Carbonyl alkylative amination for tertiary amine synthesis

2020/06/13 Keshu Zhang

Contents

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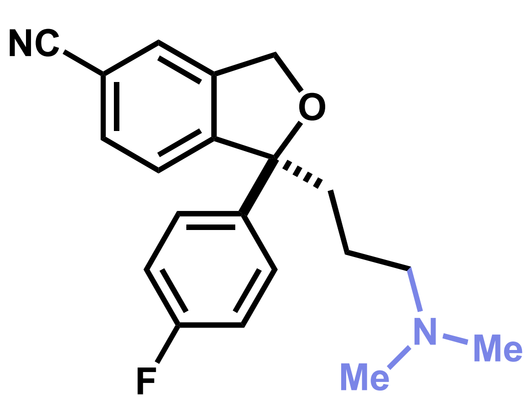
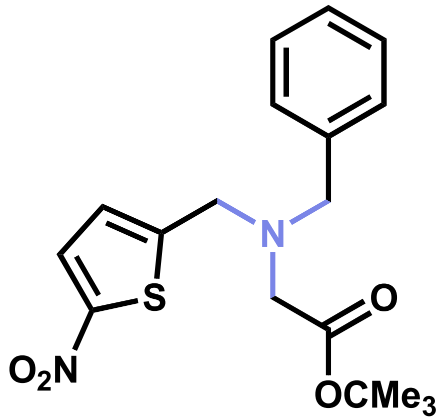
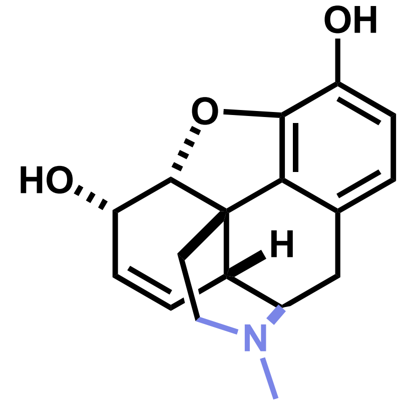
Tertiary amine



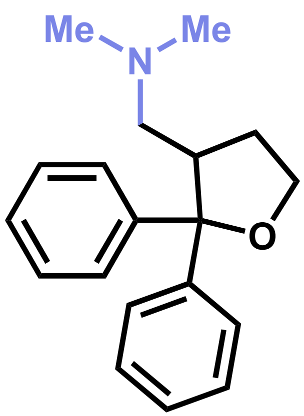
Escitalopram
Anti-depressant



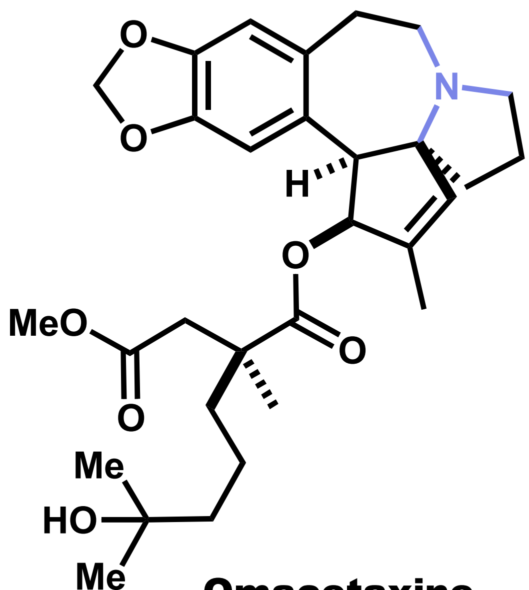
GSK4112
REV-ERBα agonist



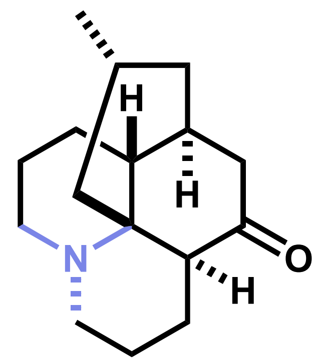
Morphine
Analgesic activity



ANAVEX2-73
Phase II trials, Alzheimer's

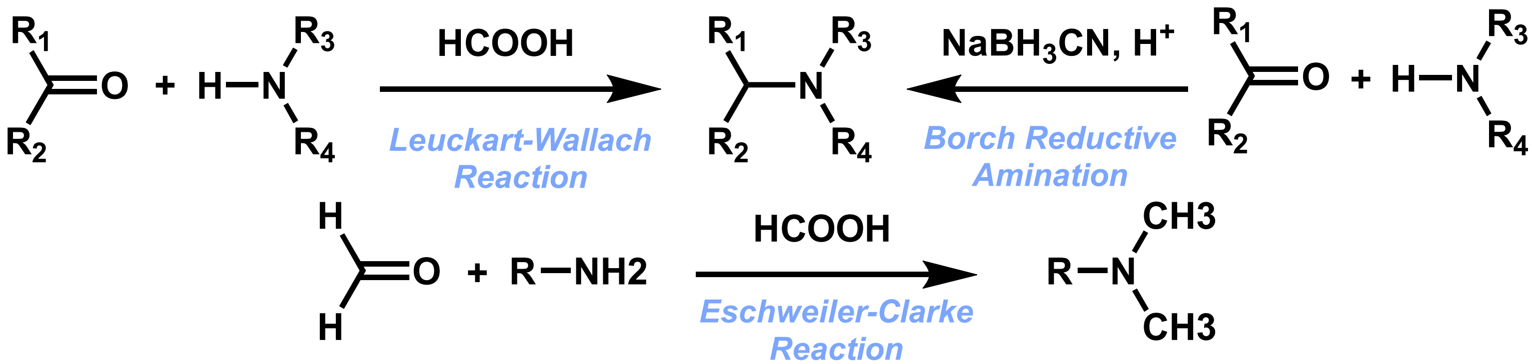


Omacetaxine
Acute myeloid leukaemia



Lycopodine
HeLa cells proliferation inhibitor

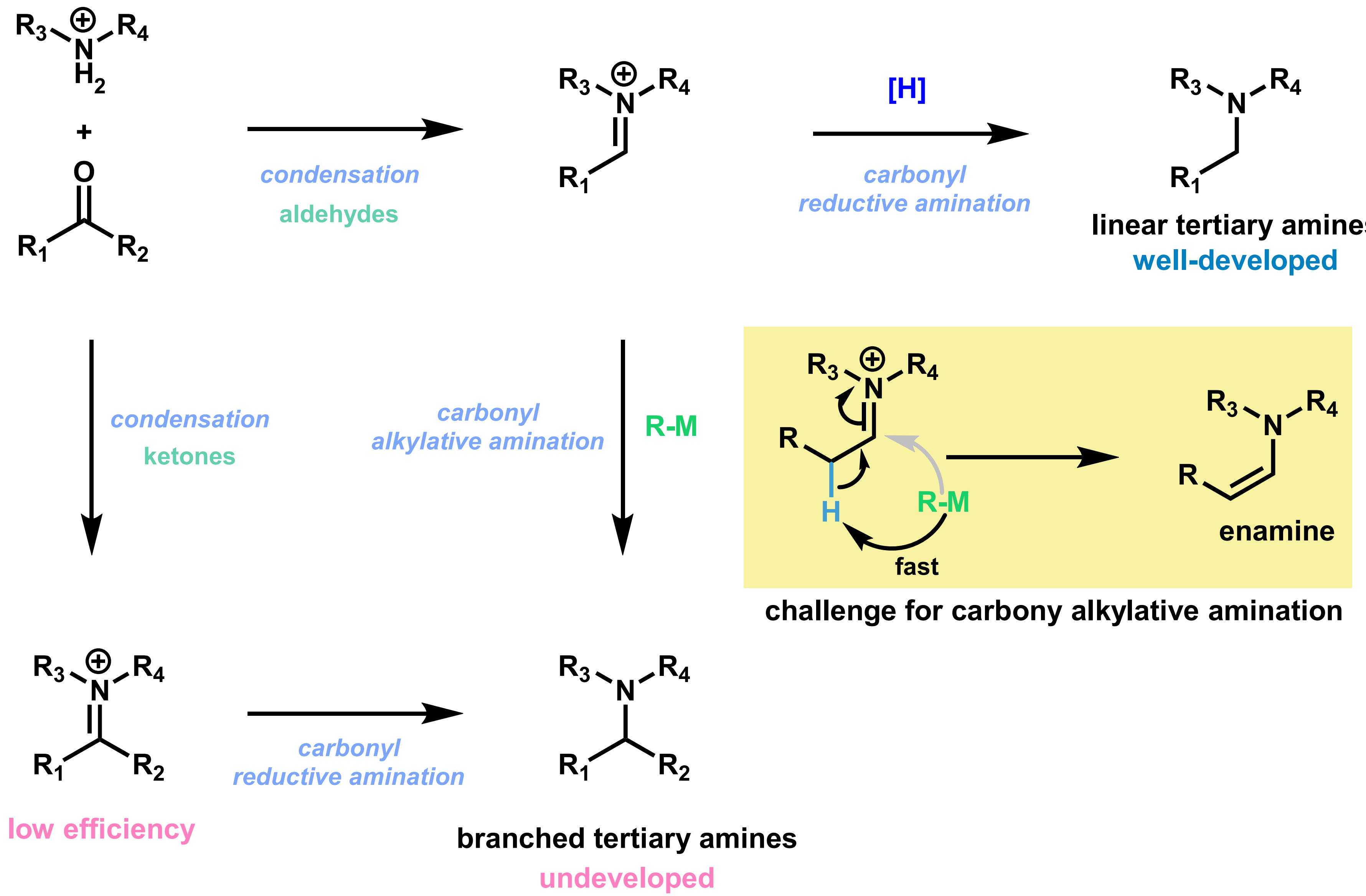
Top 10 Reactions by Frequency in the 2008 Data Set



reaction	no. of reactions	% of all reactions
N-acylation to amide	1165	16
N-containing heterocycle formation	537	7.4
N-arylation with Ar-X	458	6.3
RCO_2H deprotection	395	5.4
N-subs with alkyl-X	390	5.3
reductive amination	386	5.3
N-Boc deprotection	357	4.9
Suzuki cross-coupling reaction	338	4.6
O-substitution	319	4.4
other NH deprotection	212	2.9
total	4557	62.4

