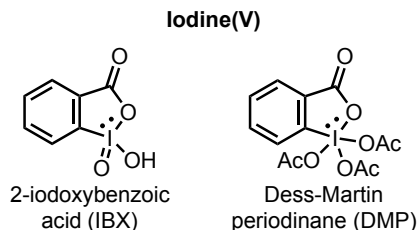# Hypervalent Iodine

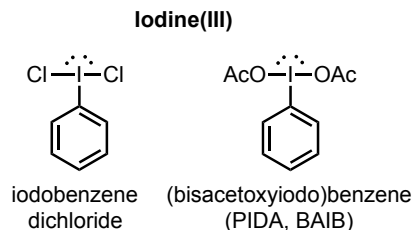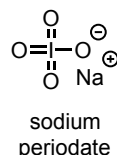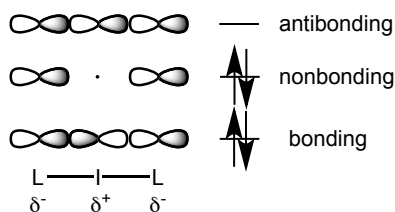## 1. Introduction

**Hypervalent refers to a main group element that breaks the octet rule and formally has more than 8 electrons in its valence shell**

**Iodine(III)**

iodobenzene dichloride

(bisacetoxyiodo)benzene (PIDA, BAIB)

**Iodine(V)**

2-iodoxybenzoic acid (IBX)

Dess-Martin periodinane (DMP)

iodosylbenzene

**Iodine(VII)**

sodium periodate
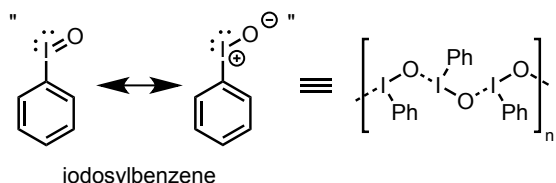
### The hypervalent molecular orbitals

— antibonding

— nonbonding

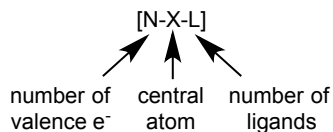— bonding

L — I — L
$\delta^-$ $\delta^+$ $\delta^-$

L–I–L bond consists of an unhybridized p orbital

2 e$^-$ come from iodine and 1 e$^-$ comes from each L, creating a 4 e$^-$, 3 center bond

Negative charge accumulates on each L, positive charge accumulates on central I
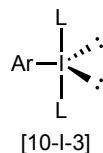
### Martin–Arduengo nomenclature

[N-X-L]

number of valence e$^-$     central atom     number of ligands

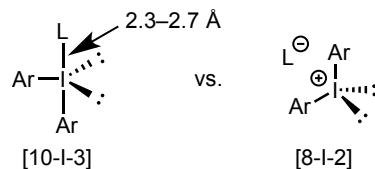### Aryl-$\lambda^3$-iodanes (ArIL$_2$)

Ar–I bond is a typical bond with sp$^2$ hybridization

I–L bonds are the hypervalent bonds

[10-I-3]

The most electronegative ligands reside in the apical (axial) positions

### Diaryl-$\lambda^3$-iodanes vs. diaryliodonium salts (Ar$_2$IL)

2.3–2.7 Å

[10-I-3]     vs.     [8-I-2]

"X-ray structural data for the overwhelming majority of iodonium salts show a significant secondary bonding between the iodine atom and the anion." (Zhdankin, *Chem. Rev.* **2008**, 5299.)

### Aryl-$\lambda^5$-iodanes (ArIL$_4$)

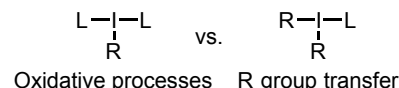Two orthogonal hypervalent L–I–L bonds with each using an unhybridized p orbital
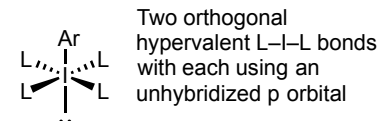
[12-I-5]

Ar–I bond is a typical bond with sp hybridization

Most electropositive substituent resides in the apical position

### General reactivity

Iodine(III) reactivity depends on the ligands attached

L—I—L   vs.   R—I—L
   R             R

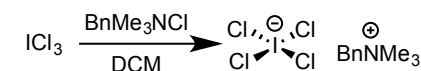Oxidative processes     R group transfer

Iodine(V) and iodine(VII)

Oxidative processes

## 2. Basic mechanisms

### Ligand exchange

Can theoretically proceed through either an associative or dissociative mechanism

Tetracoordinated species have been isolated, suggesting an associative mechanism

Kajigaeshi, *Tetrahedron Lett.* **1988**, 5783.

$ICl_3$ $\xrightarrow[\text{DCM}]{\text{BnMe}_3\text{NCl}}$

### Reductive elimination

Driven by reduction to return to univalent iodide and by an increase in entropy

Leaving group ability 10$^6$ times greater than OTf, making it a "hypernucleofuge" (reason why alkyl-$\lambda^3$-iodanes are so rare)

Kitamura, *J. Am. Chem. Soc.* **1999**, 11674.

$\xrightarrow[\text{DCM, rt}]{\text{TBAF}}$ + PhI + TMSF + TBAOTf

### Configurational isomerization

Can occur via intramolecular ligand exchange or Berry pseudorotation ($\Psi$)
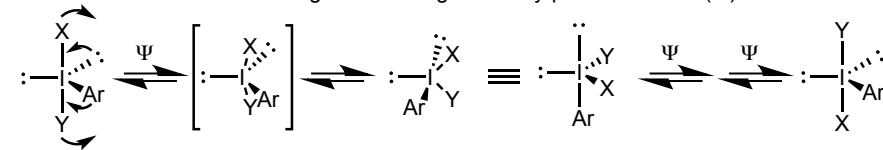
## 3. Not covered (extensively)

Basic oxidations of alcohols to the corresponding carbonyl compounds
·Can oxidize allylic alcohols to enals with IBX and do Wittigs in one pot
(Yadav, *Synth. Commun.* **2001**, 149)

Oxidative cleavage of diols using PhI(OAc)$_2$, DMP, NaIO$_4$, ect.

Halogenations using TolIF$_2$, PhICl$_2$, ect.

Reactions where PhI(OAc)$_2$ or similar reoxidizes a transition metal in a catalytic cycle

Transition metal–catalyzed cross coupling processes where an aryl, alkenyl, or alkynyl iodoinum salt serves as the organohalide
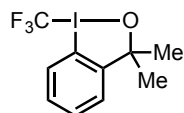
CF$_3$ transfer reagent and potentially explosive
Waser, J. *Chem. Commun.* **2011**, 102.
Haller, J. *Org. Process. Res. Dev.* **2013**, 318.

Togni's reagent
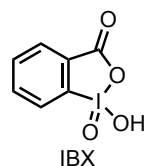
Benzylic oxidation
Oxidation to α,β-unsaturated carbonyl compounds
Oxidation of silyl enol ethers in conjunction with MPO
Cyclization of N-aryl amides, ureas, and carbamates

} Proceeds via SET

IBX

Nicolaou, *J. Am. Chem. Soc.* **2002**, 2245.
Nicolaou, *J. Am. Chem. Soc.* **2000**, 7596.
Nicolaou, *J. Am. Chem. Soc.* **2002**, 2233.
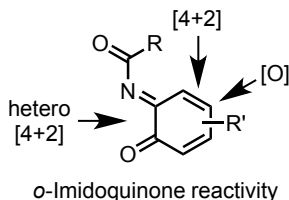Nicolaou, *Angew. Chem. Int. Ed.* **2002**, 996.

IBX proposed to be activated prior to SET:
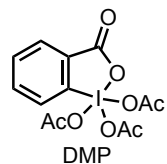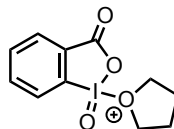
Mixtures of DMP and Ac-IBX (hydrolyzed DMP) oxidizes N-aryl amides, ureas, and carbamates to the *o*-imidoquinones

DMP

Nicolaou, *J. Am. Chem. Soc.* **2002**, 2212.
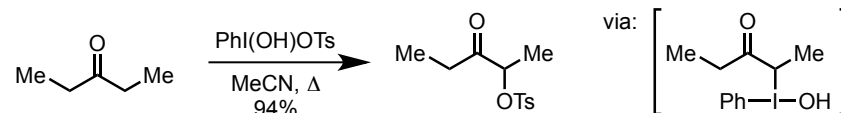Nicolaou, *J. Am. Chem. Soc.* **2002**, 2221.

hetero [4+2]

[4+2]
[O]

*o*-Imidoquinone reactivity

## 4. α-Functionalizations

**Direct α-oxytosylation of ketones.**
Koser, *J. Org. Chem.* **1982**, 2487.

PhI(OH)OTs
MeCN, Δ
94%

via:

Silyl enol ethers and silyl ketene acetals can also be used as the nucleophile

α-**Hydroxylation of ketones.**
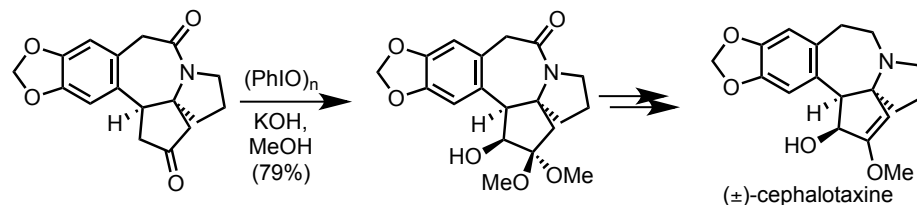Moriarty, *Tetrahedron Lett.* **1981**, 1283.

