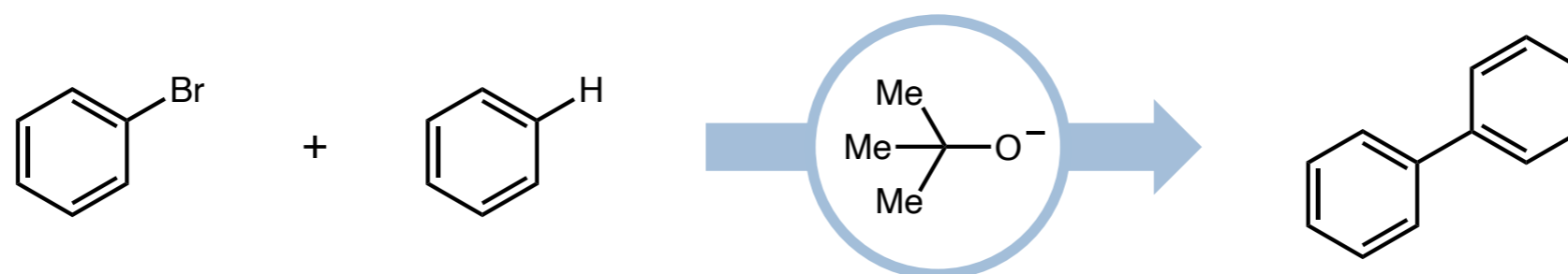


Radical Chemistry of tert-Butoxide

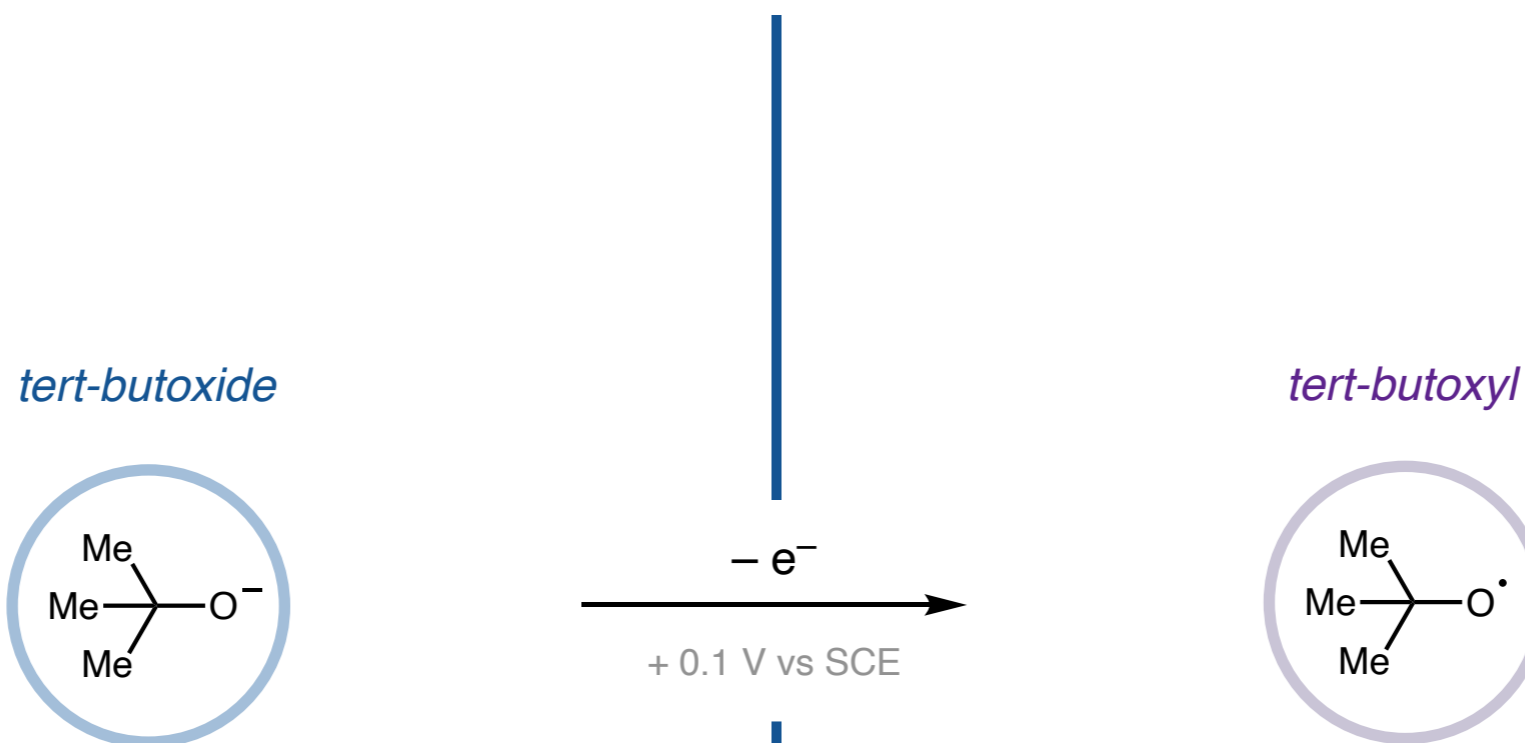


Christian Oswood
MacMillan Lab Group Meeting
March 9th, 2021

Outline

- The tert-butoxyl radical
 - HAT vs. β -scission
- Early single-electron reactivity of $t\text{-BuO}^-$
- Modern examples
 - Initial methods publication
 - Organocatalytic C–H activation cross-coupling reactions?
 - Mechanistic investigations
- $\text{KO}t\text{-Bu}$ -catalyzed $\text{C}(\text{sp}^2)\text{--H}$ silylation
 - Original publication
 - Mechanistic investigations

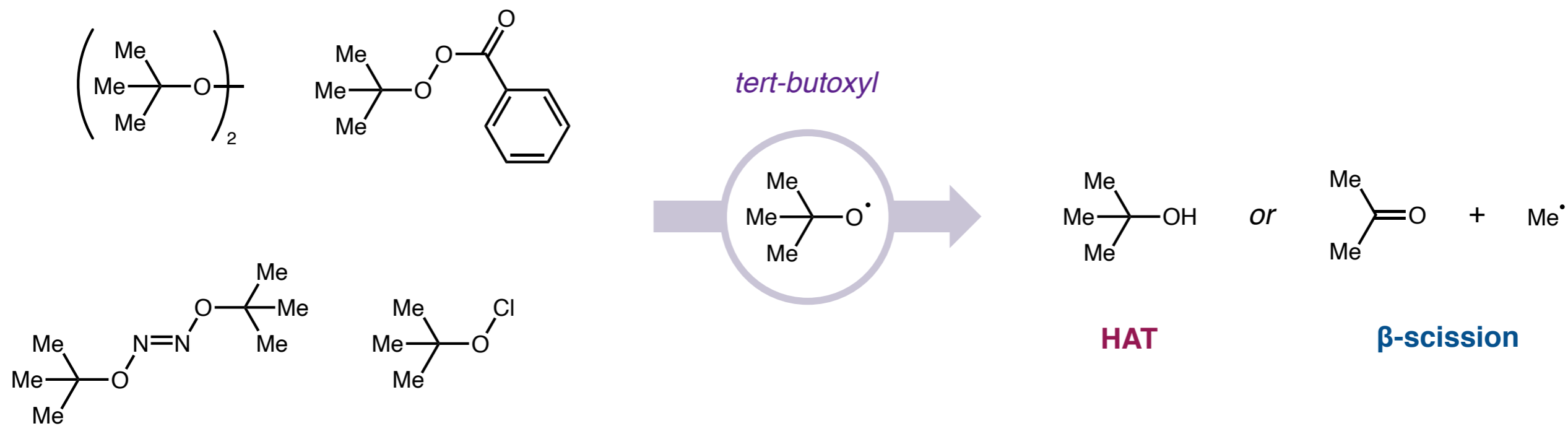
Tert-butoxide and tert-butoxyl radical



- Strong base (pKa 32.2 in DMSO)
- Bulky, non-nucleophilic

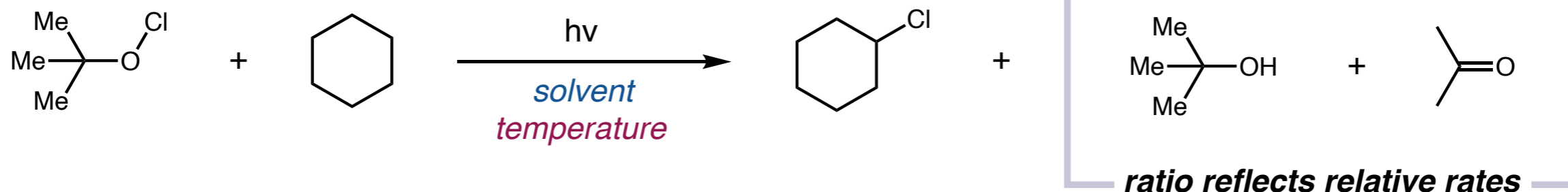
- Electrophilic radical
- Competitive HAT and β -scission

Tert-butoxyl radical



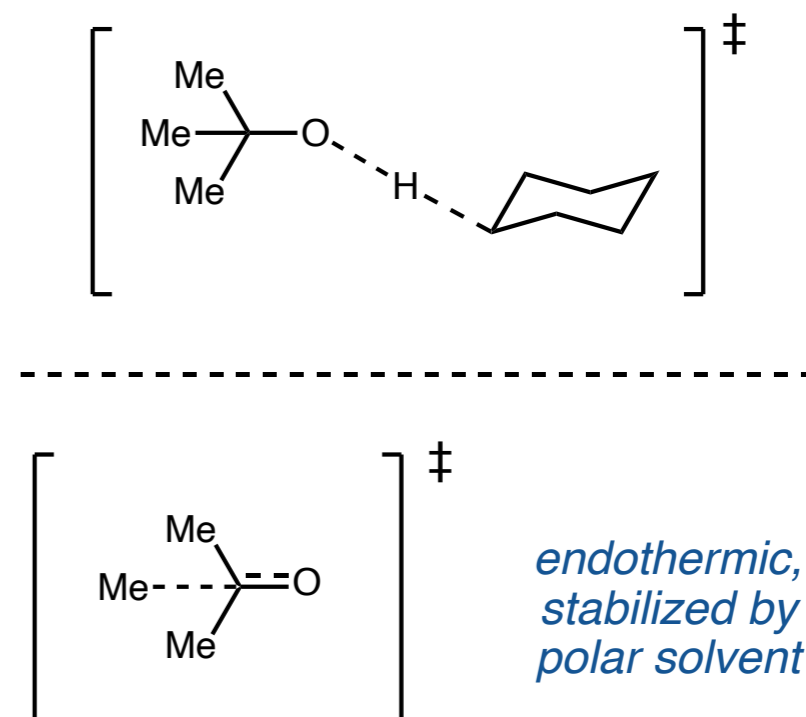
Relative rates of HAT vs. β -scission are highly solvent- and temperature- dependent

Tert-butoxyl radical: β -scission or HAT?



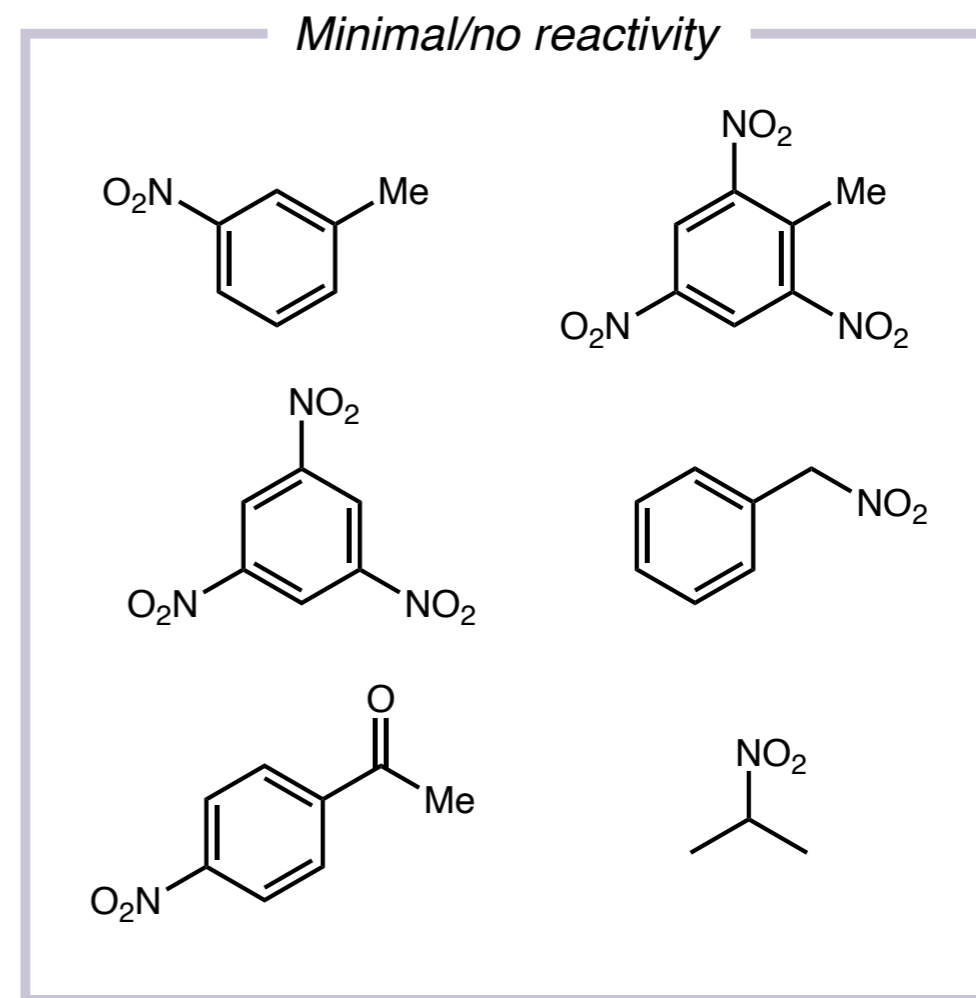
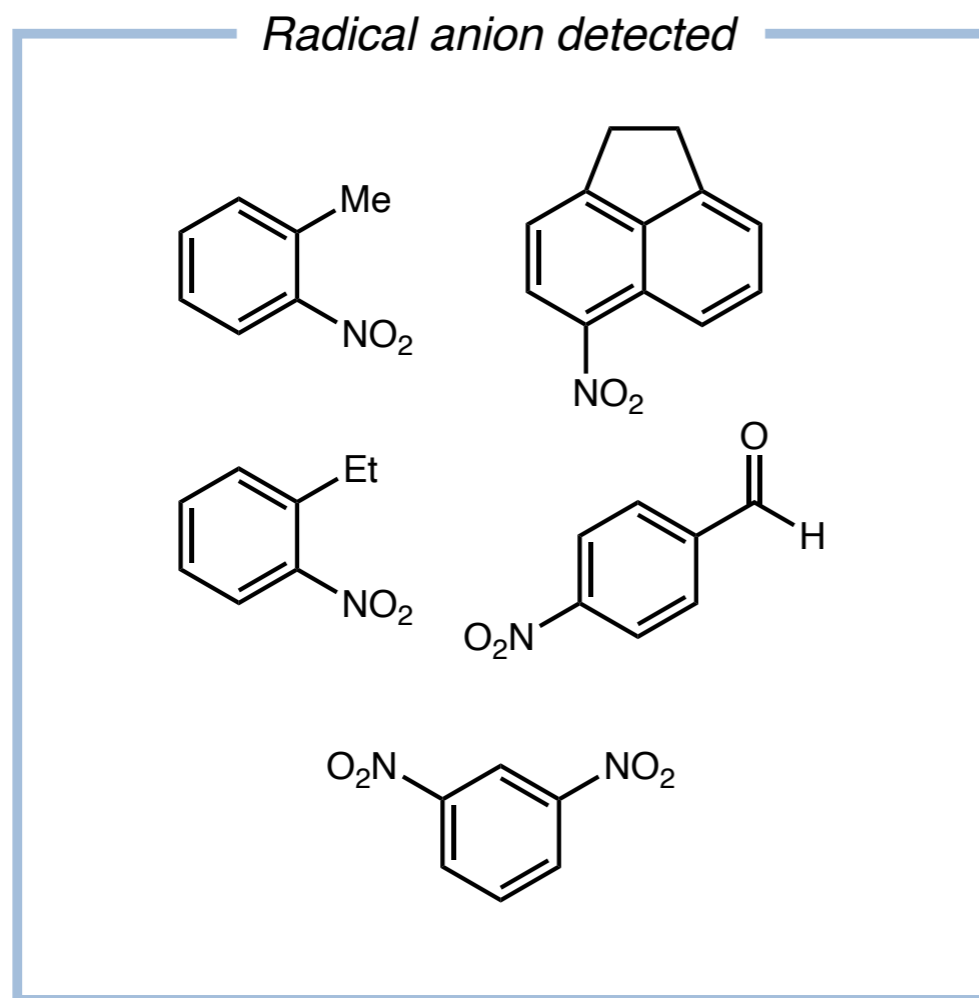
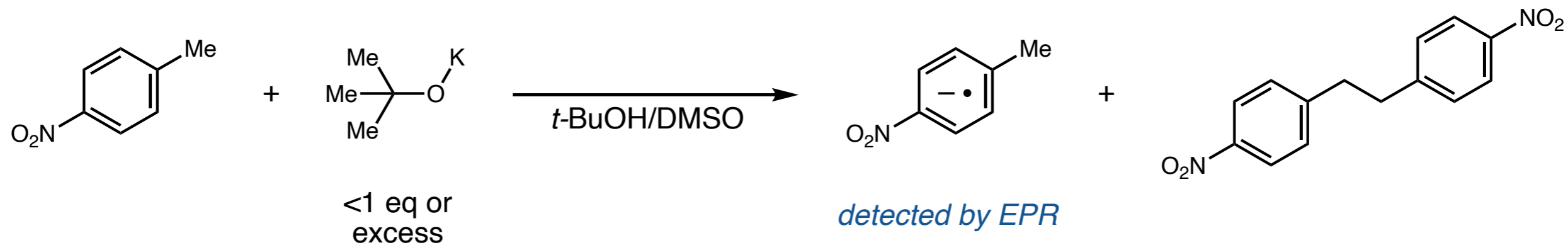
Solvent	<i>t</i> -BuOH/acetone				
	100°	70°	40°	25°	0°
None			202, 346, 584, 982 ^e		
CFC ₂ CF ₂ Cl	4.29	12.2	52.8	99	487
CH ₃ CN	(0.68) ^f	2.33	8.12	19.8	81.9
Benzene	2.82	7.62	24.7	48.6	207
<i>m</i> -C ₆ H ₄ Cl ₂	2.81	7.07	24.3	45.7	178
C ₆ H ₅ Br	2.90	7.33	25.4	45.2	162
<i>o</i> -C ₆ H ₄ Cl ₂	2.15	5.82	19.2	35.2	120
C ₆ H ₅ CN	1.90	4.87	16.9	33.4	109
C ₆ H ₅ F	2.73	6.94	22.4	43.4	127
C ₆ H ₅ Cl	2.65	5.62	16.4	28.6	91.7
CH ₃ COOH ^g	(0.65) ^f	1.34	2.90	4.87	12.6
C ₂ Cl ₄	4.14	11.1	39.0	87.8	293
<i>trans</i> -C ₂ H ₂ Cl ₂ ^g	2.26	5.55	14.2	33.0	98.9
C ₂ HCl ₂	2.01	4.87	14.2	24.6	75.7
<i>cis</i> -C ₂ H ₂ Cl ₂	1.57	3.74	9.12	16.9	52.2

