Literature Report IX

Intermolecular Anti-Markovnikov Hydroamination of Alkenes with Sulfonamides, Sulfamides, and Sulfamates

Reporter: Qing-Xian Xie
Checker: Gao-Wei Wang
Date: 2025-1-20

Lin, A.; Karrasch, M. J.; Ganley, J. M.; Hejna, B. G.; Knowles, R. R. *ACS Catal.* **2024**, 14, 13098-13104

CV of Prof. Robert R. Knowles

Background:

- **1999-2003** B. S., William & Mary
- **2003-2008** Ph. D., California Institute of Technology (Prof. David MacMillan)
- **2008-2011** Postdoc., Harvard University (Prof. Eric Jacobsen)
- **2011-2017** Associate Professor, Princeton University
- **2017-Now** Professor, Princeton University

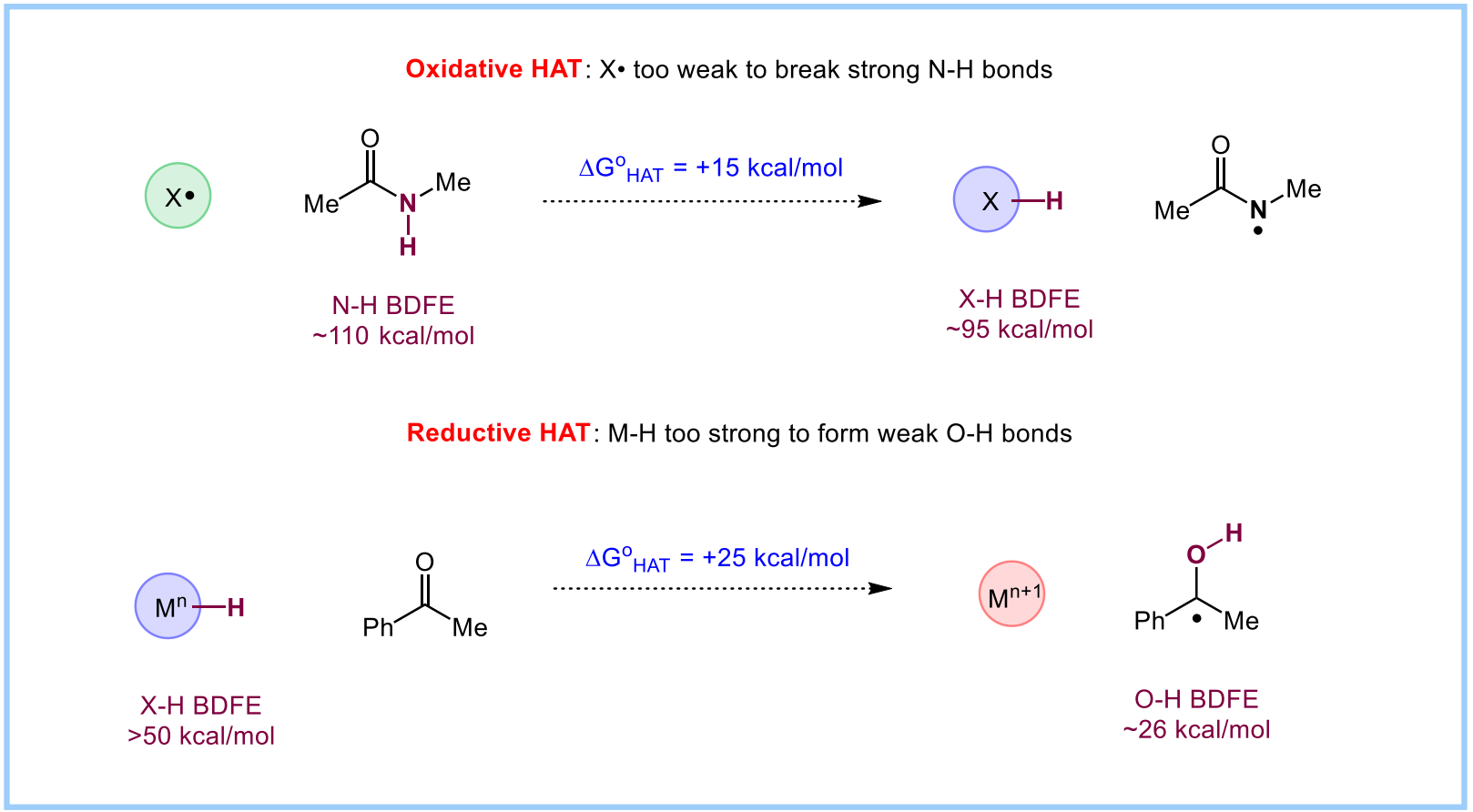
Research:

- Proton-coupled electron transfer in organic synthesis
- Enantioselective catalysis with free radical intermediates
- Catalytic olefin hydroamination

