

Anti-Markovnikov Hydroamination of Alkenes

2020/11/11

Literature Seminar

Hiroyasu Nakao

Contents

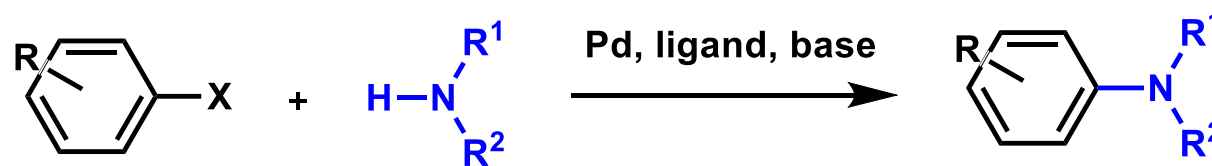
- 1. Introduction**
- 2. Hydroamination with secondary amines**
- 3. Hydroamination with primary amines**
- 4. Hydroamination with ammonia**
- 5. Summary**

Introduction

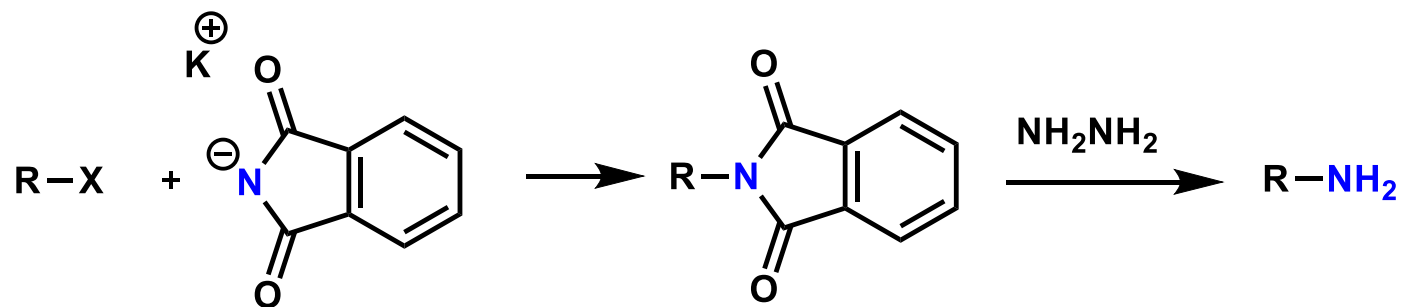
Amine synthesis



Fukuyama Amine Synthesis



Hartwig Cross Coupling

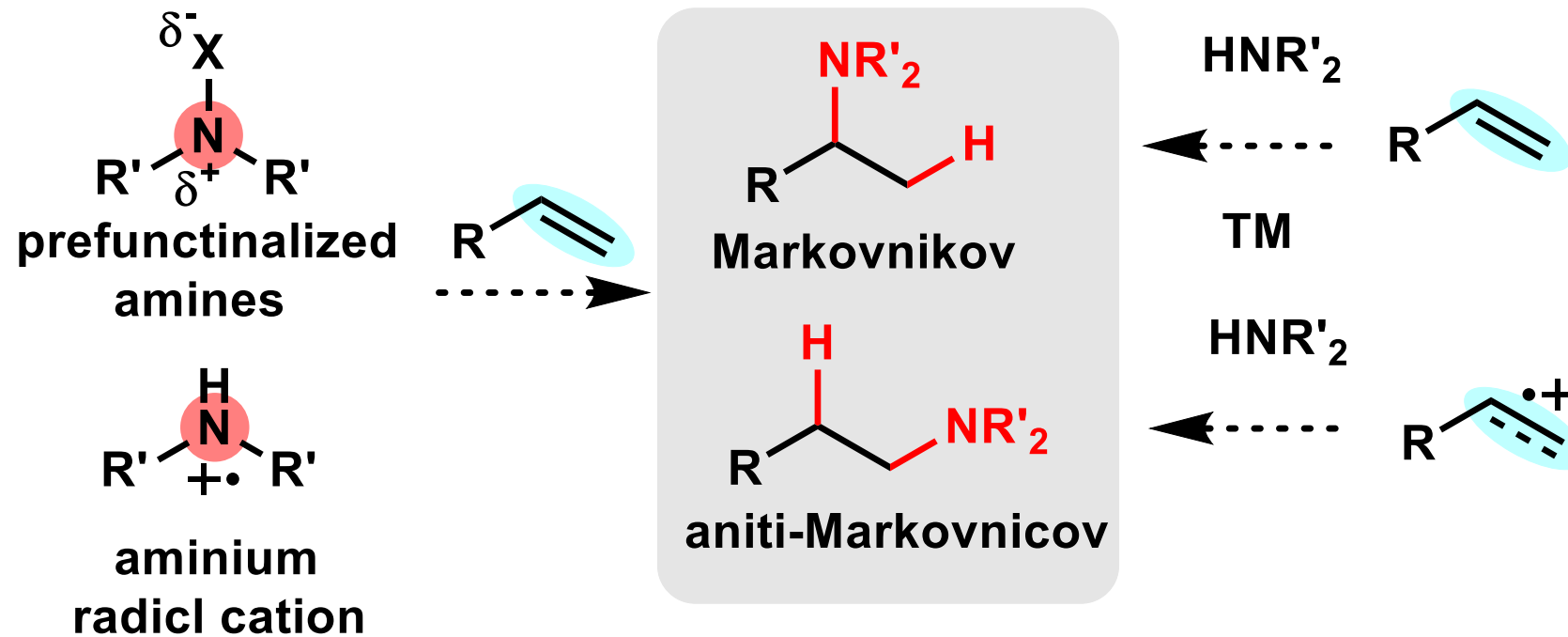


Gabriel Amine Synthesis

C-N bond formation are widely studied.

Introduction

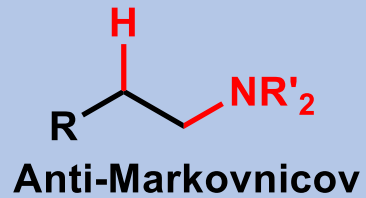
Hydroamination



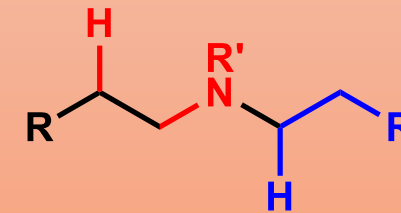
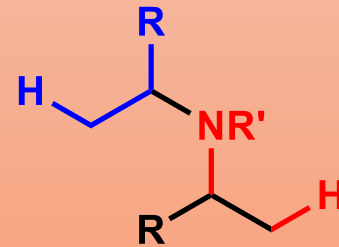
Introduction

Challenges with hydroamination

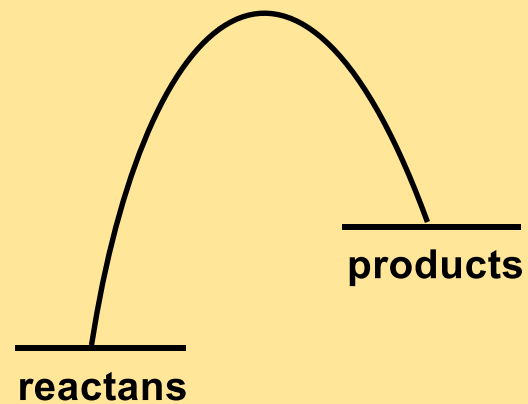
Regioselectivity



Overalkylation

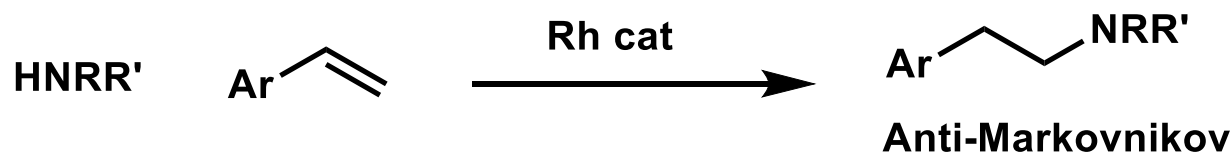
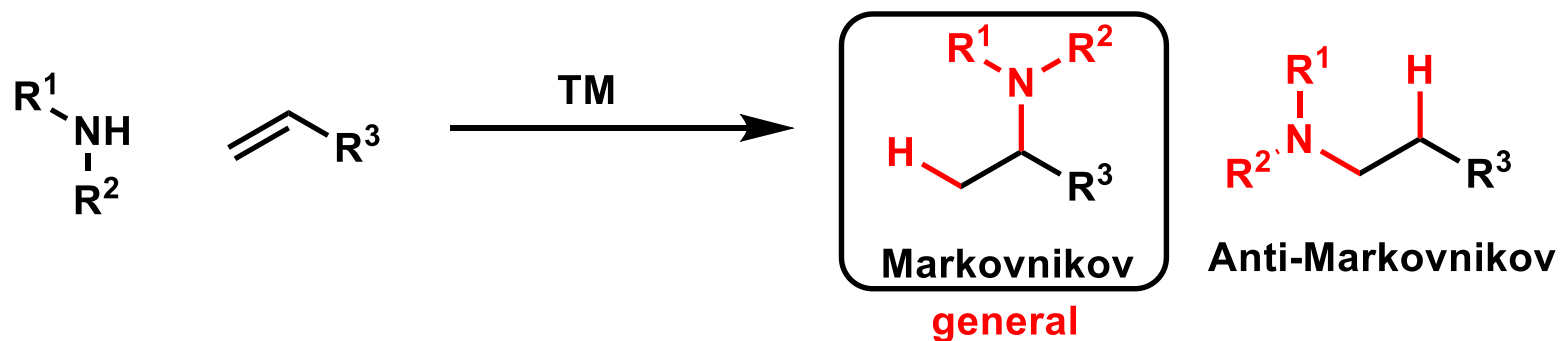


Thermodynamics



Introduction

Regioselectivity



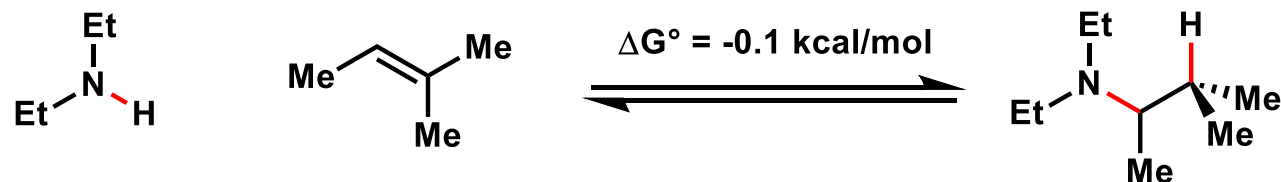
M. Utsunomiya, J. F. Hartwig, et al, *J. Am. Chem. Soc.* **2003**, 125, 19, 5608–5609.

At this time, **Anti-Markovnikov hydroamination of olefins was named as one of 10 challenges** for homogeneous catalysts.

