

Photoredox Synthesis of Amines

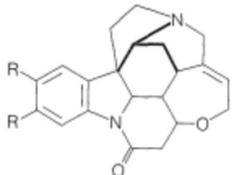
2024.05.02

Literature Seminar

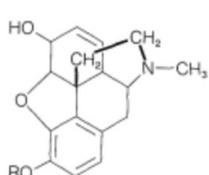
M1 Hiroki Kanamori

Importance of amines

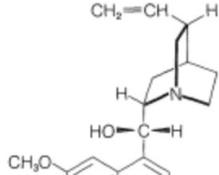
alkaloids



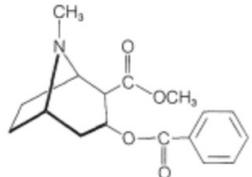
R = H, strychnine
R = OCH₃, brucine



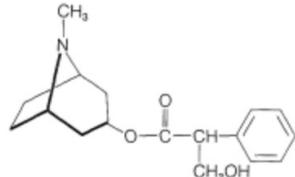
R = H, morphine
R = CH₃, codeine
(analgesic)



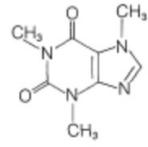
quinine
(antimicrobial)
(antimalarial)



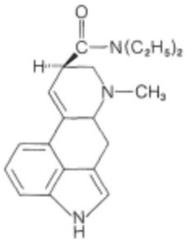
cocaine
(local anaesthetic)
(stimulant)



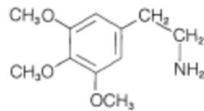
atropine
(stimulant)



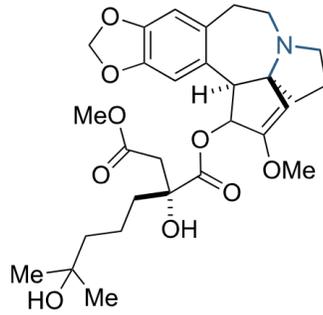
caffeine
(stimulant)



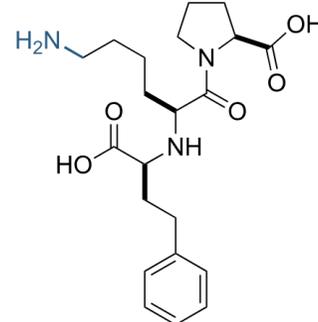
lysergic acid diethylamide (LSD)
(hallucinogen)



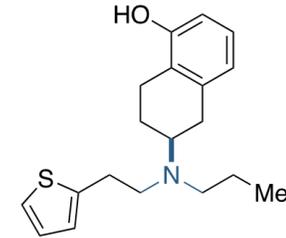
mescaline
(hallucinogen)



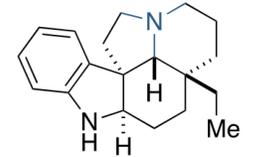
omacetaxine
acute myeloid leukaemia



lisinopril
ACE inhibitor

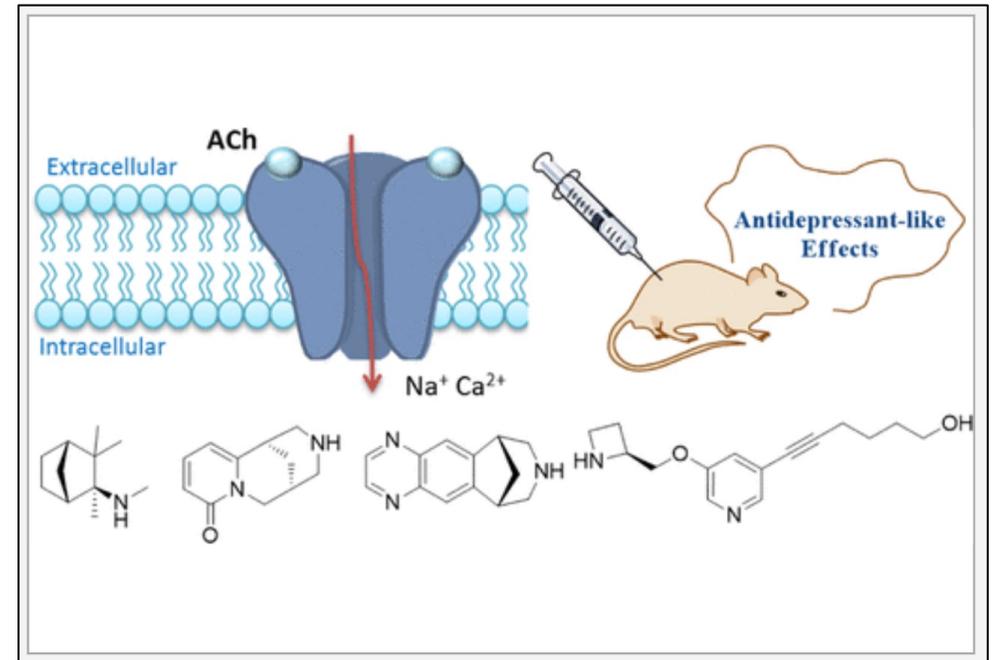


neupro
muscular skeletal disorder



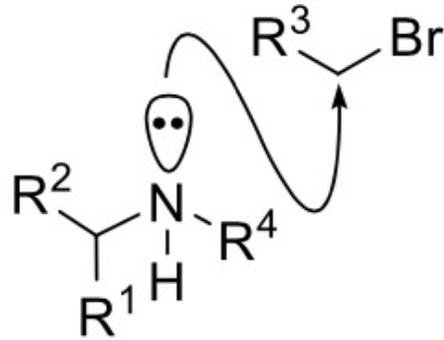
aspidospermidine
common motif in natural products

antidepressants



Methods for the synthesis of amines

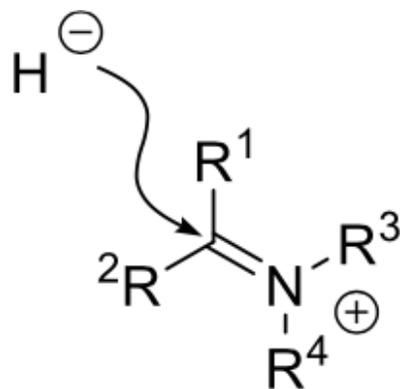
Hoffman alkylation (1850 ~)



- × overalkylation
- × separation, atom economy

Methods for the synthesis of amines

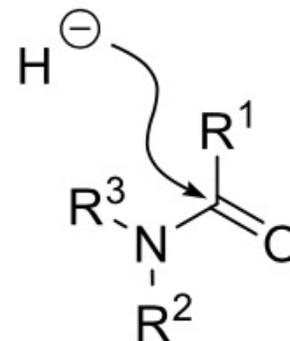
Reductive amination



Most widely used, but ...

- × poor reactivity in the case of sterically encumbered amines
- × over-reaction in the case of small, nucleophilic amines, and simple aldehydes
- × toxic byproducts

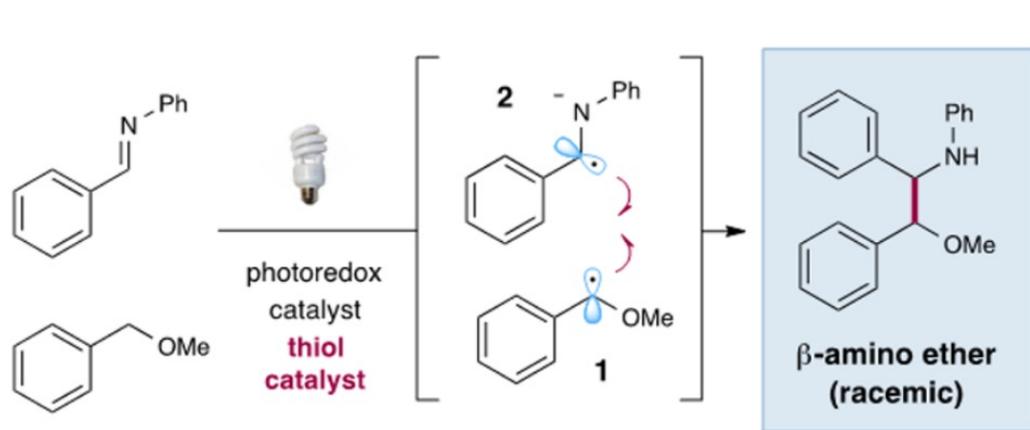
amide/nitrile reduction



- × challenging workup procedures
- × reactive aluminum hydrides with Lewis or Brønsted acids

Photoredox synthesis of β -amino ether

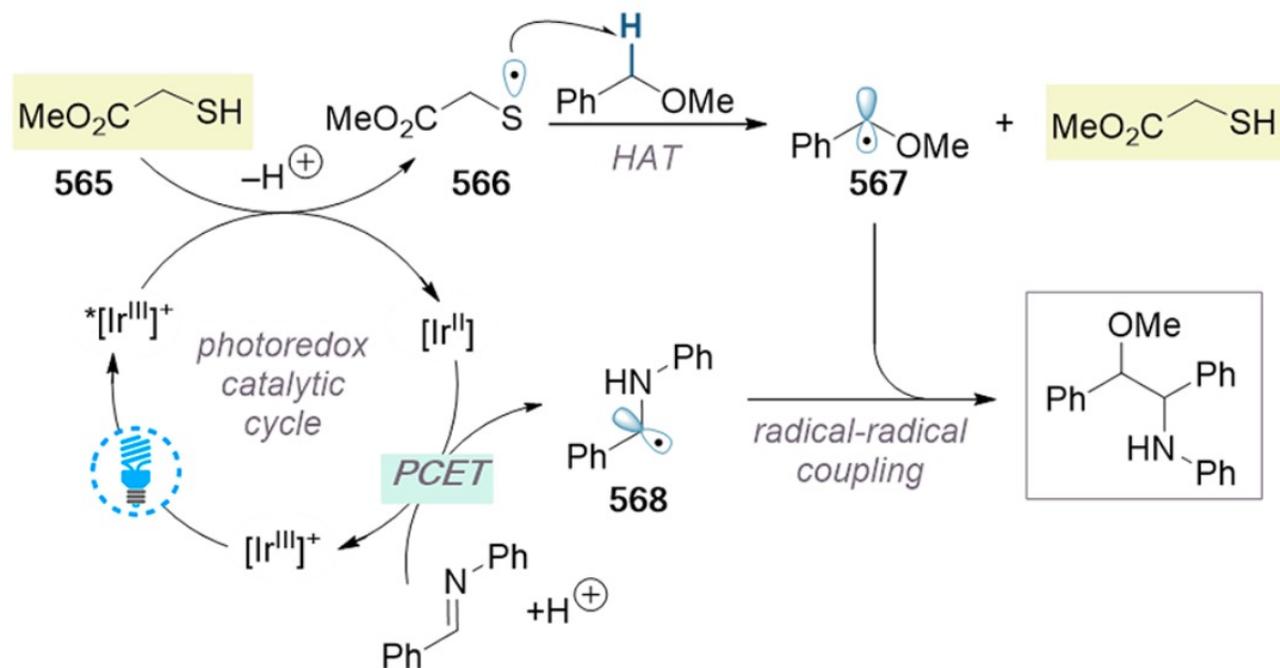
the first example of photocatalytic α -amino radical generation



radical-radical coupling

visible light

photoredox & thiol catalyst



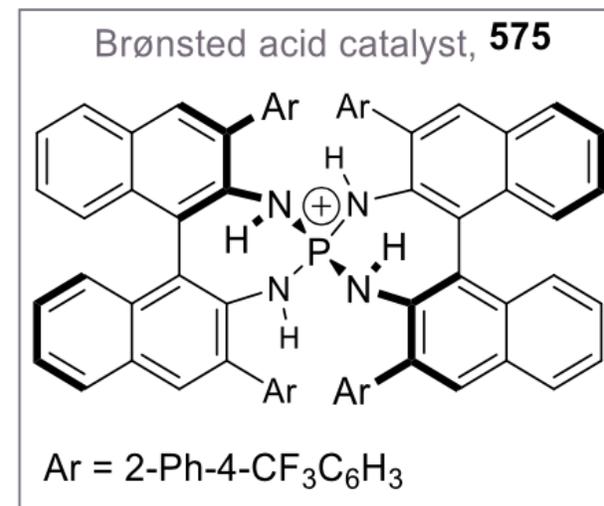
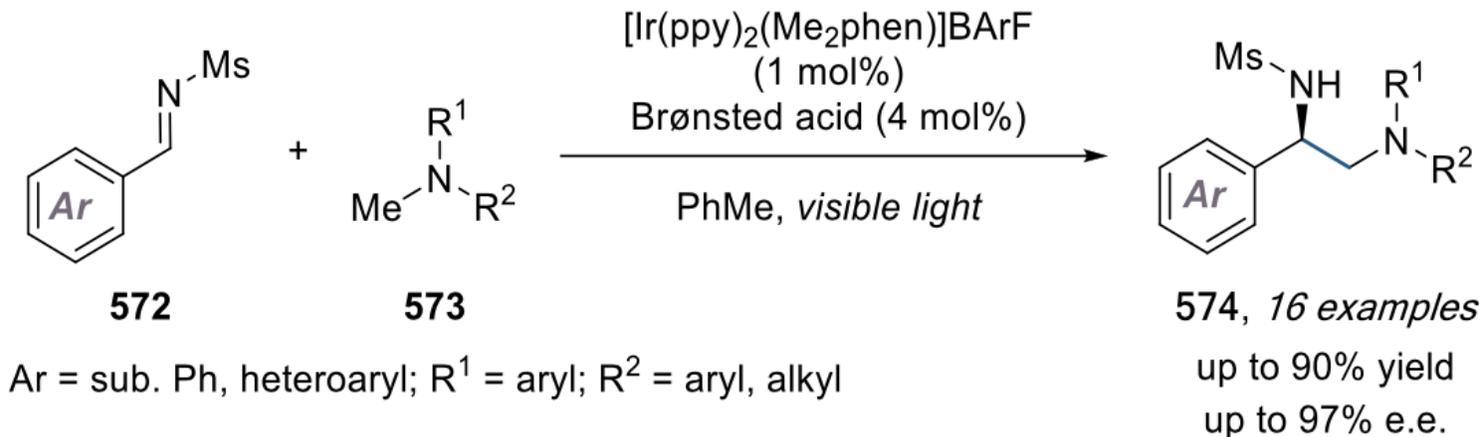
→ development of photocatalytic synthesis of amines

