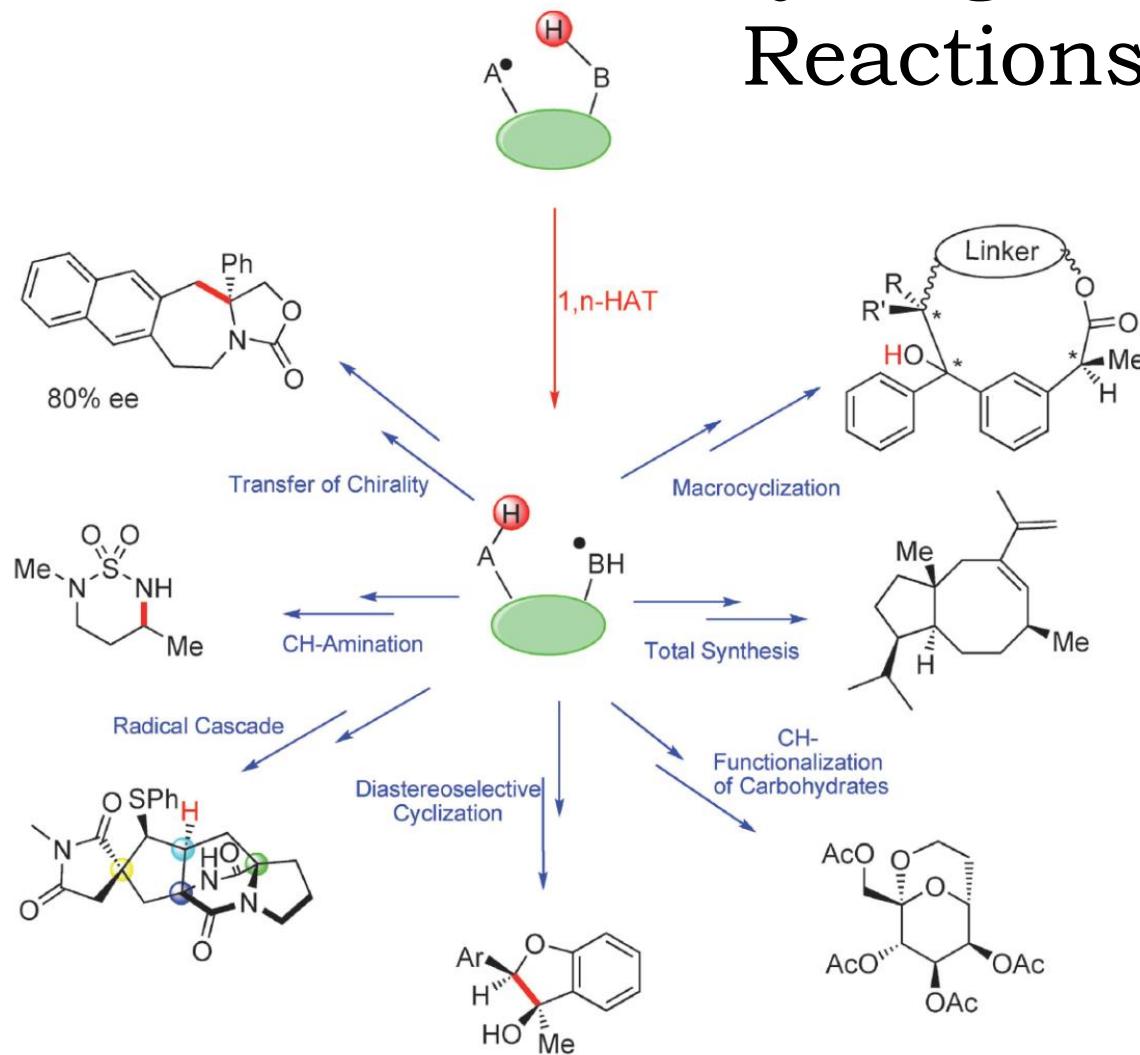


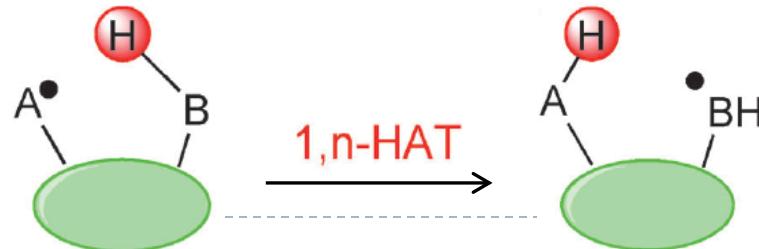


1,*n*-Hydrogen-Atom Transfer Reactions in Which *n*>5



Rong Zeng
Dong Group
5/13/2015

Hydrogen Atom Transfer (HAT):



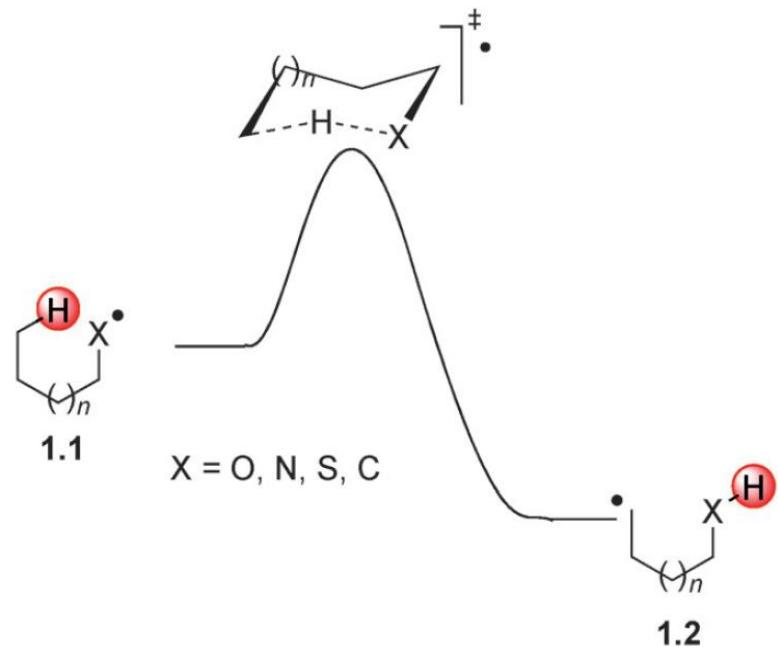
Controlled by different parameters, amongst which the **enthalpy** is crucial;

Most are **exothermic irreversible** processes;

Activation energy is also sensitive to **polar effects (O, N, S...)**;

Ideal arrangement of the three atoms is linear;

Distance between A• and B-H should be $\leq 3 \text{ \AA}$.



1,5-HAT vs 1,6-HAT

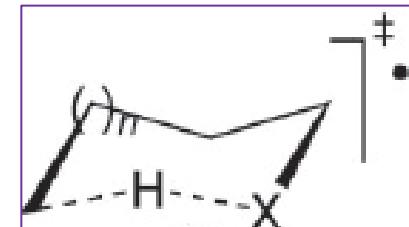
1,5-HAT are **enthalpically slightly disfavored** compared to 1,6-HAT

However:

1,5-HAT: **six-membered transition**: the C-H-X angle close to 180°.

Entropic factors: six-membered > seven-membered transition states.

So, 1,5-HAT are the most favored processes.



For reviews on radical chemistry:

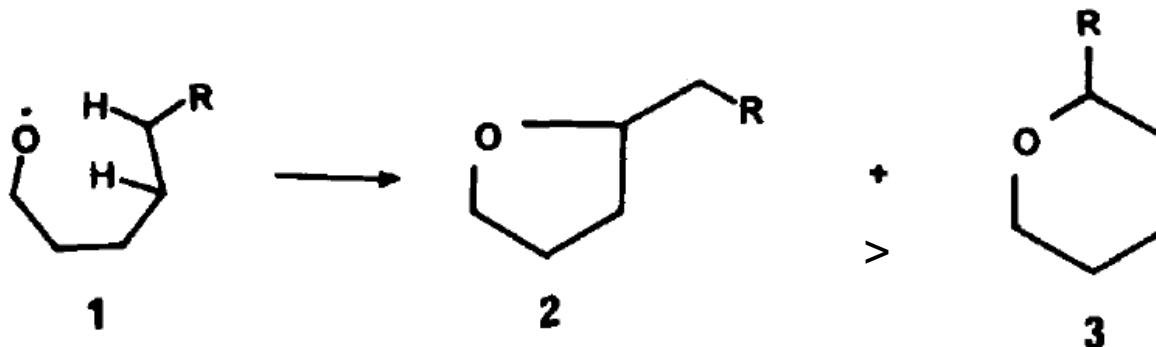
- a) G. Majetich, K. Wheless, *Tetrahedron* **1995**, *51*, 7095–7129;
- b) Ž. Čeković, J. Serb. Chem. Soc. **2005**, *70*, 287–318;
- c) L. Feray, N. Kuznetzov, P. Renaud in *Radicals in Organic Synthesis* Vol. 2 (Eds: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 246–278;
- d) J. Robertson, J. Pillai, R. K. Lush, *Chem. Soc. Rev.* **2001**, *30*, 94–103;
- e) J. Sperry, Y.-C. Liu, M.A. Brimble, *Org. Biomol. Chem.* **2010**, *8*, 29–38;
- f) A. Gansuer, T. Lauterbach, S. Narayan, *Angew. Chem. Int. Ed.* **2003**, *42*, 5556–5573;
- g) F. Dns, F. Beaufils, P. Renaud, *Synlett* **2008**, 2389–2399.
- h) S. Chiba, H. Chen, *Org. Biomol. Chem.* **2014**, *12*, 4051.

Contents

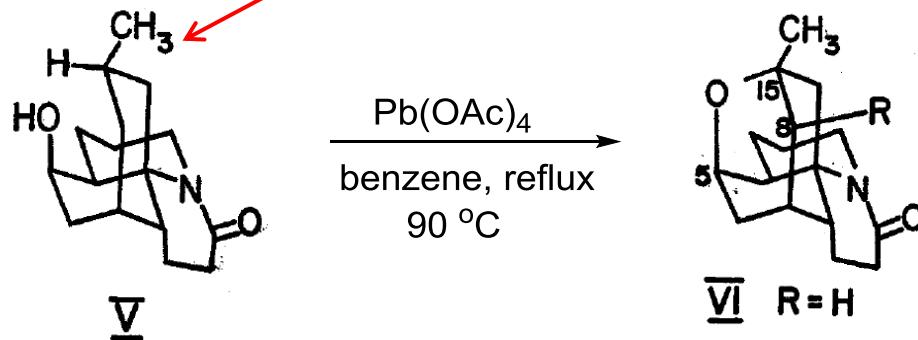
- ▶ **I,6-Hydrogen-atom transfer**
- ▶ **I,7-Hydrogen-atom transfer**
- ▶ **I,8-Hydrogen-atom transfer**
- ▶ **I,n-Hydrogen-atom transfer ($n > 8$)**

I,6-HAT involving oxygen-centered radicals

Normal linear substrates:

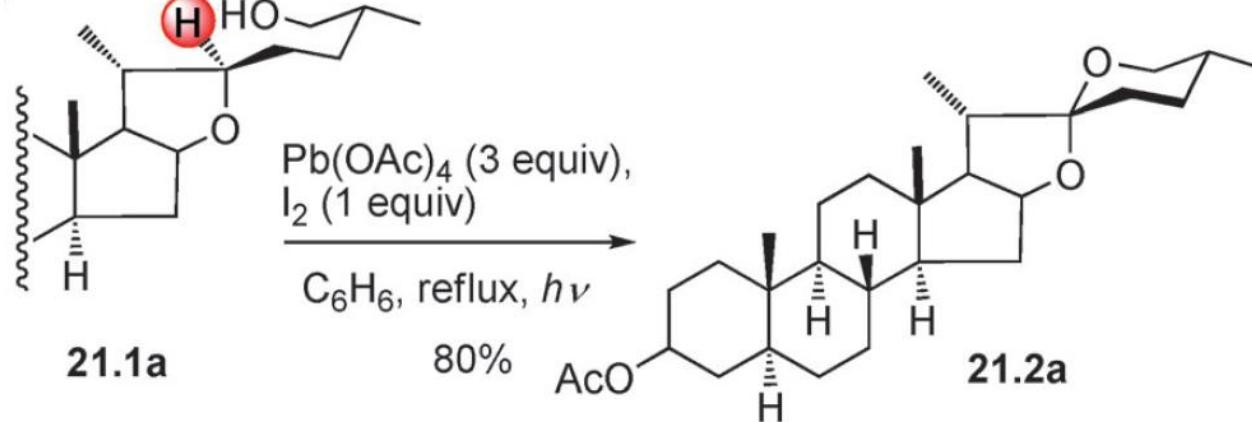


Tertiary carbon and rigid structure.



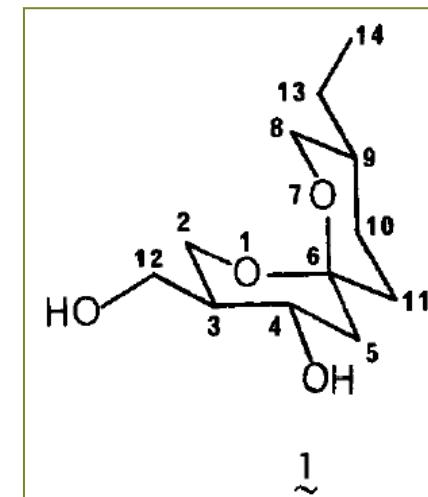
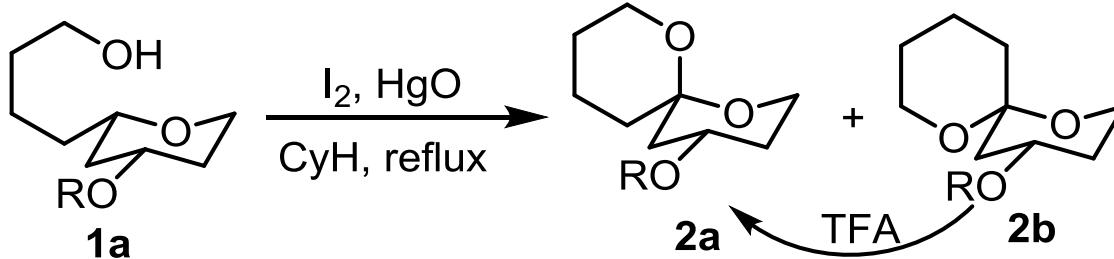
W.A. Ayer, D.A. Law, K. Piers, *Tetrahedron Lett.* **1964**, 5, 2959

Adjacent to Oxygen.



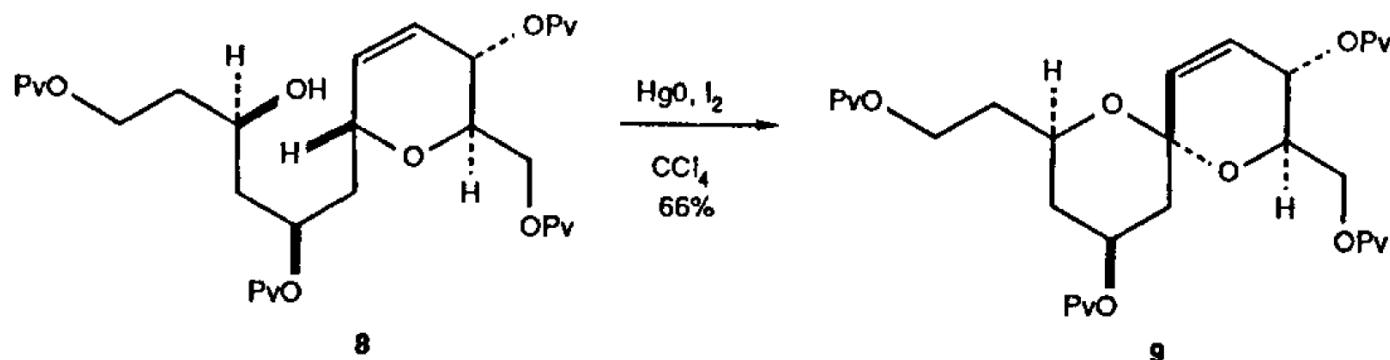
E. Suárez, et al. *Tetrahedron Lett.* **1983**, 24, 4621

(\pm)-TALARCMYCIN B

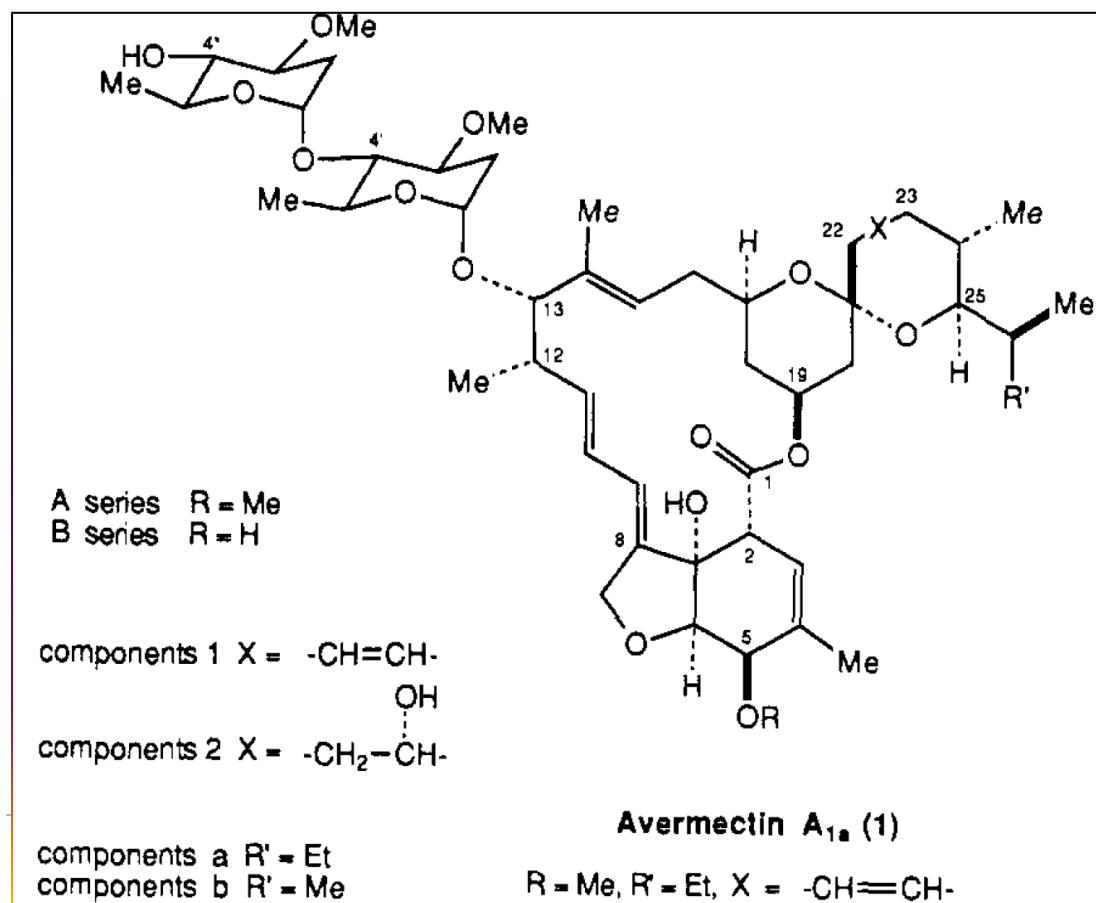


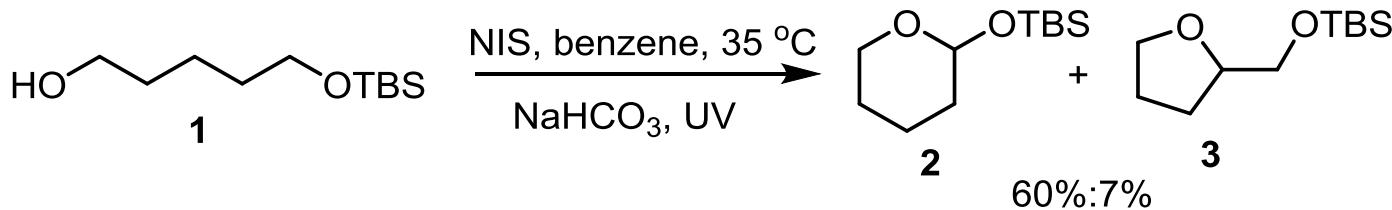
Kay, I.T.; Williams, E. G. *Tetrahedron Lett.* **1983**, 24, 5915.

Kay, I.T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, 25, 2035.

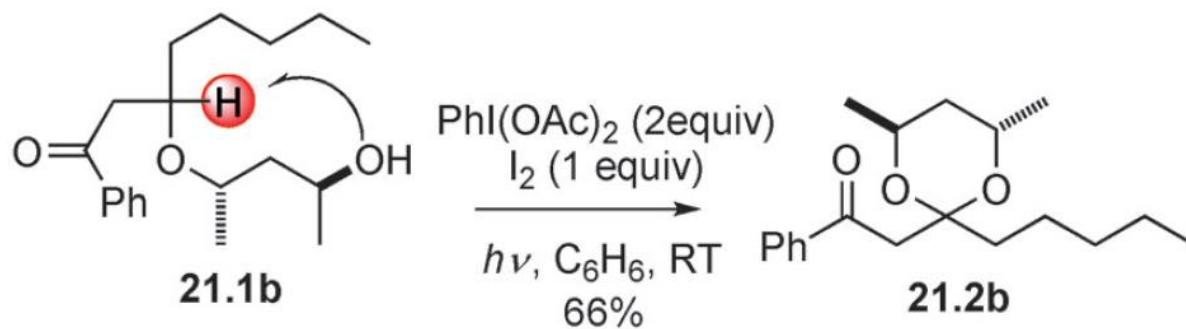


Danishefsky, S. J. et al.
Tetrahedron Lett. **1987**, *28*, 4951.
Tetrahedron Lett. **1987**, *28*, 49.
J. Am. Chem. Soc. **1989**, *111*, 2967.

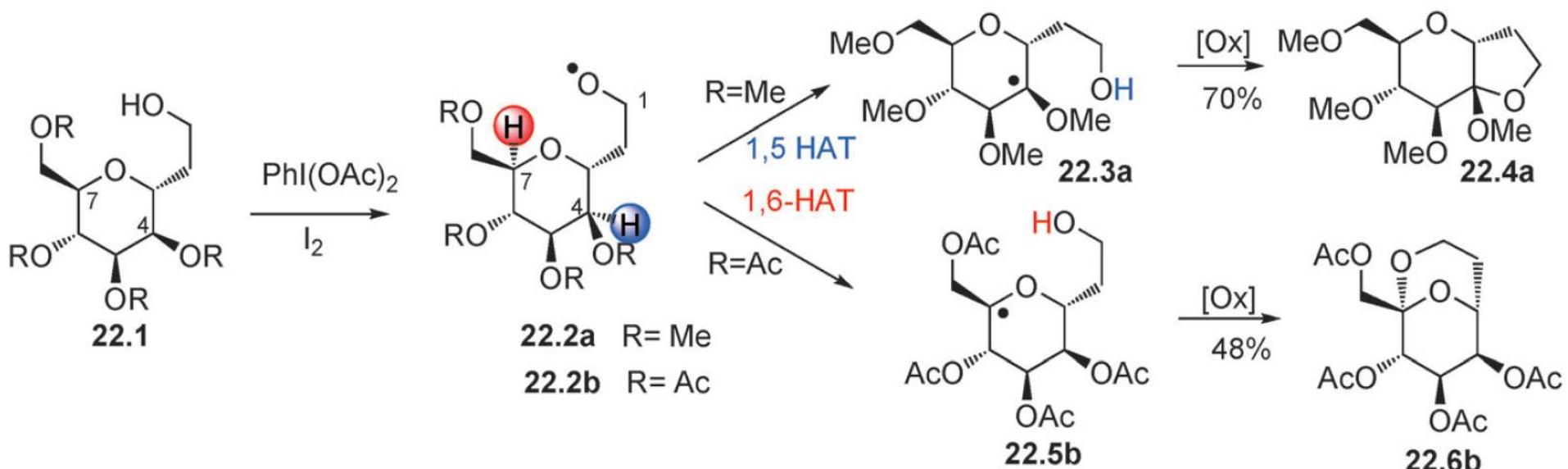




C. E. McDonald, et al, *Tetrahedron Lett.* 1989, 30, 4791



K. Furuta, T. Nagata, H. Yamamoto, *Tetrahedron Lett.* **1988**, 29, 2215.



The acetoxy group increases the BDE of the C-H bond at C4;
 The C-H bond is stronger by 1.4 kcal/mol in $\text{CH}_3\text{C(O)OCH}_2\text{H}$ than in $\text{CH}_3\text{OCH}_2\text{H}$;
 The incoming radical at C4 becomes less nucleophilic.