1) Allan M. Jordan. *et al. J. Med. Chem*. **2011**, *54,* 3451

Carbonyl alkylative amination (CAA)

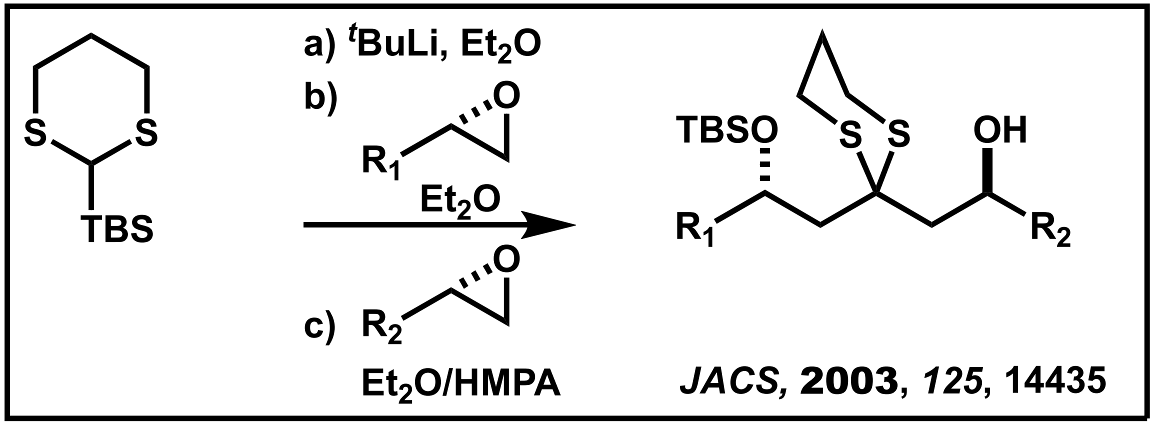


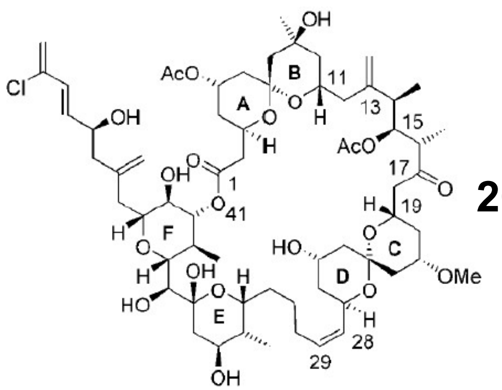
Contents

Prof. Matthew J. Gaunt

Education and career:

1995 B.S. in Chemistry @ University of Birmingham
1995-99 Ph.D in Chemistry @ University of Cambridge
Chemistry of Pd catalysts (hydrogenation, Wacker oxidation)
(Prof. Jonathan B. Spencer)
1999-01 P. D. study @ University of Pennsylvania
(Prof. Amos B. Smith III)



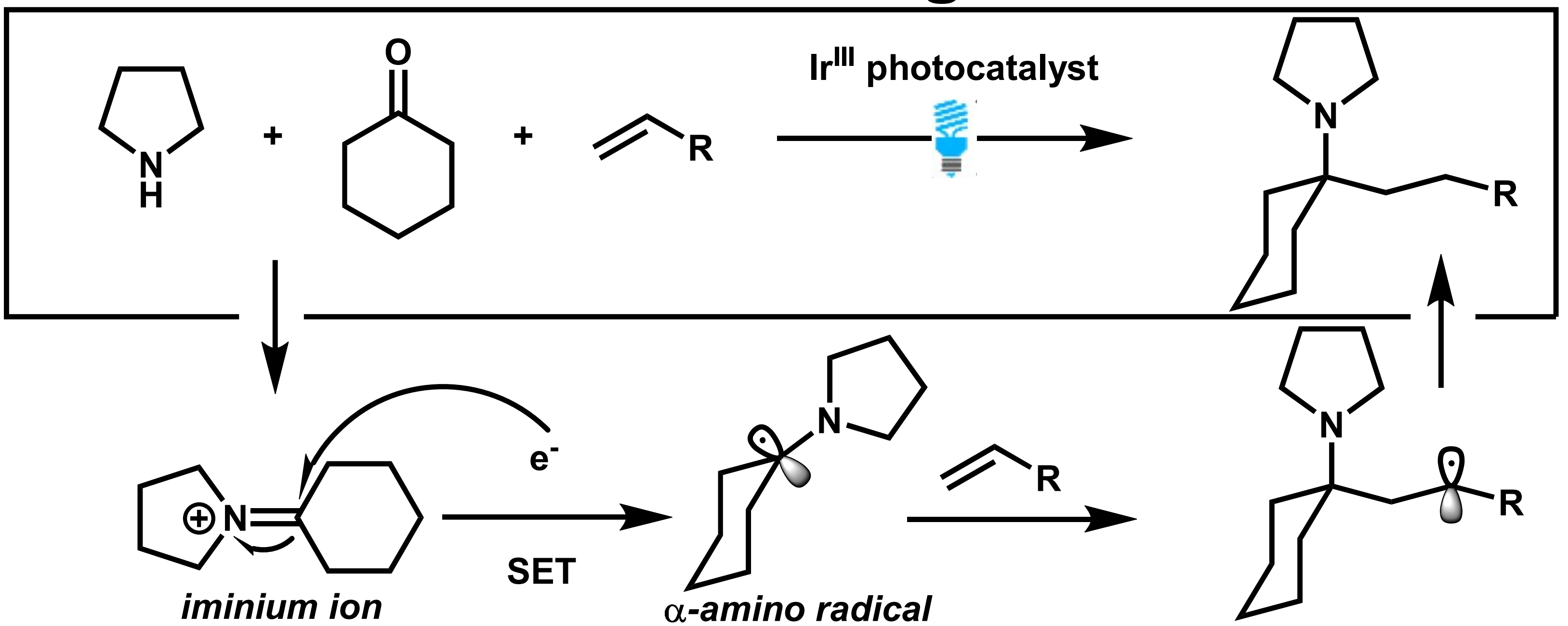


Spongistatin 1

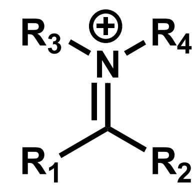
2001-03 Junior Research Fellow @ Magdalene University, Cambridge
(Prof. Steven Ley)
Total Synthesis of Spongistatin 1 (*ACIE,* **2005**, *44*, 5433)

2003 Assistant Professor, University of Cambridge
2010 Associate Professor, University of Cambridge
2012 Professor, University of Cambridge

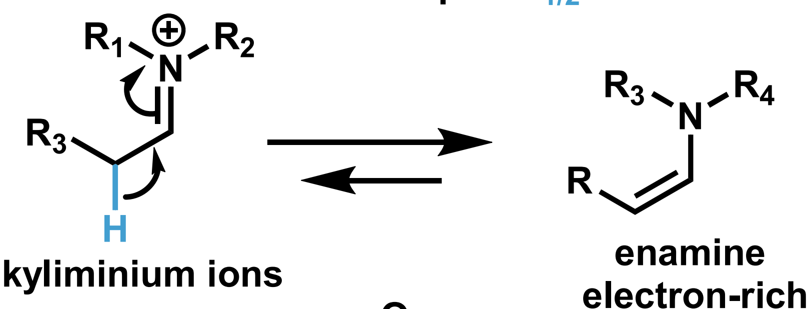
Gaunt's Design



1. Iminium ions conjugated with aromatic substituents $E_{1/2}^{red}$ = −0.8 to −1.2 V vs.SCE
   All-alkyl-iminium ion could be up to $E_{1/2}^{red}$ = −1.95 V vs.SCE

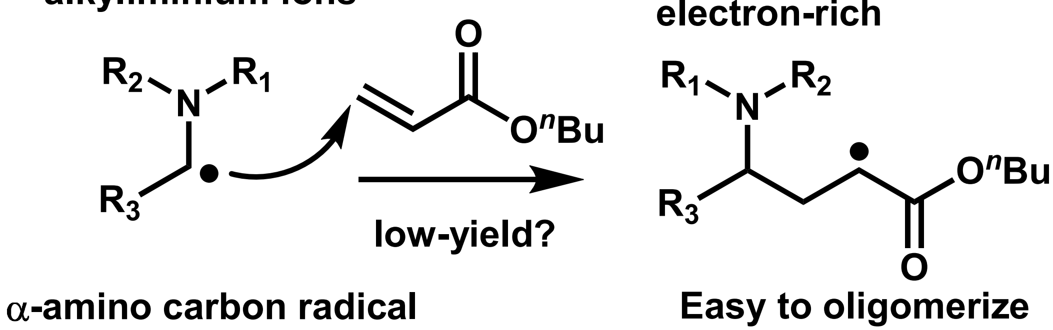


2.



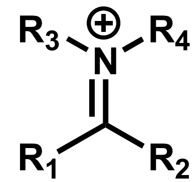
Enamine can also undergo SET reactions to form radical species

3.

