Frontiers of Chemistry

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Recent Progresses in Organic Hypervalent Iodine Chemistry

Contents.

1. Hypervalent Iodine Chemistry in Organic Synthesis

1) Introduction

- Why Hypervalent Iodine?

a. Benign Environmental Character
b. Very Useful Oxidizing Properties
c. Similar Chemistry as Transition Metal
(Ligand Exchange, Reductive Elimination etc.)

- What is Hypervalent Iodine?

a. Hypervalent Molecule: Molecules containing elements of group 15-18 bearing more electrons than the octet in the valence cell
b. Iodine: Largest, most polarizable and least electronegative halogen element (polycoordinate, multivalent compounds)
c. Hypervalent Iodine Compouds: Iodine compounds bearing more electrons than the octet in the valence cell
d. Linear 3-center-4-electron (3c-4e) bonds: Hypervalent Bonds

Ref) T. Wirth *et al.* Top. Curr. Chem. 2003 224 1-248 pp.

- Who are Frontiers in This Field?

P. J.Stang: University of Utah
- *Physical Properties and Structure of Hypervalent Iodine etc.*

V. V. Zhadakin: University of Minnesota-Duluth
- *C-C Bond Formation etc.*

A. Varvoglis: Thessaloniki University, Greece
- *Preparation and Practical Aspects of Hypervalent Iodine etc.*

T. Wirth: Cardiff University, UK
- *Chiral Hypervalent Iodine etc.*

M. Ochiai: University of Tokushima, Japan
- *Reactivities of Hypervalent Iodine etc.*

G. F. Koser: University of Akron
- *Heteroatom Bond Formation etc.*

Y. Kita: Osaka University, Japan
- *Application to Natural Product Synthesis etc.*

H. Togo: Chiba University, Japan
- *New Types of Hypervalent Iodine Reagents etc.*

T. Okuyama: Himeji Institute of Technology
- *Alkenyl Iodonium Salts etc.*

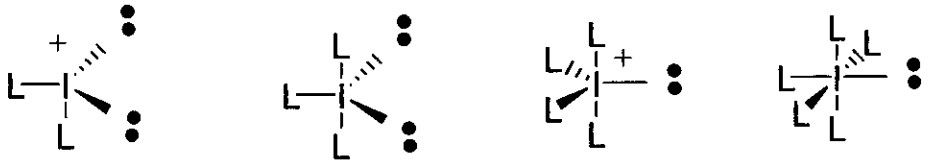
K. C. Nicolau: Scripps Research Institute
- *New Application of Pentavalent Iodines (DMP, IBX)*

P. Wipf: University of Pittsburgh
- *Oxidative Cyclization of Phenol Aanlogs etc.*

Et al.

- Classification of Hypervalent Iodine

a. Martin-Arduengo N-X-L designation
(N-Number of Electrons in Valence Cell, X-Central Atom, L-Number of Ligands)
- 4-types of polyvalent iodine are important



8-I-2 | 10-I-3 | 10-I-4 | 12-I-5

2 | 3 | 4 | 5

- Numbers of Carbon Ligands are important

- Trivalent Iodine: One Carbon Ligand in 2 or 3
- Trivalent Iodine: Two Carbon Ligand in 2 or 3
- Trivalent Iodine: Three Carbon Ligand in 3
- Pentavalent Iodone: 4 or 5

b. IUPAC Name
Iodane: hydrogen iodide
λ: compounds with nonstandard bonding number
Ex) The Most Commom $ArIL_2$ (L: Heteroatom Ligands) $(PhI(OAc)_2$ etc.)
: Aryl-λ^3-iodanes (3 means trivalent)

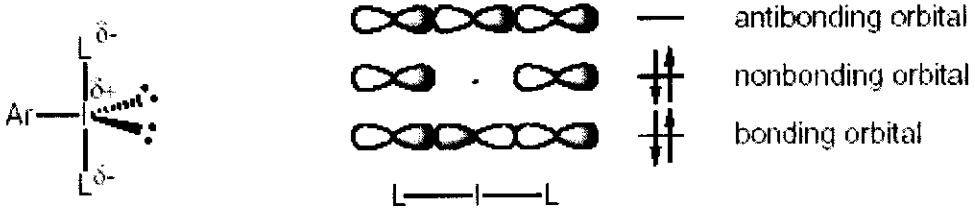
ref) P. J. Stang *et al* Chem Rev. 1996, 96, 1123-

- The Commonest Reagents of Hypervalent Iodine

N-X-L	Name	Formula	Abbreviation	
10-I-3	(Dichloroiodo)benzene	$PhICl_2$		First Discovered
10-I-3	(Diacetoxyiodo)benzene or Iodobenzene diacetate	$PhI(OAc)_2$	DIB or PIDA	
10-I-3	[bis(trifluoroacetoxy)iodo]benzene	$PhI(OCOCF_3)_2$	BTI or PIFA	
10-I-3	[Hydroxy(tosyloxy)iodo]benzene	PhI(OH)(OTs)	HTI	Koser's reagent
10-I-2	Iodosylbenzene	PhIO PhI=O		
12-I-3	Iodoylbenzene	$PhIO_2$		
8-I-2	Diaryiodonium Salts	$PhArI^+X^-$		
8-I-2	Alkenylphenyliodonium Salts	$PhI^+CH{=}CHRX^-$		
8-I-2	Alkynylphenyliodonium Salts	$PhI^+C{\equiv}CRX^-$		
12-I-5	o-Iodoxybenzoic Acid		IBX	
12-I-5	Dess Martin Periodinane		DMP	

- Representative Structures of Hypervalent Iodine

a. Aryl-λ^3-Iodanes ($PhI(OAc)_2$ etc.)

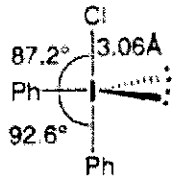


Pseudotrigonal bipyramid structure and molecular orbital of the 3c – 4e bond

b. Aryl-λ^5-Iodanes (DMP etc)

square pyramid structure

c. Diaryl-λ^3-Iodanes (Ph_2ICl) : Diphenyliodonium chloride



1 10-I-3
chloro(diphenyl)-λ^3-iodane

2 8-I-2
diphenyliodonium chloride

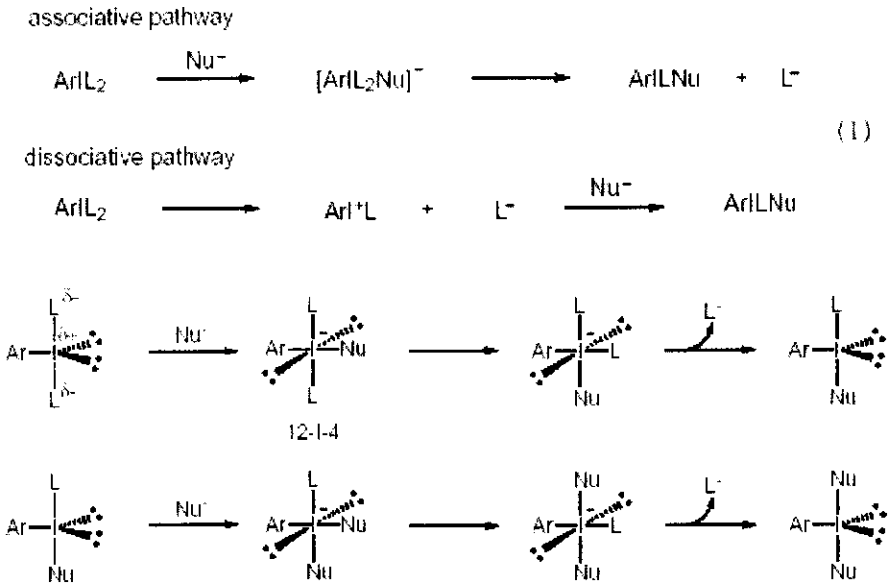
ref) M. Ochiai, Top. Curr. Chem. 2003 224 6-

2) Reactivity Patterns

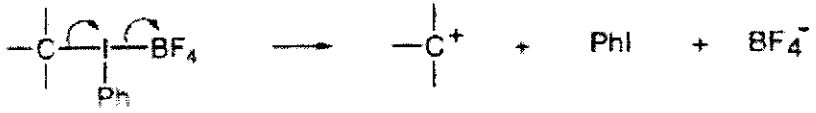
Ref) M. Ochiai, Top. Curr. Chem. 2003 224 6-

- General Aspects

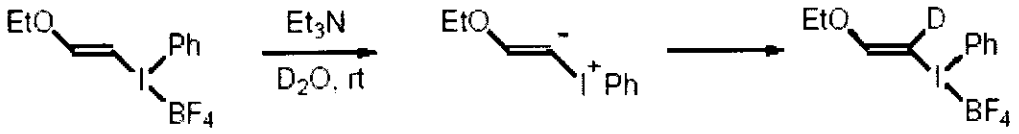
a. Ligand Exchange



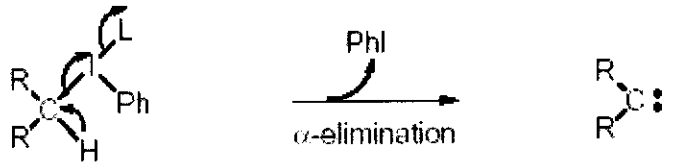
b. Hypernucleofuge: Reductive Elimination