Introduction

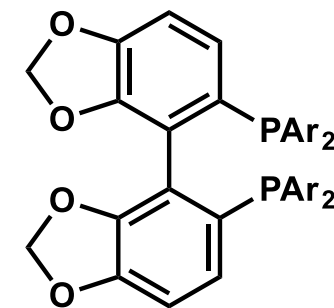
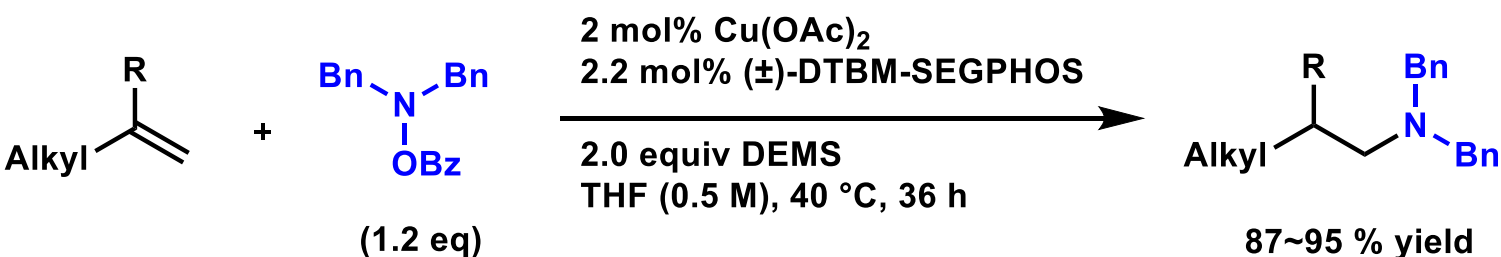
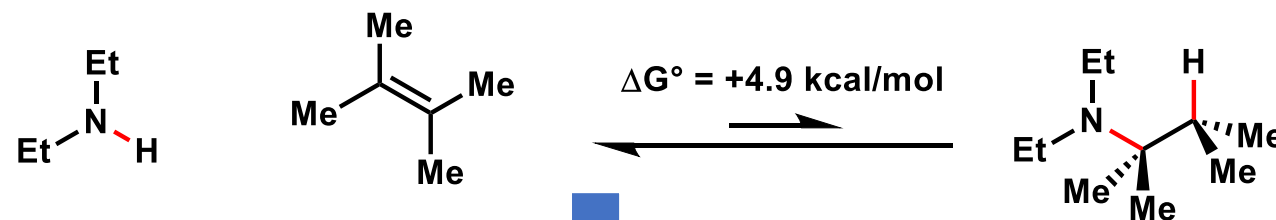
thermodynamics for intermolecular hydroamination

Trisubstituted alkenes



✘ thermodynamic instability

Tetrasubstituted alkenes



DEMS: diethoxymethylsilane

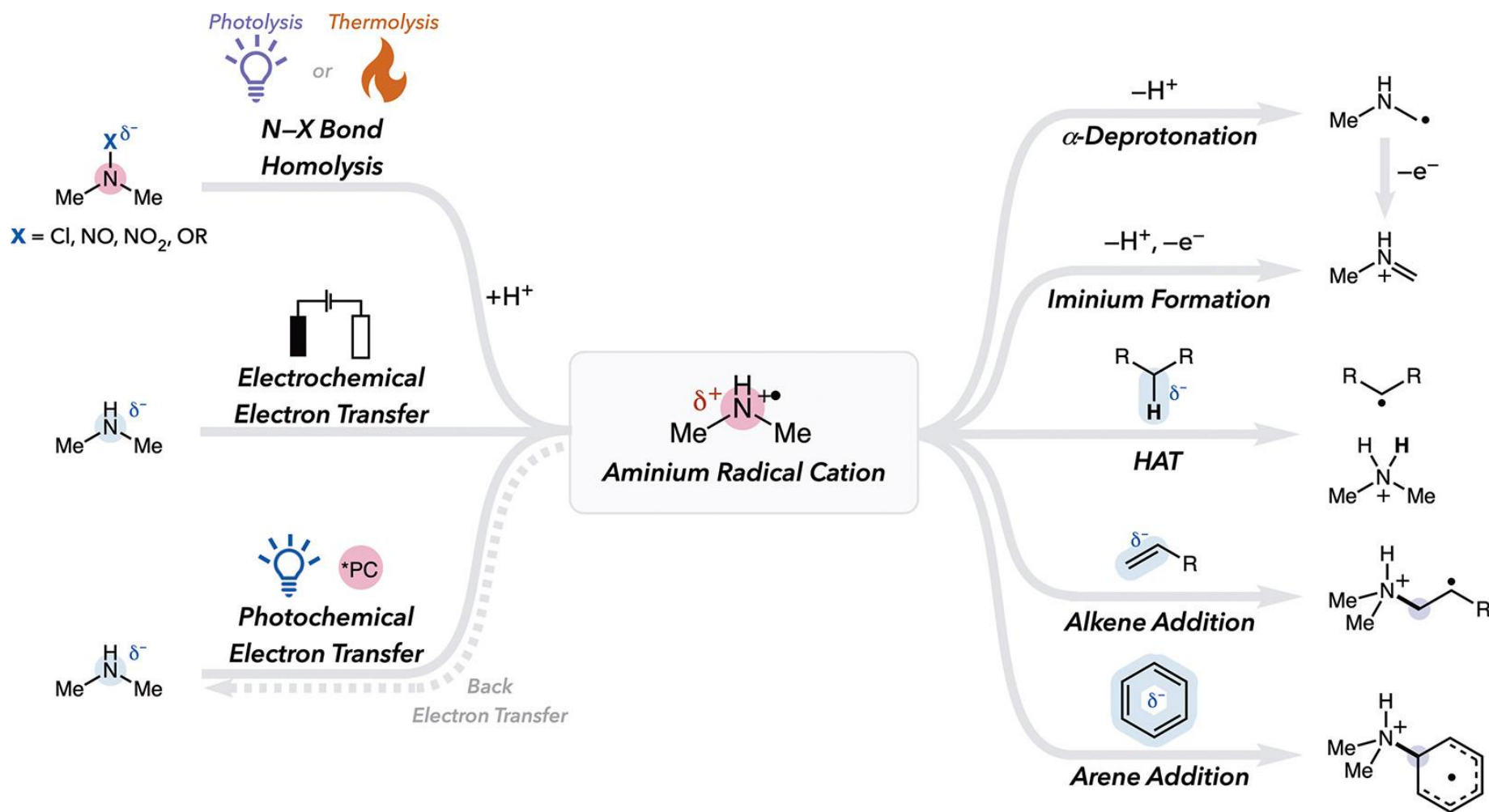
Ar = 3,5-*t*-Bu-4-MeOC₆H₂
(±)-DTBM-SEGPHOS

Shaolin. Z, et al. *J. Am. Chem. Soc.* **2013**, 135, 42, 15746–15749.

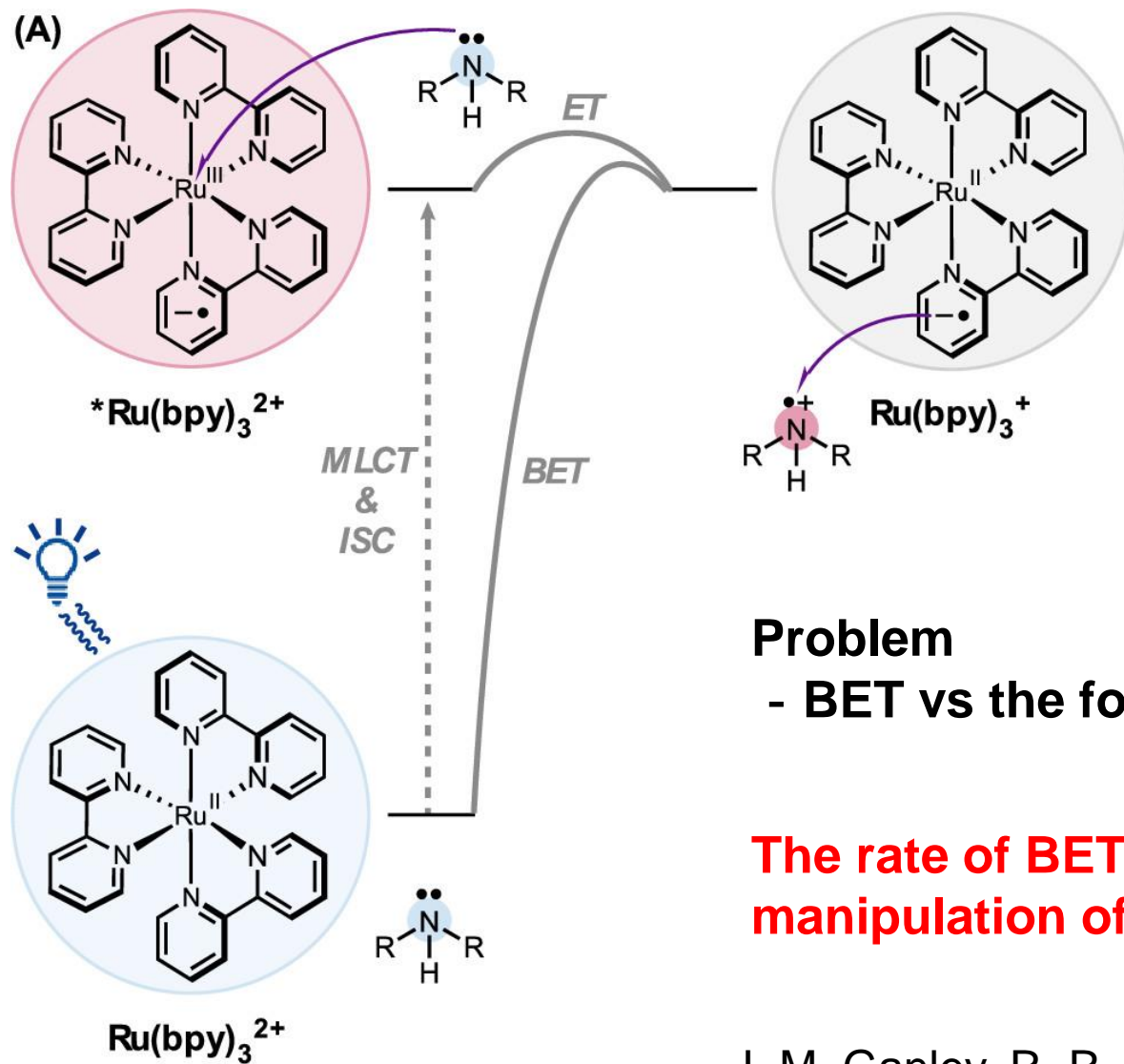
✘ the formation of stoichiometric by-products

✘ preclude the direct use of inexpensive and abundant secondary amine partners

Aminium Radical Cation (ARC)



Back Electron Transfer (BET)