Differential stabilization of transition states:



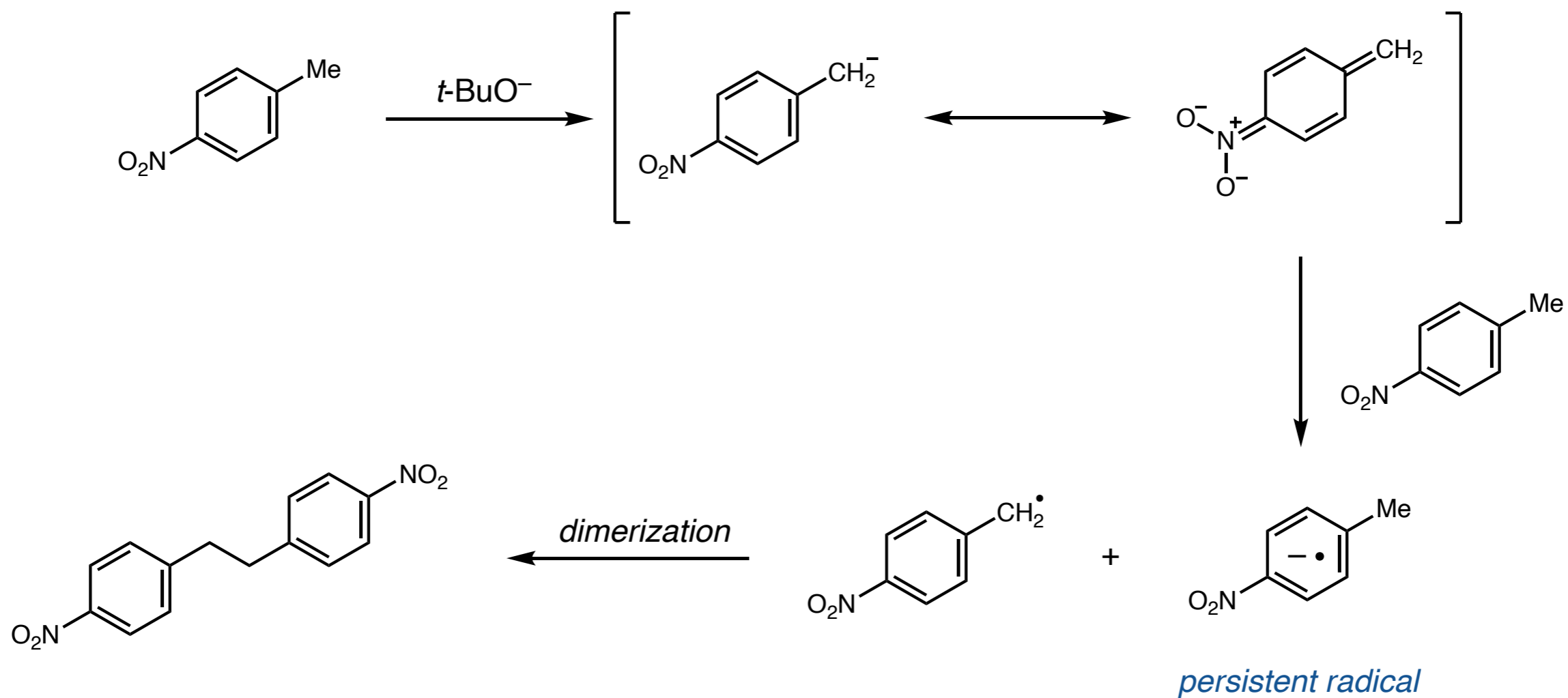
Less polar solvents favor HAT – β -scission typically disfavored

Initial publications: radical anions from KOt-Bu



Proposed mechanism

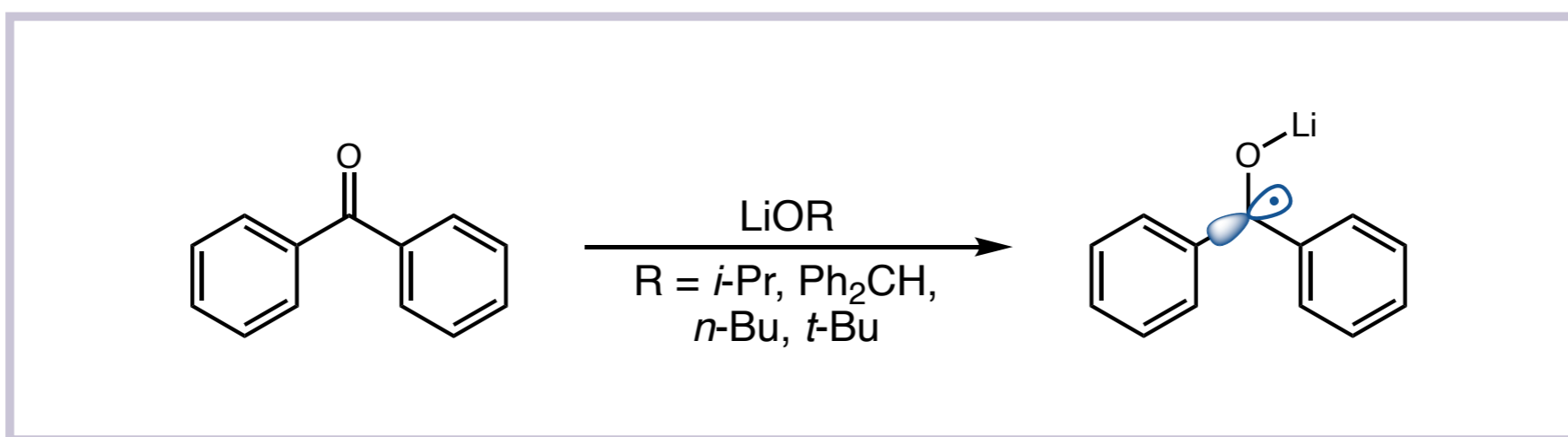
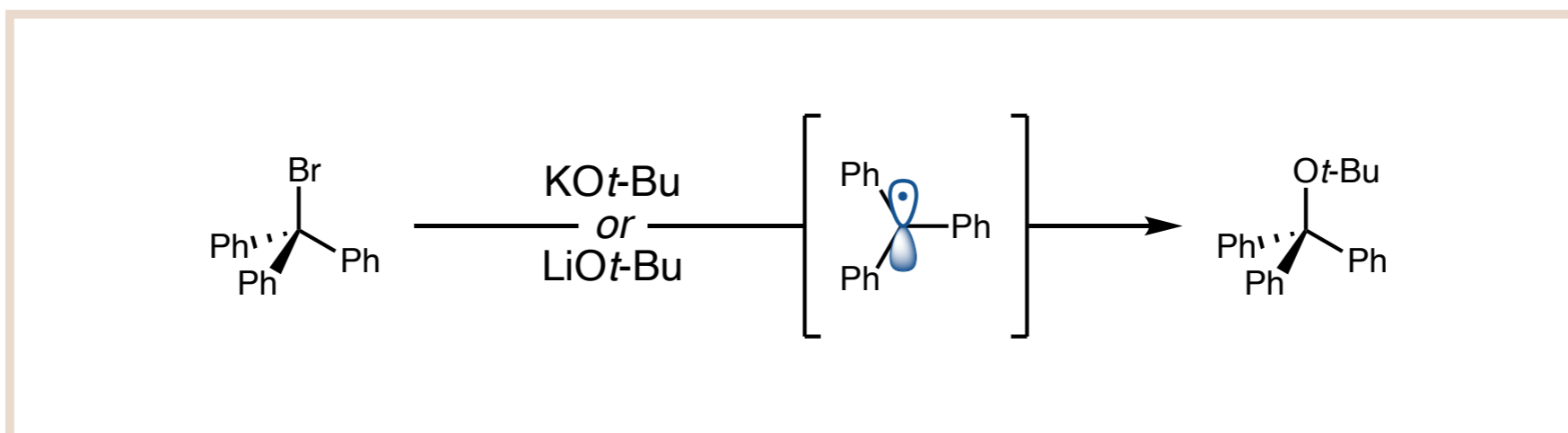
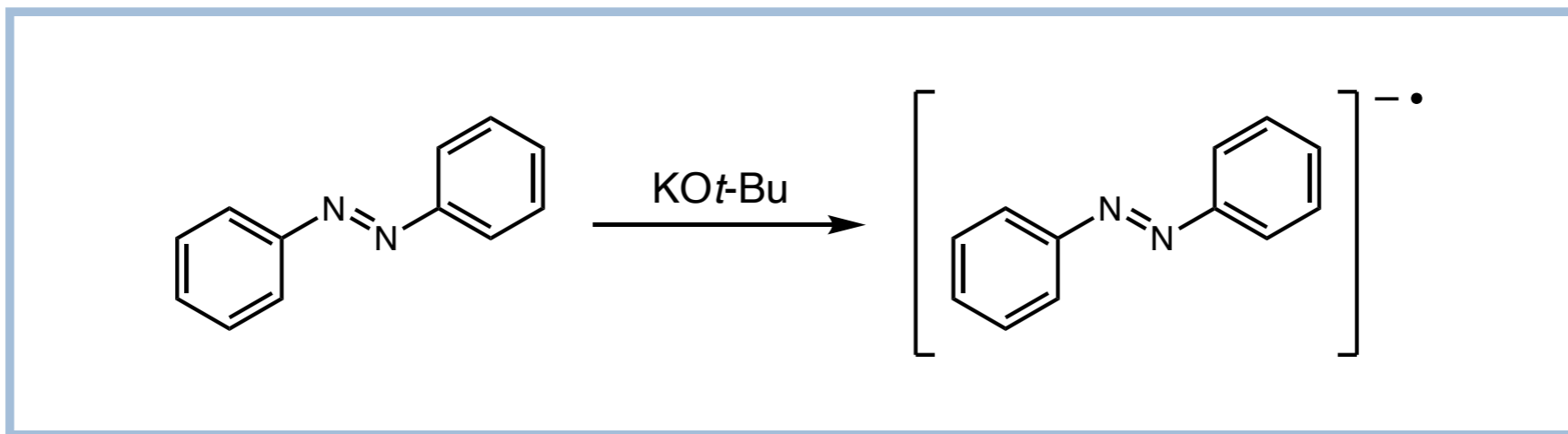
Deprotonation/disproportionation proposed for alkyl-substituted aromatics:



Russell, G. A.; Janzen, E. G. *J. Am. Chem. Soc.* **1962**, *84*, 4153.

Russell, G. A.; Janzen, E. G. *J. Am. Chem. Soc.* **1967**, *89*, 300.

Additional reductions by alkoxides

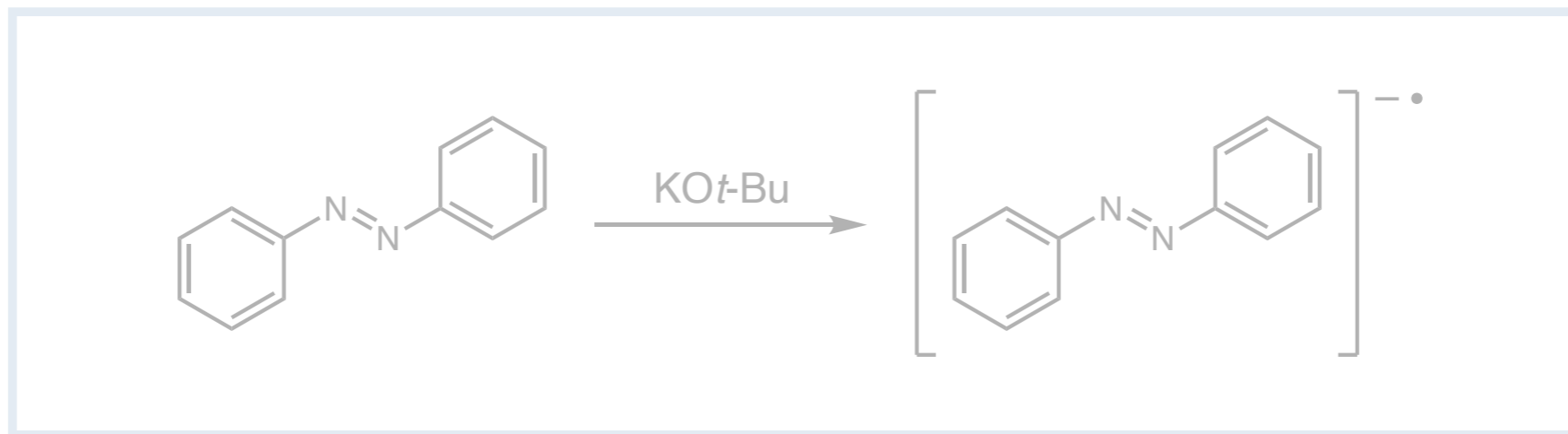


Russell, G. A.; Konaka, R.; Strom, E. T.; Danen, W. C.; Chang, K.-Y.; Kaupp, G. *J. Am. Chem. Soc.* **1968**, *90*, 4646.

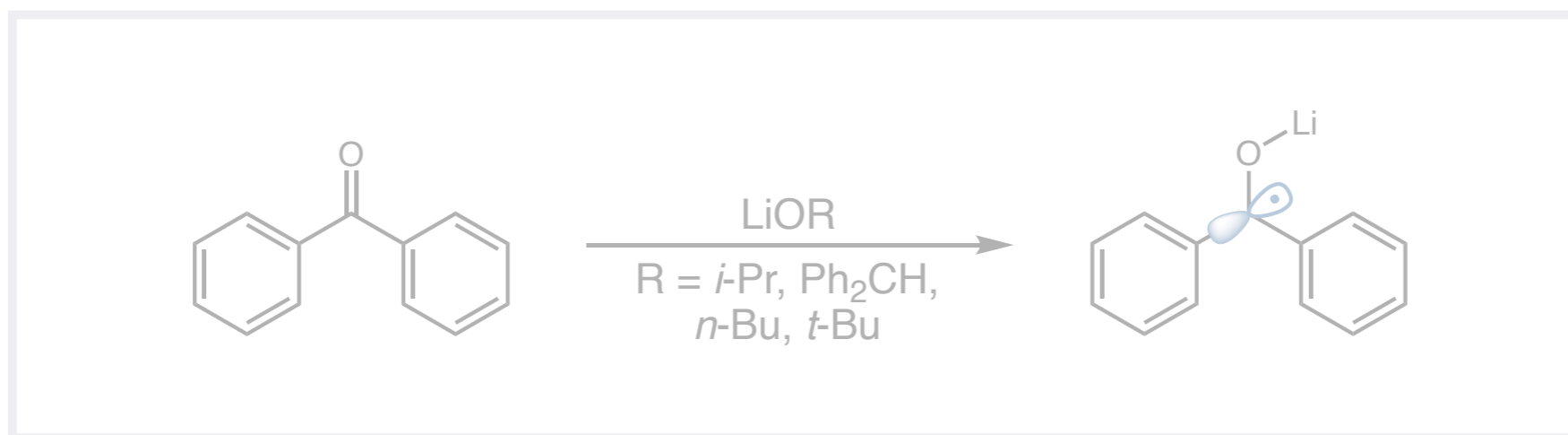
Ashby, E. C.; Goel, A. B.; DePriest, R. N. *J. Org. Chem.* **1981**, *11*, 2429.

Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1986**, *19*, 3593.

