Hypervalent Iodine in Organic Synthesis

Topic Review 16.08.2012

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Main source: Topic in Current Chemistry: Hypervalent Iodine Chemistry
Volume editor: Thomas Wirth
Springer

Outlook

Intro

Reactivity patterns

- C-C bond formation
- C-O bond formation
- C-N bond formation
- C-S bond formation
- S-O bond formation

Homolytic cleavage of I-O bond

Oxydation of phenols

Conclusion

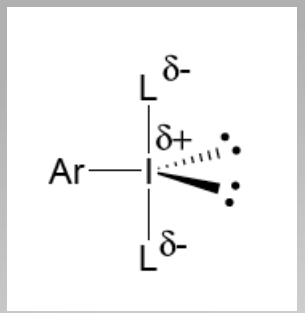
Nomenclature:

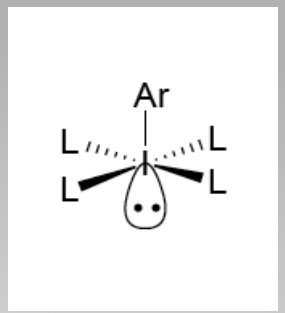
Hypervalent: Elements of groups 15-18 bearing more than 8 e^- in their valence shell. (I, Cl, P, S)

IUPAC Rules: λ for non-standard bonding

Trivalent iodine: aryl-λ^3-iodane $ArIL_2$ (10 e^-)
Pentavalent iodine: λ^5-iodane $ArIL_4$ (12 e^-)

-Pseudotrigonal bipyramid
-Lone pairs at basal positions



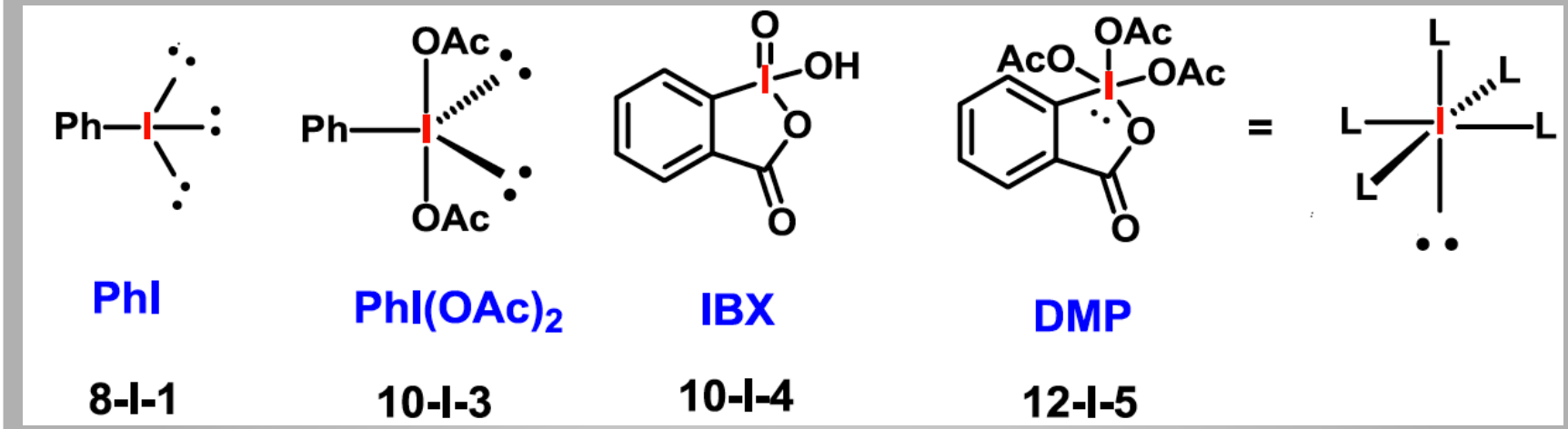


-Square pyramid
-Lone pair apical

Nomenclature: Martin-Arduengo

N-X-L

N: # of valence electrons on central atom
X: Central atom
L: # of ligand on central atom



PhI — 8-I-1

$PhI(OAc)_2$ — 10-I-3

IBX — 10-I-4

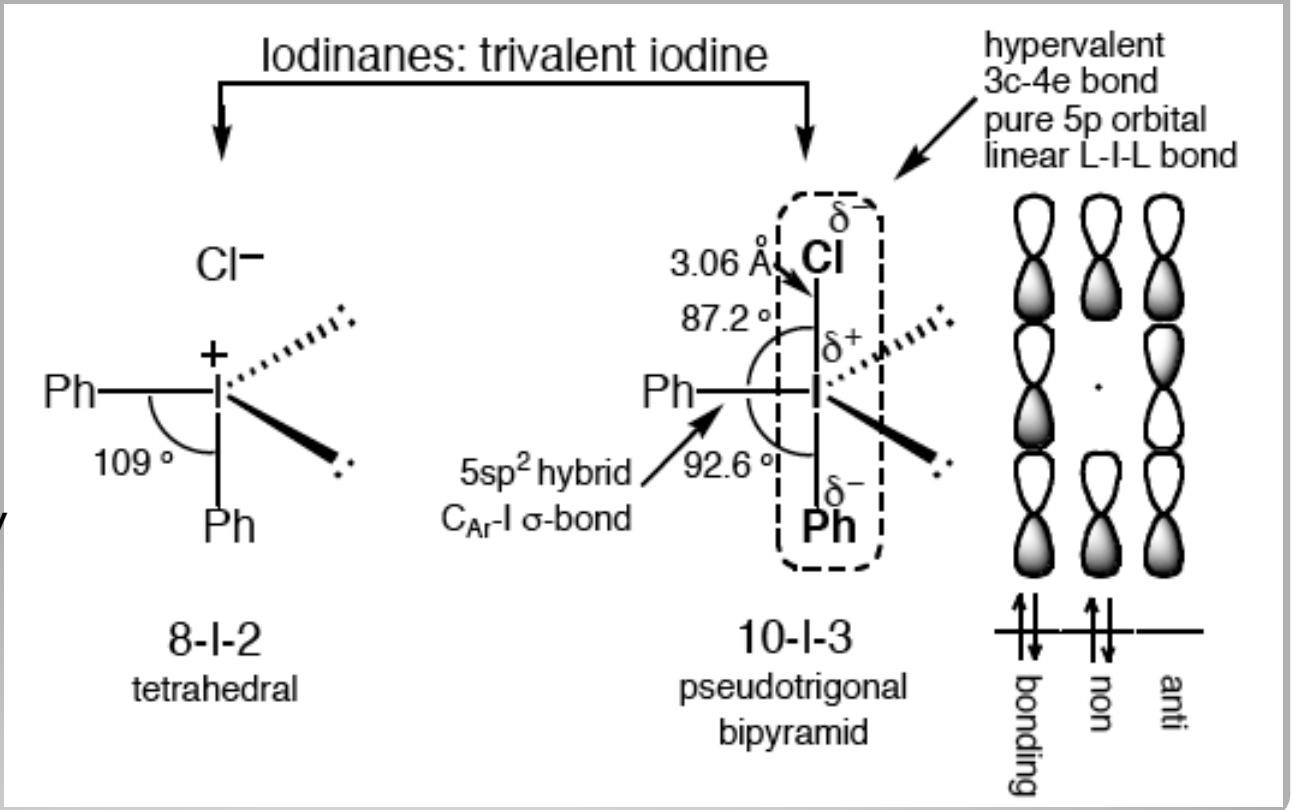
DMP — 12-I-5

C.W. Perkins, J.C. Martin, A.J. Arduengo, W. Lau, A. Alegria and J.K. Kochi, *JACS,* **1980**, *102*, 7753-7759

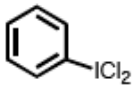
Nomenclature: Hypervalent Bond

Diphenyliodonium chloride or Chloro(diphenyl)-λ^3-Iodane?

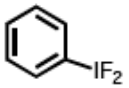
-Long C-I bond
-Polarized
-I strongly δ^+
- T-Shape X-Ray



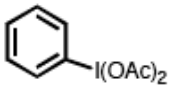
Current hypervalent Iodine



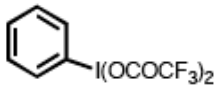
di(chloroiodo)benzene
$PhICl_2$



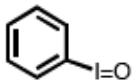
di(fluoroiodo)benzene
$PhIF_2$



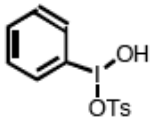
di(acetoxyiodo)benzene
$PhI(OAc)_2$
DIB
Aldrich, Fluka,
Lancaster, Merck



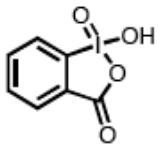
[bis(trifluroacetoxy)iodo]benzene
$PhI(OCOCF_3)_2$
BTI
Aldrich, Fluka



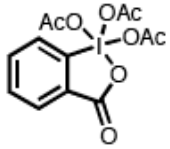
iodosylbenzene*
PhI(O)
IOB
ICN, TCI America



[(hydroxy)(tosyloxy)iodo]benzene
PhI(OH)(OTs)
HTI
Koser's Reagent
Aldrich



2-iodoxy-benzoic acid
IBX



Dess-Martin Periodinane
DMP

Current hypervalent Iodine: solid state

- Most hypervalent iodine: solid and stable to oxygen and moisture.
- An explosion can occur if heating without solvent.
- In the solid state: iodosylbenzene and other are polymeric structures
- Monomeric structures are generated in reactive solvents (MeOH) or or by activation with Lewis Acids

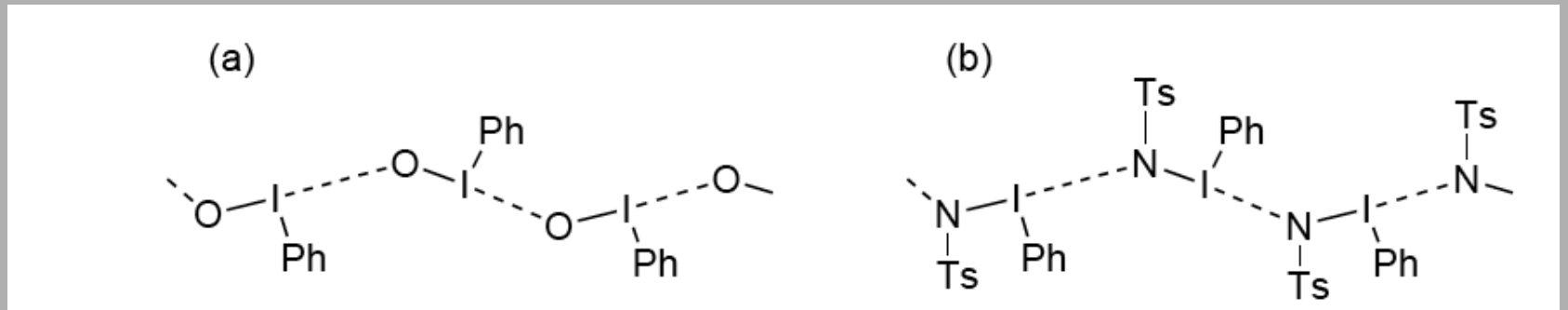
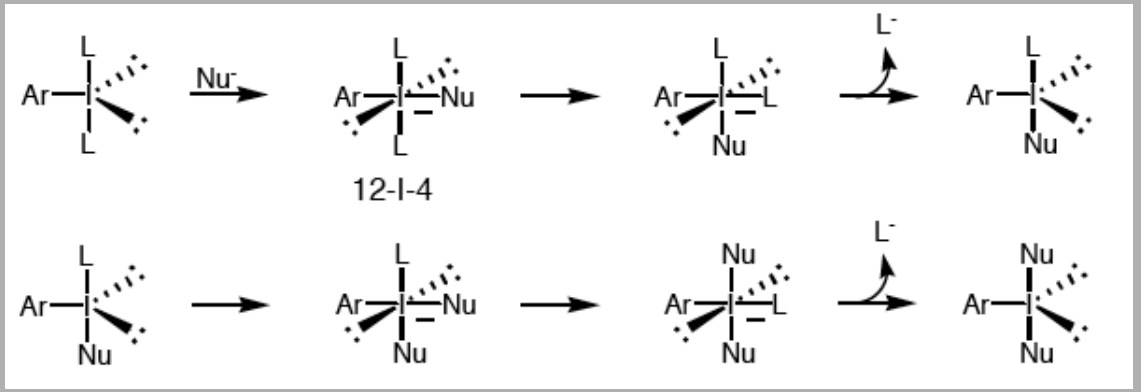


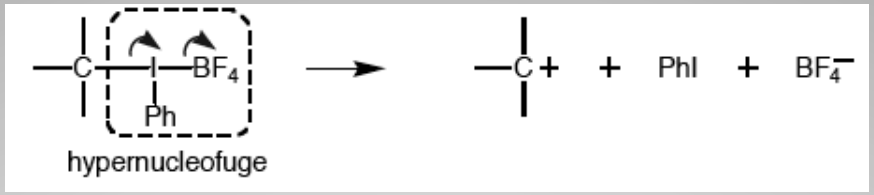
Fig. 4. Schematic solid state structures of $(PhlO)_n$ **18** (**a**) and PhlNTs (**b**)

Reactivity patterns

- Reactivity based on electrophilic nature of iodine atom:
  - nucleophilic attack:

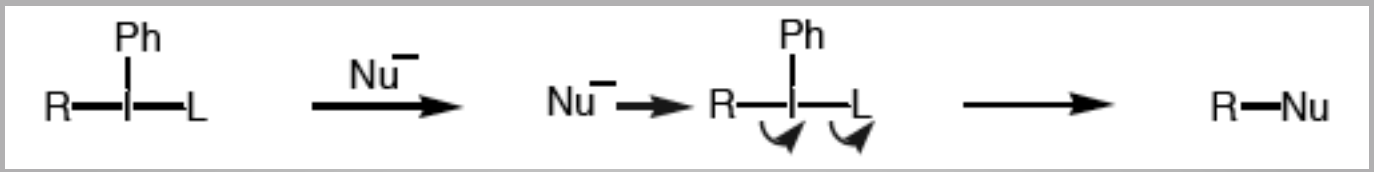


- phenyliodinio group (-IPhX) 10^6 time better leaving group than –OTf



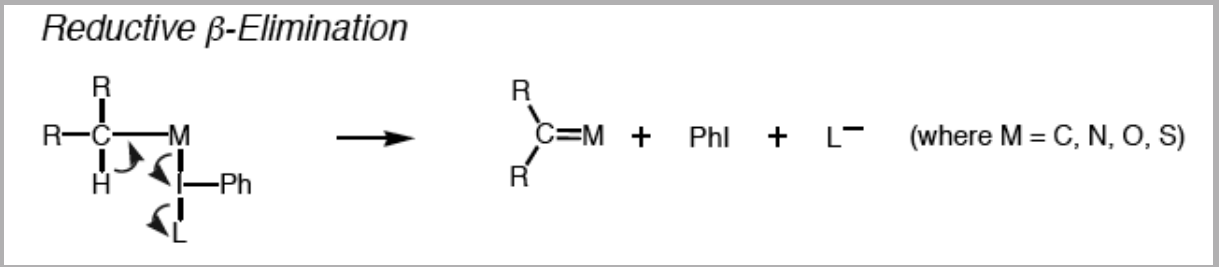
Reactivity patterns

- Number of heteroatom ligand determine reactivity
- R_2IL easily transfer 1 carbon ligand
- Reductive elmination with substitution
- Nucleophile attacks on the carbon atom attached to I(III)

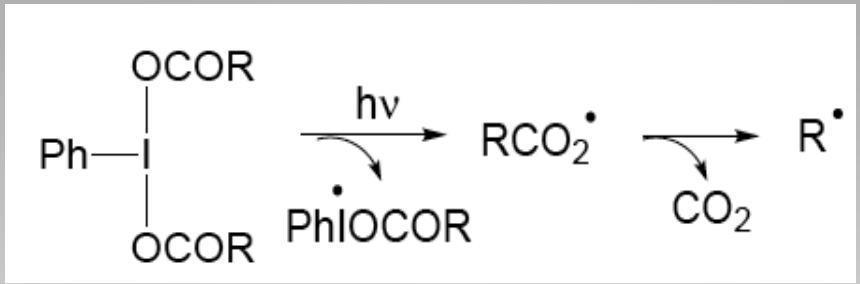


Reactivity patterns

RIL_2 used for oxydation (ligand exchange and red. elimination)

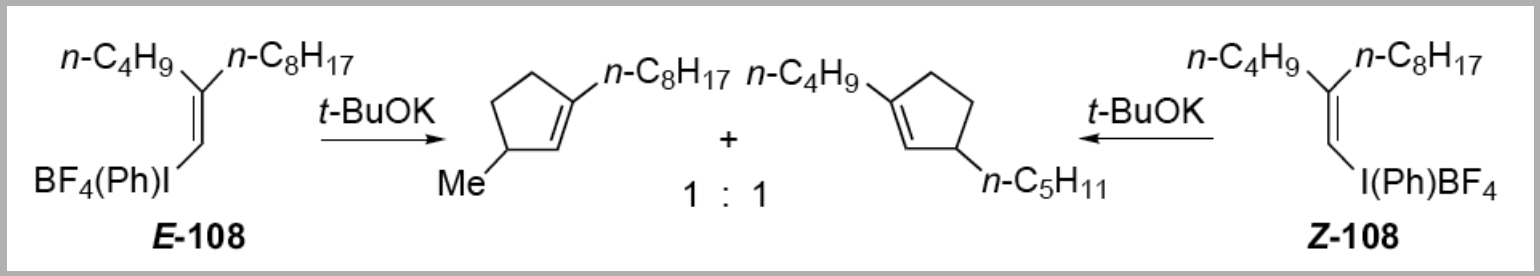


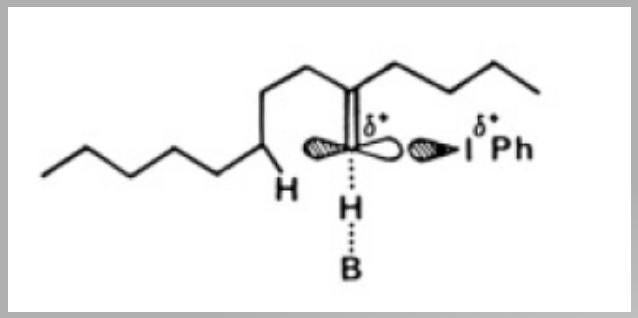
- Homolytic cleavage of I-O Bond



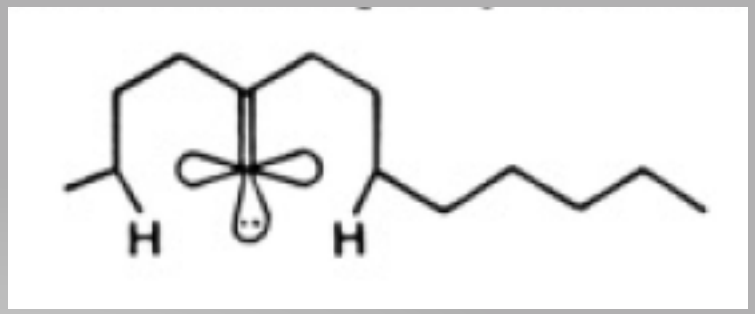
Reactivity patterns: Red. α elimination

Proof of carbene formation: rxn of alkenyliodonium salts





Selectivity in insertion expected

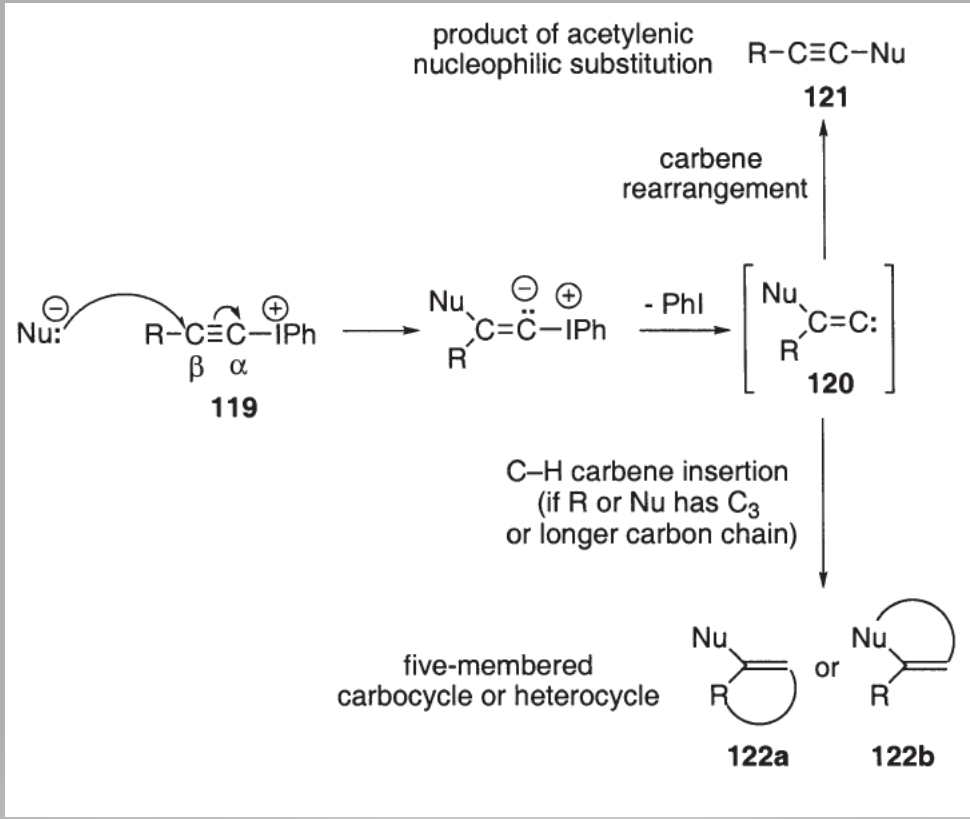


No selectivity observed!

- Elimination
- C-H insertion

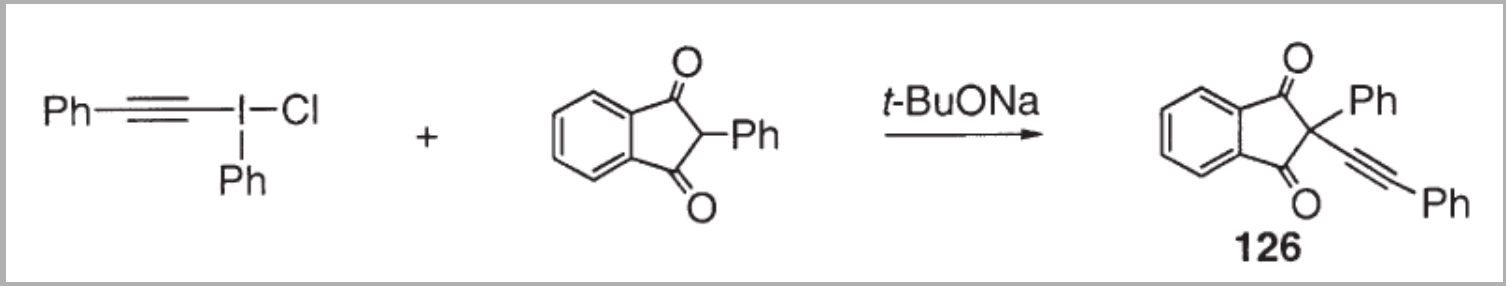
M. Ochiai, Y. Takaoka, Y. Nagao, *JACS*, **1988**, *110*, 6566-6568

Reactivity patterns: Michael addition

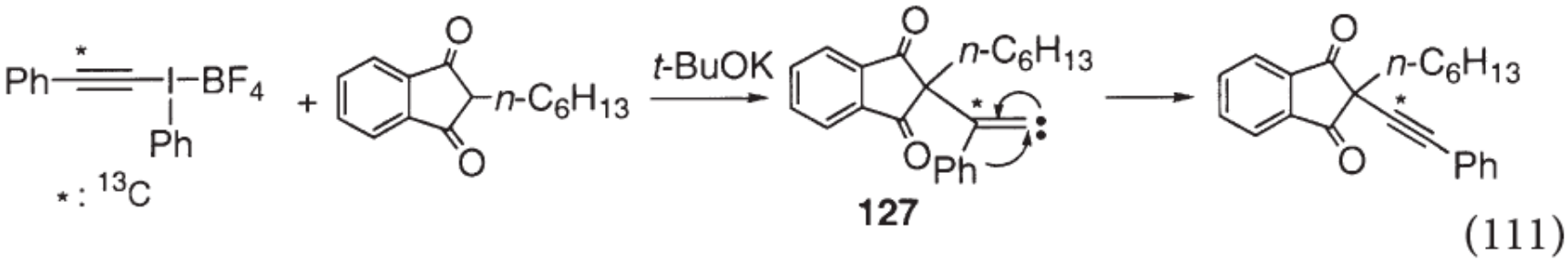


- Electron- withdrawing and hyperleaving properties enabled rxn.

