Hypervalent Bromine

~An outlaw of organic chemistry~

Literature seminar

January 10th, 2012(Tue)

Masahiro Kojima(B4)

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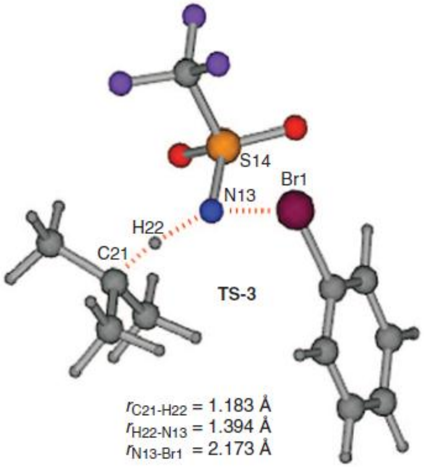
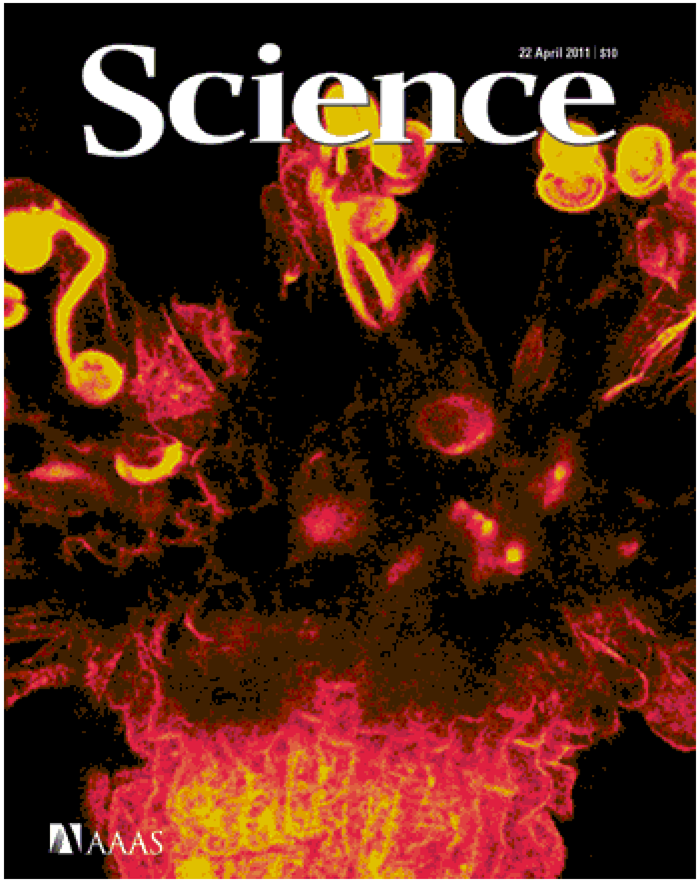
14C outlaw

20C outlaw



21C outlaw

0. Introduction



COVER False-colored two-photon microscopy image showing green fluorescent protein–labeled pollen on the stigma (the top of the pistil) of *Arabidopsis thaliana*. On page 434, Michard *et al*.

http://www.sciencemag.org/content/332/6028.cover-expansion

Reports

☐ **Polarized Gamma-Ray Emission from the Galactic Black Hole Cygnus X-1**
P. Laurent, J. Rodriguez, J. Wilms, M. Cadolle Bel, K. Pottschmidt, and V. Grinberg
Science 22 April 2011: 438-439.
Published online 24 March 2011 [DOI:10.1126/science.1200848]

This gamma-ray emission originates from a jet of relativistic particles that is formed in close proximity to the black hole.

» Abstract » Full Text » Full Text (PDF)

☐ **Selective, Nickel-Catalyzed Hydrogenolysis of Aryl Ethers**
Alexey G. Sergeev and John F. Hartwig
Science 22 April 2011: 439-443.

A catalyst that cleaves aryl-oxygen bonds but not carbon-carbon bonds may help improve lignin processing.

» Abstract » Full Text » Full Text (PDF) » Supporting Online Material

☐ **High-Performance Electrocatalysts for Oxygen Reduction Derived from Polyaniline, Iron, and Cobalt**
Gang Wu, Karren L. More, Christina M. Johnston, and Piotr Zelenay
Science 22 April 2011: 443-447.

Fuel cell catalysts synthesized from abundant metals approach the performance and durability of platinum at lower cost.

» Abstract » Full Text » Full Text (PDF) » Supporting Online Material » Podcast Interview

☐ **Highly Regioselective Amination of Unactivated Alkanes by Hypervalent Sulfonylimino-λ^3-Bromane**
Masahito Ochiai, Kazunori Miyamoto, Takao Kaneaki, Satoko Hayashi, and Waro Nakanishi
Science 22 April 2011: 448-451.

A highly reactive bromine-based reagent can add nitrogen to hydrocarbons without the need for metal catalysts.

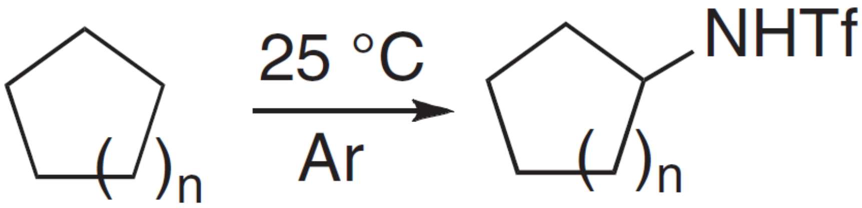
» Abstract » Full Text » Full Text (PDF) » Supporting Online Material

On April 22nd, 2011, one article was published on *Science*.

REPORTS

Highly Regioselective Amination of Unactivated Alkanes by Hypervalent Sulfonylimino-λ³-Bromane

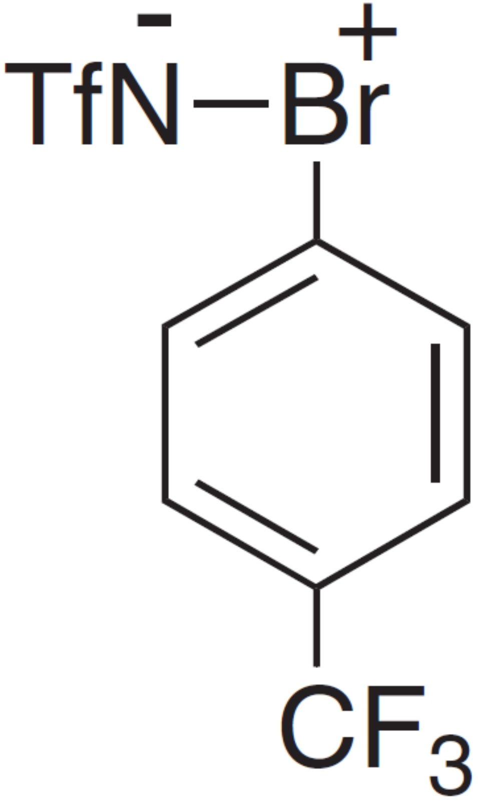
Masahito Ochiai,[1]* Kazunori Miyamoto,[1] Takao Kaneaki,[1] Satoko Hayashi,[2] Waro Nakanishi[2]*



	n	yield
3a:	n = 1	(92%)
3b:	2	91%
3c:	3	70%
3d:	4	81%
3e:	6	(65%)
3f:	11	(54%)

The article reported regioselective sp3-CH amination of functional-group-free alkanes, metal free!!

What are the active species?



Hypervalent sulfonylimino-λ^3-bromane

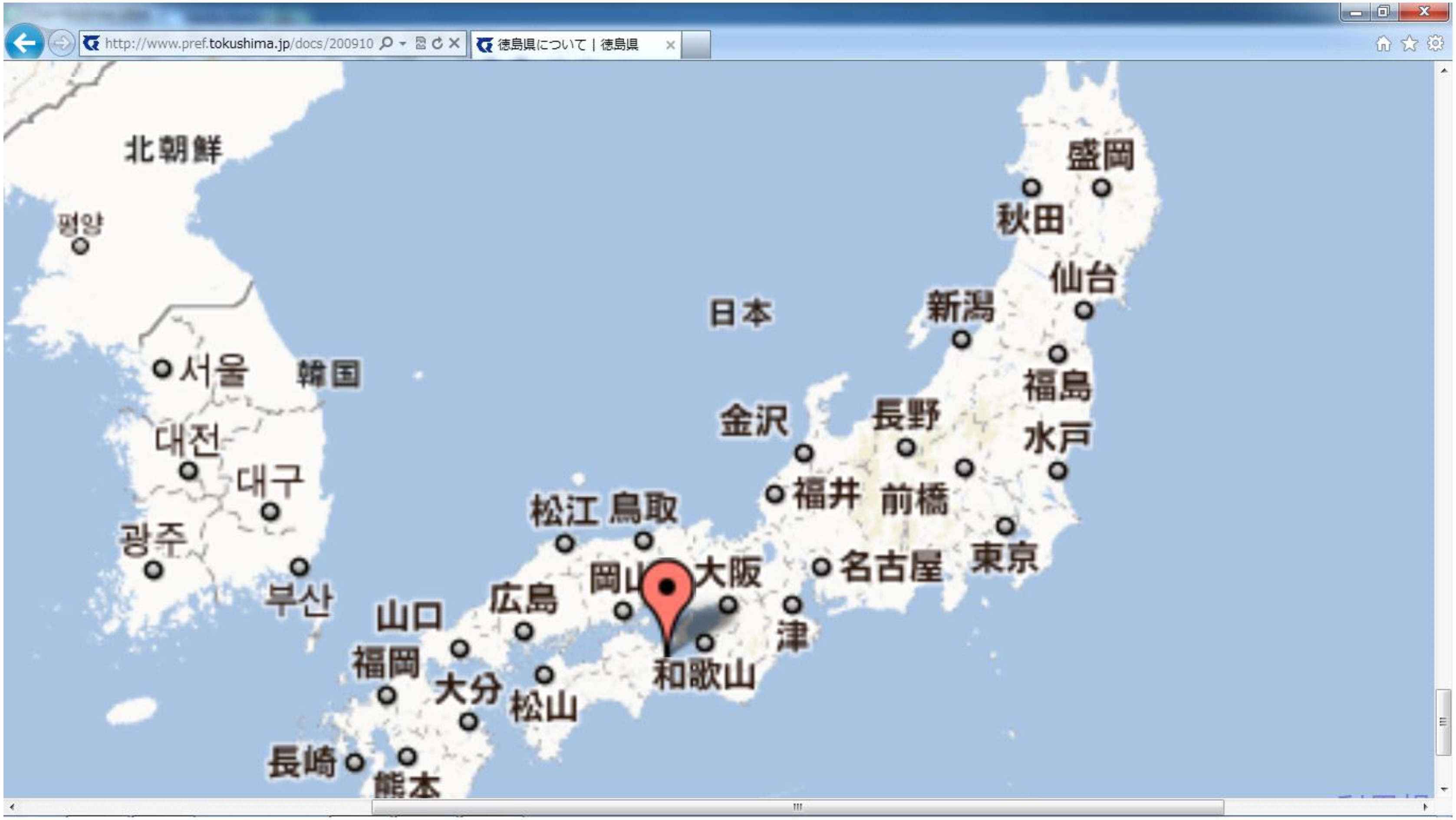
- Isolated, colorless plates
- Soluble in DCM, MeCN, acetone
- Storable under argon in refrigerator (without decomposition over 2 months!)