Additional reductions by alkoxides



No mechanisms proposed for reduction of substrates lacking acidic C–H bonds

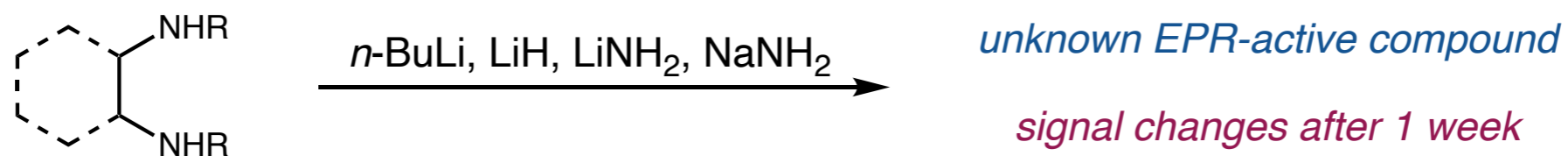


Russell, G. A.; Konaka, R.; Strom, E. T.; Danen, W. C.; Chang, K.-Y.; Kaupp, G. *J. Am. Chem. Soc.* **1968**, *90*, 4646.

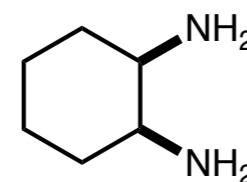
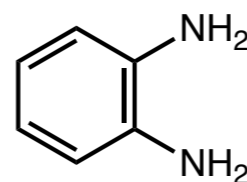
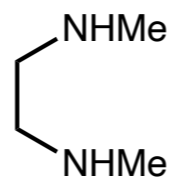
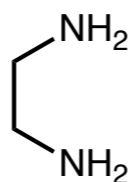
Ashby, E. C.; Goel, A. B.; DePriest, R. N. *J. Org. Chem.* **1981**, *11*, 2429.

Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1986**, *19*, 3593.

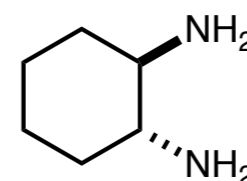
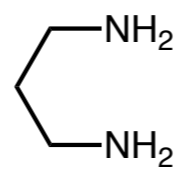
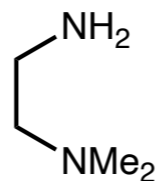
Radical chemistry of diamines and strong bases



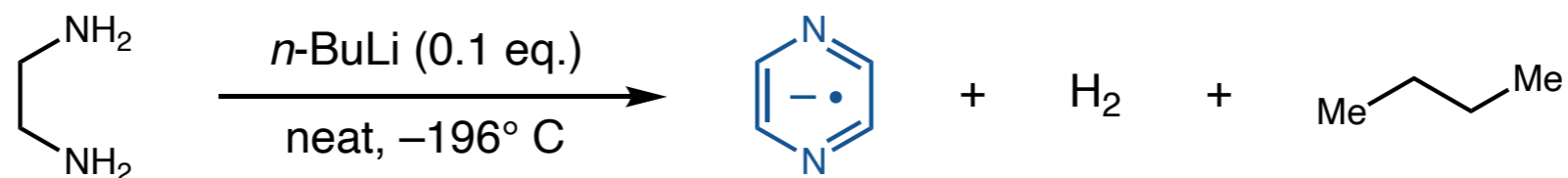
signal observed



no signal

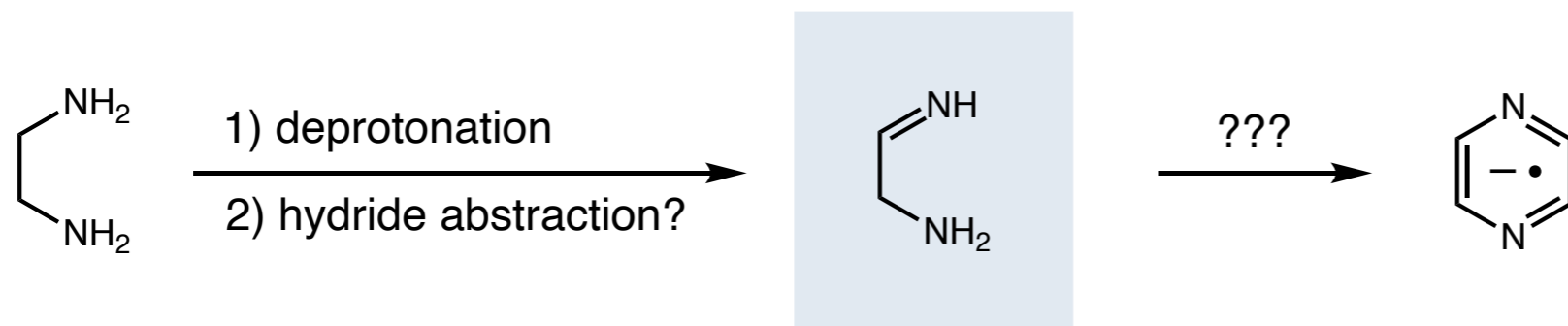


Radical chemistry of diamines and strong bases



initial signal identified as pyrazine radical anion

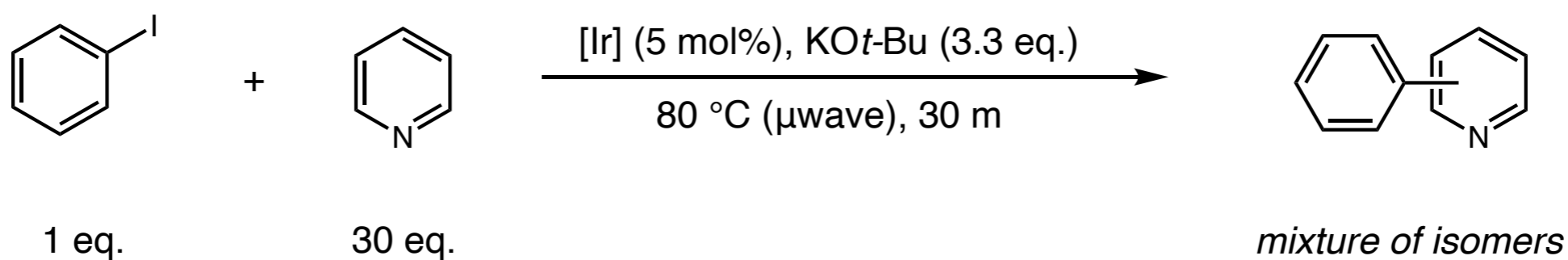
second signal tentatively assigned as dihydropyrazine isomer



“The mode of formation of pyrazine... would be largely speculation at this time.”

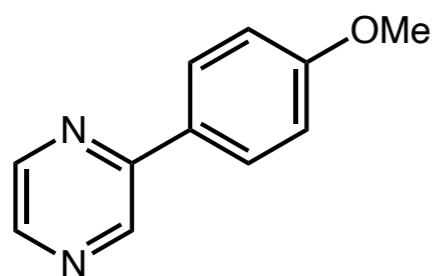
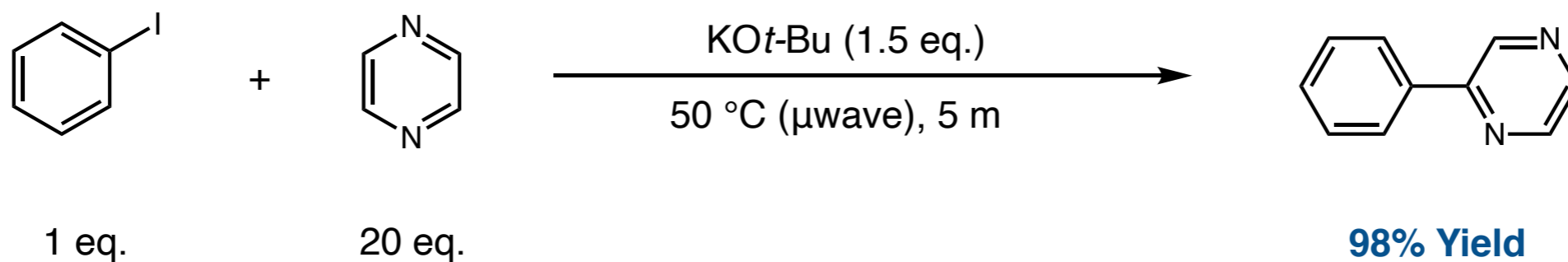
imine proposed as key intermediate

Initial methods publication

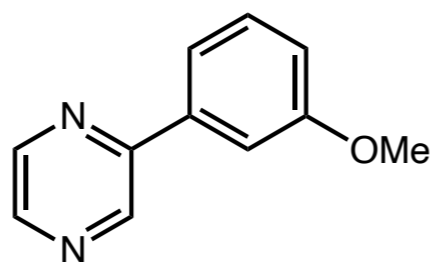


Catalyst	Yield
$[\text{Cp}^*\text{IrHCl}]_2$	30%
$[\text{IrCl}(\text{cod})]_2$	17%
$\text{IrCl}(\text{CO})(\text{PPh}_3)_2$	41%
$(\text{NH}_4)_3\text{IrCl}_6$	26%
<i>none</i>	39%

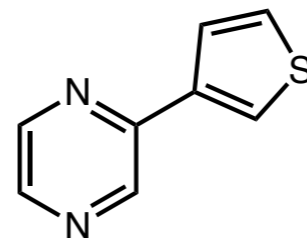
Scope



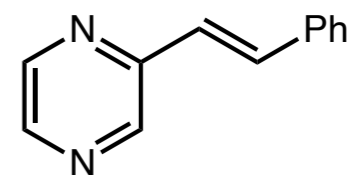
83% Yield



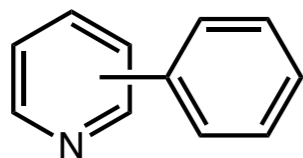
64% Yield



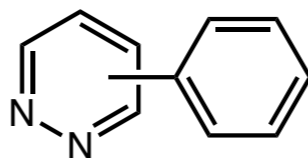
71% Yield



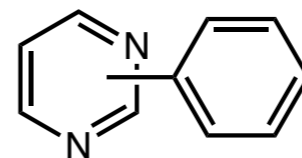
33% Yield



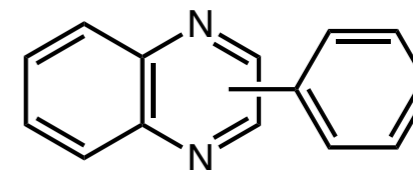
63% Yield



56% Yield



59% Yield



75% Yield

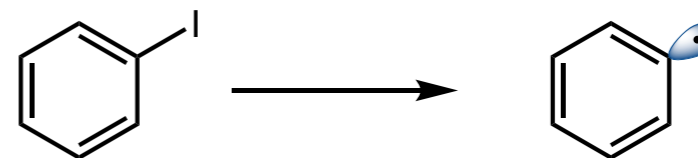
What's going on?

Trace metals?

- All glassware thoroughly cleaned
- All reagents “purified extensively”
- KO t -Bu sublimed, analyzed by ICP-AES
 - Trace Si, Al, Ca detected (<1 ppm)
 - Pd, Rh, Ru below detection limits

Mechanism?

- Aryl radical intermediate proposed

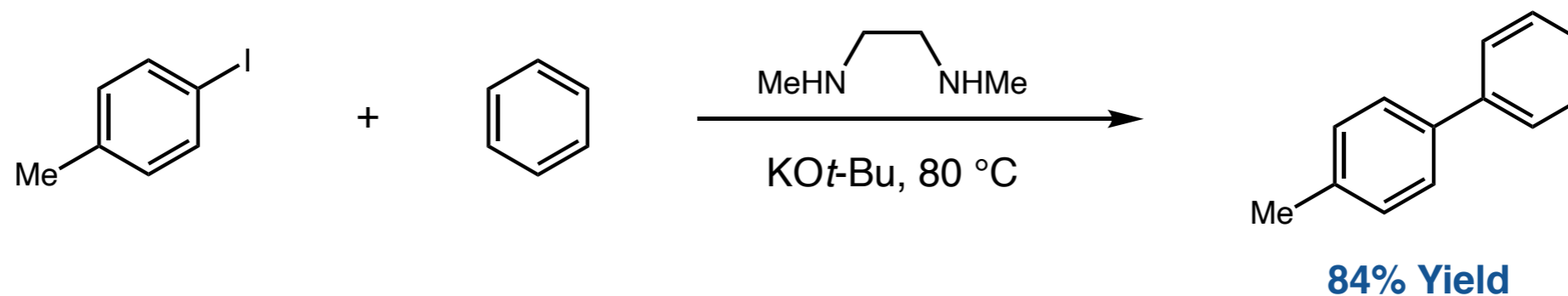


- Radical scavengers (TEMPO, galvinoxyl) completely terminate reactivity

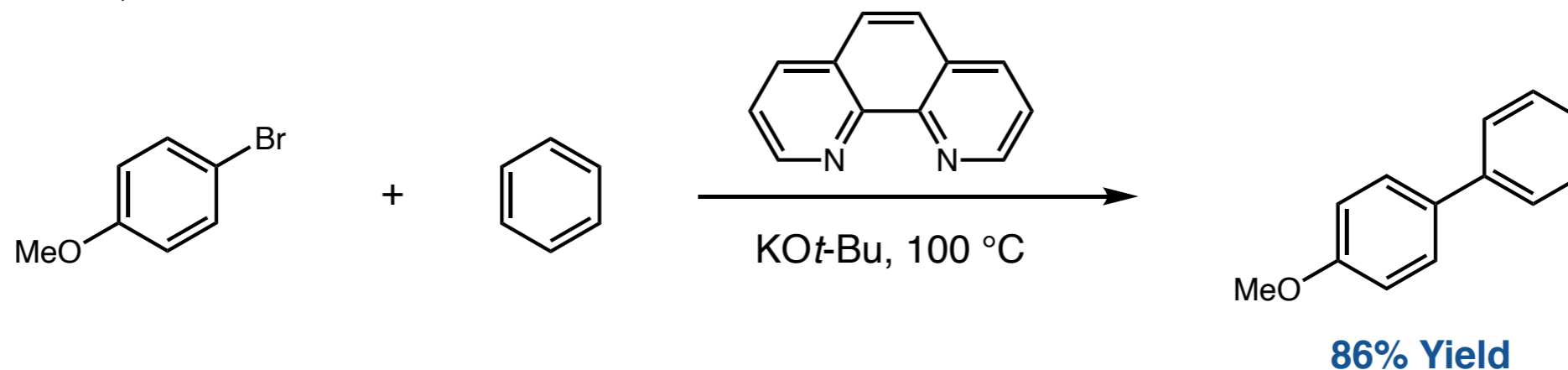
“The discovered new reactivity of t -butoxides should raise concerns to the synthetic community. Given the occasional use of t -butoxide bases and haloarenes in transition-metal-catalyzed arylation reactions... great care is urged in the analysis and interpretation of such reactions.”

2010: The year of organocatalytic C–H activation cross-coupling

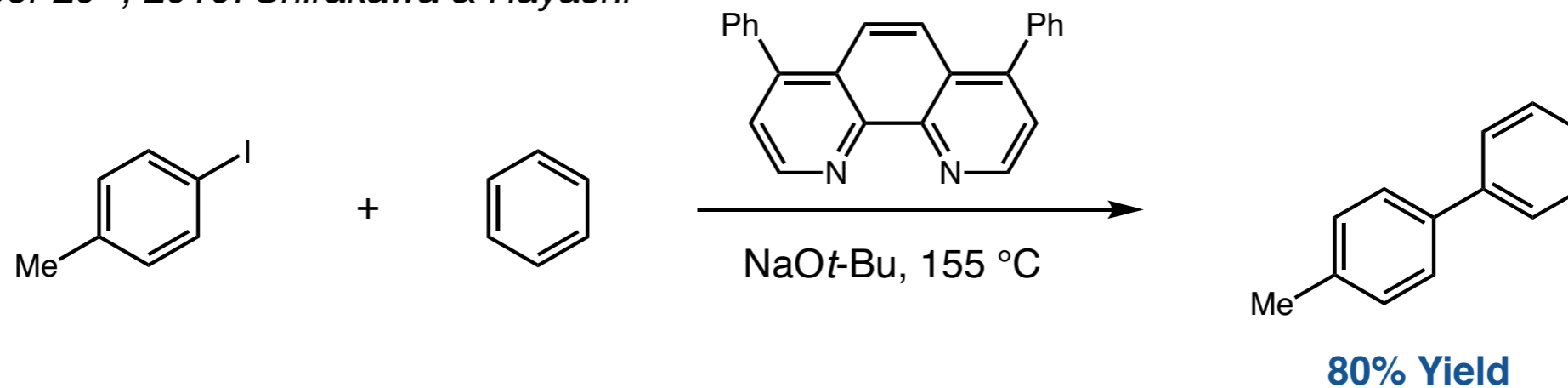
August 2nd, 2010: Lei



October 3rd, 2010: Shi



October 20th, 2010: Shirakawa & Hayashi

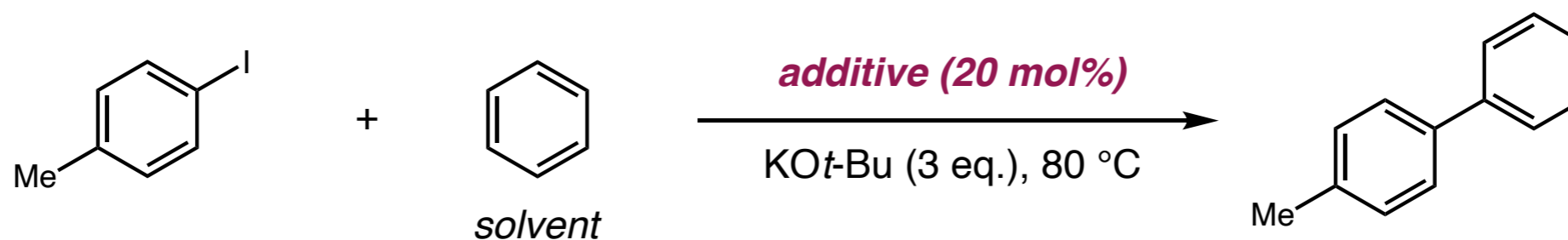


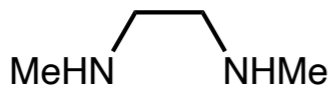
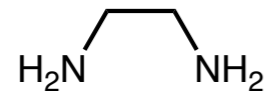
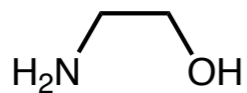
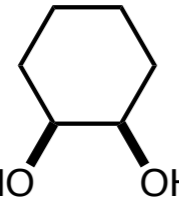
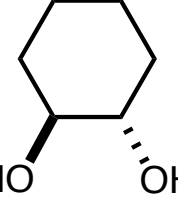
Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737.