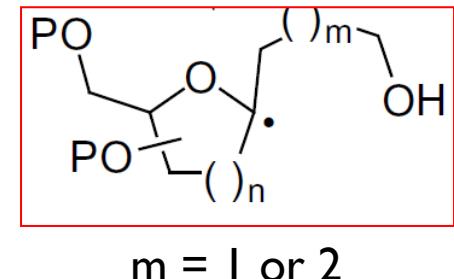
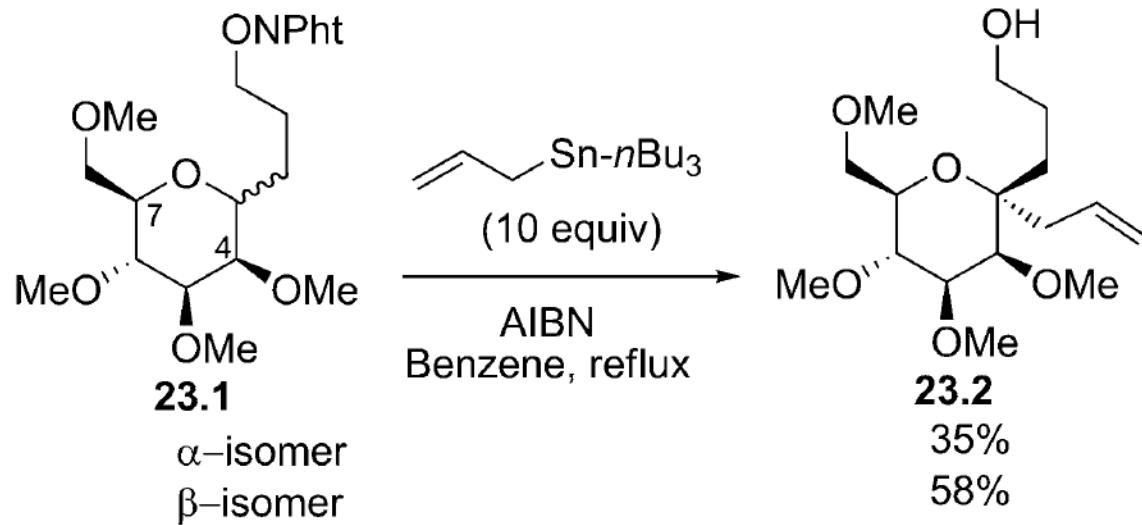
E. Suárez, et al. *Org. Lett.* **2002**, *4*, 1959.

E. Suárez, et al. *Tetrahedron* **2007**, *63*, 8910.

I. Perez-Martin, E. Suárez, *Encyclopedia of Radicals in Chemistry, Biology and Materials*, Vol. 2 (Eds.: C. Chatgilialoglu, A. Studer), Wiley-VCH, Weinheim, **2012**, pp. 1131– 1174.

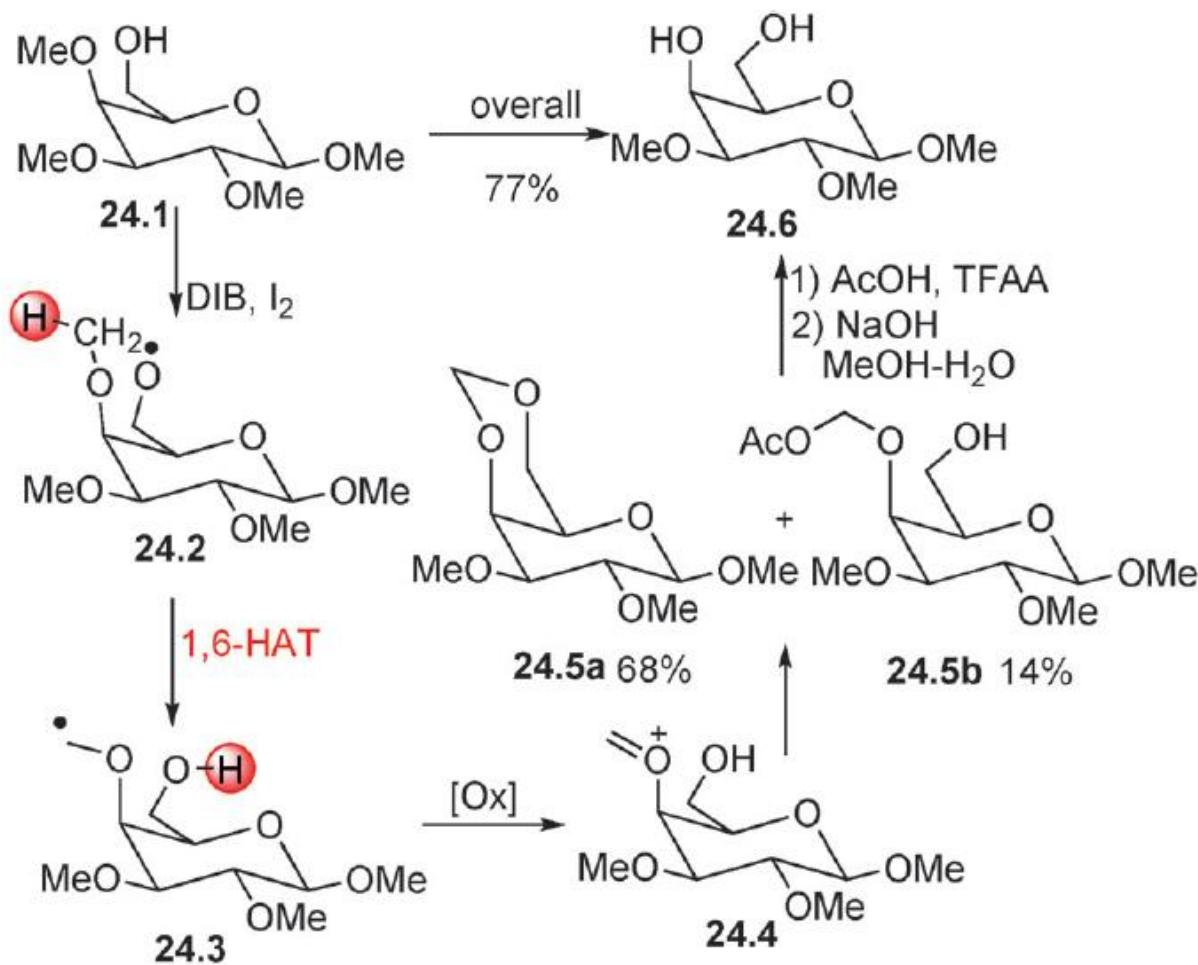
Comprehensive Handbook of Chemical Bond Energies (Ed.: Y-R. Luo), CRC Press, Boca Raton, **2007**, pp. 73 and 96.

Capture the forming radical with ATBT:



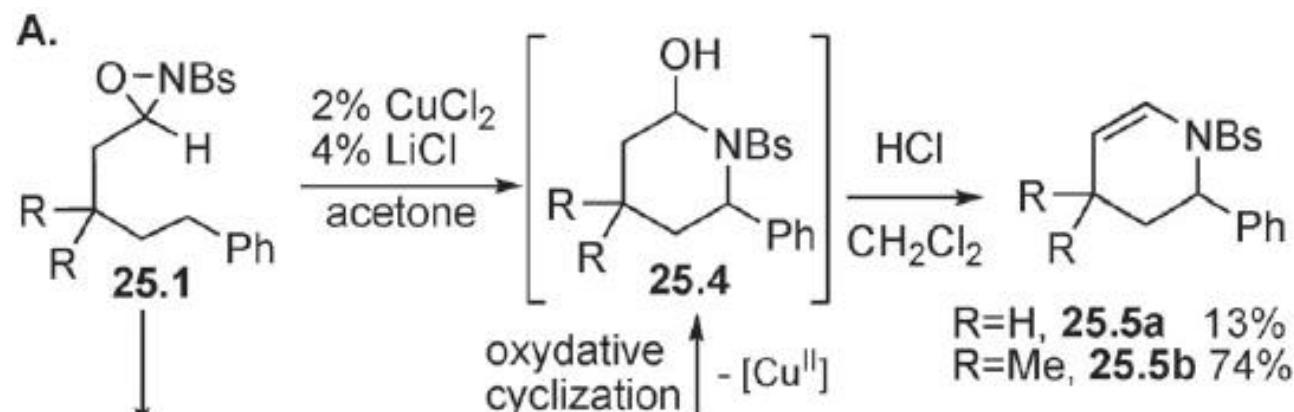
E. Suárez, et al. *Tetrahedron Lett.* **2008**, *49*, 5179

Selective de-methylation:

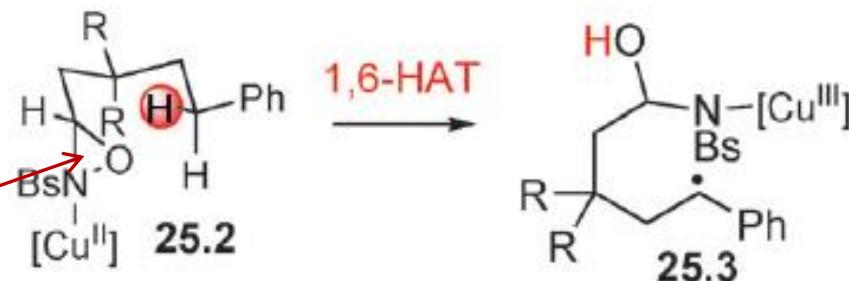


E. Suárez, et al. Org. Lett. 2004, 6, 3785

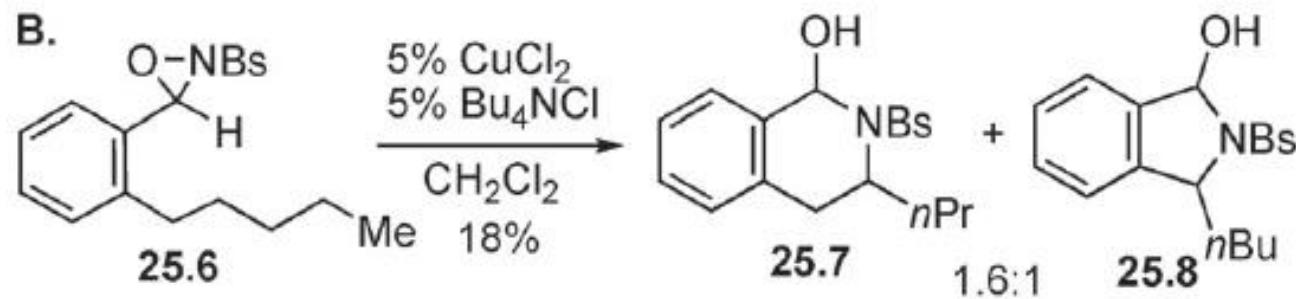
Redox process



gem-dimethyl effect

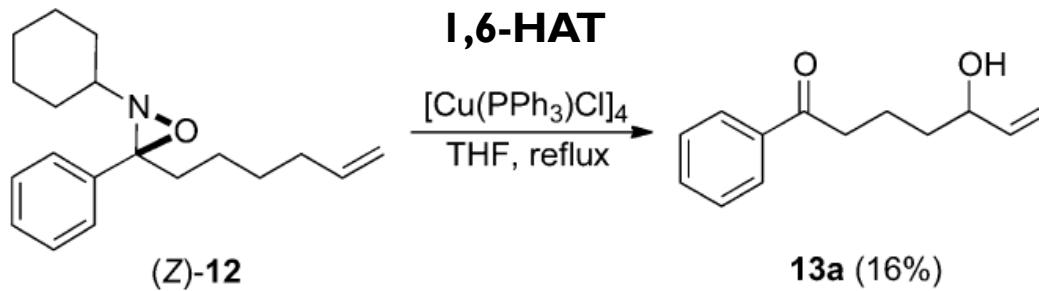
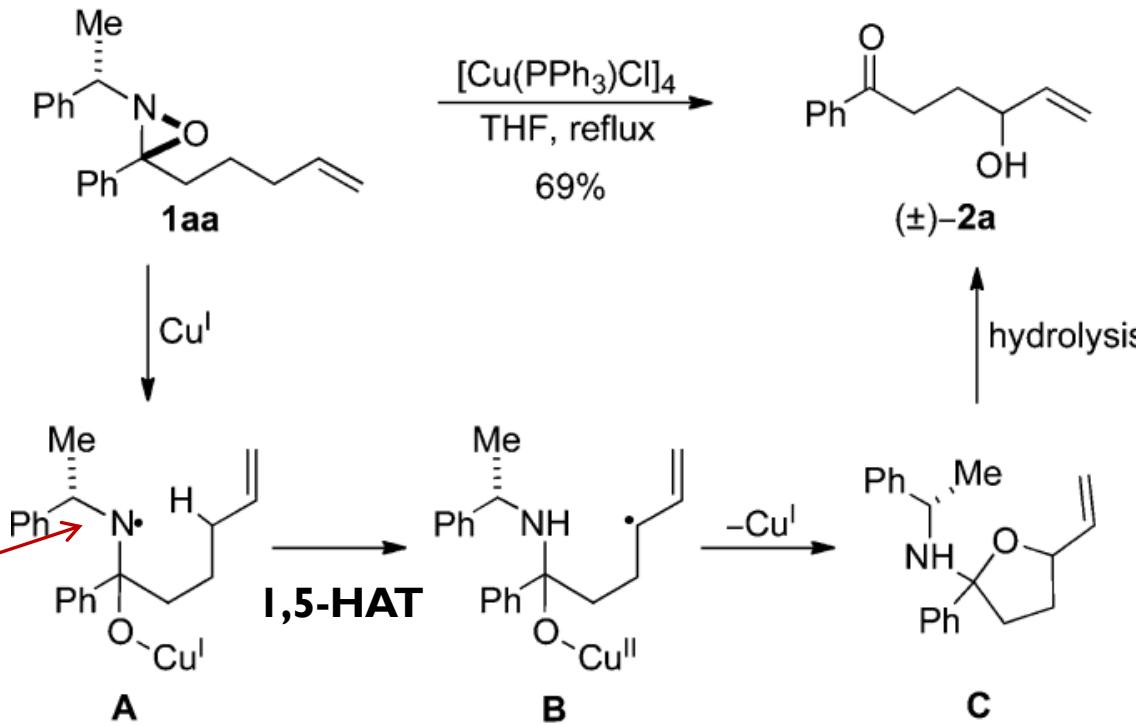


O-radical



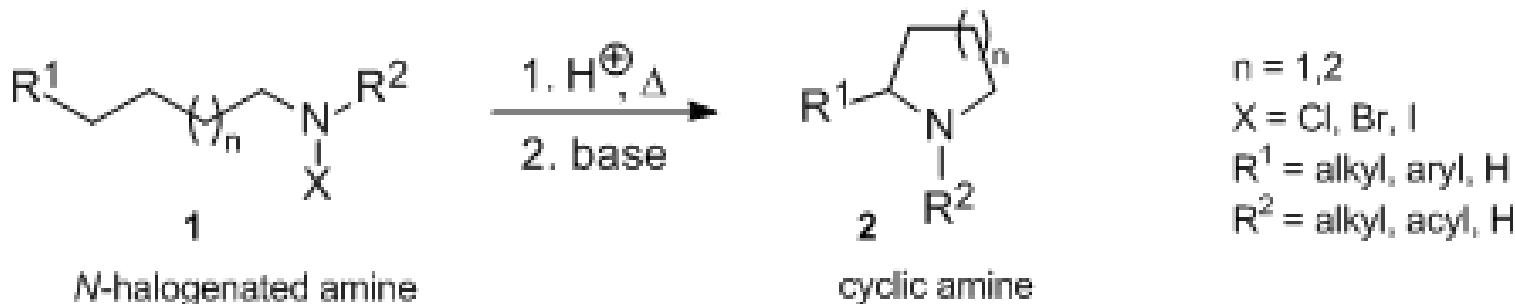
Non-Benzyllic position

I,6-HAT involving Nitrogen-centered radicals

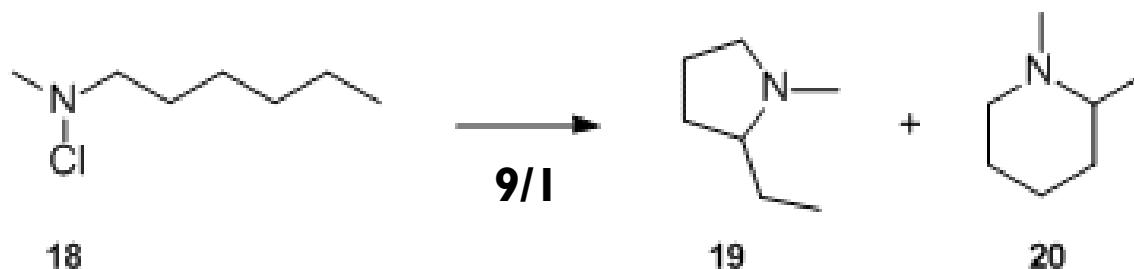


J. Aubé, et al. J. Org. Chem. 2012, 77, 7005
J. Am. Chem. Soc. 1992, 114, 5466

Hofmann–Löffler–Freytag reaction

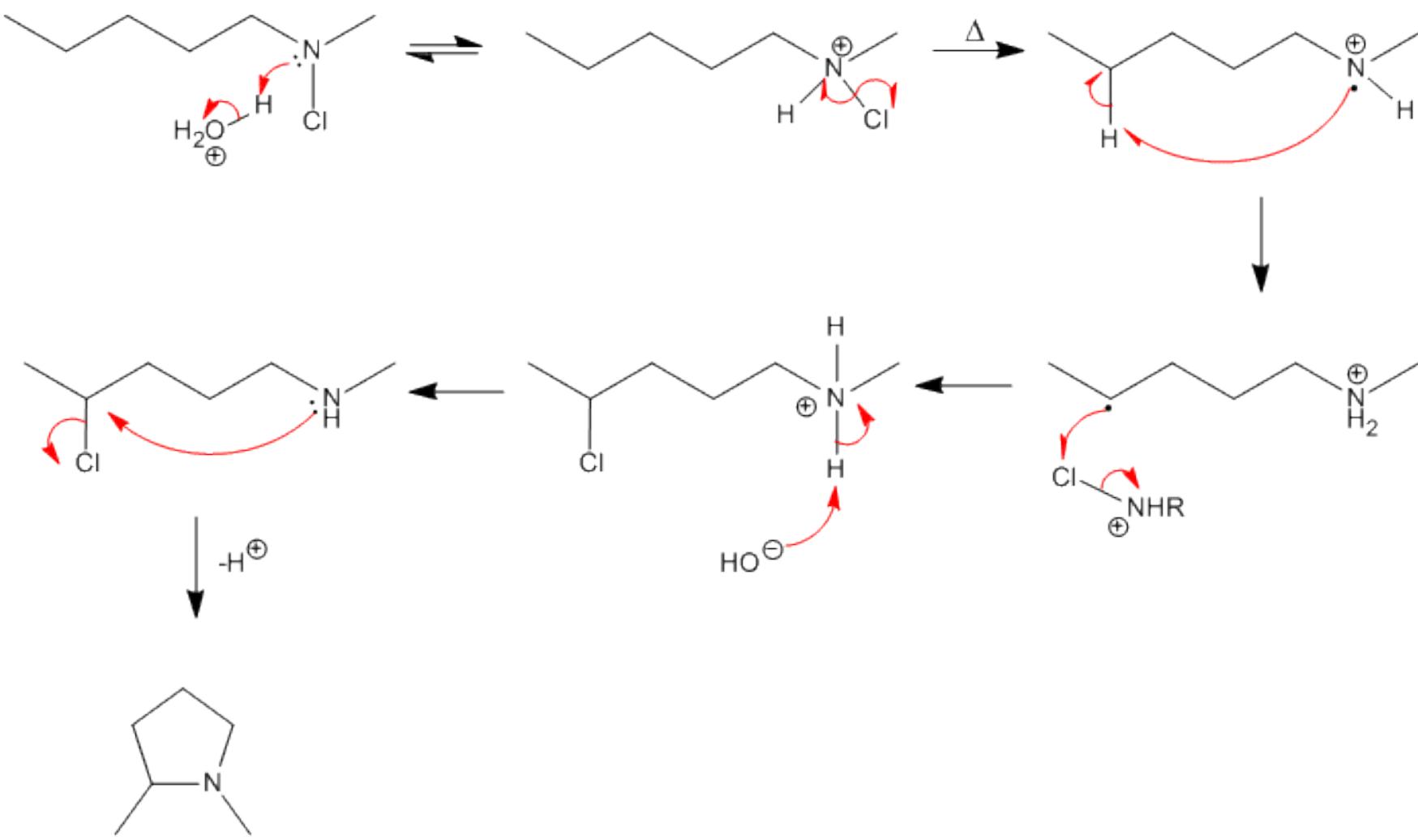


- A.W. Hofmann, *Chem. Ber.* **1883**, *16*, 558–560;
- K. Löffler, C. Freytag, *Chem. Ber.* **1909**, *42*, 3427–3431.

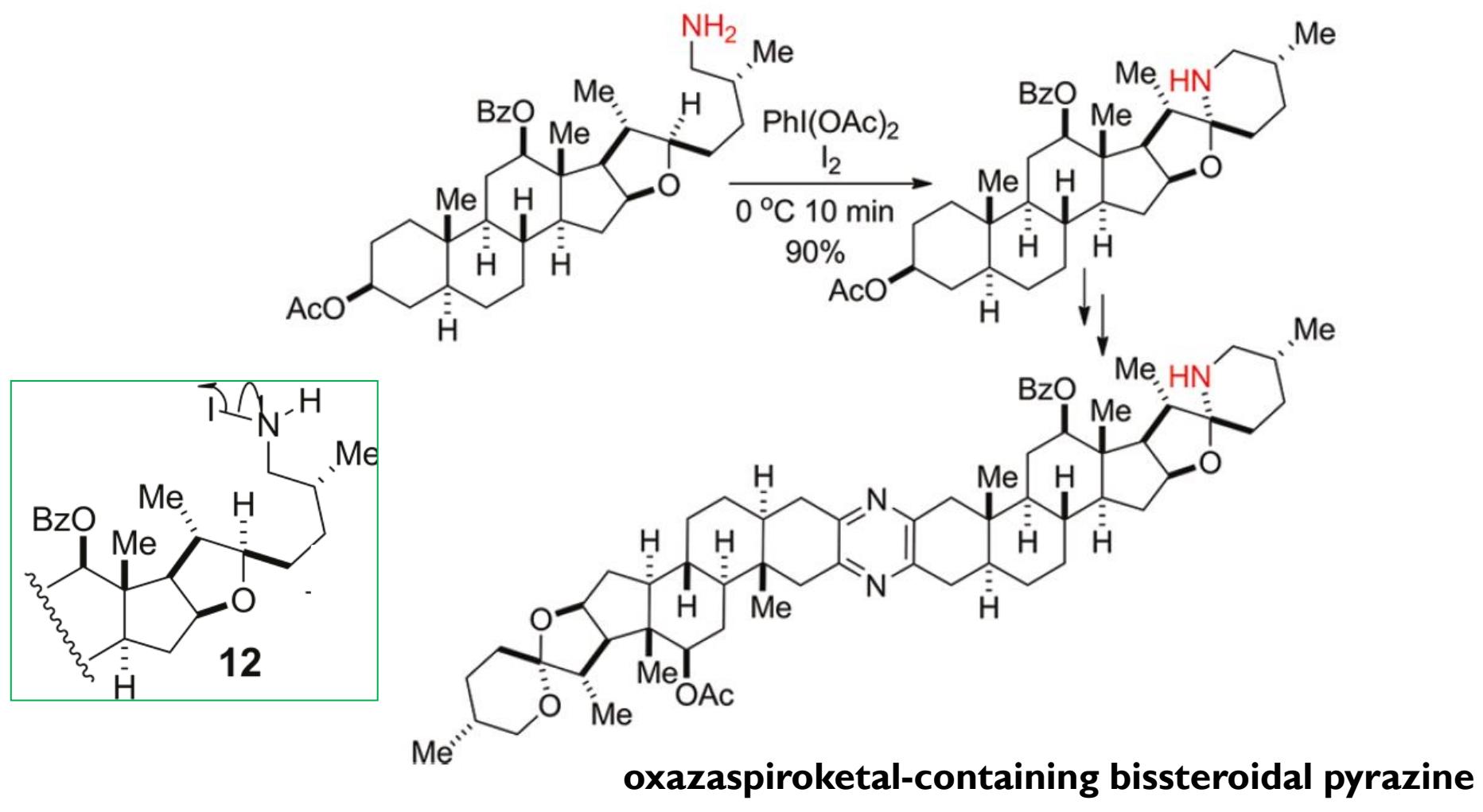


Usually, 1,5-HAT is major reaction.

