

Skeletal Editing through Direct Nitrogen Deletion of Secondary Amines

2021.5.29 Literature Seminar

M1 Junichi Taguchi

Contents

1. Introduction

2. Background

**3. Skeletal Editing through Direct Nitrogen
Deletion of Secondary Amines**

(Nature 2021, 593, 223)

Contents

1. Introduction

2. Background

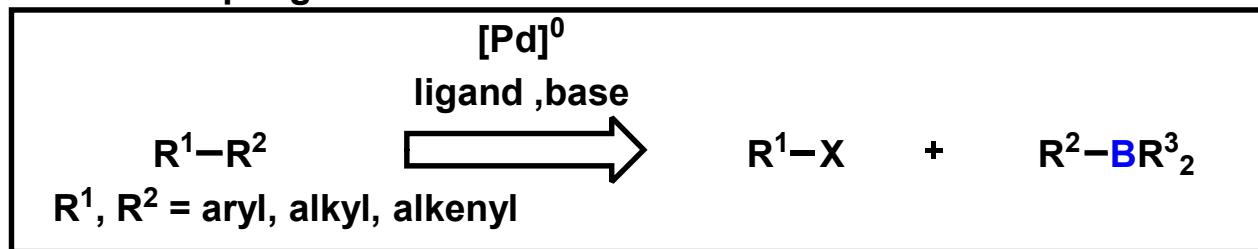
**3. Skeletal Editing through Direct Nitrogen
Deletion of Secondary Amines**

(Nature 2021, 593, 223)

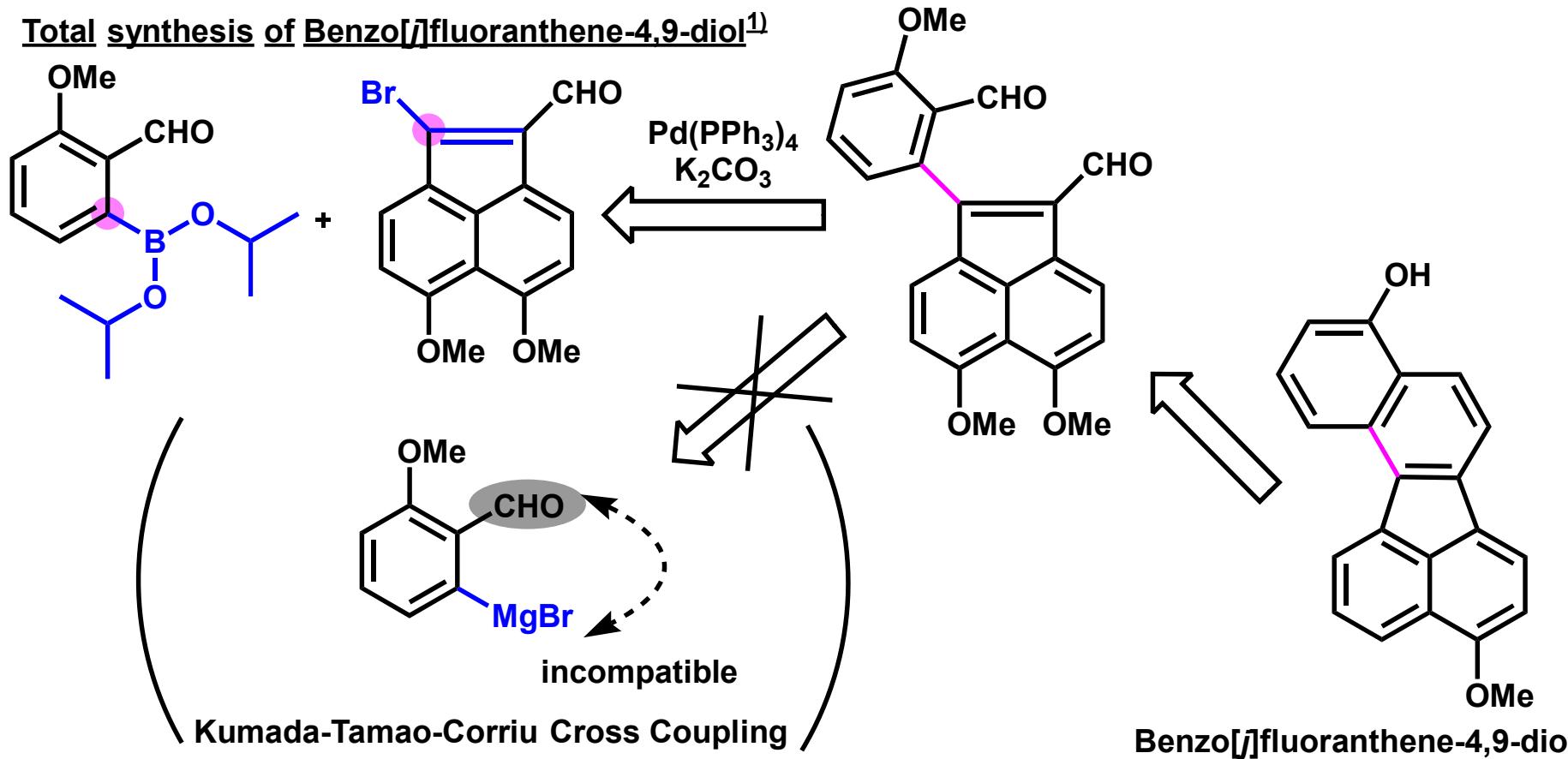
Retrosynthesis and Chemical Transformations

New chemical transformations enable new retrosynthetic disconnections.

ex) Suzuki-Miyaura cross coupling



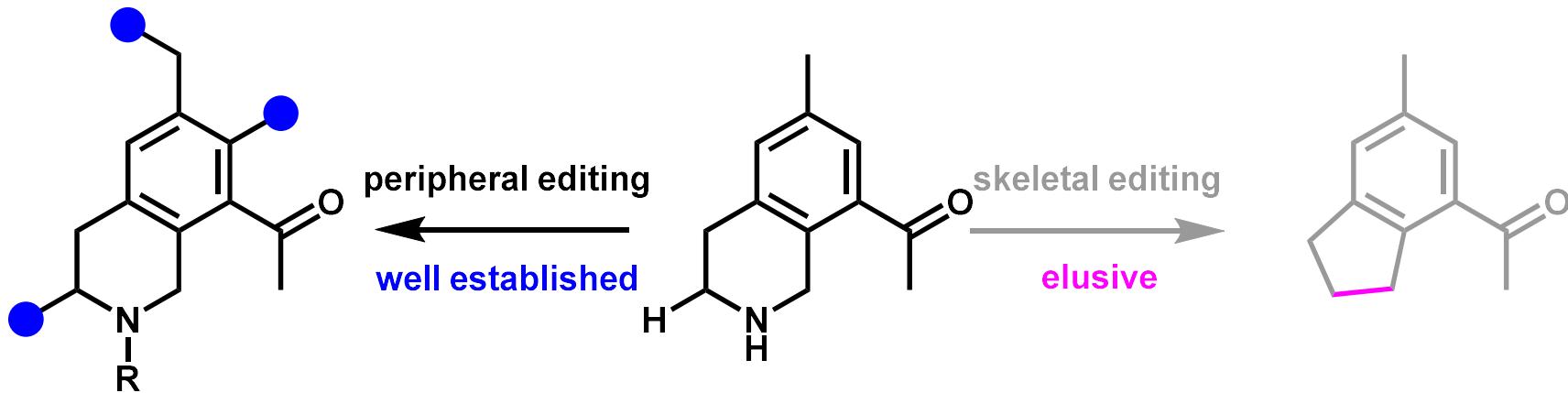
Total synthesis of Benzo[*J*]fluoranthene-4,9-diol¹⁾



1) Lahore, S.; Narkhede, U.; Merlini, L.; Dallavalle, S. *J. Org. Chem.* 2013, 78, 10860.

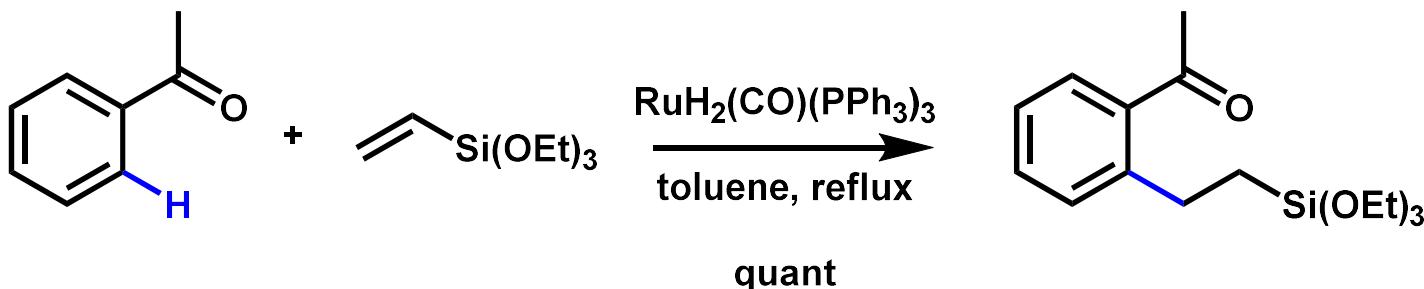
Molecular Editing and Late-stage Functionalization (1)

5



peripheral editing

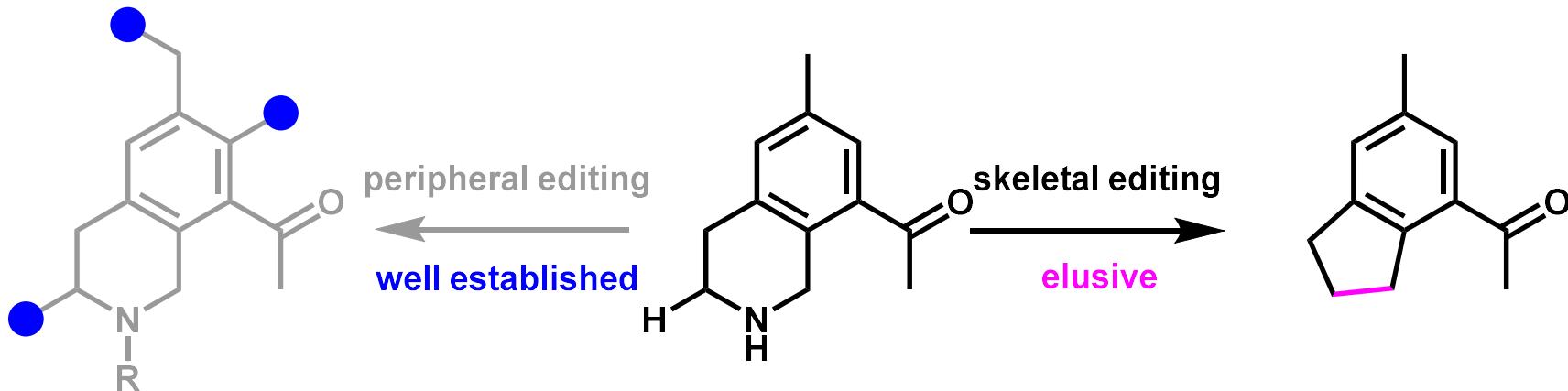
ex) Murai reaction (C-H functionalization)¹⁾



1) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* 1993, 366, 529.

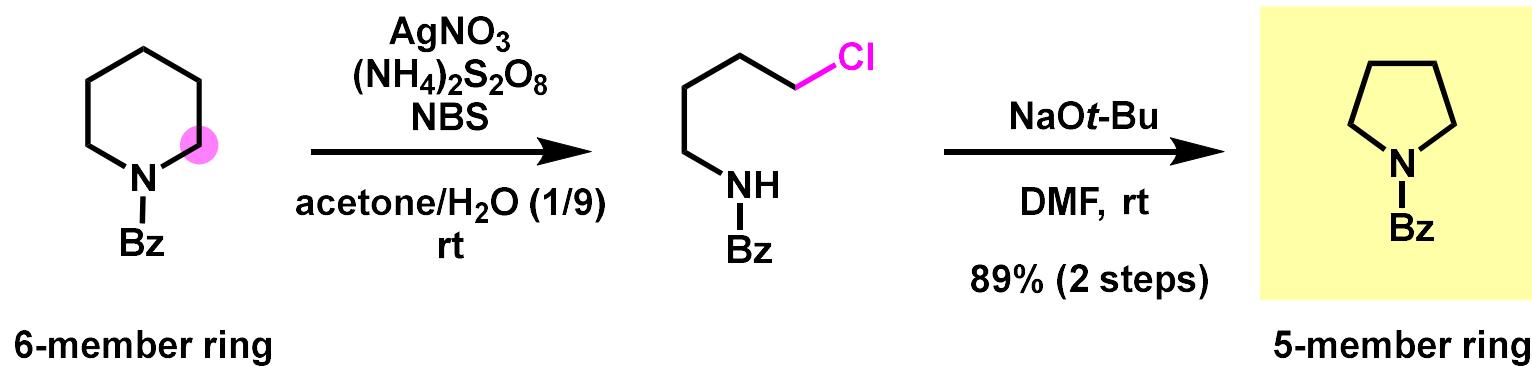
Molecular Editing and Late-stage Functionalization (2)

6



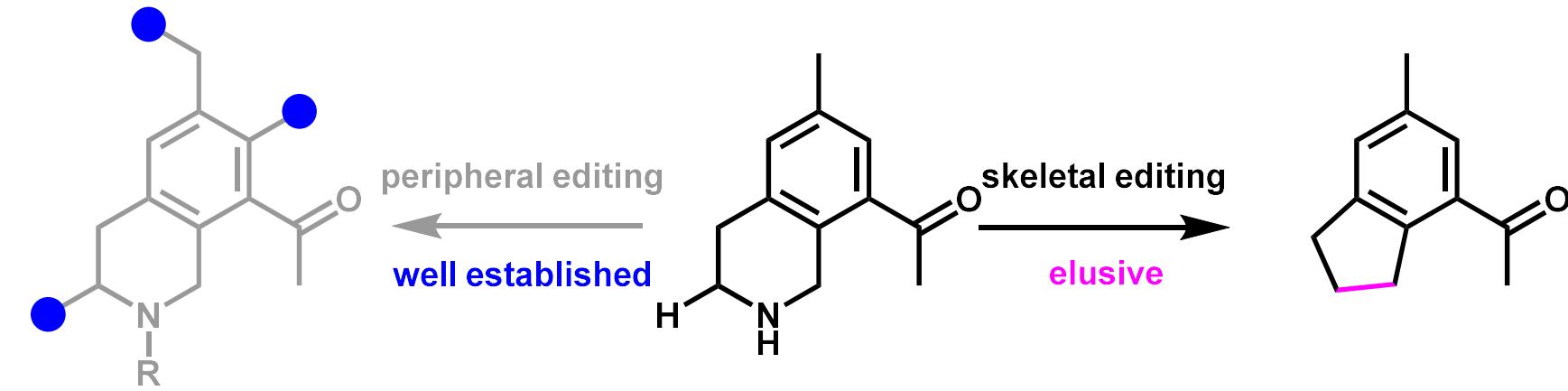
skeletal editing

ex) Deconstructive diversification of cyclic amines¹⁾



Concept of the Main Paper

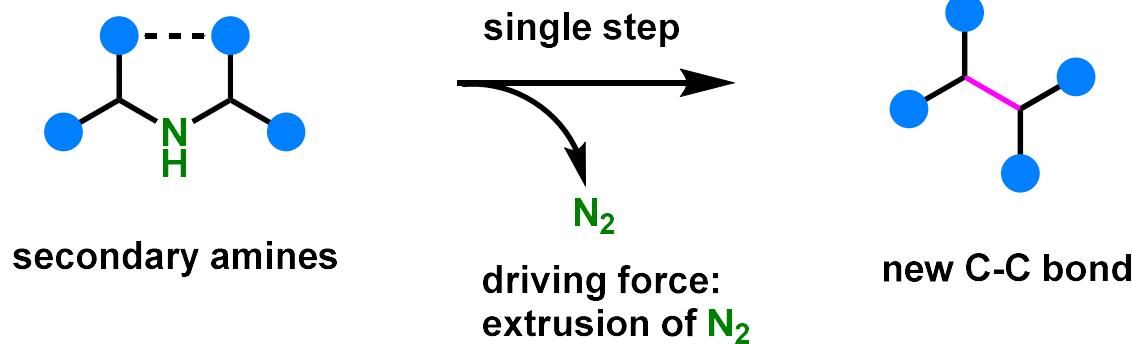
7



skeletal editing

C-N-C bond → C-C bond (single-atom skeletal editing)

"Carbons are tied with a nitrogen."

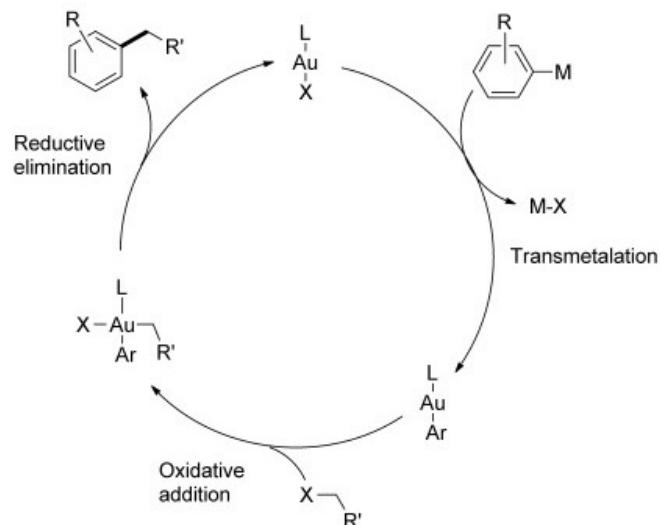


Assistant Prof. Mark D. Levin



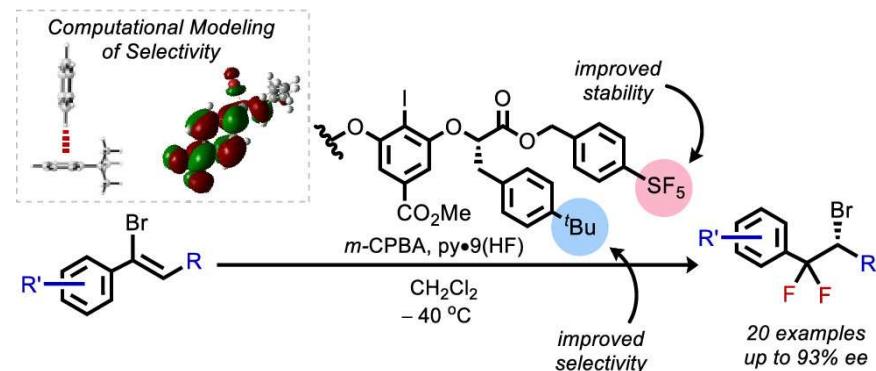
2008-2012 B.S. in Chemistry @ University of Rochester (Prof. Frontier, A. J.)
2012-2017 Ph.D. in Chemistry @ University of California, Berkeley (Prof. Toste, F. D.)
2017-2019 NIH Postdoctoral Fellow @ Harvard University (Prof. Jacobsen, E. N.)
2019- Assistant Professor @ University of Chicago

Research Interests :
catalyst design/ organometallic chemistry/
the development of synthetic methodology



Gold-Catalyzed Allylation of Aryl Boronic Acids²⁾

- 1) <https://voices.uchicago.edu/levingroup/mark/> 2) Levin, M. D.; Toste, F. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 6211. 3) Levin, M. D.; Ovian, J. M.; Read, J. A.; Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2020**, *142*, 35.