Today, I would like to focus on its relatives:

Hypervalent bromines

Front runner: Prof. Ochiai

The author of the article conducts research in…



University of Tokushima, faculty of pharmaceutical sciences
Ochiai laboratory

Professor Masahito Ochiai

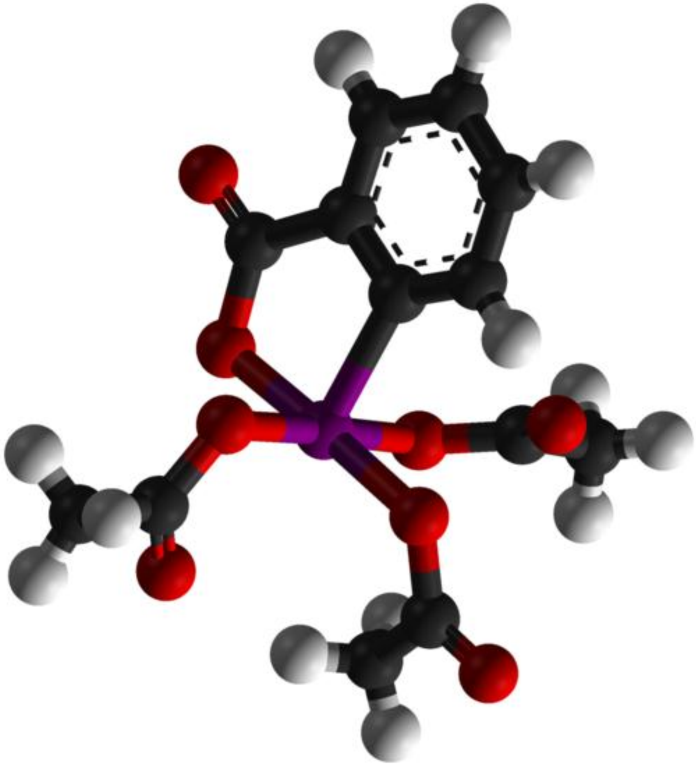
Masahito Ochiai

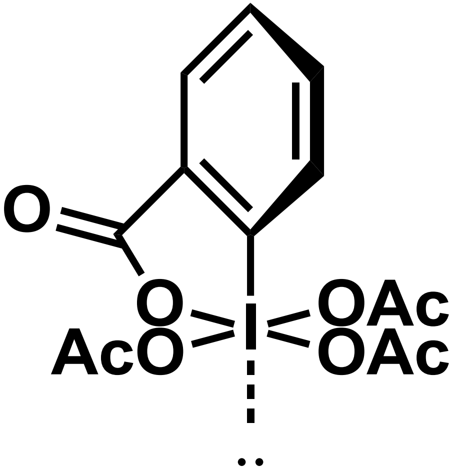
Masahito Ochiai joined the Institute for Chemical Research, Kyoto University, as a research associate in 1975. After working as a postdoctoral fellow at University of Wisconsin with Professor B. M. Trost, he moved to Gifu Pharmaceutical University as an Assistant Professor in 1989. He was promoted to Professor of Faculty of Pharmaceutical Sciences, University of Tokushima, in 1992. He received Pharmaceutical Society of Japan Award and Society of Iodine Science Award. His research interests are in the areas of synthetic organic chemistry.

He has made countless contributions in a field of hypervalent iodine chemistry, including the first report of its catalytic use.

His unique, unprecedented research area:
Chemistry of HYPERVALENT BROMINE

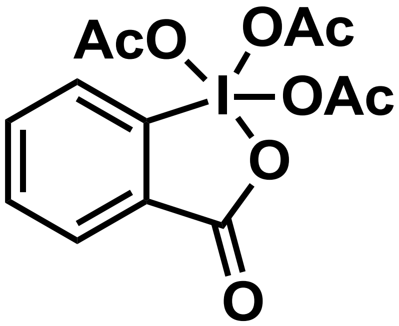
1. General aspects of hypervalent halogens





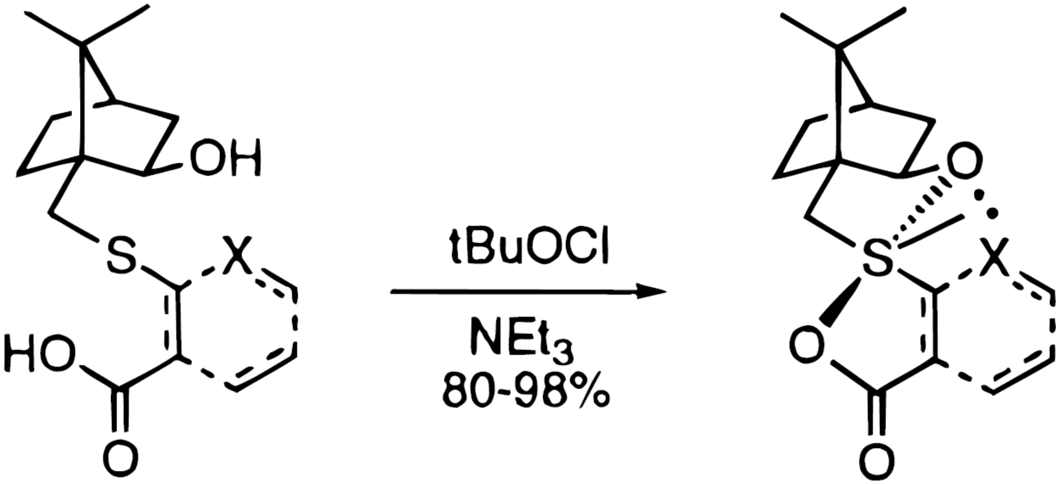
DMP

What does “hypervalent” mean??



λ^5-iodane

D.B. Dess, J.C. Martin
J. Org. Chem. **1983**, 48. 4156.



λ^4-sulforane

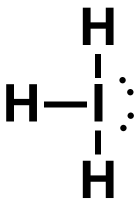
J. Zhang et al., *J. Am. Chem. Soc.* **1998**, 120, 1631.

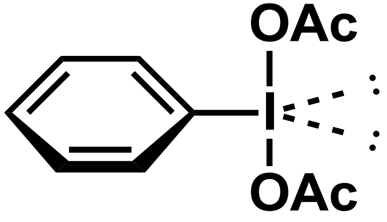
"Molecules containing elements of Groups 15 - 18 bearing more electrons than the octet in the valence shell are described as hypervalent molecules."

"Hypervalent Iodine Chemistry"
Ed. by Wirth T.,*Top. Curr. Chem.*, **2003**, Springer, 2, p1.

What is λ?? ~IUPAC rules~

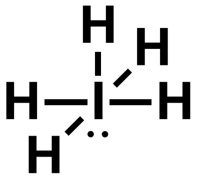
λ^3-iodanes

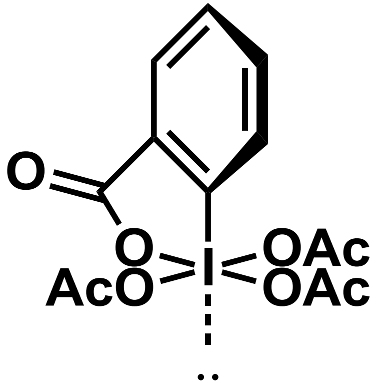




PIDA

λ^5-iodanes





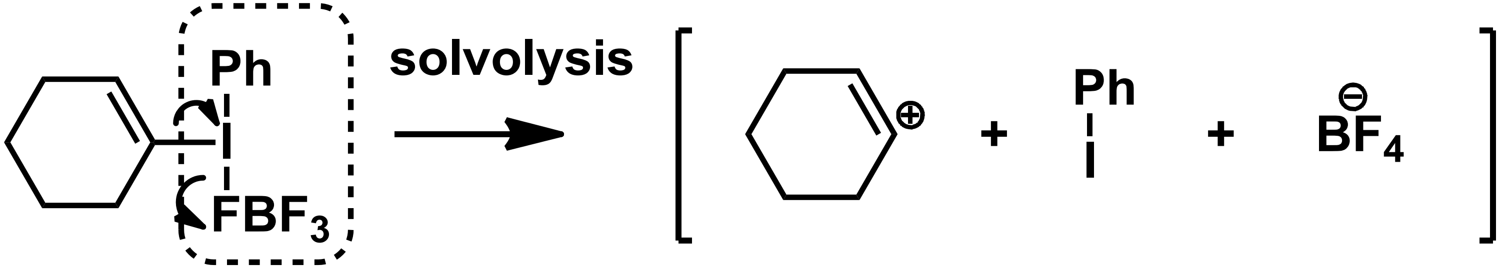
DMP

With its superscripts, λ signifies the bonding number to an atom.
Its usage is restricted to molecules with non-standard valence states.

W.H. Powell, *Pure Appl. Chem.,* **1984**, 56, 6, 769.

Hypervalent halogen as hypernucleofuge

In 1995, Ochiai et al measured the nucleofugality of trivalent iodine compounds:



Hyper-leaving group

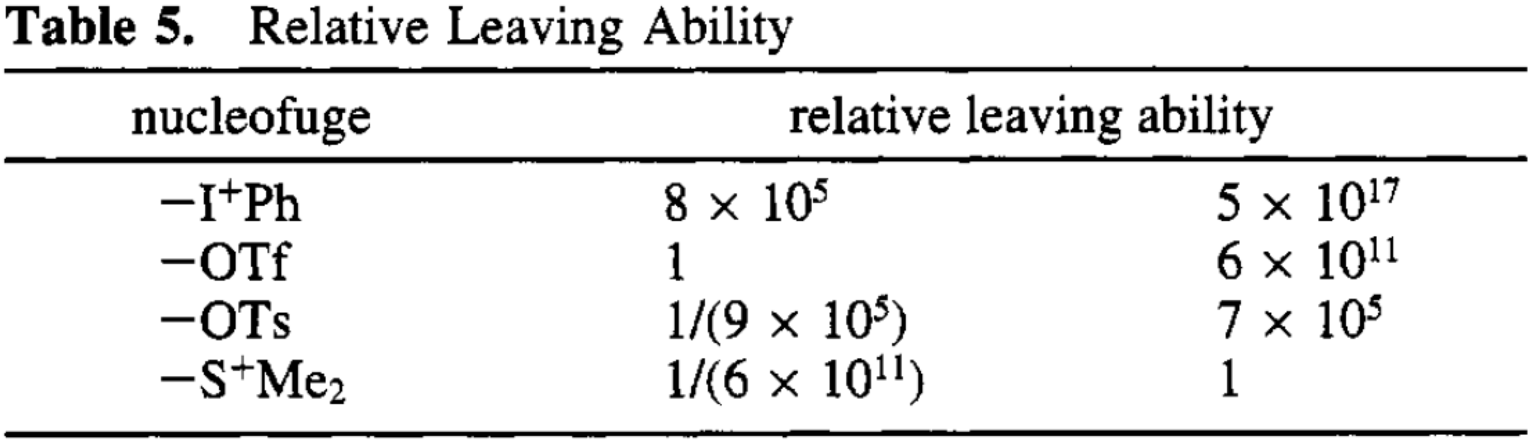


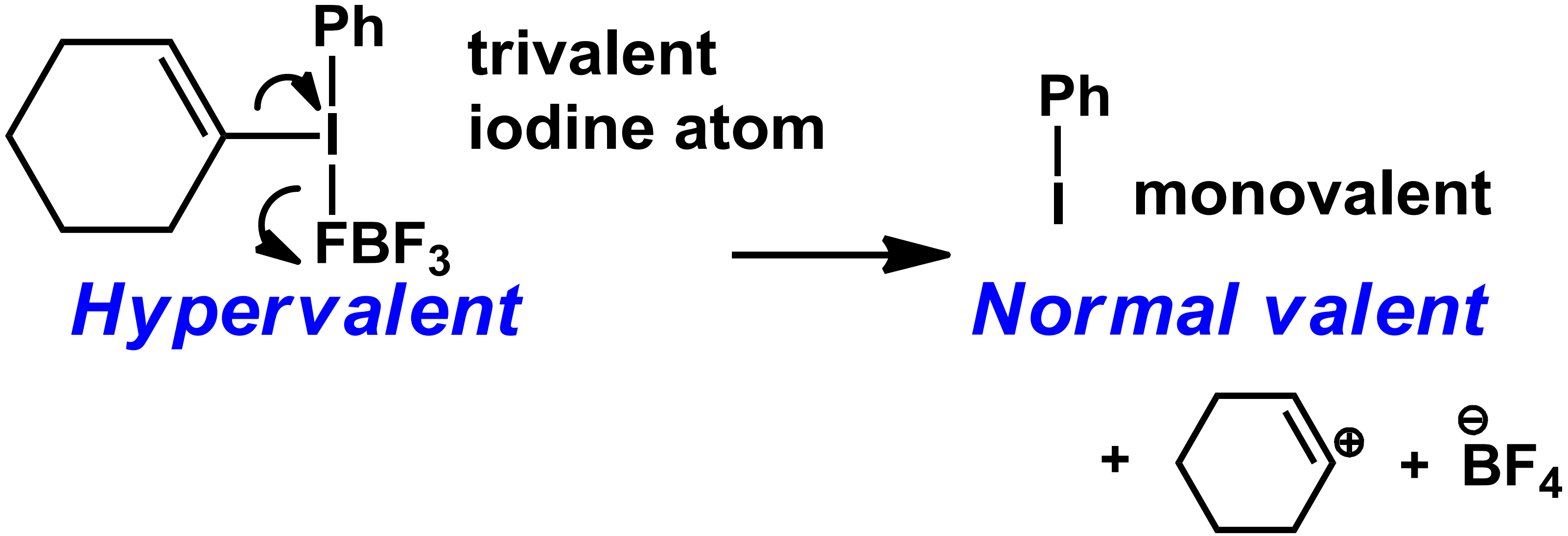
Table 5. Relative Leaving Ability

nucleofuge	relative leaving ability	
$-I^+Ph$	8×10^5	5×10^{17}
$-OTf$	1	6×10^{11}
$-OTs$	$1/(9 \times 10^5)$	7×10^5
$-S^+Me_2$	$1/(6 \times 10^{11})$	1

Leaving ability of phenyl-λ^3-iodanyl group is 10^6 times greater than TfO^- !!

M. Ochiai et al., *J. Am. Chem. Soc.* **1995**, 127, 3360.

Key step = Reductive elimination



trivalent iodine atom

Hypervalent

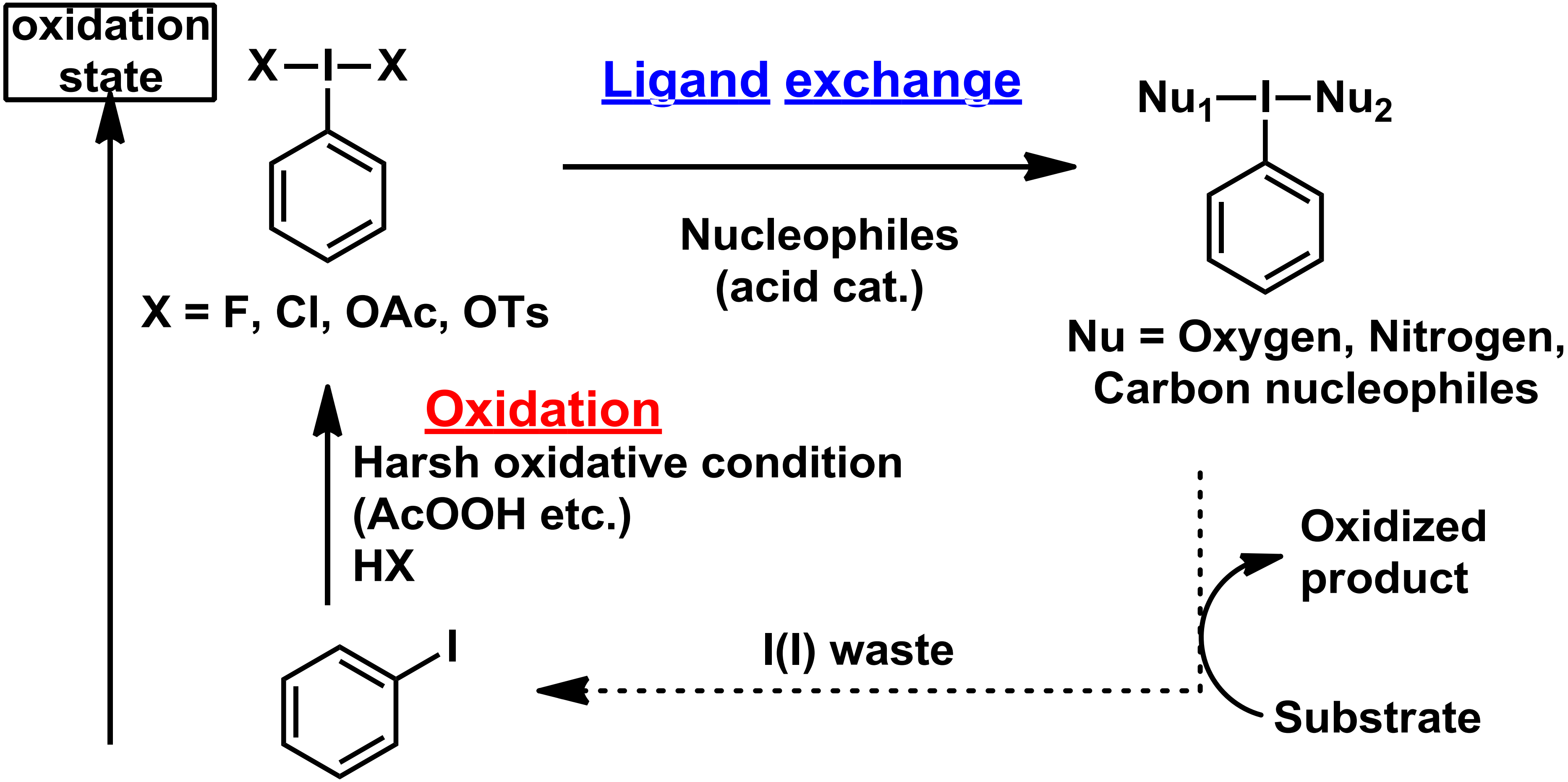
monovalent

Normal valent

Leaving process of Ph(BF_4)I involves energetically preferred reduction of hypervalent iodine atom to normal valency.

This process also associates with increase in entropy, as 1 hypervalent molecule decomposes to 3 components.

Preparations



oxidation state

X—I—X

X = F, Cl, OAc, OTs

Ligand exchange

Nucleophiles
(acid cat.)

Nu_1—I—Nu_2

Nu = Oxygen, Nitrogen,
Carbon nucleophiles

Oxidation

Harsh oxidative condition
(AcOOH etc.)
HX

I

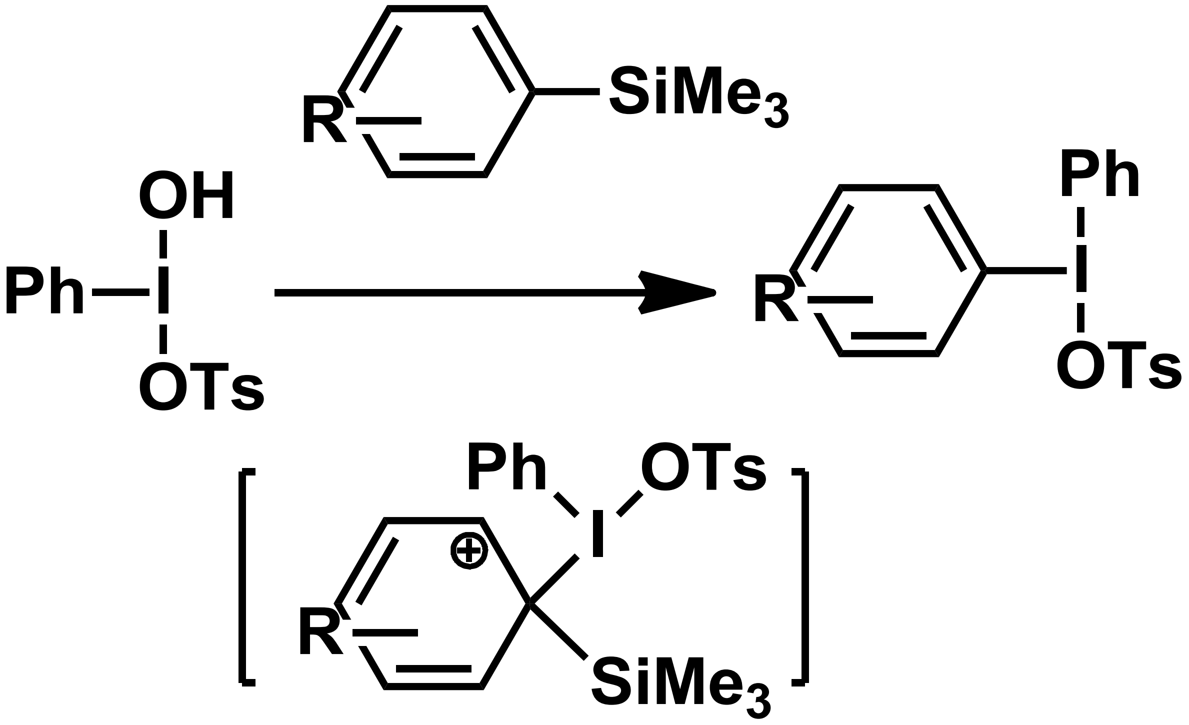
I(I) waste

Oxidized product

Substrate

Synthesis of polyvalent iodine reagents generally requires 2 steps.

Preparations ~Ligand exchange~

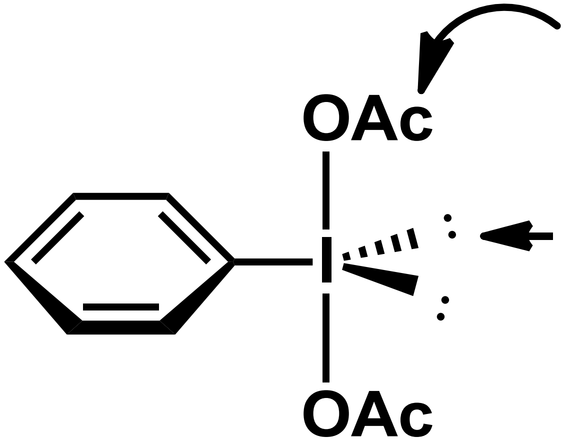


Silicon directed ipso substitution gives Ar_2IL.

Si, Ge, Sn, boronic acids are used.

G.F. Koser et. al., *J. Org. Chem.* **1980**, 45, 1543.