Contents

Introduction

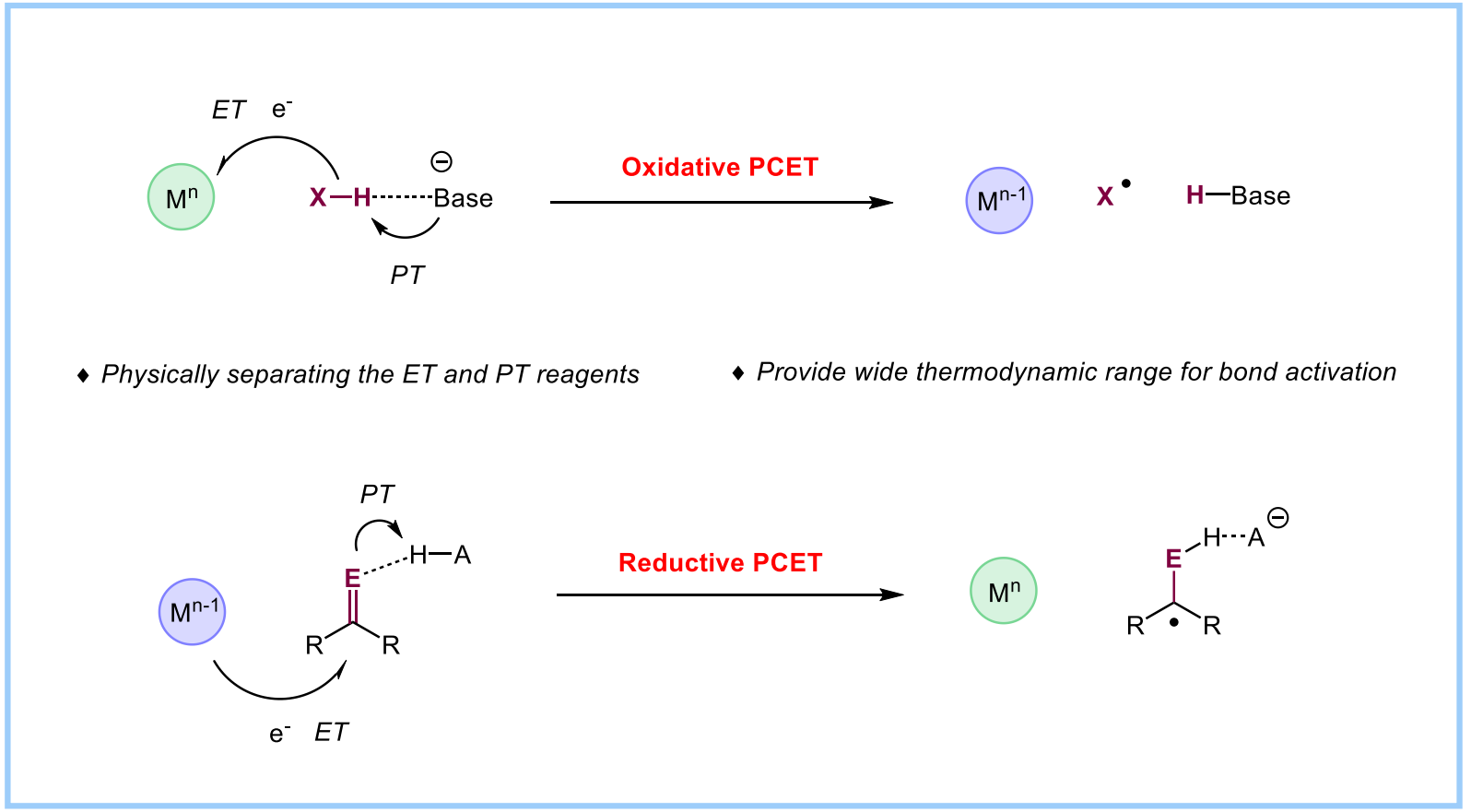
Thermodynamically limited HAT reactions



Gentry, E. C.; Knowles, R. R.* *Acc. Chem. Res.* **2016**, *49*, 1546-1556

Introduction

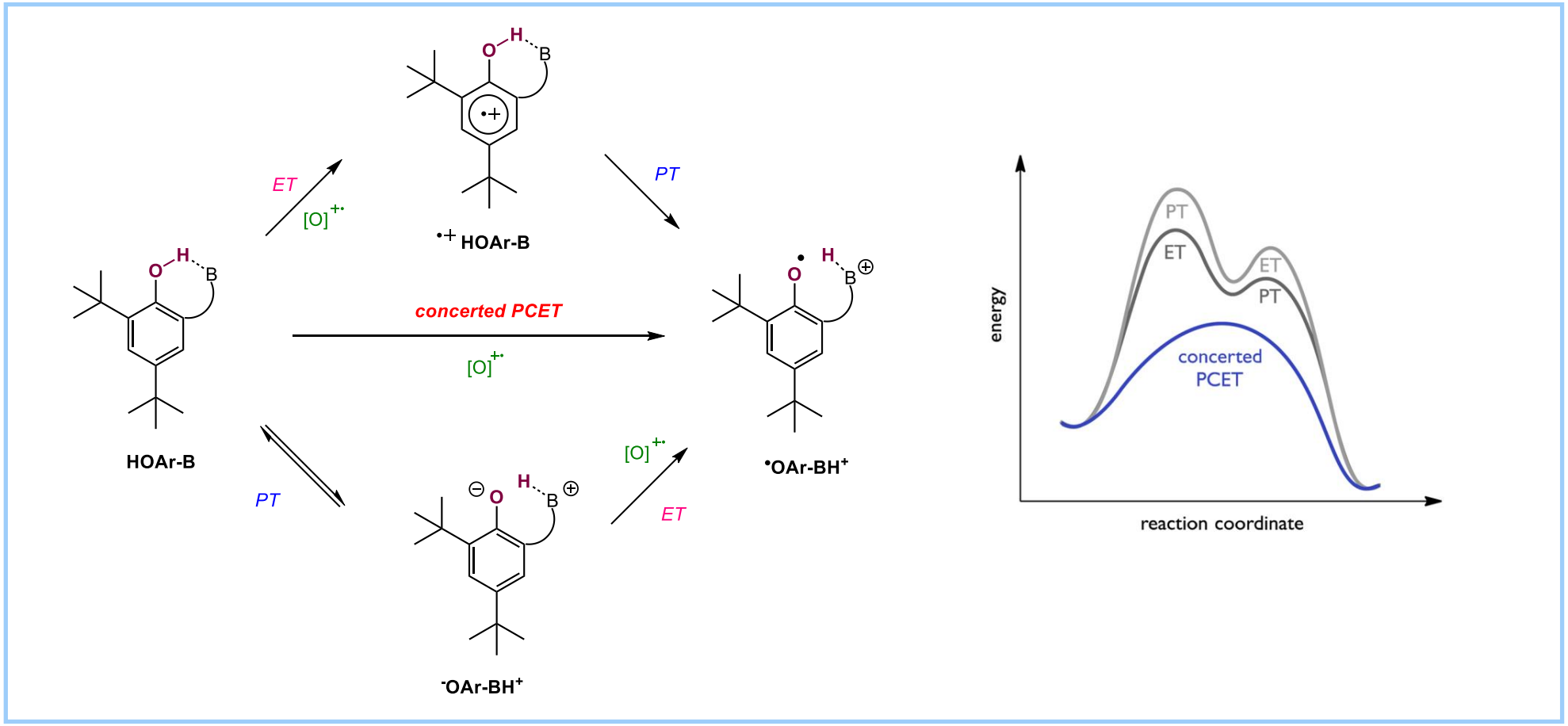
Multi-site proton-coupled electron transfer



Gentry, E. C.; Knowles, R. R.* *Acc. Chem. Res.* **2016**, *49*, 1546-1556

Introduction

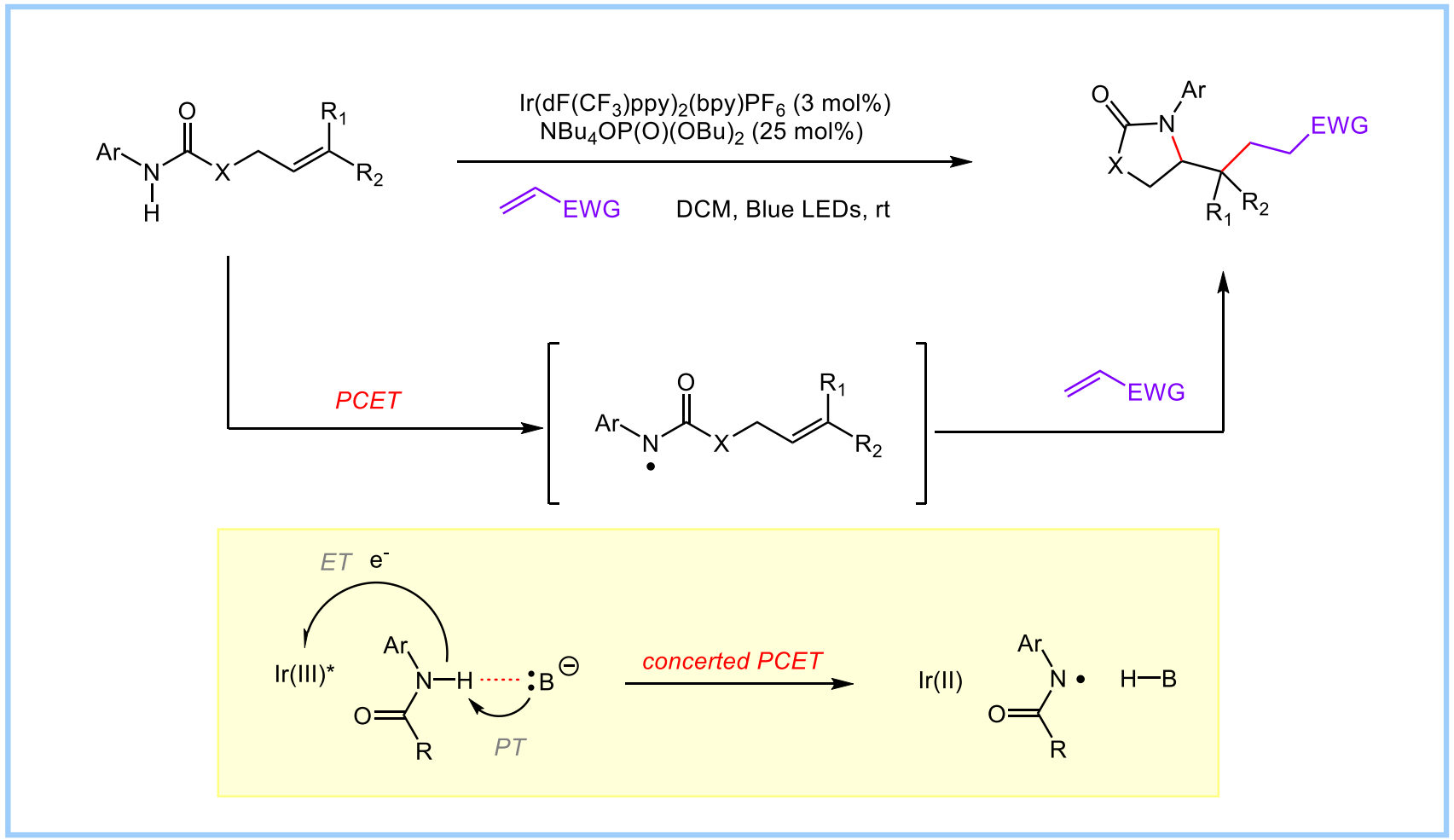
Three pathways of PCET mechanism



Rhile, I. J.; Markle, T. F.; Nagao, H.; Rotter, K; Mayer, J. M.* *J. Am. Chem. Soc.* **2006**, *128*, 6075-6088

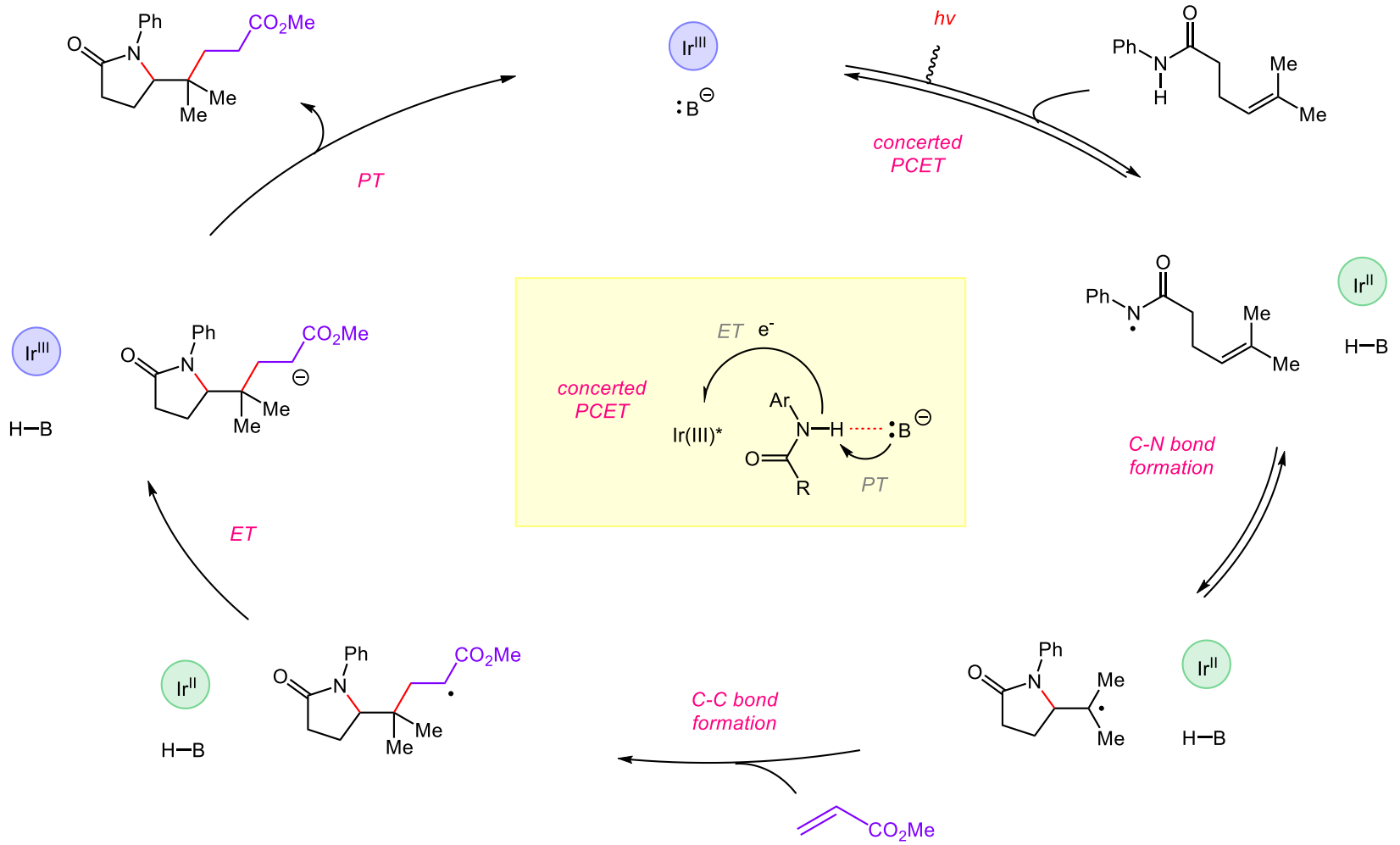
Proton-Coupled Electron Transfer in Organic Synthesis