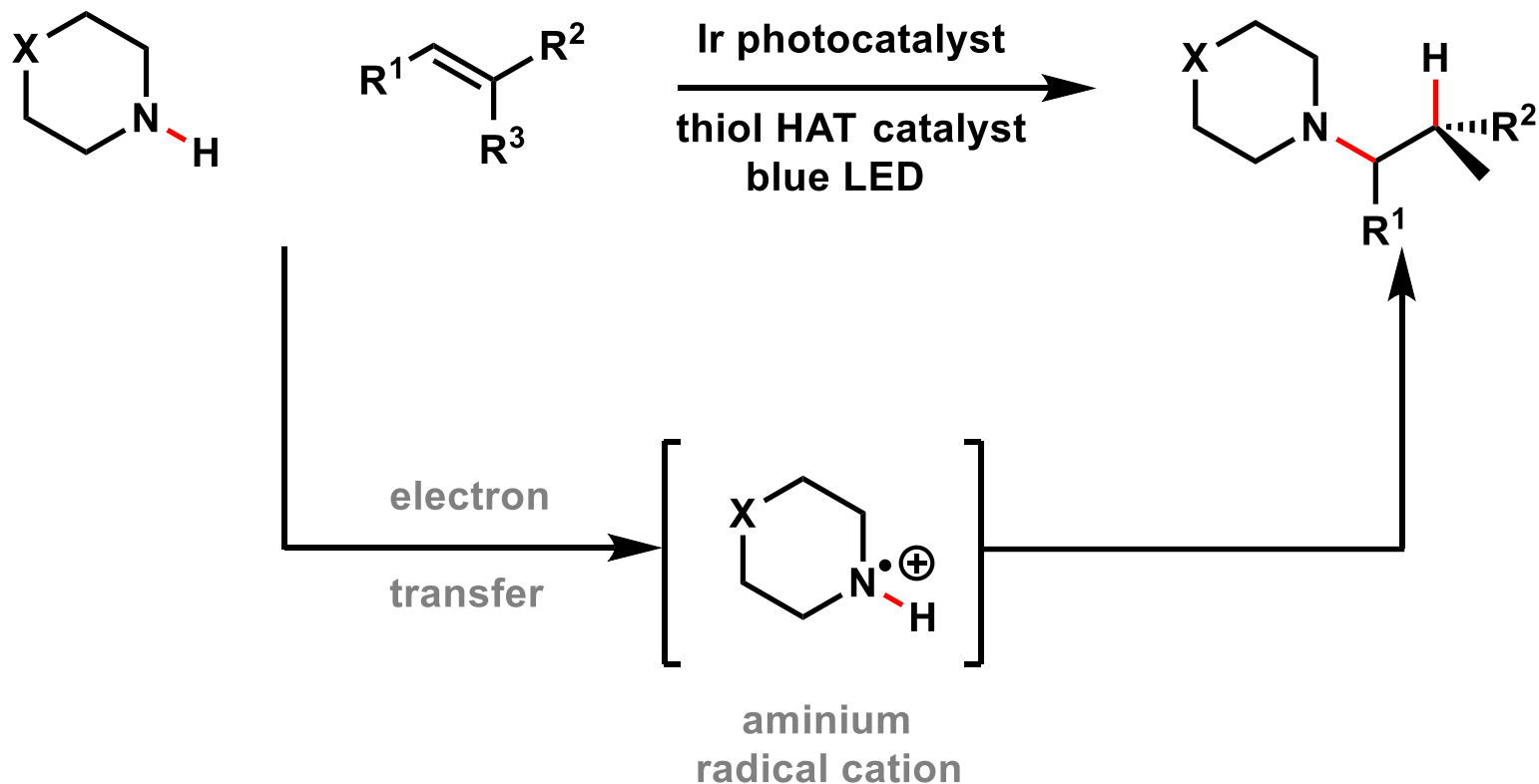
Problem

- BET vs the forward reactions of the aminium radical cation.

The rate of BET can be modulated through careful manipulation of the ligand architecture of the catalyst.

Secondary Alkyl Amines

This work: photo-driven intermolecular hydroamination with ARCs

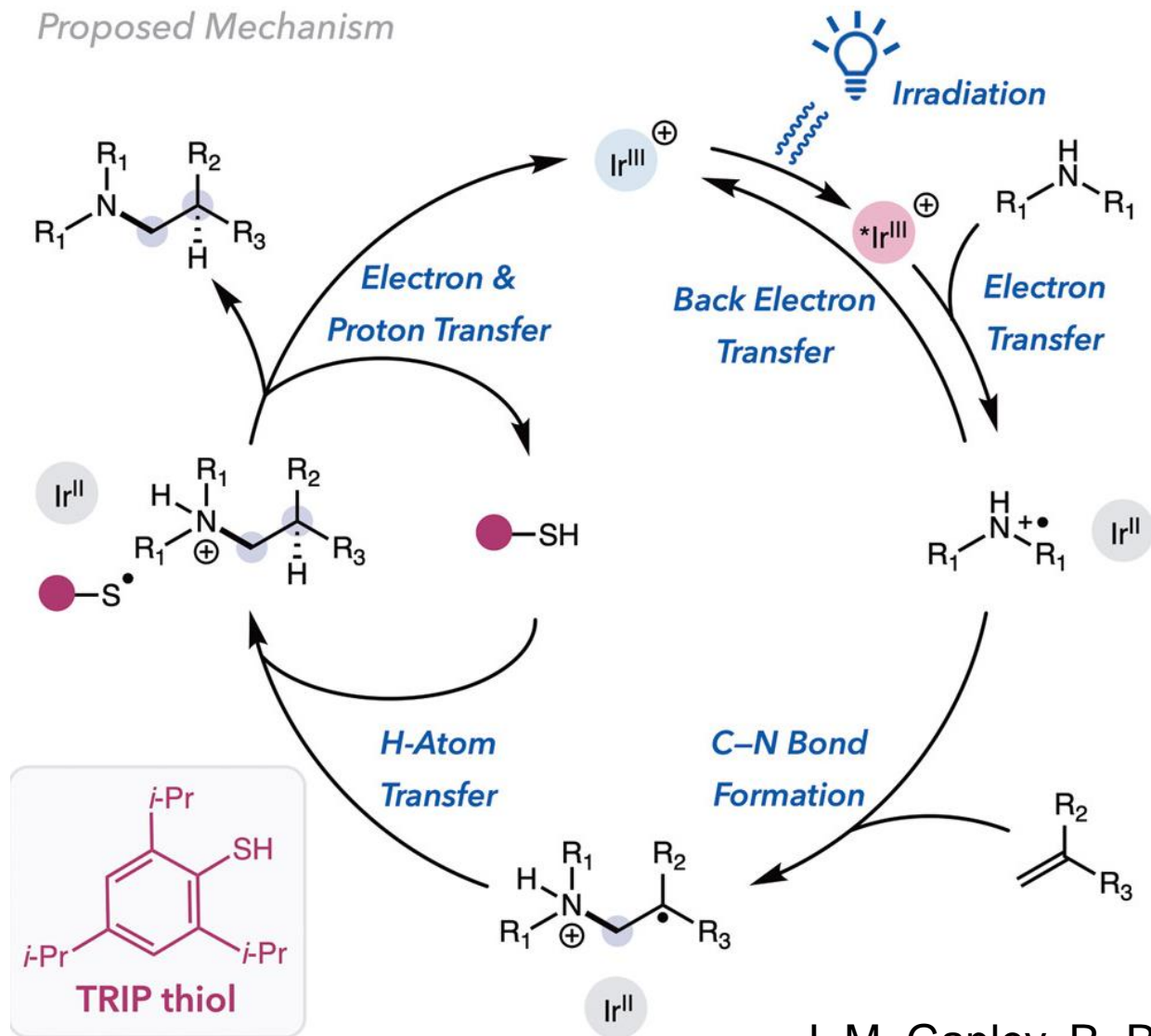


- ✓ Atom economy
- ✓ Mild condition

- ✓ Regioselectivity

Proposed Mechanism

Proposed Mechanism



this thiyl radical
($E_{1/2} = +0.07$ V vs Fc⁺/Fc in MeCN)

piperidine
($E_{p/2} = +0.56$ V vs Fc⁺/Fc in MeCN)

[Ir(dF(Me)ppy)₂(dtbbpy)]PF₆
($E_{1/2}(\text{Ir(III)*}/\text{Ir(II)}) = +0.59$ V vs Fc⁺/Fc in MeCN)

Optimization

entry	photocatalyst	amine	solvent	yield (%)
1	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (A)	piperidine	dioxane	34
2	[Ir(dF(CF ₃)ppy) ₂ (dtbbpy)]PF ₆ (B)	piperidine	dioxane	86
3	[Ir(dF(CF ₃)ppy) ₂ (dtbbpy)]PF ₆ (B)	diethylamine	dioxane	4
4	[Ir(dF(Me)ppy) ₂ (dtbbpy)]PF ₆ (E)	diethylamine	dioxane	17
5	[Ir(dF(Me)ppy) ₂ (dtbbpy)]PF ₆ (E)	diethylamine	THF	6
6	[Ir(dF(Me)ppy) ₂ (dtbbpy)]PF ₆ (E)	diethylamine	MeCN	4
7	[Ir(dF(Me)ppy) ₂ (dtbbpy)]PF ₆ (E)	diethylamine	CH ₂ Cl ₂	0
8	[Ir(dF(Me)ppy) ₂ (dtbbpy)]PF ₆ (E)	diethylamine	toluene	60

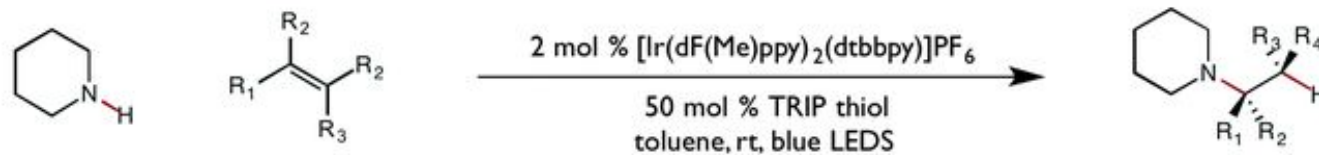
entry	change from entry 10	yield (%)
9	no light	0
10	no photocatalyst	0
11	no thiol	0
12	24 hr reaction time	73
13	piperidine in place of HNEt ₂	88
14	piperidine, 10 mol% thiol	95