Catalytic Enantioselective Synthesis of Difluorinated Alkyl Bromides³⁾

Contents

1. Introduction

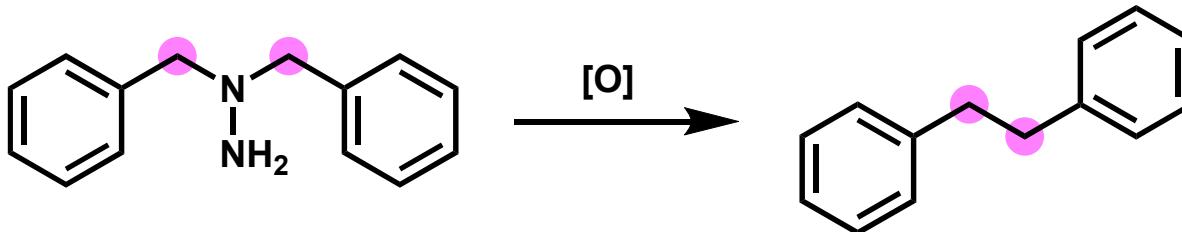
2. Background

3. Skeletal Editing through Direct Nitrogen
Deletion of Secondary Amines

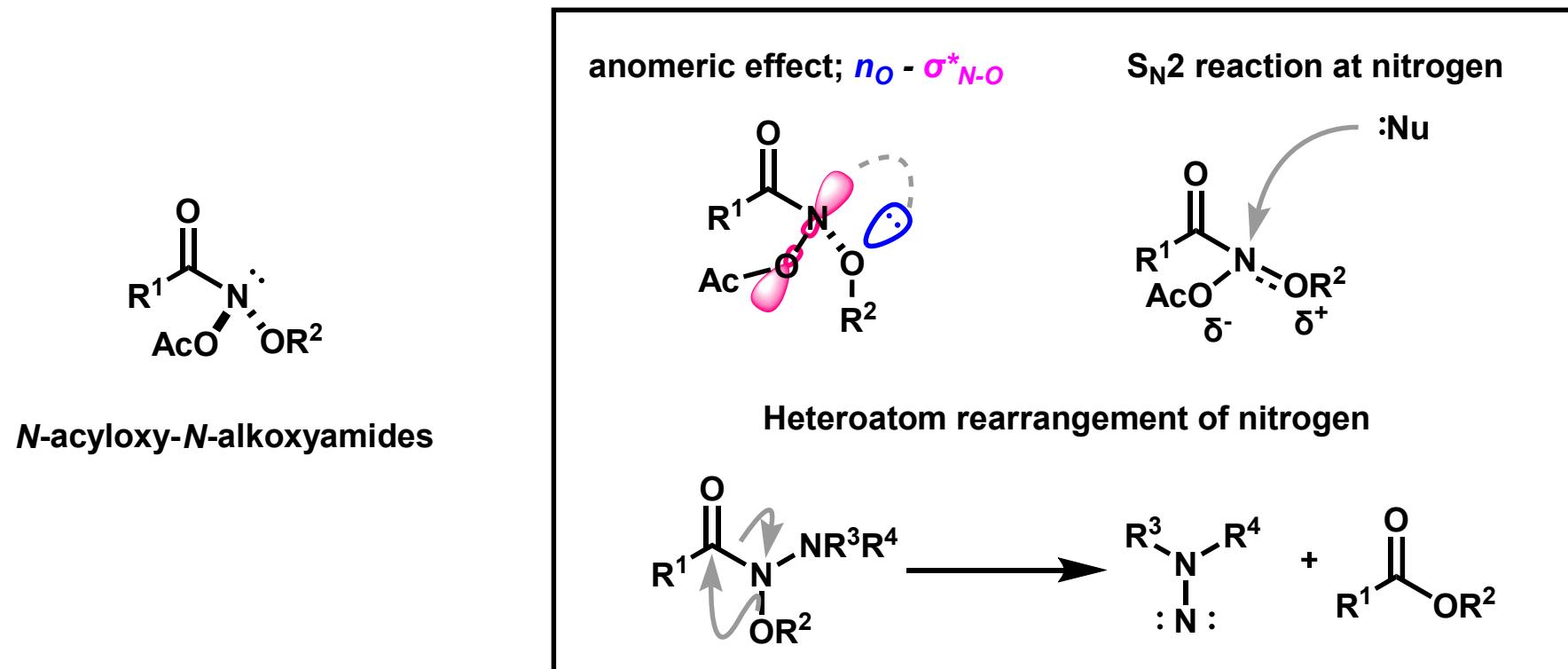
(*Nature* 2021, 593, 223)

Background

1. C-C bond-forming by the oxidation of 1,1-disubstituted hydrazines



2. Properties and reactivity of *N*-acyloxy-*N*-alkoxyamides

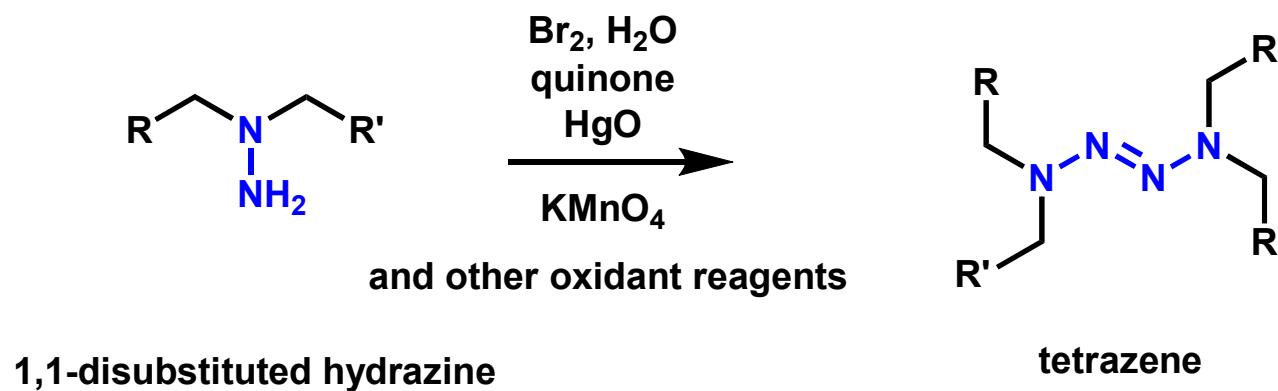


1) Glover, S. A. *Tetrahedron* 1998, 54, 7229. 2) Glover, S. A.; Rauk, A.; Buccigross, J. M.; Campbell, J. J.; Hammond, G. P.; Mo, G.; Andrews, L. E.; Gillson, A. E. *Can. J. Chem.* 2005, 83, 1492.

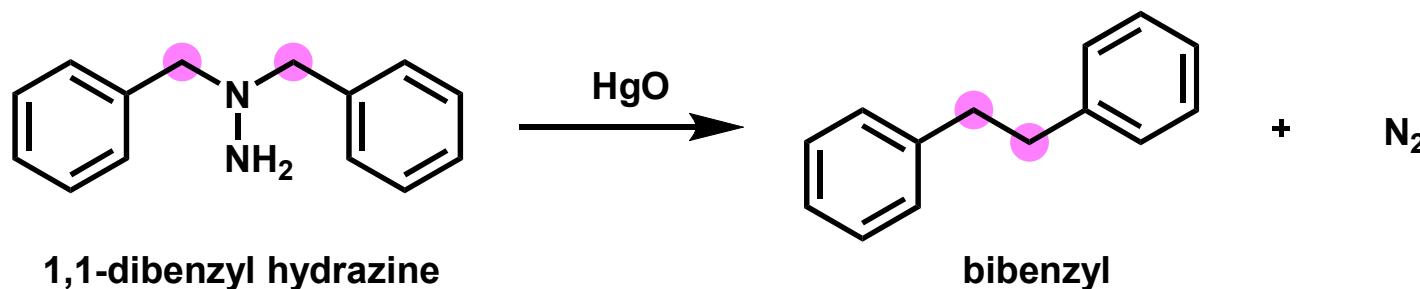
1. Oxidation of 1,1-Dibenzylhydrazines (1)

11

1. The oxidation of 1,1-disubstituted hydrazines to the corresponding tetrazene¹⁾



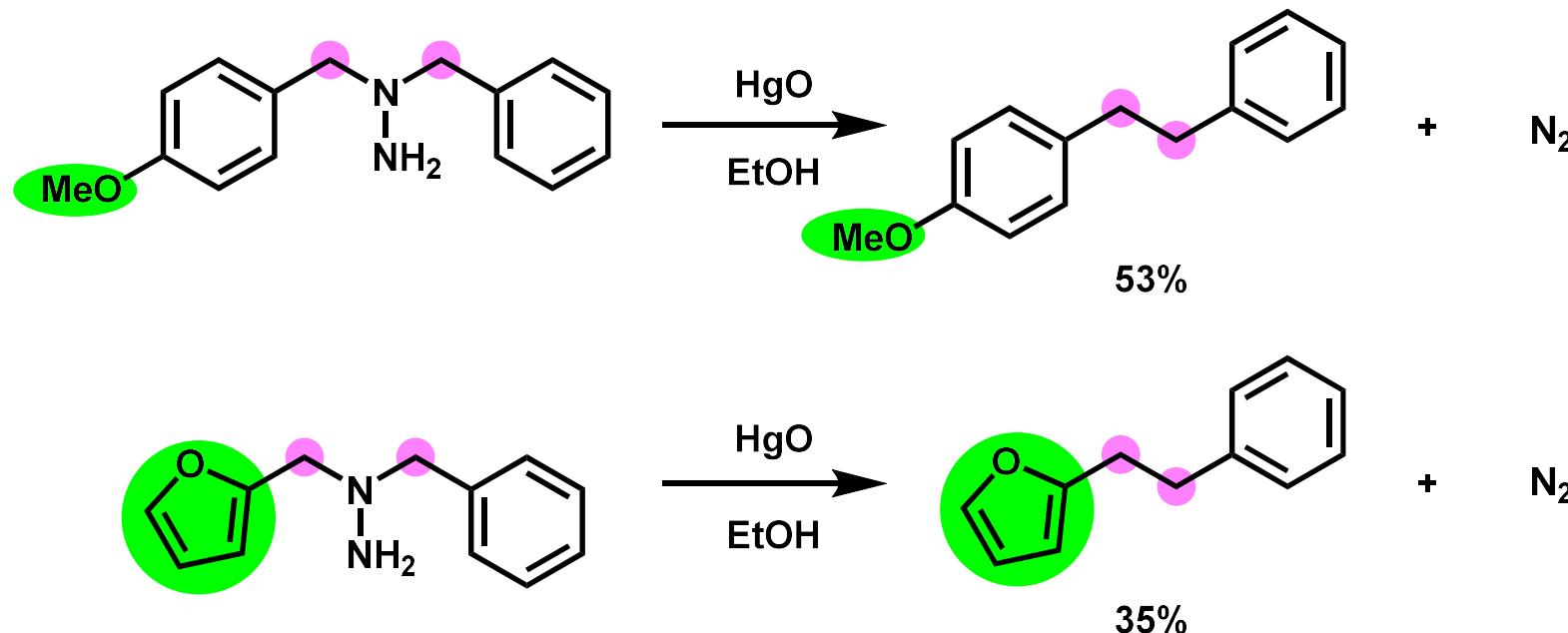
2. The first oxidation of a 1,1-disubstituted hydrazine to bibenzyl (in 1900 by Busch and Weiss)²⁾



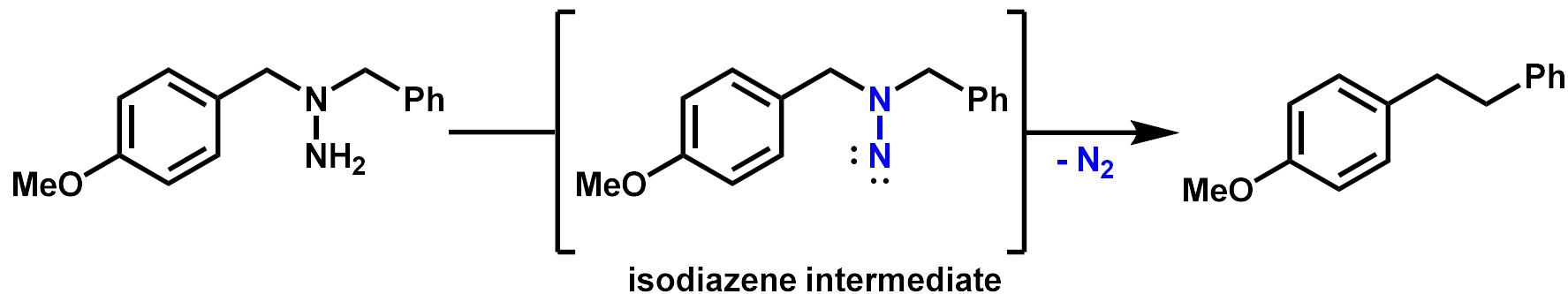
1) Hinman, R. L.; Hamm, K. L. *J. Am. Chem. Soc.* **1959**, *81*, 3294. 2) Busch, M.; Weiss, B. *Ber.* **1900**, *33*, 2701.

1. Oxidation of 1,1-Dibenzylhydrazines (2)

The oxidation of 1,1-disubstituted hydrazines to "mixed" bibenzyls¹⁾



It has been suggested that the reaction proceeds by way of an isodiazene intermediate²⁾



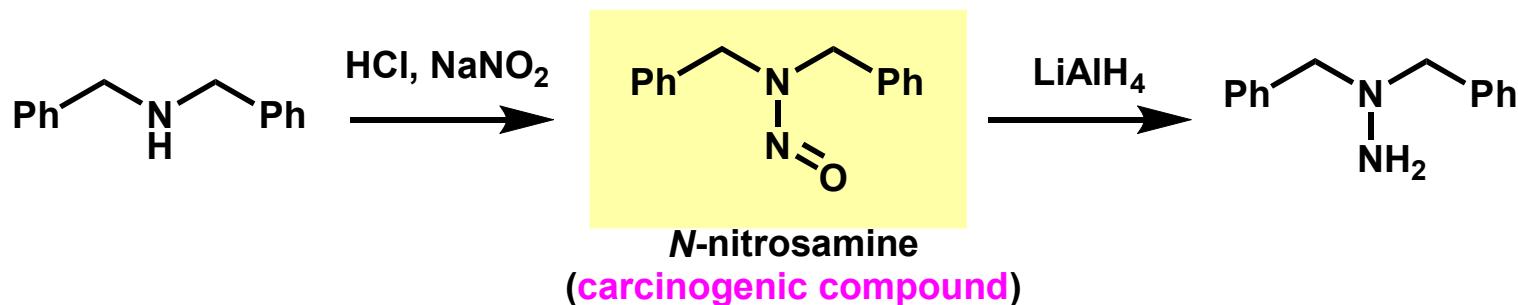
1) Hinman, R. L.; Hamm, K. L. *J. Am. Chem. Soc.* **1959**, *81*, 3294. 2) Kenner, J.; Knight, E.C. *Ber.* **1936**, *69*, 341.

1. Oxidation of 1,1-Dibenzylhydrazines (3)

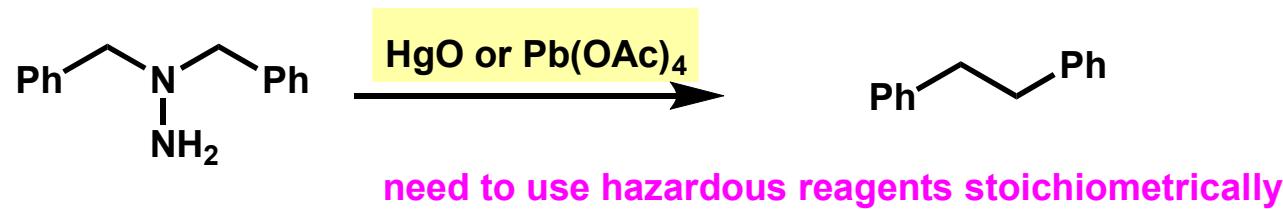
13

Preparation of 1,1-disubstituted hydrazines

General procedure:

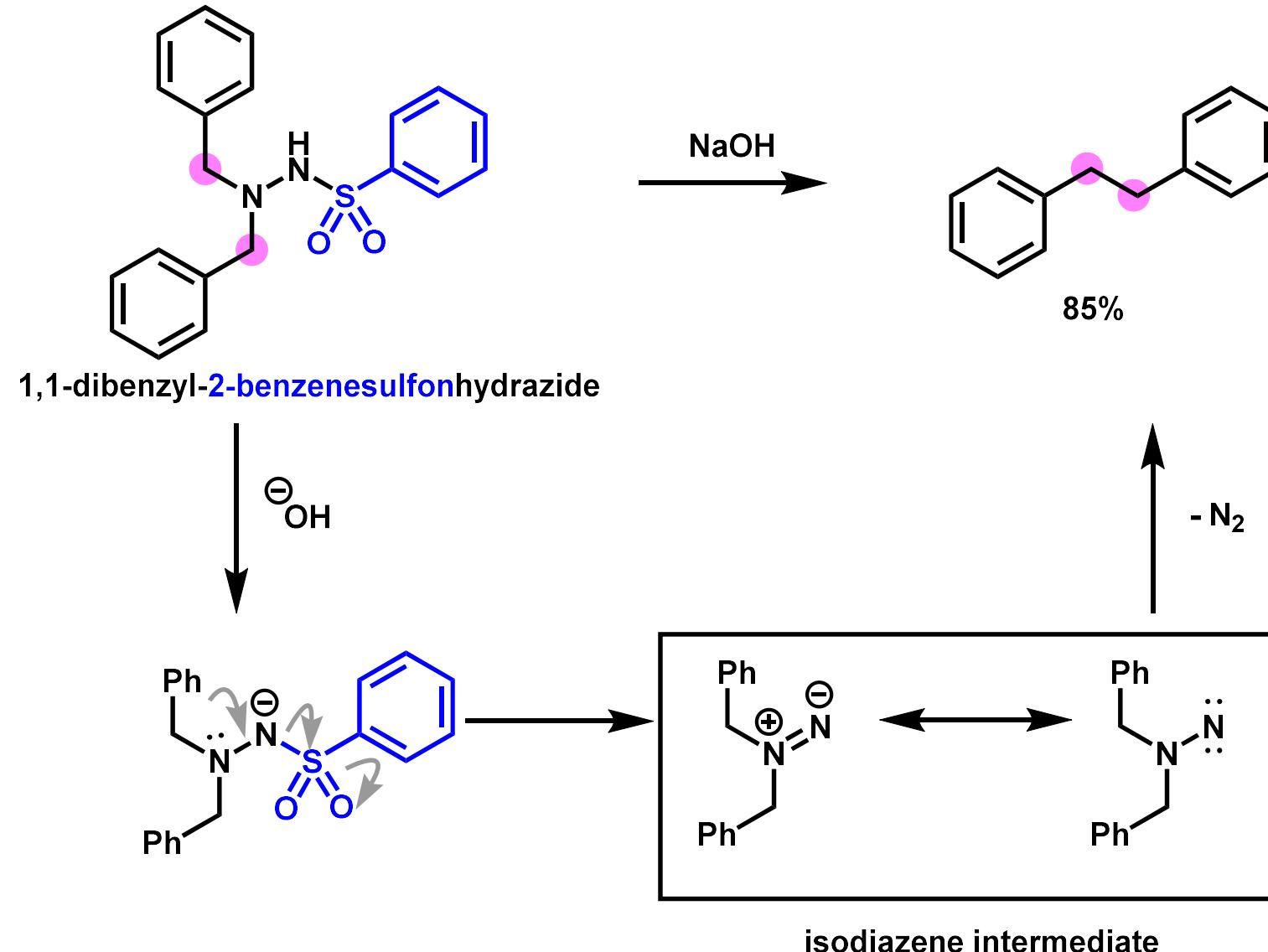


The oxidant reagent



1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, 593, 223. 2) Hinman, R. L.; Hamm, K. L. *J. Am. Chem. Soc.* **1959**, 81, 3294. 3) Pavel, G.; Mikhail, K. *Tetrahedron Lett.* **2018**, 59, 3532.

