THE YANG RESEARCH GROUP

KNOWLES GROUP

Synthetic Organic Chemistry and Catalysis

PCET

Yuzhong Gao

2023·5·26

Robert R. Knowles

Employment

Professor of Chemistry, Princeton University	Mar. 2017 – present
Assistant Professor of Chemistry, Princeton University	July 2011 – Mar. 2017
NIH NRSA Postdoctoral Fellow, Harvard University Advisor: Eric Jacobsen	Dec. 2008 – June 2011

Education

Doctor of Philosophy, California Institute of Technology Advisor: David MacMillan	July 2003 – Oct. 2008
Bachelor of Science in Chemistry, College of William and Mary Advisors: Robert Hinkle and David Kranbuehl	Sep. 1999 – May 2003

Research

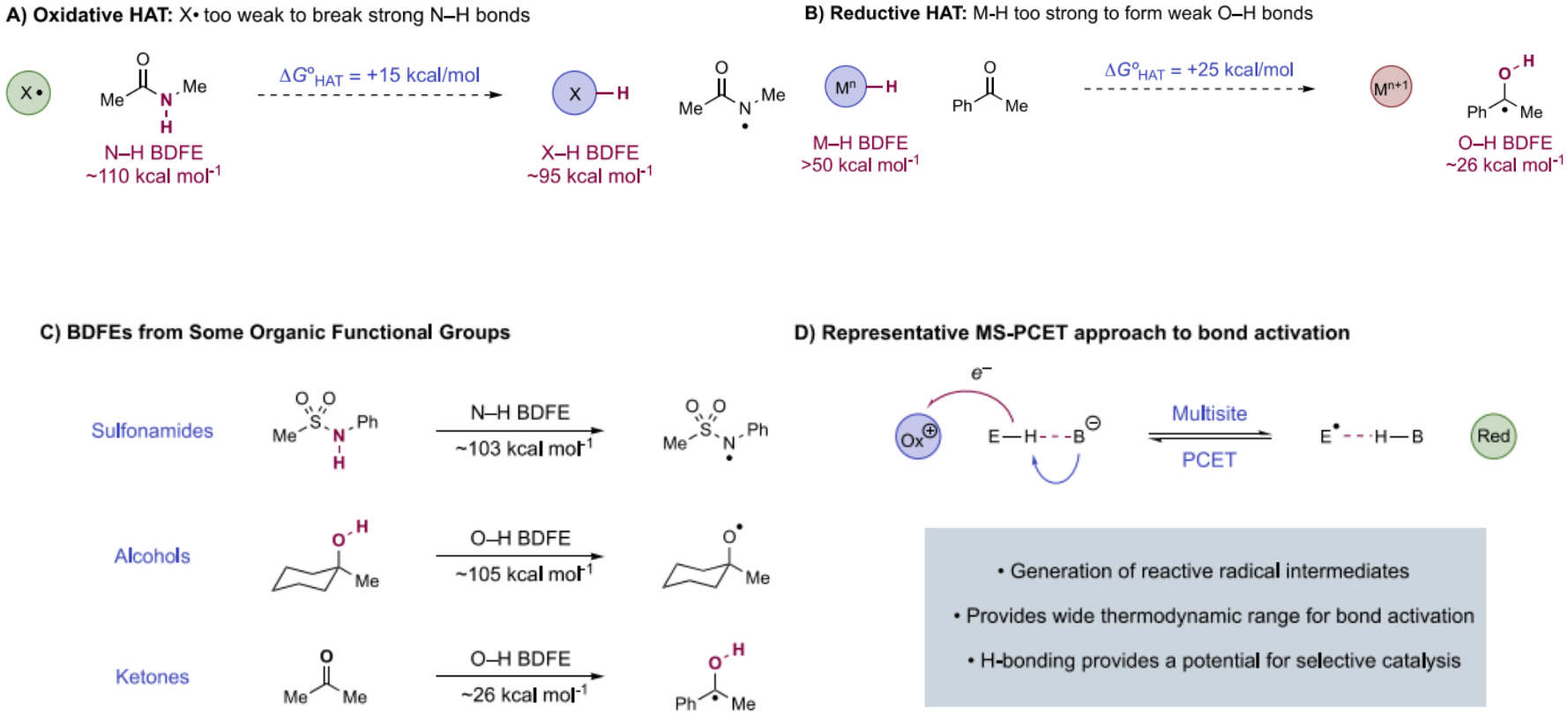
Radical methods for olefin hydroamination

Proton-Coupled Electron Transfer

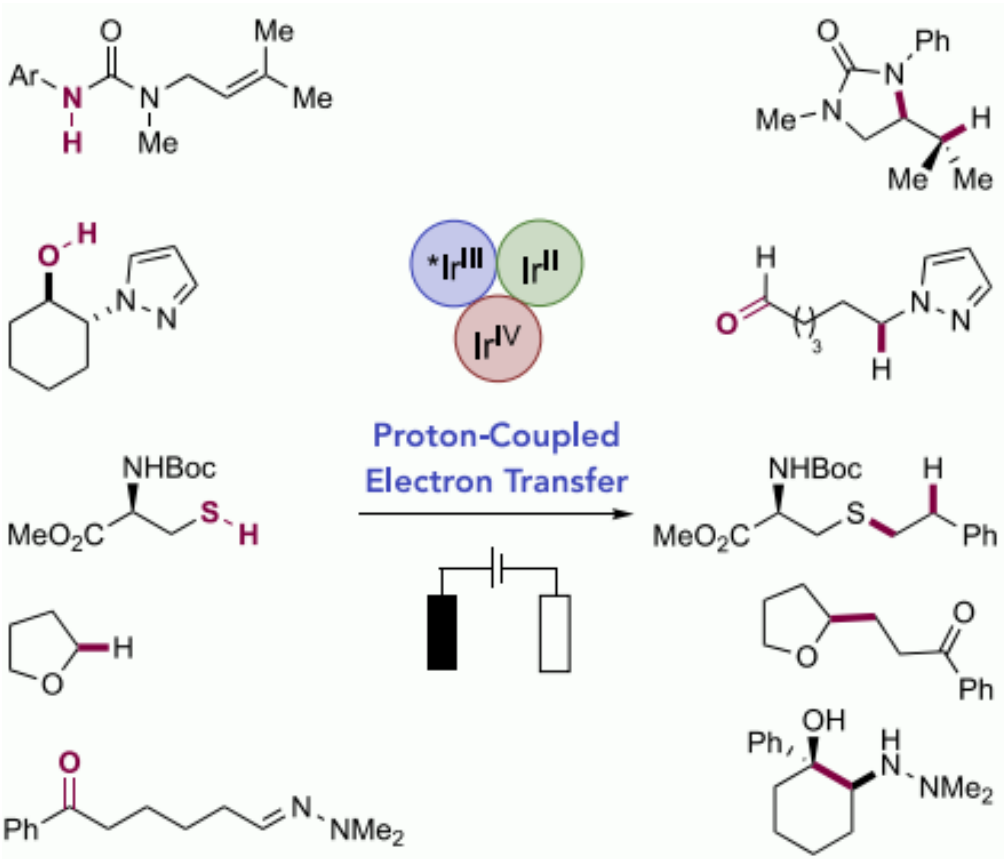
Asymmetric catalysis via radical intermediates

目录

Background



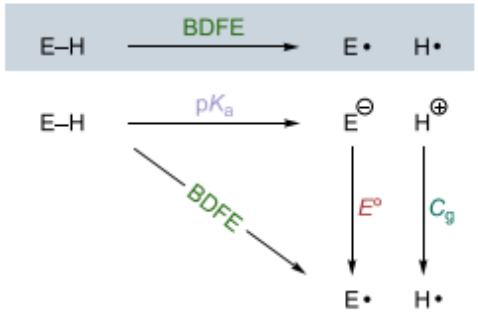
BDFE: 为均裂目标键，产生自由基中间体和质子所需的能量



- Catalytic generation of reactive free radicals
- Photochemical and electrochemical approaches

Background

A) Conventional BDFE of an E–H bond:

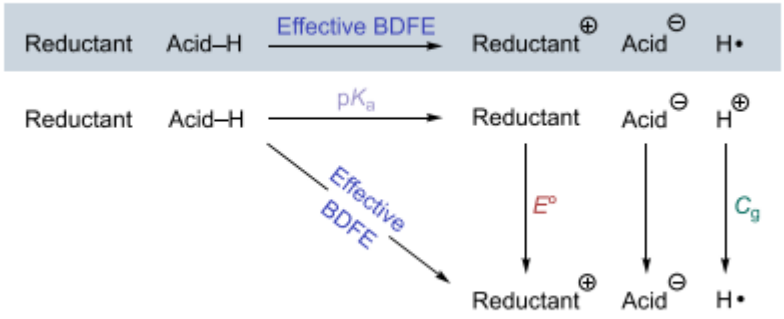


E–H Bond BDFE (kcal mol^{-1}) = 1.37 pK_a (E–H) + 23.06 $E°$(E•/E$^-$) + C_g (1)

C) Oxidative MS-PCET reaction thermodynamics:

$\Delta G°_{PCET}$ (kcal mol^{-1}) = $BDFE_{(E–H)}$ – Effective $BDFE_{(Oxidant,Base–H)}$ (3)

B) Effective BDFE of a MS-PCET reductant / acid pair:



Effective BDFE (kcal mol^{-1}) = 1.37 pK_a (Acid–H) + 23.06 $E°$(Reductant$^+$/Reductant) + C_g (2)

Background

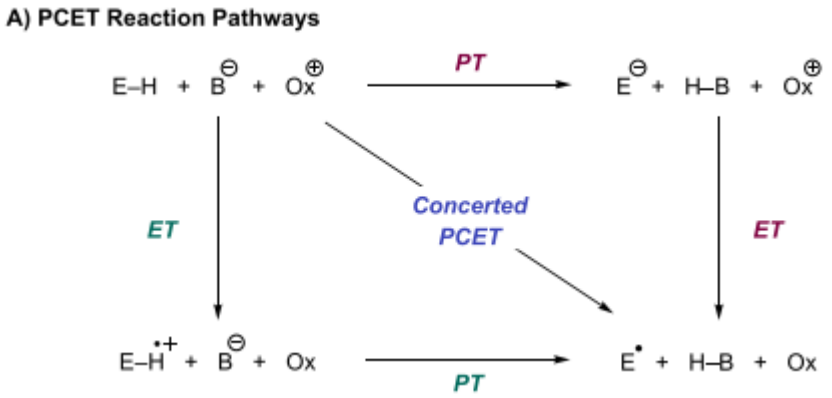
Oxidative Multisite-PCET Pairs

Oxidant	Base	$E_{1/2}$ (V)	pK_a	Effective BDFE
$[Fe^{III}(bpy)_3]^{3+}$	pyridine	+0.70	12.5	87
$*[Ru^{II}(bpy)_3]^{2+}$	acetate	+0.39	23.5	96
$*[Ru^{II}(bpz)_3]^{2+}$	lutidine	+1.07	14.1	100
$*[Ir^{III}(dF(CF_3)ppy)_2(bpy)]^{+}$	DMAP	+1.04	18	103
*1-cyanonapthalene	lutidine	+1.50	14.1	110

Reductive Multisite-PCET Pairs

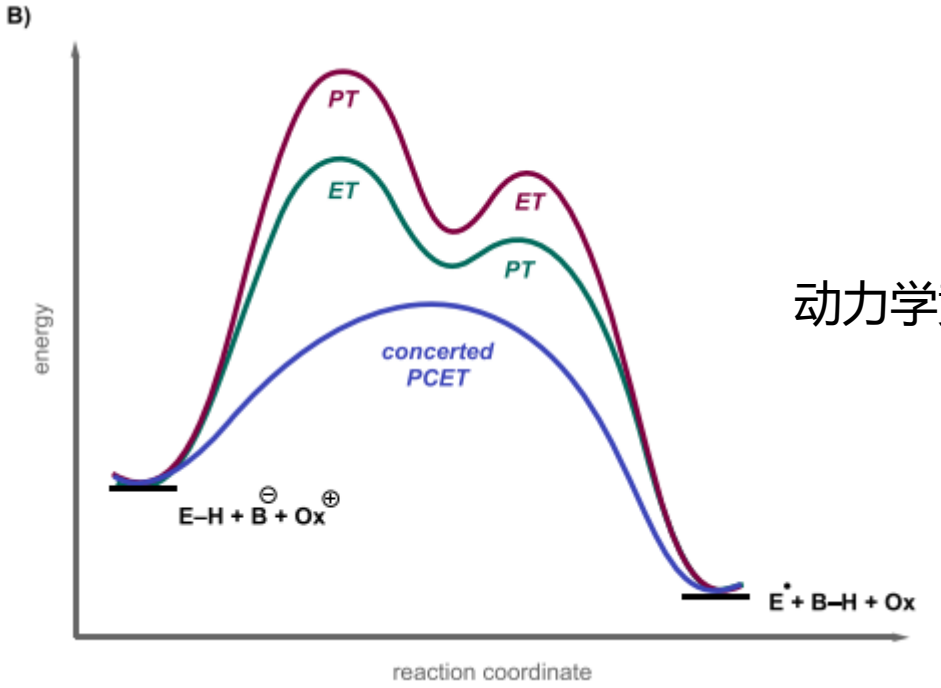
Reductant	Acid	$E_{1/2}$ (V)	pK_a	Effective BDFE
Cp_2Co	$PhCO_2H$	–1.34	21.5	54
Cp^*_2Co	lutidinium	–1.47	14.1	40
$[Ru^{I}(bpy)_3]^{+}$	pyridinium	–1.71	12.5	33
$[Ru^{I}(bpy)_3]^{+}$	*p*-TsOH	–1.71	8.6	27
$*Ir(ppy)_3$	$(PhO)_2PO_2H$	–2.11	13	24

Background



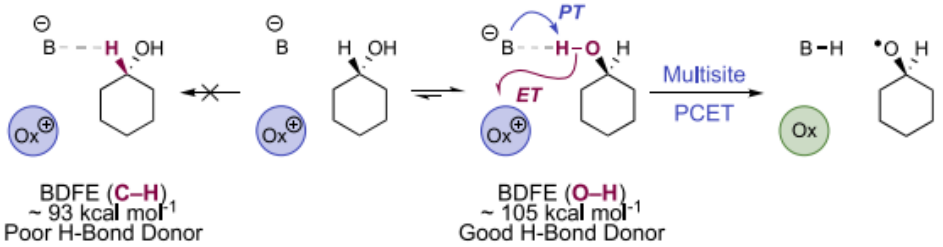
当两种中间体相对于反应物的能量都明显高时，协同途径通常会占主导地位

协同PCET避免了高能中间体的产生

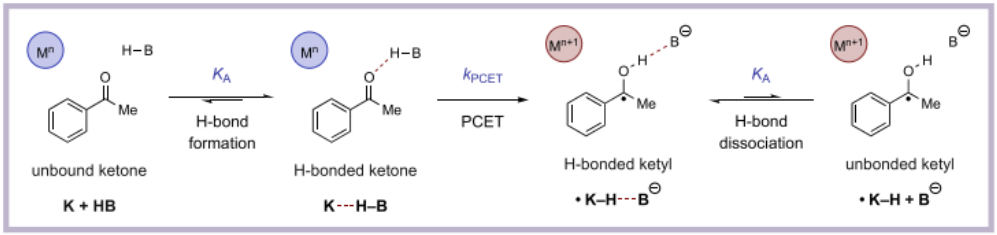


动力学竞争

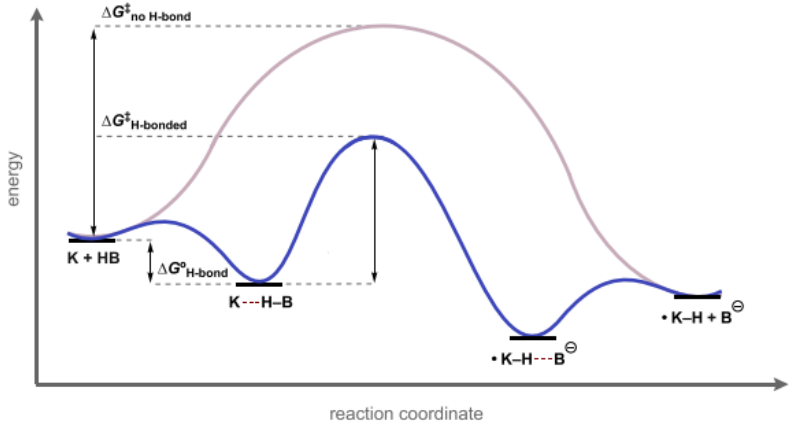
Background



- Hydrogen bonding selects for MS-PCET with polar bonds
- Enables contra-thermodynamic selectivity in bond homolysis

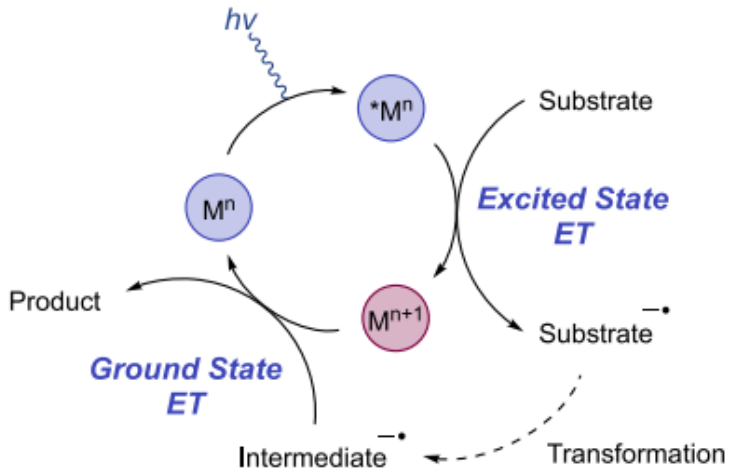


协同PCET有效降低反应能垒



Background

A) Photocatalytic Oxidative Quenching:



B) Photocatalytic Reductive Quenching:

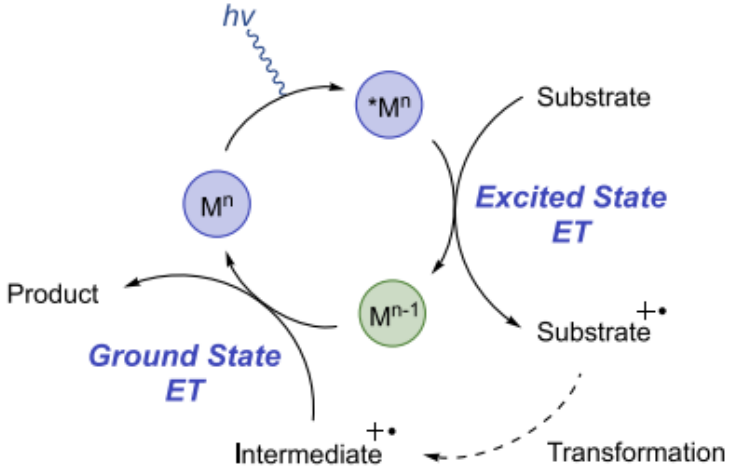
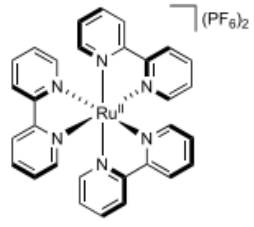
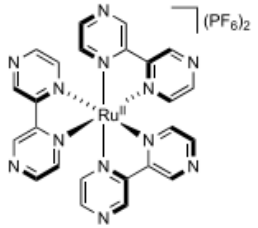


Chart 1. Structures of Photocatalysts Discussed in This Review[a]

Ruthenium:

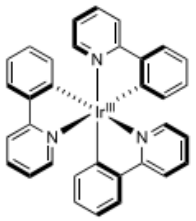


[Ru(bpy)$_3$](PF$_6$)$_2$ ([**Ru-1**](PF$_6$)$_2$)

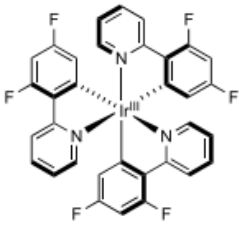


[Ru(bpz)$_3$](PF$_6$)$_2$ ([**Ru-2**](PF$_6$)$_2$)

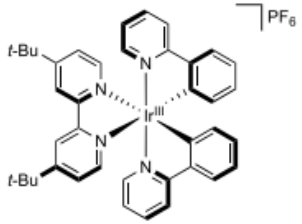
Iridium:



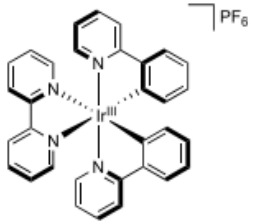
Ir(ppy)$_3$ (**Ir-1**)



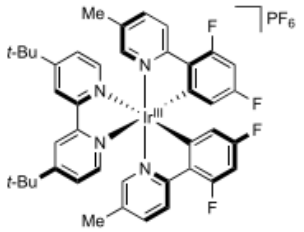
Ir(dFppy)$_3$ (**Ir-2**)



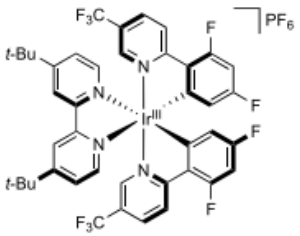
[Ir(ppy)$_2$(dtbbpy)]PF$_6$ ([**Ir-3**]PF$_6$)



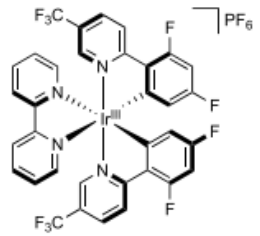
[Ir(ppy)$_2$(bpy)]PF$_6$ ([**Ir-4**]PF$_6$)



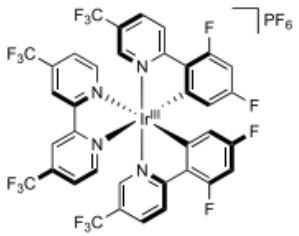
[Ir(dF(Me)ppy)$_2$(dtbbpy)]PF$_6$ ([**Ir-5**]PF$_6$)



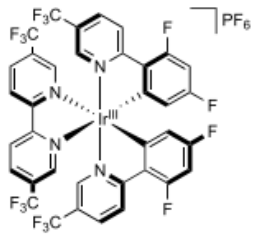
[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ ([**Ir-6**]PF$_6$)



[Ir(dF(CF$_3$)ppy)$_2$(bpy)]PF$_6$ ([**Ir-7**]PF$_6$)

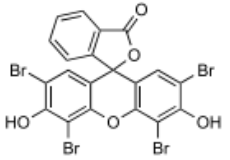


[Ir(dF(CF$_3$)ppy)$_2$(4,4'-d(CF$_3$)bpy)]PF$_6$ ([**Ir-8**]PF$_6$)

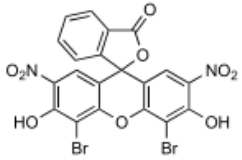


[Ir(dF(CF$_3$)ppy)$_2$(5,5'-d(CF$_3$)bpy)]PF$_6$ ([**Ir-9**]PF$_6$)

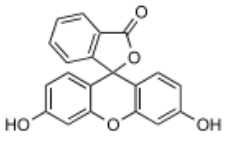
Fluorescein:



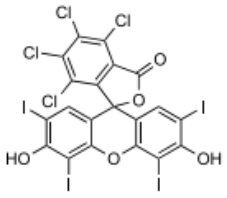
Eosin Y (EY)



Eosin B (EB)

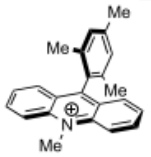


Fluorescein (Fl)

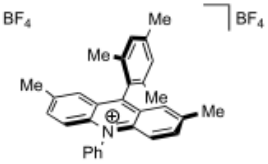


Rose bengal (RB)

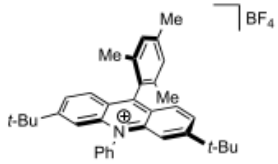
Acridine- and Phenothiazine-derived:



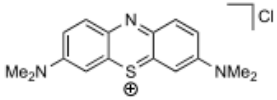
***N*-Me Mes-Acr$^+$ ([**Acr-1**]ClO$_4$) ([**Acr-1**]BF$_4$)**



***N*-Ph Mes-Me$_2$-Acr$^+$ ([**Acr-2**]BF$_4$)**

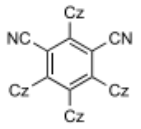


***N*-Ph Mes-*t*-Bu$_2$-Acr$^+$ ([**Acr-3**]BF$_4$)**

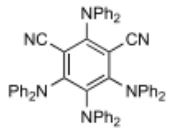


Methylene Blue$^+$ ([MB]Cl)

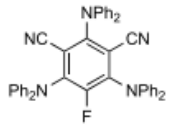
Cyanoarene:



4CzIPN
Cz = *N*–Carbazolyl



4DPAIPN



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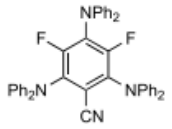

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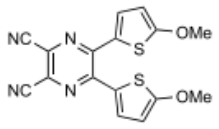


DPZ

[a]Photocatalysts are separated into subclasses of ruthenium, iridium, fluorescein, acridine, and cyanoarene-based structures.

Table 1. Ground-State and Excited-State Redox Potentials for Photocatalysts Discussed in This Review

photocatalyst	ground-state redox potentials		excited-state redox potentials	
	$E^\circ_{ox}(PC^+/PC)^a$	$E^\circ_{red}(PC/PC^-)^a$	$E^\circ_{ox}(PC^+/{}^*PC)^a$	$E^\circ_{red}({}^*PC/PC^-)^a$
[Ru(bpy)$_3$](PF$_6$)$_2$ ([Ru-1](PF$_6$)$_2$)	+0.88[b,64]	−1.71[b,64]	−1.19[b,64]	+0.39[b,64]
[Ru(bpz)$_3$](PF$_6$)$_2$ ([Ru-2](PF$_6$)$_2$)	+1.48[b,65]	−1.18[b,65]	−0.64[b,65]	+1.07[b,65]
Ir(ppy)$_3$ (Ir-1)	+0.39[b,66]	−2.57[b,66]	−2.11[b,66]	−0.07[b,66]
Ir(dFppy)$_3$ (Ir-2)	+0.69[67]	−2.51[67]	−1.82[67]	0.00[67]
[Ir(ppy)$_2$(dtbbpy)]PF$_6$ ([Ir-3]PF$_6$)	+0.83[b,68]	−1.89[b,68]	−1.34[b,68]	+0.28[b,68]
[Ir(ppy)$_2$(bpy)]PF$_6$ ([Ir-4]PF$_6$)	+0.87[b,46]	−2.43[b,46]	−1.79[b,46]	+0.23[b,46]
[Ir(dF(Me)ppy)$_2$(dtbbpy)]PF$_6$ ([Ir-5]PF$_6$)	+1.11[b,68]	−1.81[b,69]	−1.30[b,68]	+0.59[b,68]
[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ ([Ir-6]PF$_6$)	+1.31[b,68]	−1.75[b,68]	−1.59[b,68]	+0.51[b,68]
[Ir(dF(CF$_3$)ppy)$_2$(bpy)]PF$_6$ ([Ir-7]PF$_6$)	+1.38[70]	−1.64[70]	−1.30[70]	+1.04[70]
[Ir(dF(CF$_3$)ppy)$_2$(4,4′-d(CF$_3$)bpy)]PF$_6$ ([Ir-8]PF$_6$)	+1.55[29]	−1.18[29]	−0.89[29]	+1.27[29]
[Ir(dF(CF$_3$)ppy)$_2$(5,5′-d(CF$_3$)bpy)]PF$_6$ ([Ir-9]PF$_6$)	+1.56[29]	−1.07[29]	−0.81[29]	+1.30[29]
Eosin Y (EY)	–	−1.44[b,c,71]	−1.49[b,c,72]	+0.45[b,c,71]
fluorescein (Fl)	–	−1.60[b,c,71]	−1.64[b,c,72]	+0.36[b,c,72]
rose bengal (RB)	–	−1.34[b,c,72]	−1.40[b,c,72]	+0.47[b,c,72]
***N*-Me Mes-Acr$^+$ClO$_4^-$ and *N*-Me Mes-Acr$^+$BF$_4^-$ ([Acr-1]ClO$_4$ and ([Acr-1]BF$_4$)**	–	−0.93[b,73]	–	+1.70[d]/+1.50[e,b,73,74]
***N*-Ph Mes-Me$_2$-Acr$^+$ ([Acr-2]BF$_4$)**	–	−0.96[b,75]	–	+1.71[b,75]
***N*-Ph Mes-*t*-Bu$_2$-Acr$^+$ ([Acr-3]BF$_4$)**	–	−0.97[b,76]	–	+1.70[b,76]
methylene blue$^+$Cl$^-$ ([MB]Cl)	+0.75[b,f,45]	−0.68[b,f,45]	−1.11[d]/−1.06[e,b,f,45]	+1.18[d]/+1.22[e,b,f,45]
4CzIPN	+1.11[b,77]	−1.59[b,78]	−1.56[b,77]	+0.97[b,78]
4DPAIPN	+0.65[b,79]	−2.03[b,79]	−1.90[b,79]	+0.52[b,79]
3DPAFIPN	+0.92[b,77]	−1.97[b,78]	−1.76[b,77]	+0.72[b,78]
3DPA2FBN	+0.86[b,g,77]	−2.30[b,g,77]	−1.98[b,g,77]	+0.54[b,g,77]
DPZ	+0.99[b,g,80]	−1.83[b,g,81]	−1.55[b,82]	+0.53[b,g,81]

[a]Potentials measured in V vs Fc$^+$/Fc and measured in MeCN unless indicated. [b]Converted to Fc$^+$/Fc from the reference electrode used in the original report according to Addison and co-workers.[83] [c]Measured in 1:1 MeCN:H$_2$O. [d]From the singlet excited state. [e]From the triplet excited state. [f]Measured in H$_2$O. [g]Measured in CH$_2$Cl$_2$.