PCET promoted N-H bond-weakening



Choi, G. J.; Knowles, R. R.* *J. Am. Chem. Soc.* **2015**, *137*, 9226-9229

Proton-Coupled Electron Transfer in Organic Synthesis



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Proton-Coupled Electron Transfer in Organic Synthesis

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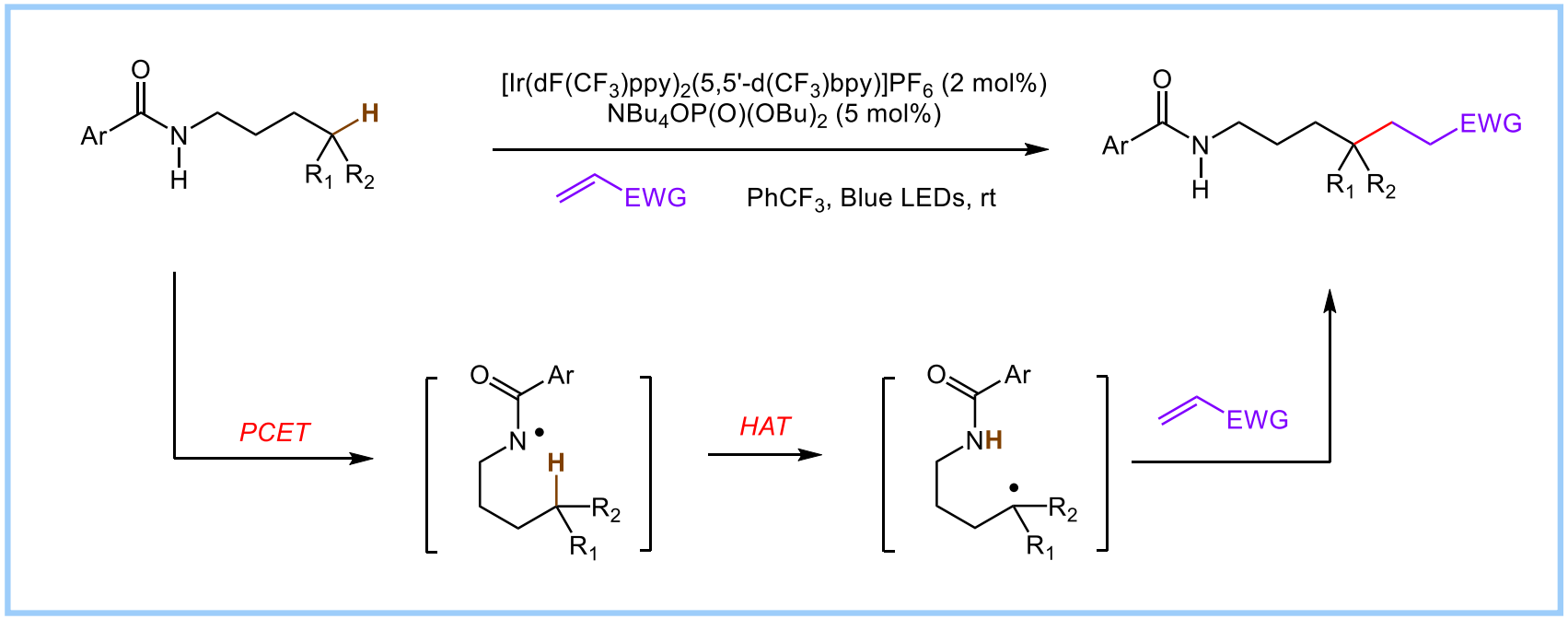
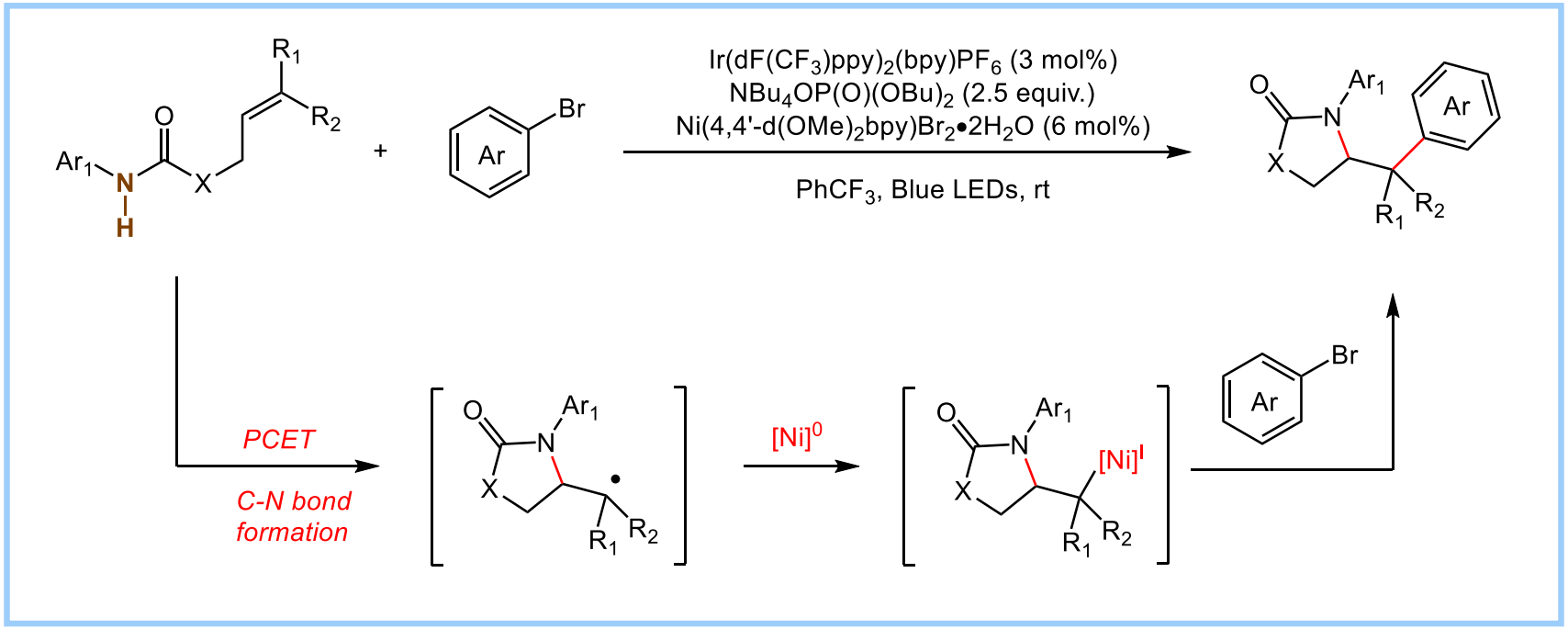


Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R.* *Nature* **2016**, *539*, 268-271

