Catalytic alkylation of remote C–H bonds enabled by proton-coupled electron transfer

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Checker: Shubo Hu

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Nature **2016**, *539*, 268

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- Amide-directed photoredox-catalysed C-C bond formation at unactivated sp^3 C-H bonds
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Introduction

Brief introduction of Robert R. Knowles

- B.S. in Chemistry, College of William and Mary, 2003;
- Ph.D. with David MacMillan, Caltech, 2008;
- NIH Postdoctoral Fellow with Eric Jacobsen, Harvard University, 2008–2011;
- Assistant Professor of Chemistry, Department of Chemistry, Princeton University, 2011-present.

Robert R. Knowles

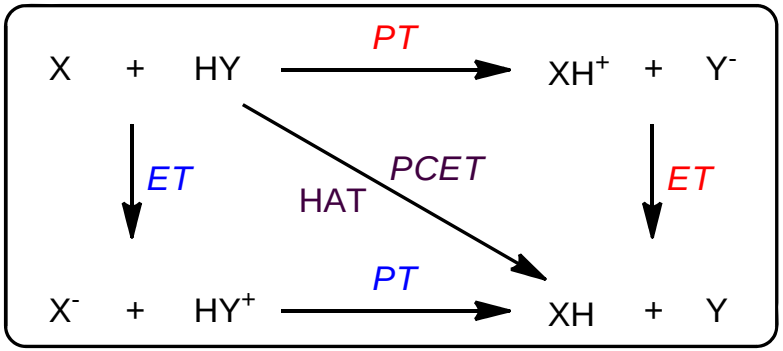
Research

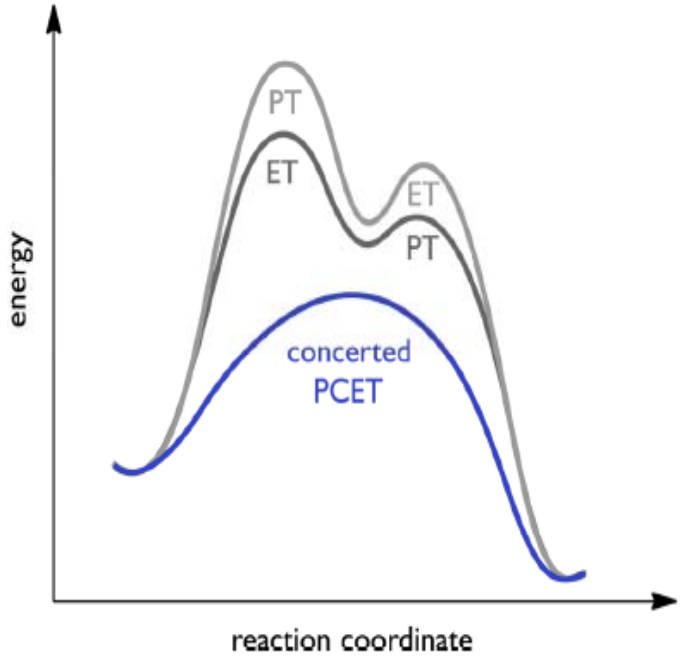
Synthetic organic chemistry; Asymmetric catalysis

Proton-coupled electron transfer (PCET) reaction

Introduction

Proton-coupled electron transfer (PCET)

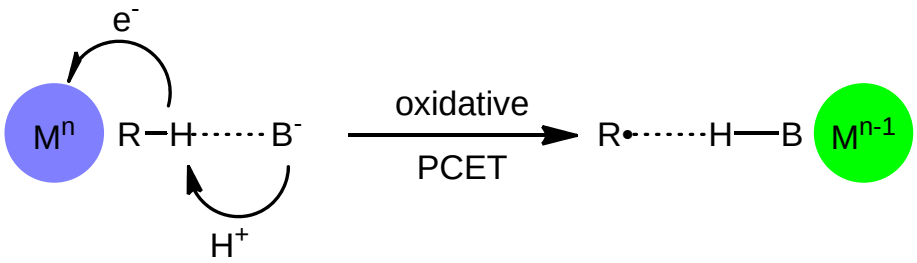




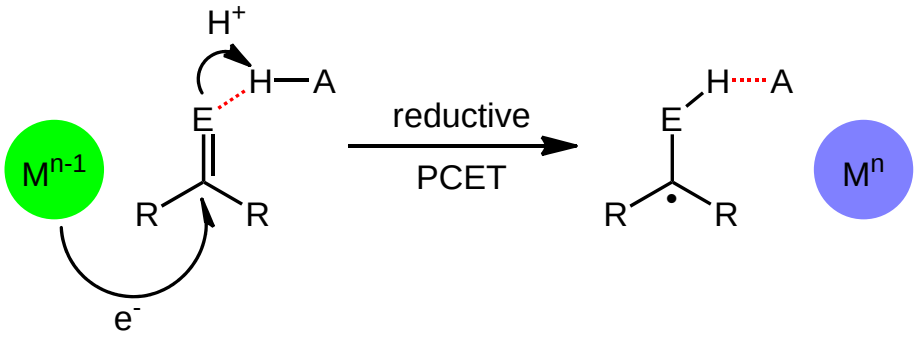
Redox events in which an electron and proton are exchanged in a concerted elementary step are commonly referred to as proton-coupled electron transfers (PCETs). PCETs are known to operate in numerous important biological redox processes, as well as recent inorganic technologies for small molecule activation.

Introduction

Proton-coupled electron transfer (PCET)



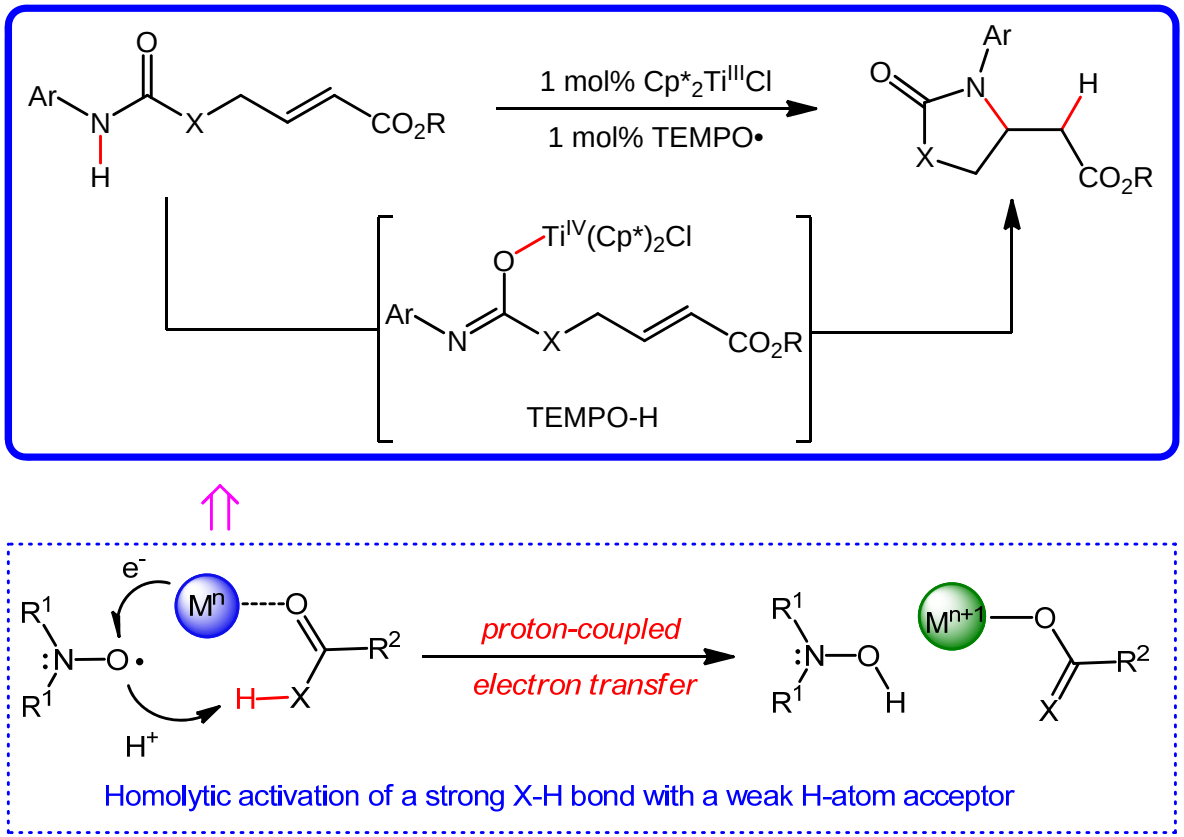
- New strategy for challenging homolytic bond activation
- Unique opportunity for selective radical catalysis



Knowles, R. R. *et al. Acc. Chem. Res.* **2016**, *49*, 1546.