A R₁ = CF₃, R₂ = H

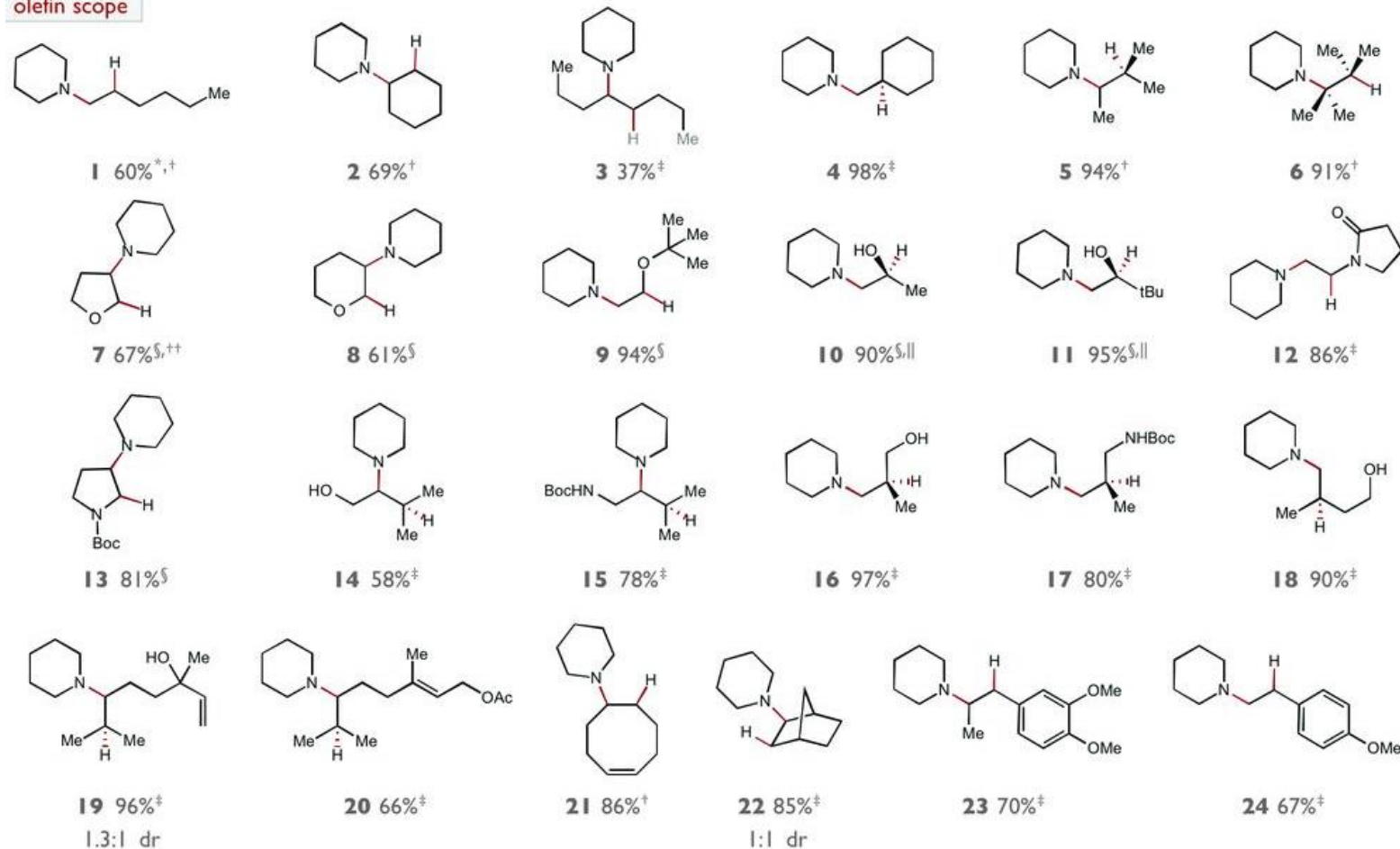
B R₁ = CF₃, R₂ = tBu

C R₁ = Me, R₂ = tBu

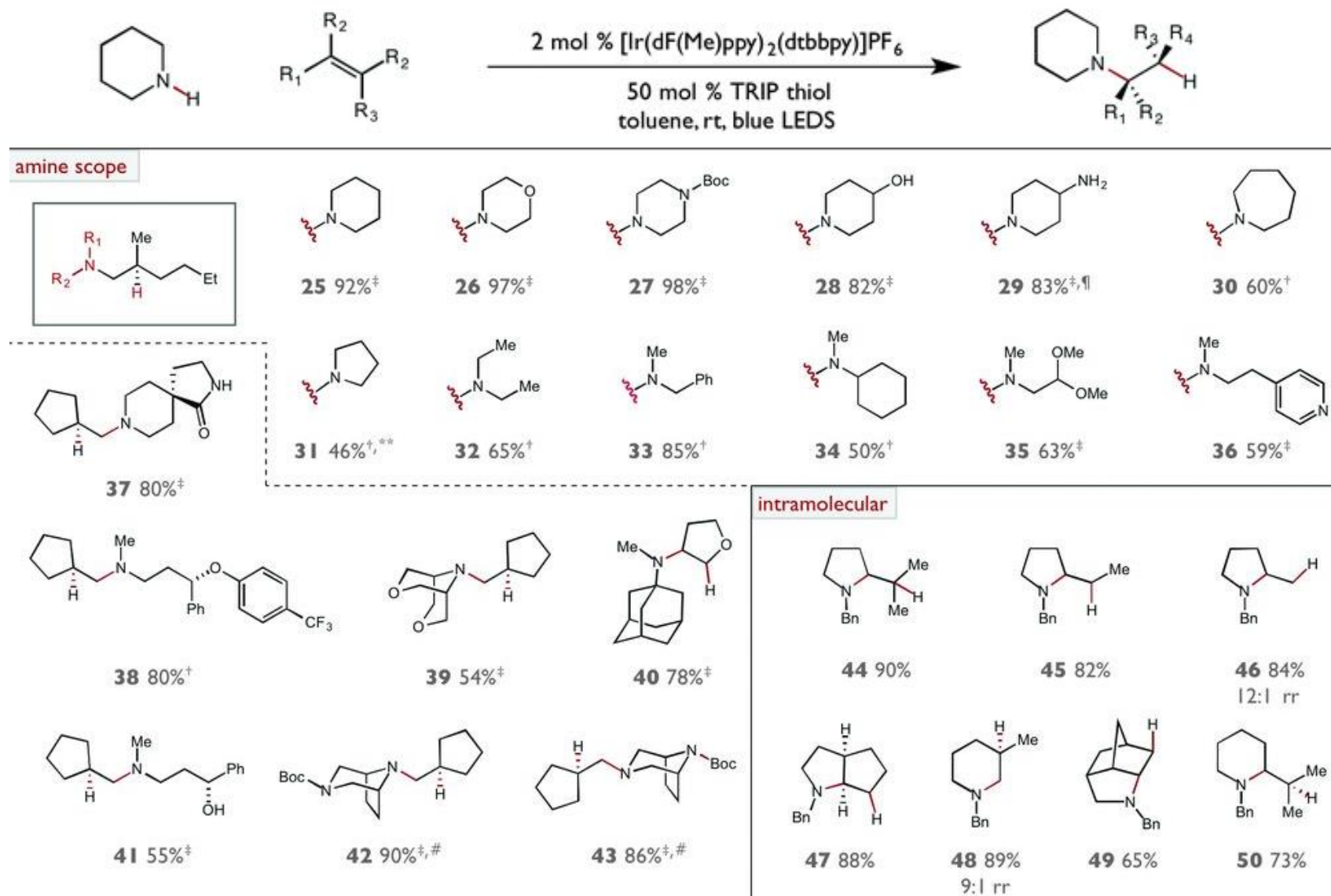
Substrate Scope



olefin scope



Substrate Scope

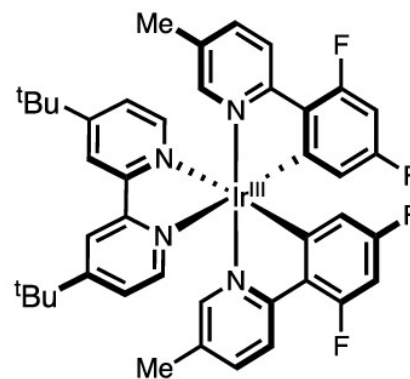


The differences of Ir catalysts

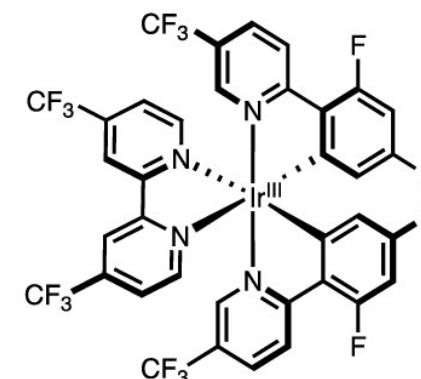
(A) Diethylamine & $[\text{Ir}(\text{dF}(\text{Me})\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$



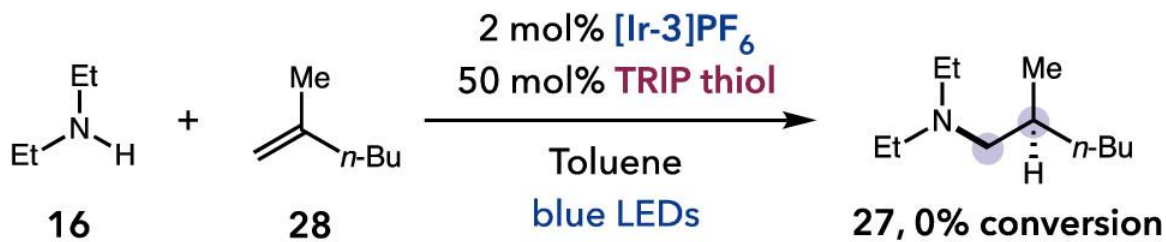
[Ir-2]PF₆



[Ir-3]PF₆



(B) Diethylamine & $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(4,4'\text{-d}(\text{CF}_3)\text{-bpy})]\text{PF}_6$



$[\text{Ir}(\text{dF}(\text{Me})\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$

$E_{1/2}(\text{Ir}^{\text{III}*/\text{II}}) = +0.59 \text{ V vs Fc}^+/\text{Fc}$

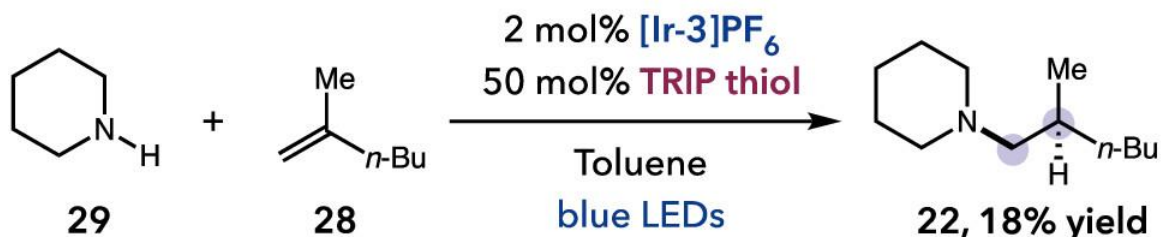
$E_{1/2}(\text{Ir}^{\text{III}/\text{II}}) = -1.81 \text{ V vs Fc}^+/\text{Fc}$

$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(4,4'\text{-d}(\text{CF}_3)\text{-bpy})]\text{PF}_6$

$E_{1/2}(\text{Ir}^{\text{III}*/\text{II}}) = +1.27 \text{ V vs Fc}^+/\text{Fc}$

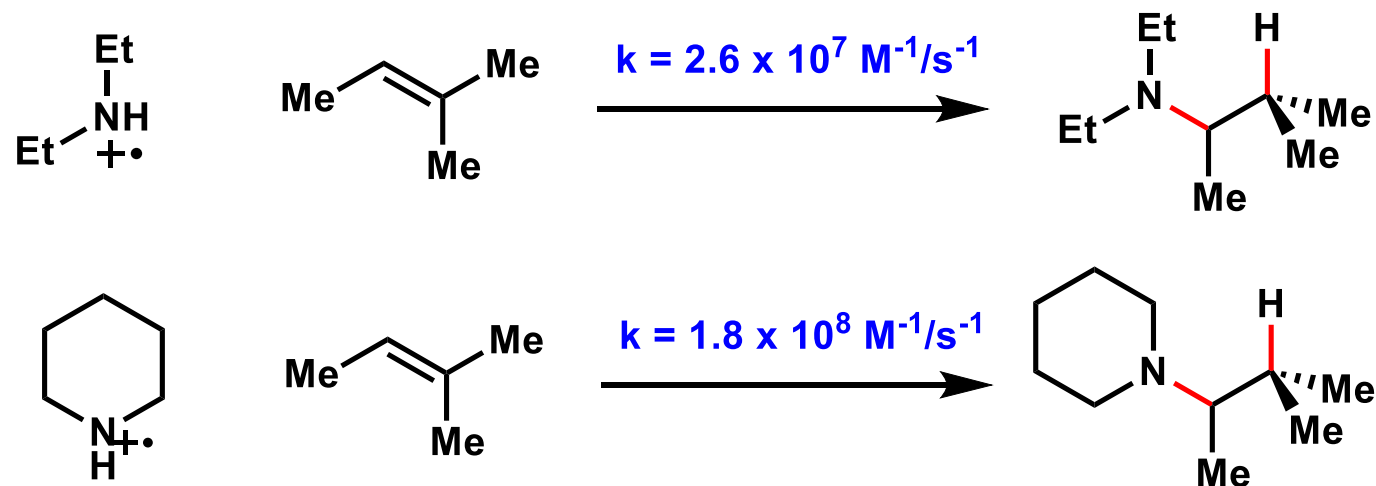
$E_{1/2}(\text{Ir}^{\text{III}/\text{II}}) = -1.18 \text{ V vs Fc}^+/\text{Fc}$

(C) Piperidine & $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(4,4'\text{-d}(\text{CF}_3)\text{-bpy})]\text{PF}_6$



Why did the reaction stop under [Ir-3]cat condition?