Sun, C.-L.; Li, H.; Yi, D.-G.; Yi, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J.; *Nat. Chem.* **2010**, *2*, 1044.

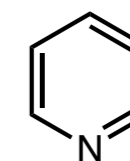
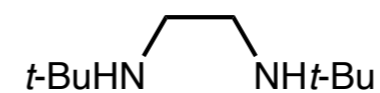
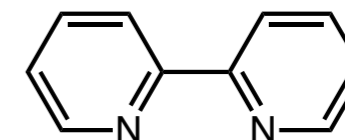
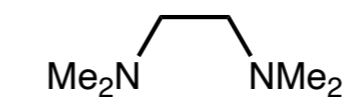
Shirakawa, E.; Itoh, K.; Higashina, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537.

Lei: DMEDA as additive



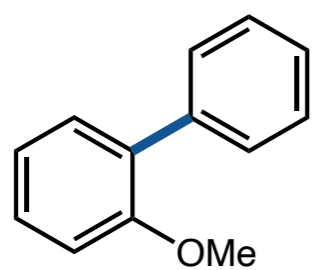
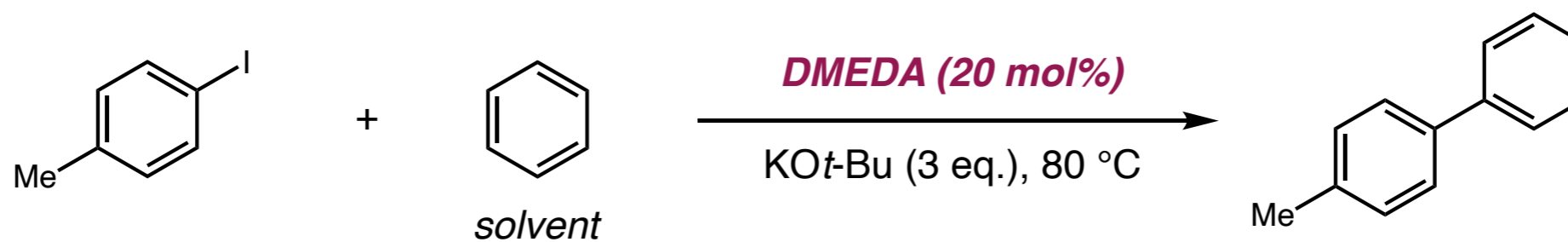
Additive	Yield
—	trace
	84%
	81%
	67%
	81%
	22%

Ineffective additives:

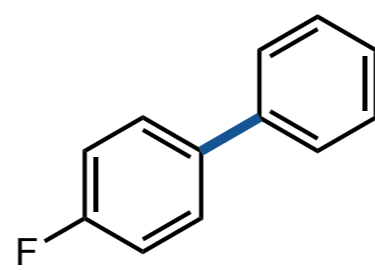


X-H bond necessary for reactivity?

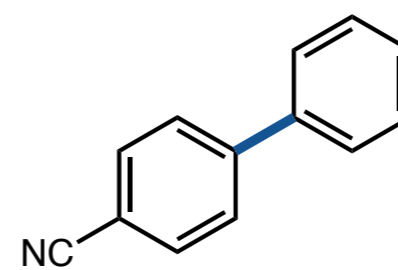
Lei: DMEDA as additive



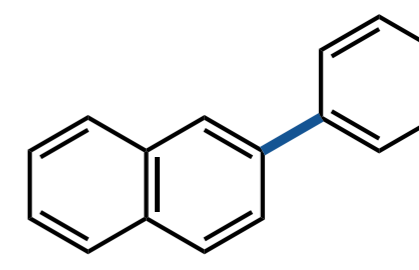
60% Yield



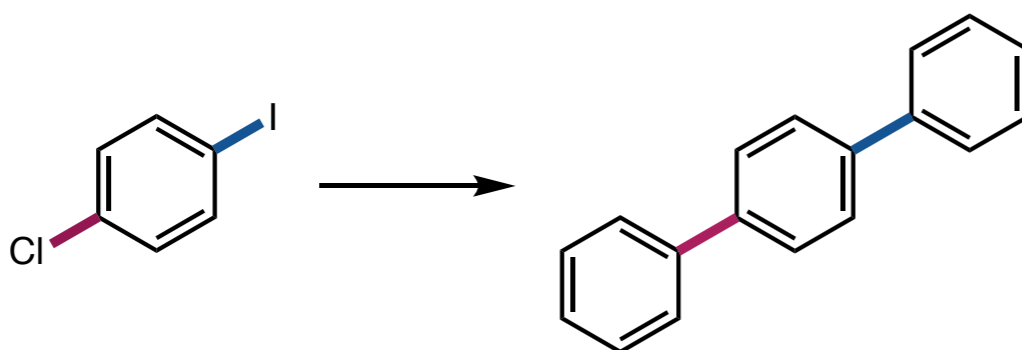
68% Yield



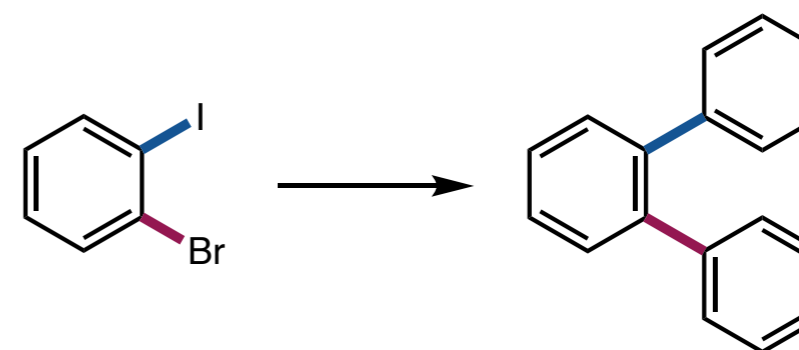
71% Yield



88% Yield

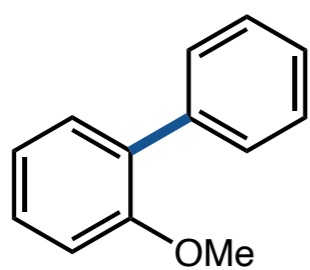
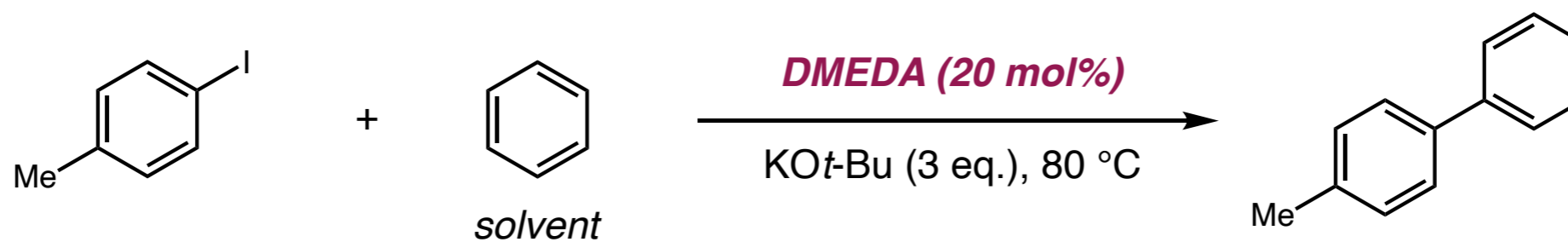


71% Yield

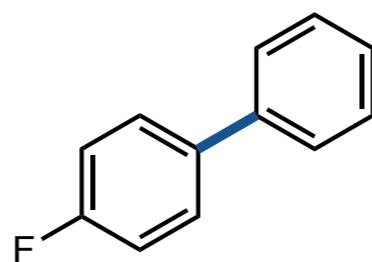


30% Yield

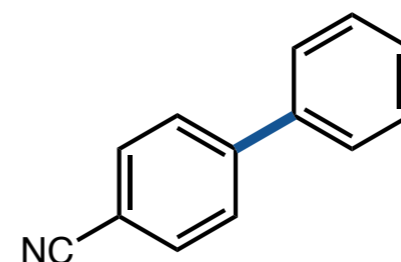
Lei: DMEDA as additive



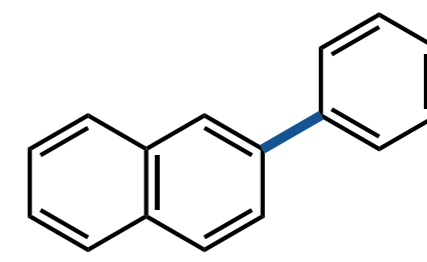
60% Yield



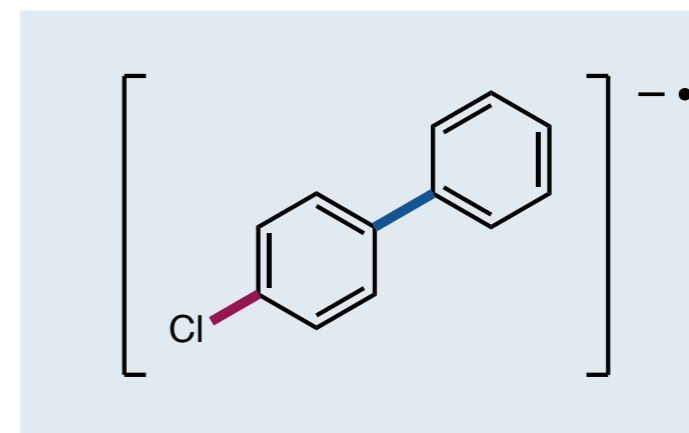
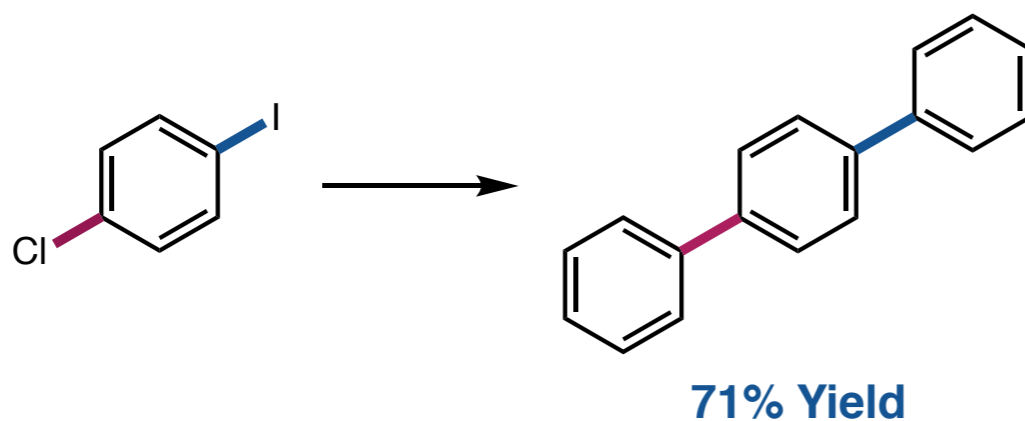
68% Yield



71% Yield



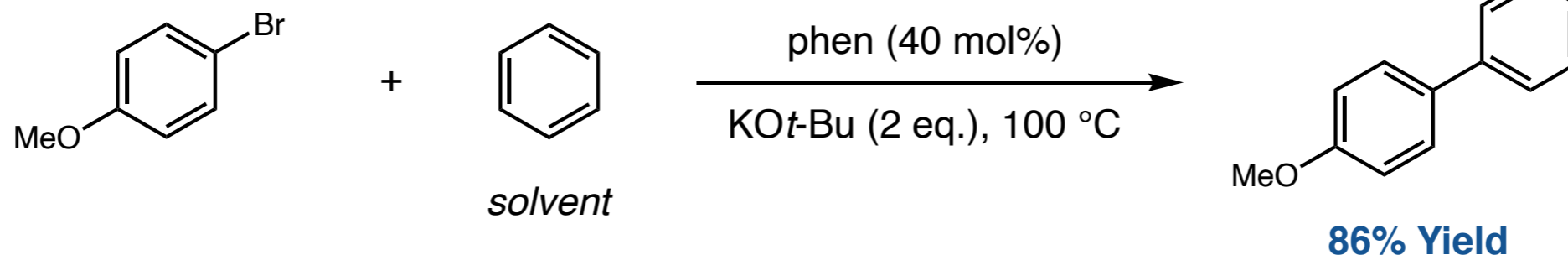
88% Yield



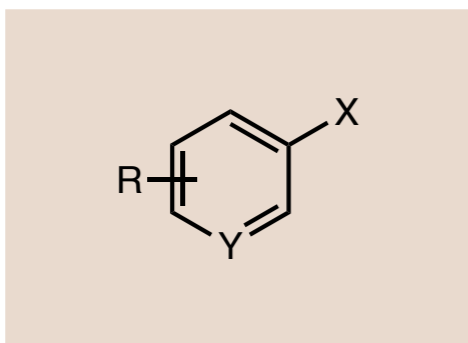
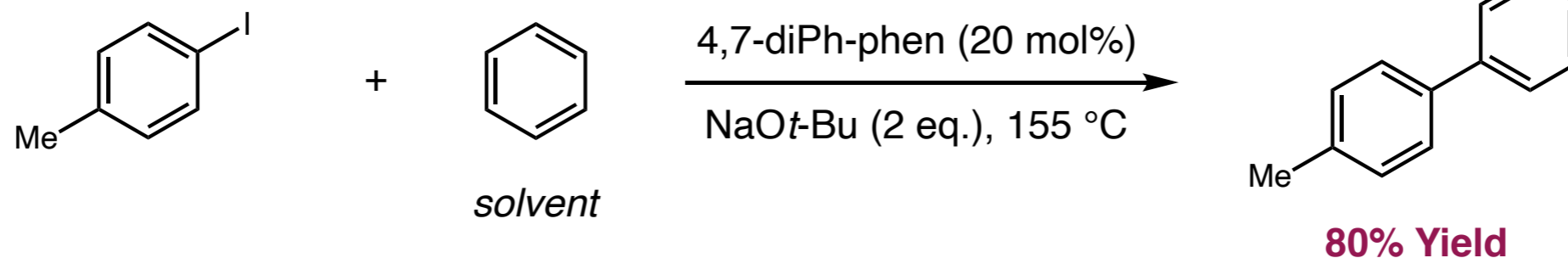
Aryl radical anion proposed as intermediate

Shi, Shirakawa & Hayashi: phen additive

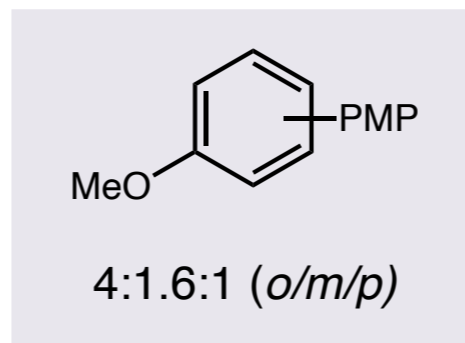
Shi's conditions:



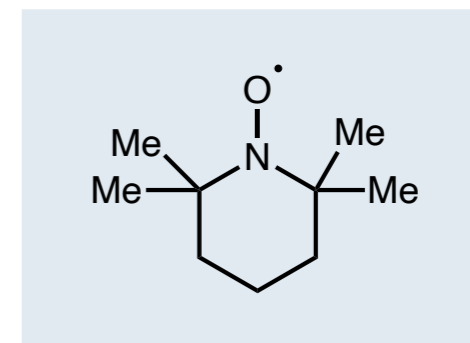
Shirakawa & Hayashi's conditions:



**(hetero)aryl iodides, bromides
competent coupling partners**



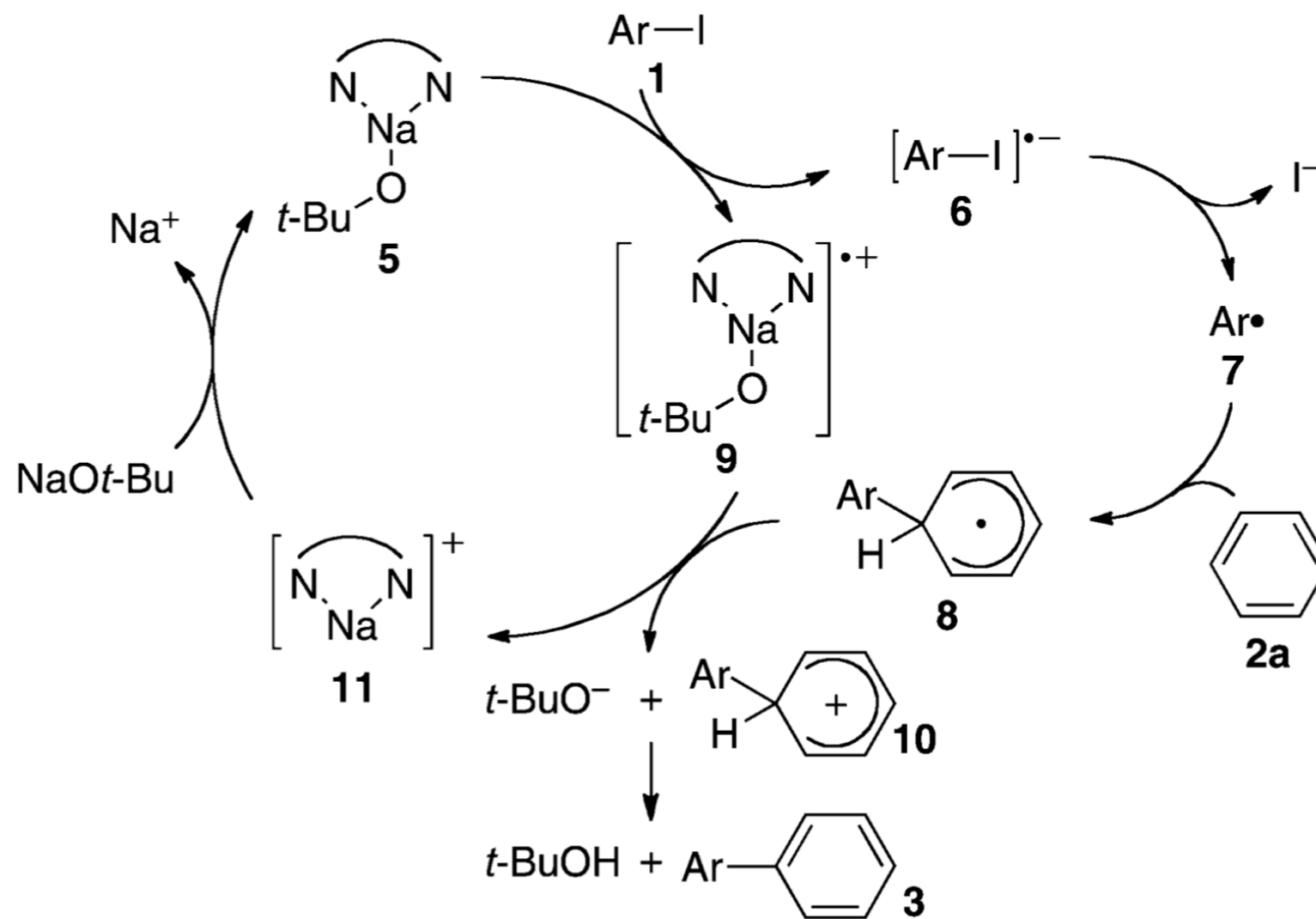
**C-H coupling partners show
low regioselectivity**



**no reactivity with
added radical inhibitors**

Shi, Shirakawa & Hayashi: phen additive

Shirakawa & Hayashi's proposed mechanism:



Mechanistic investigations and critiques

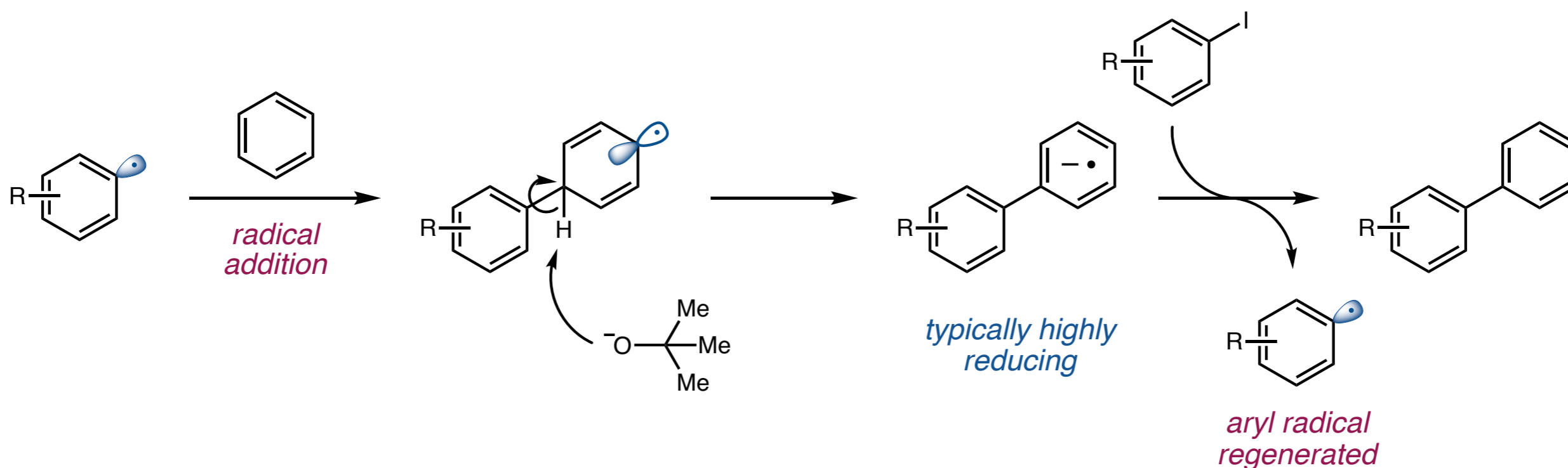
- All three transformations have very similar conditions, scopes
- Described as organocatalysis and C–H activation without strong confirmation of mechanism
- Diamine additive critical for effective reaction, but role not fully described



Result: numerous mechanistic investigations/critiques

Mechanistic investigations and critiques

April 2011: Studer and Curran propose a unified radical chain mechanism



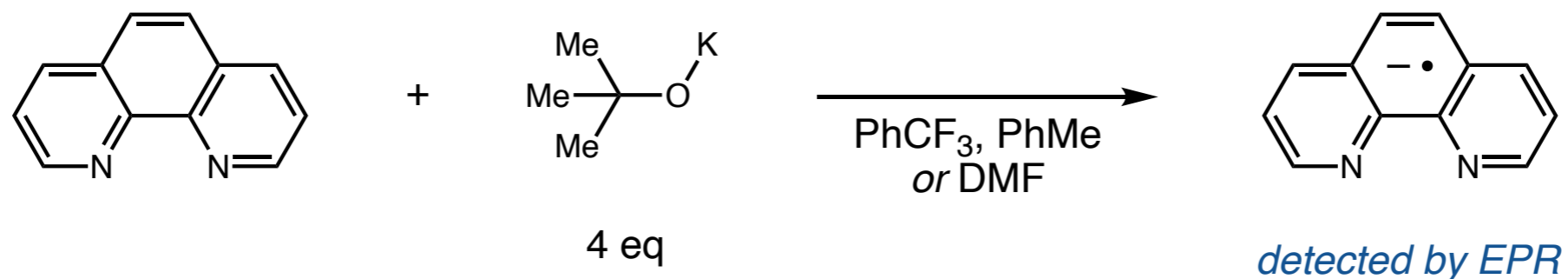
"[Initiation] steps are typically endothermic and can even be difficult to identify when the chains are long. The oxidation of (complexed) tert-butoxide is a plausible initiation step."

Mechanistic investigations and critiques

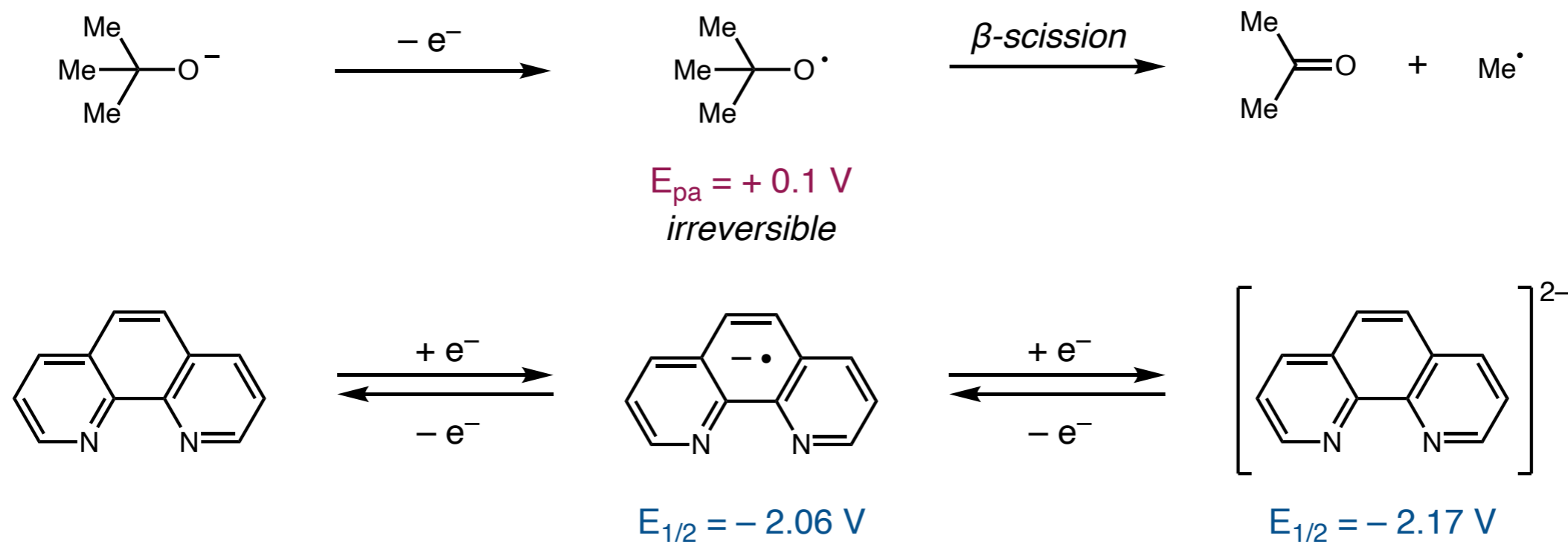
Regardless of chain character, how does aryl radical generation occur?

Aryl radical generation with phen

Reduction of phen by KOt-Bu:

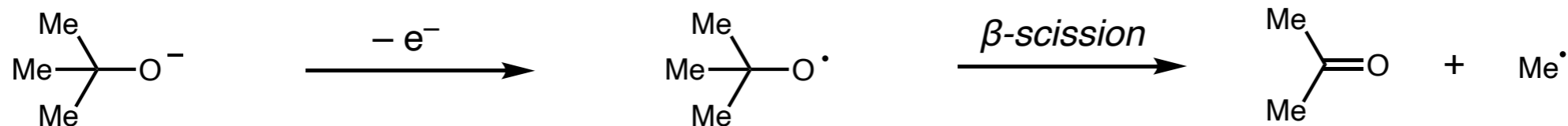


CV studies show outer-sphere ET is unfavorable: inner-sphere process?

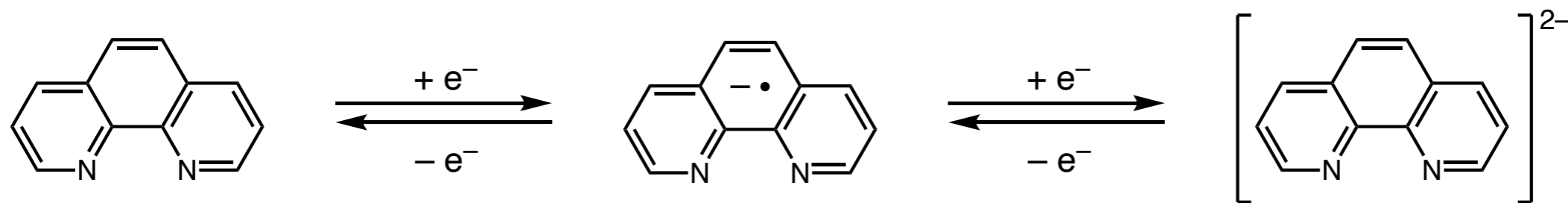


Aryl radical generation with phen

CV studies show outer-sphere ET is unfavorable: inner-sphere process?



$E_{pa} = +0.1 \text{ V}$
irreversible



$E_{1/2} = -2.06 \text{ V}$

$E_{1/2} = -2.17 \text{ V}$

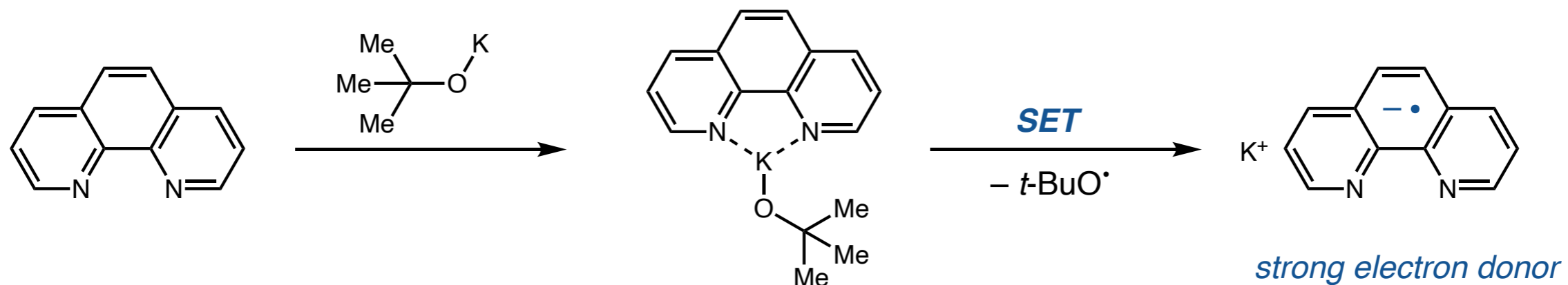
Potentials for aryl iodide line up, aryl bromide less favorable:



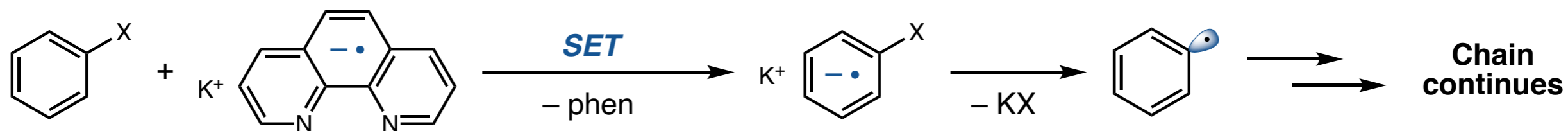
$E_{pc} = -1.72 \text{ V}$

$E_{pc} = -2.72 \text{ V}$

Aryl radical generation with phen

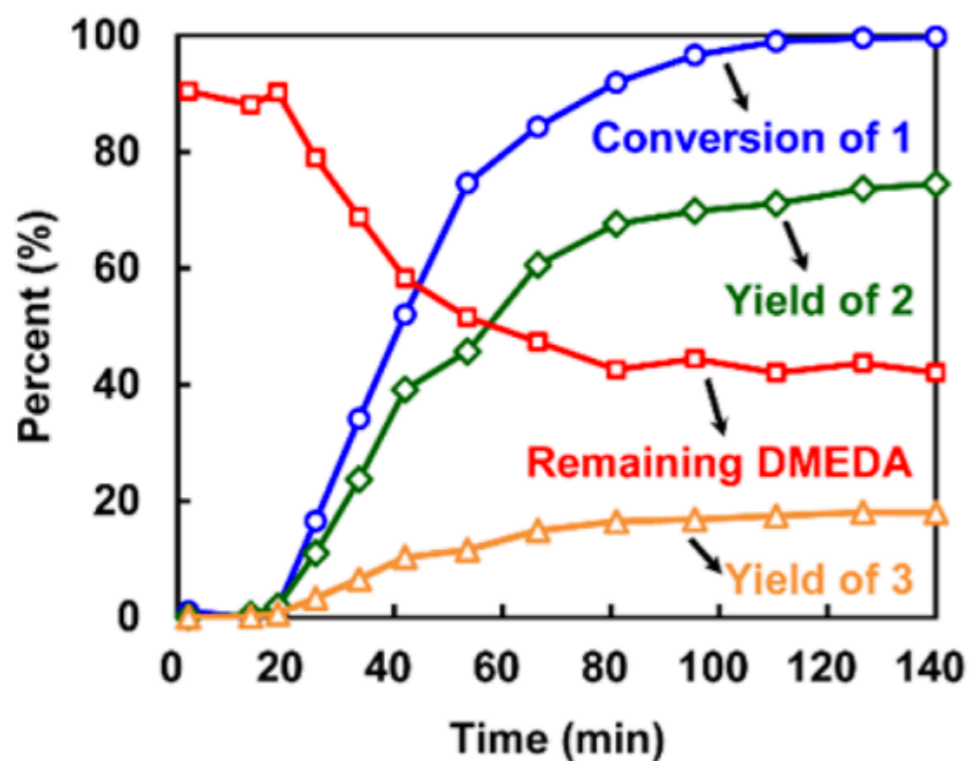
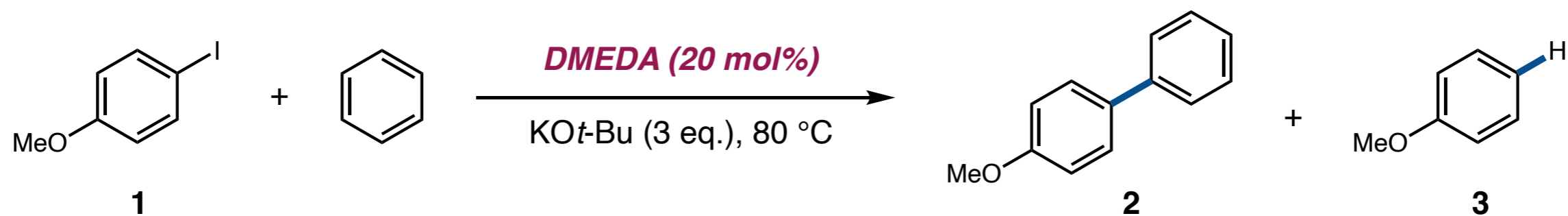