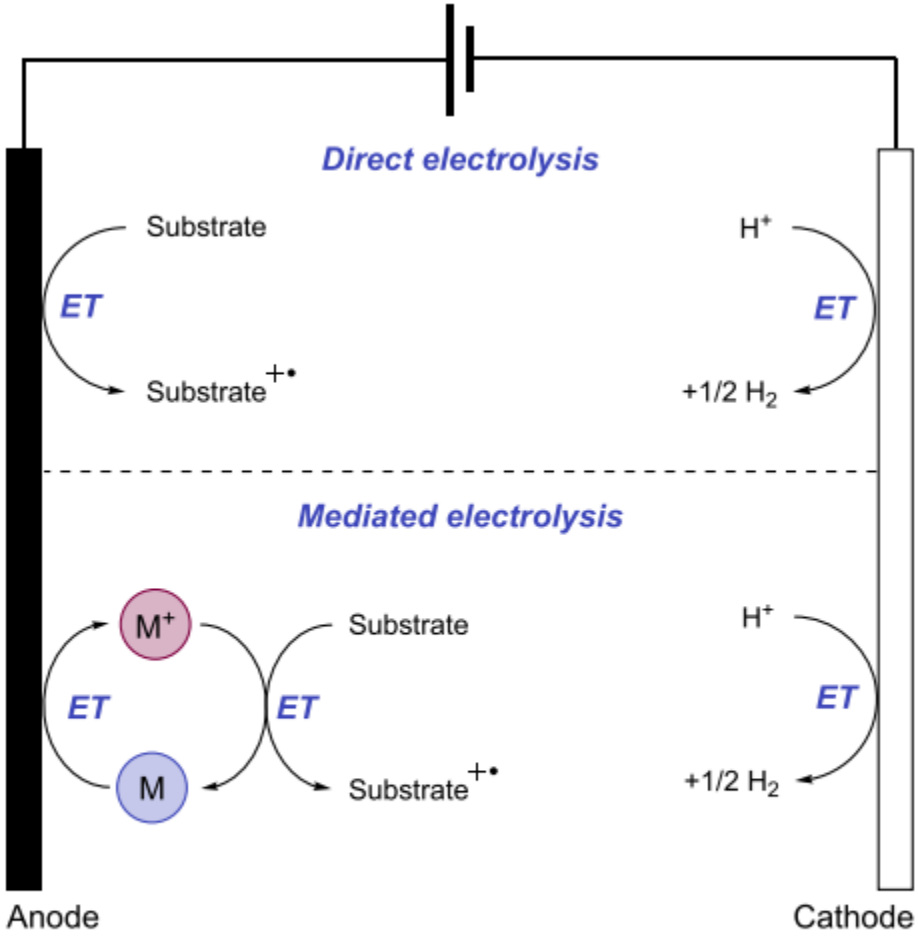
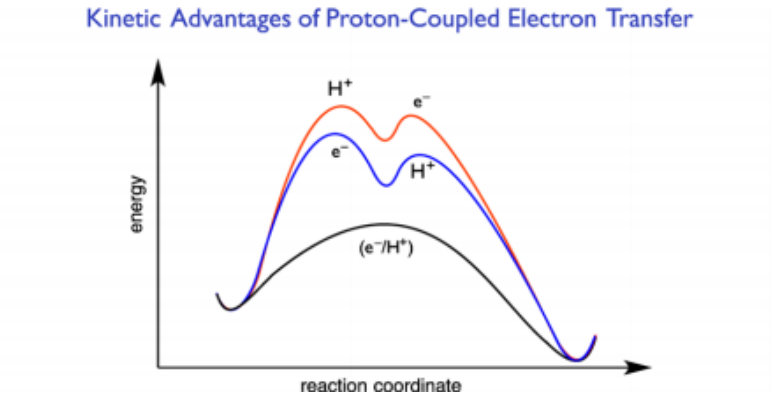
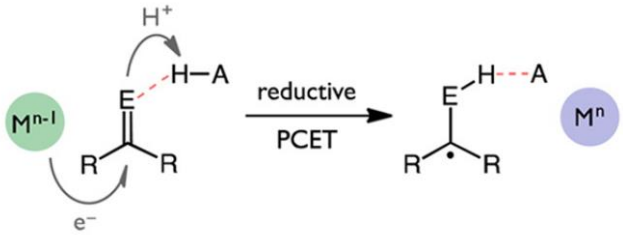
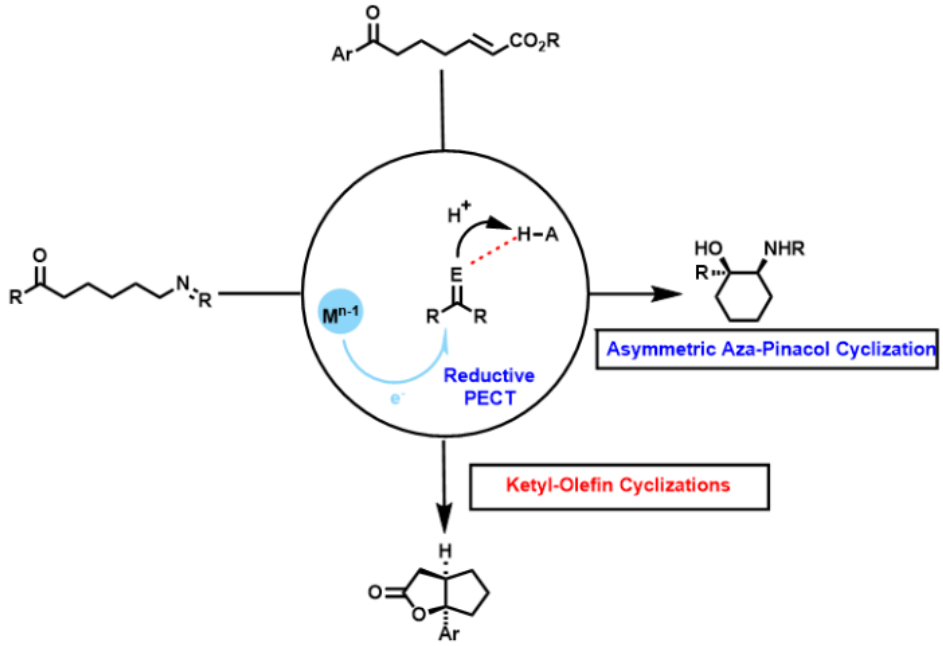


Figure 8. General schemes for substrate activation through direct and mediated electrolysis.

Reduction PCET







Reduction PCET---Ketyl-Olefin

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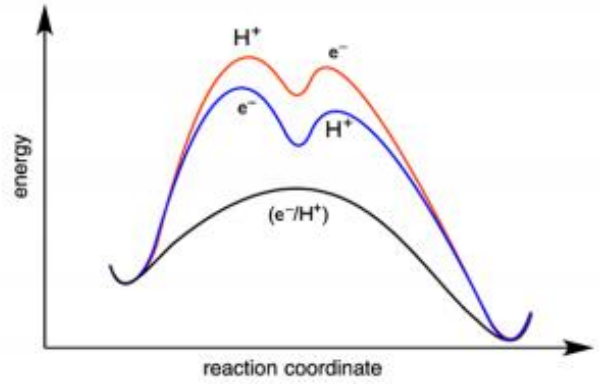
Catalytic Ketyl-Olefin Cyclizations Enabled by Proton-Coupled Electron Transfer

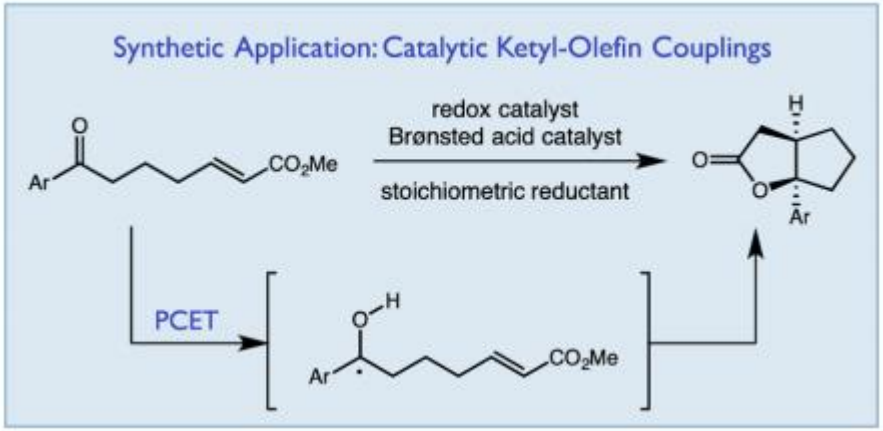
Kyle T. Tarantino, Peng Liu, and Robert R. Knowles*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

Kinetic Advantages of Proton-Coupled Electron Transfer



Synthetic Application: Catalytic Ketyl-Olefin Couplings



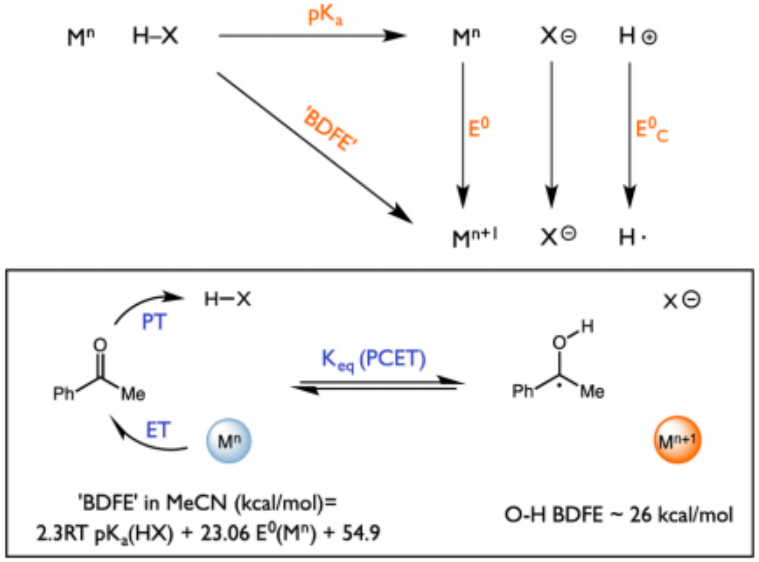
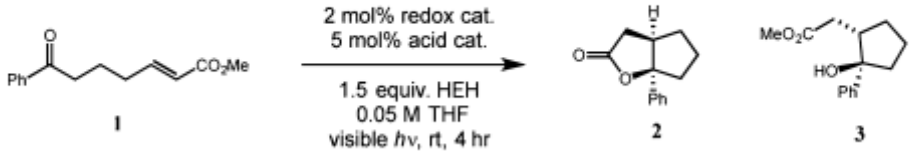


Figure 2. Thermodynamic cycle for determination of formal BD values and application to ketyl PCET.

Table 1. Optimization of the Ketyl-Olefin Coupling[a]

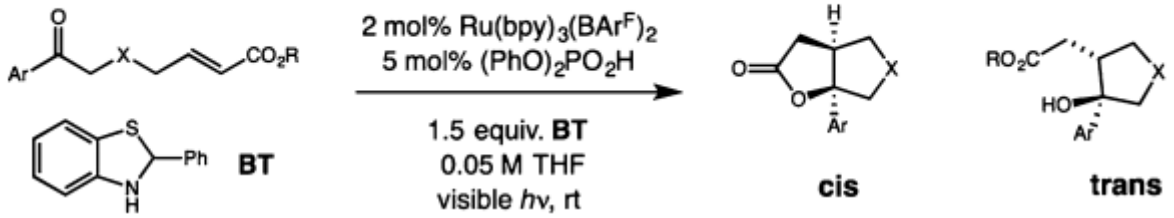


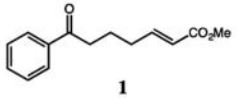
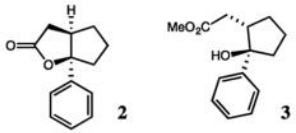
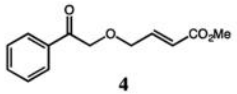
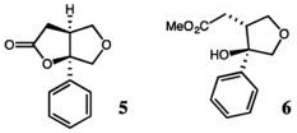
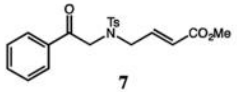
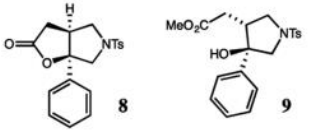
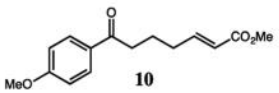
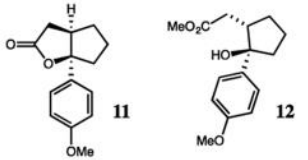
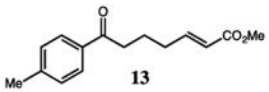
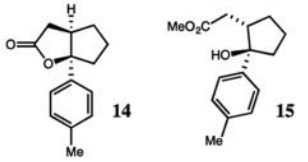
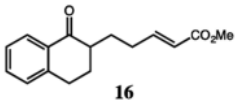
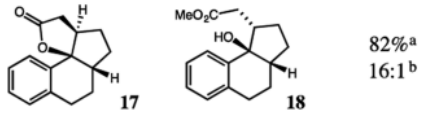
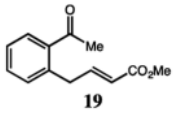
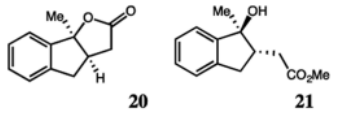
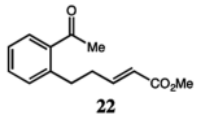
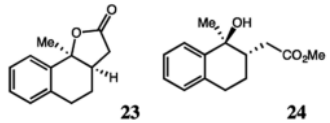
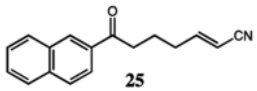
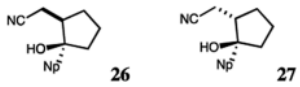
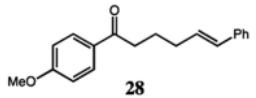
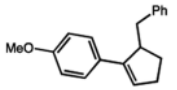
1 2 3

entry	acid catalyst	redox catalyst	'BDFE'	% yield	2:3
1	none	$Ru(bpy)_3(BAr^F)_2$	–	0	–
2	BzOH	$Ru(bpy)_3(BAr^F)_2$	45	0	–
3	$NEt_3 \cdot HBF_4$	$Ru(bpy)_3(BAr^F)_2$	41	0	–
4	lutidine·HBF_4	$Ru(bpy)_3(BAr^F)_2$	35	0	–
5	$(PhO)_2PO_2H$	$Ru(bpy)_3(BAr^F)_2$	33	78	4.6:1
6	*p*TSA	$Ru(bpy)_3(BAr^F)_2$	27	74	4.3:1
7	$(PhO)_2PO_2H$	$Ir(ppy)_2(dtbpy)PF_6$	29	93	4.8:1
8	$(PhO)_2PO_2H$	*fac*-$Ir(ppy)_3$	24	92	4.8:1
9	lutidine·HBF_4	$Ir(ppy)_2(dtbpy)PF_6$	31	74	4.9:1
10[b]	$(PhO)_2PO_2H$	$Ru(bpy)_3(BAr^F)_2$	33	89	10:1

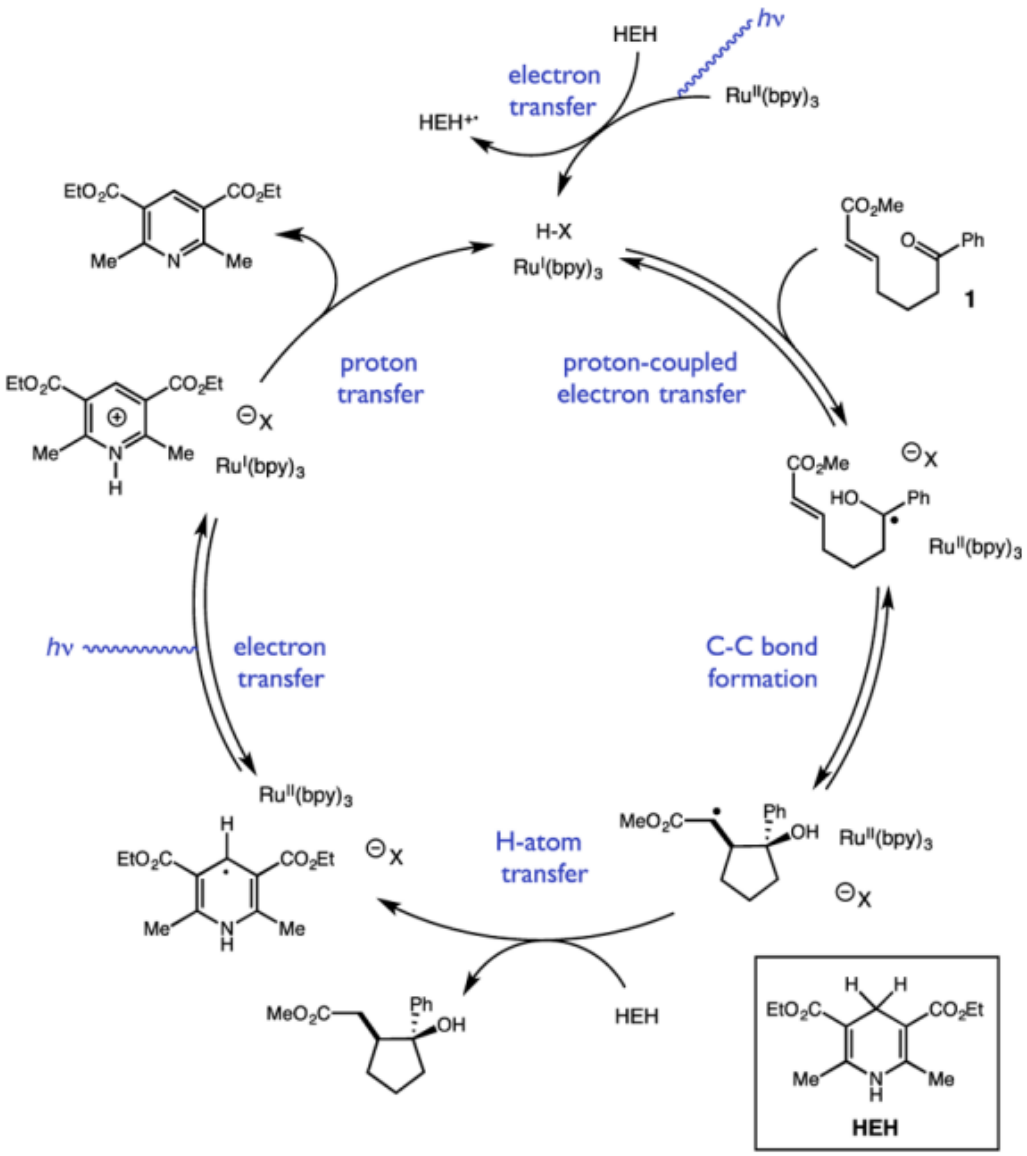
[a]Yields and isomeric ratios were determined by GC analysis of crude reaction mixtures relative to calibrated internal standards. Visible light irradiation was provided by 26 W fluorescent lamps. Formal BDFE values ('BDFE') calculated using the thermodynamic cycle presented in Figure 2 from pK_a and potential data in MeCN. For details, see Supporting Information. [b]BT used in place of HEH.

Table 2. Substrate Scope of the Ketyl-Olefin Coupling[c]



entry	substrate	products	yield (cis:trans)
1	 1	 2 3	73% 11:1
2	 4	 5 6	87% 4.8:1
3	 7	 8 9	80% 3.4:1
4	 10	 11 12	78% 12:1
5	 13	 14 15	86% 6:1
6	 16	 17 18	82%[a] 16:1[b]
7	 19	 20 21	96% 2:1
8	 22	 23 24	78% 1.2:1
9	 25	 26 27	64% 10:1
10	 28	 29	68%

Scheme 1. Proposed Catalytic Cycle



Stern–Volmer:

猝灭过程显示出对每种成分的一级依赖性

H、D的二苯基磷酸猝灭:

KIE—1.22±0.02

Reduction PCET---Aza-Pinacol Cyclization

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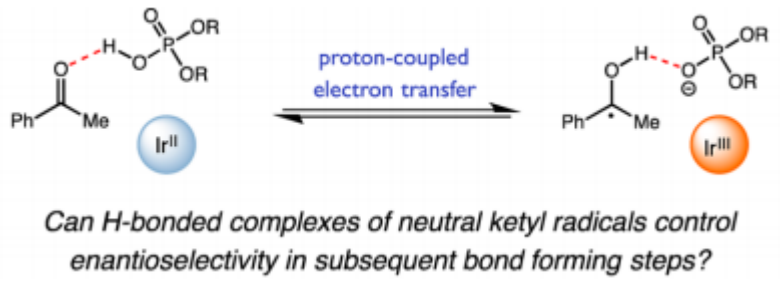
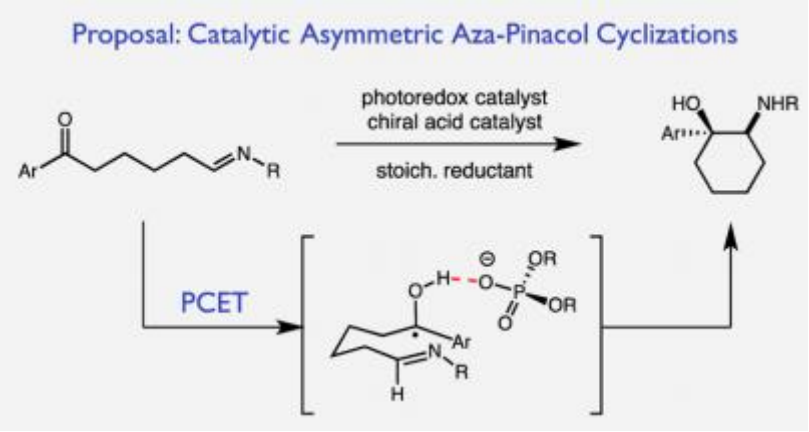
Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization

Lydia J. Rono, Hatice G. Yayla, David Y. Wang, Michael F. Armstrong, and Robert R. Knowles*

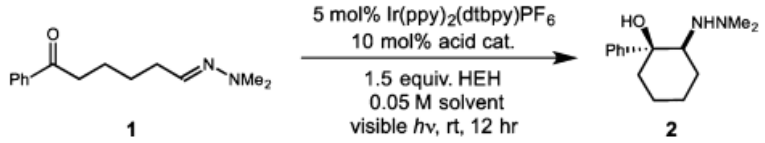
Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States





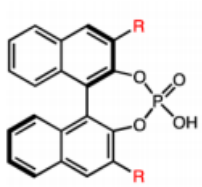
手性磷酸可能会使这些反应具有不对称选择性

Table 1. Asymmetric Aza-Pinacol Optimization Studies[a]

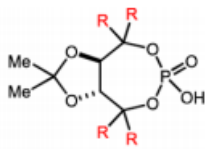


entry	acid catalyst	solvent	% yield	% ee
1	$(PhO)_2PO_2H$	THF	91	–
2	**3**	THF	89	0
3	**4**	THF	84	30
4	**5**	THF	96	58
5	**6**	THF	80	68
6	**7**	THF	84	82
7	**8**	THF	92	89
8	**9**	THF	90	0
9	**10**	THF	85	0
10	**8**	DME	90	88
11	**8**	C_6H_6	30	86
12	**8**	CH_2Cl_2	99	88
13	**8**	MeCN	77	81
14	**8**	dioxane	94	92
15[b]	**8**	dioxane	90	92

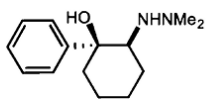
[a]Optimization reactions performed on 0.05 mmol scale. Yields and ee determinations obtained by chiral GC analysis. Visible light irradiation provided by 26-W fluorescent lamps unless otherwise noted. [b]Reaction irradiated by blue LEDs for 3 h at rt using 2 mol % of the photocatalyst.



