The Minisci Reaction

Radical Additions to Electron-Deficient Heterocycles

Jake Ganley
Department of Chemistry
Princeton University

Knowles Group

Literature Group Meeting
August 27, 2021

Reviews Covering the Minisci Reaction

Minisci, F.; Fontana, F.; Vismara, E. J. Substitutions by Nucleophilic Free Radicals: A New General Reaction of Heteroaromatic Bases. *J. Heterocyclic Chem.* **1990**, *27*, 79–96.

- Original conception and early developments

Duncton, M. A. J. Minisci reactions: Versatile CH-functionalizations for medicinal chemists. *Med. Chem. Commun.* **2011**, *2*, 1135–1161.

- Synthesis and functionalization of complex molecules

Tauber, J.; Imbri, D.; Opatz, T. Radical Addition to Iminium Ions and Cationic Heterocycles. *Molecules* **2014**, *19*, 16190–16222.

- Theoretical background & FMO analysis

Proctor, R. S. J.; Phipps, R. J. Recent Advances in Minisci-Type Reactions. *Angew. Chem. Int. Ed.* **2019**, *58*, 13666–13699.

- Modes of radical generation and control of stereochemistry

Sun, A.; McAtee, R.; McClain, E. J.; Stephenson, C. R. J. Advancements in Visible-Light-Enabled Radical C(sp)2–H Alkylation of (Hetero)arenes. *Synthesis* **2019**, *51*, 1063–1072.

- Photochemical modes of radical generation

Chemical Science

Organic LETTERS

Letter

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EDGE ARTICLE

The Acid-Free Cyclopropanol-Minisci Reaction Reveals the Catalytic Role of Silver–Pyridine Complexes

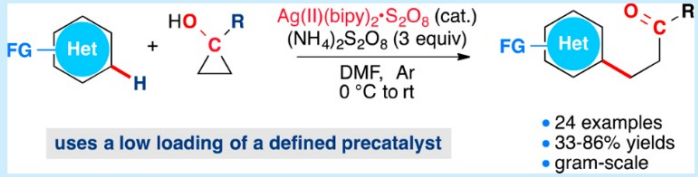
Andrei Nikolaev,[§] Claude Y. Legault,[†] Minhao Zhang,[§] and Arturo Orellana*[,§]

[§]Department of Chemistry, York University, 4700 Keele Street, Toronto, Ontario M3J 1P3, Canada

[†]Department of Chemistry, University of Sherbrooke, 2500 Boulevard de l'Universite, Sherbrooke, Québec J1K 2R1, Canada

Supporting Information

ABSTRACT: A well-defined homogeneous silver precatalyst can be utilized for the direct C–H functionalization of a wide range of aromatic nitrogen heterocycles with cyclopropanols under acid-free conditions. This reaction can be conducted on gram-scale and with low catalyst loadings (as low as 1%), which is rare for silver-catalyzed Minisci-type reactions. Moreover, reactivity trends, as well as steric and calculated electronic properties of the heterocycles, strongly suggest that silver–heterocycle complexes formed in situ behave as redox active catalysts and as Lewis acid activators of the heterocycle and that the electronic nature of the heterocyclic substrates tunes the reactivity of the resulting complexes.



Metal- and Acid-F… Using Trioxane as Soluble Oxidant

Jacob M. Ganley,[†,⊥] Melodie Christensen,[§] Yu-hong Lam,[∥] Zhengwei Peng,[∥] Angie R. Angeles,*[,‡,#] and Charles S. Yeung*[,†]

Cite This: J. Org. Chem. XXXX, XXX, XXX–XXX

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Visible-Light-Mediated Direct Decarboxylative Acylation of Electron-Deficient Heteroarenes Using α-Ketoacids …sci C–H alkylation of …ted alkyl halides using

Sabyasachi Manna and Kandikere Ramaiah Prabhu*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, Karnataka, India

…chen Wang,[a] Hongjian Song,[a] Yuxiu Liu[a]

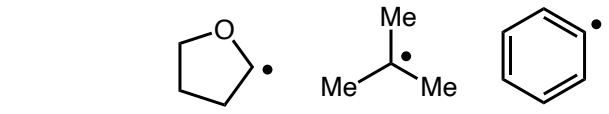
The Minisci Reaction

Radical Additions to Electron-Deficient Heterocycles

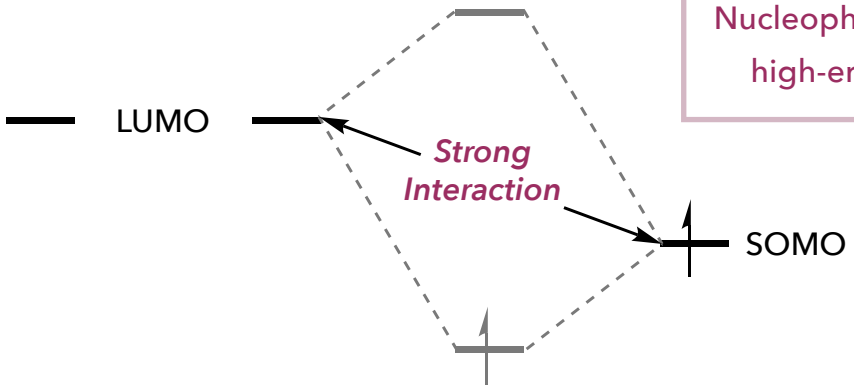
Outline

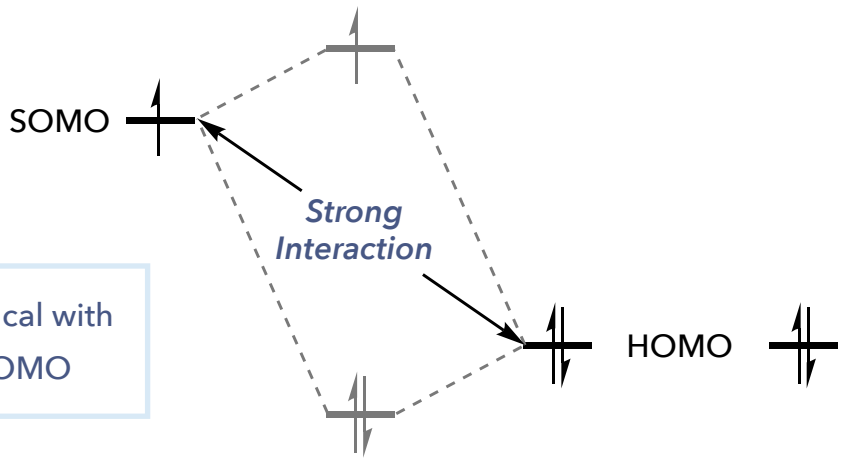
1. Historical context and reaction development
2. Mechanistic features governing selectivity
3. Recent innovations in the Minisci reaction

Radical Electrophilicity/Nucleophilicity



Nucleophilic radical with high-energy SOMO



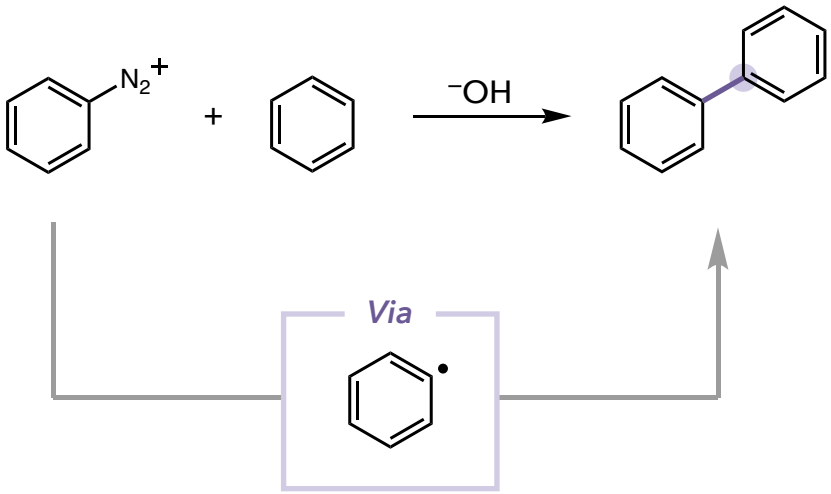


Electrophilic radical with low-energy SOMO

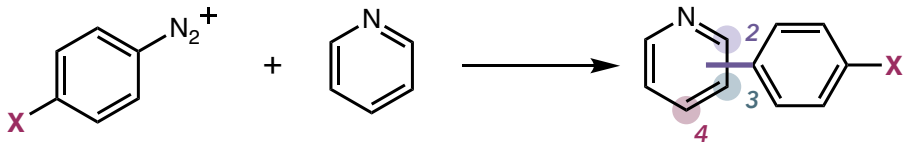
Tauber, J.; Imbri, D.; Opatz, T. *Molecules* **2014**, *19*, 16190–16222.

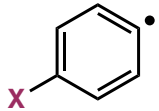
Arylation of Pyridine

Gomberg-Bachmann-Hey Reaction



Nucleo/Electrophilic Radicals





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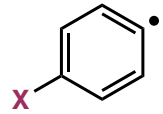
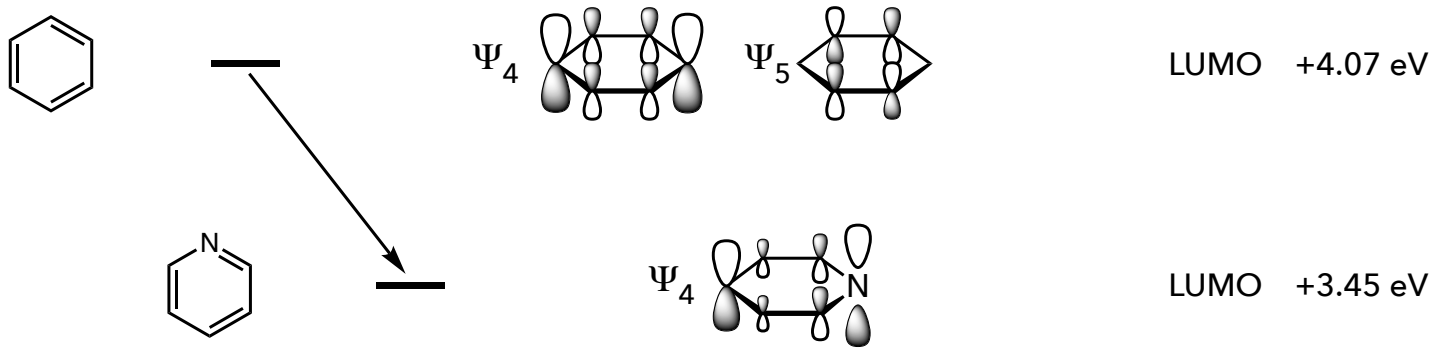
X = H	52 : 30 : 18
X = Me	56 : 28 : 16
X = NO_2	44 : 43 : 13



Me > H >> NO_2

Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1924**, *46*, 2339–2343. Abramovitch, R.; Saha, J. *J. Chem. Soc.* **1964**, *301*, 2175–2187. Lynch, B.; Chang, H. *Tet. Lett.* **1964**, *5*, 2965–2968. Dou, B.; Lynch, B. *Tet. Lett.* **1965**, *6*, 897–901.

FMO Analysis of Neutral Arenes/Pyridinium



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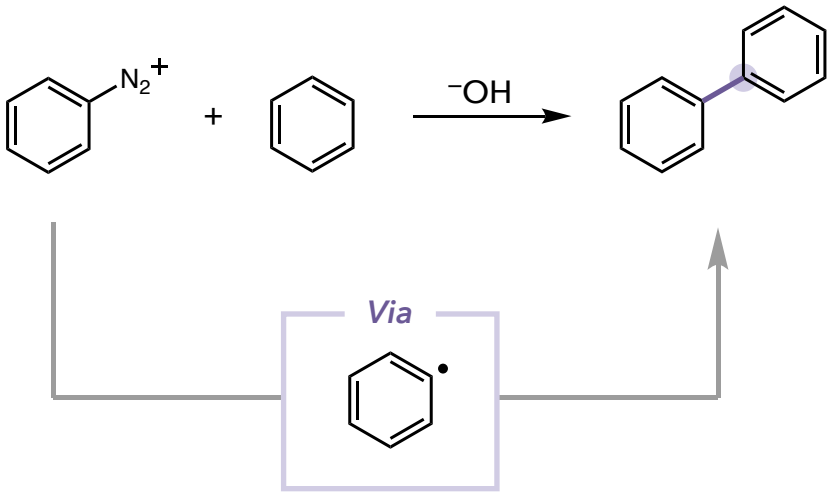
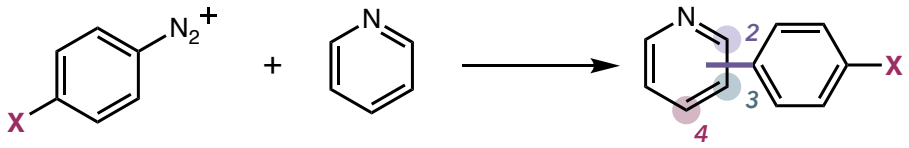
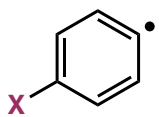


Nucleo/Electrophilic Radicals





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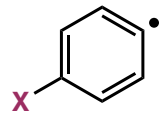
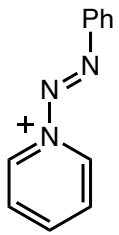
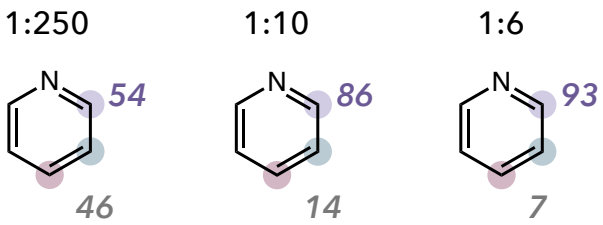