Proton-Coupled Electron Transfer in Organic Synthesis

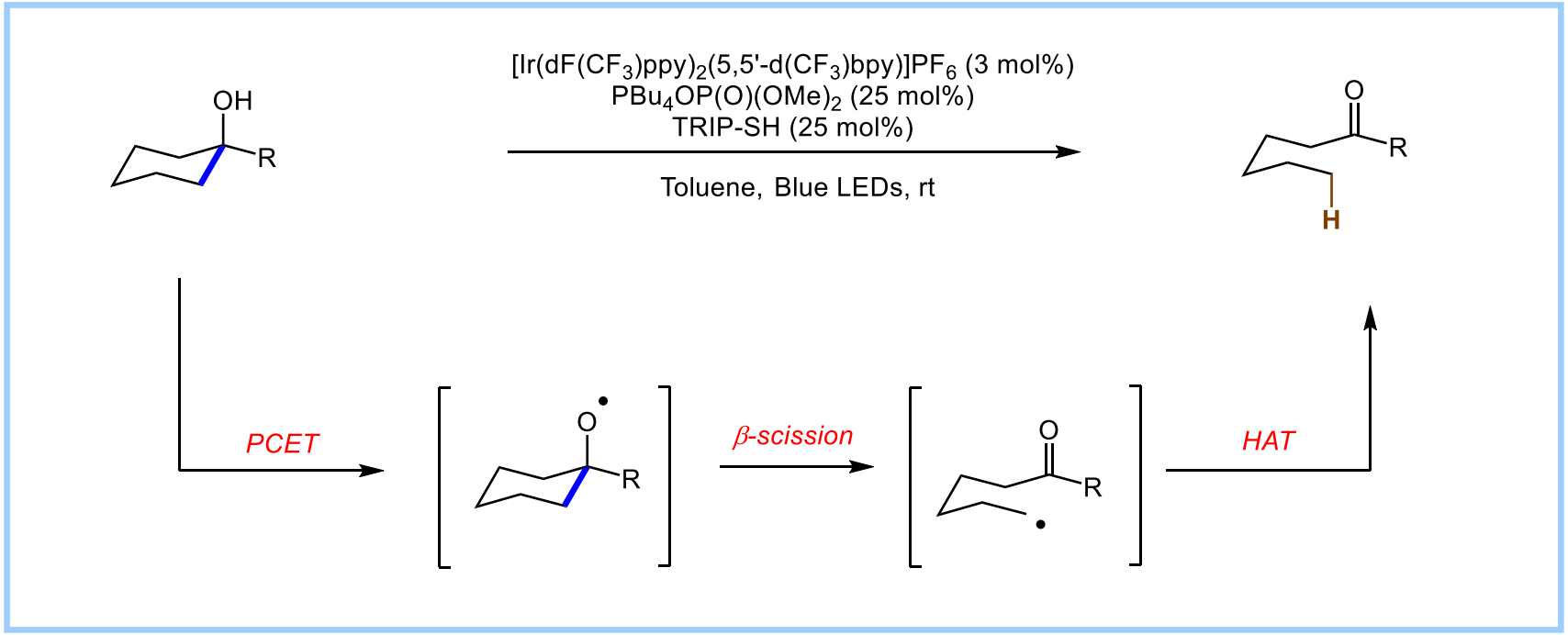
PCET promoted N-H bond-weakening



Zheng, S.; Gutierrez-Bonet, A.; Molander, G. A.* *Chem* **2019**, *5*, 339-352

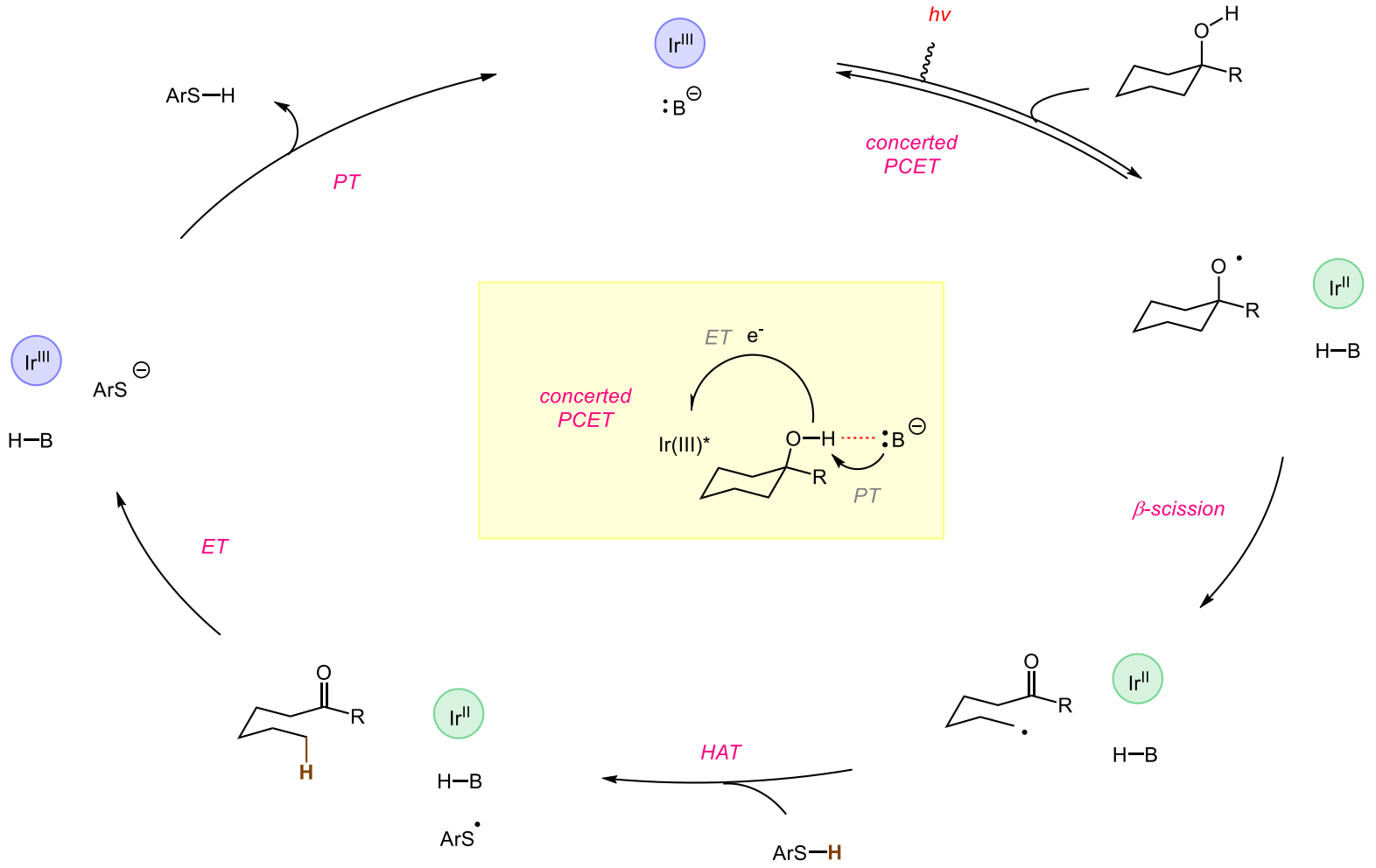
Proton-Coupled Electron Transfer in Organic Synthesis

PCET promoted O-H bond-weakening



Ota, E.; Wang, H.; Frye, N. L.; Knowles, R. R.* *J. Am. Chem. Soc.* **2019**, *141*, 1457-1462

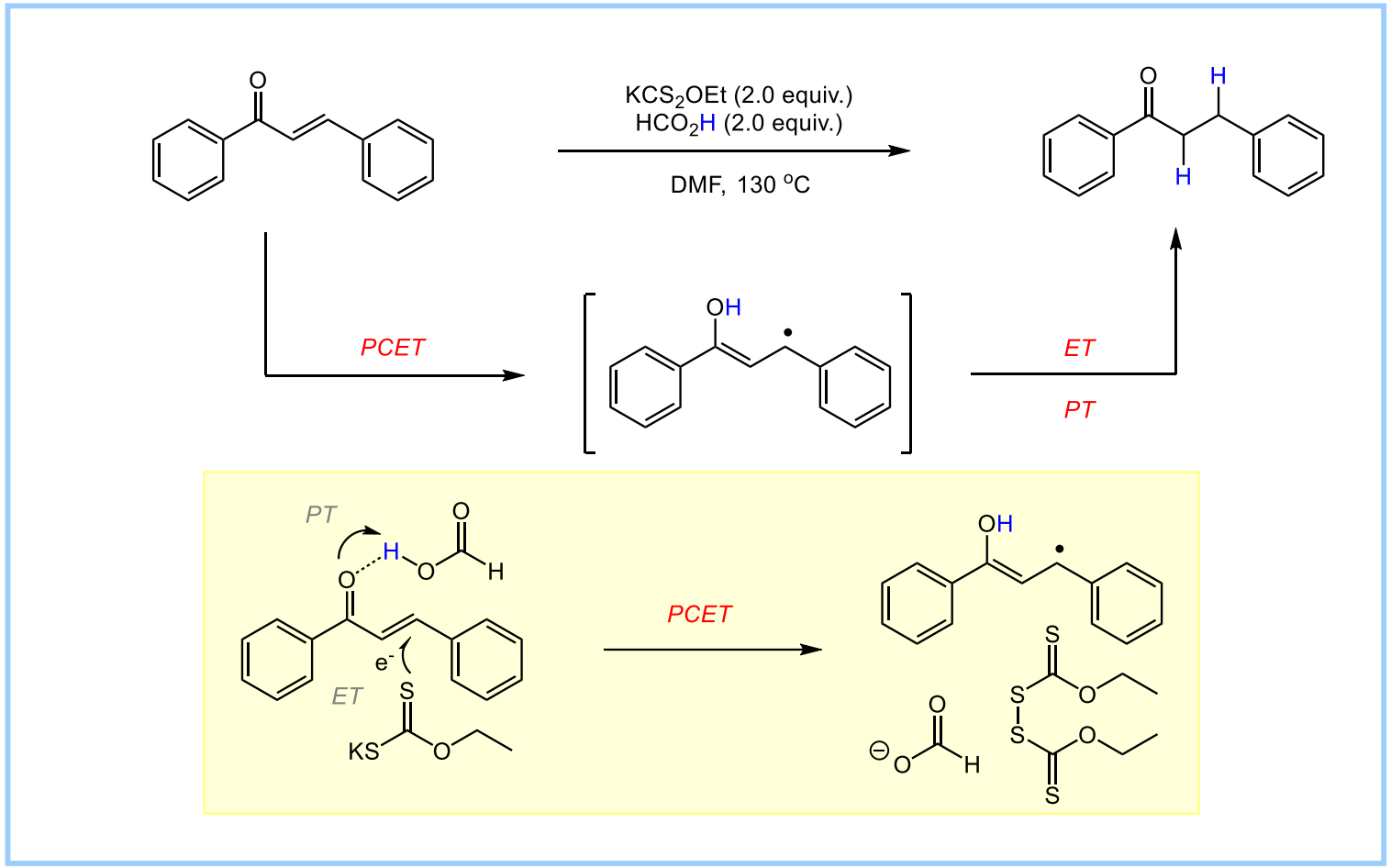
Proton-Coupled Electron Transfer in Organic Synthesis