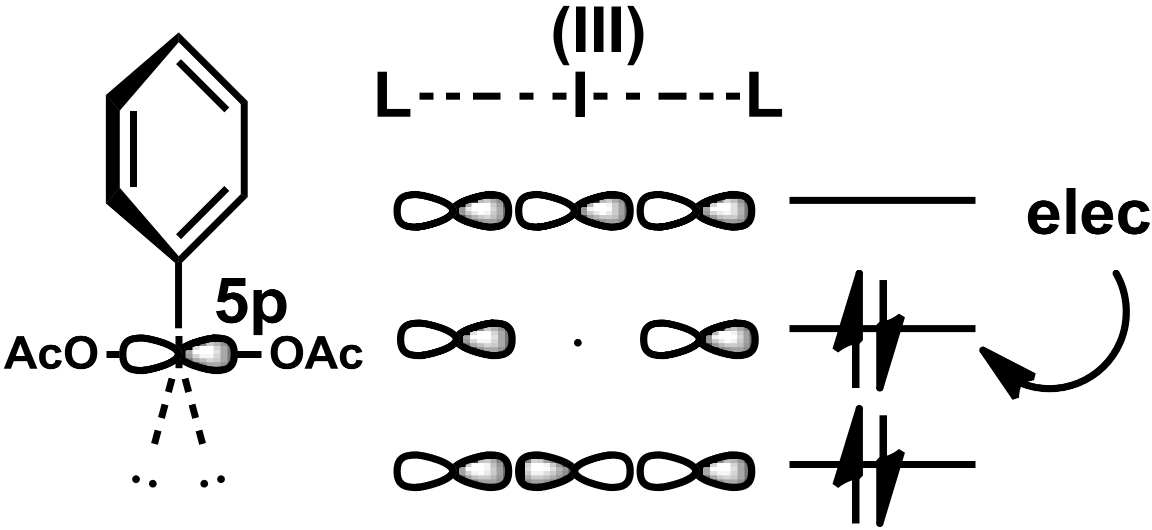
Structure ~two heteroatom ligands~



Heteroatom ligands at apical positions: 3c-4e bonds

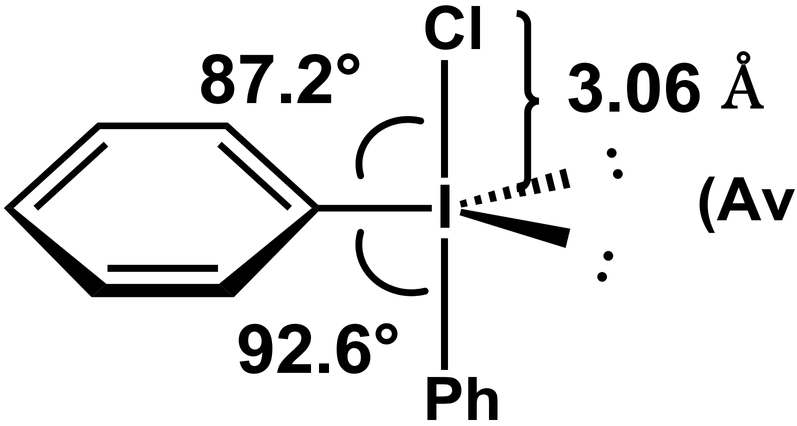
Lone pairs and aryl substituents at equatorial positions

Pseudotrigonal bipyramid structure



3c-4e bonds:
electron deficient I atom

Structure ~two carbon ligands~

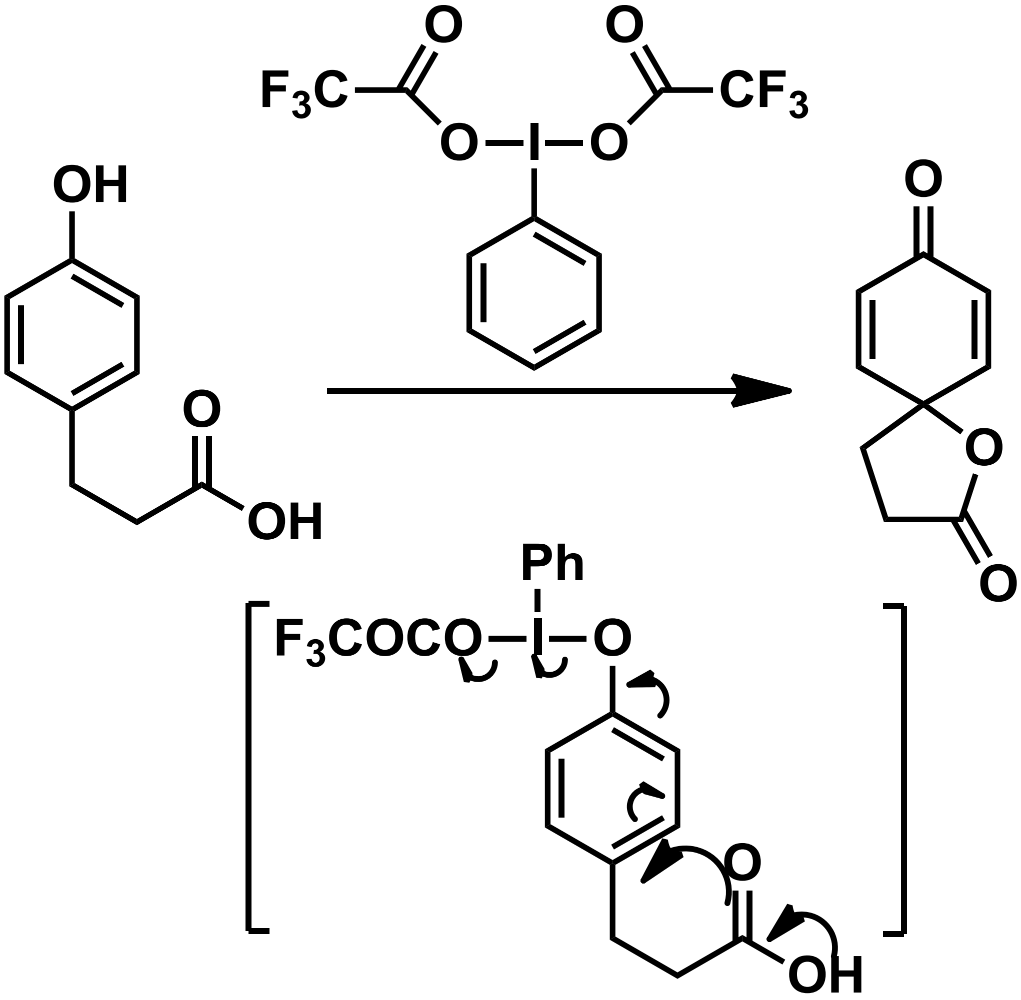


(Average bond length of I-Cl: 2.56 Å)

λ_3-iodanes with two carbon ligands transfer its carbon ligands to nucleophiles through reductive elimination of ArI.

Alcock N.W. et. al., *J. Chem. Soc. Dalton.* **1977**, 217.

Typical reaction: Oxidative cyclization



I(III) induced dearomatizing, oxidative **cyclization**

Y. Tamura et al., *J. Org. Chem.* **1987**, 52, 3927.

Iodine vs Bromine ~Why is Br so promising?~

Electronegativity(Pauling)

I < Br

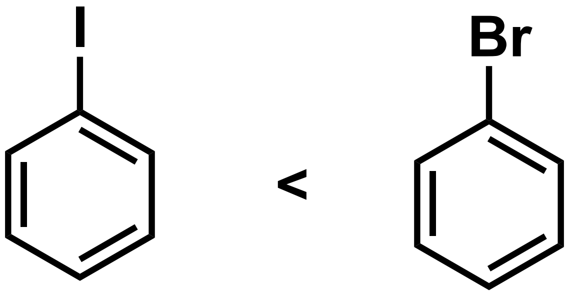
2.66 2.96

Covalent radius (Å)

I > Br

1.33 1.14

Ionization potential

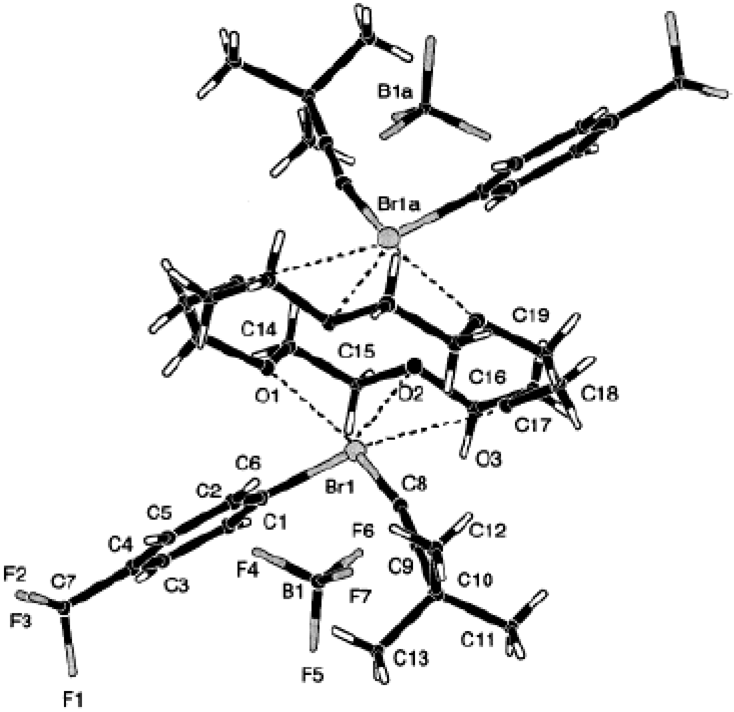


8.69 eV 8.98 eV

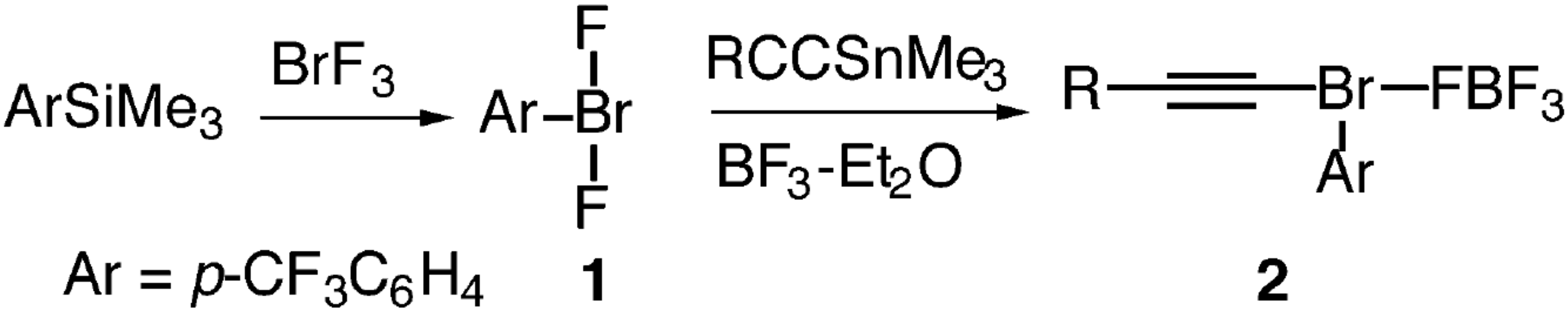
Bromine is smaller, more electron negative an atom than iodine, so:

- **Synthesis of Br(III) compound requires harder oxidation process.**
- **Smaller atom size contributes to distorted structure=high reactivity.**
- **Br(III) compound is more likely to undergo reductive elimination.**