Me > H >> NO_2

Additions to Pyridiniums

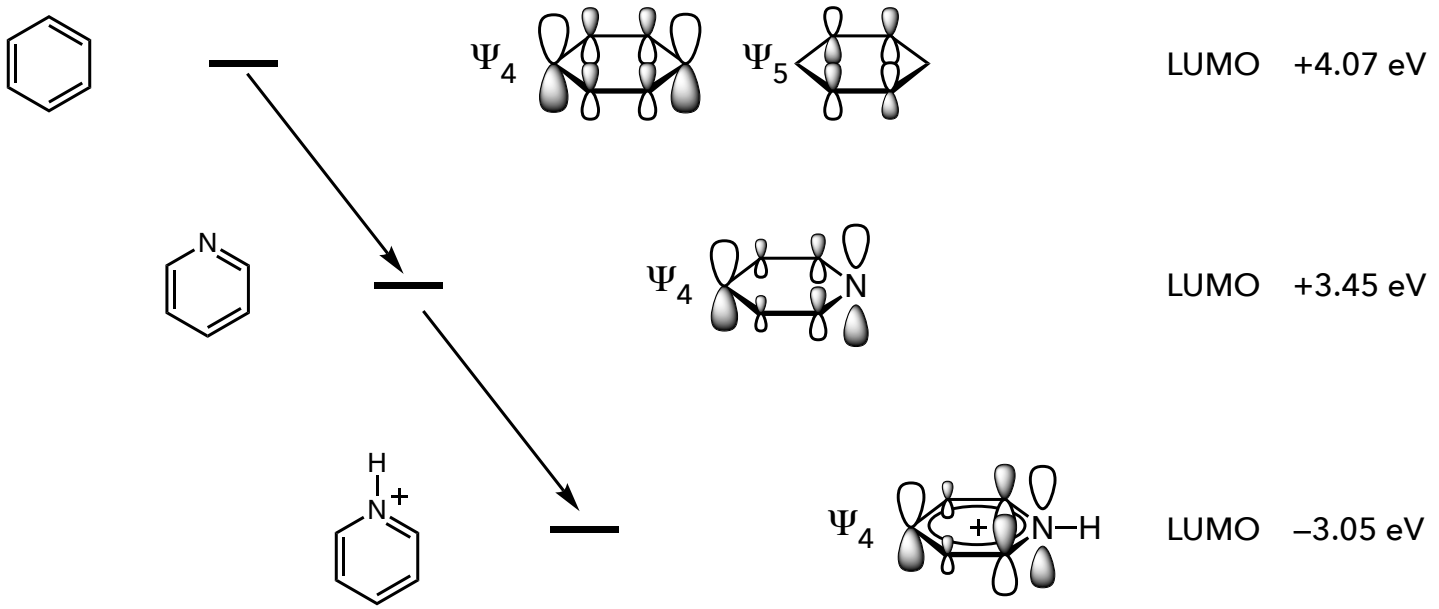


Ratio Diazonium:Pyridine



Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1924**, *46*, 2339–2343. Abramovitch, R.; Saha, J. *J. Chem. Soc.* **1964**, *301*, 2175–2187. Lynch, B.; Chang, H. *Tet. Lett.* **1964**, *5*, 2965–2968. Dou, B.; Lynch, B. *Tet. Lett.* **1965**, *6*, 897–901.

FMO Analysis of Neutral Arenes/Pyridinium



HF/6-31G* level of theory

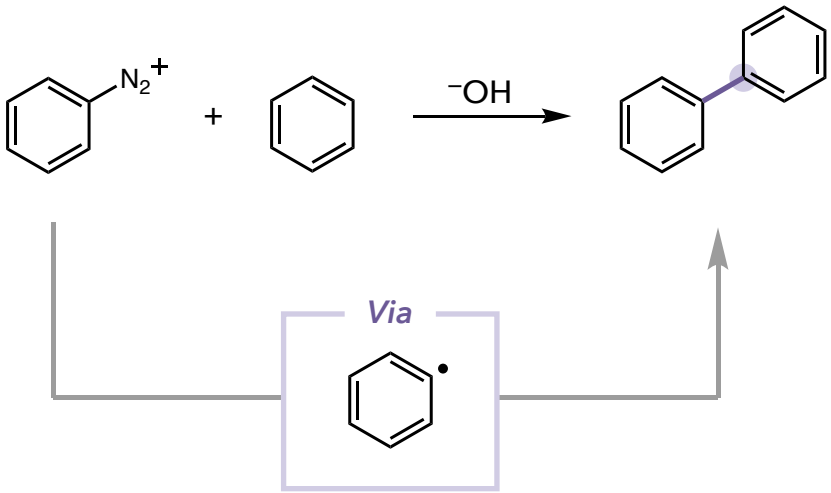
Frontier Molecular Orbital Theory

- Correctly predicts preferential reactivity at 2- and 4-positions of pyridinium
- Explains higher reactivity of cationic form due to lower LUMO

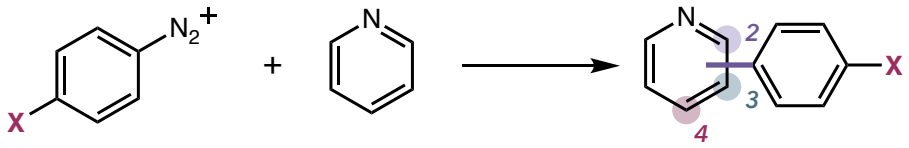
Tauber, J.; Imbri, D.; Opatz, T. *Molecules* **2014**, *19*, 16190–16222.

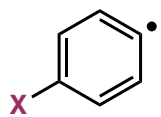
Arylation of Pyridine

Gomberg-Bachmann-Hey Reaction



Nucleo/Electrophilic Radicals





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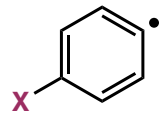
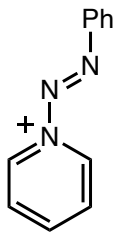
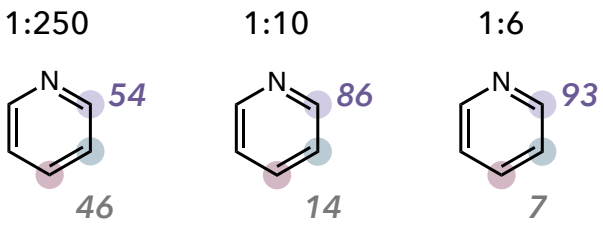


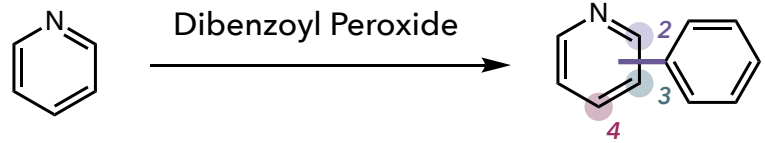
Me > H >> NO_2

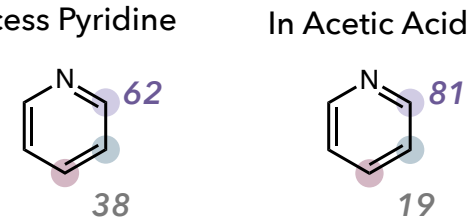
Additions to Pyridiniums



Ratio Diazonium:Pyridine







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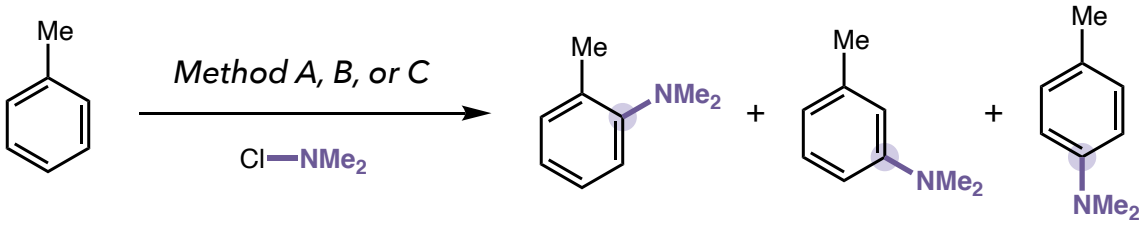
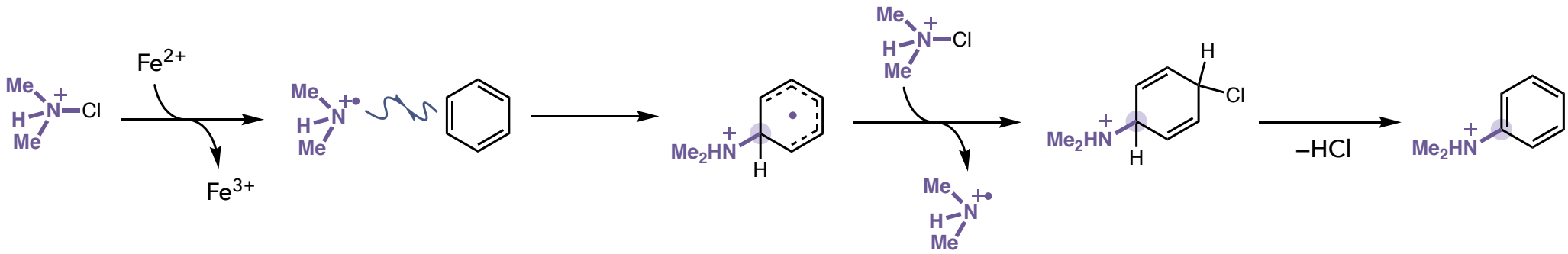
Electrophilic Amination of Arenes

Bock/Kompa, 1965



Method A: Na_2SO_4/Sulfuric Acid, 100 °C (80% yield)
Method B: UV irradiation in Sulfuric Acid (61% yield)
Method C: $AlCl_3$, 100 °C (50% yield)

Minisci, 1965

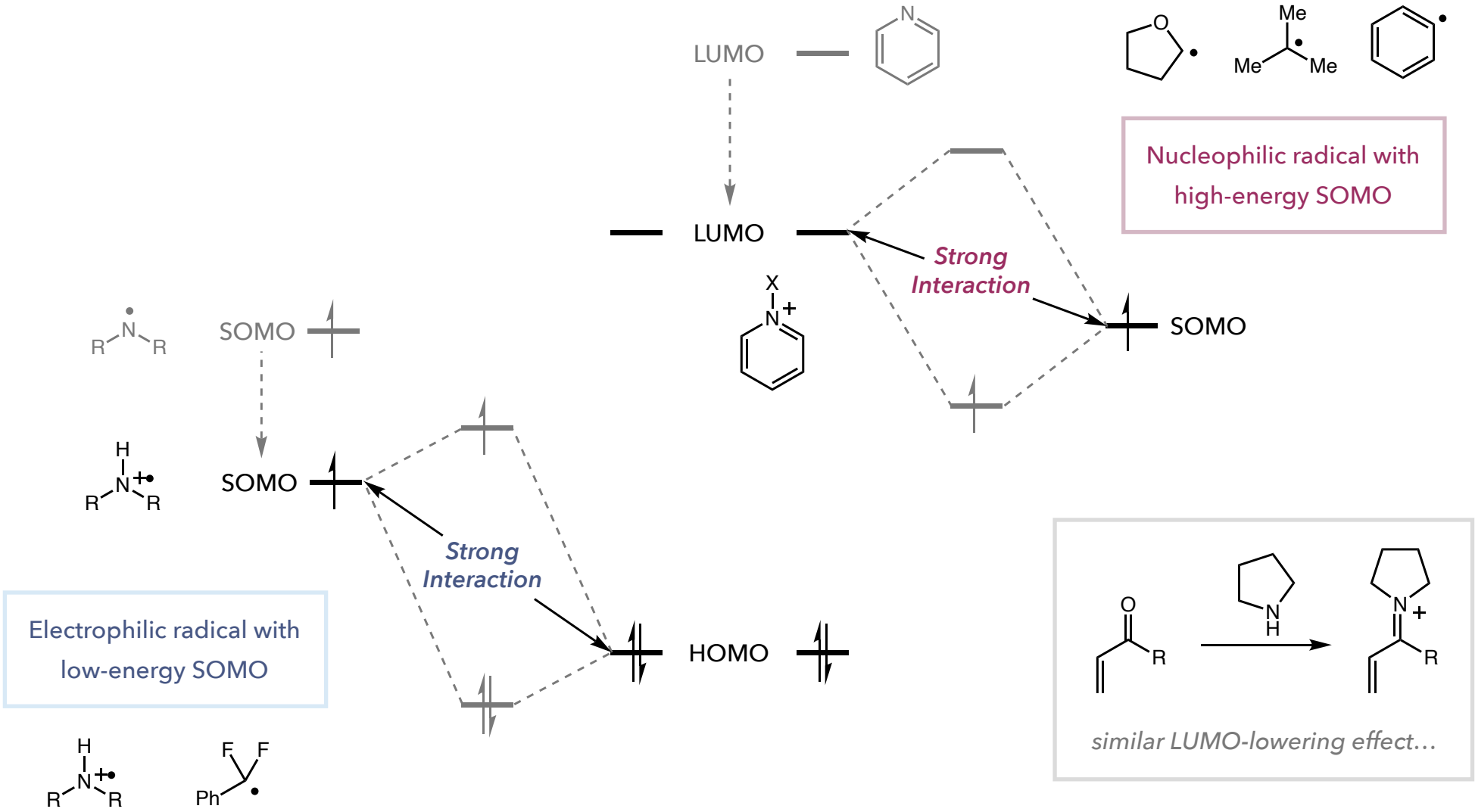


Key Mechanistic Features

- Redox system for radical initiation • Protonation of amines renders it electrophilic
- Significant polar component to reaction selectivity