Contents

1. Introduction
2. Enantioselective photocatalytic reaction
3. Carbonyl alkylative amination
4. Reductive amination

Enantioselective photocatalytic reaction

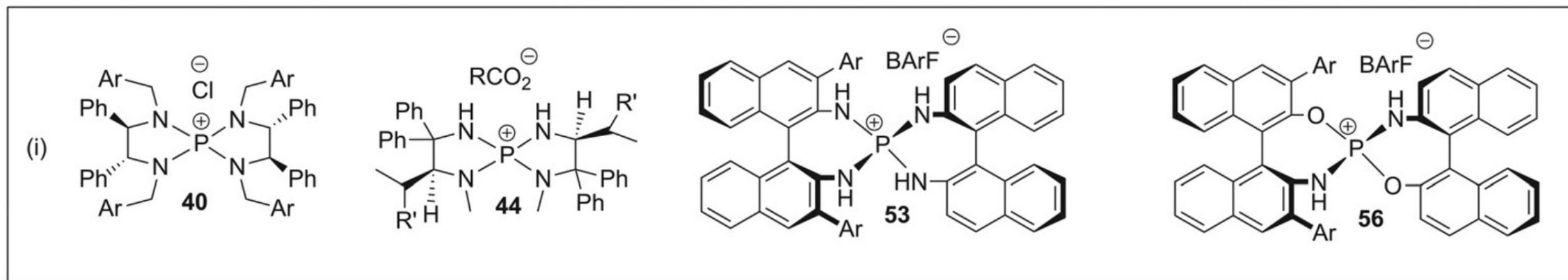
Ooi (2015)



absolute stereocontrol
synergistic catalysis
visible light

P-spiro chiral aminophosphonium salts

a new class of organocatalysts

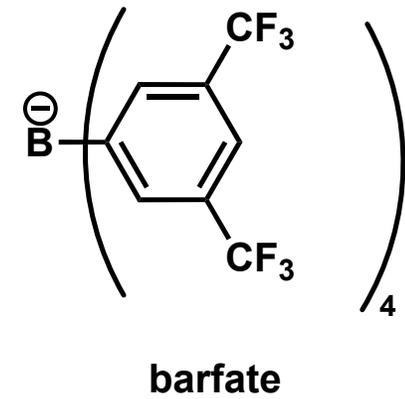
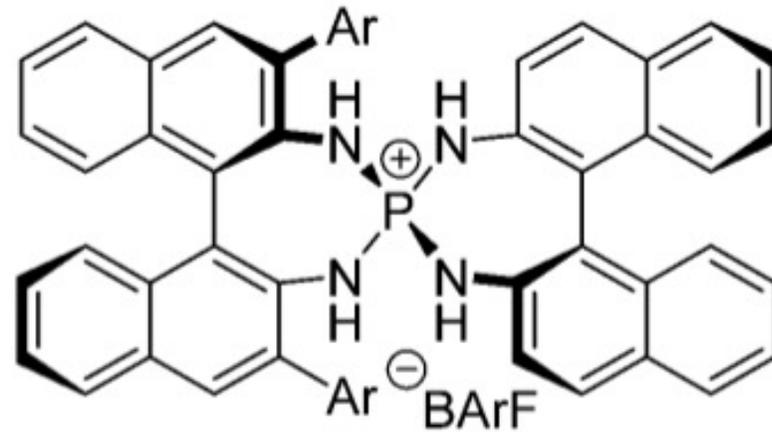


excellent yields & outstanding stereoselectivity

structurally modifiable

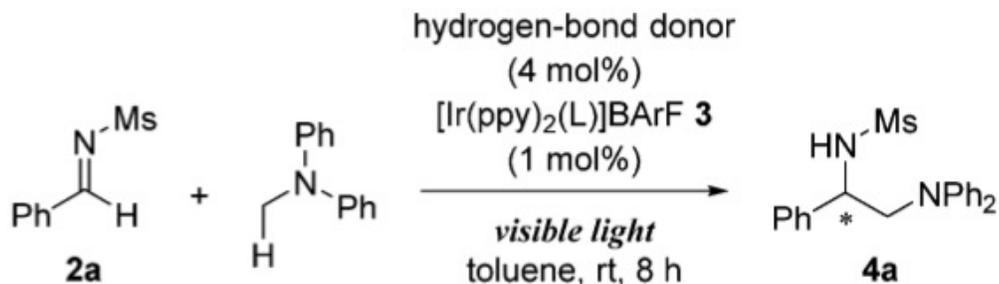
readily accessible

Chiral catalyst design

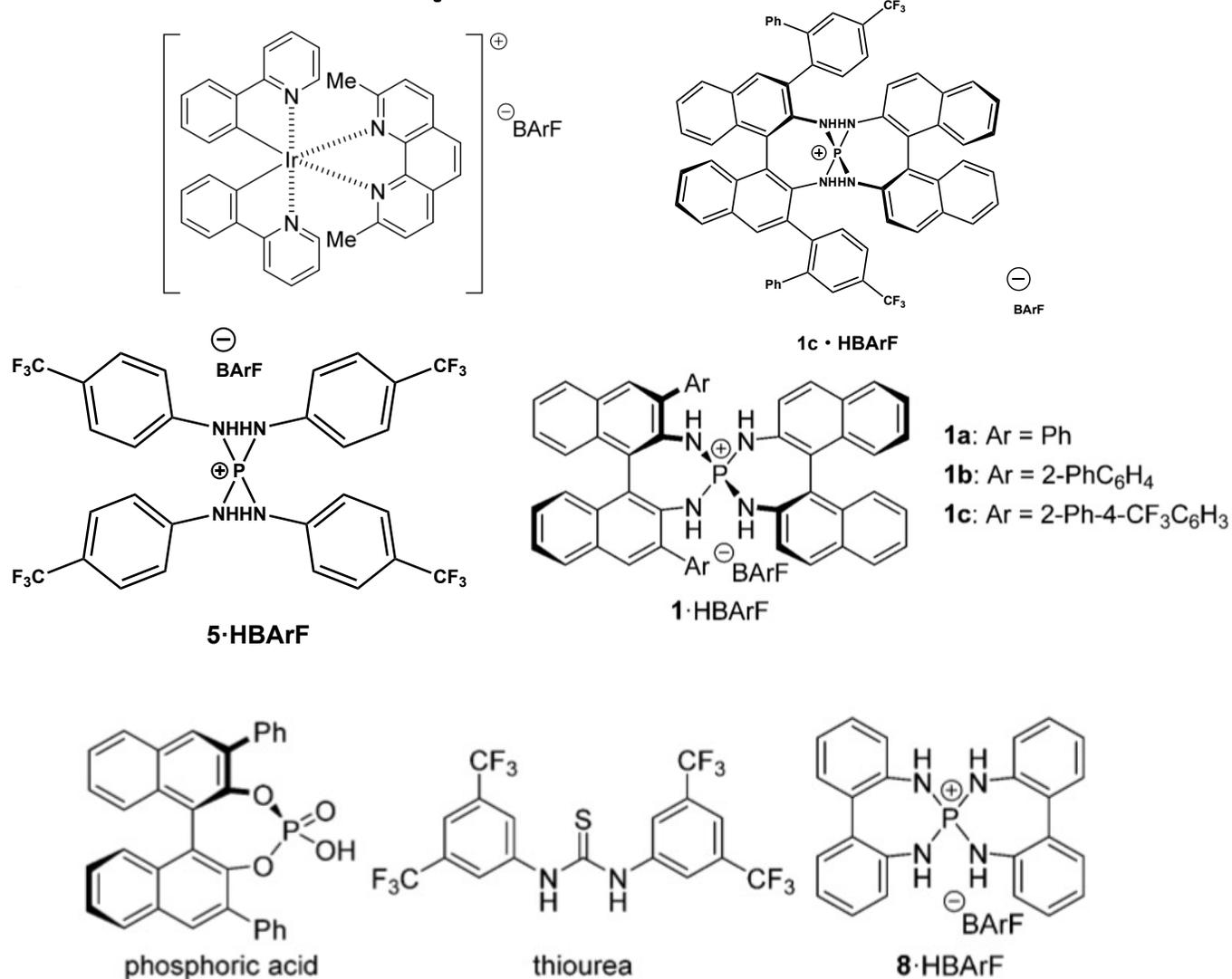


- charged Brønsted acid catalyst
→ efficient acidity to protons
- double H-bond donor
- positive charge
→ for catalytic ion-pairing with anion radical

Comparison of H-bond donor & photosensitizer



entry	H-bond donor	L (3) ^b	yield (%) ^c	ee (%) ^e
1	5·HBArF	bpy (3a)	21	—
2	5·HBArF	none	0	—
3 ^d	5·HBArF	3a	0	—
4	none	3a	6	—
5	5·HBArF	phen (3b)	46	—
6	5·HBArF	Me ₂ phen (3c)	79	—
7	Bu ₄ N·BARf	3c	7	—
8	phosphoric acid	3c	9	—
9	benzoic acid	3c	12	—
10	3,3'-Ph ₂ -BINOL	3c	11	—
11	thiourea	3c	21	—
12	Et ₃ N·HBArF	3c	40	—
13	2,6-lutidine·HBArF	3c	56	—
14	8·HBArF	3c	59	—
15	1a·HBArF	3c	56	53
16	1b·HBArF	3c	79	89
17	1c·HBArF	3c	89	94