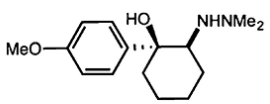
3 R = H
4 R = 2-naphthyl
5 R = Mesityl
6 R = 2,4,6-*i*Pr$_3$C$_6$H$_2$
7 R = *i*Pr$_3$Si
8 R = Ph$_3$Si



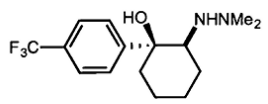
9 R = Ph
10 R = 2-naphthyl



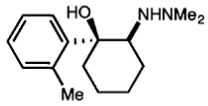
2[a] 83%, 93% ee



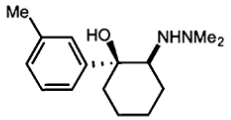
11 86%, 94% ee



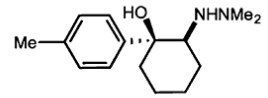
12 58%, 90% ee



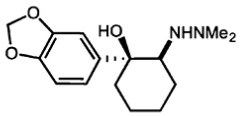
13[b] 63%, 94% ee



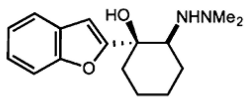
14 78%, 90% ee



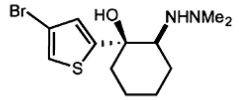
15 81%, 95% ee



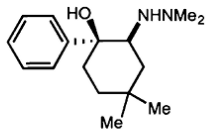
16 96%, 94% ee



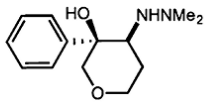
17 53%, 82% ee



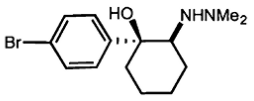
18 69%, 85% ee



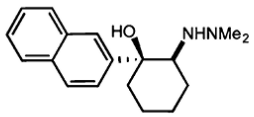
19 78%, 90% ee



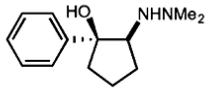
20[c] 85%, 83% ee



21 77%, 95% ee

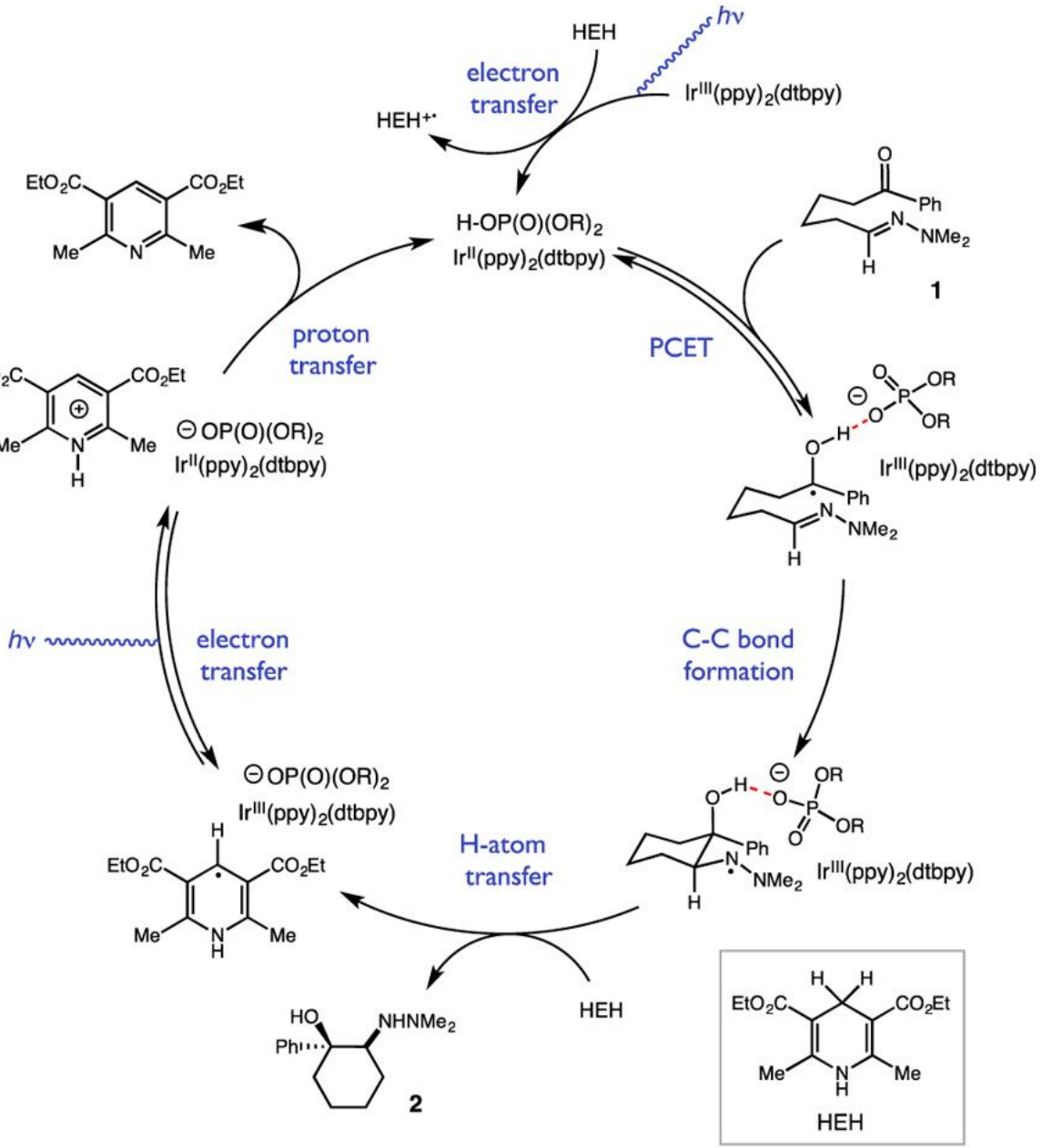


22[d] 45%, 91% ee



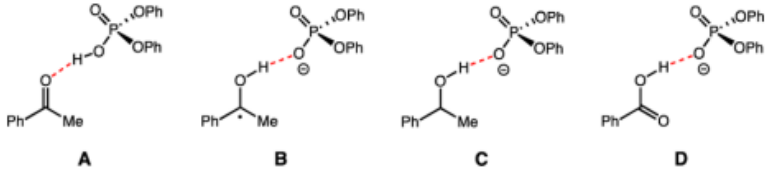
23[e] 71%, 77% ee

Scheme 1. Proposed Catalytic Cycle



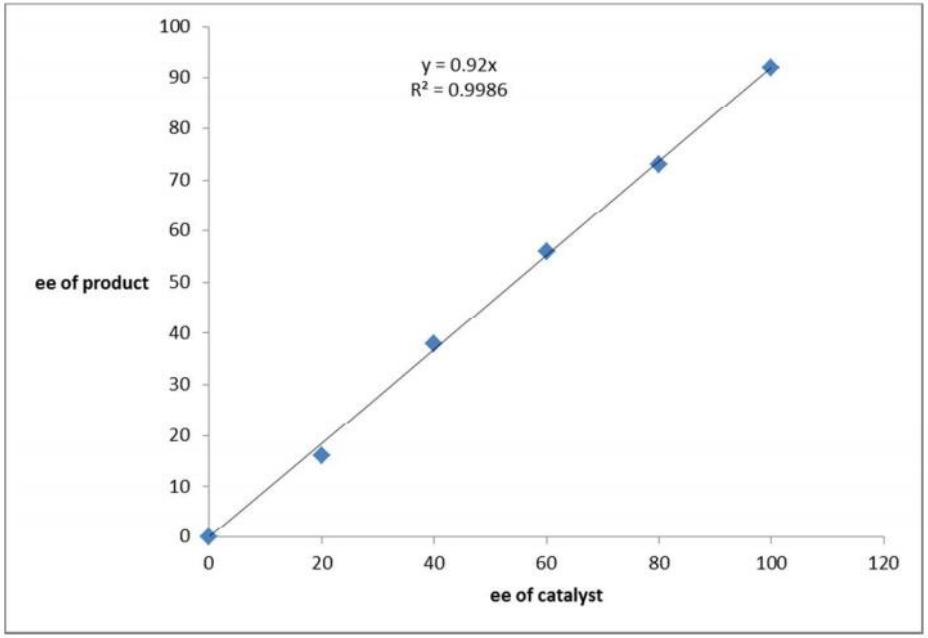
DFT

Table 3. DFT Evaluation of Ketyl-phosphate H-Bonding

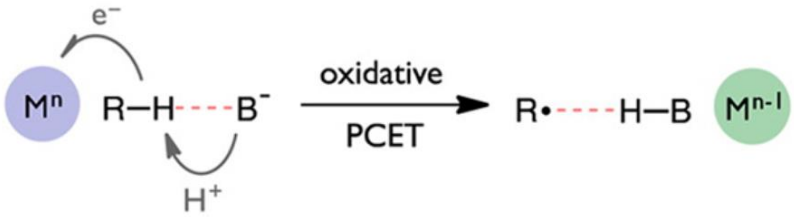


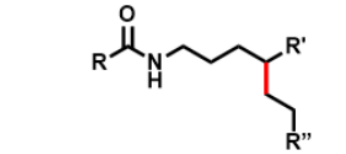
complex	$\Delta E_{\text{H-bond}}{}^{a,b}$	d OH···O (Å)^{a}	O−H pK_a(MeCN)	Mulliken charge (H)^{a}
A	−9.2	1.642	13	0.39
B	−14.4	1.629	20	0.59
C	−10.4	1.737	~38^{c}	0.51
D	−12.6	1.551	21.5	0.60

Figure S1. Product **2** ee vs ee of the catalyst **8**

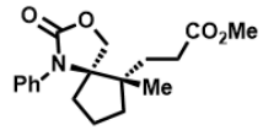


Oxidation PCET---Amine

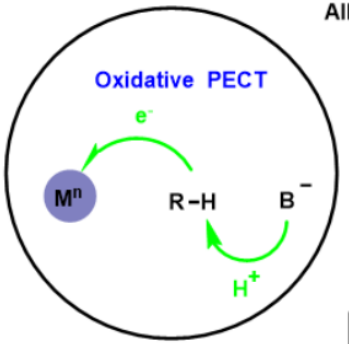


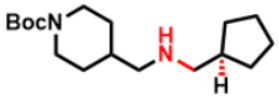


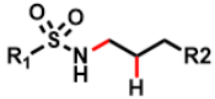
Alkylation of remote C–H bonds



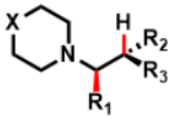
Alkene Carboaminations

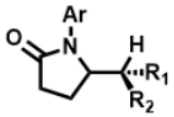


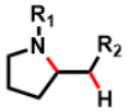


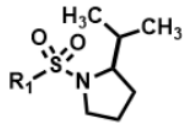


Anti-Markovnikov Hydroamination









Intermolecular Hydroaminations

Oxidation PCET---Alkene Carboaminations

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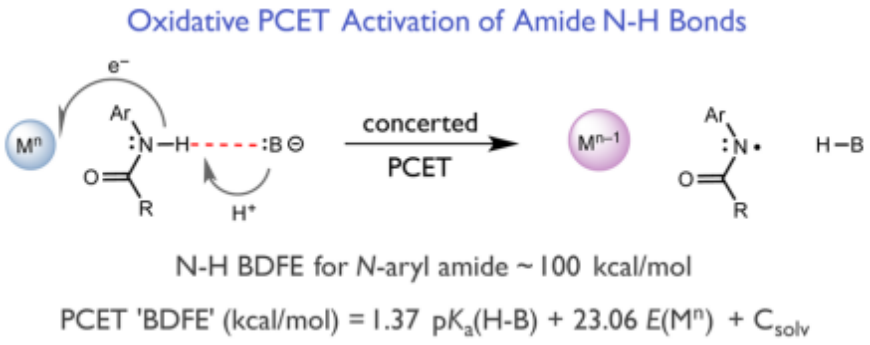
Catalytic Alkene Carboaminations Enabled by Oxidative Proton-Coupled Electron Transfer

Gilbert J. Choi and Robert R. Knowles*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States



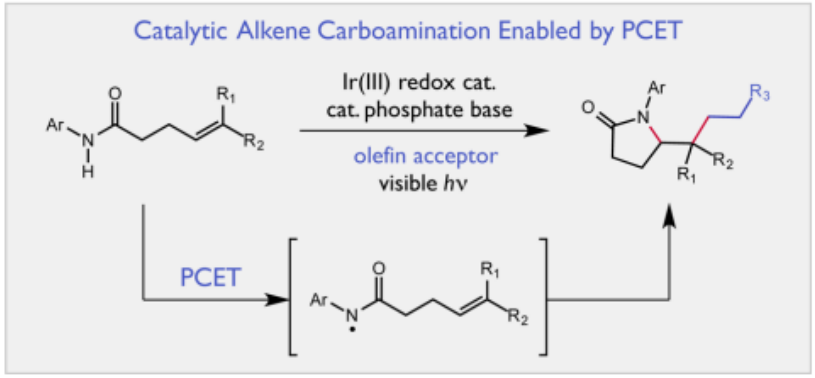
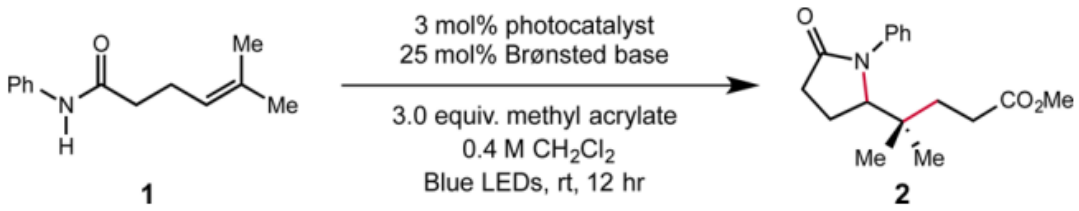


Figure 1. PCET activation of amide N–H bonds and application to the development of a catalytic protocol for alkene carboamination.

选择性均裂N-芳基酰胺的N-H键,不受较弱C-H的影响

Table 1. Reaction Optimization[a]

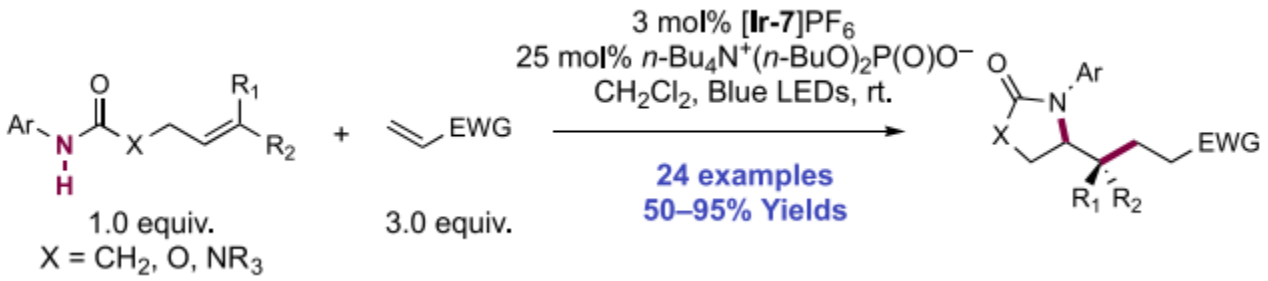


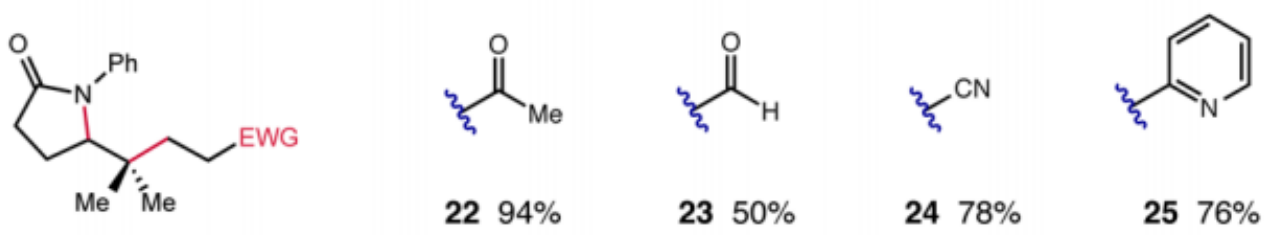
Entry	Photocatalyst	Base	"BDFE"[b]	Yield (%)
1	$Ir(ppy)_2(phen)PF_6$	$NBu_4OP(O)(OBu)_2$	80	0
2	$Ir(ppy)_2(phen)PF_6$	lutidine	82	0
3	$Ir(Fmppy)_2(dtbbpy)PF_6$	$NBu_4OP(O)(OBu)_2$	82	0
4	$Ir(Fmppy)_2(dtbbpy)PF_6$	lutidine	83	0
5	$Ir(Fmppy)_2(phen)PF_6$	$NBu_4OP(O)(OBu)_2$	83	trace
6	$Ir(Fmppy)_2(phen)PF_6$	lutidine	85	0
7	$Ir(ppy)_2(phen)(PF_6)$	DMAP	87	trace
8	$Ir(Fmppy)_2(dtbbpy)PF_6$	DMAP	89	0
9	$Ir(Fmppy)_2(phen)PF_6$	DMAP	90	6
10	$Ir(ppy)_2(phen)PF_6$	NBu_4OBz	92	20
11	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	$NBu_4OP(O)(OBu)_2$	92	76
12	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	lutidine	93	22
13	$Ir(Fmppy)_2(dtbbpy)PF_6$	NBu_4OBz	93	56
14	$Ir(Fmppy)_2(phen)PF_6$	NBu_4OBz	95	35
15	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	$NBu_4OP(O)(OBu)_2$	97	92
16	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	lutidine	98	24
17	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	DMAP	99	34
18	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	DMAP	103	16
19	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	NBu_4OBz	104	76
20	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	NBu_4OBz	108	50

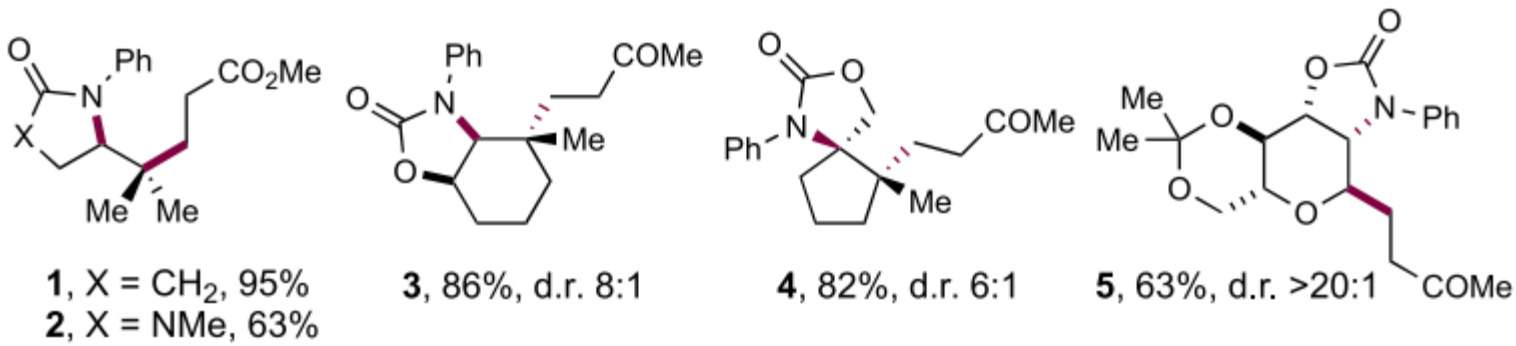
"BDFE" values significantly lower than the strength of the substrate N–H bond were not successful catalysts for carboamination

N-arylamide derivatives
(N–H BDFEs ~ 100 kcal/mol)

Scheme 1. Photocatalytic Alkene Carboamidation of N-Aryl Amides through Concerted PCET (Knowles, 2015)

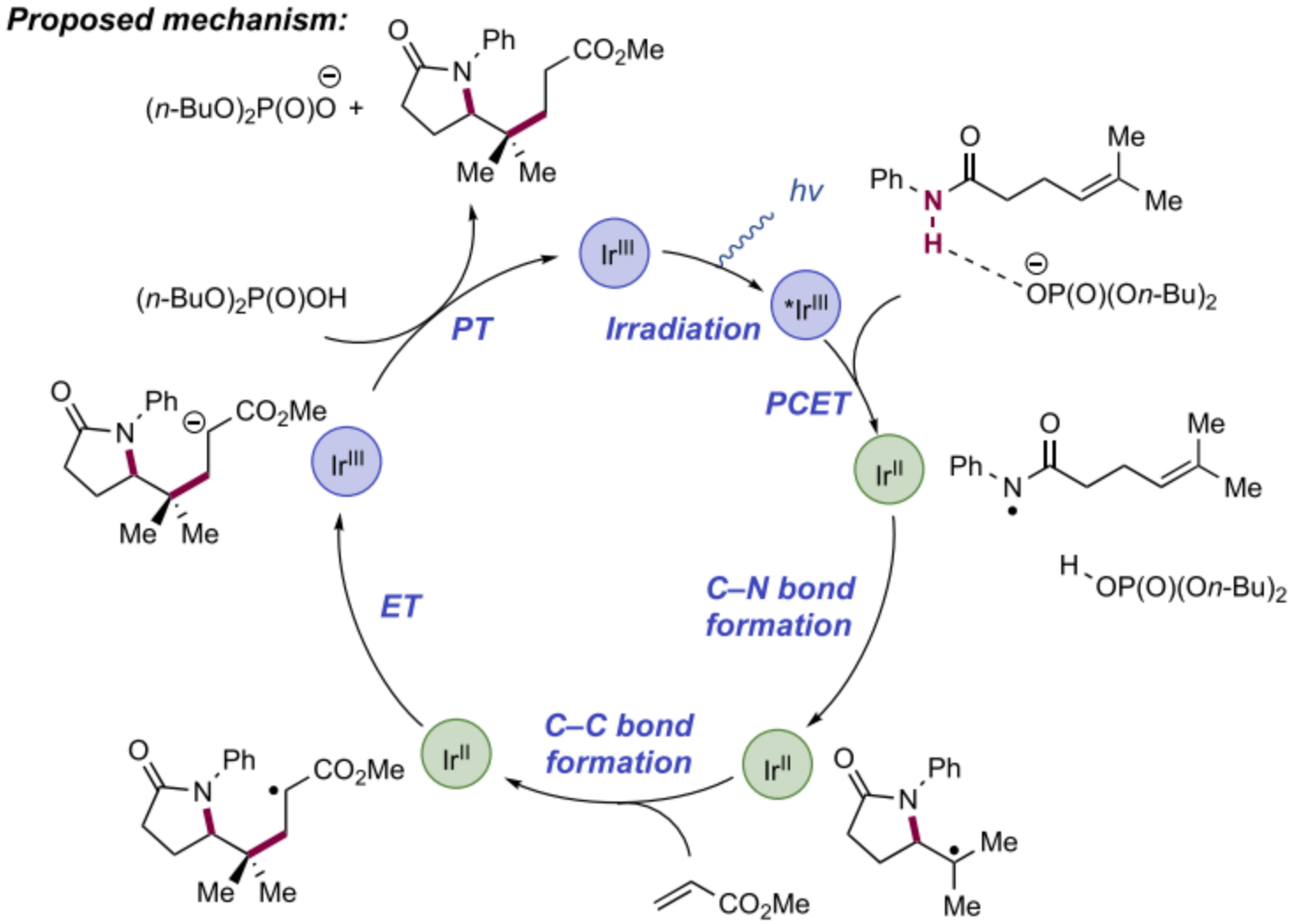






以前未报道

Proposed Catalytic Cycle



KIE

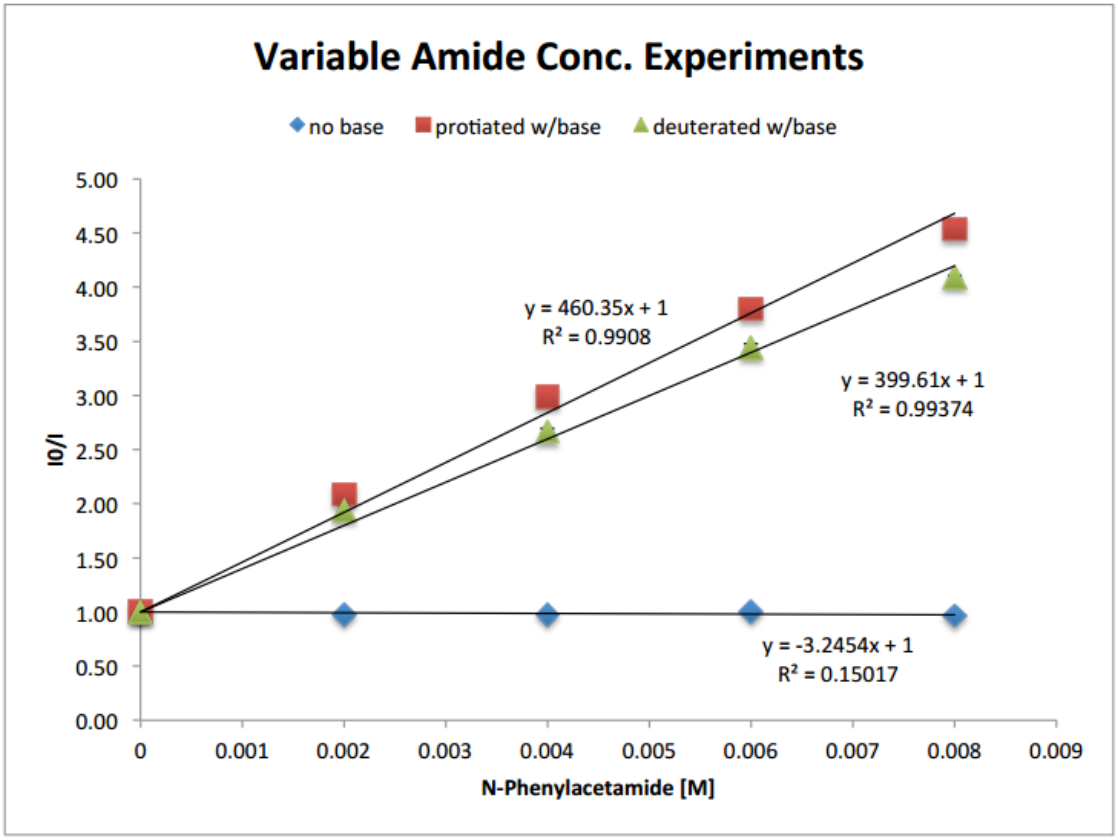


Fig. S1. Stern-Volmer plot of $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$, $NBu_4(BuO)_2PO_2$, and variable acetanilide. The error in the slope was calculated (from LINEST analysis) to be 460.3 ± 12.2 for protiated acetanilide and 399.6 ± 8.8 for deuterated acetanilide.

$$k_H/k_D = 460.3 \pm 12.2 / 399.6 \pm 8.8 = 1.15 \pm 0.04$$

酰胺(MeCN中的pKa≈32)

磷酸碱基(δpKaH≈20)

Sterm-Volmer

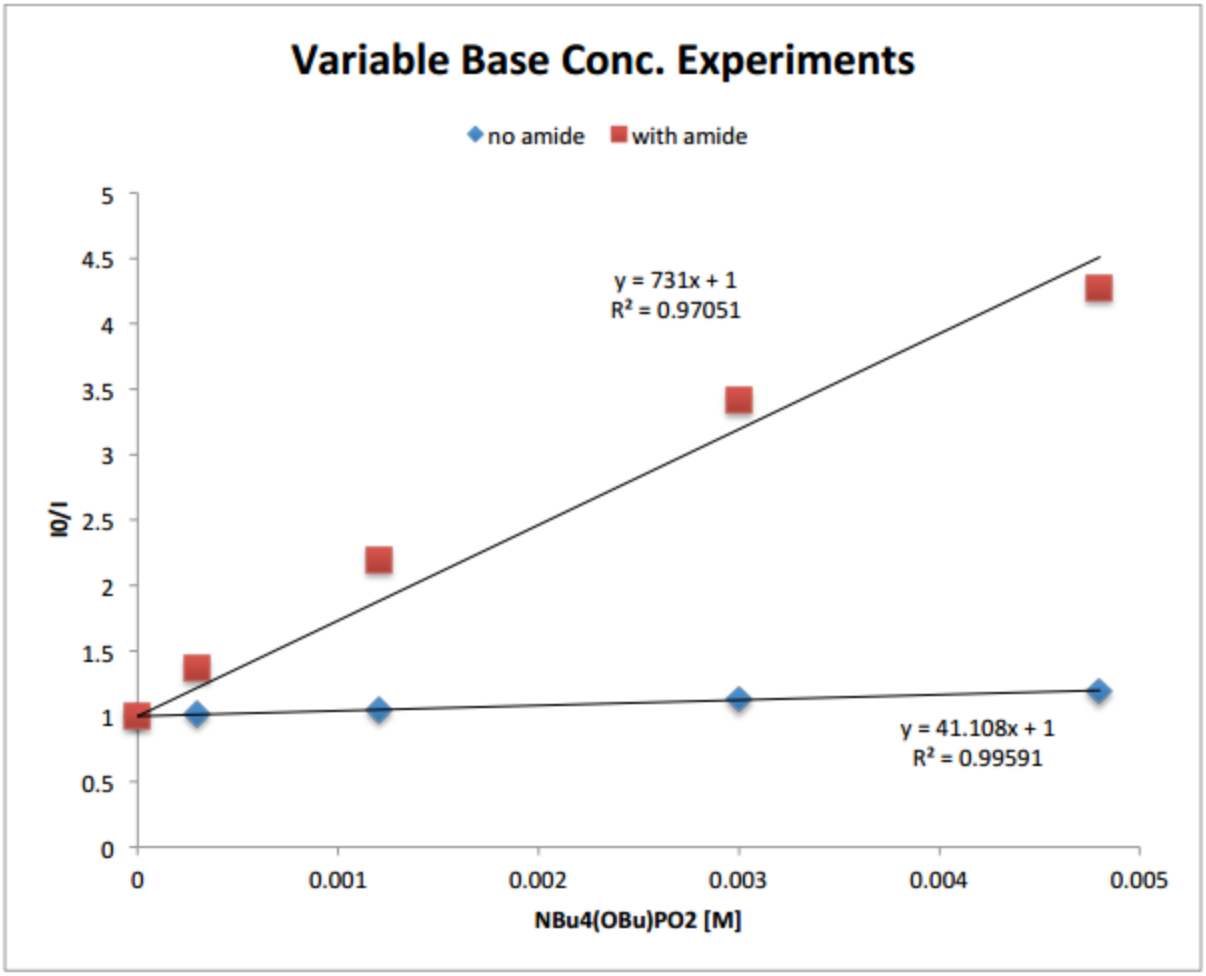


Fig. S2. Stern-Volmer plot of $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$, 0.01 M acetanilide, and variable $NBu_4(BuO)_2PO_2$.