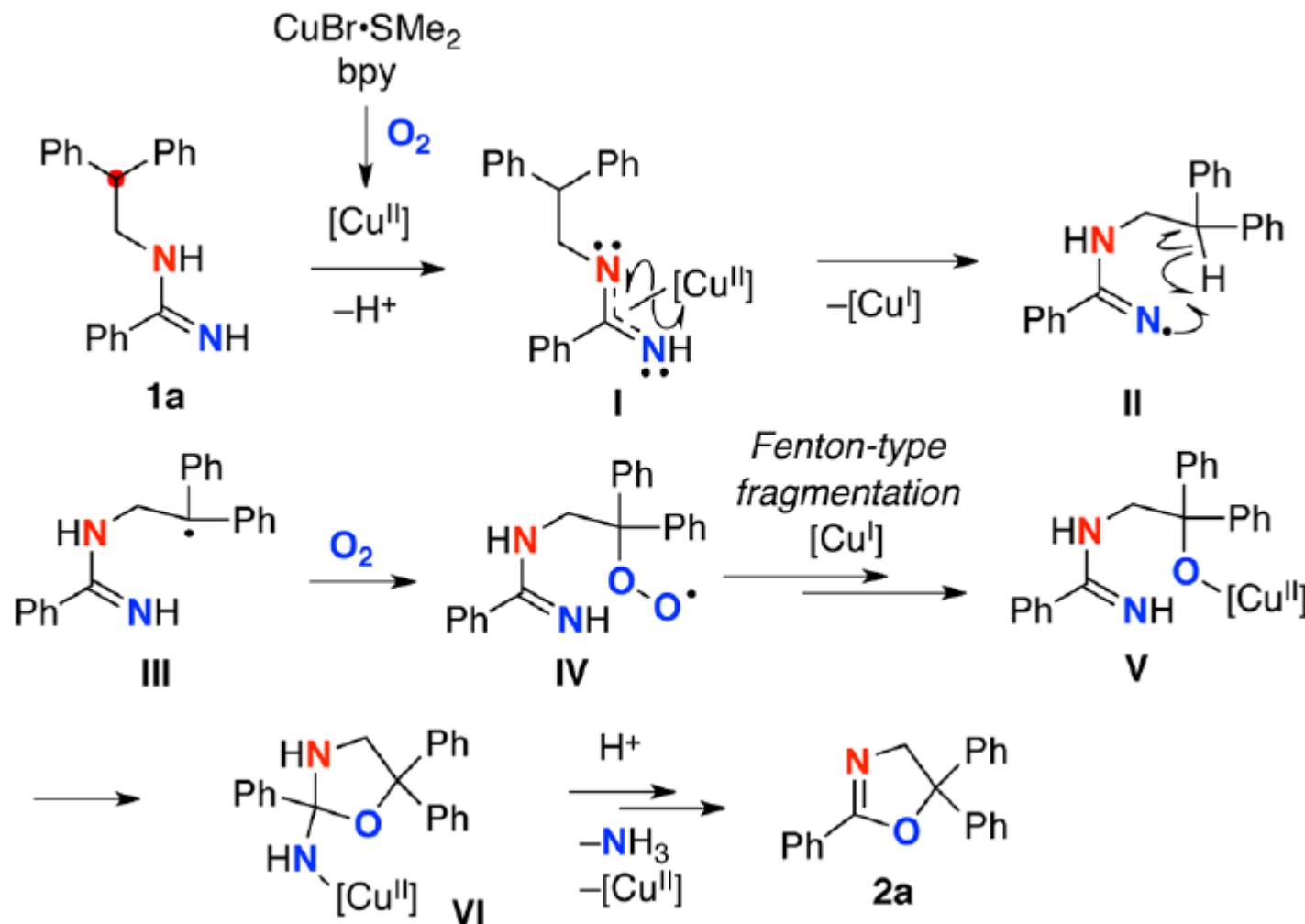
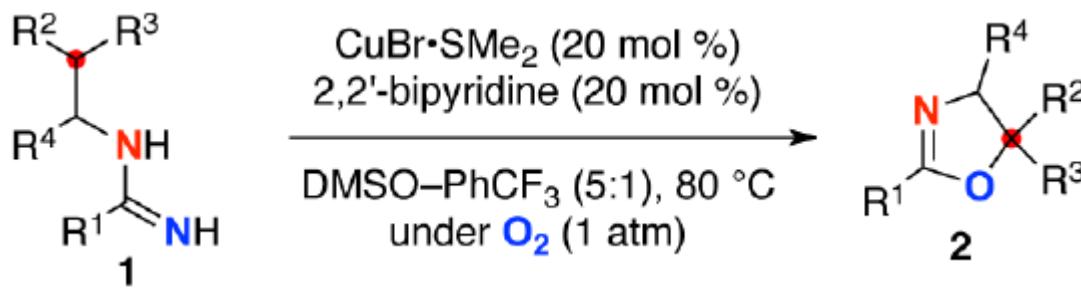
For more details, see: M. E. Wolff, *Chem. Rev.*, **1963**, *63*, 55.

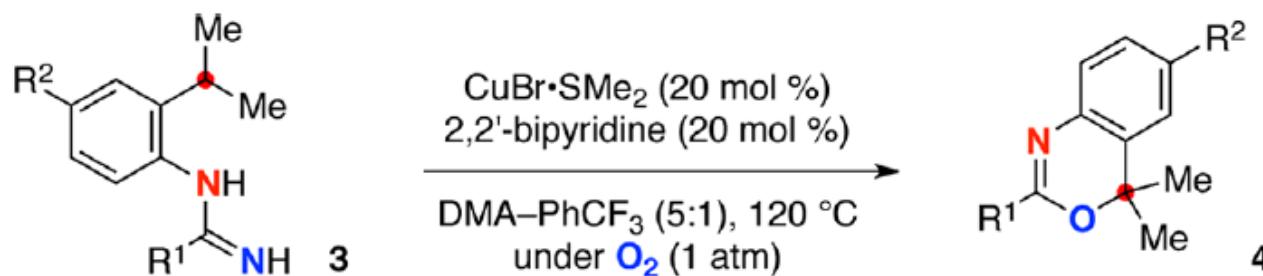


Recent interesting developments on 1,6-HAT :



M. Koag, S. Lee, Org. Lett. 2011, 13, 4766





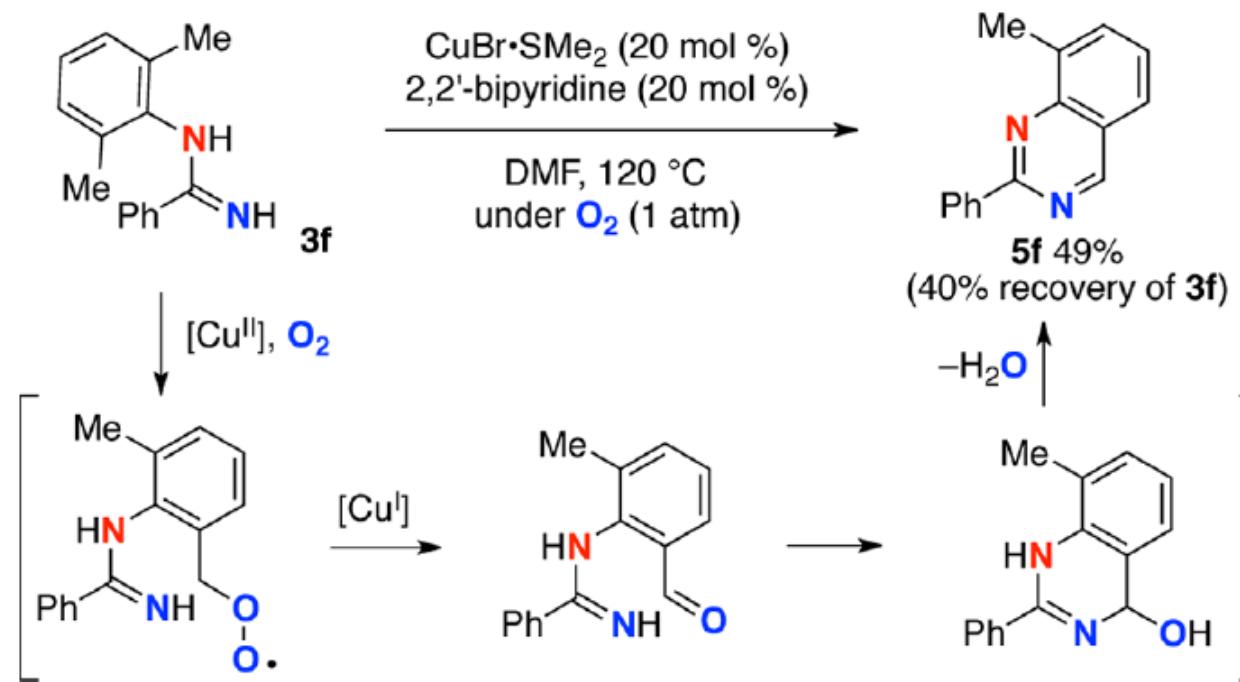
4a ($R^1 = \text{Ph}$, $R^2 = \text{H}$): 67%

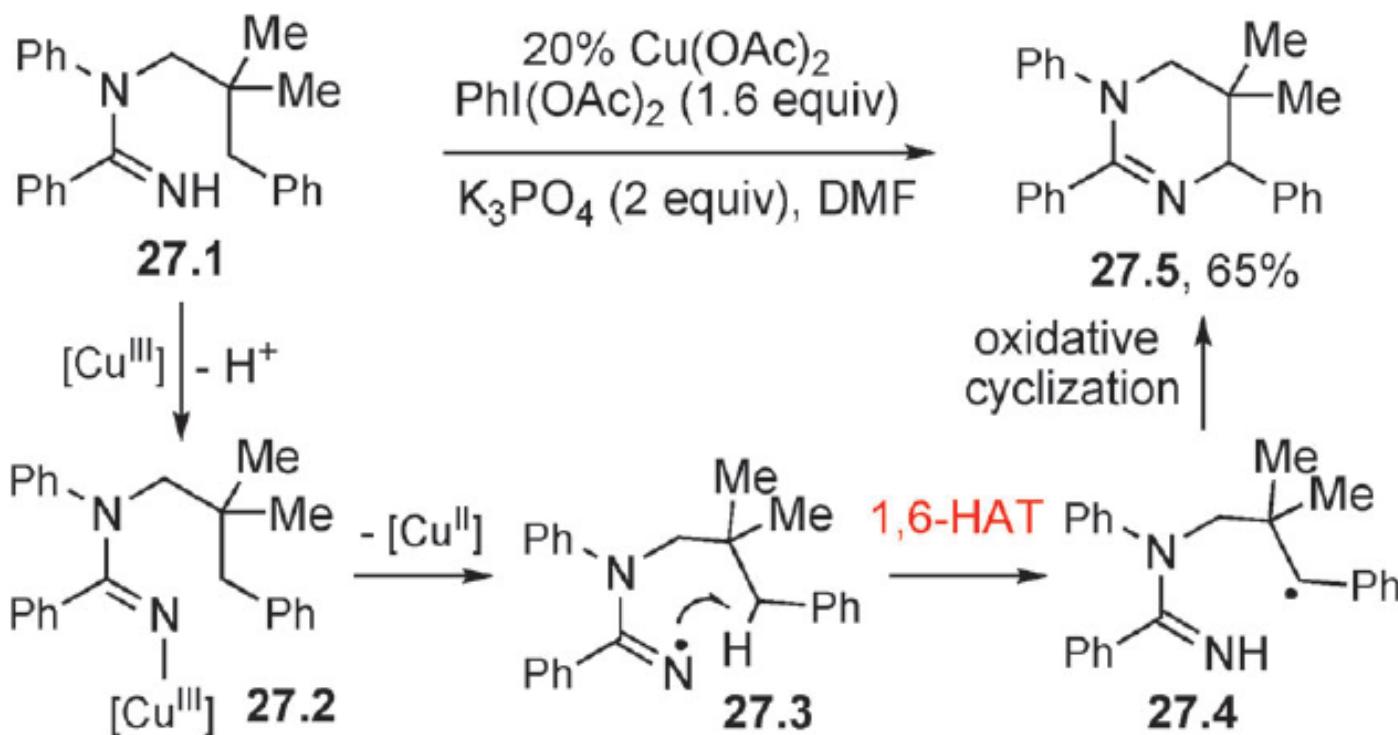
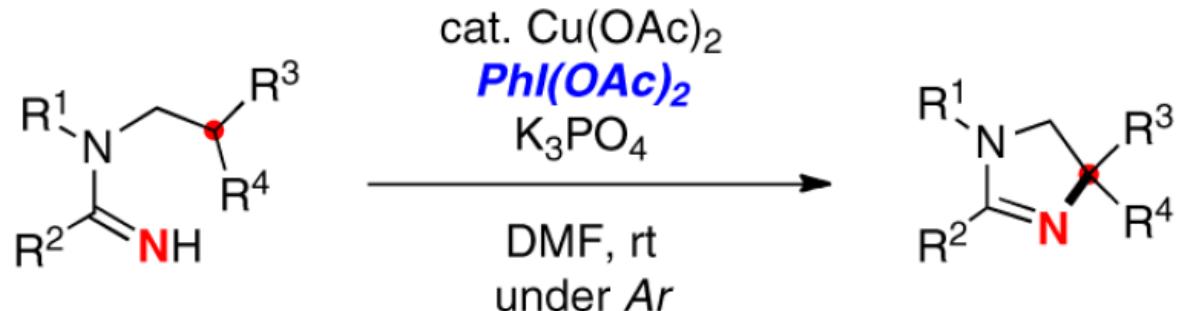
4b ($R^1 = 4\text{-CF}_3\text{C}_6\text{H}_4$, $R^2 = \text{H}$): 68%

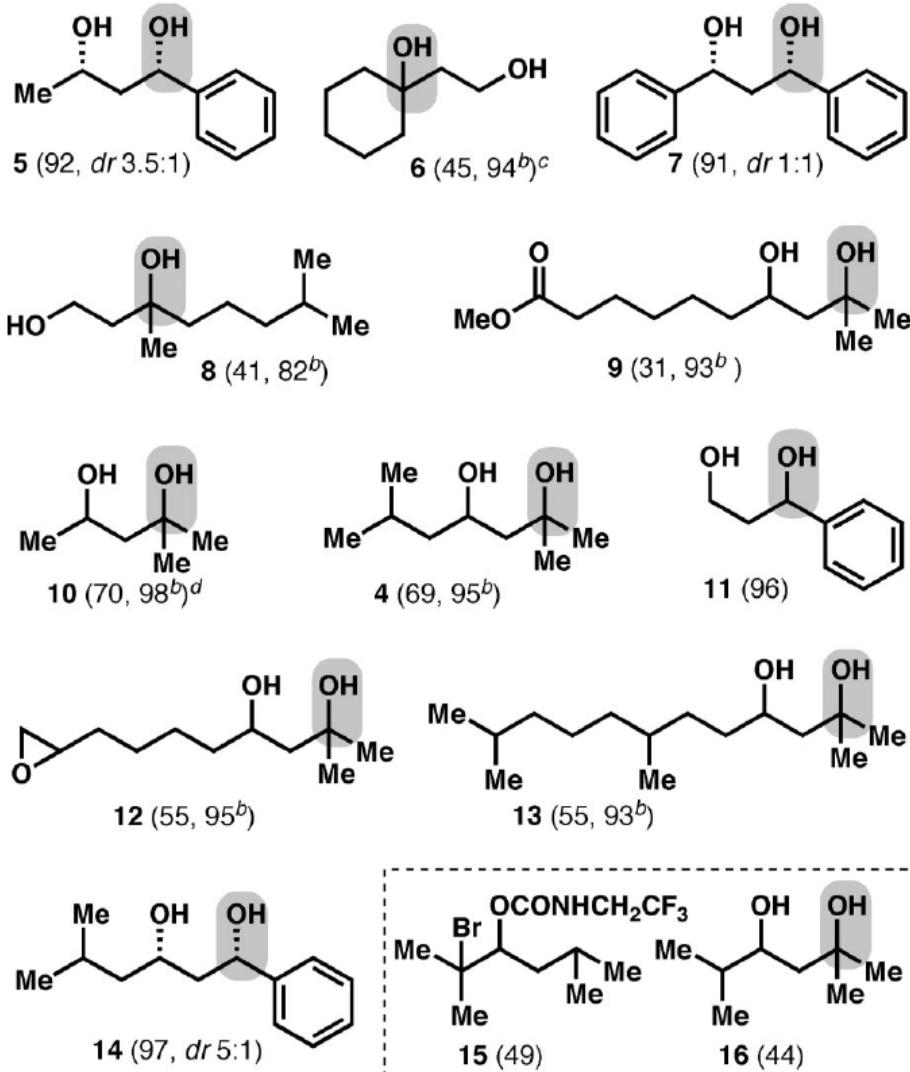
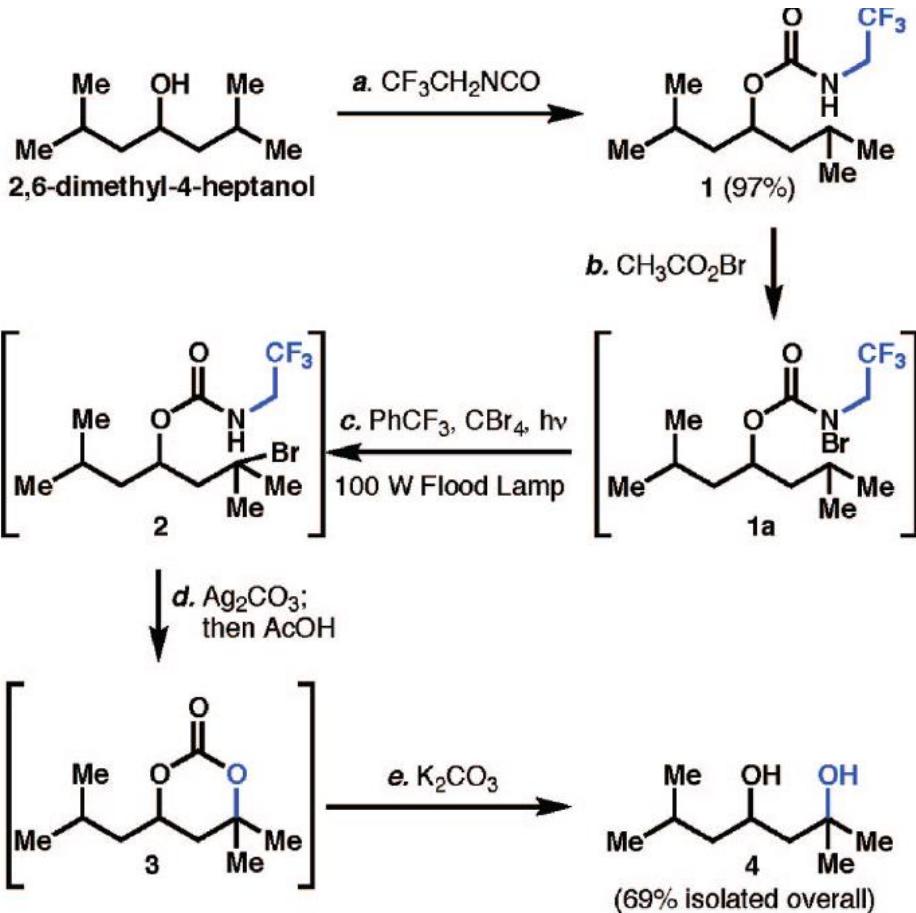
4c ($R^1 = 2\text{-thienyl}$, $R^2 = \text{H}$): 42%

4d ($R^1 = \text{Ph}$, $R^2 = \text{Br}$): 72%

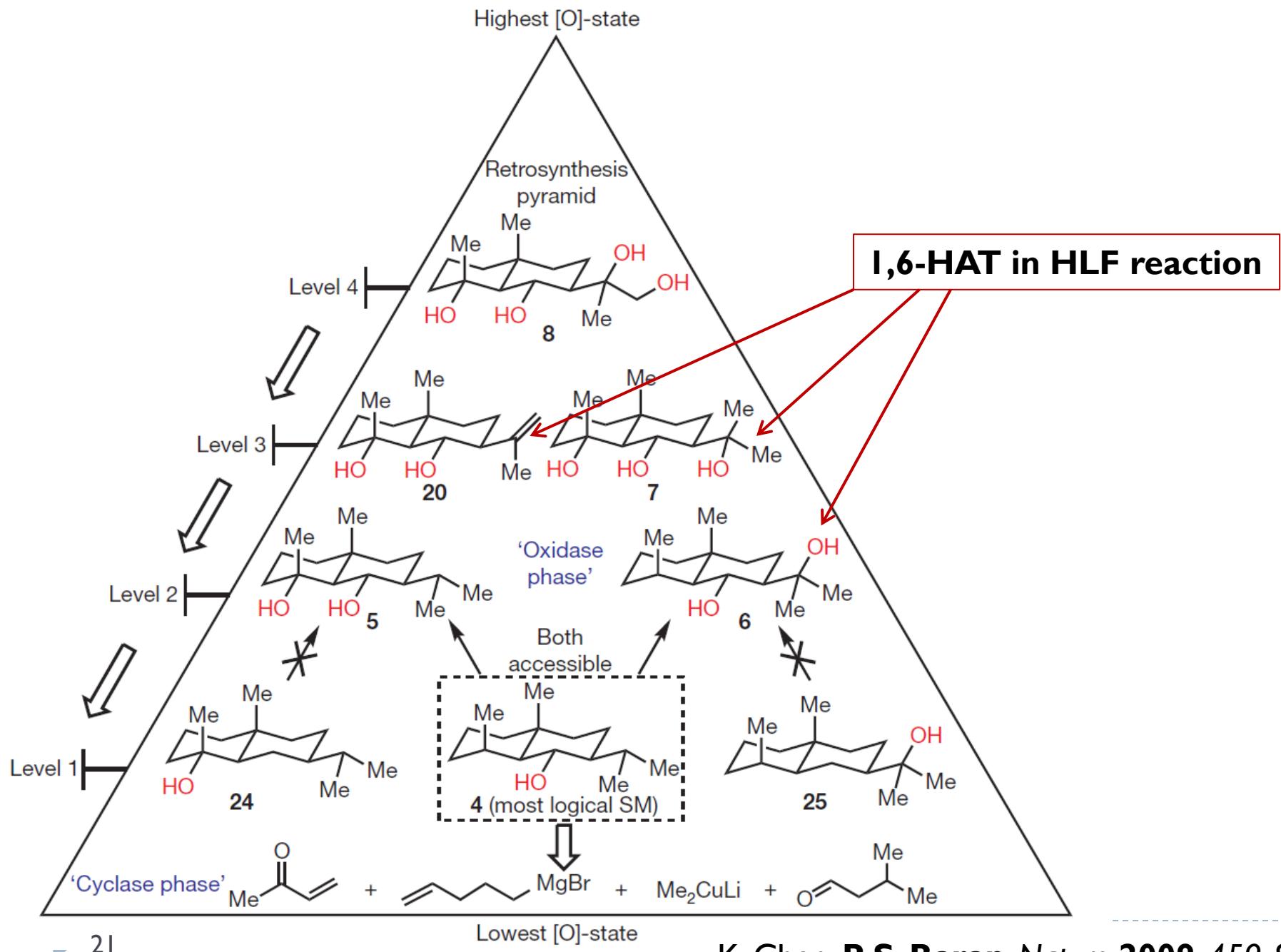
4e ($R^1 =$, $R^2 = \text{H}$): 65%



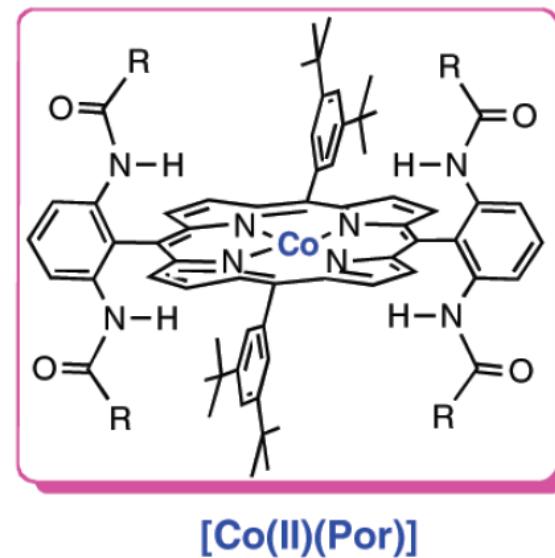
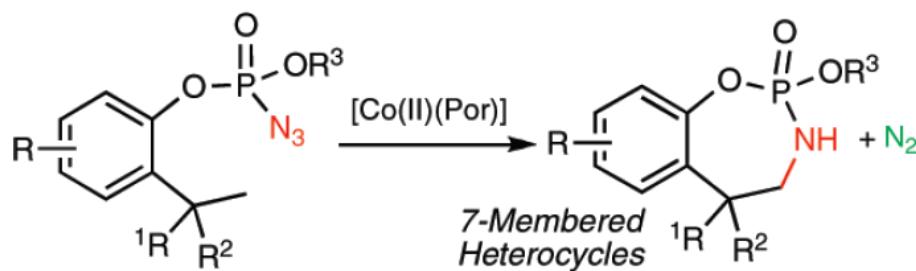
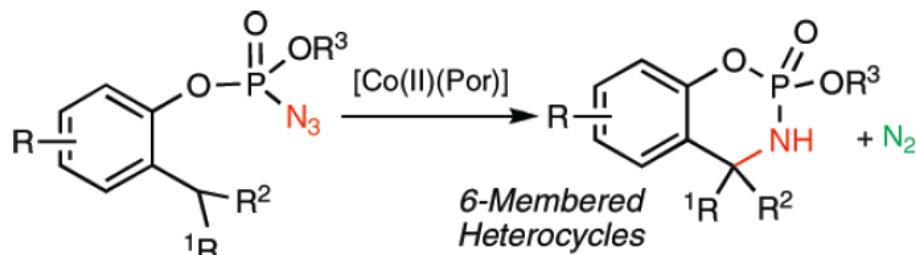
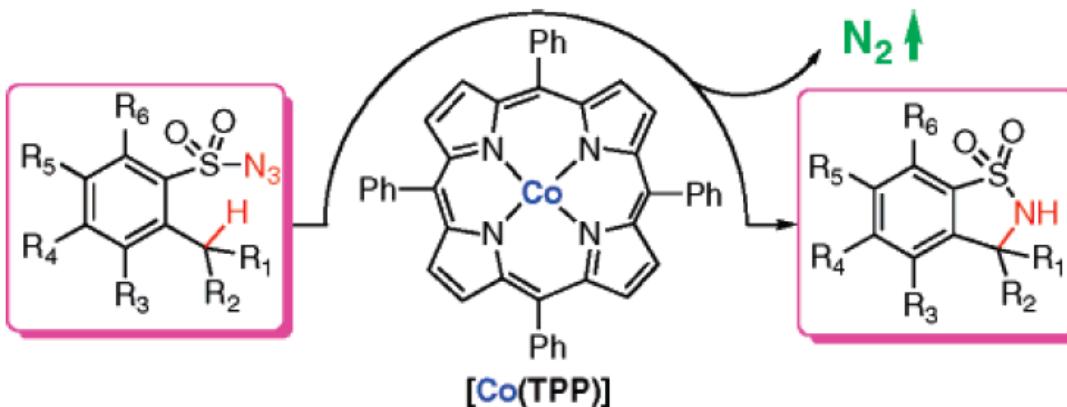




