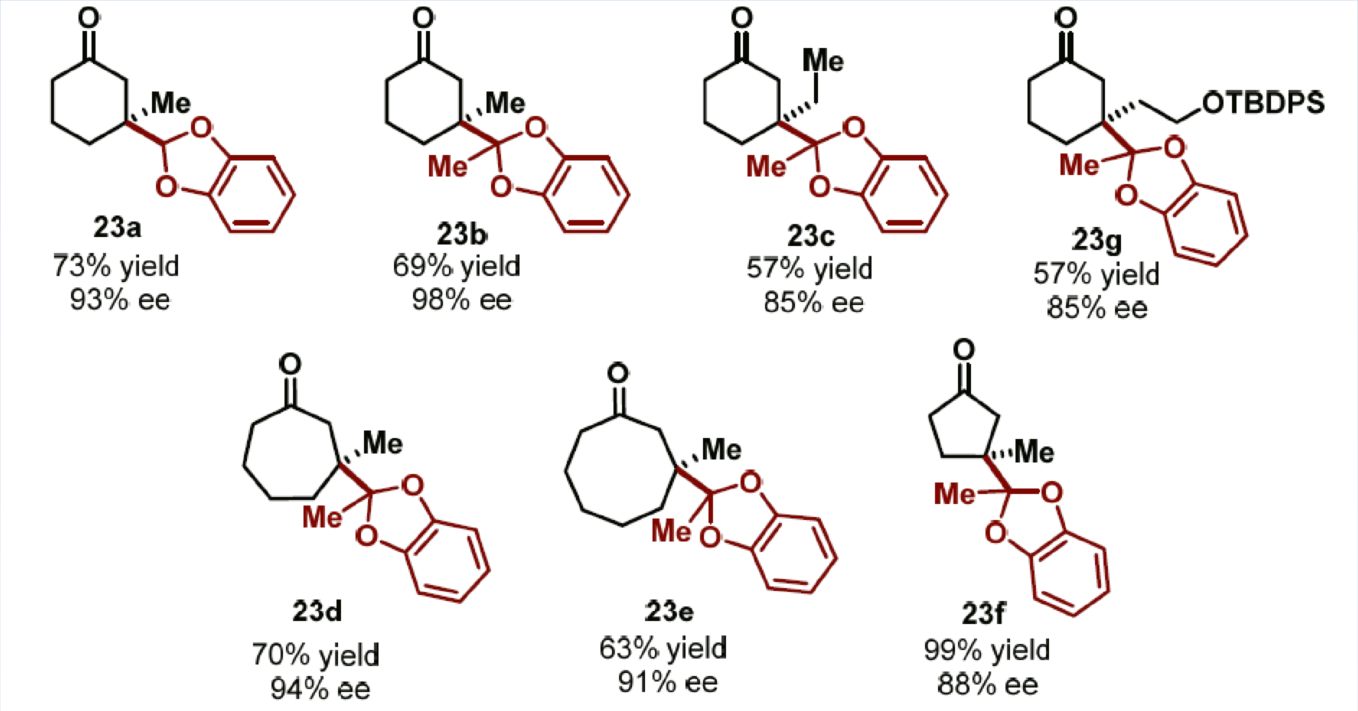


Organocatalysts tested



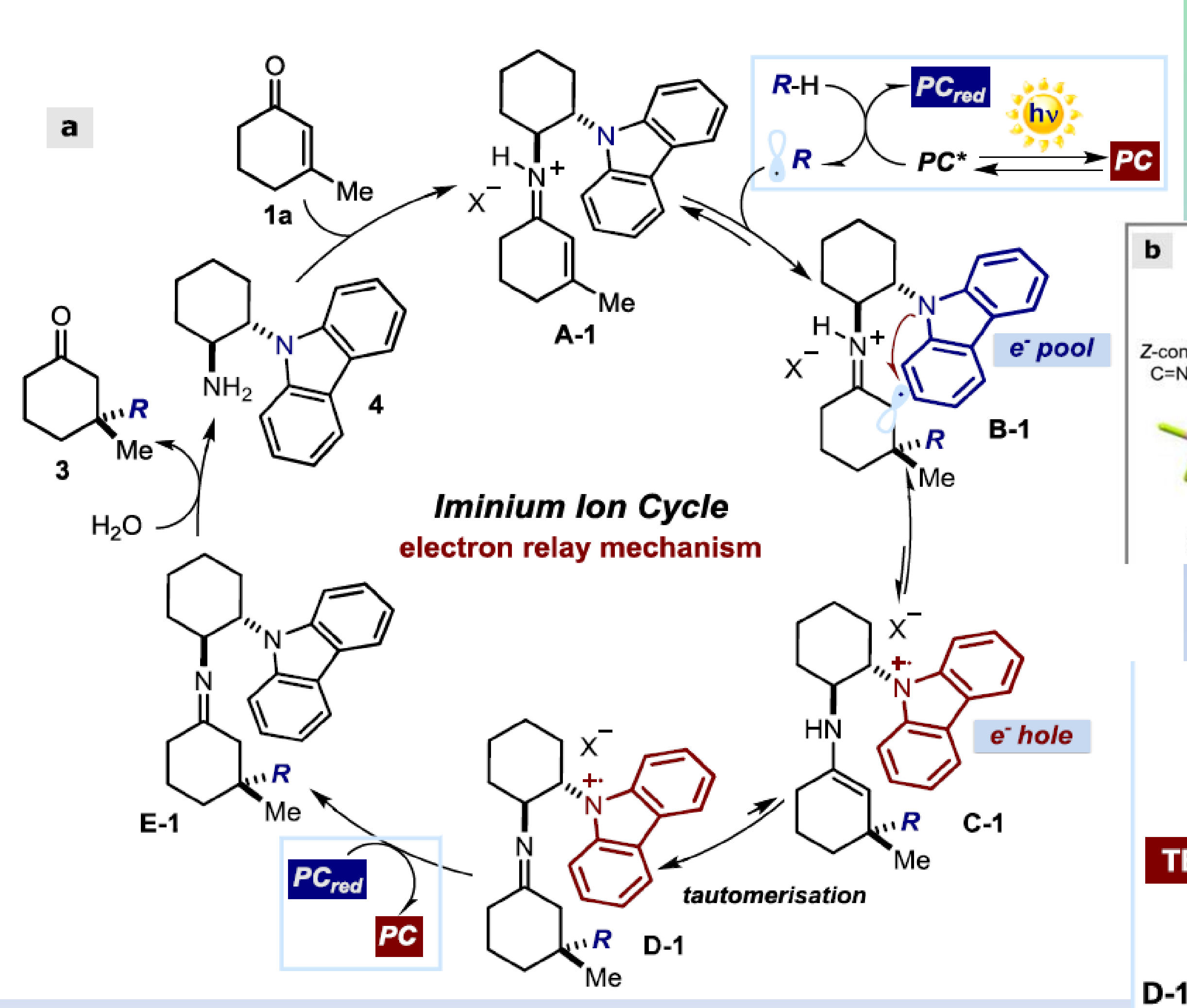
Enantioselective reactions

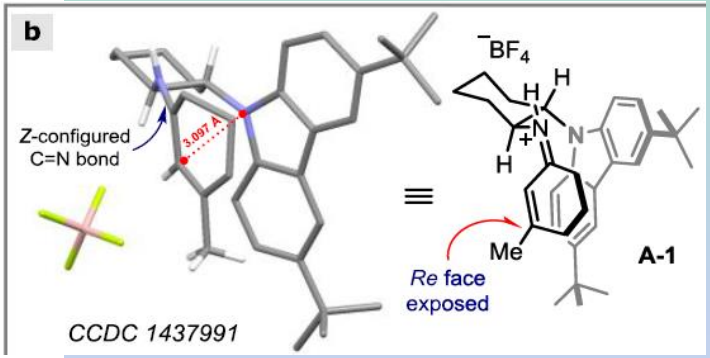


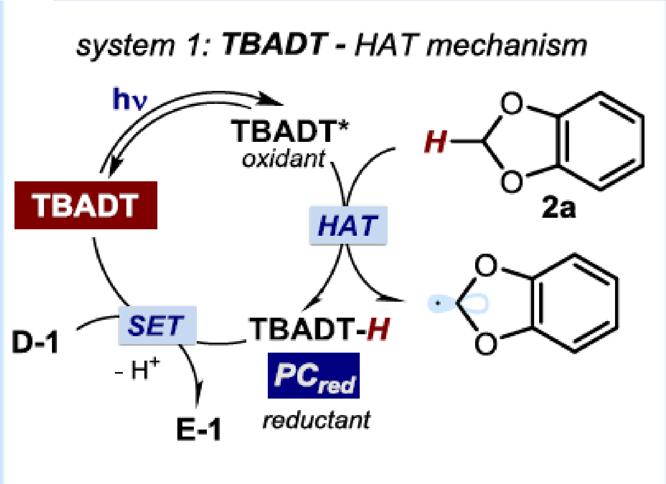


Nature **2016**, *532*, 218

Mechanistic proposal







Nature **2016**, *532*, 218

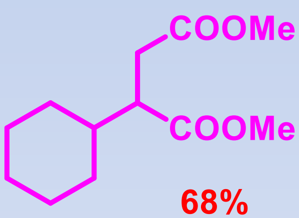
Solar Light Photocatalysis

*A Green Approach to Synthesis - **Window-Ledge Chemistry***