Oxidation PCET---Olefin Hydroamidation

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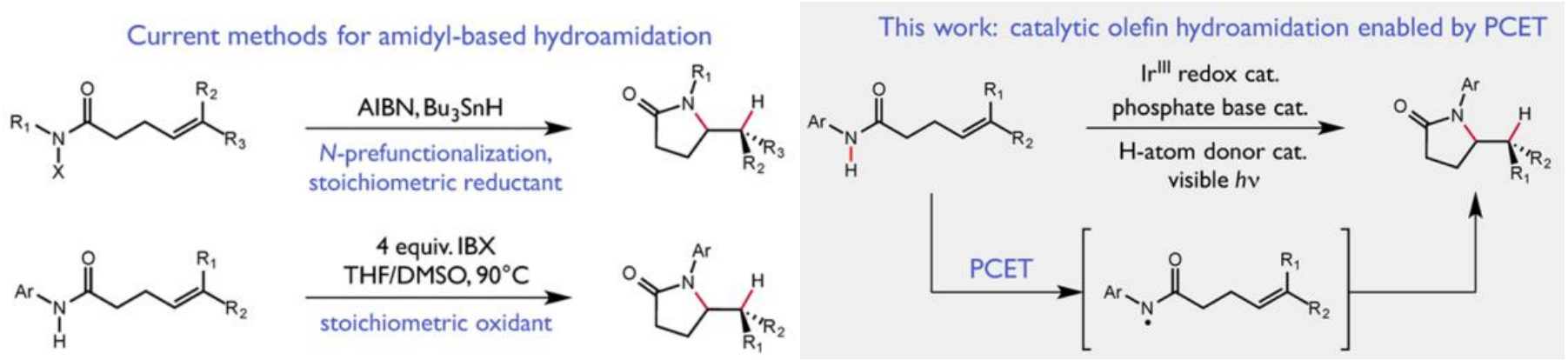
Catalytic Olefin Hydroamidation Enabled by Proton-Coupled Electron Transfer

David C. Miller, Gilbert J. Choi, Hudson S. Orbe, and Robert R. Knowles*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

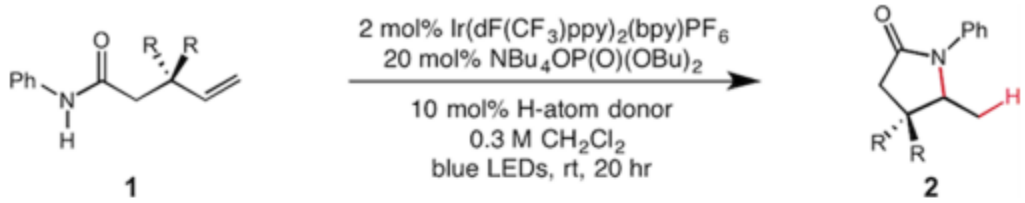
Supporting Information



Previous：强氧化剂

Now：氧化还原中性条件

Table 1. Optimization Studies[a]



entry	R	H-atom donor	yield (%)
1	H	none	24
2	Me	none	0
3	H	phenol	18
4	H	2,4,6-tBu-phenol	19
5	H	4-aminopyridine	21
6	H	diphenyl acetonitrile	28
7	H	Ph_3SiH	16
8	H	thiophenol	95
9	H	2-naphthalenethiol	45
10	H	4-trifluoromethyl thiophenol	86
11	H	2,4,6-iPr-thiophenol	83

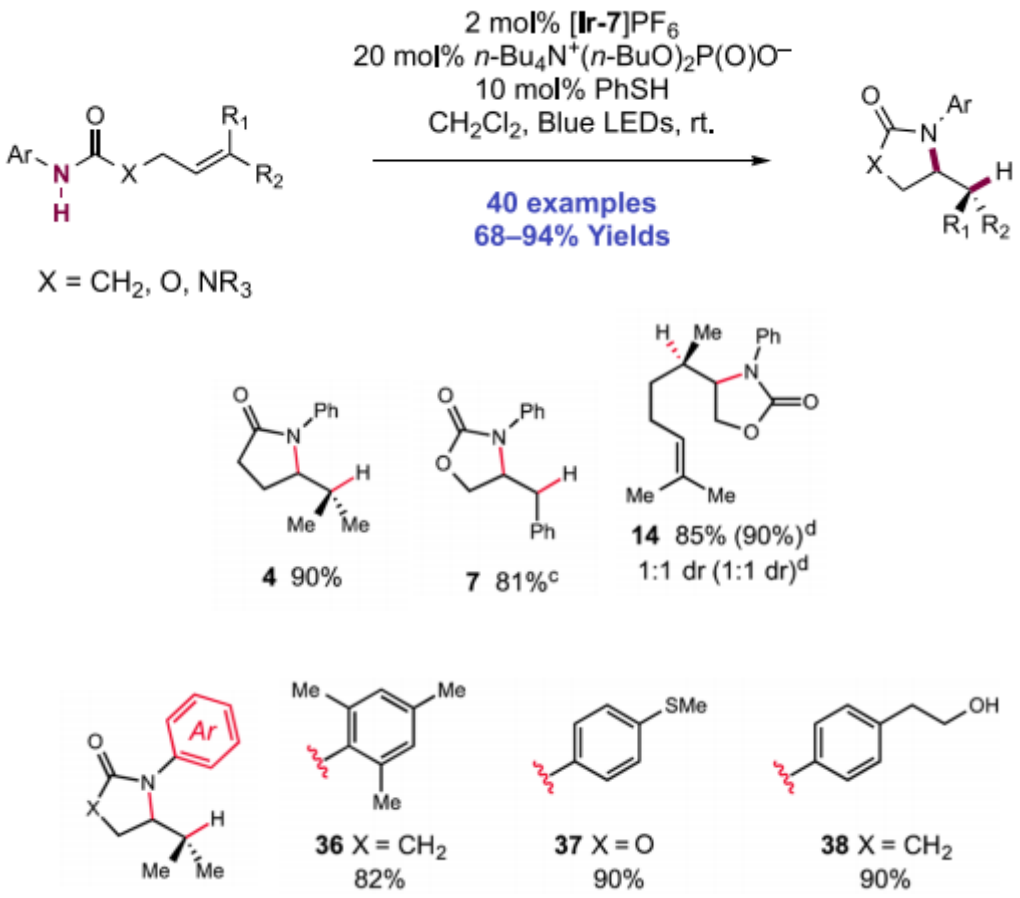
entry	R	change from best conditions (entry 8)	yield (%)
12	H	no light	0
13	H	no photocatalyst	0
14	H	no $NBu_4OP(O)(OBu)_2$	0
15	Me	none	89

[a]Optimization reactions run on 0.1 mmol scale. Yields determined by ^1H NMR analysis of the crude reaction mixture relative to an internal standard. Irradiation supplied by 4 W blue LED strips.

具有选择性：
硫酚的成功有些令人惊讶，因为硫醇是已知的多位PCET激活的底物，而硫酚S−H键(S−H BDFE≈79千卡/摩尔)比酰胺底物的N−H键(N−H BDFE≈99千卡/摩尔)弱20千卡/摩尔

DFT计算猜测：
酰胺磷酸氢键络合物的形成比硫酚−磷酸氢键络合物更有利5.2Kcal/mol

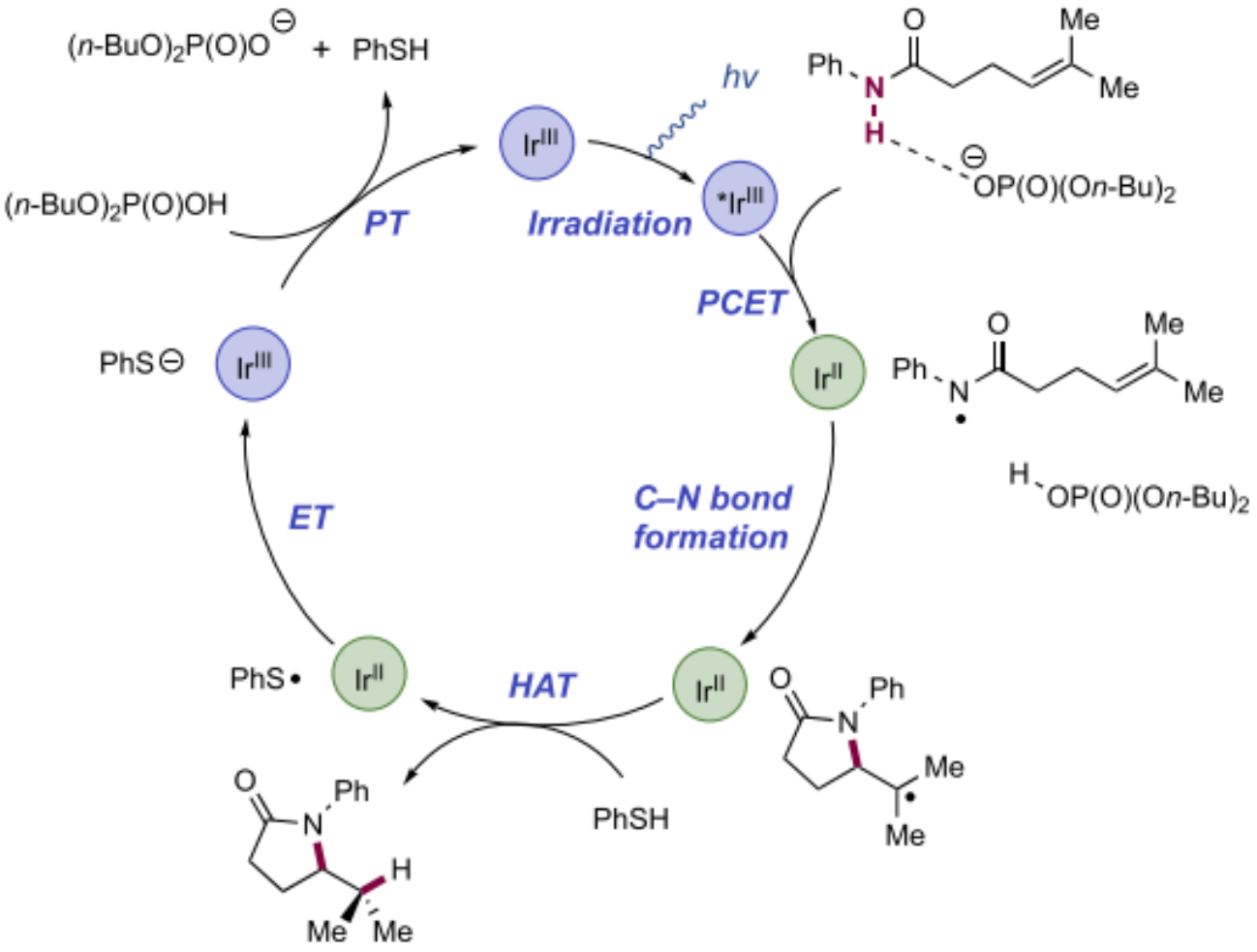
Scheme 2. Photocatalytic Alkene Hydroamidation of N-Aryl Amides through Concerted PCET (Knowles, 2015)



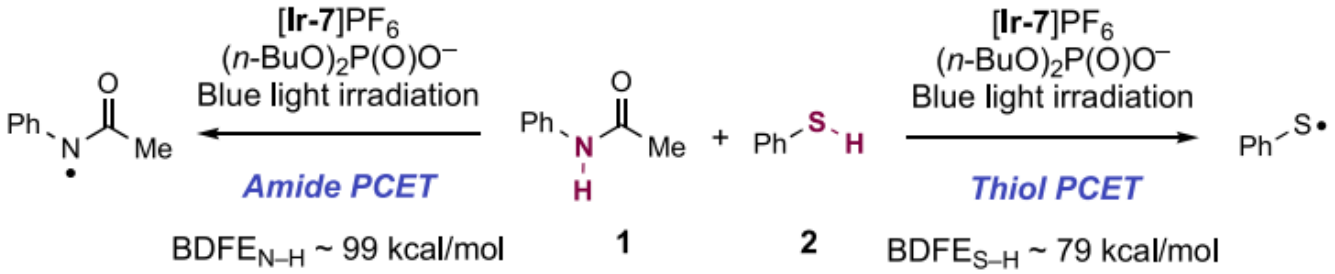
局限性：不适合分子间偶联或高效率地形成更大的环

Proposed Catalytic Cycle

Proposed mechanism:



Scheme 3. Observed Rate Law for Ir(III) Luminescence Quenching in a Model Hydroamidation System (Knowles,2019)



Experimental rate law for *Ir(III) quenching:

$$\frac{d[\text{Ir(III)*}]}{dt} = [\text{amide}]^1[\text{phosphate}]^1[\text{thiol}]^0$$

DOI: 10.1021/jacs.9b08398
J. Am. Chem. Soc. 2019, 141, 16574−16578

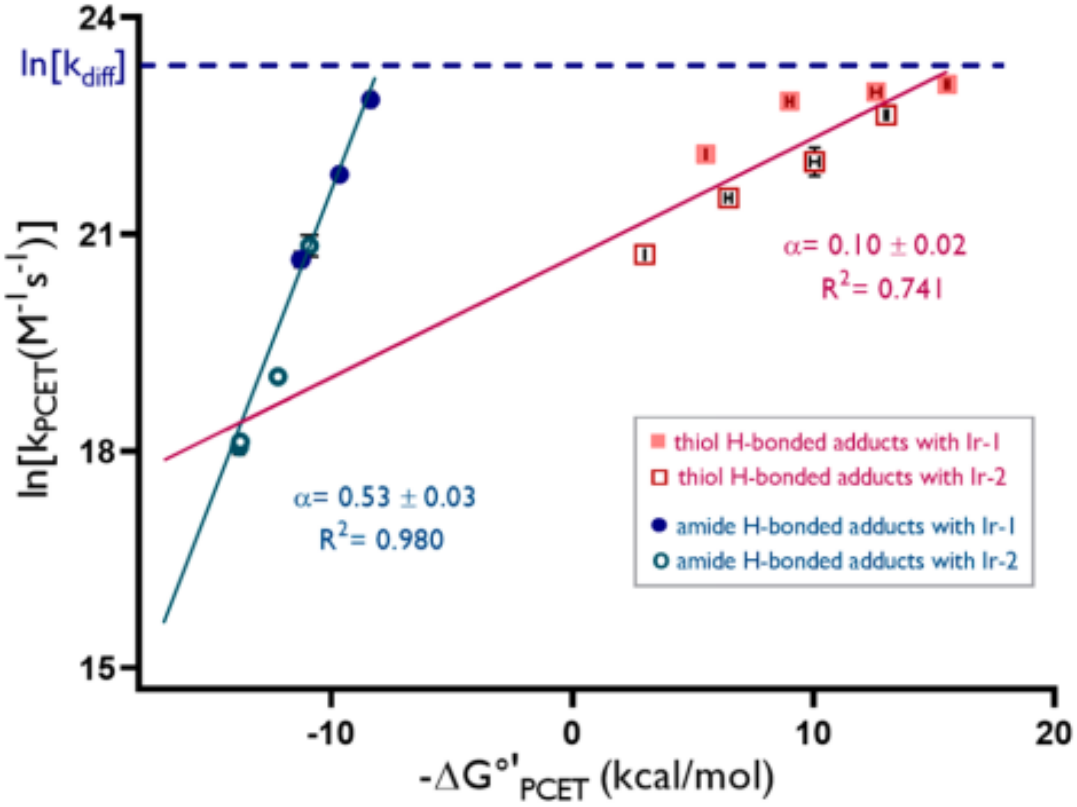
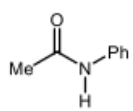


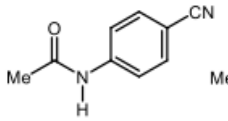
Figure 2. Rate-driving force relationships.

Table 1. Kinetic and H-Bonding Equilibrium Data

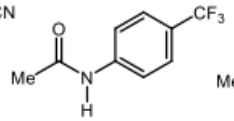
entry	amide/thiol	*Ir(III)	$BDFE_{N-H/S-H}$ (kcal/mol)[6,8]	K_A (M^{-1})	$\Delta G^{\circ\prime}_{PCET}$ (kcal/mol)	k_{PCET} (M^{-1} s^{-1})
1	**A1**	**Ir-1**	98.9	1050	8.4	8.4×10^9
2	**A1**	**Ir-2**	98.9	1050	10.9	1.1×10^9
3	**A2**	**Ir-1**	101.1	3550	11.3	9.3×10^8
4	**A2**	**Ir-2**	101.1	3550	13.8	6.8×10^7
5	**A3**	**Ir-1**	101.6	1390	11.2	9.3×10^8
6	**A3**	**Ir-2**	101.6	1390	13.7	7.5×10^7
7	**A4**	**Ir-1**	100.0	1500	9.7	3.0×10^9
8	**A4**	**Ir-2**	100.0	1500	12.2	1.8×10^8
9	**T1**	**Ir-1**	79.1	200	−12.4	9.5×10^9
10	**T1**	**Ir-2**	79.1	200	−9.8	3.6×10^9
11	**T2**	**Ir-1**	76.9	44	−15.6	1.0×10^{10}
12	**T2**	**Ir-2**	76.9	44	−13.0	7.0×10^9
13	**T3**	**Ir-1**	84.0	5600	−5.5	4.0×10^9
14	**T3**	**Ir-2**	84.0	5600	−3.0	1.0×10^9
15	**T4**	**Ir-1**	81.3	2150	−8.8	8.3×10^9
16	**T4**	**Ir-2**	81.3	2150	−6.3	2.2×10^9



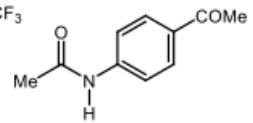
A1



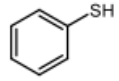
A2



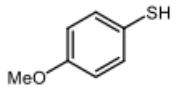
A3



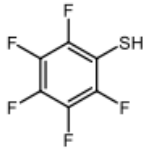
A4



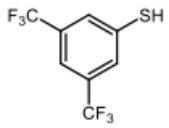
T1



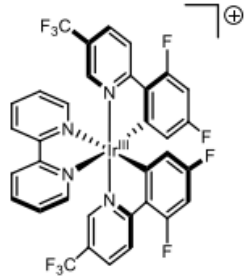
T2



T3



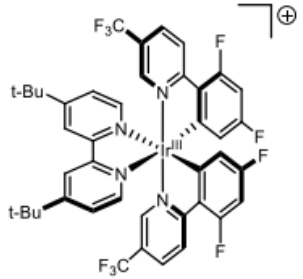
T4



Ir-1

$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$

$E_{1/2}(Ir^{*III/II}) = +0.94$ V vs. Fc^+/Fc

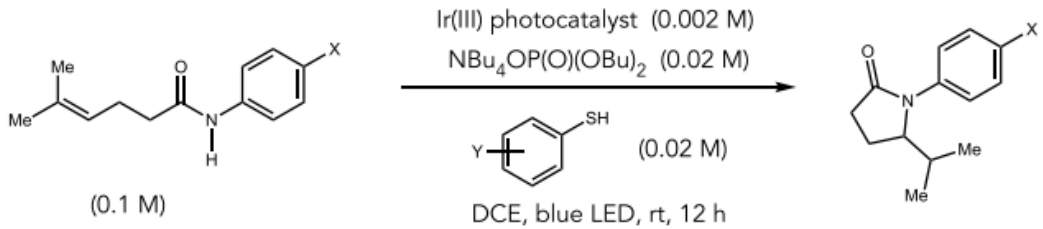


Ir-2

$[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$

$E_{1/2}(Ir^{*III/II}) = +0.83$ V vs. Fc^+/Fc

Table 2. Correlation of Selectivity Factor Q_0 with Catalytic Reaction Outcomes



$$Q_0 = \frac{k_{\text{PCET amide}}[\text{amide}\bullet\text{phosphate}]_0}{k_{\text{PCET thiol}}[\text{thiol}\bullet\text{phosphate}]_0}$$

entry	thiol	amide X =	*Ir(III)	$k_{\text{PCET amide}}$ (M^{-1} s^{-1})	$K_{\text{A amide}}$ (M^{-1})	$k_{\text{PCET thiol}}$ (M^{-1} s^{-1})	$K_{\text{A thiol}}$ (M^{-1})	Q_0	% yield[b]	% recovery[b]
1	PhSH	H	**Ir-1**	8.4×10^9	1050	9.5×10^9	200	96:4	100	0
2	PhSH	COMe	**Ir-1**	3.0×10^9	1500	9.5×10^9	200	91:9	100	0
3	PhSH	CN	**Ir-1**	9.3×10^8	3550	9.5×10^9	200	87:13	100	0
4	PhSH	H	**Ir-2**	1.1×10^9	1050	3.6×10^9	200	86:14	100	0
5	PhSH	COMe	**Ir-2**	1.8×10^8	1500	3.6×10^9	200	62:38	80	9
6	PhSH	CN	**Ir-2**	6.8×10^7	3550	3.6×10^9	200	57:43	8	85
7	3,5-$(CF_3)_2C_6H_3SH$	H	**Ir-1**	8.4×10^9	1050	8.3×10^9	2100	78:22	95	0
8	3,5-$(CF_3)_2C_6H_3SH$	H	**Ir-2**	1.1×10^9	1050	2.2×10^9	2100	64:36	85	0
9	3,5-$(CF_3)_2C_6H_3SH$	COMe	**Ir-1**	3.0×10^9	1500	8.3×10^9	2100	56:44	60	30
10	3,5-$(CF_3)_2C_6H_3SH$	CN	**Ir-1**	9.3×10^8	3550	8.3×10^9	2100	47:53	13	62

$$Q = \frac{k_{\text{PCET amide}}[\text{amide}\bullet\text{phosphate}]}{k_{\text{PCET thiol}}[\text{thiol}\bullet\text{phosphate}]}$$

Oxidation PCET--- Alkylation

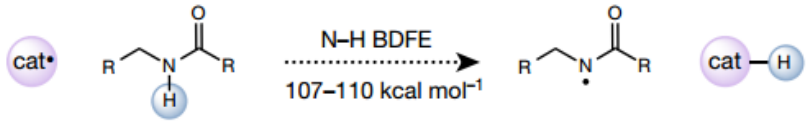
LETTER

doi:10.1038/nature19811

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

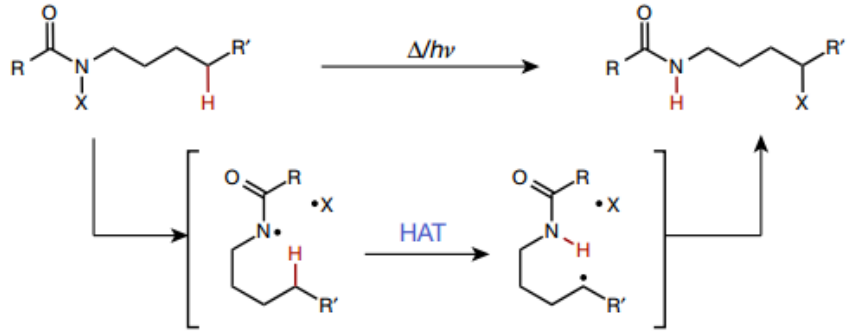
Gilbert J. Choi[1], Qilei Zhu[1]*, David C. Miller[1]*, Carol J. Gu[1] & Robert R. Knowles[1]

a Challenges in catalytic homolysis of strong N–H bonds



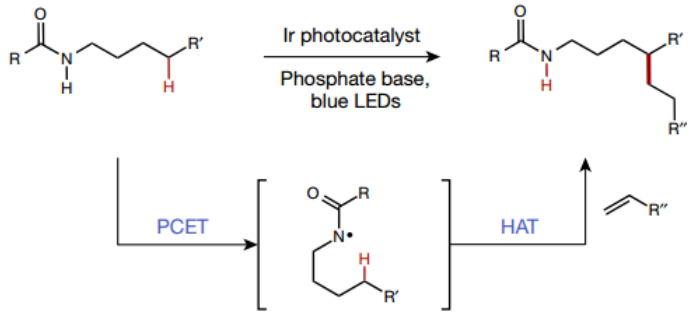
No known catalysts for selective homolysis of *N*-alkyl amide N–H bonds