Proposed mechanism

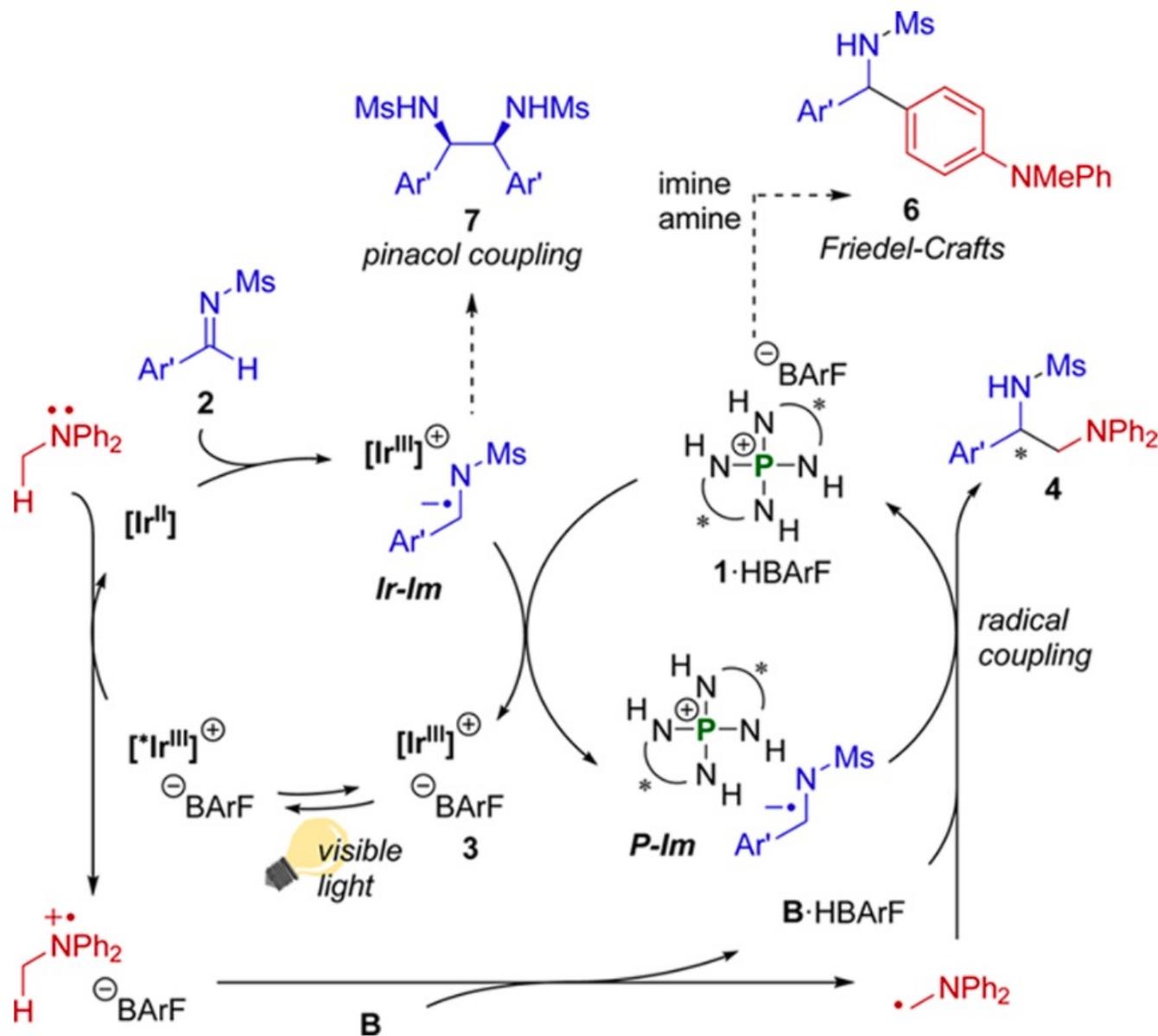
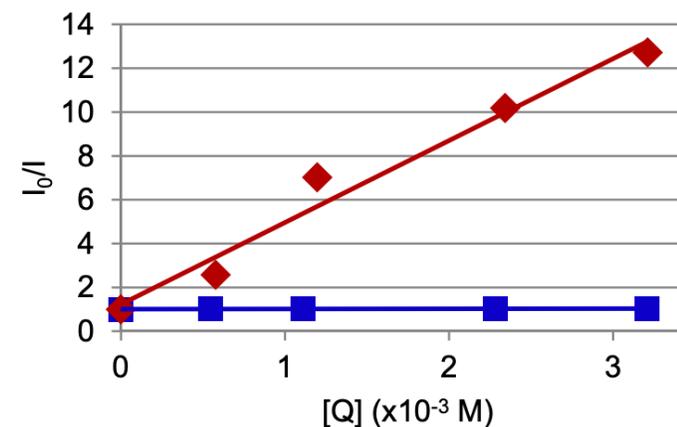
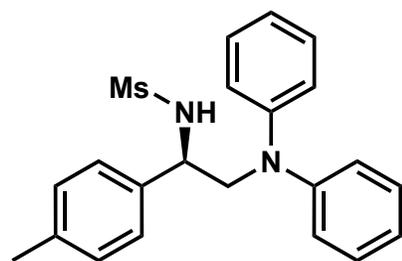
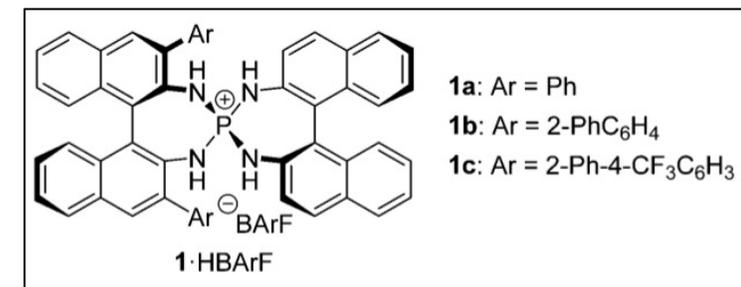
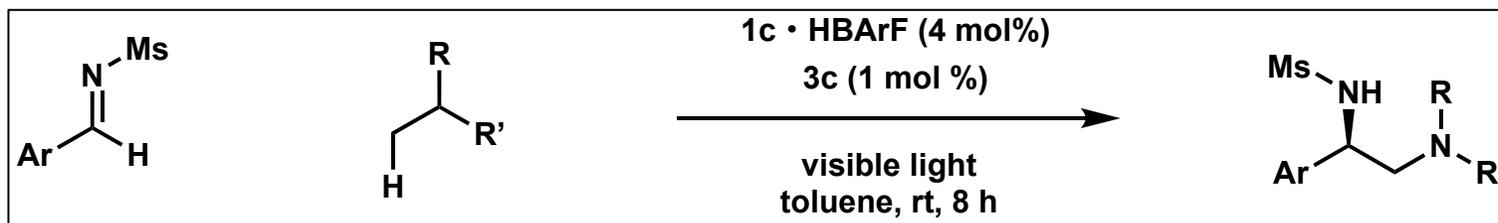


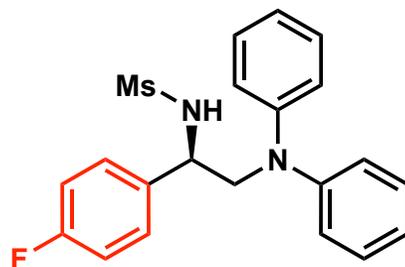
Fig. S2. Stern-Volmer Plots (■ = *N*-Ms benzaldimine (2); (a) Ir(bpy)₂(Me₂phen) (3c).



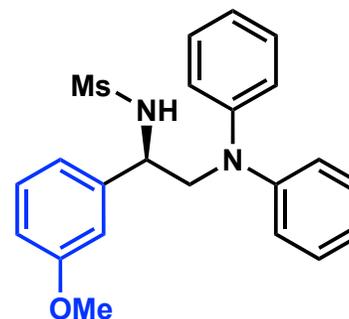
Substrate scope



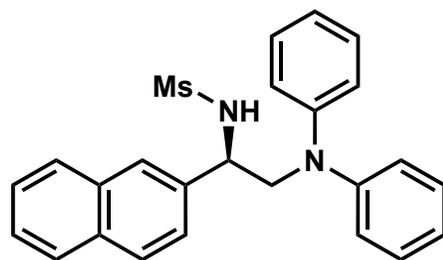
85 %
97 % ee



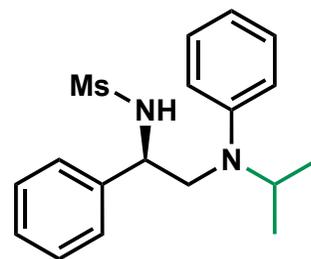
90 %
91 % ee



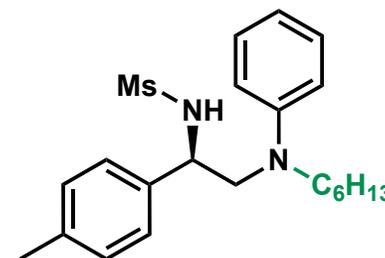
75 %
85 % ee



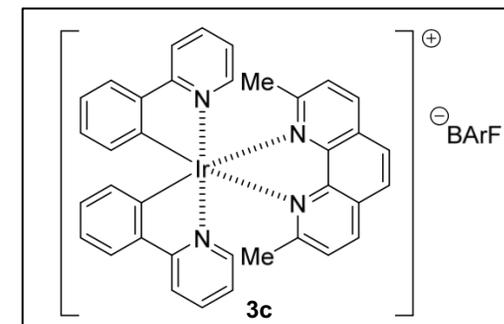
64 %
90 % ee



73 %
91 % ee



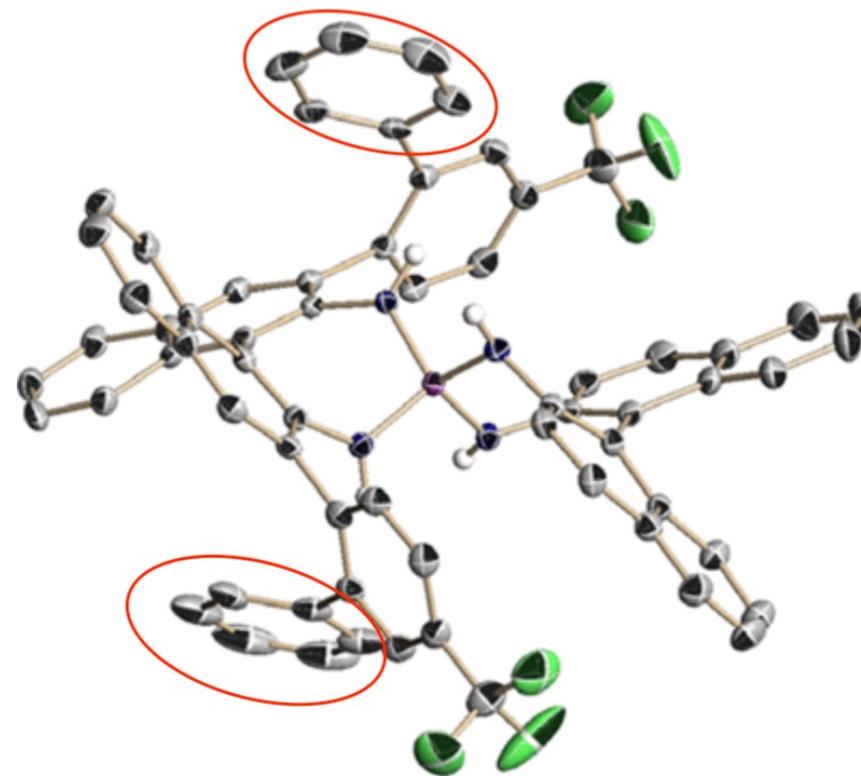
65 %
91 % ee



Enantioselectivity

entry	solvent	ϵ_r	yield (%)	ee (%)
1	toluene	2.38	89	94
2	Et ₂ O	4.33	54	93
3	THF	7.58	15	76
4	CH ₂ Cl ₂	8.93	56	92
5	MeCN	37.5	no reaction	–

Catalytic efficiency was higher in a less coordinating solvent



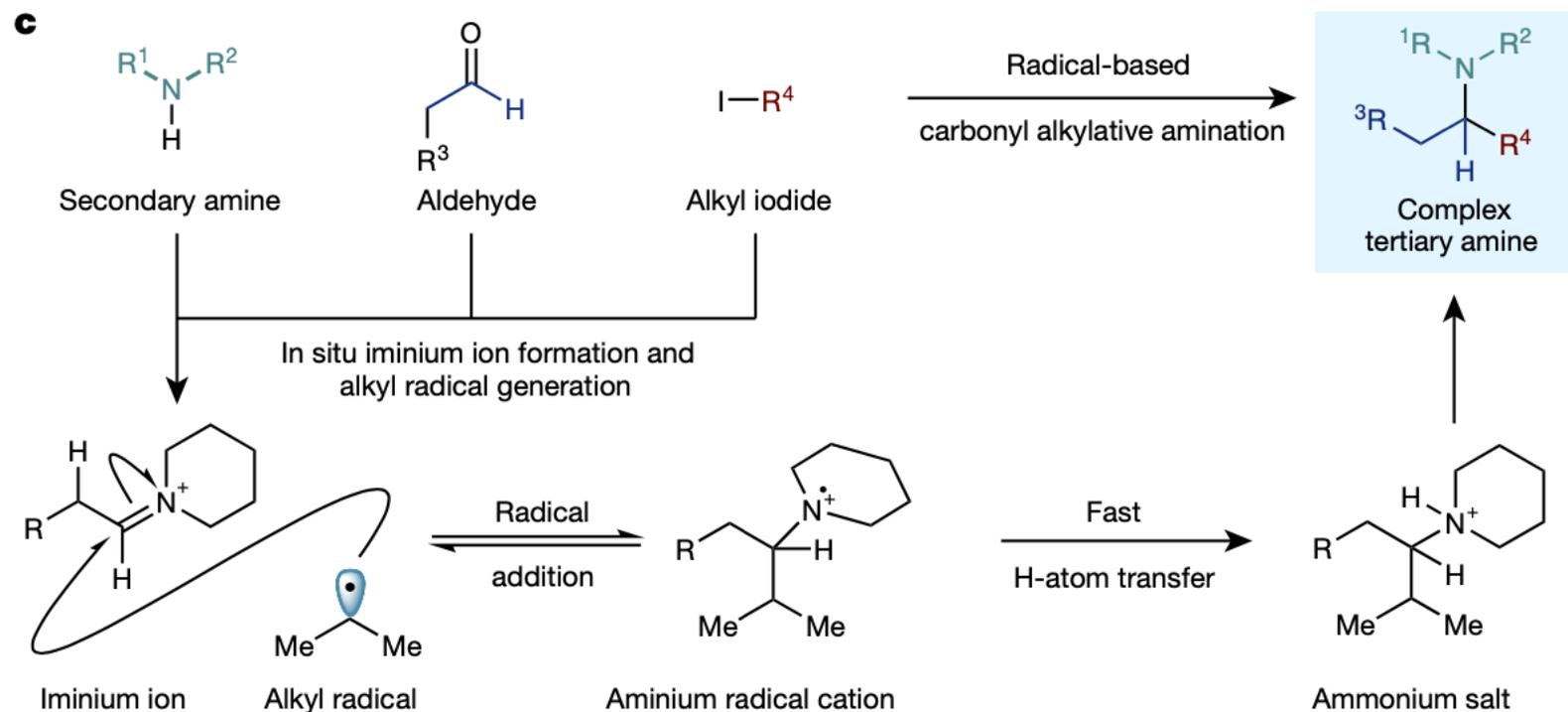
2-phenyl groups

→ cavity over the ionic H-bonding site

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Carbonyl alkylative amination