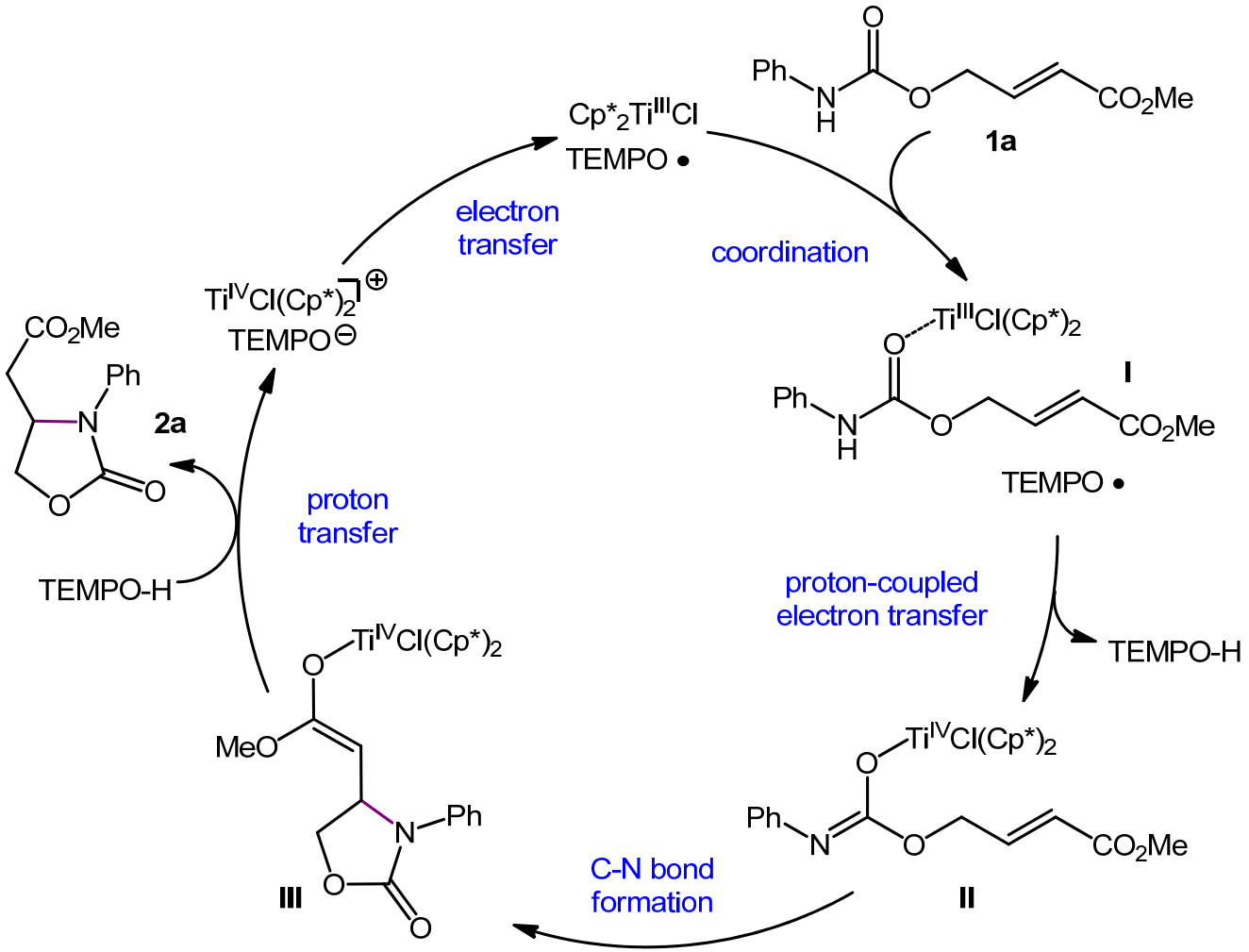
Introduction

Conjugate amination enabled by homolytic bond-weakening



Knowles, R. R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6440.

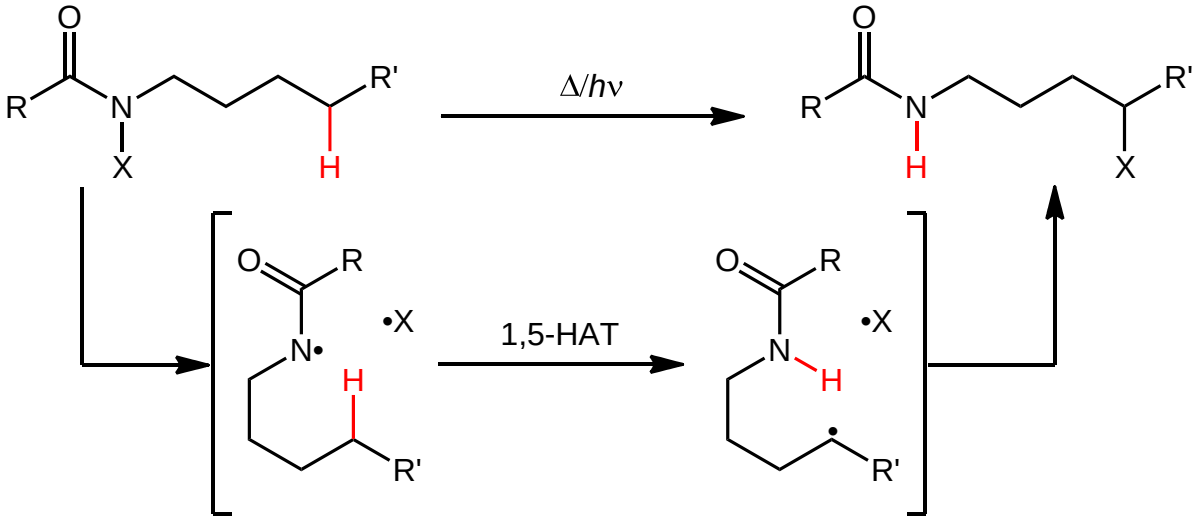
Introduction



Knowles, R. R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6440.

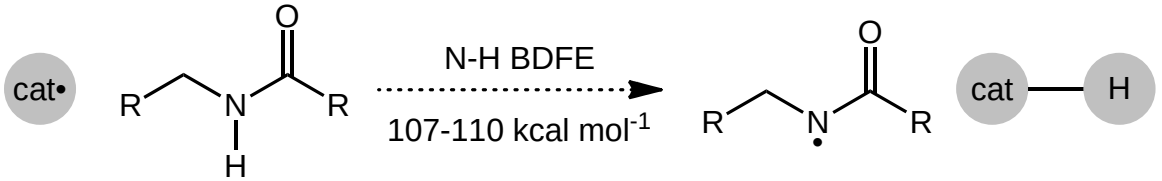
Remote sp^3 C-H bonds activation by PCET