Only tertiary C-H or benzylic C-H bonds



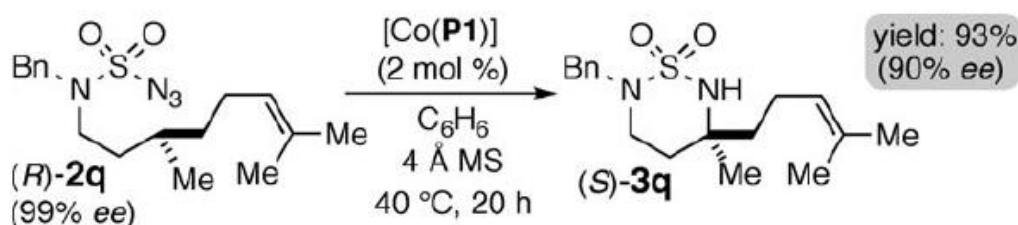
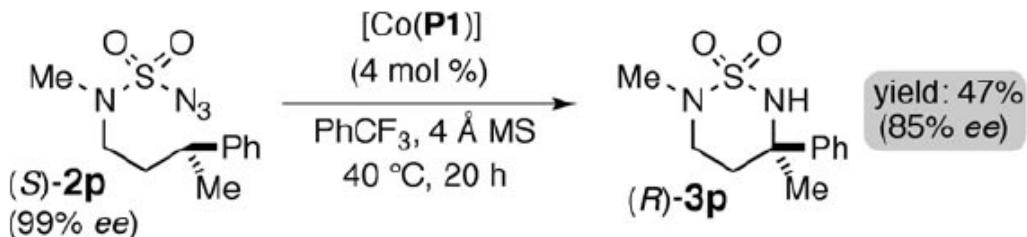
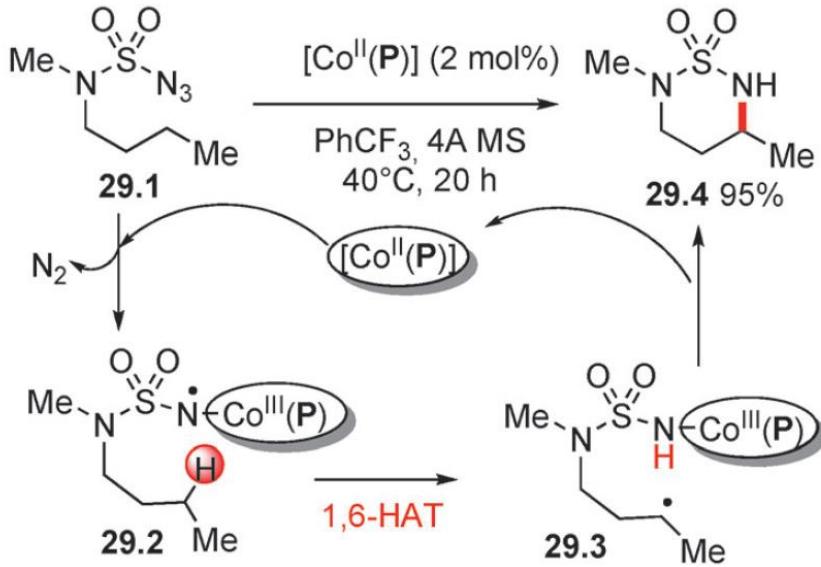
Metallated-imido radicals



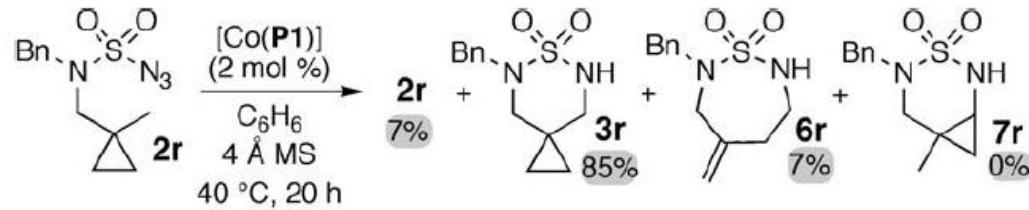
X. P. Zhang, et al. *Org. Lett.* **2007**, *9*, 4889;

Org. Lett. **2010**, *12*, 1248;

Organometallics **2010**, *29*, 389.

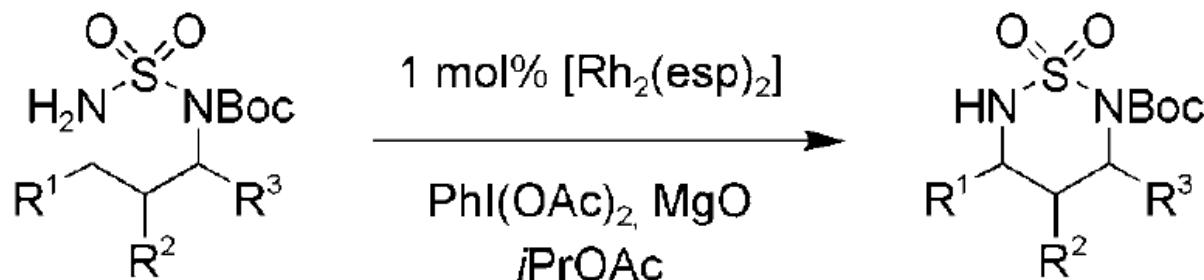


partial racemization



DFT calculations & EPR spectroscopy:
“nitrene radical anion ligand” bearing
the almost entire spin density on the
nitrogen atom

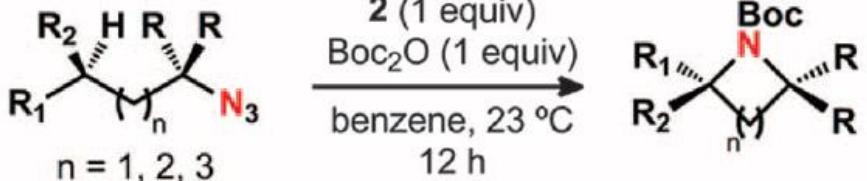
X. P. Zhang, et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 10192;
J. Am. Chem. Soc. **2011**, *133*, 12264.
Angew. Chem. Int. Ed. **2014**, *53*, 7028



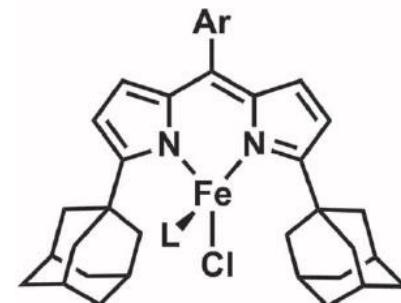
Concerted mechanism involving nitrenoid intermediates

For reviews on C-H amination:

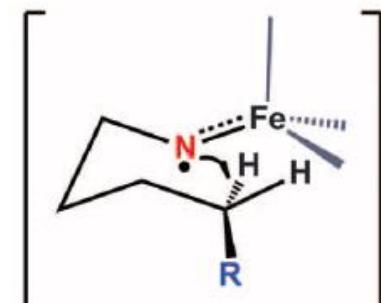
- a) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061 – 5074;
- b) H. M. L. Davies, J. R. Manning, *Nature* **2008**, 451, 417 – 424;
- c) H. M. L. Davies, *Angew. Chem. Int. Ed.* **2006**, 45, 6422 – 6425;
- d) C. G. Espino, J. Du Bois in *Modern Rhodium-Catalyzed Organic Reactions* (Ed.: P.A. Evans), Wiley-VCH, Weinheim, **2005**, pp. 379 – 416;
- e) H. M. L. Davies, M. S. Long, *Angew. Chem. Int. Ed.* **2005**, 44, 3518 – 3520;
- f) J. A. Halfen, *Curr. Org. Chem.* **2005**, 9, 657 – 669;
- g) P. Müller, C. Fruit, *Chem. Rev.* **2003**, 103, 2905 – 2919.



Entry	Azide	Product(s)	Conv. (%) ^{*†}
1			45
2			82
3			52 (1.0:0.9)
4			47 (1.0:1.5)
5			47 (1.0:1.5)



Ar = (1) Mes
(2) 2,6-Cl₂C₆H₃

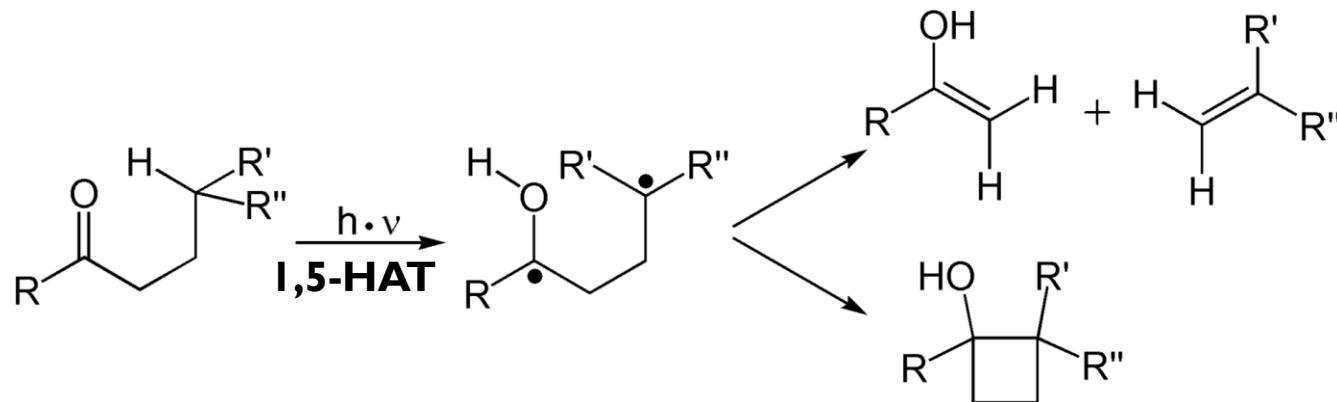


Fe^{III} radical imido

E.T. Hennessy, T.A. Betley,
Science 2013, 340, 591

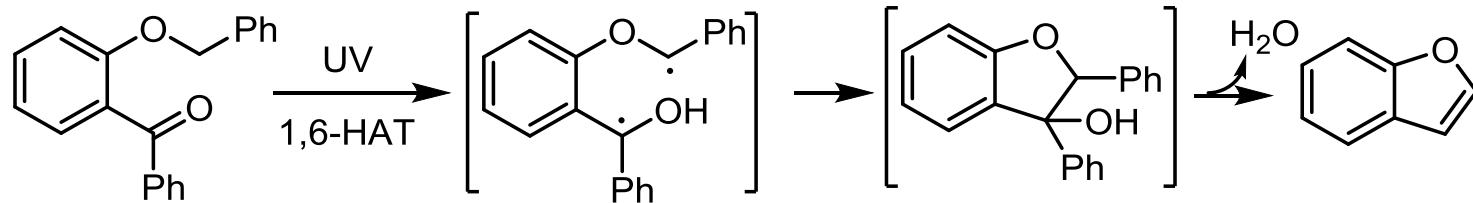
* Yields determined by ¹H NMR using ferrocene or trimethoxybenzene as internal standards. † Ratios determined by integration of GC/MS peaks.

Norrish–Yang rearrangement of ketones



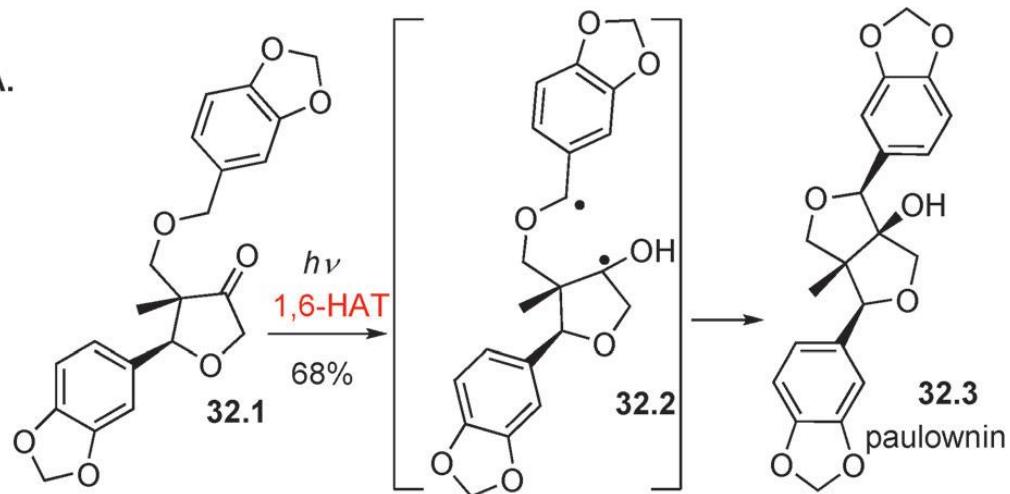
For general reviews, see:

- N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052 – 1103;
- T. Bach, J. P. Hehn, *Angew. Chem. Int. Ed.* **2011**, *50*, 1000 – 1045;
- A. G. Griesbeck, *Synlett* **2003**, 0451 – 0472;
- P. Wessig, Pablo in *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed. (Eds.: W. Horspool, F. Lenci), **2004**, 57/1 – 57/20;
- P. Wessig in *Handbook of CH Transformations*, Vol. I (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**, pp. 569–579.



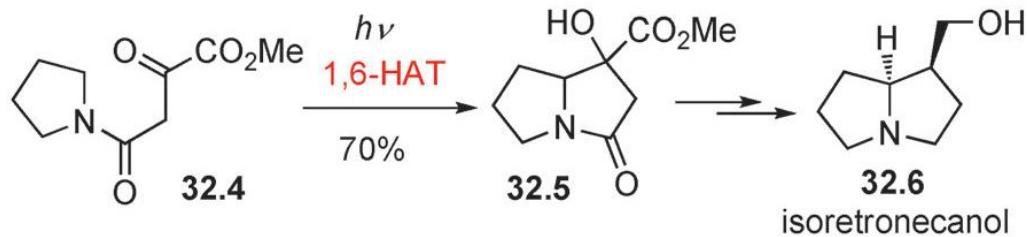
G. R. Lappin, J. S. Zannucci, *J. Org. Chem.* **1971, *36*, 1808.**

A.



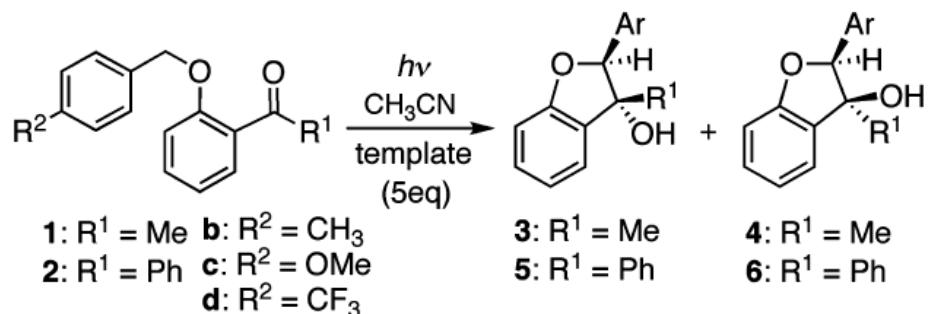
G. A. Krauss, L. Chen, *J. Am. Chem. Soc.* **1990, *112*, 3464**

B.



J. C. Gramain, R. Remuson, D. Valle, *J. Org. Chem.* **1985, *50*, 710.**

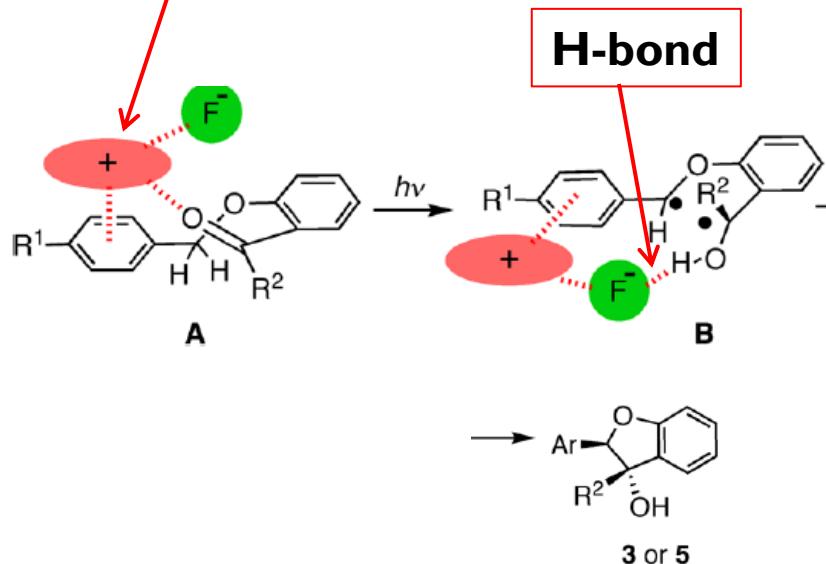
Additive effect:



entry	substrate	template	time (h)	conv (%)	3:4 or 5:6 ^a
1	1b	—	24	35	20:80
2	1b	Bu ₄ NF	24	84	93:7
3	1c	—	24	70	11:89
4	1c	Bu ₄ NF	24	99	94:6
5	1d	—	24	33	23:77
6	1d	Bu ₄ NF	24	6	59:41
7	2b	—	3	100	37:63
8	2b	Bu ₄ NF	3	99	88:12
9	2c	—	3	100	42:58
10	2c	Bu ₄ NF	3	57	88:12
11	2d	—	3	100	45:55
12	2d	Bu ₄ NF	3	92	72:28

^a Determined by ¹H NMR spectra.

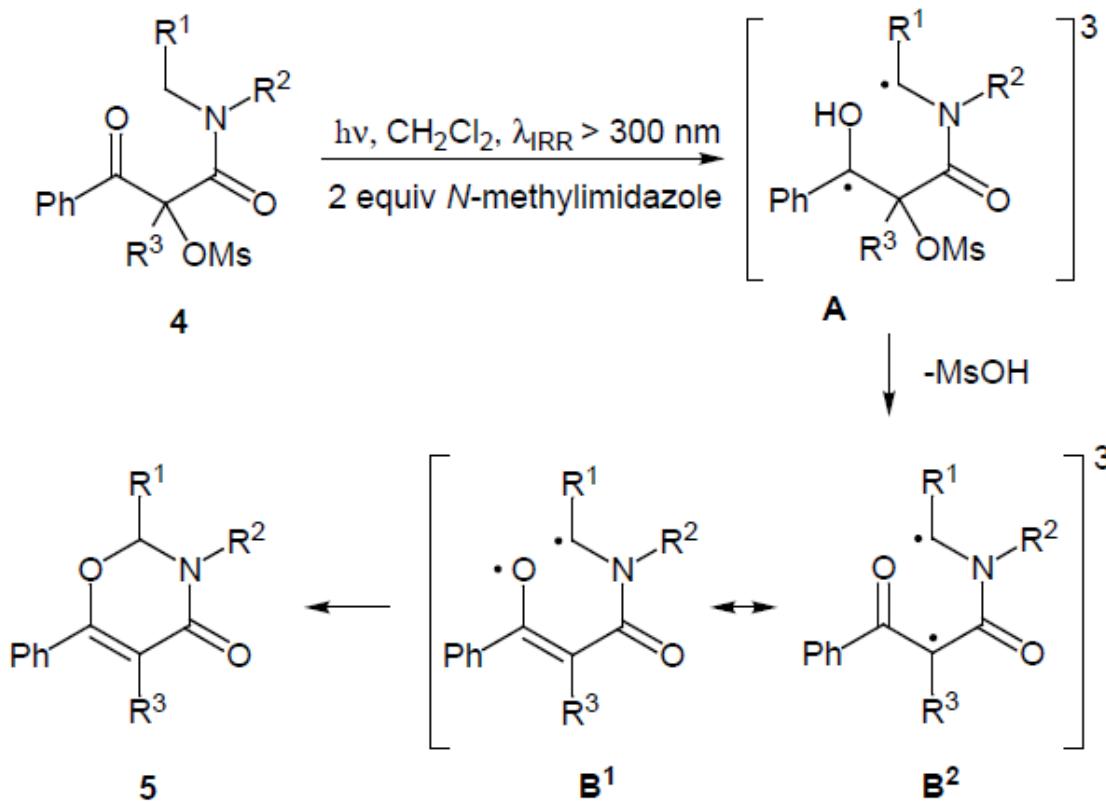
dual interactions



$\text{AcO}^- \geq \text{F}^- > \text{Cl}^- > \text{Br}^-$

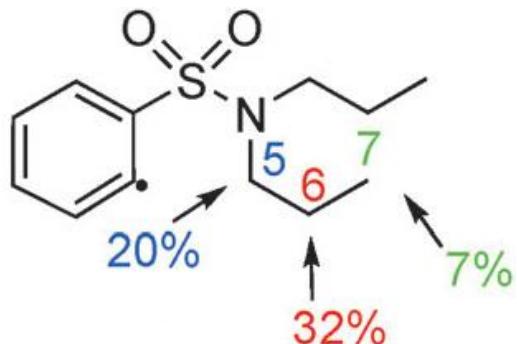
S. Yamada, A. Iwaoka, Y. Fujita, S. Tsuzuki, Org. Lett. **2013**, *15*, 5994

Alpha-LG

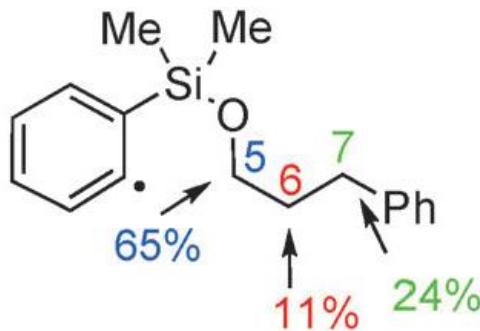


P. Wessig, J. Schwarz, U. Lindemann, M. C. Holthausen, *Synthesis* **2001**, 1258

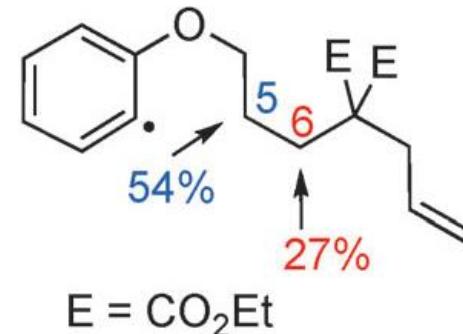
I,6-HAT involving carbon-centered radicals



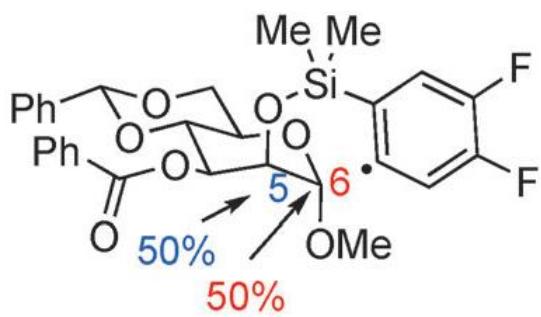
S. H. Pines, et al, *J. Org. Chem.*
1978, 43, 1337.