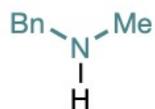
streamlined synthesis of complex tertiary amines

metal-free and modular transformation

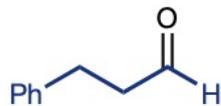
abundant feedstocks

Optimization and controls

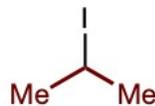
a



Secondary amine **1a**



Aldehyde **2a** (2 equiv.)



Alkyl iodide **3a** (3 equiv.)

Conditions

4 Å MS, CH₂Cl₂



4a

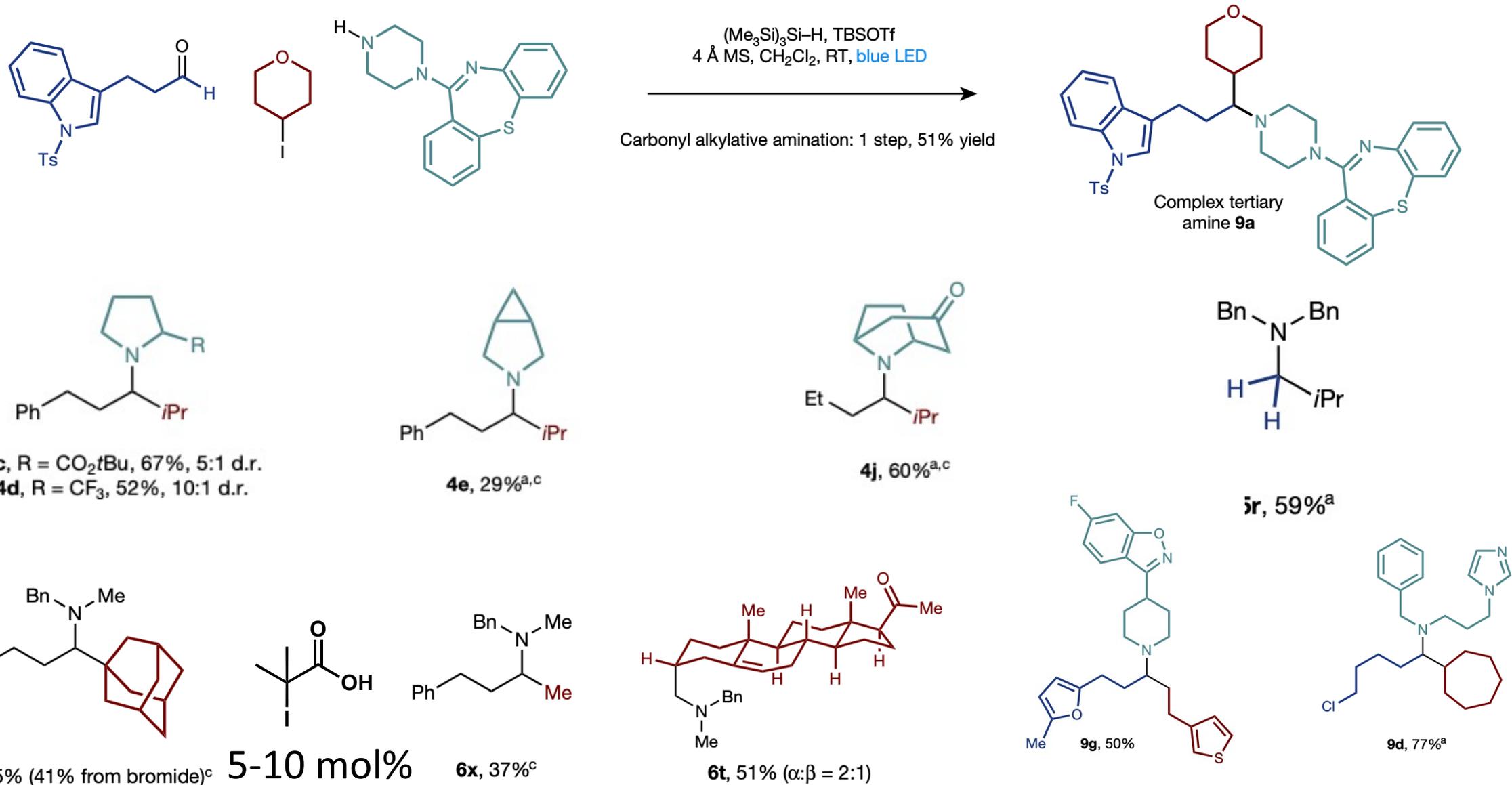
Conditions	Yield of 4a by ¹ H NMR	Conditions	Yield of 4a by ¹ H NMR
1. Bu ₃ Sn-H, AIBN, 70 °C	Trace	5. 2 equiv. (Me ₃ Si) ₃ Si-H, 1 equiv. TBSOTf, RT, 8 h 40 W blue LED	92% (80% isolated)
2. (Me ₃ Si) ₃ Si-H, AIBN, 70 °C	<10%	6. (Me ₃ Si) ₃ Si-H, RT, 40 W blue LED	82%
3. (Me ₃ Si) ₃ Si-H, AIBN, TBSOTf, 70 °C	75% (plus 25% reductive amination)	7. (Me ₃ Si) ₃ Si-H, TBSOTf, RT, 40 W blue LED, 455 nm filter	86%
4. Bu ₃ Sn-H, AIBN, TBSOTf, 70 °C	0% (84% reductive amination)		

TTMSS : HAT

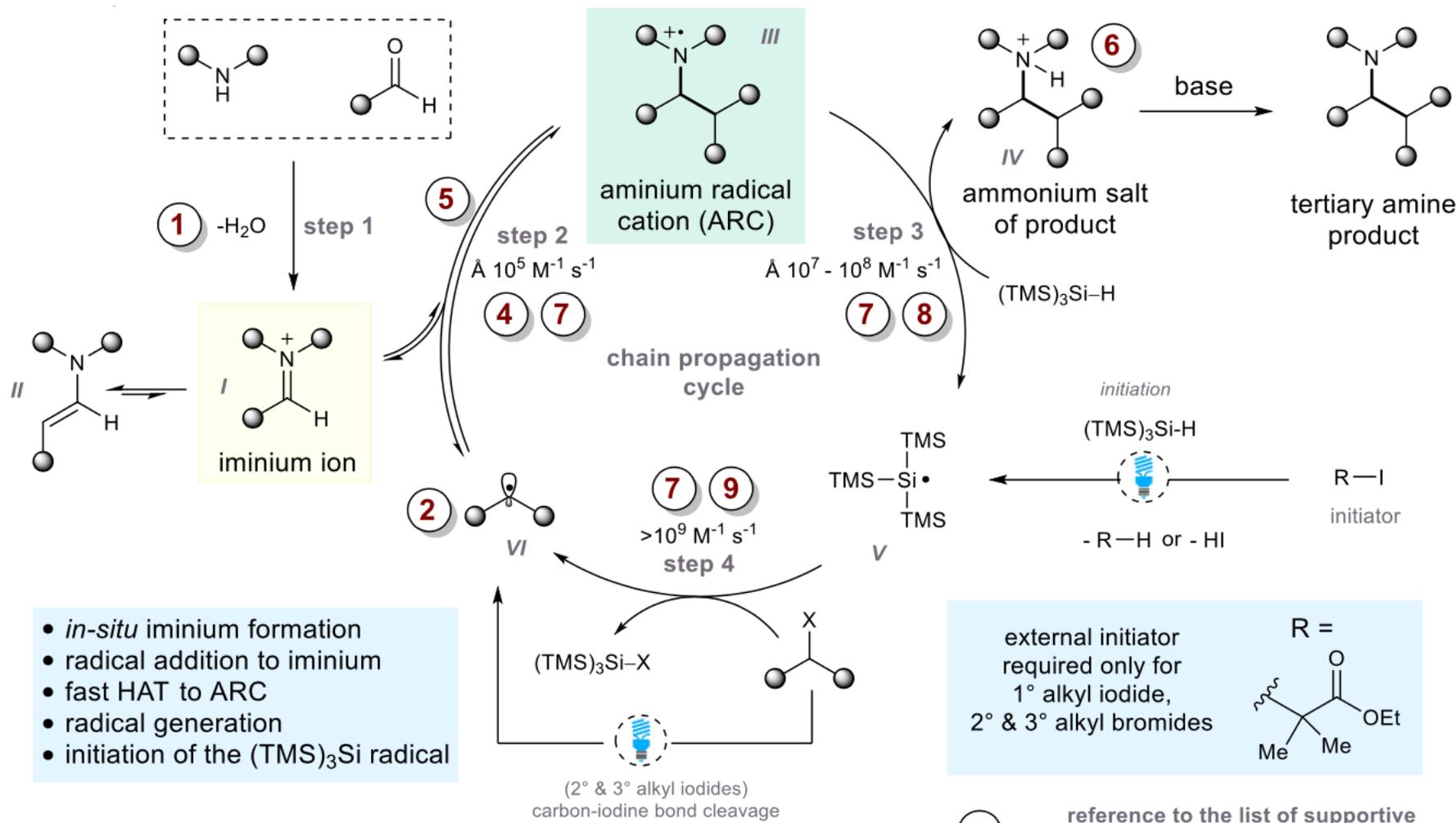
TBSOTf : Lewis acid

light : visible light

Substrate scope



Proposed mechanism



- *in-situ* iminium formation
- radical addition to iminium
- fast HAT to ARC
- radical generation
- initiation of the $(\text{TMS})_3\text{Si}$ radical

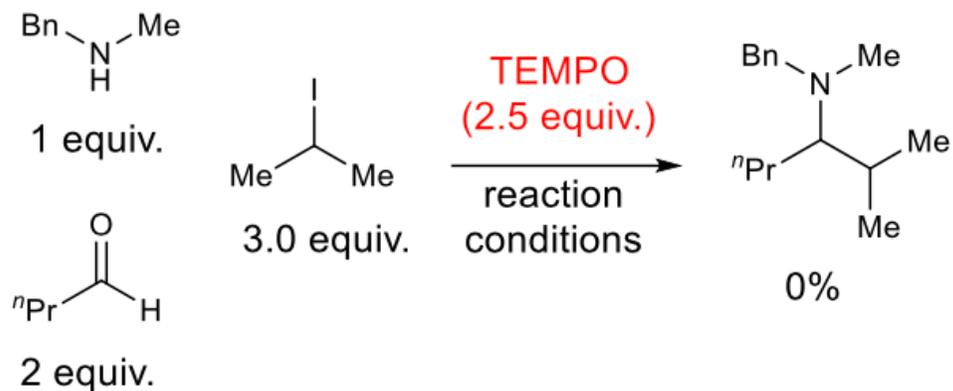
external initiator required only for 1° alkyl iodide, 2° & 3° alkyl bromides