(PhIO)$_n$ or
PhI(OAc)$_2$
KOH,
MeOH

H$_3$O$^+$

40–70%
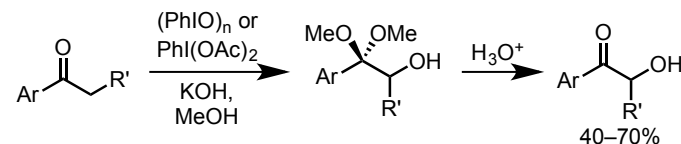
**Oxygenation installed on more hindered face.**
Moriarty, *J. Org. Chem.* **1987**, 153.

PhI(OAc)$_2$
MeOH, KOH
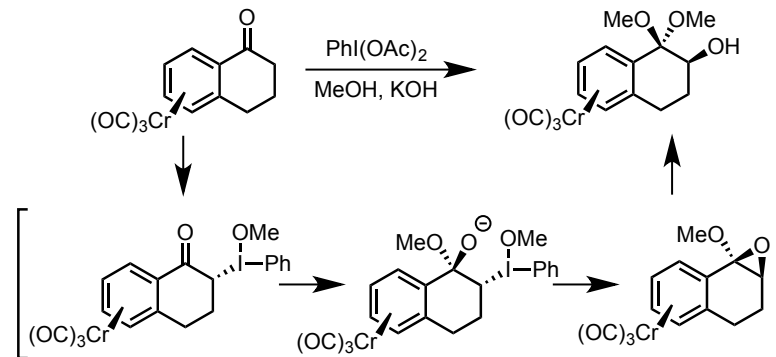
**Used in the total synthesis of cephalotaxine.**
Hanaoka, *Tetrahedron Lett.* **1986**, 2023.
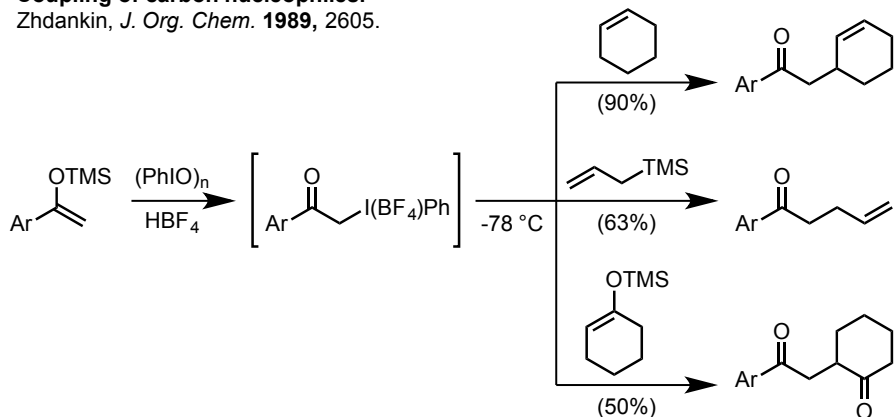
(PhIO)$_n$
KOH,
MeOH
(79%)

(±)-cephalotaxine
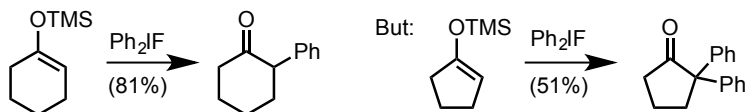
# Hypervalent Iodine

**α-Oxidations of ketones can also occur under catalytic conditions.**
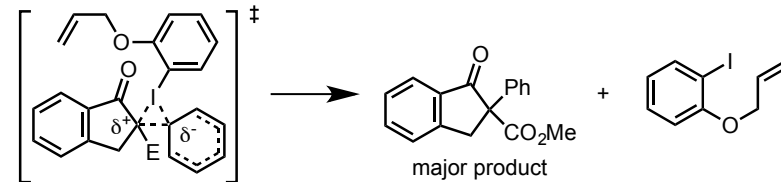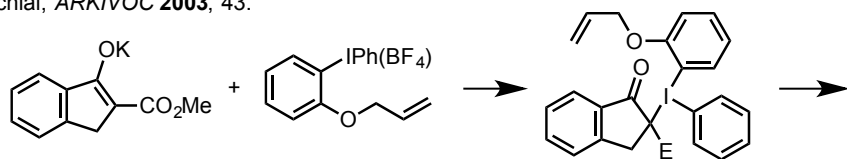Ochiai, *J. Am. Chem. Soc.* **2005**, 12244.



43–63%
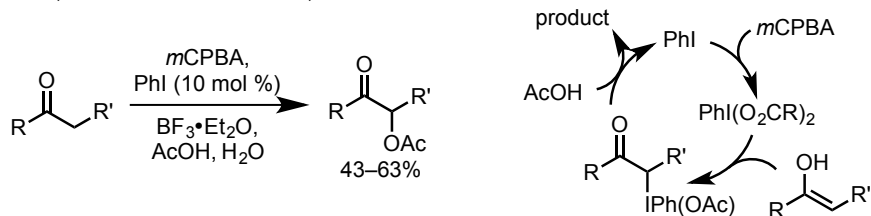
**Coupling of carbon nucleophiles.**
Zhdankin, *J. Org. Chem.* **1989,** 2605.



(90%)

(63%)

(50%)

**Phenylation of silyl enol ethers.**
Koser, *J. Org. Chem.* **1991**, 5764.
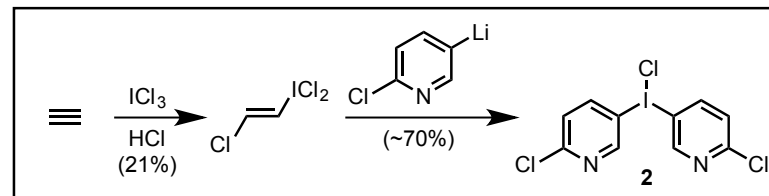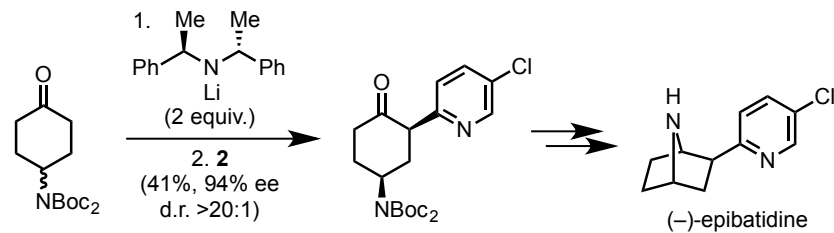


(81%)

But:

(51%)

**A mechanistic study reveals that the more electron deficient aryl group migrates in unsymmetrical salts.**
Ochiai, *ARKIVOC* **2003**, 43.



‡

major product

**Used in the synthesis of the indole core of tabersonine.**
Rawal, *J. Am. Chem. Soc.* **1998**, 13523.



(94%)

TiCl$_3$,
NH$_4$OAc
(89%)

1. K$_2$S$_2$O$_8$,
H$_2$SO$_4$, KI
2. AgF

**1**

tabersonine
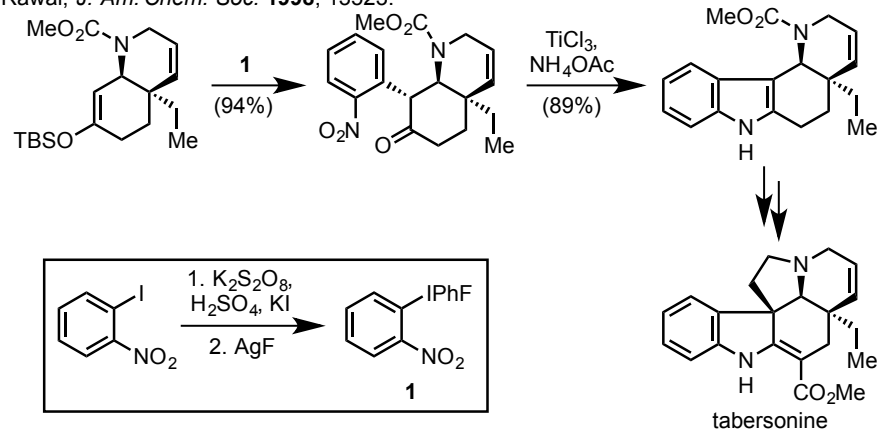
**α-Arylation in a more modern setting.**
Aggarwal, *Angew. Chem. Int. Ed.* **2005**, 5516.