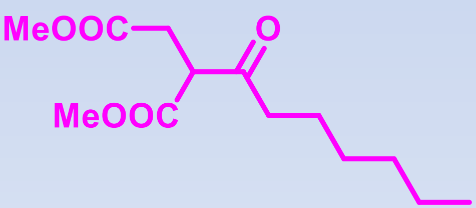
**Reaction Mixture
(Volume: 100 mL)**

Chem. Commun. **2009**, *7351*

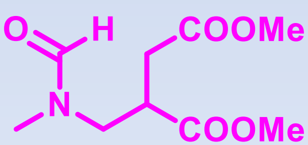
Acc. Chem. Res. **2016**, 49, 2232



68%
1.55 g in 5 days



90%
10.5 g in 9 days

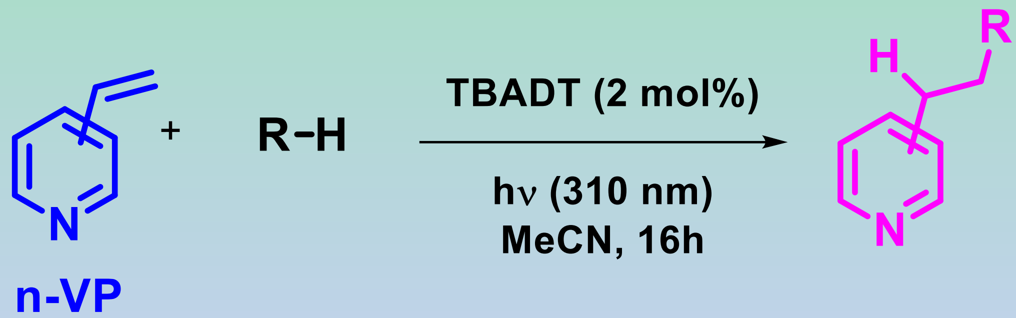


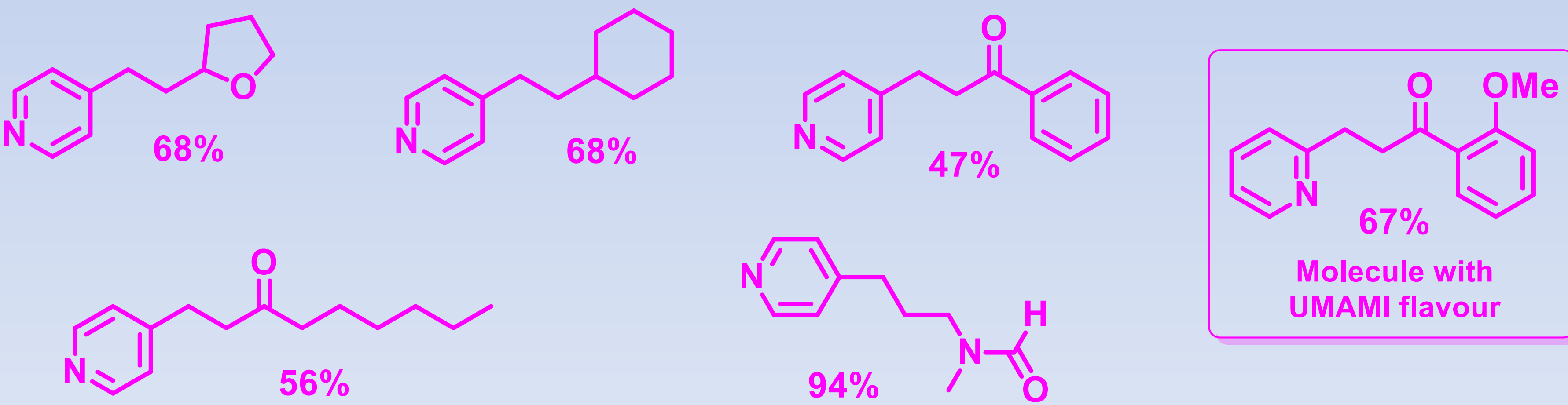
64%
1.39 g in 4 days

Extending the reaction to VinylAromatics

Radical addition onto Vinylpyridines (n-VP)

vs





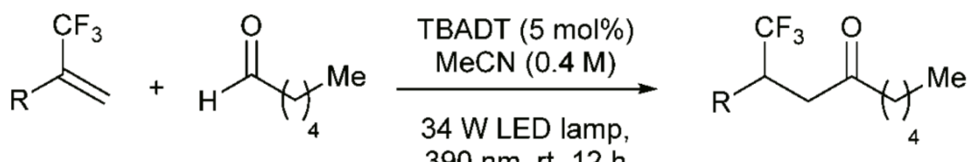
Chem. Eur. J. **2017**, *23*, 6527

Photocatalytic hydroacylation of trifluoromethyl alkenes†

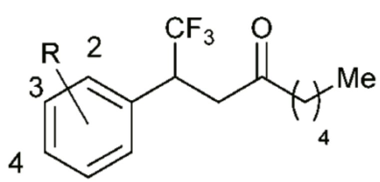
Cite this: *Chem. Commun.*, 2019, 55, 12691

Pei Fan, Chang Zhang, Yun Lan, Zhiyang Lin, Linchuan Zhang and Chuan Wang *

Table 2 Evaluation of the substrate scope of the TBADT-catalyzed hydroacylation by varying the structure of trifluoromethyl alkenes[a,b]