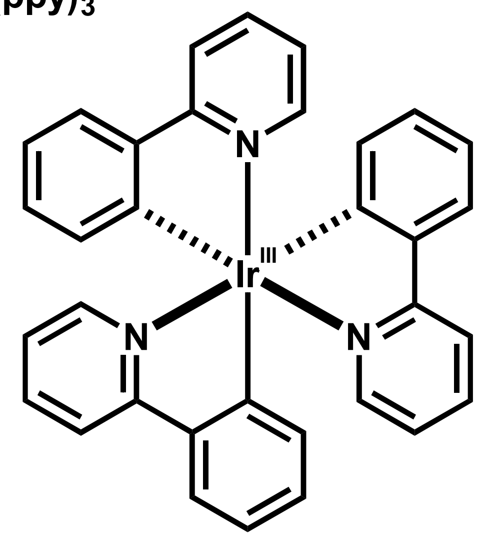


Problems for the photocatalytic olefinhydroaminoalkylation

1. Conjugated with multiple aromatic substituents $E_{1/2}^{red}$ = −0.8 to −1.2 V vs.SCE
   All-alkyl-iminium ion could be up to $E_{1/2}^{red}$ = −1.95 V vs.SCE

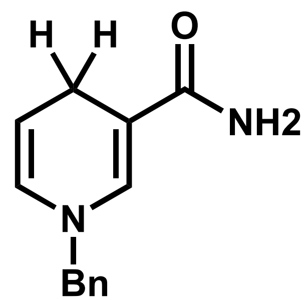


fac-Ir(ppy)$_3$



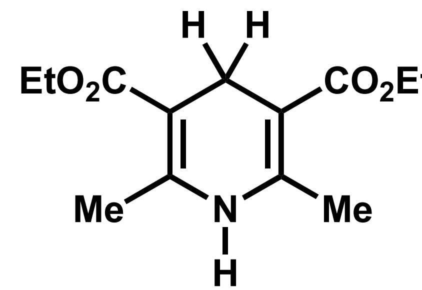
[Ir^{III}(ppy)$_3$]* / [Ir^{II}(ppy)$_3$]$^-$, $E_{1/2}^{red}$ = +0.31 V
(excite by 40W blue lamp)
[Ir^{III}(ppy)$_3$] / [Ir^{II}(ppy)$_3$]$^-$, $E_{1/2}^{red}$ = –2.19 V

Hantzsch esters (HE) and BNAH



BNAH
1-Benzyl-1,4-dihydronicotinamide

$E_{1/2}^{red}$ = +0.76 V vs.SCE



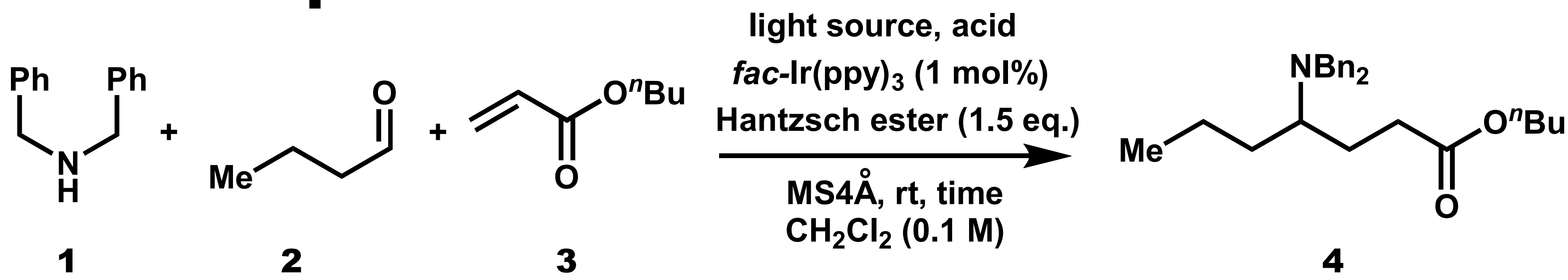
HE

$E_{1/2}^{red}$ = +1.00 V vs.SCE

* Hydrogen donors * SET catalysts
* Effective excited state reductants

1) W. Xiao, *et al. Org. Biomol. Chem.*, **2019**, *17*, 6936

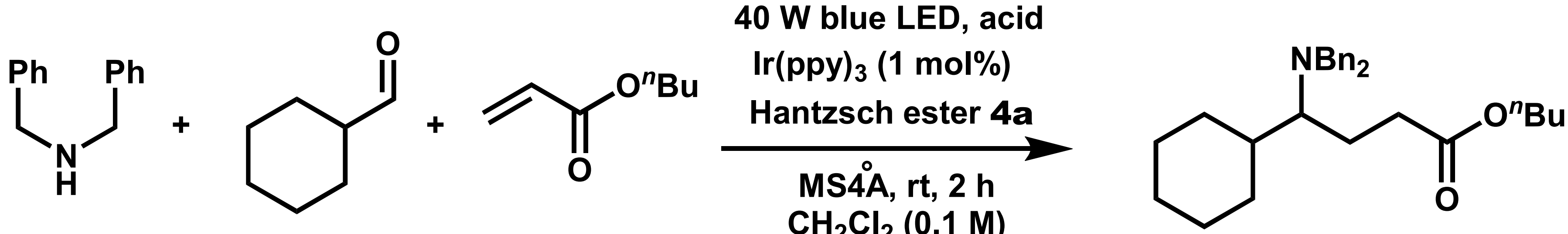
Optimization for Reaction conditions



Entry	1 / 2 / 3 eq.	light source	time	acid	yield[a]
1	1.0 / 2.0 / 2.0	30 W CFL	14 h	trace[b]	66%
2	1.0 / 2.0 / 2.0	30 W CFL	14 h	trace[b]	0%[c]
3	1.0 / 2.0 / 2.0	40 W blue LED	13 h	trace[b]	99%
4	1.0 / 1.1 / 1.1	40 W blue LED	14 h	trace[b]	99%
5	1.0 / 1.1 / 1.1	40 W blue LED	2 h	trace[b]	98%
6	1.0 / 1.1 / 1.1	40 W blue LED	2 h	-[d]	0%
7	1.0 / 1.1 / 1.1	40 W blue LED	2 h	butyric acid (0.1 eq.)	97%
8	1.0 / 1.1 / 1.1	40 W blue LED	2 h	propanoic acid (0.1 eq.)	99%
9	1.0 / 1.1 / 1.1	40 W blue LED	2 h	propanoic acid (0.1 eq.)	0%[e]
10	1.0 / 1.1 / 1.1	-	2 h	propanoic acid (0.1 eq.)	0%

a) Yield determined by ^{1}H NMR (internal standard : 1,1,2,2-tetrachloroethane) b) *n*-butyraldehyde readily generates trace amounts of butyric acid. c) Without Hantzsch ester. d)n-butyraldehyde freshly distilled e) Without *fac*-Ir(ppy)$_3$.