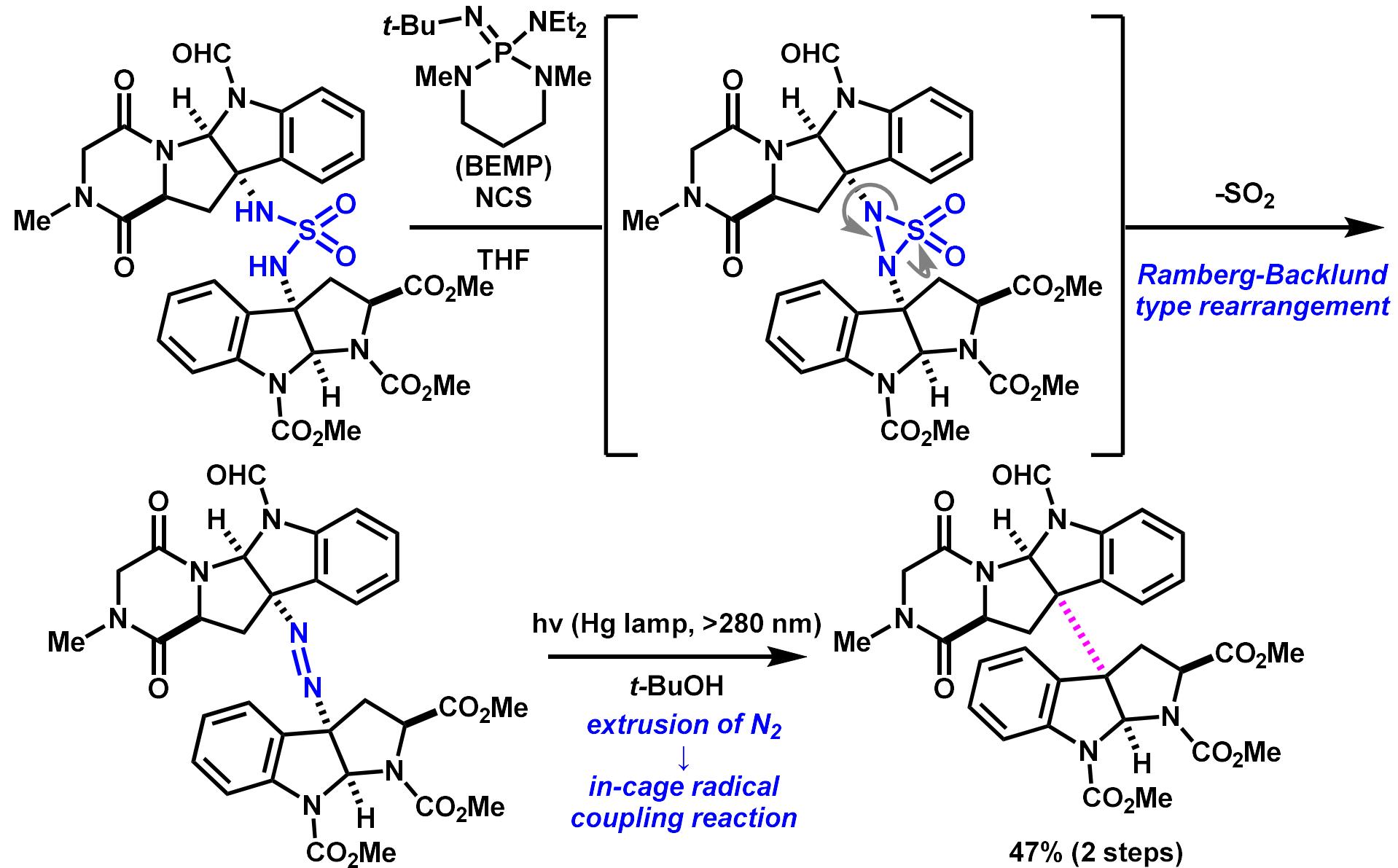
1. Alkaline Decomposition of 1,1-Dibenzyl-2-benzenesulfonhydrazine



1) Carpino, L. A. *J. Am. Chem. Soc.* **1957**, *79*, 4427. 2) Kenner, J.; Knight, E.C. *Ber.* **1936**, *69*, 341.

1. Fragmentation of Dialkyl Diazenes

15



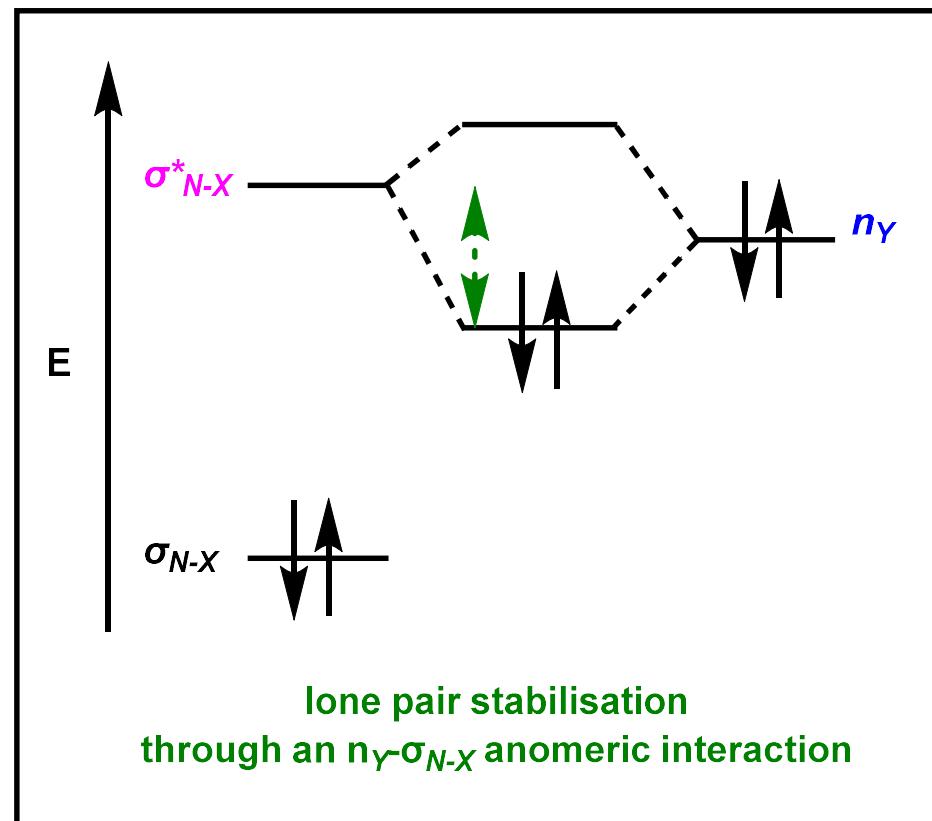
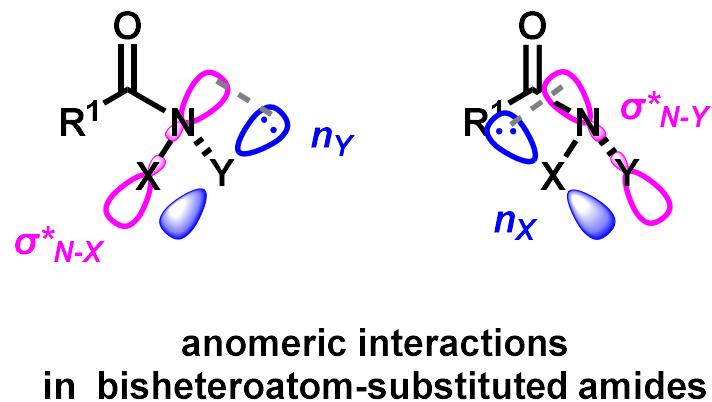
See also 090711_LS_Daisuke URABE and 170121_PS_Daiki Kuwana

1) Movassaghi, M.; Ahmad, O. K.; Lathrop, S. P. *J. Am. Chem. Soc.* **2011**, 133, 13002.

2. Anomeric Amides

anomeric effect:

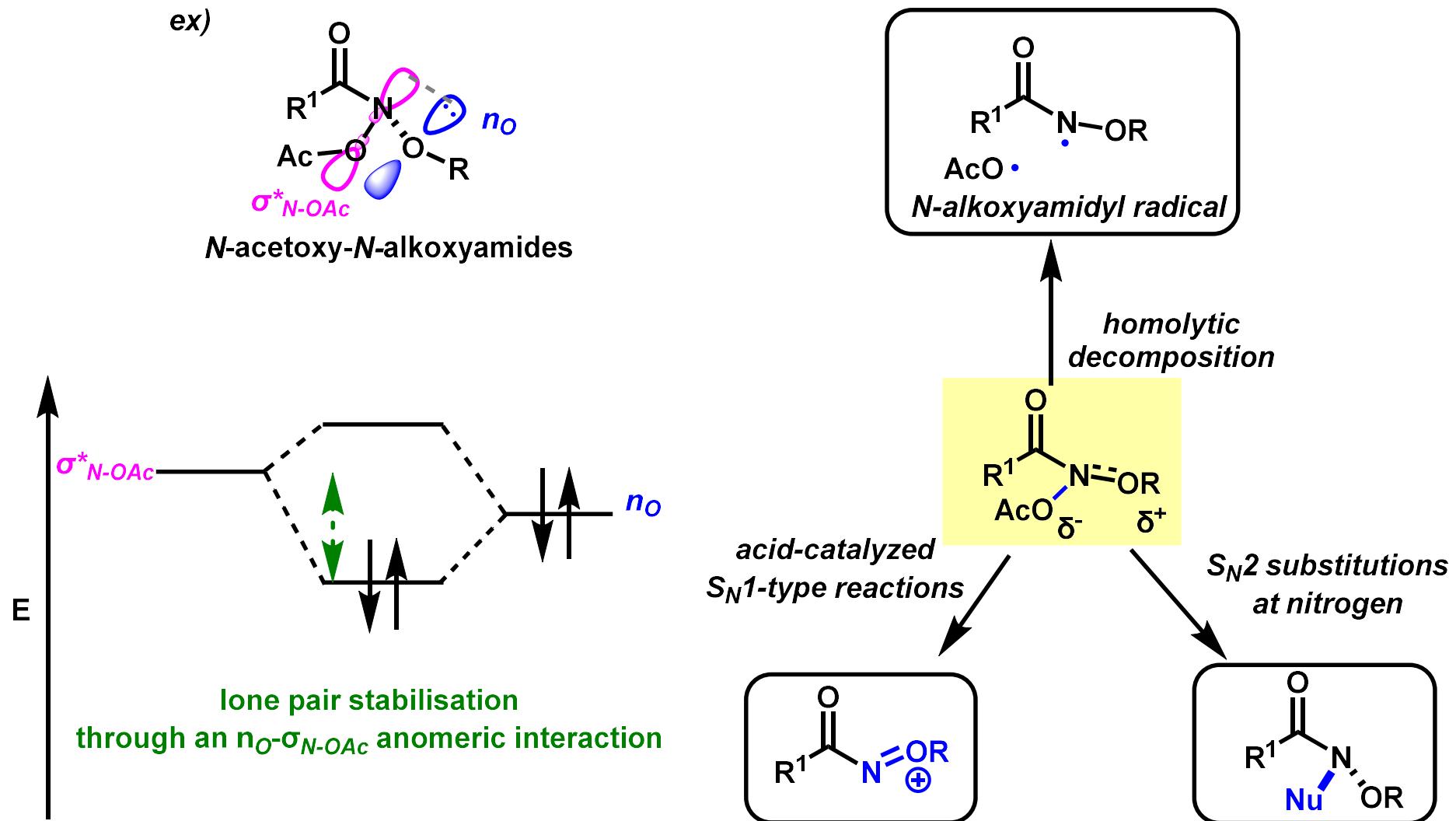
stabilising electronic interaction involving overlap between the lone pair (n) on one heteroatom with the σ^* orbital of the bond between the central carbon atom and the second heteroatom.



1) Glover, S. A. *Tetrahedron* 1998, 54, 7229.

2. *N*-Acyloxy-*N*-alkoxyamides

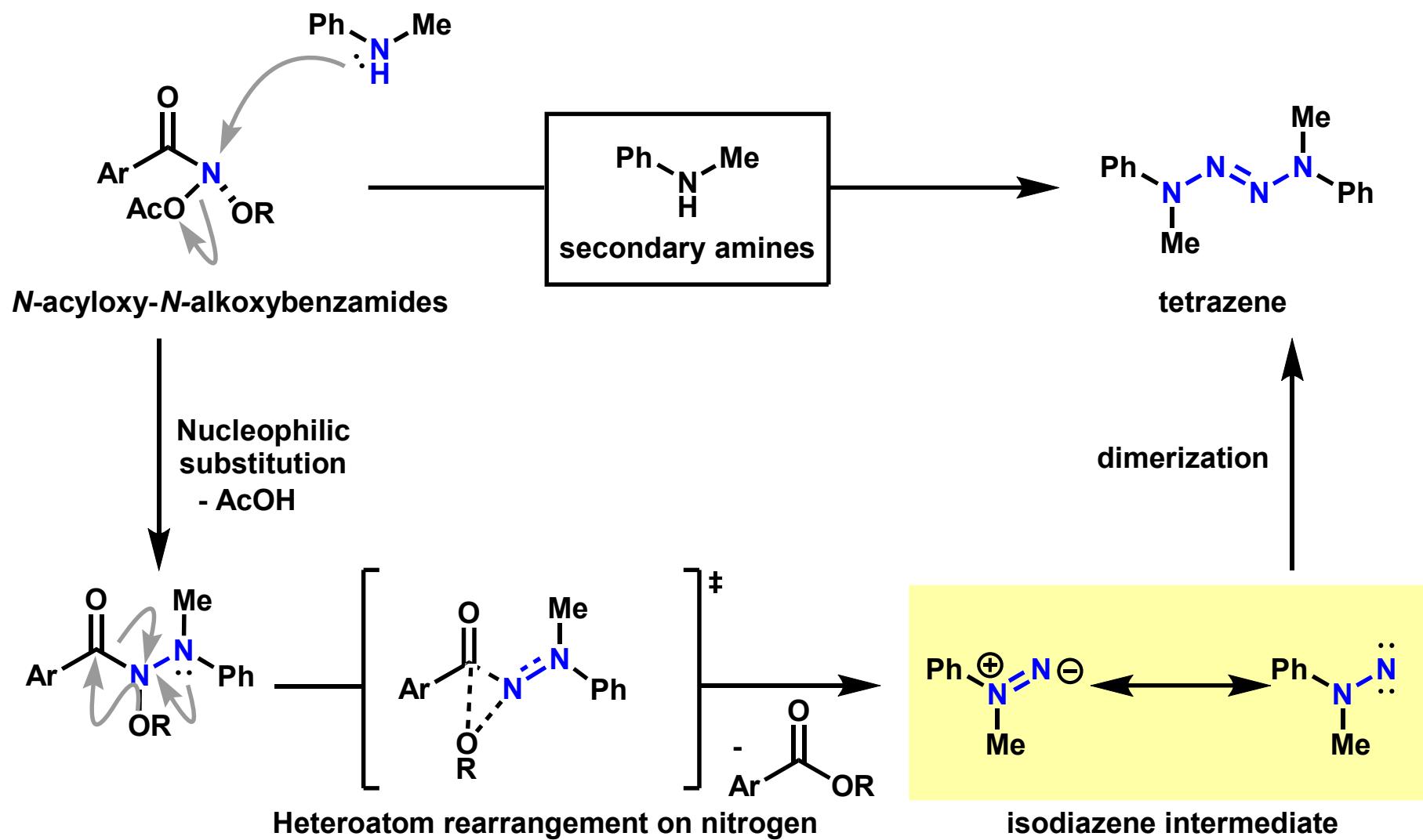
17



1) Glover, S. A. *Tetrahedron* 1998, 54, 7229.

2. S_N2 Substitutions at Nitrogen

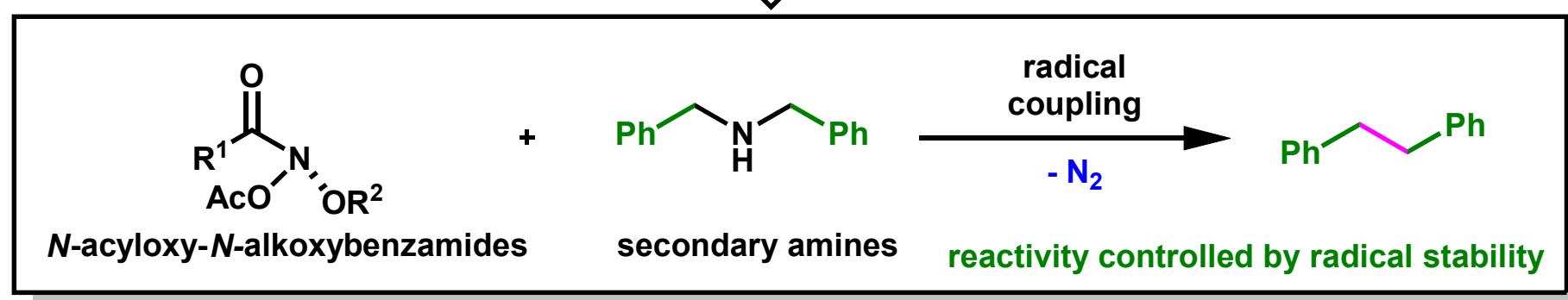
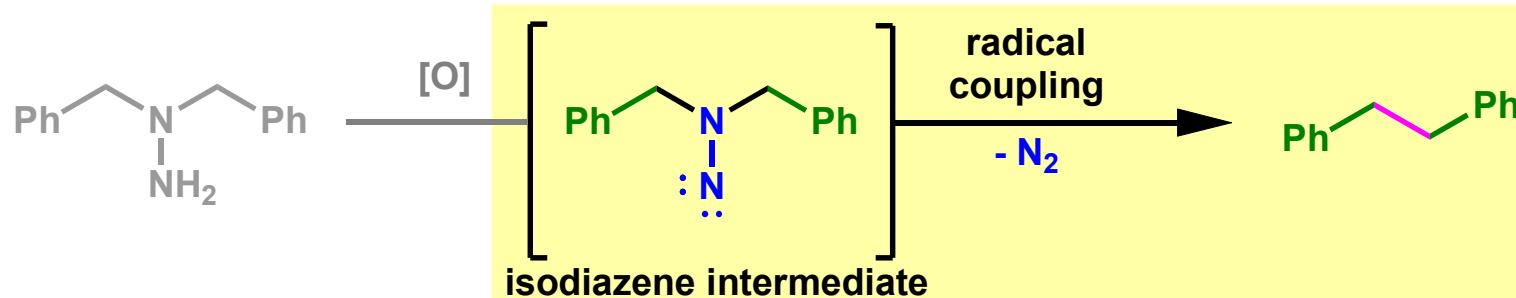
18



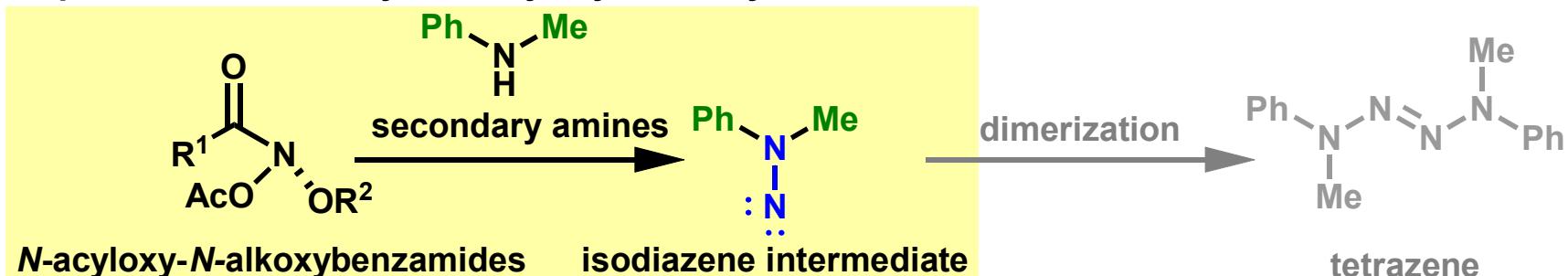
1) Glover, S. A. *Tetrahedron* **1998**, *54*, 7229. 2) Glover, S. A.; Rauk, A.; Buccigross, J. M.; Campbell, J. J.; Hammond, G. P.; Mo, G.; Andrews, L. E.; Gillson, A. E. *Can. J. Chem.* **2005**, *83*, 1492.