b Classical Hofmann–Löffler–Freytag reactions



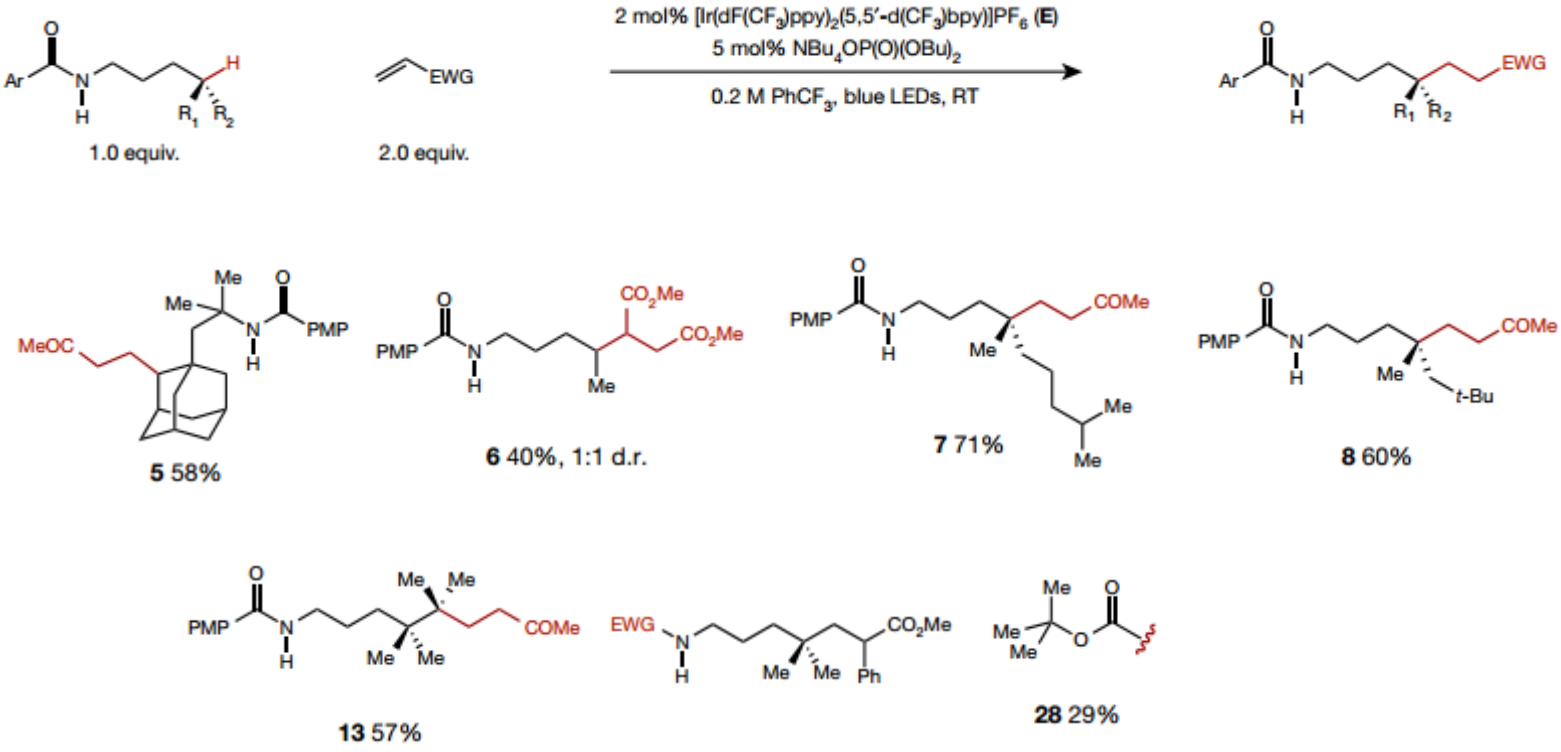
• *N*-functionalization required • No methods for C–C bond formation

c Catalytic C–H alkylation enabled by PCET

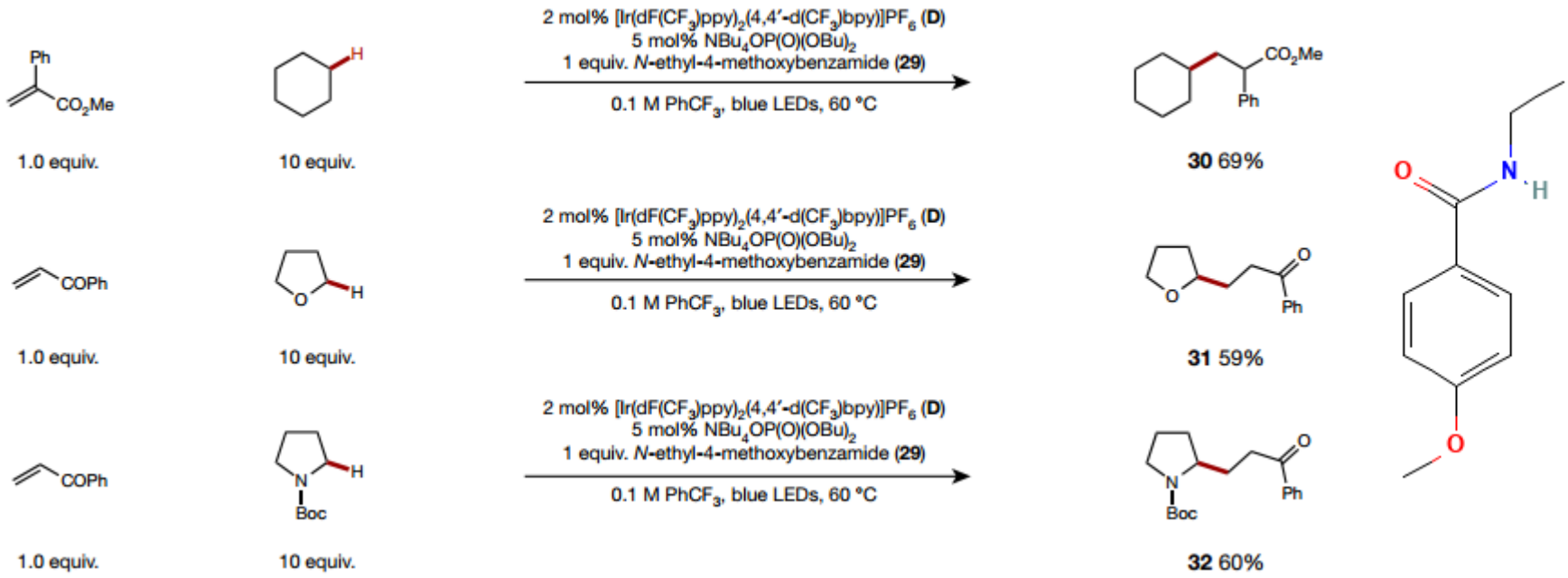


Directed alkylation of remote C–H bonds enabled by amide PCET

Scheme 4. Catalytic alkylation of remote C–H bonds enabled by proton-coupled electron transfer (Knowles,2016)

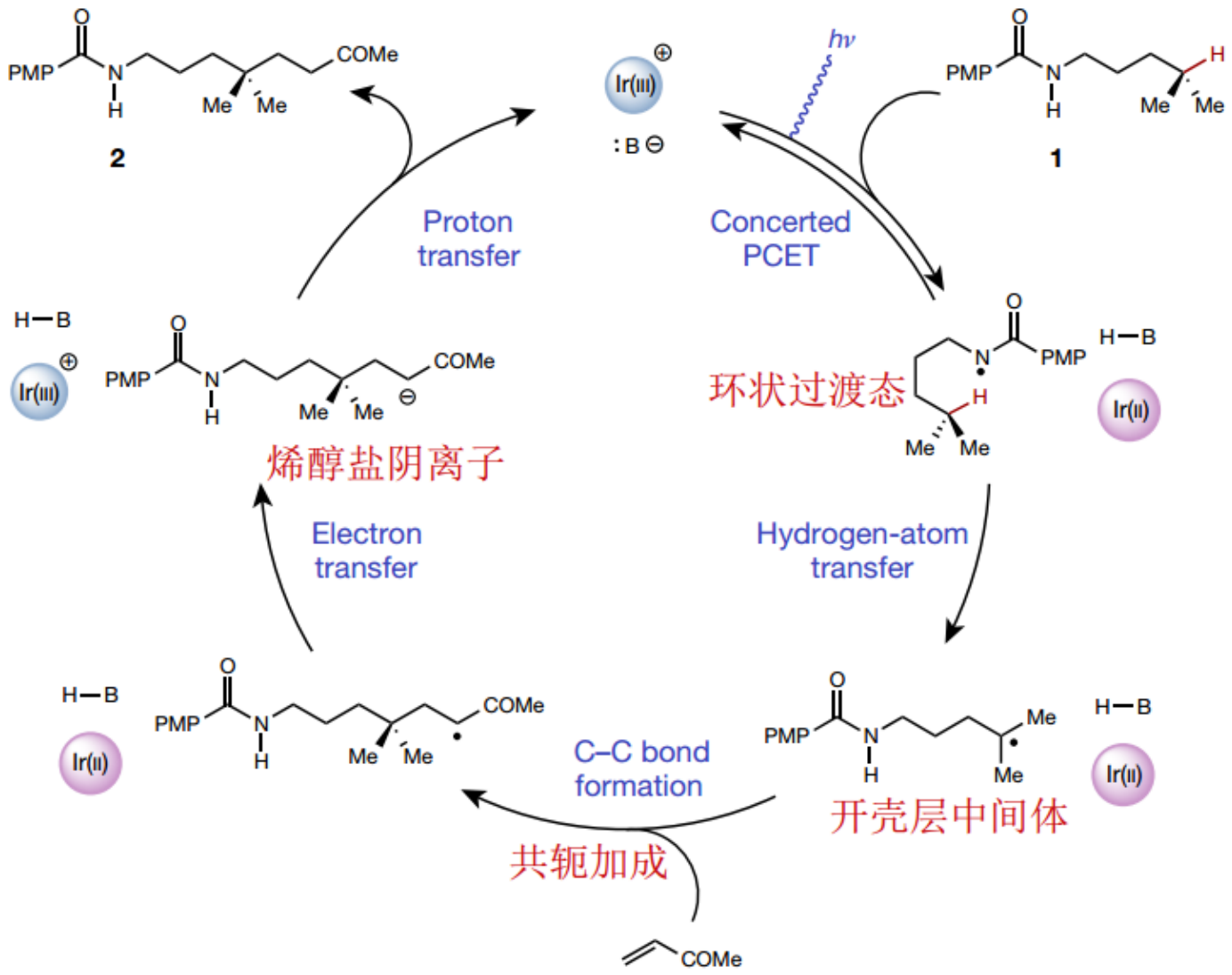


分子间C－H官能化



分子间C–H官能化同样适用，烷烃过量

Proposed Catalytic Cycle



Oxidation PCET--- N-Alkyl Amides

ACS Catalysis

Letter

Cite This: *ACS Catal.* 2019, 9, 4502–4507

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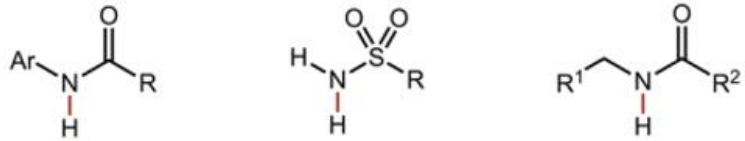
PCET-Enabled Olefin Hydroamidation Reactions with *N*-Alkyl Amides

Suong T. Nguyen, Qilei Zhu, and Robert R. Knowles*

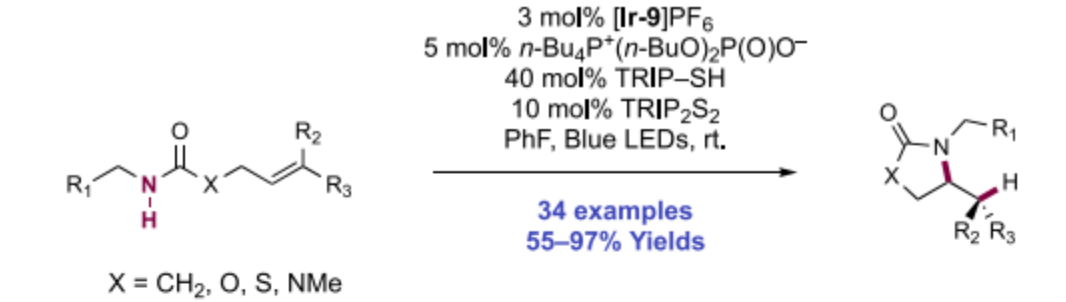
Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

a) BDFEs of N–H bonds in common amine derivatives

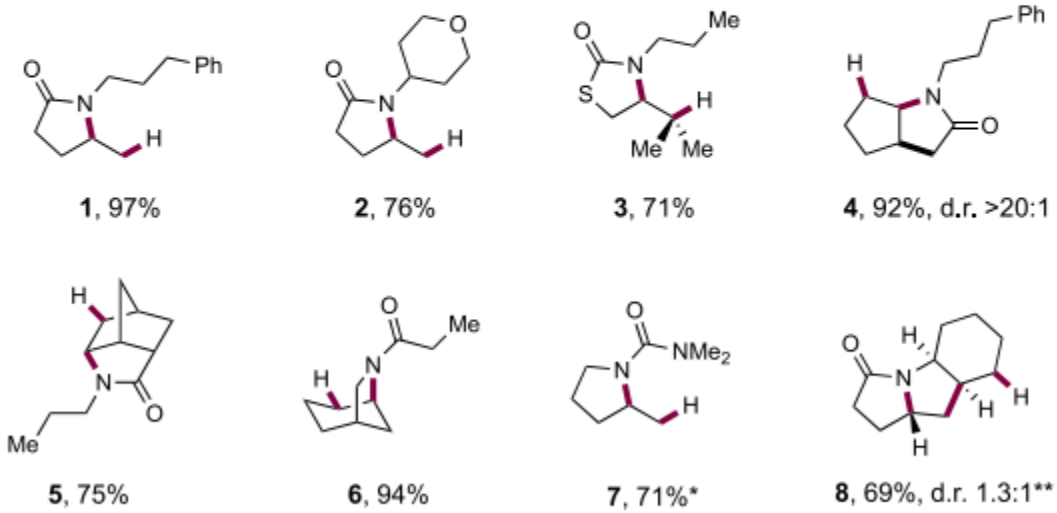


N-H BDFEs	~100 kcal/mol	~105 kcal/mol	~110 kcal/mol

Scheme 5. Catalytic Intramolecular Alkene Hydroamidations of N-Alkyl Amides (Knowles, 2019)



Selected examples:

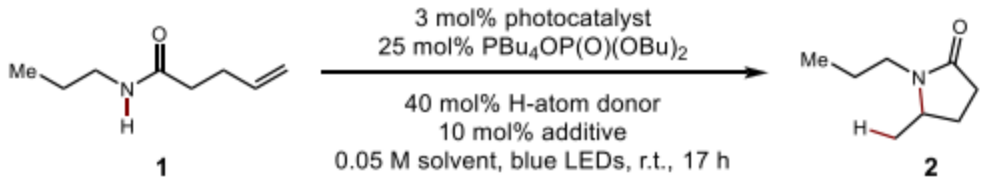


1, 97% **2**, 76% **3**, 71% **4**, 92%, d.r. >20:1

5, 75% **6**, 94% **7**, 71%* **8**, 69%, d.r. 1.3:1**

[a]*25 mol% n-$Bu_4P^+(t\text{-}BuO)_2P(O)O^-$, 80 mol% TRIP-SH. **Without TRIP-SH, 30 mol% $TRIP_2S_2$.

Table 1. Reaction Optimization[a]

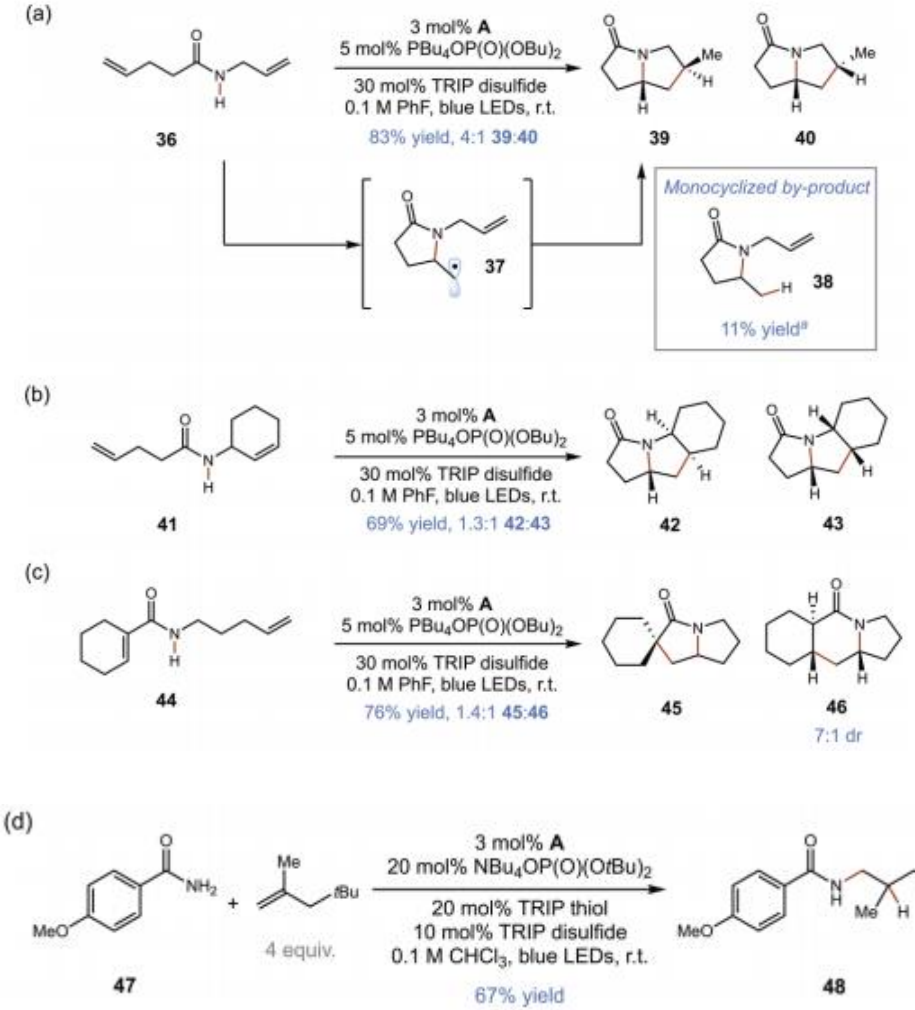


entry	solvent	PC	H-atom donor	additive	yield (%)[b]
1	PhF	**A**	TRIP thiol	-	44
2	PhF	**B**	TRIP thiol	-	26
3	PhF	**C**	TRIP thiol	-	10
4	PhF	**A**	thiophenol	-	32
5	PhF	**A**	tri(*t*Bu)thiophenol	-	33
6	PhF	**A**	*t*Dodecanethiol	-	8
7	PhF	**A**	TRIP thiol	TRIP disulfide	95
8	PhMe	**A**	TRIP thiol	TRIP disulfide	46
9	$PhCF_3$	**A**	TRIP thiol	TRIP disulfide	73
10	CH_2Cl_2	**A**	TRIP thiol	TRIP disulfide	51
11	$CHCl_3$	**A**	TRIP thiol	TRIP disulfide	62
			change from entry 7		
12	60 mol % TRIP thiol, no TRIP disulfide				58
13	no TRIP thiol, 30 mol % TRIP disulfide				81
14	5 mol % phosphate base				80
15	0.1 M PhF				85
16	5 mol % phosphate base and 0.1 M PhF				97
17	no light				0
18	no photocatalyst				0
19	no phosphate base				0
20	no TRIP thiol and/or TRIP disulfide				0

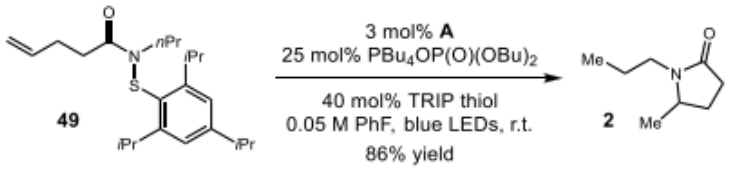
TRIP硫醇和TRIP二硫化物共同催化反应

在加倍反应浓度的同时降低磷酸盐碱的含量保持了反应活性，增强了制备规模反应的实用性

Scheme 1. Polycyclization Cascade and Intermolecular Anti-Markovnikov Hydroamidation Reaction†



Scheme 2. Olefin Hydroamidation with *N*-Thioamide



PCET--- Secondary alkyl amines

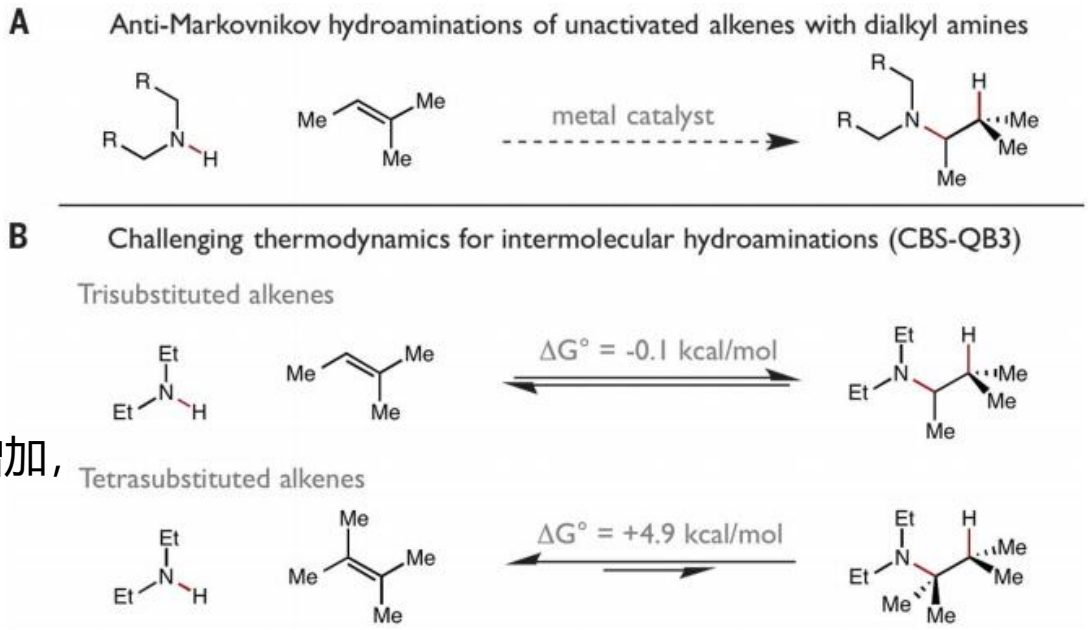
REPORT

PHOTOCHEMISTRY

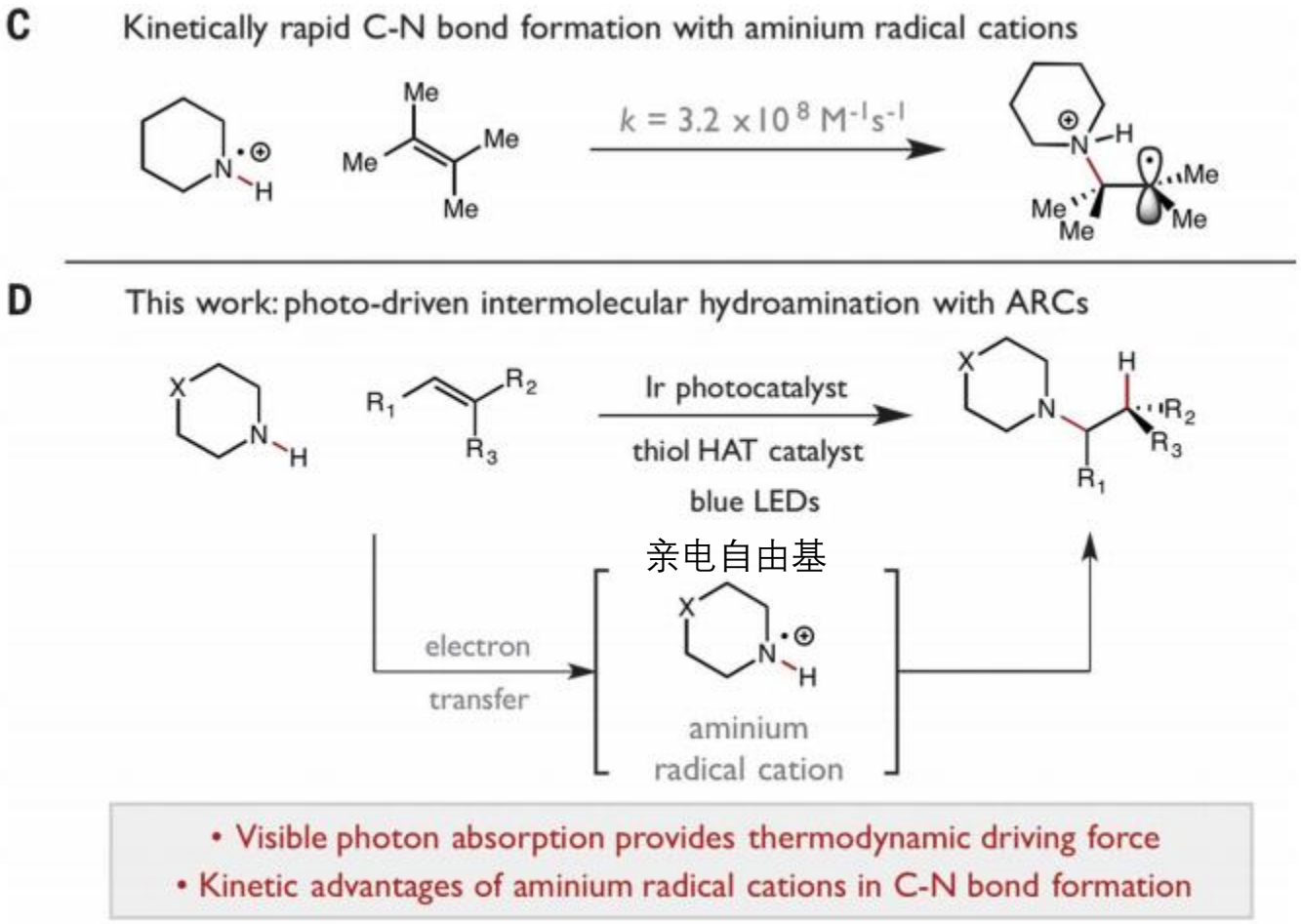
Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines

Andrew J. Musacchio,[1] Brendan C. Lainhart,[1*] Xin Zhang,[1*] Saeed G. Naguib,[1]
Trevor C. Sherwood,[2] Robert R. Knowles[1]†