Michael addition

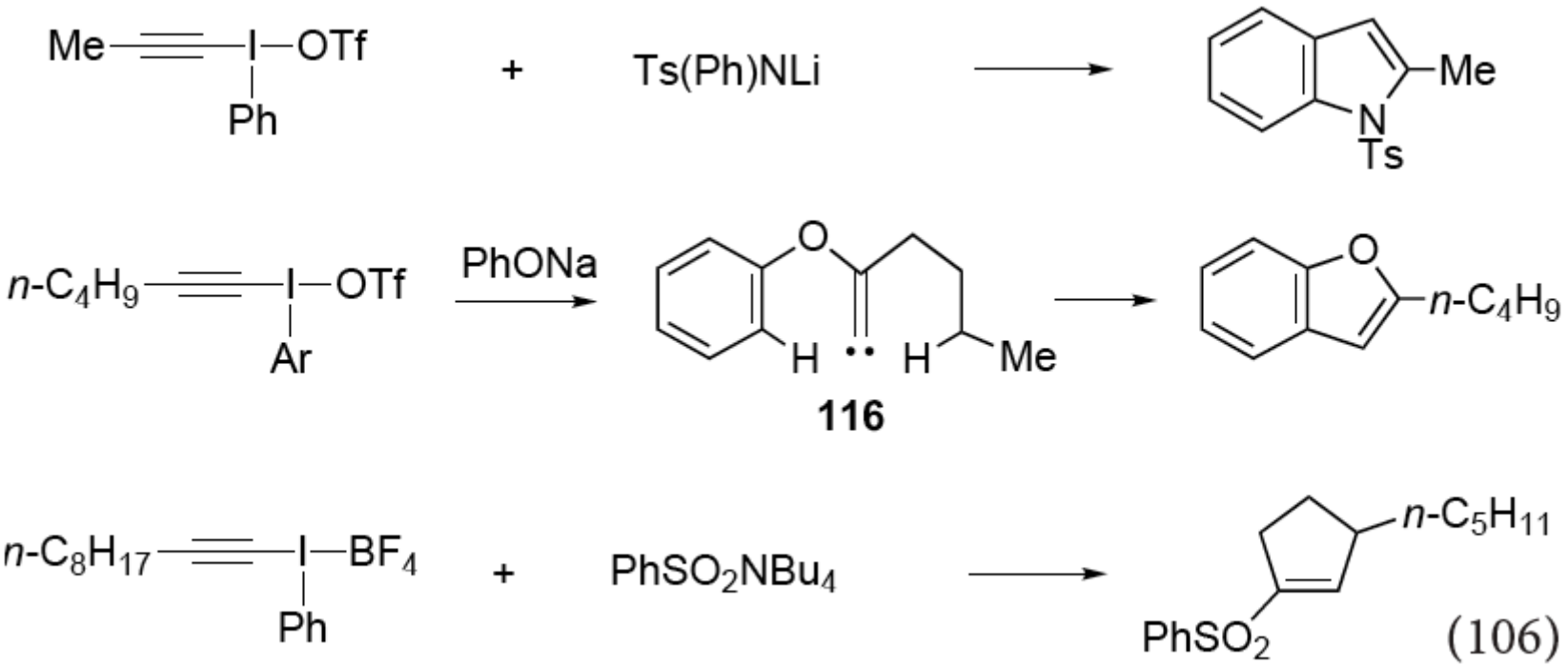


Proof for carbene mechanism
1,2-Ar shift



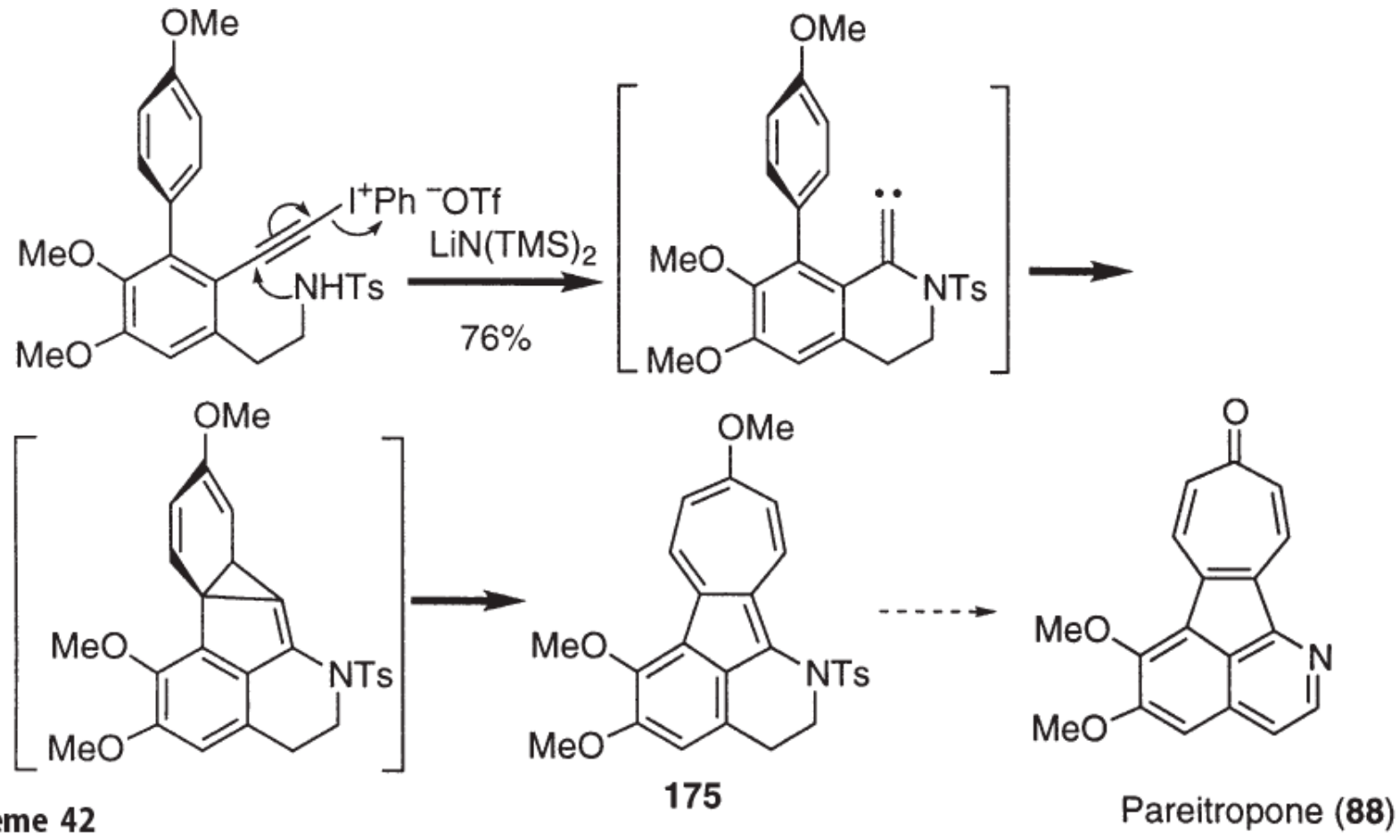
(111)

Tandem Michael/Carbene insertion reaction



1,5-carbene insertion

Tandem Michael/Carbene insertion reaction



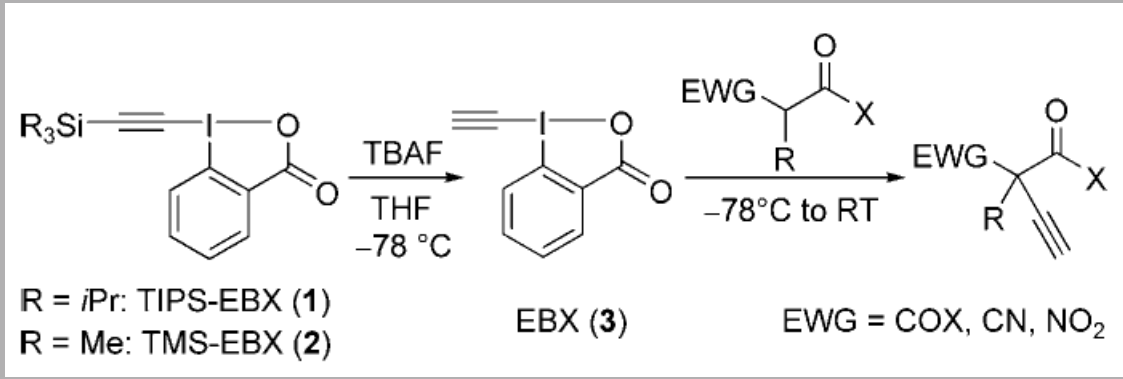
Scheme 42

175

Pareitropone (**88**)

K. S. Feldman, T. D. Cutarelli, and R. Di Florio, *J. Org. Chem.* **2002**, 67, 8528-8537

Waser group: Acetylene transfer



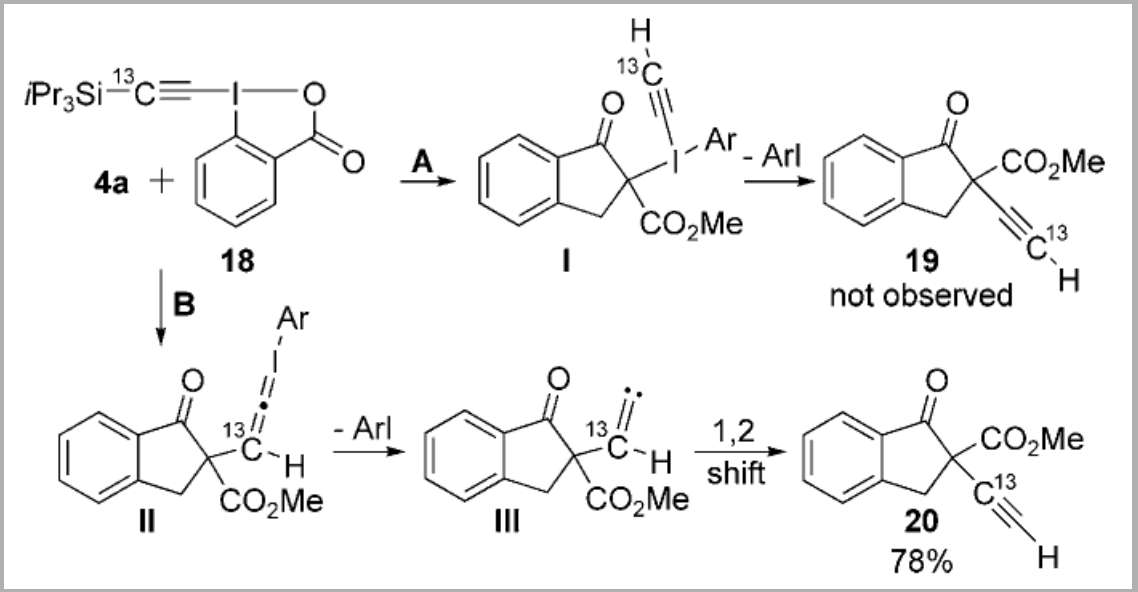
(triisopropylsilyl)ethynyl-1,2-benziodoxol-3(1H)-one: TIPS-EBX

TBAF: activating agent and base

EBX could never be isolated

First alkynylation of acyclic keto and cyano substrate -> quaternary center

Waser group: Labelling experiment



Similar mechanism as alkynyliodonium salts

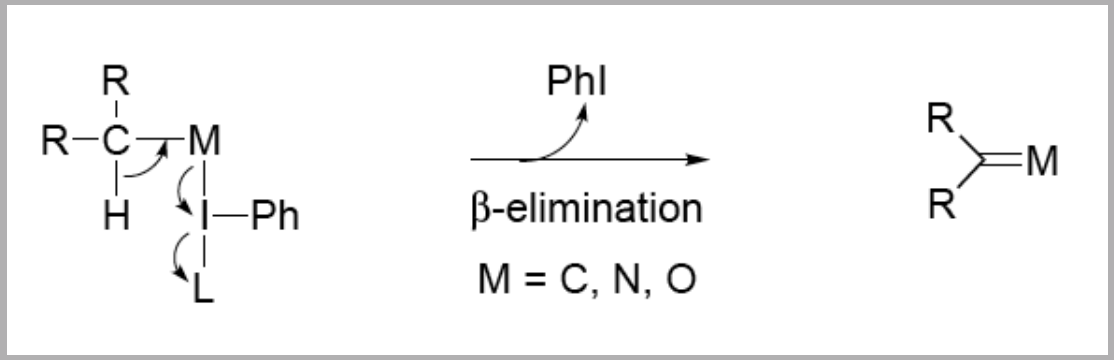
No need of strong base, milder conditions!

Developped also Au-catalyzed ethynylation of heteroaromatics

D. Fernandez Gonzalez, J.P. Brand, and J. Waser, *Chem. Eur. J.* **2010**, 16, 9457-9461

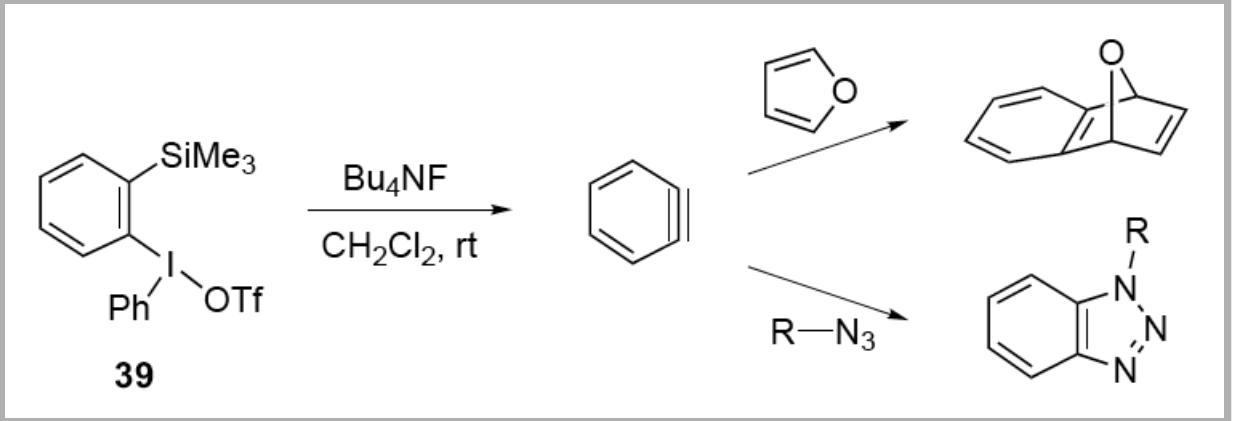
Red. β elimination: C-C bond formation

Reactivity used in multiple bond formation

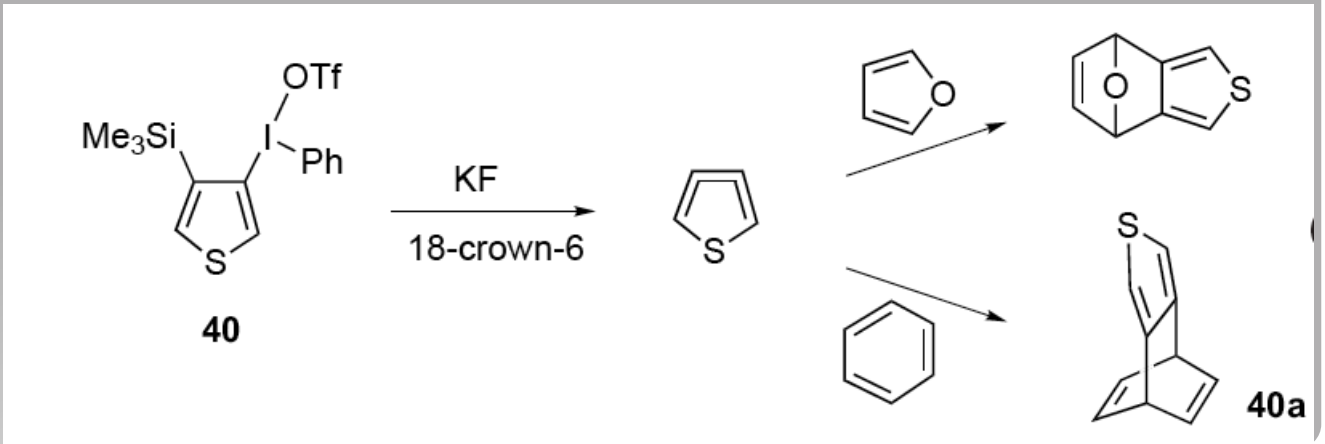


Red. β elimination: C-C bond formation

Benzyne formation



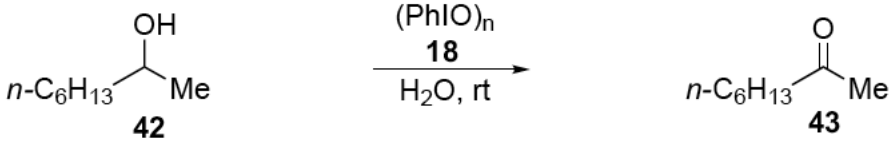
Cumulene trapping



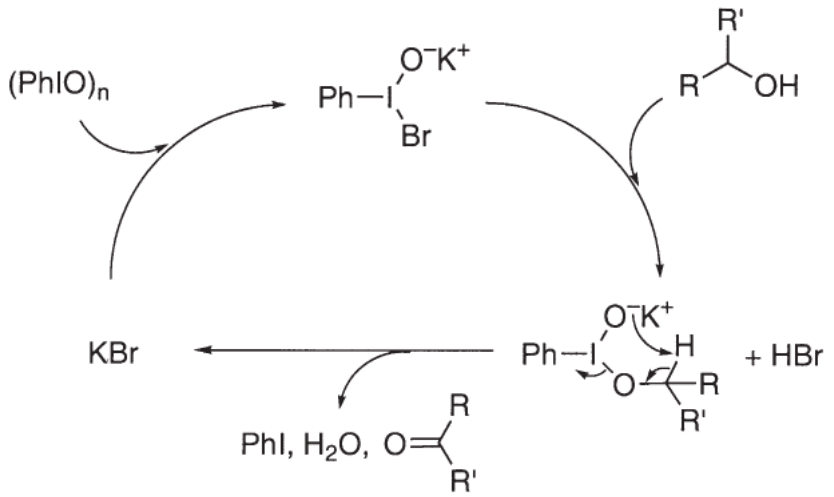
X-S Ye, W-K Li, and H.N.C. Wong, *JACS*, **1996**, *118*, 2511-2512

Red. β-elimination: C-O bond formation

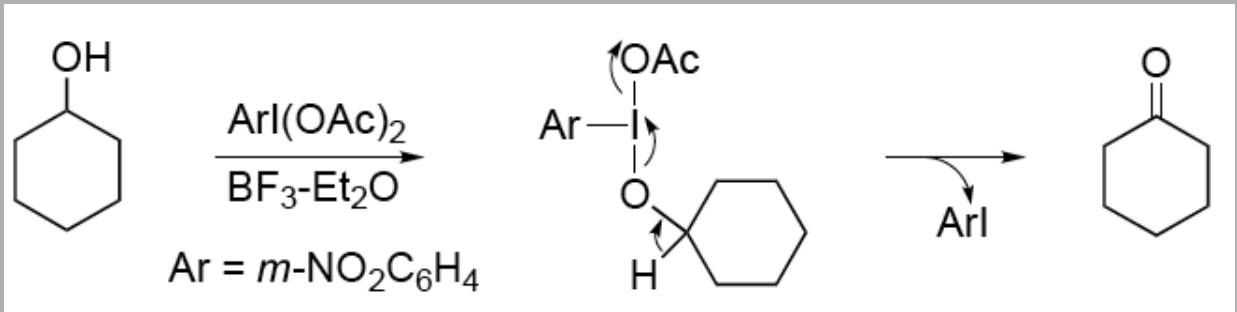
KBr enables depolimerization of 18 and allows reaction in water



additive (equiv)	time (h)	yield (%)
none	48	trace
KBr (0.2)	24	94
KBr (1)	8	98



Red. β-elimination: C-O bond formation

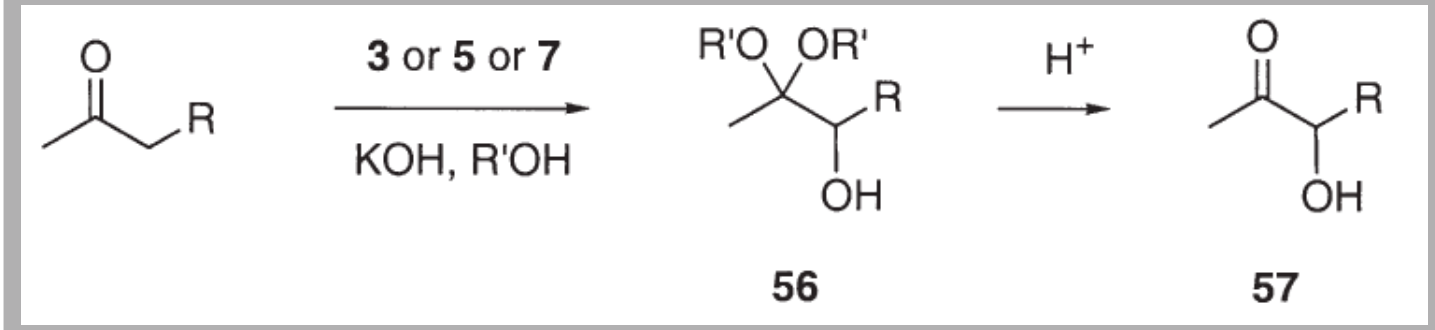


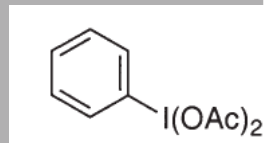
Presence of a Lewis acid accelerate the reaction by complexation to the acetoxy-ligand

Influence on:
1. ligand exchange
2. reductive elimination

C-O bond formation

Formation of α-hydroxy ketones





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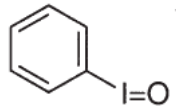

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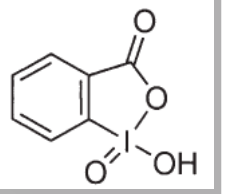
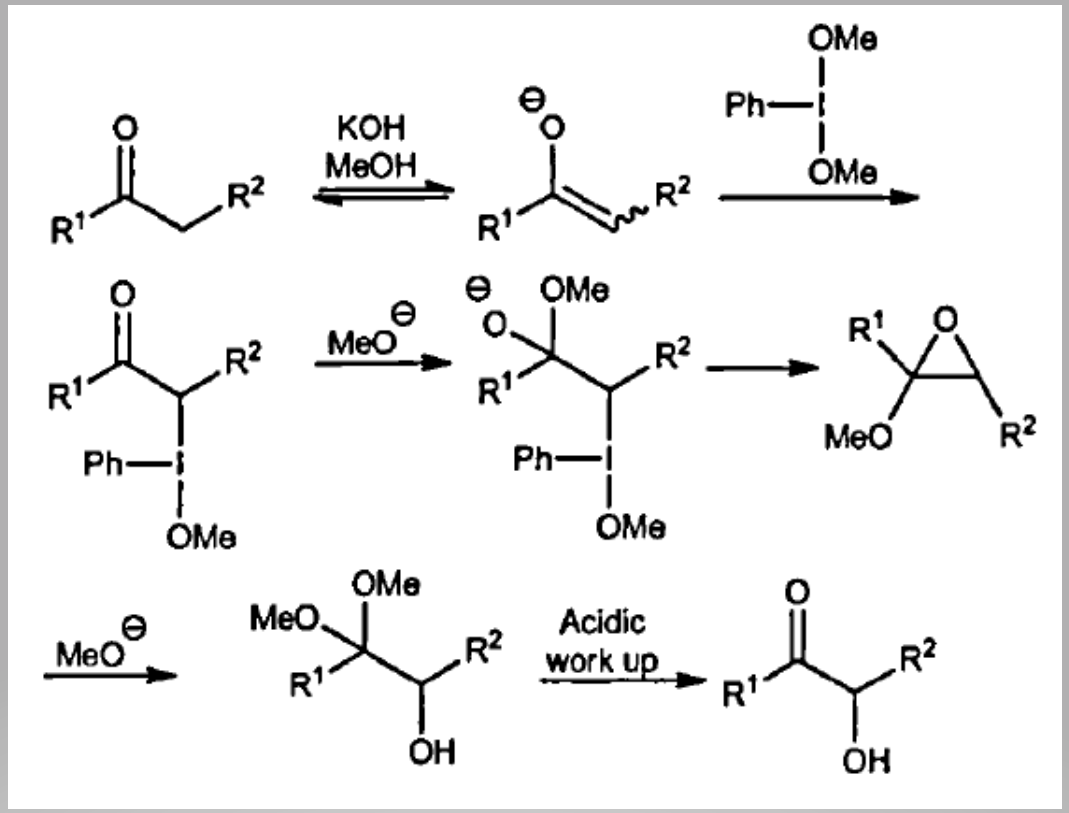
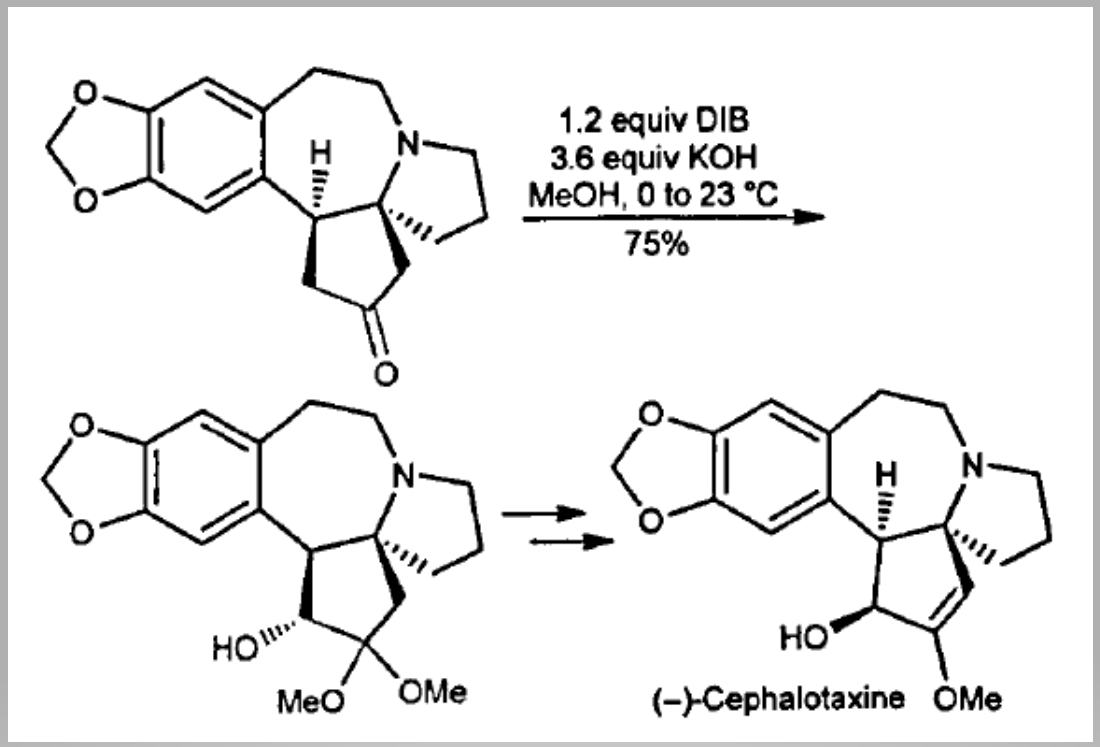