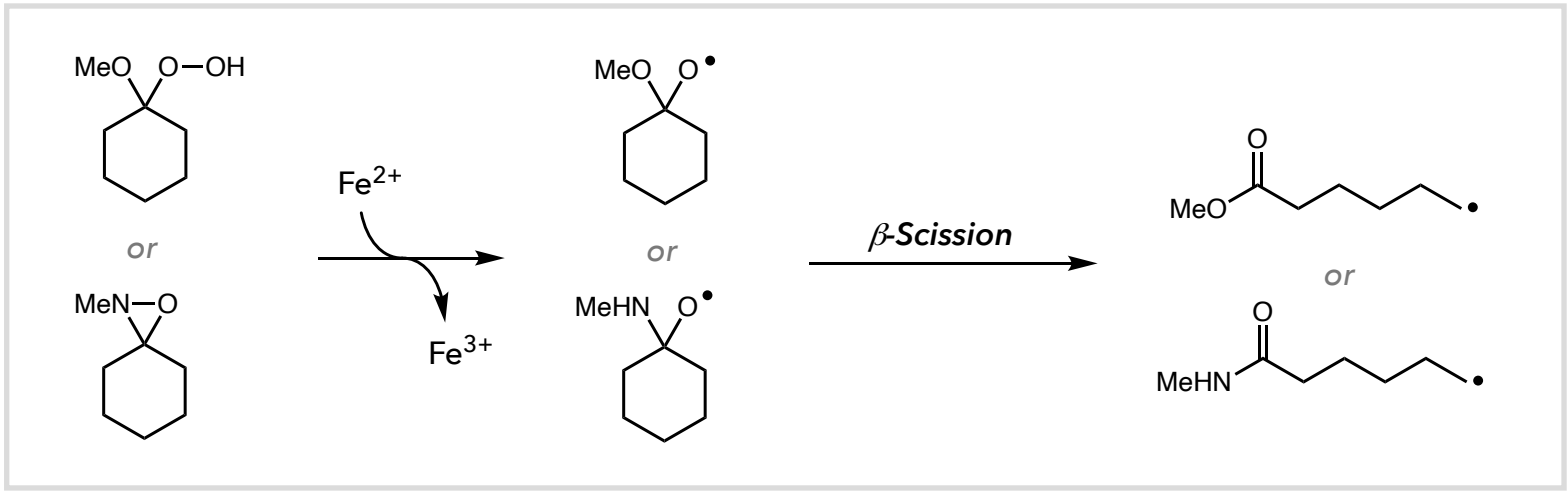
Bock, H.; Kompa, K. L. *Angew. Chem. Int. Ed.* **1965**, *4*, 783–783. Minisci, F.; Galli, R. *Tet. Lett.* **1965**, *8*, 433–436. Minisci, F. *Chim. Ind. (Milano)* **1967**, *49*, 705–719.

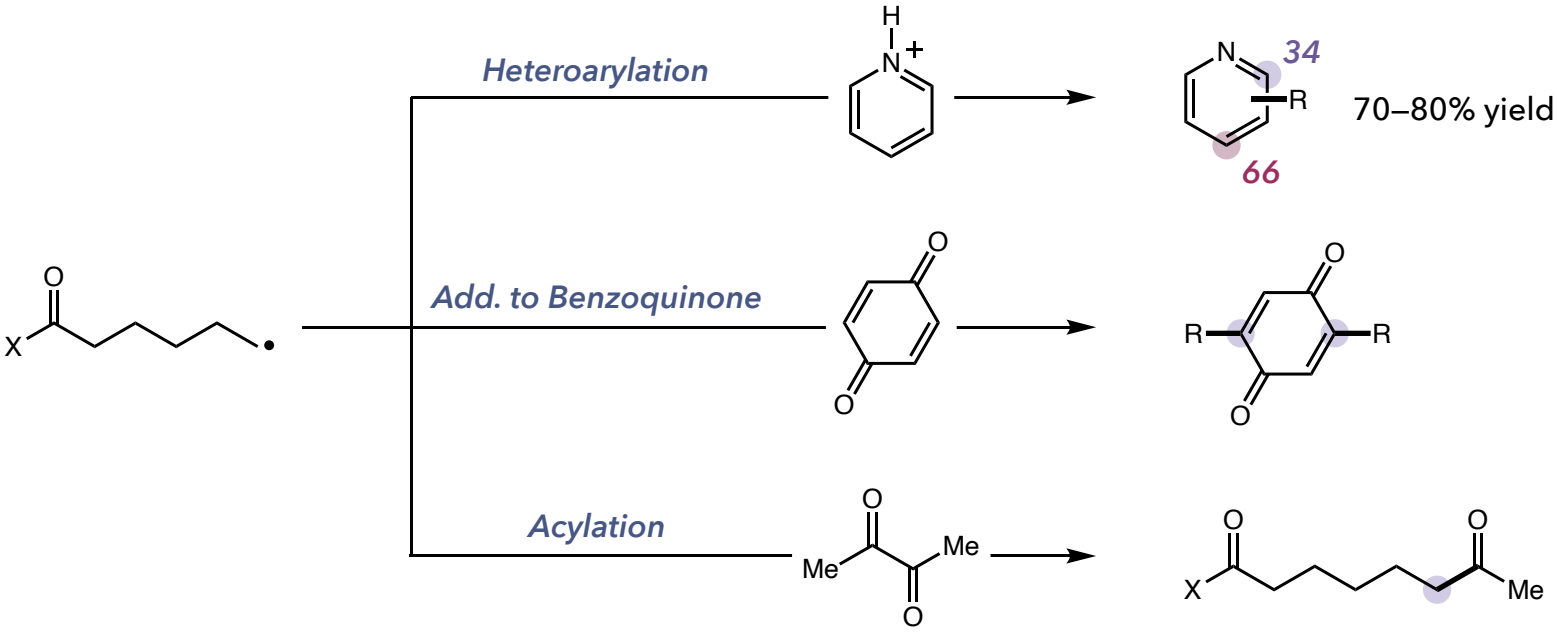
Radical Electrophilicity/Nucleophilicity



Tauber, J.; Imbri, D.; Opatz, T. *Molecules* **2014**, *19*, 16190–16222.

Investigating the Nucleophilic Behavior of Alkyl Radicals

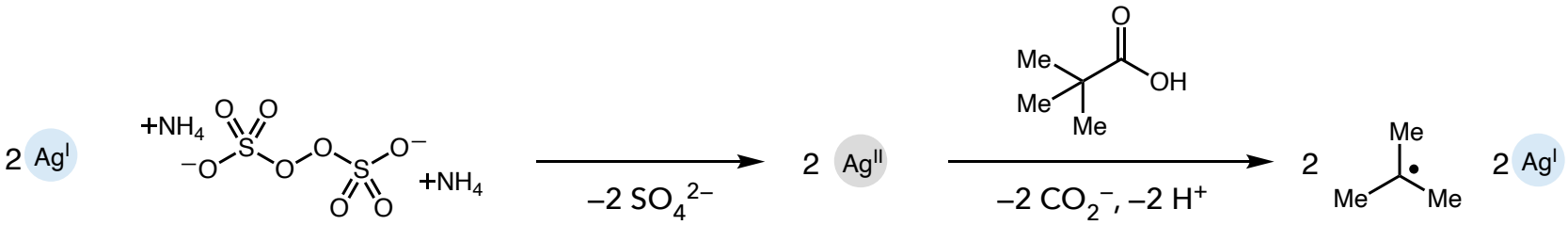




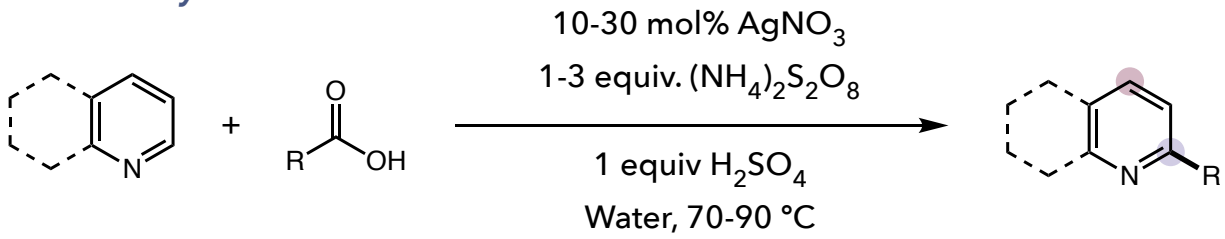
Minisci, F.; Galli, R.; Cecere, M.; Malatesta, V.; Caronna, T. *Tet. Lett.* **1968**, *54*, 5609–5612.

Advent of "The Minisci Reaction"

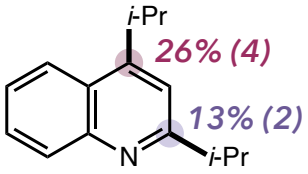
Ag Catalyzed Decarboxylation



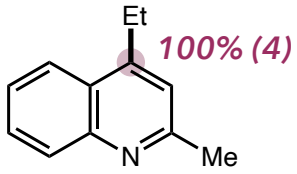
Alkylation of Heterocycles



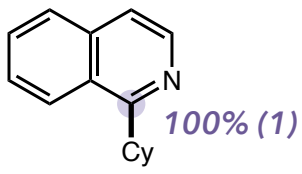
61% (2-, 4-)



99% yield

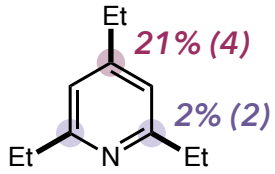


98% yield



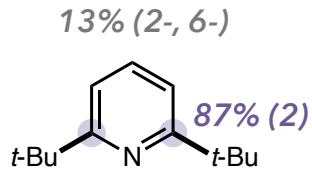
84% yield

73% overalk.

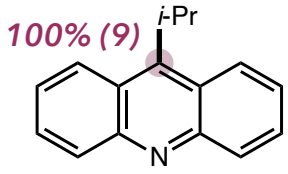


98% yield

13% (2-, 6-)



93% yield



66% yield

Anderson, J.; Kochi, J. *J. Am. Chem. Soc.* **1970**, *92*, 1651–1659. Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. *Tetrahedron* **1971**, *27*, 3575–3579.

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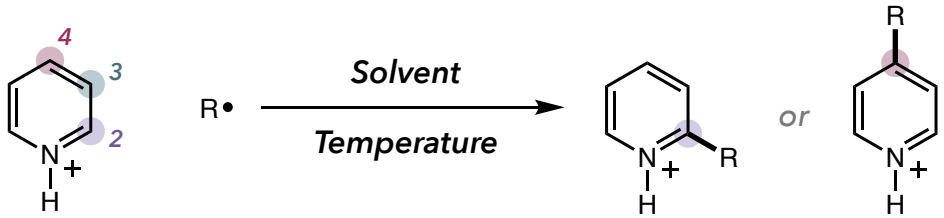
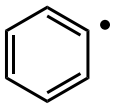
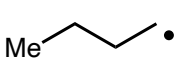
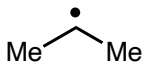
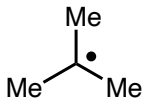
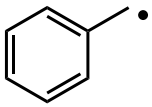
Outline

1. Historical context and reaction development
2. Mechanistic features governing selectivity
3. Recent innovations in the Minisci reaction

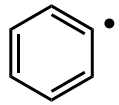
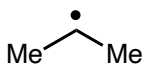
Regioselectivity in the Additions of Radicals to Pyridinium



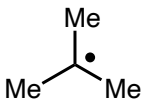
Solvent Effects

radical	solvent	2 4 (3)
	water	64 : 32 (4)
	benzene	70 : 24 (6)
	water	56 : 74
	benzene	75 : 25
	water	32 : 68
	benzene	72 : 28
	water	23 : 77
	benzene	71 : 29
	water, benzene, MeCN, DMSO…	no reaction (bibenzyl formation)

Kinetic Isotope Effects

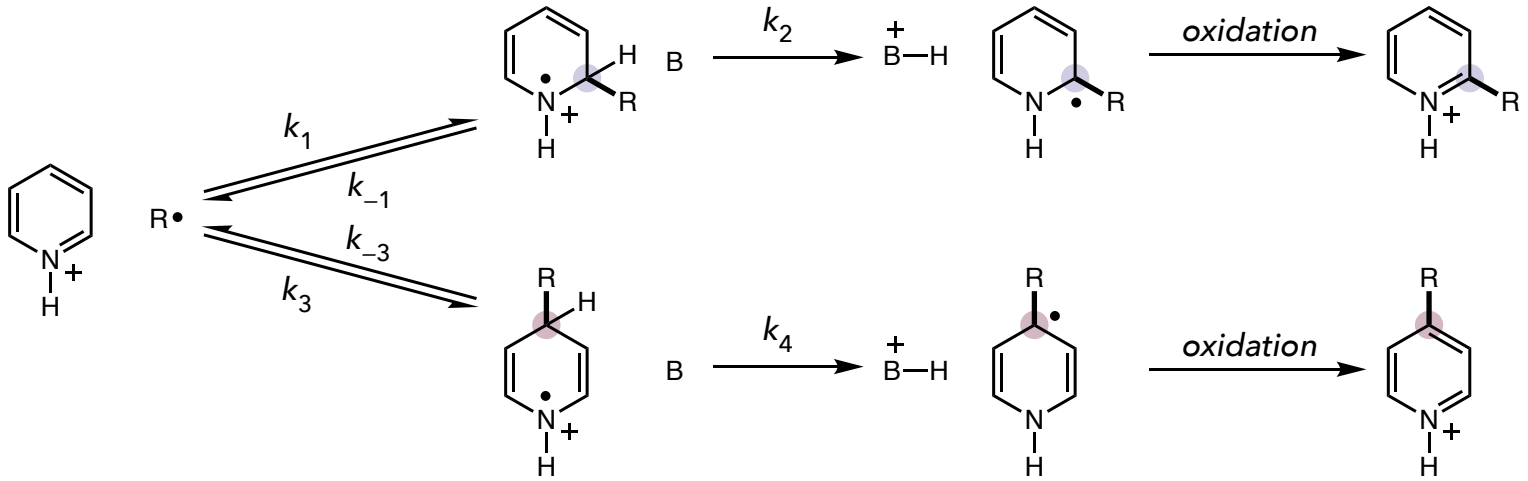
radical	solvent	Py(H) 2	Py(H) 4	Py(D) 2	Py(D) 4	k_H/k_D 2	k_H/k_D 4
	water	64 : 32		61 : 31		1.0	1.0
	benzene	70 : 24		70 : 24		1.0	1.0
	water	31 : 69		30 : 70		3.9	4.2
	benzene	72 : 28		77 : 23		1.7	1.9

Temperature Effects

radical	temperature	2	4
	20 °C	33 : 67	
	60 °C	29 : 71	
	100 °C	23 : 77	

Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1987**, *52*, 730–736.