BET vs C-N bond formation



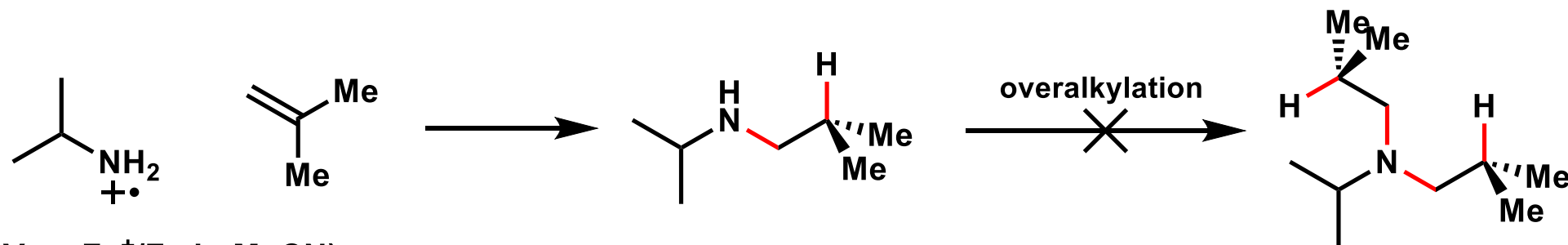
Knowles hypothesized that the divergent outcomes for cyclic and acyclic amines may arise from differences in the kinetic competition between **BET and C-N bond formation for the respective photocatalysts and ARCs.**

[Ir-2]catalyst
BET **vs** C-N bond formation

[Ir-3]catalyst
BET **>** C-N bond formation

Primary Alkyl Amine

Next, Knowles proposed...



($E_{p/2} = +1.16 \text{ V vs Fc}^+/\text{Fc}$ in MeCN)

Kinetic framework may enable the development of a method for hydroamination with primary amines that avoids overalkylation

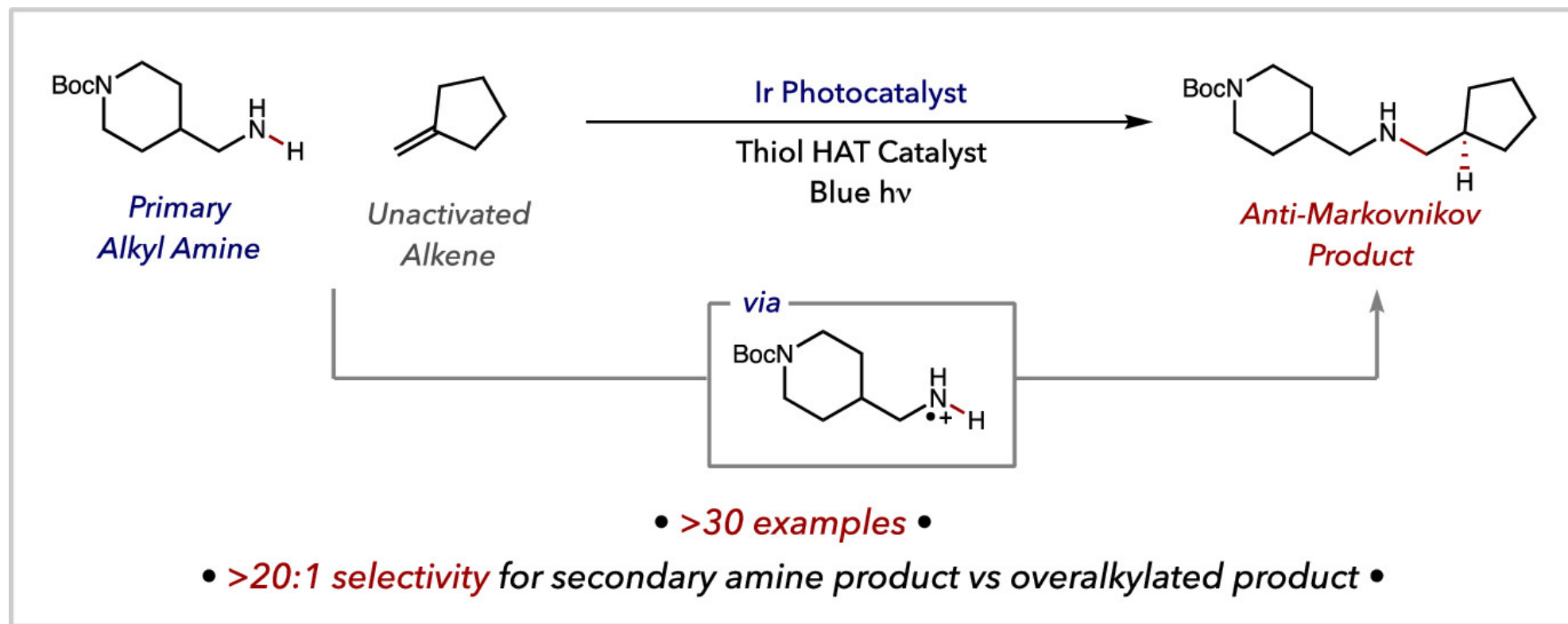
But it was unclear whether the primary ARC would undergo productive C–N bond formation.



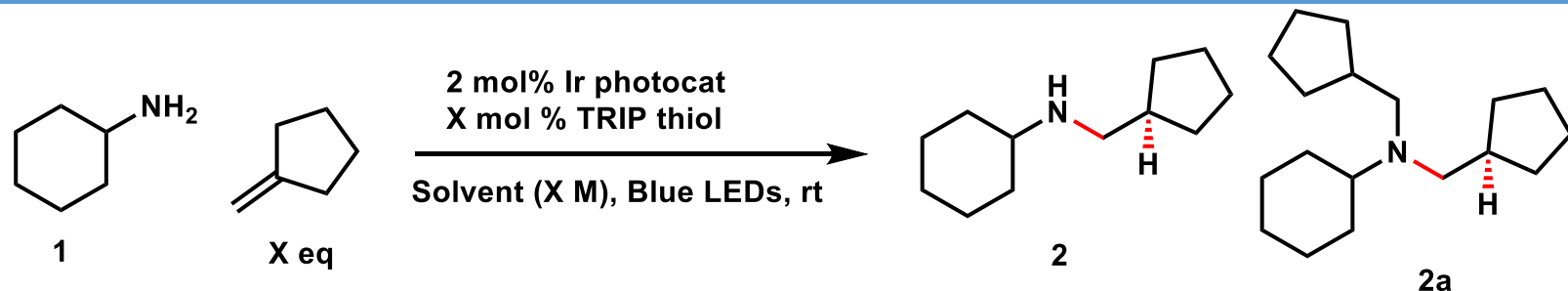
Challenging with primary amines

Primary Alkyl Amine

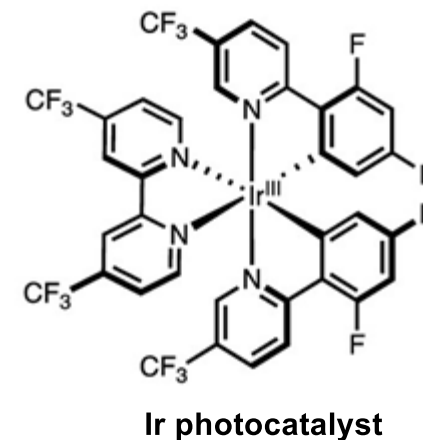
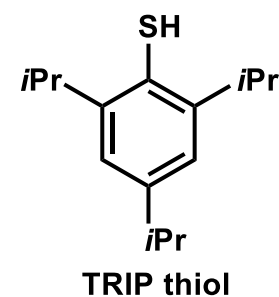
Anti-Markovnikov Hydroamination of unactivated Alkenes with Primary Alkyl Amines



Optimization



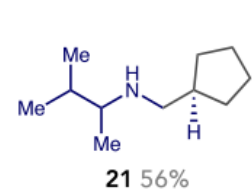
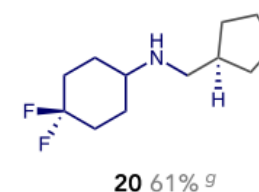
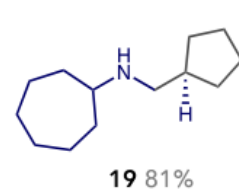
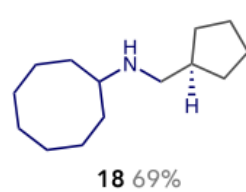
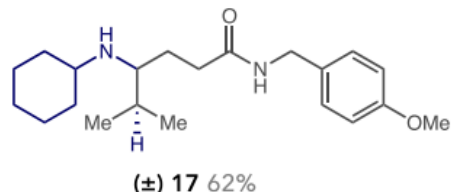
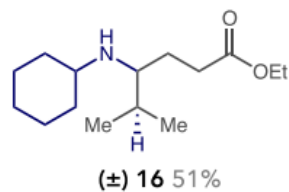
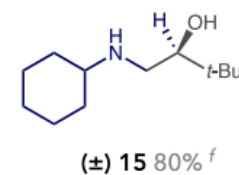
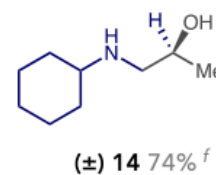
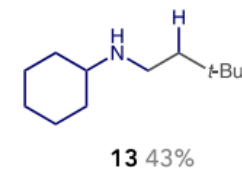
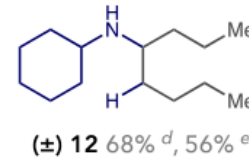
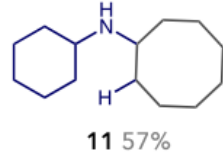
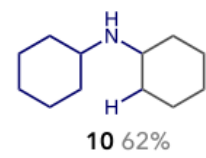
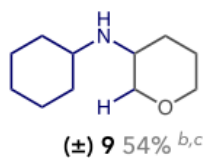
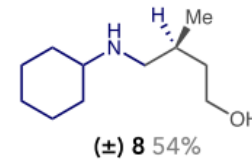
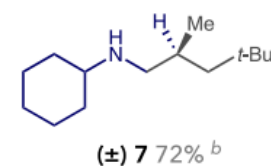
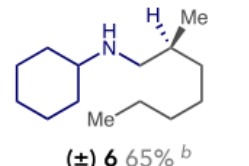
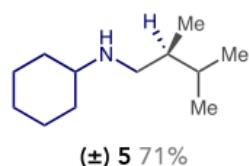
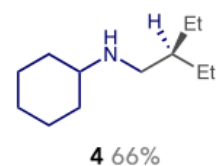
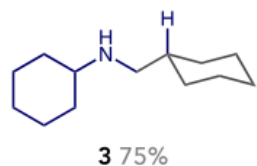
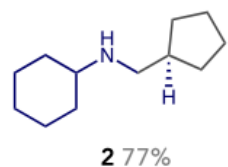
entry	solvent	TRIP thiol (mol%)	concn (M)	equiv alkene	yield (%)	
					2	2a
1	PhMe	30	0.05	6	8	0
2	EtOAc	30	0.05	6	34	0
3	dioxane	30	0.05	6	84	2
4	dioxane	30	0.2	3	69	2
5 ^b	dioxane	30	0.05	6	8	0
6 ^c	dioxane	30	0.05	6	76	2
7	dioxane	0	0.05	6	0	0
8 ^d	dioxane	30	0.05	6	0	0
9 ^e	dioxane	30	0.05	6	0	0