2. Alkynyl(aryl)-λ^3-bromanes



Synthesis

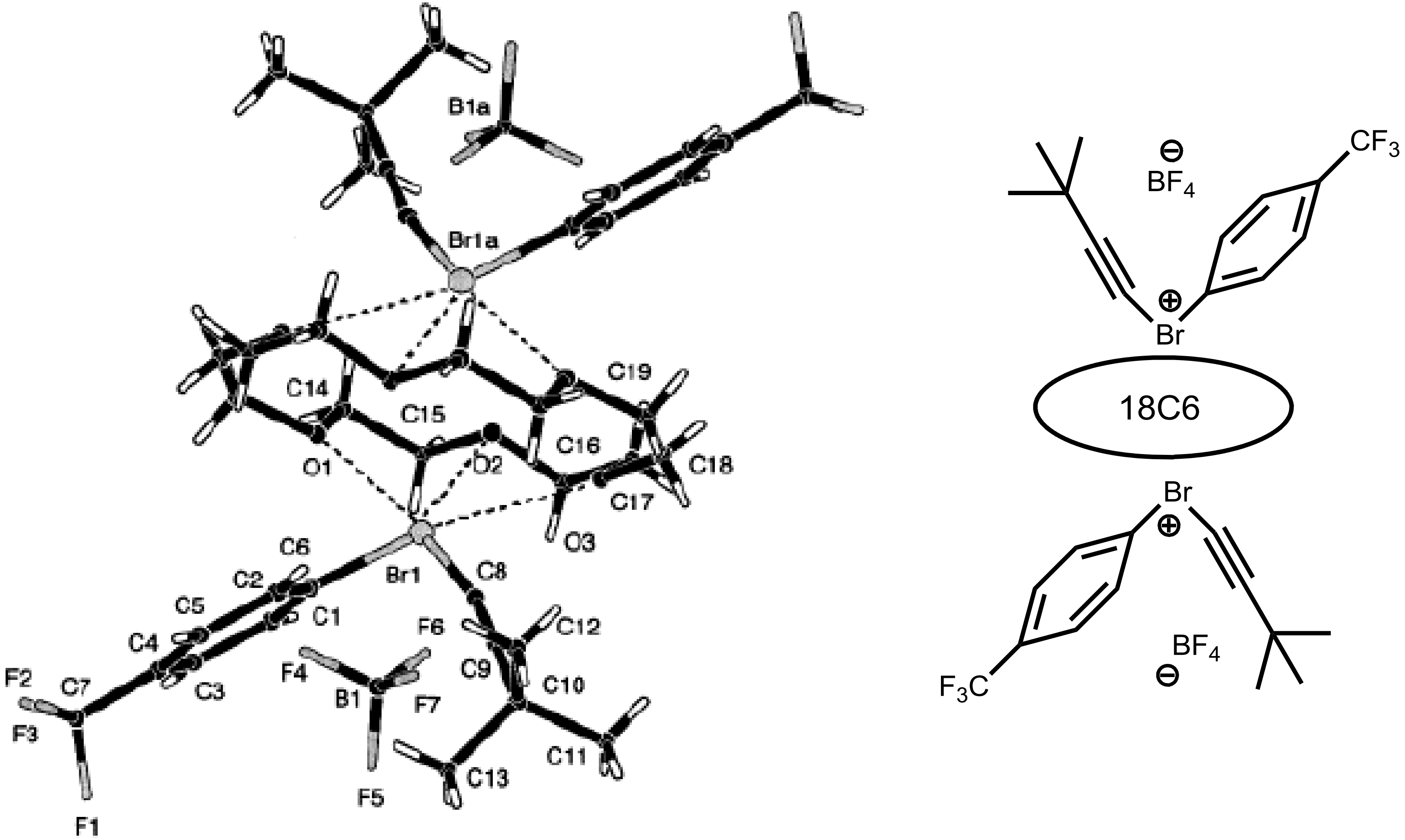


seven examples, 76-89% yield

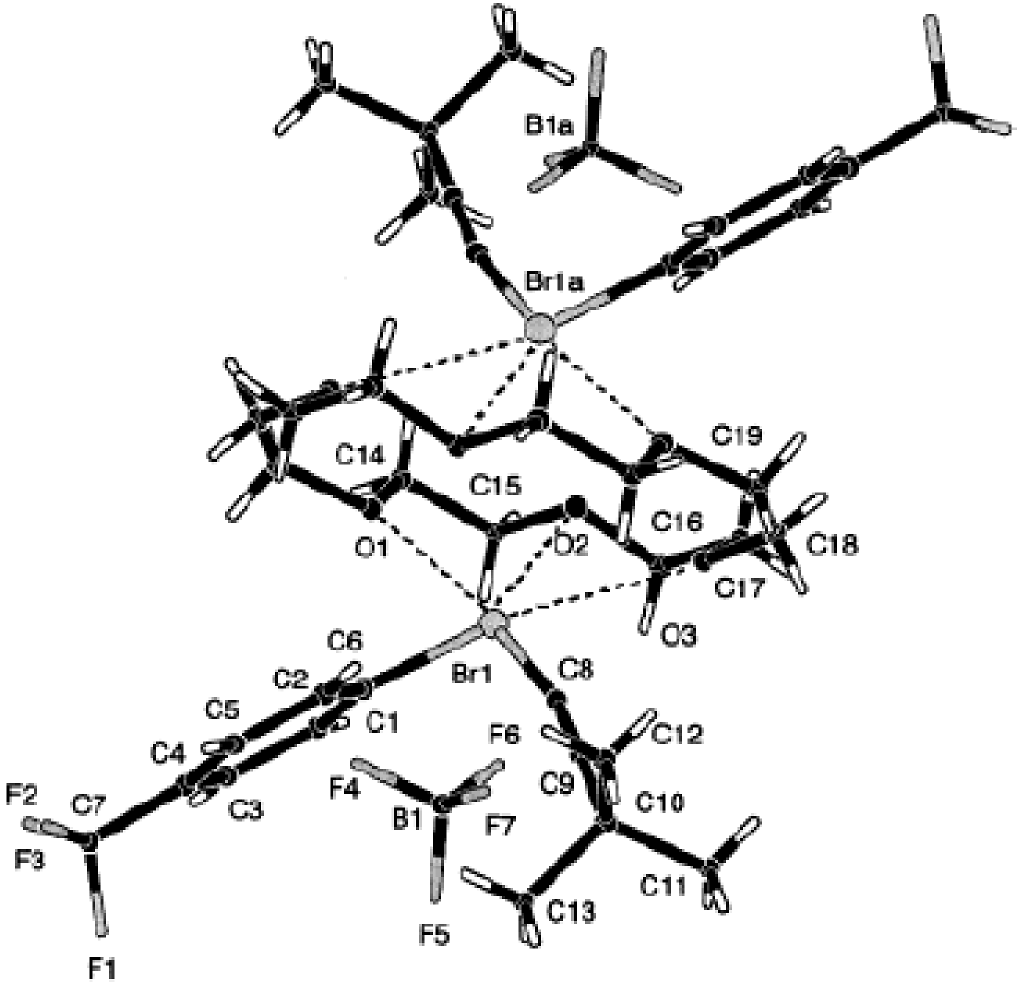
In 2003, Ochiai et al suceeded in synthesizing Alkynyl(aryl)-λ^3-bromane for the first time!!

M. Ochiai et al., *J. Am. Chem. Soc.* **2003**, 125, 15304.

Structure



X-ray analysis of its crown ether(18C6) complex



- ***Pentagonal, planar coordination around Br***
  (O1,2,3, Br1, C1,8)

- ***Bent, longer triple bond***

Br1-C8-C9 angle: 167.3°

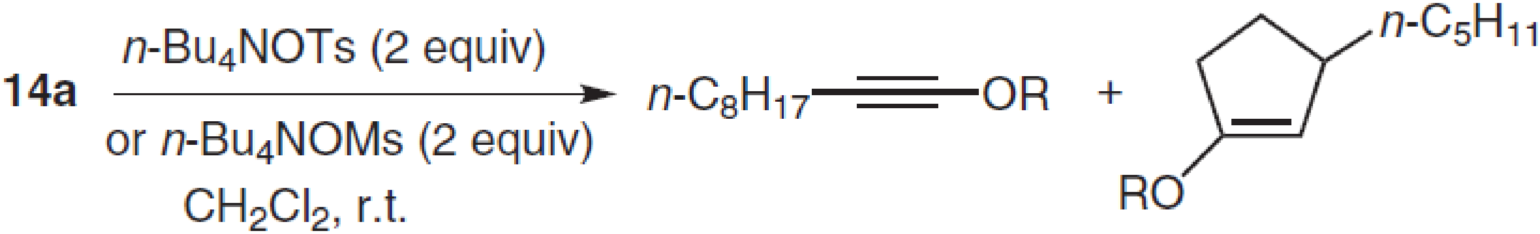
C8-C9: 1.211 Å

(1.181 Å on average triple bond)

↓

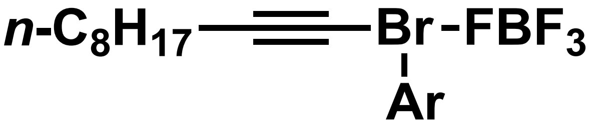
Polarization of π-electrons by positive partial charge on Br(III)

Reactions: Michael-carbene rearrangements



18a (R = Ts, 55%)
18b (R = Ms, 68%)

19a (R = Ts, 5%)
19b (R = Ms, 5%)

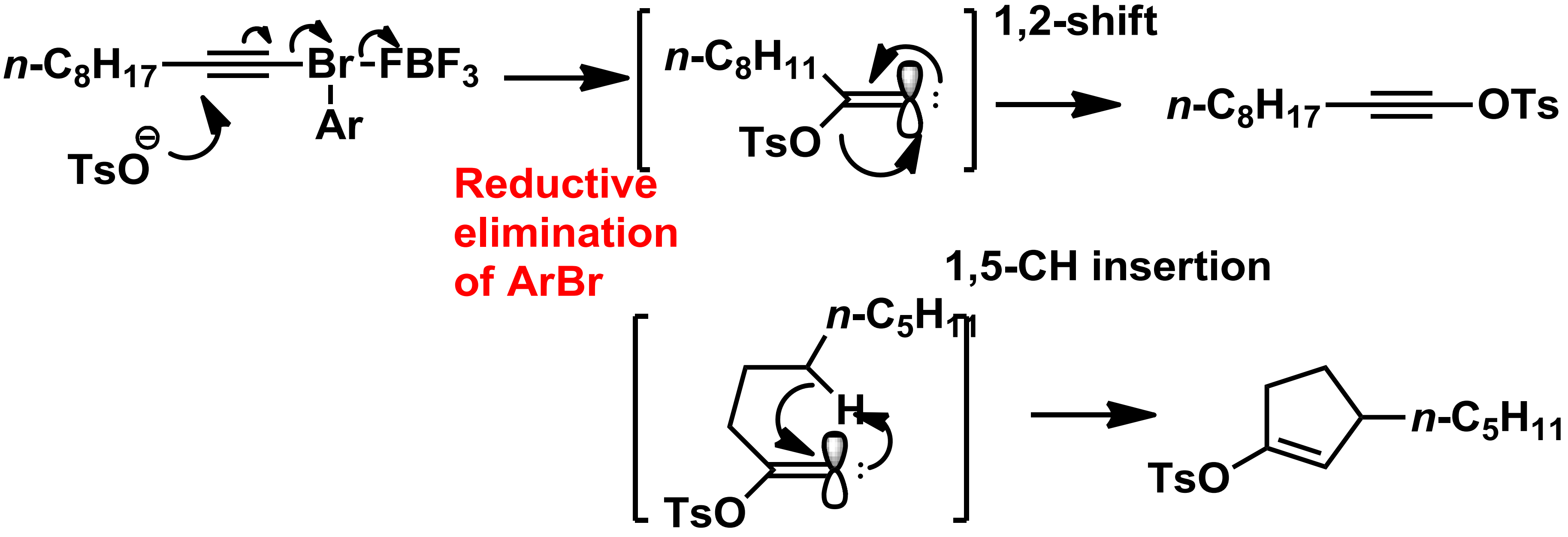


$n\text{-}C_8H_{17}\text{—}C{\equiv}C\text{—}\underset{Ar}{Br}\text{—}FBF_3$

14a

Weak nucleophiles like TsO$^-$ undergo Michael addition (not reported in λ^3-iodanes)

Reaction mechanisms

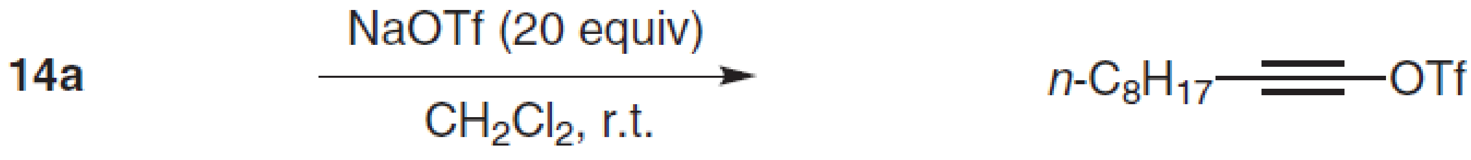


Reductive elimination of ArBr

1,2-shift

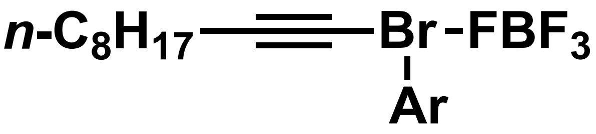
1,5-CH insertion

Triflate anion as Nucleophile!!



$$\mathbf{14a} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, r.t.}]{\text{NaOTf (20 equiv)}} n\text{-C}_8\text{H}_{17}\text{−C≡C−OTf}$$

23 (72%)



$$n\text{-C}_8\text{H}_{17}\text{−C≡C−}\underset{\text{Ar}}{\text{Br}}\text{−FBF}_3$$

14a

Even triflate anion works as nucleophile toward alkynyl(aryl)-λ^3-bromane

Actually, this was the first report of 23(alkynyl triflate) synthesis!!