Phenanthroline acts as an electron relay to facilitate aryl halide reduction

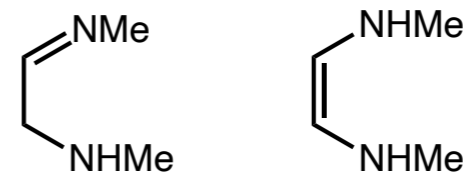


- Reduction of aryl halide proposed to potentially occur from phen^{2-}

Aryl radical generation with DMEDA

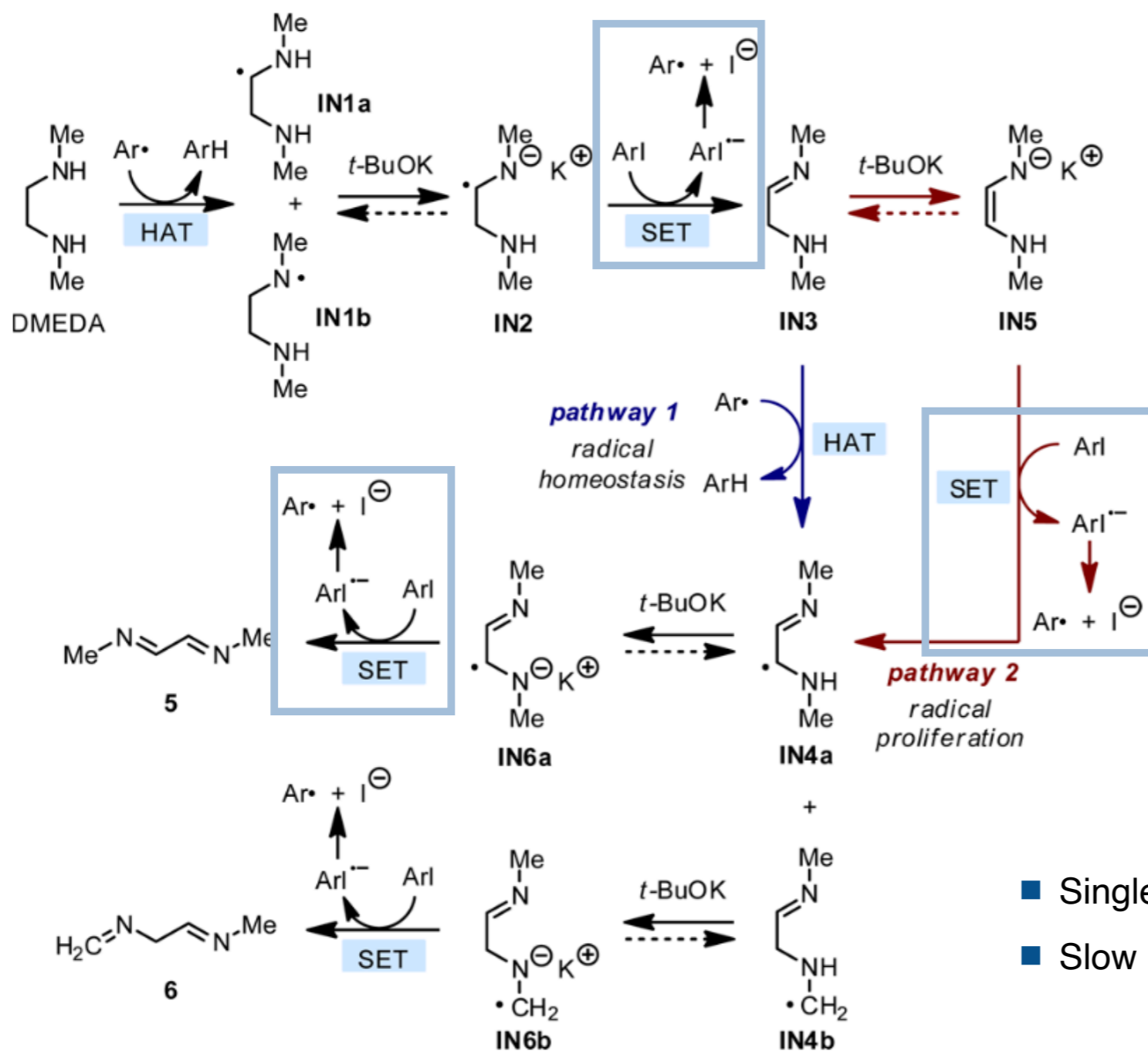


- Induction period followed by rapid reactivity
- Diamine consumed in proportion to protodehalogenation
- Imine/enamine implicated as potential e^- , H^\bullet donors



Aryl radical generation with DMEDA

Proposed radical initiation network:



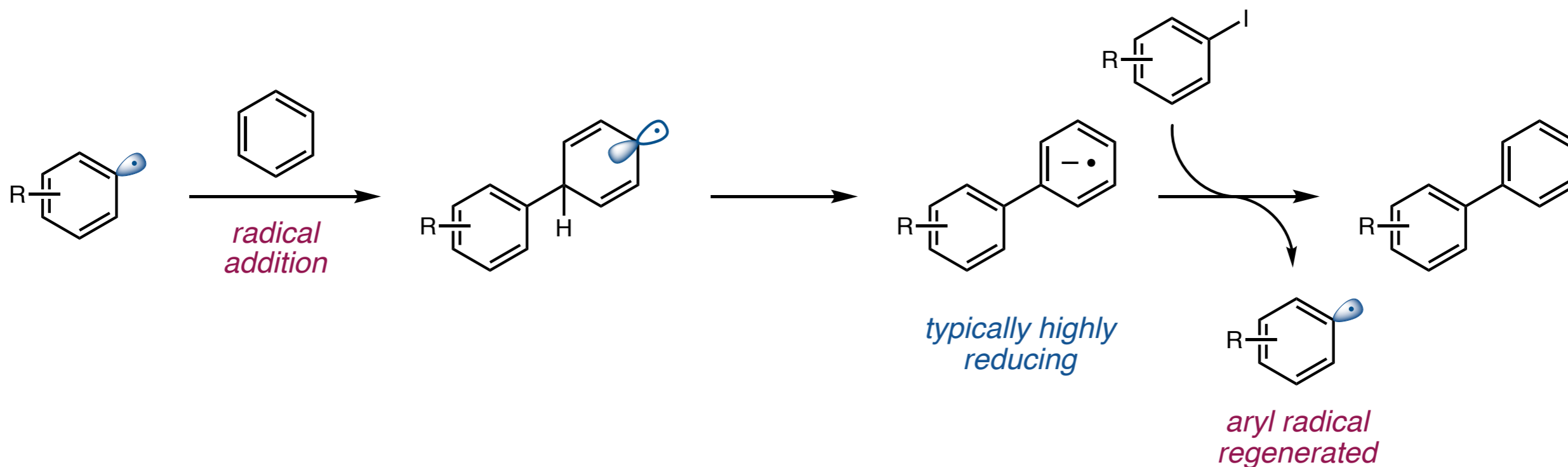
Results supported by:

- computational models
- kinetic experiments
- competence of monoimine

- Single molecule of DMEDA generates 2-3 eq. of Ar•
- Slow initial production of Ar• results in induction period

Mechanistic investigations: conclusions

Radical chain mechanism: base-promoted homolytic aromatic substitution



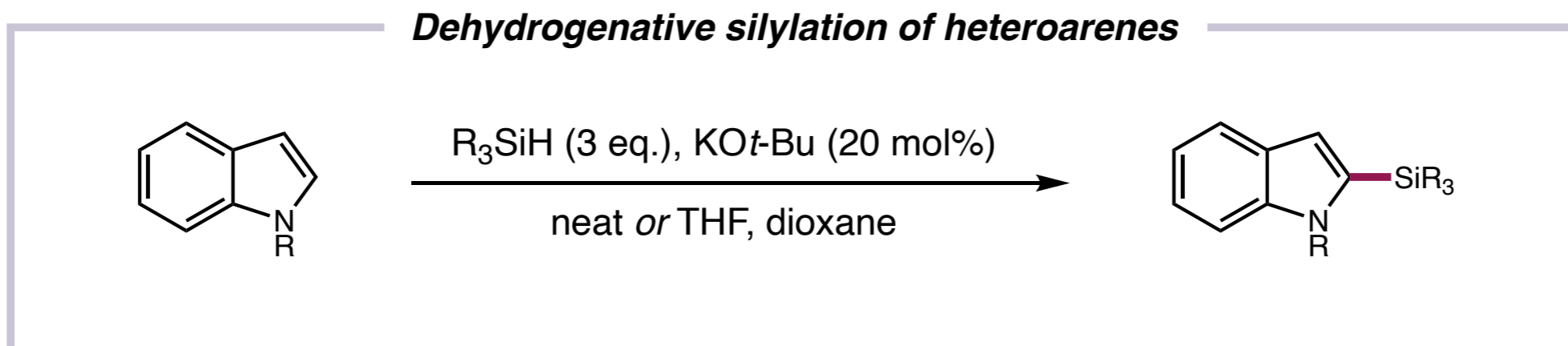
(Hopefully) uncontroversial mechanistic statements:

- Bond-forming step is attack of aryl radical on C–H partner, followed by deprotonation to generate radical anion
- Radical chain mechanism generally accepted, but initiation step(s) highly debated, likely additive-dependent.

Outline

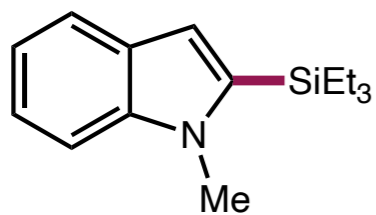
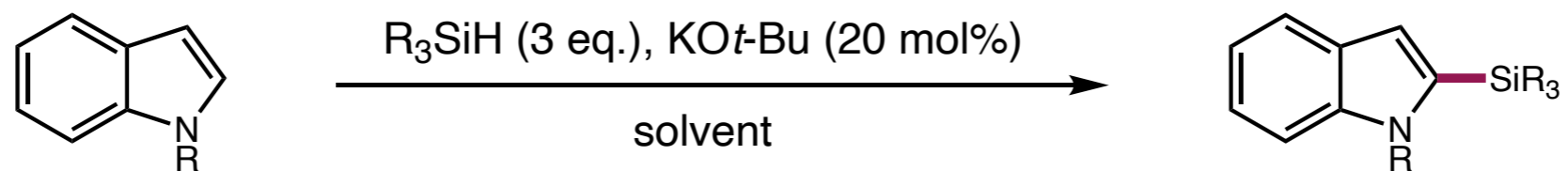
- The tert-butoxyl radical
 - HAT vs. β -scission
- Early single-electron reactivity of $t\text{-BuO}^-$
- Modern examples
 - Initial methods publication
 - Organocatalytic C–H activation cross-coupling reactions?
 - Mechanistic investigations
- $\text{KO}t\text{-Bu}$ -catalyzed $\text{C}(\text{sp}^2)\text{--H}$ silylation
 - Original publication
 - Mechanistic investigations

Heteroaryl C–H silylation promoted by *KOt*-Bu

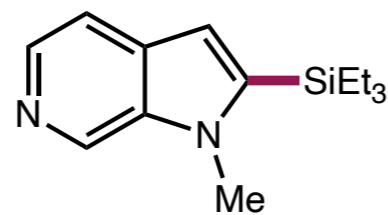


- Stoichiometric organometallic reagents, transition metal catalyst, H_2 acceptors not required
- Mild conditions (neat or minimal solvent, moderate temperatures)
- Good scope of e^- -rich heteroarenes with generally high regioselectivity

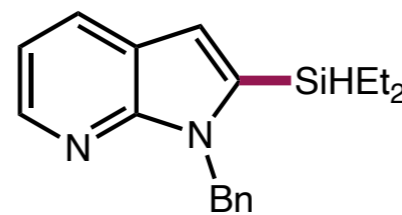
Heteroaryl scope



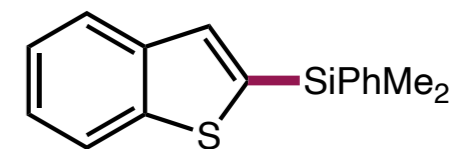
78% Yield
(24 indole examples)



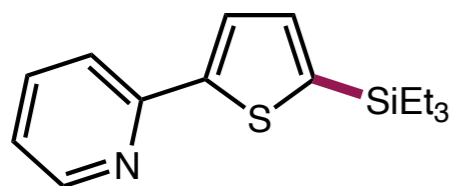
50% Yield



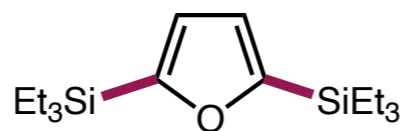
56% Yield



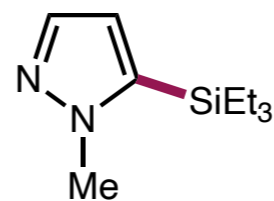
87% Yield



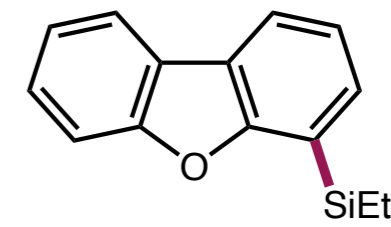
94% Yield



73% Yield

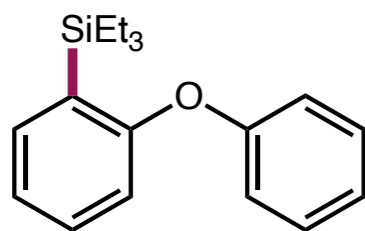
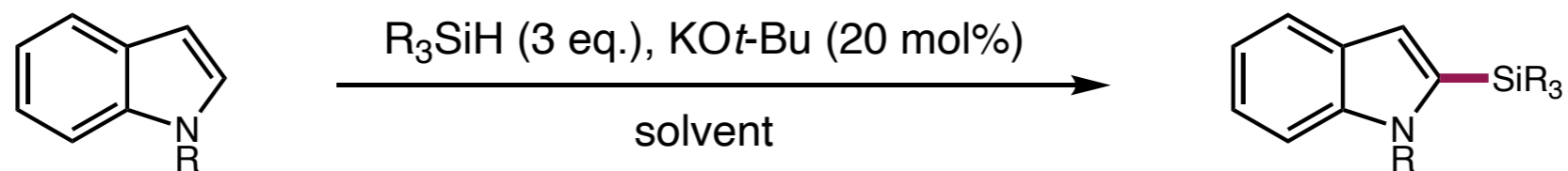


71% Yield

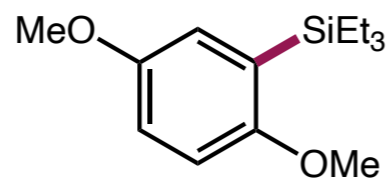


71% Yield

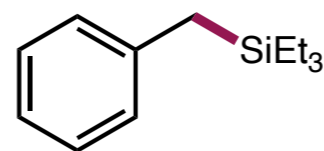
Other scope



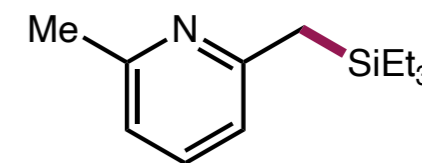
55% Yield



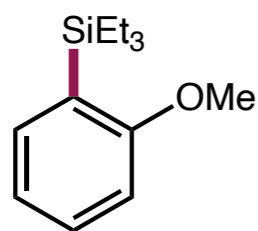
42% Yield
8% bis-[Si]



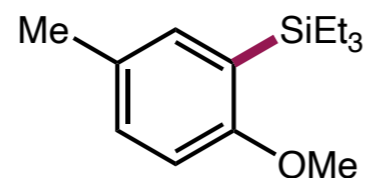
24% Yield



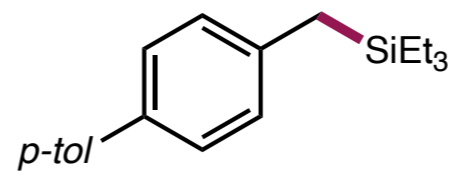
53% Yield



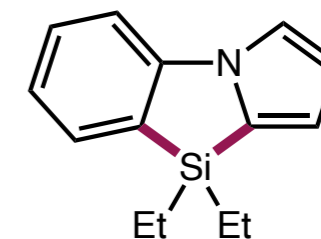
43% Yield



42% Yield



43% Yield



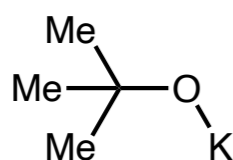
43% Yield

Initial mechanistic insights

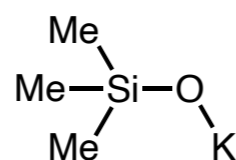
Control experiments:

- No difference in reactivity between commercial KO*t*-Bu vs. sublimed or freshly prepared
- All reaction components analyzed by ICP-MS: >0.1 ppm levels of trace metals

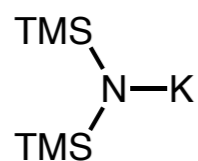
Only effective bases:



88% Yield



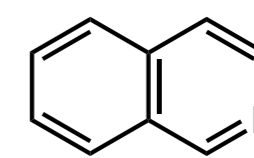
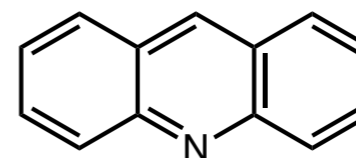
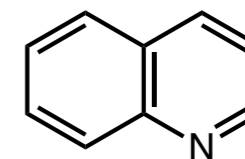
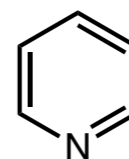
79% Yield



75% Yield

KOEt

14% Yield



*Electron-poor heterocycles unreactive:
evidence against sila-Minisci reactivity*

Detailed mechanistic investigations...