C-O bond formation



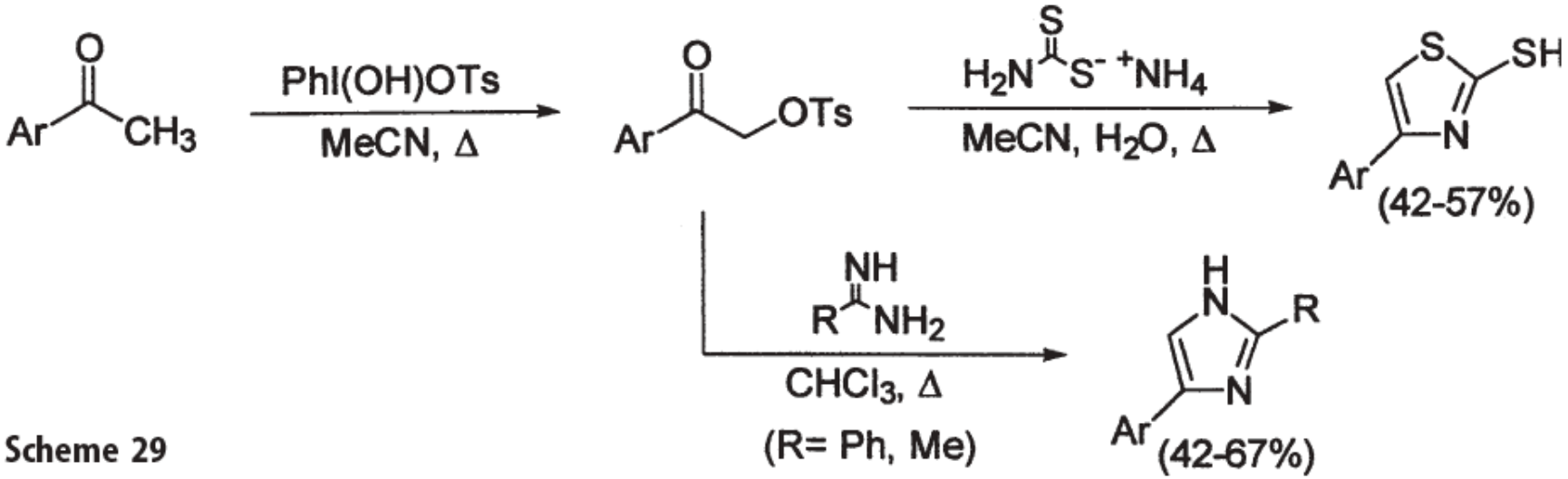
C-O bond formation



W. D. Z. li and Y. Q. Wang, *Org. Lett.*, **2003**, 5, 2931

C-O bond formation

- 1 pot-2 step rection
- preparation of imidazole and and 2-mercaptothiazole



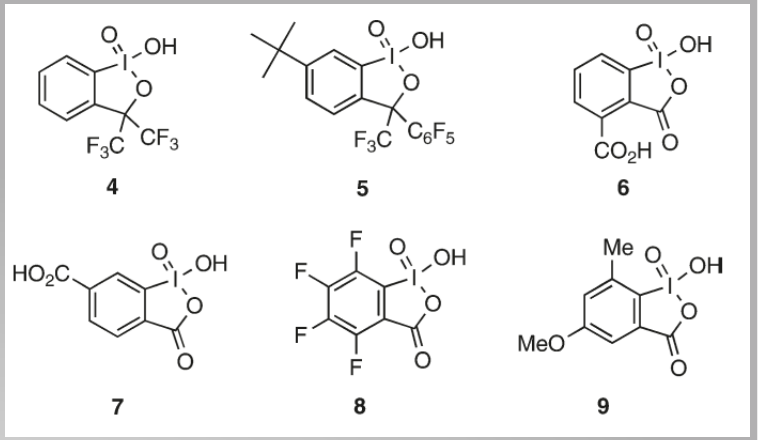
Scheme 29

Zhang P-F, Chen Z-C (2000) Synthesis 1219
Zhang P-F, Chen Z-C (2001) Synthesis 2075
Zhang P-F, Chen Z-C (2001) Synth Commun 31:415

Red. β-elimination: C-O bond formation IBX and DMP (λ^{5})

- Among best reagent for alcohols oxydation
- High protecting and functional groups tolerence
- Not perfect reagents: Explosive (233°C)
- IBX improvement: better solubility, stability, activity

- Improved solubility into org. Solvent
- Polymer supported: easy to remove
- Problem of activity!

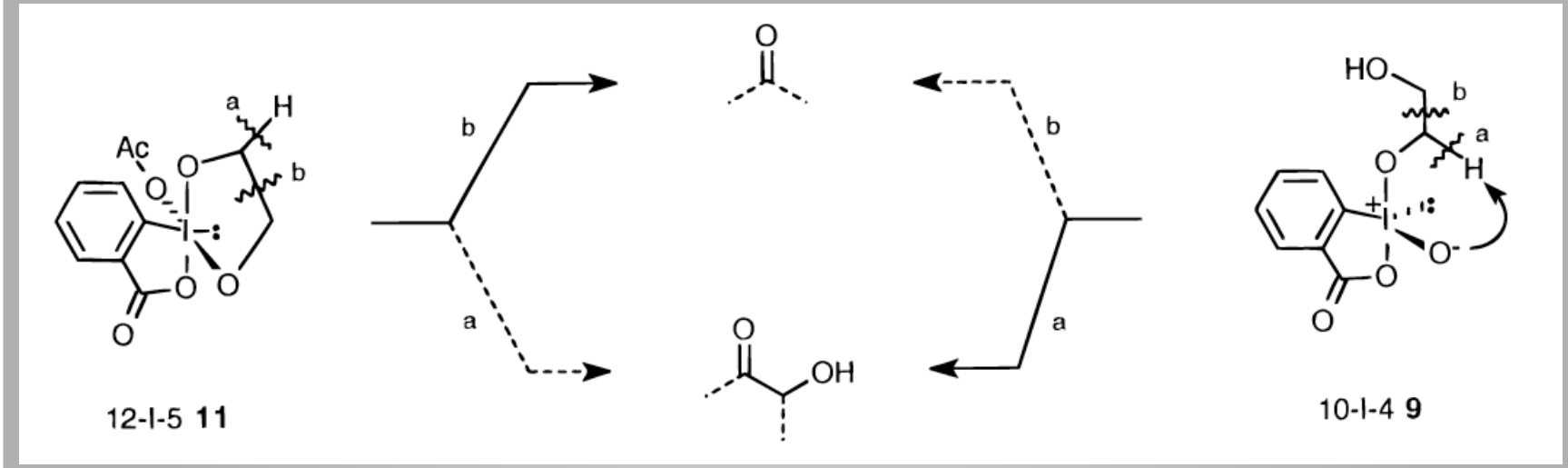


Red. β-elimination: C-O bond formation

- IBX soluble in DMSO while DMP in current org. solvent

-DMP replaced by IBX (modification/optimization)

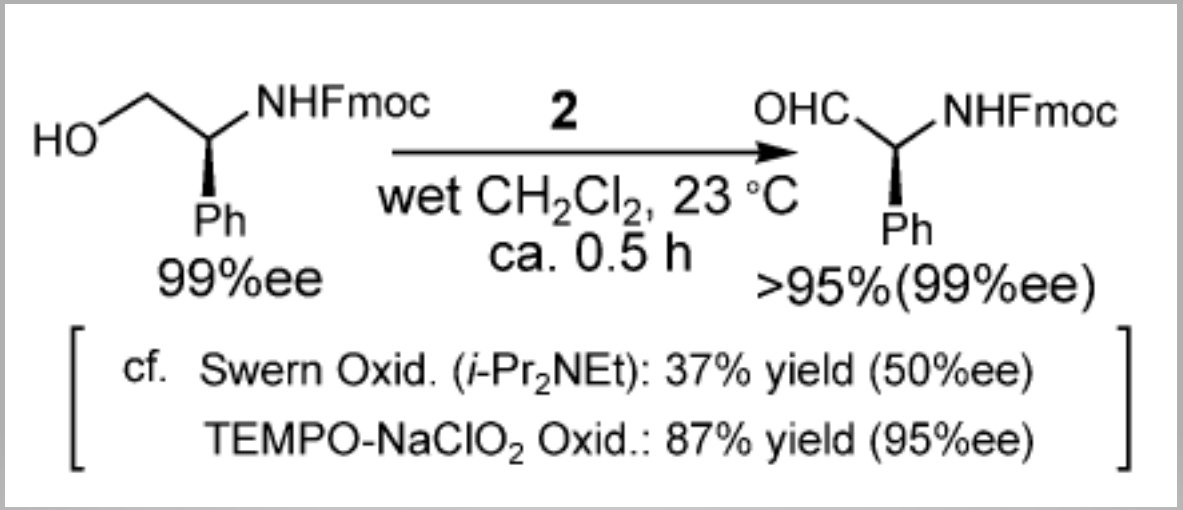
- Difference in reactivity: Cleaves 1.2-diols while IBX doesn't!



S. De Munari, M. Frigerio, and M. Santagostino, *J. Org. Chem.* **1996**, *61*, 9272-9279

Red. β-elimination: C-O bond formation, DMP

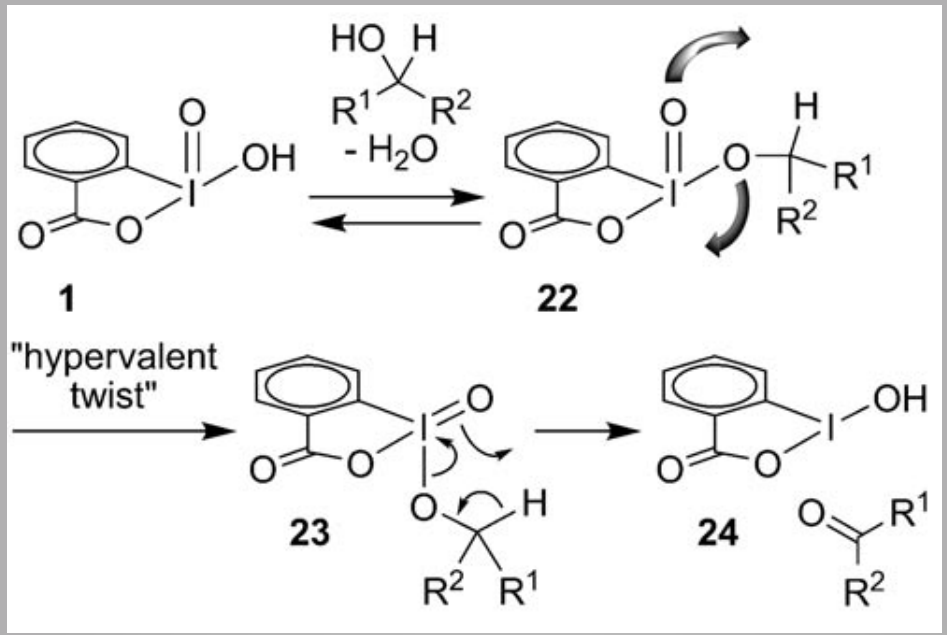
- No epimerization observed!
- React with alcohol selectively
- High e^- density on the amine diminish acidy at α position



- Epimerization-free reaction also possible with IBX!

Red. β-elimination: C-O bond formation, IBX

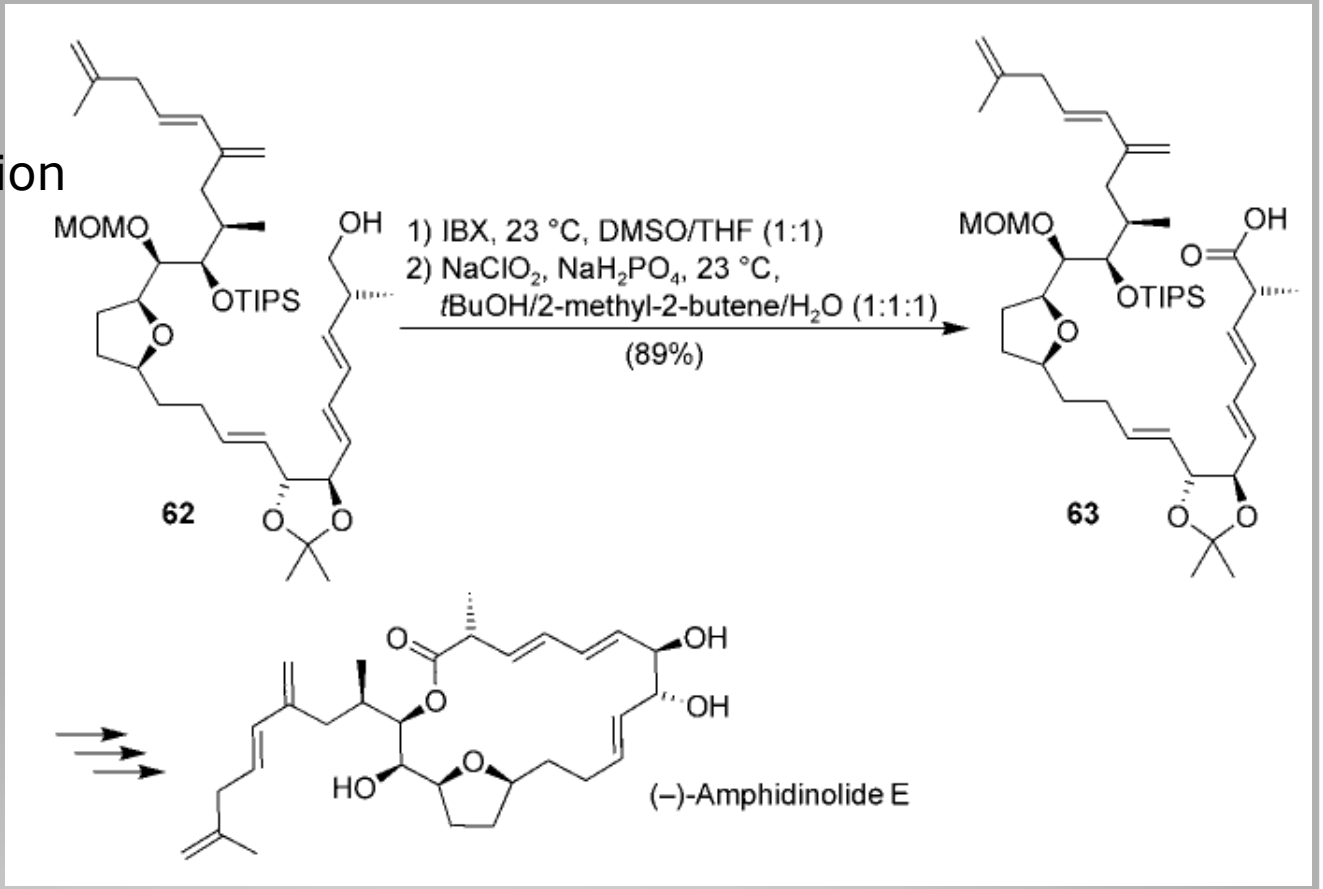
- Hypervalent twist mechanism



- Suggested by calculations
- For electronic reason, 22 has to rearrange to 23

Red. β-elimination: C-O bond formation, IBX

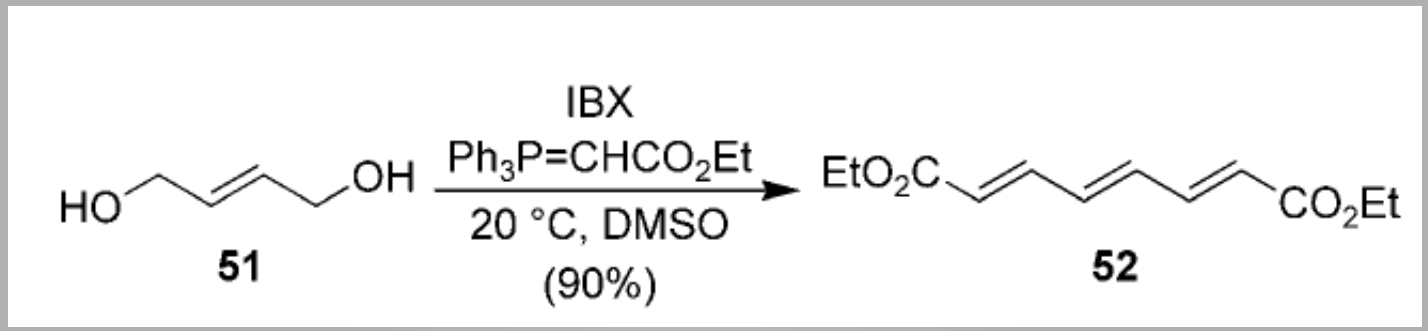
- DMP failed!
- No epimerization



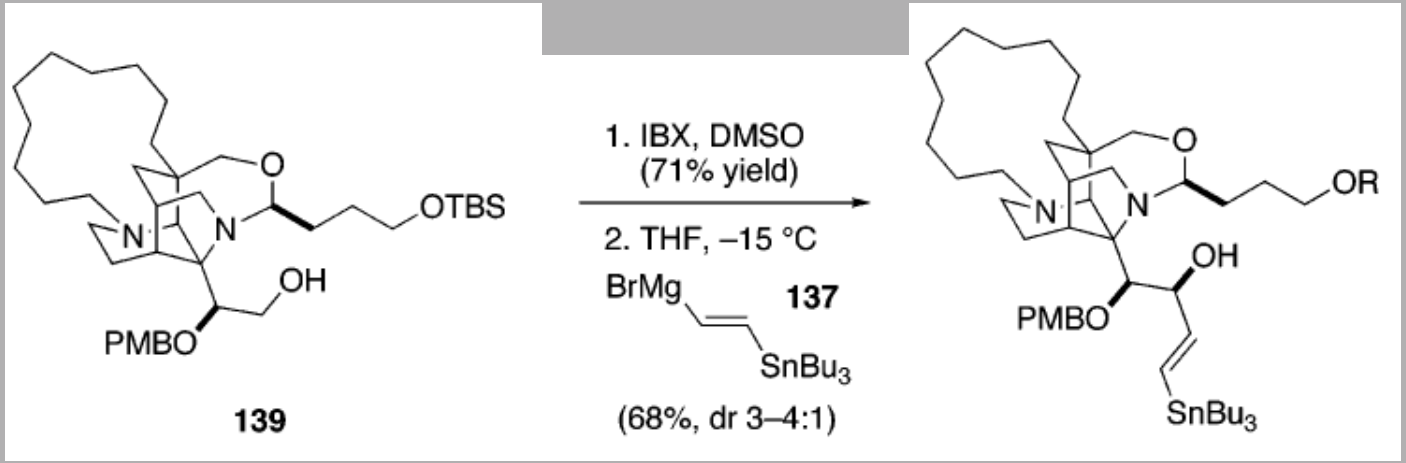
C.H. Kim, H.J. An, W.K. Shin, W.Yu, S.K. Woo, S.K. Jung, and E. Lee, *Angew. Chem. Int. Ed.* **2006**, 45, 8019-8021

Red. β-elimination: C-O bond formation, IBX

- Tandem oxydation/Wittig
- No need of isolation of unstable aldehyde



Red. β-elimination: C-O bond formation, IBX



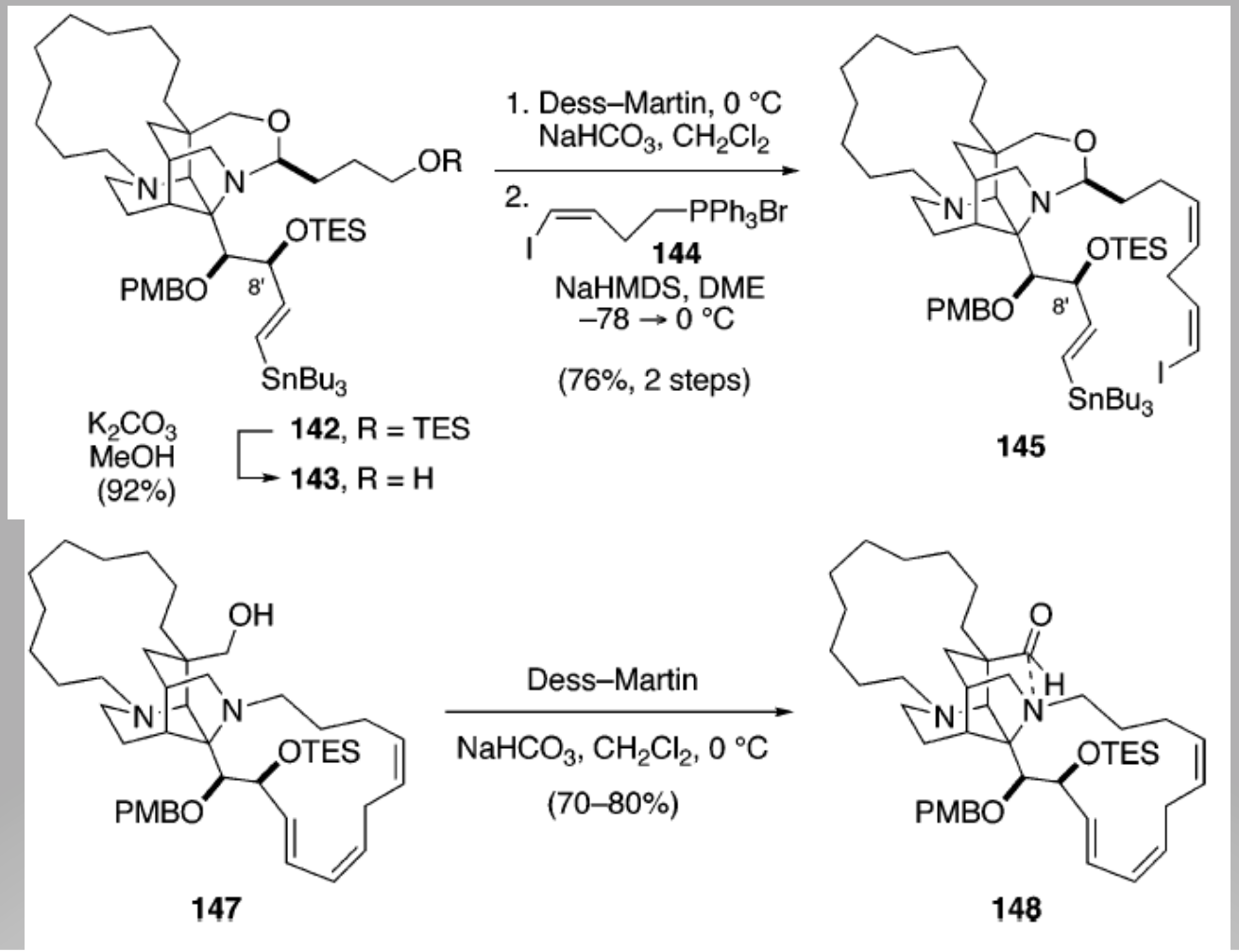
Synthesis of Sarain A featuring 3 hypervalent iodine oxydation steps at a late stage

Presence of 1 tertiary amine and N-O acetal!