(2 equiv.)
2. **2**
(41%, 94% ee
d.r. >20:1)

(–)-epibatidine

ICl$_3$
HCl
(21%)

(~70%)

**2**

# Hypervalent Iodine

## 5. Azidonation, aziridination, and amination

**(Di)azidonation of silyl enol ethers.**
Magnus, *J. Am. Chem. Soc.* **1992**, 767.



β-Azidonation pathway:
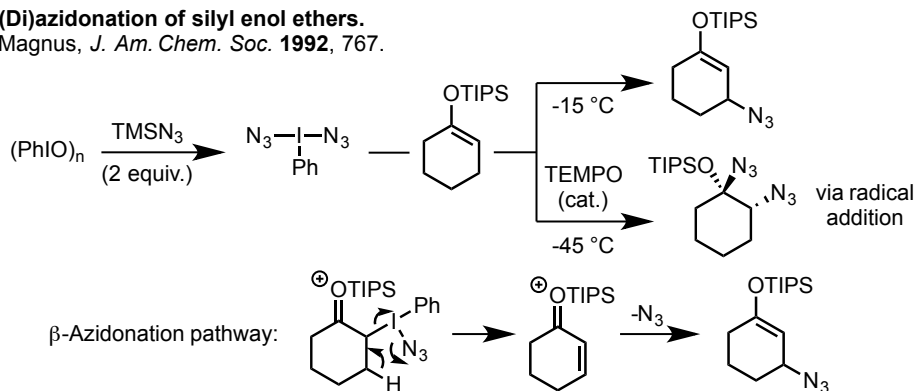


**Azidonation of *N,N*-dimethylanilines.**
Magnus, *Synthesis* **1998**, 547.

via:
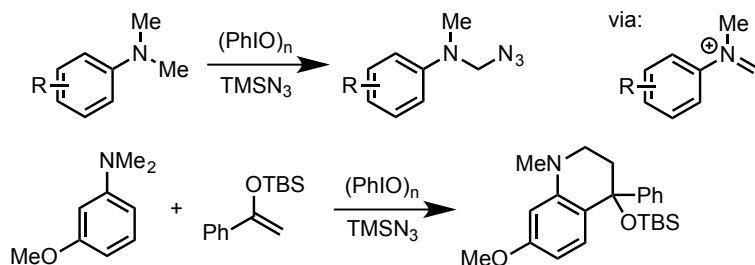


**Substrate controlled amination of allyl silanes.**
Panek, *J. Am. Chem. Soc.* **1997**, 6040.
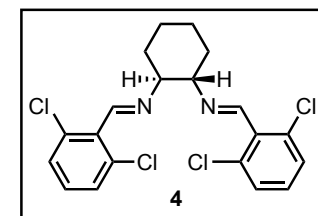


60–65%
> 30:1 de

But:

64%
2:1 ds

Rationale:
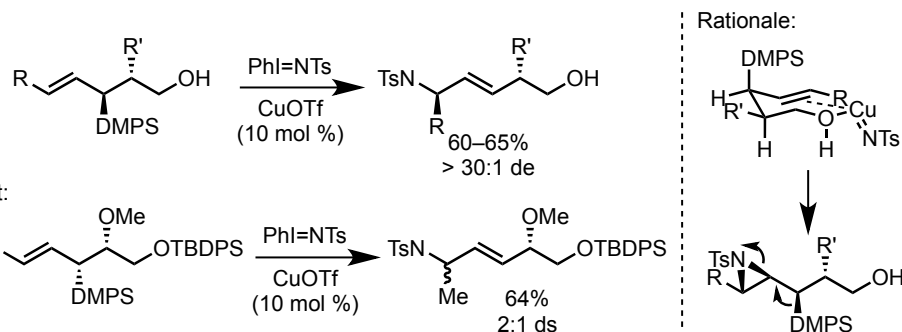


**Enantioselective aziridination.**
Evans, *J. Am. Chem. Soc.* **1993**, 5328.
Evans, *J. Am. Chem. Soc.* **1994**, 2742.



PhI=NTs
CuOTf
(5 mol %)
**3**
(6 mol %)

60–76%
94–97% ee
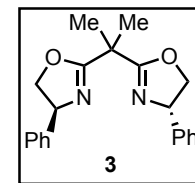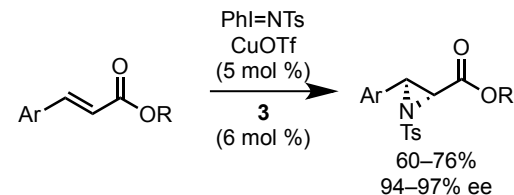
**An alternative ligand for enantioselective aziridination.**
Jacobsen, *J. Am. Chem. Soc.* **1993**, 5326.



PhI=NTs
CuOTf
(10 mol %)
**4**
(11 mol %)

50–79%
58–98% ee
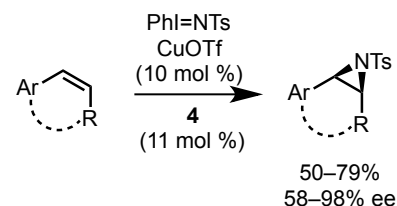
**DuBois' nitrene chemistry proceeds through an iminoiodinane.**
DuBois, *Tetrahedron* **2009**, 3042.



$PhI(OAc)_2$
-2 AcOH

[Rh] cat.
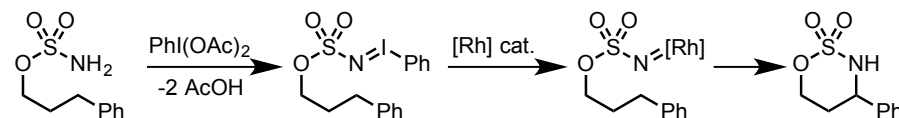
**Aryl C–H insertions can take place without the presence of transition metals.**
Tellitu, *J. Org. Chem.* **2005**, 2256.



$PhI(O_2CCF_3)_2$
$CF_3CH_2OH$
(70%)

$Mo(CO)_6, \Delta$
(76%)
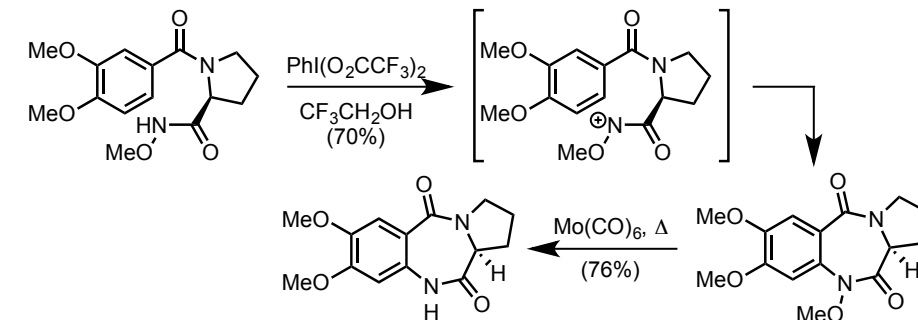
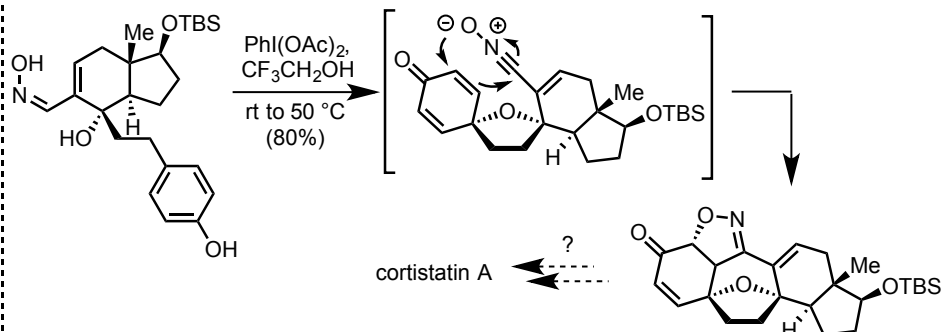# 6. Oxidative dearomatization of phenols

**There are several possible mechanisms.**
Quideau, *Tetrahedron* **2010**, 2235.



A radical pathway has also been proposed.
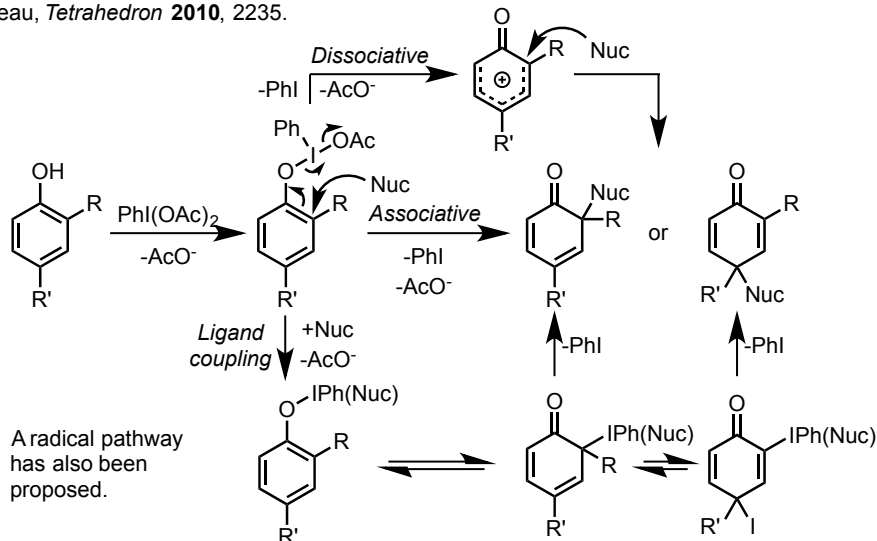
**Oxidative dearomatization often initiates cascade sequences (eg. diazonamide A).**
Harran, *Angew. Chem. Int. Ed.* **2003**, 4961.
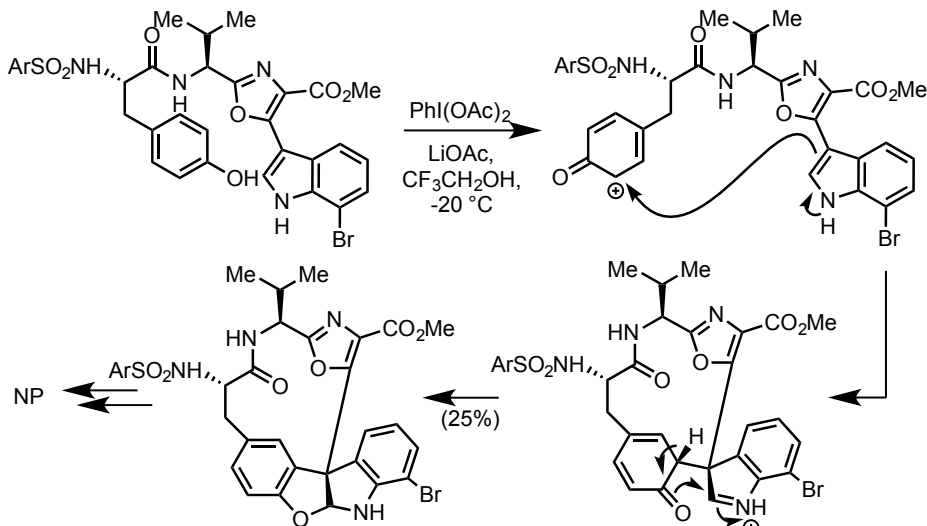