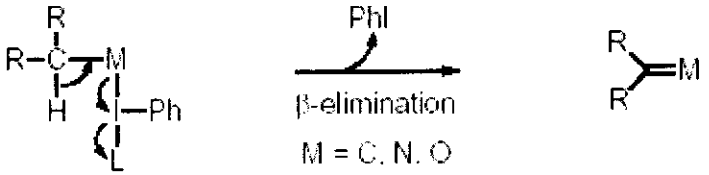
c. Electronic Nature: Strong Electron Withdrawing Effect



d. Reductive α-Elimination

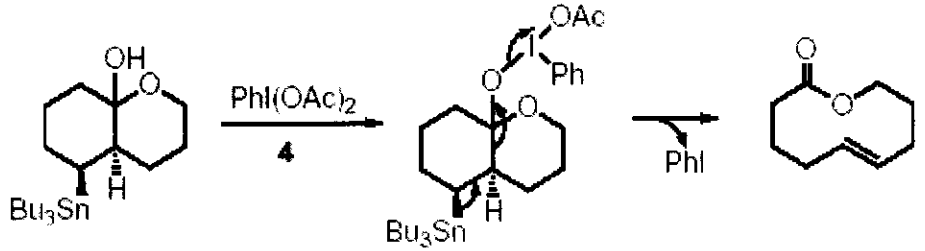


e. Reductive β-elimination

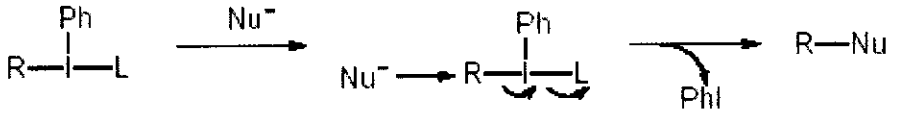


- Major Reactive Pathway for Oxidation

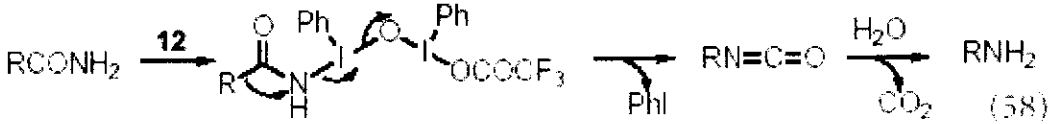
f. Reductive Elimination with Fragmentation



g. Reductive Elimination with Substitution

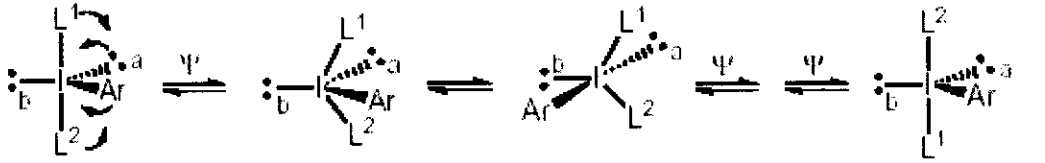


h. Reductive Elimination with Rearrangement



(58)

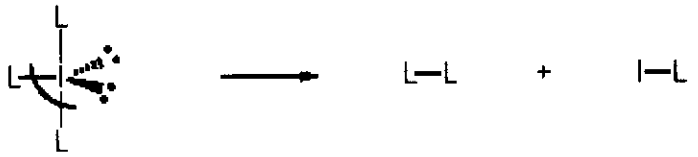
i. Pseudorotation



72TBP SP TBP **72'**TBP

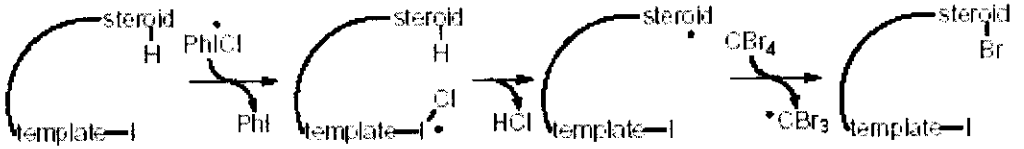
(64)

j. Ligand Coupling on Iodine(III)

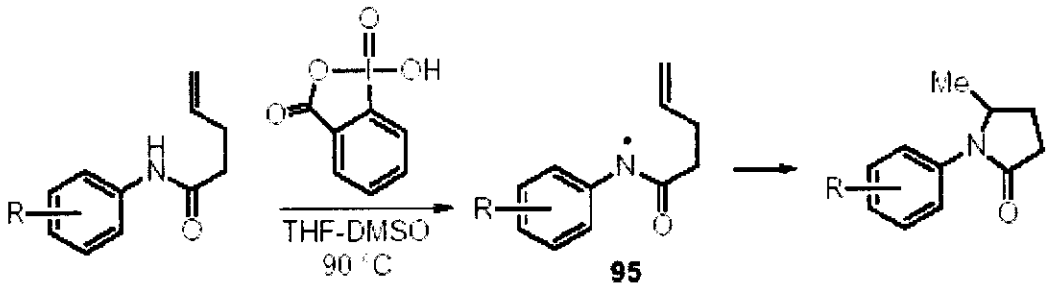


L: carbon and heteroatom ligands

k. Homolytic Cleavage



l. Single-Electron Transfer

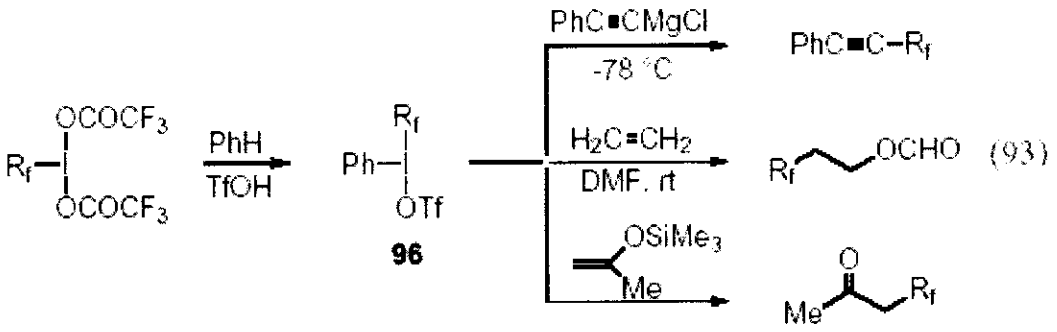


R = *o*-OMe, *o*-F, *m*-Et, *m*-Br, *p*-Et (88)

- Two Carbon Ligand Trivalent Iodine Compounds

a. Alkyl(aryl)-λ^3-Iodanes

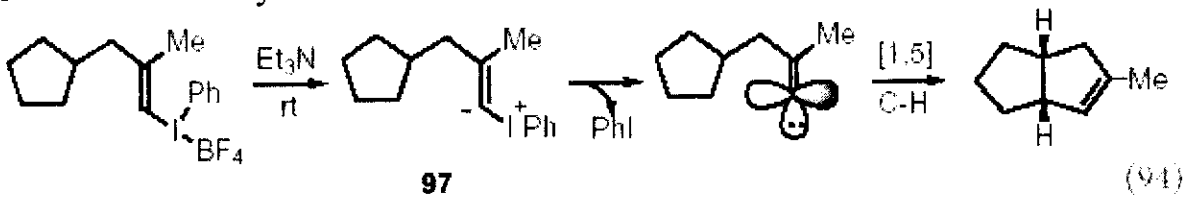
- Because of hypernucleofugality these compounds are generally labile



(93)

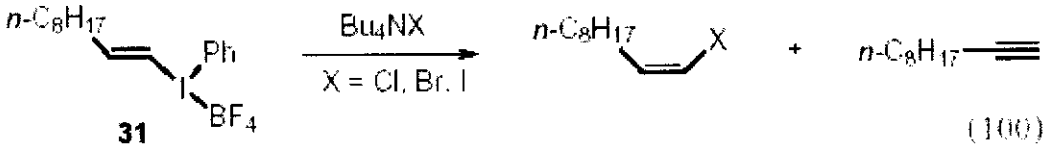
b. Alkenyl(aryl)-λ^3-Iodanes (Alkenyl phenyl iodonium salts)

- Generation of Alkylidene Carbenes



(94)

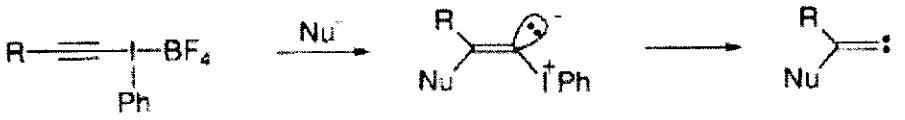
- Nucleophilic Vinylic Substitution



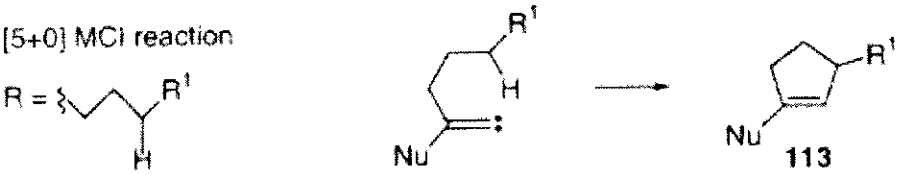
(100)

c. Alkynyl(aryl)-λ^3-Iodanes (Alkynyl phenyl iodonium salts)

- Michael-Carbene Insertion Reaction

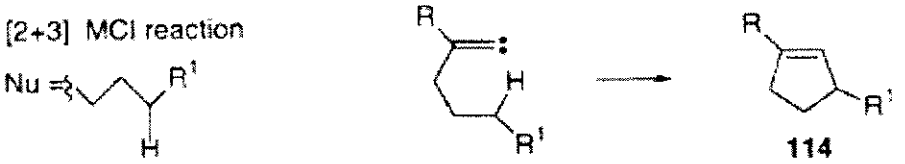


[5+0] MCI reaction

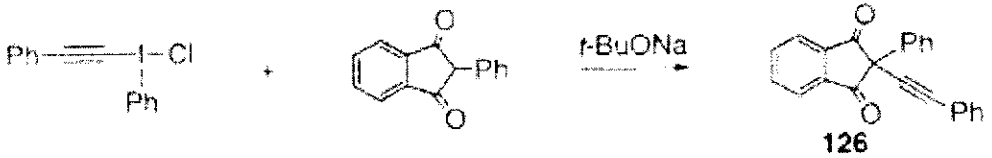


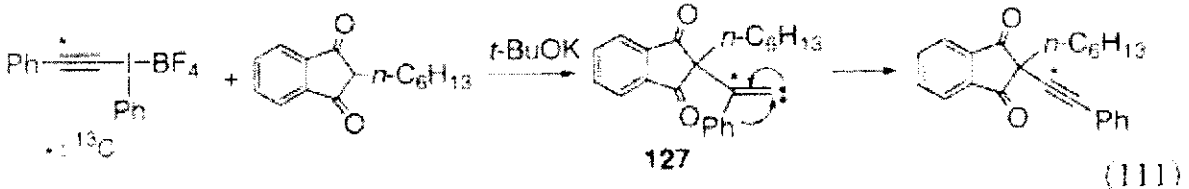
(104)