Key Point in This Lecture

1. C-C bond-forming by the oxidation of 1,1-disubstituted hydrazines



2. Properties and reactivity of *N*-acyloxy-*N*-alkoxyamides



1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* 2021, 593, 223.

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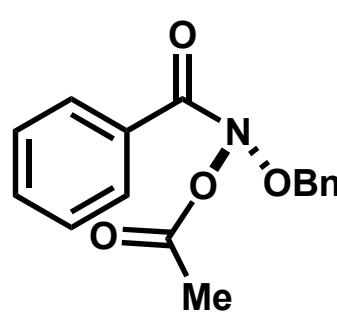
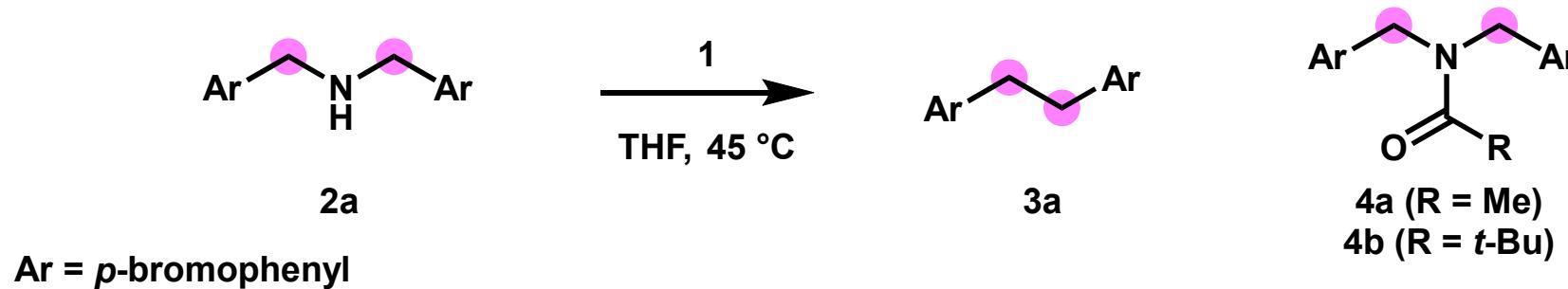
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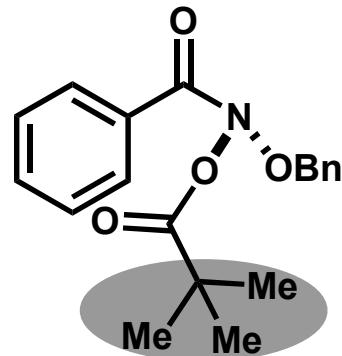
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(*Nature* 2021, 593, 223)

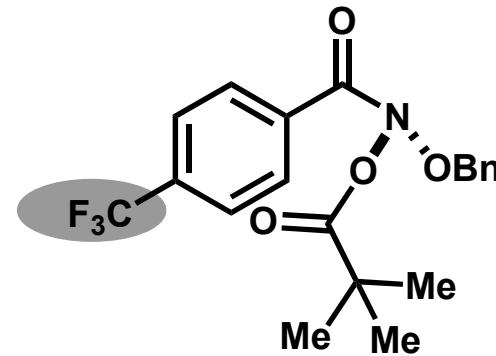
Optimization of the Reagent



2:1 3a/4a
35%^a



>20:1 3a/4b
57%^a

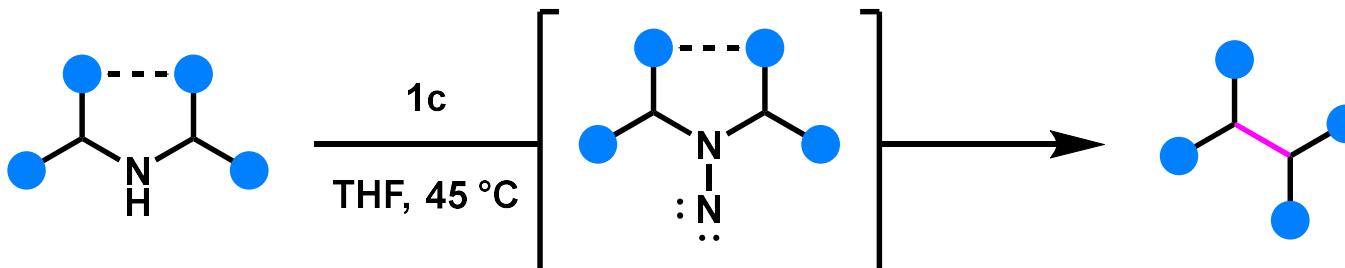


>20:1 3a/4b
74%^b

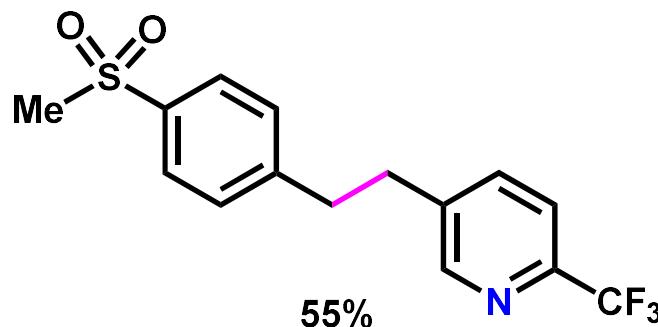
The yield stated are NMR yield.

^aThe reaction time was 18 h. ^bThe reaction time was 5 h.

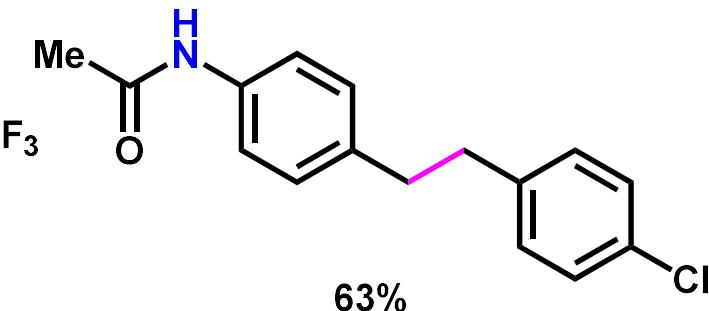
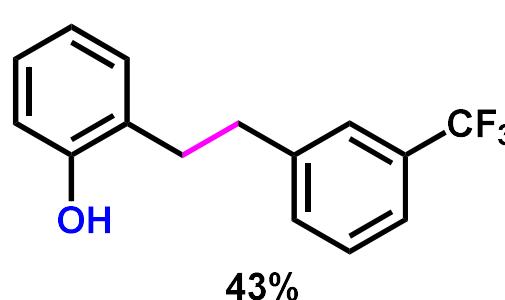
Substrate Scope (1)



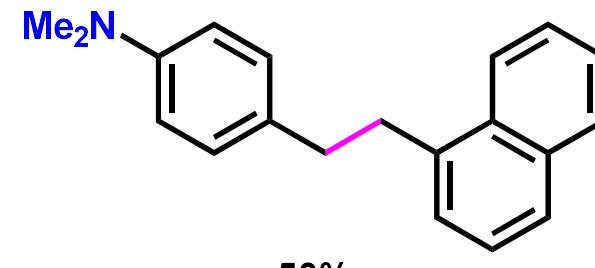
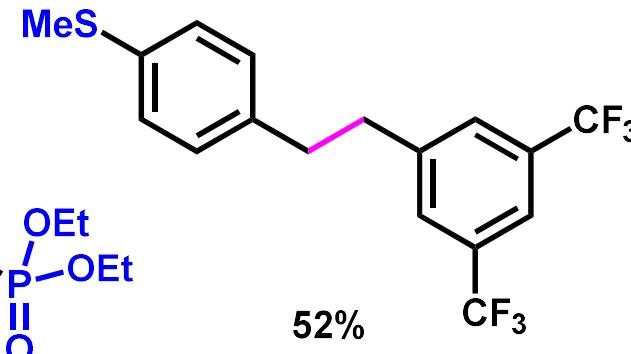
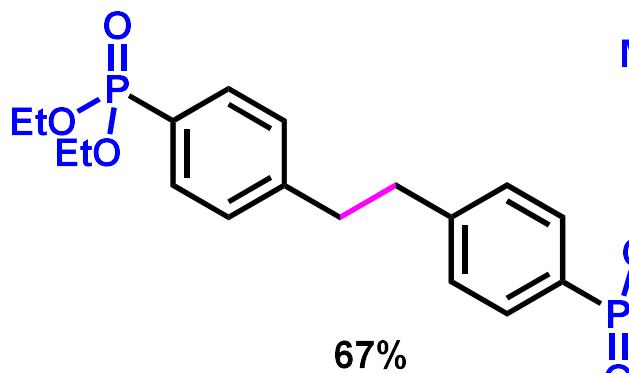
basic nitrogen heterocycles



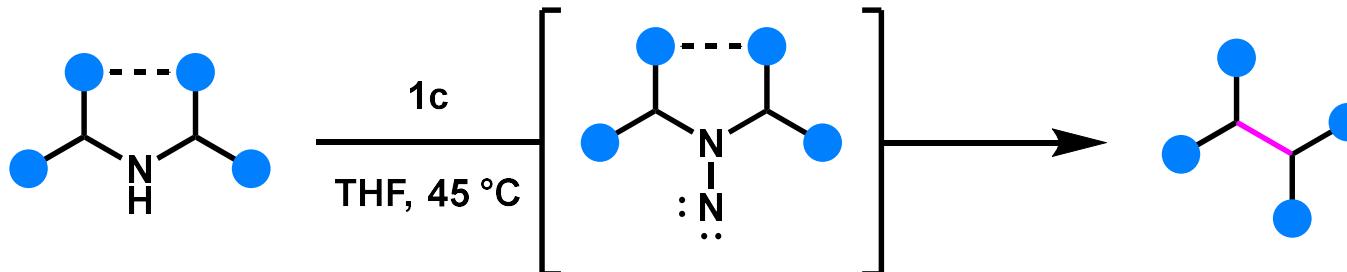
unprotected protic functionality



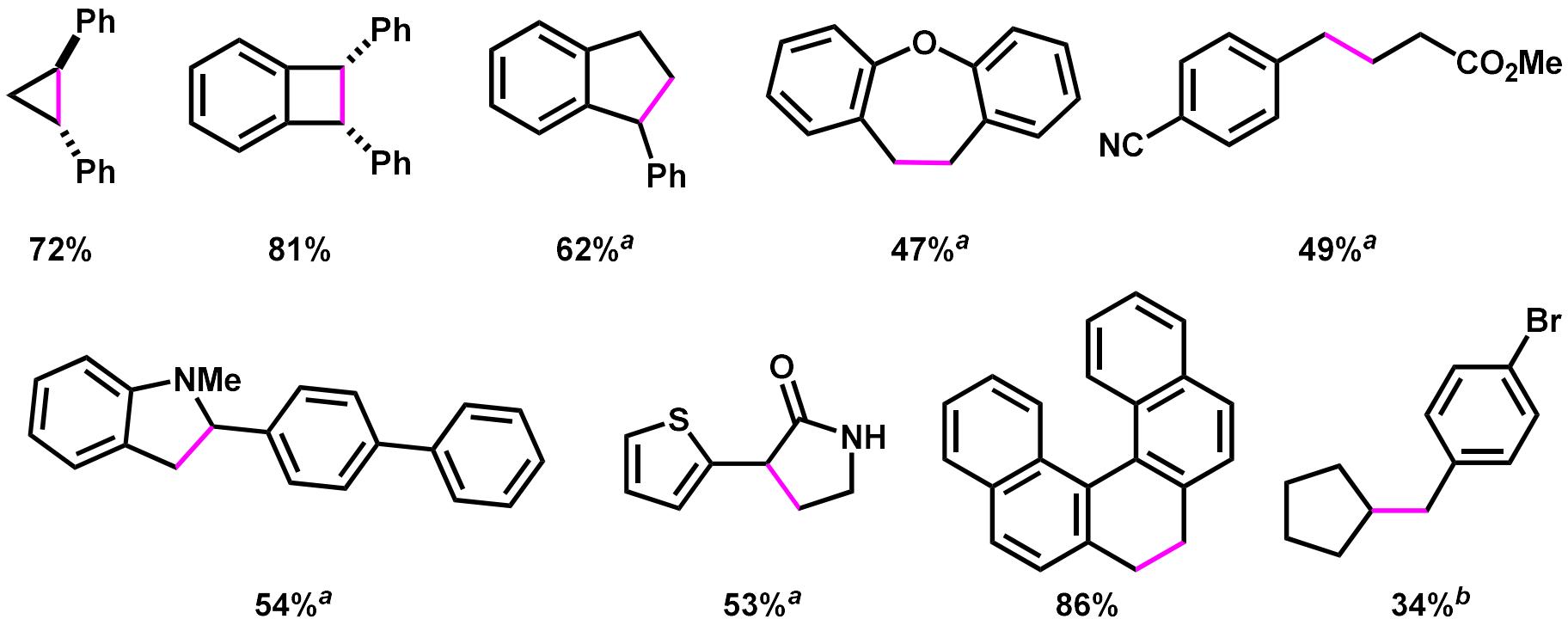
reducing or Lewis basic functionality



Substrate Scope (2)

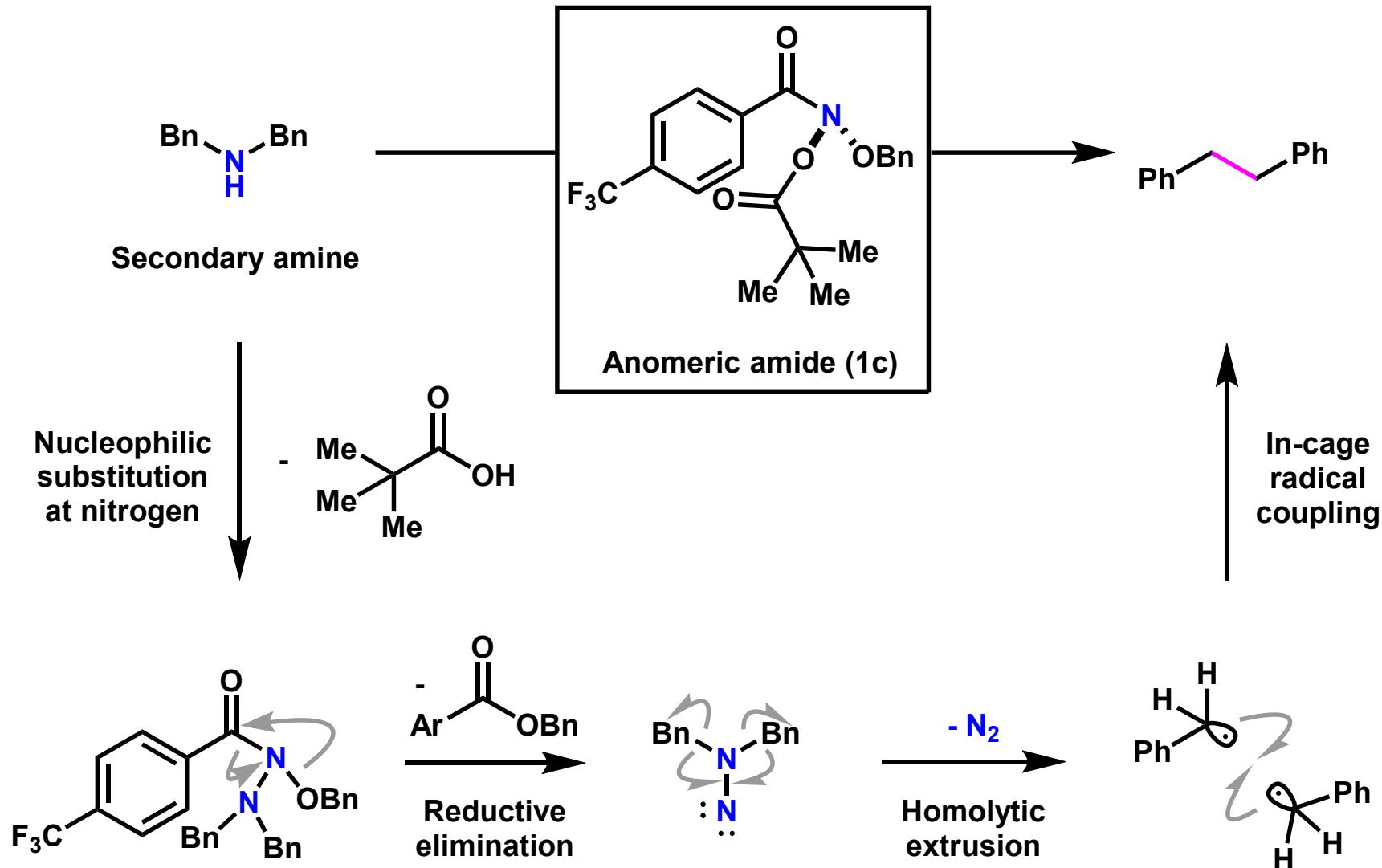


skeletal diversity



^a2 equivalents trimethylamine were added. ^b2 equivalents 1c

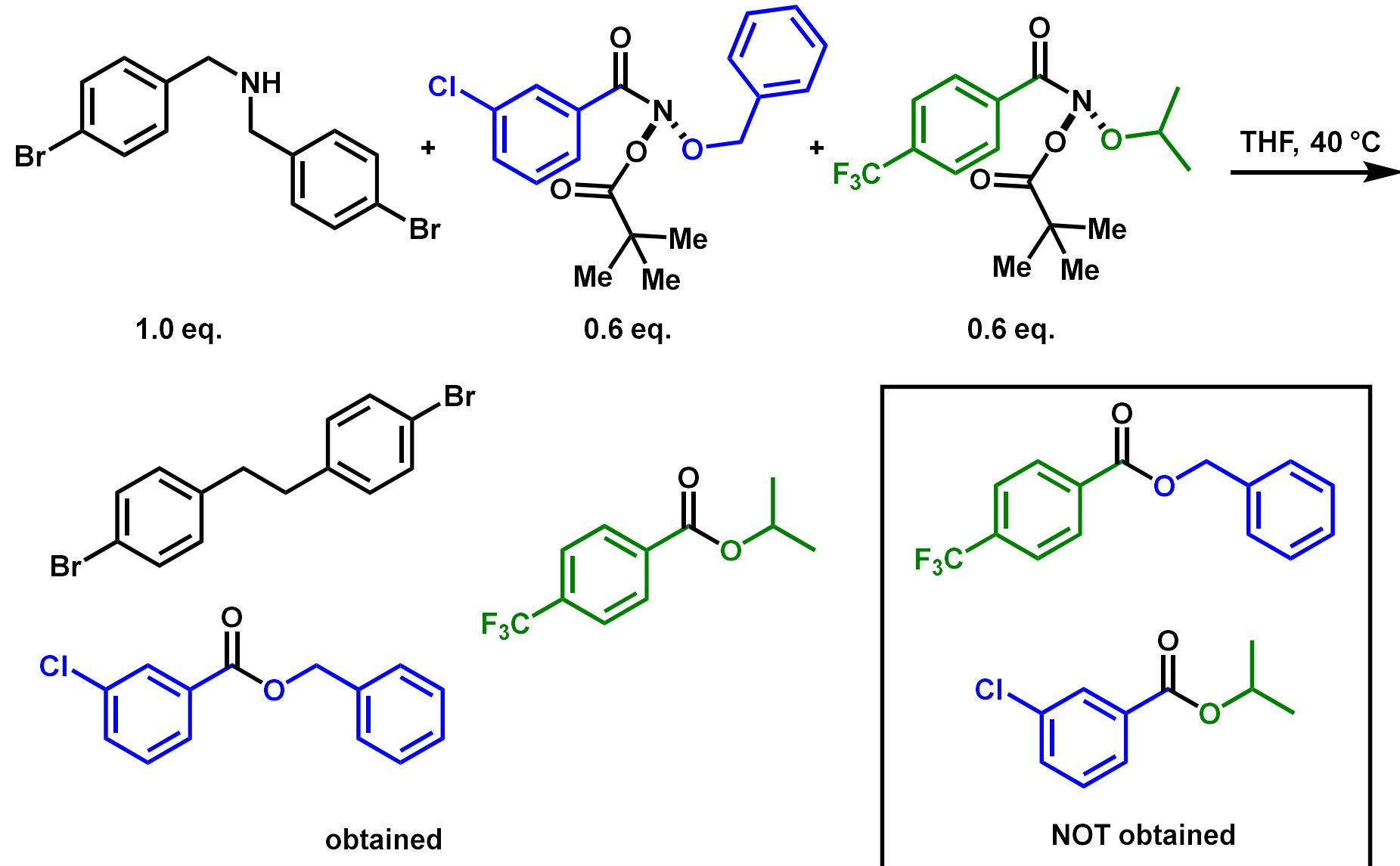
Proposed Reaction Mechanism



1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* 2021, 593, 223.