Ota, E.; Wang, H.; Frye, N. L.; Knowles, R. R.* *J. Am. Chem. Soc.* **2019**, *141*, 1457-1462

Proton-Coupled Electron Transfer in Organic Synthesis

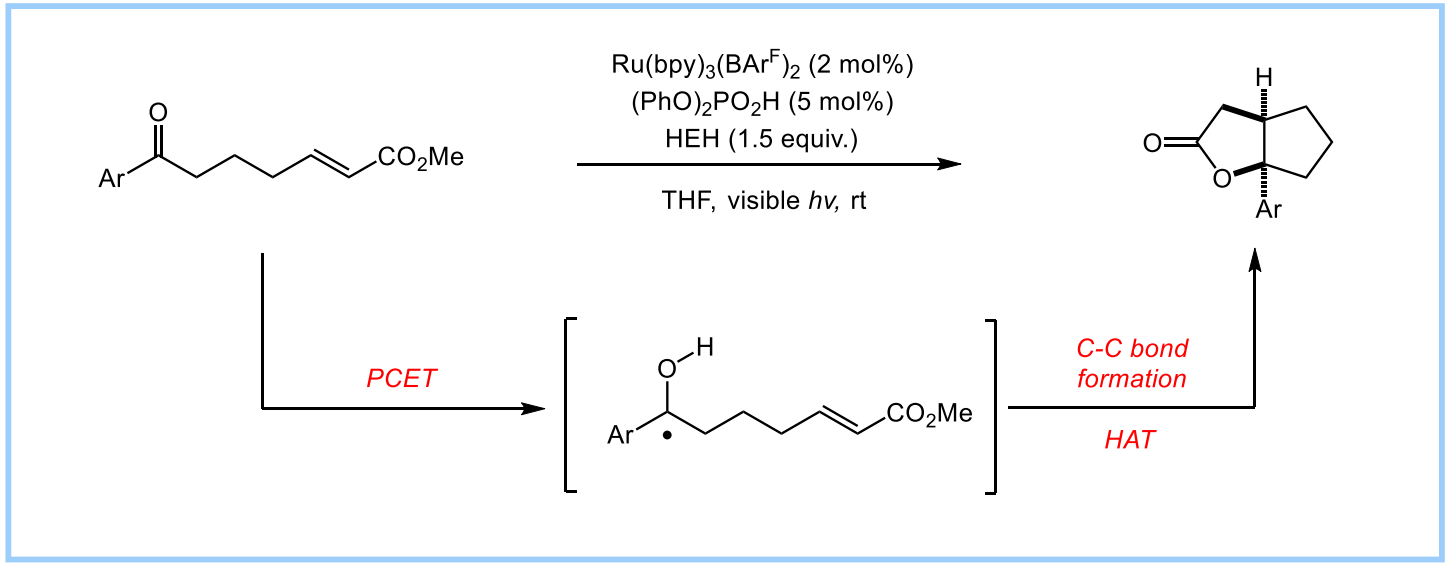
PCET promoted reduction of C=C bond



Prasanna, R.; Guha, S.; Sekar, G.* *Org. Lett*. **2019**, *21*, 2650-2653

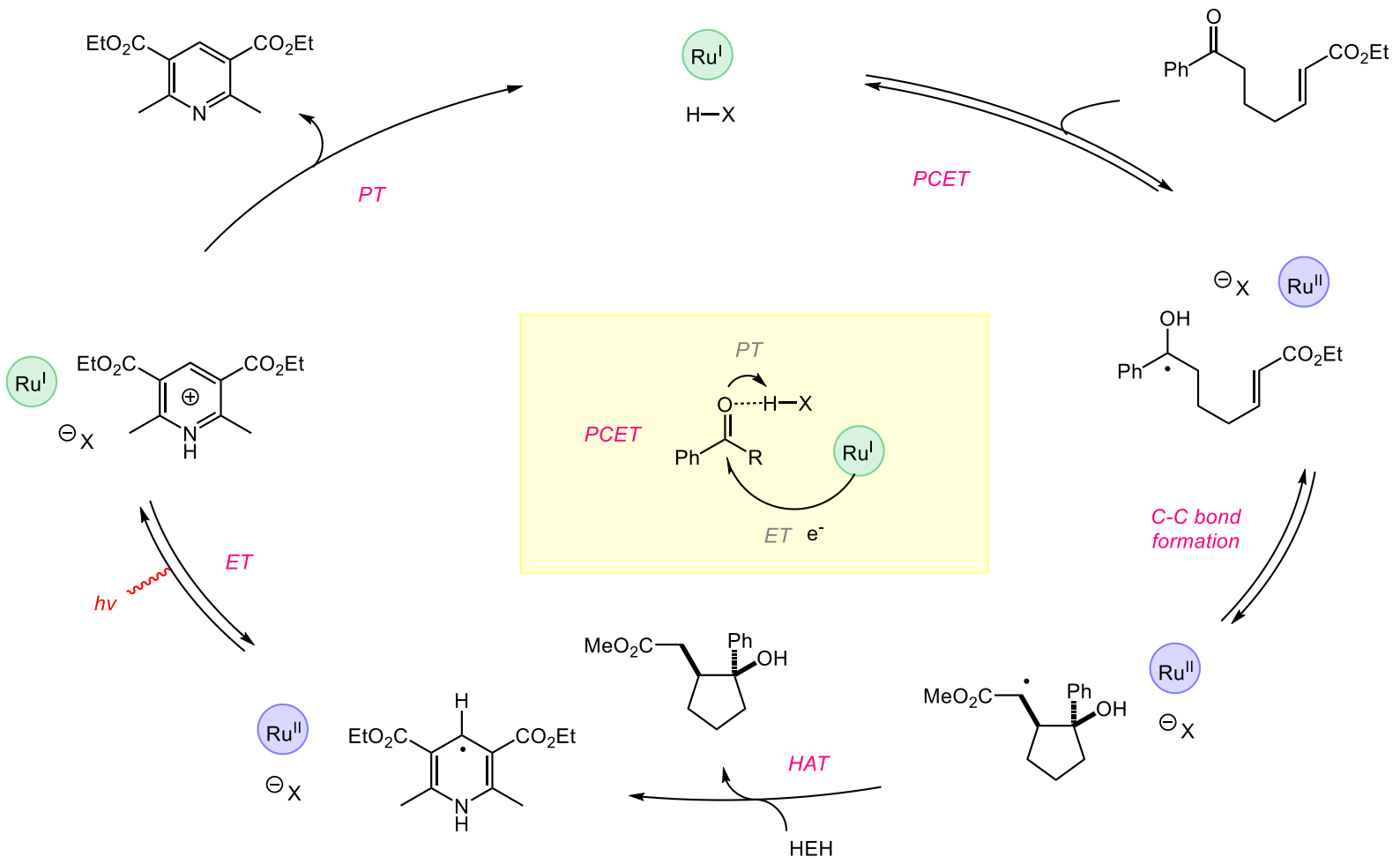
Proton-Coupled Electron Transfer in Organic Synthesis