Classical Hofmann-Löffler-Freytag reactions



- *N*-functionalization required
- No methods for the C-C bond formation

Challenges in catalytic homolysis of strong N-H bonds

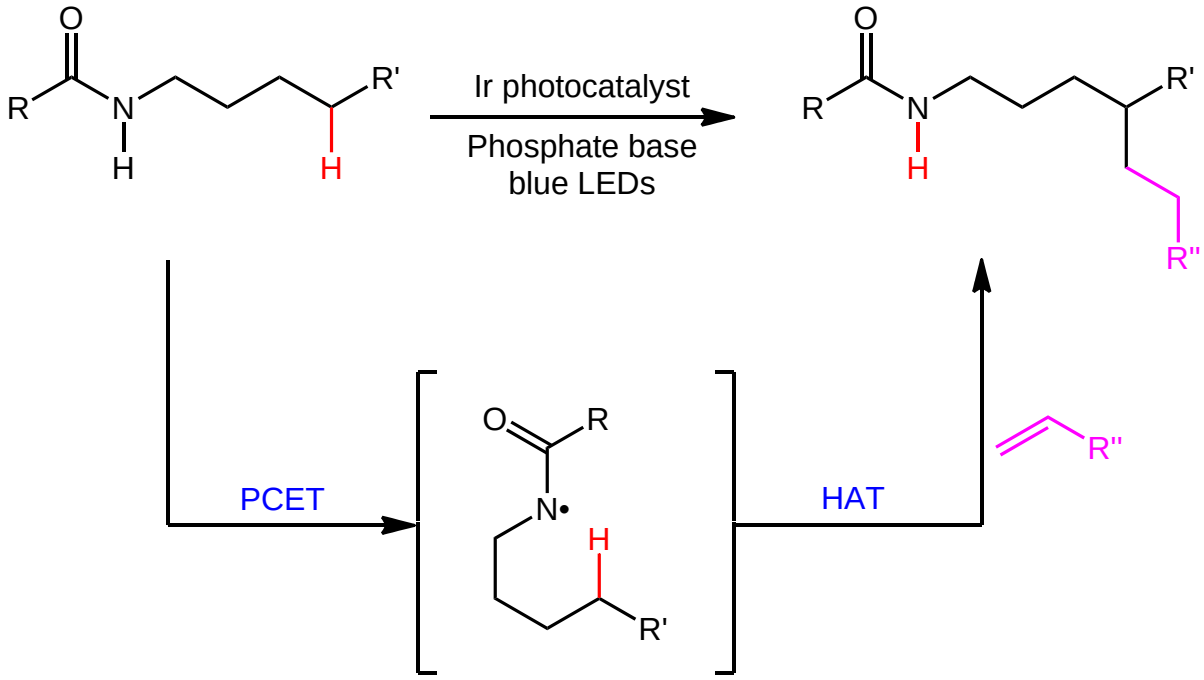


- No known catalysts for selective homolysis of strong *N*-alkyl amide N-H bonds

Knowles, R. R. *et al. Nature* **2016**, *539*, 268.

Remote sp^3 C-H bonds activation by PCET

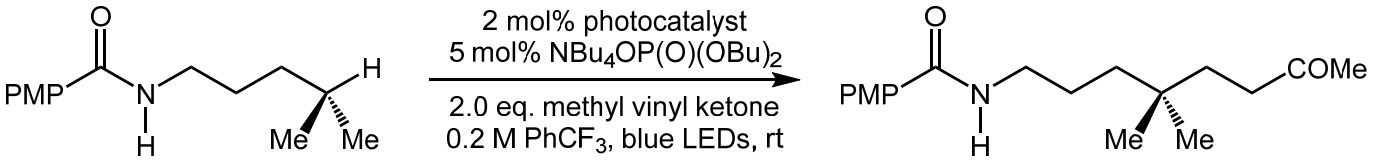
Catalytic C-H alkylation enabled by PCET



- Excited-state iridium oxidant and a weak phosphate base cooperatively serve to remove both a proton and an electron from an amide substrate.
- Undergo a catalytic variant of the classical Hofmann–Löffler–Freytag reaction.

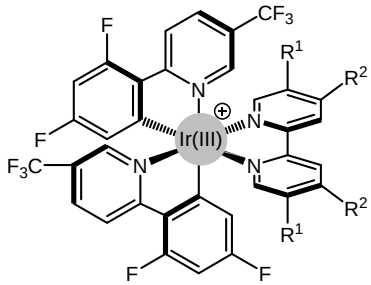
Knowles, R. R. *et al. Nature* **2016**, *539*, 268.

Optimization studies



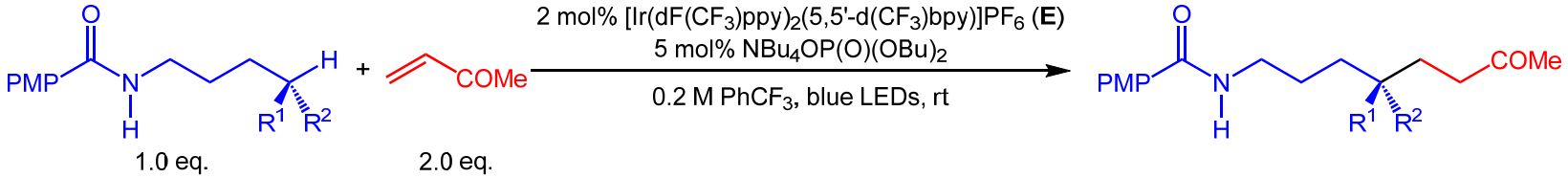
Entry	Photocatalyst	Yield (%)
1	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (**A**)	28
2	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**B**)	10
3	$[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dFbpy)]PF_6$ (**C**)	25
4	$[Ir(dF(CF_3)ppy)_2(4,4'\text{-}dCF_3bpy)]PF_6$ (**D**)	78
5	$[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)]PF_6$ (**E**)	82

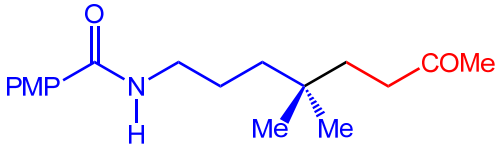
Entry	Change from entry 5	Yield (%)
6	No light	0
7	No photocatalyst	0
8	No $NBu_4OP(O)(OBu)_2$	0
9	0.5 mol % photocatalyst	26
10	1.0 eq. of methyl vinyl ketone	69
11	20 mol% phosphate	58
12	0.4 M $PhCF_3$	76