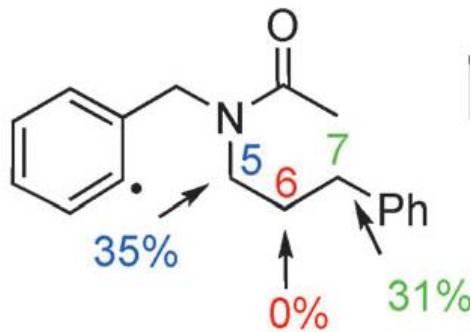
Curran, D. P. et al,
Tetrahedron Lett. **1992, 33,**
2295



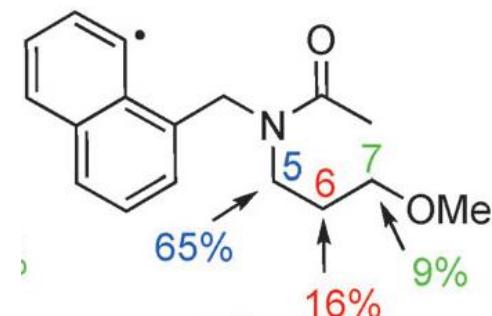
D. P. Curran, et al, *J. Am.*
Chem. Soc. **1993, 115, 6051**



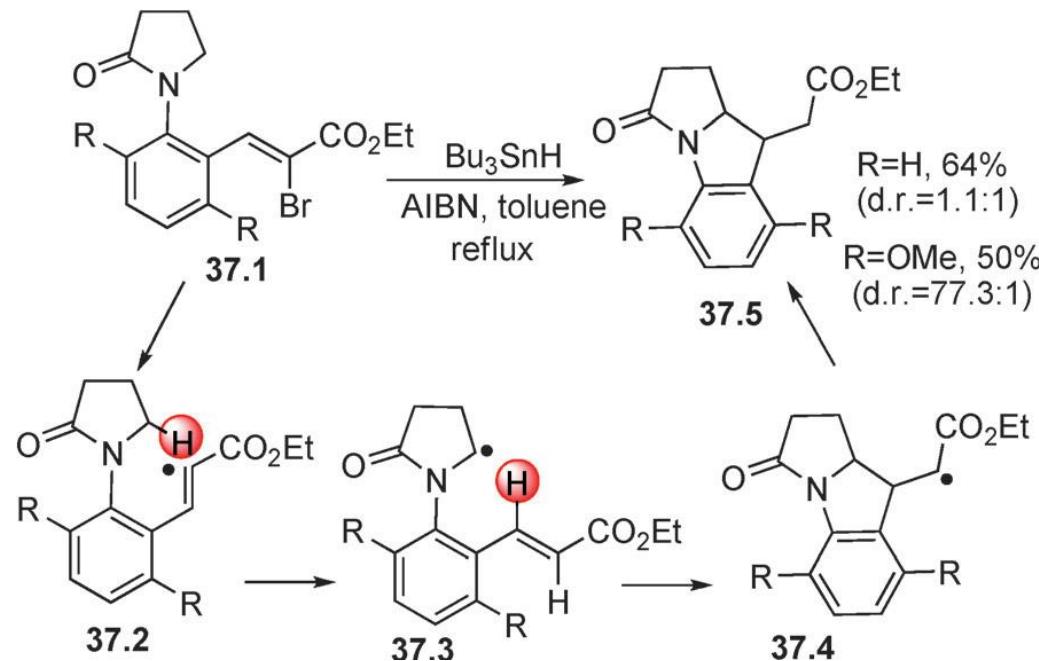
D. P. Curran, et al. *Tetrahedron Lett.* **1994, 35, 6623**



A. De Mesmaeker, et al.
Tetrahedron Lett. **1992, 33, 3613**
Synlett **1991, 621**

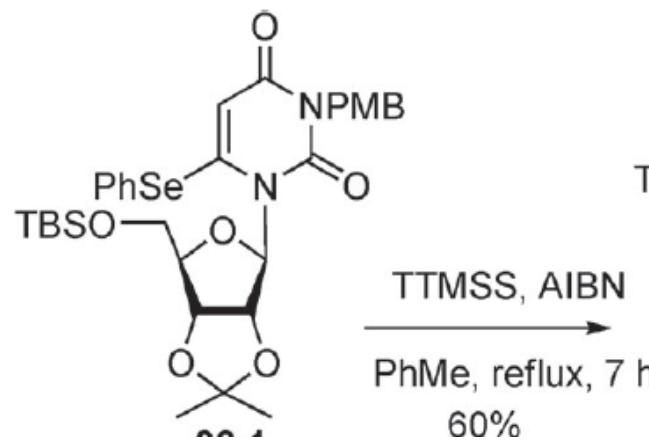


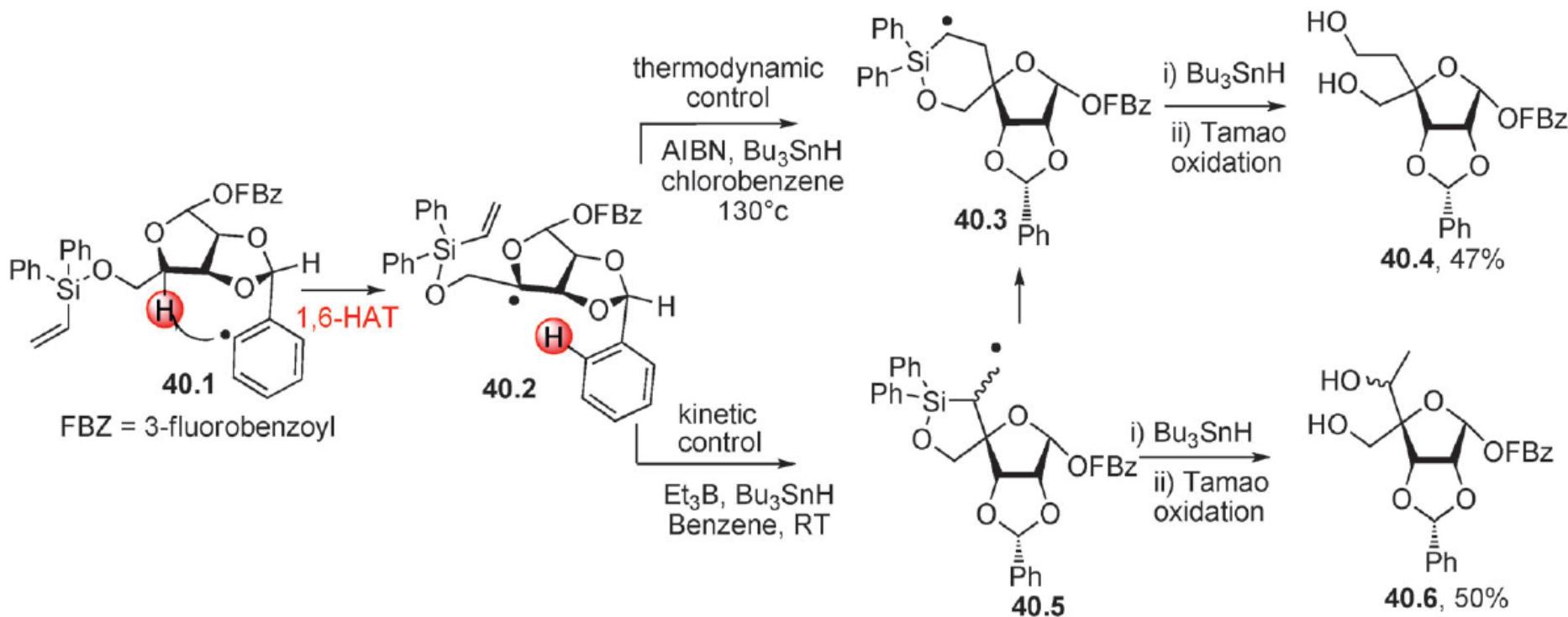
Exclusive 1,6-HAT involving carbon-centered radicals



G. M. Allan, A. F. Parsons, J. F. Pons,
Synlett 2002, 1431

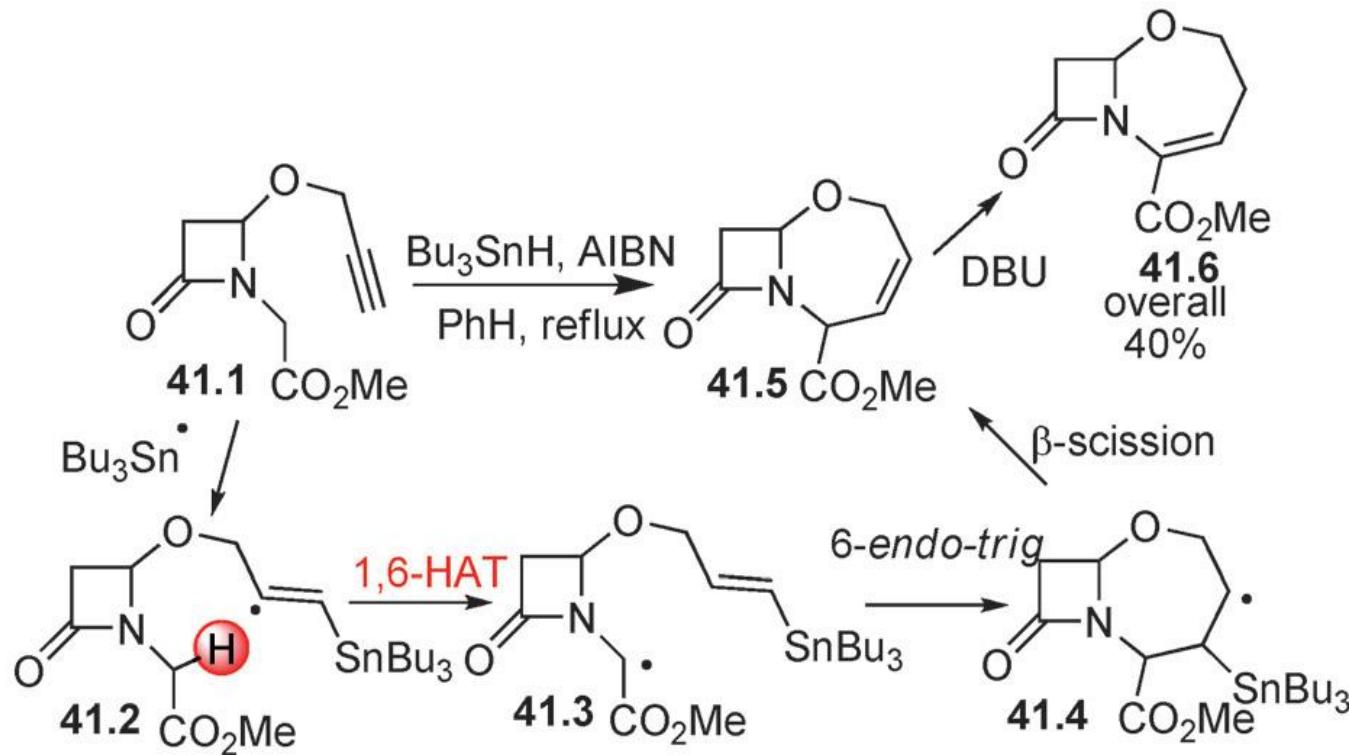
Y. Yoshimura, Y. Yamazaki, K. Wachi, S. Satoh, H. Takahata, *Synlett* 2007,
111





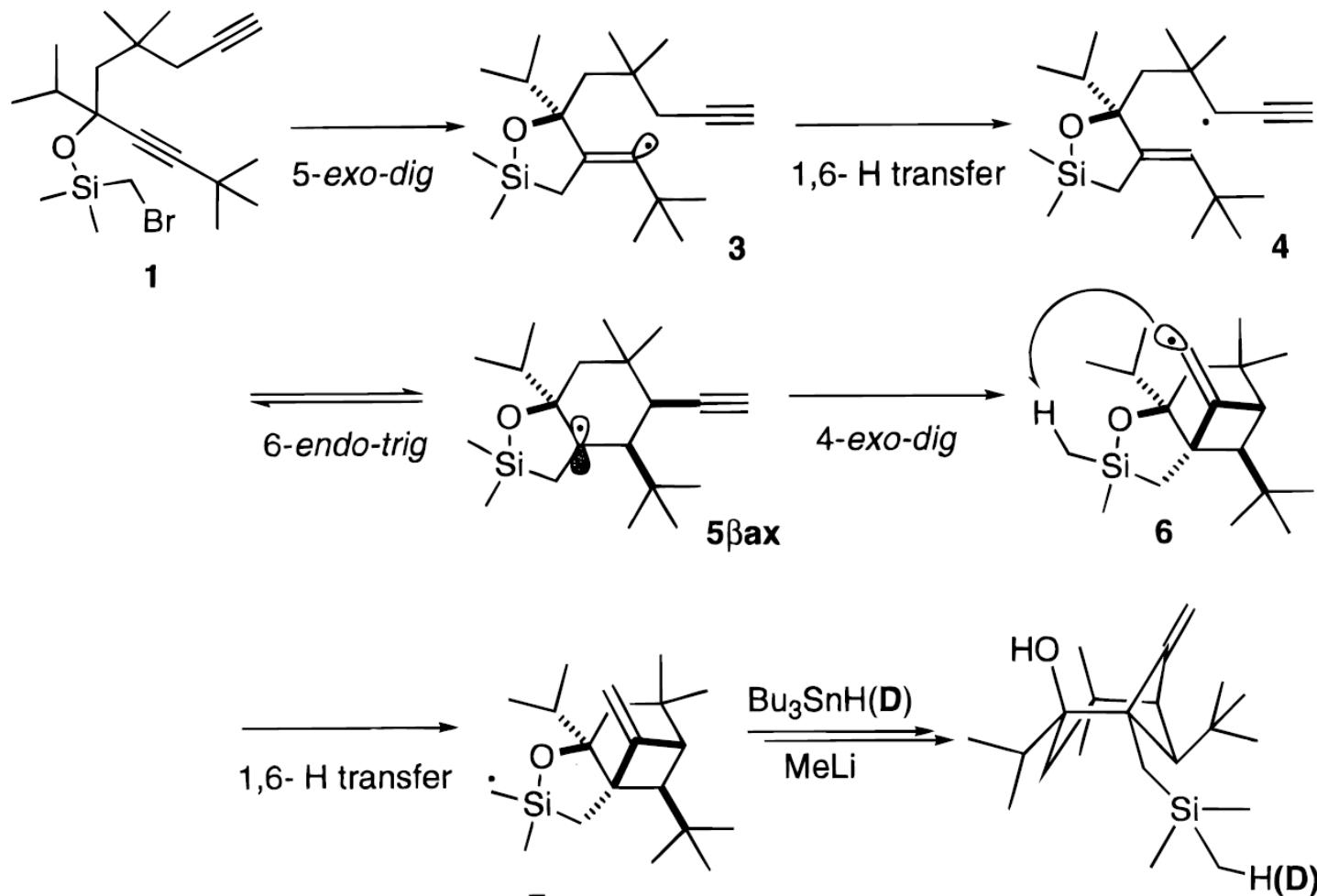
N. Sakaguchi, S. Hirano, A. Matsuda, **S. Shuto**, Org. Lett. **2006**, 8, 3291

Combination of radical addition/1,6-HAT/radical cyclization



E. Bosch, M. D. Bachi, J. Org. Chem. 1993, 58, 5581.

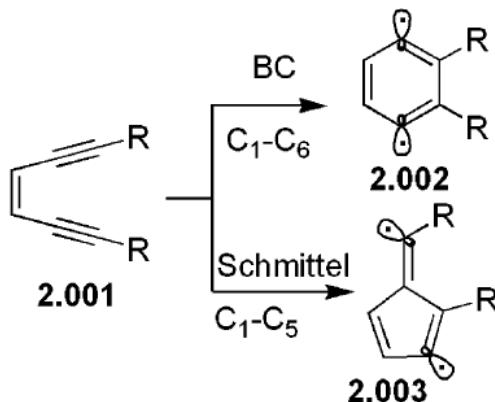
Radical Cascades



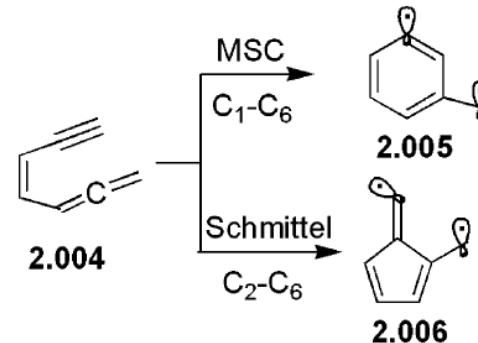
M. Malacria, et al. J. Am. Chem. Soc. 1997, 119, 5037
J. Org. Chem. 1999, 64, 819

1,6-HAT in rearrangements involving biradicals

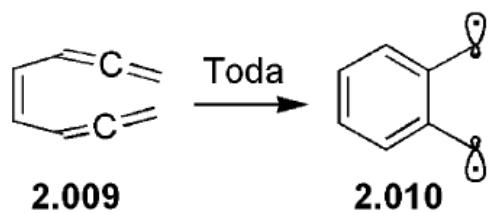
Cyclization of Enediyne



Cyclization of Ene-yne-allene



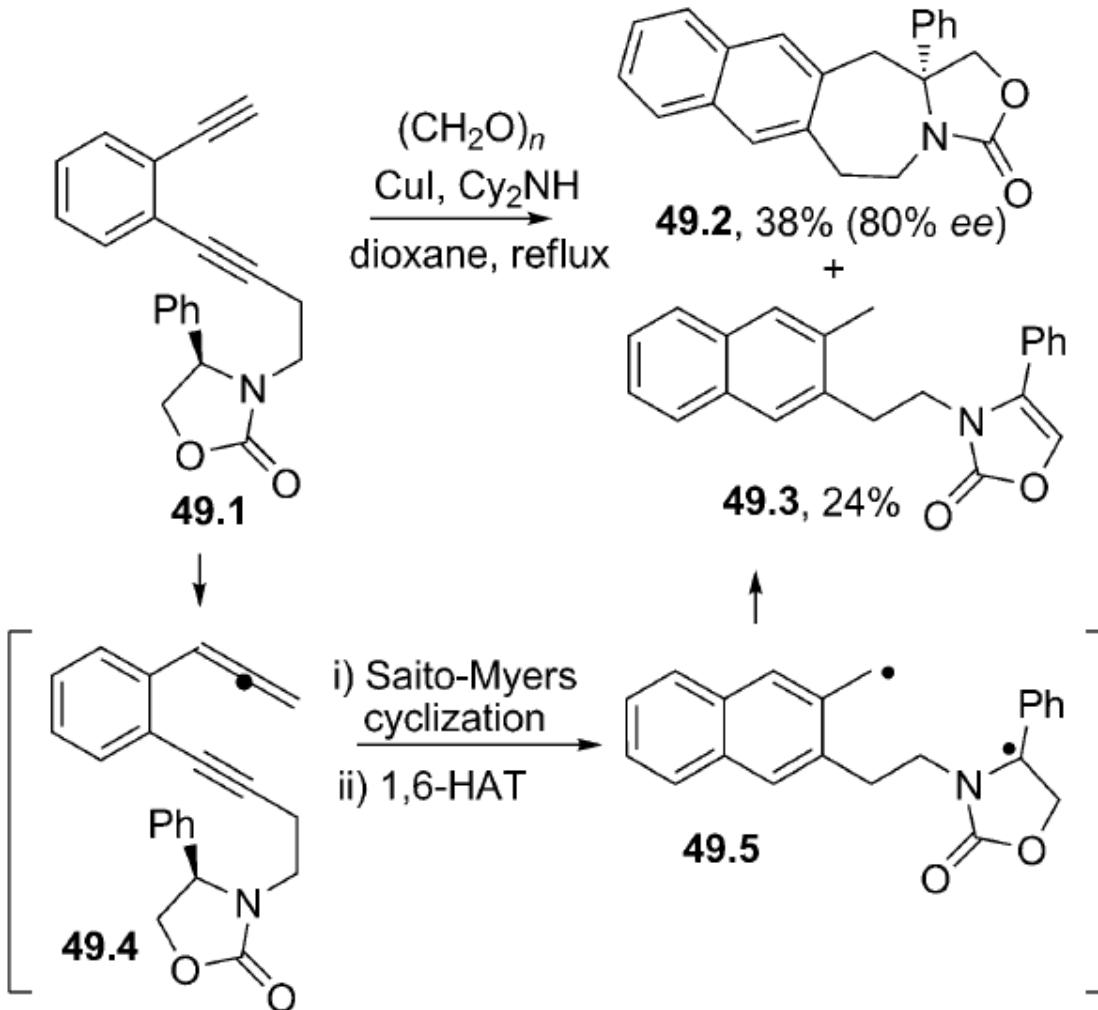
Cyclization of Ene-bisallenes



For reviews, see:

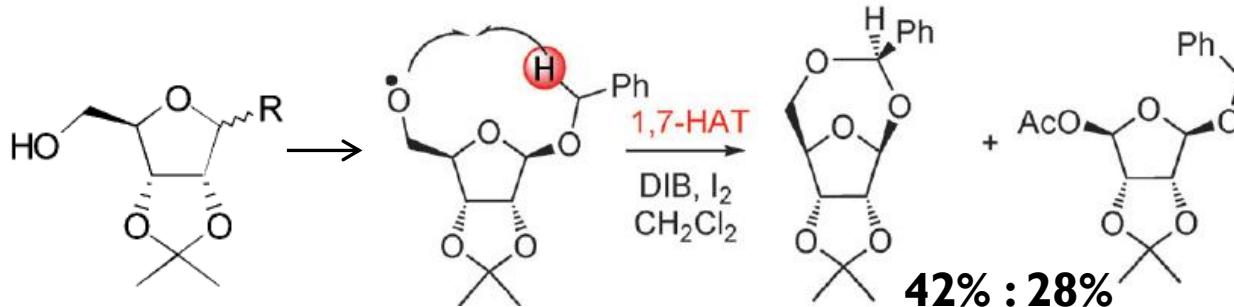
- A. Basak**, et al. *Chem. Rev.* **2007**, *107*, 2861
- I.V. Alabugin**, et al. *Org. Biomol. Chem.* **2012**, *10*, 3974.

Typical examples:

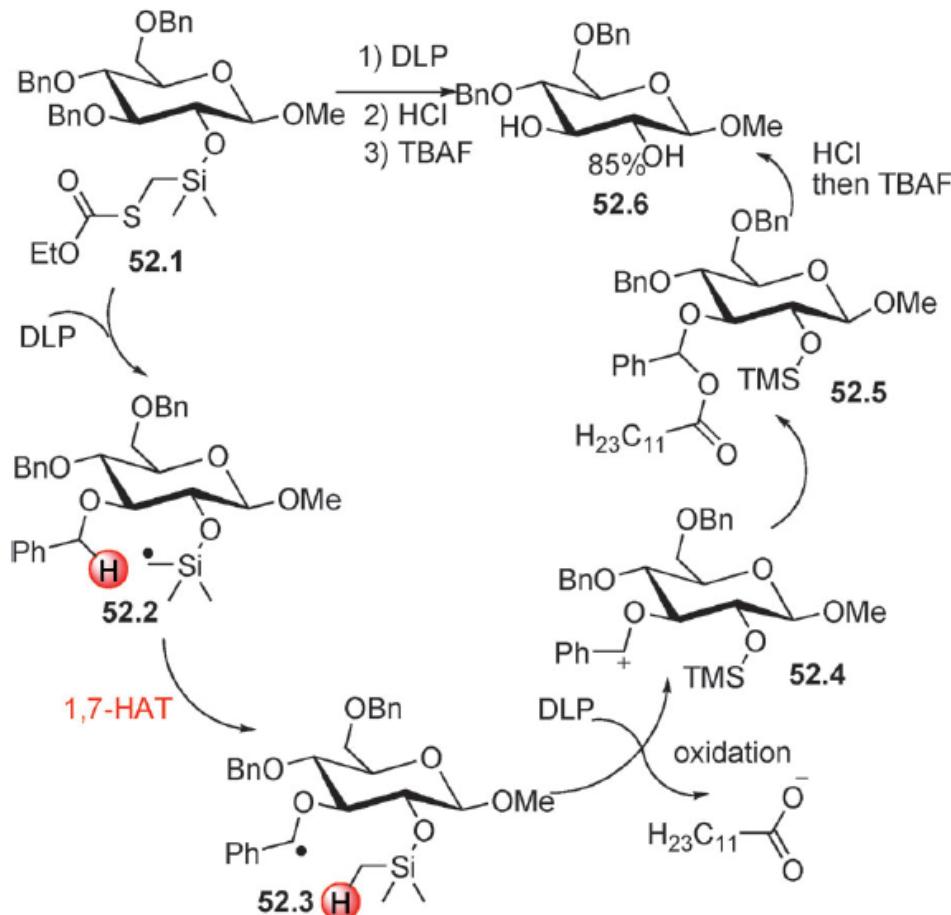


S. Mondal, M. Nechab, N. Vanthuyne, **M. P. Bertrand**, *Chem. Commun.* **2012**, *48*, 2549

1,7-Hydrogen-atom transfer



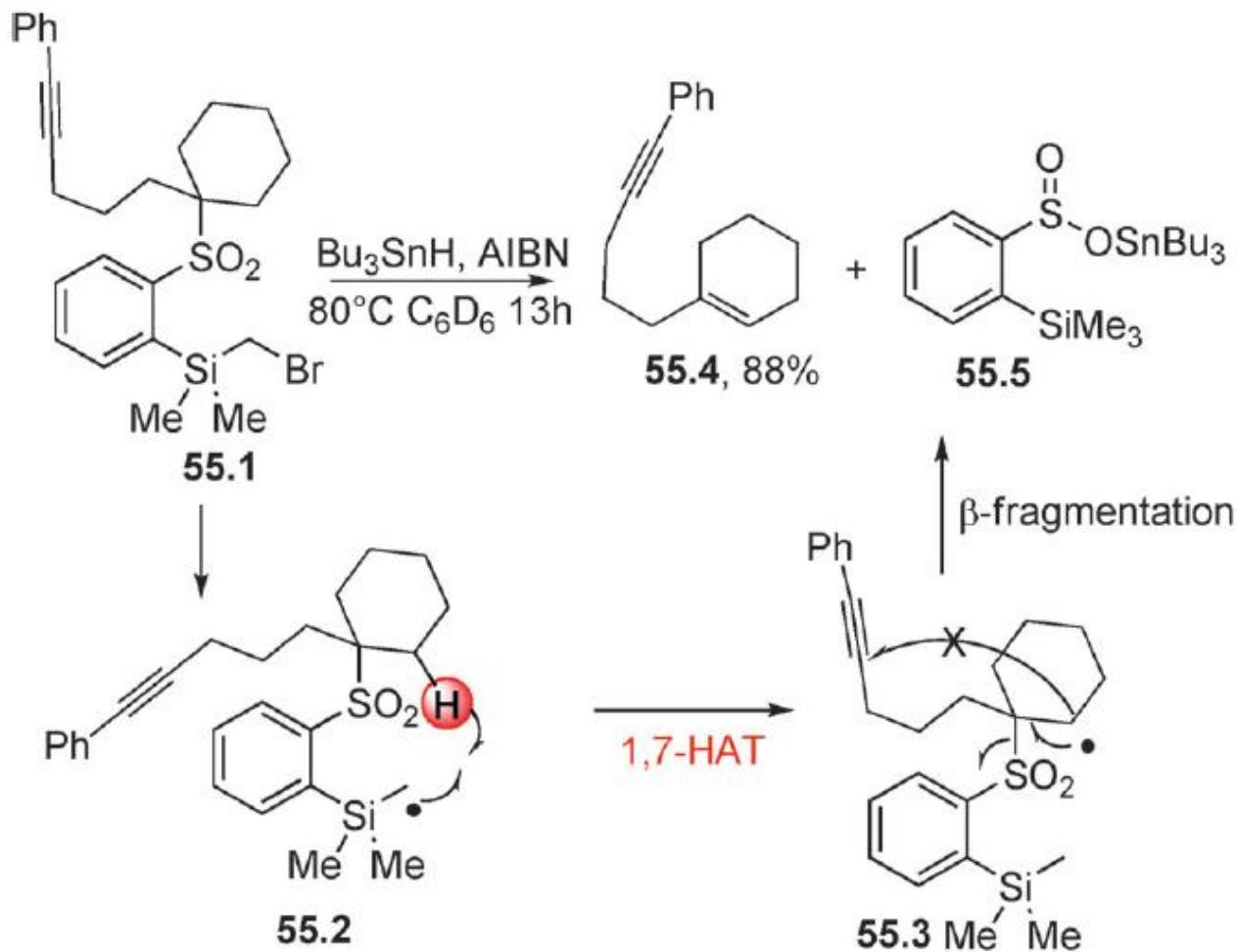
A. Boto, D. Hernández, R. Hernández, E. Suárez, *J. Org. Chem.* **2003**, *68*, 5310