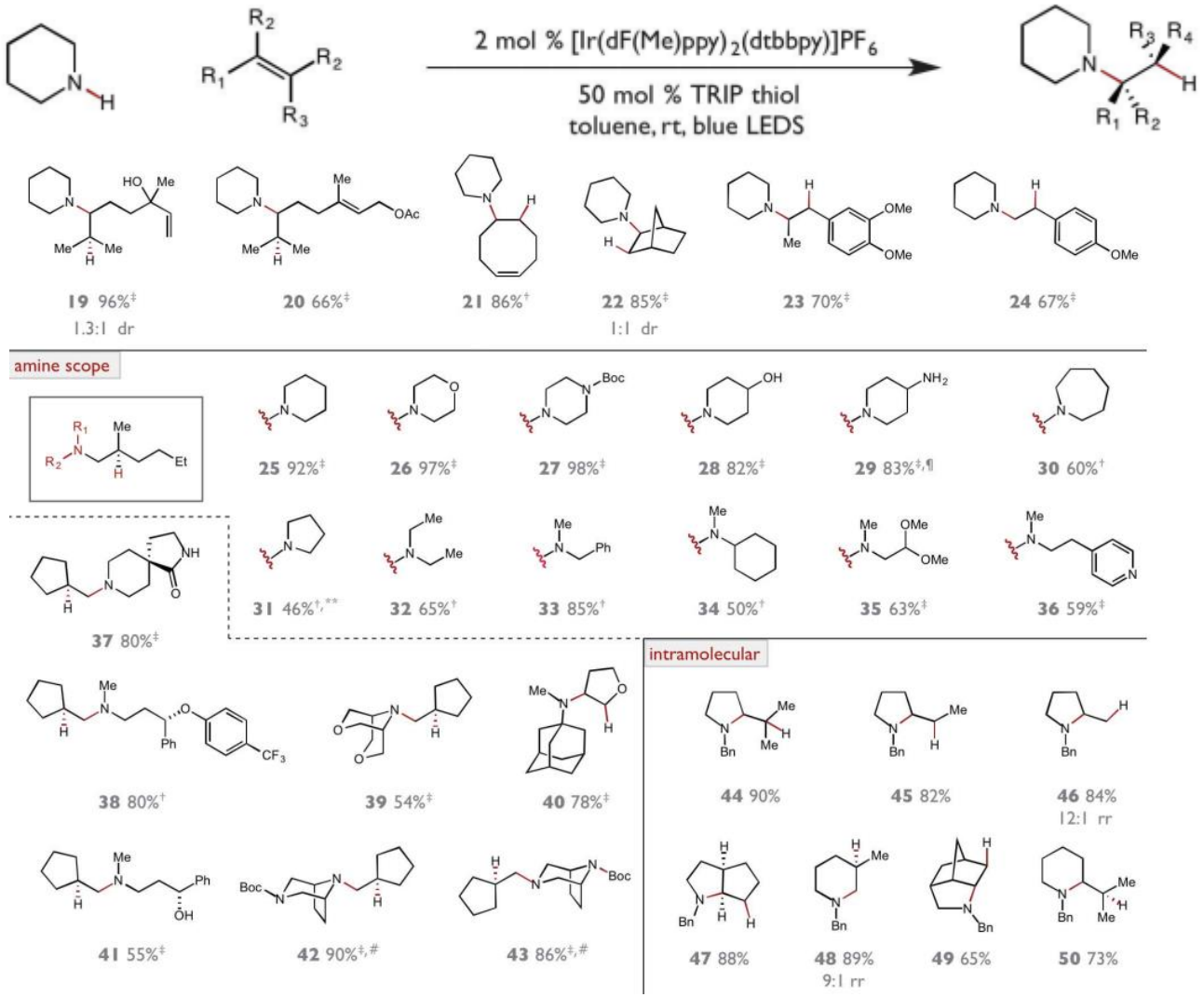
能量变大



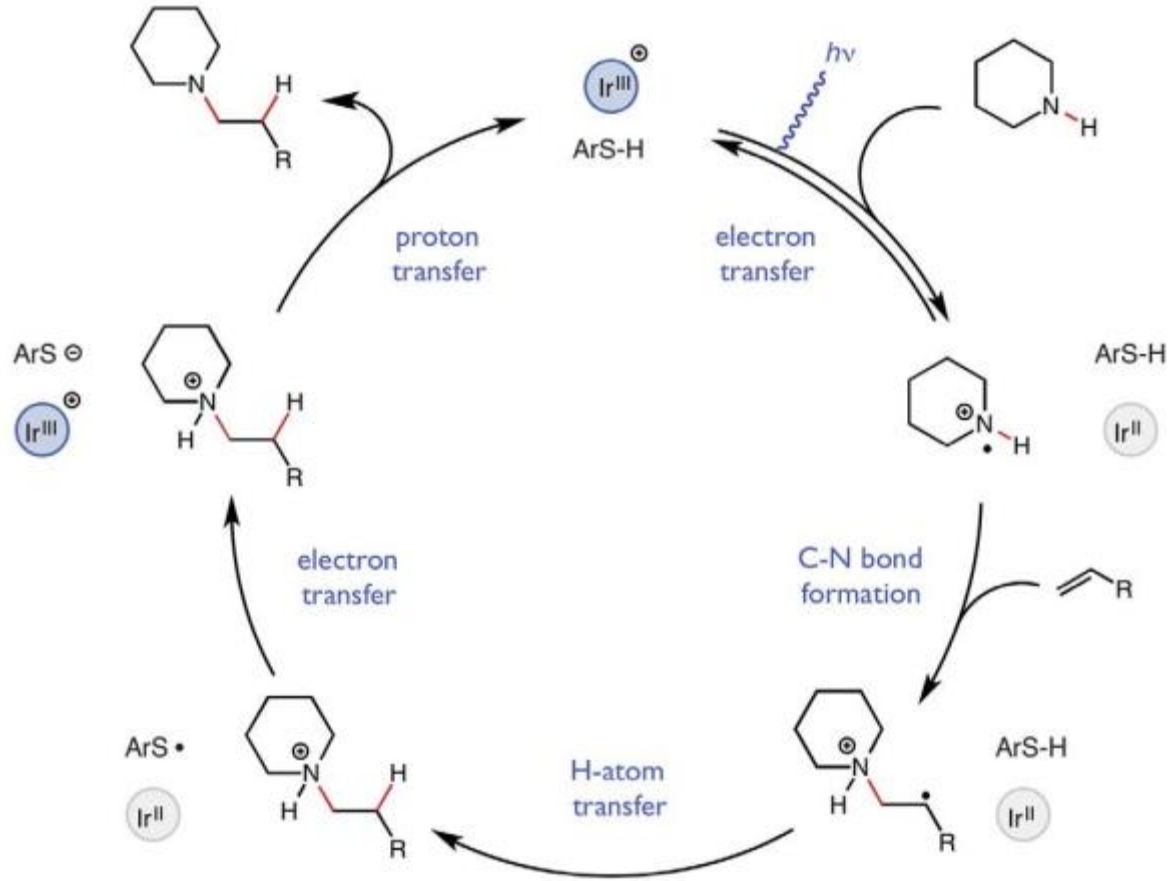
随着反应伙伴的空间分布的增加，类似的胺化变得越来越不利


C
Kinetically rapid C-N bond formation with aminium radical cations
k = 3.2 x 10 8 M-1s-1
D
This work: photo-driven intermolecular hydroamination with ARCs
Ir photocatalyst
thiol HAT catalyst
blue LEDs
亲电自由基
electron
transfer
aminium
radical cation
• Visible photon absorption provides thermodynamic driving force
• Kinetic advantages of aminium radical cations in C-N bond formation

Scheme 6. Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines



Proposed Catalytic Cycle



闭壳的氨离子中间体

PCET--- Primary alkyl amines

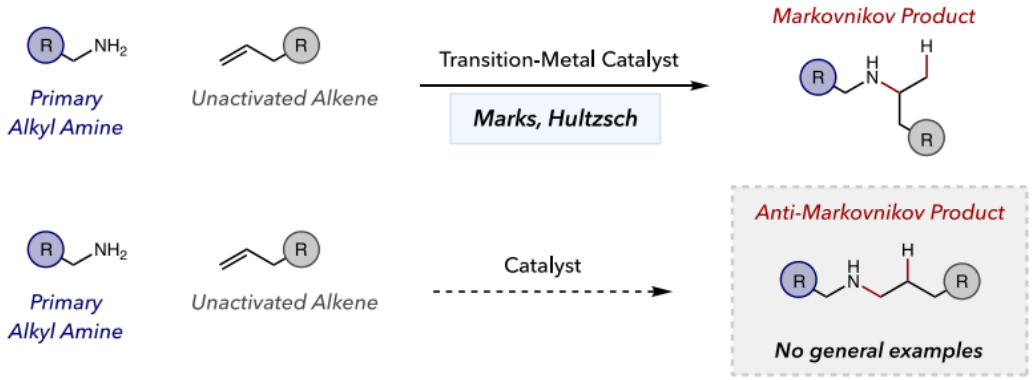
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: J. Am. Chem. Soc. 2019, 141, 16590−16594
pubs.acs.org/JACS

Anti-Markovnikov Hydroamination of Unactivated Alkenes with Primary Alkyl Amines

David C. Miller,[†,‡] Jacob M. Ganley,[†,‡] Andrew J. Musacchio,[†] Trevor C. Sherwood,[§] William R. Ewing,[§] and Robert R. Knowles*[,†]

[†]Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States
[§]Discovery Chemistry, Bristol−Myers Squibb, Lawrenceville, New Jersey 08543, United States

(A) Intermolecular Hydroamination of Unactivated Alkenes with Primary Amines



大多为马氏规则产物

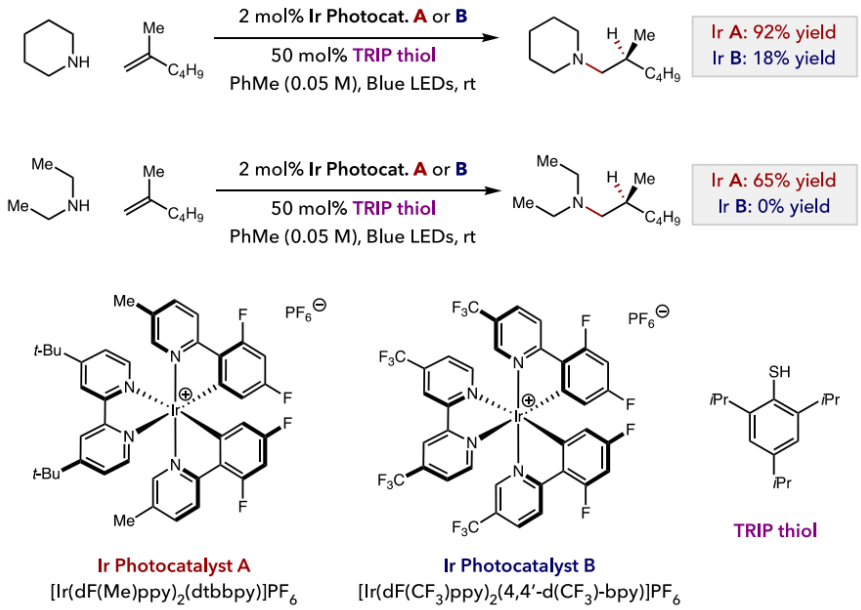


Figure 2. Observation of divergent reactivity between cyclic and acyclic amines with photocatalysts **A** and **B**.

光催化剂氧化程度影响反应产率

伯胺、仲胺之间氧化电位有巨大差异

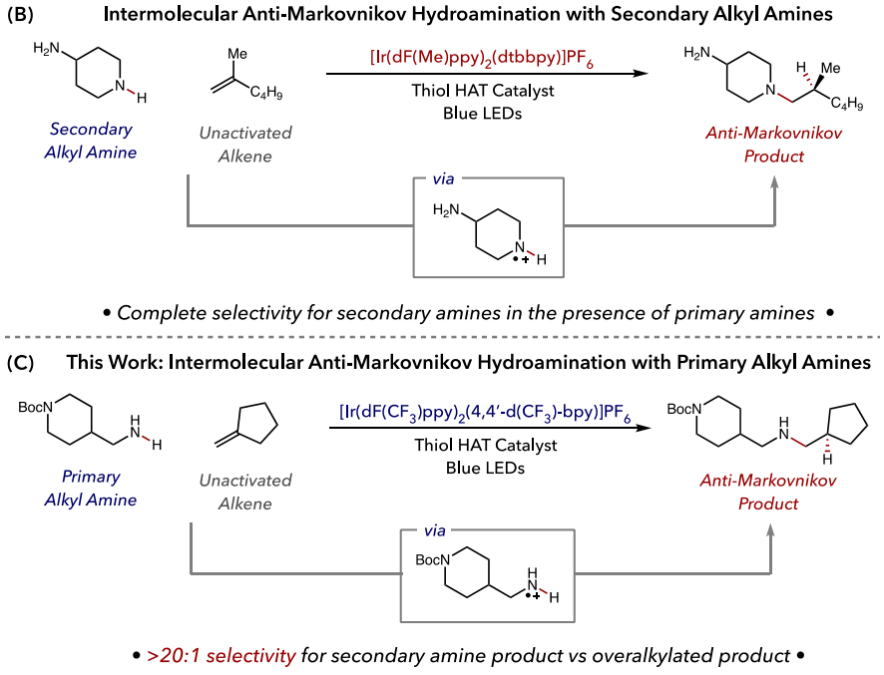
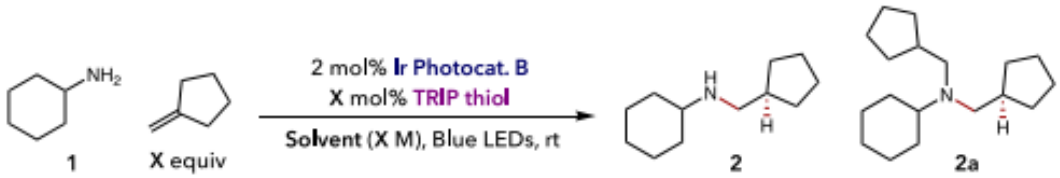


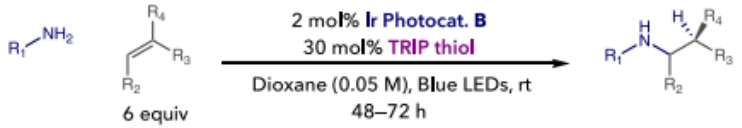
Table 1. Reaction Optimization[a]



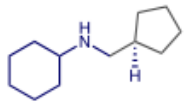
entry	solvent	TRIP thiol (mol%)	concn (M)	equiv alkene	yield (%) 2	yield (%) 2a
1	PhMe	30	0.05	6	8	0
2	EtOAc	30	0.05	6	34	0
3	dioxane	30	0.05	6	84	2
4	dioxane	30	0.2	3	69	2
5[b]	dioxane	30	0.05	6	8	0
6[c]	dioxane	30	0.05	6	76	2
7	dioxane	0	0.05	6	0	0
8[d]	dioxane	30	0.05	6	0	0
9[e]	dioxane	30	0.05	6	0	0

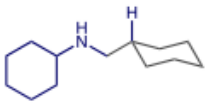
[a]Optimization reactions were performed on a 0.2 mmol scale and run for 24 h. Yields were determined via GC analysis of the crude reaction mixture relative to biphenyl as an internal standard. [b]**1**·HCl used instead of **1**. [c]**1**·HCl used with 1 equiv LiOH. [d]0 mol% Ir photocatalyst **B**. [e]No irradiation.

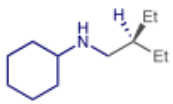
Table 2. Scope of the Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes[a]

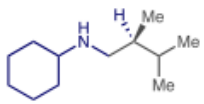


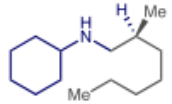
Alkene Scope

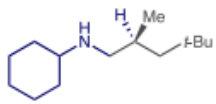

2 77%

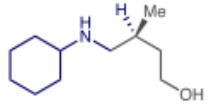

3 75%

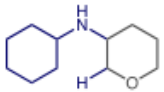

4 66%

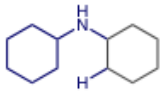

(±) 5 71%

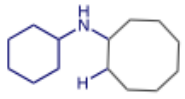

(±) 6 65% [b]

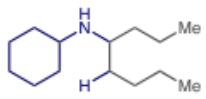

(±) 7 72% [b]

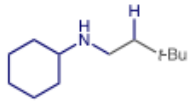

(±) 8 54%

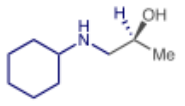

(±) 9 54% [b,c]

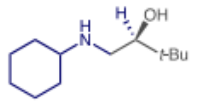

10 62%

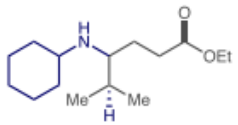

11 57%

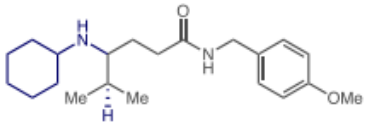

(±) 12 68% [d], 56% [e]

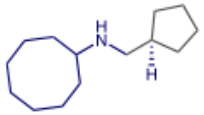

13 43%

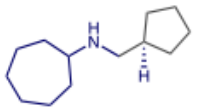

(±) 14 74% [f]

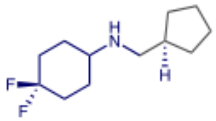

(±) 15 80% [f]

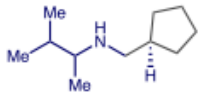

(±) 16 51%


(±) 17 62%

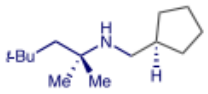

18 69%

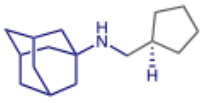

19 81%

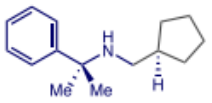

20 61% [g]


21 56%

Amine Scope


22 59%


23 73%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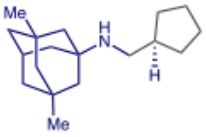
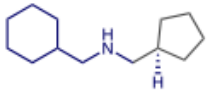
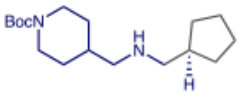
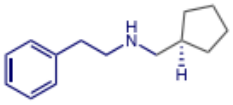
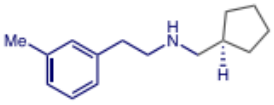
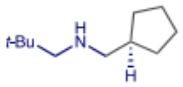

25 67% [g]

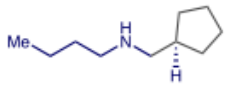

26 74%

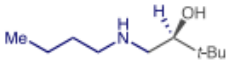

27 56% [g]


28 56%


29 49%


30 59%


31 43%


(±) 32 57% [f]

Oxidation PCET--- Anti-Markovnikov Hydroamination

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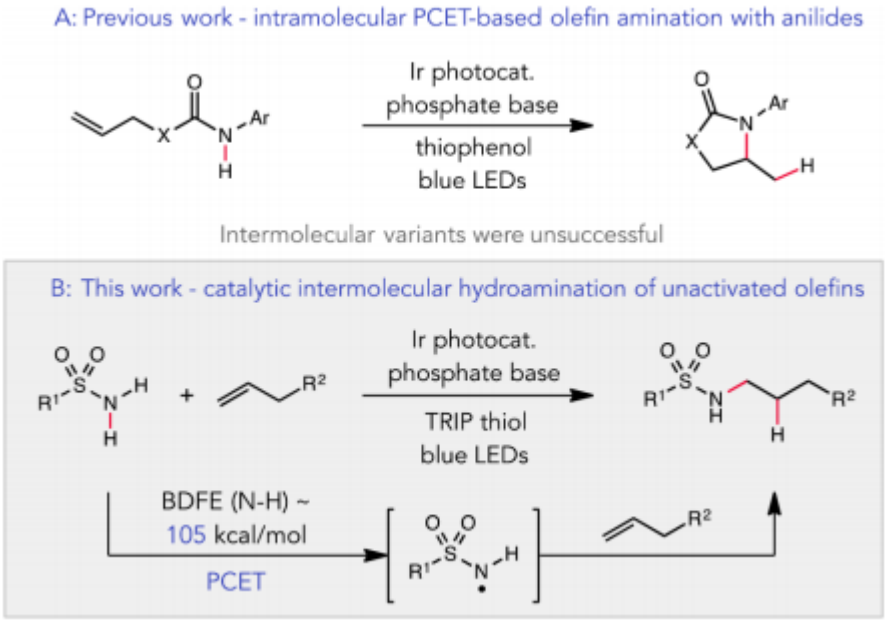
Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer

Qilei Zhu, David E. Graff, and Robert R. Knowles*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States



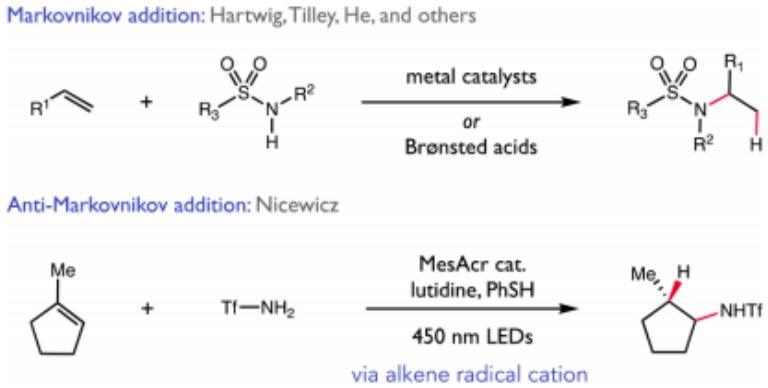
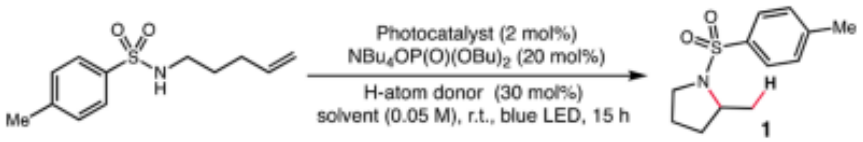


Figure 2. Prior work in intermolecular olefin hydroamination with sulfonamides.

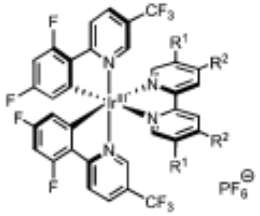
富电子烯烃与磺酰胺和各种唑的
分子间加氢胺化的催化方法

Table 1. Reaction Sensitivity Screen[a]



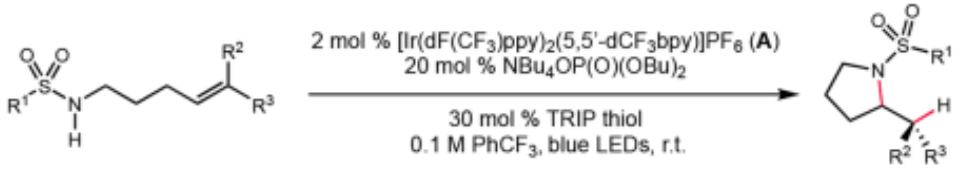
entry	H-atom donor	photocatalyst	solvent	yield (%)
1	2,4,6-TRIP thiophenol	A	$PhCF_3$	78
2	thiophenol	A	$PhCF_3$	47
3	*tert*-dodecanethiol	A	$PhCF_3$	16
4	BHT	A	$PhCF_3$	<1
5	Ph_2CHCN	A	$PhCF_3$	<1
6	2,4,6-TRIP thiophenol	B	$PhCF_3$	71
7	2,4,6-TRIP thiophenol	C	$PhCF_3$	77
8	2,4,6-TRIP thiophenol	D	$PhCF_3$	38
9	2,4,6-TRIP thiophenol	A	$PhCF_3$	6
10	2,4,6-TRIP thiophenol	A	CH_2Cl_2	32
11	2,4,6-TRIP thiophenol	A	$ClCH_2CH_2Cl$	13
12	2,4,6-TRIP thiophenol	A	THF	<1
	Change from Best Conditions (Entry 1)			
13	no light			<1
14	no photocatalyst			<1
15	no $NBu_4OP(O)(OBu)_2$			1
16	no 2,4,6-TRIP thiophenol			1

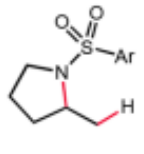
[a]Reactions were run on 0.05 mmol scale, and yields are determined by GC analysis relative to an internal standard. Photocatalysts:



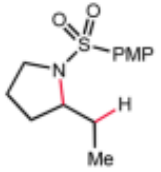
A: $R^1 = CF_3$, $R^2 = H$;
B: $R^1 = H$, $R^2 = CF_3$;
C: $R^1 = CO_2Me$, $R^2 = H$;
D: $R^1 = H$, $R^2 = CO_2Me$;
E: $R^1 = H$, $R^2 = {}^tBu$;

Table 2. Scope of the Intramolecular Amination[a]

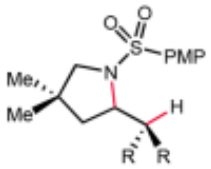




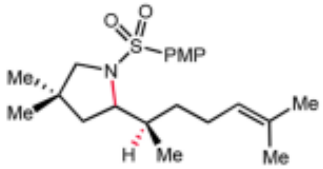
1 Ar = 4-tol, 86%
2 Ar = PMP, 92%



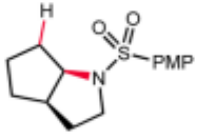
3 91%



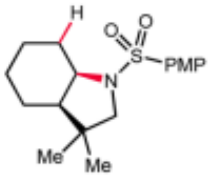
4 90% R = H
5 92% R = Me



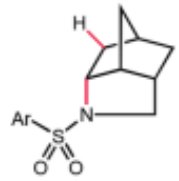
6 81% (1:1 dr)



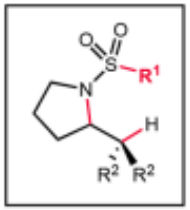
7 85%
>20:1 dr

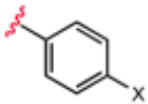


8 89%
>20:1 dr

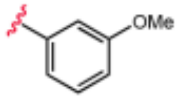


9 86% Ar = 4-tol,
10 88% Ar = PMP

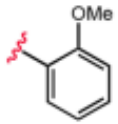




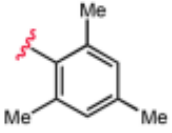
$R^2 = R^2$ = Me:
11 X = OMe, 96%
12 X = Me, 74%
13 X = H, 66%
14 X = Cl, 69%
15 X = Br, 66%
16 X = CF_3, 65%
17 X = CN, 57%



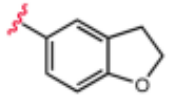
18 R^2 = Me 86%



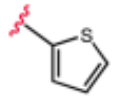
19 R^2 = Me 47%



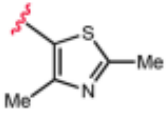
20 R^2 = Me 83%
21 R^2 = H 82%



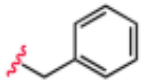
22 R^2 = Me 90%



23 R^2 = Me 89%
24 R^2 = H 79%



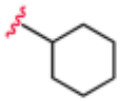
25 R^2 = Me 81%



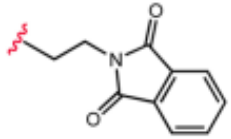
26 R^2 = Me 81%

27 R^2 = Me 69%

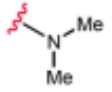
28 R^2 = Me 70%



29 R^2 = Me 67%

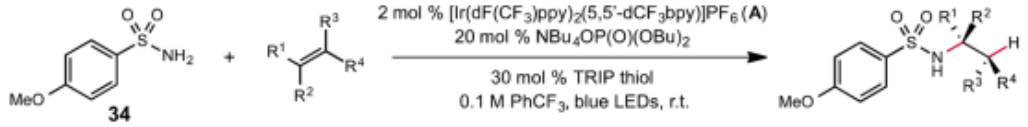


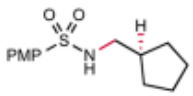
30 R^2 = Me 77%
31 R^2 = H 76%



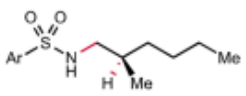
32 R^2 = Me 91%
33 R^2 = H 80%

Table 3. Scope of the Intermolecular Hydroamination

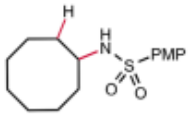




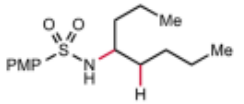
35 64%[b]



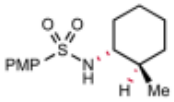
36 82% Ar = PMP
37 15% Ar = 4-tol[a]



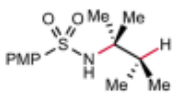
38 75%



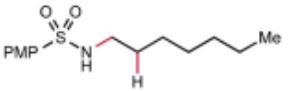
39 from *cis*-4-octene: 86%
from *trans*-4-octene: 79%



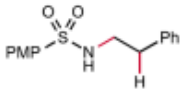
40 60%
trans:*cis* = 2:1



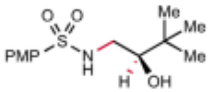
41 89%



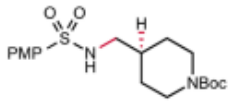
42 60%



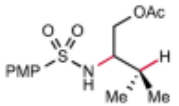
43 26%[a]



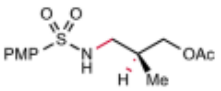
44 59%



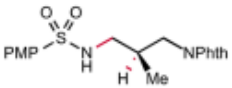
45 85%



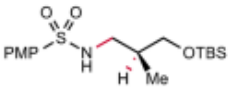
46 45%



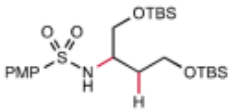
47 67%



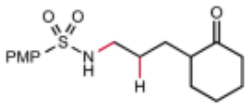
48 78%



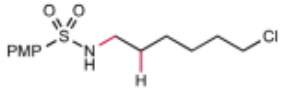
49 80%



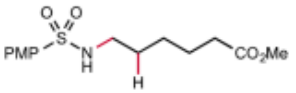
50 48%



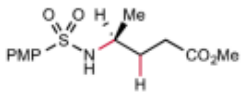
51 52%



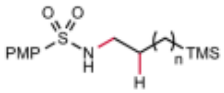
52 50%



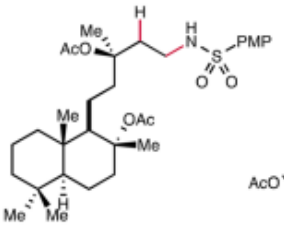
53 51%



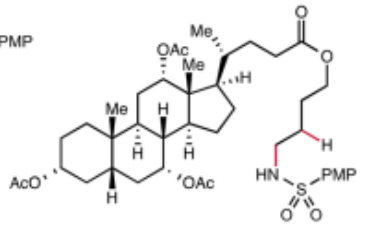
54 44% (3:1 regioisomer)