R =

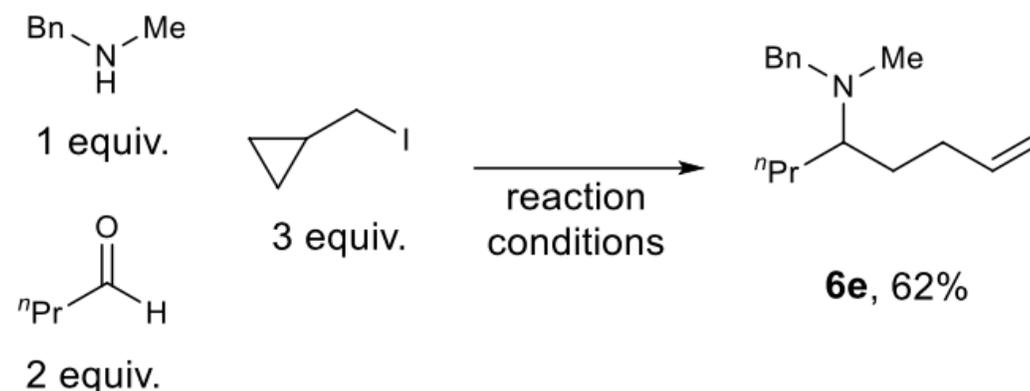
X ≡ reference to the list of supportive mechanistic experiments/observations below

Mechanistic study

b Radical inhibition experiment



c Radical trap experiment

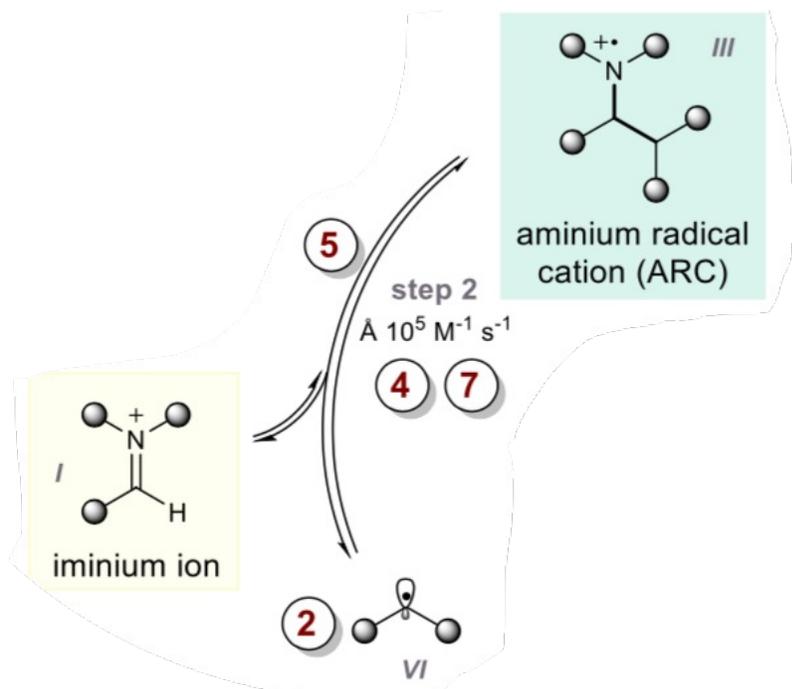


d Radical clock experiment



+ the reaction efficiency dropped under air

Evidence in support of the proposed mechanism

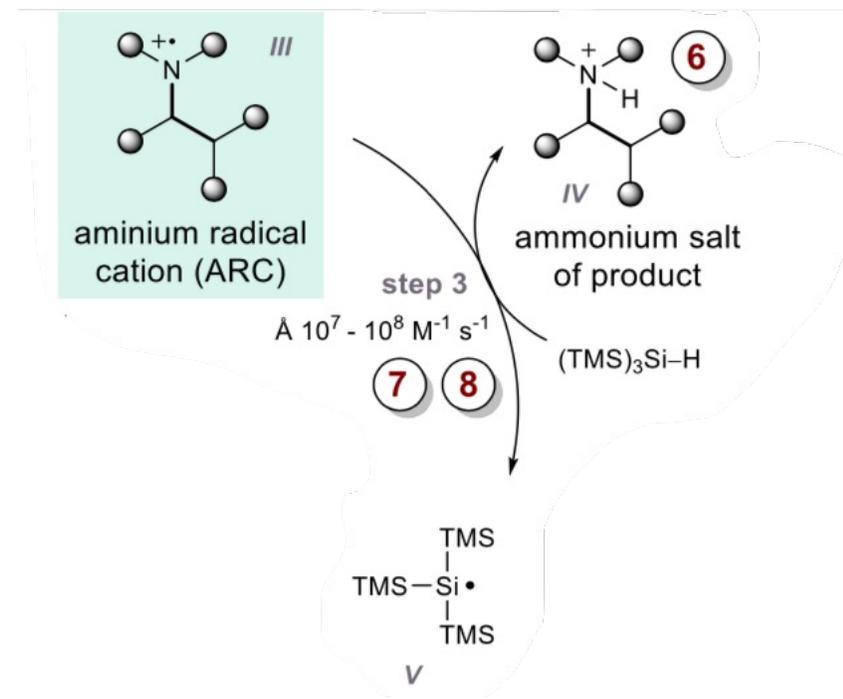


adding an alkyl radical to an iminium ion :

$$\Delta G = - 6.2 \text{ kcal mol}^{-1}$$

$$\Delta G^{\text{TS}} = + 2.7 \text{ kcal mol}^{-1}$$

the length of the forming C–C bond
(2.3609 Å)

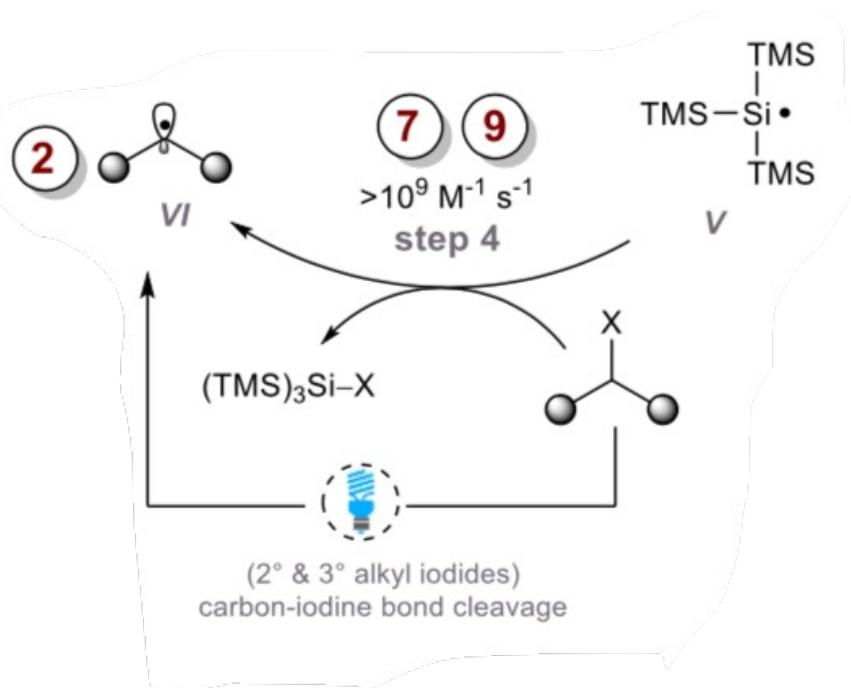


a strong dependence on the choice of silane
BDE:

$$\text{TTMSS } 84 \text{ kcal mol}^{-1}$$

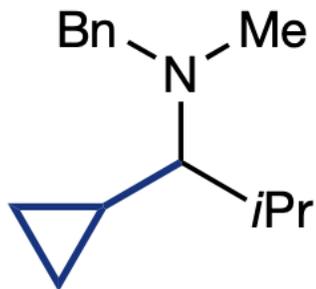
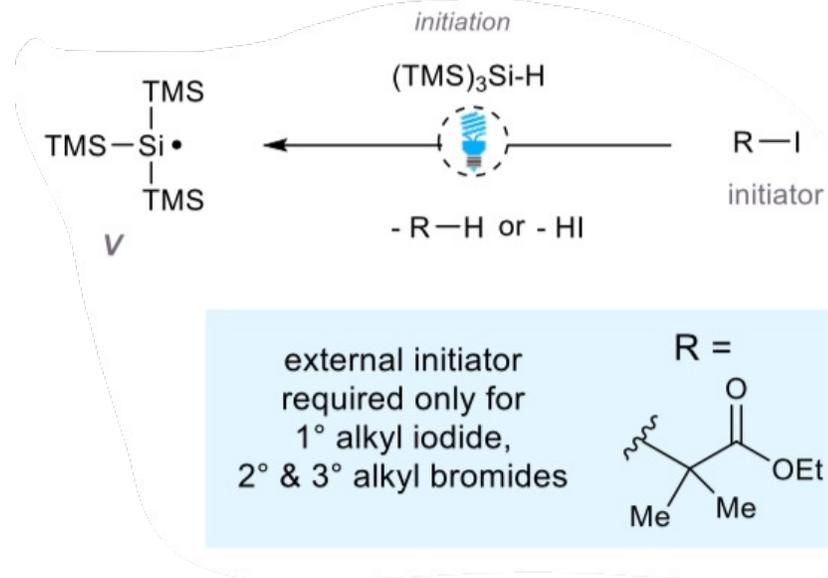
$$\text{ammonium ion } 95 \text{ kcal mol}^{-1}$$

Evidence in support of the proposed mechanism



The halogen abstraction

$3^\circ > 2^\circ > 1^\circ$ and $\text{R-I} > \text{R-Br}$



No ring-opened product was observed
 formation of an α -amino radical does not occur.

Studies into the role of visible light

- Control experiment in the dark afforded no product.

Light is required for the reaction

- The reaction proceeds efficiently in the presence of 455 nm long-pass filter.

The reaction does not require high-energy UV-light

- The reaction is also operative under thermal conditions.

The main role of light is thought to be to provide a room temperature **initiation** pathway for the silane-mediated radical chain mechanism.