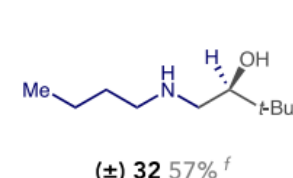
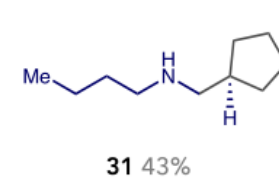
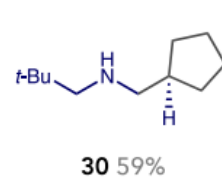
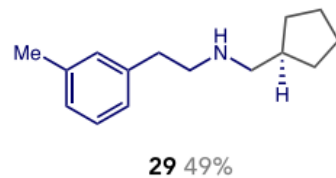
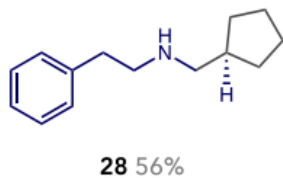
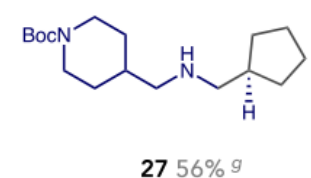
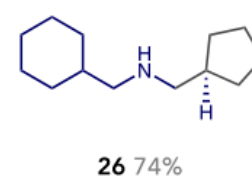
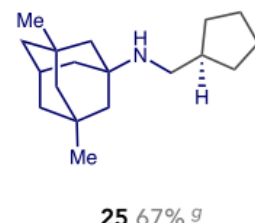
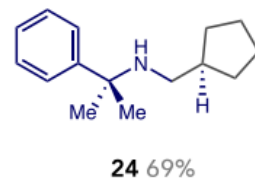
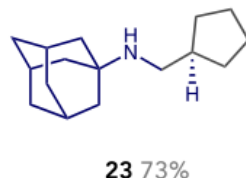
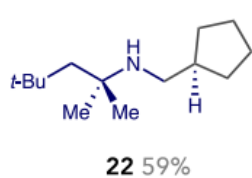
a Optimization reactions were performed on a 0.2 mmol scale and run for 24 h.
 b 1·HCl used instead of 1.
 c 1·HCl used with 1 equiv LiOH.
 d 0 mol% Ir photocatalyst B.
 e No irradiation.

Substrate scope

Alkene Scope

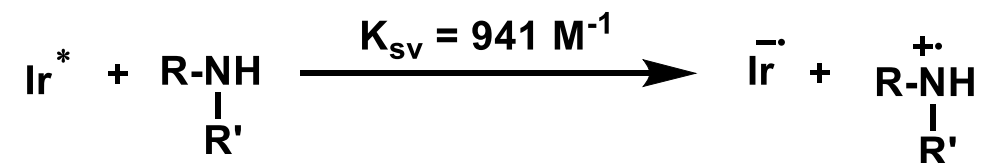
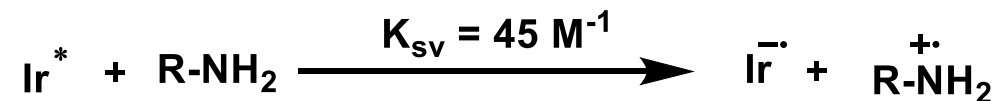


Amine Scope



BET vs C-N formation

Stern-Volmer equation



Secondary amine product also quenches the excited state of the photocatalyst even more efficiently than the primary amine starting materials

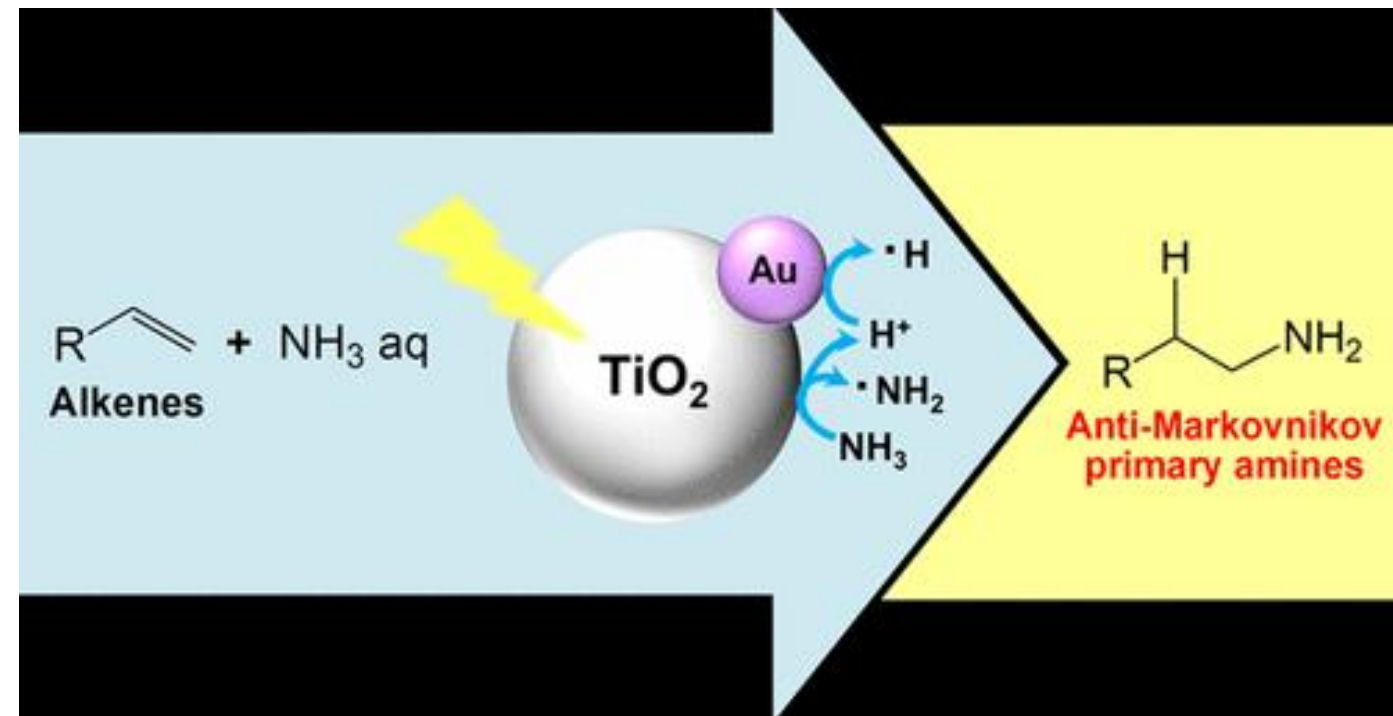


Using BET process limit the reaction channels available to an otherwise kinetically competent radical intermediate.

Hydroamination of Alkenes with Ammonia

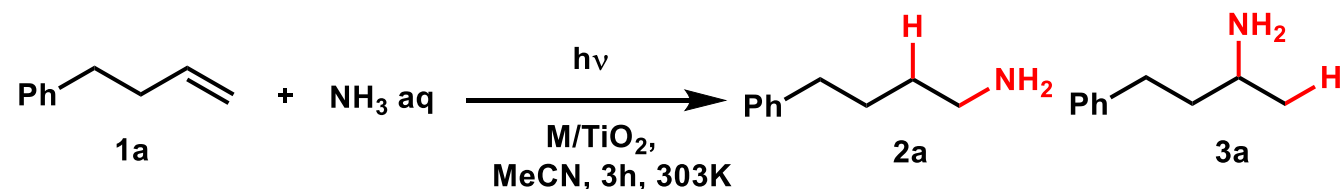
Recently achievement

Anti-Markovnikov Hydroamination of Alkenes with Aqueous Ammonia by Metal-Loaded Titanium Oxide Photocatalyst