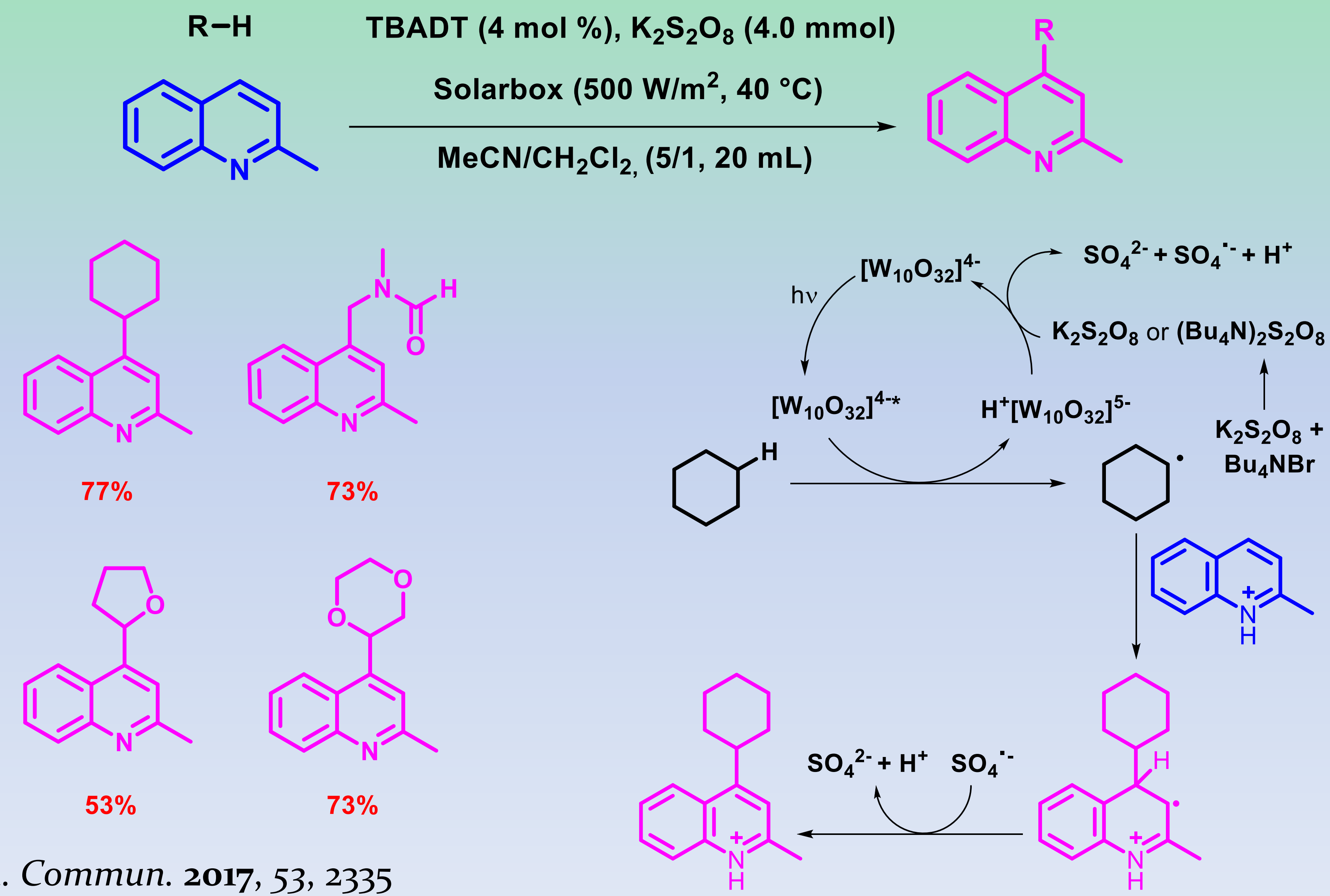
1a-t **2a** **3aa-sa**



3aa	R= 4-MeO,	80%	**3ha**,	R= 3-BzNH,	72%
3ba	R= 2-MeO,	61%	**3ia**,	R= 3-AcNH,	90%
3ca	R= 2-F-4-MeO,	86%	**3ja**,	R= 4-$MeCO_2$,	83%
3da	R= 3-MeO-4-Cl,	81%	**3ka**,	R= 4-CN,	59%
3ea	R= 3-Br-4-MeO,	65%	**3la**,	R= 4-Ms,	71%
3fa	R= 3-BnO,	71%	**3ma**,	R= 4-NH_2CO,	51%
3ga	R= 4-TBSO,	78%			