[2+3] MCI reaction



- Michael-Carbene Rearrangement Reaction



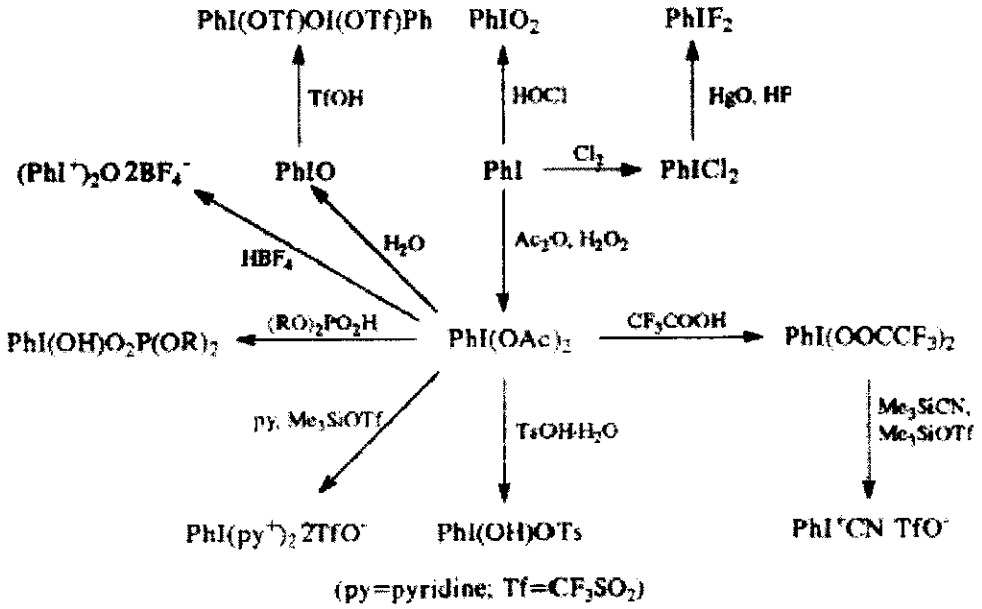


(111)

3) Preparations

- Trivalent Iodine Compounds

Preparative Methods for Hypervalent Iodine Reagents Derived from Iodobenzene



Ref) A. Varvoglis *et al* Tet. 1997, 53, 1179-

- Two Carbon Ligand Trivalent Iodine Compounds

Preparative Approaches for Some Important Classes of 8-I-2 Phenyliodonium Reagents

Ar_2I^+ : from ArH + ArI + oxidant; or $PhIL_2$ + ArH

PhI^+R_f : from C_6H_6 + R_fIL_2

$PhI^+CH{=}CHR$: from silyl or stannyl alkenes + $PhIL_2$

$PhI^+C{\equiv}CR$: from silyl or stannyl alkynes + $PhIL_2$

PhI^+C^-XY : from CH_2XY and $PhIL_2$

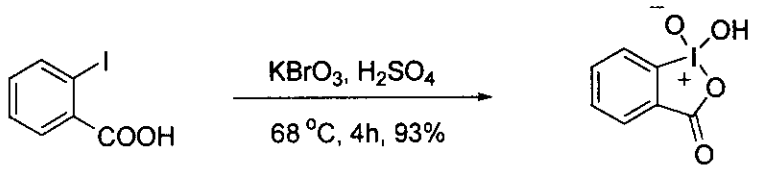
$PhI^+N^-SO_2R$: from NH_2SO_2R and $PhIL_2$

(for other dipoles, see text)

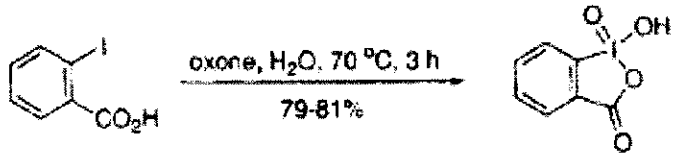
Ref) A. Varvoglis *et al* Tet. 1997, 53, 1179-

- Pentavalent Iodine Compounds

a. Preparation of IBX

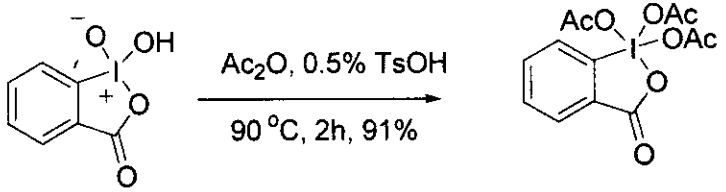


ref) I.R. Ireland *et al* JOC 1993, 58, 2889-



ref) M. Frigerio *et al* JOC 1999, 64, 4537-

b. Preparation of Dess-Martin Reagents



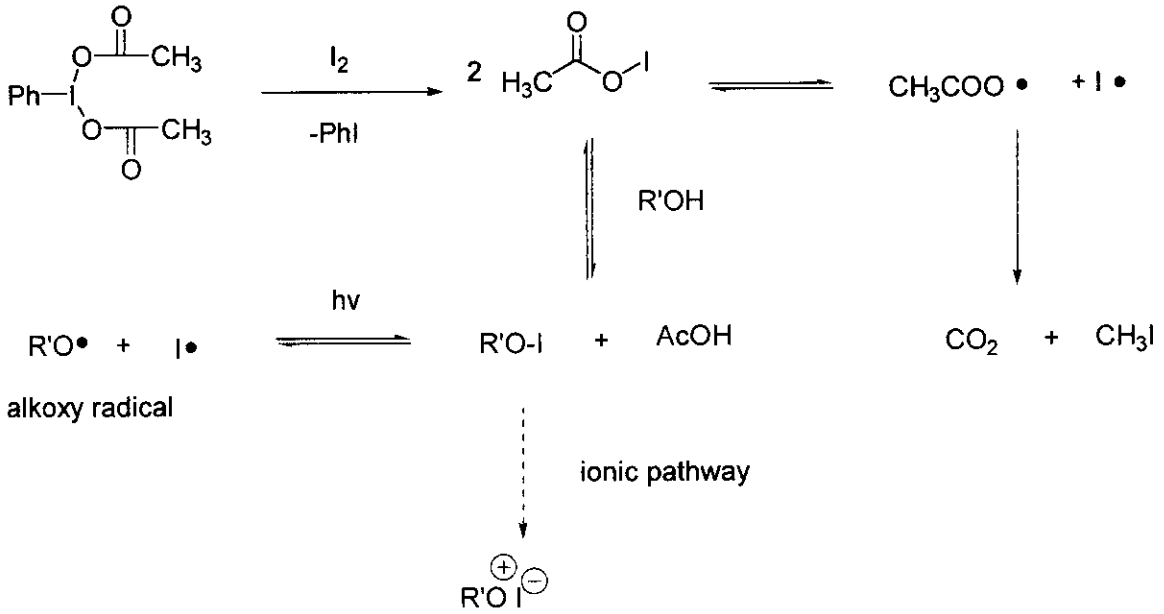
ref) I.R. Ireland *et al* JOC 1993, 58, 2889-

2. Recent Progresses

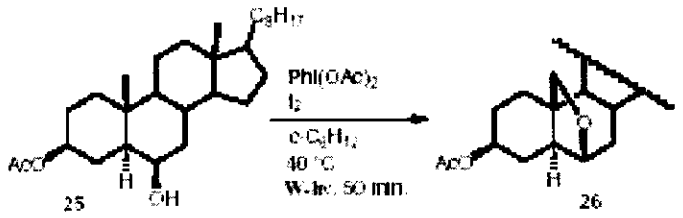
1) One-Carbon Ligand Trivalent Iodines
- Generation of Radicals

Review) H. Togo *et al.* Synlett 2001, 565-
J. Hartung *et al.* Eur. J. Org. 2001, 619-

a. Alkoxy Radical by Suarez's Condition ($PhI(OAc)_2$, I_2)