Other oxydation methods failed!

N. K. Garg, L. E. Overman and al. *JACS*, **2007**, 129, 11987-12002

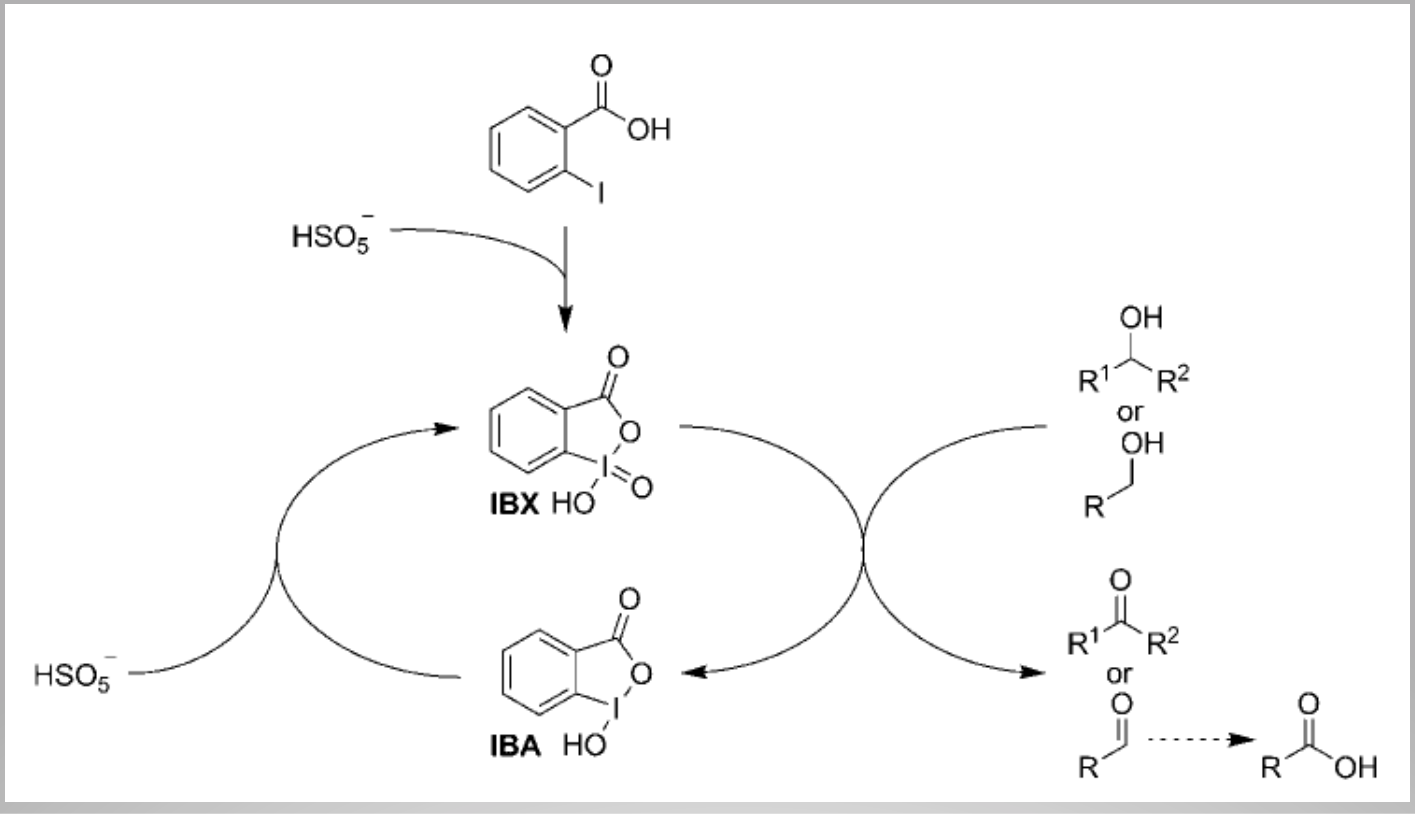
Red. β-elimination: C-O bond formation, IBX



N. K. Garg, L. E. Overman and al. *JACS*, **2007**, 129, 11987-12002

Red. β-elimination: C-O bond formation, IBX

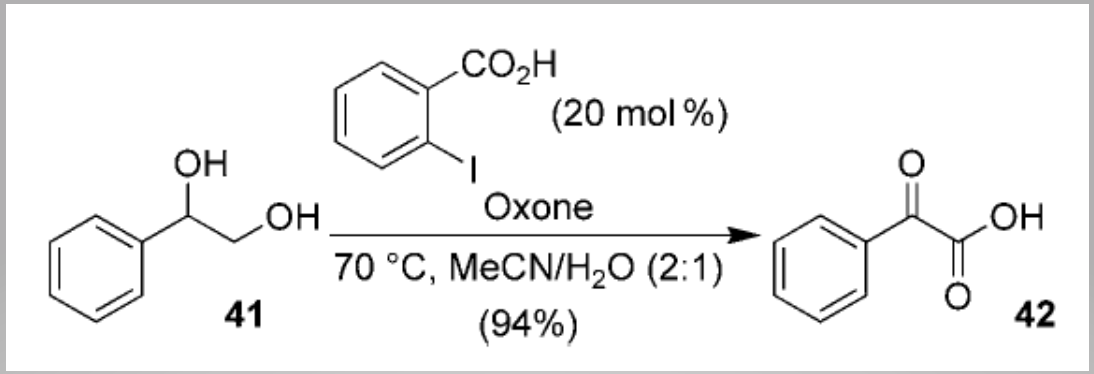
Catalytical use of IBX in biphasic mixture or under phase transfer Catalysis / oxone oxydation)



A. P. Thottumkara, M. S. Bowsher, T. K. Vinod, *Org. Lett.* **2005**, 7, 2933-2936

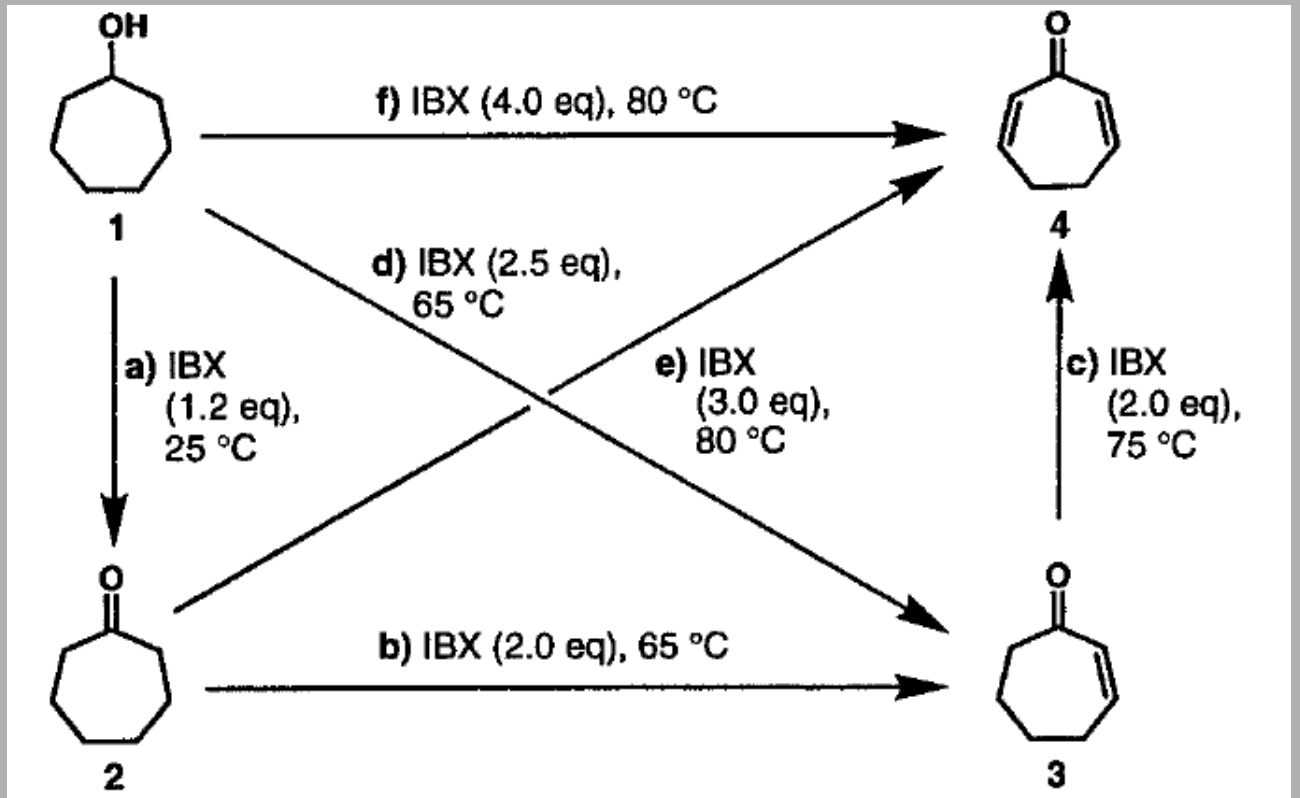
Red. β-elimination: C-O bond formation

- Primary alcohols oxydized to the carboxylic acid
  - First oxydation performed by IBX
  - Second oxydation performed by Oxone
- Secondary alcohols to the ketone



A. P. Thottumkara, M. S. Bowsher, T. K. Vinod, *Org. Lett.* **2005**, 7, 2933-2936

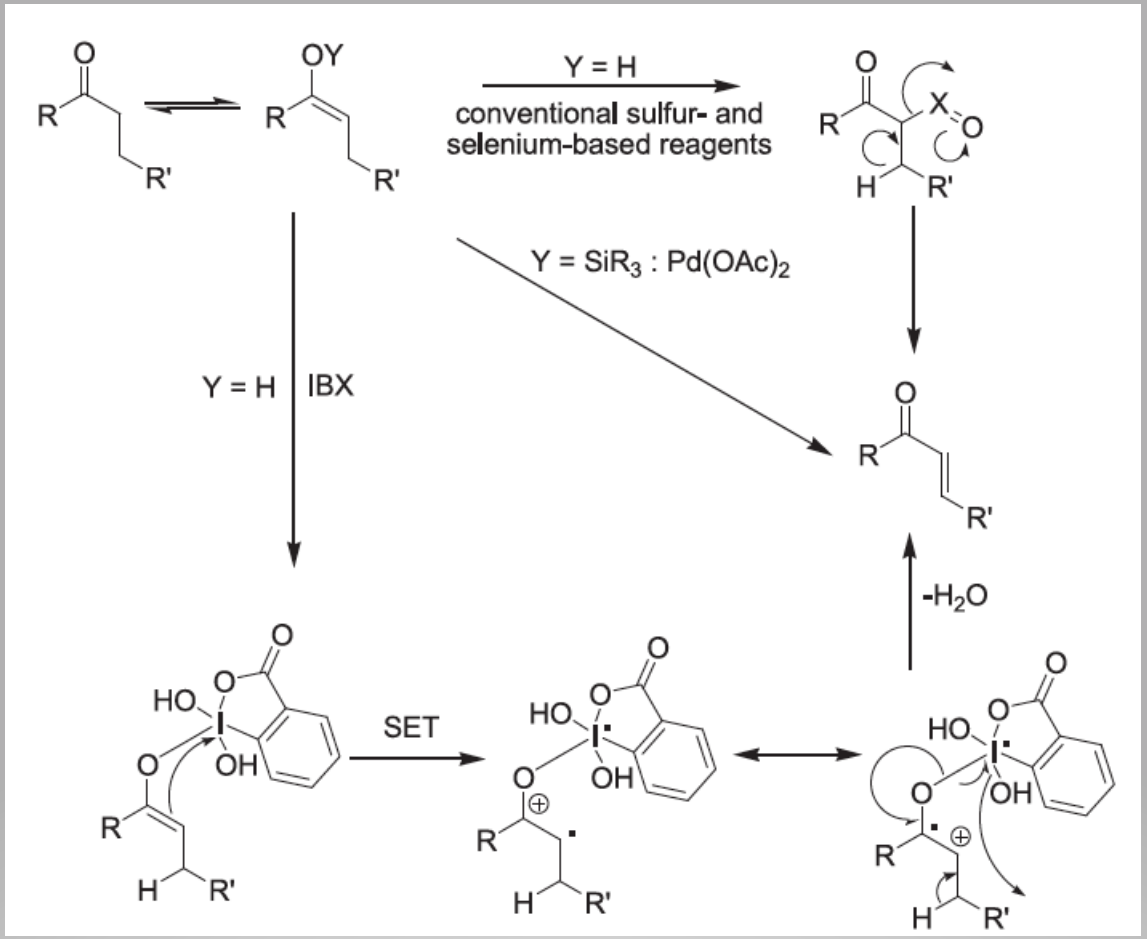
IBX: Enone formation



[a] Reagents and conditions: (a) IBX (1.2 equiv), DMSO, 25 °C, 3 h, 98%; (b) IBX (2.0 equiv), DMSO, 65 °C, 6 h, 88%; (c) IBX (2.5 equiv), DMSO, 75 °C, 12 h, 74%; (d) IBX (2.5 equiv), DMSO, 65 °C, 6 h, 82%; (e) IBX (3.0 equiv), DMSO, 80 °C, 15 h, 81%; (f) IBX (4.0 equiv), DMSO, 80 °C, 22 h, 76%.

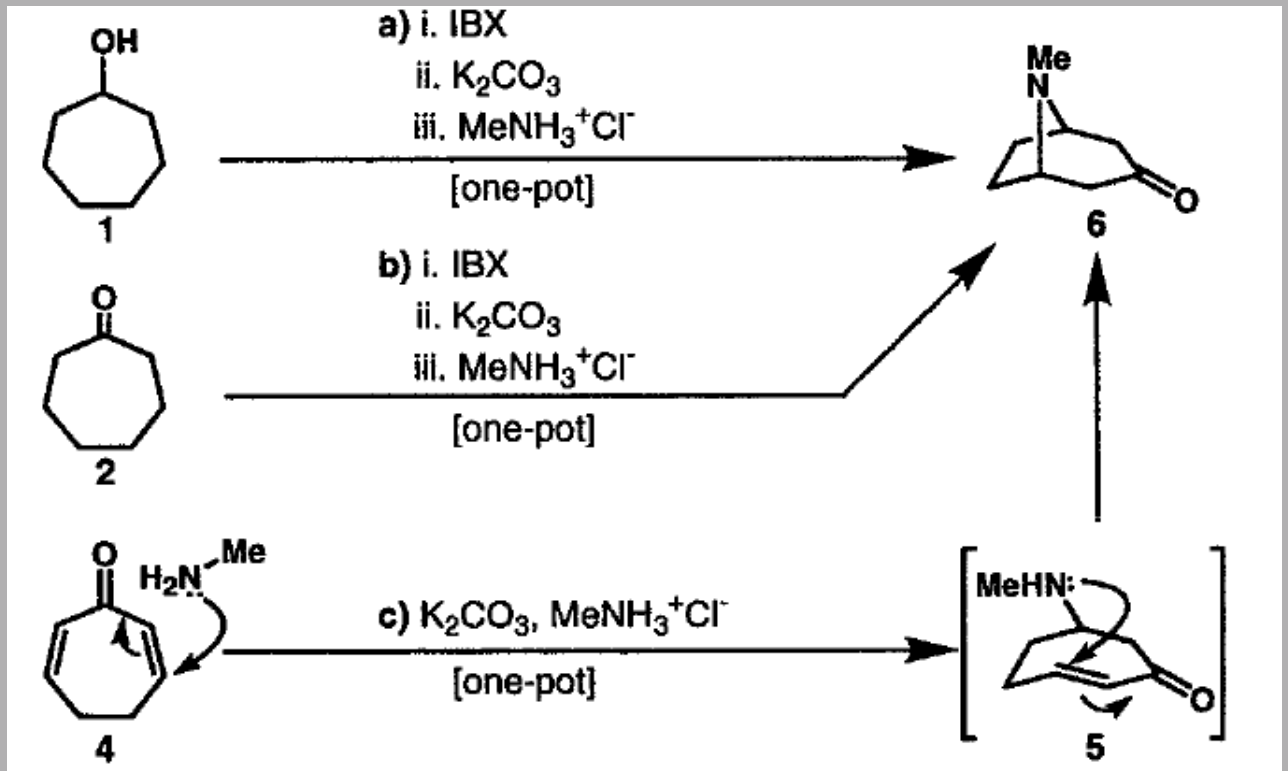
K.C Nicolaou, T. Montagnon, P.S Baran, Y.-L Zhong, *JACS,* **2002**, 124, 2245-2258

IBX enone formation



K.C Nicolaou, T. Montagnon, P.S Baran, Y.-L Zhong, *JACS,* **2002**, 124, 2245-2258
S. F. Kirsch an A. Duschek, *Angew. Chem. Int. Ed.* **2011**, *50*, 1524-1552

IBX enone formation: tropinone

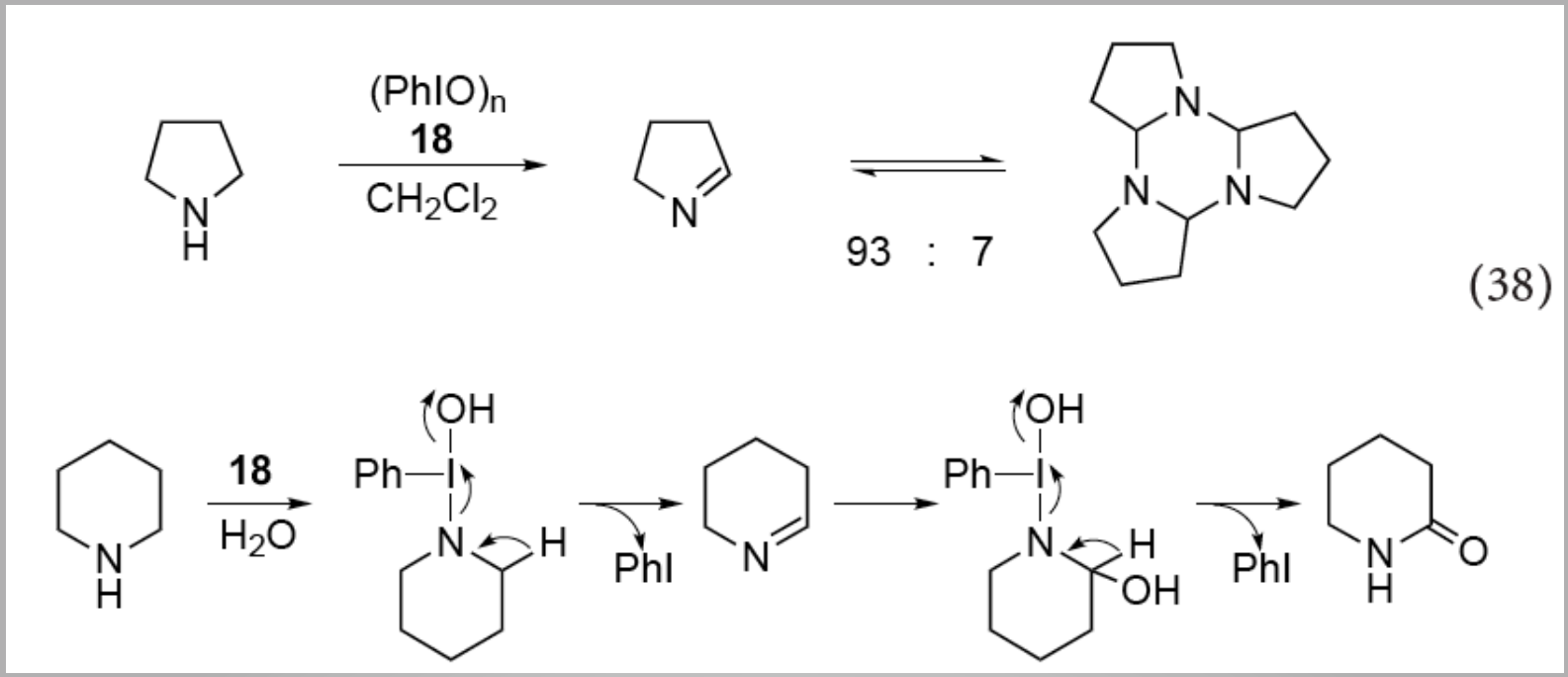


[a] Reagents and conditions: (a) IBX (4.0 equiv), DMSO, 25−85 °C, 22 h, cool to 25 °C, add K_2CO_3 followed by $MeNH_3^+Cl^-$, 3 h, 58%; (b) IBX (3.0 equiv), DMSO, 80 °C, 22 h, cool to 25 °C, add K_2CO_3 followed by $MeNH_3^+Cl^-$, 3 h, 59%; (c) K_2CO_3, $MeNH_3^+Cl^-$, MeOH, 25 °C, 2 h, 72%.

K.C Nicolaou, T. Montagnon, P.S Baran, Y.-L Zhong, *JACS,* **2002**, 124, 2245-2258

Red. β-elimination: C-N bond formation

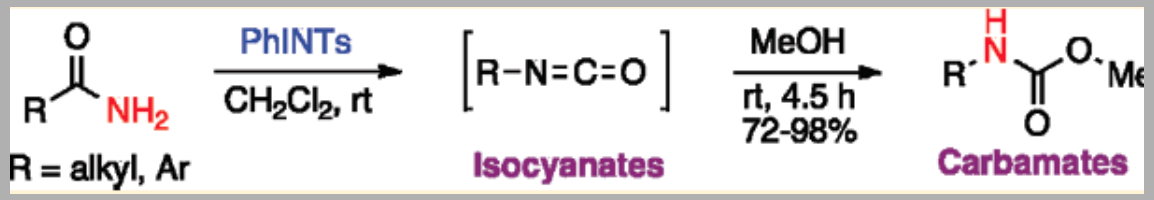
Oxydation of amine to imine



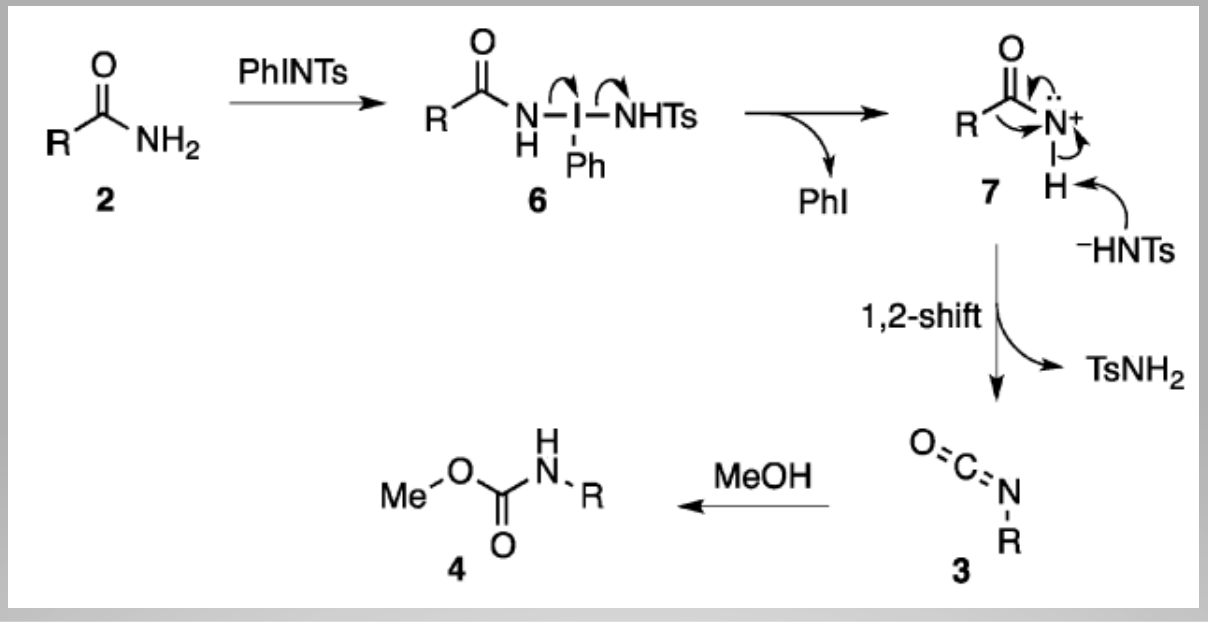
Reaction in water yielded piperidone

M. Ochiai, M. Inanage, Y. Nagao, RM. Moriarty, RK Vaid, Duncan MP, *Tetrahedron*, **1998**, 29, 6917-6919
RM Moriarty, RK Vaid, Duncan MP, M. Ochiai, M. Inenaga, Y. Nagao, , *Tetrahedron*, **1998**, 29, 6913-6917