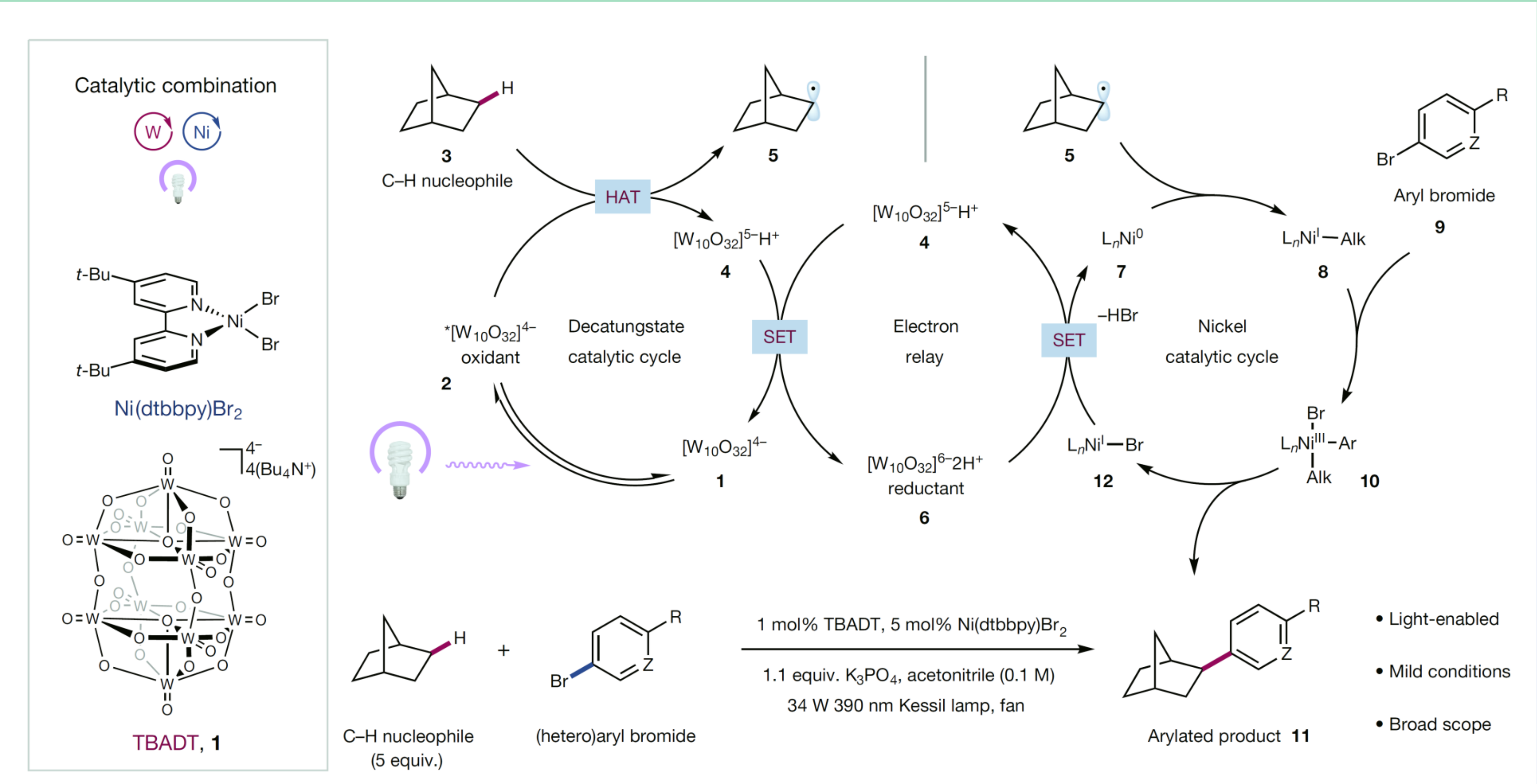
Photocatalytic Minisci-type reactions

Cross-Dehydrogenative Coupling of Heteroaromatics and H-Donors



Chem. Commun. **2017**, *53*, 2335

Direct arylation of strong aliphatic C–H bonds



MacMillan et al *Nature* **2018**, *560*, 70

Organic Letters

Letter

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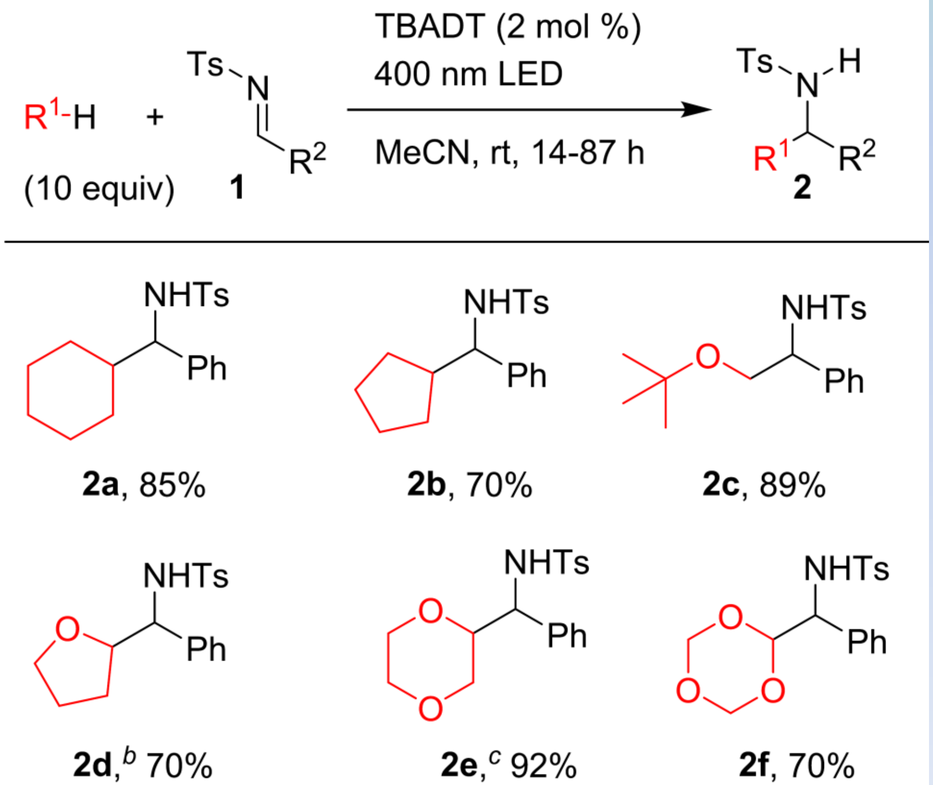
pubs.acs.org/OrgLett

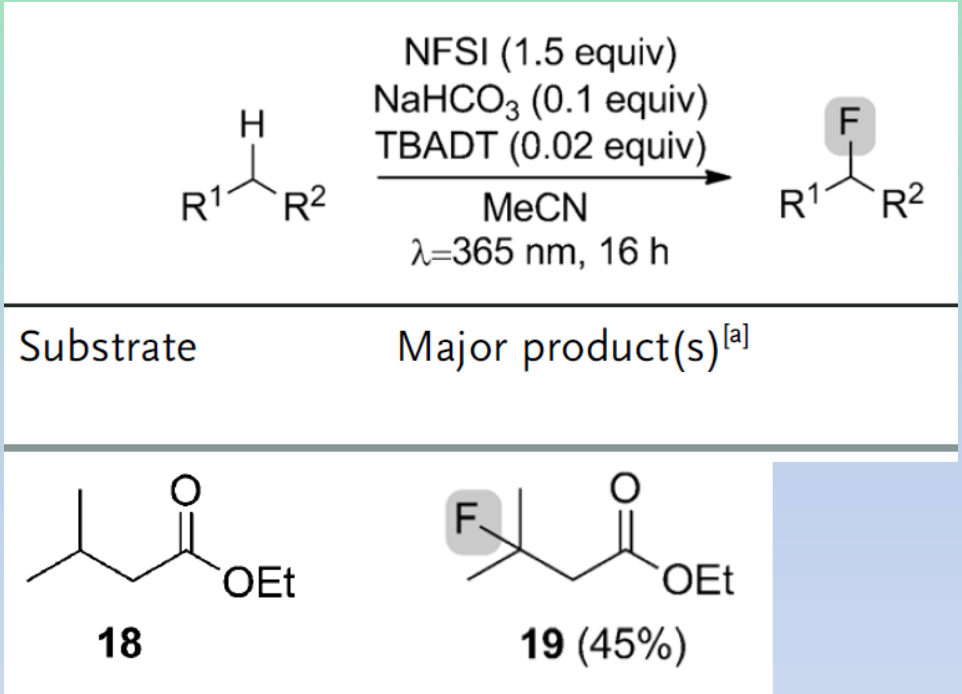
Radical Addition to *N*-Tosylimines via C−H Activation Induced by Decatungstate Photocatalyst