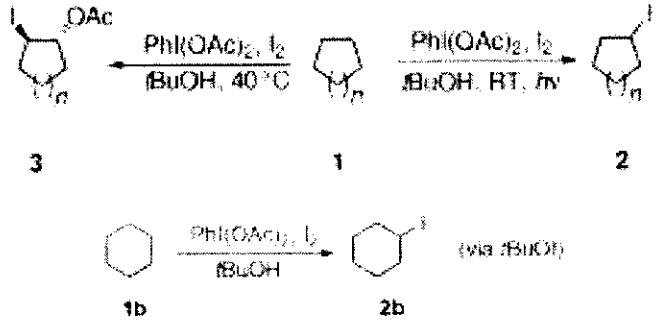


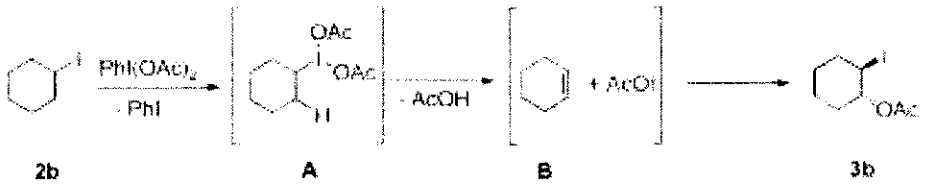
b. Suarez's Work



ref) E. Suarez *et al.* TL, 1984, 25, 1953

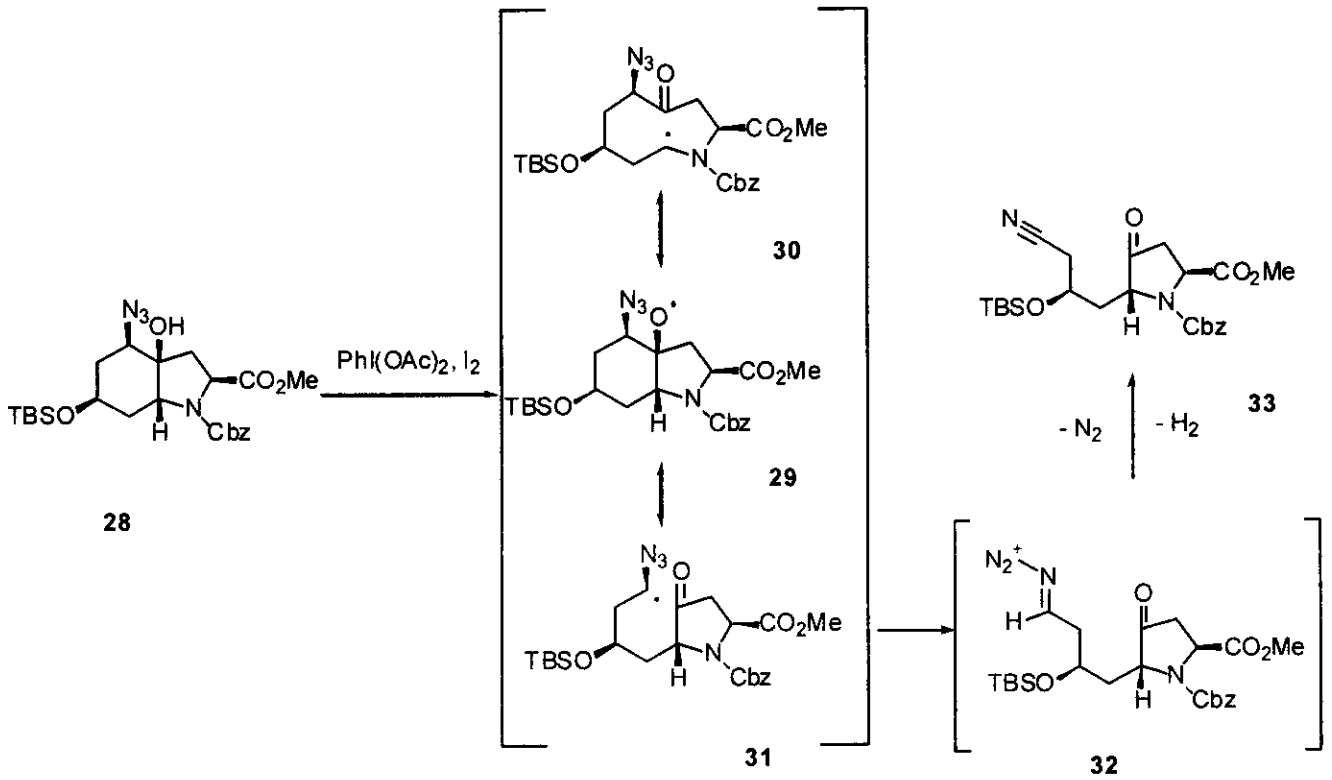
c. Barluega's Work





ref) J. Barluenga *et al.* ACIEE 2002, 41. 14. 2556-

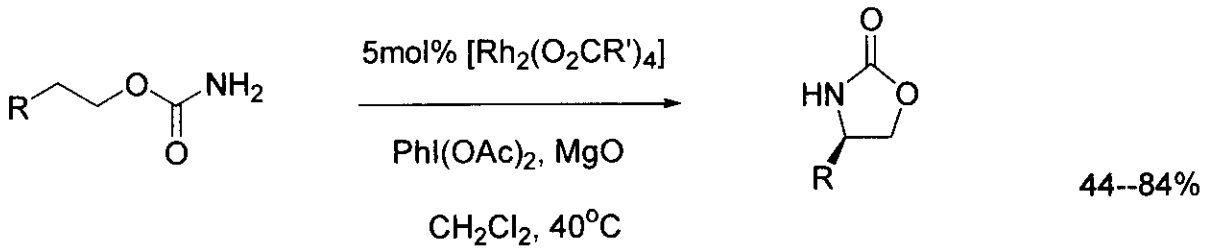
d. Our Group's Work



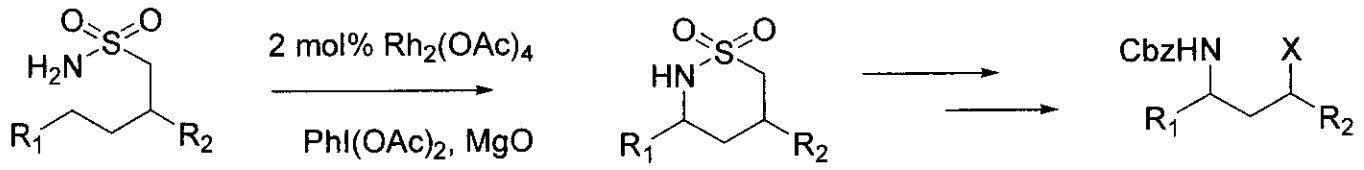
Wipf, P.; Mareska, D. A. *Terahedron Lett.* **2000**, *41*, 4723.

- Generation of Carbene or Nitrene Species

a. Du Bois's Work (Nitrene Species Generation)

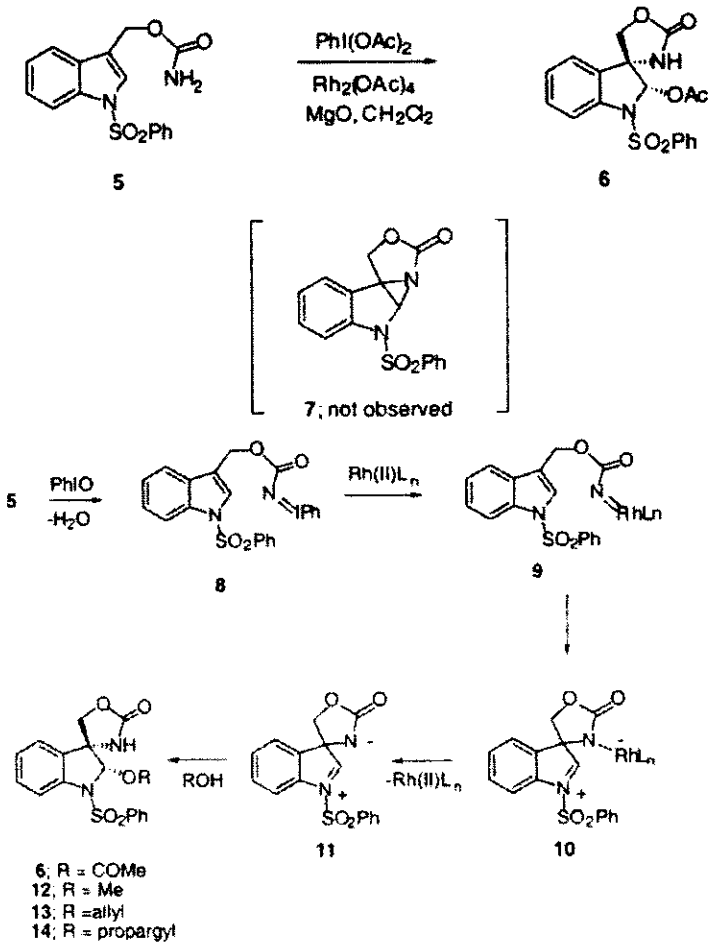


J. Du Bois *et al* ACIEE 2001, 40. 598-



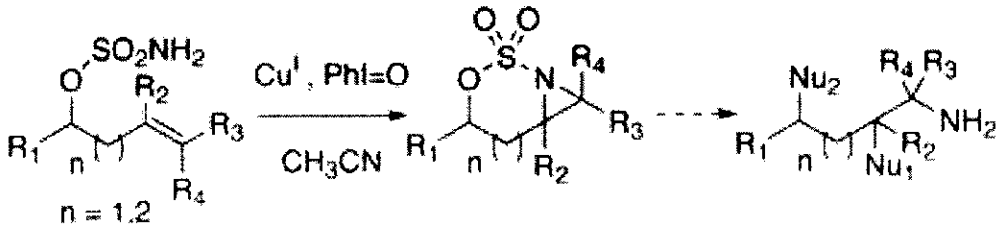
J. Du Bois *et al* JACS 2001, 40. 598-

b. Padwa's Work



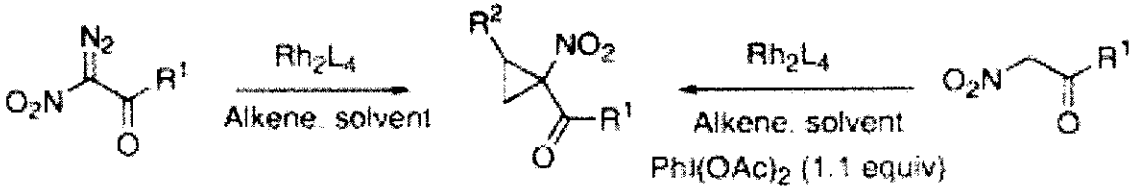
Ref) A. Padwa *et al.* Org. Lett. 2002, 4, 13, 2137

c. Dauban's Work



ref) P. Dauban *et al* Org. Lett. 2002, 4, 15, 2481-

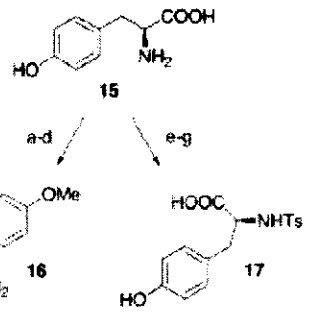
d. Charette's Work (Carbene Species Generation)



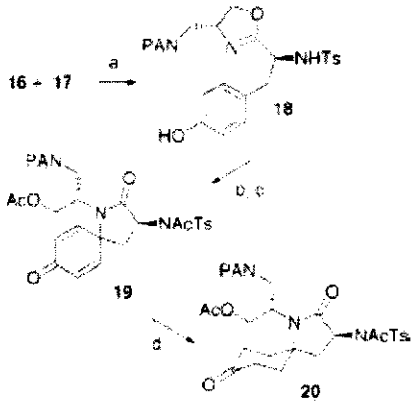
ref) A. B. Charette *et al.* Org. Lett. 2003, 5, 13, 2327-