Kinetic Model to Account for Regioselectivity



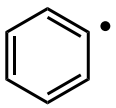
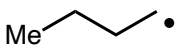
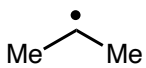
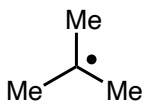
2-selectivity

$$k_{obs} = \frac{k_1 k_2[B]}{k_{-1} + k_2[B]}$$

4-selectivity

$$k_{obs} = \frac{k_3 k_4[B]}{k_{-3} + k_4[B]}$$

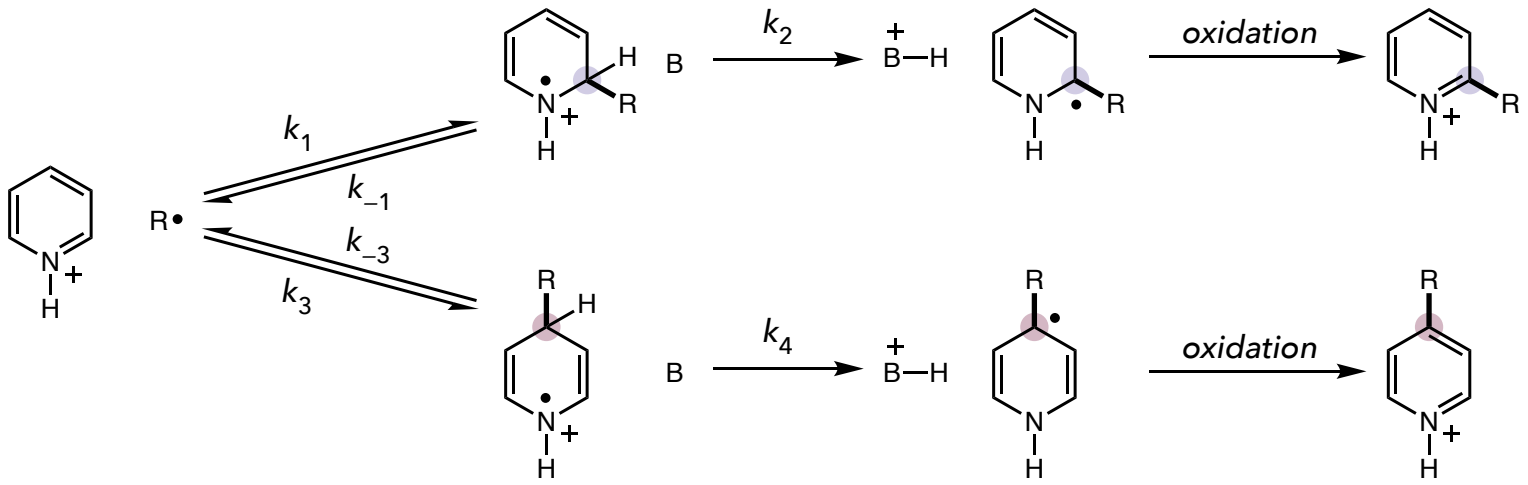
Solvent Effects

radical	solvent	2 4 (3)
	water	64 : 32 (4)
	benzene	70 : 24 (6)
	water	56 : 74
	benzene	75 : 25
	water	32 : 68
	benzene	72 : 28
	water	23 : 77
	benzene	71 : 29

- Magnitude of solvent effect trends Ph < *n*-Bu < *i*-Pr < *t*-Bu
- Either related to *solvation of polar transition states* (k_1 vs k_3) or to the *reversibility of addition* ($k_{-1}/k_2[B]$ or $k_{-3}/k_4[B]$)

Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1987**, *52*, 730–736.

Kinetic Model to Account for Regioselectivity



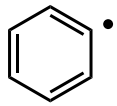
2-selectivity

$$k_{obs} = \frac{k_1 k_2[B]}{k_{-1} + k_2[B]}$$

4-selectivity

$$k_{obs} = \frac{k_3 k_4[B]}{k_{-3} + k_4[B]}$$

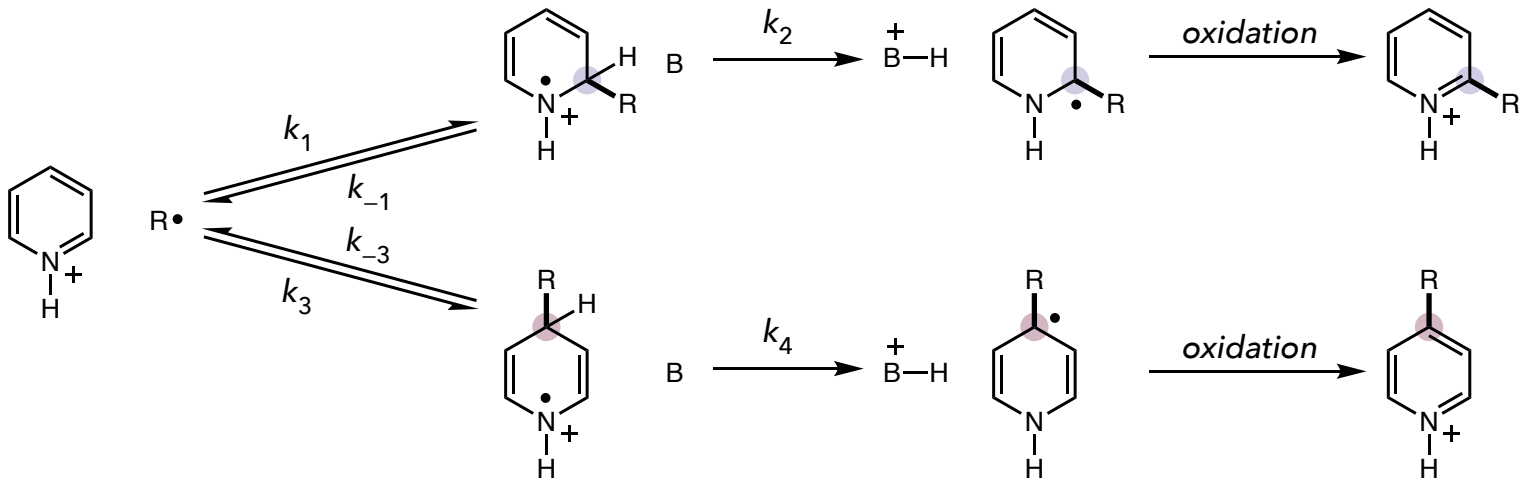
Kinetic Isotope Effects

radical	solvent	Py(H) 2 : 4	Py(D) 2 : 4	k_H/k_D 2	k_H/k_D 4
	water	64 : 32	61 : 31	1.0	1.0
	benzene	70 : 24	70 : 24	1.0	1.0

- ***No isotope effect*** observed for Ph radical (k_{-1} << k_2[B] and k_{-3} << k_4[B])
- ***Addition to the pyridinium is largely irreversible***, regioselectivity determined by k_1 vs k_3

Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1987**, *52*, 730–736.

Kinetic Model to Account for Regioselectivity



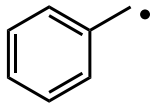
2-selectivity

$$k_{obs} = \frac{k_1 k_2[B]}{k_{-1} + k_2[B]}$$

4-selectivity

$$k_{obs} = \frac{k_3 k_4[B]}{k_{-3} + k_4[B]}$$

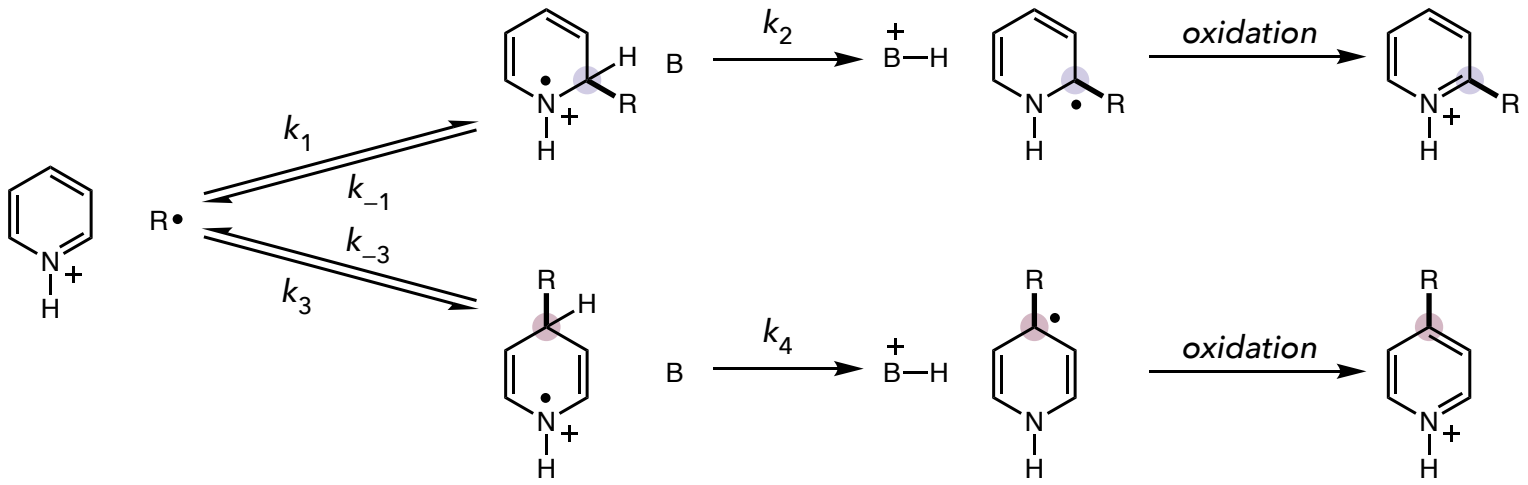
Solvent Effects

radical	solvent	2 ● 4 ● (3 ●)
	water, benzene, MeCN, DMSO…	no reaction (bibenzyl formation)

- No desired product observed for benzyl radical in any solvent
- *Low enthalpy of addition* renders $k_{-1} >> k_2[B]$ and $k_{-3} >> k_4[B]$, allowing for *irreversible dimerization*

Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1987**, *52*, 730–736.

Kinetic Model to Account for Regioselectivity



2-selectivity

$$k_{obs} = \frac{k_1 k_2 [B]}{k_{-1} + k_2 [B]}$$

4-selectivity

$$k_{obs} = \frac{k_3 k_4 [B]}{k_{-3} + k_4 [B]}$$

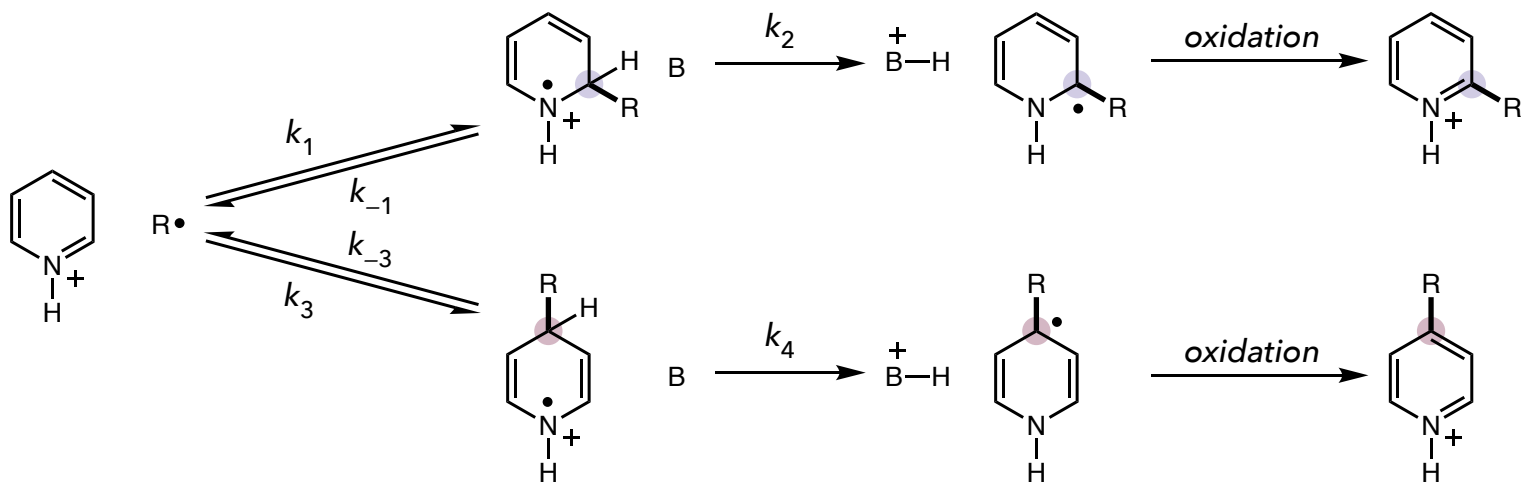
Kinetic Isotope Effects

radical	solvent	Py(H) 2	Py(H) 4	Py(D) 2	Py(D) 4	k_H/k_D 2	k_H/k_D 4
Me, Me	water	31	69	30	70	3.9	4.2
	benzene	72	28	77	23	1.7	1.9

- *Isotope effect* and *regioselectvity* are both significantly affected by reaction medium
- Solvent and base catalysis mainly influence the *reversibility of the radical addition*
- Poorly solvated radical ion pair in benzene undergoes α-deprotonation faster than in water

Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1987**, *52*, 730–736.