PCET promoted reduction of C=O bond



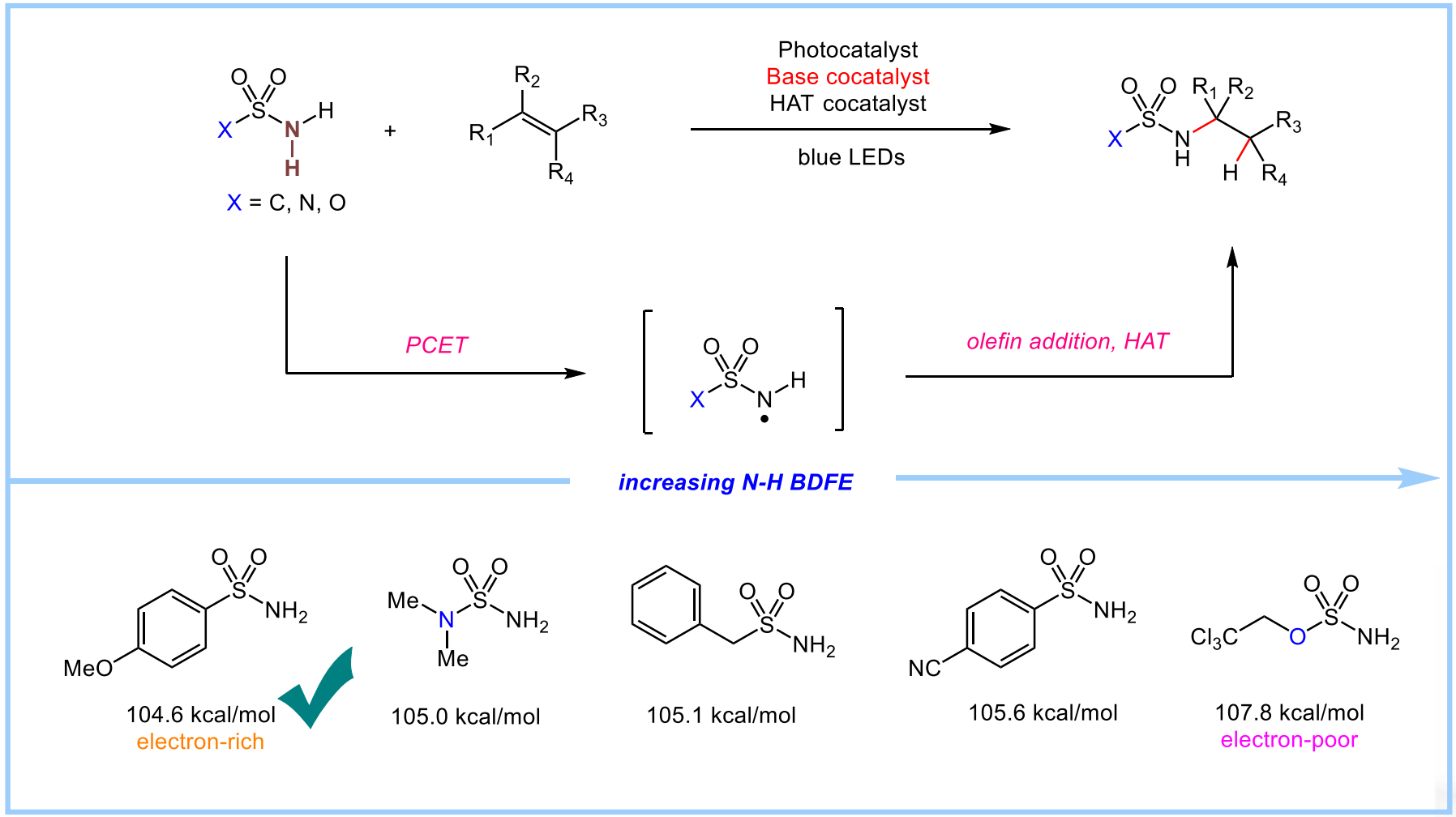
Tarantino, K. T.; Liu, P.; Knowles, R. R.* *J. Am. Chem. Soc.* **2013**, *135*, 10022-10025

Proton-Coupled Electron Transfer in Organic Synthesis



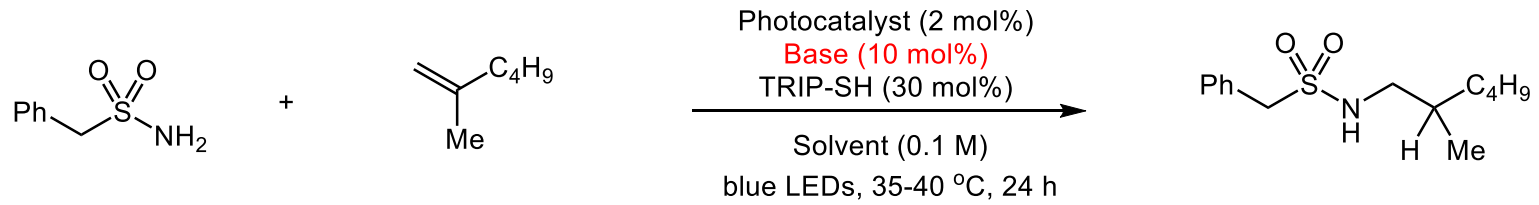
Choi, G. J.; Knowles, R. R.* *J. Am. Chem. Soc.* **2015**, *137*, 9226-9229

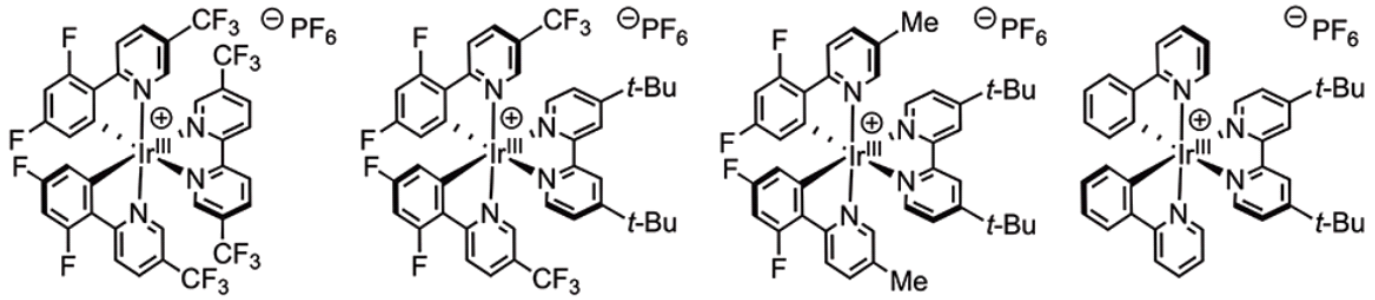
Project Synopsis



Zhu, Q.; Graff, D. E.; Knowles, R. R.* *J. Am. Chem. Soc.* **2018**, *140*, 741-747

Optimization of Reaction Conditions





[**Ir-A**]PF_6
$E_{1/2}(*Ir^{III}/Ir^{II})$= +1.30 V[b]

[**Ir-B**]PF_6
$E_{1/2}(*Ir^{III}/Ir^{II})$= +0.81 V[b]

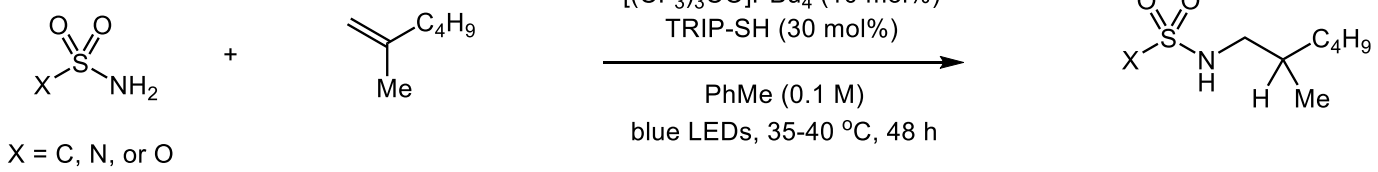
[**Ir-C**]PF_6
$E_{1/2}(*Ir^{III}/Ir^{II})$= +0.59 V[b]

[**Ir-D**]PF_6
$E_{1/2}(*Ir^{III}/Ir^{II})$= +0.28 V[b]

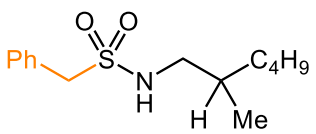
Optimization of Reaction Conditions

Entry	Base	Photocatalyst	Solvent	Yield (%)
1	$NBu_4[(BuO)_2OPO]$	[**Ir-A**]PF_6	PhMe	2
2	$NBu_4[(CF_3)_3CO]$	[**Ir-A**]PF_6	PhMe	85
3	$PBu_4[(CF_3)_3CO]$	[**Ir-A**]PF_6	PhMe	97
4	$PBu_4[BzO]$	[**Ir-A**]PF_6	PhMe	41
5	$PBu_4[BuO]$	[**Ir-A**]PF_6	PhMe	6
6	2,6-lutidine	[**Ir-A**]PF_6	PhMe	0
7	$PBu_4[(CF_3)_3CO]$	[**Ir-B**]PF_6	PhMe	92
8	$PBu_4[(CF_3)_3CO]$	[**Ir-C**]PF_6	PhMe	51
9	$PBu_4[(CF_3)_3CO]$	[**Ir-D**]PF_6	PhMe	2
10	$PBu_4[(CF_3)_3CO]$	[**Ir-A**]PF_6	$PhCF_3$	74
11	$PBu_4[(CF_3)_3CO]$	[**Ir-A**]PF_6	DCM	19
12	$PBu_4[(CF_3)_3CO]$	[**Ir-A**]PF_6	MeCN	10
13	$PBu_4[(CF_3)_3CO]$	[**Ir-A**]PF_6	THF	4

Substrate Scope



Alkyl sulfonamides



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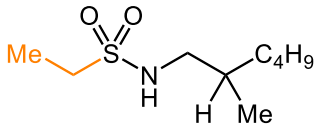

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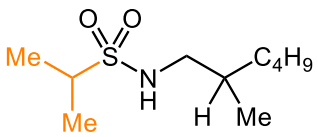