A R^1 = H, R^2 = H
B R^1 = H, R^2 = *t*-Bu
C R^1 = F, R^2 = H
D R^1 = H, R^2 = CF_3
E R^1 = CF_3, R^2 = H

Substrate scope

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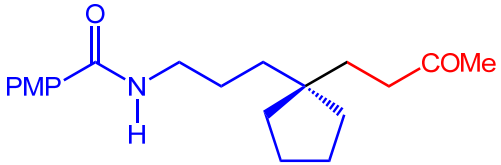
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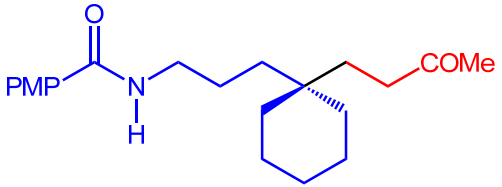
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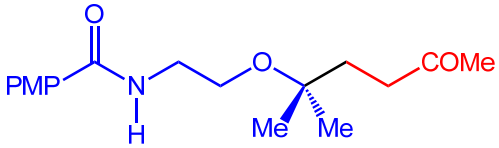
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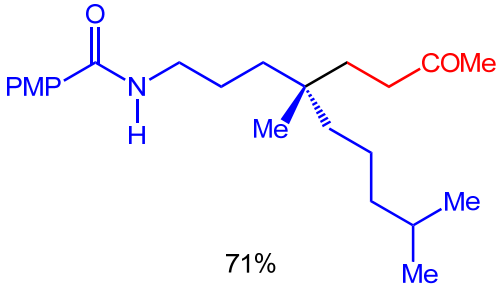
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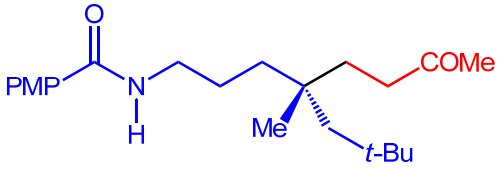
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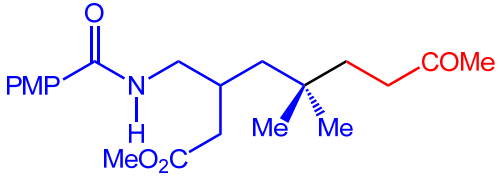
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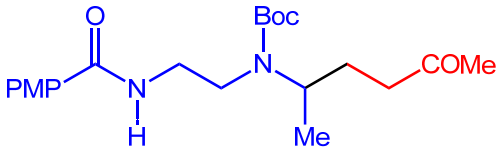
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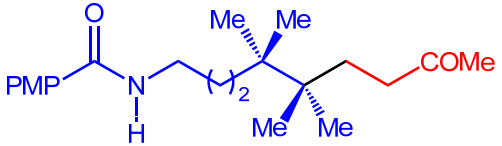
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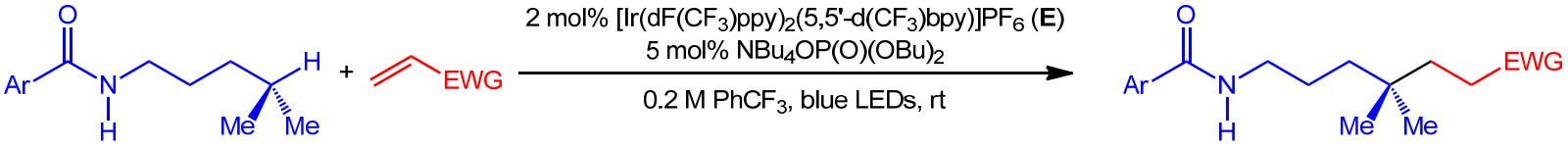
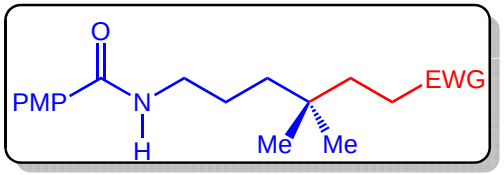
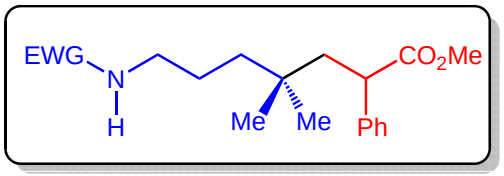
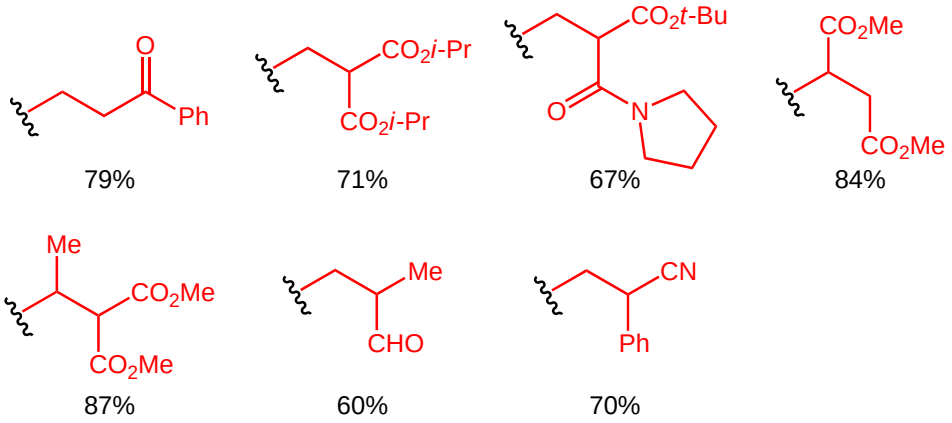
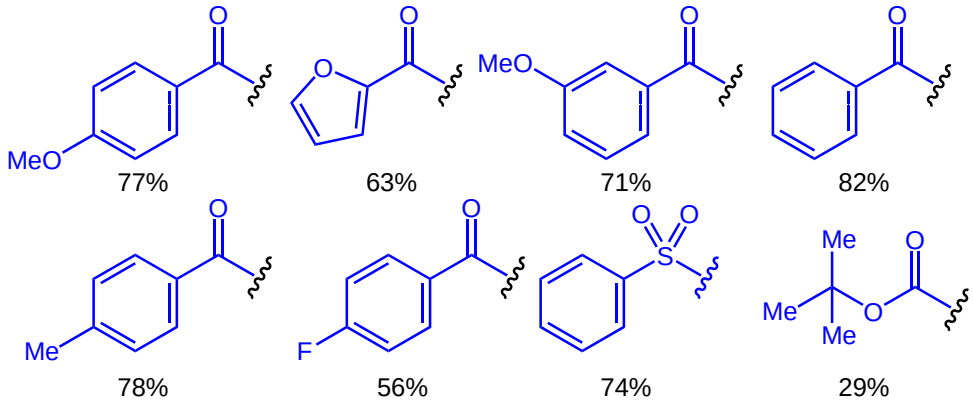
Substrate scope