**Can also be used in conjuction with 1,3-dipolar cycloadditions.**
Sorensen, *Org. Lett.* **2009**, 5394.



cortistatin A

**And Diels-Alder reactions.**
Danishefsky, *J. Am. Chem. Soc.* **2006**, 16440.



(±)-11-*O*-debenzoyltashironin
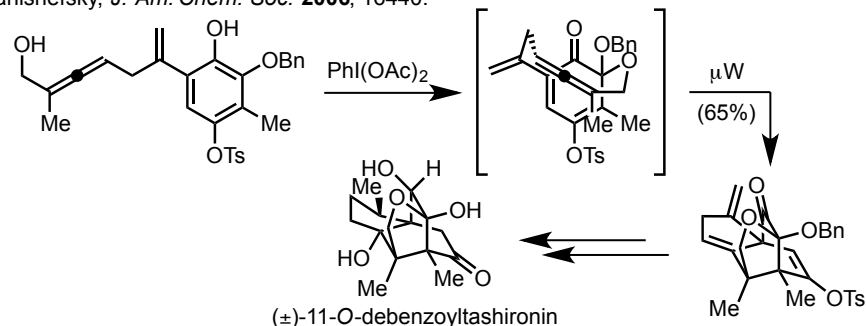
**IBX can directly oxidize electron–rich phenols to *o*-quinones.**
Pettus, *Org. Lett.* **2002**, 285.



20–99%

Authors propose:

# Hypervalent Iodine

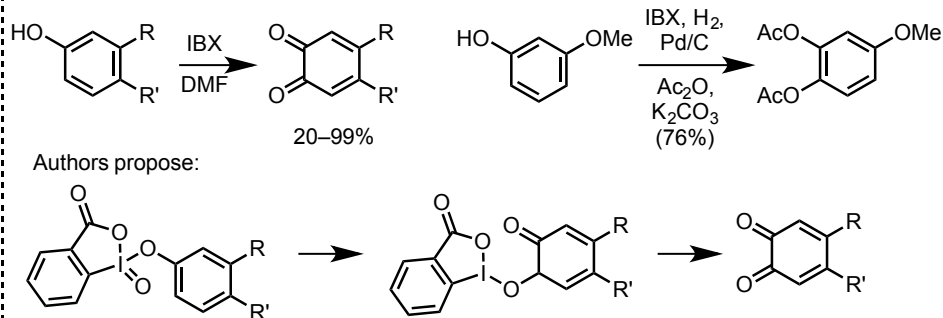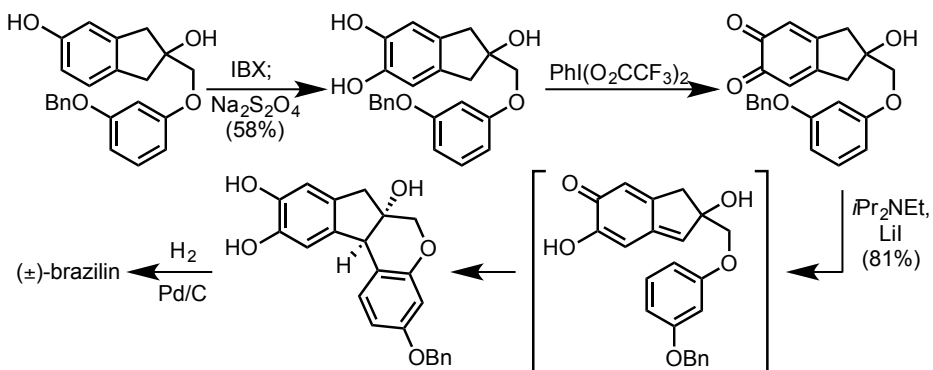**The use of oxidative dearomatization can be more subtle.**
Pettus, *Org. Lett.* **2005**, 5841.

IBX;
Na$_2$S$_2$O$_4$
(58%)

PhI(O$_2$CCF$_3$)$_2$

*i*Pr$_2$NEt,
LiI
(81%)

H$_2$
Pd/C

(±)-brazilin

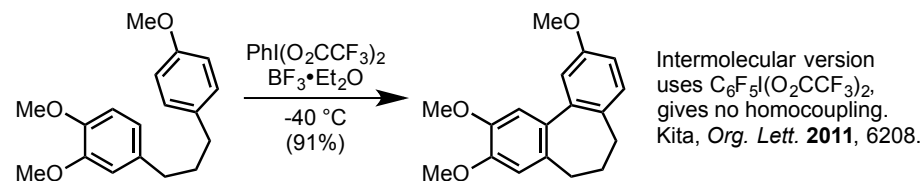# 7. Aryl charge transfer complexes

**Nucleophilic substitution can also occur on *para*-substituted aryl ethers via a charge transfer complex.**
Kita, *J. Am. Chem. Soc.* **1994**, 3684.

PhI(O$_2$CCF$_3$)$_2$
(CF$_3$)$_2$CHOH
or CF$_3$CH$_2$OH

CF$_3$CO$_2$$^\ominus$
Ph—I—O$_2$CCF$_3$

SET

SET

Nuc

Nuc = TMSN$_3$, TMSOAc,
1,3-dicarbonyls
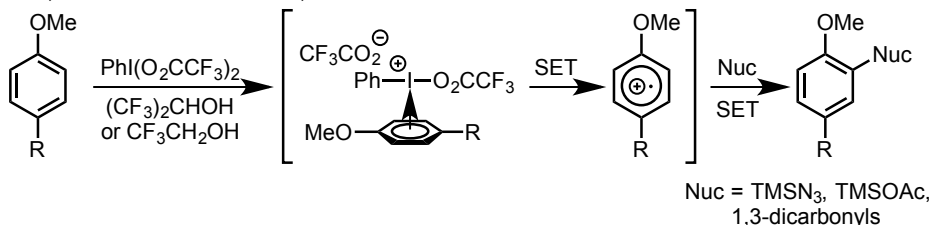
**Intramolecular biaryl coupling of electron–rich aryl ethers.**
Kita, *J. Org. Chem.* **1998**, 7698.

PhI(O$_2$CCF$_3$)$_2$
BF$_3$•Et$_2$O
-40 °C
(91%)

Intermolecular version
uses C$_6$F$_5$I(O$_2$CCF$_3$)$_2$,
gives no homocoupling.
Kita, *Org. Lett.* **2011**, 6208.

**Can also be used to add nucleophiles to heterocycles.**
Kita, *J. Org. Chem.* **2007**, 109.

PhI(O$_2$CCF$_3$)$_2$
TMSCN
BF$_3$•Et$_2$O
(83%)

PhI(O$_2$CCF$_3$)$_2$
TMSCN
BF$_3$•Et$_2$O
(79%)
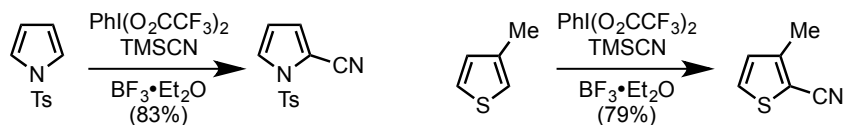
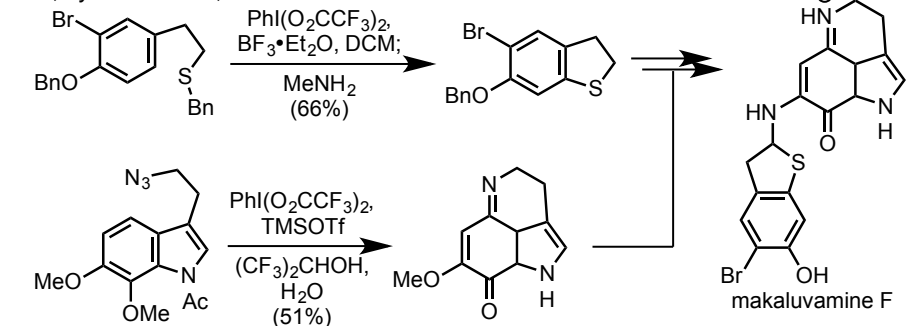**Possible involvement of CT complex in dimerization of indoles at the 2 position?**
Kita, *Org. Lett.* **2006**, 2007.

PhI(O$_2$CCF$_3$)$_2$,
TMSBr
DCM
-78 °C to -40 °C

74%          29%
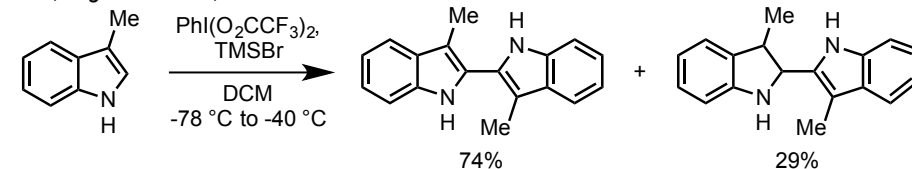
**Application of charge transfer chemistry in total synthesis.**
Kita, *Synthesis* **1999**, 885.