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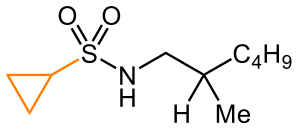

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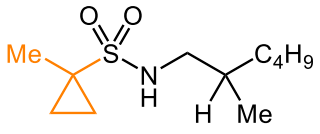

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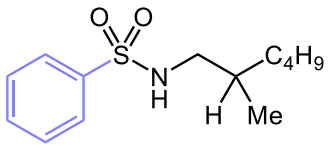
Aryl sulfonamides



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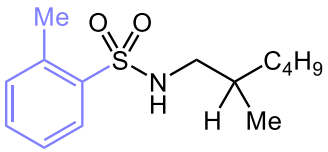

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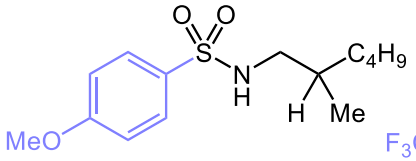

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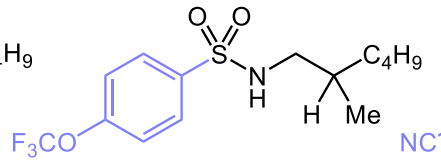

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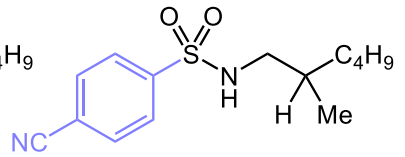

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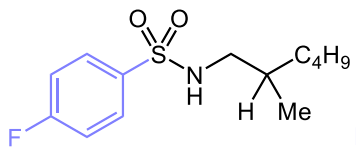
Substrate Scope



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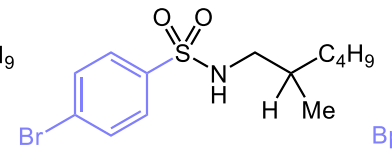

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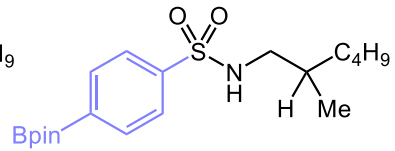

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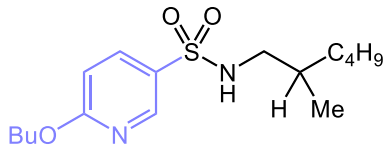

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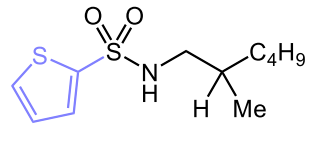

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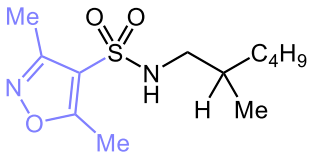

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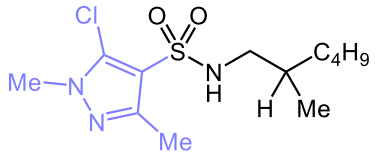

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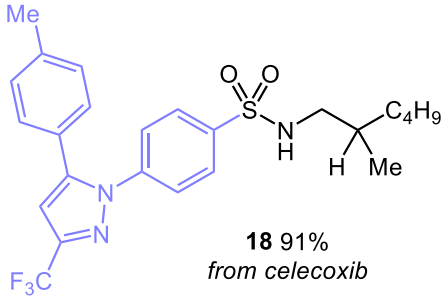
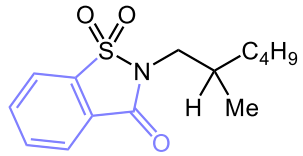
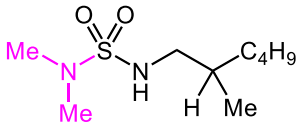


18 91%
from celecoxib



19 64%
from saccharin

Sulfamides



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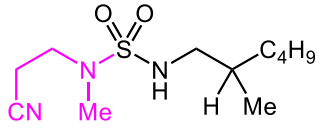

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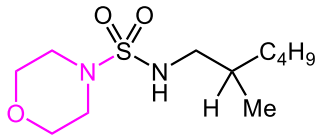

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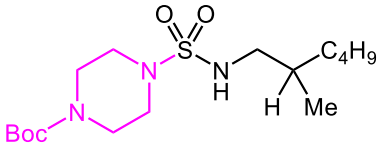

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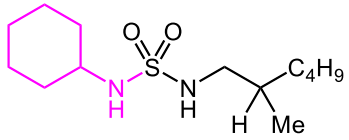
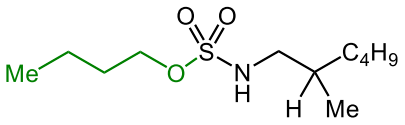


24 72%

Sulfamates



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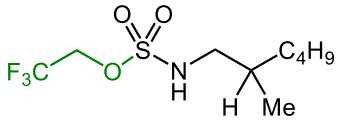

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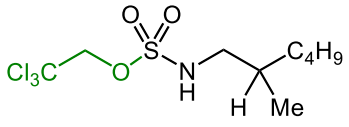

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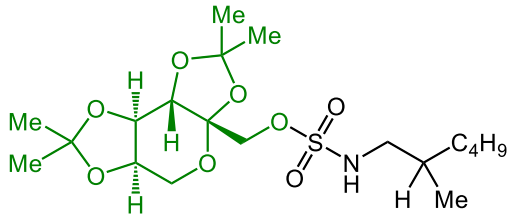
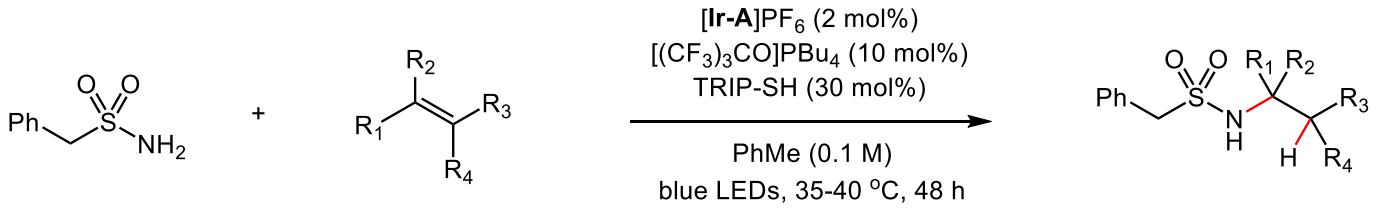
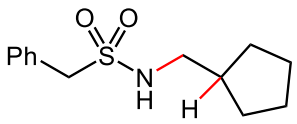


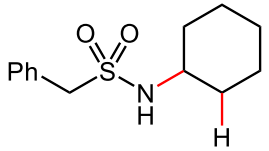
28 99% (1:1 dr)
from topiramate

Substrate Scope





29 82%



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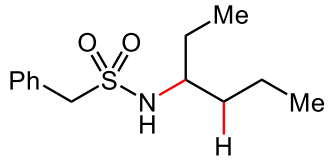
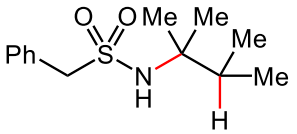
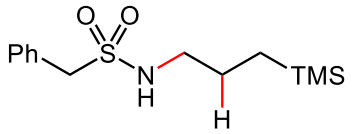


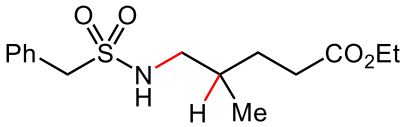
31 *from trans-3-hexene 72%*
from cis-3-hexene 73%