- Oxidative Cyclization of Phenols

a. Ciufolini's FR901483 Synthesis



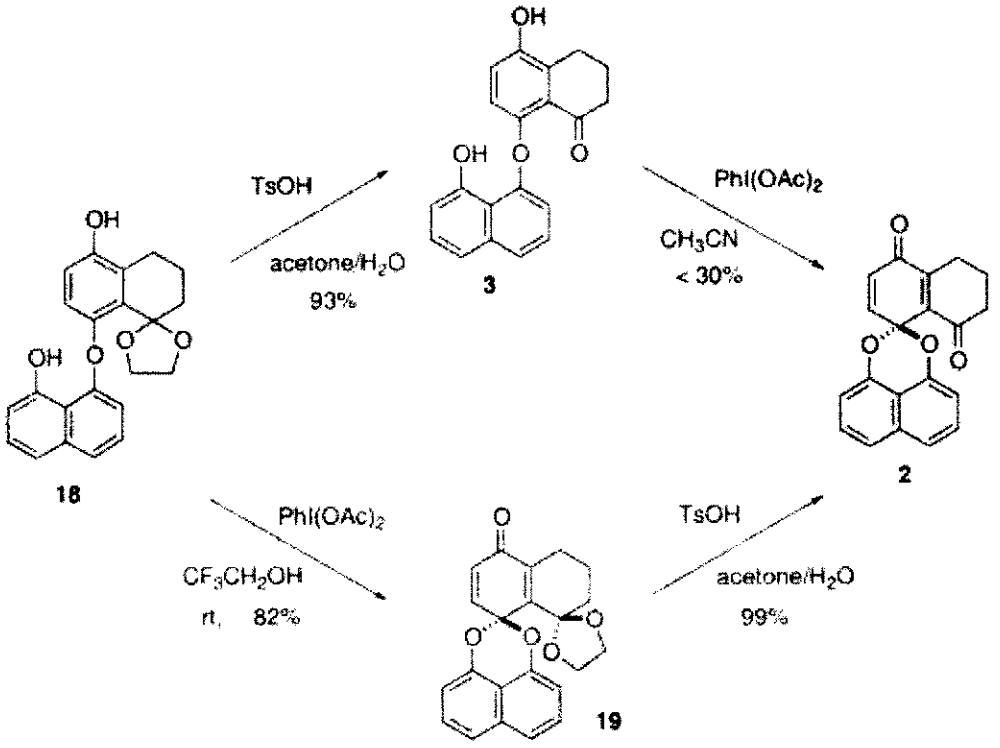
[a] Reagents: (a) MeOOCCl, $NaHCO_3$, H_2O/THF (1:1), 99%; (b) Me_2SO_4, K_2CO_3, acetone, 99%; (c) LAH, THF, 85%; (d) aqueous KOH, 86%; (e) EtOH, HCl_{gas}, 100%; (f) TsCl, aqueous Na_2CO_3, $CHCl_3$, 98%; (g) aqueous NaOH, 98%.



[a] Reagents: (a) CCl_4, PPh_3, NEt_3, MeCN, pyridine (1:1:1), 73%; (b) PhIO(OAc)$_2$, CF_3CH_2OH, then solid $NaHCO_3$; (c) Ac_2O, pyridine, 41% (for b + c); (d) H_2, PtO_2, EtOAc, 96%. PAN = *p*-anisyl

ref) M. A. Ciufolini *et al.* JACS 2001, 123, 7534-7538

b. Wipf's Diepoxin-σ Synthesis

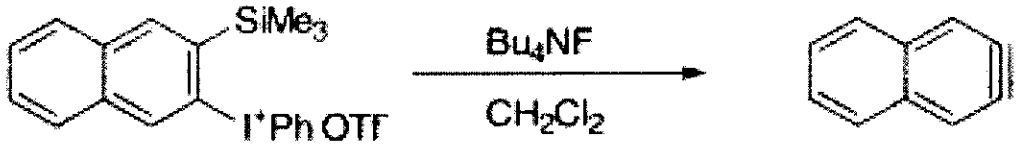


Ref) P. Wipf et al JOC 2000, 6319-

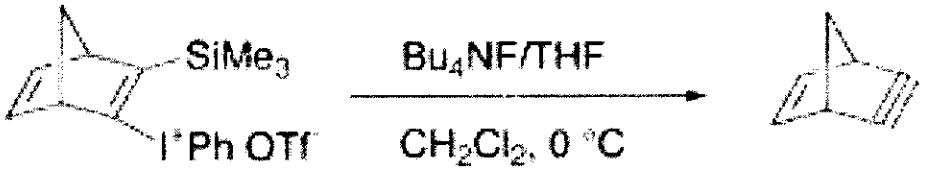
2) Two-Carbon Ligands Trivalent Iodines (Iodonium Salts)

Rev.) P. J. Stang *et al.* J. Org. Chem. 2003. 68. 2997-

- Kitamura's Work (Benzyne or Alkyne Generation)



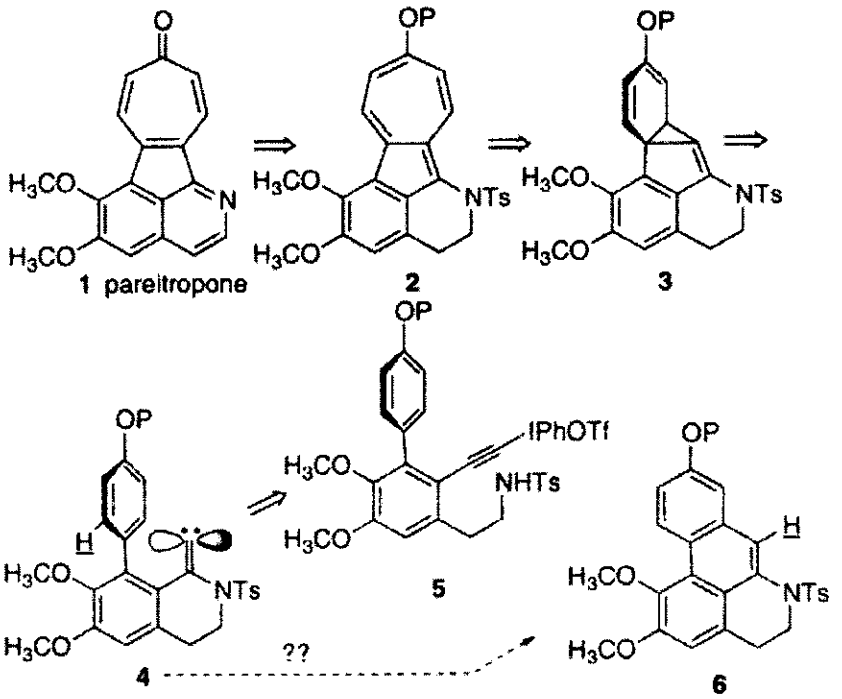
T. Kitamura *et al.* JOC 1998, 63, 8579-8581



T. Kitamura *et al* JOC 1999, 64, 680-

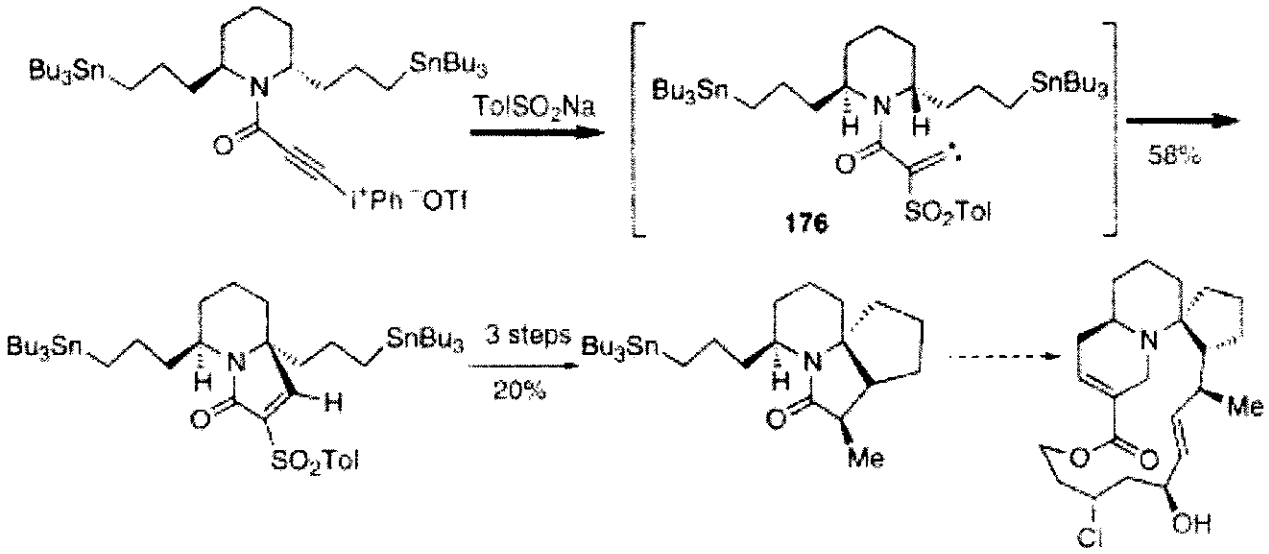
- Feldman's Work

a. Paretrione Synthesis



K. S. Feldman *et al.* JACS 2002 124 11601-

b. Halichorin Synthesis

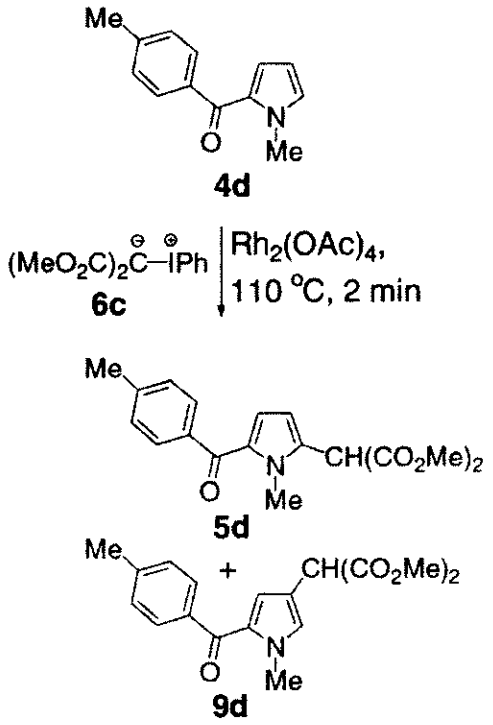


Scheme 43

Halichlorine (89)

Ref) Feldman et al, (2001)
FIU (Forum on Iodine Utilization) Report:
the 4th Symposium on Iodine Utilization: 5