Acid screen for reaction conditions

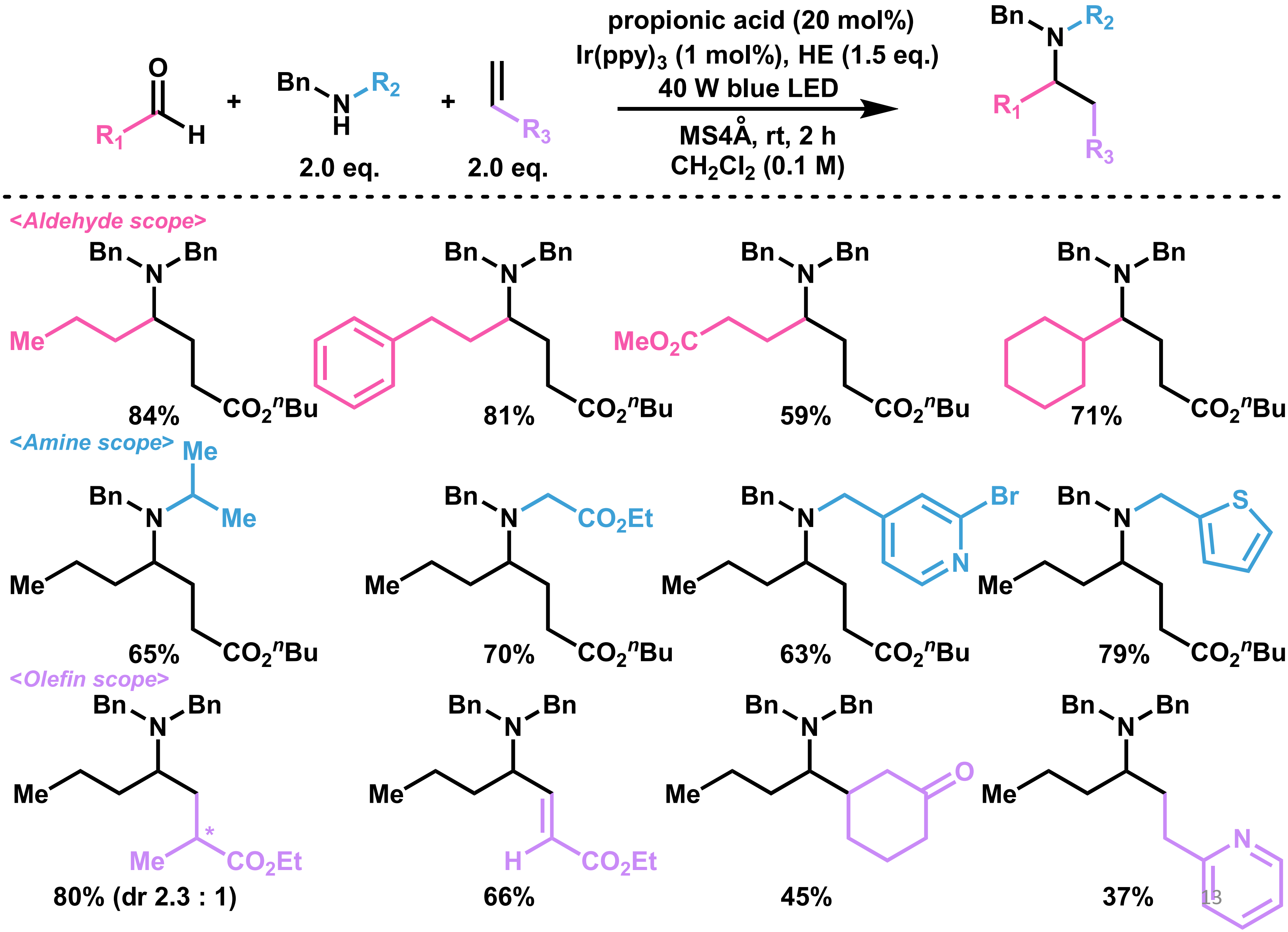


1 + **2** (1.1 eq.) + **3** (1.1 eq.) → **4**

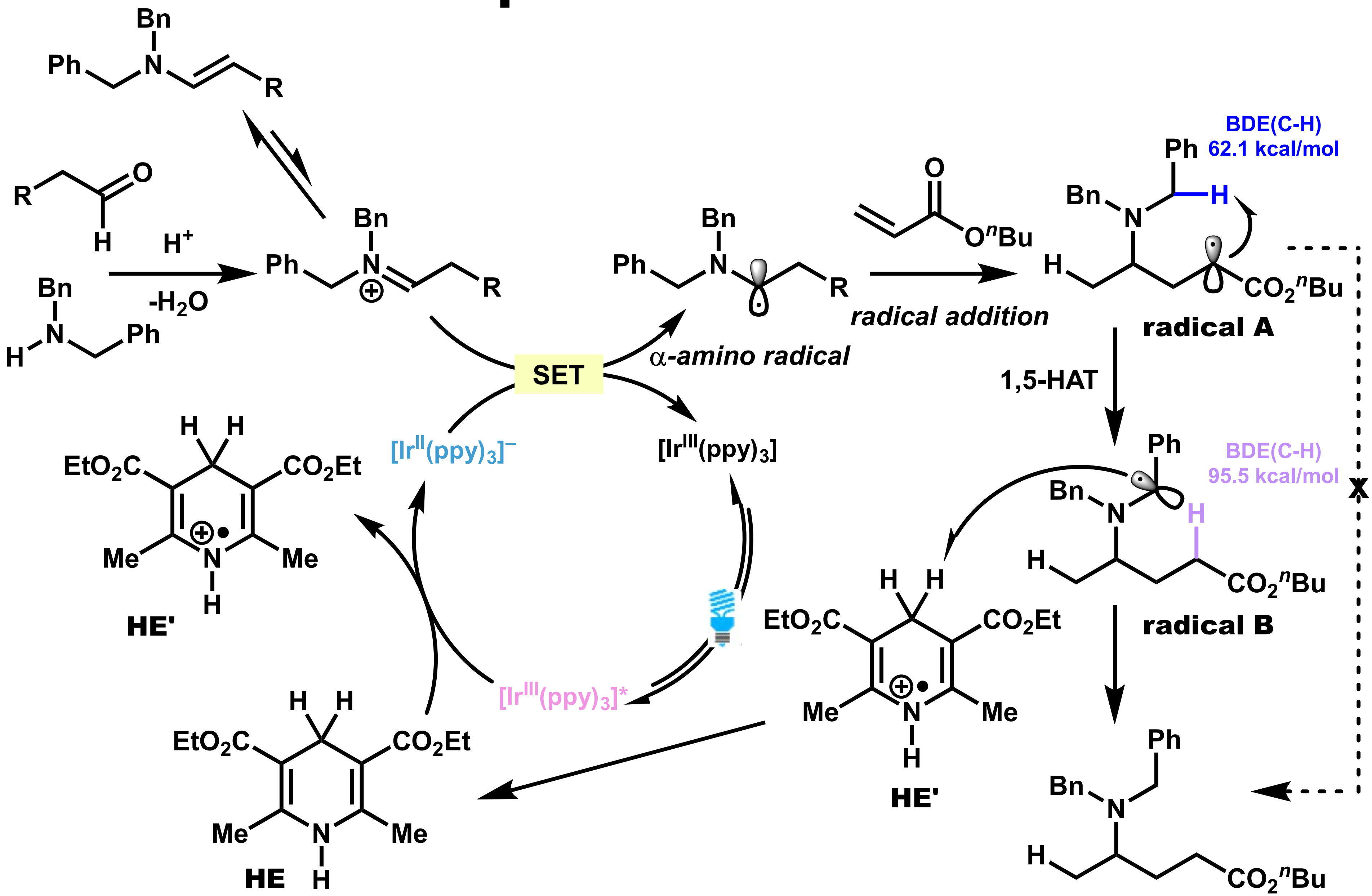
Entry	acid	eq.	yield[a]
1	TFA	0.1	47%
2	CSA (*rac*)	0.1	43%
3	octanoic acid	0.2	61%
4	adamantanecarboxylic acid	0.2	63%
5	PPTS	0.2	53%
6	HFIP	0.2	36%
7	propanoic acid	0.1	55%
8	propanoic acid	0.2	66%
9	propanoic acid	0.5	62%
10	propanoic acid	1.0	57%
11	propanoic acid	20 mol%	71%

a) Yield determined by ^{1}H NMR (internal standard : 1,1,2,2-tetrachloroethane).

Substrate Scope

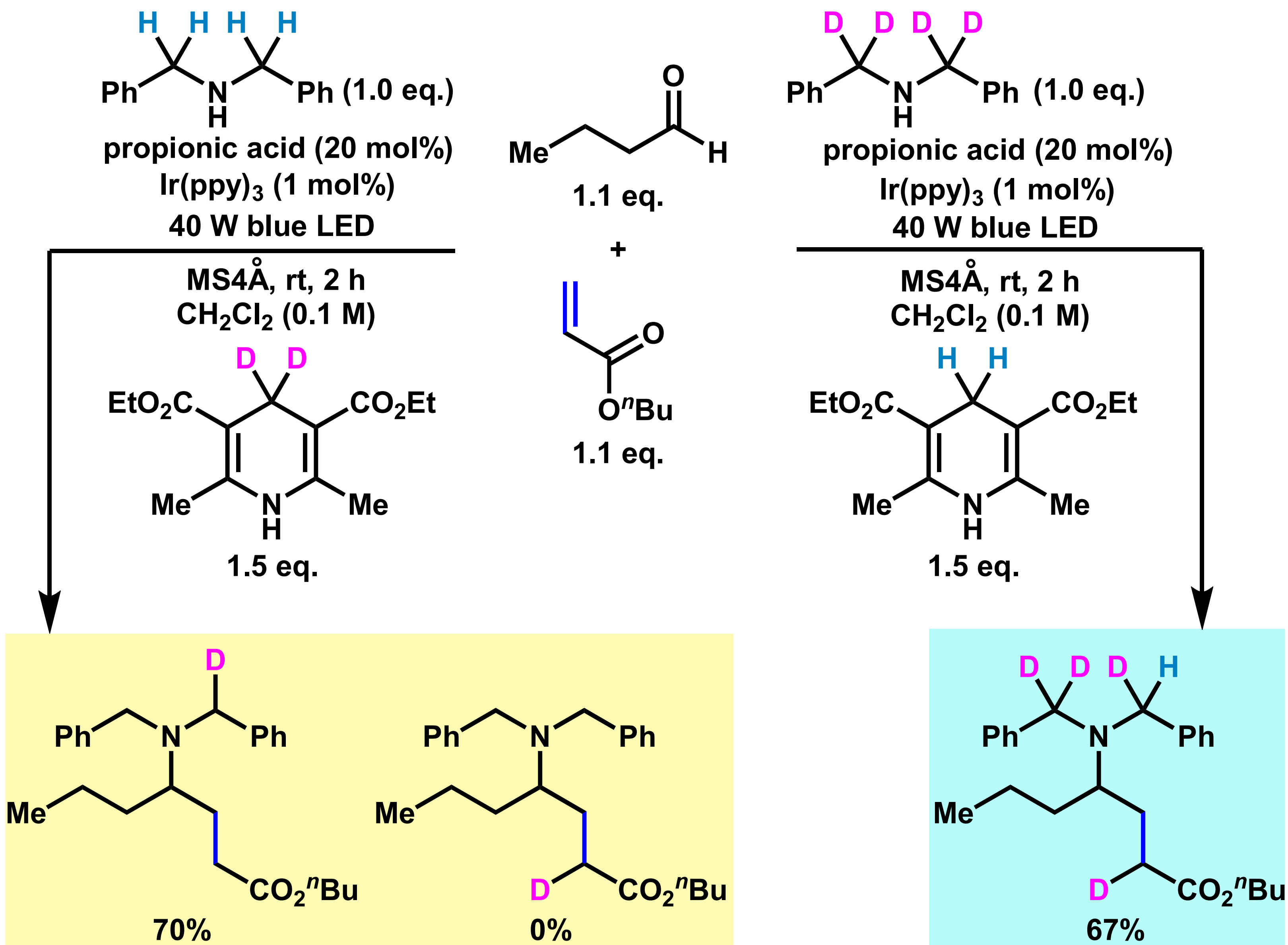


Proposed Mechanism



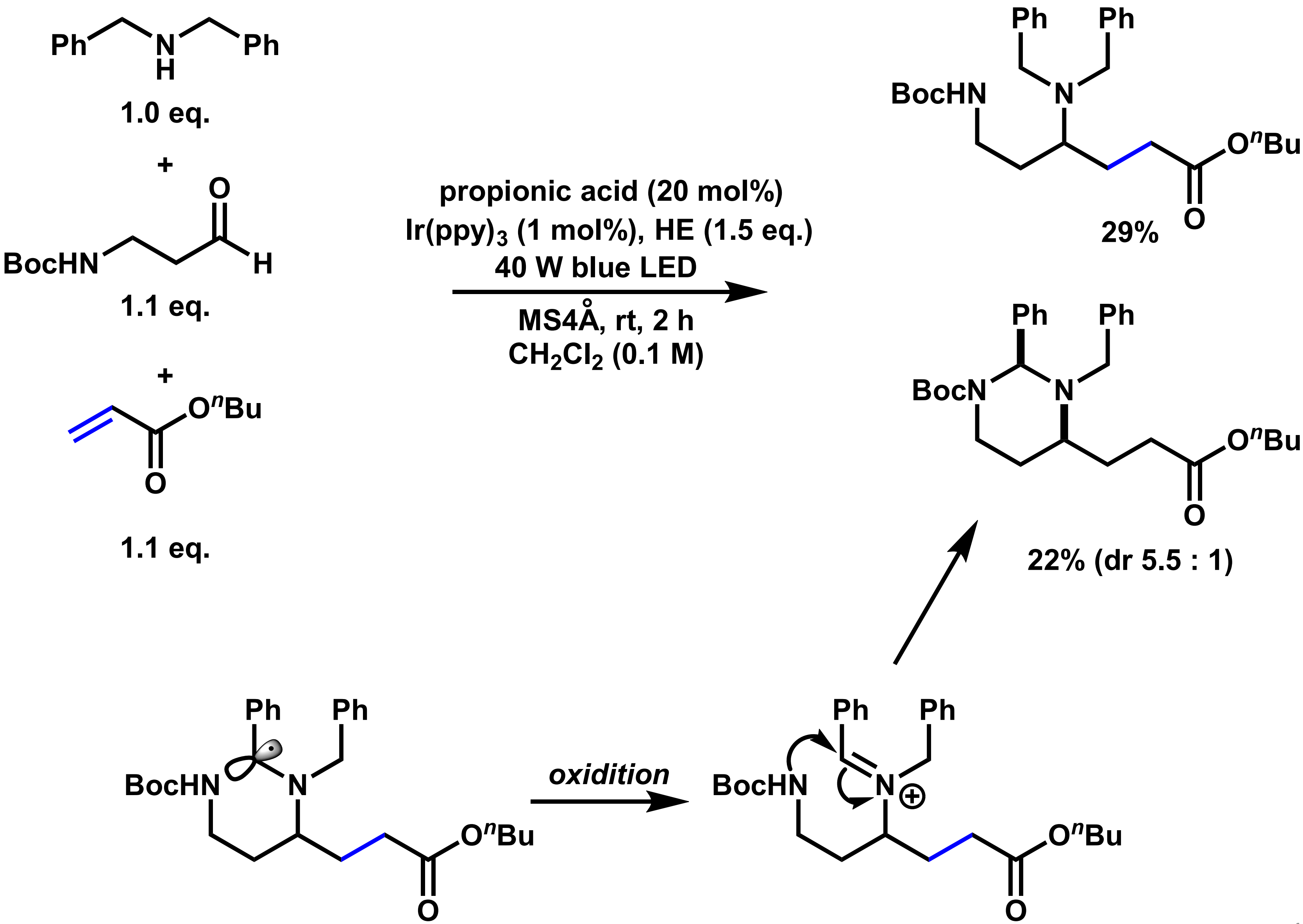
1) Aaron Trowbridge, Dominik Reich, Matthew J. Gaunt. *Nature,* **2018**, *561*, 522.