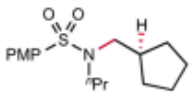
55 n = 0, 42%
56 n = 1, 49%



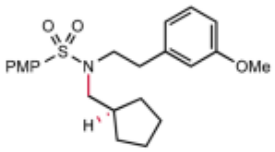
Sclareol derivative
57 50%[b]



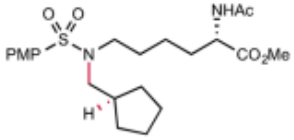
Cholic acid derivative
58 47%[b]



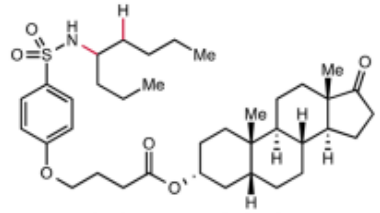
59 57%



60 53%

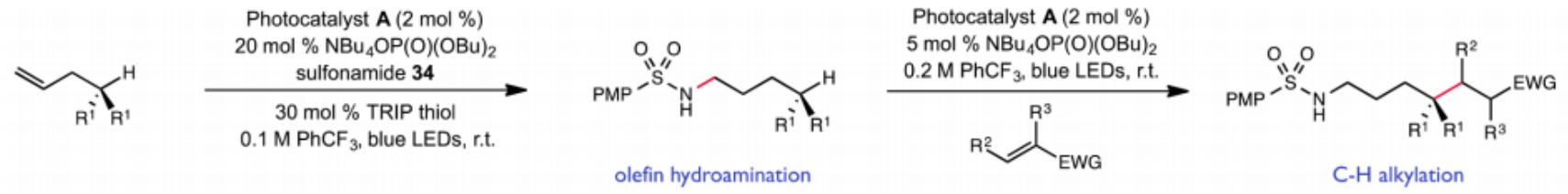


61 46%



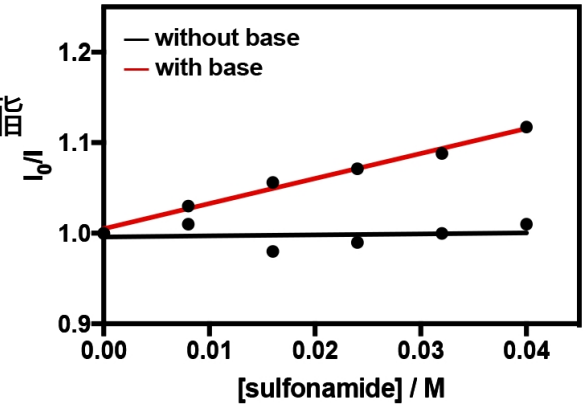
Androsterone derivative
62 57%

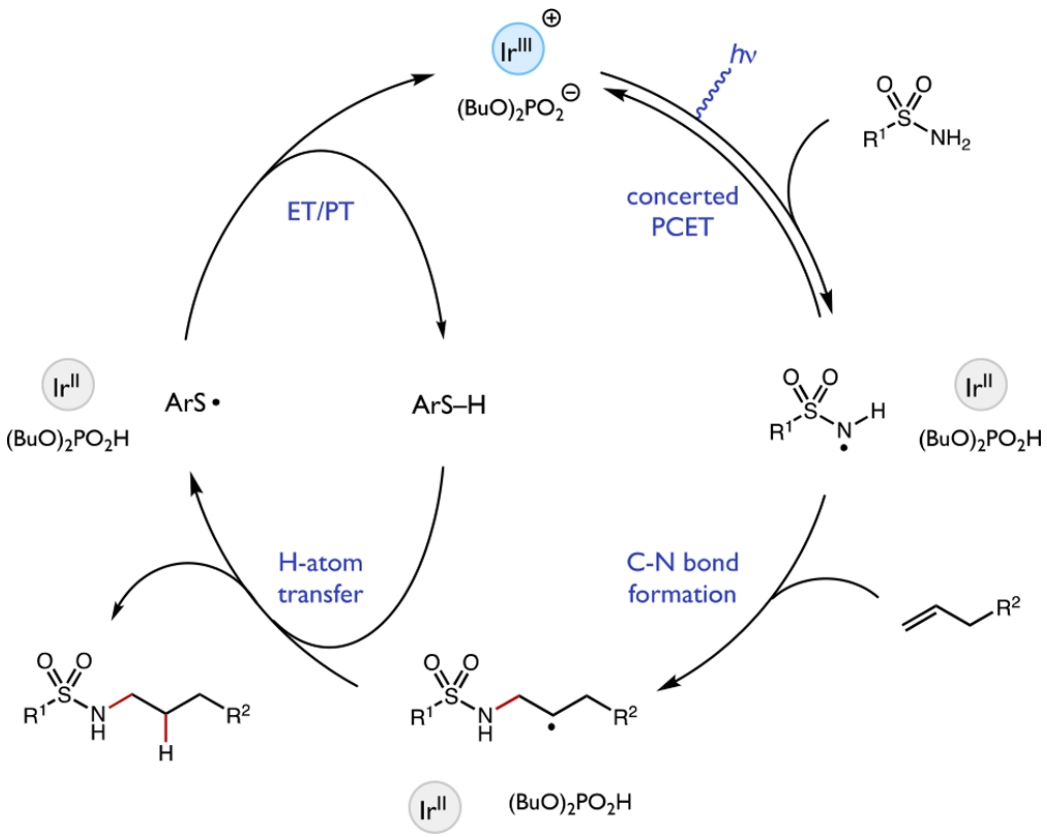
Scheme 1. Tandem Amination/C–H Alkylation[a]

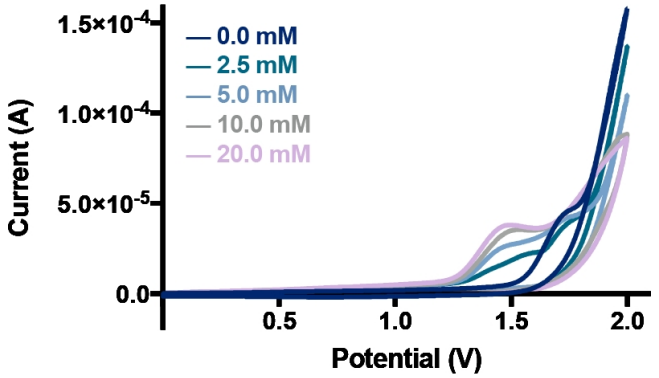


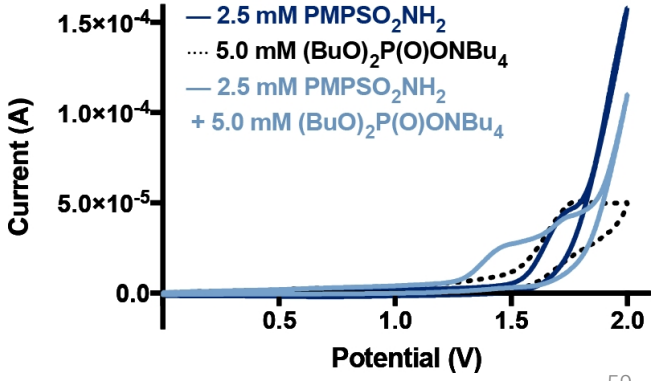
Alkene	Products		Alkene	Product
63	**64**	**65**	**66**	**67**
I st step: 75%	2nd step: 83%	2nd step: 70%	I st step: 74%	2nd step: 78%

不同浓度的磺酰胺
恒定浓度的磷酸二丁酯
光催化剂的猝灭









该烷基通过HAT被硫醇助催化剂还原

Oxidation PCET---Enantioselective Hydroamination

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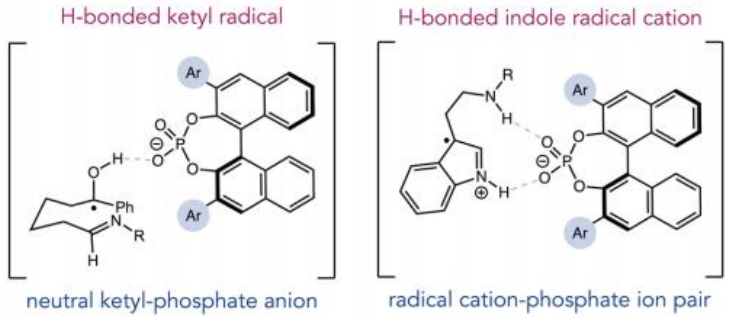
Communication

Enantioselective Hydroamination of Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer

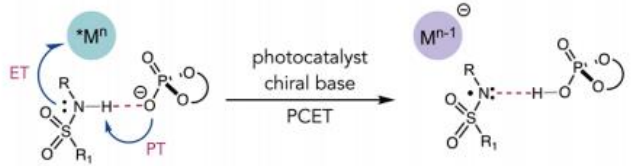
Casey B. Roos, Joachim Demaerel, David E. Graff, and Robert R. Knowles*

Cite This: *J. Am. Chem. Soc.* 2020, 142, 5974–5979
Read Online

(a) Previous Work: Electrostatic contributions to hydrogen bonding interactions



(b) Hypothesis: Hydrogen bonding in PCET successor complex



Can we extend this principle to neutral radical interfaces?

(c) This Work: Enantioselective C-N bond formation enabled by PCET

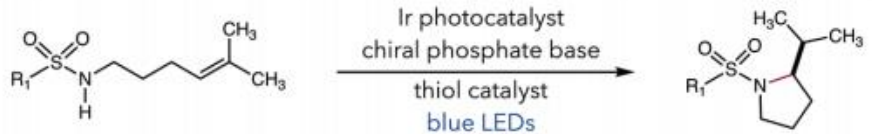
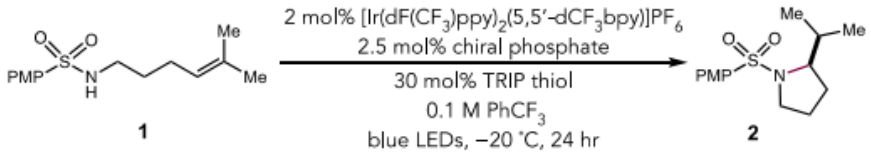
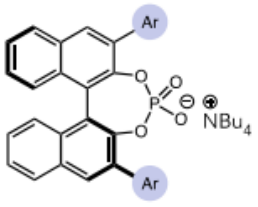


Table 1. Optimization Studies[a]

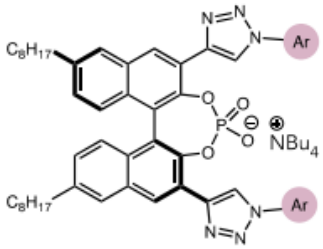


Entry	Phosphate	Yield (%)	er
1	**P1**	54	55:45
2	**P2**	30	52:48
3	**P3**	96	35:65
4	**P4**	62	86:14
5	**P5**	97	93:7
6	**P6**	98	87:13
7	**P7**	85	95:5

Chiral phosphate bases:

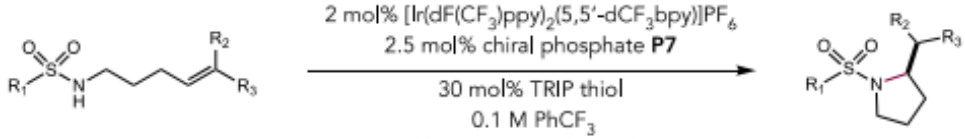


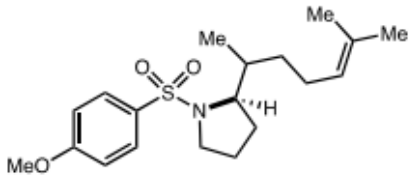
P1 Ar = C_6H_5
P2 Ar = (2,4,6-*i*Pr)C_6H_2
P3 Ar = 9-phenanthryl



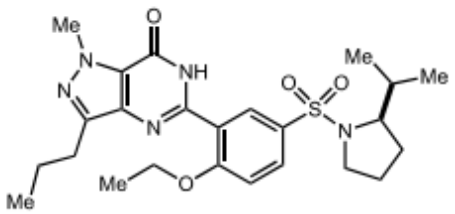
P4 Ar = 9-phenanthryl
P5 Ar = C_6H_5
P6 Ar = (2,6-*i*Pr)C_6H_3
P7 Ar = (3,5-Ph)C_6H_3

Entry	Change from Entry 7	Yield (%)	er
8	room temperature	93	89:11
9	thiophenol H-atom donor	81	94:6
10	10 mol% **P7**	89	95:5
11	no base	<1	-
12	no thiol	<5	-
13	no photocatalyst	<1	-
14	no light	<1	-

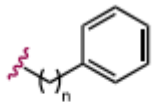




from cis: **28** 85%
96:4 er; 1.5:1 dr



22 50%, 96:4 er[c]



15 n = 1 98%, 91:9 er
16 n = 2 98%, 96:4 er

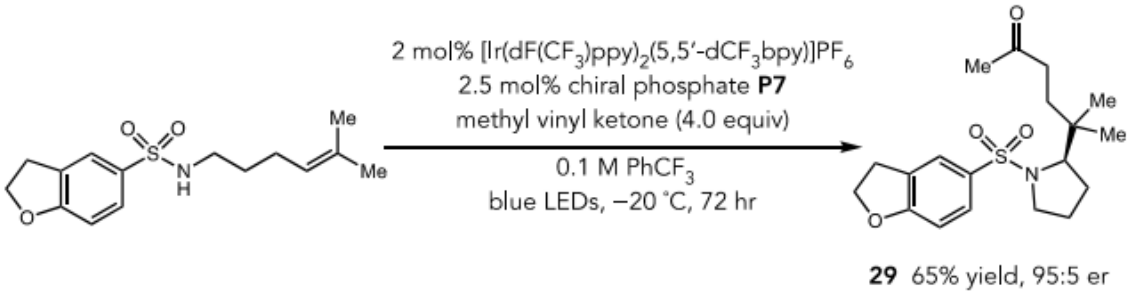
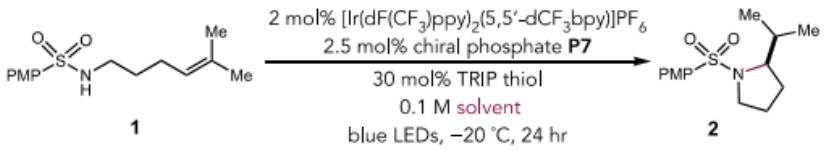


Figure 2. Carboamination reaction.

这种氢化胺化反应的对映选择性对溶剂介电常数不敏感

非离子对机制

Table 3. Enantioselectivity as a Function of Solvent Dielectric

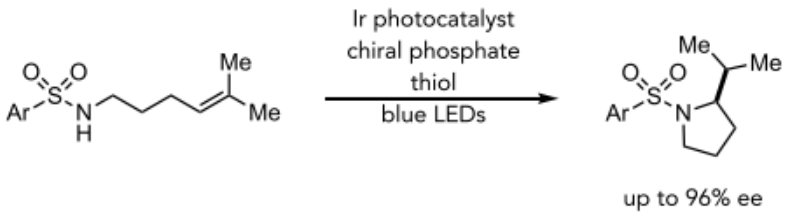


entry	solvent	yield (%)	er	ε
1	toluene	85	93:7	2.4
2	fluorobenzene	77	94:6	5.5
3	tetrahydrofuran	45	94:6	7.5
4	dichloromethane	54	94:6	8.9
5	acetonitrile	15	94:6	36.6
6	*N*,*N*-dimethylformamide	trace	83:17	38.3
7	propylene carbonate	trace	85:15	66.2

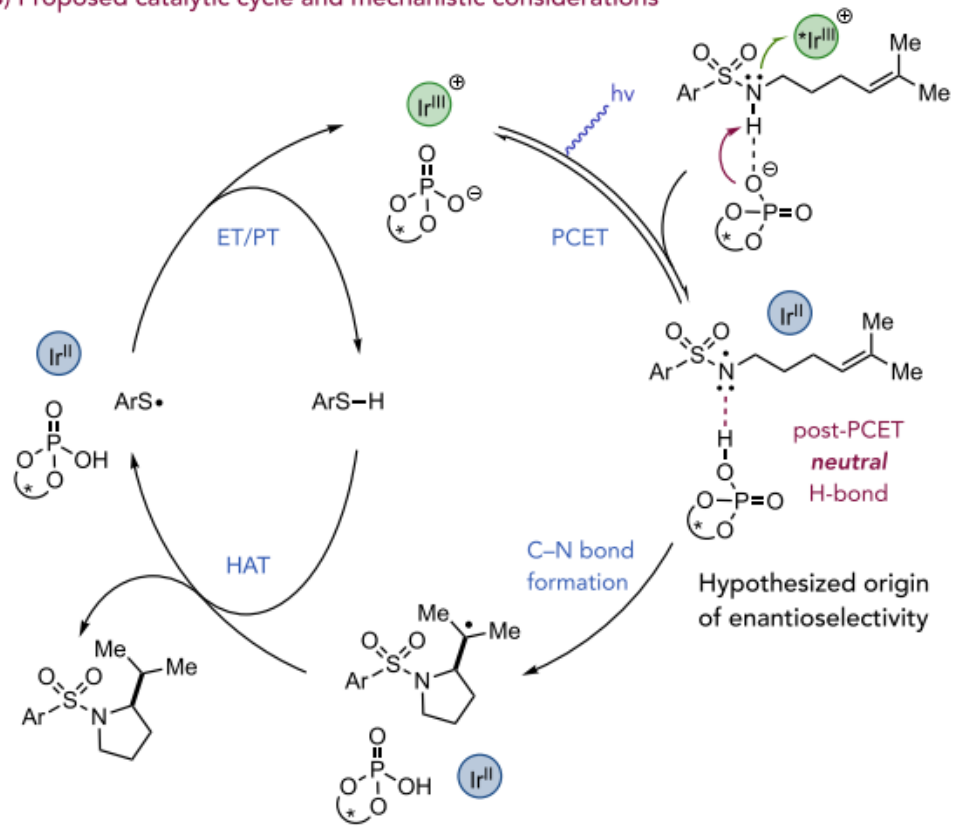
[a]Reactions were conducted on a 0.05 mmol scale, and yields were determined by NMR analysis relative to an internal standard. Enantioselectivity determined by HPLC analysis on a chiral stationary phase.

非共价相互作用(NCIs)

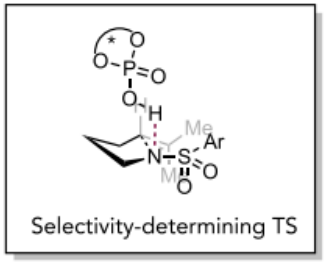
A) Overview of enantioselective hydroamination of alkenes with sulfonamides



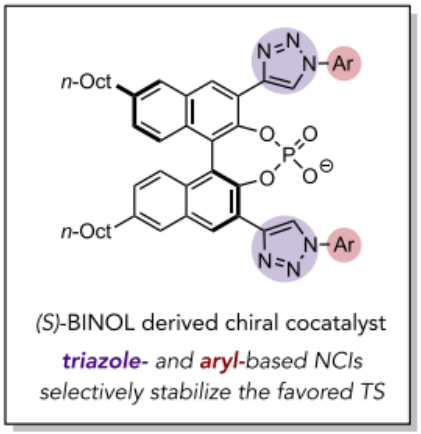
B) Proposed catalytic cycle and mechanistic considerations



C) This work: experiments, computational studies, and data science-based analysis



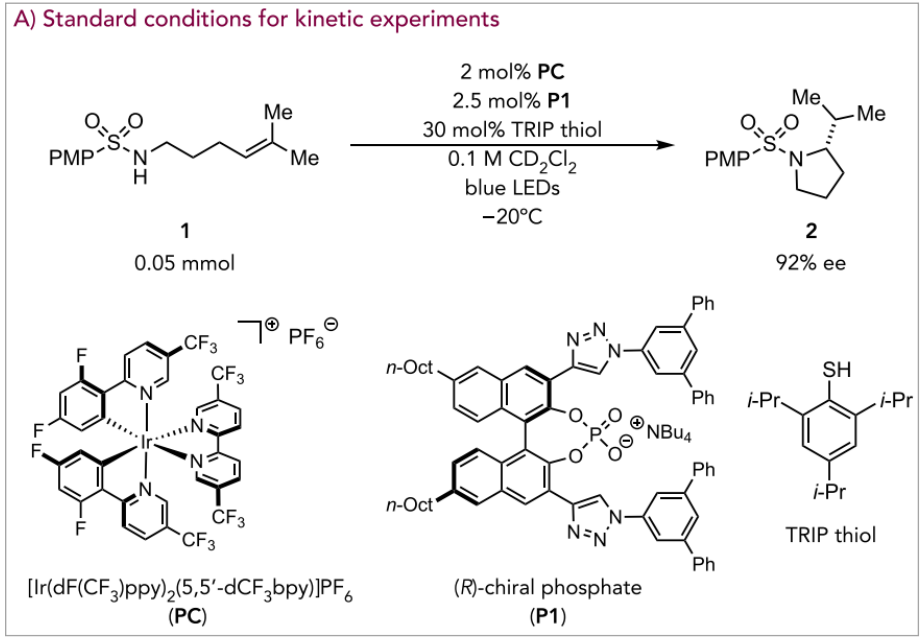
- Experimentally and computationally supported enantiodetermining C–N bond formation.
- TS calculations and statistical modeling reveal the primary and secondary network of NCIs that govern enantioselectivity.

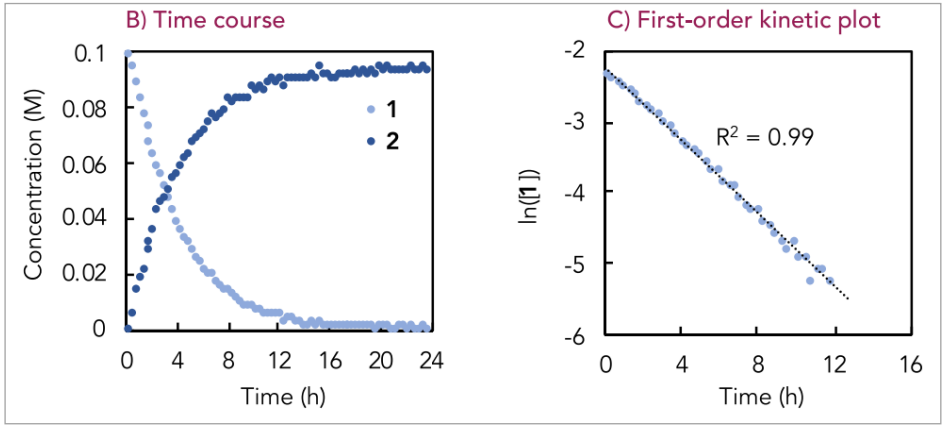


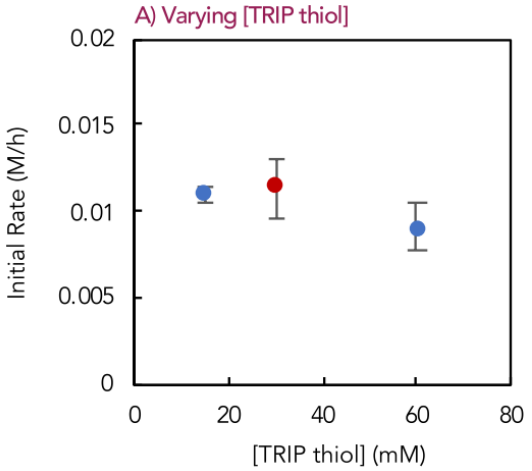
Key mechanistic questions:

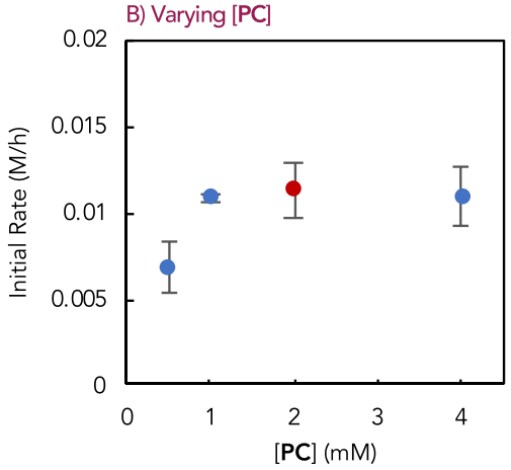
- What is the enantiodetermining step of the catalytic cycle?
- Can a molecular model be constructed to support the hypothesis and account for enantioinduction across a range of substrates and chiral cocatalysts?