Mechanistic Experiments (1)

1. Crossover experiment

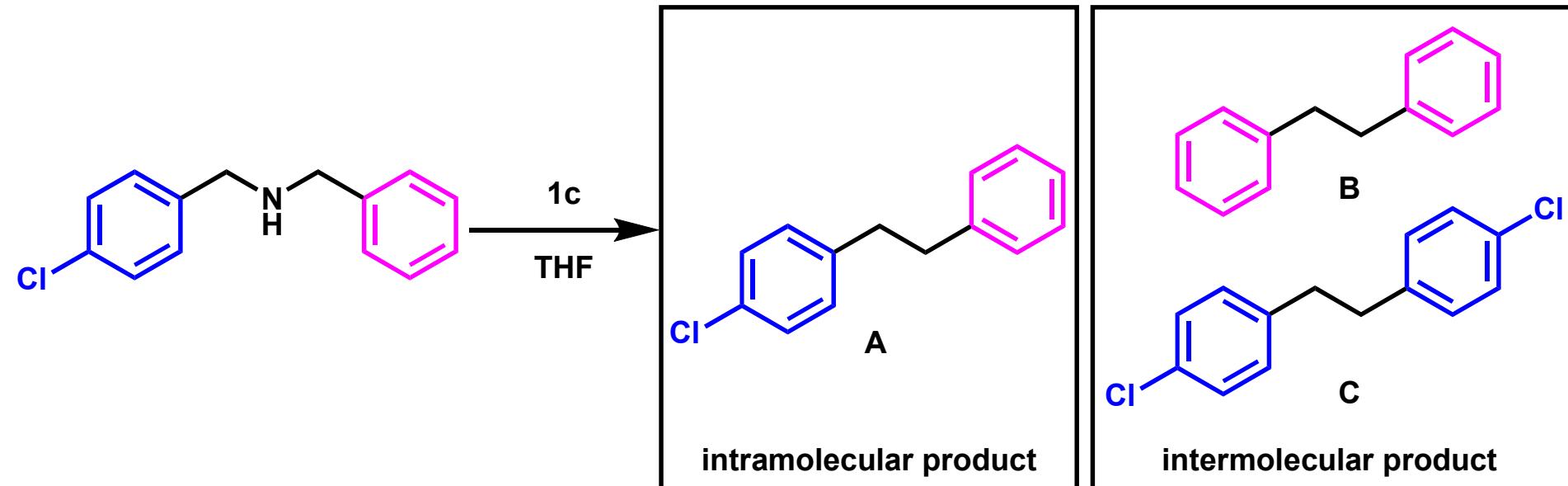


1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, 593, 223.

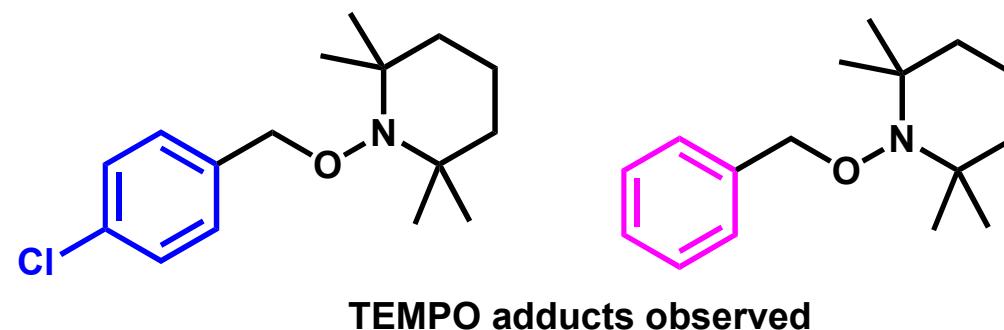
Mechanistic Experiments (2)

26

2. Scavenging of intermolecular products



No additive: A:B:C = 93:4:3
TEMPO (1.0 eq.): A:B:C = 100:0:0



TEMPO adducts observed

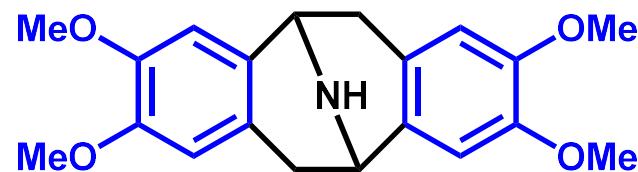
The result suggests largely in-cage C-C bond formation.

1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* 2021, 593, 223.

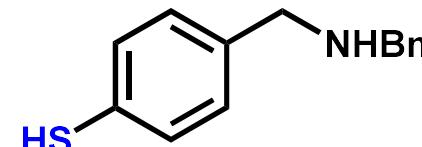
Limitations and Side Reactions (1)

1. Oxidation Sensitivity (→decomposition)

The anomeric amide can function as an oxidant.



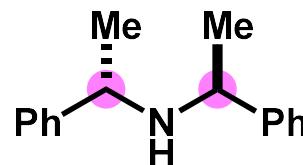
highly electron rich aromatics



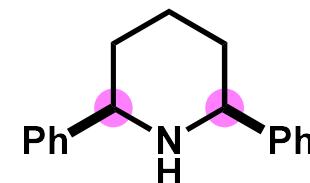
thiols

2. Steric hindrance (→no reaction)

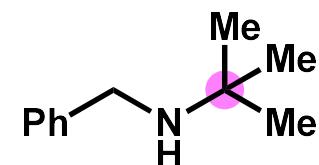
Steric hindrance makes it difficult for the anomeric amide to approach nitrogen.



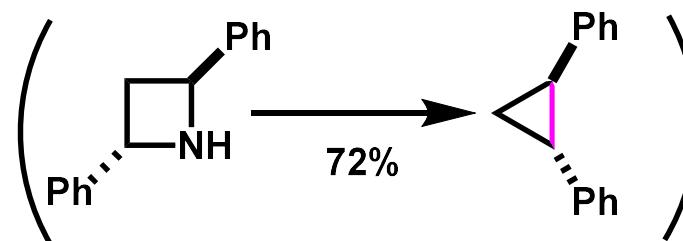
acyclic bis- α -secondary amine



cyclic bis- α -secondary amine
(dependent of the ring size)



acyclic α -tertiary amine



1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, 593, 223.

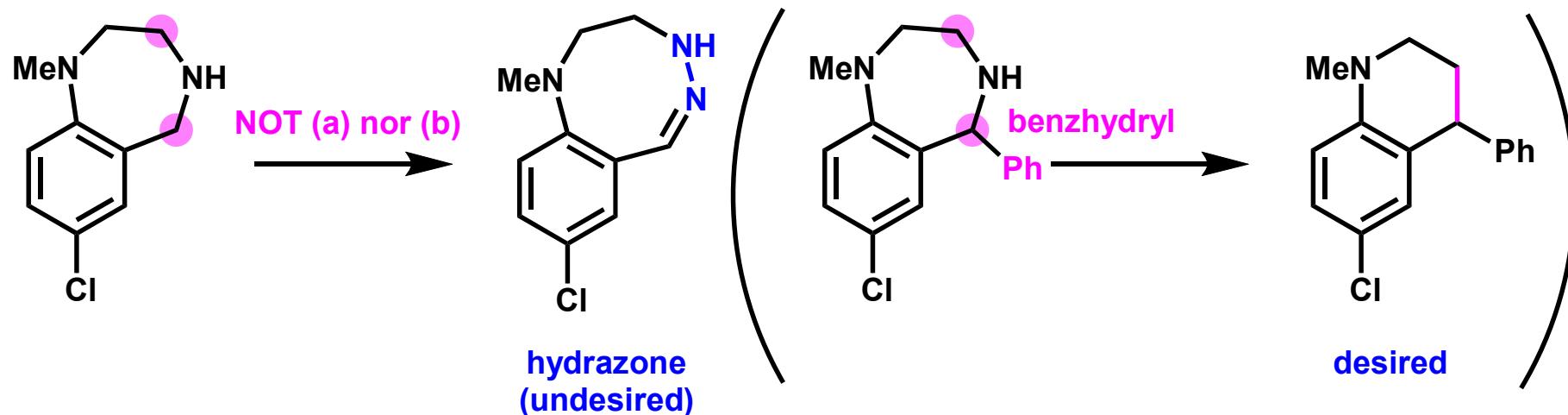
Limitations and Side Reactions (2)

3. Stabilizing elements (\rightarrow rearrangement to a hydrazone)

acyclic systems: a single benzylic substituent

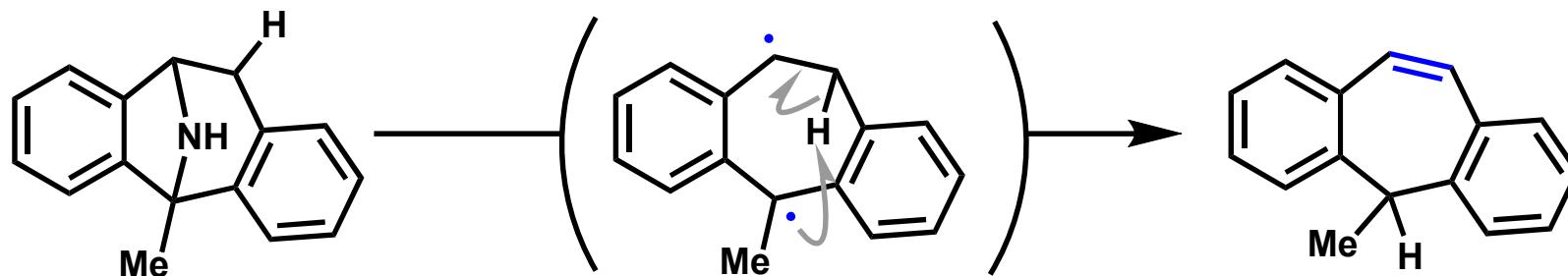
cyclic systems: (a) both substituents (●) must bear stabilizing elements (e.g. benzylic, allylic, etc.)

(b) one substituent must be benzhydral



4. Fragmentation processes

Even in cases where productive diradical formation occurs, competitive fragmentation processes (β -alkyl or β -H scission) can predominate rather than nitrogen deletion.

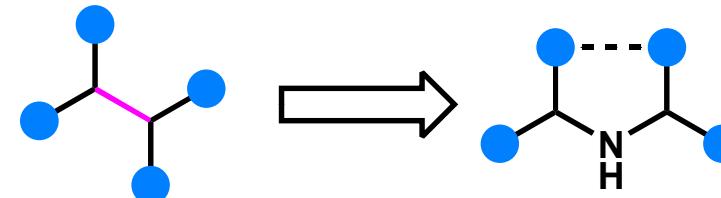


1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* 2021, 593, 223.

New Retrosynthetic Logic

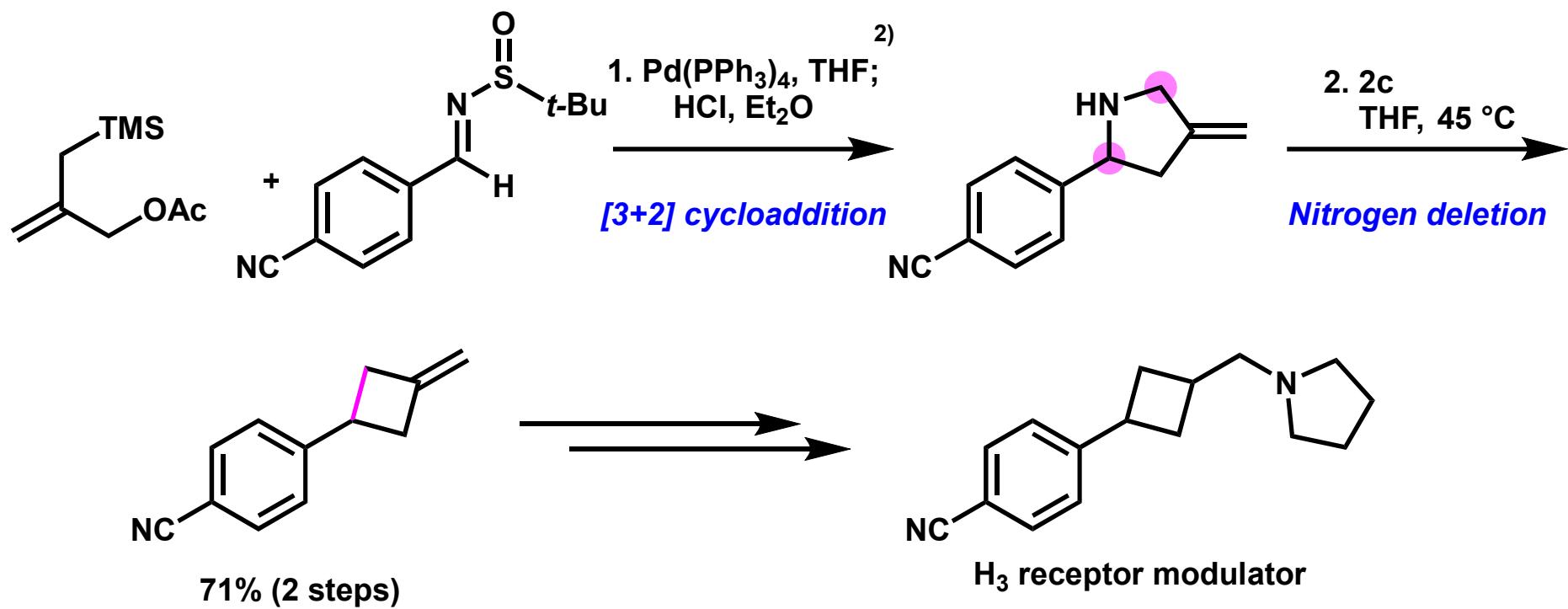
29

C-C bond → C-N-C bond



Advantages:

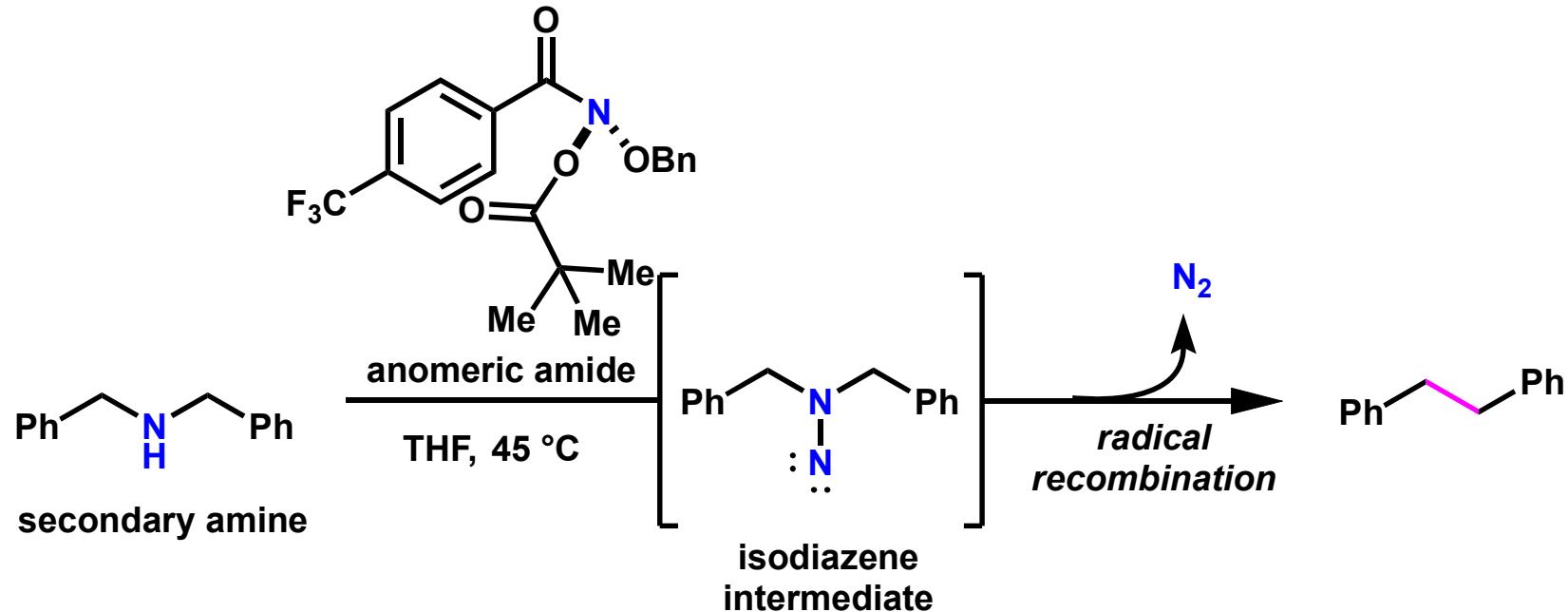
1. Reliability and broad scope iminium-based transformations
2. Broad functional-group tolerance



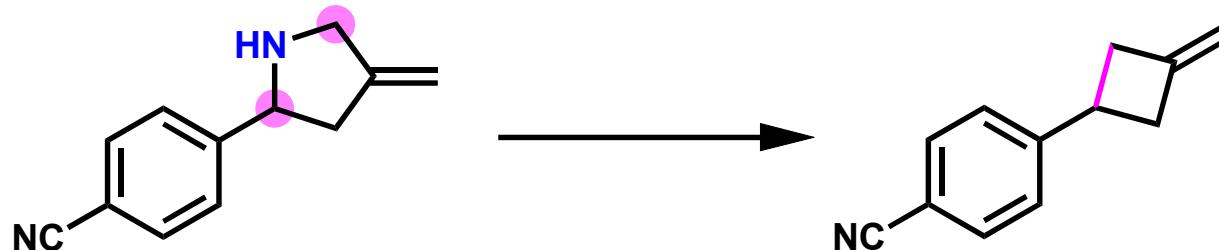
1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, 593, 223. 2) Procopiou, G.; Lewis, W.; Harbottle, G.; Stockman, R. A. *Org. Lett.* **2013**, 15, 2030.