“Detailed mechanistic investigations by experimental and computational methods are under way”

Potassium *tert*-Butoxide-Catalyzed Dehydrogenative C–H Silylation of Heteroaromatics: A Combined Experimental and Computational Mechanistic Study

Wen-Bo Liu,^{†,#} David P. Schuman,^{†,#} Yun-Fang Yang,^{‡,#} Anton A. Toutov,[†] Yong Liang,[‡] Hendrik F. T. Klare,[⊥] Nasri Nesnas,[§] Martin Oestreich,[⊥] Donna G. Blackmond,[∇] Scott C. Virgil,[†] Shibdas Banerjee,^{||} Richard N. Zare,^{||} Robert H. Grubbs,[†] K. N. Houk,^{*,‡} and Brian M. Stoltz^{*,†}

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[‡]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

[⊥]Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 115, 10623 Berlin, Germany

[§]Department of Chemistry, Florida Institute of Technology, 150 West University Boulevard, Melbourne, Florida 32901, United States

^{||}Department of Chemistry, Stanford University, Stanford, California 94305, United States

[∇]Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States

Ionic and Neutral Mechanisms for C–H Bond Silylation of Aromatic Heterocycles Catalyzed by Potassium *tert*-Butoxide

Shibdas Banerjee,^{†,#} Yun-Fang Yang,^{‡,#} Ian D. Jenkins,^{||,#} Yong Liang,[‡] Anton A. Toutov,[§] Wen-Bo Liu,[§] David P. Schuman,[§] Robert H. Grubbs,[§] Brian M. Stoltz,[§] Elizabeth H. Krenske,^{*,⊥} Kendall N. Houk,^{*,‡} and Richard N. Zare^{*,†}

[†]Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

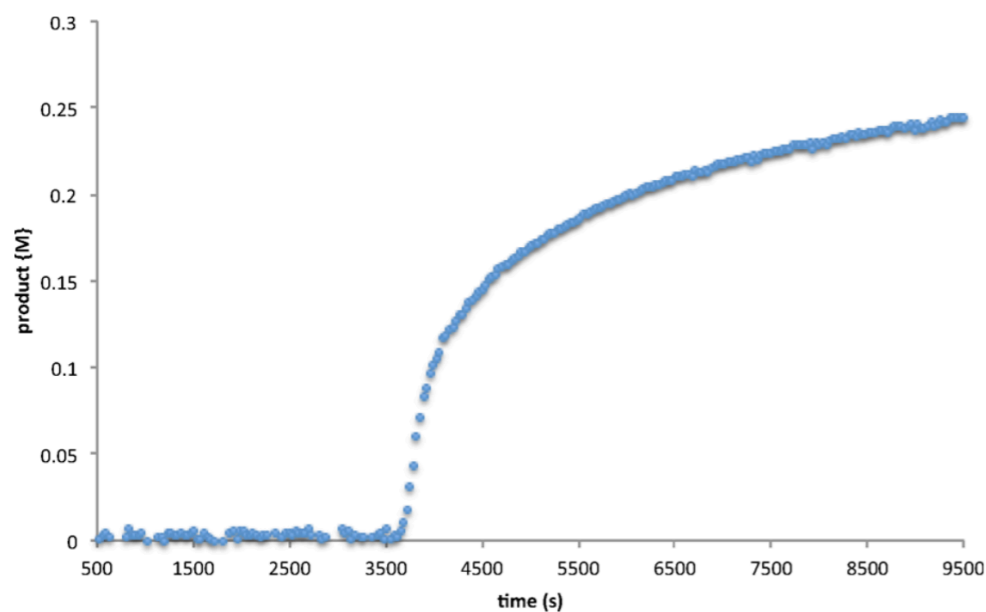
[‡]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

^{||}Eskitis Institute, Griffith University, Nathan, QLD 4111, Australia

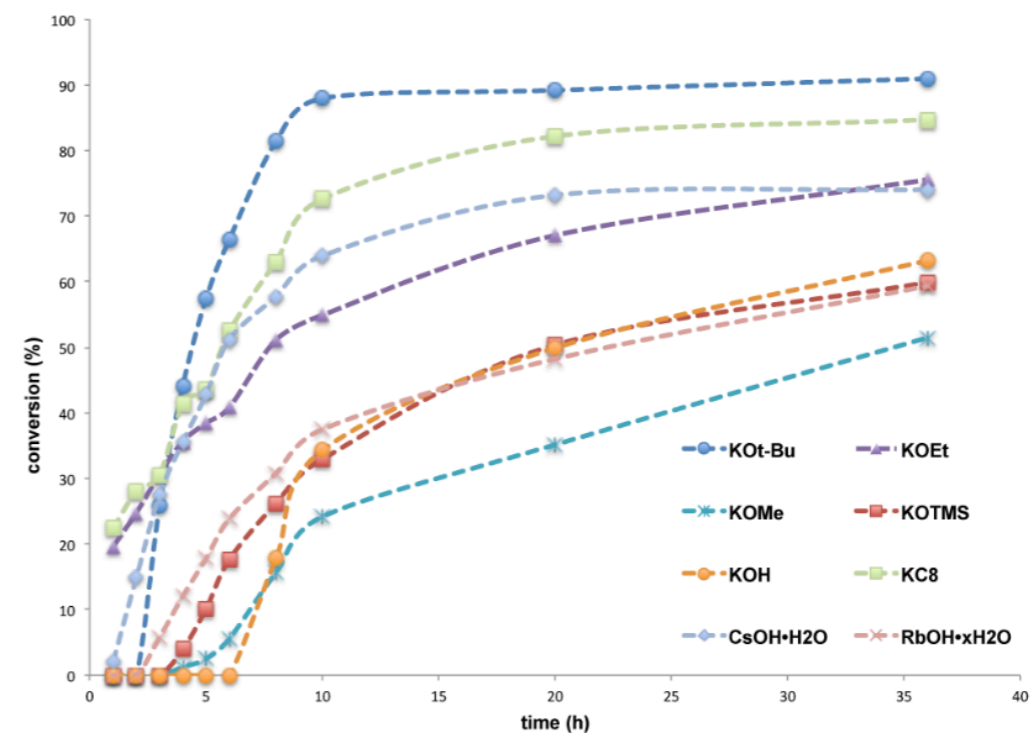
[⊥]School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, QLD 4072, Australia

[§]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

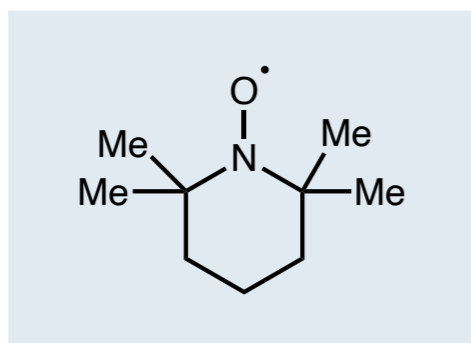
Initial hints of a silyl radical chain



Long induction period followed by rapid product formation

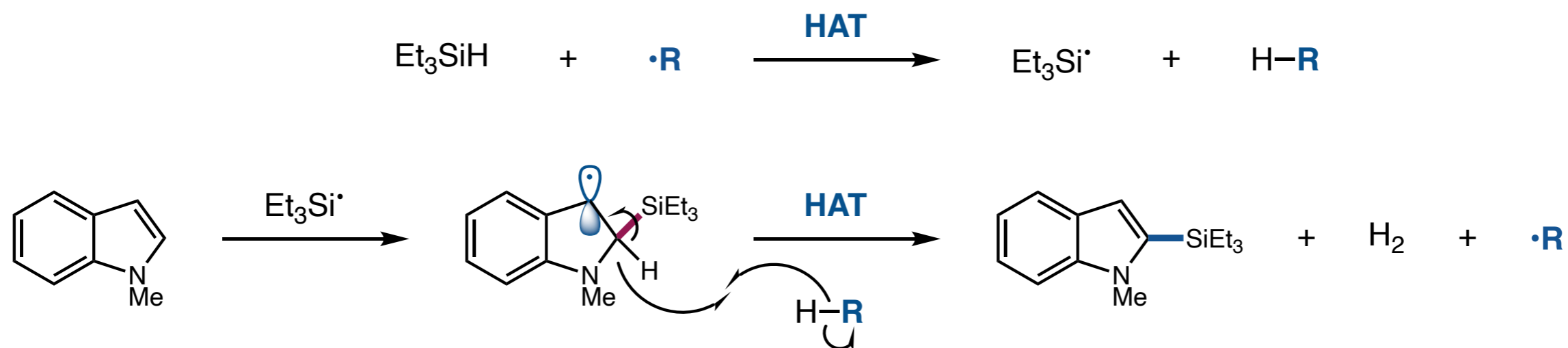


Choice of additive affects induction period length



Addition of TEMPO restarts induction period, reaction resumes after TEMPO consumed to TEMPO-TES

Proposed radical mechanism

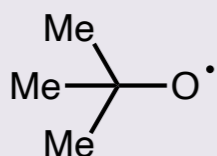


Key questions:

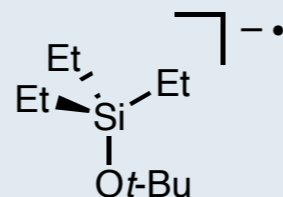
- What is the identity of $\cdot\text{R}$?
- How is it initially generated?

Identity of radical initiator/propagator

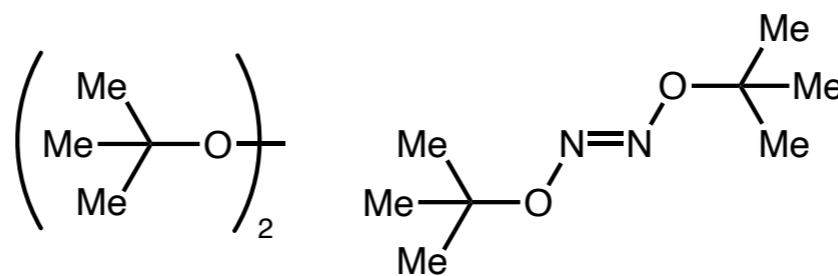
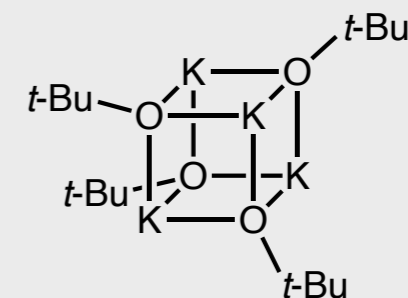
tert-butoxyl radical



silicate radical anion



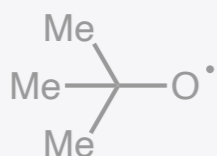
KOt-Bu tetramer



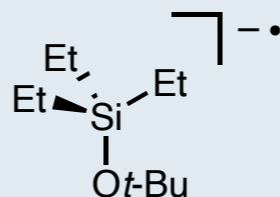
typical t-BuO• sources ineffective at promoting reaction

Identity of radical initiator/propagator

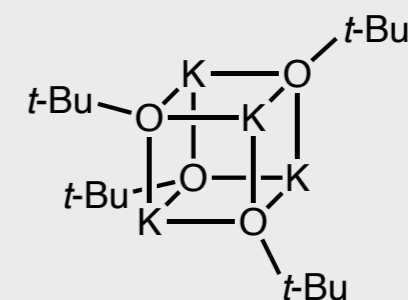
tert-butoxyl radical



silicate radical anion



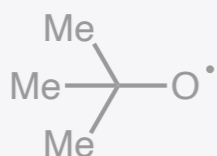
KOt-Bu tetramer



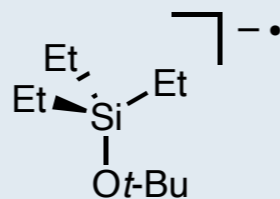
- Pentacoordinate silicate Si–H stretch detected in reaction mixture (ReactIR)
- *t*-BuOSiEt₃ detected by GC after work-up
- Feasible formation via *t*-BuO[−] coordination, then HAT

Identity of radical initiator/propagator

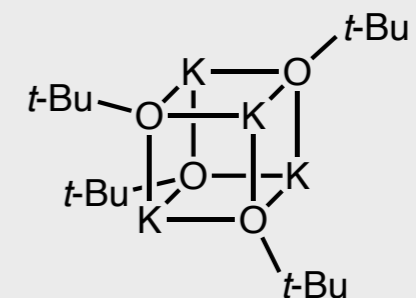
tert-butoxyl radical



silicate radical anion

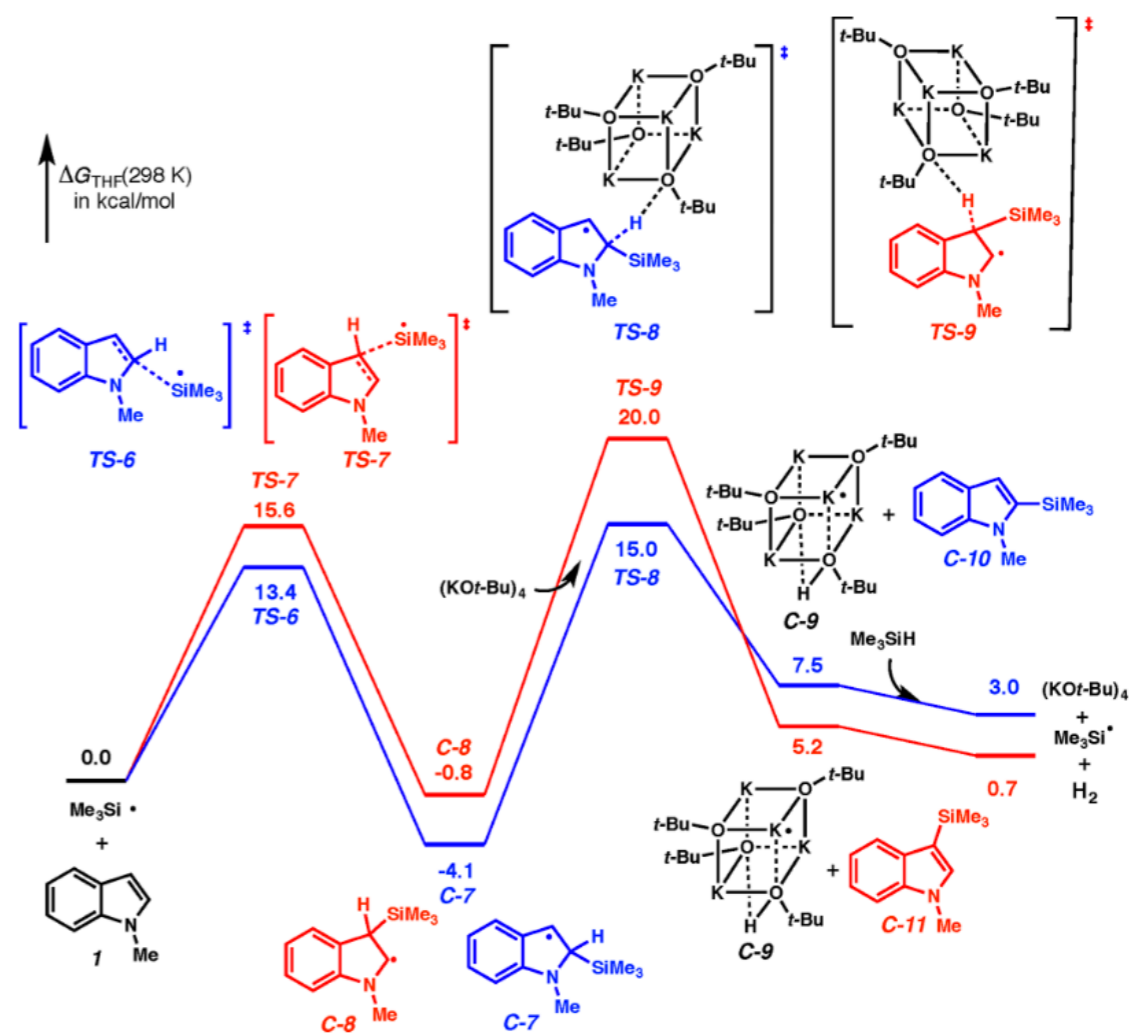
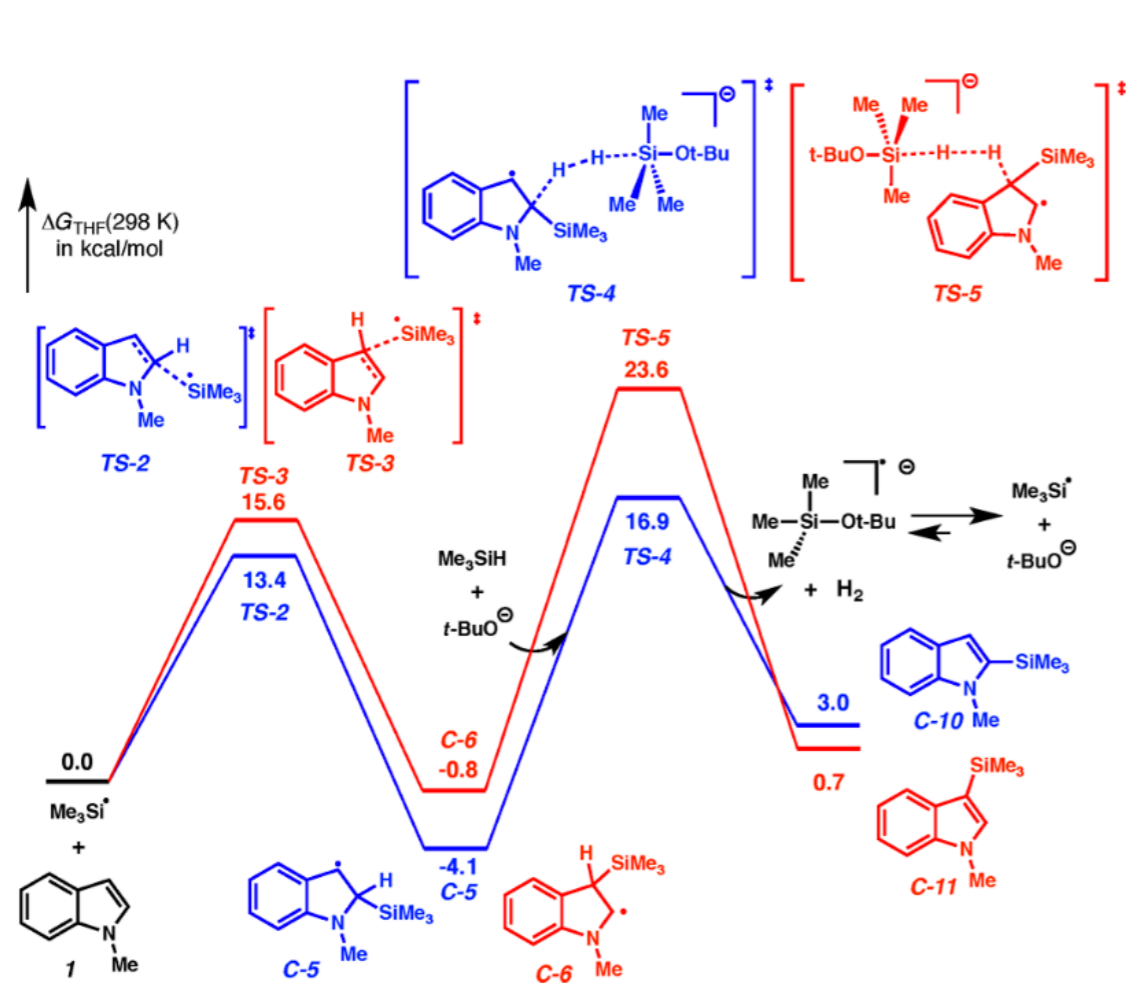