Vyacheslav I. Supranovich, Vitalij V. Levin, and Alexander D. Dilman*

Scheme 2. Reactions of *N*-Tosylimines[a]



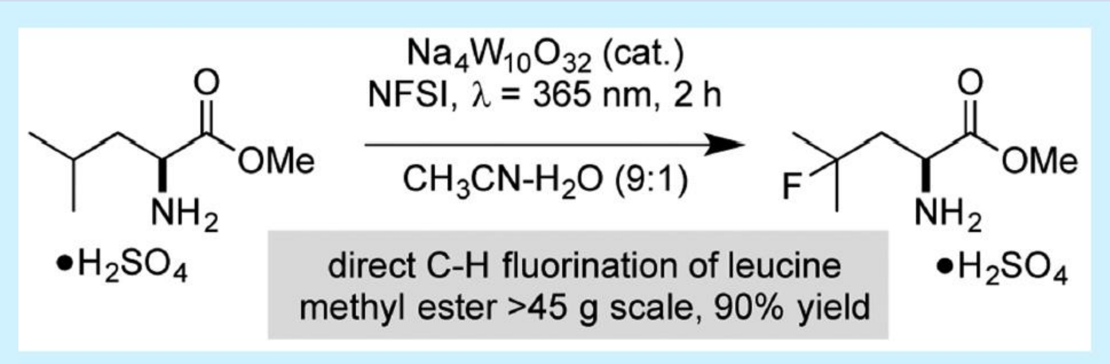
Photocatalytic C-H Fluorination



NFSI: *N*-fluorobenzenesulfonimide

$(PhSO_2)_2N{-}F$

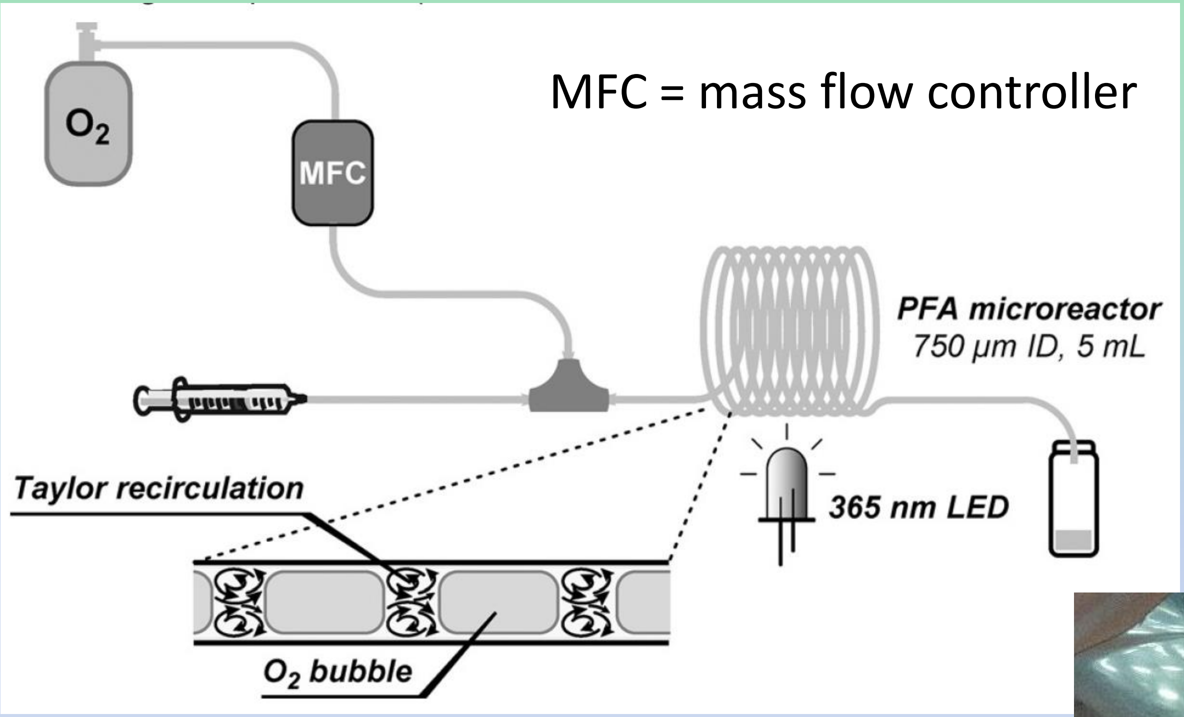
Britton et al.
Angew. Chem. Int. Ed. **2014**, *53*, 4690