The role of visible-light

Hypothesis 1 : ruled out

light-mediated homolysis of the C–I bond of the alkyl iodide

Hypothesis 2 : ruled out

excited state enamine reduces alkyl iodide

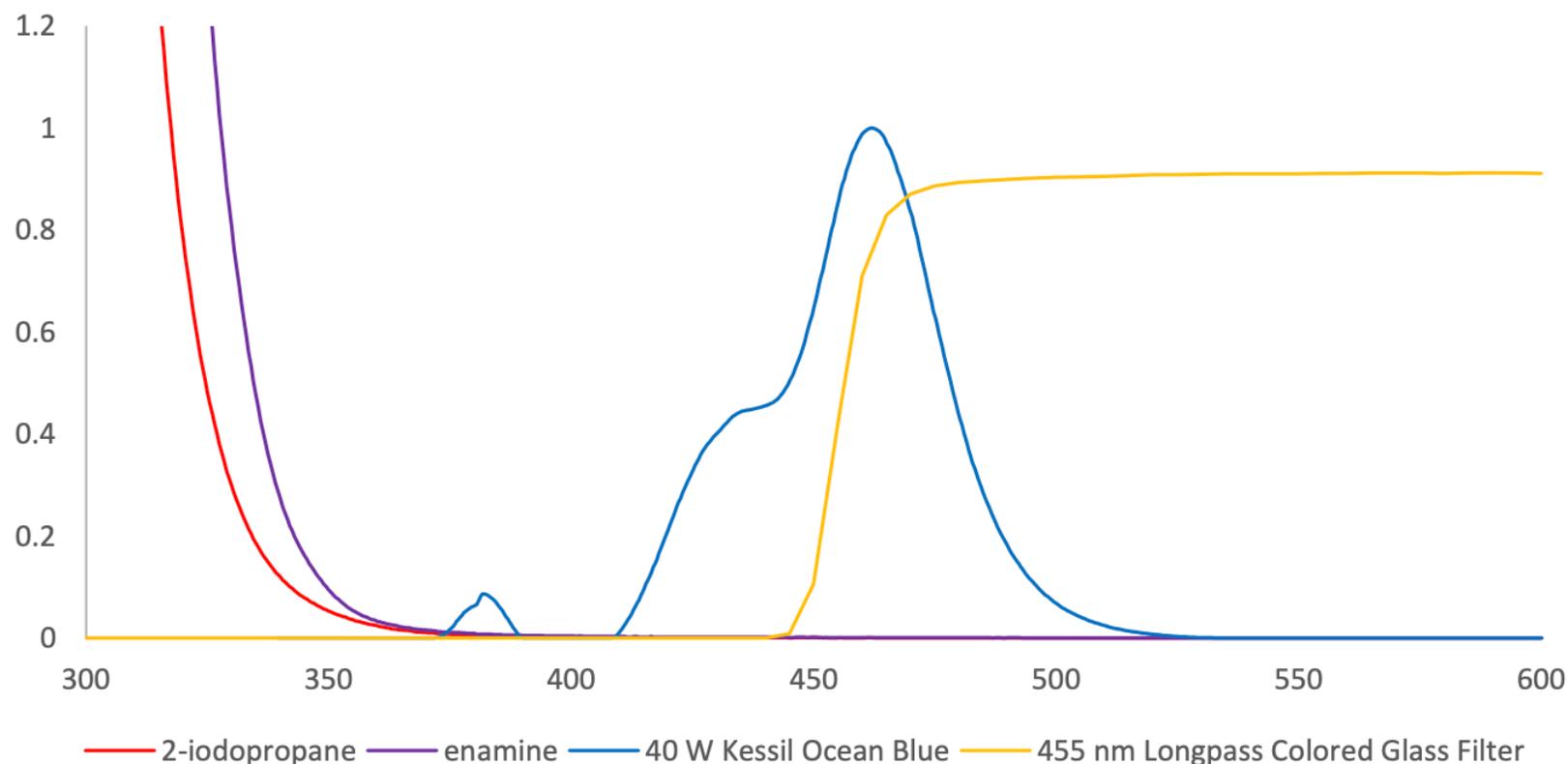
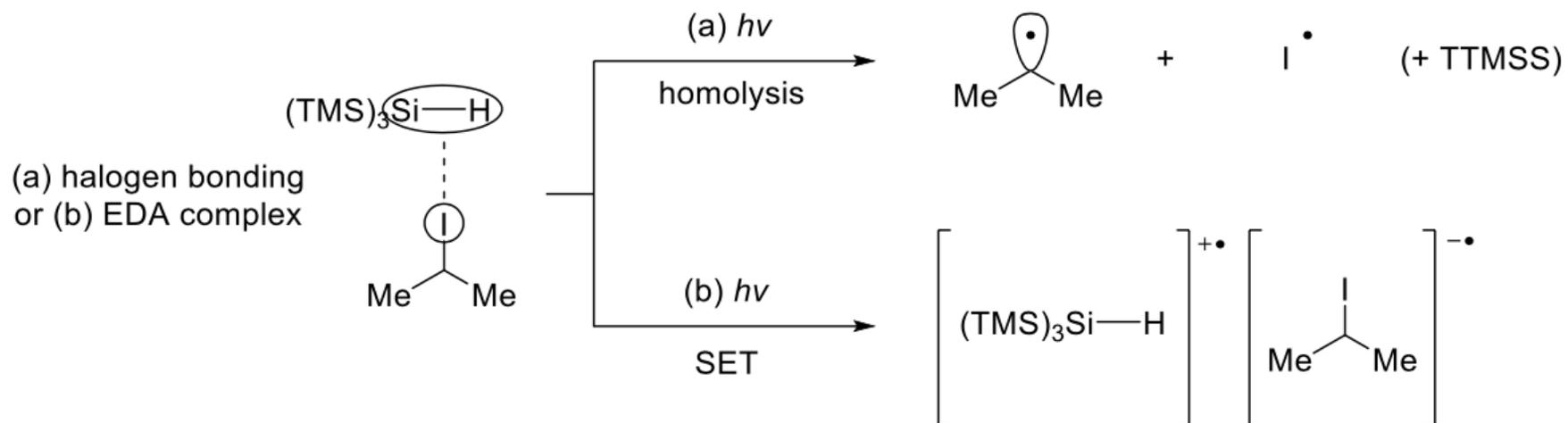


Figure S3. Absorption spectra of 2-iodopropane & enamine versus the emission of the Kessil lamp.

The role of visible-light



Hypothesis 3 : ruled out

interaction between TTMSS and alkyl iodide
(halogen bonding or EDA complex)

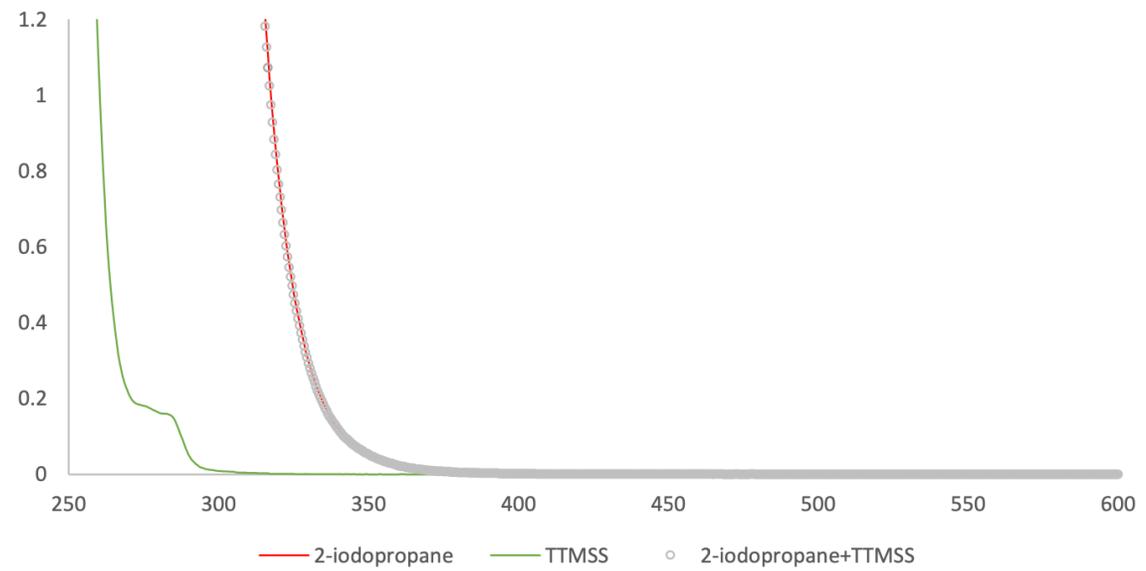


Figure S4. Absorption spectra of 2-iodopropane, TTMSS and their mixture.

The role of visible-light

Hypothesis 4 : ruled out

EDA complex between the iminium ion and TTMSS

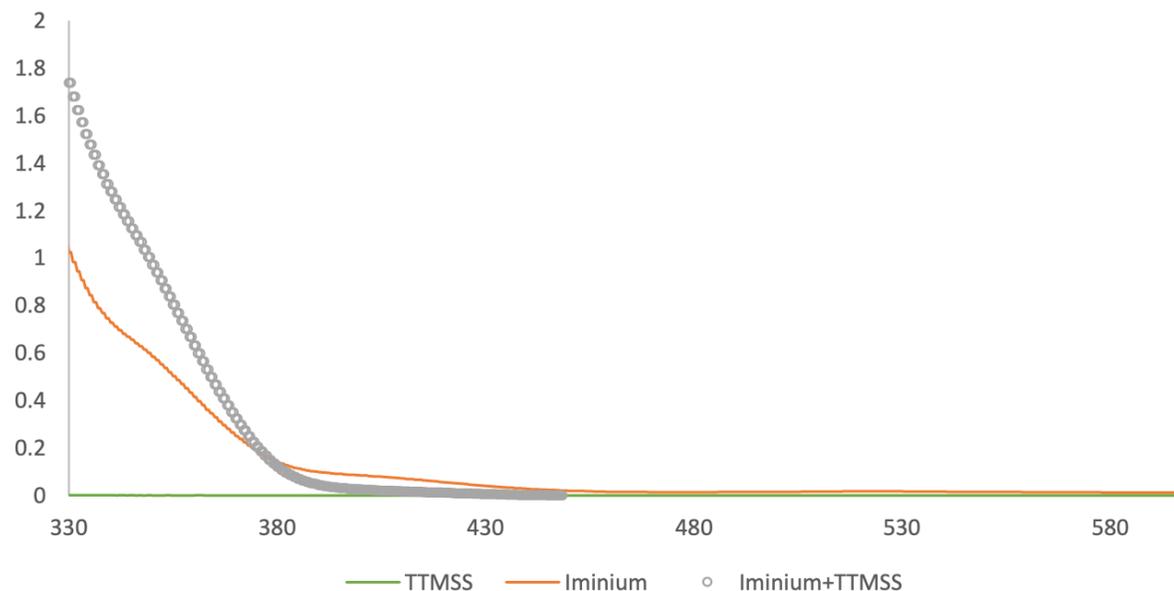


Figure S5. Absorption spectra iminium ion, TTMSS and their mixture.

Hypothesis 5 : ruled out

EDA complex between enamine and alkyl iodide

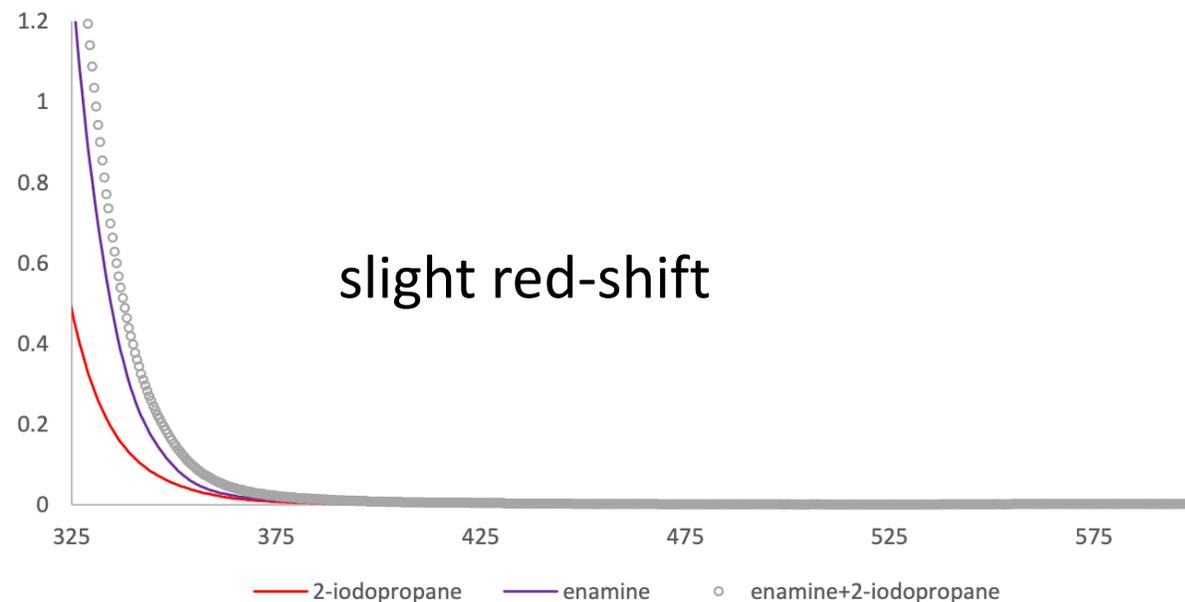
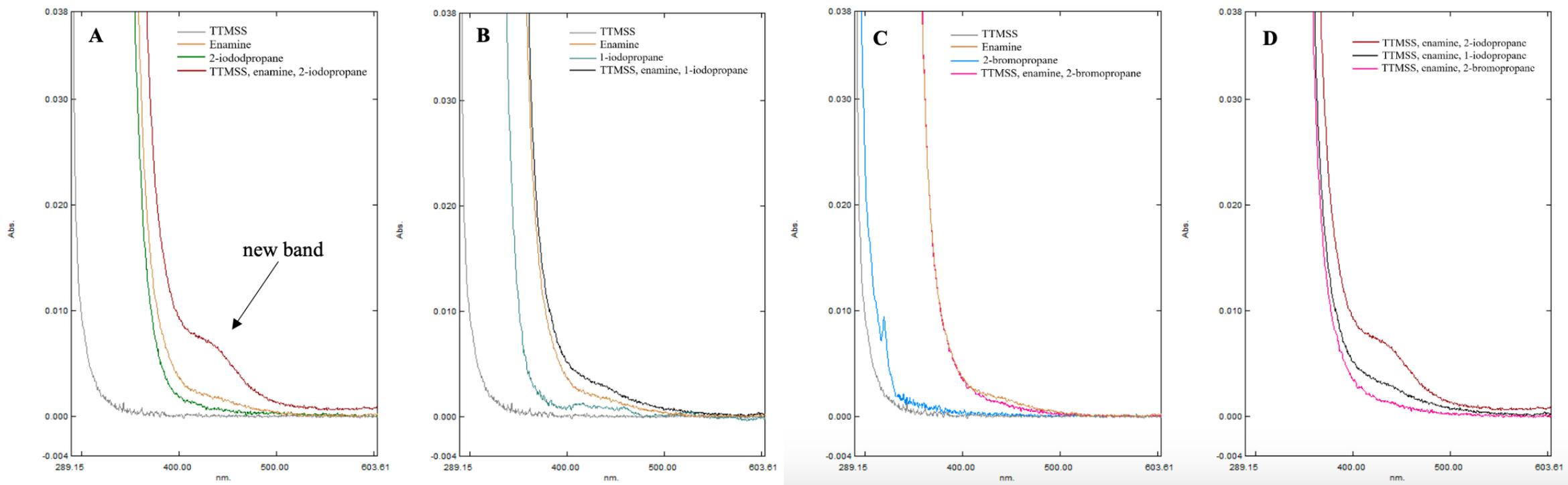
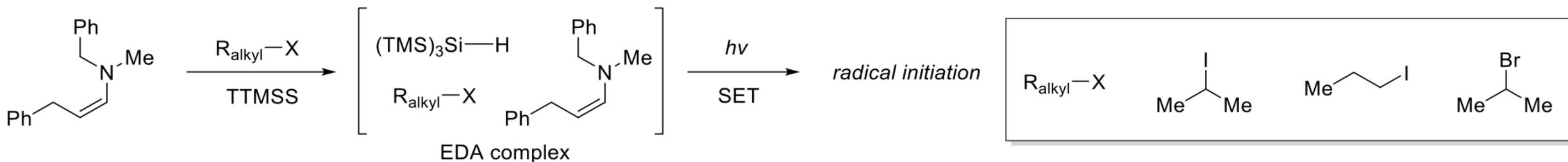


Figure S6. Absorption spectra of 2-iodopropane, enamine and their mixture.