Summary

- straightforward nitrogen deletion



- high functional-group tolerance
- valuable tool for C-C bond constructions and ring synthesis

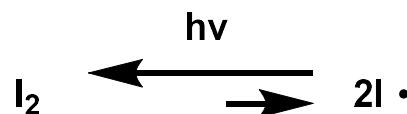


Appendix

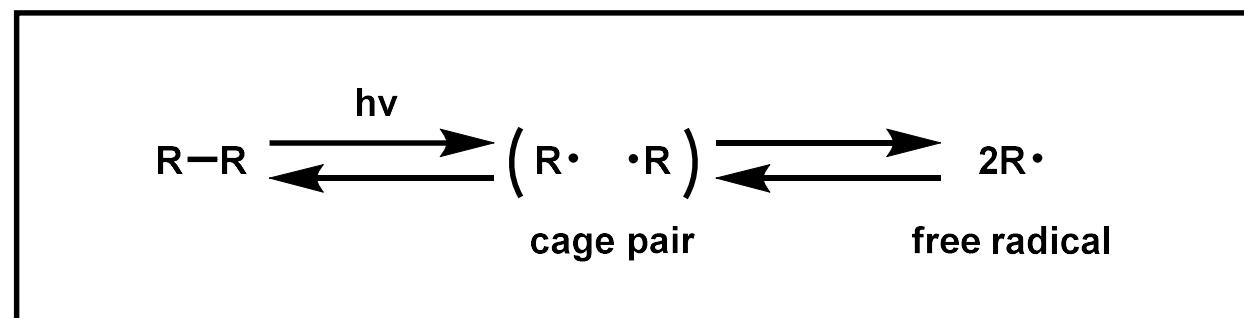
Cage Effect

32

Frank and Rabinowitch (1934)



"Cage effect" was introduced to explain the reason why the efficiency of I_2 photodissociation was lower in solution than in the gas phase.

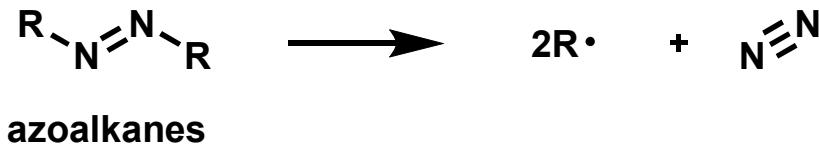


It was proposed that the solvent temporarily encapsulates the reactive R• atoms in a "solvent cage", causing them to remain as colliding neighbors before they recombine or diffuse apart.

1) Braden, D. A.; Parrack, E. E.; Tyler, D. R. *Coordin. Chem. Rev.* **2001**, *211*, 279.

Preceding Study (Azoalkanes)

Activation parameters

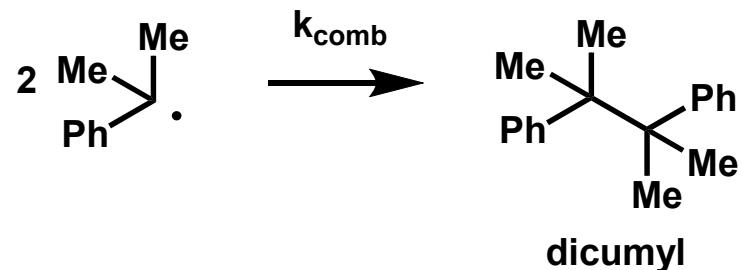
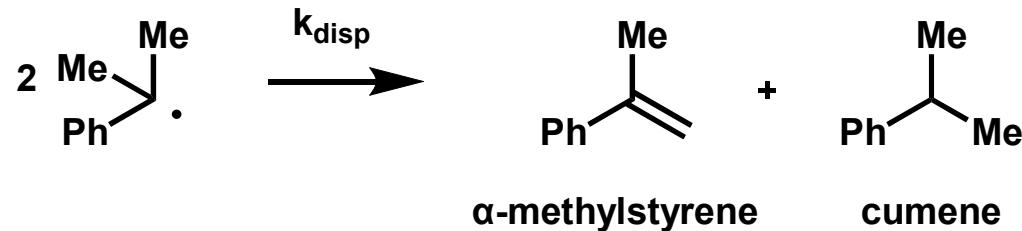
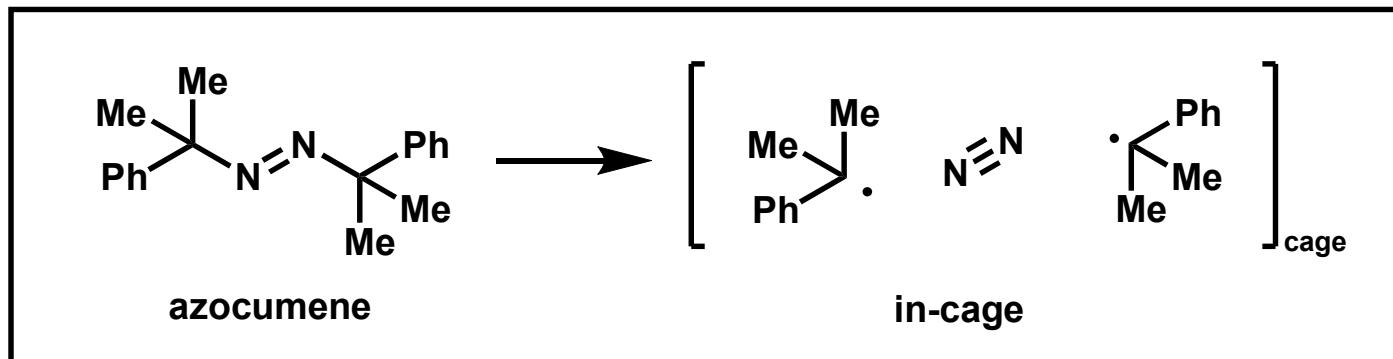


R in RN ₂ R	ΔH^* , kcal./ mole	ΔS^* , e.u.	Phase	Ref.
CH ₃	52.3	12.2	Vapor	9
CH ₃ CH ₂	49.5	12.2	Vapor	10
(CH ₃) ₂ C	44	16-17	Vapor	11
PhCH ₂	36	5	Vapor	12
Ph(CH ₃)CH	32.2	7.2	Dodecane	13

1) Nelsen, S. F.; Bartlett, P. D. *J. Am. Chem. Soc.* **1966**, *88*, 137.

Preceding Study (Azocumene)

Azocumene decomposition: radical coupling rate

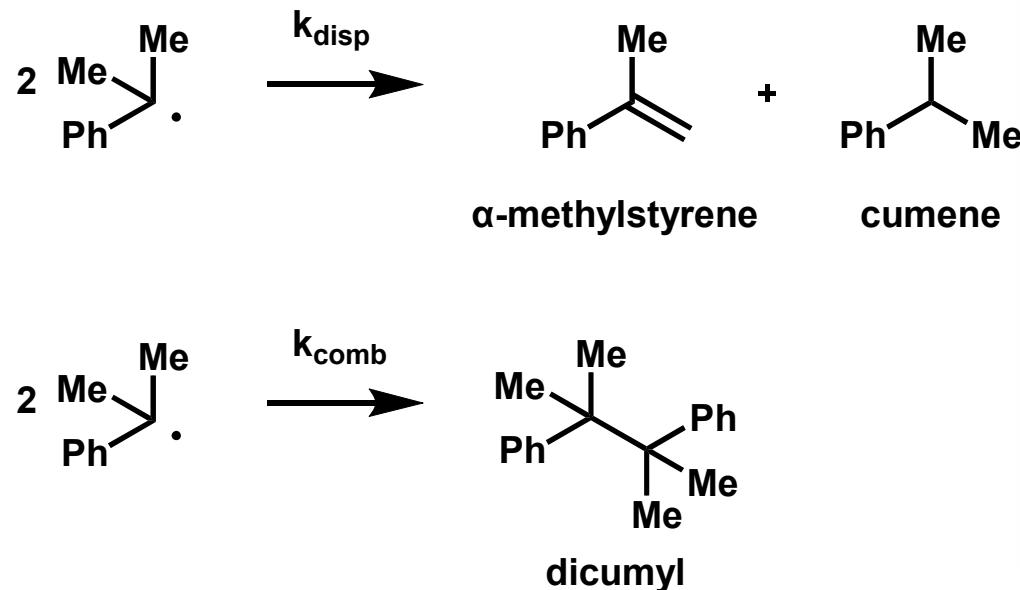


$k_{\text{disp}}/k_{\text{comb}}$ ratios were determined from the amount of cumene formed, with *p*-methylanisole as an internal standard.

1) Nelsen, S. F.; Bartlett, P. D. *J. Am. Chem. Soc.* **1966**, *88*, 137.

Preceding Study (Azocumene)

Azocumene decomposition: radical coupling rate¹⁾



Temp., °C.	—V.p.c. peak areas—			Initial azocumene, mmole	$k_{\text{disp}}/k_{\text{comb}}$	$(\text{Cu-mene})/(AMS)$
	Cumene	AMS	PMA ^a			
20.5 ^b	26.1	32.7	44.1	0.0436	0.054	0.80
	41.8	41.5	71.0		0.055	1.01
20.5 ^b	52.3	52.6	90.9	0.0436	0.054	0.99
	45.1	45.6	78.9		0.054	1.00
46.8	40.5	31.0	68.1	0.0436	0.056	1.31
	49.2	36.0	73.2		0.063	1.36
46.8	42.0	33.0	63.5	0.0436	0.062	1.27
60.0	26.4	22.7	52.2	0.0413	0.046	1.17
	30.2	...	56.2		0.049	...
60.0	30.5	23.6	49.5	0.0413	0.056	1.30
	55.0	45.8	93.7		0.054	1.20
"170" ^c	34.1	33.6	57.0	0.0413	0.054	1.01
	63.4	63.5	81.5		0.072	1.00

^a 0.0356 mmole of *p*-methylanisole was used as internal standard in all runs. ^b Photolytic decomposition using a 450-w. Hanovia lamp and Corning 7-37 filter. ^c Direct injection into v.p.c. injection port at 170°; temperature control is not good, but a very rapid thermal decomposition must have taken place in the injection port.

No significant variation of the amounts of disproportionation and combination was observed with temperature

→ [The activation energies for the two processes must be very close.](#)

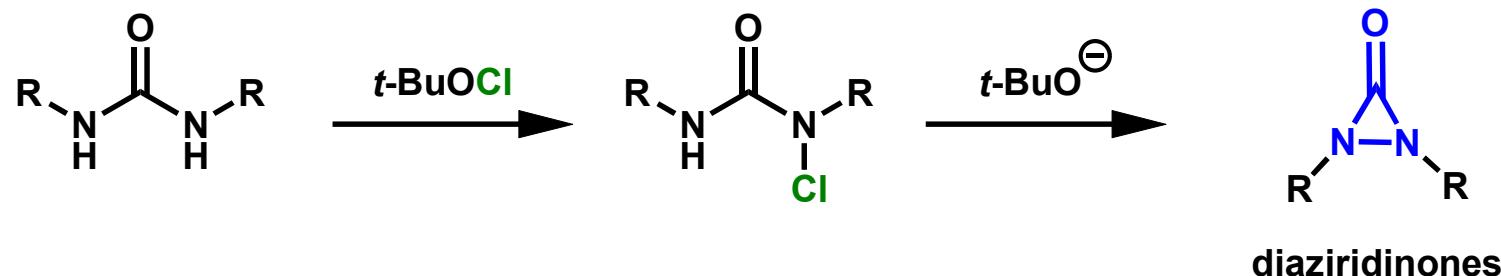
In the comparison of isobutyl, sec-butyl, *t*-butyl radicals the relative values of $k_{\text{disp}}/k_{\text{comb}}$ were 1:5.4:11.0

→ All radicals coupling occurred at the same rate.²⁾

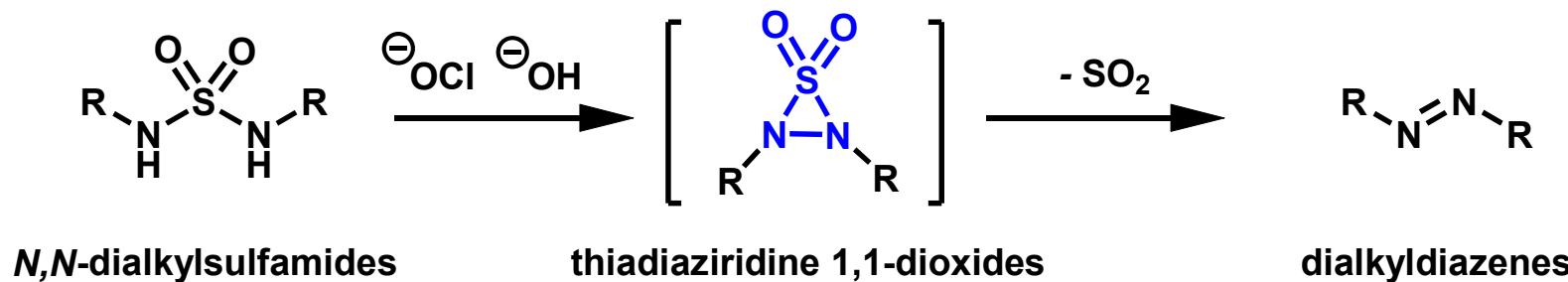
1) Nelsen, S. F.; Bartlett, P. D. *J. Am. Chem. Soc.* **1966**, *88*, 137. 2) Kraus, J.; Calvert, J. *J. Am. Chem. Soc.* **1957**, *79*, 5921.

Preceding Study (Thiadiaziridine 1,1-Dioxides)³⁶

Greene et al (1964)¹⁾: Studies toward formation of N-N bonds

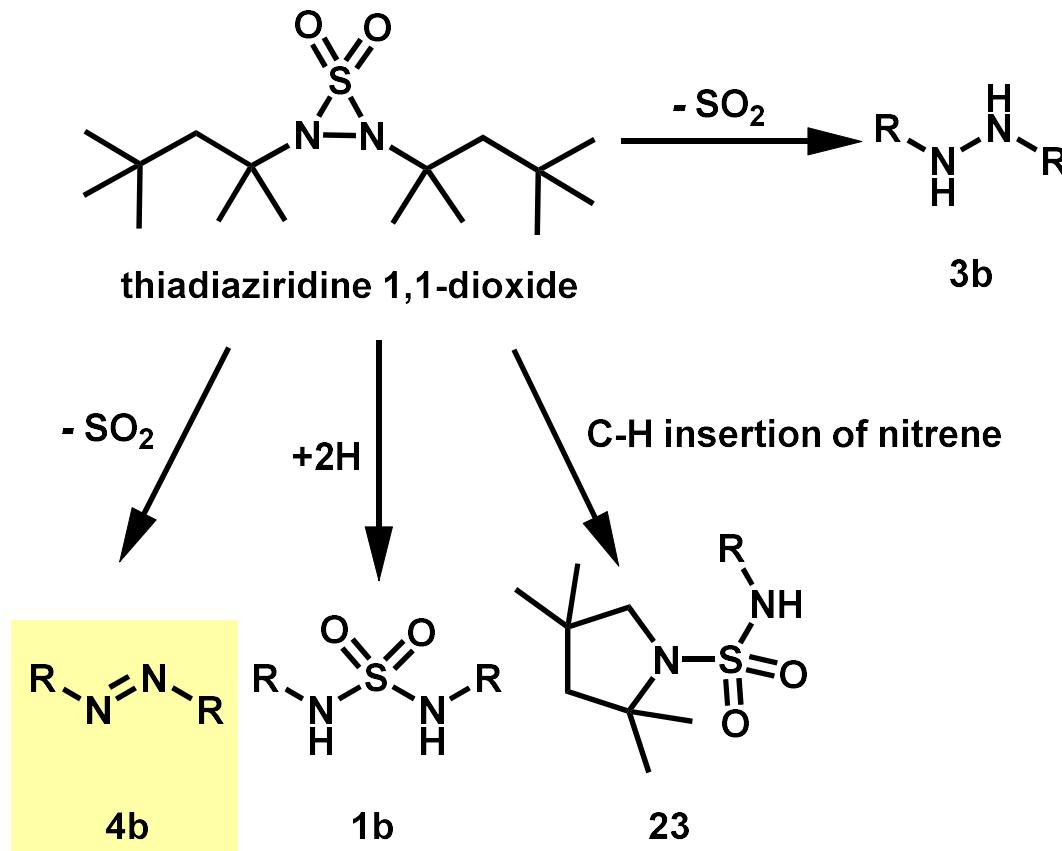


Ohme et al (1965)²⁾



1) (a) Greene, F. D.; Stowell, J. C. *J. Am. Chem. Soc.* **1964**, 86, 3569. (b) Greene, F. D.; Stowell, J. C.; Bergmark, W. J. *Org. Chem.* **1969**, 34, 2254. 2) Ohme, R.; Schmidt, E. *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 433.

Preceding Study (Thiadiaziridine 1,1-Dioxides)³⁷



mild conditions: No reaction
 more rigorous conditions: Diazene 4b was obtained.

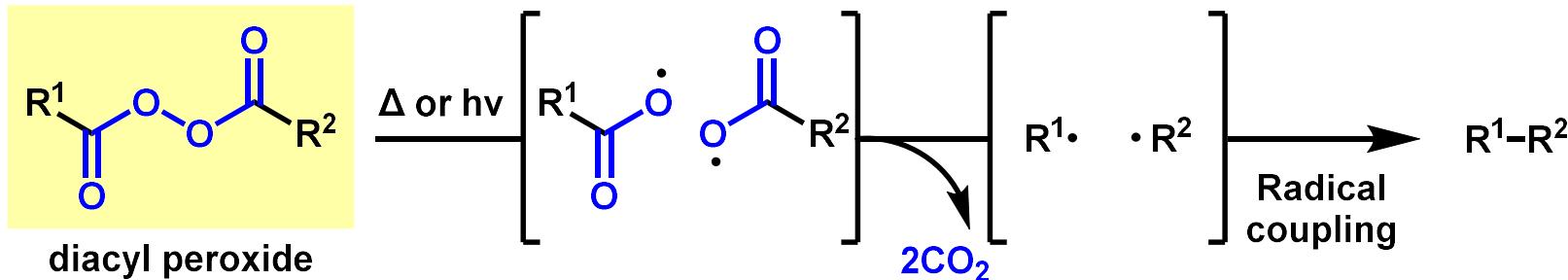
reagents	conditions ^a	products ^b
HOAc	24 h, 60 °C	NR
C ₆ H ₅ OH	48 h, 80 °C	NR
C ₆ H ₅	4 h, 80 °C	NR
HCl	1 h, 50 °C, 3 M	NR
NaOH	2 M, 1 h, RT	NR
Cl ₂	1 h, RT	NR
H ₂ O ₂	3 h, 36 °C	NR
KMnO ₄	3 h, 36 °C	NR
(t-BuNH-) ₂	2 h, 80 °C	NR
diphenylketene	24 h, RT	NR
(MeO ₂ CC=) ₂	24 h, 60 °C	NR
HCl	12 M, 30 min, 60 °C	4b
HCl gas	30 min, 25 °C	4b
picric acid	24 h, RT	4b
NaOH	30 min, 80 °C	4b
NaOCH ₃	30 min, 60 °C	4b
Cl ₂	1 h, 50 °C	4b
t-BuOCl	3 h, 36 °C	4b
C ₆ H ₅ Cl	2 h, 25 °C	4b
LiAlH ₄	1 h, 35 °C	4b + 1b (4:1)
C ₆ H ₅ SH	excess, 3 h, C ₆ H ₆ , reflux	1b
Bu ₃ SnH	24 h, RT	1b
H ₂	24 h, RT, Pd/C, 50 psi	1b
Nap ⁻	140 h, RT	1b
CH ₃ MgI	2 h, 35 °C	1b
C ₆ H ₅ CH ₂ MgCl	2 h, 35 °C	1b
H ₂ O	THF or C ₆ H ₅ , 24 h, reflux	3b·H ₂ SO ₄
cumene	24 h, reflux	23
cumene	24 h, 75 °C	23 + 1b (3.5:1)
PhNCO	72 h, 80 °C	23 + 24 (2.5:1)
C ₆ H ₅ CH ₃	48 h, reflux	23
C ₆ H ₅	72 h, reflux	23
C ₆ H ₅ SH	24 h, C ₆ H ₆ , reflux, 1 equiv	1b + 23 (1:1)

^a RT = room temperature. ^b NR = no reaction.

1) Timberlake, J. W.; Alender, J.; Garner, A. W.; Hodges, M. L.; Özmeral, C.; Szilagyi, S. *J. Org. Chem.* 1981, 46, 2082.