Red. β-elimination: Hofmann rearrangement



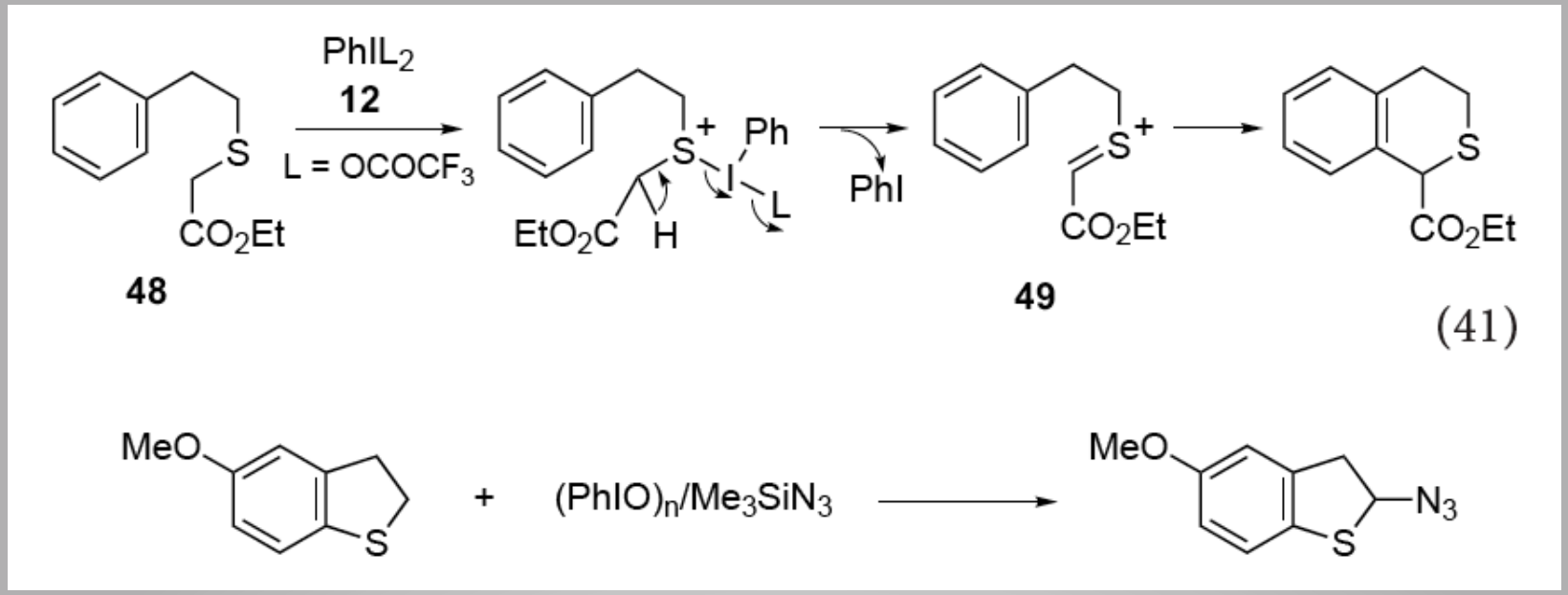
- 1,2-shift of Nitrenium nitrogen



A. Yoshimura, M. W. Luedtke, and V. Zhdankin, *J. Org. Chem,* **2012**, 77, 2087-2091

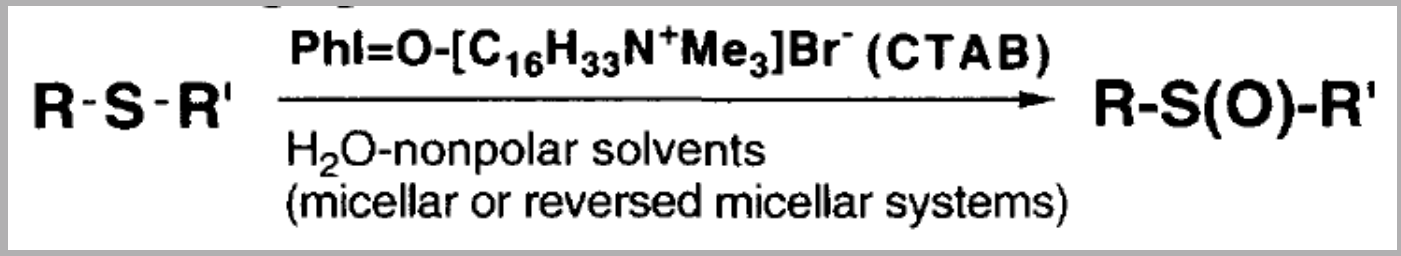
Red. β-elimination: C-S bond formation

Isothiochromane

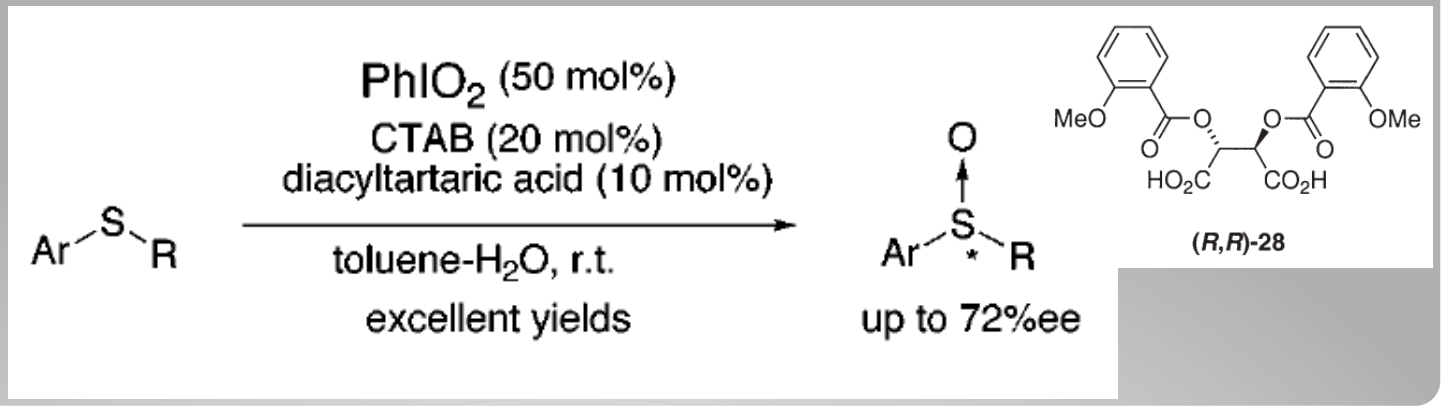


Red. β-elimination: S-O bond formation

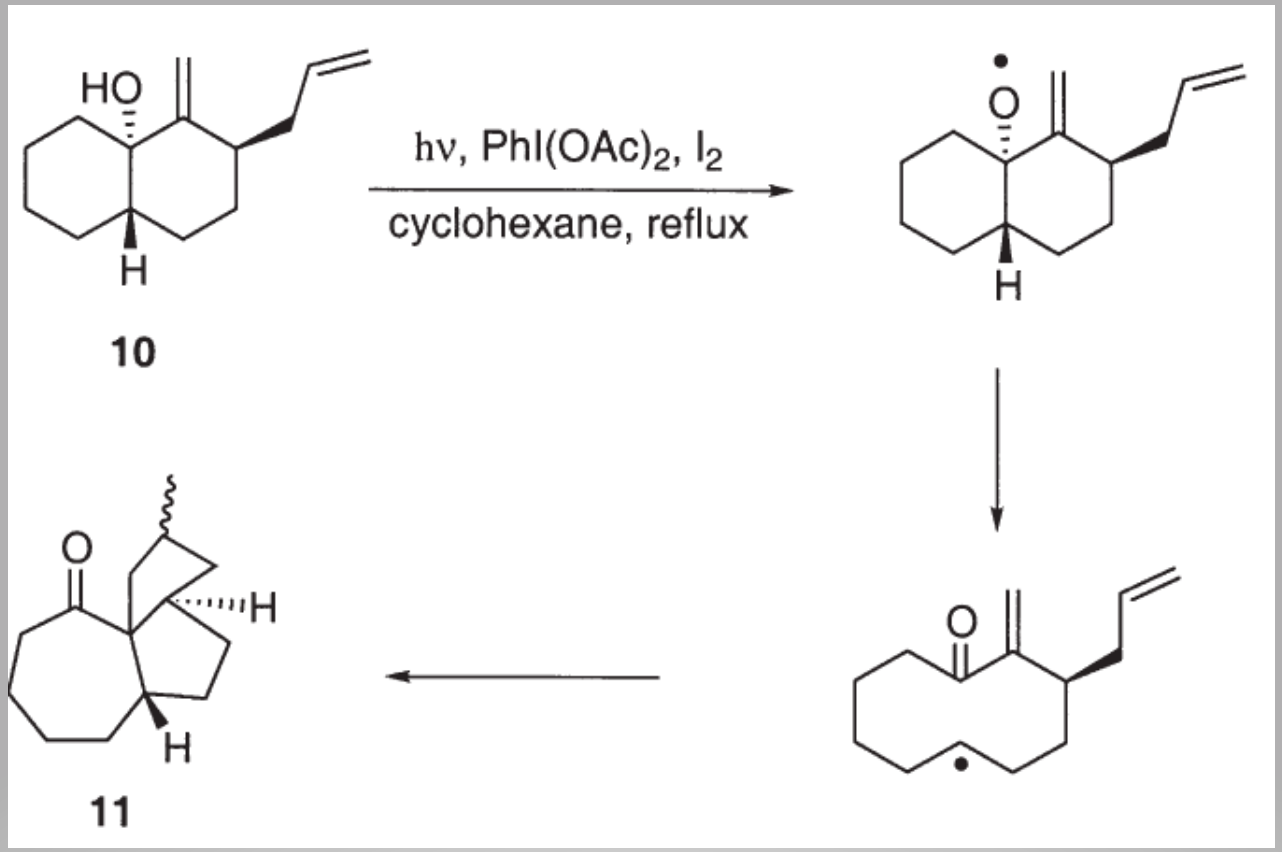
- Harsh conditions give mixture of sulfoxide and sulfone
- Miscellar system allows mild conditions in apolar system with iodosobenzene!



- Catalytic asymmetric version has been investigated



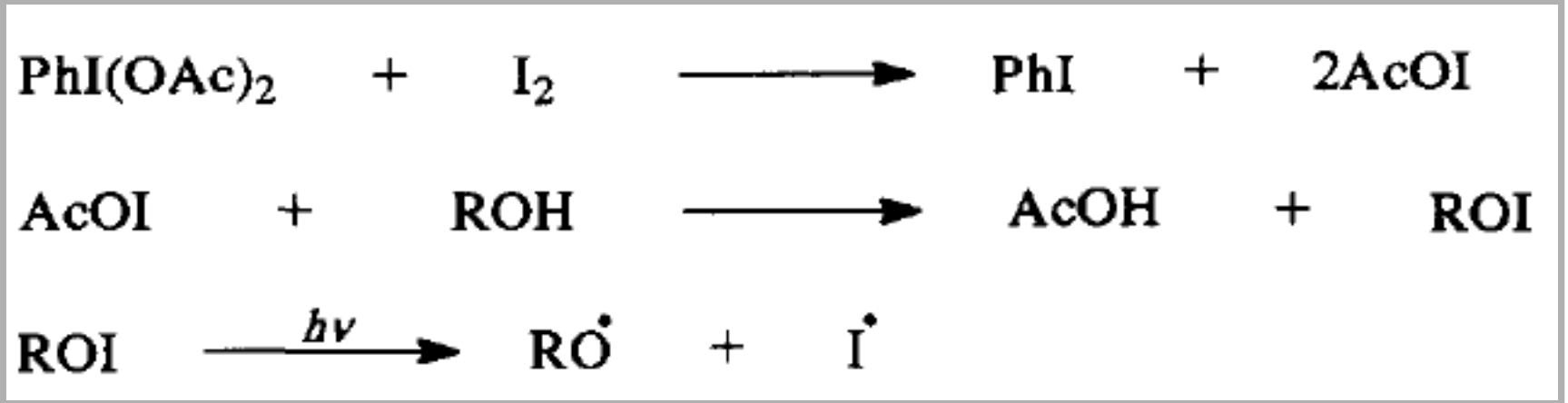
I-L homolytic cleavage



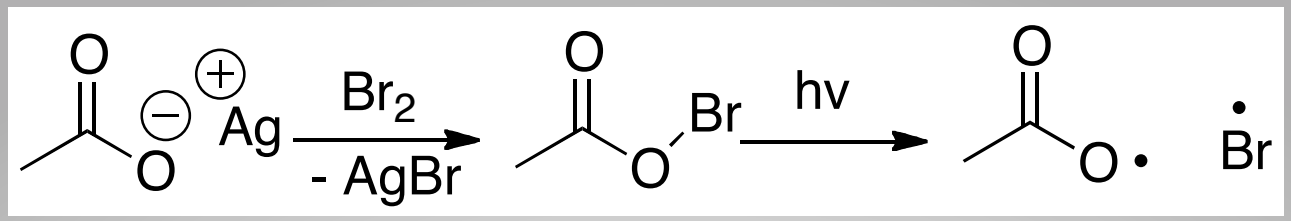
C.E. Mowbray, G. Pattenden, *Tettrahedron Letters*, **1993**, 34, 127

I-L homolytic cleavage

Proposed mechanism: formation of acetyl hypoiodite

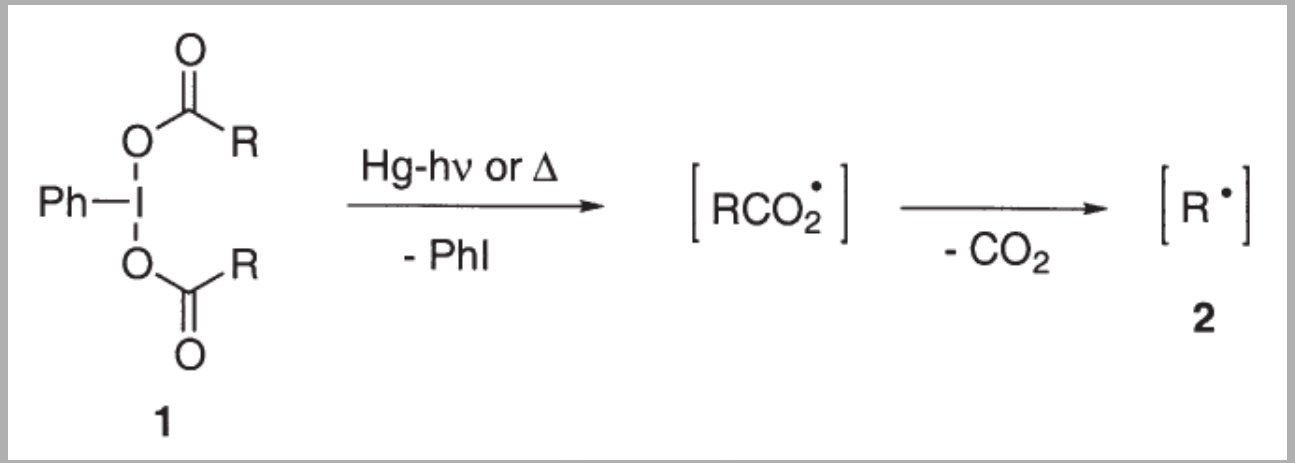


Analogy to the Hunsdiecker reaction



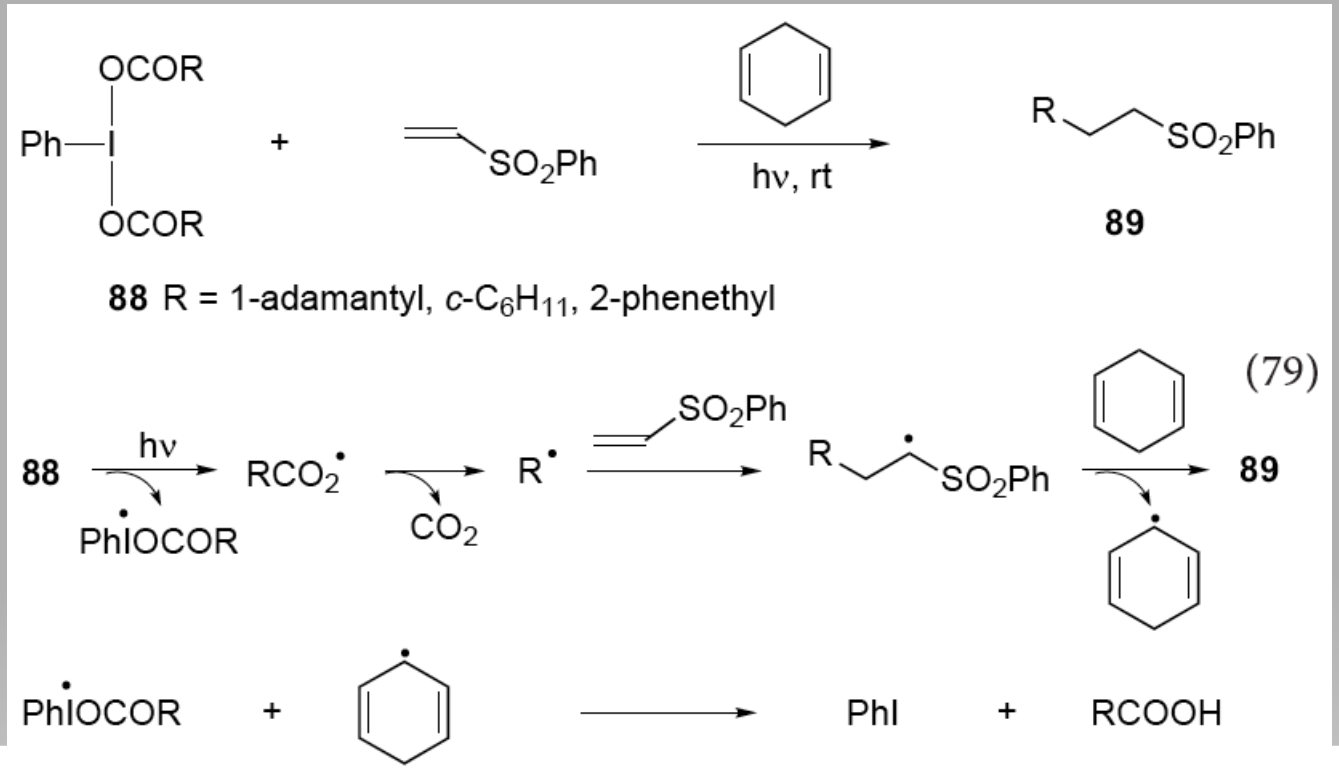
J.L. Courtneidge, J. Lusztyk, D. Page, *Tetrahedron Letters,* **1994**, 35, 1003

Homolytic cleavage of O-I bond



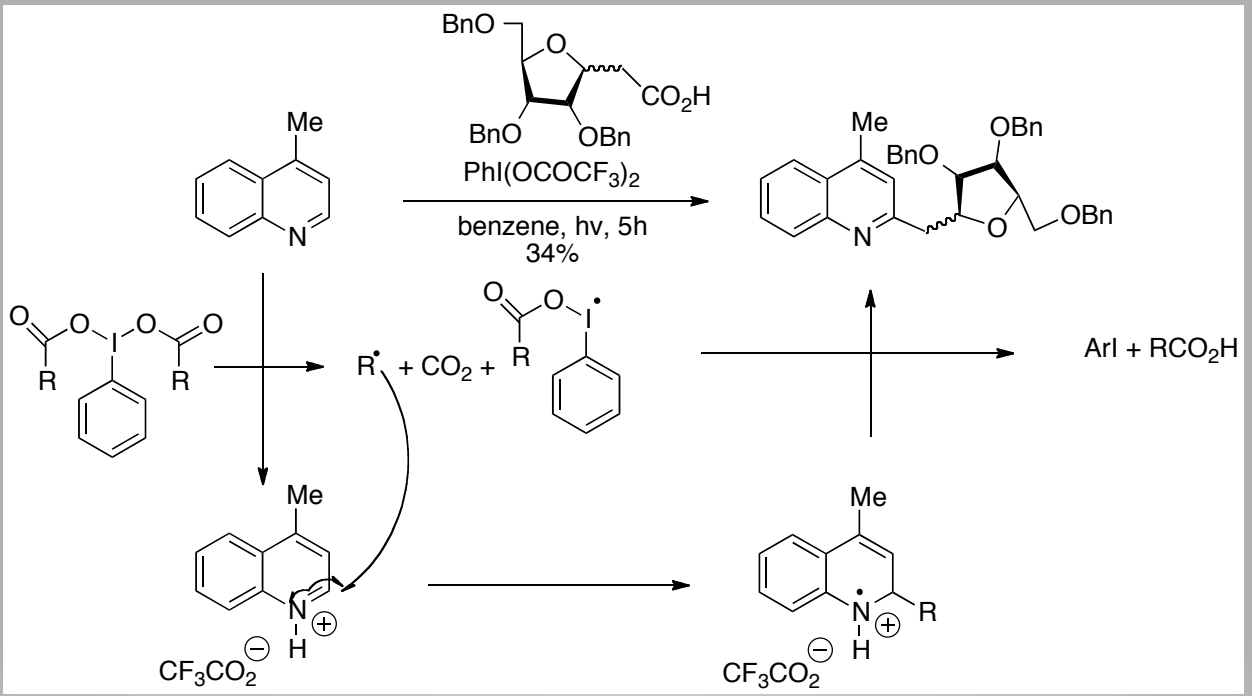
Homolytic cleavage of the I-O bond

- Bond dissociation energy not known but assumed to be smaller than than organoiodane
- Heating or light irradiation induce homolytic cleavage



Homolytic cleavage of the I-O bond

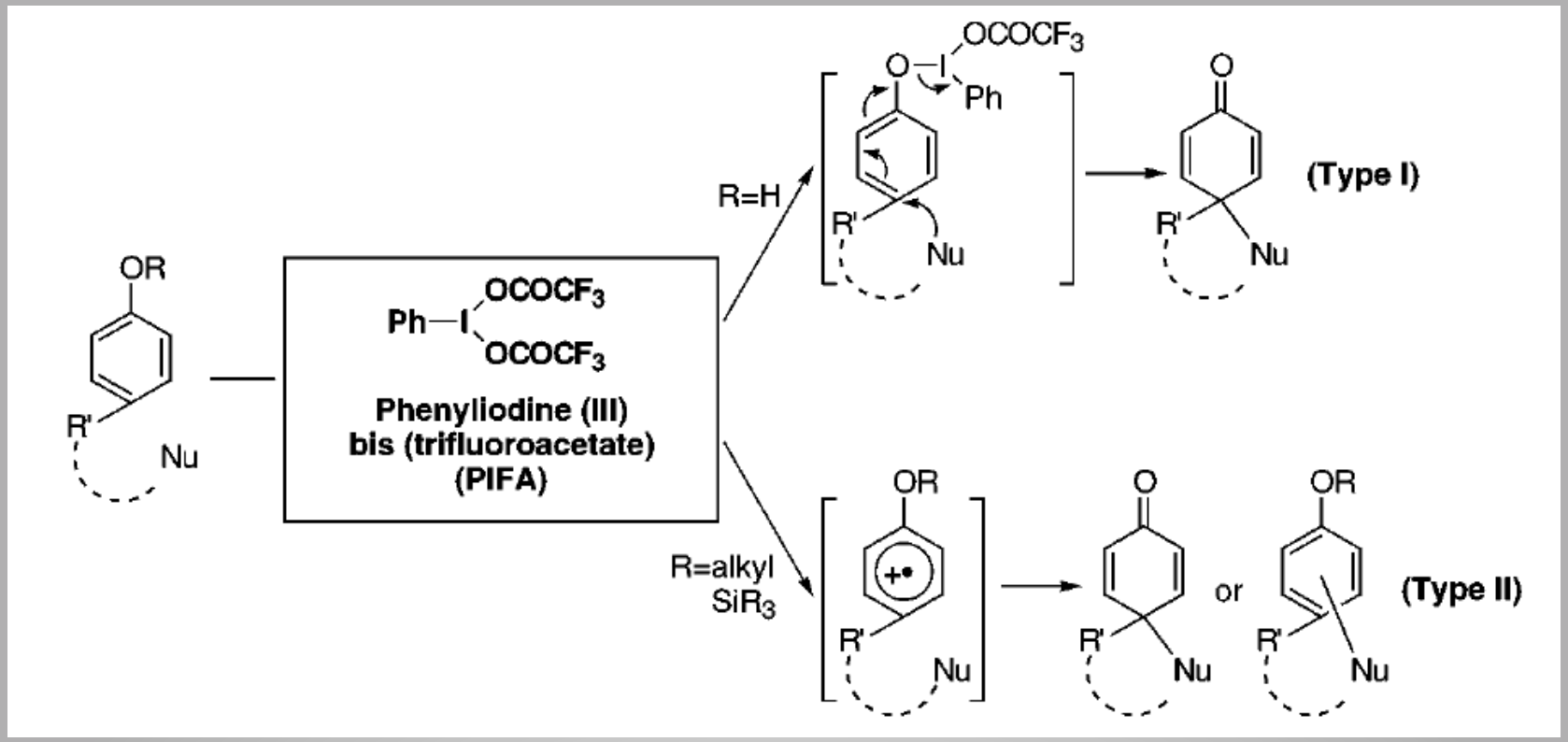
Alkylation of heterobases (lepitine) with C-nucleosides derivatives