- ✓ regioselectivity
- ✓ synthesis of primary amine
- ✓ mild condition

Optimization

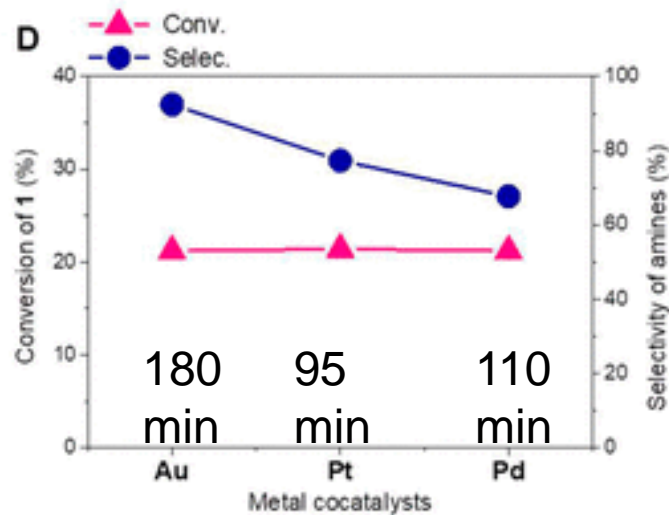
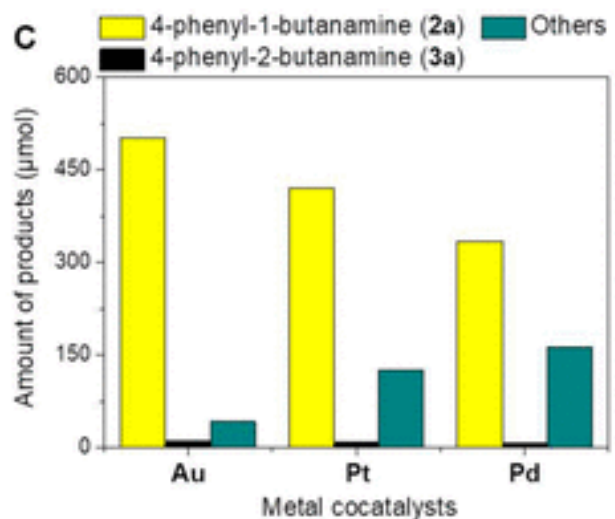
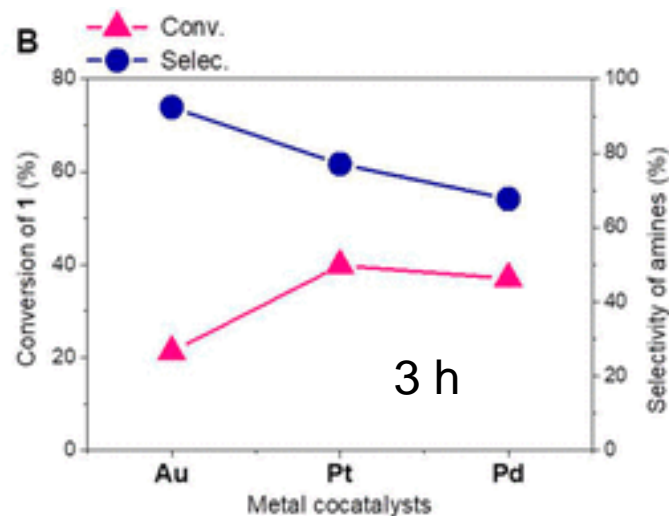
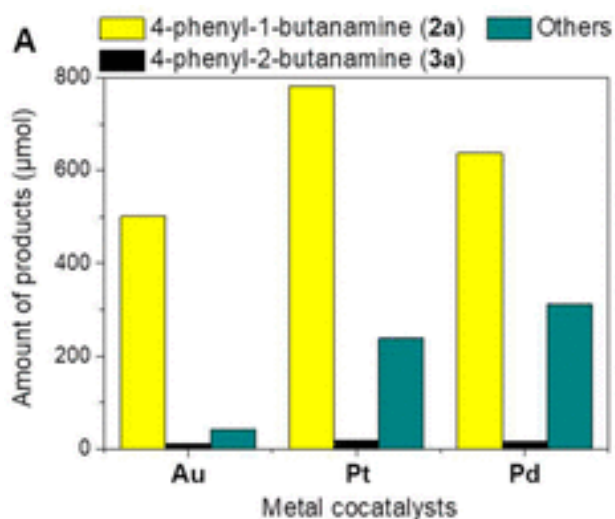


entry	catalyst	obtained products/ μmol			conversion ^c (%)	yield of amines ^d (%)	selectivity for amines ^e (%)	regioselectivity ^f (%)
		2a	3a	others ^b				
1	TiO ₂	5.63		2.66	0.318	0.216	67.9	
2			1.79	1.76	0.136	0.068	50.4	
3	Au(0.1)/TiO ₂	501	10.8	42.3	21.2	19.6	92.4	97.9
4	Pt(0.1)/TiO ₂	781	18.6	238	39.8	30.7	77.1	97.7
5	Pd(0.1)/TiO ₂	638	16.4	312	37.0	25.1	67.7	97.5
6 ^g	Au(0.1)/TiO ₂	14.6	0.454	10.2	1.00	0.578	57.6	97.0

^g water was used instead of MeCN

Acetonitrile was crucial to make the liquid phase homogenous.

Loaded Metals

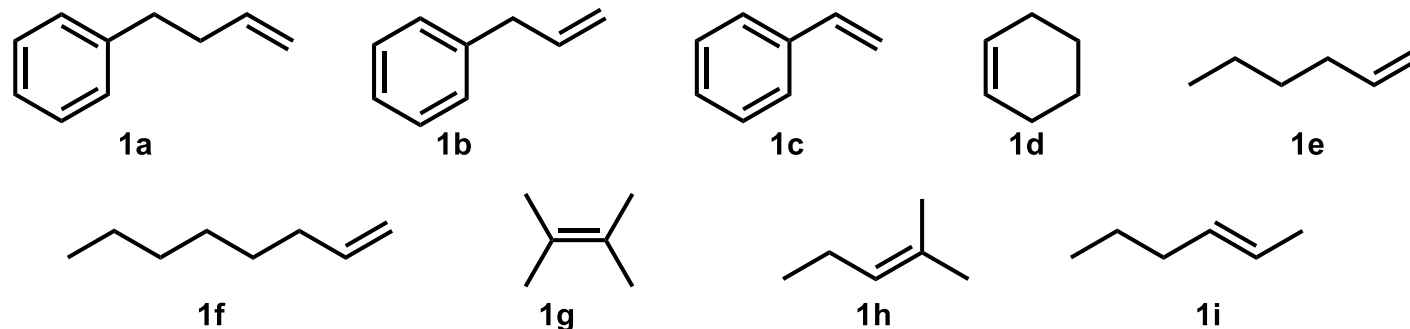
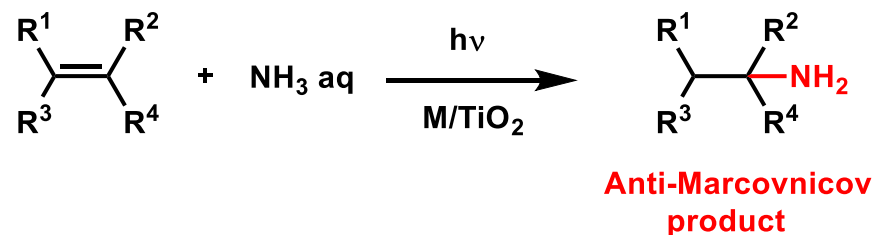


(A), alkene conversion, and selectivity to amine (B) with the M(0.1)/TiO₂ photocatalysts (M = Pt, Au, and Pd) in the same reaction time, 3 h. the reaction time was controlled as follows: 95 min for Pt(0.1)/TiO₂, 180 min for Au(0.1)/TiO₂, and 110 min for Pd(0.1)/TiO₂, respectively (C, D).

Au-loaded photocatalyst
highest regioselectivity

Pt- and Pd-loaded photocatalyst
high reaction rate even for byproduct formation

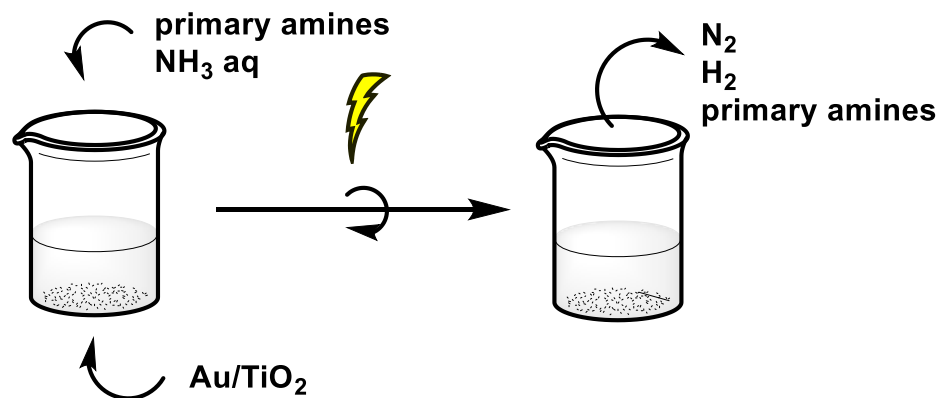
Substrate scope



entry	alkenes	time (h)	conversion	yield of amines (%)	selectivity fo amines (%)	regioselectivity (%)
1	1a	18	99.9	92.7 (88.9)	92.7	97.9
2	1b	18	99.9	91.5	91.5	99.6
3	1c	12	>99.9	74.5	74.5	>99.9
4	1d	15	98.1	44.8	44.8	
5	1e	9	98.3	41.7	42.5	97.0
6	1f	9	99.9	68.3	69.6	97.3
7	1g	9	>99.9	92.0	92.0	
8	1h	9	>99.9	95.8	95.8	98.1
9	1i	18	98.1	43.5	44.4	72.3

Overalkylation

The experiment about overreaction



The photocatalyst can predominantly activate not amines but ammonia, and the amide radical does not react with amines.

entry	amines	initial amount of amines /mmol	obtained products/ μmol						conversion ^c (%)
			N ₂	H ₂	2a	3a	imines	other amines ^b	
1	4-phenyl-1-butanamine (2a)	2.48	1.34	4.17	2475	–	–	–	0.20
2	4-phenyl-2-butanamine (3a)	2.42	1.31	4.06	8.32	2408	–	–	0.57

^a Catalyst: Au(0.1)/TiO₂ 150 mg, aqueous ammonia (28%, 1.6 mL, 23.7 mmol), solvent: acetonitrile (4.0 mL, 73.1 mmol), wavelength of the irradiated light: $\lambda \geq 300$ nm, light intensity: 40 mW cm⁻² measured at 360 \pm 40 nm in wavelength, reaction time: 3 h, reaction temperature: 303 K, TiO₂ used; anatase, 300 m²g⁻¹ (ST-01, Ishihara Sangyo Kaisha), ^b other amines: secondary and tertiary amines, ^c conversion of amine (**2a** and **3a**), which was calculated from the initial and final amounts of **2a** and **3a**, respectively.

Thermodynamic stability

entry	anti-Markovnikov products	$\Delta_f G^\circ / \text{kJmol}^{-1}$	Markovnikov products	$\Delta_f G^\circ / \text{kJmol}^{-1}$
1	4-phenyl-1-butanamine (2a)	212.2	4-phenyl-2-butanamine (3a)	209.7
2	3-phenyl-1-propanamine (2b)	203.8	1-phenyl-2-propanamine (3b)	201.3
3	2-phenylethanamine (2c)	195.3	1-phenylethanamine (3c)	192.9
4	Cyclohexanamine (2d)	90.5	–	–
5	1-hexanamine (2e)	66.1	2-hexanamine (3e)	63.7
6	1-octanamine (2f)	82.9	2-octanamine (3f)	80.5
7	2-hexanamine (2i)	63.7	3-hexanamine (3i)	63.7

^a Data were calculated by the Joback method at the web site: <https://www.chemeo.com/>.