PhI(O$_2$CCF$_3$)$_2$,
BF$_3$•Et$_2$O, DCM;
MeNH$_2$
(66%)

PhI(O$_2$CCF$_3$)$_2$,
TMSOTf
(CF$_3$)$_2$CHOH,
H$_2$O
(51%)

makaluvamine F

# 8. Radical processes

**Remote steroidal C–H functionalization.**
Breslow, *J. Am. Chem. Soc.* **1991**, 8977.

PhICl$_2$
CBr$_4$,
h$\nu$
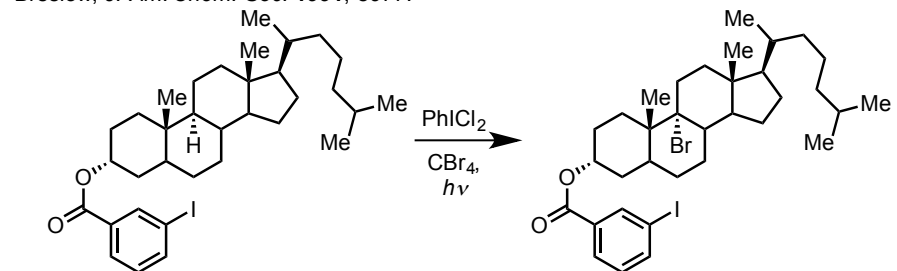
**A variant of the Hofmann-Löffler-Freytag reaction.**
Suárez, *Tetrahedron Lett.* **1985**, 2493.

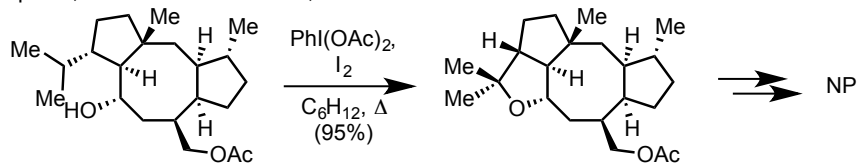PhI(OAc)$_2$,
I$_2$
C$_6$H$_{12}$, Δ
(77%)
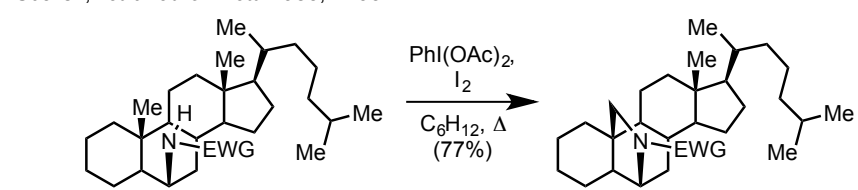
**Suárez conditions can also generate alkoxy radicals.**
Pattenden, *Tetrahdron Lett.* **1993**, 127.



(58%)
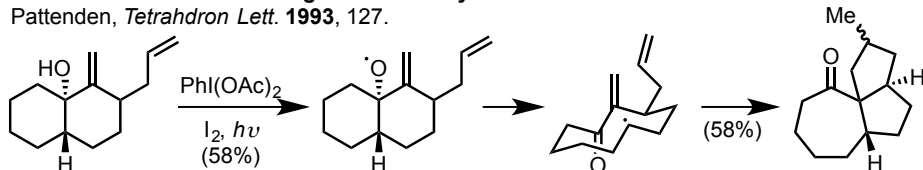
**β-Fragmentation paths can also lead to 2-dioxolanes.**
Suárez, *J. Org. Chem.* **1998**, 4697.



1. PhI(OAc)$_2$, I$_2$, *hv*
2. NaOMe
(79%)
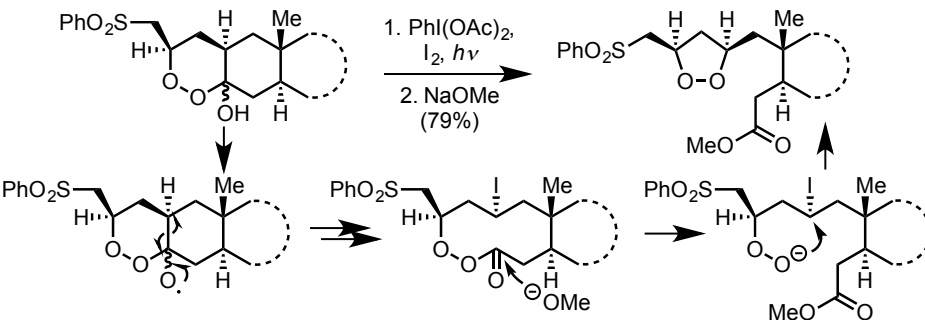
**En route to (+)-epoxydictymene.**
Paquette, *Tetrahedron Lett.* **1997**, 195.



PhI(OAc)$_2$, I$_2$
C$_6$H$_{12}$, Δ
(95%)

NP

**PhI(O$_2$CR)$_2$ can be decarboxylated to give radicals.**
Togo, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2417.

R = alkyl, RC(O)

PhI(O$_2$CCF$_3$)$_2$
*hv* or Δ
(13-88%)

Radical generation:

PhI(O$_2$CR)$_2$ →(*hv* or Δ, -PhI) [RCO$_2^{\bullet}$] →(-CO$_2$) R$^{\bullet}$
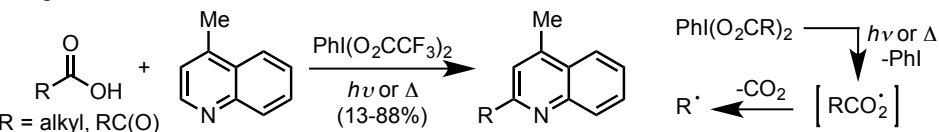
**Similar reaction can perform C–H amidation.**
Zhdankin, *Tetrahedron Lett.* **1997**, 21.



TMSOTf;
RC(O)NH$_2$,
pyr
(63–75%)

PhCl, Δ
(PhCO$_2$)$_2$
cat.

R = *p*-ClC$_4$H$_6$ (58%)
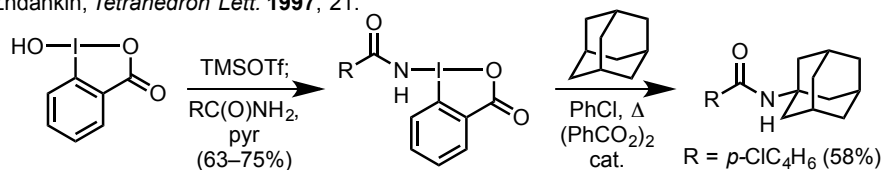
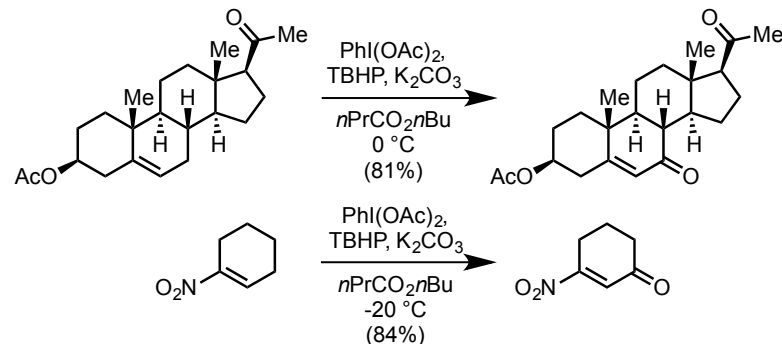**TBHP undergoes a complicated decomposition pathway in the presence of PhI(OAc)$_2$.**
Milas, *J. Am. Chem. Soc.* **1968**, 4450.



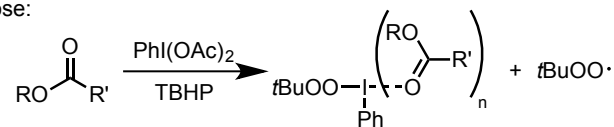PhI(OAc)$_2$ →(TBHP, -80 °C, - 2 AcOH) PhI(OO*t*Bu)$_2$ →(-PhI) 2 *t*BuOO$^{\bullet}$ ⇌ *t*BuOOOO*t*Bu
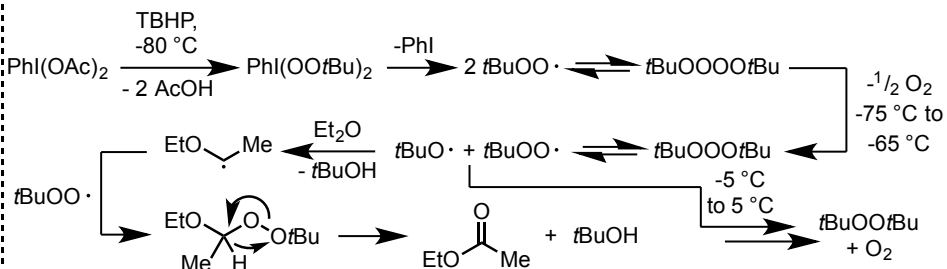
**A stable (alkylperoxy)iodane that oxidizes allyl and benzyl ethers.**
Ochiai, *J. Am. Chem. Soc.* **1996**, 7716.



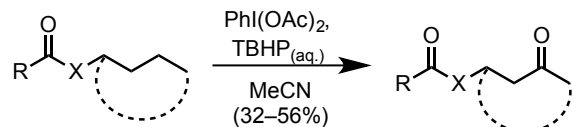TBHP
BF$_3$•Et$_2$O
(90%)

Cs$_2$CO$_3$ (10–76%)

K$_2$CO$_3$ (21–84%)
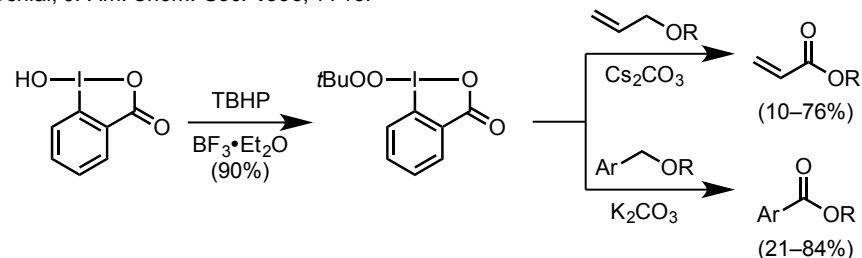
**Allylic oxidation of alkenes to enones.**
Yeung, *Org. Lett.* **2010**, 2128.