Kinetic Model to Account for Regioselectivity



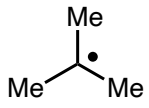
2-selectivity

$$k_{obs} = \frac{k_1 k_2 [B]}{k_{-1} + k_2 [B]}$$

4-selectivity

$$k_{obs} = \frac{k_3 k_4 [B]}{k_{-3} + k_4 [B]}$$

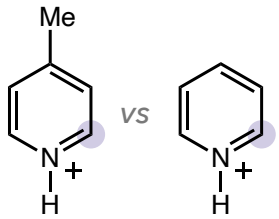
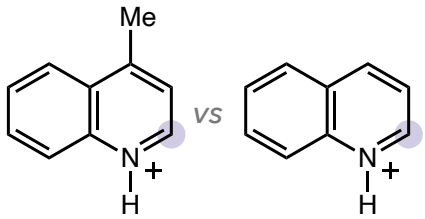
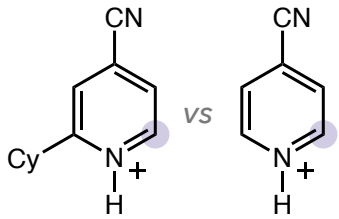
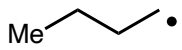
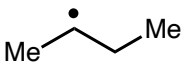
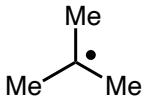
Temperature Effects

radical	temperature	2 : 4
	20 °C	33 : 67
	60 °C	29 : 71
	100 °C	23 : 77

- Increasing the *temperature* of the reaction in water *increases reversibility of radical addition*
- Increasing the reversibility *increases the amount of the 4-isomer*
- Similarly, increasing the reaction pH *(decreasing base catalysis) favors 4-isomer*

Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1987**, *52*, 730–736.

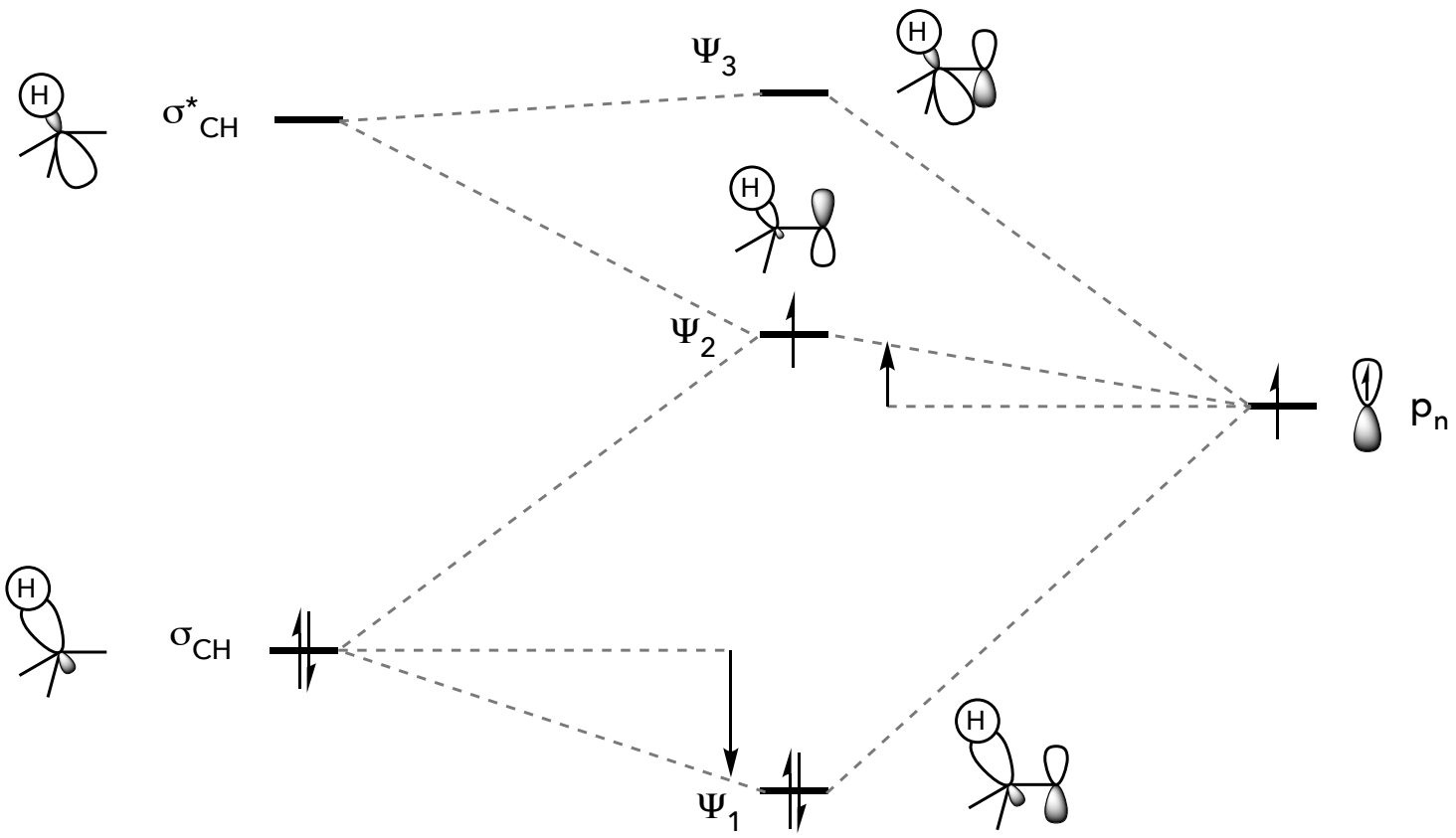
Deactivation of Arene by Alkylation

			
	0.53 : 1.0	––	––
	0.32 : 1.0	0.70 : 1.0	0.33 : 1.0
	0.28 : 1.0	0.60 : 1.0	0.20 : 1.0
	0.15 : 1.0	0.16 : 1.0	< 0.10 : 1.0

- Introduction of an inductively donating *alkyl group deactivates the ring* towards further alkylation
  - The degree of activation increases with the *nucleophilic character* of the attacking radical

Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocyclic Chem.* **1990**, *27*, 79–96.

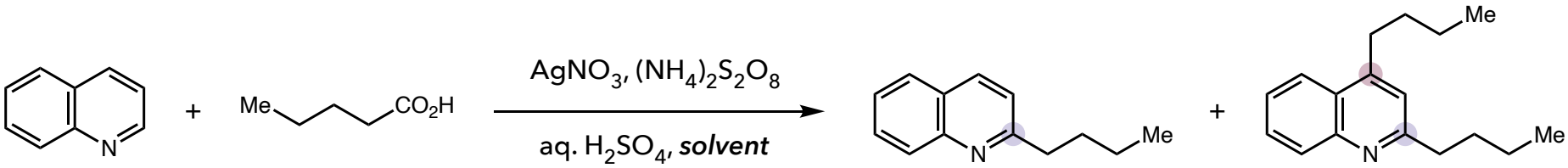
Nucleophilicity of Alkyl Radicals



- *Hyperconjugation* with adjacent σ(C–H)-orbitals *raises the SOMO energy*
- Nucleophilicity of radicals trends primary < secondary < tertiary
- Similarly, hyperconjugation with *heteroatom lone pairs* also raises the SOMO energy

Tauber, J.; Imbri, D.; Opatz, T. *Molecules* **2014**, *19*, 16190–16222.

Circumventing Overalkylation with Biphasic Reaction Conditions

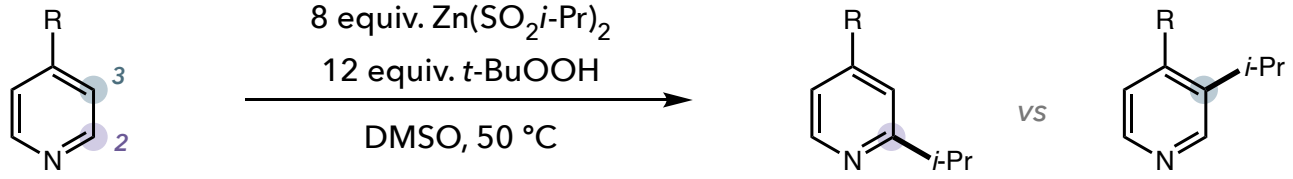


Conversion (%)	*Solvent*	*Monoalkyl (%)*	*Dialkyl (%)*
38	H_2O	100	––
87	H_2O	67	33
31	$PhCl/H_2O$	100	––
63	$PhCl/H_2O$	100	––

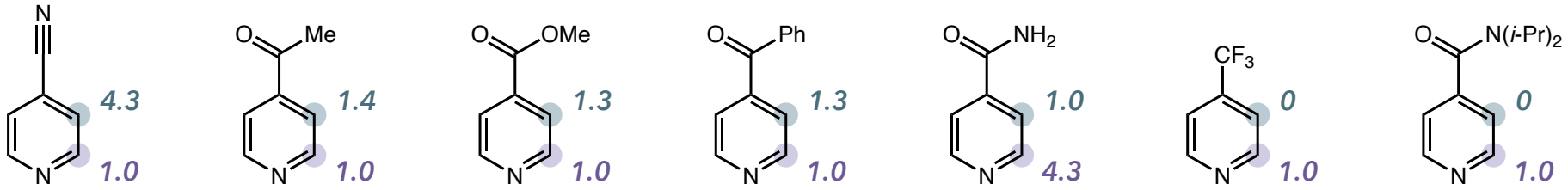
- Introduction of an alkyl group *increases the lipophilicity* of the product
- Extraction into the organic solvent *inhibits further alkylation*

Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocyclic Chem.* **1990**, *27*, 79–96.

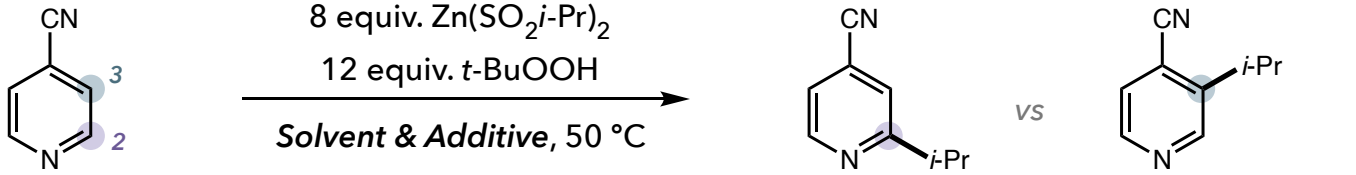
Substituent, Solvent, and Acid Effects in Regioselectivity



"innate reactivity" *"conjugate reactivity"*



Solvent & Additive Effects



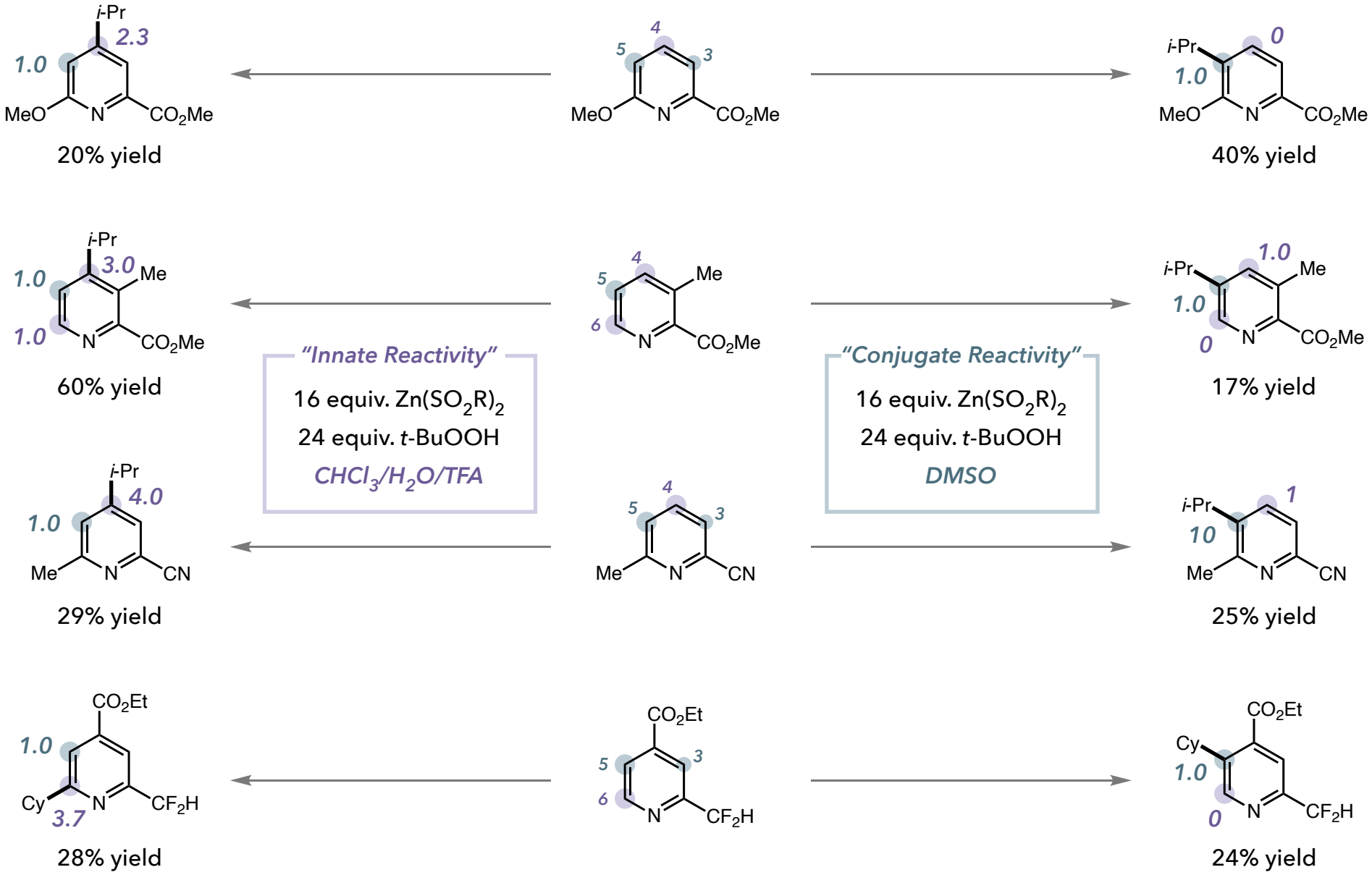
"innate reactivity" *"conjugate reactivity"*

	2 : 3
DMSO	1.0 : 4.3
$CHCl_3$:H_2O	3.0 : 1.0
DMSO + H_2SO_4	6.6 : 1.0
$CHCl_3$:H_2O + TFA	5.0 : 1.0

- Addition of acid & switch of solvent reduces influence of *"conjugate reactivity"*

O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122–12134.