De-protection:

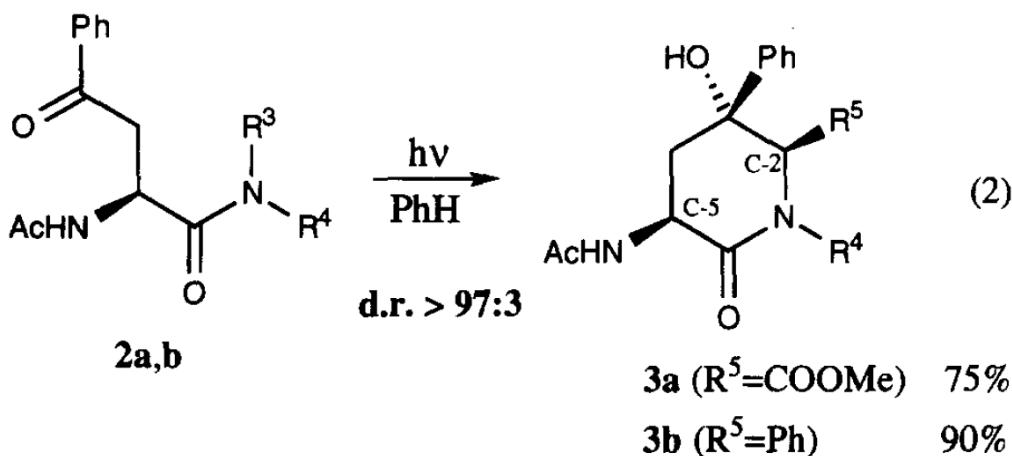
A. Attouche, D. Urban, J.-M. Beau, *Angew. Chem. Int. Ed.* **2013**, *52*, 9572

Reductive Desulfonylation



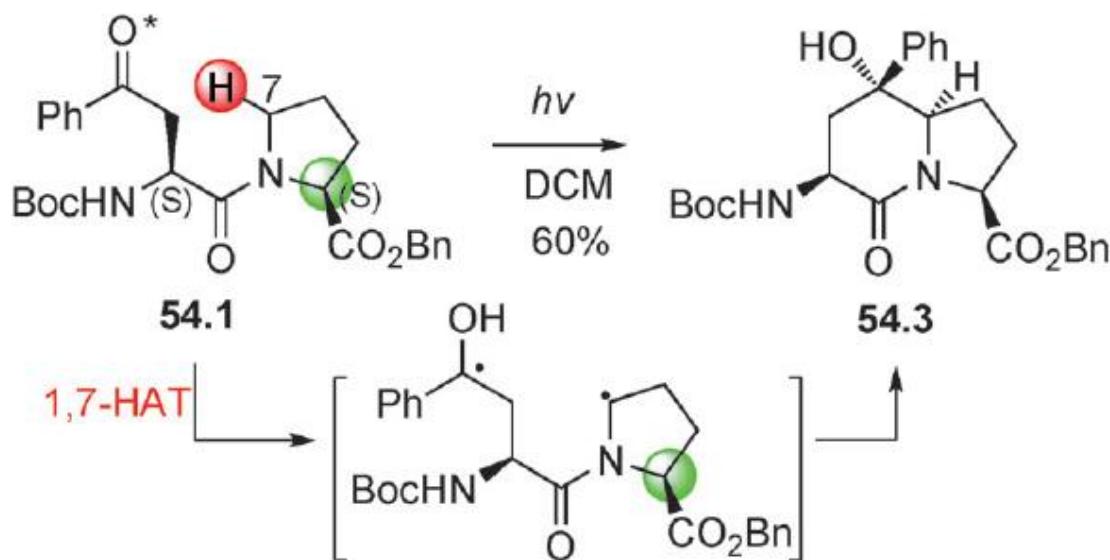
P. C. Van Dort, P. L. Fuchs, *J. Org. Chem.* 1997, 62, 7142.

Norrish type II photocyclizations



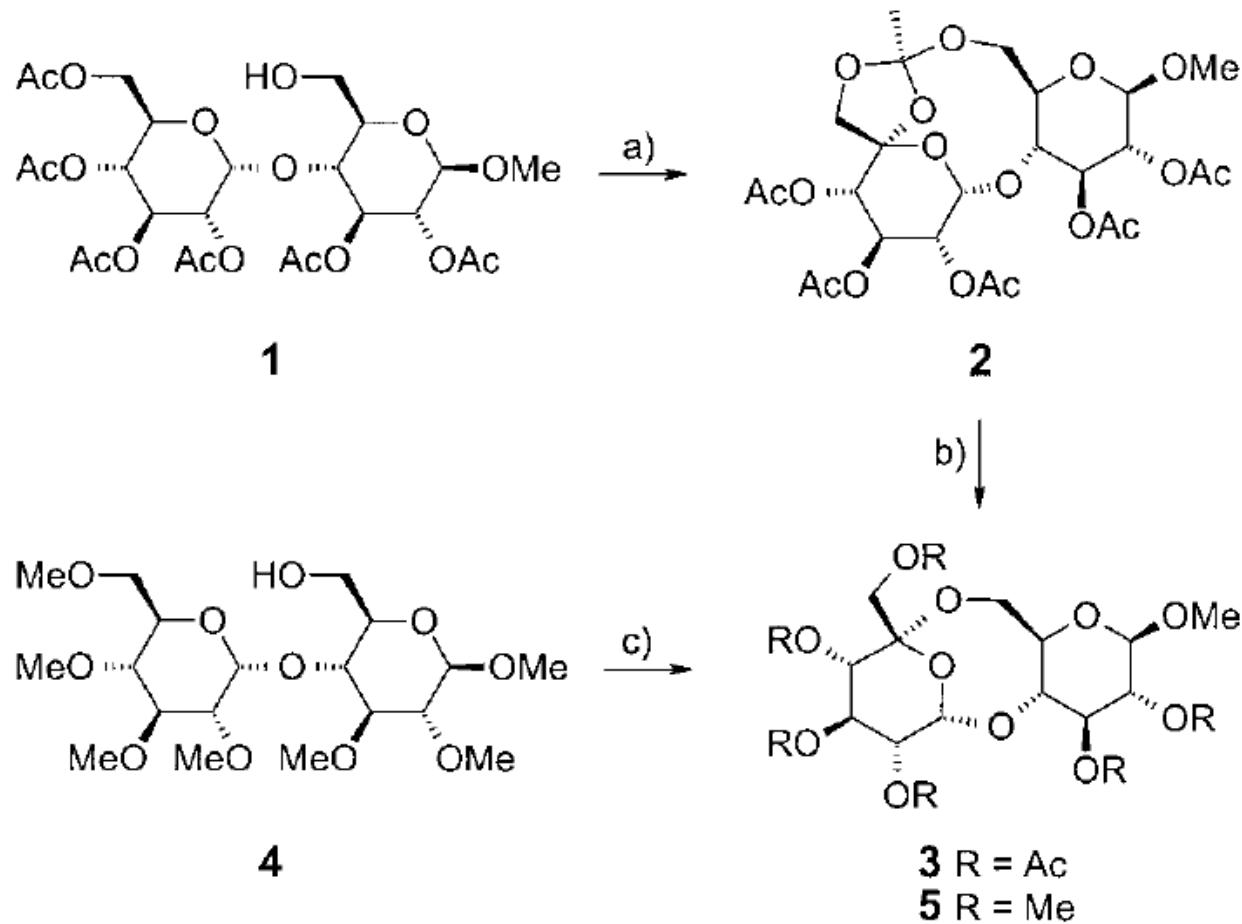
A. G. Griesbeck, et al, Tetrahedron Lett. 1999, 40, 3137

P. Wessig, et al.
Tetrahedron **1998**, *54*, 2529.
Tetrahedron Lett. **1999**, *40*, 5987

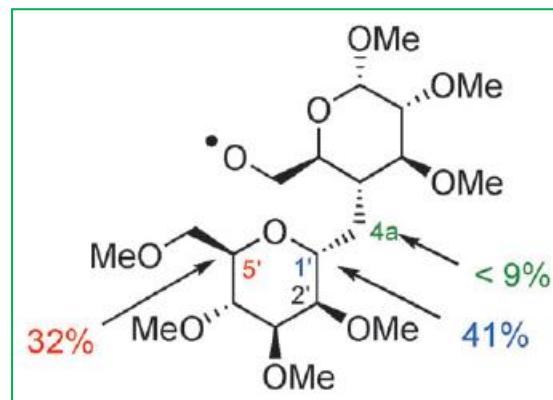
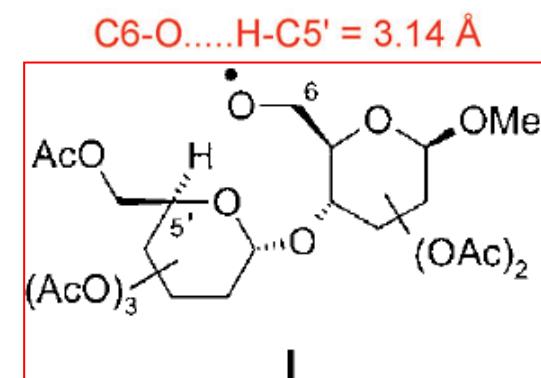


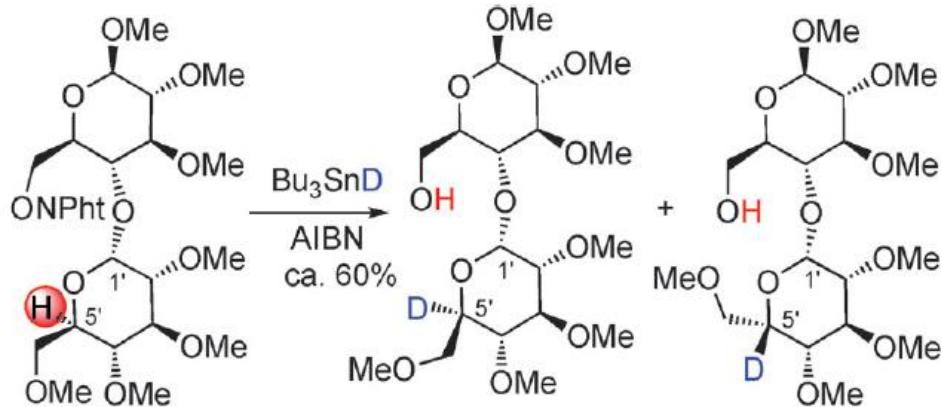
1,8-Hydrogen-atom transfer

Most examples involve oxygen-centered radicals.

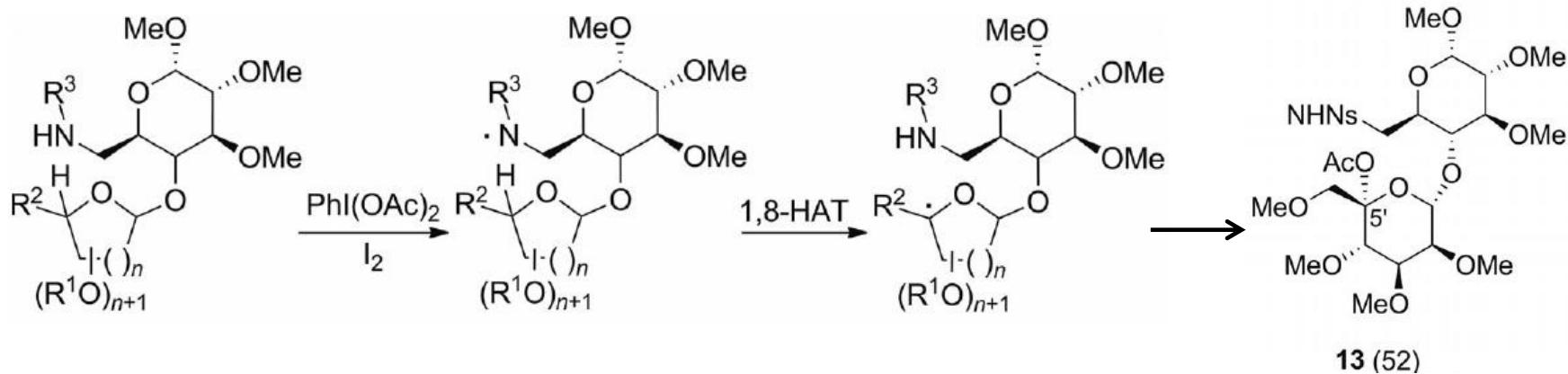


Scheme 1. IHA under oxidative conditions. a) DIB (1.5 equiv), iodine (0.7 equiv), CH_2Cl_2 , $h\nu$, 25°C , 90 min, 62 %; b) CDCl_3 , RT, 60 h, 100 %; c) DIB (1.7 equiv), iodine (0.5 equiv), CH_2Cl_2 , 25°C , 90 min, 56 %. DIB = (diacetoxido)benzene.



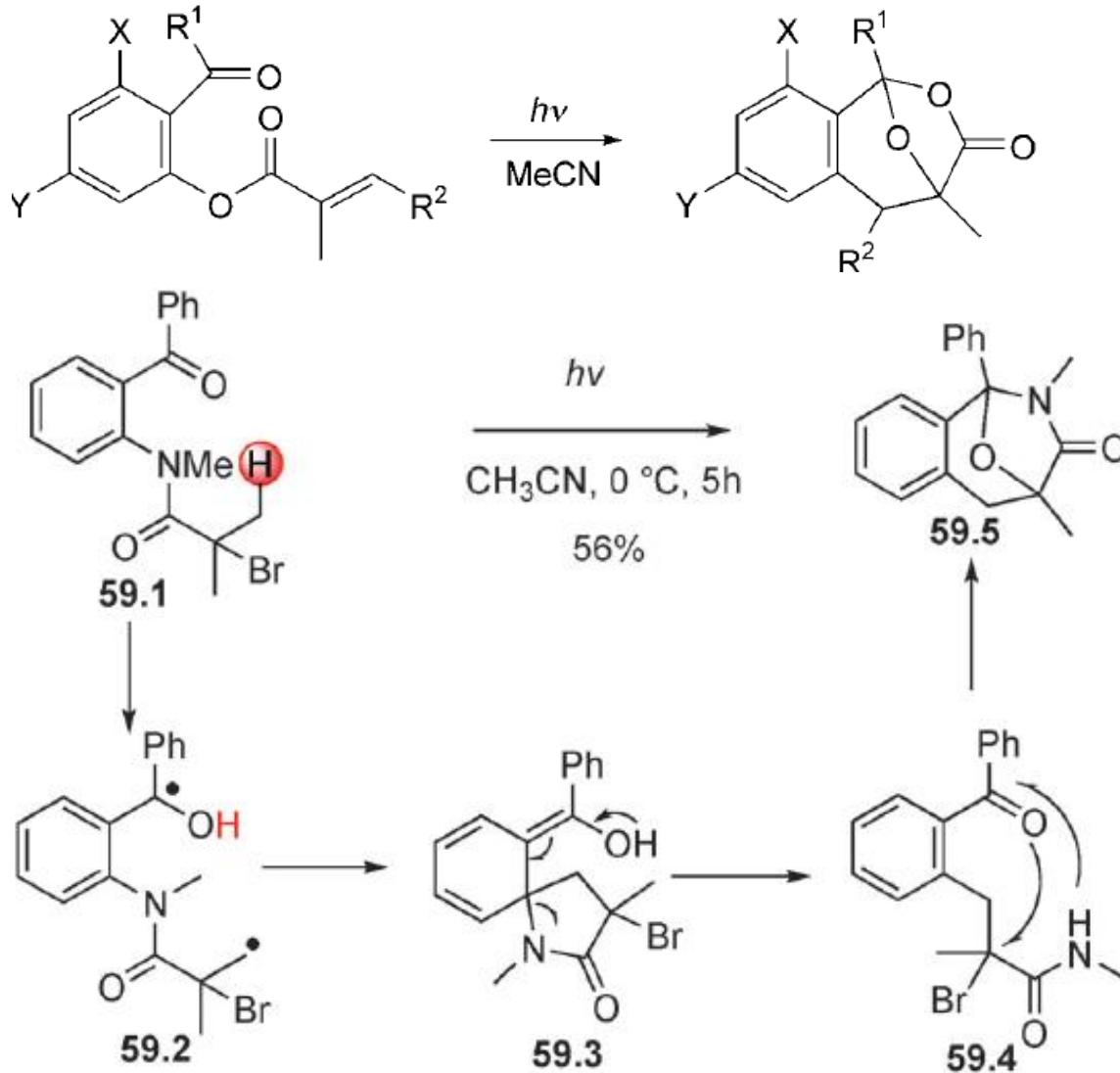


E. Suárez, et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 856; *Org. Lett.* **2007**, *9*, 1785;
Chem. Eur. J. **2008**, *14*, 10369; *J. Org. Chem.* **2008**, *73*, 7710; *Eur. J. Org. Chem.* **2010**, 5248.



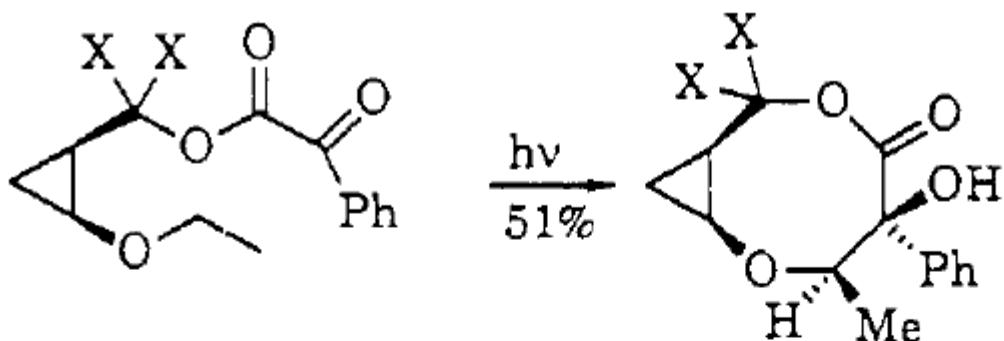
E. Suárez, et al. *Eur. J. Org. Chem.* **2011**, 7339

Norrish type II photocyclizations



T. Nishio, et al. *Helv. Chim. Acta* **2005**, *88*, 2603.

Long-distance 1,n-HAT ($n \geq 9$)