Preceding Study (Diacyl Peroxides)

Decomposition of diacyl peroxides with radical coupling

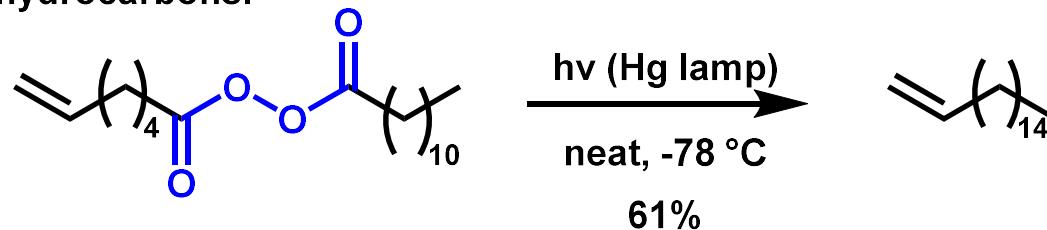


In practice, this approach is not often used because...

- all diacyl peroxides are explosive.
- side reactions (e.g. hydrogen abstraction) and crossover radical coupling often occur.

Schäfer et al (1985)²

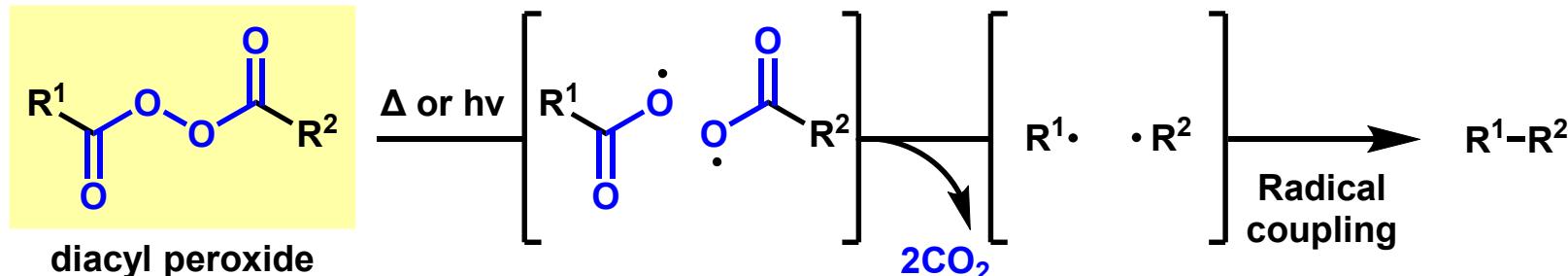
Low temperature (- 78 °C) photolysis of aliphatic diacyl peroxides for the efficient synthesis of long chain aliphatic hydrocarbons.



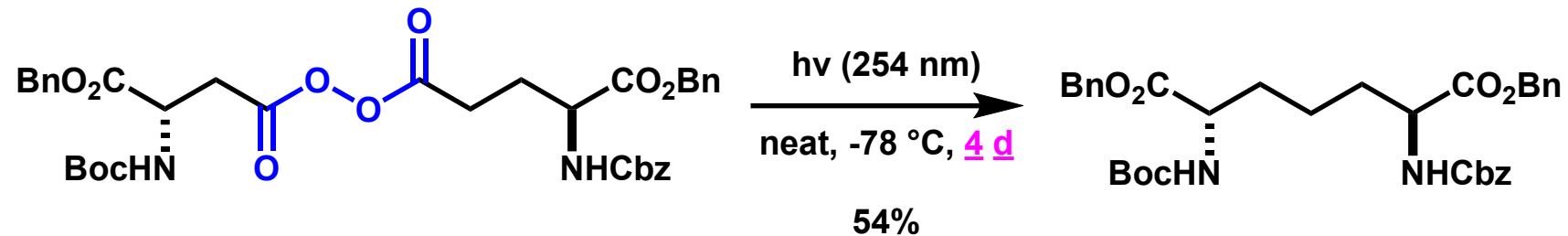
1) Spantulescu, M. D.; Jain, R. P.; Derksen, D. J.; Vedera, J. C. *Org. Lett.* 2003, 5, 2963. 2) Feldhues, M.; Schäfer, H. J. *Tetrahedron* 1985, 41, 4213.

Preceding Study (Diacyl Peroxides)

Decomposition of diacyl peroxides with radical coupling

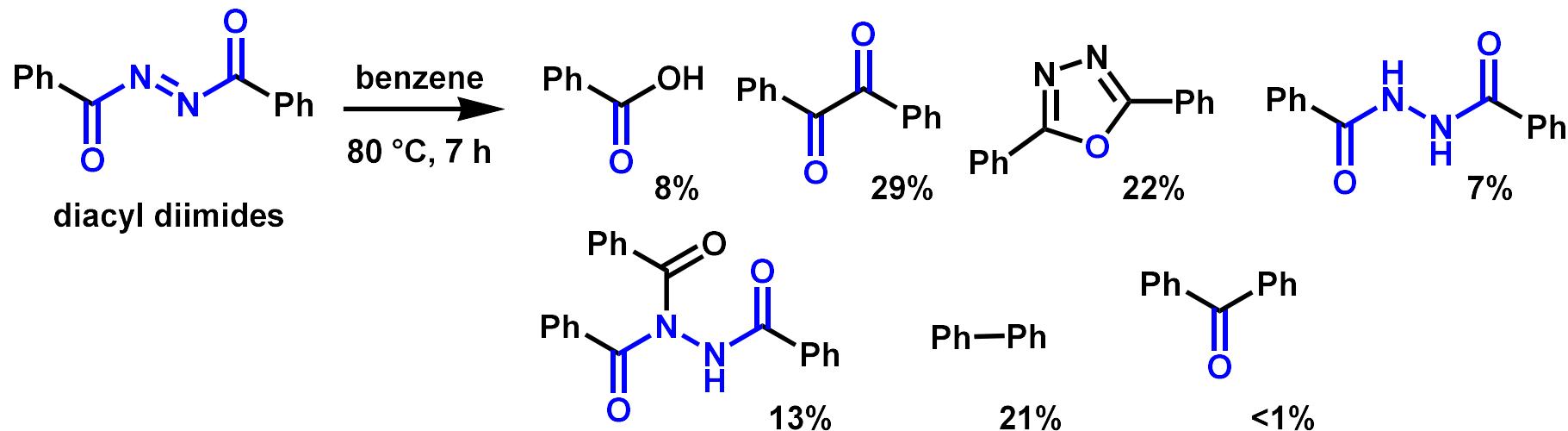
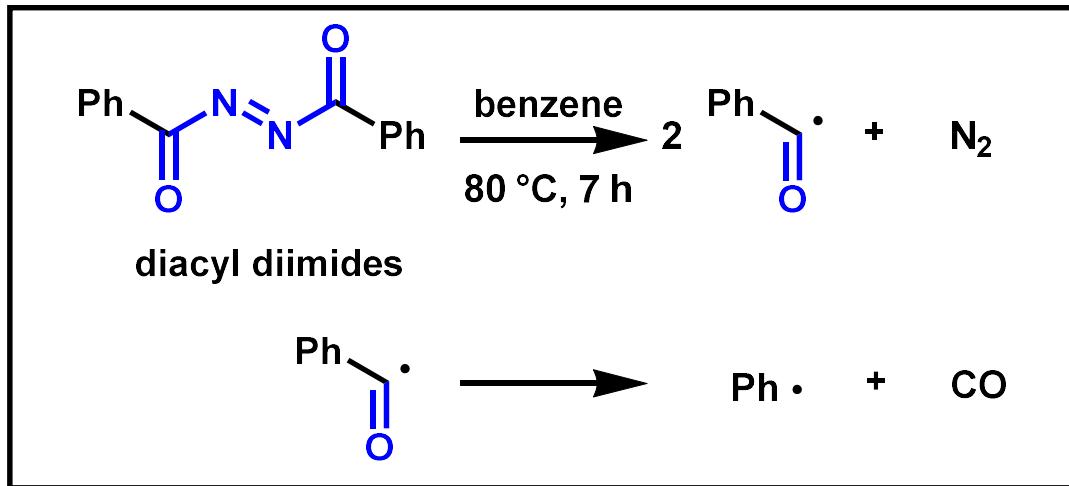


Application: Synthesis of functionalized amino acids¹⁾



1) Spantulescu, M. D.; Jain, R. P.; Derksen, D. J.; Vederas, J. C. *Org. Lett.* 2003, 5, 2963.

Preceding Study (Azodibenzoyl)



The products of the diimides are complex, numerous, and dependent on the nature of the solvent.

1) Mackay, D.; Marx, U. F.; Waters, W. A. *J. Chem. Soc.* **1964**, 4793.

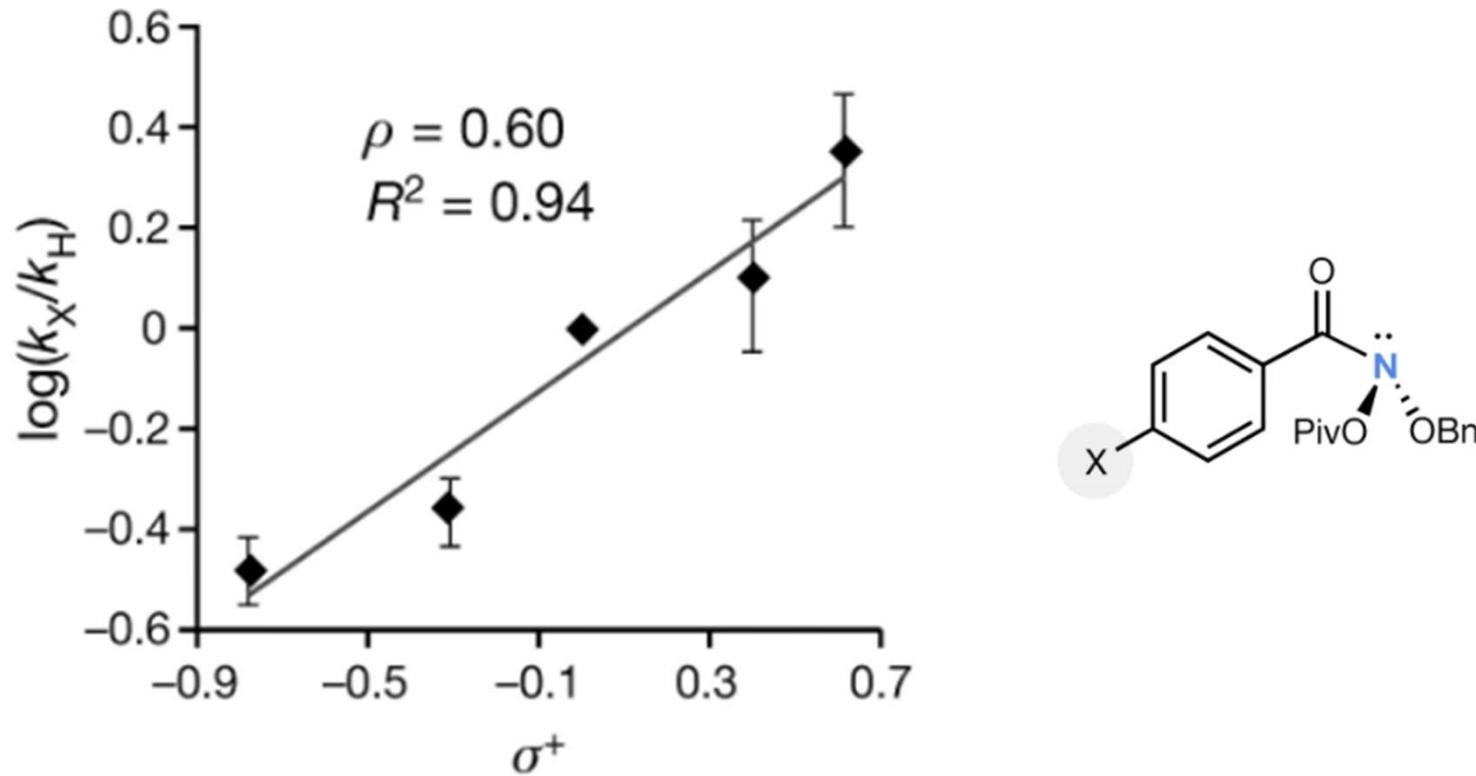
Preceding Study (Azodibenzoyl)

(All yields are in moles per hundred moles of starting material.)

Reactants, concentrations, conditions	Gases	PhCO ₂ H	PhCHO	Diphenyl- (PhCO) ₂ N oxadiazole	(PhCONH) ₂	PhCONH	(PhCO) ₂ N Other products
<i>A. Silver Oxide Oxidations</i>							
PhCO-NH-NH ₂ (0.03 mole), benzene (1%), 7 hr., 80°	71 total 3.6 CO ₂	31	5*	12	1	2	4 Ph ₂
PhCO-NH-NH ₂ (0.01 mole), cumene (3%), 76 hr.	76 total	47	<1 ^b	3	1	2	1 bicumyl ^b
(PhCONH) ₂ (0.01 mole), benzene (2%)	71 total	100	trace ^b	22			4 Ph ₂
<i>B. Photolytic Decompositions of Azodibenzoyl</i>							
0.01 mole, benzene (1%), 7 hr., 80°	51 total 6 CO ₂ +ve CO ^c	8	none ^b	29 ^b	22	7	13 21 Ph ₂ ^b <1 PhCOPh ^b
0.01 mole, cumene (10%), 8 hr., 140—150°	32	trace ^b	10 ^d	25	10		No bicumyl ^b
0.001 mole, no solvent, 5 hr., 100°	62 total +ve CO ^c	trace	trace	24 ^b	19 ^b	8	7 No Ph ₂ ^b No PhCOPh ^b
<i>C. Thermal Decompositions of Azodibenzoyl^f</i>							
0.02 mole, toluene (4%), 6 hr., 110°	5.5 CO ₂			9	22	4	7 C ₂₁ H ₁₆ N ₂ O ₂ ^e
0.03 mole, ethylbenzene (7%), 4 hr., 110°					40	6	
0.02 mole, chlorobenzene (4%), 3 hr., 132°	26 CO ₂	5	1*	6	25	6	
0.01 mole, chlorobenzene (0.5%), 3 hr., 132°	17 CO ₂	2		5	19	14	2
0.03 mole, nitrobenzene (4%), 2 hr., 150°	34 CO ₂ +ve			2	2	5	2 PhCONHPh
0.02 mole, tetrachloroethylene (4%), 7 hr., 121°	+ve CO ₂	8			24	2	HCl
0.02 mole, o-dichlorobenzene (5%), 4 hr., 135°	14 CO ₂	7			11		
0.002 mole, no solvent, 2 hr., 200° (by D. M.)	trace			9	24		

* Identified as 2,4-dinitrophenylhydrazone. ^b Detected or estimated by vapour phase chromatography. ^c Detected by the colour reaction with dodecamolybdophosphoric acid-palladium chloride reagent. ^d Estimated by chromatography on alumina. ^e M. p. 135°, not depressed in admixture with authentic 3-benzoyl-2,5-diphenyl-2,3-dihydro-1,3,4-oxadiazole (see ref. 18). ^f Experimental work by U. F. M.

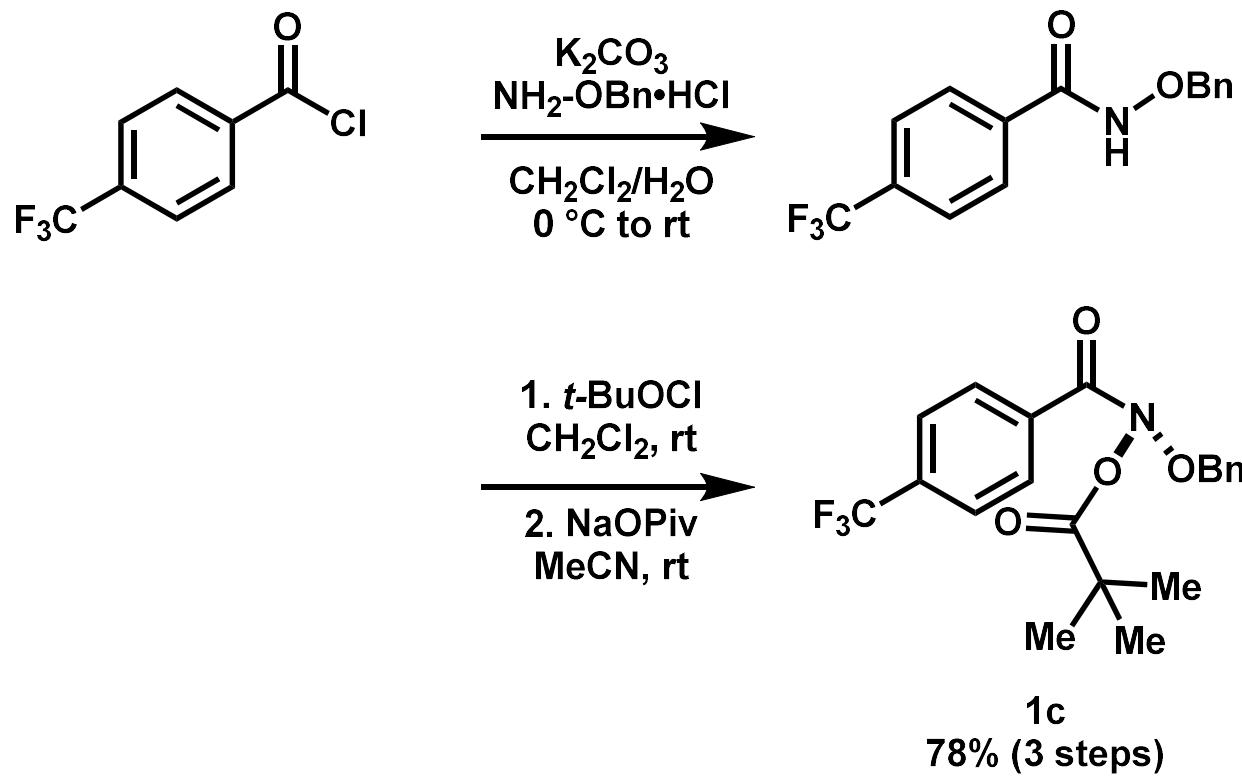
Hammet Plot



Hammet plot indicates the electronic origin of the increased rate of reaction with reagent 1c.

1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, 593, 223.