Predicting and Tuning Regioselectivity



O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122–12134.

The Minisci Reaction

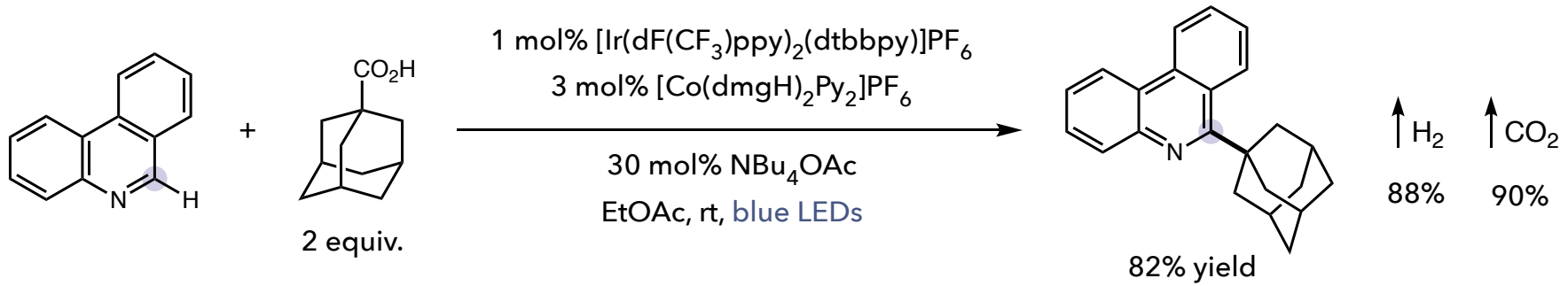
Radical Additions to Electron-Deficient Heterocycles

Outline

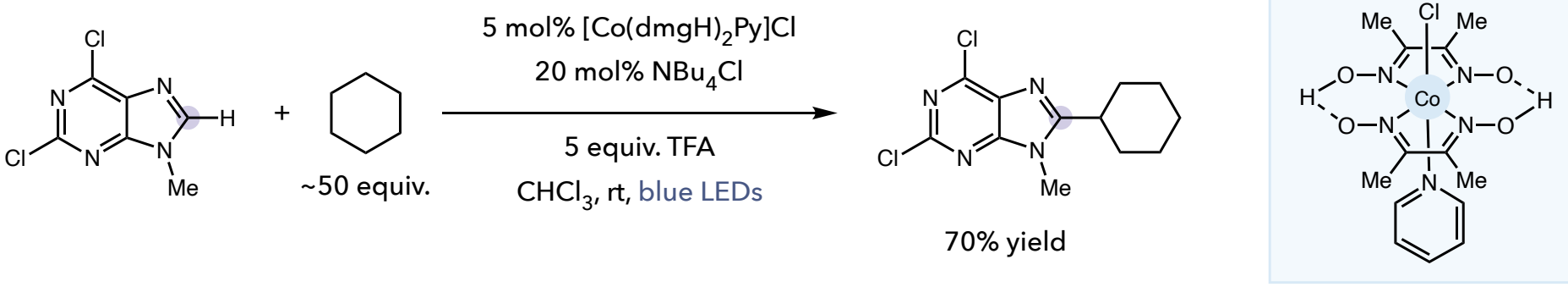
1. Historical context and reaction development
2. Mechanistic features governing selectivity
3. Recent innovations in the Minisci reaction

Dehydrogenative Coupling with H_2 Release

Decarboxylative Radical Generation



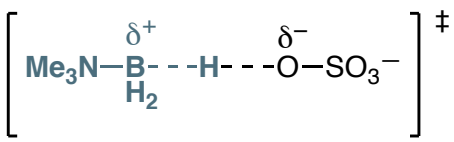
Chlorine Radical Generation



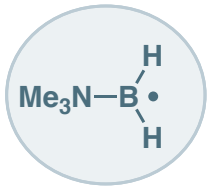
- Net oxidative reaction with no chemical oxidant, solely *driven by light and the release of H_2*

Tian, W.-F.; Hu, C.-H.; He, K.-H.; He, X.-Y.; Li, Y. *Org. Lett.* **2019**, *21*, 6930–6935. Huang, C.-Y.; Li, J.; Li, C.-J. *Nat. Comm.* **2021**, *12*, 1–9.

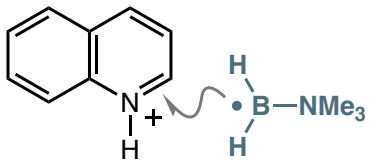
Nucleophilicity of Boryl Radicals



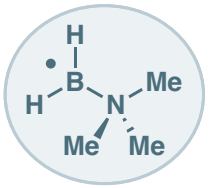
Polarized HAT transition state



Precedented nucleophilic HAT reagent

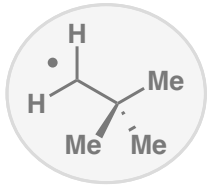


Nucleophilic addition to arenes?

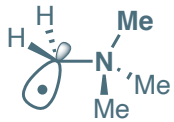
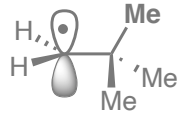


Boryl Radical

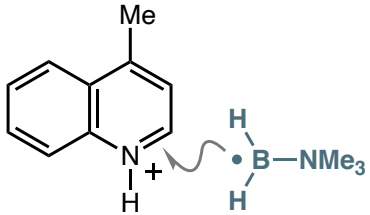
vs



Neopentyl Radical

	Boryl Radical	Neopentyl Radical
Ionization Potential (eV)	5.65	8.14
Hirshfield Charge	–0.38	–0.006
Radical Configuration	 *σ-radical*	 *π-radical*
Structural Features	B–N = 1.619 Å	C–C = 1.502 Å

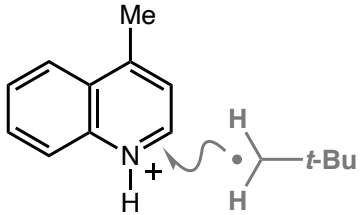
Minisci Borylation



$\Delta G° = -11.0$ kcal mol^{-1}

$\Delta G^{‡} = 5.4$ kcal mol^{-1}

Minisci Alkylation

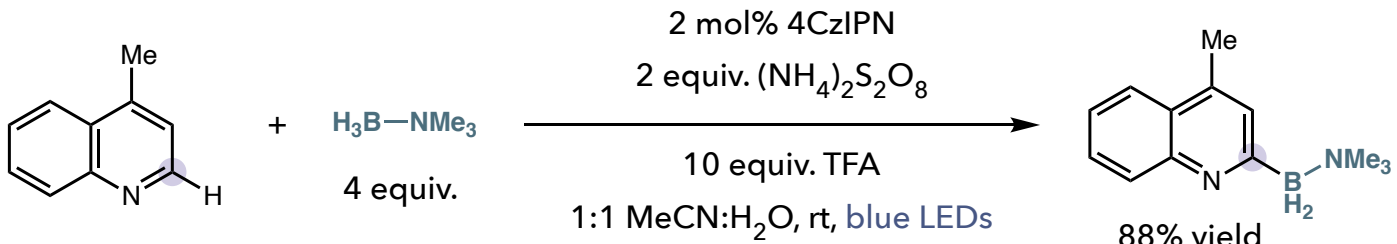


$\Delta G° = 4.7$ kcal mol^{-1}

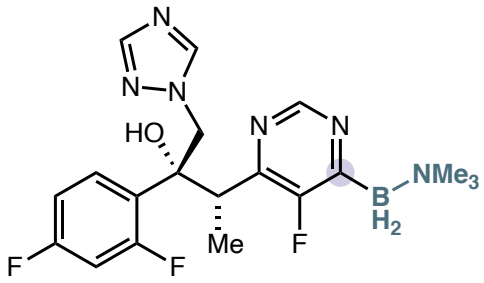
$\Delta G^{‡} = 20.1$ kcal mol^{-1}

Kim, J. H.; Constantin, T.; Simonetti, M.; Llaveria, J.; Sheikh, N. S.; Leonori, D. *Nature* **2021**, *595*, 677–683.

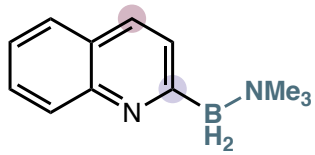
Minisci-Type Borylation of Nitrogen Heterocycles



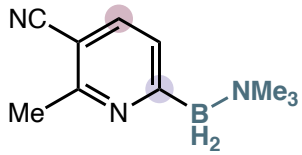
88% yield
(65% w/o 4CzIPN)



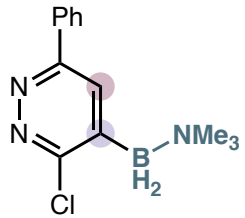
46% yield



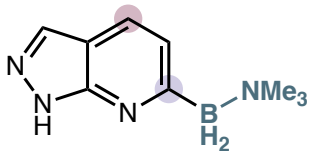
63% yield (3:1)



73% yield (2:1)

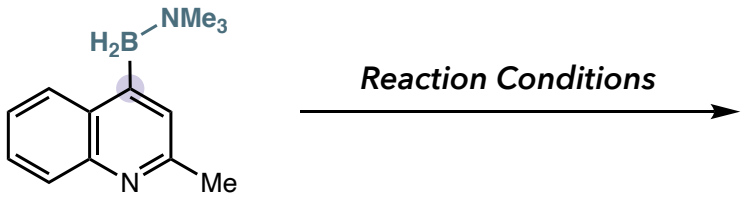


73% yield (8:1)



61% yield (1.7:1)

Derivatization of Boryl Group



Oxidation to Phenol

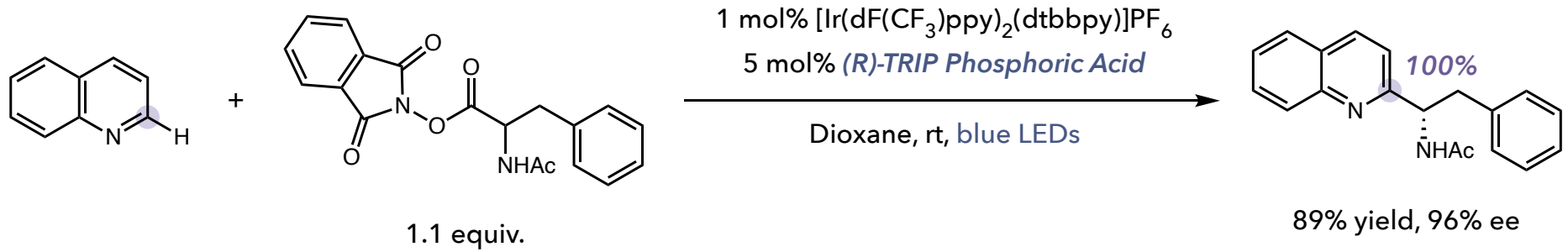
Suzuki-Miyaura cross-coupling

Chan-Lam etherification

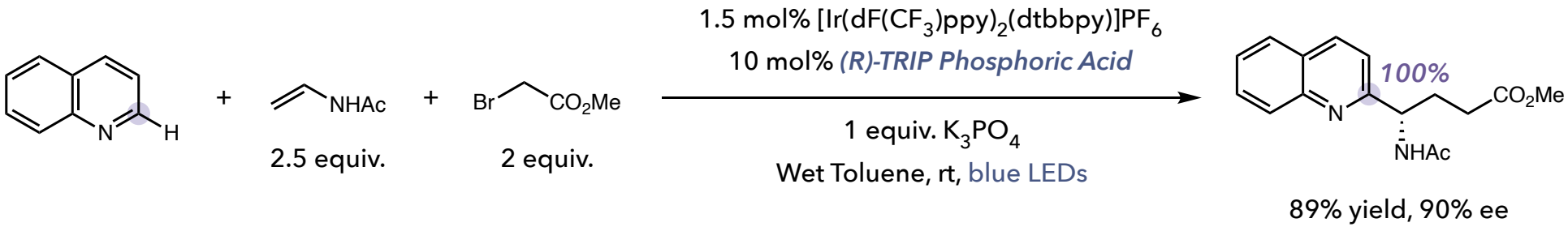
Kim, J. H.; Constantin, T.; Simonetti, M.; Llaveria, J.; Sheikh, N. S.; Leonori, D. *Nature* **2021**, *595*, 677–683.