KOt-Bu tetramer



- Also apparently an option

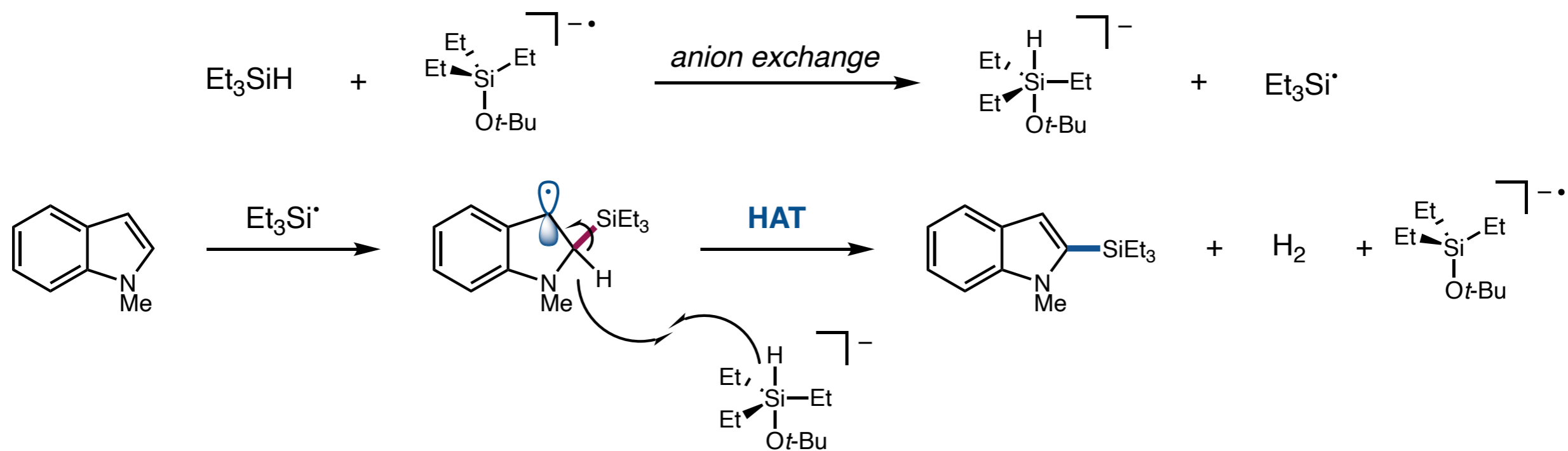
Identity of radical initiator/propagator



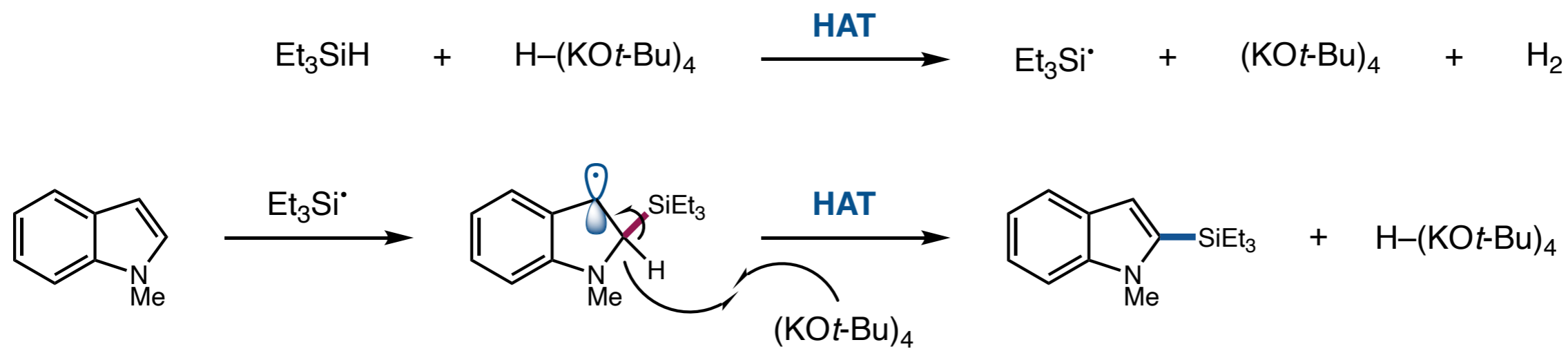
Both pathways energetically feasible, tetramer has slightly lower barriers

Revised radical chain mechanism

Silicate-mediated chain:

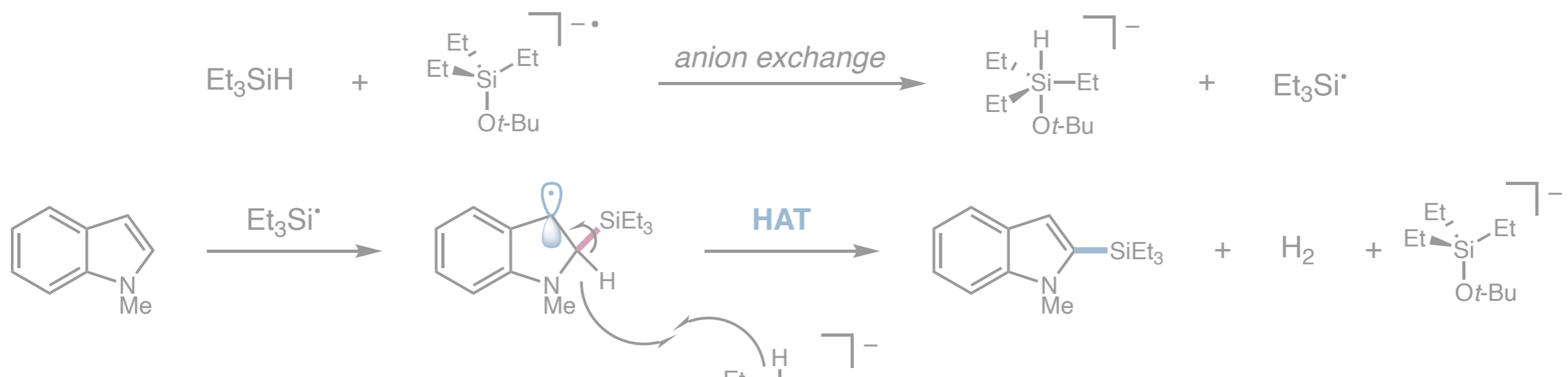


Tetramer-mediated chain:



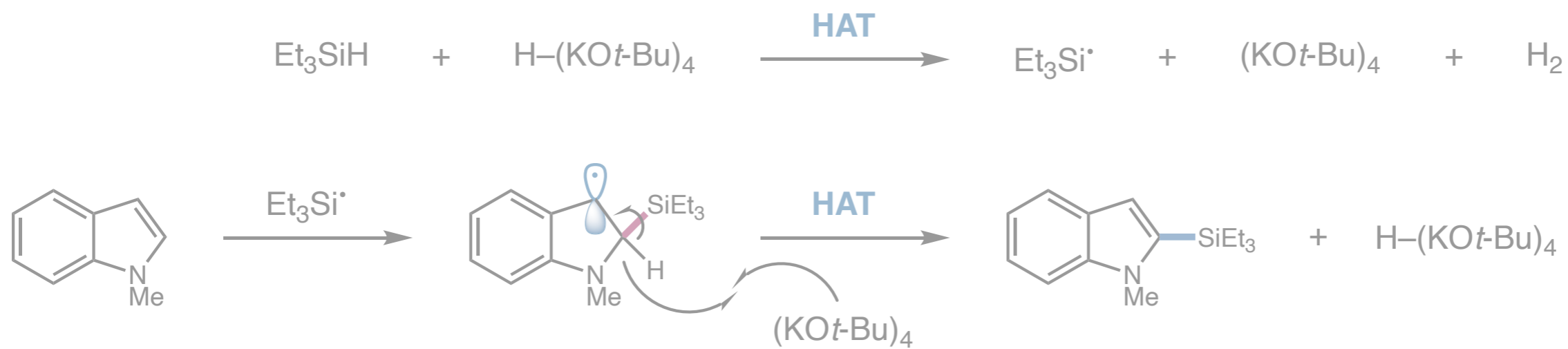
Revised radical chain mechanism

Silicate-mediated chain:

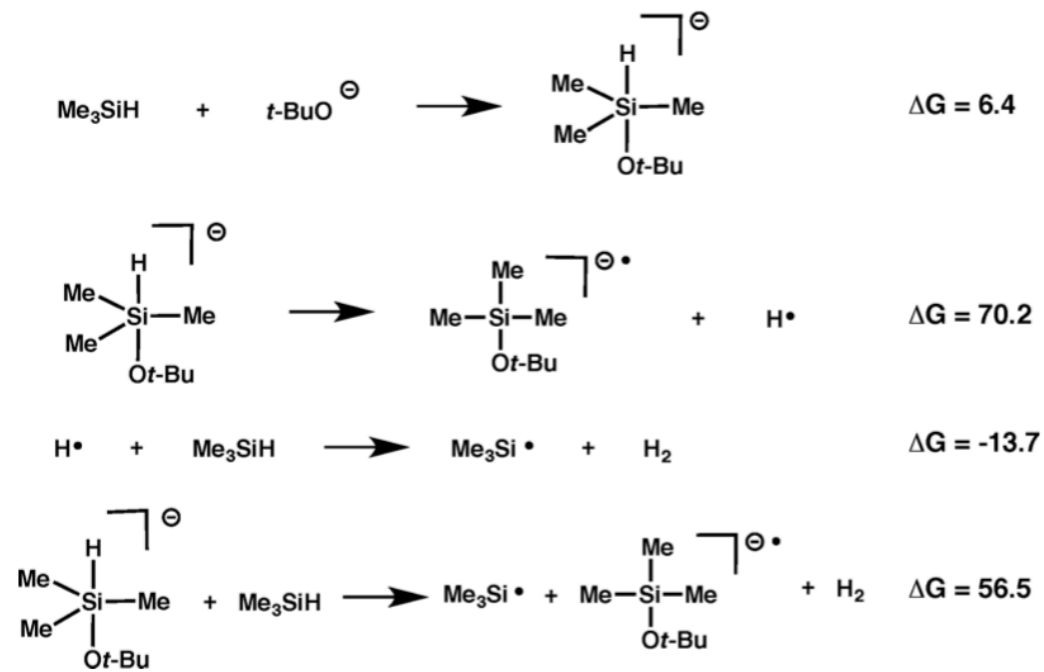


What is the pathway leading to chain initiation?

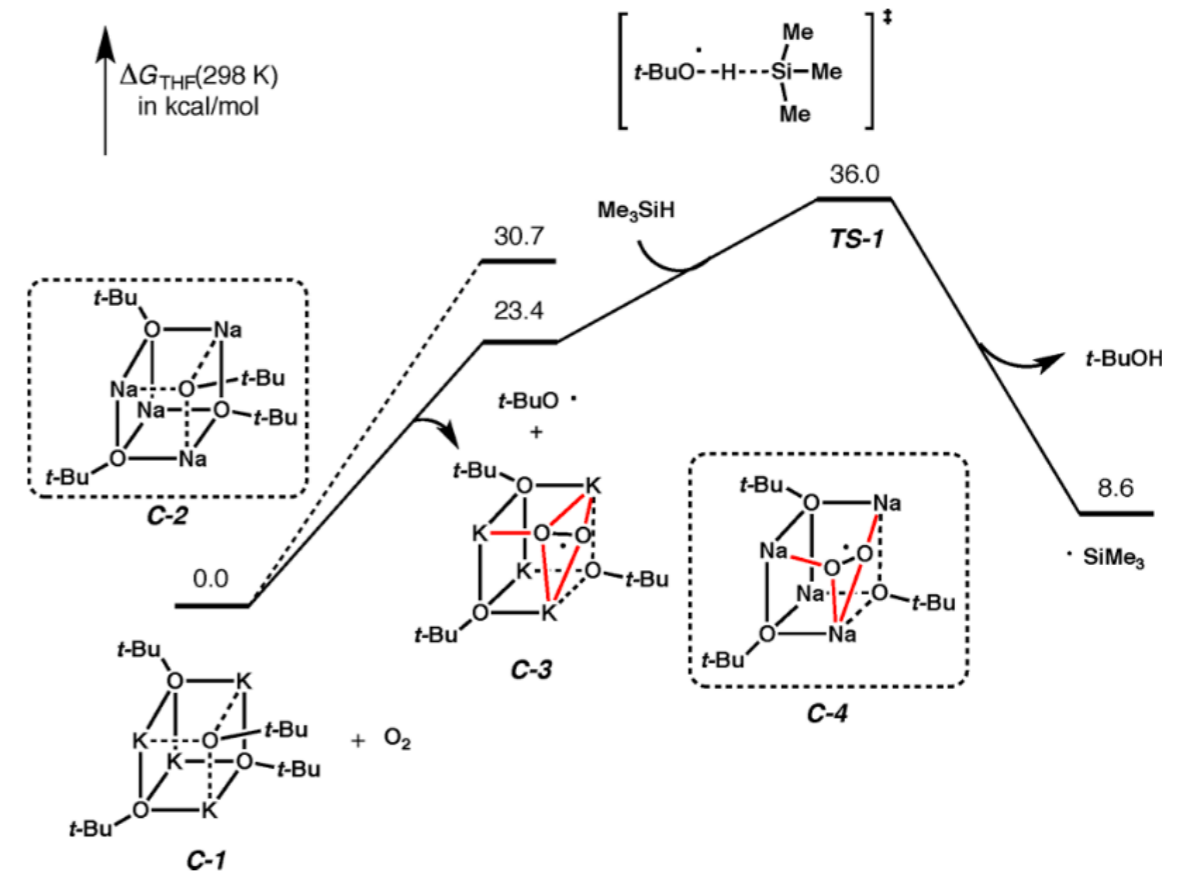
Tetramer-mediated chain:



Chain initiation



Homolysis of silicate is highly endothermic



Initiation by $(\text{KOt-Bu})_4$ & trace O_2 has lower barriers

Mechanistic conclusions

- Likely a radical chain mechanism, with nucleophilic silyl radical addition as the bond-forming step
- Hypervalent silicates and $\text{KO}t\text{-Bu}$ tetramers are both energetically reasonable chain-carrying species
- Chain initiation may be due to trace oxygen, but very endothermic Si–H homolysis is also possible

More references

Additional mechanistic investigations/debates:

Cuthbertson, J.; Gray, V. J.; Wilden, J. D. *Chem. Comm.* **2014**, 50, 2575.

Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2014**, 136, 17818.

Drapeau, M. P.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M. *Angew. Chem. Int. Ed.* **2015**, 54, 10587.

Patil, M. *J. Org. Chem.* **2016**, 81, 632.

Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2016**, 138, 7402.

Review of KOt-Bu-promoted bond-forming reactions:

Madasu, J.; Shinde, S.; Das, R.; Patel, S.; Shard, A. *Org. Biomol. Chem.* **2020**, 18, 8346.

Outline

- The tert-butoxyl radical
 - HAT vs. β -scission
- Early single-electron reactivity of $t\text{-BuO}^-$
- Modern examples
 - Initial methods publication
 - Organocatalytic C–H activation cross-coupling reactions?
 - Mechanistic investigations
- $\text{KO}t\text{-Bu}$ -catalyzed $\text{C}(\text{sp}^2)\text{--H}$ silylation
 - Original publication
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