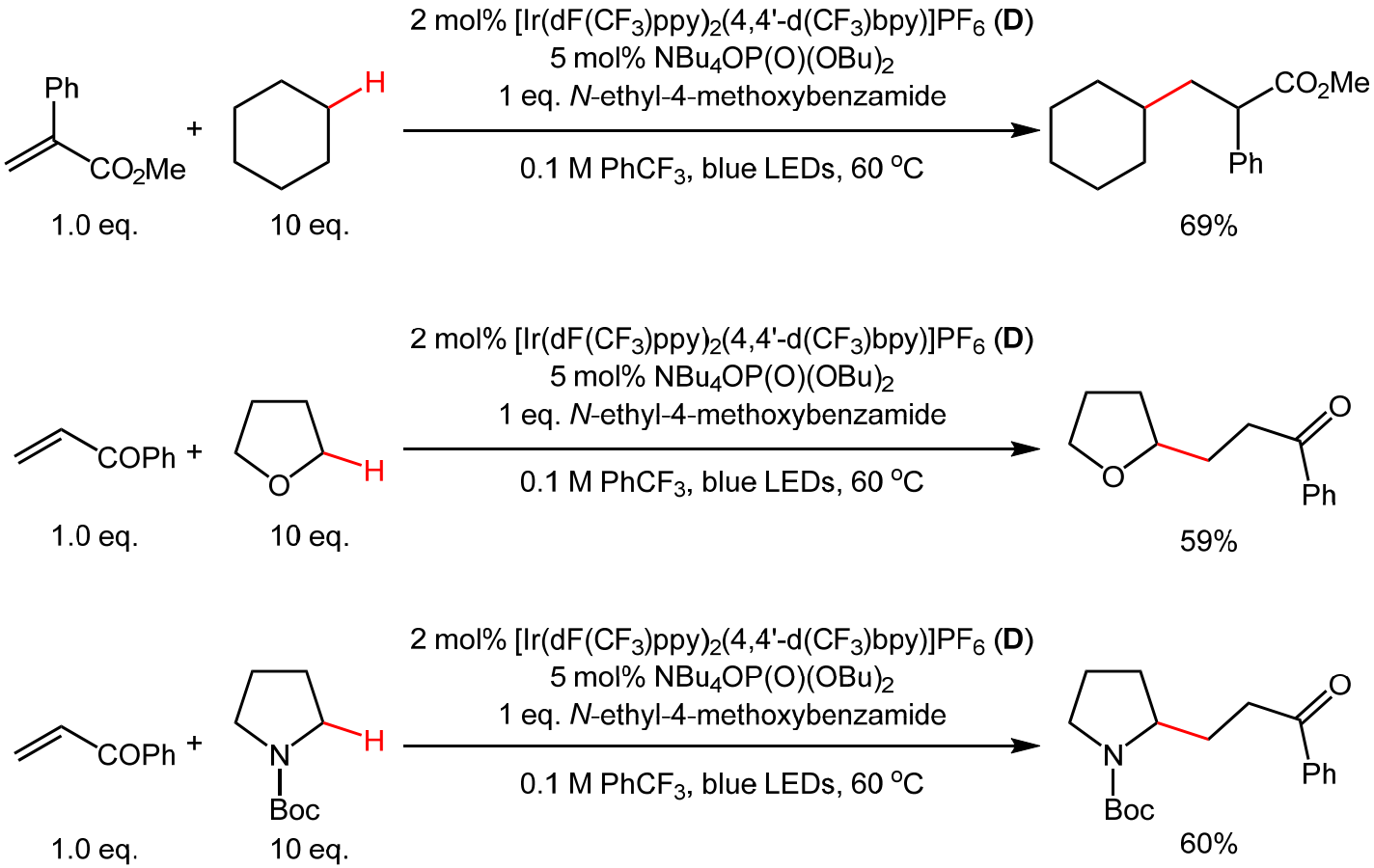




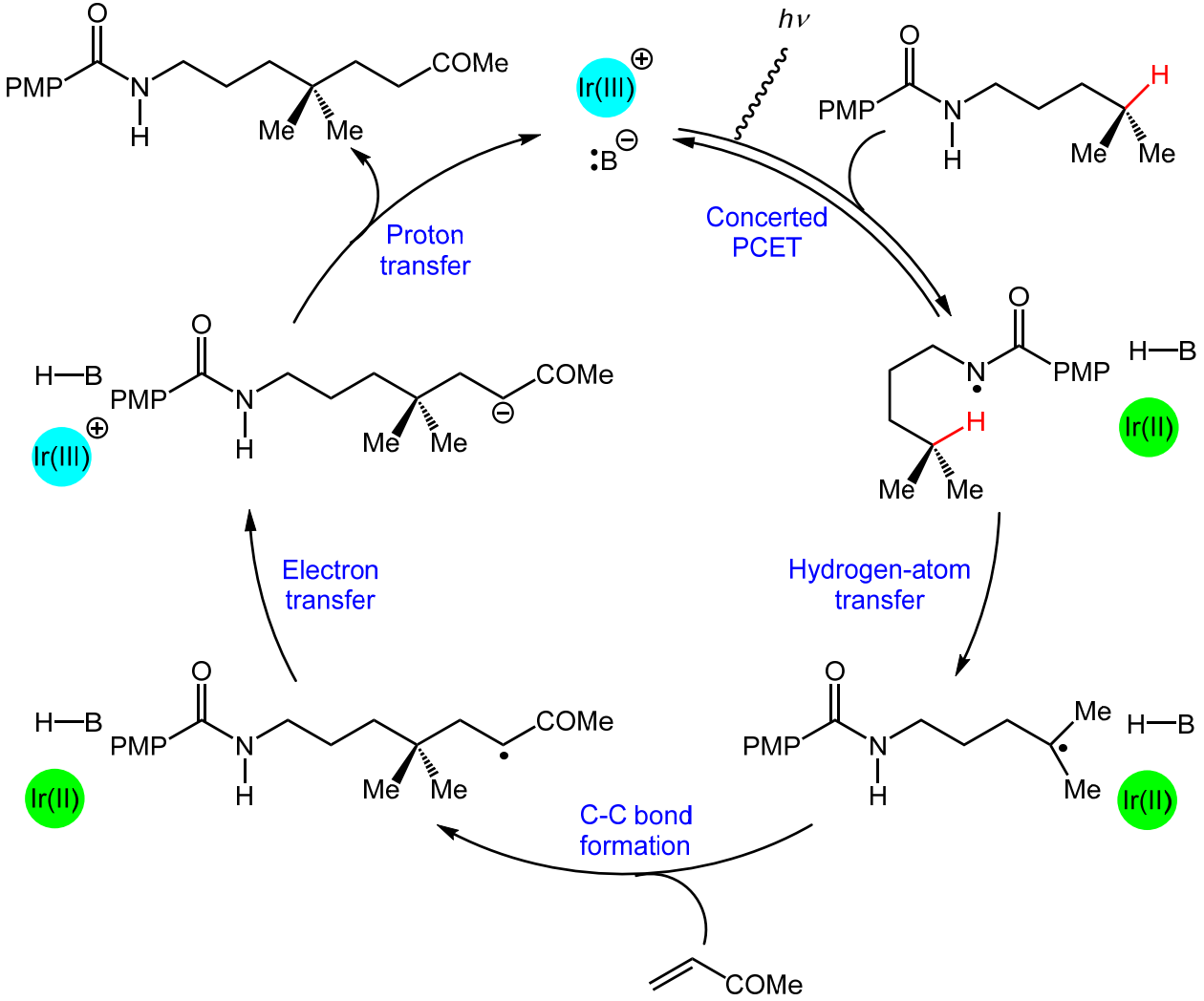


Substrate scope

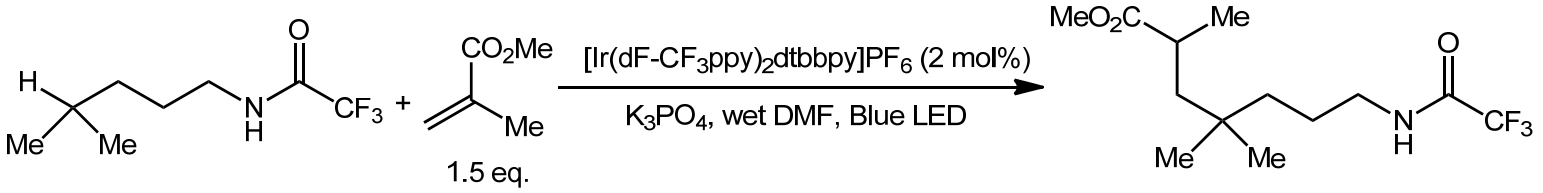
Intermolecular C-H alkylations



Proposed catalytic cycle



Remote sp^3 C-H bonds activation by Rovis



Solvent Effects

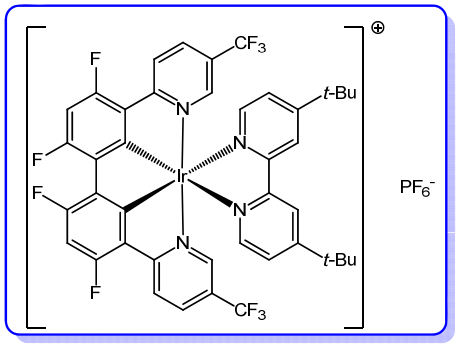
DMF: 40%
$CHCl_3$: 56%
DCE: 54%
Dioxane, THF, DME: messy
DMSO: 40%
DMA: 45%
Acetone: 48%
t-Amyl Alchol: 35%
HFIP: 0%
t-Amyl Alchol/$PhCF_3$: 70%
MeCN: 65%, 55% with $[Ir(ppy)_2(dtbpy)]PF_6$
PhMe, PhH, PhCl: 0%
$PhCF_3$: 71%