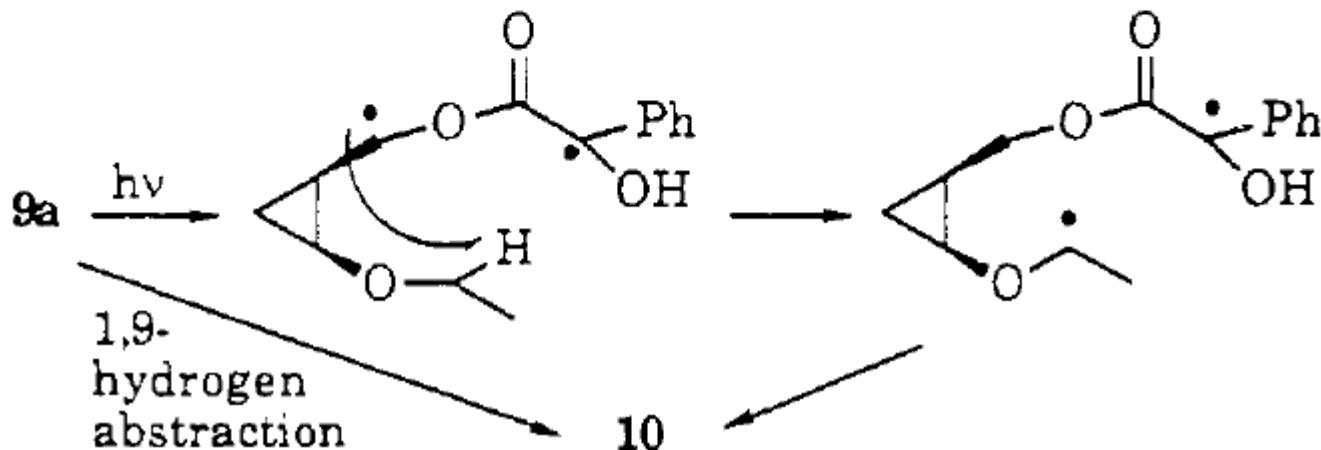


9a: $X = H$

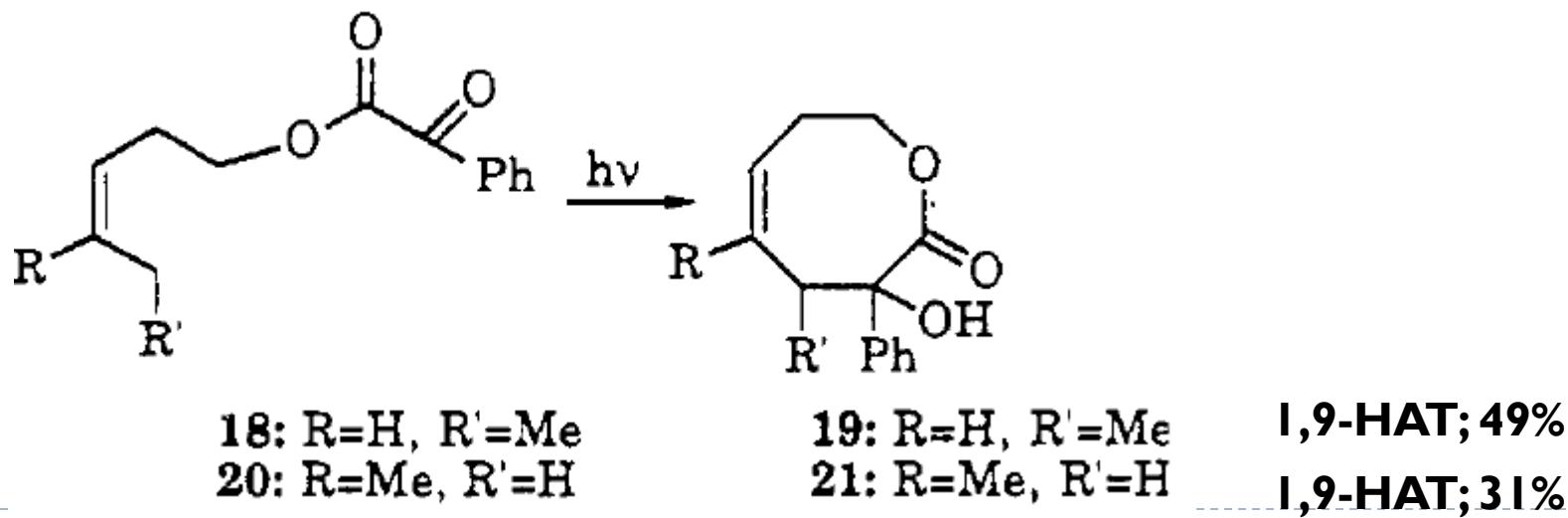
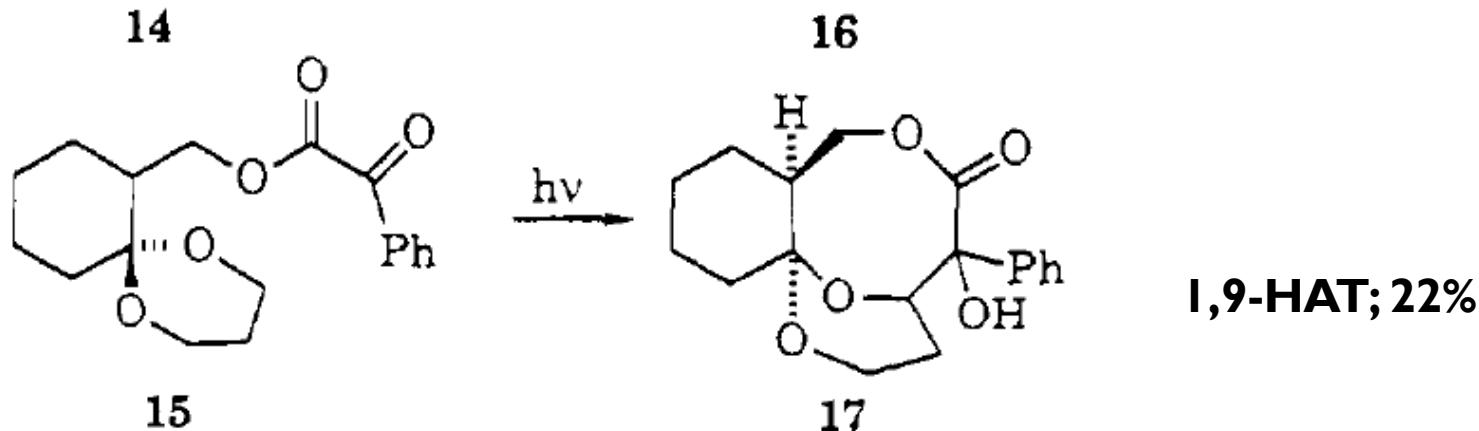
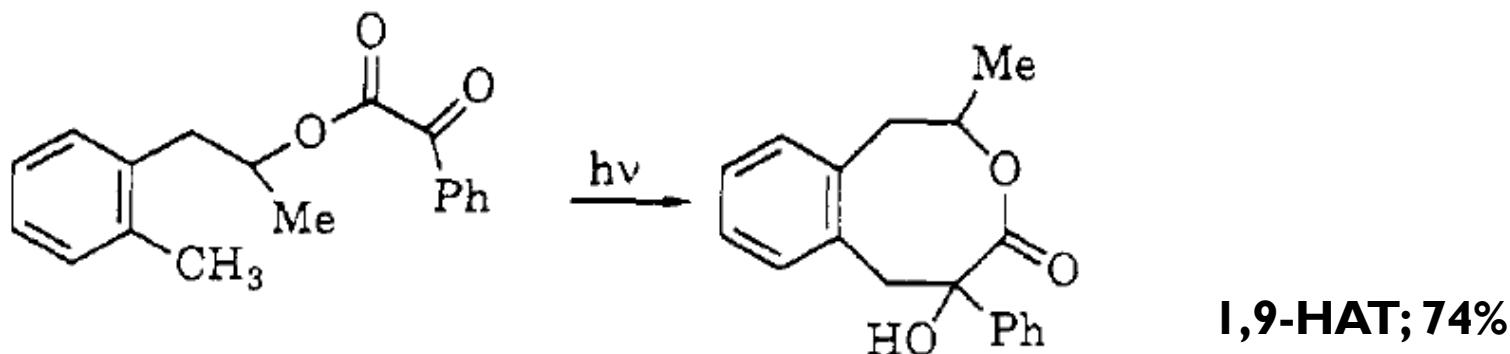
9b: $X = D$

10: $X = H$

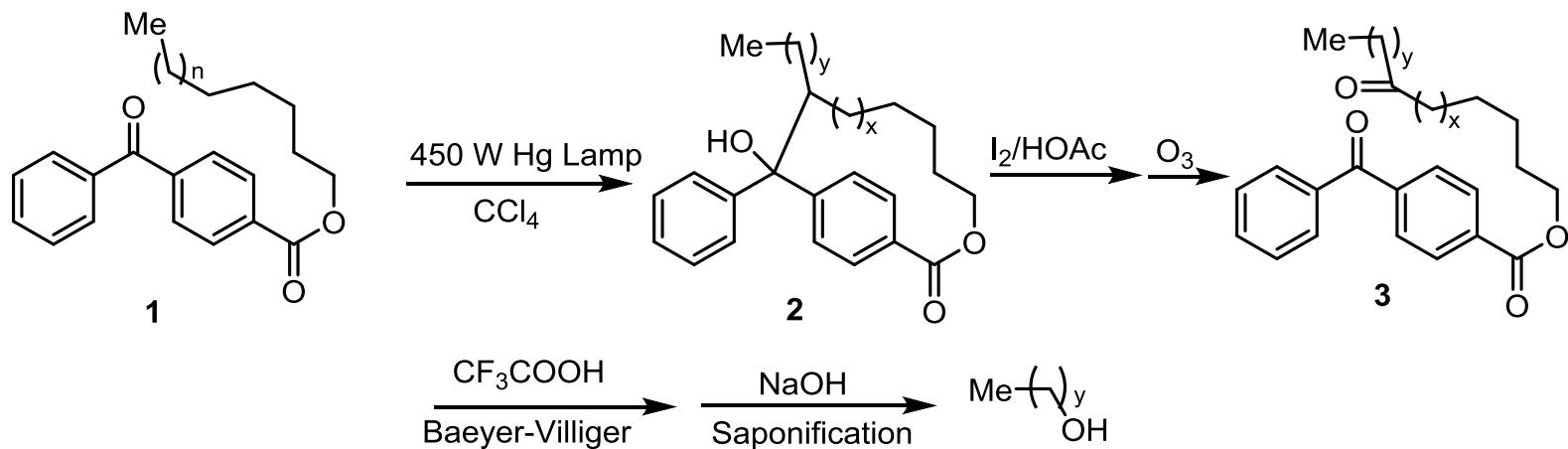
11: $X = D$



G.A. Krause, Y. Wu, J. Am. Chem. Soc. 1992, 114, 8705



Breslow's transformations



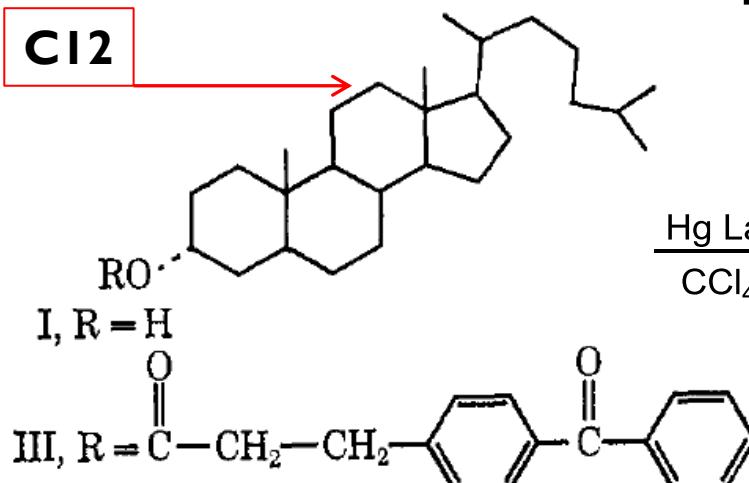
Oxidation site	Number of carbons in ester alkyl chain				
	C-14	C-16 ^d	C-16 ^d	C-18	C-20
C-8					
C-9	1.4	1.1	1.4	0.1	<2
C-10	3	7.8	8	8	5
C-11	11	12	10	17 ± 3 ^c	15
C-12	49 ^a	13	8	21	20
C-13	22 ^b	10	3	18	19 ± 3 ^c
C-14	0	56 ^a	66 ^a	12	19
C-15		7 ^b	10 ^b	5	13
C-16		0	0	13 ^a	8
C-17				6 ^b	0.7
C-18				0	0
C-19					0 ^b
C-20					

^a Measured amount of ethanol doubled in accord with selectivity against ethyl migration in the Baeyer–Villiger reaction. Not corrected for steam distillation work-up, making these values minimum values. ^b Measured by nmr analysis of IV. ^c Reproducibility of measurements within one experiment at least ± 1% except where noted. ^d Typical reproducibility between completely different runs.

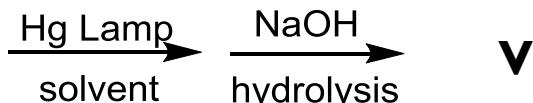
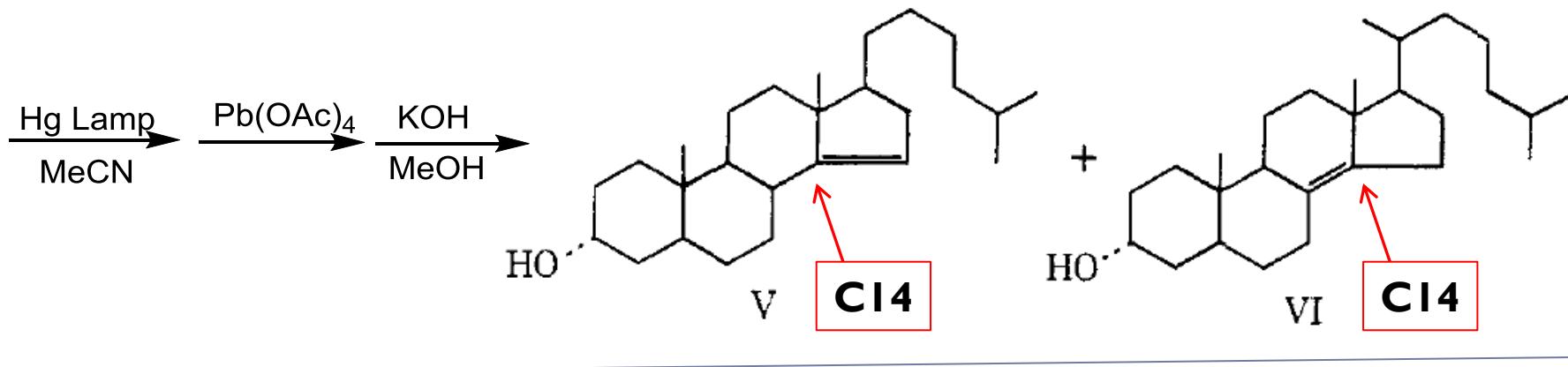
Breslow's transformations

Cholestanol

Cl2



Together with chlorination product

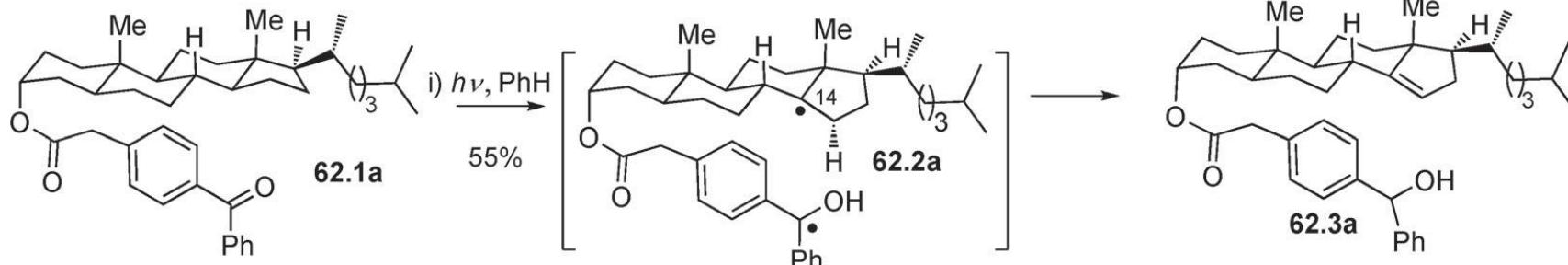


MeCN: 10%
Acetone: 20%
Benzene: 35%

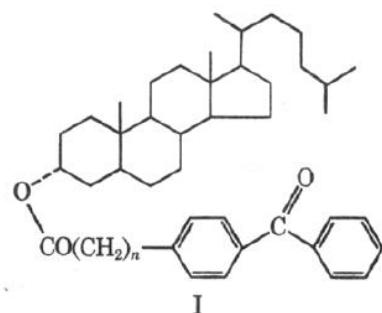
Directly dehydrogenation
w/o C-C bond formation

Breslow's transformations

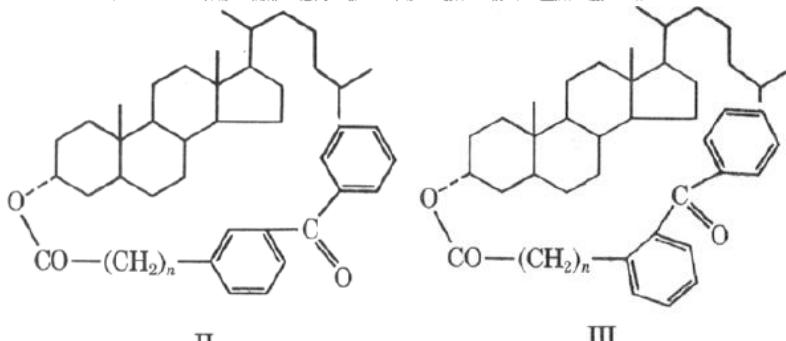
A.



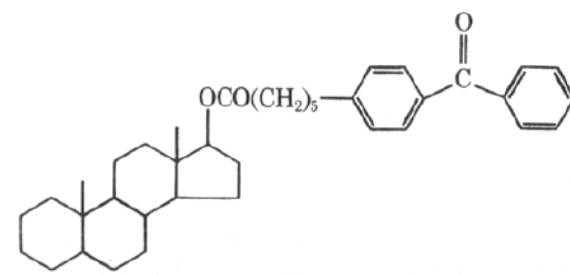
Substrate	% direct olefin	% lactone	Olefin distribution						
			$\Delta 6$	$\Delta 7$	$\Delta 14$	$\Delta 8(14)$	$\Delta 16$	$\Delta 5$	$\Delta 9(11)$
Ia, IIa, IIIa, IIIb, VIa-c	None	None							
Ib	55	0					100		
Ic	35	50					100		
Ic (lactone cleavage)			20	49			31		
Id (in benzene)	55	10				43		57	
Id (in acetone)	55					30		70	
IIb	5	95	28	16				30	34
IIb (lactone cleavage)									



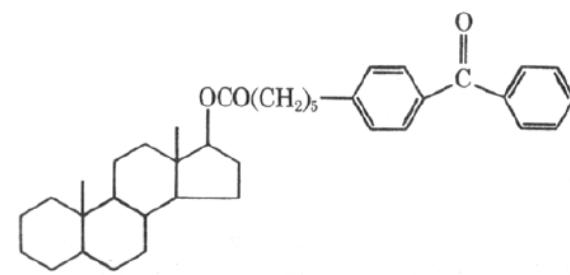
a, n = 0; b, n = 1; c, n = 2; d, n = 4



a, n = 0; b, n = 1

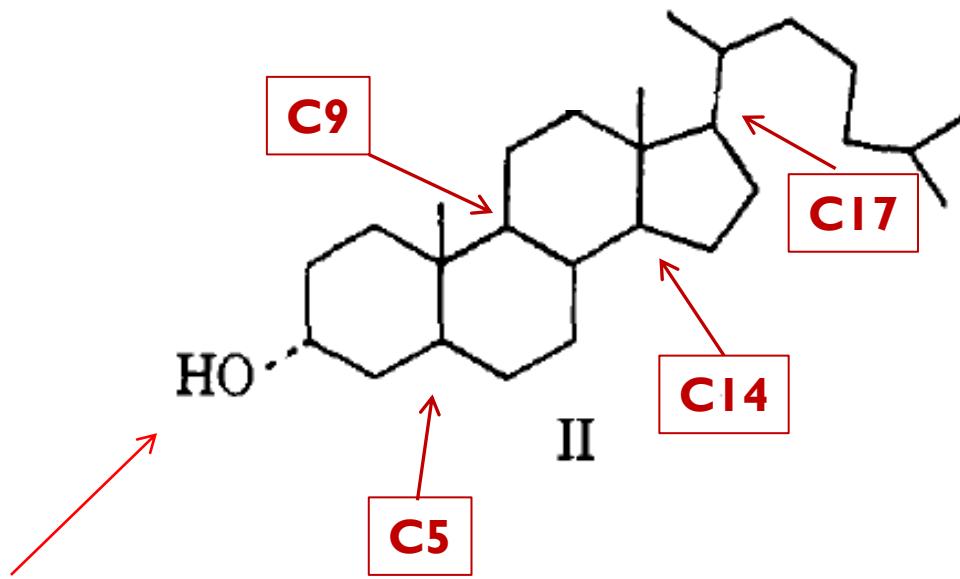


a, n = 0; b, n = 1



IV

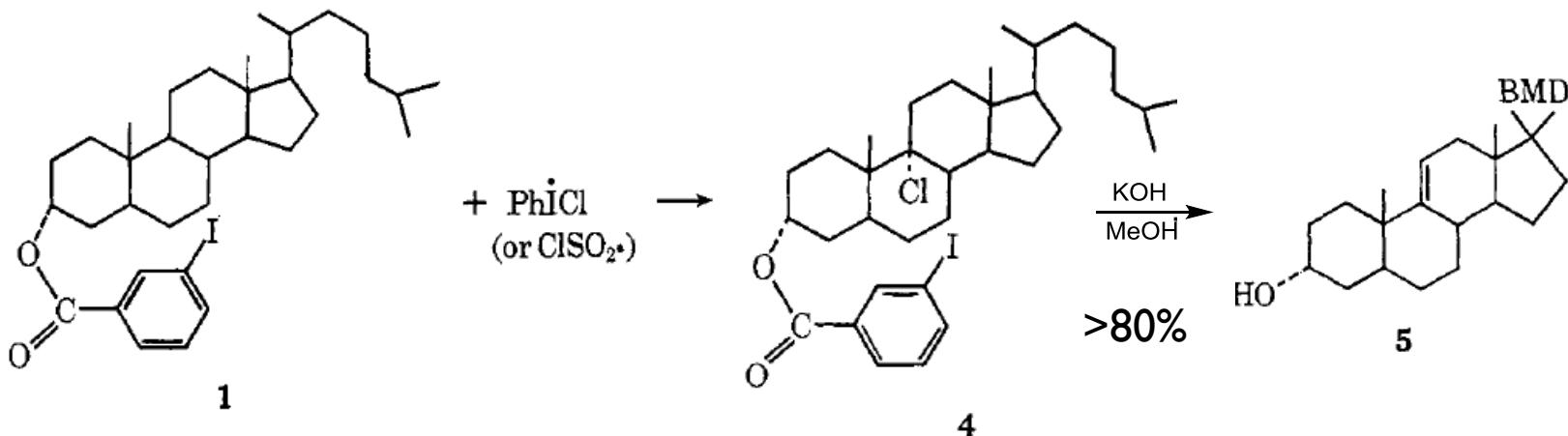
Other position?



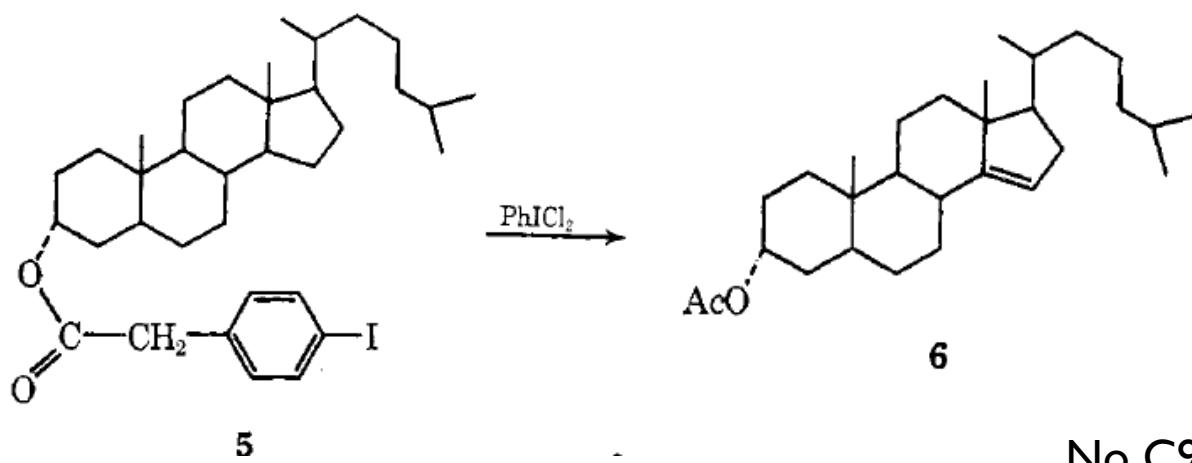
Poor selectivity.

OH, OAc, or $\text{OCO}(\text{CH}_2)_n(\text{C}_6\text{H}_4)\text{CO}(\text{C}_6\text{H}_5)$

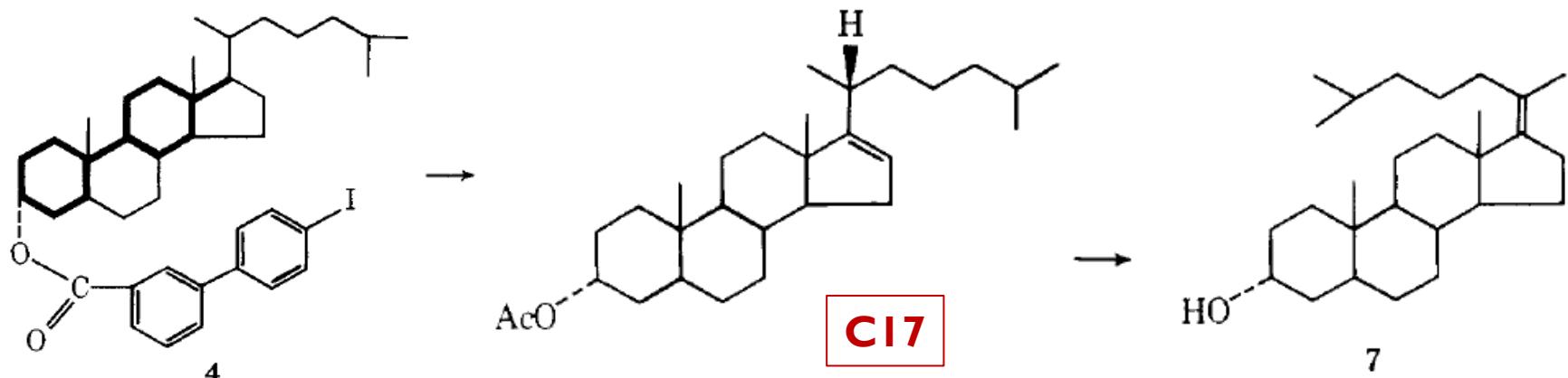
R. Breslow, et al. *J. Am. Chem. Soc.* 1972, 94, 3276.