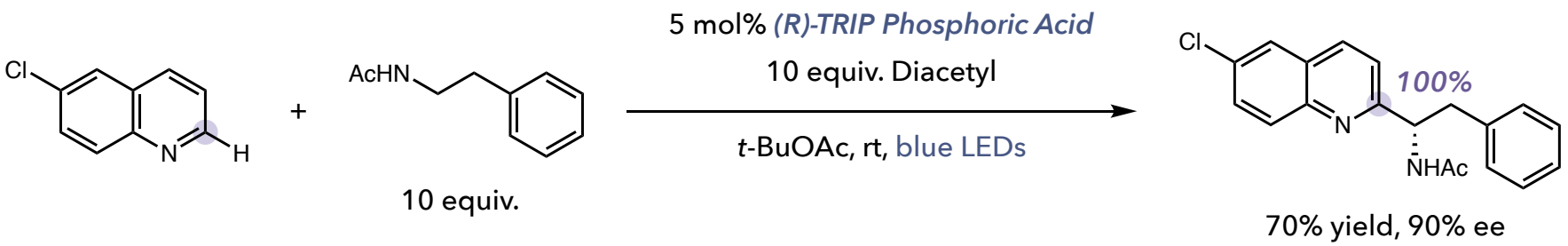
Enantioselective Minisci Reaction

Original Phipps Report, 2018



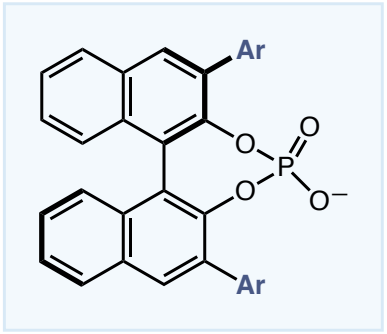
Follow Up Reports



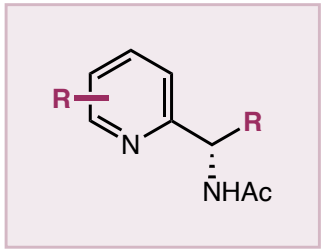


Proctor, R. S. J.; Davis, H. J.; Phipps, R. *Science* **2018**, *360*, 419–422. Zheng, D.; Studer, A. *Angew. Chem. Int. Ed.* **2019**, *58*, 15803–15807.
Proctor, R. S. J.; Chuentragool, P.; Colgan, A. C.; Phipps, R. *J. Am. Chem. Soc.* **2021**, *143*, 4928–4934.

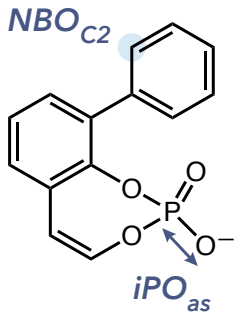
Multivariate Linear Regression Analysis

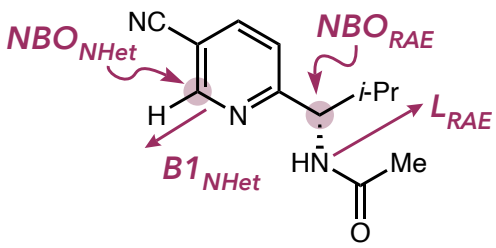


8 phosphoric acids



7 heteroarene products





Build training set → Develop model

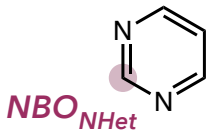
$$\Delta\Delta G^{\ddagger} = 0.73 - 0.30(iPO_{as}) + 0.18(NBO_{C2}) + 0.17(NBO_{RAE}) + 0.26(NBO_{NHet}) - 0.21(L_{RAE}) + 0.30(B1_{NHet})$$

L_{RAE} = distance along bond axis

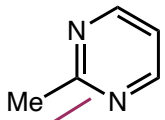
$B1_{NHet}$ = minimum radius perpendicular to bond axis

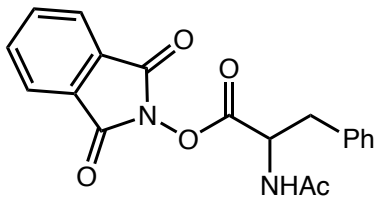
NBO_{RAE} = natural bond orbital

iPO_{as} = asymmetric IR stretch



or



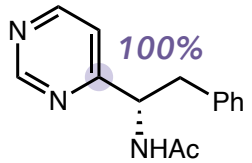


1.1 equiv.

1 mol% $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$

5 mol% (R)-TRIP Phosphoric Acid

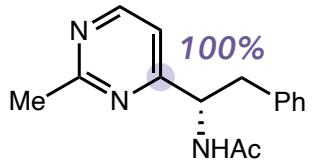
Dioxane, rt, blue LEDs



44% yield, 88% ee

(predicted 89% ee)

or

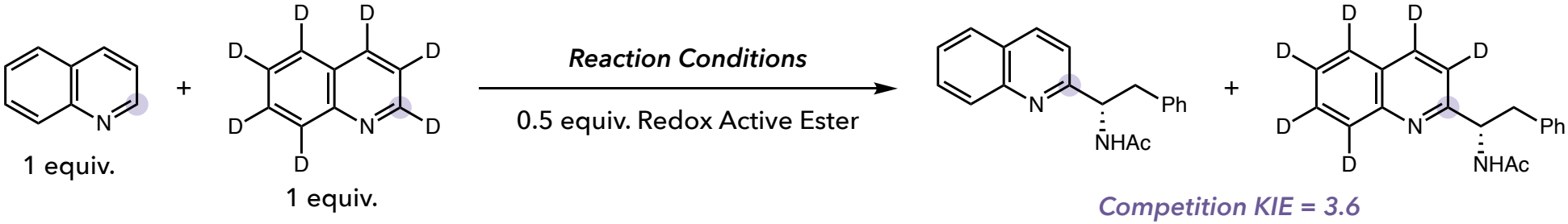


45% yield, 94% ee

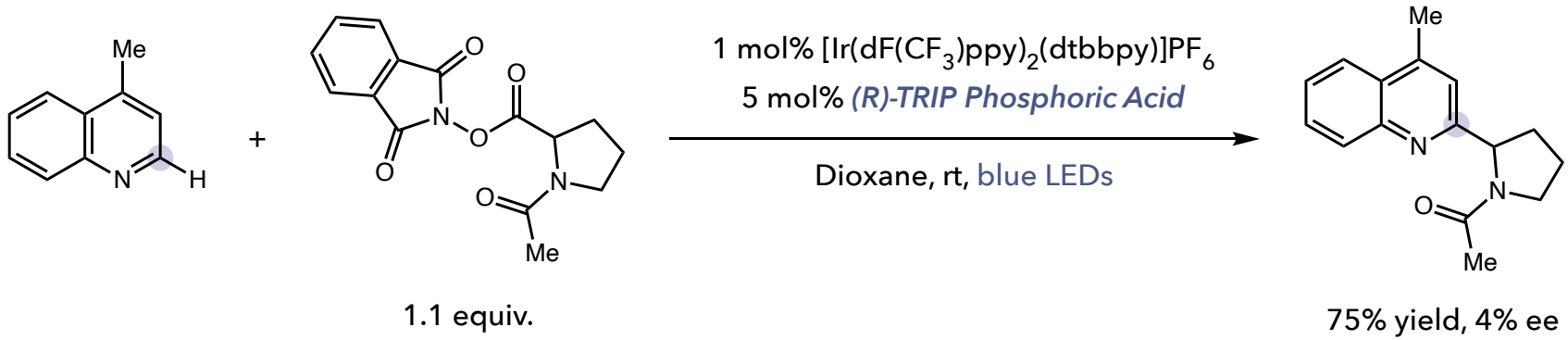
(predicted 94% ee)

Reid, J. P.; Proctor, R. S. J.; Sigman, M. S.; Phipps, R. J. *J. Am. Chem. Soc.* **2019**, *141*, 19178–19185.

Additional Mechanistic Experiments



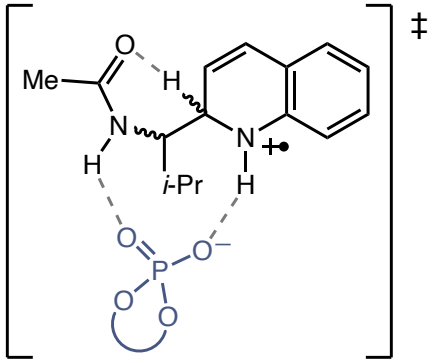
- Consistent with Minisci's measured KIE of α-THF radical and reversibility *dependence on radical stability*
- Suggests a *Curtin-Hammett situation*- radical addition is reversible and *deprotonation is selectivity determining*



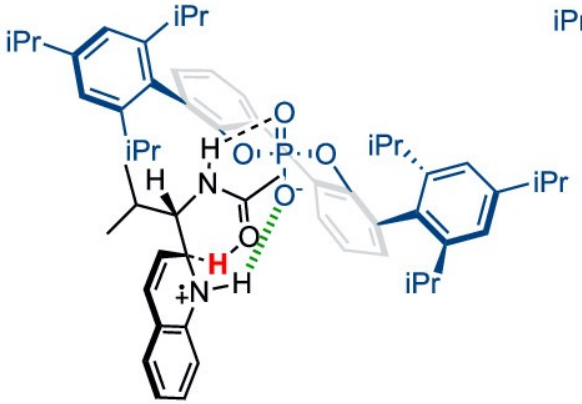
- Suggests the free N–H bond participates with the phosphate during enantiodetermining deprotonation

Proctor, R. S. J.; Davis, H. J.; Phipps, R. *Science* **2018**, *360*, 419–422.

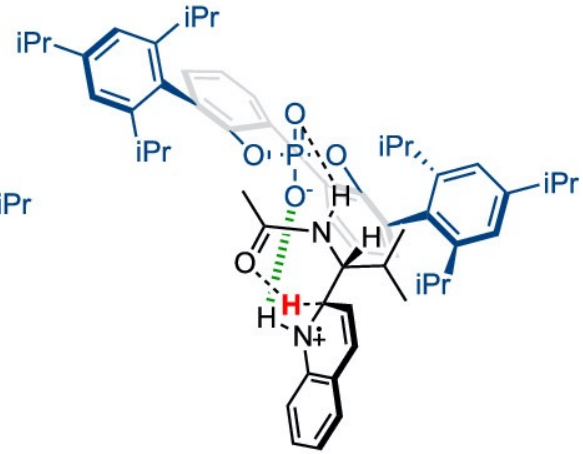
Summarized Computational Study



lowest energy calculated transition state



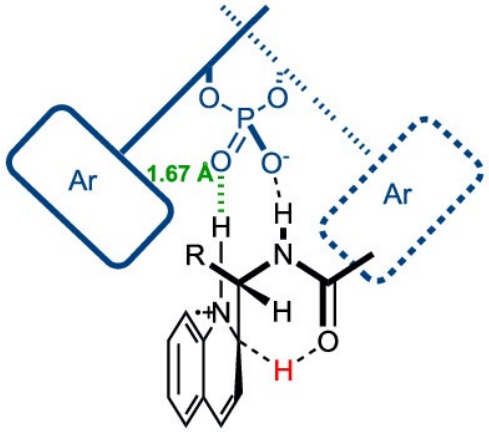
***R,S*-INT**
0.0 kcal/mol



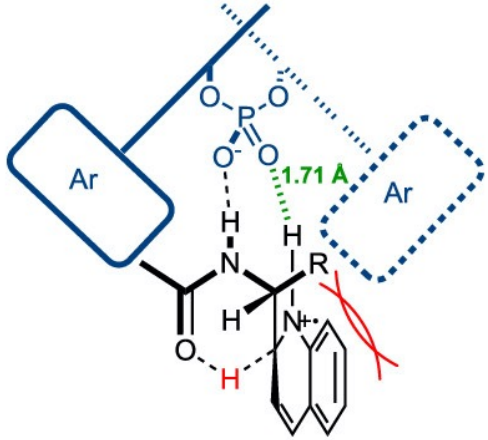
***S,R*-INT**
1.2 kcal/mol

Enantioselectivity Model Rationalizes

- Selectivity dependence on ***B1***$_{NHet}$ and ***L***$_{RAE}$
- Poor performance of carbamate & TFA PG
- Superior performance of *N*-Ac vs *N*-Piv
- High regioselectivity for 2-position
- Correlation between regio- & enantioselectivity