Base

K_2CO_3: 0%
K_2HPO_4: 0%
KOAc: 0%
Cs_2CO_3: 54%
Na_3PO_4: 65%
K_3PO_4: 71%
NaOH: 0%

Concentration

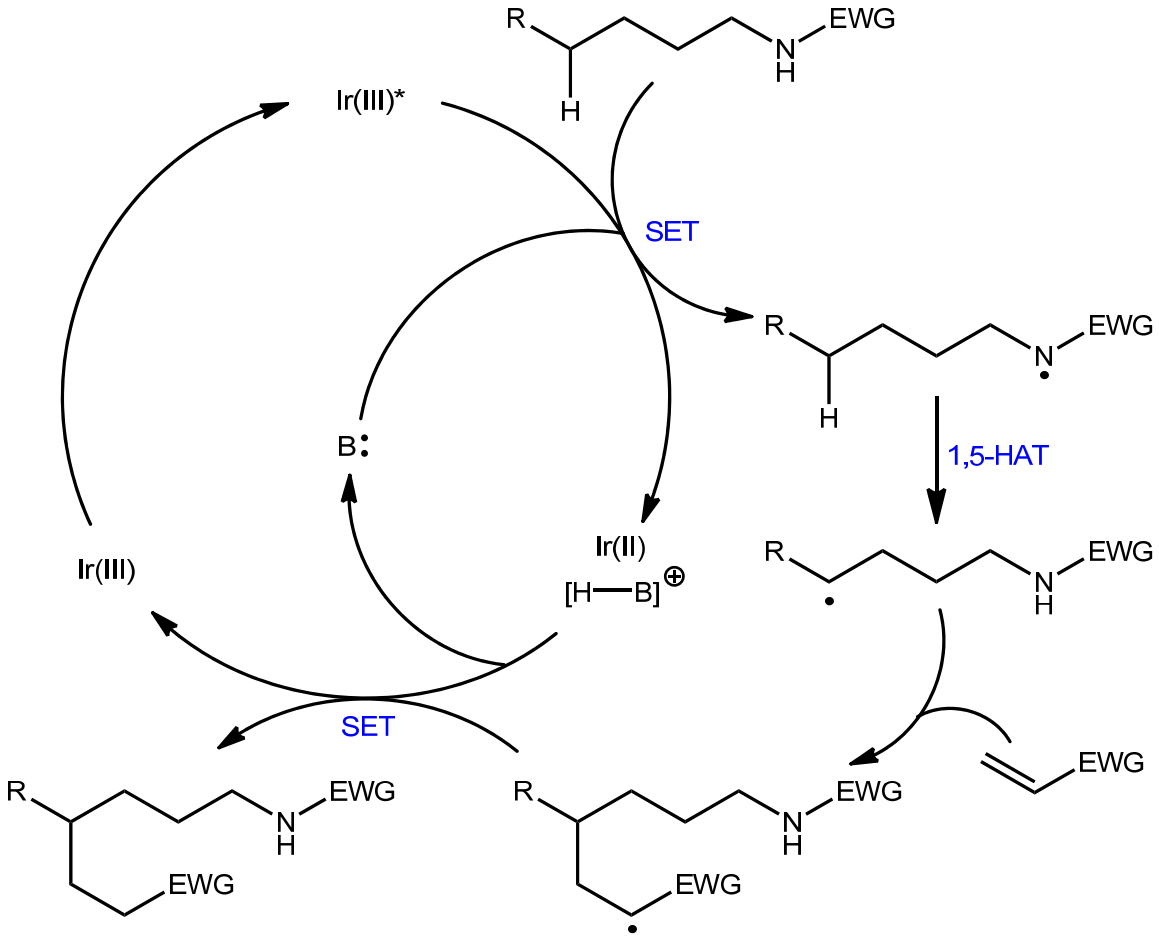
0.4 M: >90% (75%)
0.2 M: >90% (71%)
0.13 M: 78%
0.10 M: 71%
0.05 M: 22%
0.03 M: 0%



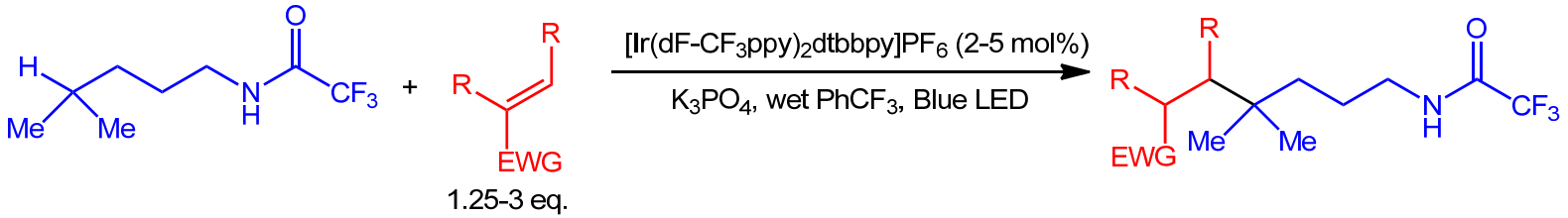
No product was observed with other photocatalysts!

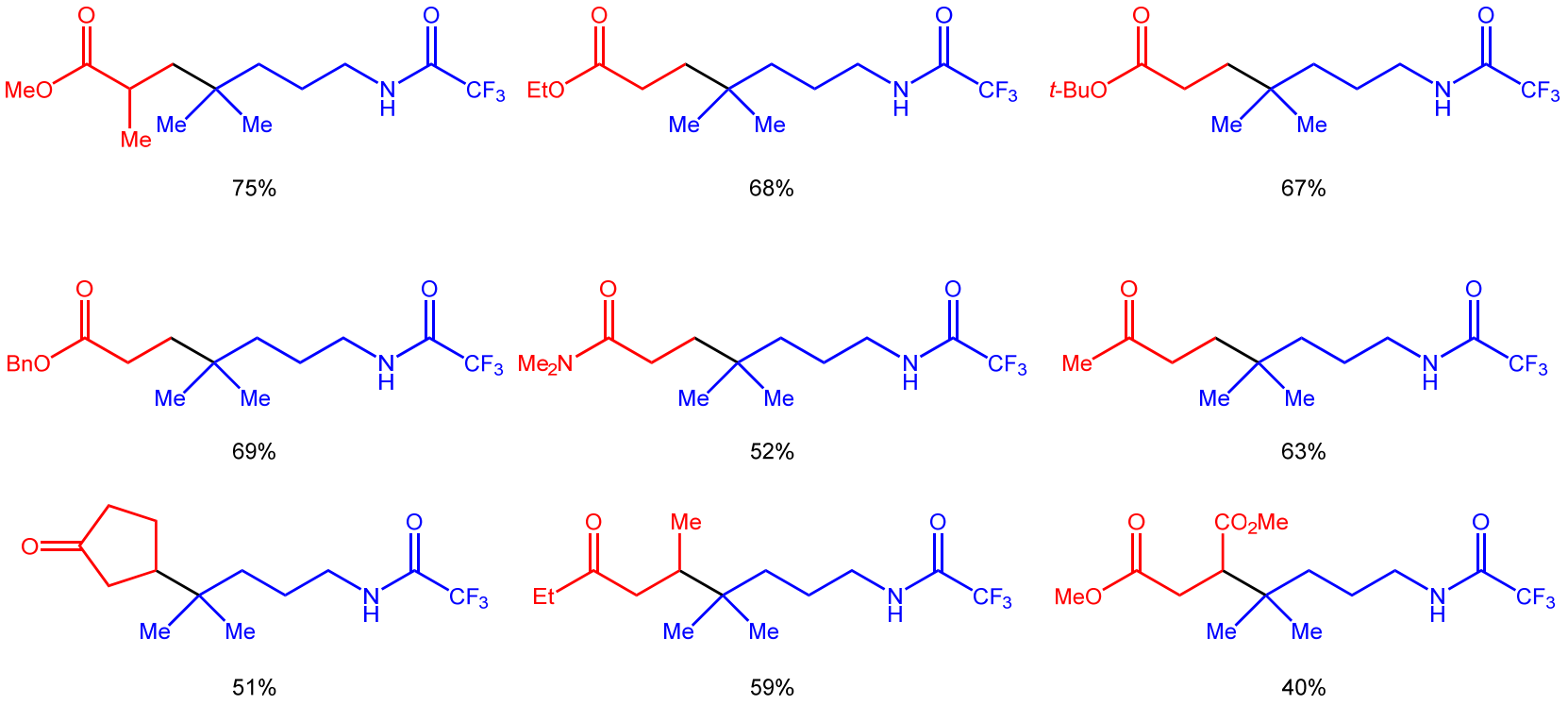
Rovis, T. *et al. Nature* **2016**, *539*, 272.