Deuterium-labelling studies



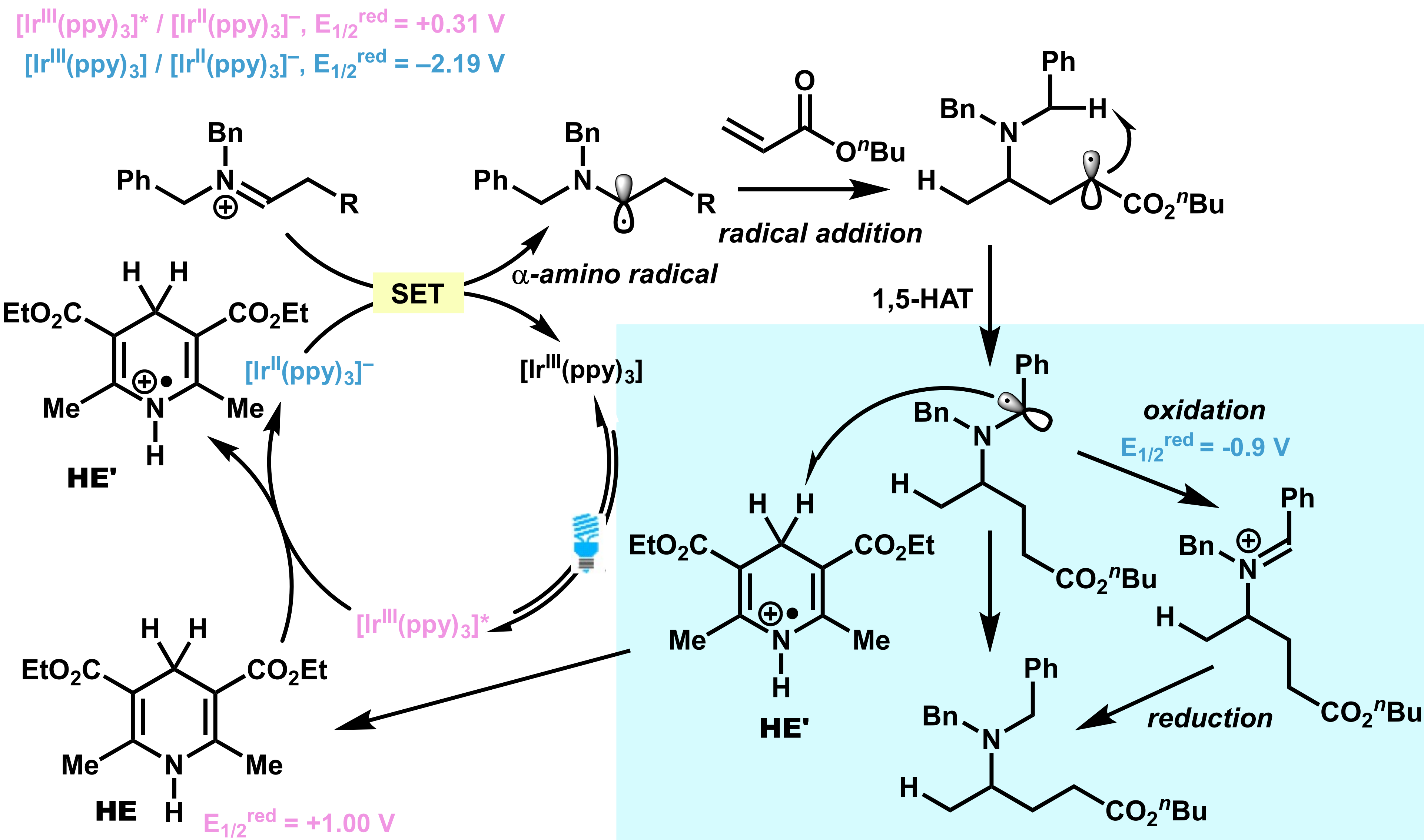
1) Aaron Trowbridge, Dominik Reich, Matthew J. Gaunt. *Nature,* **2018**, *561*, 522.

Iminium-ion redox-relay mechanism



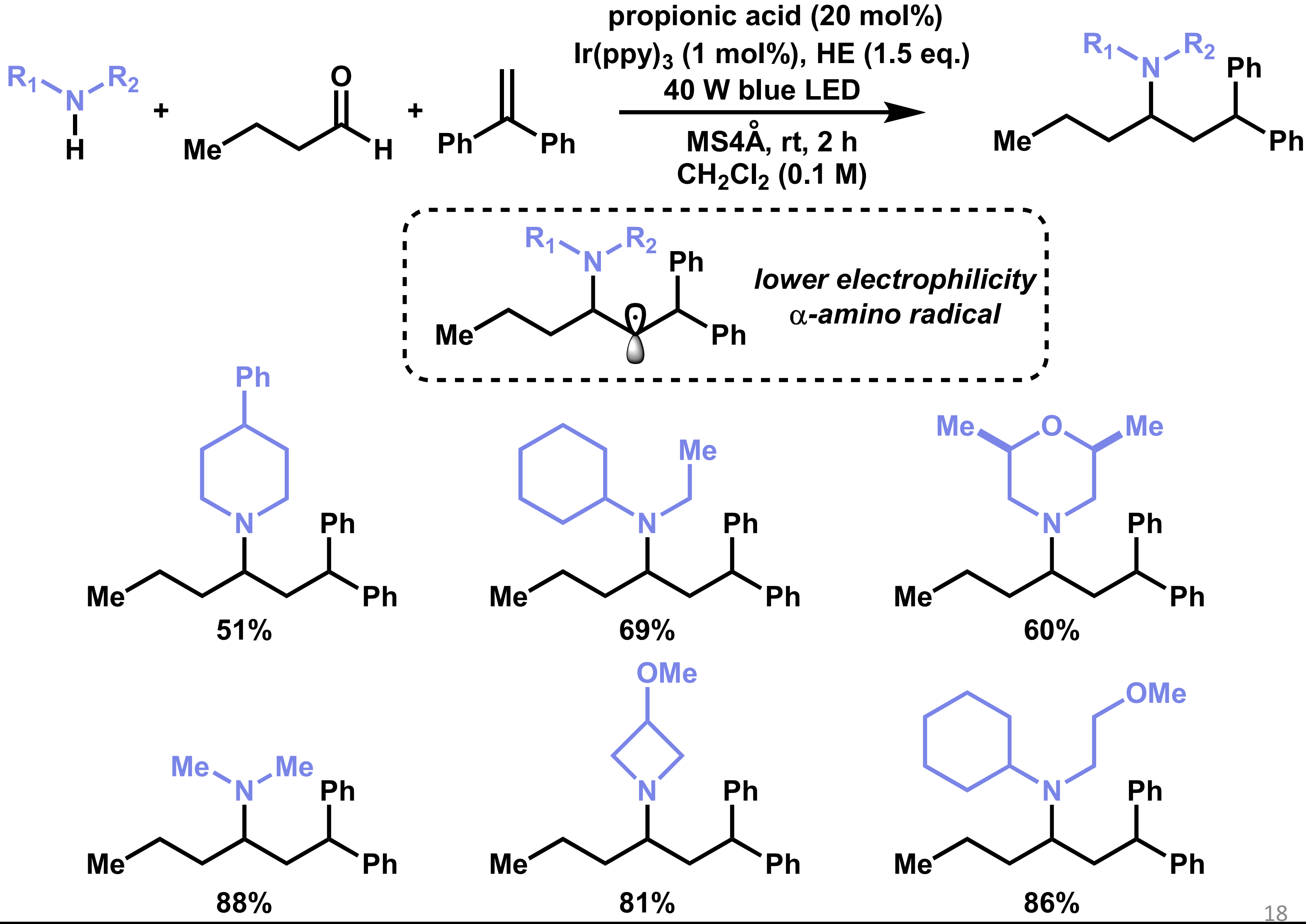
1) Aaron Trowbridge, Dominik Reich, Matthew J. Gaunt. *Nature,* **2018**, *561*, 522.

Proposed Mechanism



1) Aaron Trowbridge, Dominik Reich, Matthew J. Gaunt. *Nature,* **2018**, *561*, 522.

Scope of the multicomponent photocatalytic synthesis of tertiary alkylamines



1) Aaron Trowbridge, Dominik Reich, Matthew J. Gaunt. *Nature,* **2018**, *561*, 522.