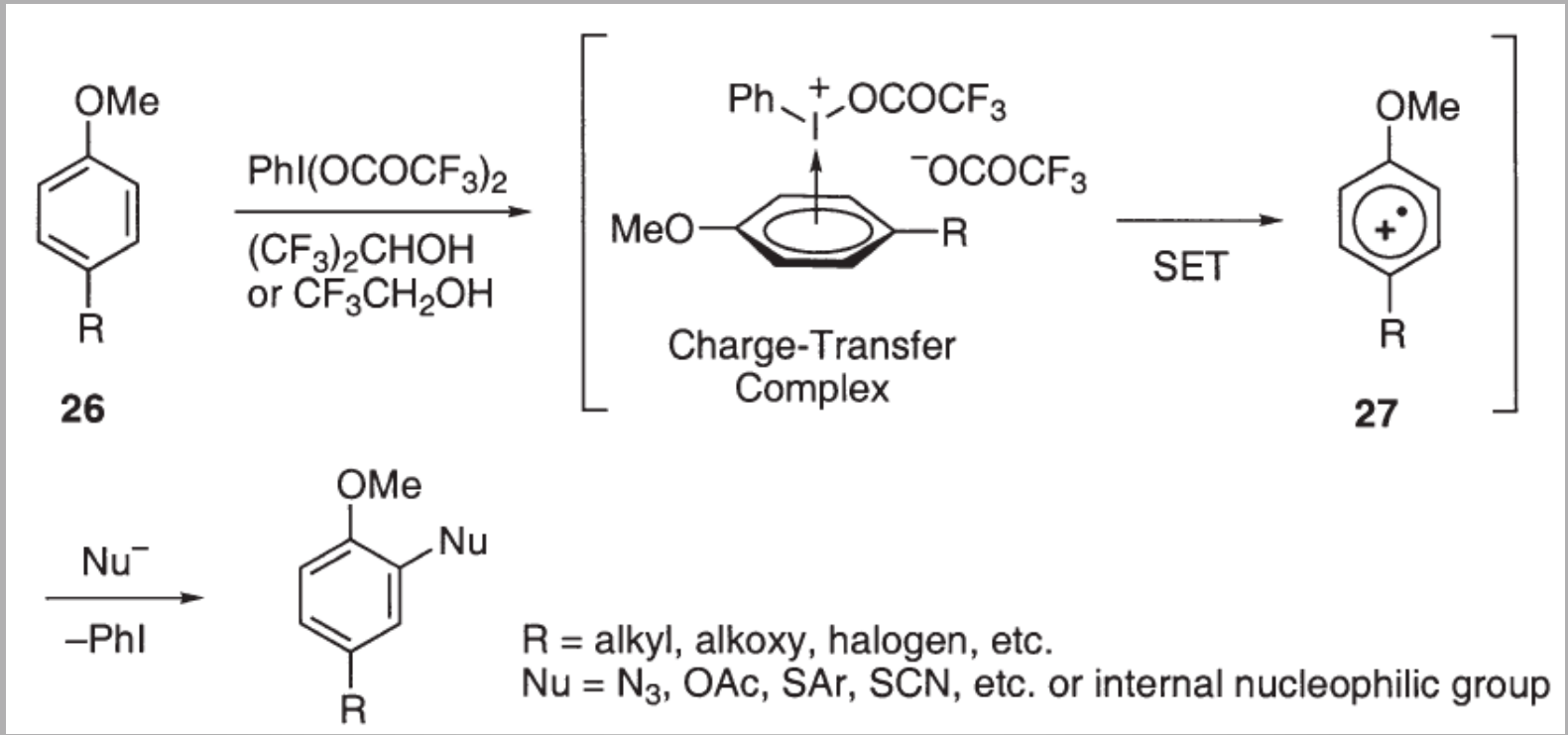
Class of product investigated for antivirus and antitumor activity

H. Togo, M. Aoki and M. Yokoyama, *Tett. Lett.*. **1991**, 32, 6559-6562

Oxydation of phenol and phenol ether



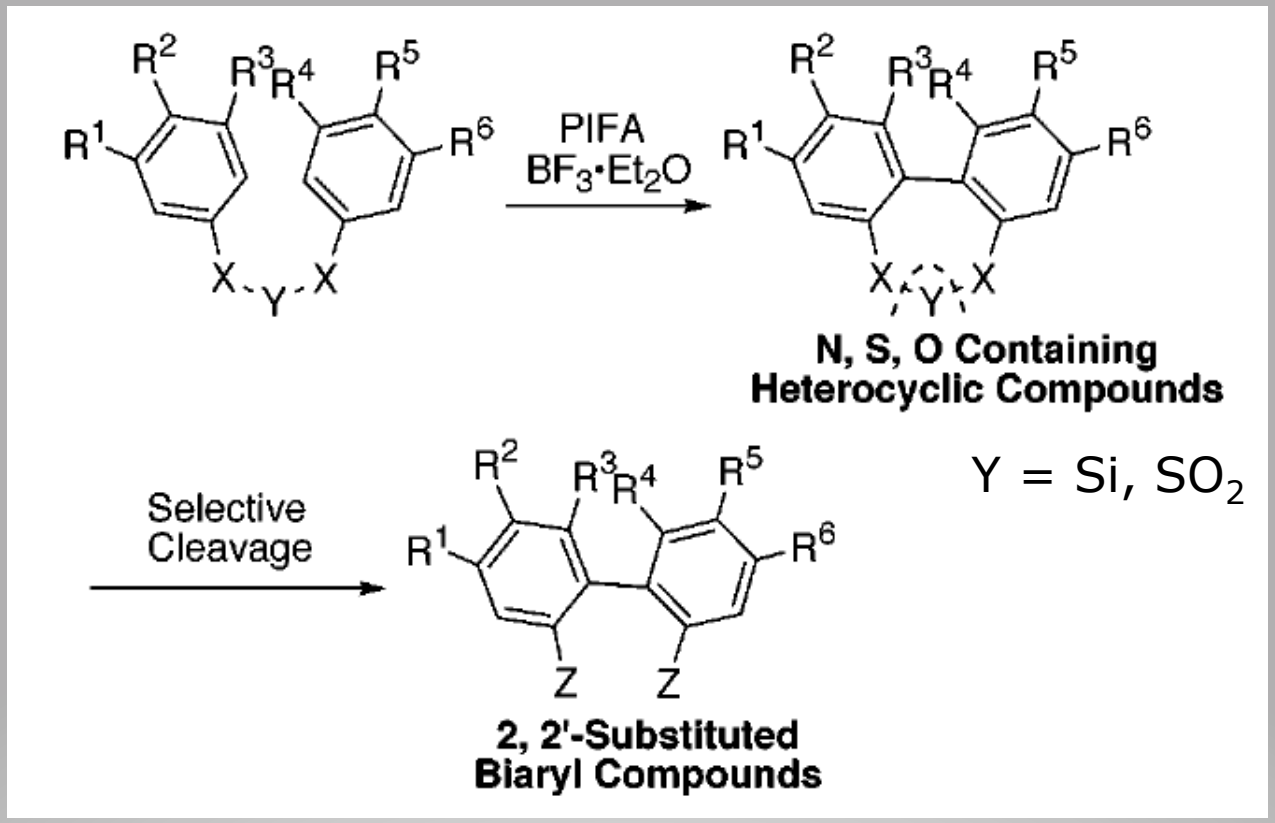
Oxydation of phenol ethers



- Poorly nucleophilic solvents
- Ortho substitution with *para*-substituted phenol ether

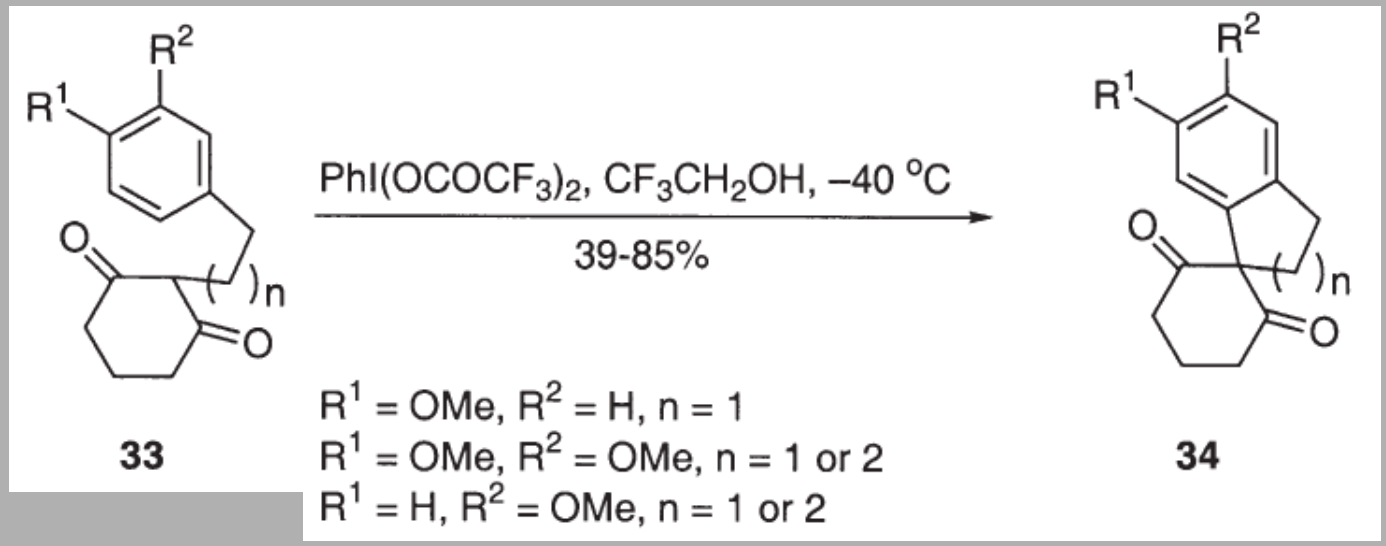
Oxydation of phenol ethers

Oxydative biaryl coupling



T. Takada, M. Arisawa, M. Gyoten, R. Hamada, H. Tohma and Y. Kita, *J. Org. Chem.* **1998**, 7698-7706

Oxydation of phenol ethers

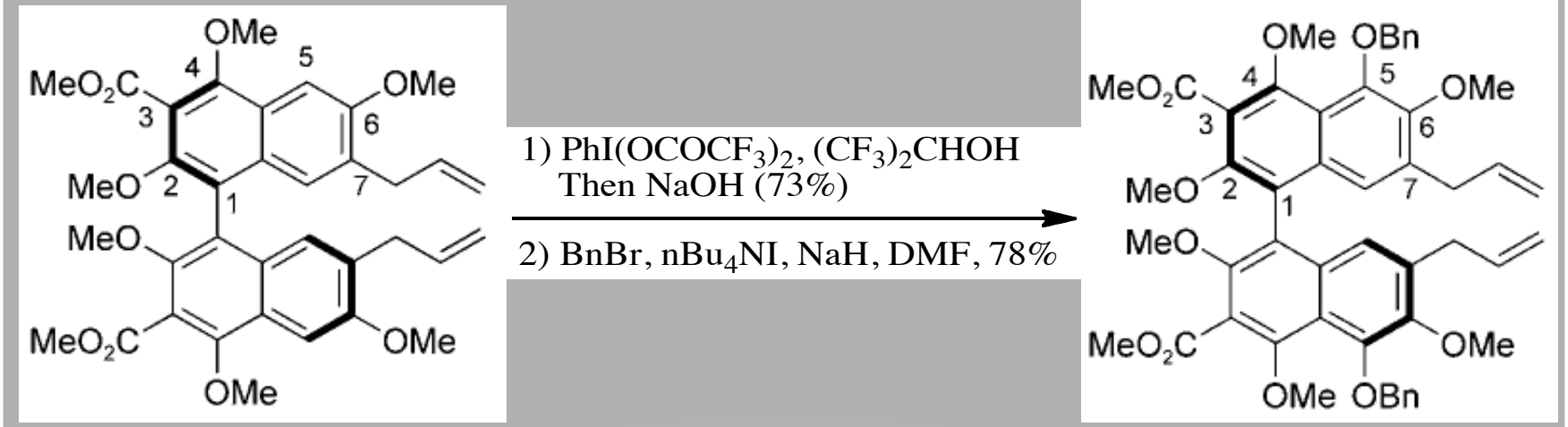


- Scaffold present in naturally occuring products (cannabis)

T. Takada, M. Arisawa, M. Gyoten, R. Hamada, H. Tohma and Y. Kita, *J. Org. Chem.* **2001**, 59-65

Oxydation of phenol ethers

Total synthesis of Hypocrellin A

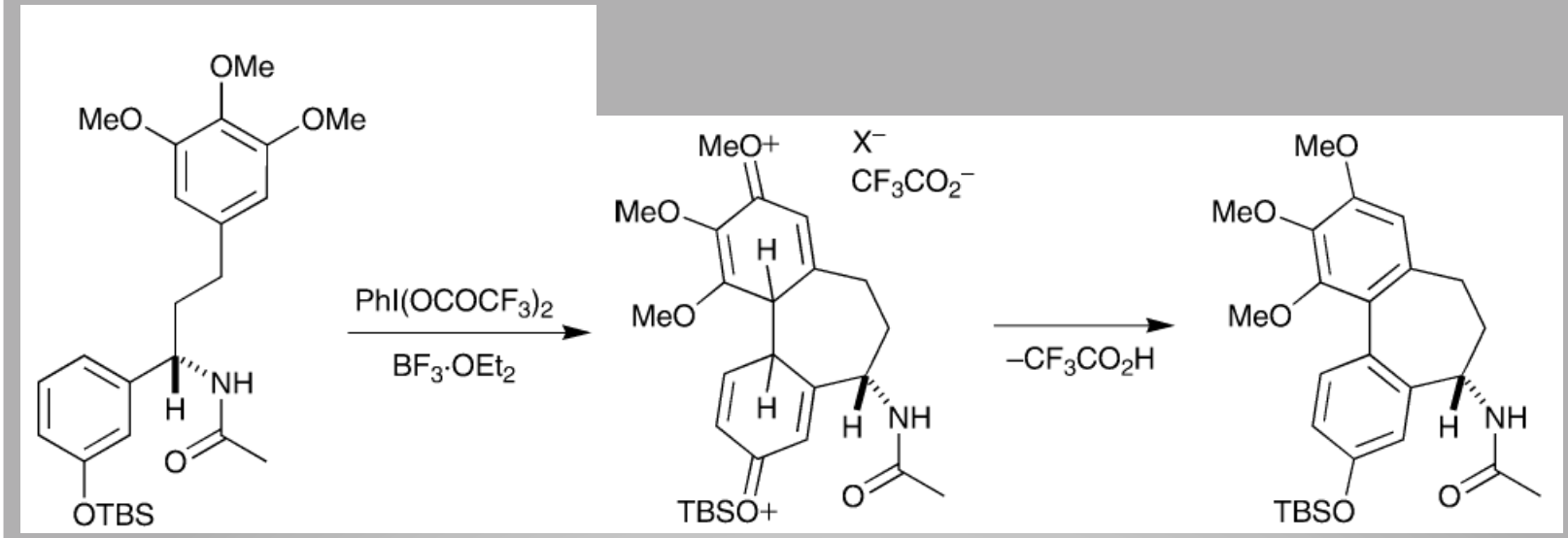


- Light induced activity against tumor cell light

E.M. O'Brien, B.J. Morgan and M.C. Kozlowski, *Angew. Chem. Int. Ed.*, **2008**, 47, 6877-6880

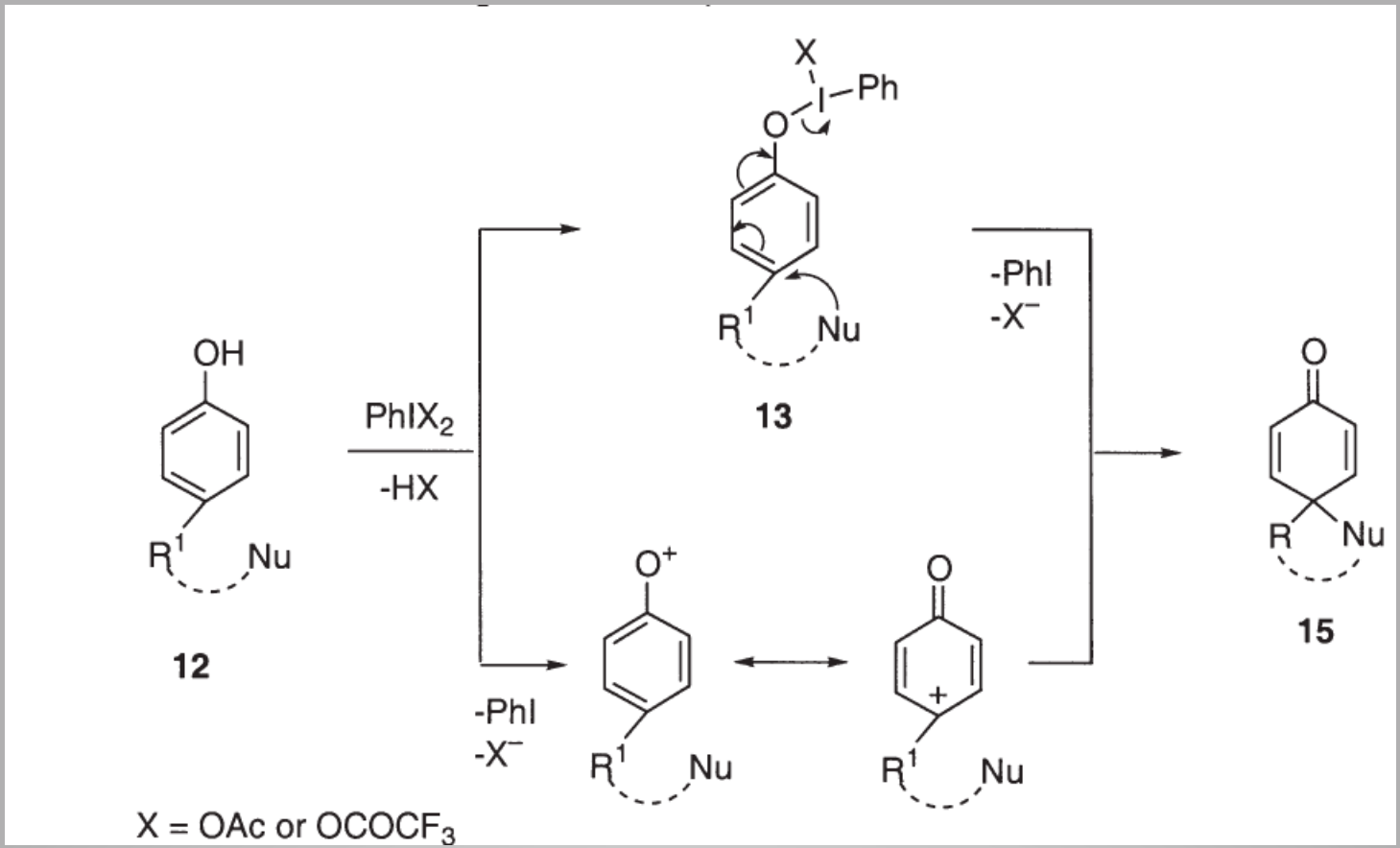
Oxydation of phenol ether

- Total synthesis of (S)-(-)-N-acetylcolchinol
- Tubulin polymerisation inhibitor (clinical trial AstraZeneca)



K. Jarowicki, P.J. Kocienski, E. Sliwinski and F.T Boyle.*Org. Biomol. Chem.,***2006**, 4, 2193-2207

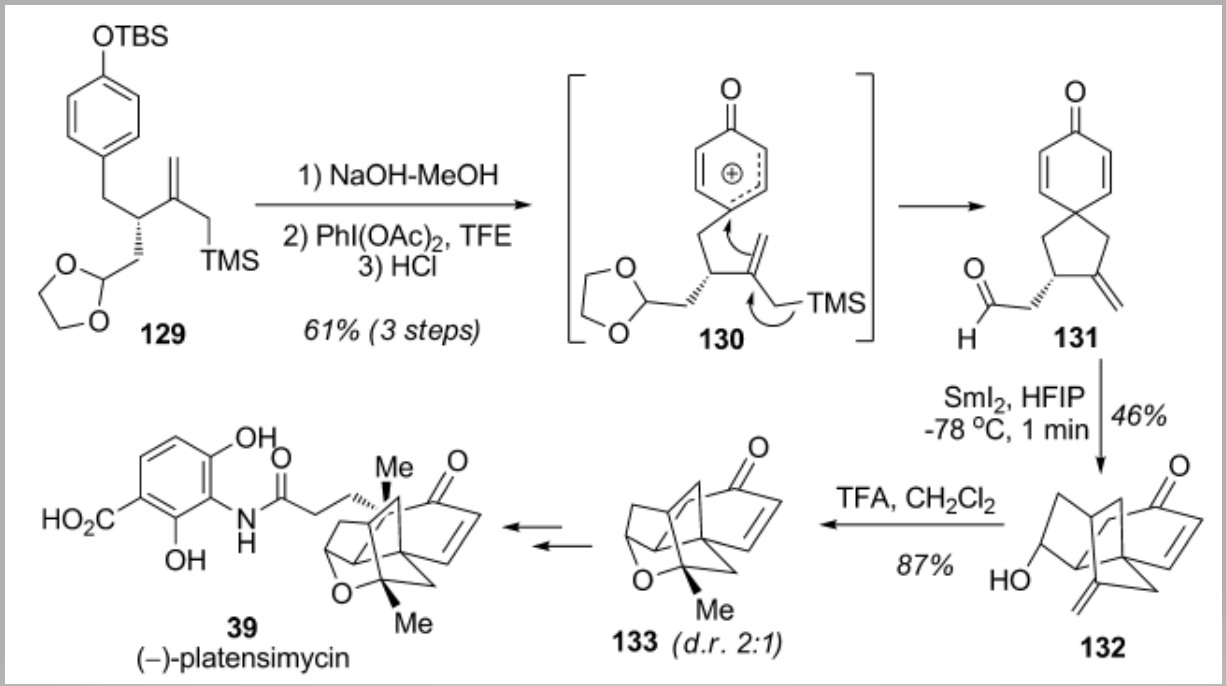
Oxydation of phenol



Nu = alcohols, fluoride ion, amides, allylsilane and e⁻rich aromatics

Oxydation of phenol

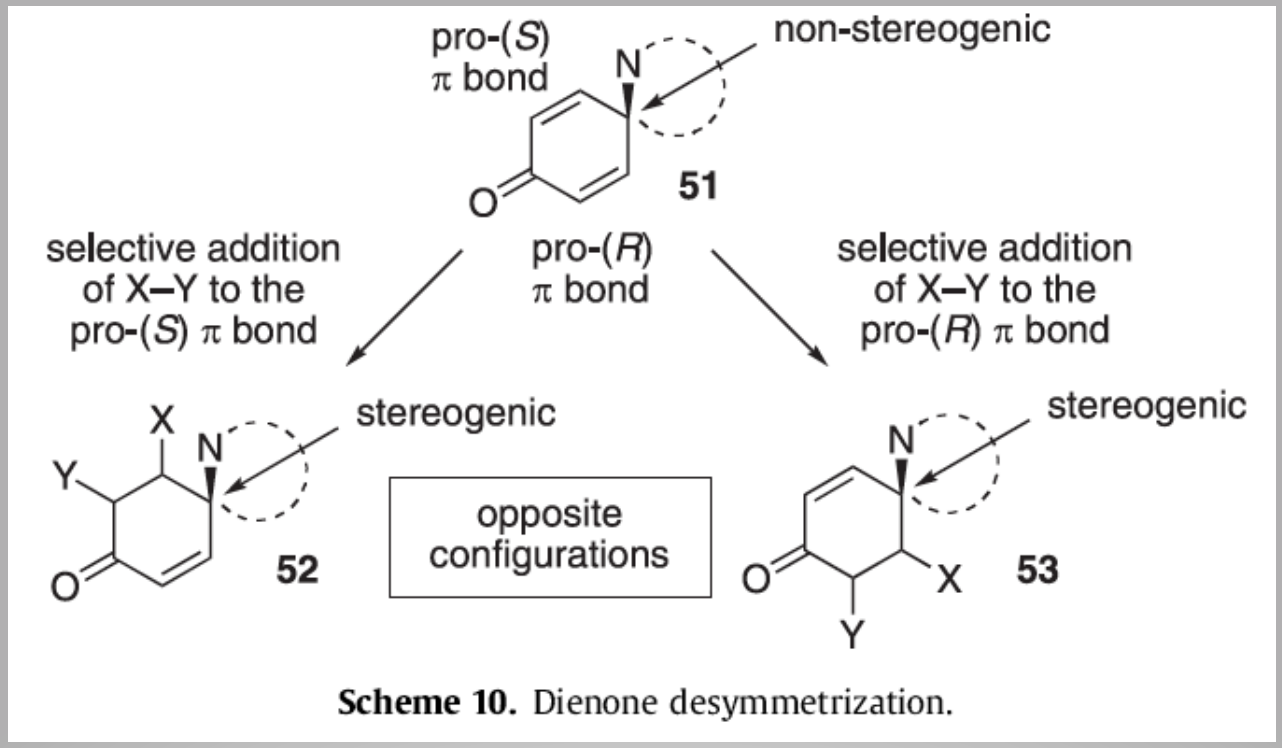
Total Synthesis of Platensimycin



- Allylsilane used a nucleophile

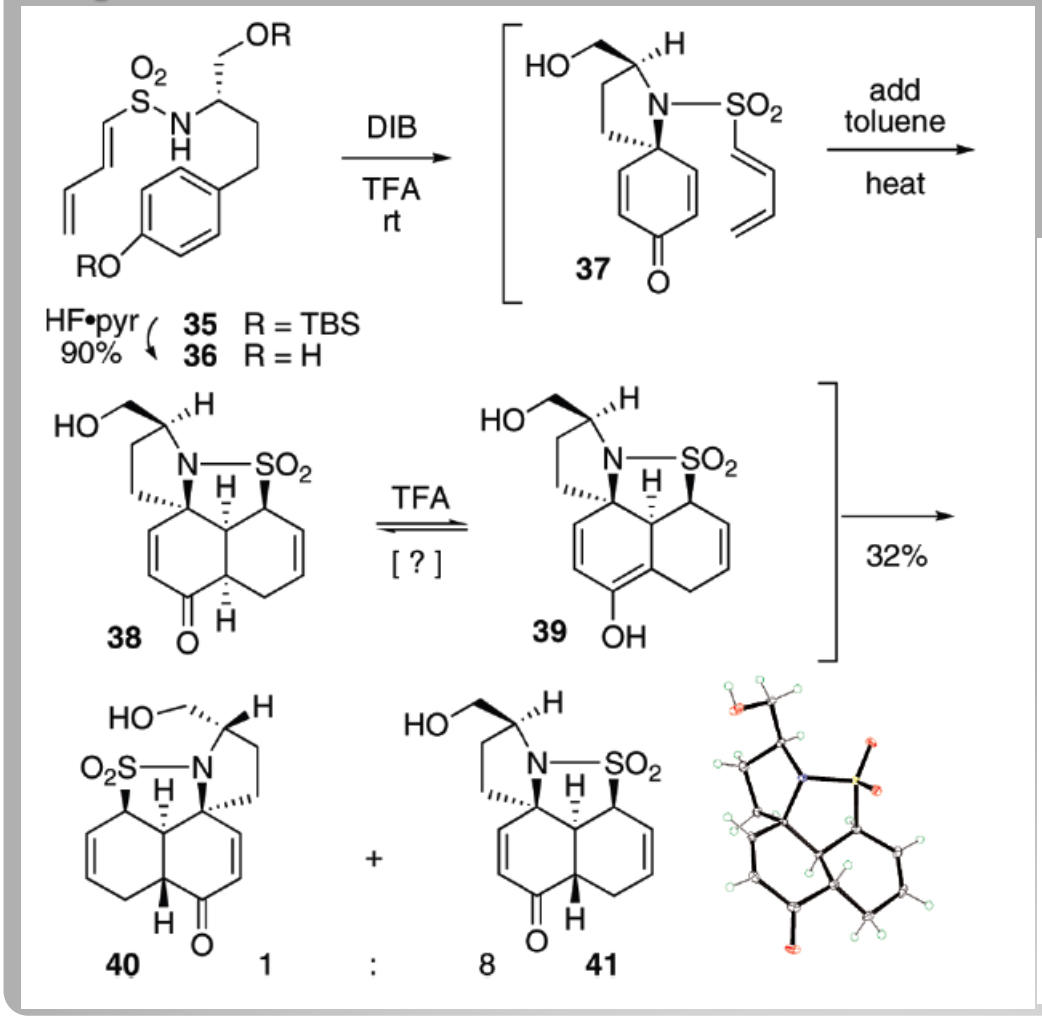
K. C. Nicolaou, D. J. Edmonds, A. Li, and G.S. Tria, *Angew. Chem. Int. Ed.* **2007**, 46, 3942-3945