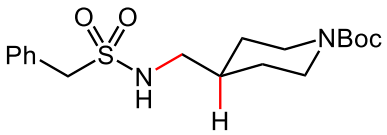
32 94%



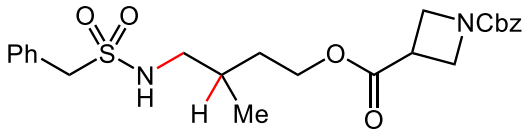
33 82%



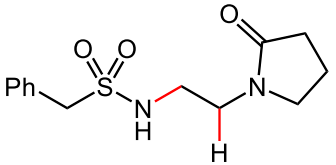
34 90%



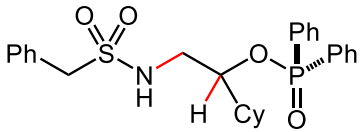
33 72%



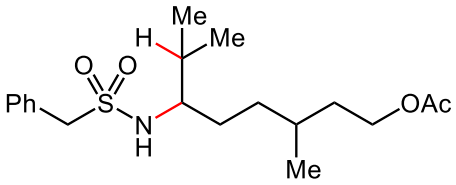
34 65%



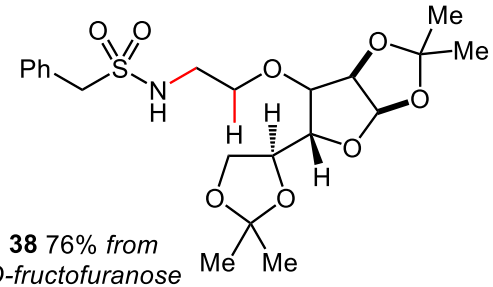
35 64%



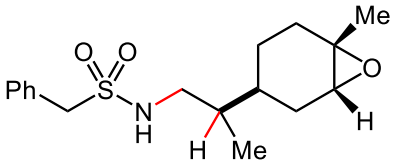
36 60%



37 90% (1:1 dr)
from citronellol

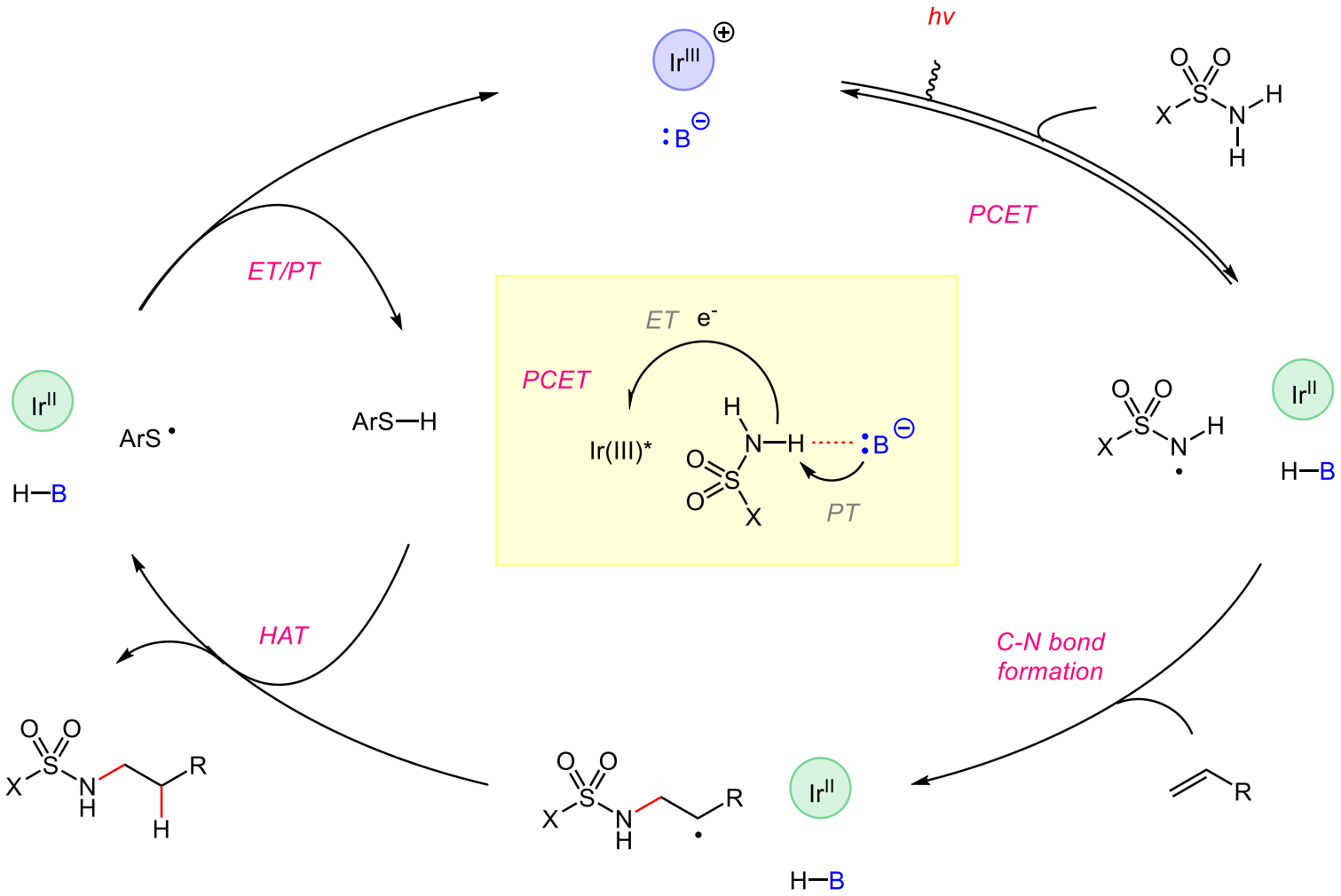


38 76% *from*
D-fructofuranose

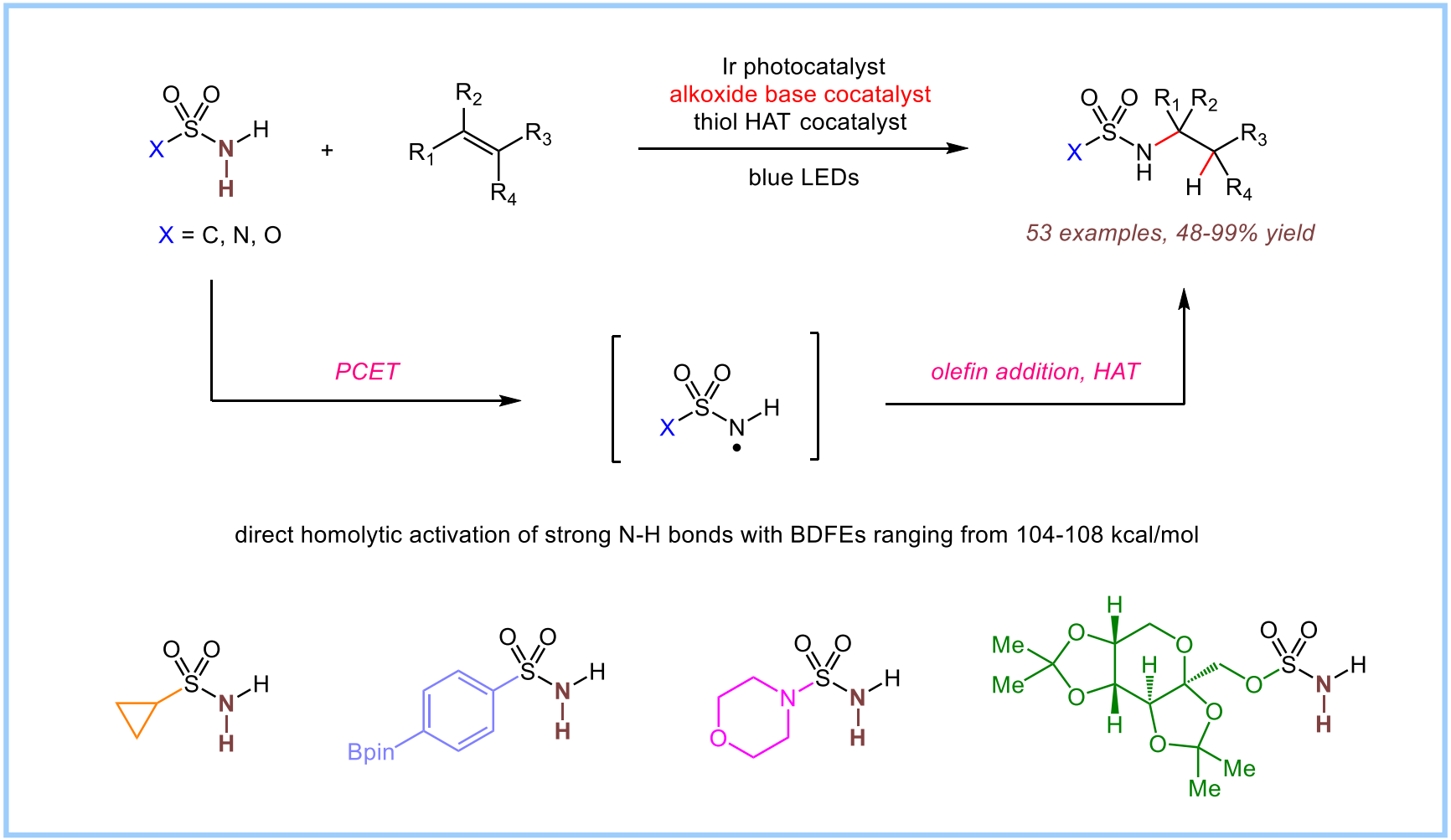


39 70% (1:1 dr)
from cis-(-)-limonene oxide

Proposed Mechanism



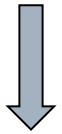
Summary


Ir photocatalyst
alkoxide base cocatalyst
thiol HAT cocatalyst
blue LEDs
X = C, N, O
53 examples, 48-99% yield
PCET
olefin addition, HAT
direct homolytic activation of strong N-H bonds with BDFEs ranging from 104-108 kcal/mol
Bpin

Writing strategy

首段写作思路

磺胺类化合物在药物中的应用



以往合成磺胺类化合物合成策略

Writing strategy

末段写作思路

实现多种类型磺胺与烯烃的反马氏氢胺化

↓

成功关键在于碱的选择

↓

PCET在烯烃官能团化中具有较大潜力

Representative examples

- We previously leveraged this strategy to generate sulfonamidyl radicals under the joint action of [Ir(dF(CF_3)ppy)2(5,5′-d(CF_3)bpy)]PF_6 ([Ir-A]PF_6) photocatalyst and tetrabutylammonium dibutyl phosphate base cocatalyst for the….(联合作用)

- While notable, all three protocols are restricted in scope with respect to either the alkene or sulfonamide component. (受限制的)

- Additional mechanistic work aimed at elucidating the precise nature of the electron and proton transfer steps involved in N-radical formation will require further investigation. (精确的机制)

Acknowledgment

Thanks
for your attention !