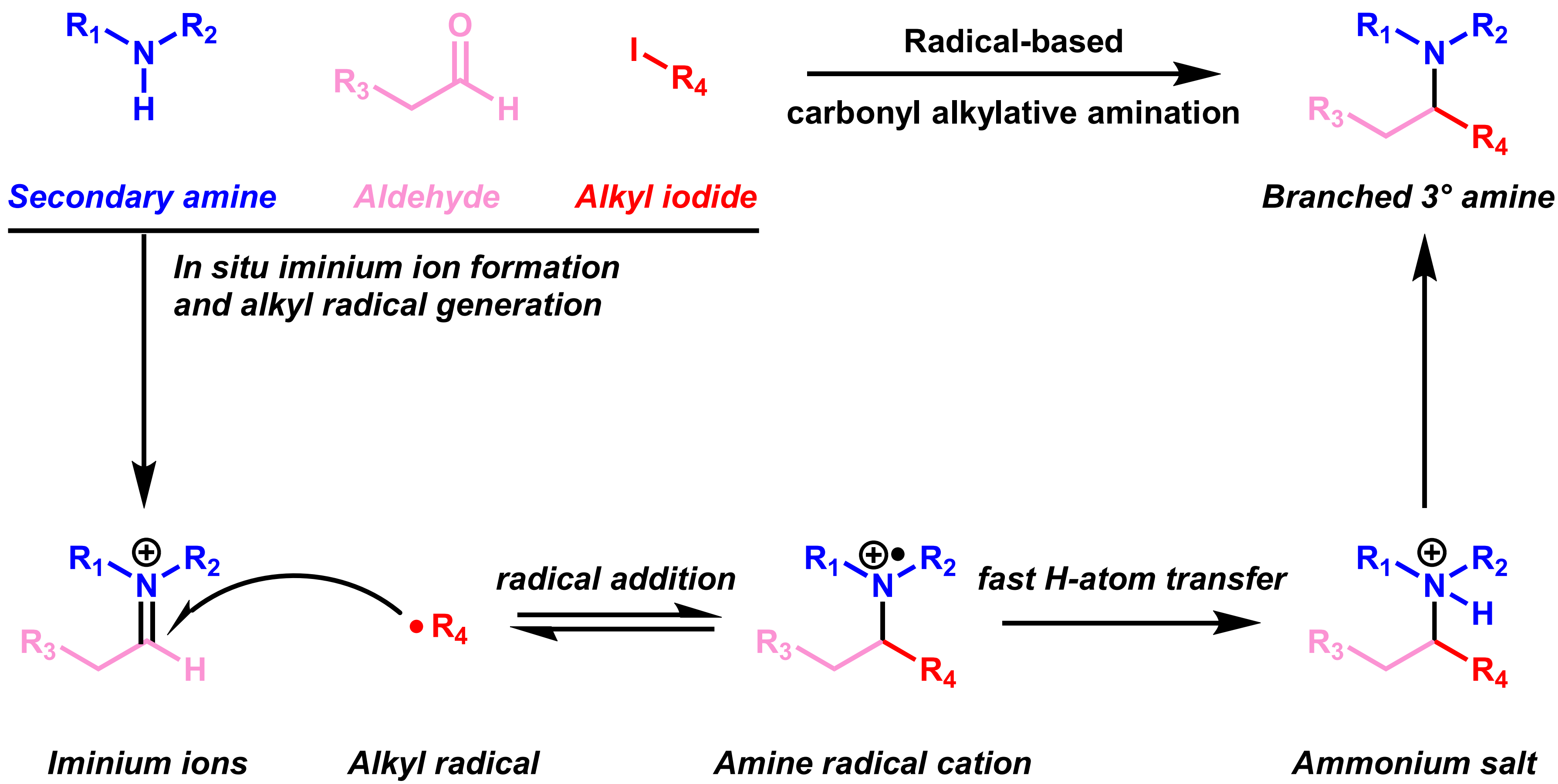
Contents

1. Introduction

2. Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation
   A, Trowbridge.; D, Reich.; Matthew J. Gaunt.
   Nature, **2018**, *522, 527*.

3. **A general carbonyl alkylative amination for tertiary amine synthesis (main paper)**
   R, Kumar.; N, Flodén.; W, Whitehurst.; Matthew J. Gaunt.
   Nature, **2020**, *581,* 415.

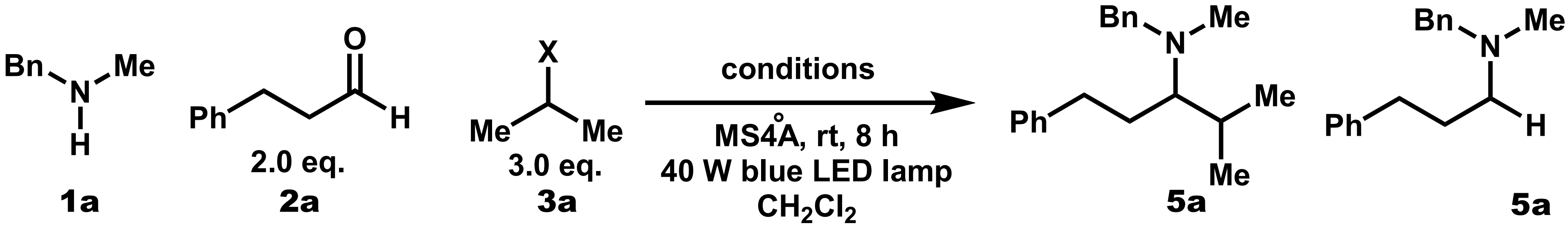
Gaunt's Design



- Metal-free
- Radical initiator-free
- Commerical feedstocks

1) Roopender Kumar, Nils J. Flodén, William G. Whitehurst, Matthew J. Gaunt, *Nature,* **2020**, *581*, 415.

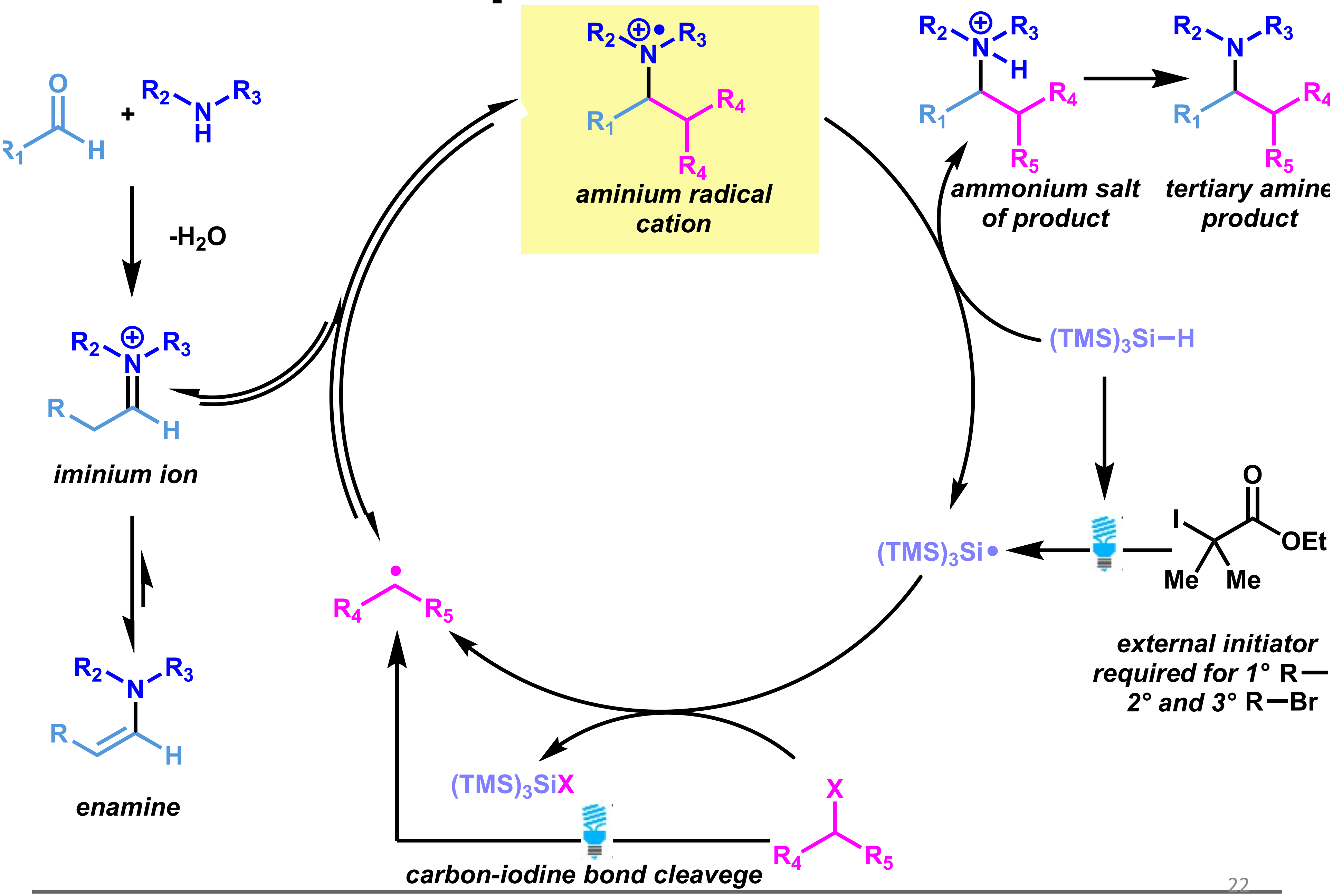
Optimization for Reaction conditions



Entry	1a / 2a / 3a eq.	HAT reagent (2.0 eq.)	acid (1.0 eq.)	X	conc.	yield 5a	yield 5b
1	1.0 / 1.0 / 2.0	$(TMS)_3SiH$	-	I	0.1 M	23%	10%
2	1.0 / 1.0 / 2.0	$(TMS)_3SiH$	-	I	0.05 M	55%	22%
3	1.0 / 1.0 / 2.0	$(TMS)_3SiH$	-	I	0.03 M	61%	17%
4	1.0 / 1.0 / 3.0	$(TMS)_3SiH$	-	I	0.03 M	70%	20%
5	1.0 / 2.0 / 3.0	$(TMS)_3SiH$	-	I	0.03 M	82%	15%
6	1.0 / 2.0 / 3.0	Et_3SiH	-	I	0.03 M	16%	14%
7	1.0 / 2.0 / 3.0	$(EtO)_3SiH$	-	I	0.03 M	9%	trace
8	1.0 / 2.0 / 3.0	Ph_3SiH	-	I	0.03 M	5%	66%
9	1.0 / 2.0 / 3.0	$PhSiH_3$	-	I	0.03 M	10%	37%
10	1.0 / 2.0 / 3.0	$(TMS)_3SiH$	TBSOTf	I	0.03 M	92%	trace
11	1.0 / 2.0 / 3.0	$(TMS)_3SiH$	TBSOTf	Br	0.03 M	81%	13%
12	1.0 / 2.0 / 3.0	-	TBSOTf	I	0.03 M	0%	0%