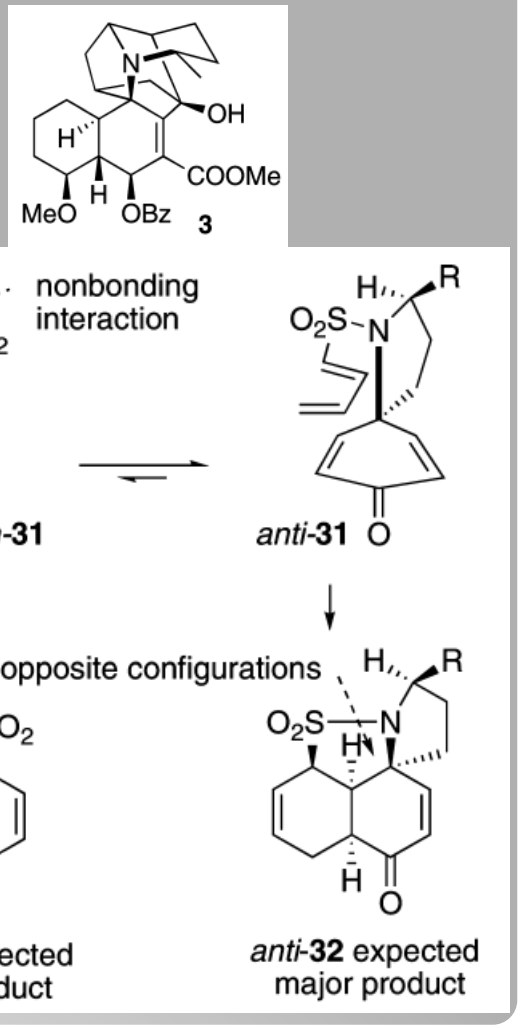
Oxydation of phenol: desymmetrisation



Scheme 10. Dienone desymmetrization.

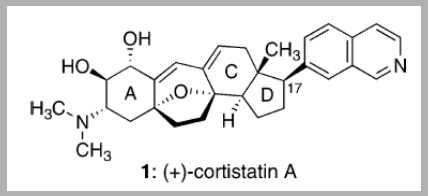
Synthesis of Himandrine core



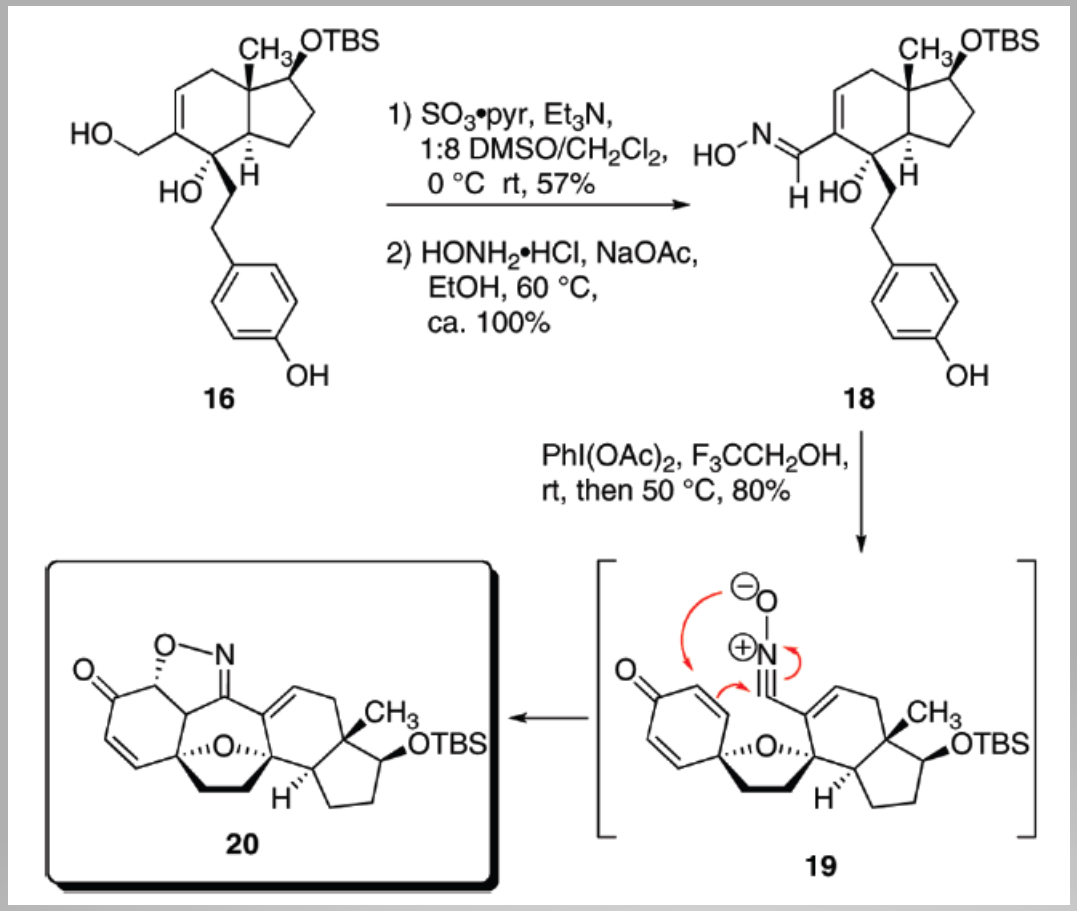


H. Liang and M.A. Cuifolini, *Org. Lett.* **2010**, 12, 1760-1763

Oxydation of phenol ethers



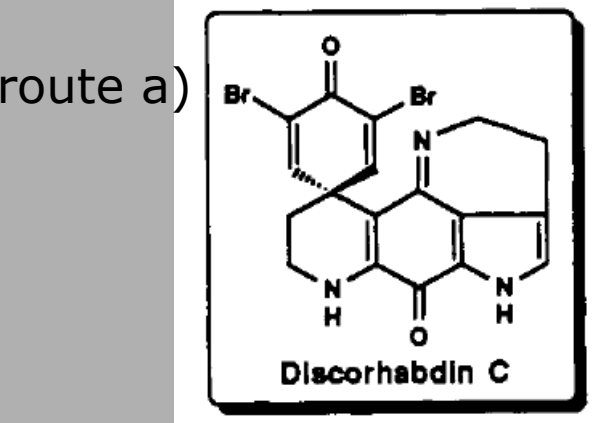
1: (+)-cortistatin A

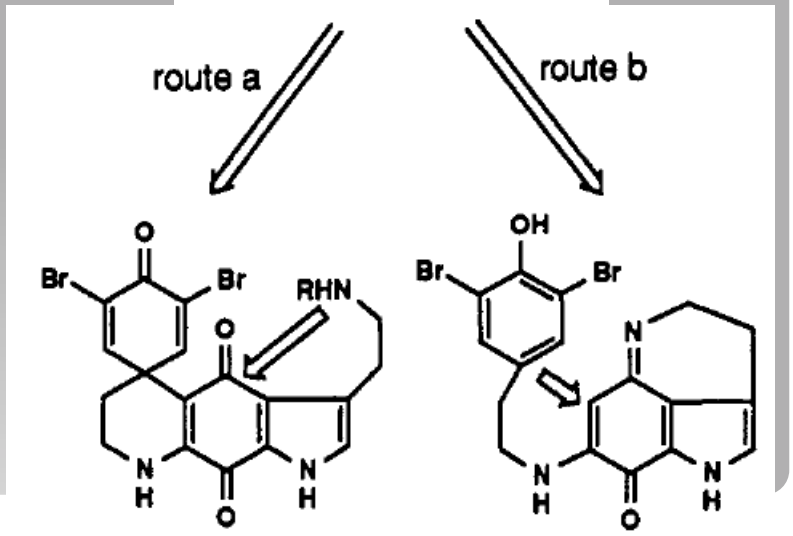


J. L. Frie, C. S. Jeffrey, E. J. Sorensen, *Org. Lett.* **2009**, 11, 5394-5397
J. P. Parikh, W. E Doering, *JACS*, **1967**, 89, 5505

Oxydation of phenol: Discorhabdin Story

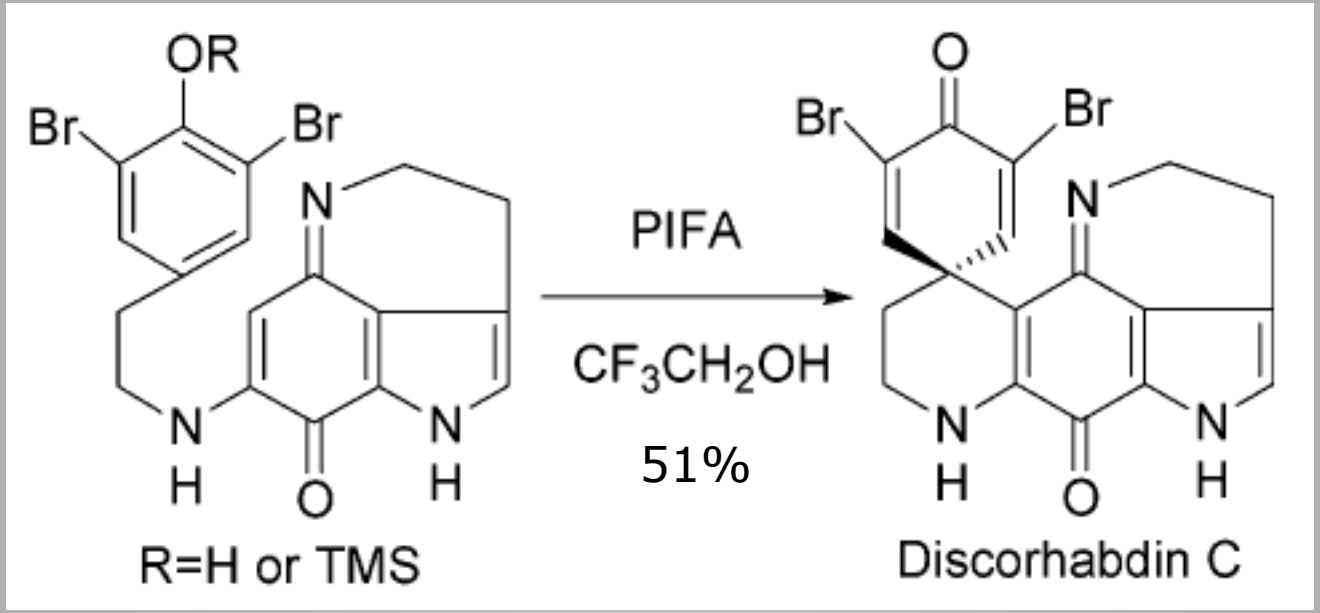
- Imine formation proved impossible (route a)
- First form imine and then oxydation





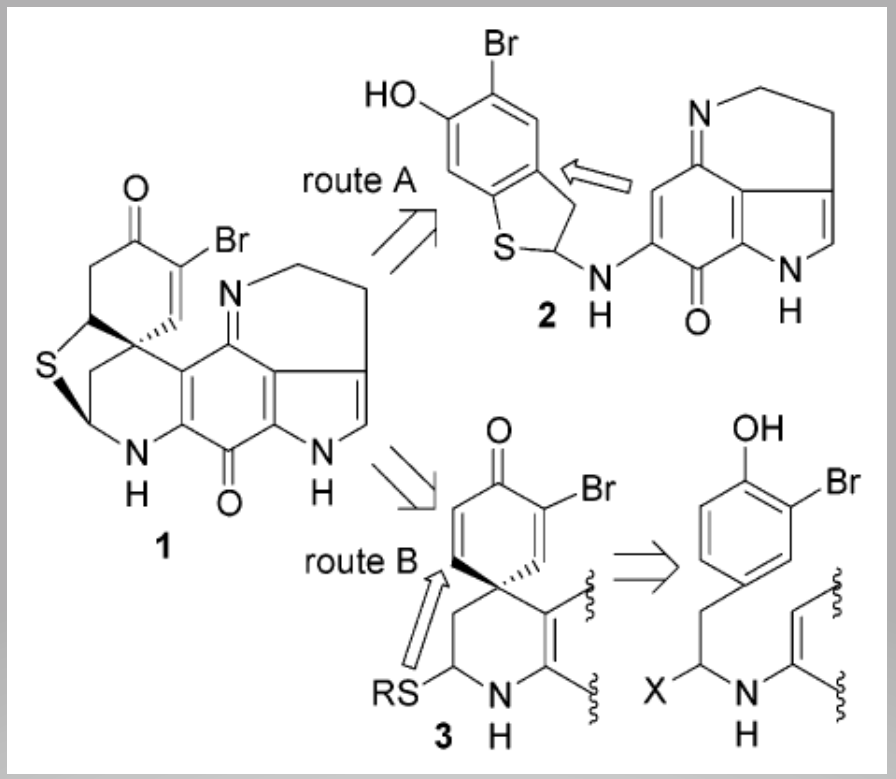
Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka and T. Yakura, *J. Am. Chem. Soc.*, **1992**, 114, 2175-2180

Oxydation of phenol: Discorhabdin C



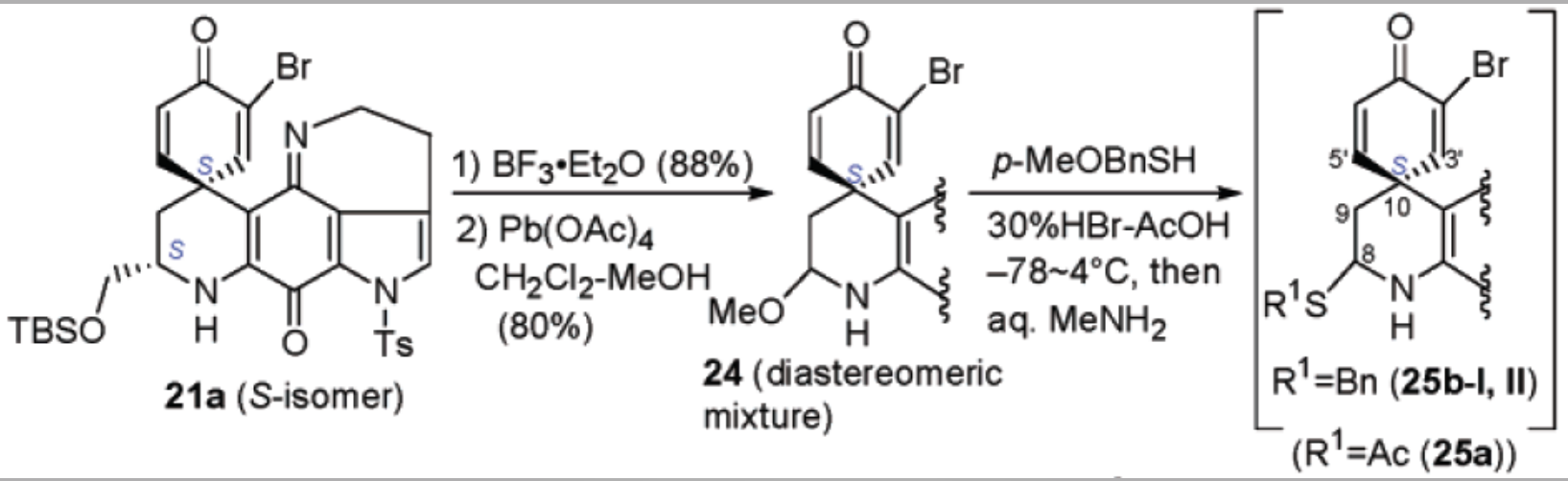
Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka and T. Yakura, *J. Am. Chem. Soc.*, **1992**, 114, 2175-2180

Oxydation of phenol: Discorhabdin A



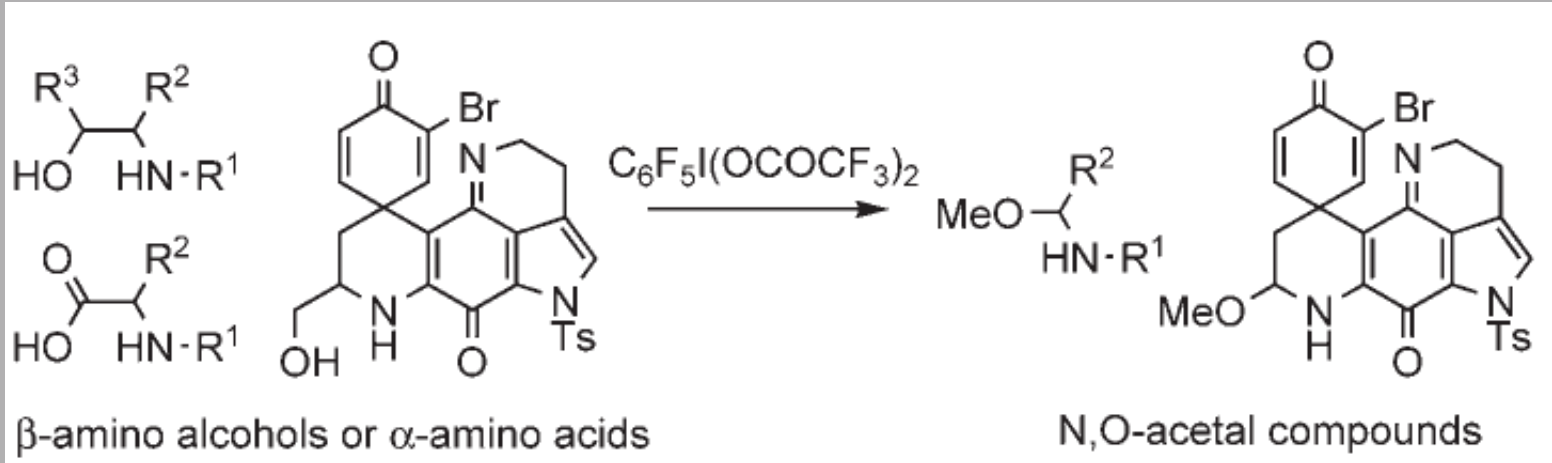
H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, Y. Kiyonon, M. Egi, and Y. Kita, *J. Am. Chem. Soc.*, **2003**, 114, 11235-11240

Oxydation of phenol: Discorhabdin A



H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, Y. Kiyonon, M. Egi, and Y. Kita, *J. Am. Chem. Soc.*, **2003**, 114, 11235-11240

Oxydation of phenol: Discorhabdin A

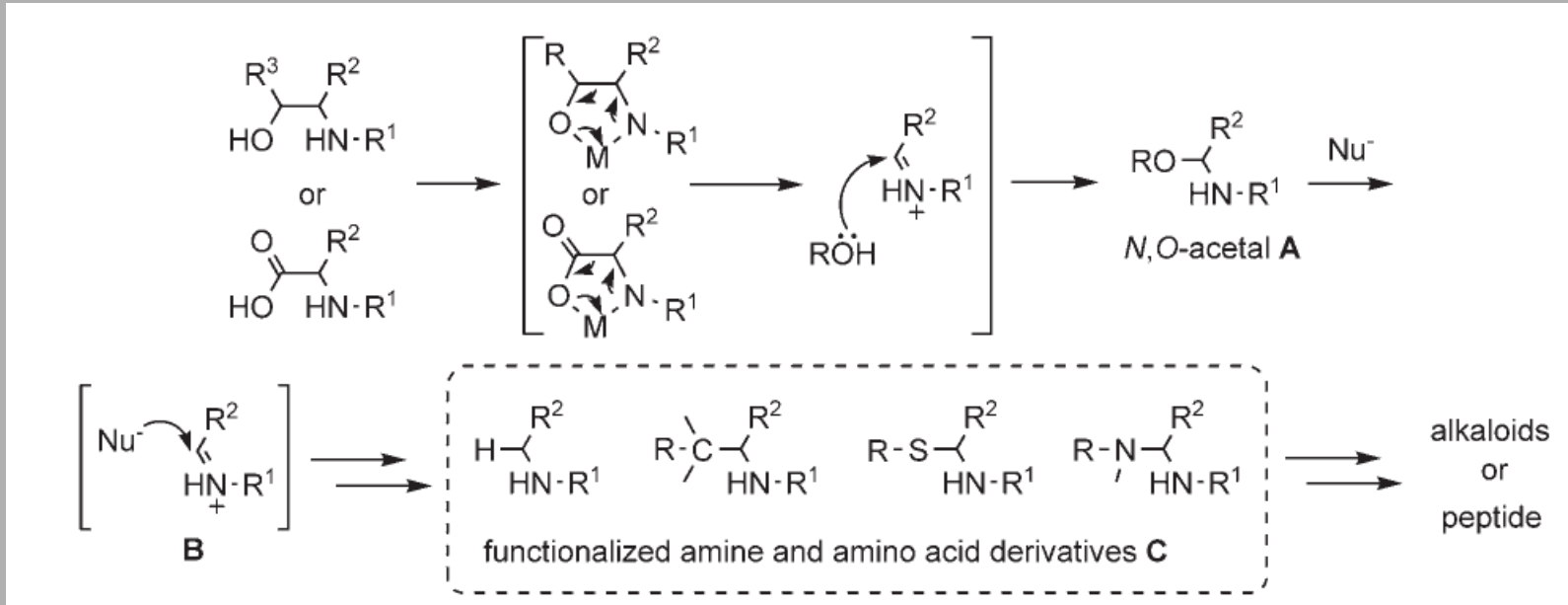


β-amino alcohols or α-amino acids

N,O-acetal compounds

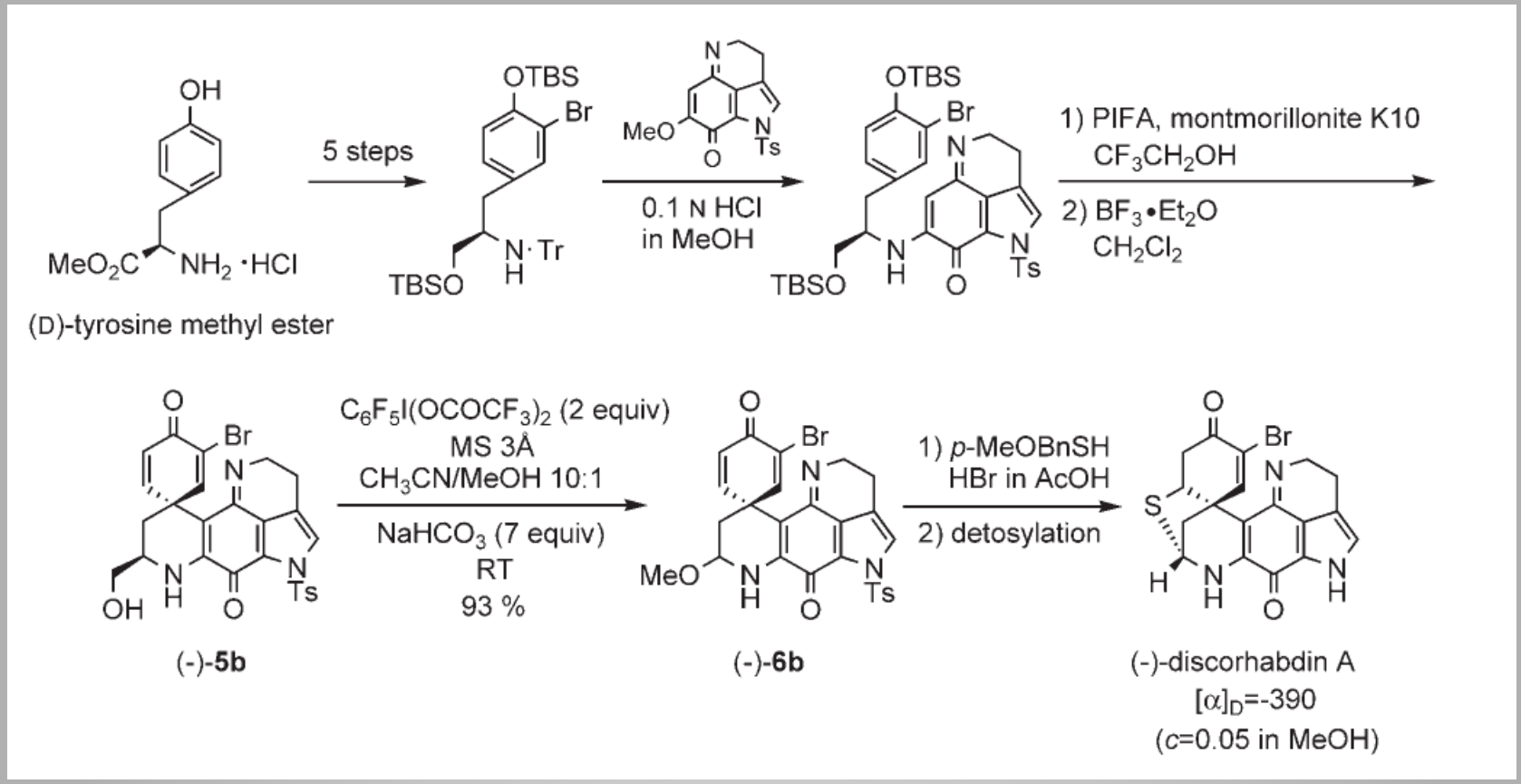
Scheme 3. Fragmentation reaction by $C_6F_5I(OCOCF_3)_2$.