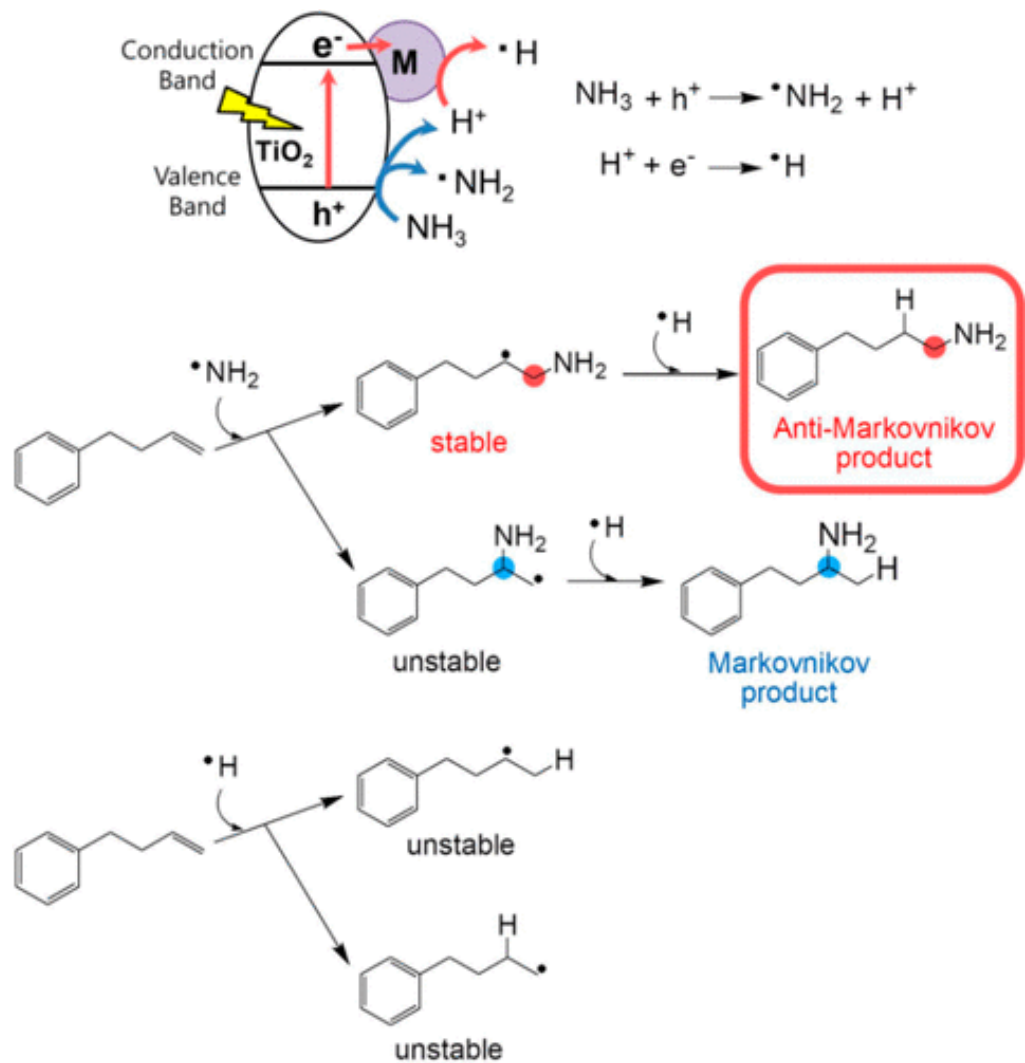
thermodynamic stability

Anti-Markovnikov products < Markovnikov products

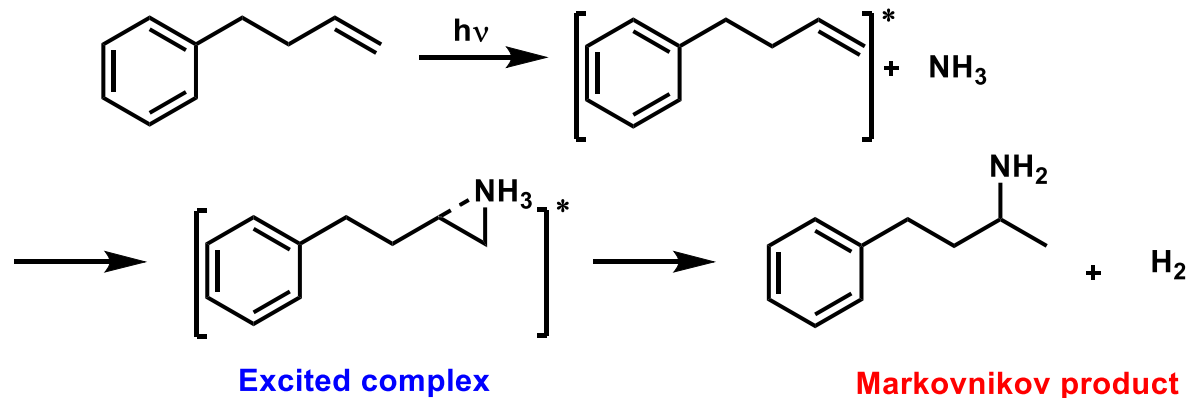


Why were anti-Markovnikov products obtained despite thermodynamic instability of the anti-Markovnikov products?

Regioselectivity



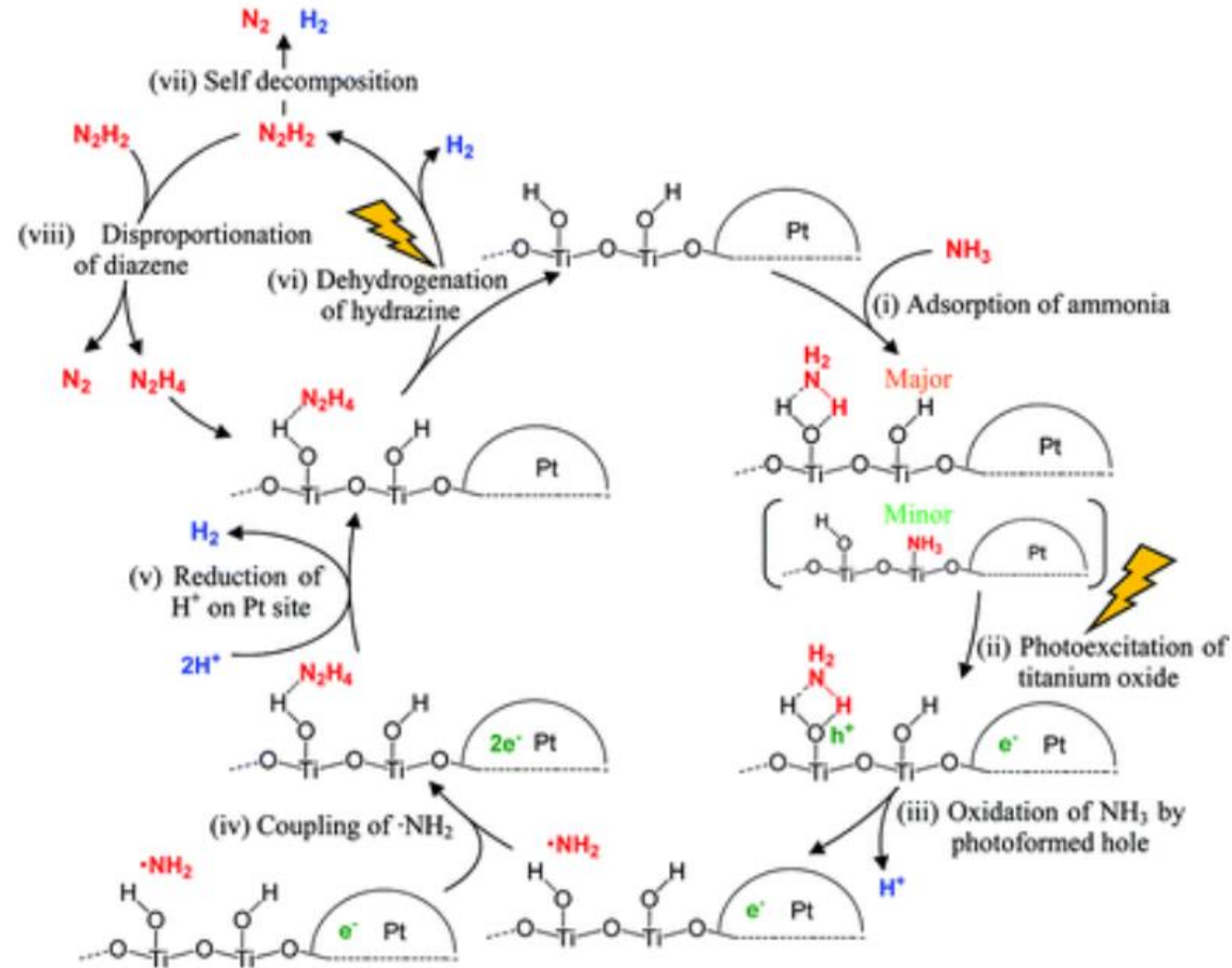
Markovnikov product



Possibly an alkene molecule is directly photoexcited to form an excited complex with ammonia.

Amide radical generation process

(a) Wet condition

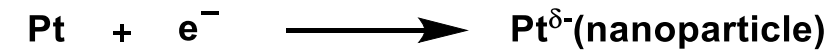
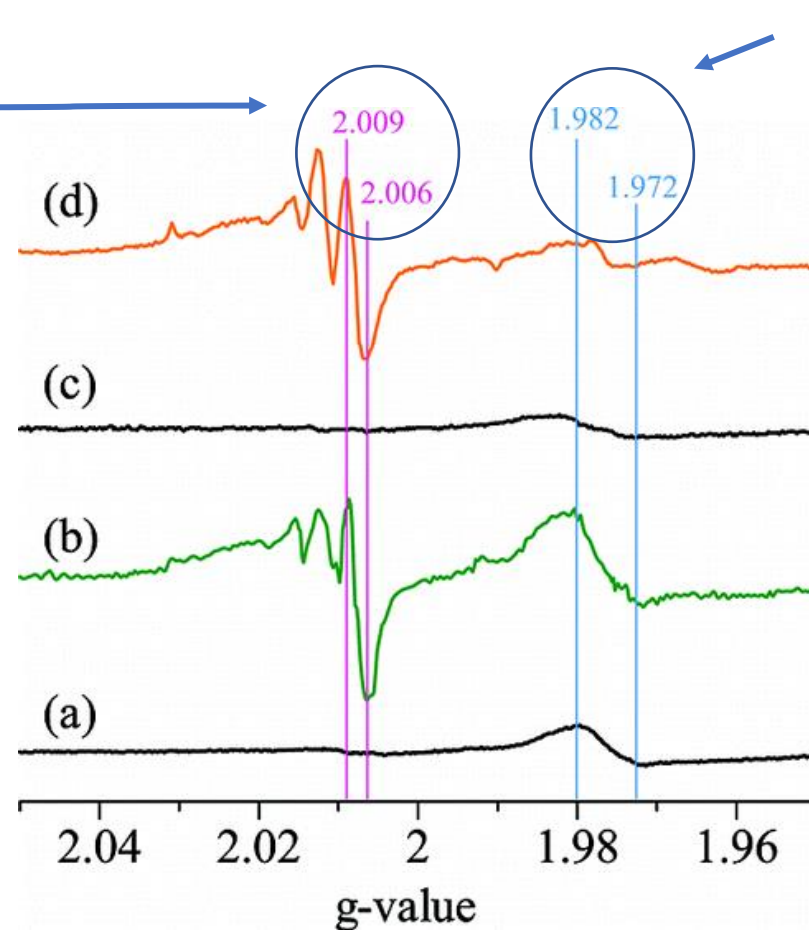


Amide radical generation process

Amide radical generation process



ESR spectra of the $\text{TiO}_2(\text{A/R})$ sample adsorbing ammonia before photoirradiation (a) under photoirradiation (b) the $\text{Pt}(0.1)/\text{TiO}_2(\text{A/R})$ sample adsorbing ammonia before photoirradiation (c) under photoirradiation (d).



✓ Amide radical is produced from NH_3 .

✓ Pt plays a role of restricting reduction of Ti^{4+} .

Summary

- **Anti-Markovnikov hydroamination of secondary and primary amines is accomplished by using different Ir photocatalyst.**
- **Using BET process limit the reaction channels available to an otherwise kinetically competent radical intermediate.**
- **Hydroamination with ammonia is accomplished by using metal-loaded titanium oxide.**