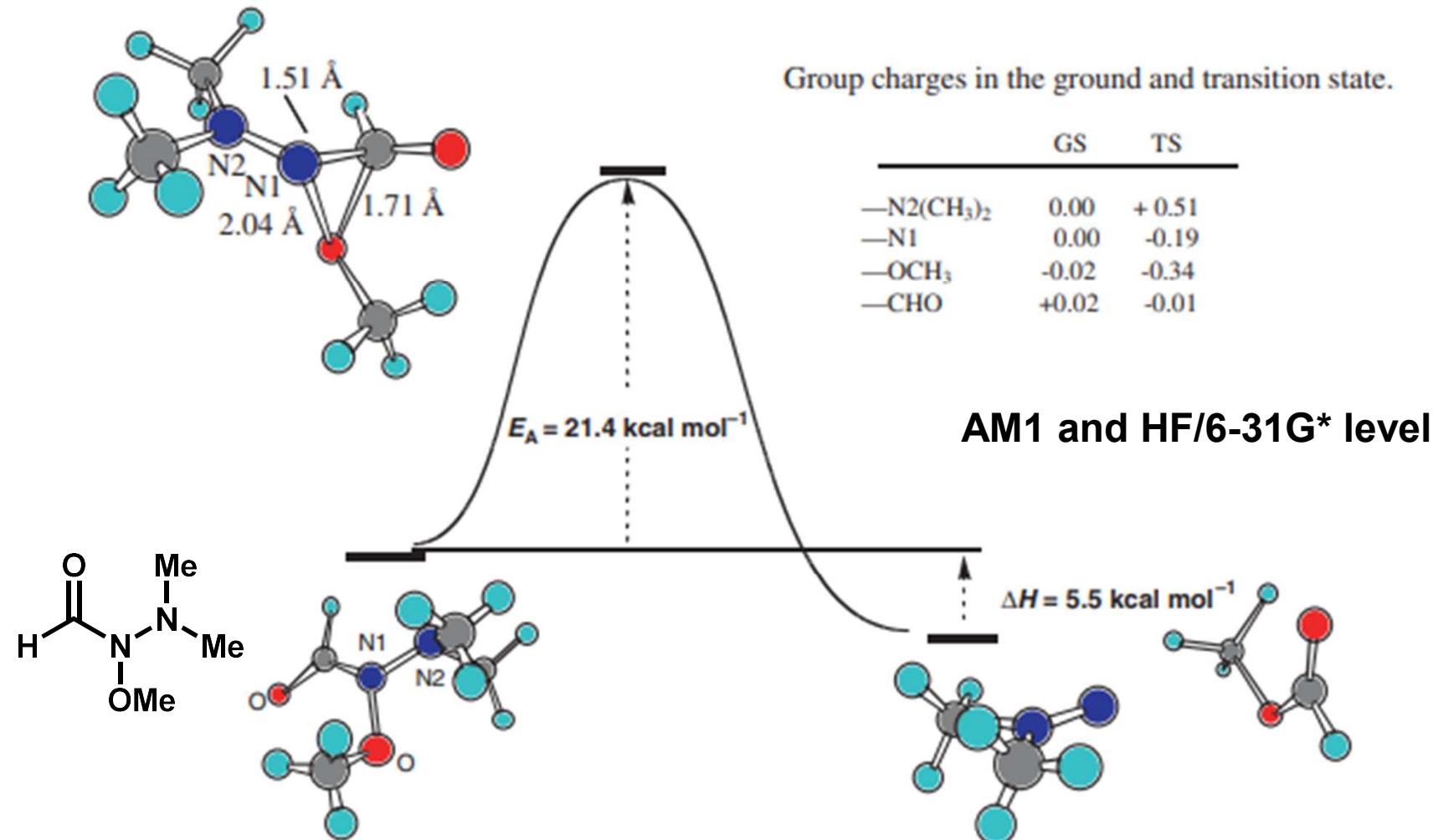
Preparation of the Reagent



Decagram scale
No chromatography

1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, 593, 223.

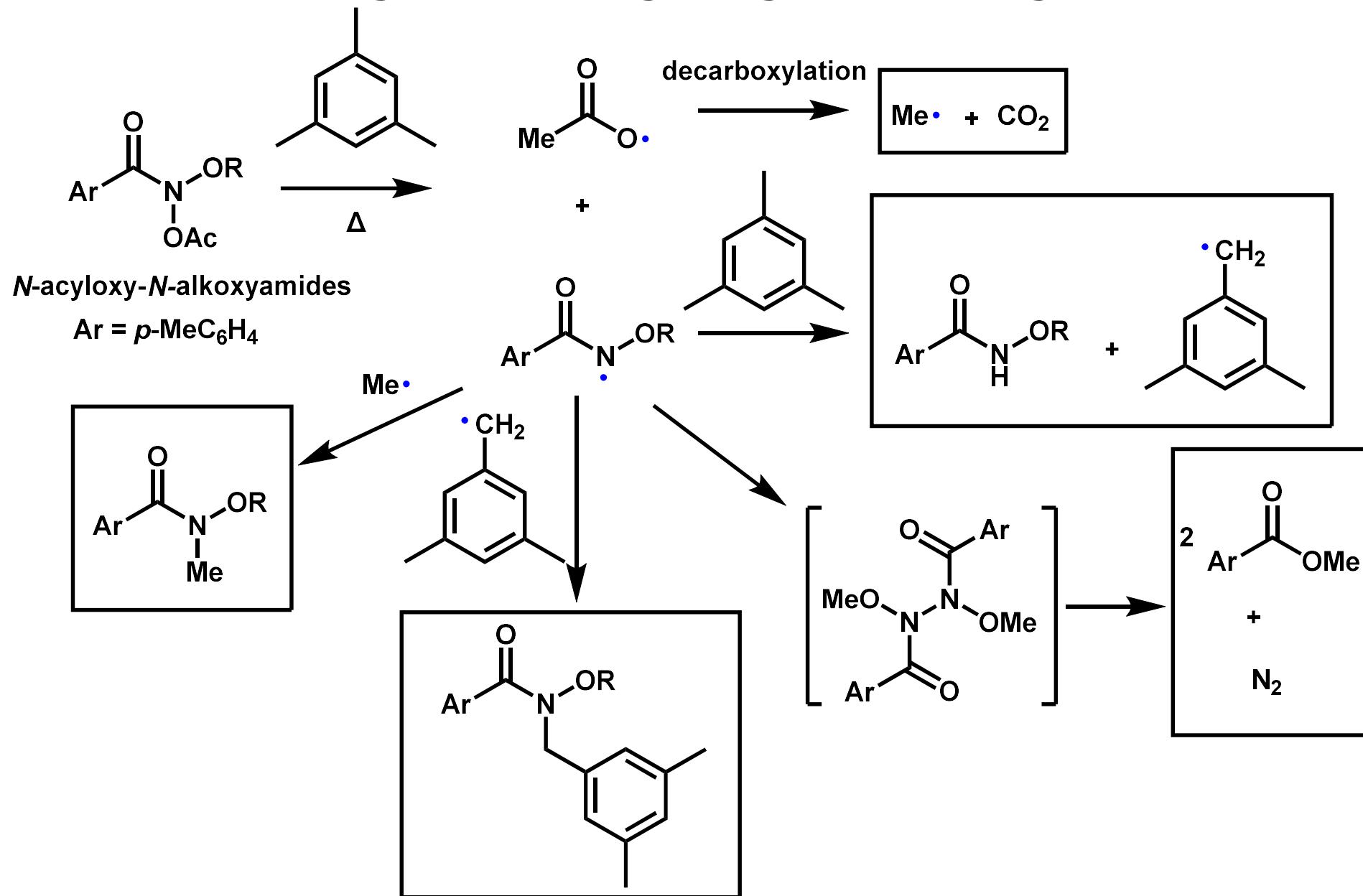
Transition State for a HERON Reaction



The transition-state geometry shows that the N-C bond is intact, and the carbonyl bond is virtually unaltered. In essence, this reaction represents an intramolecular $\text{S}_{\text{N}}2$ reaction on the amide carbonyl.

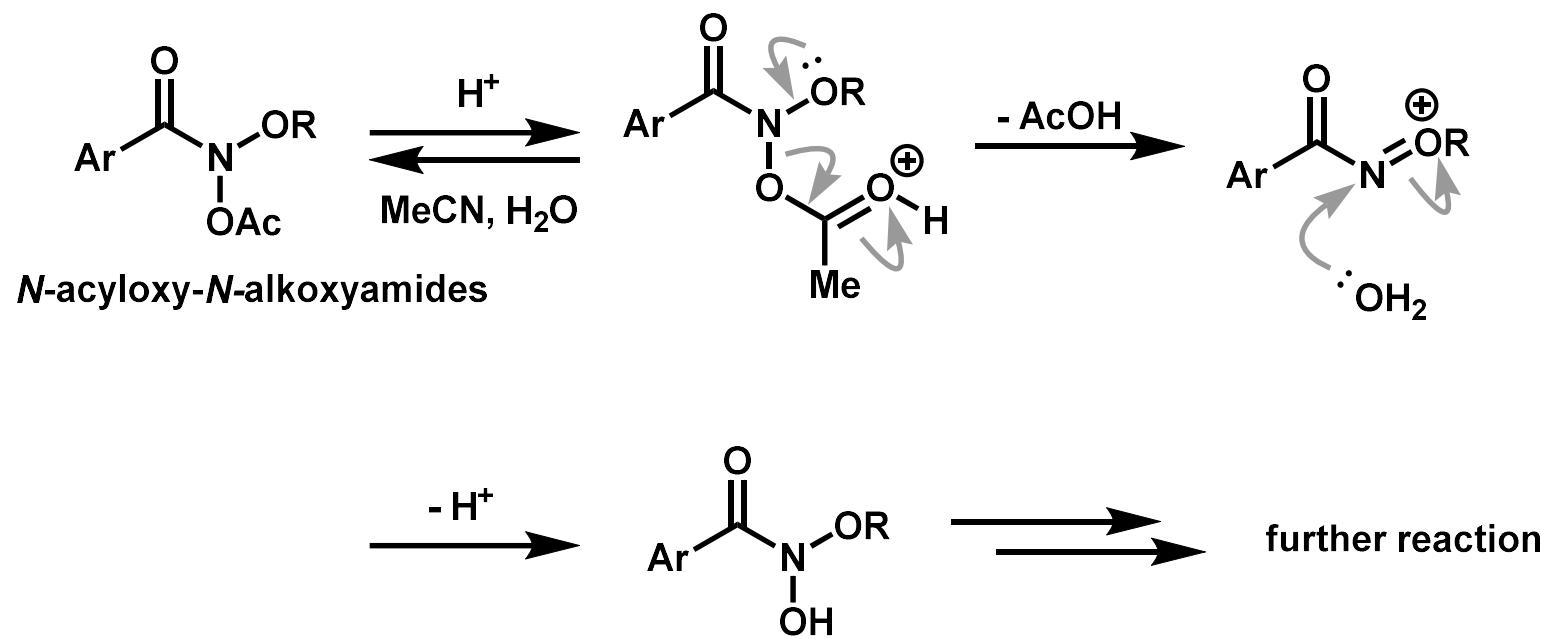
1) Glover, S. A.; Rauk, A.; Buccigross, J. M.; Campbell, J. J.; Hammond, G. P.; Mo, G.; Andrews, L. E.; Gillson, A. E. *Can. J. Chem.* **2005**, 83, 1492.

Reactivity of *N*-Acyloxy-*N*-alkoxyamides



1) Glover, S. A. *Tetrahedron* 1998, 54, 7229.

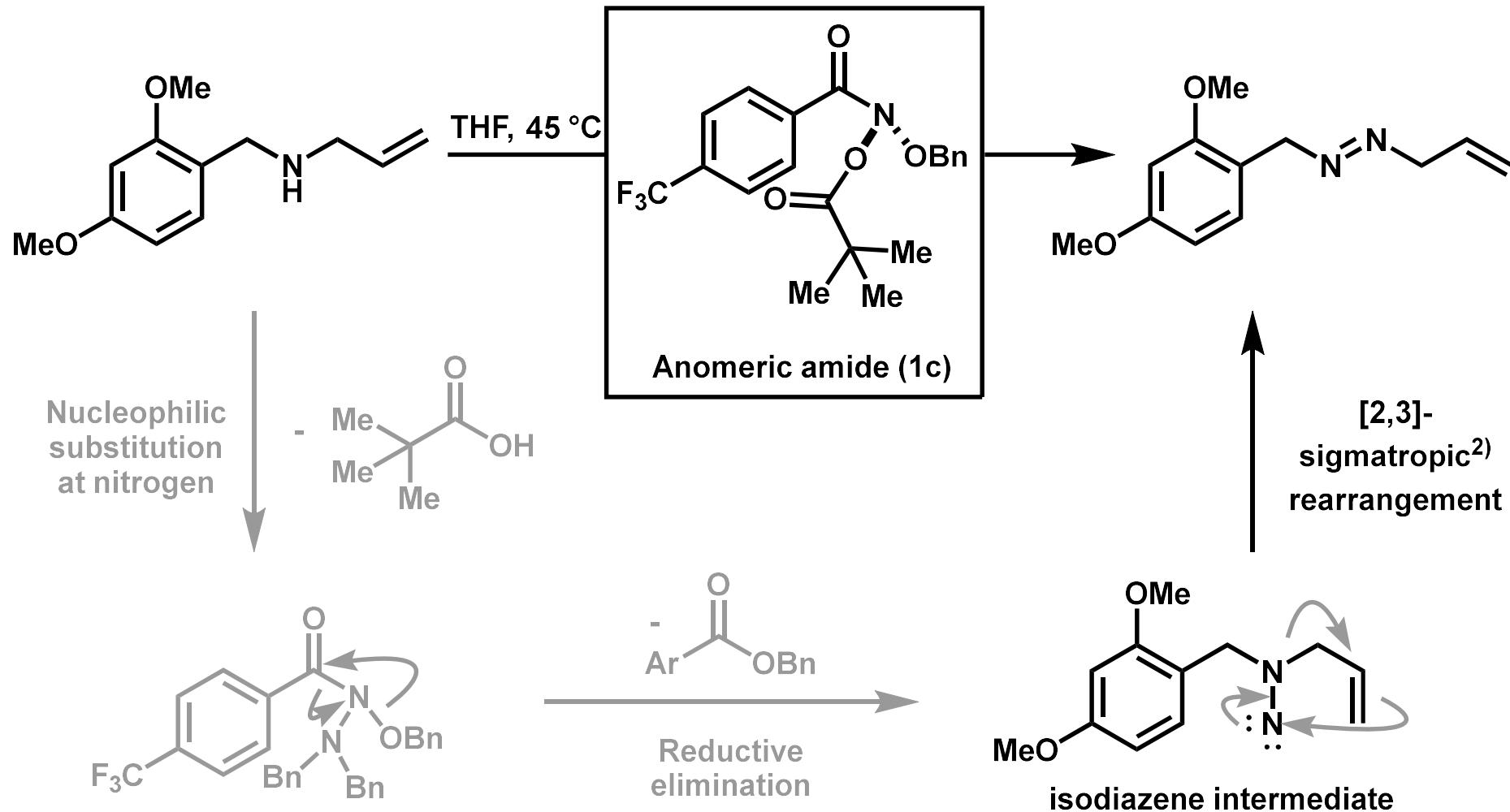
Reactivity of *N*-Acyloxy-*N*-alkoxyamides



1) Glover, S. A. *Tetrahedron* 1998, 54, 7229.

Mechanistic Experiments (3)

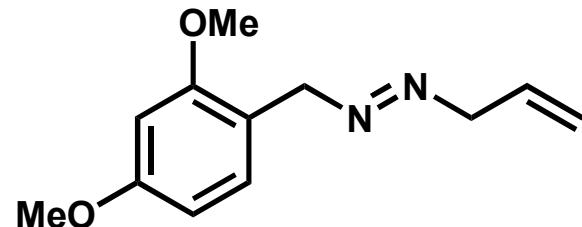
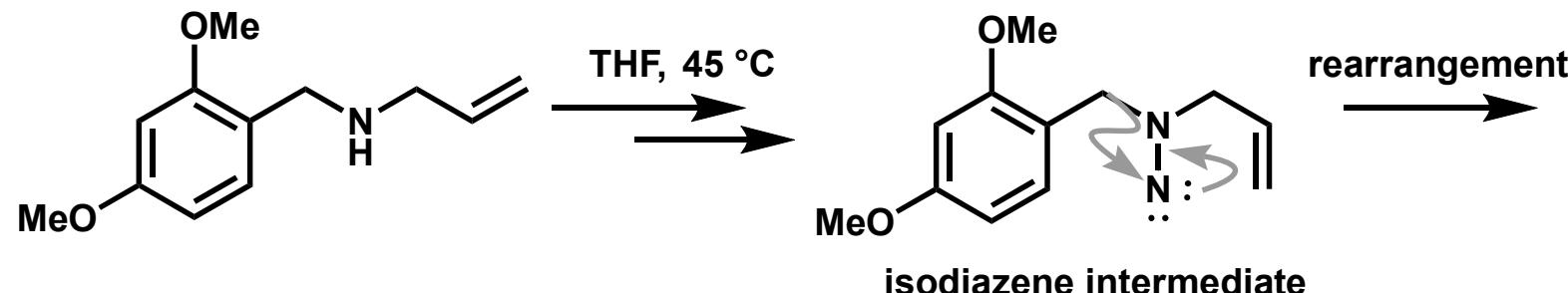
3. Evidence for the isodiazene intermediate



1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, 593, 223. 2) Strick, B. F.; Mundal, D. A.; Thomson, R. J. *J. Am. Chem. Soc.* **2011**, 133, 14252.

Mechanistic Experiments (3)

3. Evidence for the isodiazene intermediate (my proposal)

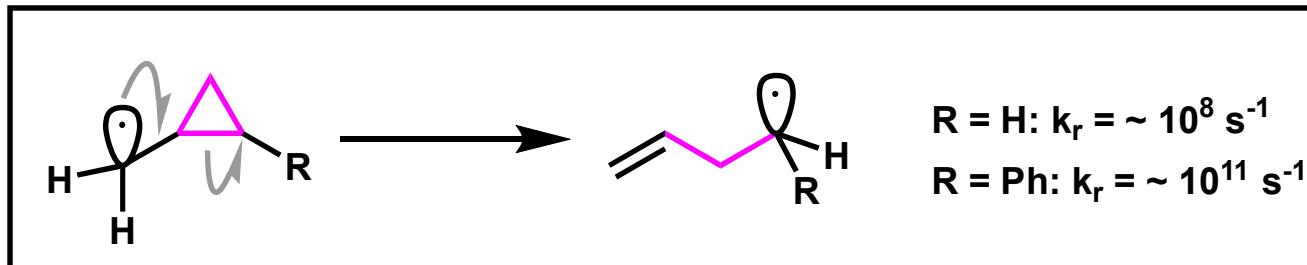
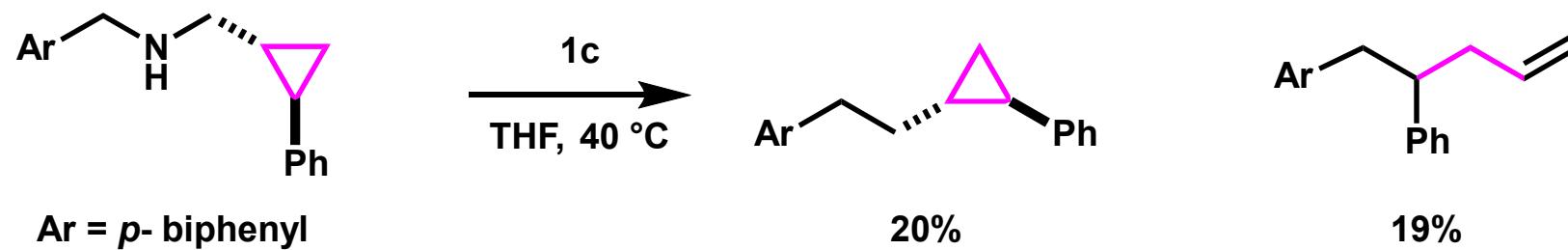
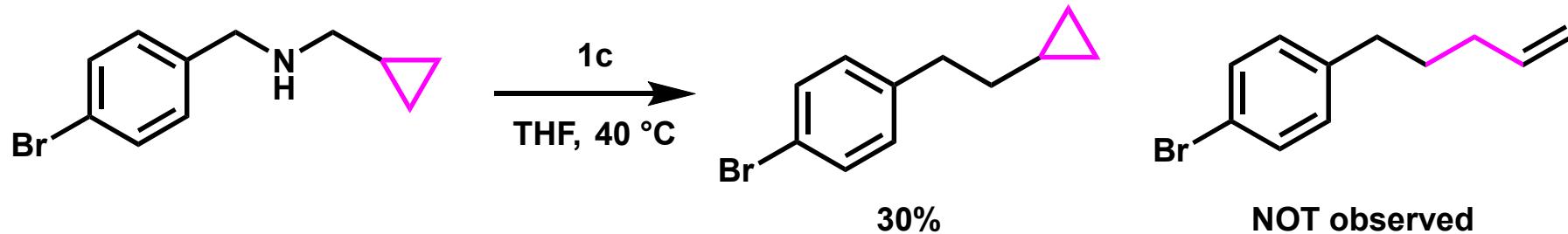


**There is another possible reaction mechanism.
In my opinion, this is not a firm evidence for
the isodiazene intermediate.**

1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, 593, 223.

Mechanistic Experiments (4)

4. Radical clock experiment



The result also suggests largely in-cage C-C bond formation.
A competitive non-radical pathway cannot be excluded categorically .

1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, *593*, 223.