Oxydation of phenol: Discorhabdin A



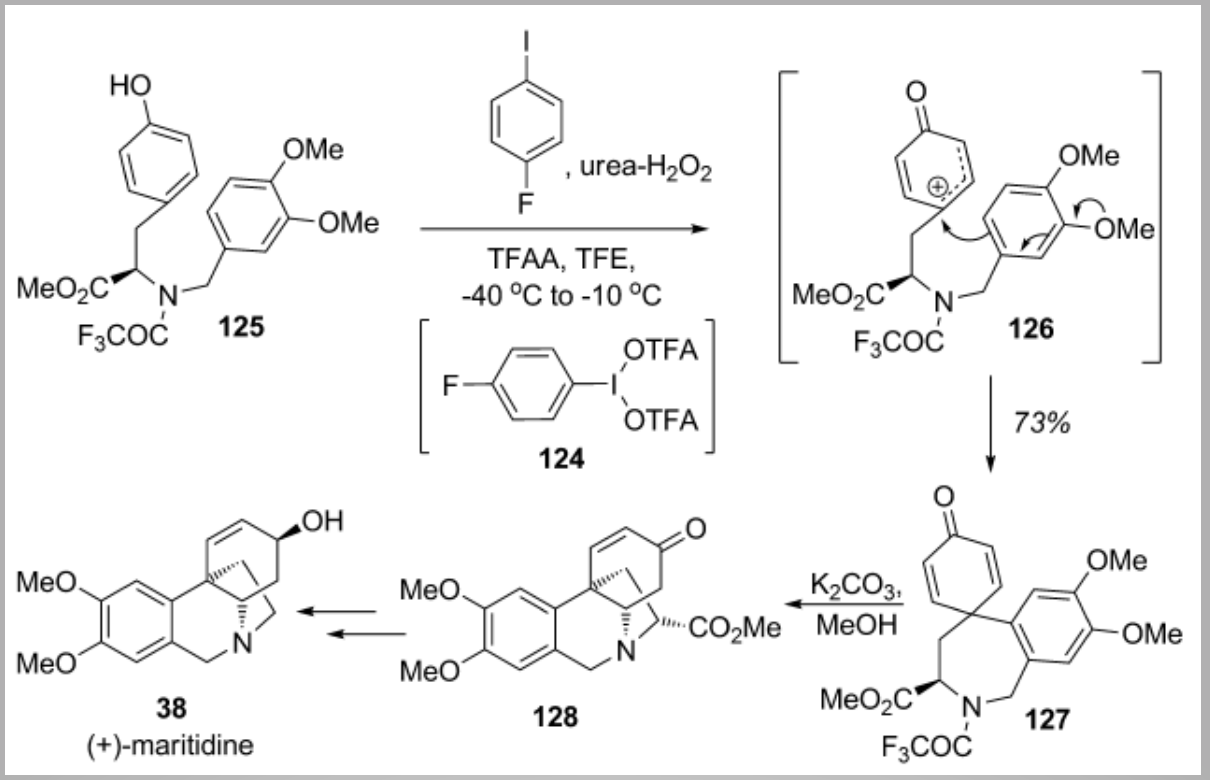
Scheme 1. Synthesis and efficient use of N,O-acetals.

Oxydation of phenol: Discorhabdin A



Y. Harayama, M. Yoshida, D. Kamimura, Y. Wada, and Y. Kita, *Chem. Eur. J.* **2006**, 12, 4893-4899

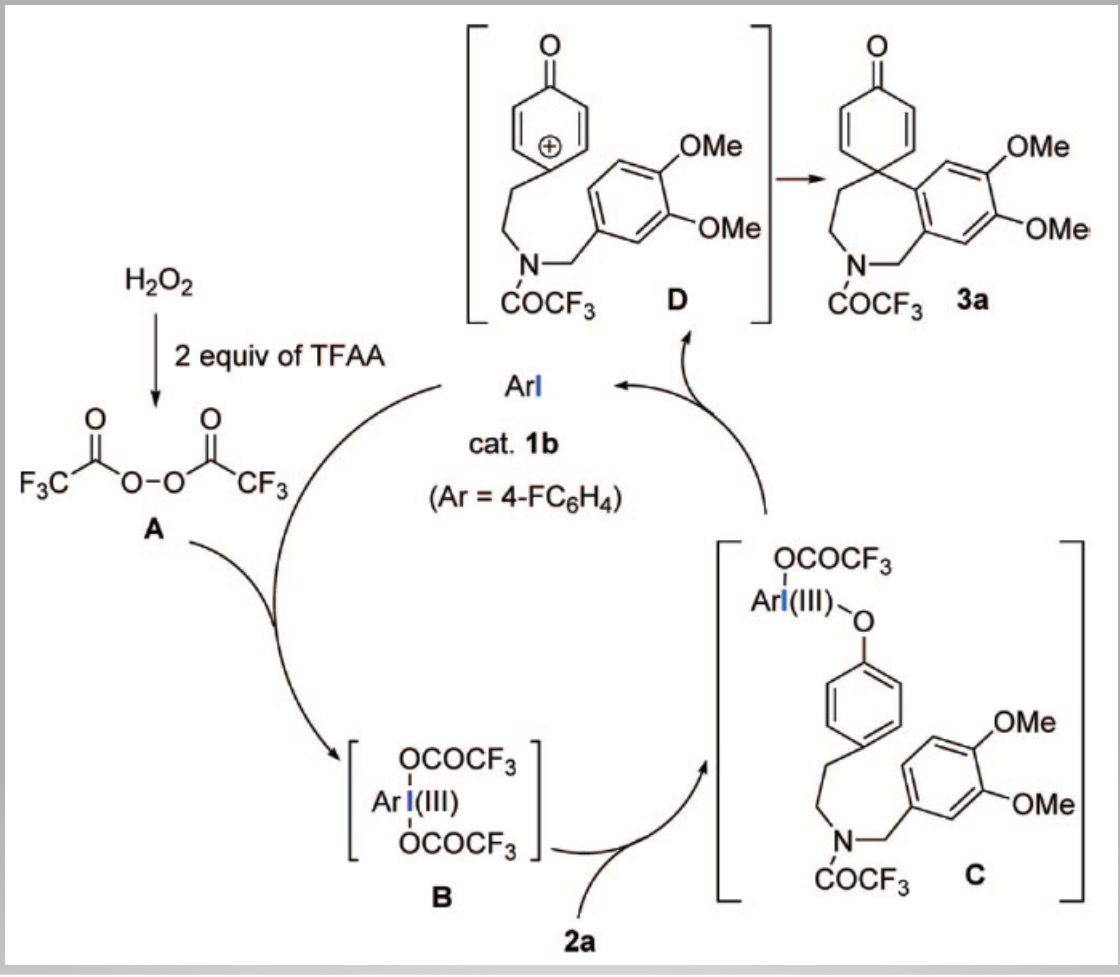
Oxydation of phenol: (+)-maritidine



First catalystic C-C bond formation using hypervalent iodine

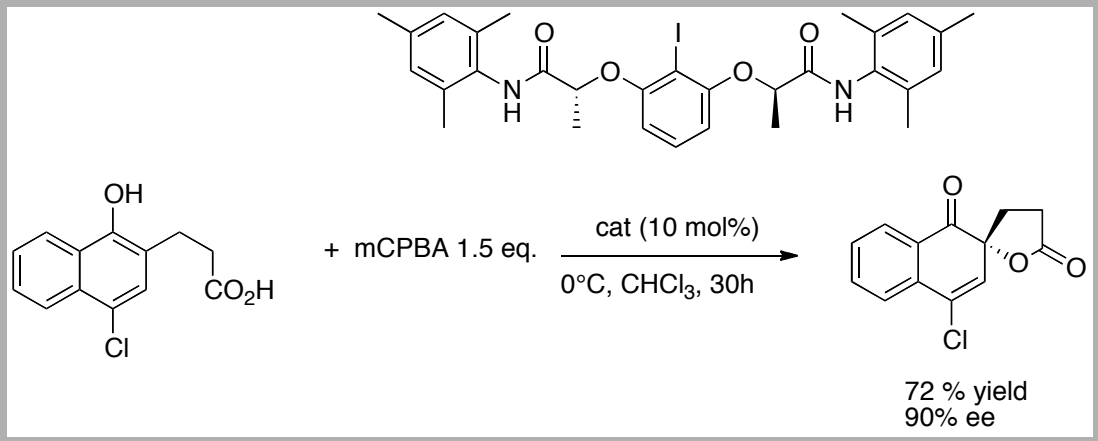
T. Dohi, Y. Minamitsuji, A. Maruyama, S. Hirose and Y. Kita, *Org. Lett.*, **2008**, 10, 3559-3562

Catalytic oxydation of phenol



T. Dohi, Y. Minamitsuji, A. Maruyama, S. Hirose and Y. Kita, *Org. Lett.*, **2008**, 10, 3559-3562

Kita spirolactonisation

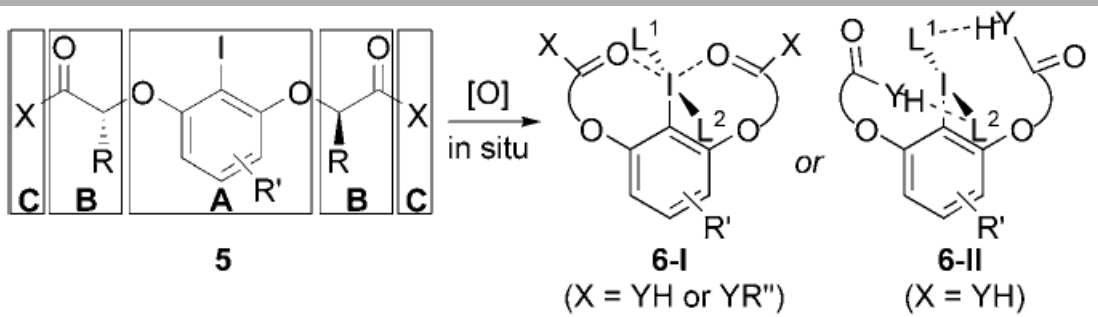


In situ formation of hypervalent iodine

Best ee obtained over all

M. Uyanik, T. Yasui, and K. Ishihara, *Angew. Chem. Int. Ed.* **2010**, 49, 2175-2177

Kita spirolactonisation



Scheme 2. Design of conformationally flexible iodoarene **5** (precatalyst) and iodosylarene **6** (catalyst).

- C_2 symmetrical catalyst flexible

- A : Iodoaryl moiety
- B : Chiral linker
- C : group allowing secondary interaction (H-Bridge , n- σ*)

M. Uyanik, T. Yasui, and K. Ishihara, *Angew. Chem. Int. Ed.* **2010**, 49, 2175-2177

Conclusion

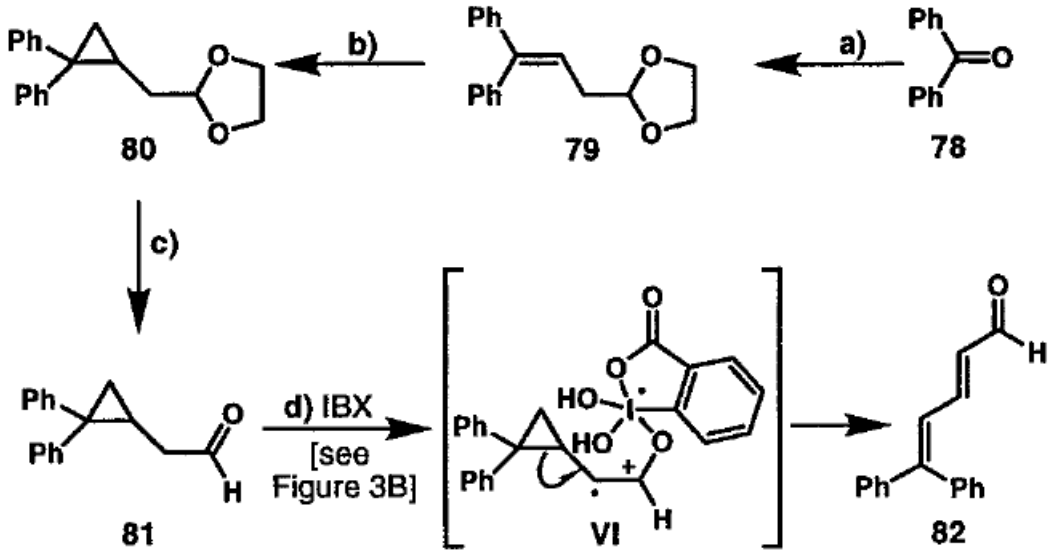
- Only a short overview on hypervalent Iodine:
  - Aziridination
  - Metal catalyzed reactions
- Research focusing on:
  - Green Chemistry
  - Enantioselective reactions
  - Catalytic reactions
  - IBX analogs
- Mild and selective reagent usefull for sensitive substrates in total synthesis

"... A motto in our research group became *when in doubt, think hypervalent iodine*."

Robert M. Moriarty

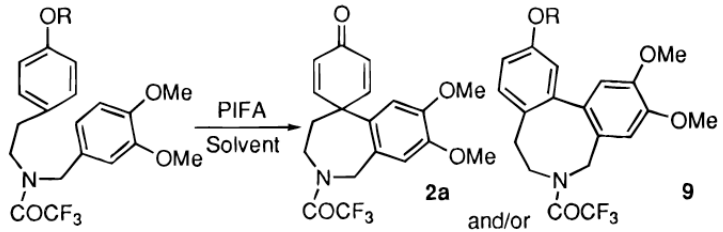
IBX proof of radical

Scheme 5. Reaction of Cyclopropyl Aldehyde **81** with IBX Leads to the Ring-Opened Dienal **82**, Thus Supporting the Intermediacy of Radical Species (i.e., **VI**)[a]



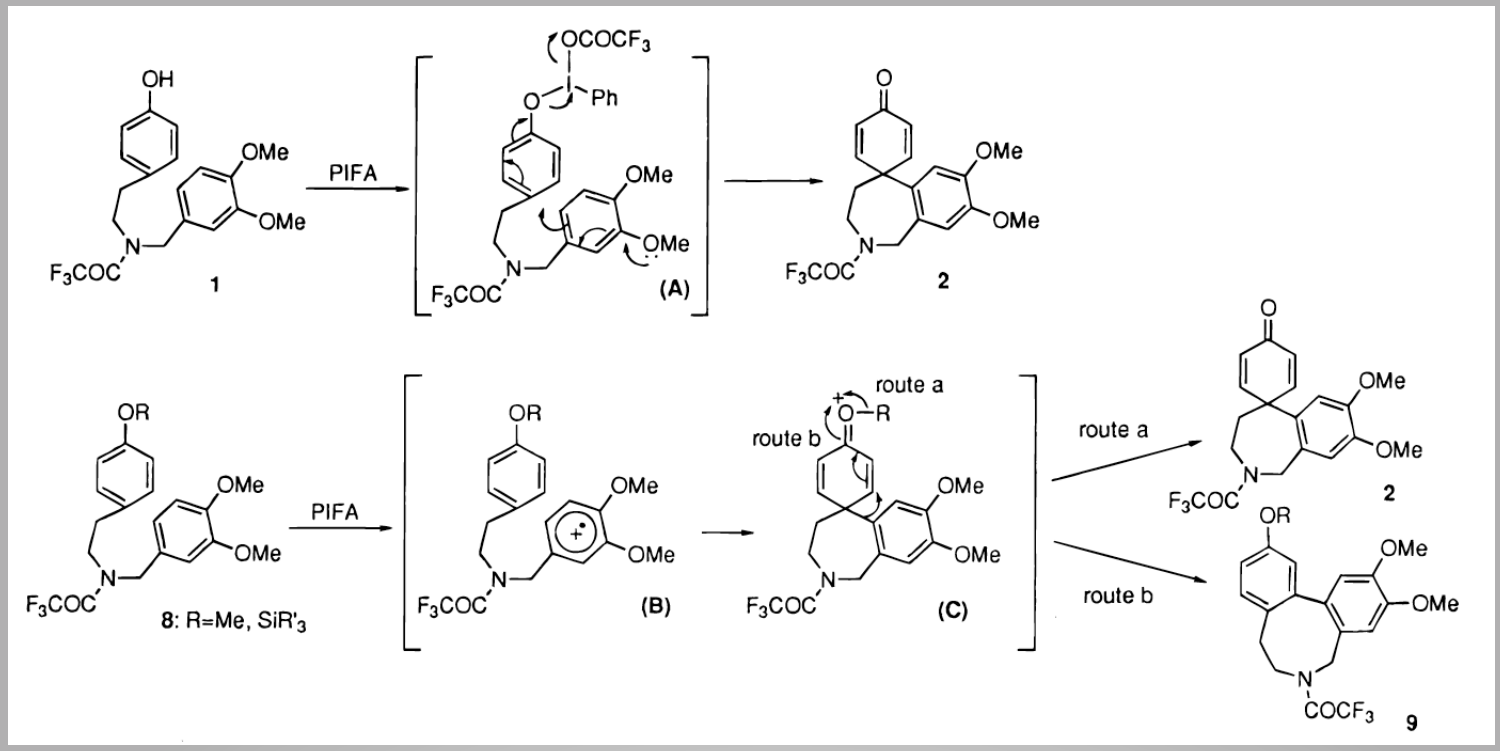
[a] Reagents and conditions: (a) [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide[43] (2.0 equiv), *t*-BuOH (2.0 equiv), THF, 25 °C, 72 h, 43%; (b) Zn−Ag couple,[44] CH_2I_2 (1.3 equiv), Et_2O, reflux, 22 h, 78%; (c) AcOH:H_2O 1:1, 25 °C, 12 h, 81%; (d) IBX (2.0 equiv), DMSO, 70 °C, 7 h, 98%.

J. AM. CHEM. SOC. ■ VOL. 124, NO. 10, 2002



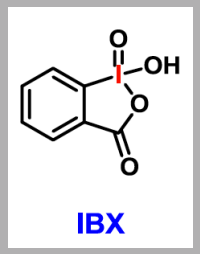
entry	substrate	R	solvent	reaction time	**2a** (%)	**9** (%)
1	**1a**	H	CF_3CH_2OH	5 min	61	
2	**8a**	TMS		30 min	57	
3	**8b**	TBDMS		4.5 h	66	
4	**8c**	TBDPS		4 h	23	12
5	**8d**	$PhCH_2$		24 h		48
6	**8e**	Me		30 min		47
7	**8e**		$(CF_3)_2CHOH$	1 h		42
8	**8e**		CH_3CN	3.5 h	33	23
9	**8e**		CH_2Cl_2	24 h	22	

J. Org. Chem. **1996,** *61,* 5857−5864

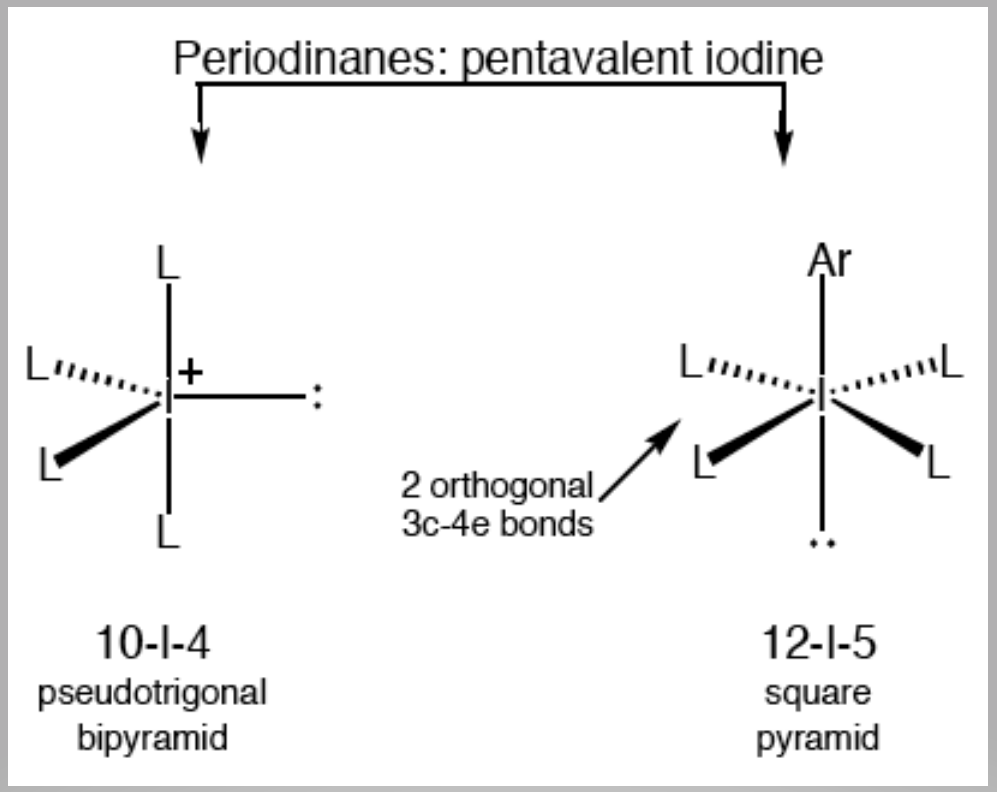


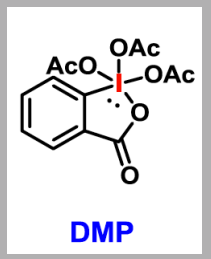
J. Org. Chem. **1996,** *61,* 5857−5864

Nomenclature: Hypervalent Bond



IBX





DMP