PhI(OAc)$_2$,
TBHP, K$_2$CO$_3$
*n*PrCO$_2$*n*Bu
0 °C
(81%)

PhI(OAc)$_2$,
TBHP, K$_2$CO$_3$
*n*PrCO$_2$*n*Bu
-20 °C
(84%)

Authors propose:

RO–C(O)–R' →(PhI(OAc)$_2$, TBHP) *t*BuOO–I(Ph)–(O–C(O)R')$_n$ + *t*BuOO$^{\bullet}$

**Oxidation of unactivated C–H bonds.**
Yeung, *Org. Lett.* **2011**, 4308.

Proposed intermediate:
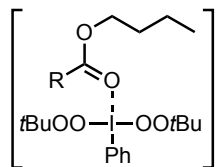


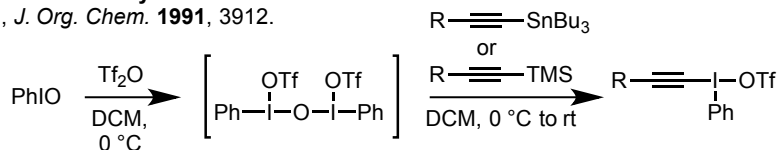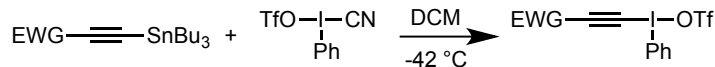## 9. Alkynyl(aryl)-λ³-iodanes

Although not commerically available, there a many ways to synthesize.

**For R = alkyl or Ph.**
Fujita, *Tetrahedron Lett.* **1985,** 4501.
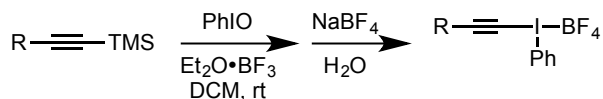


**For R = TMS or alkyl.**
Stang, *J. Org. Chem.* **1991**, 3912.



**For electron poor alkynes.**
Stang, *J. Am. Chem. Soc.* **1994**, 93.
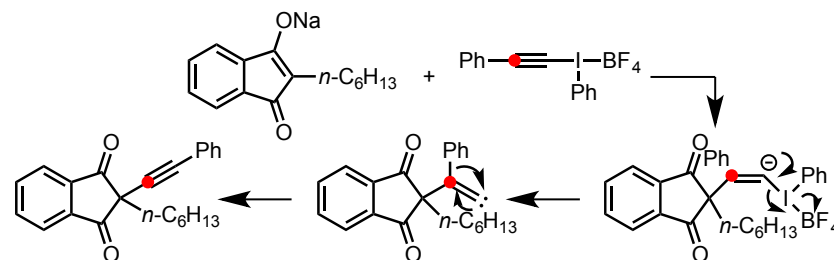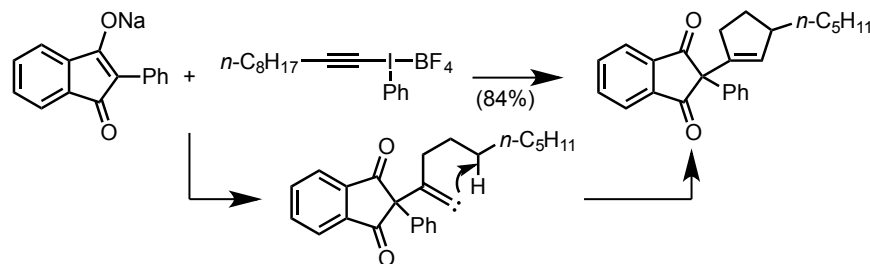


**Alkynylation of of nucleophiles with alkynyl(aryl) iodonium salts.**
Beringer, *J. Org. Chem.* **1965**, 1930.



(73%)
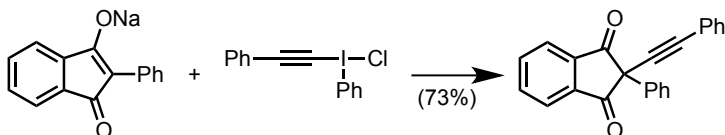
**Shown to not proceed through the originally proposed α-carbon attack ($^{13}$C labeling).**
Ochiai, *J. Am. Chem. Soc.* **1986**, 8281.



**Can be utilized in a conjugate addition–carbene insertion cascade.**
Ochiai, *J. Am. Chem. Soc.* **1986**, 8281.



(84%)

**Provides a route to amino cyclopropanes.**
Lee, *Synlett* **2001**, 1656.



(76%)
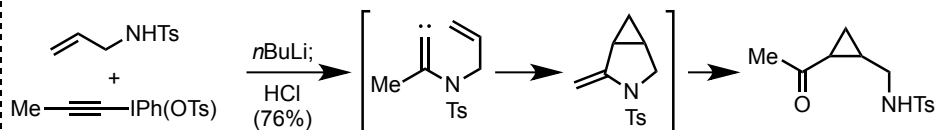
**With a cascade ending with a formal Stevens shift.**
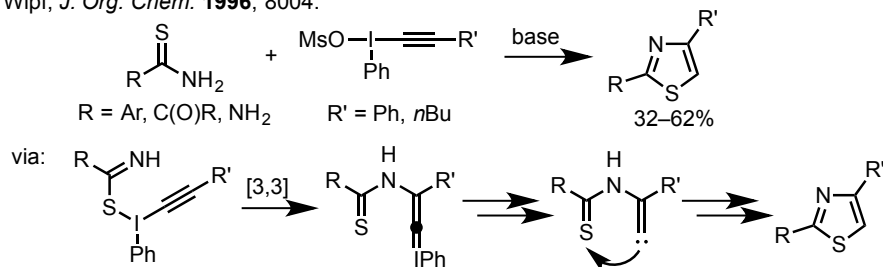Feldman, *Org. Lett.* **2000**, 2603.



41%          27%

# Hypervalent Iodine
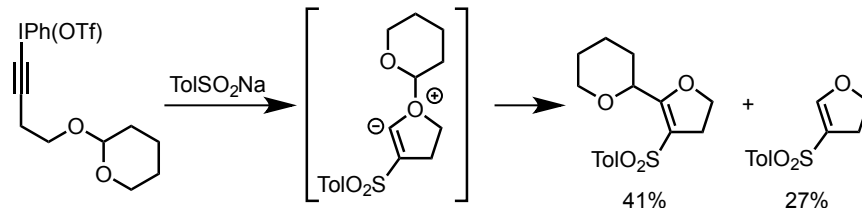
**Used in key step of pareitropone synthesis.**
Feldman, *J. Org. Chem.* **2002**, 8528.



pareitropone
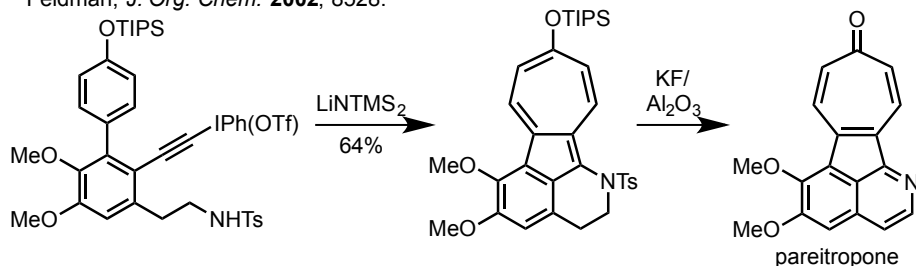
**Cyclocondensation with thioamides to thiazoles.**
Wipf, *J. Org. Chem.* **1996**, 8004.

R = Ar, C(O)R, NH$_2$      R' = Ph, *n*Bu      32–62%
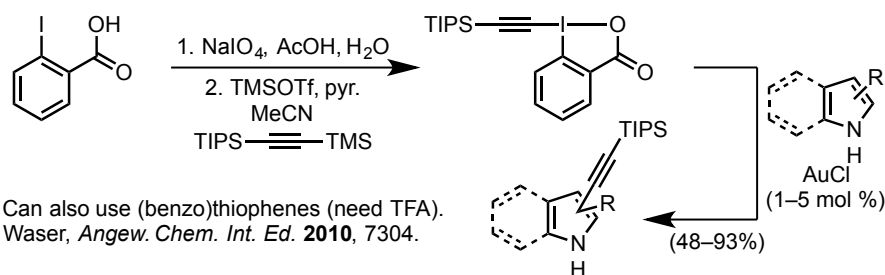
via: [3,3]



**Counterintuitive regiochemical outcome in Diels–Alder reactions.**
Stang, *J. Org. Chem.* **1997**, 5959.



major          minor
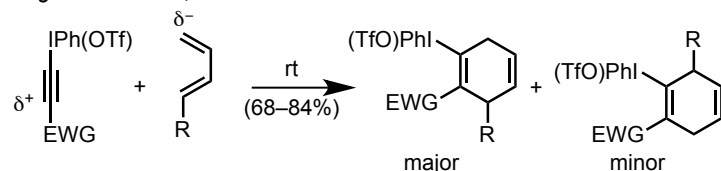
**Benziodoxoles in direct alkynylations of pyrroles and indoles.**
Waser, J. *Angew. Chem. Int. Ed.* **2009**, 9346.