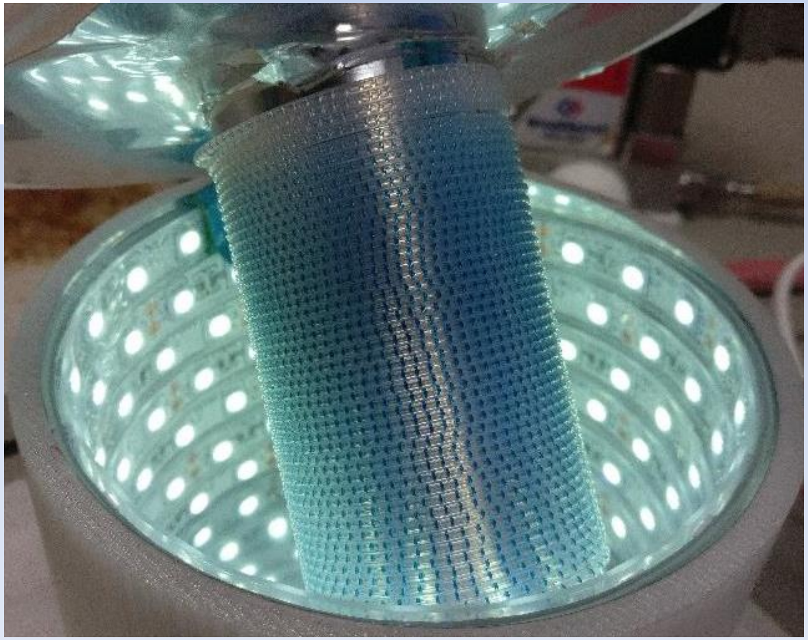
Britton et al.
Org. Lett. **2015**, *17*, 5200

Key step in the Synthesis of Odanacatib

Selective C(sp^3)-H Aerobic Oxidation

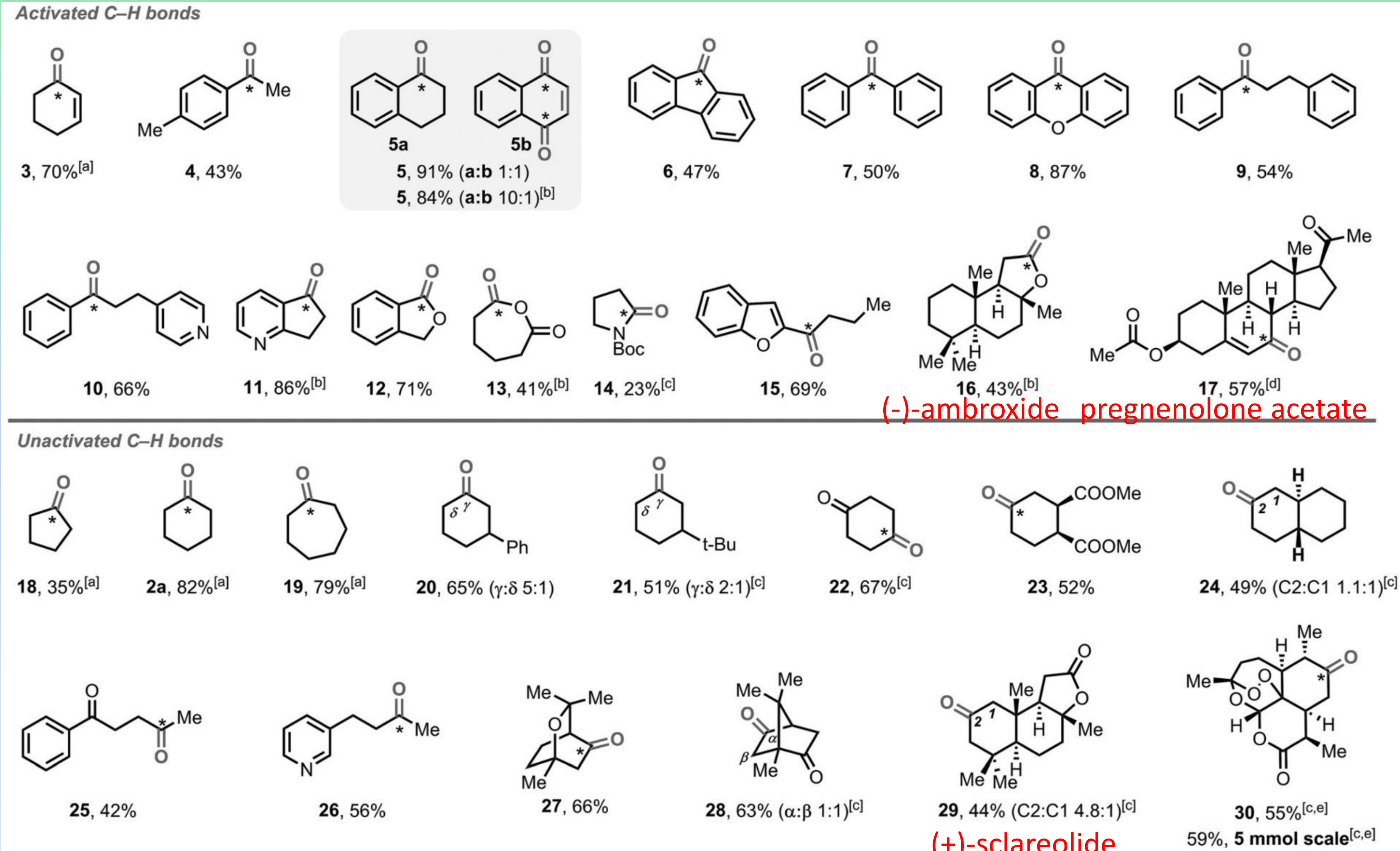


Prof. NOEL
Eindhoven (Netherlands)