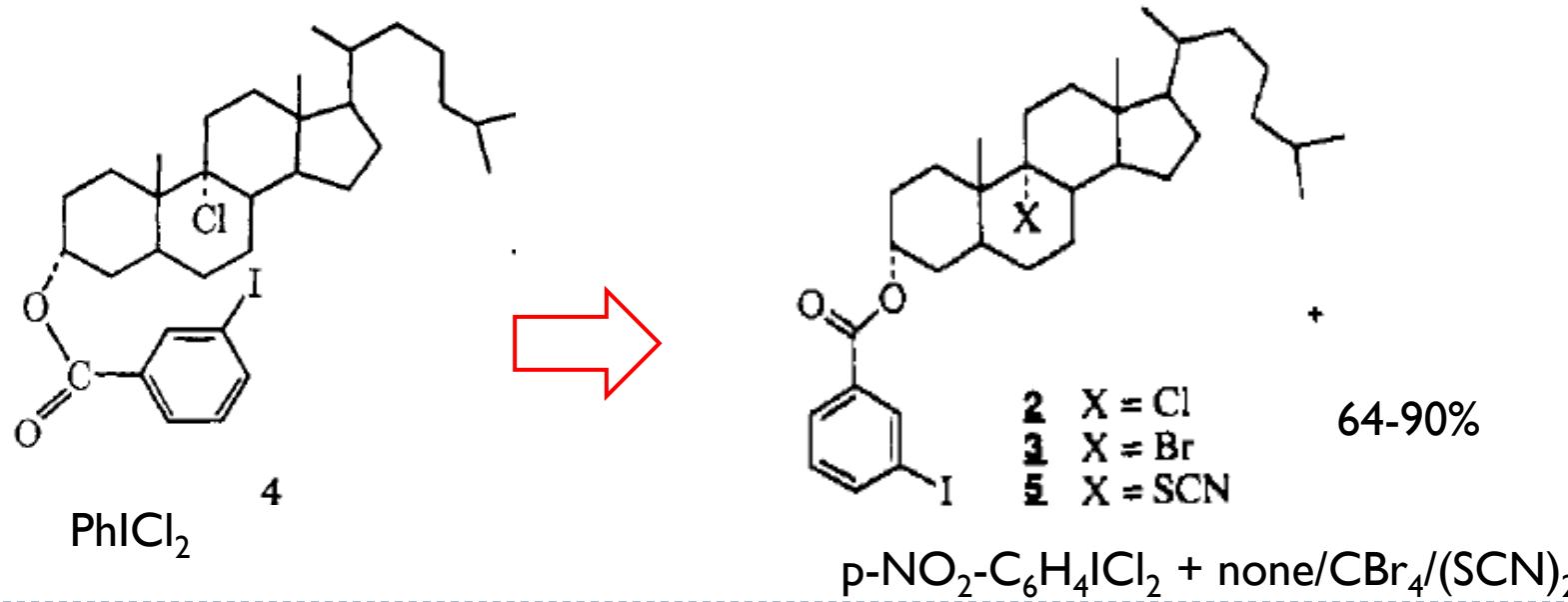
No C14 product



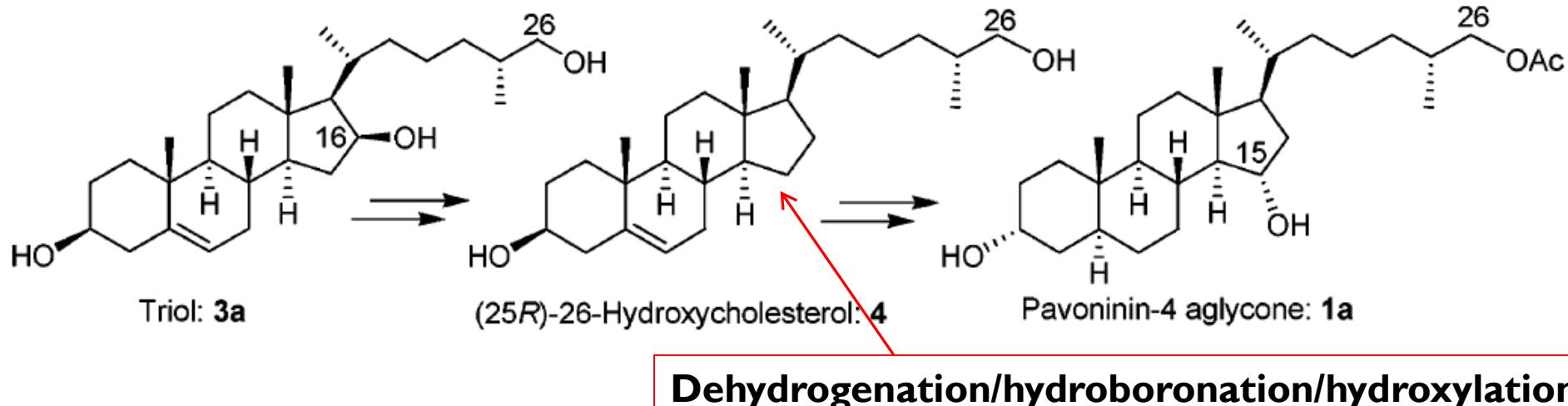
R. Breslow, et al. *J. Am. Chem. Soc.* **1974**, *96*, 1973.
J. Am. Chem. Soc. **1974**, *96*, 6791.
J. Am. Chem. Soc. **1974**, *96*, 6792.



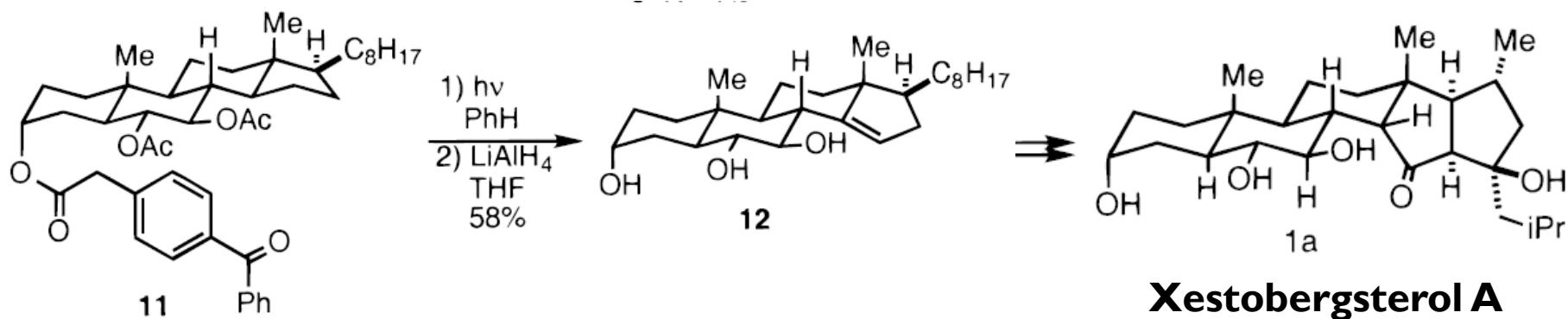
R. Breslow, et al. *J. Am. Chem. Soc.* **1975, **97**, 6580.
J. Am. Chem. Soc. **1977**, **99**, 905.**



► **R. Breslow, et al. *J. Am. Chem. Soc.* **1991**, **113**, 8977.**



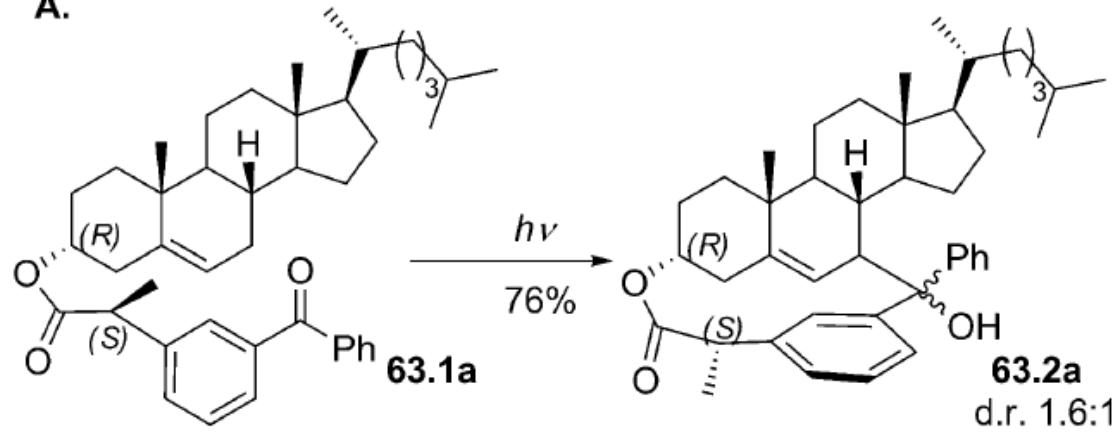
H. Gong, J. R. Williams, *Org. Lett.* **2006**, 8, 2253.



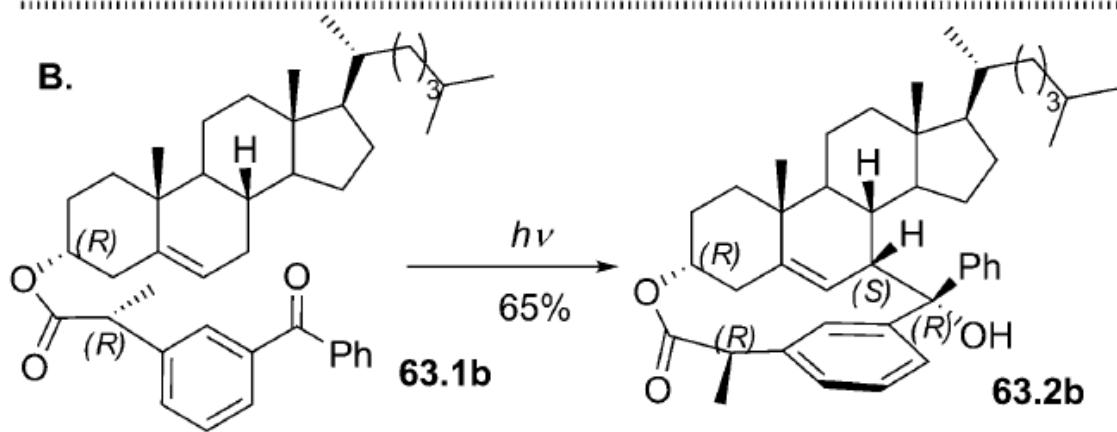
M. E. Jung, T.W. Johnson, *Org. Lett.* **1999**, 1, 1671.

C7

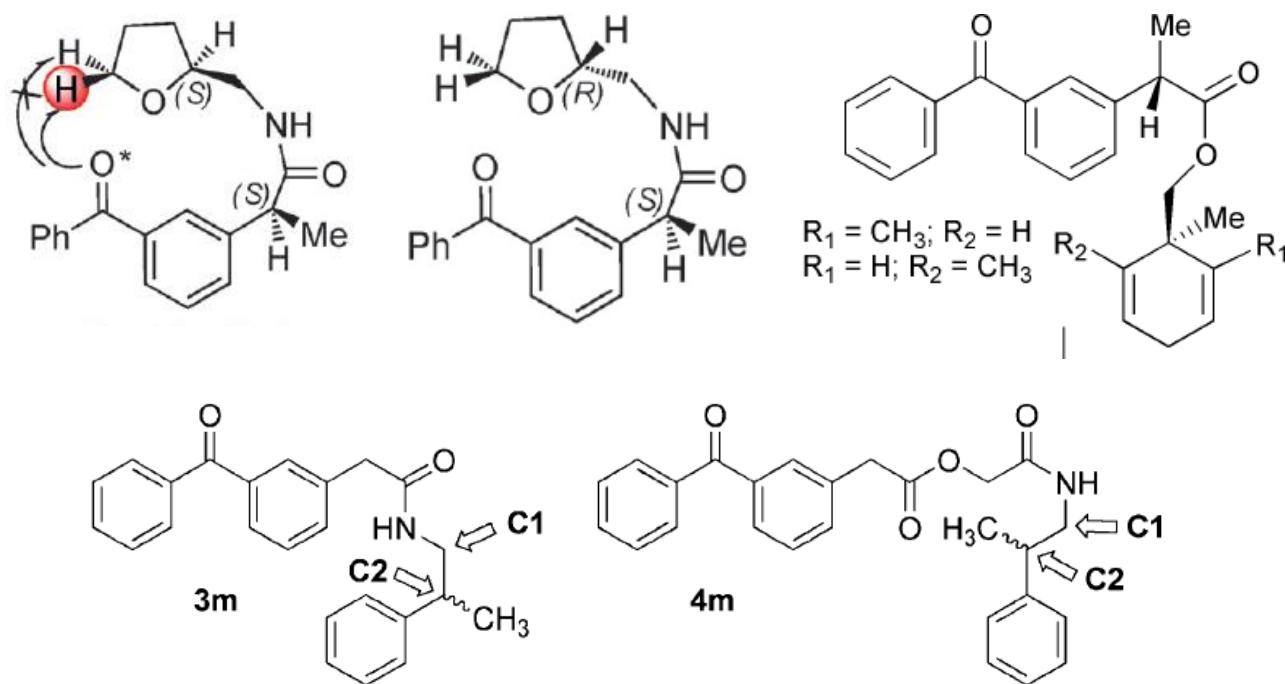
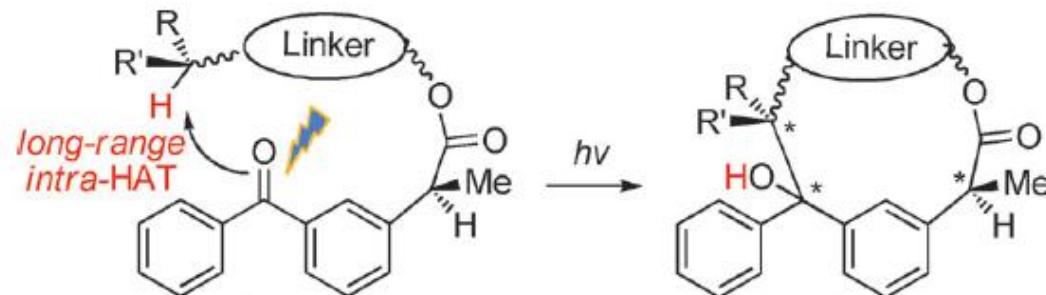
A.



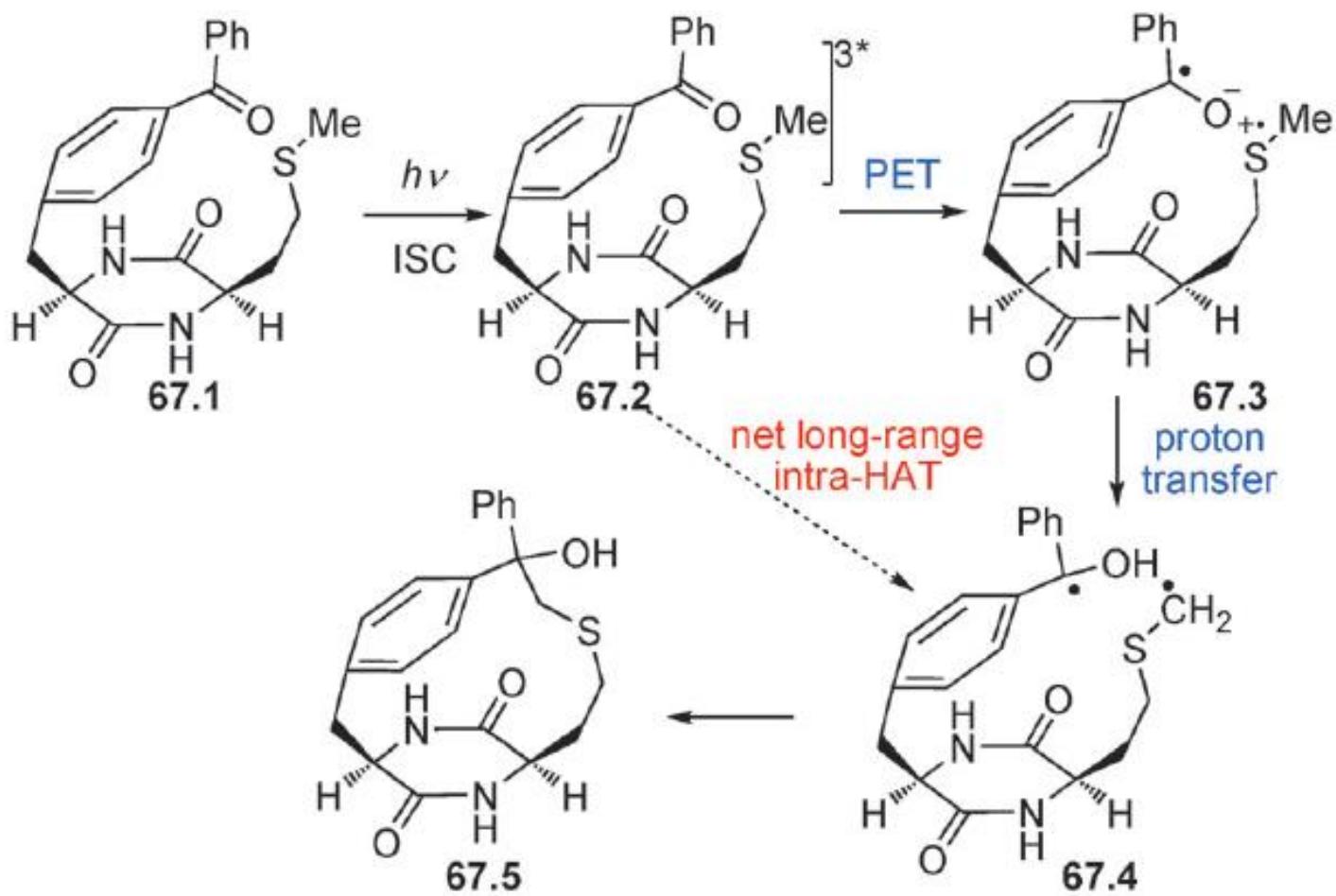
B.



M.A. Miranda, et al. *Org. Lett.* 2006, 8, 4597.



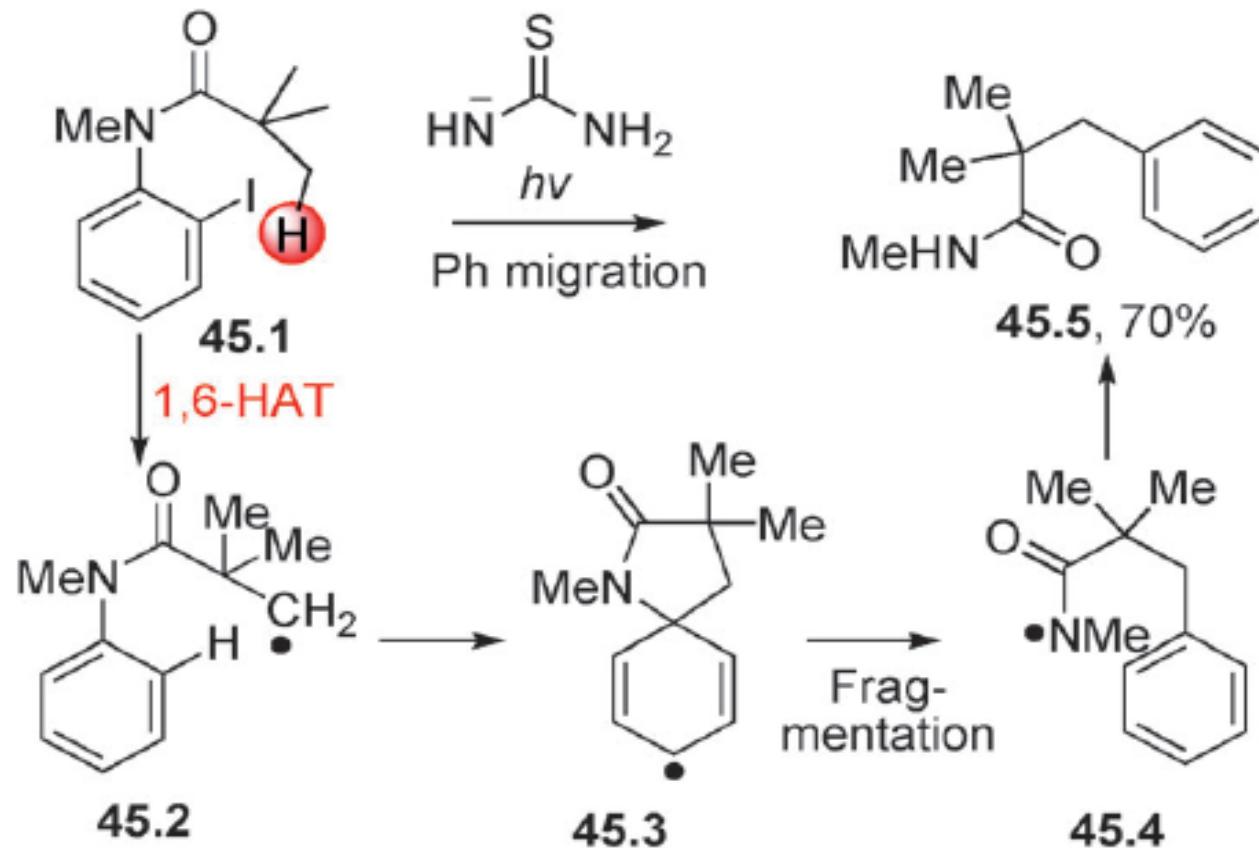
M.A. Miranda, et al. *Chem. Commun.* **2002**, 280; *Chem. Commun.* **2003**, 1592; *Angew. Chem. Int. Ed.* **2003**, 42, 2531; *Chem. Commun.* **2003**, 1088; *J. Am. Chem. Soc.* **2007**, 129, 7407; *Org. Lett.* **2008**, 10, 4409; *Chem. Eur. J.* **2006**, 12, 553



A. Lewandowska-Andralojc, et al. Photochem. Photobiol. 2013, 89, 14

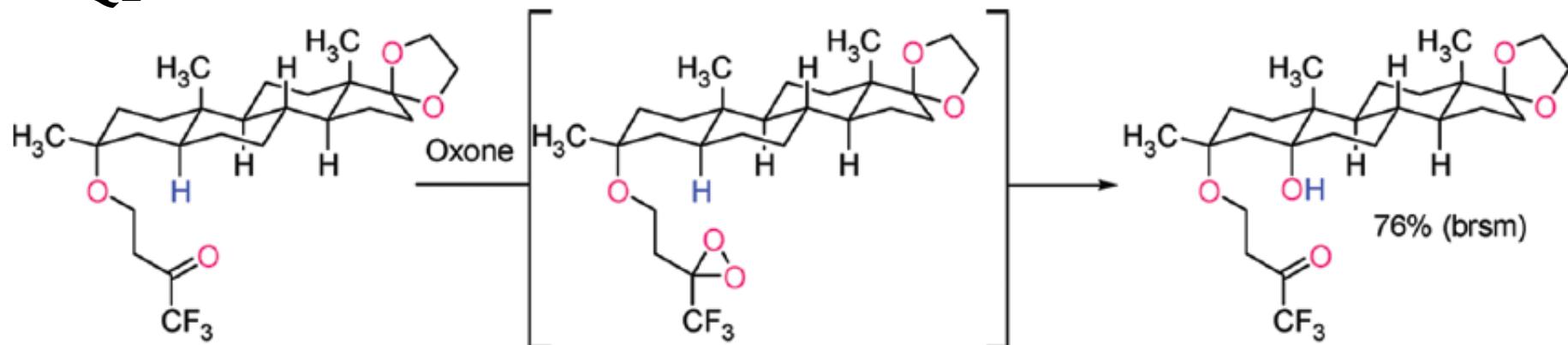
Thank you for your attention!

Q1

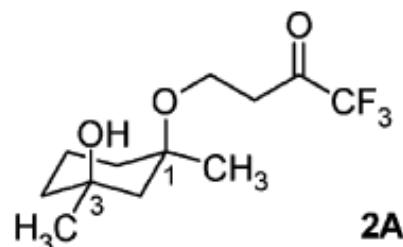
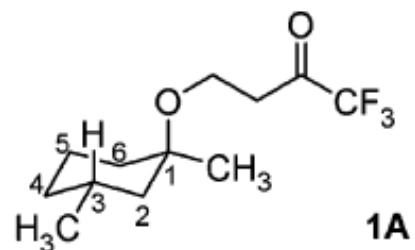


J. Org. Chem. **2009**, *74*, 1223

Q2



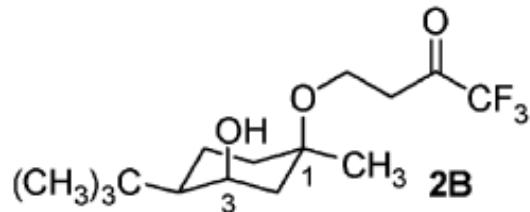
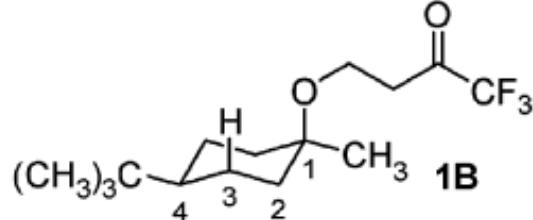
1



51 (31)

74

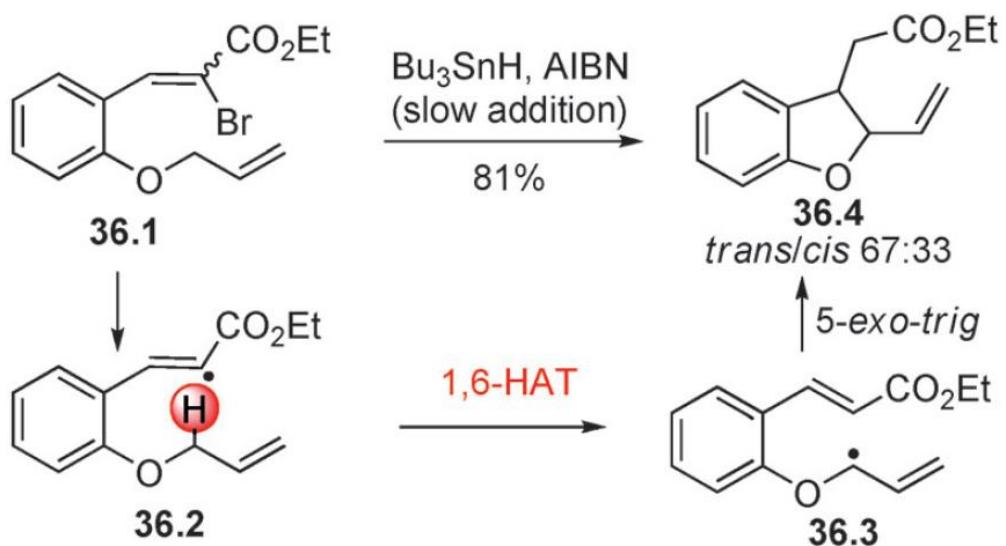
2^c



14 (43)

25

S. Kasuya, S. Kamijo, M. Inoue, *Org. Lett.* **2009**, *11*, 3630.



H. Lin, A. Schall, O. Reiser, *Synlett* 2005, 2603