1. NaIO$_4$, AcOH, H$_2$O
2. TMSOTf, pyr.
MeCN
TIPS≡TMS
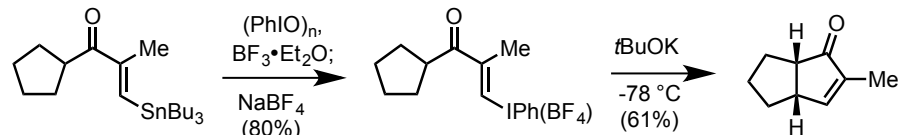
AuCl
(1–5 mol %)
(48–93%)

Can also use (benzo)thiophenes (need TFA).
Waser, *Angew. Chem. Int. Ed.* **2010**, 7304.
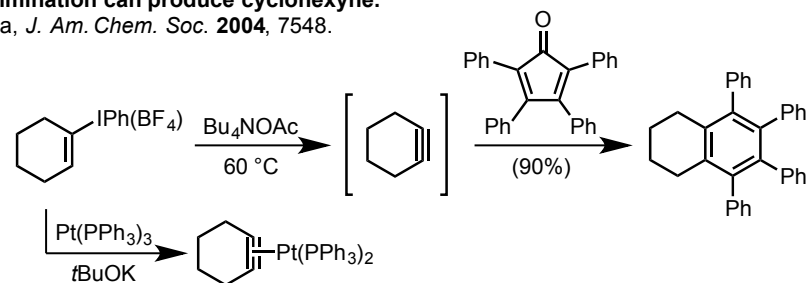
## 10. Alkenyl(aryl)-λ$^3$-iodanes

**Alkenyl iodonium salts can be synthesized analogously to the alkynyl iodonium salts and undergo similar chemistry via base-induced alkylidinecarbenes.**
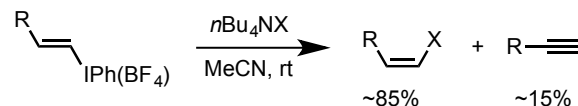Ochiai, *J. Am. Chem. Soc.* **1988**, 6565.

(PhIO)$_n$,
BF$_3$•Et$_2$O;
NaBF$_4$
(80%)

*t*BuOK
-78 °C
(61%)



**β-Elimination can produce cyclohexyne.**
Fujita, *J. Am. Chem. Soc.* **2004**, 7548.

Bu$_4$NOAc
60 °C
(90%)

Pt(PPh$_3$)$_3$
*t*BuOK



**Direct S$_N$2 reaction of vinyliodonium salts and isotopic labeling studies provide evidence for β-elimination.**
Ochiai, *J. Am. Chem. Soc.* **1991**, 7059.

*n*Bu$_4$NX
MeCN, rt

R–X  ~85%     R≡  ~15%

Mechanistically:
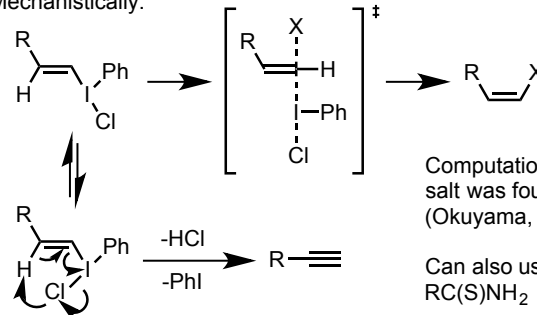


Computationally, the σ* of the vinyliodonium salt was found to be lower in energy than the π*.
(Okuyama, *Can. J. Chem.* **1999**, 577)

Can also use: AcOH, DMF, ArSH, R$_2$S, R$_2$Se, RC(S)NH$_2$

-HCl
-PhI
R≡

(X = F proceeds via alkylidinecarbene)

## 11. Iodonium ylides
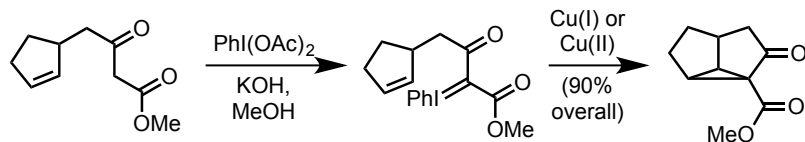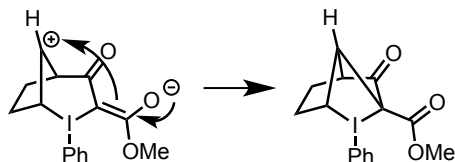
**Iodonium ylides as an alternative to α-diazo dicarbonyl compounds in intramolecular cyclopropanations.**
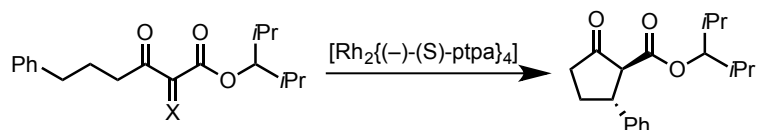Moriarty, *J. Am. Chem. Soc.* **1989**, 6443.



Authors propose:



**Transition metal–catalyzed iodonyl ylide chemistry proceeds through metal carbenoids.**
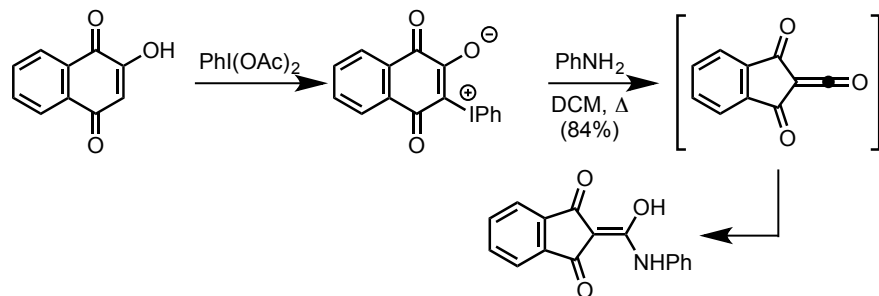Müller, *Helv. Chim. Acta.* **1995**, 947.



Iodonium ylides perform the same chemistry
as the corresponding diazo species
(albiet in slightly lower yields).

X = N$_2$ (89%, 69% ee)
X = IPh (78%, 67% ee)

**Iodonium ylides can also undergo Wolff rearrangements.**
Spyroudi, *J. Org. Chem.* **2003**, 5627.



**Mixed phosphonium–iodonium ylides.**
Zhadankin, *J. Org. Chem.* **2003**, 1018.
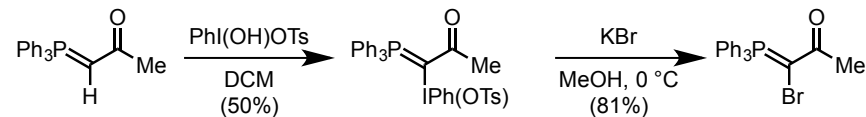


Can also use PhSLi and PhSO$_2$Na

**Iodonium ylides undergo a net 1,3-dipolar cycloadditions upon photolysis.**
Hadjiarapoglou, *Tetrahedron Lett.* **2000**, 9299.



**Intermolecular transylidation can generate reactive alkyl iodonium ylides.**
Hadjiarapoglou, *Synlett* **2004**, 2563.



34%     46%

**A mechanistic controversy arising from an I to O Ph migration.**
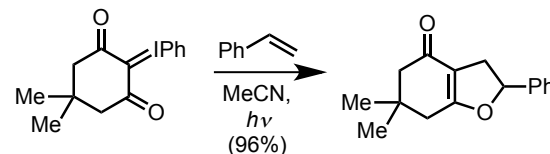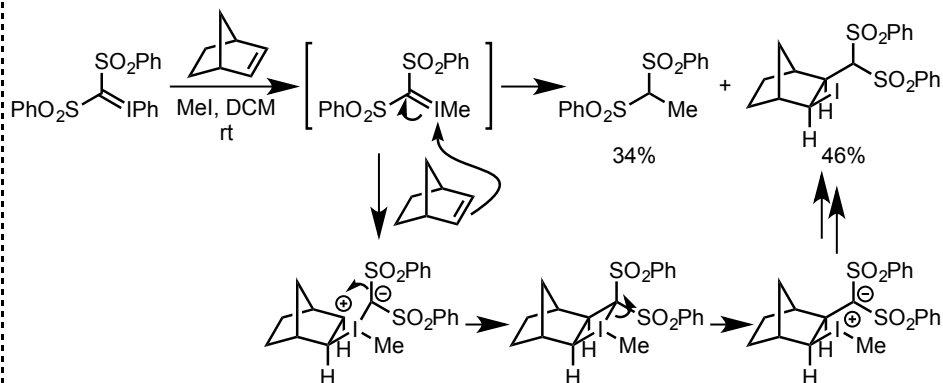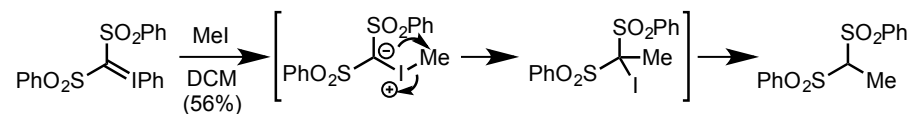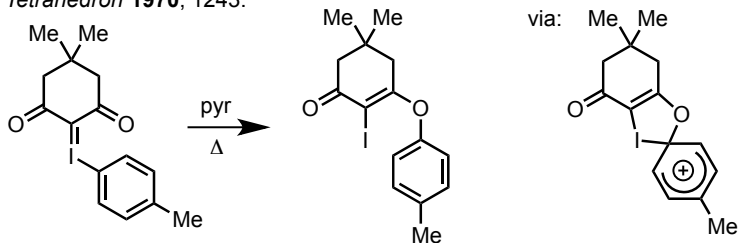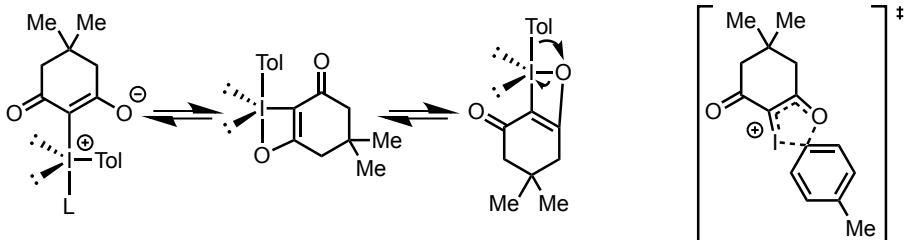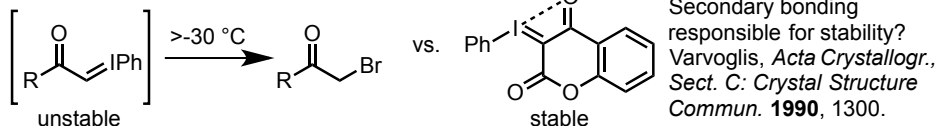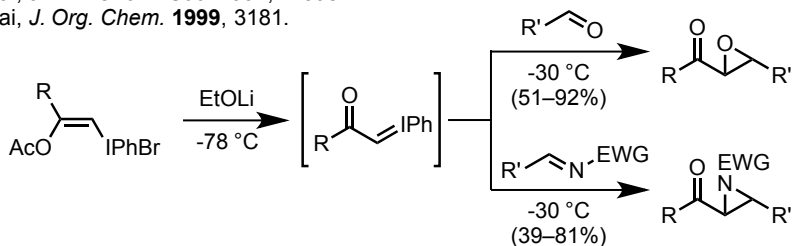Nozaki, *Tetrahedron* **1970**, 1243.