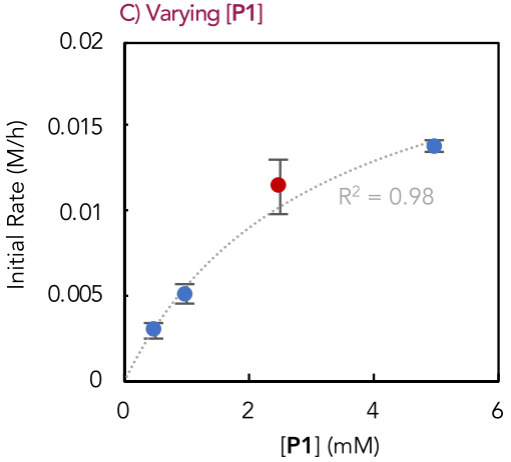
https://doi.org/10.1021/jacs.2c07099
J. Am. Chem. Soc. 2022, 144, 18948−18958





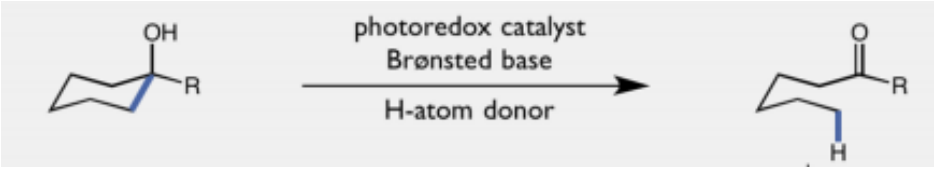




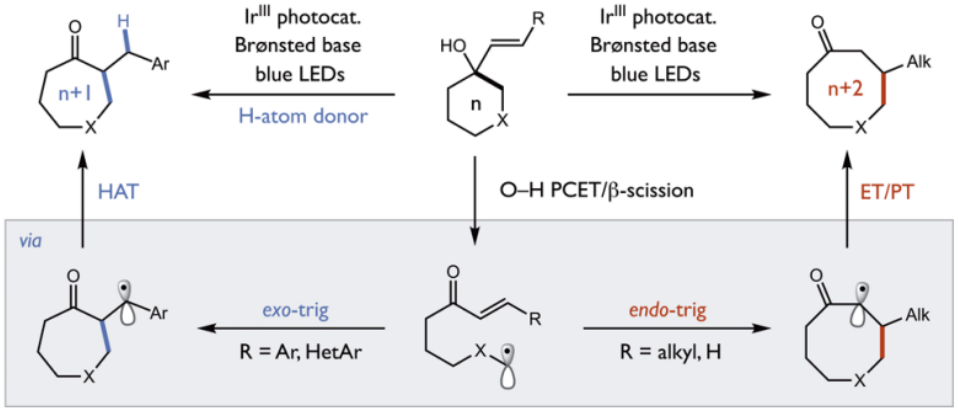


排除了对映体选择性在可逆的C-N键形成之后的HAT步骤中建立

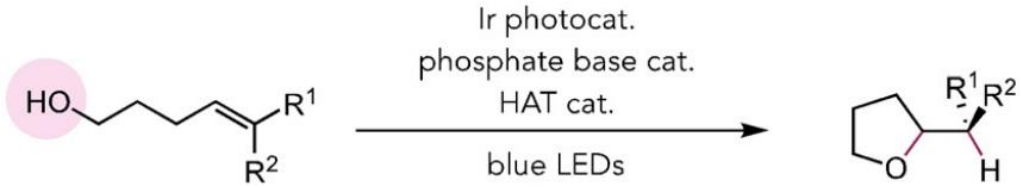
Oxidation PCET---O-H Bonds



J. Am. Chem. Soc. 2016, 138, 10794−10797



J. Am. Chem. Soc. 2019, 141, 8752−8757



Angew. Chem. Int. Ed. 2020, 59, 11845 – 11849

Oxidation PCET---Ring-Opening of Cyclic Alcohols

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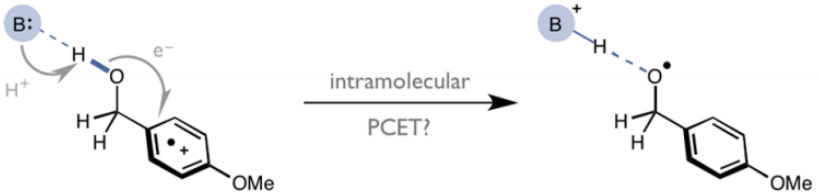
Catalytic Ring-Opening of Cyclic Alcohols Enabled by PCET Activation of Strong O–H Bonds

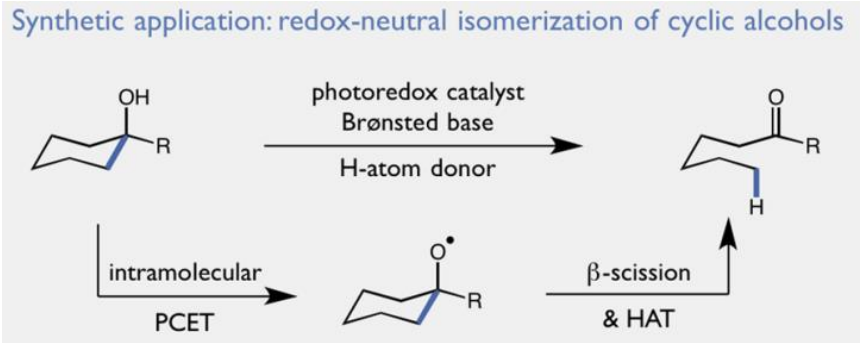
Hatice G. Yayla, Huaiju Wang, Kyle T. Tarantino, Hudson S. Orbe, and Robert R. Knowles*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

Bacchioici, Bietti, and Steenken:

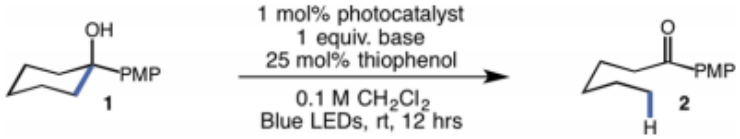


This work:



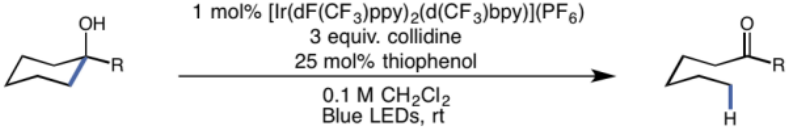
允许从空间上远离芳烃自由基阳离子的醇产生烷氧基自由基，提供了选择性裂解远端C-C键的方法

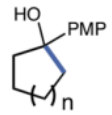
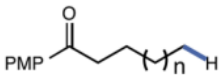
Table 1. Reaction Optimization[a]

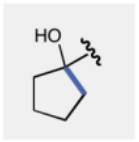


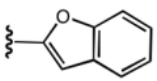
entry	photocatalyst	base	yield (%)
1	$[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ (**A**)	collidine	0
2	$[Ir(dF(CF_3)ppy)_2(bpy)](PF_6)$ (**B**)	collidine	9
3	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	collidine	79
4	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	pyridine	6
5	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	$TBA^+ (PhO)_2POO^-$	4
6	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	$TBA^+ CF_3COO^-$	48
7	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	$TBA^+ PhCOO^-$	8
8	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	collidine (2 equiv)	83
9	$[Ir(dF(CF_3)ppy)_2(5,5'd(CF_3)bpy)](PF_6)$ (**C**)	collidine (3 equiv)	91

Table 2. Substrate Scope[a]

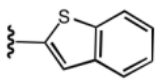


Starting material	Product	Yield
		**3** n = 0 71% **4** n = 1 86% **2** n = 2 89% **5** n = 3 90% **6** n = 4 81% **7** n = 6 92% **8** n = 8 85%

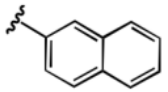




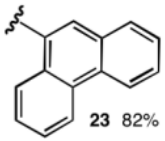
20 84%



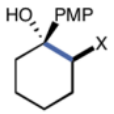
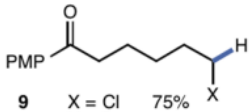
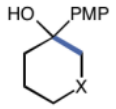
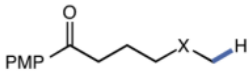
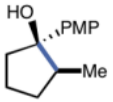
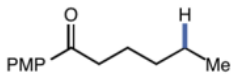
21 86%

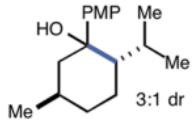
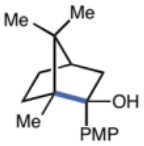
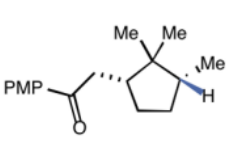
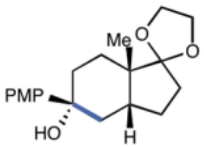
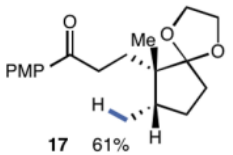


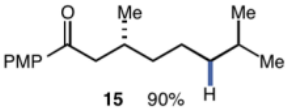
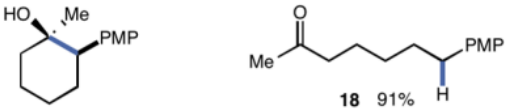
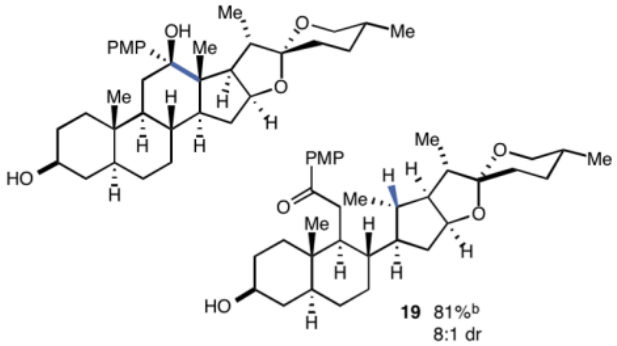
22 41%

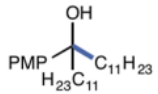
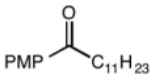
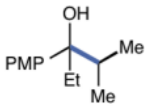
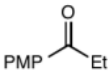


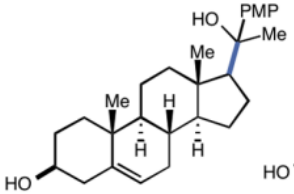
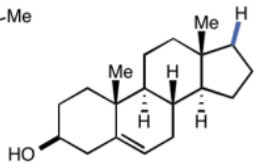
23 82%

Starting material	Product
	 **9** X = Cl 75% **10** X = Br 63%
	 **11** X = O 98% **12** X = NBoc 88% **13** X = $C(Me)_2$ 94%, 8.5:1 rr
	 **14** 97%

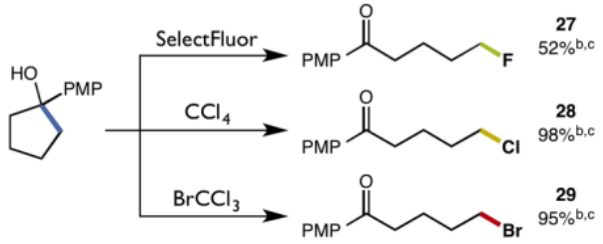
Starting material	Product
	3:1 dr
	 **16** 91%, 6:1 dr
	 **17** 61%

Starting material	Product
	 **18** 91%
	**19** 81%[b] 8:1 dr

Starting material	Product
	 **24** 84%
	 **25** 93%

Starting material	Product
	2:1 dr
	**26** 72%[b]

Halogenation reactions

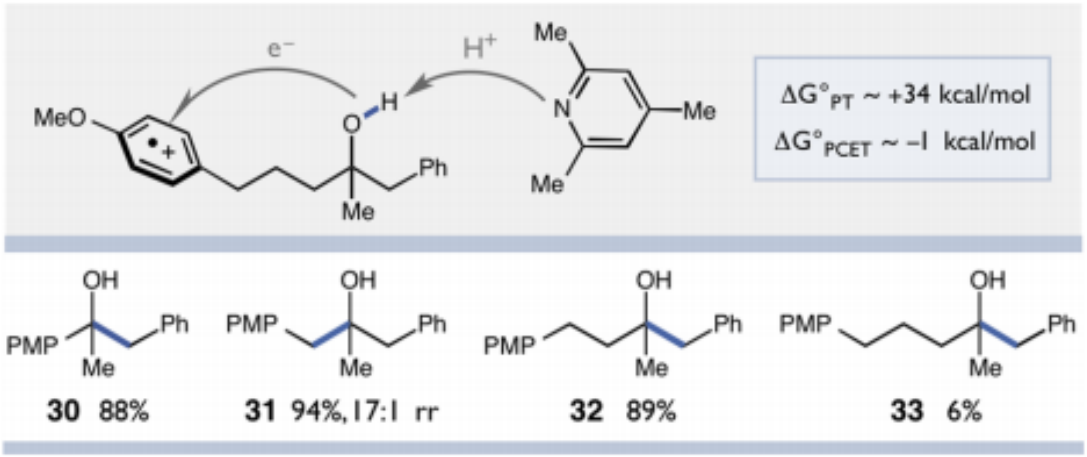


27 52%[b,c]

28 98%[b,c]

29 95%[b,c]

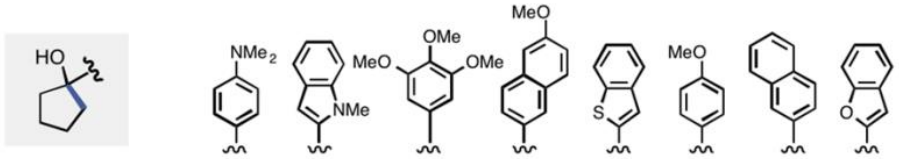
局限性：R为苯基or非芳基叔烷基醇不成功



叔烷醇中，三甲基吡啶无法对羟基去质子化

Figure 3. Distal C–C bonds cleaved via long-range PCET.

热力学可以用来准确预测给定PCET过程的可行性



Base	$E_{p/2}$ (V)	0.39	0.69	0.92	0.96	1.18	1.22	1.24	1.27
2-MeO-pyridine	'BDFE'	77	84	90	91	96	97	97	98
pK_a = 9.9	Yield (%)	0	0	0	0	0	0	<5	8
pyridine	'BDFE'	81	88	93	94	99	100	101	101
pK_a = 12.5	Yield (%)	0	0	0	<5	6	16	5	19
CF_3COO^-	'BDFE'	81	88	93	94	99	100	101	101
pK_a = 12.5	Yield (%)	0	0	0	0	23	87	97	18
collidine	'BDFE'	84	91	97	98	103	104	104	105
pK_a =15	Yield (%)	0	0	<5	7	86	86	41	84

effective BDFE = 23.06 $E_{1/2}(Ar^{0/\bullet+})$ + 1.37 pK_a(base) + 54.9 (rt in MeCN)

Figure 4. Effective BDFE correlations with reactivity.

Oxidation PCET---Ring Expansions of Cyclic Alcohols

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: J. Am. Chem. Soc. 2019, 141, 8752–8757
pubs.acs.org/JACS

Catalytic Ring Expansions of Cyclic Alcohols Enabled by Proton-Coupled Electron Transfer

Kuo Zhao,[†,‡] Kenji Yamashita,[†,‡] Joseph E. Carpenter,[§] Trevor C. Sherwood,[§] William R. Ewing,[§] Peter T. W. Cheng,[§] and Robert R. Knowles*[,†]

[†]Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States
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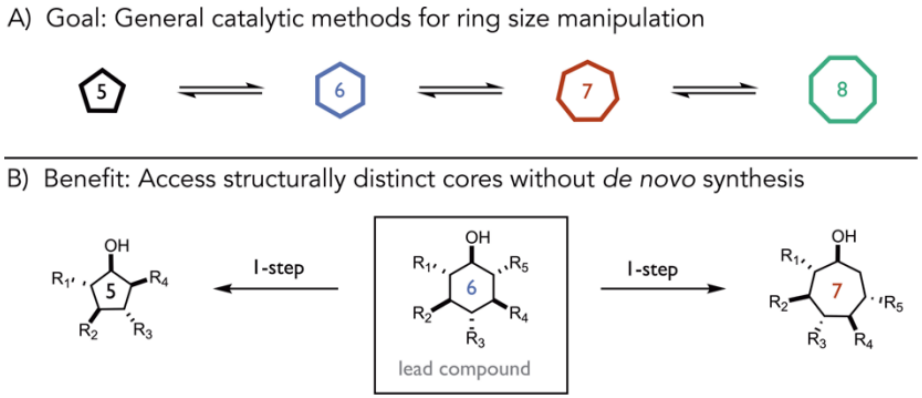


C) This work: Catalytic ring-expansion of cyclic allylic alcohols by O–H PCET

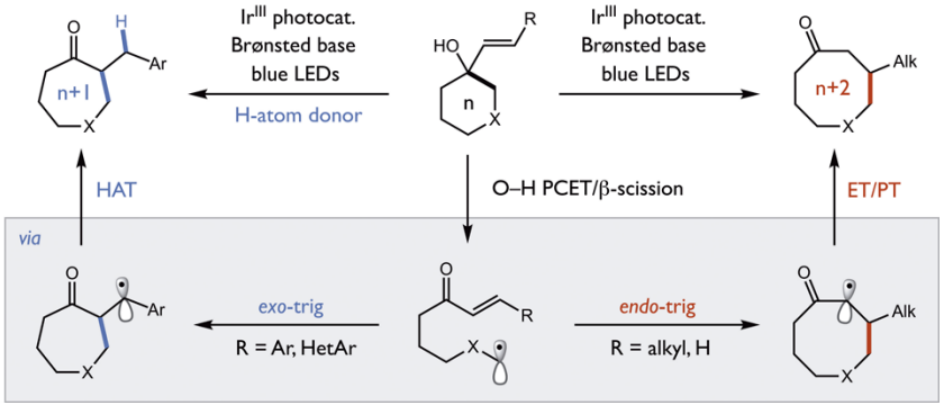


Table 1. Optimization Studies[a]

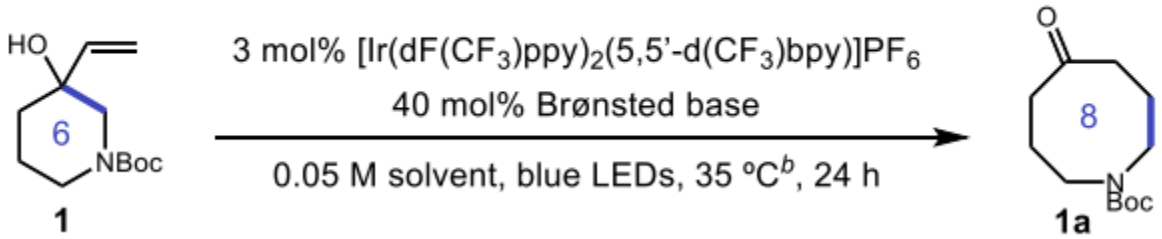
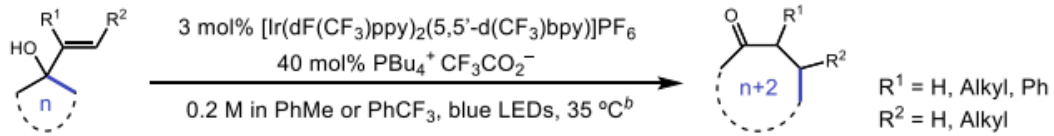
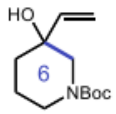
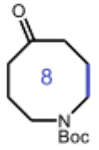
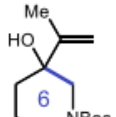
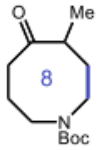
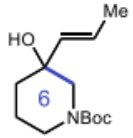
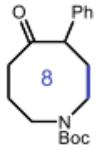
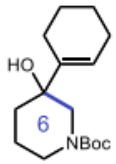
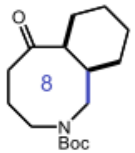
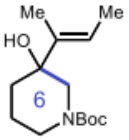
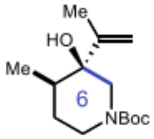
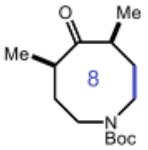
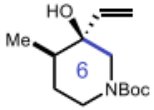
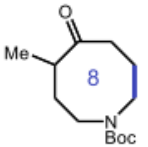
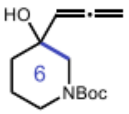
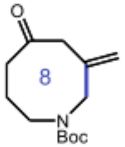
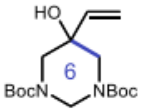
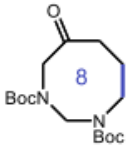
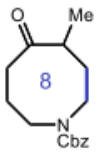
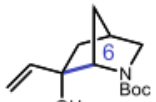
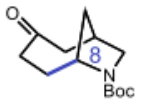


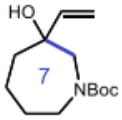
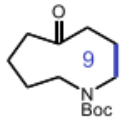
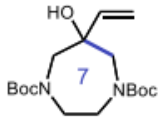
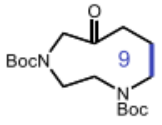
Table 2. Scope of *n*+2 Ring Expansion[a]

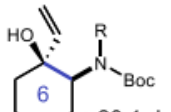
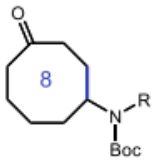


Starting material	Product	Yield
 **1**	 **1a**	84%[b]
 **2**	 **2a**	82%[b]
 **3**	 **3a**	79%[b]
 **4**	 **4a**	83%[c]
 **5**	 **5a**	92%[c,d] >20:1 d.r.

Starting material	Product	Yield
 **6**	 **6a**	83%[c,d] >20:1 d.r.
 **7** >20:1 d.r.	 **7a**	73%[c,d] >20:1 d.r.
 **8** >20:1 d.r.	 **8a**	62%[c]
 **9**	 **9a**	70%[b]
 **10**	 **10a**	70%[b]

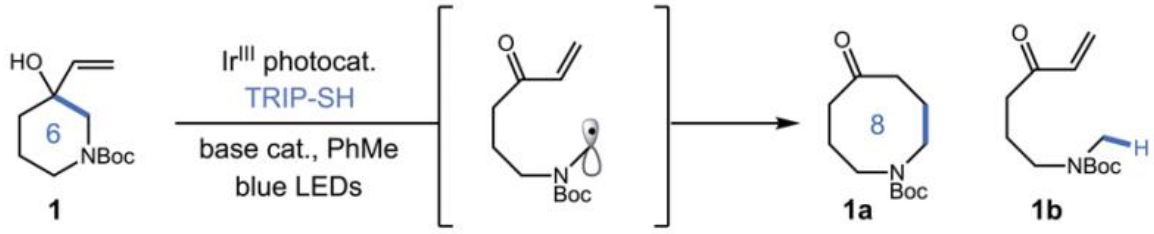
Starting material	Product	Yield
 **11**	 **11a**	75%[b]
 **12** >20:1 dr	 **12a**	44%[c,e]

Starting material	Product	Yield
 **13**	 **13a**	48%[c]
 **14**	 **14a**	58%[c]

Starting material	Product	Yield
 **15** R = Me **16** R = Bn >20:1 dr		**15a** 45%[c] **16a** 55%[f]

A) Regioselectivity in additions of alkyl radicals to cinnamates (Sparling et al.)

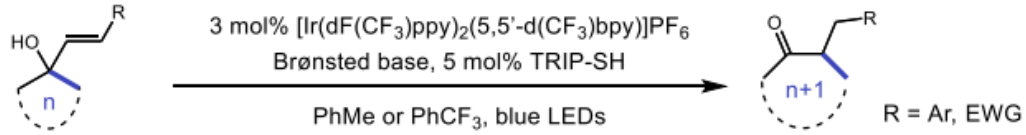
B) Competition between cyclization and radical reduction

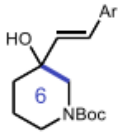
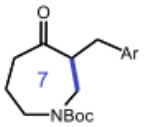
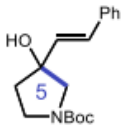
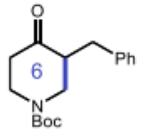
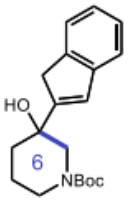
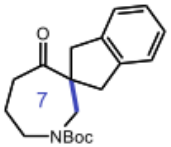
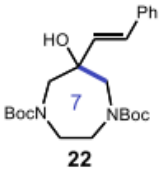


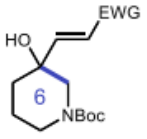
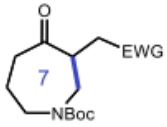
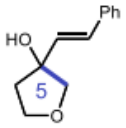
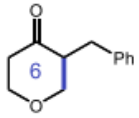
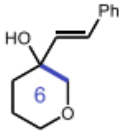
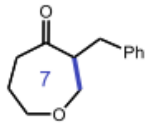
	1a	1b
with 25 mol% TRIP-SH	60%	23%
with 5 mol% TRIP-SH	88%	11%

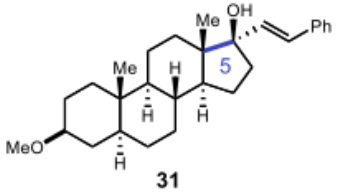
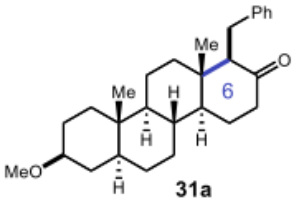
Figure 2. (a) Unconventional regioselectivity in radical additions to cinnamates. (b) Results of competition experiments.

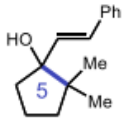
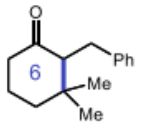
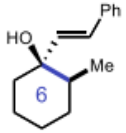
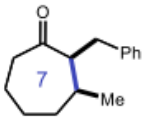
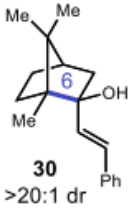
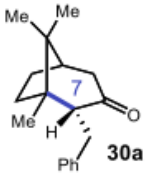
Table 3. Scope of *n*+1 Ring Expansion[a]



Starting material	Product	Yield
		**17a** 80%[b,c] **18a** 70%[c,d] **19a** 53%[c,d]
17 Ar = Ph **18** Ar = 4-*t*-BuC_6H_4 **19** Ar = 4-CO_2MeC_6H_4		
 **20**	 **20a**	70%[b,e,f]
 **21**	 **21a**	76%[b,c]
 **22**	 **22a**	82%[c,d]

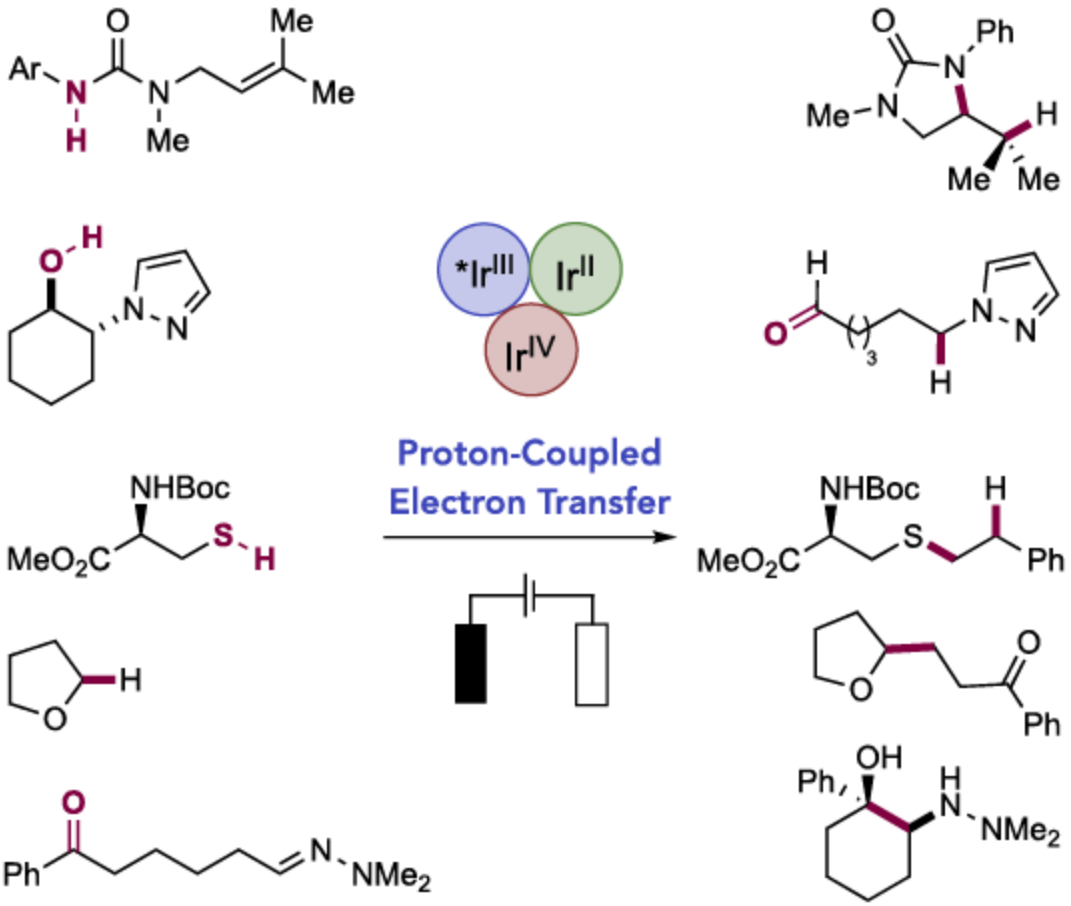
Starting material	Product	Yield
		**23a** 66%[b,c,g] **24a** 77%[b,c,g] **25a** 80%[b,c,g]
23 EWG = C(O)Me **24** EWG = 2-Pyridyl **25** EWG = 2-Pyrimidinyl		
 **26**	 **26a**	74%[d,f]
 **27**	 **27a**	67%[j]

Starting material	Product	Yield
 **31**	 **31a**	61%[i,j] >20:1 dr

Starting material	Product	Yield
 **28**	 **28a**	78%[j]
 **29** >20:1 dr	 **29a**	70%[h,j] 1.7:1 dr
 **30** >20:1 dr	 **30a**	77%[h,j] >20:1 dr

闭环产物可以通过改变烯烃受体的取代模式选择性地提供n+1或n+2扩环产物

Summary



- Catalytic generation of reactive free radicals
- Photochemical and electrochemical approaches

Thanks for watching!