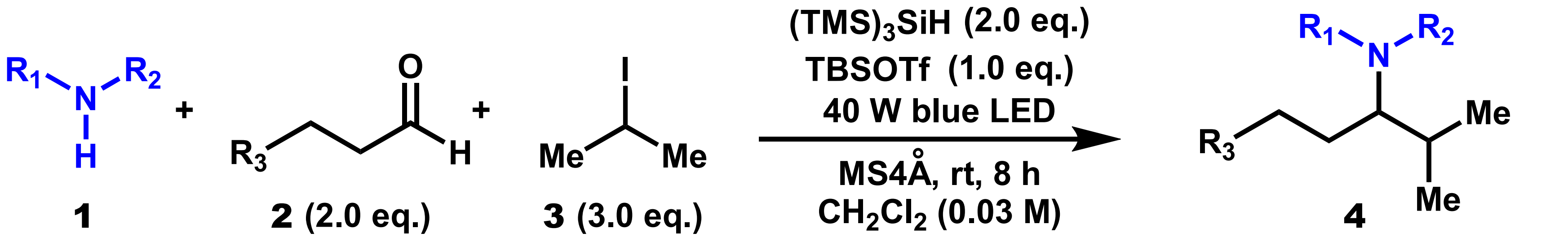
a) Yield determined by ^1H NMR (internal standard : 1,1,2,2-tetrachloroethane)

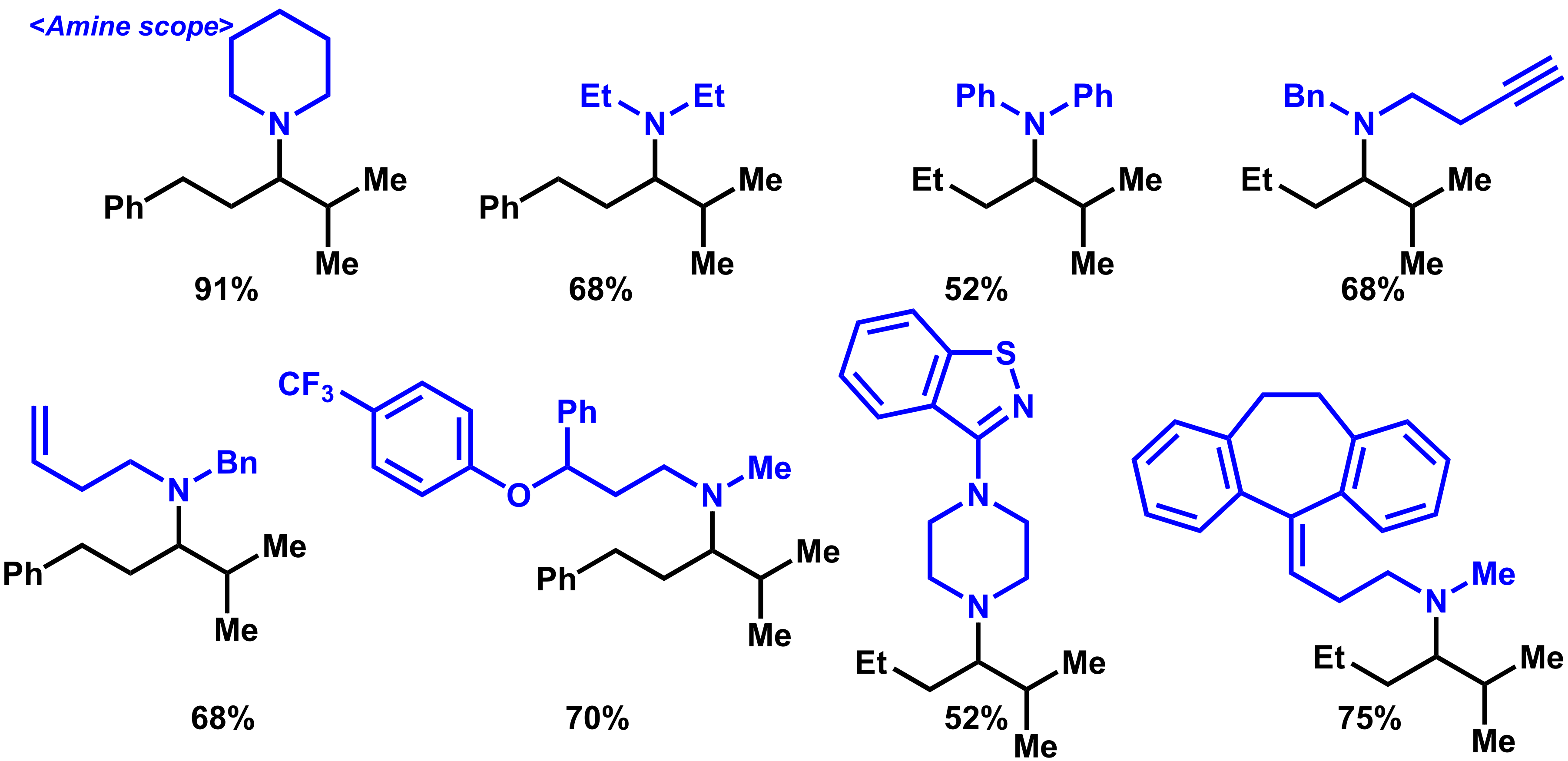
Proposed Mechanism



1) Roopender Kumar, Nils J. Flodén, William G. Whitehurst, Matthew J. Gaunt, *Nature*, **2020**, *581*, 415.

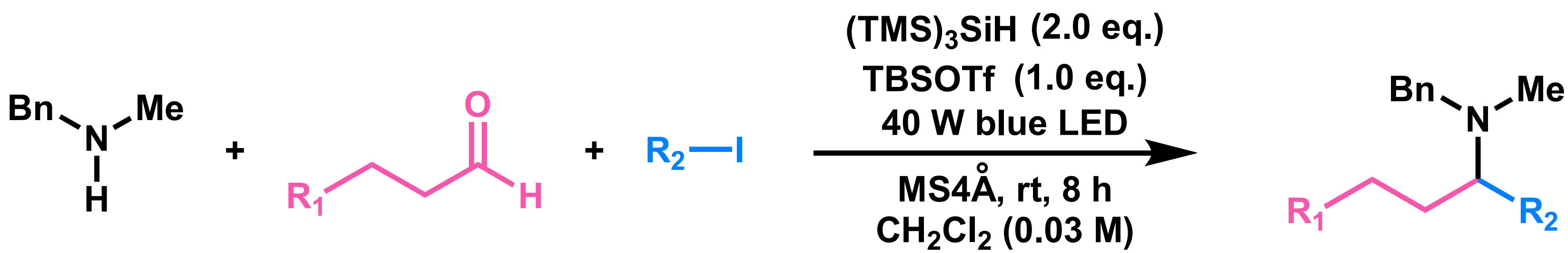
Substrate scope





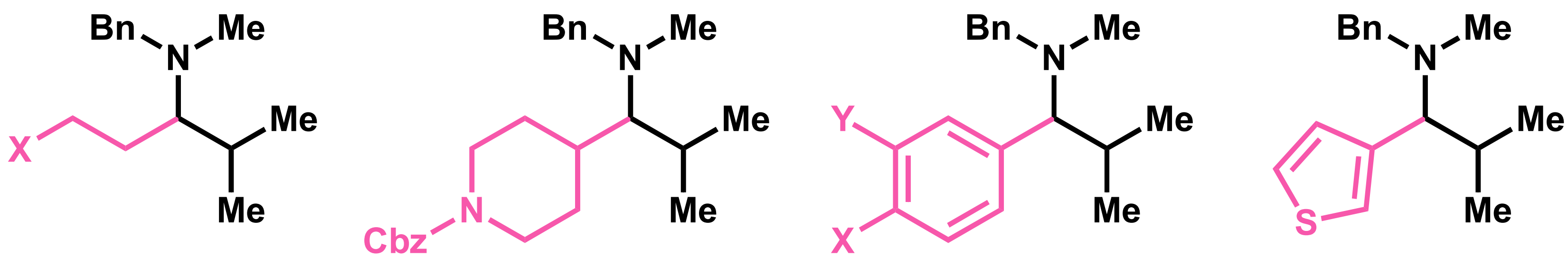
1) Roopender Kumar, Nils J. Flodén, William G. Whitehurst, Matthew J. Gaunt, *Nature,* **2020**, *581*, 415.