pyr
Δ

via:

Bakalbassis, *J. Org. Chem.* **2006**, 7060.

Moriarty, *J. Org. Chem.* **2005,** 2893.

Tol

‡

**Monocarbonyl iodonium ylides.**
Ochiai, *J. Am. Chem. Soc.* **1997**, 11598.
Ochiai, *J. Org. Chem.* **1999**, 3181.

EtOLi
-78 °C

R'CHO
-30 °C
(51–92%)

R'—CH=N—EWG
-30 °C
(39–81%)

>-30 °C

vs.

Secondary bonding responsible for stability?
Varvoglis, *Acta Crystallogr., Sect. C: Crystal Structure Commun.* **1990**, 1300.

unstable

stable

# 12. Chiral iodanes for enantioselective transformations

**Chiral 1,1'-spirobiindane iodine(III) reagent dearomatizes phenols enantioselectively.**
Kita, *Angew. Chem. Int. Ed.* **2008**, 3787.

**5**
(0.55 equiv)

(81–86%)
80–86% ee)

**5**
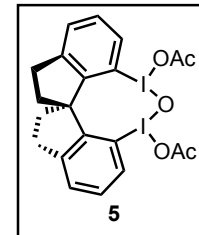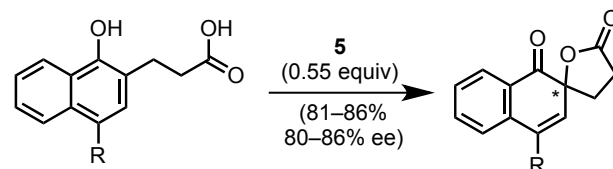
Reaction can also be ran catalytically with mCPBA as the stoichiometric oxidant and AcOH as an additive: gives 70% with 69% ee

**An alternative, conformationally flexible iodoarene catalyzes the same reaction.**
Ishihara, *Angew. Chem. Int. Ed.* **2010**, 2175.

**6**
(10 mol%),
*m*CPBA

(59–92%
83–90% ee)

**6**
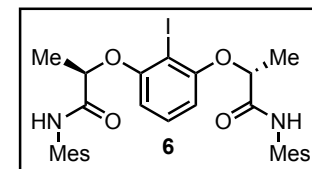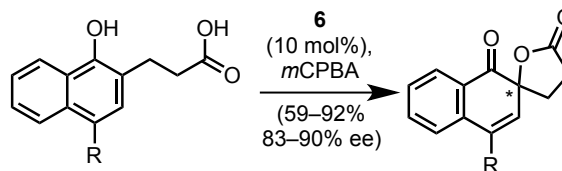
Proposed active oxidant:

or
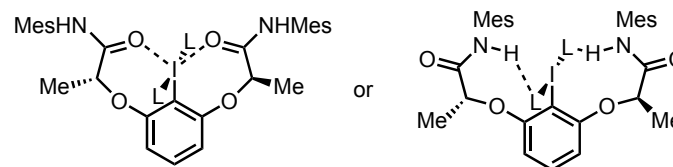
**A related lactate–derived reagent promotes and "enatiodifferentiating endo-selective oxylactonization."**
Fujita, *Angew. Chem. Int. Ed.* **2010**, 7068.

**7** (1.5 equiv.),
AcOH

BF$_3$•Et$_2$O,
-80 to -40 °C

**7**

57–88%
75–96% ee

3–8%
6–51% ee

via:
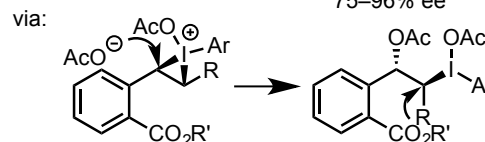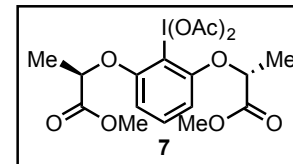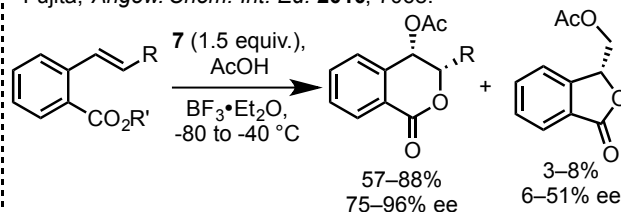
# 13. Miscellaneous reactivity

**Room temperature benzylic oxidation using catalytic iodine.**
Zhdankin, *Chem. Eur. J.* **2009**, 11091.

Ar–R $\xrightarrow[\substack{\text{Oxone}\\ \text{MeCN, H}_2\text{O}}]{\substack{\text{PhI (5 mol \%)}\\ \text{RuCl}_3 \text{ (0.16 mol \%)}}}$ Ar–C(=O)–R

23–95%

Oxone → Ru(III) / Ru(V)=O cycle; PhIO₂ / PhIO; Ar–CH₂R → Ar–C(=O)–R

---

**Utilization of allenyl iodanes in propargylations.**
Ochiai, *J. Am. Chem. Soc.* **1991**, 1319.
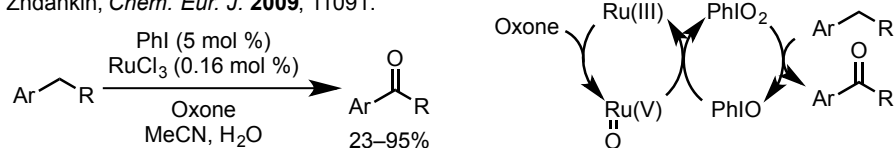Ochiai, *Chem. Commun.* **1996**, 1933.

R–C₆H₄–I(OAc)₂ $\xrightarrow[\substack{\text{BF}_3\cdot\text{Et}_2\text{O}\\ \text{MgSO}_4\\ -20\ ^\circ\text{C}}]{\text{TMS}–\text{CH}_2–C\equiv C–R'}$ [ AcO–I(R–C₆H₄)=C=C=CH₂ with R' ] $\xrightarrow[-20\ ^\circ\text{C}]{[3,3]}$ R–C₆H₄(I)–CH₂–C≡C–R'

*ipso* and *meta* propargylation if *ortho* positions are both substituted

If R = *m*-NO₂
R"OH or MeCN
(100 equiv.)

R"O–CH₂–C≡C–Ar  or  AcHN–CH₂–C≡C–Ar

---
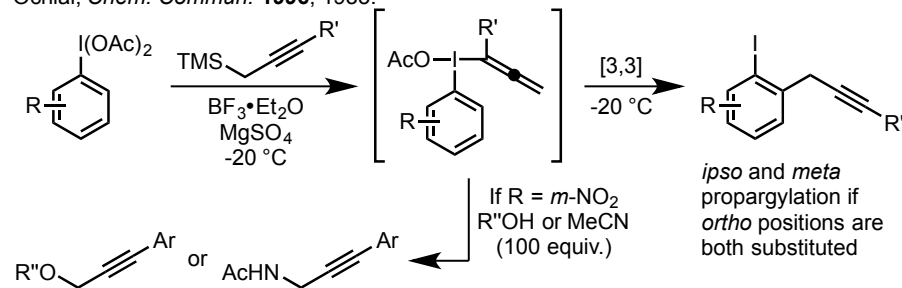
**One last application of hypervalent iodine in total synthesis.**
Moriarty, *J. Med. Chem.* **1998**, 468.

4-Ph-cyclohexanone $\xrightarrow[\substack{\text{KOH,}\\ \text{MeOH}\\ (40\%)}]{\text{PhI(OAc)}_2}$ 3-Ph-cyclopentane-CO₂Me $\rightarrow$ tricyclic ketone-CO₂H $\xrightarrow[\substack{\text{I}_2,\ \text{AIBN}\\ (92\%)}]{\text{PhI(OAc)}_2}$ iodo ketone

iodo ketone $\Leftarrow$ CONH₂ compound $\xrightarrow[(90\%)]{\text{PhI(OH)OTs}}$ NH₂ compound

NH₂ compound $\xrightarrow[\substack{\text{K}_2\text{CO}_3\\ (22\%)}]{\text{Br}-(\text{CH}_2)_n-\text{Br}}$ N-bridged compound ≡

 (analog)