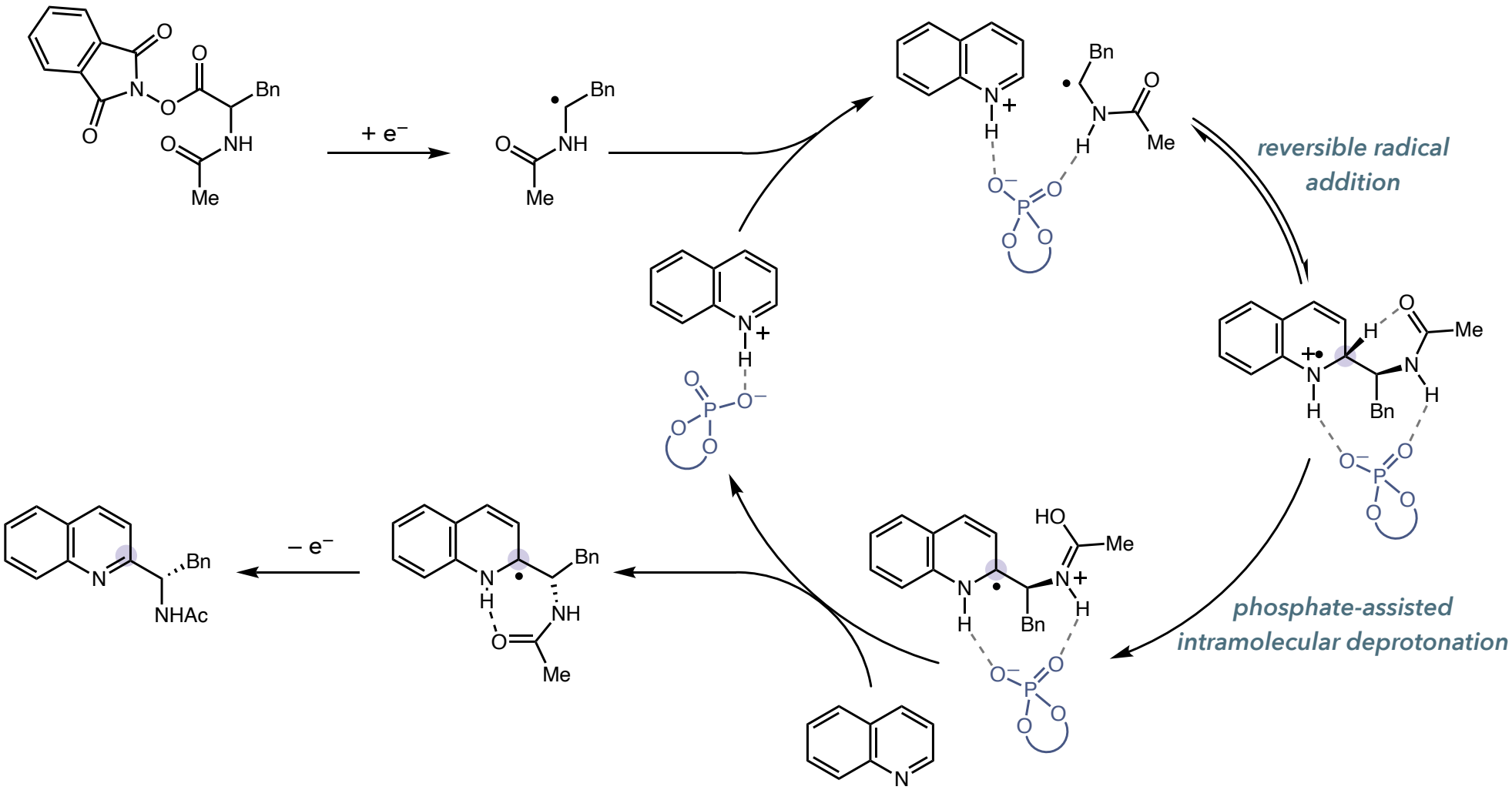
***R,S*-INT**
0.0 kcal/mol



***S,R*-INT**
1.2 kcal/mol

Ermanis, K.; Colgan, A. C.; Proctor, R. S. J.; Hadry, B. W.; Phipps, R. J.; Goodman, J. M. *J. Am. Chem. Soc.* **2020**, *142*, 21091–21101.

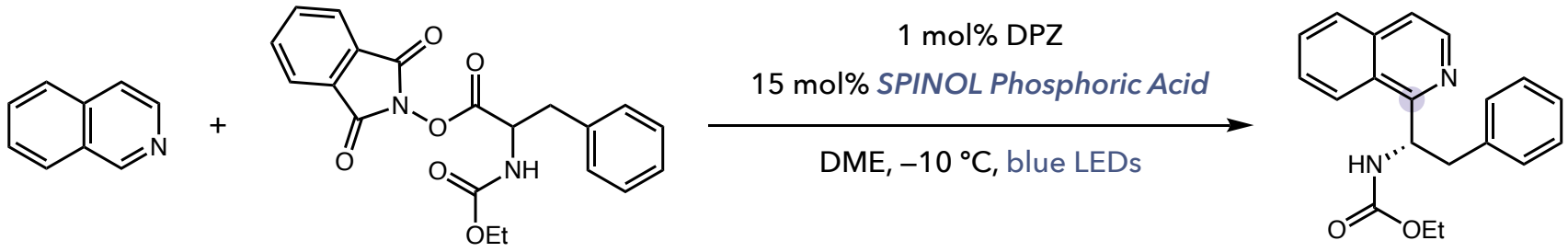
Proposed Reaction Mechanism



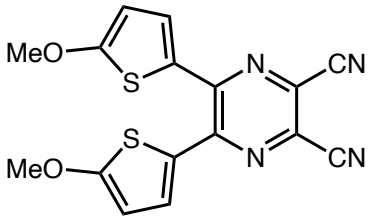
Ermanis, K.; Colgan, A. C.; Proctor, R. S. J.; Hadry, B. W.; Phipps, R. J.; Goodman, J. M. *J. Am. Chem. Soc.* **2020**, *142*, 21091–21101.

Asymmetric Minisci Reaction with Isoquinolines

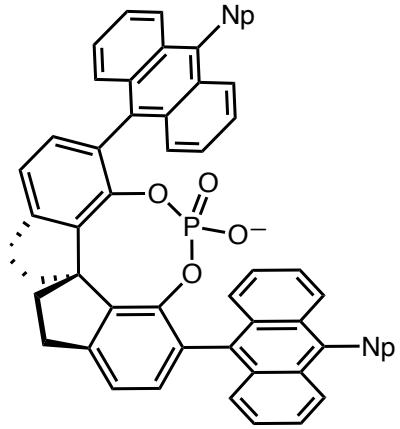
Zhiyong Jiang, 2018



DPZ Photocatalyst



SPINOL Phosphoric Acid



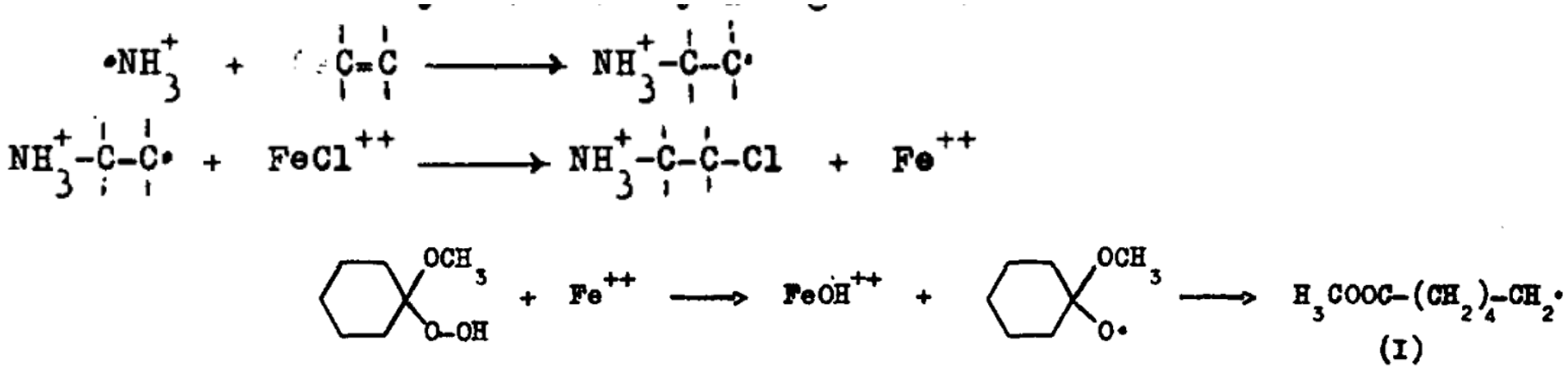
Differentiating Features

- Organic vs Ir photocatalyst
- Carbamate PG (deprotonation step?)
- Complementary (if narrow) scope of arene
- Completely different binding pocket

Liu, X.; Liu, Y.; Chai, G.; Qiao, B.; Zhao, X.; Jiang, Z. *Org. Lett.* **2018**, *20*, 6298–6301.

Conclusions

1) We stand on the *shoulders of giants* who explored much of the fundamental radical reactivity that we use today



$$Ag(II) + RCO_2H \longrightarrow Ag(I) + RCO_2\cdot + H^+$$

$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

Fine Chemicals from Lignosulfonates. 1. Synthesis of Vanillin by Oxidation of Lignosulfonates

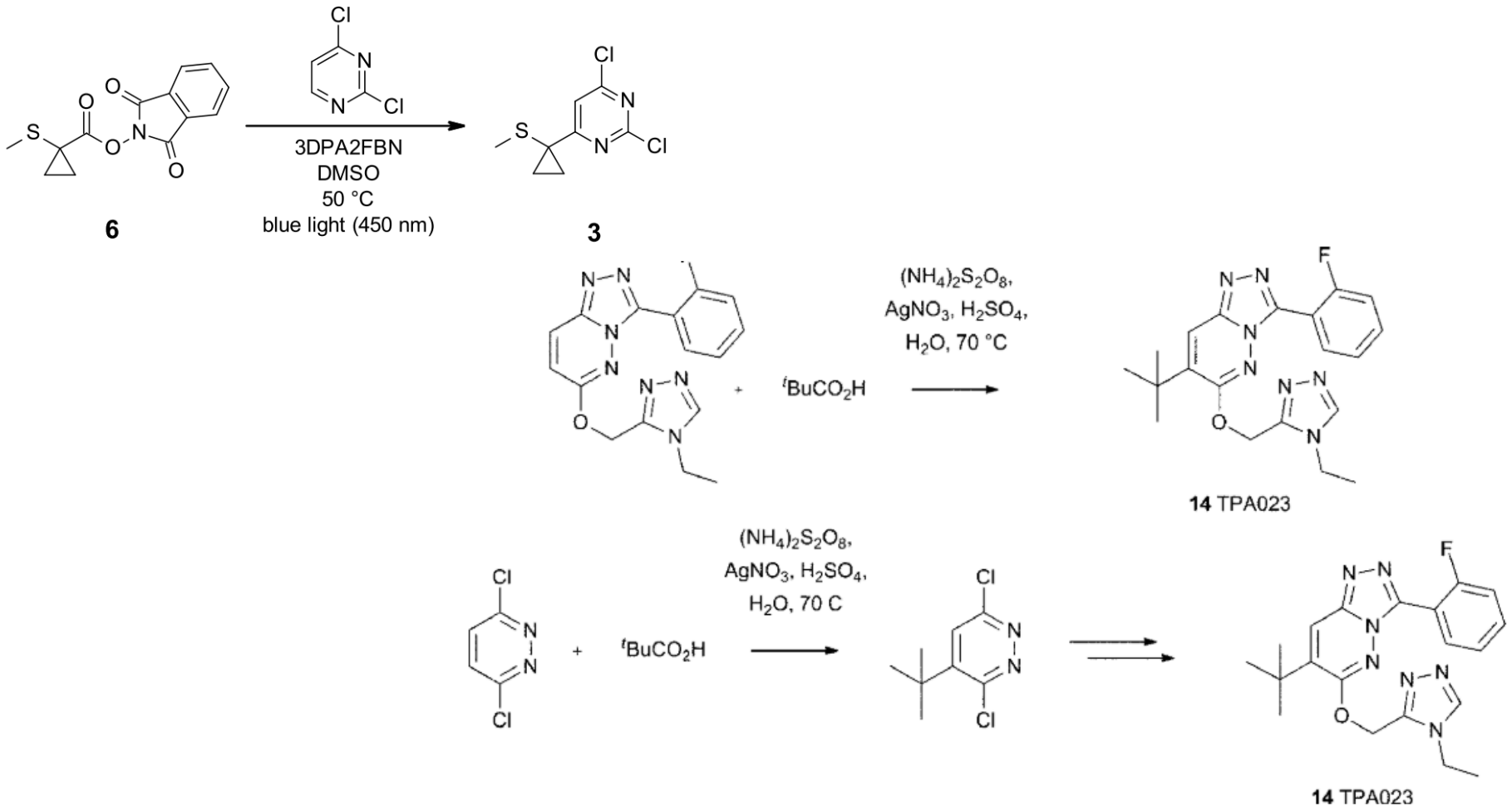
Hans-René Bjørsvik*
Borregaard Synthesis, P.O. Box 162, N-1701 Sarpsborg, Norway

Francesco Minisci
Dipartimento di Chimica del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy

Conclusions

2) The Minisci reaction is a powerful method for ***assembling desirable molecules*** (sp^2–sp^3 bonds, basic heterocycles)

Photoredox Minisci Reaction Using Large-Scale Photoflow Equipment

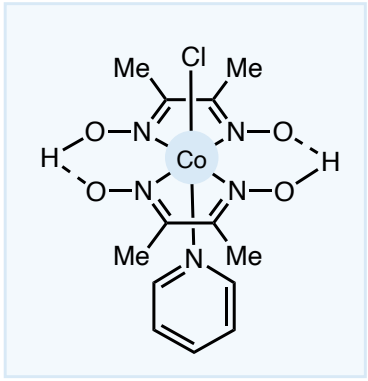


Scheme 11 Synthesis of TPA023, an α2/α3 selective $GABA_A$ agonist.[40]

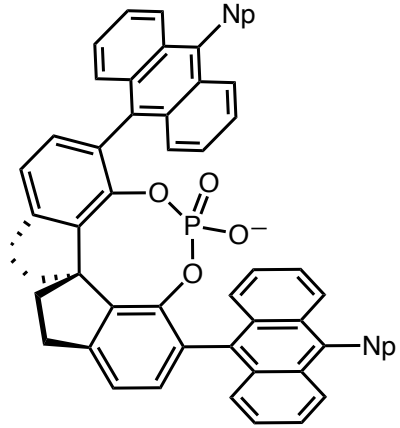
Conclusions

3) Interfacing with *modern catalysis* (Photoredox, CPA, Co H_2 evolution, electrocatalysis) has led to new innovations

Cobaloxime Hydrogen Evolution Catalyst



SPINOL Phosphoric Acid



4) *Photoredox catalysis* has drastically diversified the classes of substrates that can be used as radical precursors

5) The Minisci reaction *deserves to be respected* as more than just an afterthought in a photoredox paper!

Future Directions

- Catalytic control over regioselectivity & enantioselectivity (atroposelective?)
- Further improving reactivity of heterocycles (beyond quinoline, isoquinoline, and pyridine)
- Complementary reactivity and selectivity with other catalysts (Lewis Acids? Frustrated Lewis Pairs?)
- Catalytic, out-of-equilibrium deracemization enabled by Proton-Coupled Electron Transfer™