M. Ochiai. *Synlett* **2009**, 2, 159.

Outstanding Michael acceptor efficiency

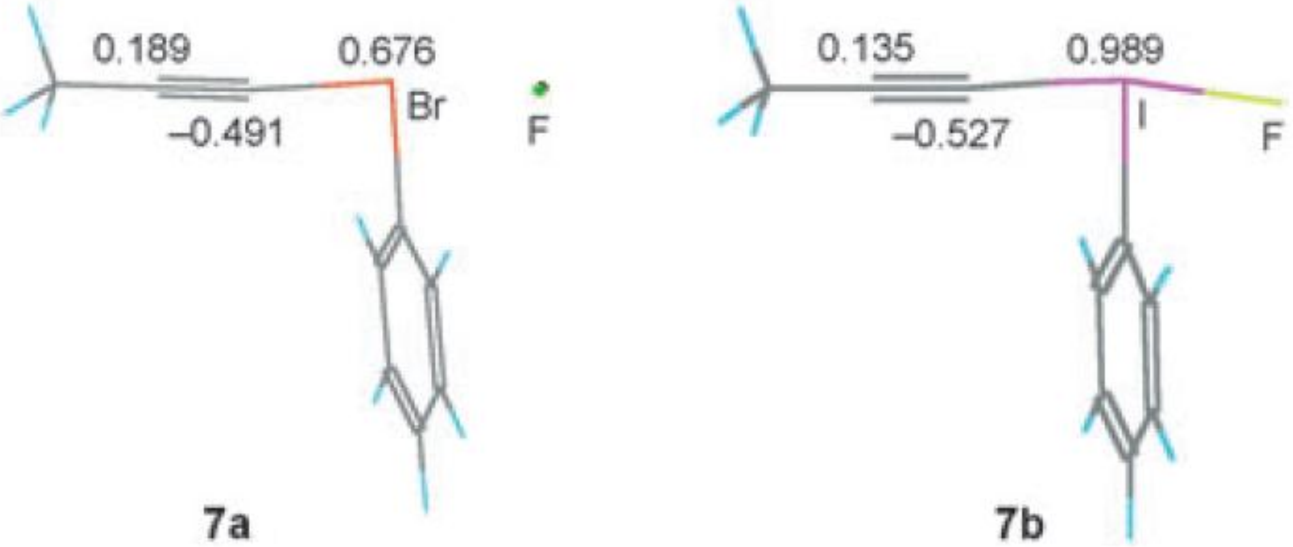


Figure 1. Mulliken atomic charges at Cα, Cβ, Br, and I calculated with the B3LYP/LanL2DZ method (Gaussian 03W).

Calculation indicates β-carbon of λ^3-bromane is more positively charged than that of iodane.

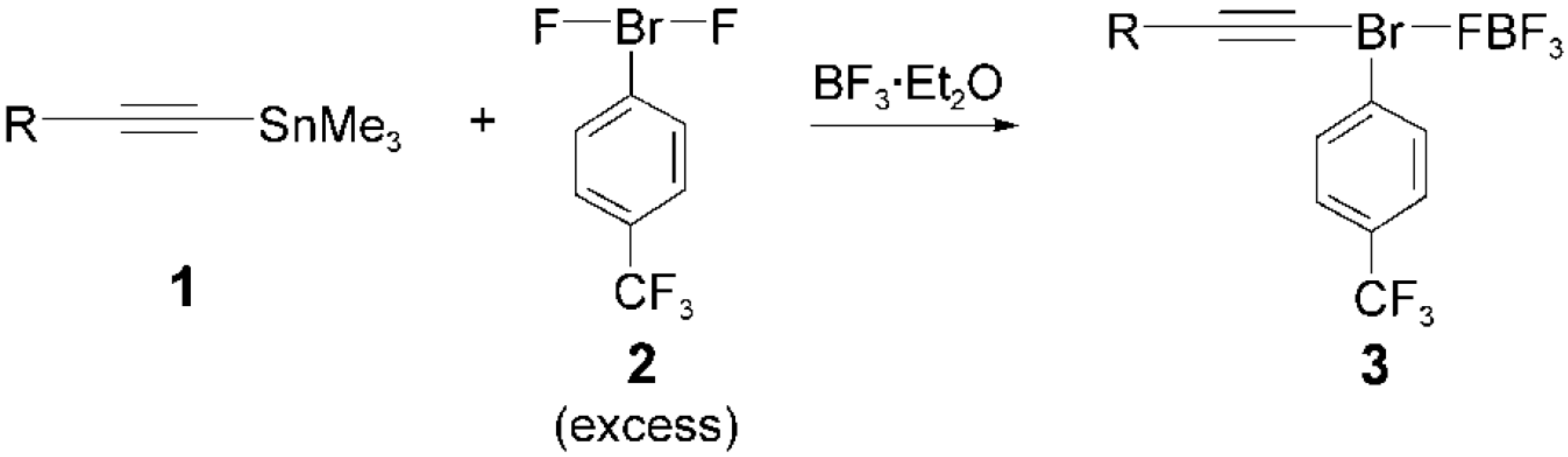
↑

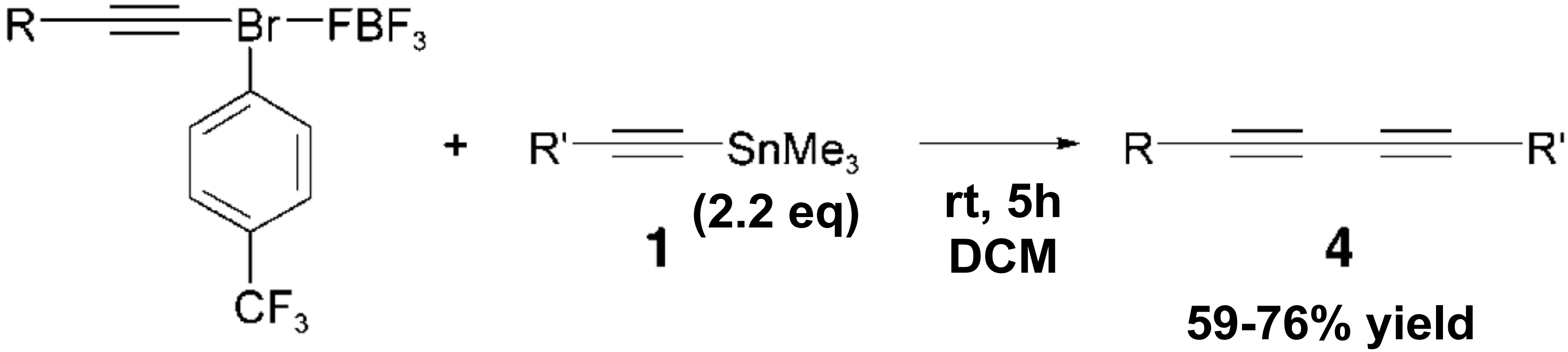
Electron-withdrawing inductive effect

σ_I = 1.63 for $PhBr(FBF_3)$

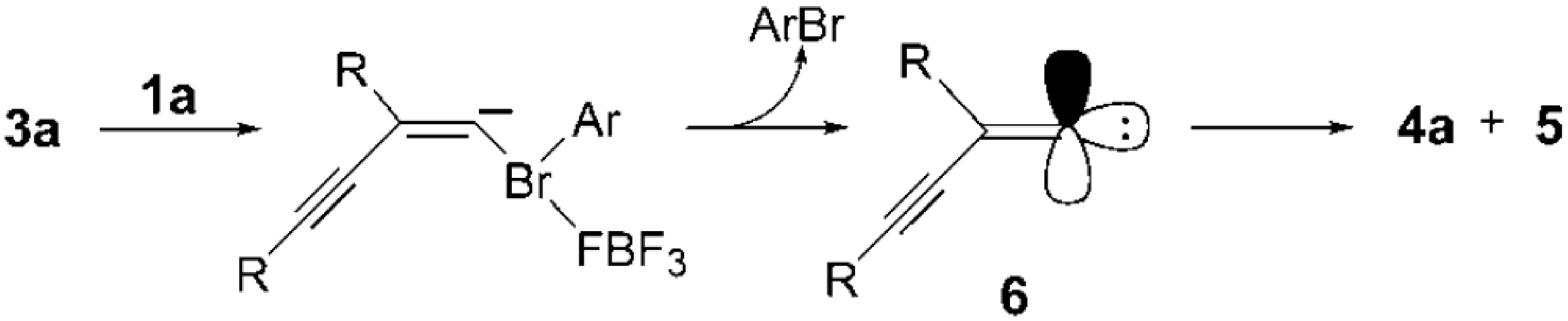
σ_I = 1.35 for $PhI(FBF_3)$

Application: Coupling of alkynyl stannanes

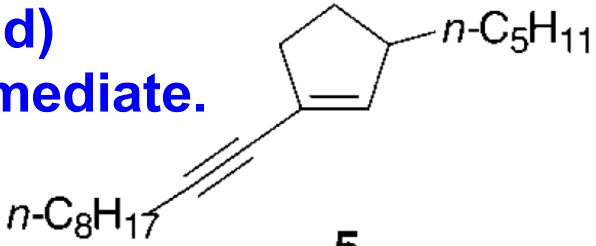




Mechanism of coupling reaction



Cyclopentenyl byproducts (ca. 4% yield) suggests the alkylidene carbene intermediate.