Angew. Chem. Int. Ed. **2018,** *57,* 4078

Selective C(sp^3)-H Aerobic Oxidation



(+)-sclareolide

artemisinin

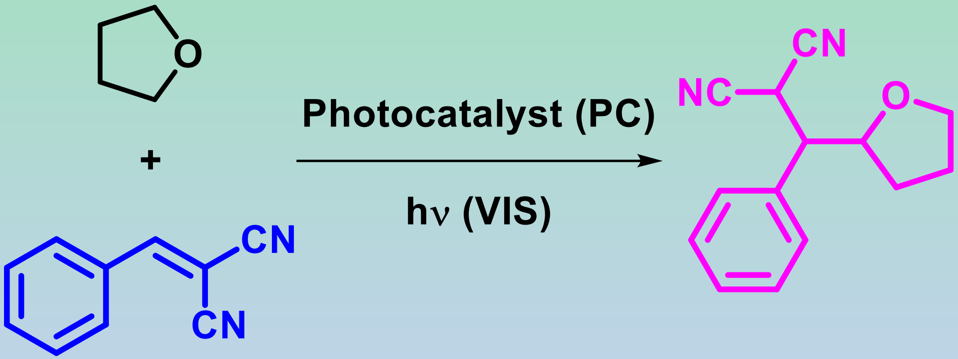
Angew. Chem. Int. Ed. **2018,** *57*, 4078

Conclusions & Perspectives

- TBADT is one of the best *green* photocatalyst in organic synthesis:
  - Robust (in most cases a 2 mol% is used); Inexpensive
  - Versatile (C-H bonds can be activated in various organic molecules);
  - Offers quite unique selectivities;

- Development of visible light absorbing POMs for HAT reactions

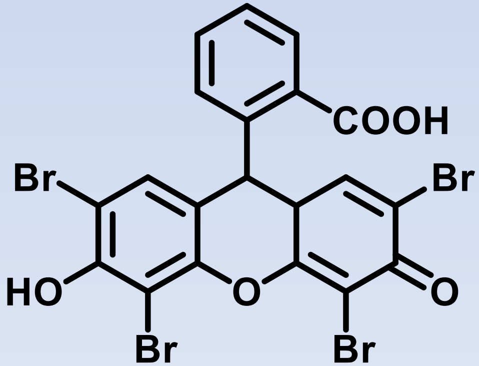
Visible light HAT



Exploiting low-energy light!!

97%, PC = Eosin Y

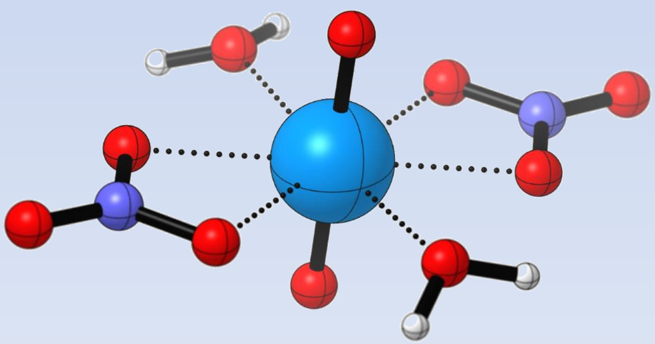
(THF as the solvent)



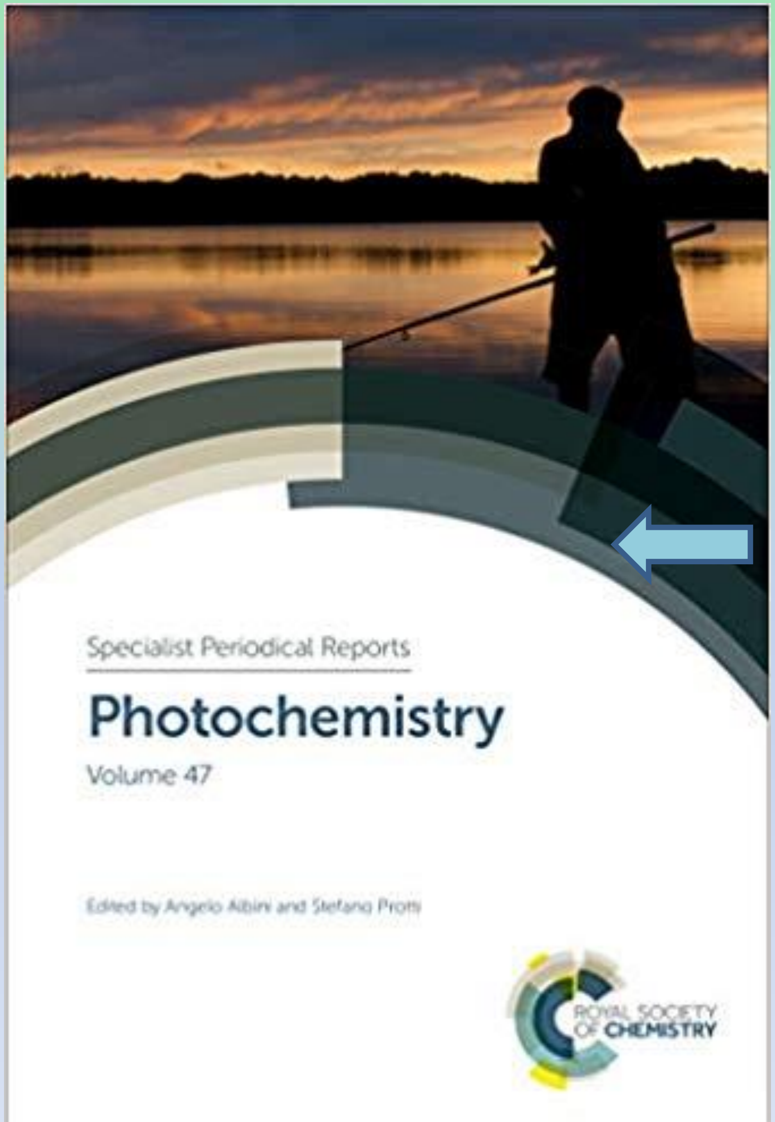
Wu, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 8514

60%, PC = $[UO_2](NO_3)_2$

(5 equiv. THF)



ACS Catal. **2019**, *9*, 3054



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