- Alkenyl C-H Insertion of Iodonium Ylides

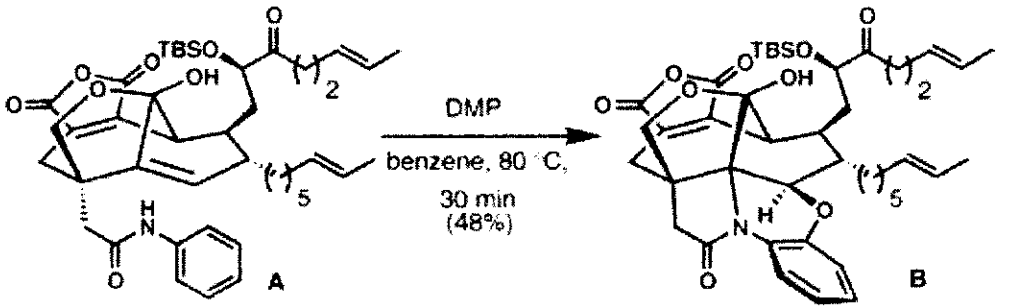


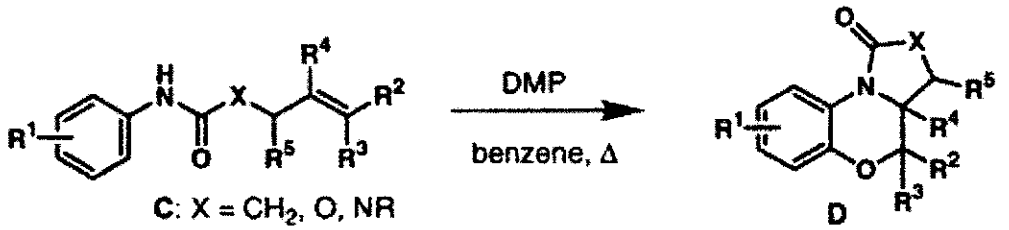
Ref) L. P. Hadjiarapoglou et al Org. Lett. 2003 Vol.5 1511-

3) Pentavalent Iodines

- Nicolau's Extensive Works

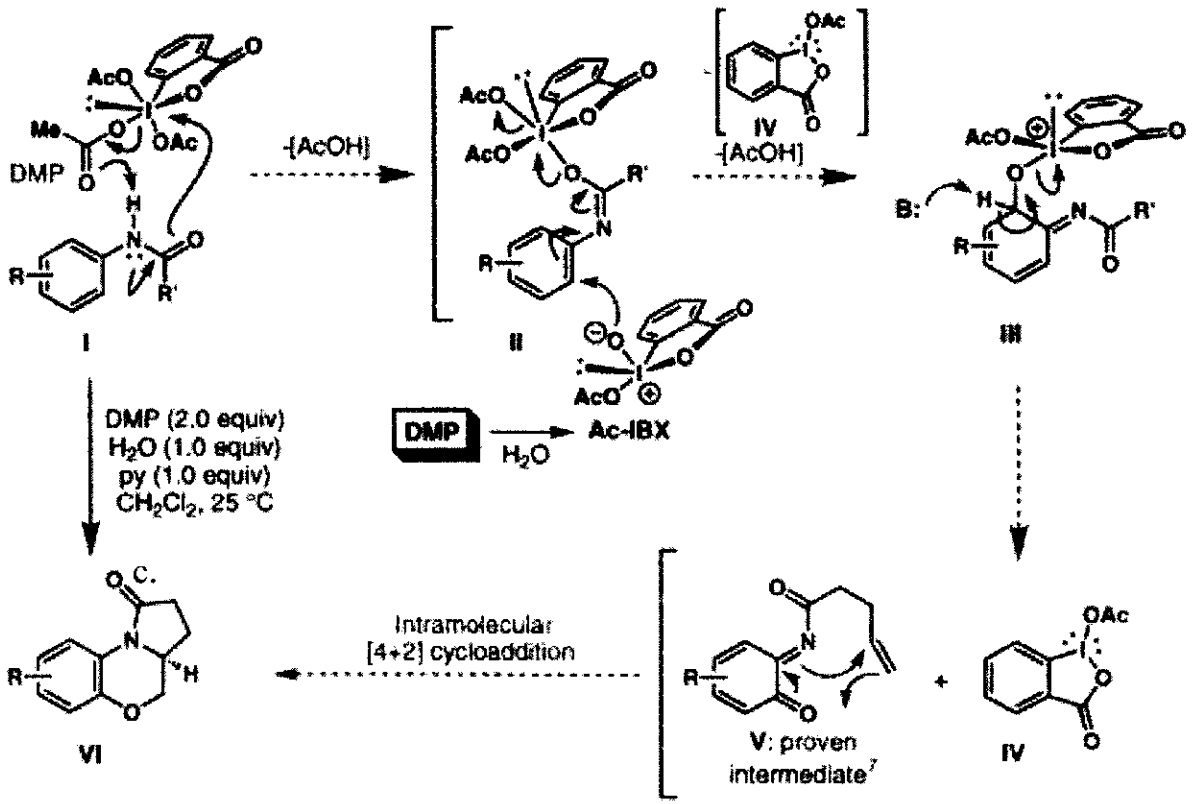
a. Serendipitous Discovery





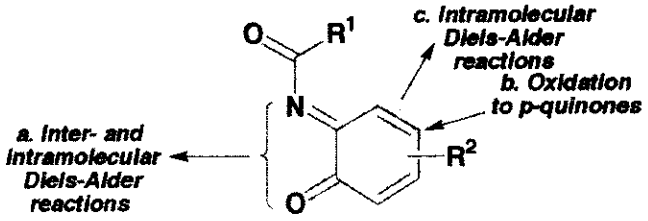
Ref) K. C. Nicolau *et al.* ACIEE 2000, 39, 622

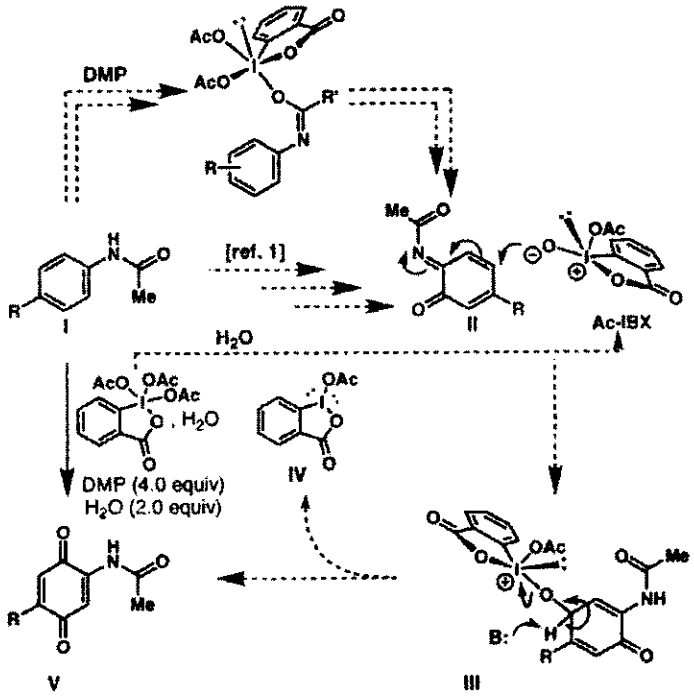
b. Proposed Mechanism



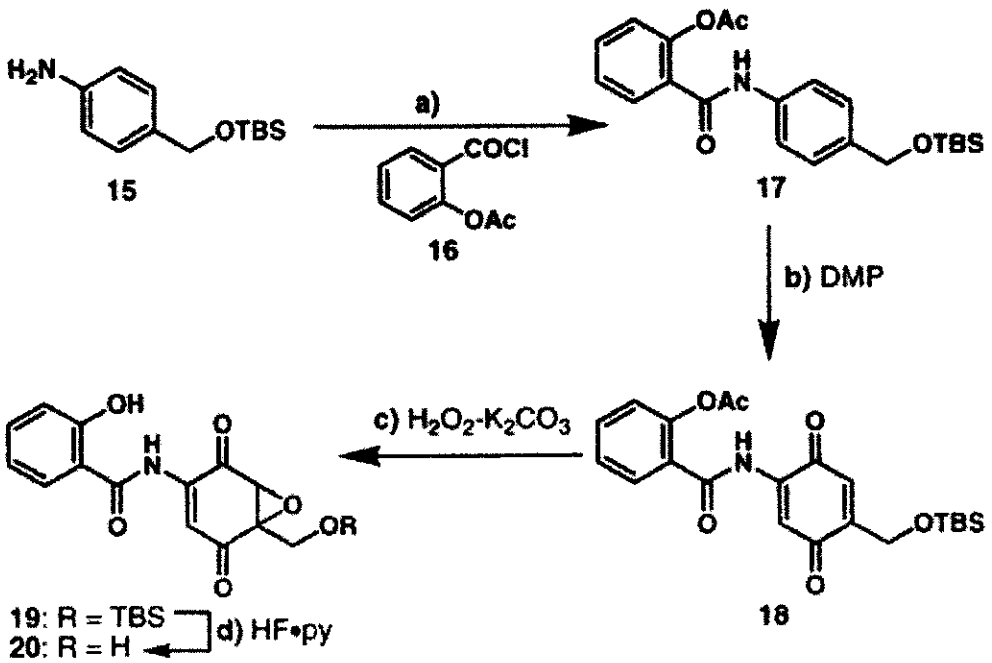
Ref) K. C. Nicolau *et al.* JACS 2002, 2213-