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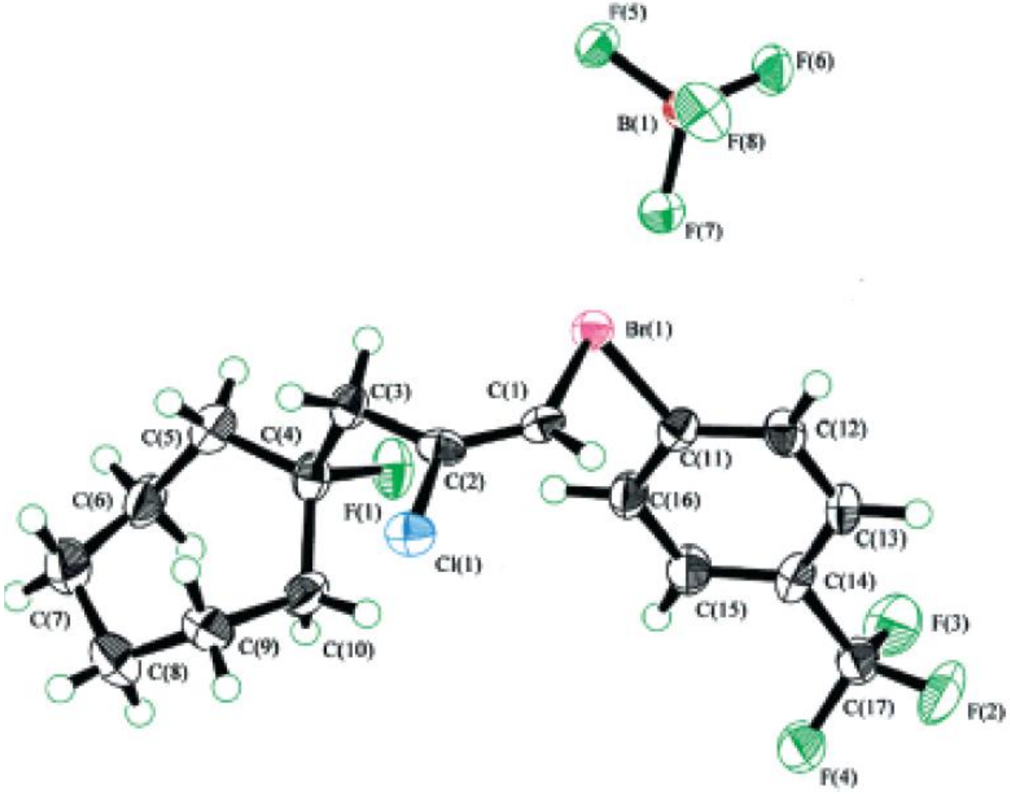
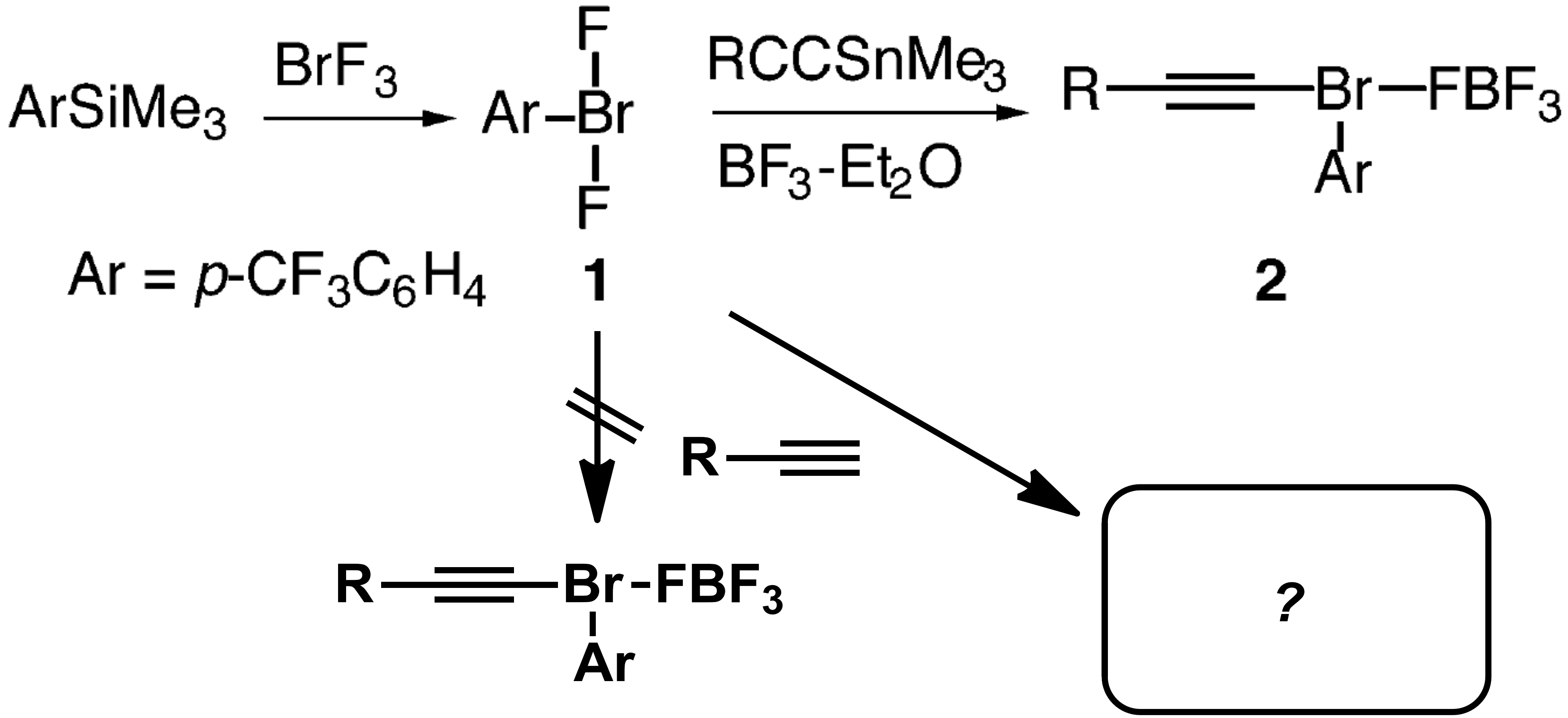
M. Ochiai et al., *Angew. Chem. Int. Ed.* **2005**, 44, 406.

3. Alkenyl(aryl)-λ³-bromanes



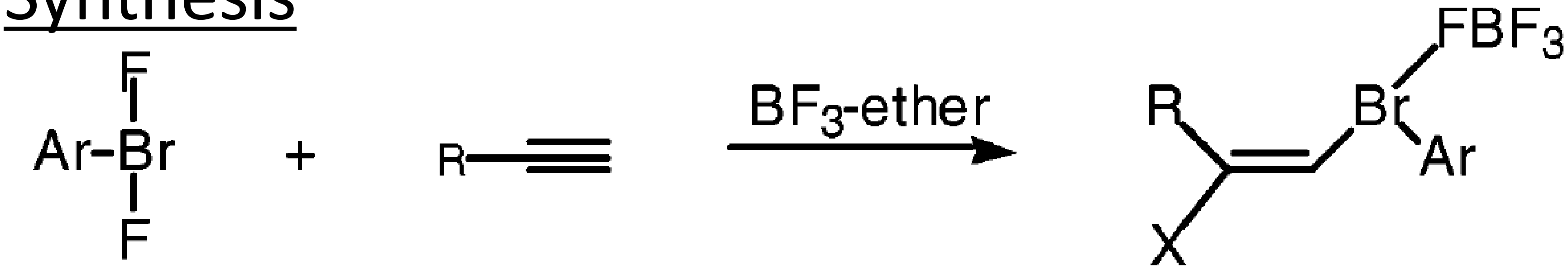
Terminal alkyne instead of alkynyl stannane?

Scheme 1



Ligand exchange did not proceed with terminal alkyne. But...

Synthesis



1

Ar = p-$CF_3C_6H_4$

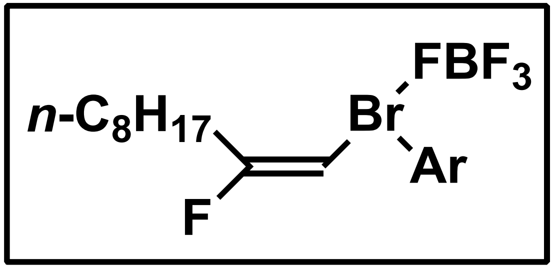
2: X = F

3a: R = n-C_8H_{17}, X = EtO

3b: R = n-C_8H_{17}, X = Cl

9 Alkyne examples, 40-88% yield
86-97% (*E*)-selective

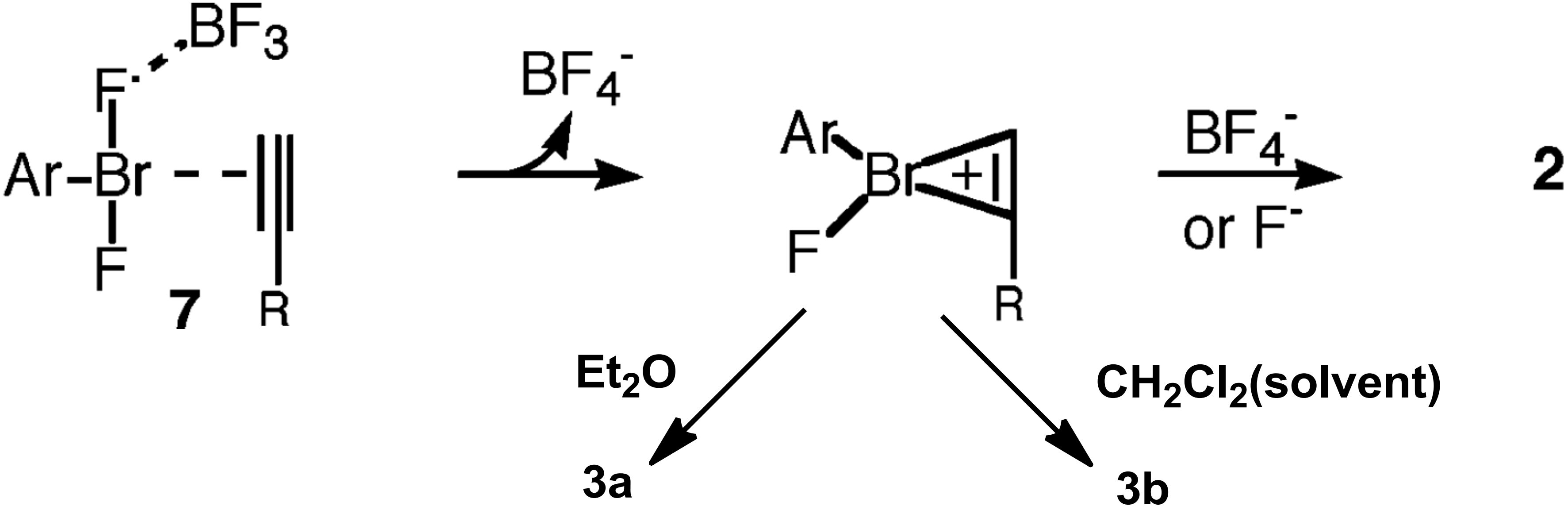
They succeeded in first isolation of β-halovinyl-λ^3-bromane.



Isolated as stable oil:
No decomposition over 1 month in a refrigerator

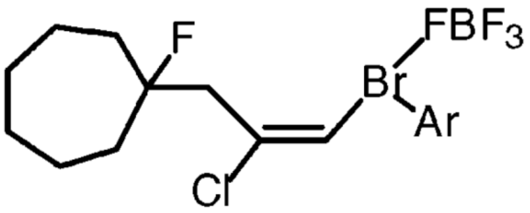
M. Ochiai et. al., *J. Am. Chem. Soc.* **2005**, 127, 10460.