Substrate scope



1 **2** (2.0 eq.) **3** (3.0 eq.) **4**

<*Aldehyde scope*>



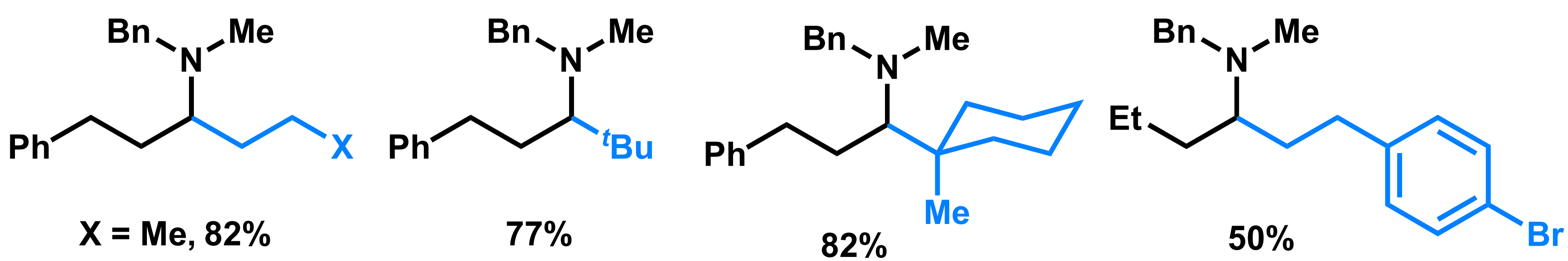
X = Me, 76% X = CO_2Me, 63%
X = CH_2CH_2Cl, 73%

62%

Y = H : X = Br, 70%; X = CF_3, 52%
X = H : Y = F, 60%; Y = CO_2Me, 56%

47%

<*Alkyl iodide scope*>



X = Me, 82%
X = Ph, 76%

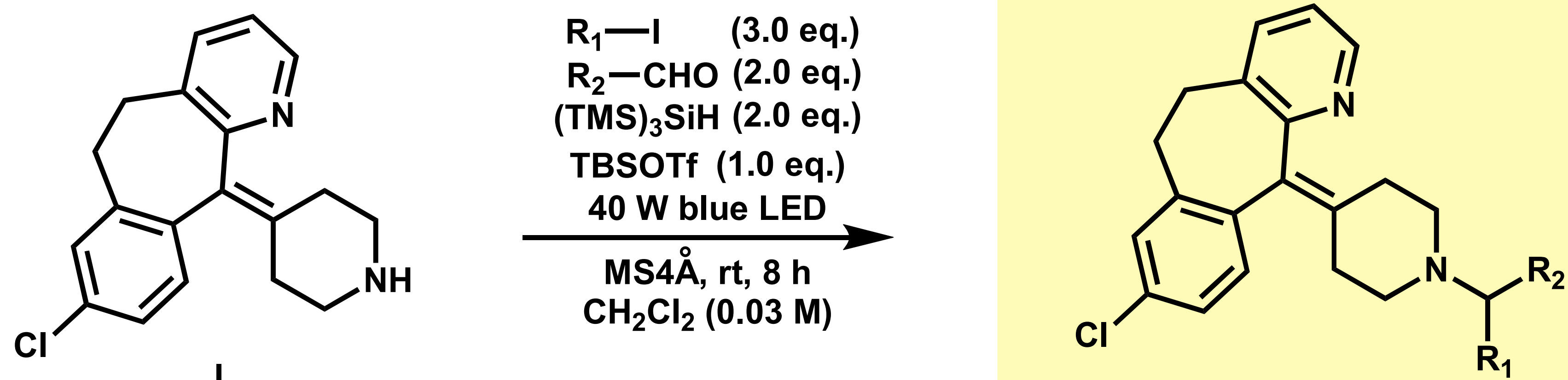
77%

82%

50%

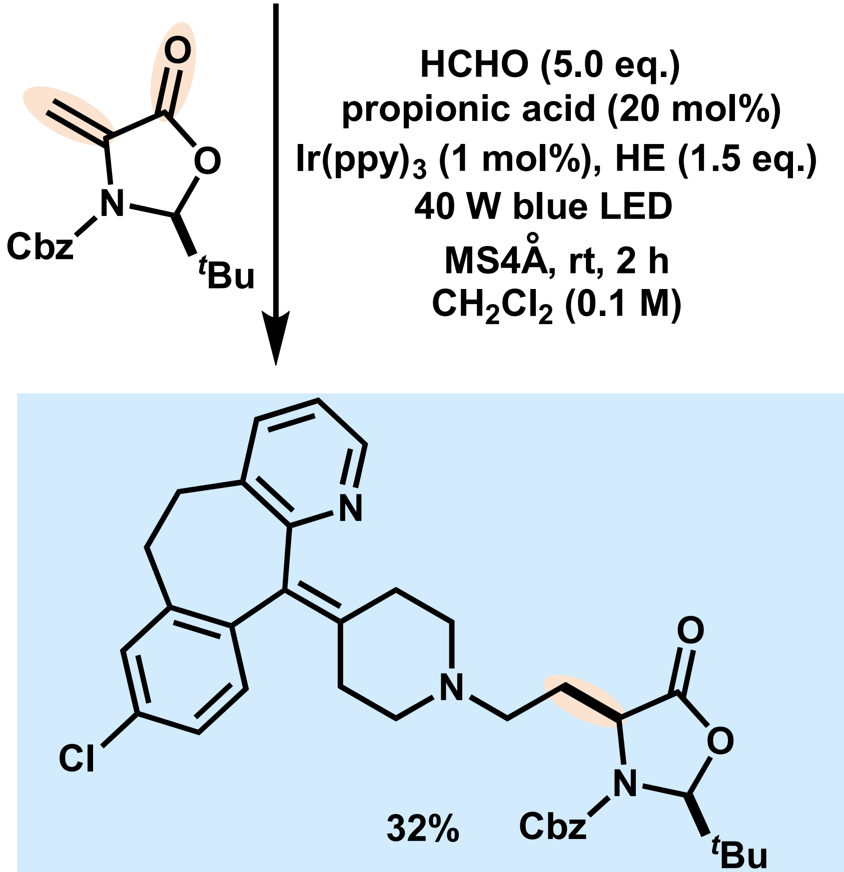
1) Roopender Kumar, Nils J. Flodén, William G. Whitehurst, Matthew J. Gaunt, *Nature*, **2020**, *581*, 415.

Expanding Substrate Scope



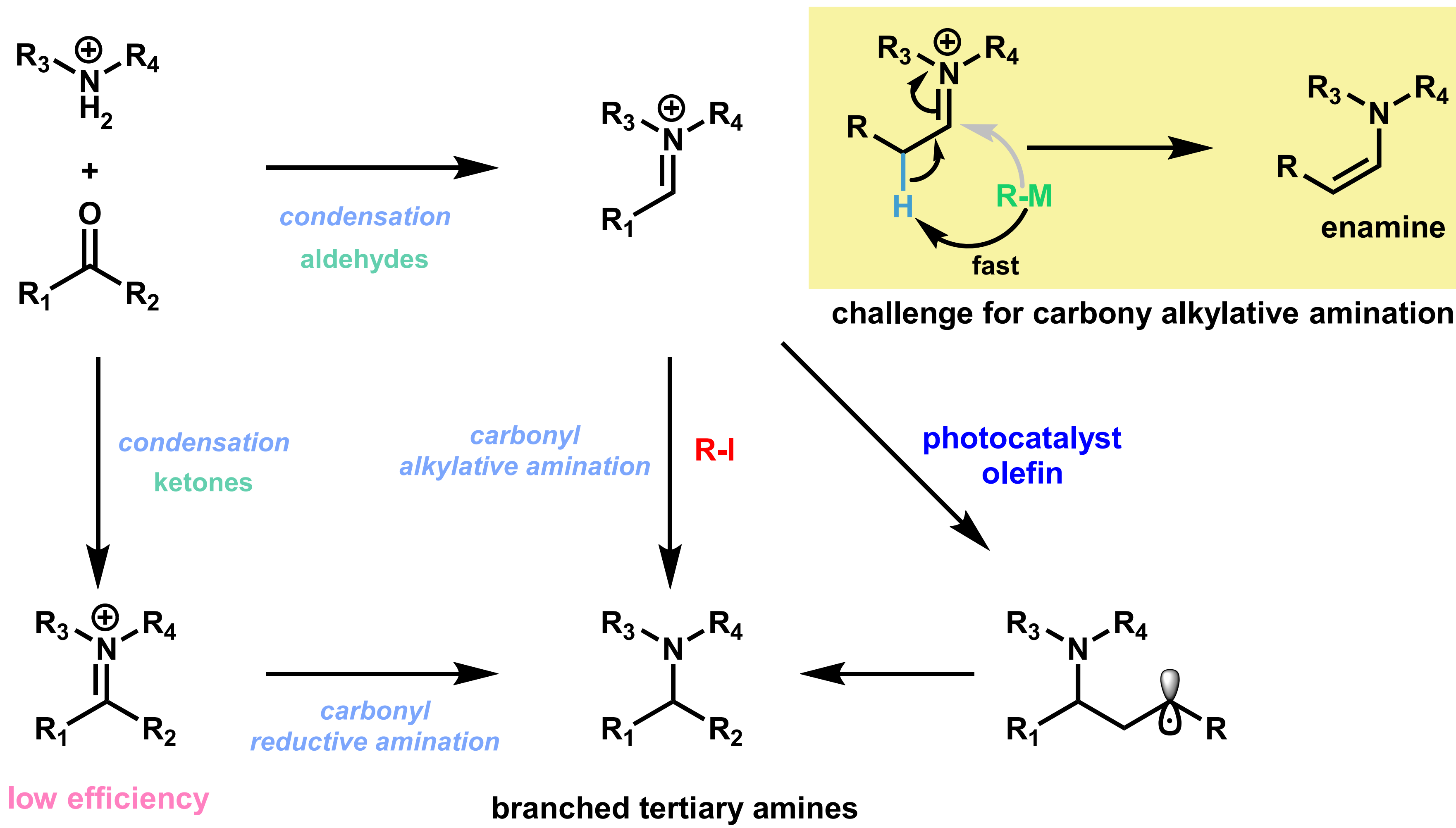
N-substituted desloratadine derivatives improved antagonism at histamine H1 receptor

R_1	R_2	yield
^{i}Pr	4-THP	46%
^{i}Pr	^{n}Pr	64%
^{t}Bu	^{n}Pr	67%
$MeOCH_2CH_2$	4-THP	42%
$MeOCH_2$	Cyclobutyl	51%
^{i}Pr	H	41%
^{i}Pr	D	45%
CD_2CD_3	^{n}Pr	23%



1) Roopender Kumar, Nils J. Flodén, William G. Whitehurst, Matthew J. Gaunt, *Nature*, **2020**, *581*, 415.

Summary



condensation
aldehydes
challenge for carbony alkylative amination
fast
R-M
enamine
condensation
ketones
carbonyl
alkylative amination
R-I
photocatalyst
olefin
carbonyl
reductive amination
low efficiency
branched tertiary amines