d. o-Azidoquinones and p-Quinones as Versatile Chemical Intermediates



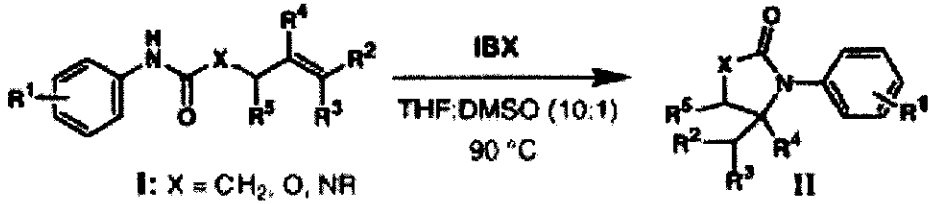


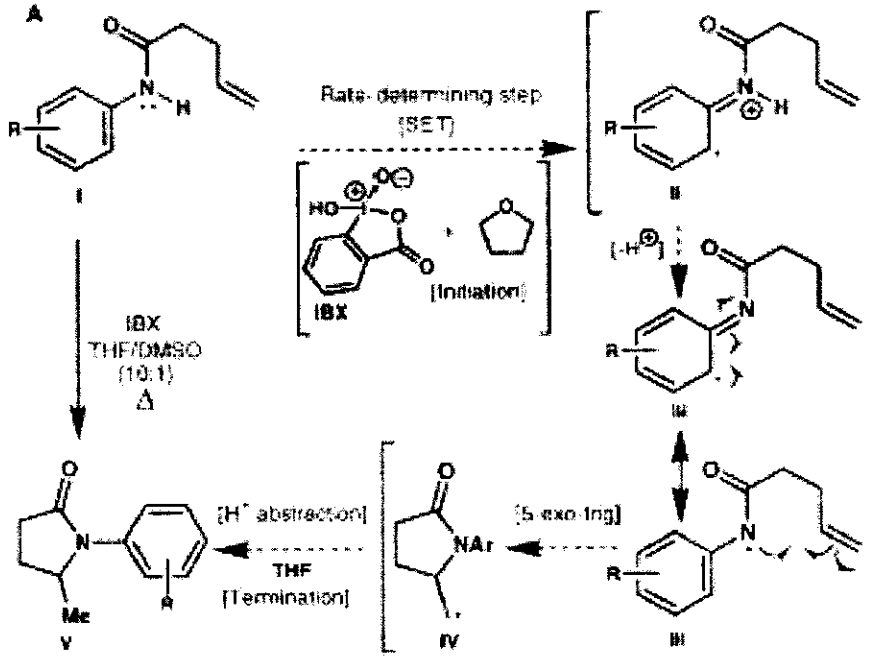
■ Total Synthesis of Epoxyquinomycin B



Ref) K. C. Nicolau *et al* JACS 2002, 124, No. 10 2221-

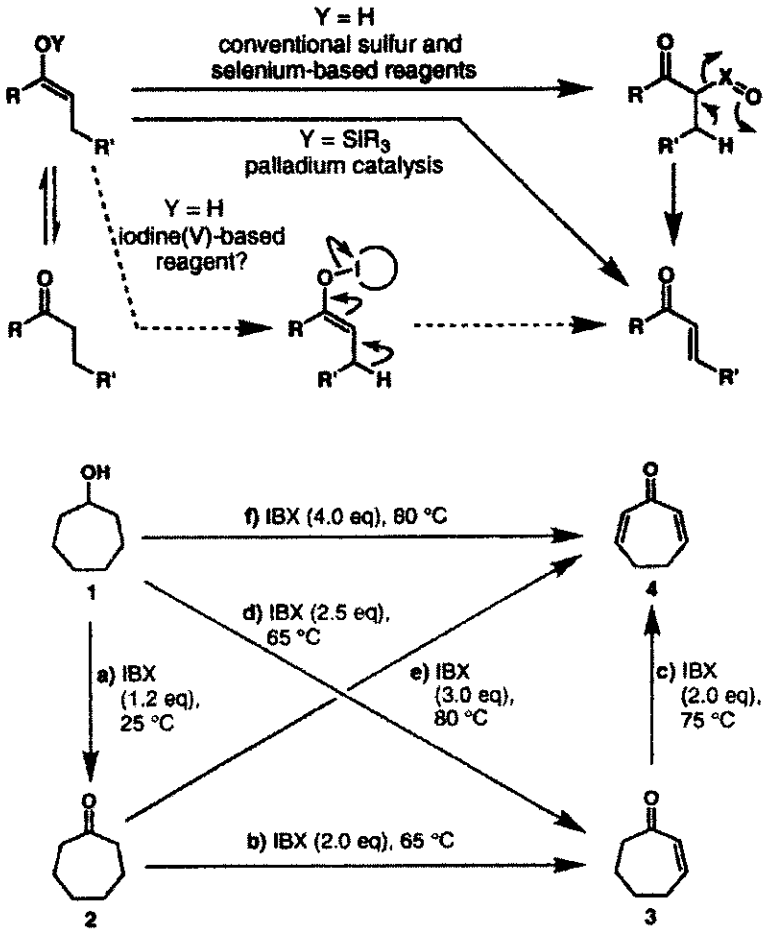
e. IBX Mediated Cyclizations



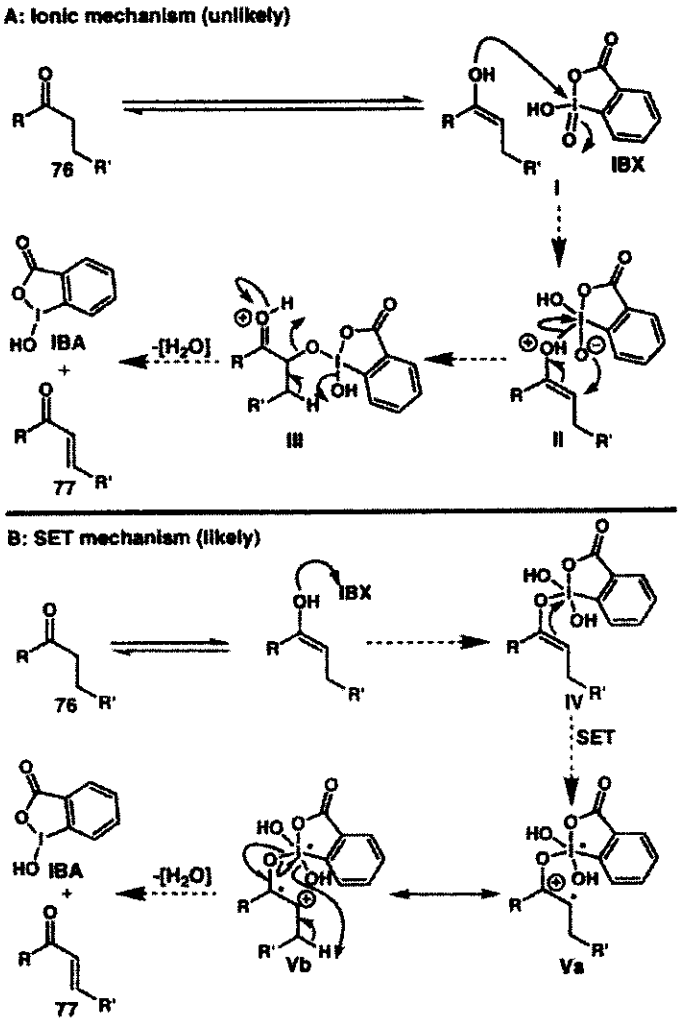


Ref) K. C. Nicolau *et al* JACS 2002, 124, No. 10 2233-

f. IBX as a Chemospecific Tool for S.E.T. Based Oxidation



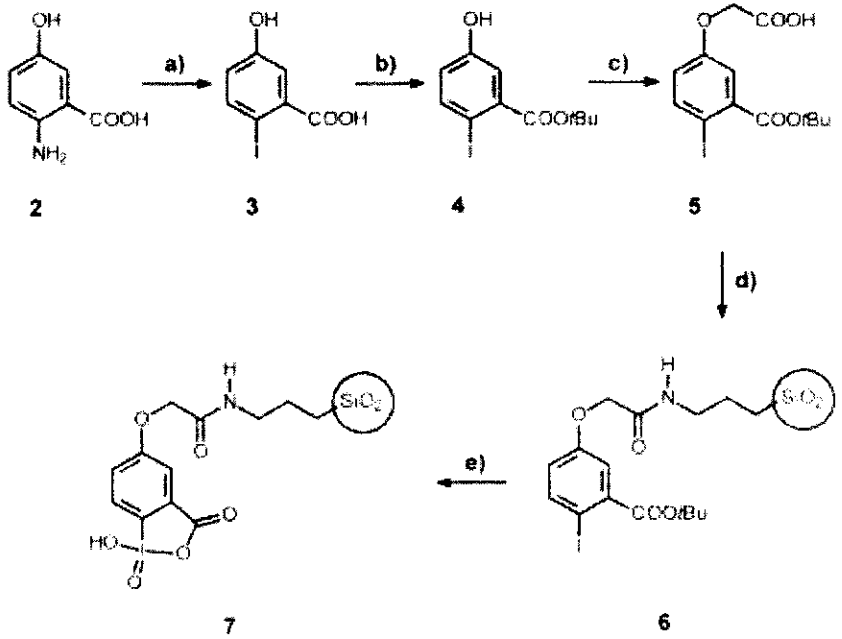
Ref) K. C. Nicolau *et al* JACS 2002, 124, No. 10 2245-


A: Ionic mechanism (unlikely)
76
IBX
I
II
III
IBA
-[H2O]
77
B: SET mechanism (likely)
IBX
IV
SET
Vb
Va
IBA
-[H2O]
77

- Various Analogs of IBX

a. Polymer-Supported IBX

- Easy Recovery of IBX



a) $NaNO_2$, H_2SO_4, KI, 90 %; b) *N,N*-dimethylformamide di-*tert*-butyl acetal 50 %; c) NaH, $BrCH_2COOEt$, then NaOH; 84 %; d) aminopropylsilica gel, DIC, HOBt, 92 %; e) trifluoroacetic acid (10 %), then oxone; DIC=diisopropylcarbodiimide, HOBt=1-hydroxy-1*H*-benzotriazole.