New band observed

Hypothesis 6

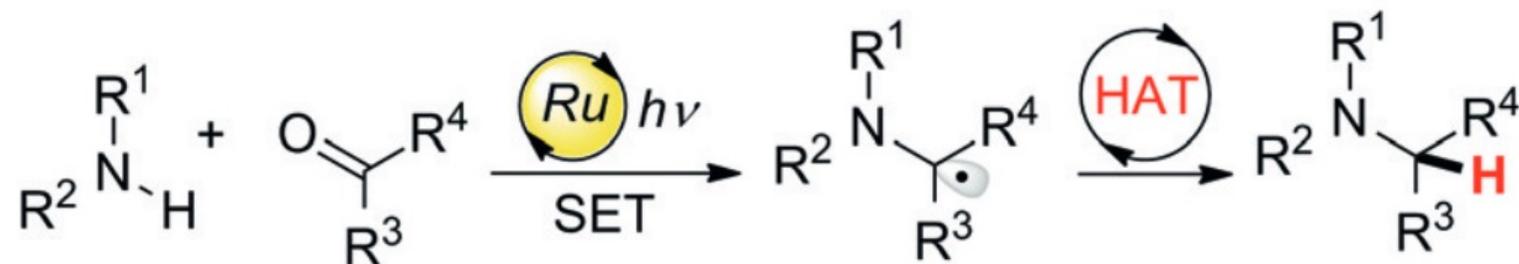
excitation of reaction mixture (enamine, TTMSS, alkyl halide)



Contents

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Reductive amination

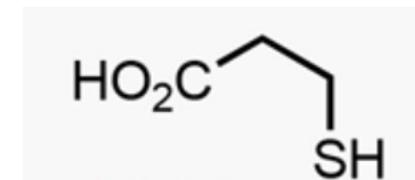
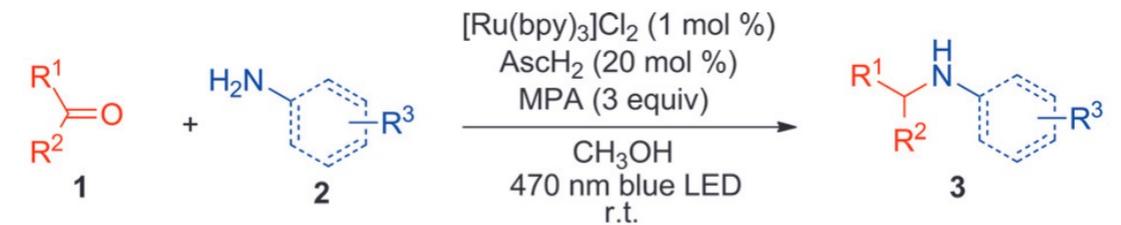


visible light

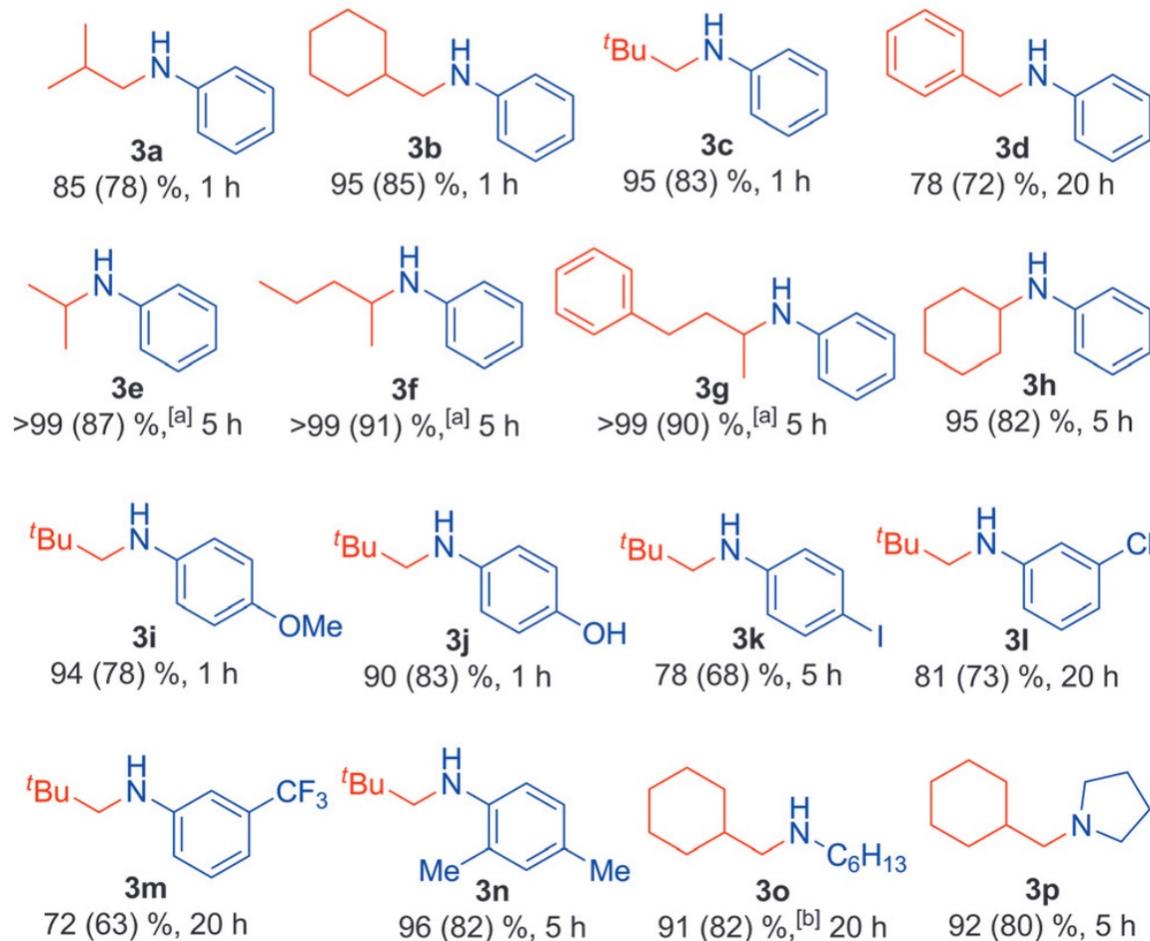
temporal & spatial control

scalable

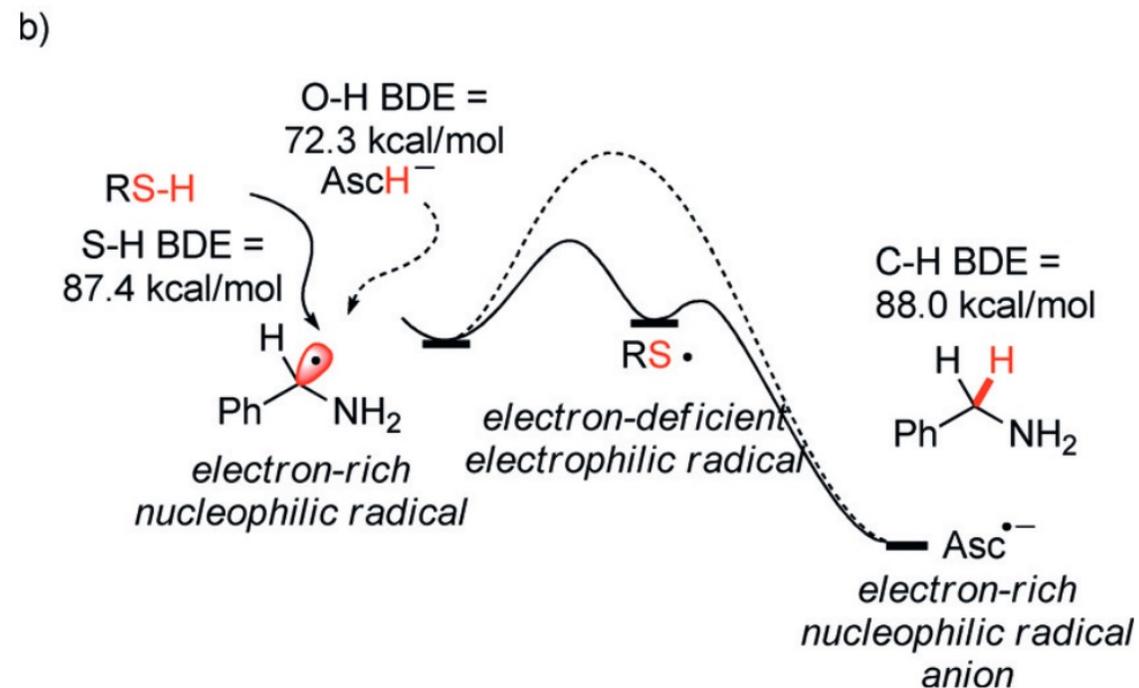
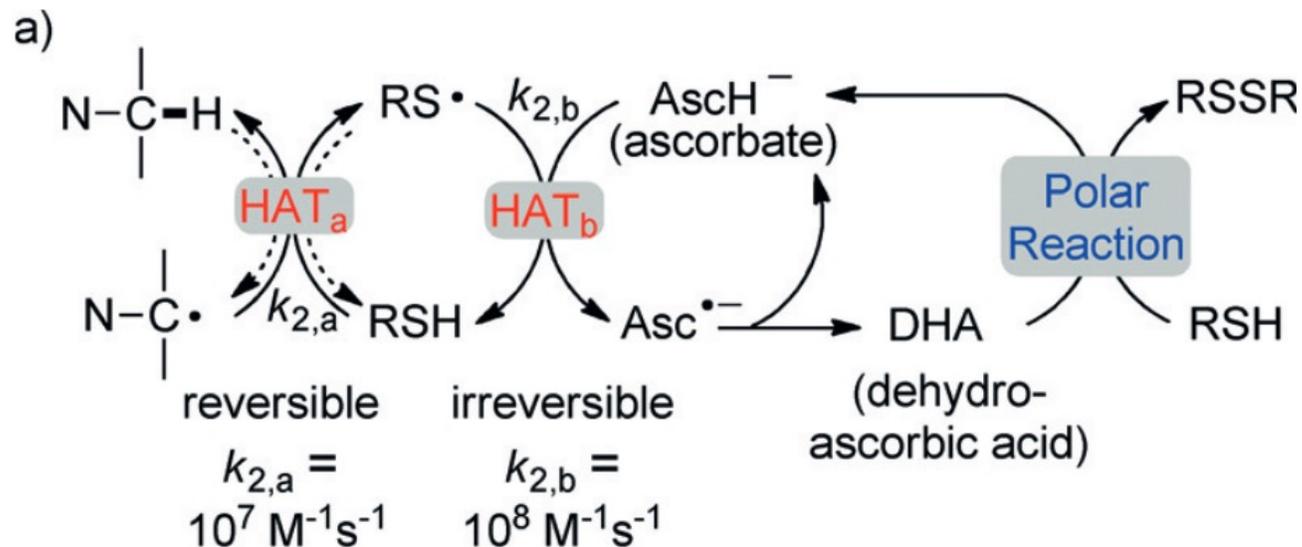
Substrate scope