Proposed photocatalytic cycle

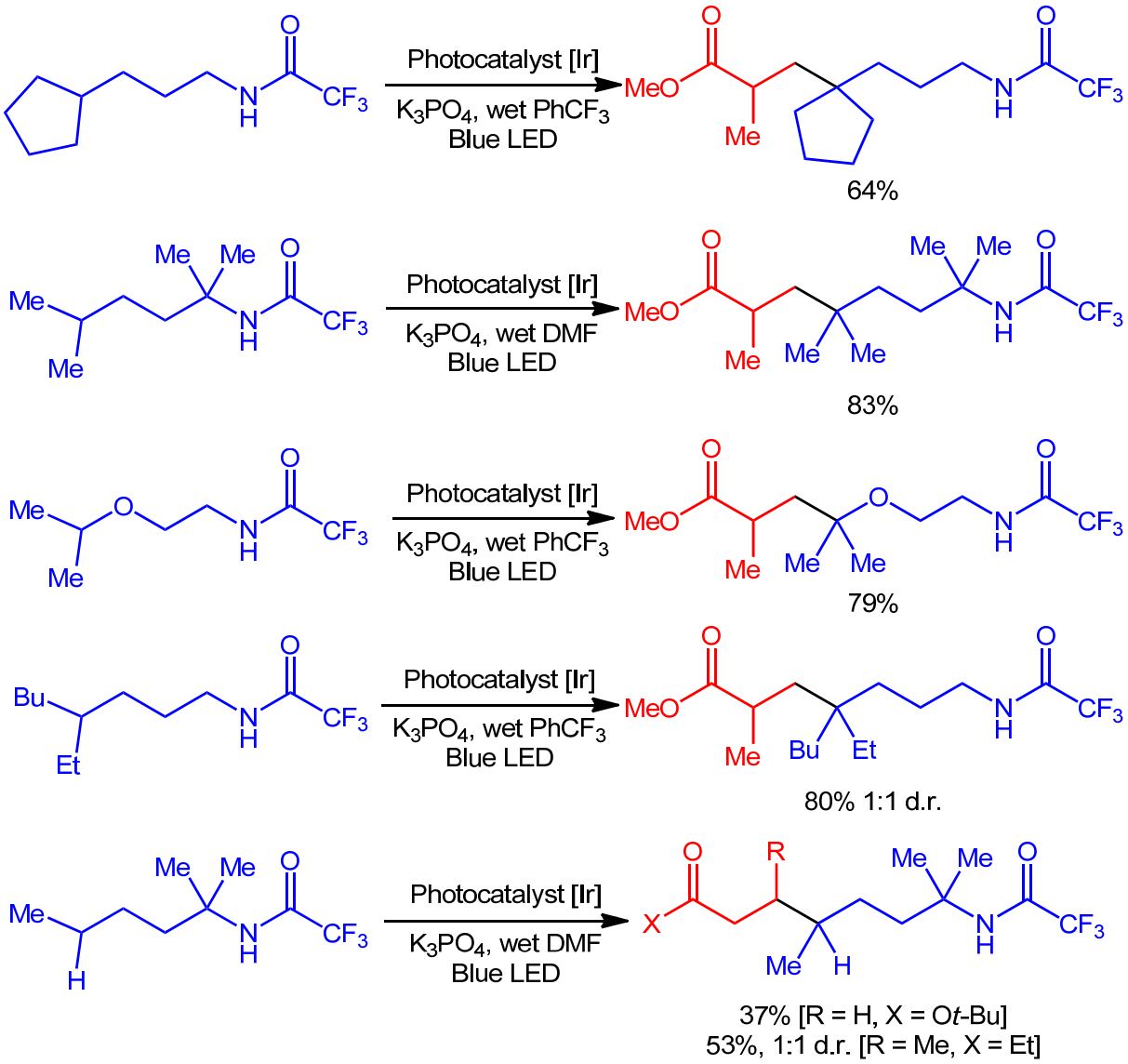


Substrate scope

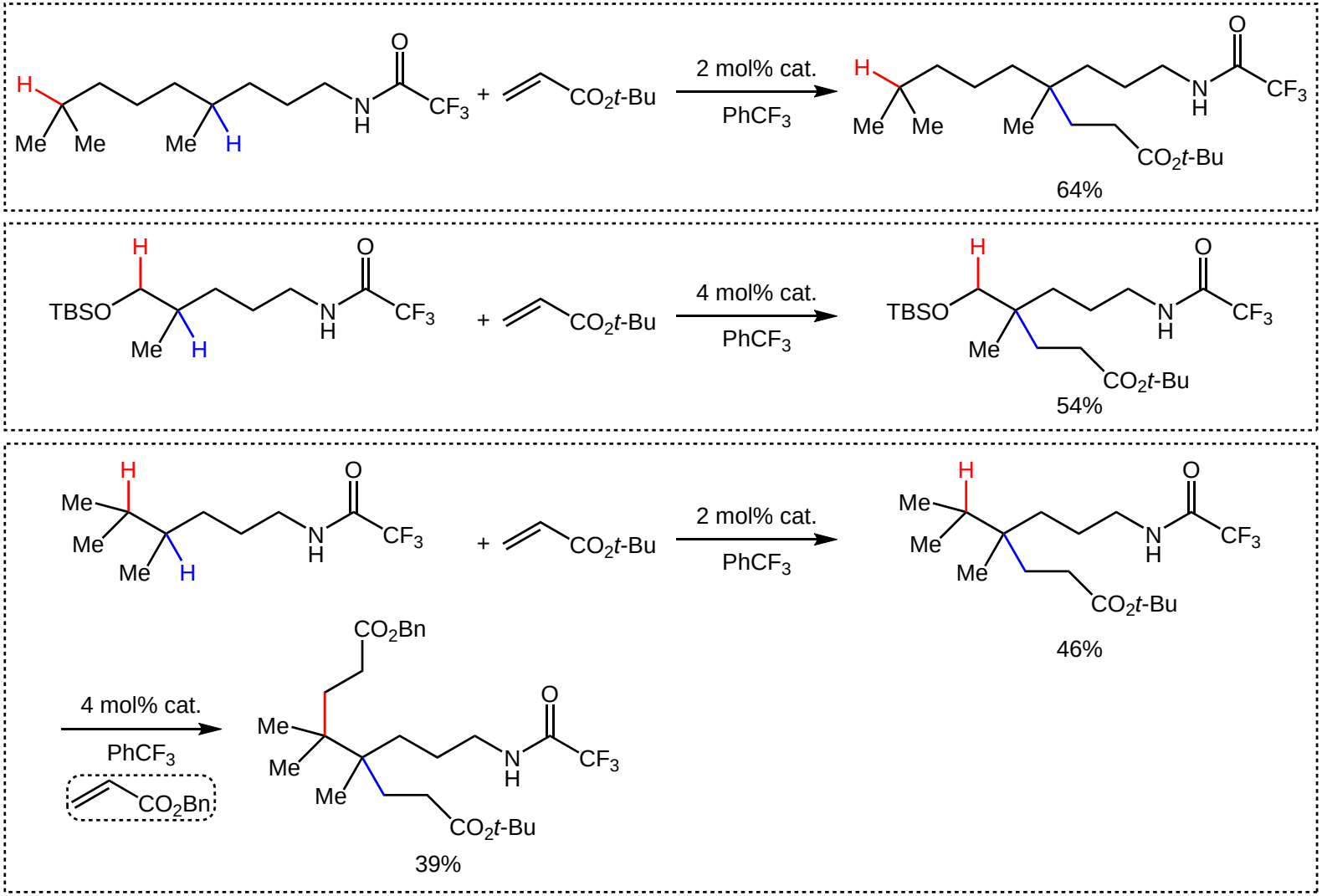




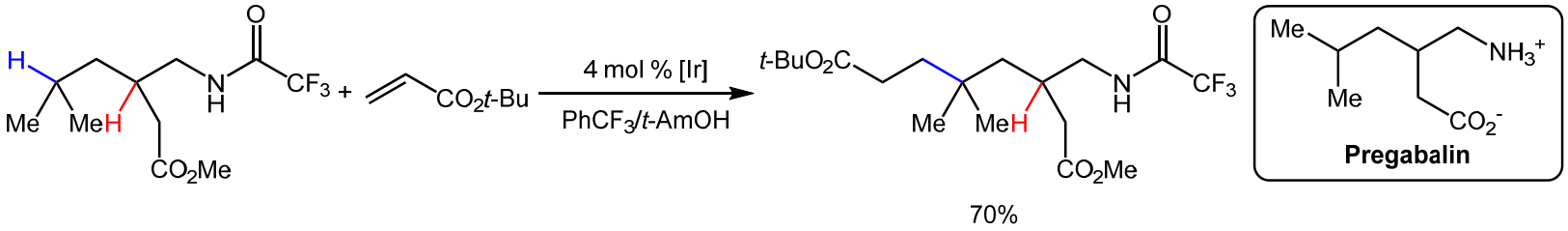
Substrate scope

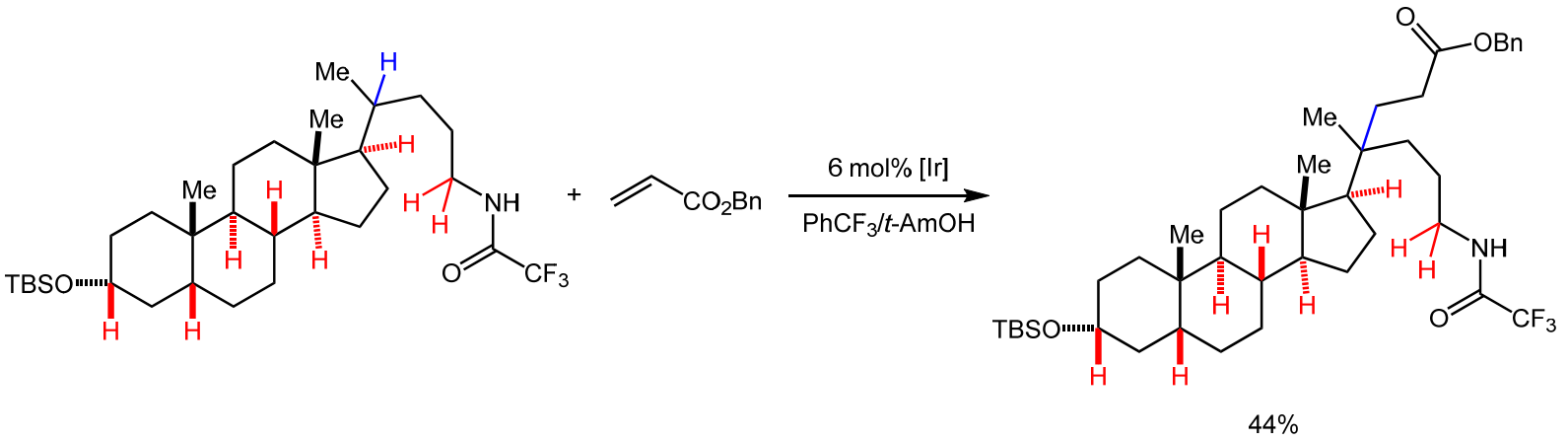


Regioselective functionalization

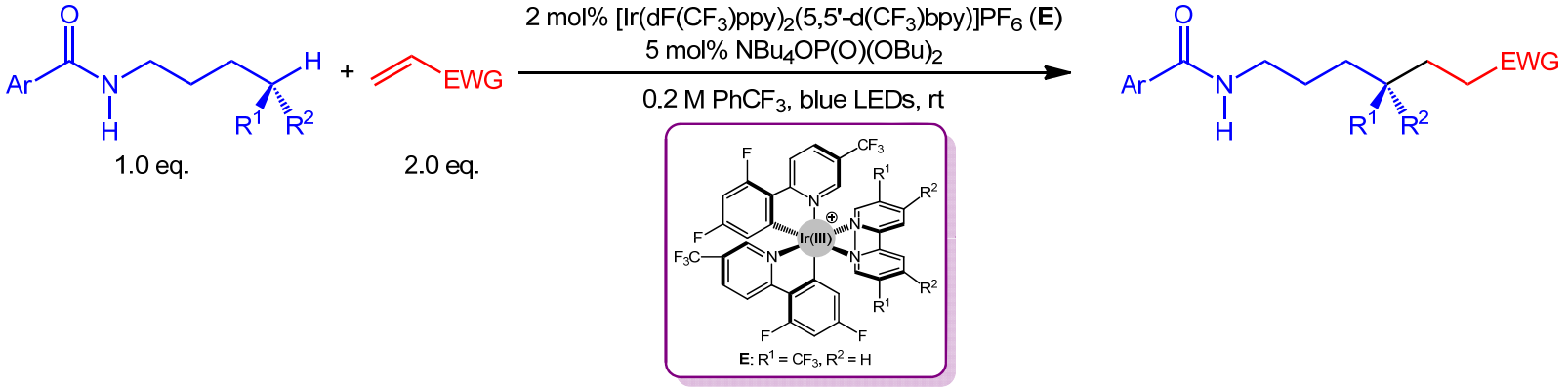


Regioselective functionalization

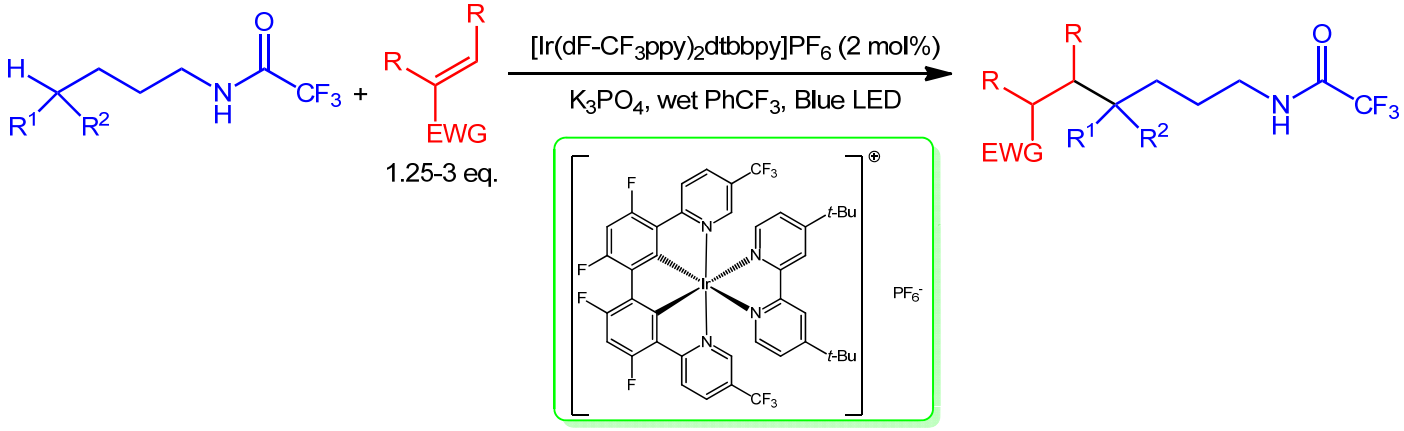




Summary



Knowles, R. R. *et al. Nature* **2016**, *539*, 268.



Rovis, T. *et al. Nature* **2016**, *539*, 272.

The first paragraph

Despite advances in hydrogen atom transfer (HAT) catalysis, there are currently no molecular HAT catalysts that are capable of homolysing the strong nitrogen–hydrogen (N–H) bonds of *N*-alkyl amides. The motivation to develop amide homolysis protocols stems from the utility of the resultant amidyl radicals, which are involved in various synthetically useful transformations, including olefin amination and directed carbon–hydrogen (C–H) bond functionalization. In the latter process—a subset of the classical Hofmann–Löffler–Freytag reaction—amidyl radicals remove hydrogen atoms from unactivated aliphatic C–H bonds. Although powerful, these transformations typically require oxidative *N*-prefunctionalization of the amide starting materials to achieve efficient amidyl generation. Moreover, because these *N*-activating groups are often incorporated into the final products, these methods are generally not amenable to the direct construction of carbon–carbon (C–C) bonds.

The first paragraph

Here we report an approach that overcomes these limitations by homolysing the N–H bonds of *N*-alkyl amides *via* proton-coupled electron transfer. In this protocol, an excited-state iridium photocatalyst and a weak phosphate base cooperatively serve to remove both a proton and an electron from an amide substrate in a concerted elementary step. The resultant amidyl radical intermediates are shown to promote subsequent C–H abstraction and radical alkylation steps. This C–H alkylation represents a catalytic variant of the Hofmann–Löffler–Freytag reaction, using simple, unfunctionalized amides to direct the formation of new C–C bonds. Given the prevalence of amides in pharmaceuticals and natural products, we anticipate that this method will simplify the synthesis and structural elaboration of amine-containing targets. Moreover, this study demonstrates that concerted proton-coupled electron transfer can enable homolytic activation of common organic functional groups that are energetically inaccessible using traditional HAT-based approaches.