Ref) A. Giannis *et al.* ACIEE 2001, 40. No.23 4393-

b. IBX-Amides

- Increase the Solubility and Stability

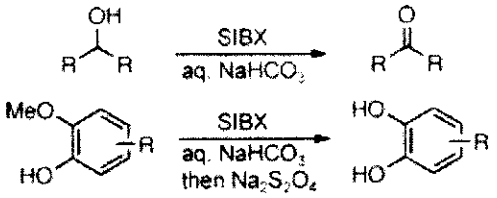
3a-g **4a-g** (45-73%)

a: R = (*S*)-CH(CH$_3$)CO$_2$CH$_3$
b: R = (*R*)-CH(CH$_3$)CO$_2$CH$_3$
c: R = (*S*)-CH(CH$_2$Ph)CO$_2$CH$_3$
d: R = (*S*)-CH(*i*-Bu)CO$_2$CH$_3$
e: R = CH$_2$CH$_2$CO$_2$H
f: R = CH(CH$_3$)CH$_2$CO$_2$H
g: R = (*R*)-CH(Ph)CH$_3$

ref) V. V. Zhadakin *et al* ACIEE 2003, 42, 2194-

c. SIBX (Stabilized IBX)

- A Mixture of Benzoic Acid(22%), Isophthalic Acid (29%), IBX (49%)

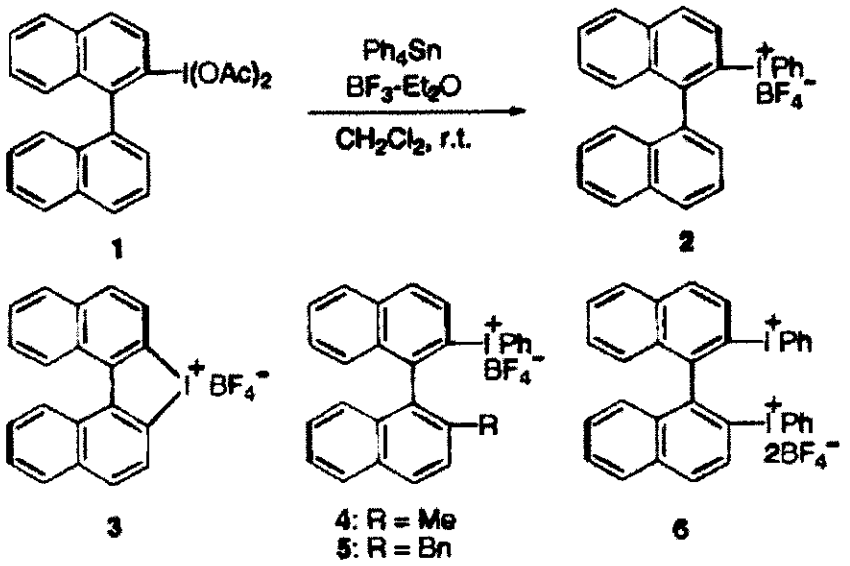


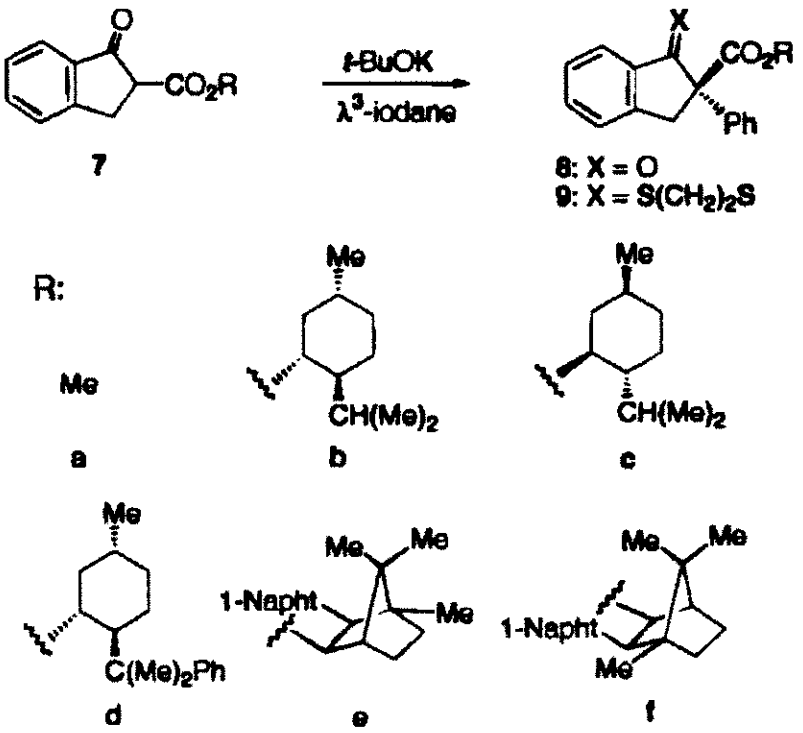
R = alkyl, allyl or benzyl group

Ref) S. Quideau *et al.* Org. Lett. 2003, 5, 16, 2903-2906

3) Chiral Hypervalent Iodines

- **Ochiai's Chiral Diaryliodonium Salts** (JACS 1999, 121. 9233-)

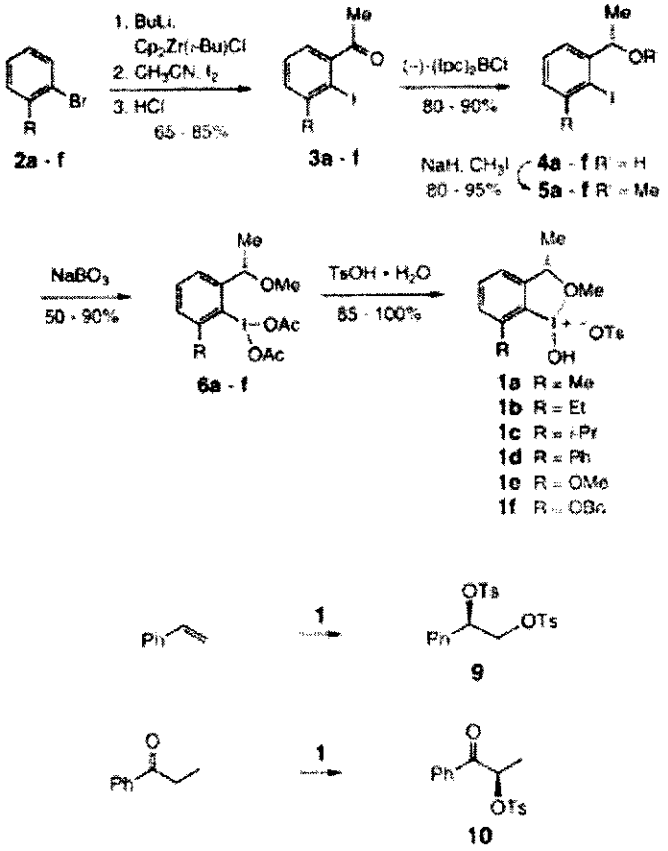




- Showed only 34-53% ee

- Wirth's Ortho-Substituted Chiral Hypervalent Iodines

(Eur. J. Org. Chem. 2001, 1569-)

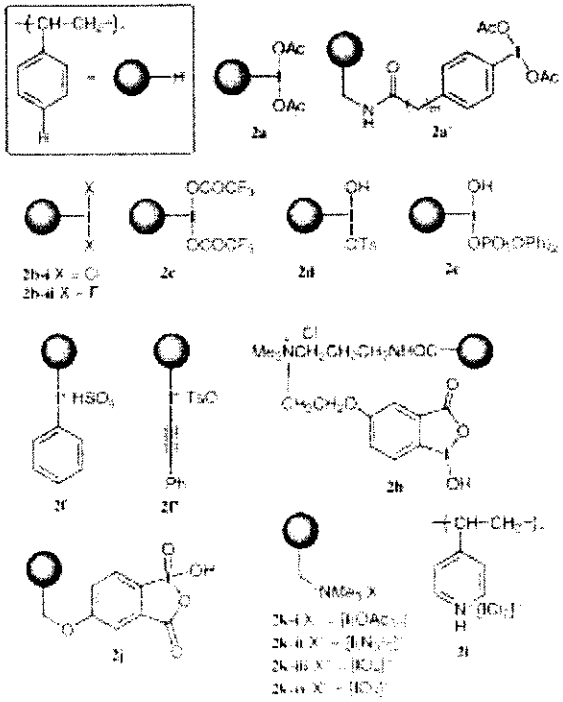


- Showed only less than 40% ee

4) Polymer Supported Hypervalent Iodine Reagents

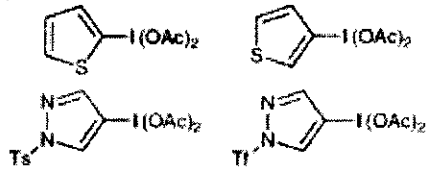
Rev) H. Togo et al. Synlett 2002, No.12 1966-

- Reaction can be monitored by standard methods such as TLC, GC, HPLC, etc
- Reaction products can be obtained by simple filtration to remove the polymer-supported reagents
- Regeneration and reuse of the recovered polymer-supported reagents are possible, thus providing an environmentally benign system
- Low toxicity and low explosiveness due to the polymer can be achieved



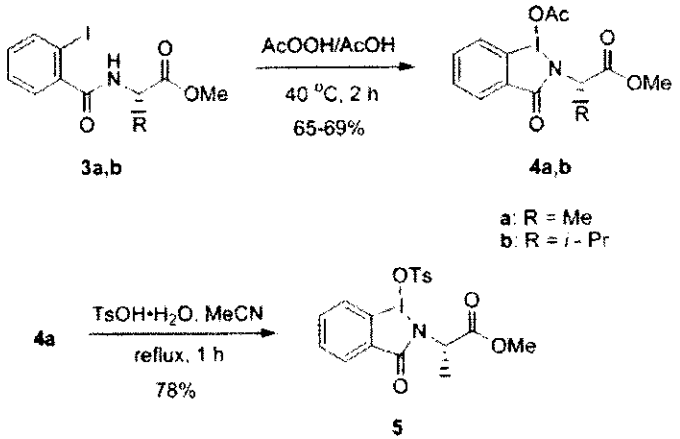
5) New Hypervalent Iodine Heterocycles

- (Diacetoxyiodo)arens Bearing Heteroaromatics



ref) H. Togo et al. JOC 2000, 65, 8391-

- New N-Functionalized Benzoidazole



Ref) V. V. Zhadakin et al. Org. Lett. 2003, Vol.5, No.9 1583-1586

3. Future Aspects

1) Development of New Classes of Hypervalent Iodine Compounds

2) Asymmetric Synthesis Using Chiral Hypervalent Iodines

3) Catalytic Use of Hypervalent Iodines with Cheaper Co-oxidants

4) New Chemistry with Other Reagents

5) Discoveries of New Reactivity in Known Reagents

6) Practical Use in Organic Synthesis including Easy Recoveries

7) Wide Applications in Total Synthesis via Tuning Reactivities