MPA



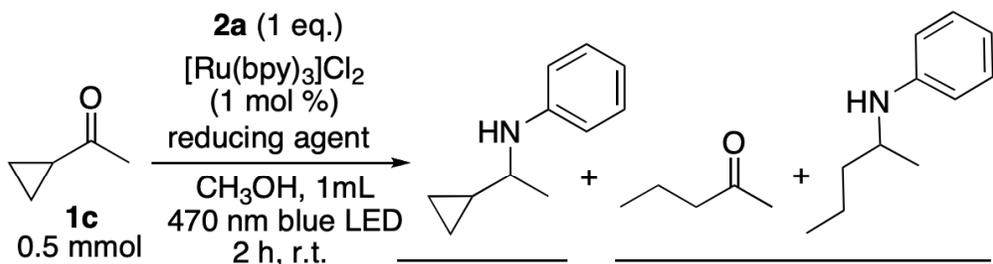
Proposed mechanism



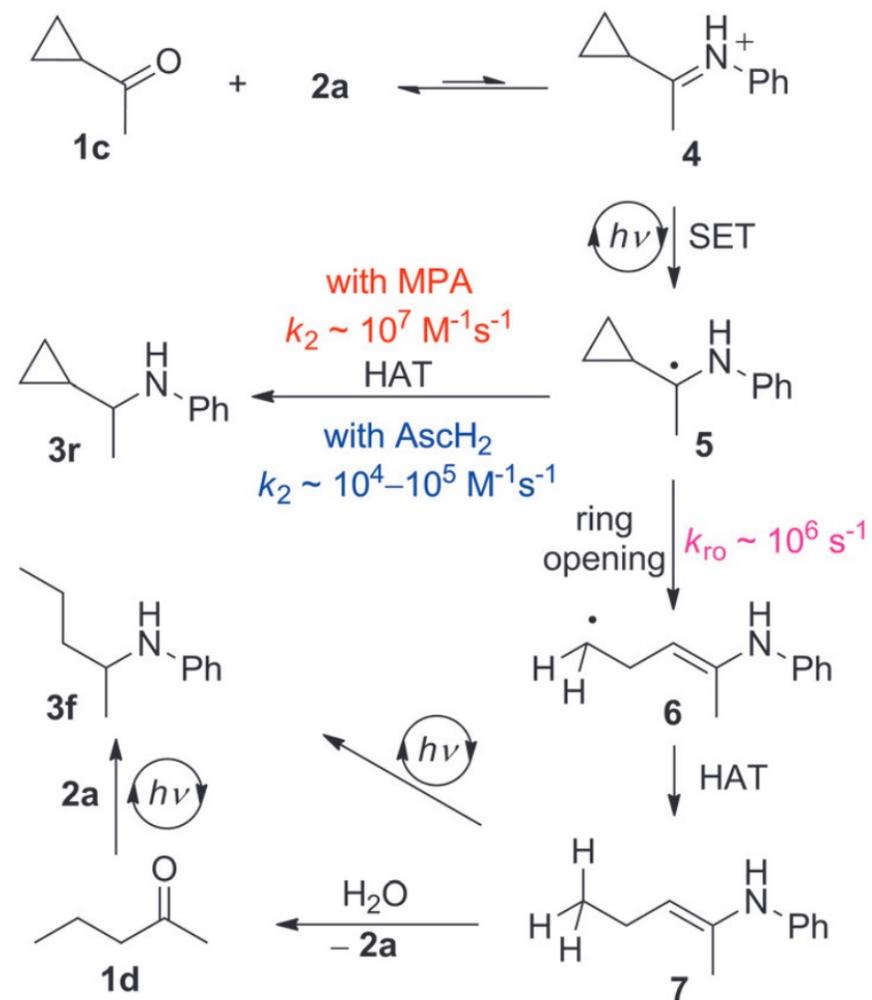
without AscH_2 : no product formation at all

- the inefficient reductive quenching of $^3\text{MLCT}$ -excited $[\text{Ru}(\text{bpy})_3]^{2+}$ by MPA
- the reversible nature of the HAT between MPA and α -amino alkyl radicals

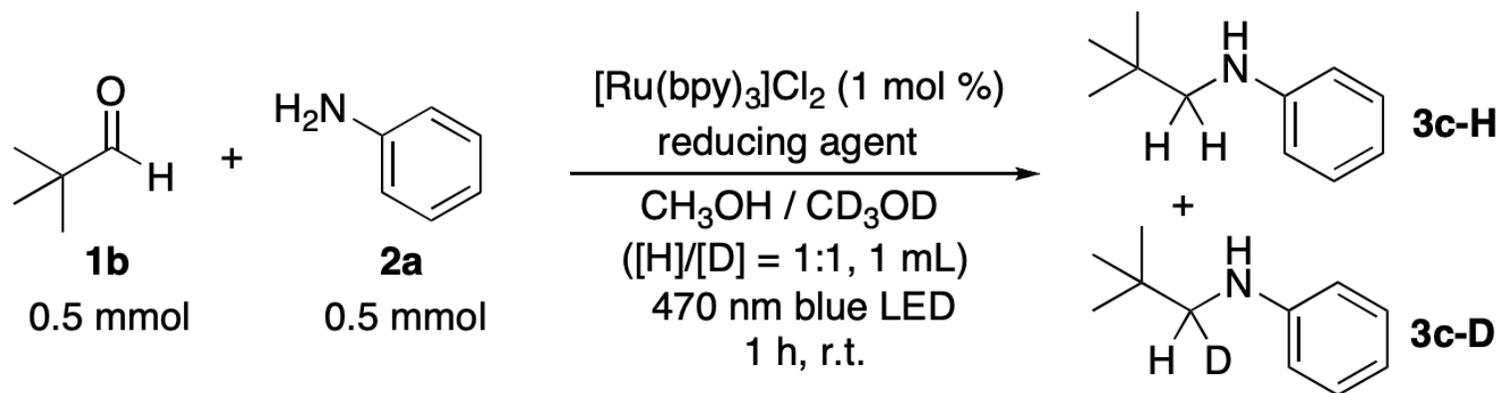
Mechanistic study



reducing agent	3r	1d	3f	$P_{rr} : P_{ro} = k_{rr}[\text{H-Donor}]/k_{ro}$	k_{rr}
AsCH_2 (20 mol %), MPA (3 eq., 1.5M)	41(25)%	~1%	3%	$41 / (1 + 3) = 10$	$10 k_{ro} / [\text{H-Donor}] = \sim 10^7 \text{M}^{-1}\text{s}^{-1}$
AsCH_2 (1.5 eq., 0.75M)	< 1%	16%	~1%	$< 1 / (16 + 1) = 0.06$	$< 0.06 k_{ro} / [\text{H-Donor}] = 8 \times 10^4 \text{M}^{-1}\text{s}^{-1}$ $10^4 \sim 10^5 \text{M}^{-1}\text{s}^{-1}$



kinetic isotope effect studies



reducing agent	yield	product ratio (3c-H : 3c-D) analyzed by ESI-MS
AsCH_2 (20 mol %), MPA (3 eq.)	83 %	70 / 30 = 2.3
AsCH_2 (1.5 eq.)	60 %	92 / 8 = 11.5

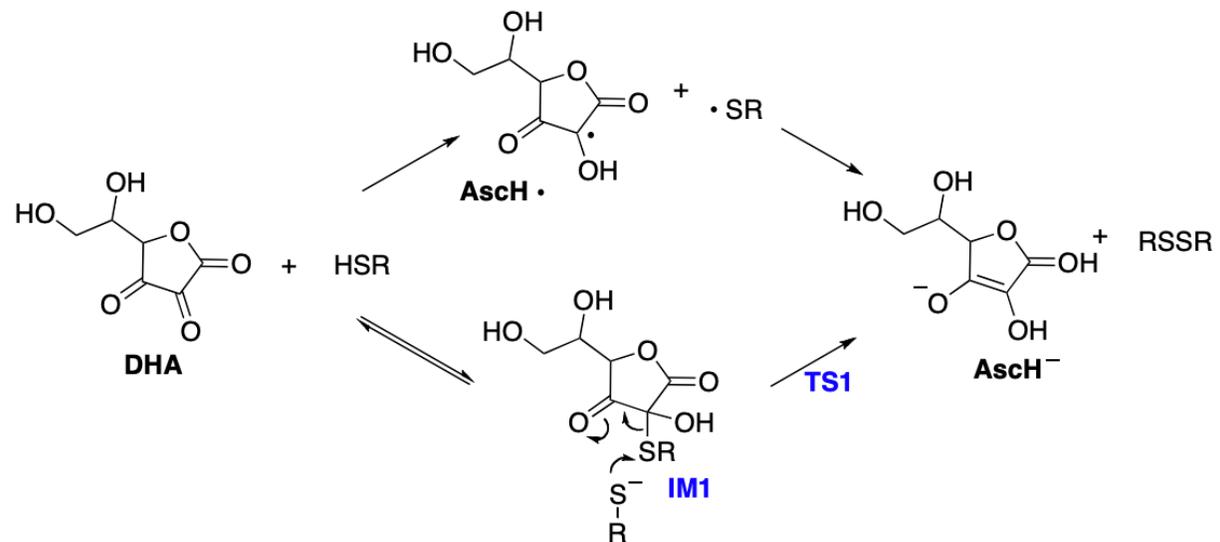
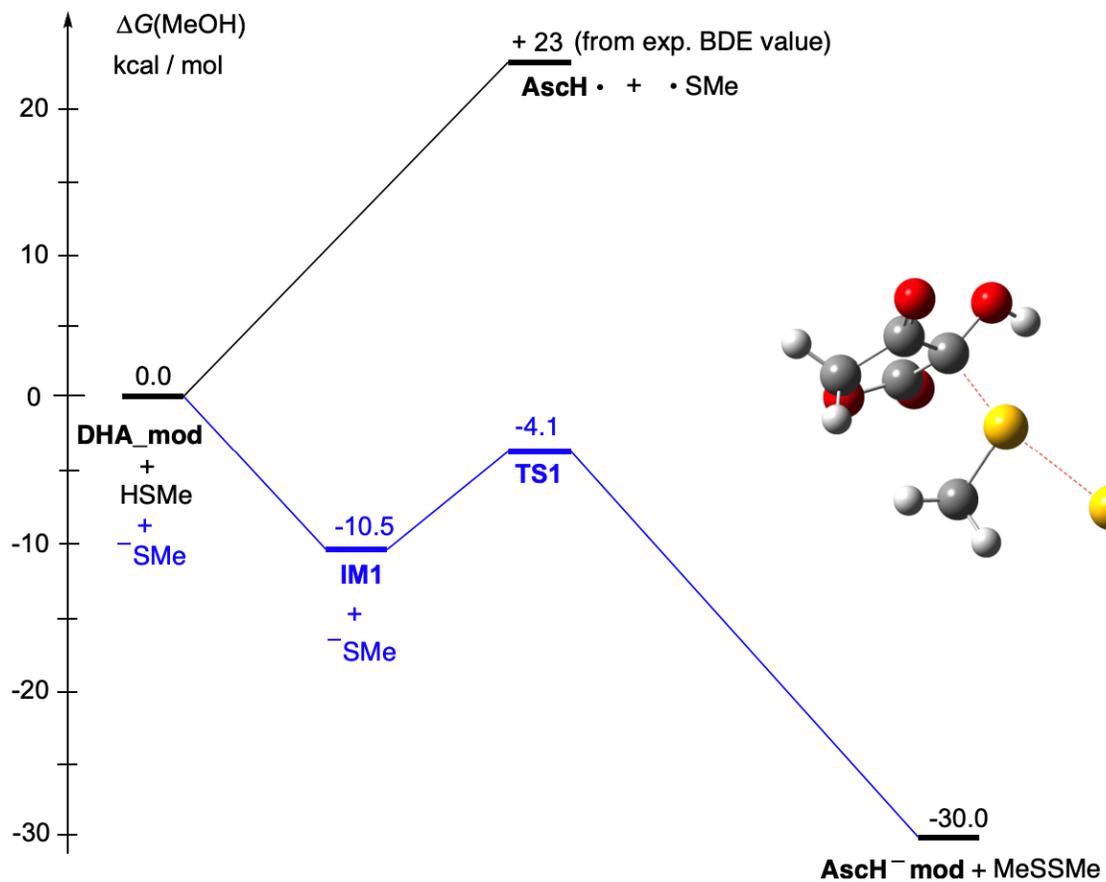
low H/D KIE (2.3)

→ relatively low vibrational frequency of S-H bond

large KIE (11.5)

→ significant contribution of proton tunneling

DFT calculation



Summary

photoredox synthesis of amines :

- visible light
- HAT (thiol, silane)
- photocatalyst (Ir, Ru)
- stereocontrol