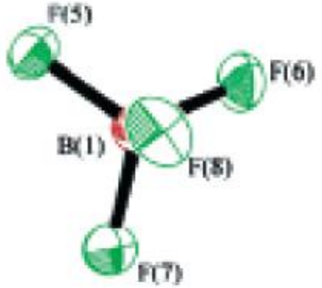
Reaction mechanisms

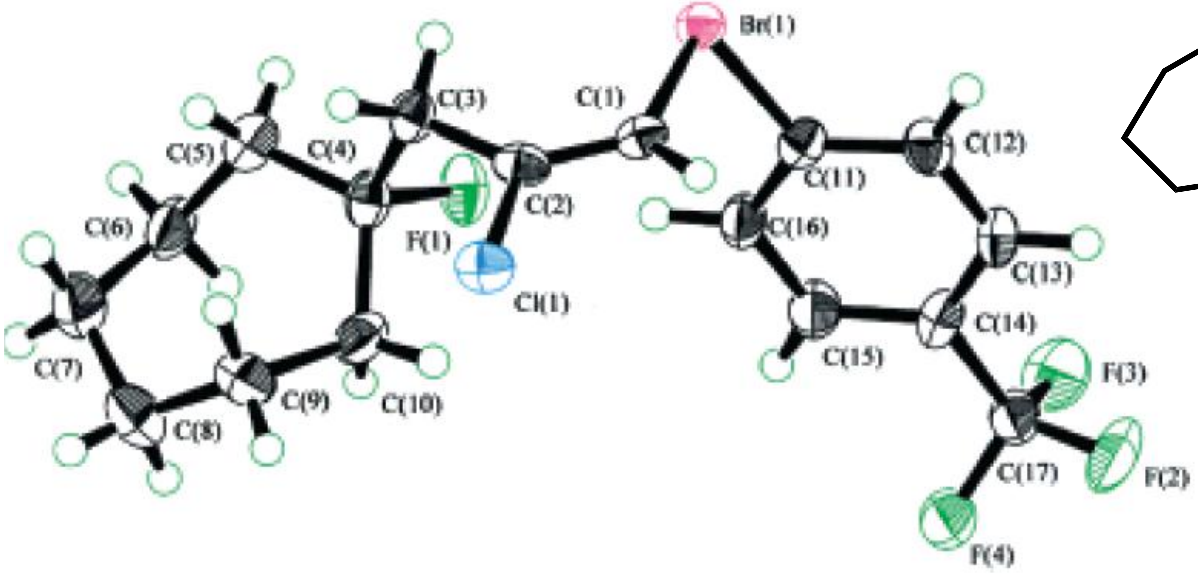


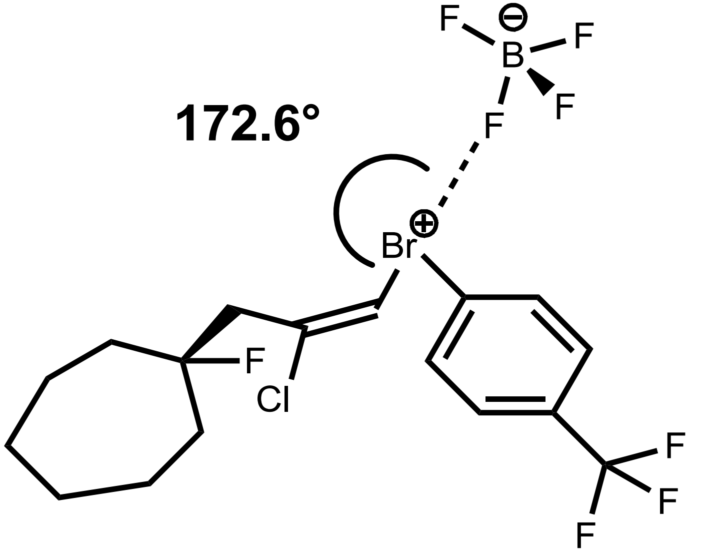
Employing BF_3•*i*-Pr_2O (bulkier Lewis acid) and $CHCl_3$ (less nucleophilic solvent) suppresses side reactions.

Structure



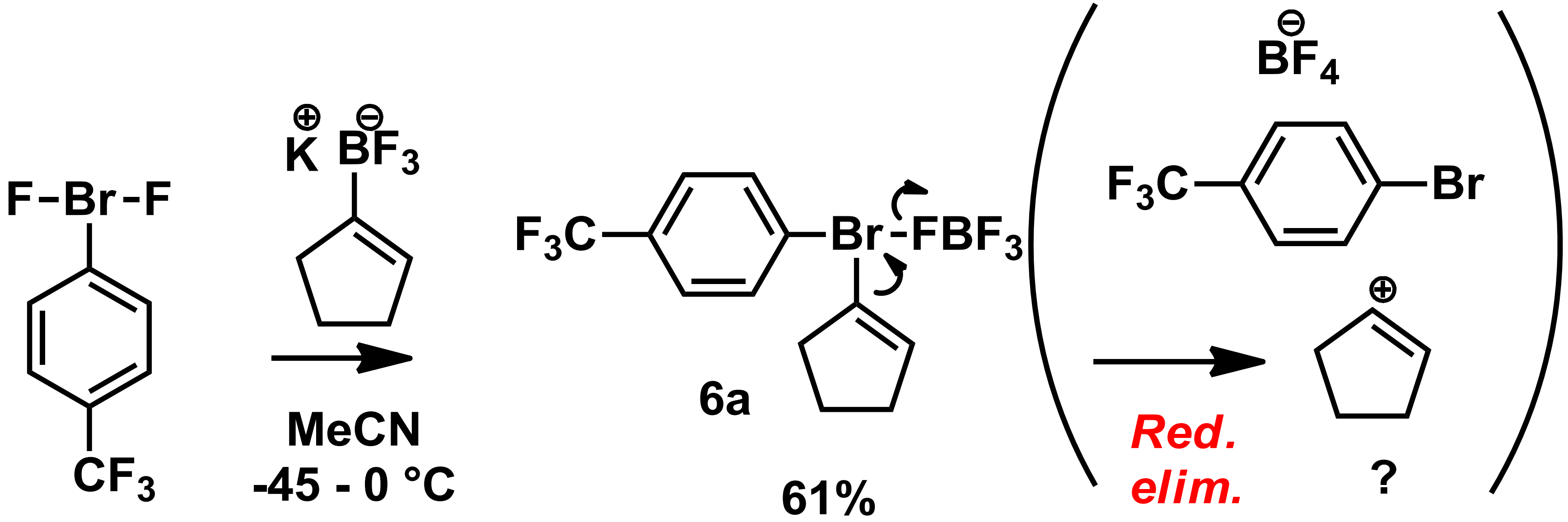






T-shaped structure with F atom of BF_4^- at apical position.

Application: Generation of cyclopent-1-enyl cation

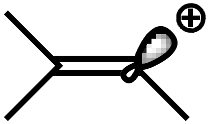


Note: cyclopentenyl cation generation has been sought by a number of researchers for more than 30 years!

W.D. Pfeifer et. al., *J. Am. Chem. Soc.* **1971**, 93, 1513.
L.R. Subramanian, ZM. Hanack *J. Org. Chem.* **1977**, 42, 174.
M. Slegt et. al., *J. Org. Chem.* **2006**, 71, 2227.

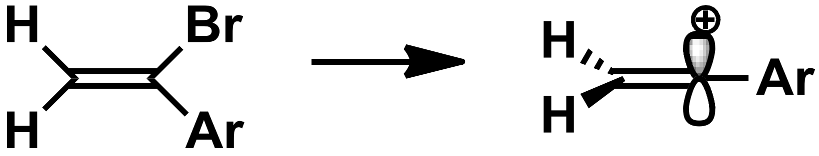
Background stories of vinyl cation

Until mid 1960s, vinyl cations are thought to be too unstable to exist.



Positive charge on sp^2 carbon(?)

In 1964, Grob and Cseh reported first vinyl cation generation.



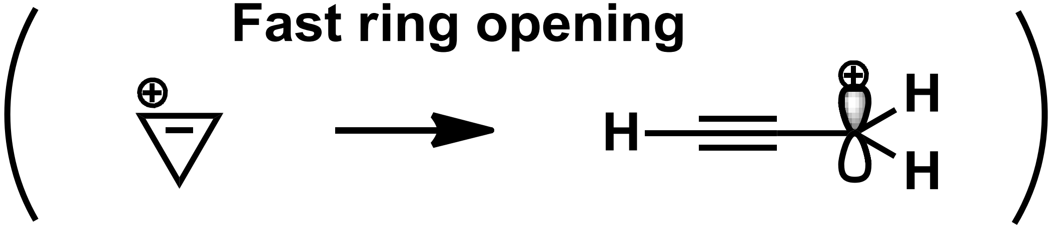
C.A. Grob, G. Cseh *Helv. Chim. Acta.* **1964**, 47, 194.

Vinyl cation prefers sp, digonal structure.

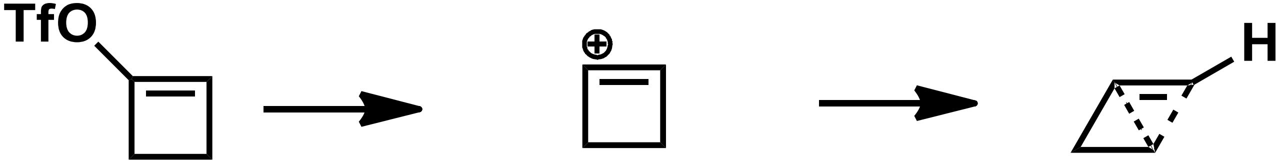
According to calculations, sp form is 40.3 kcal/mol more stable than sp^2.

Z. Rappoport, P.J. Stang Ed., "Dicoordinated Carbocations," Wiley, Chichester (1997).

What if *sp* cannot be? ~Cyclic vinyl cations~

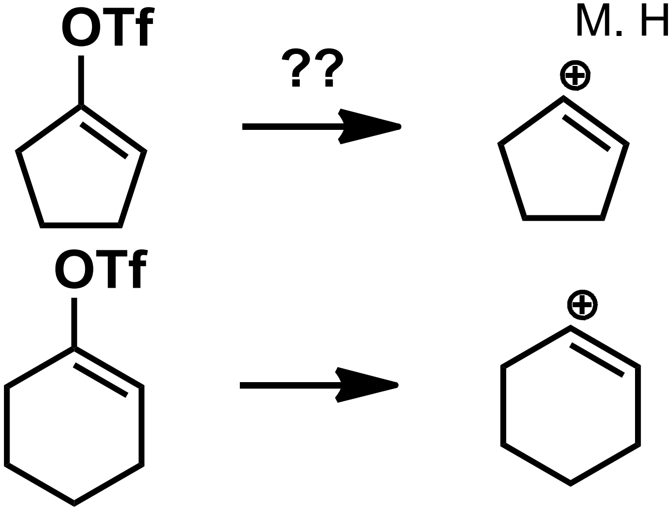


Fast ring opening



stable 3-center-2-electron bridged structure

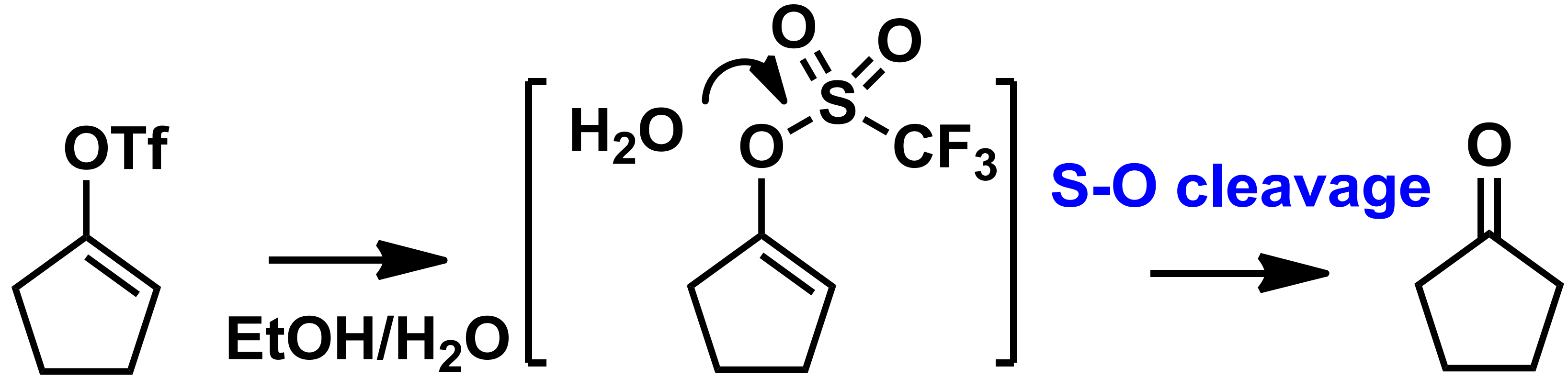
M. Hanack et. al., *J. Am. Chem. Soc.* **1979**, 101, 100.

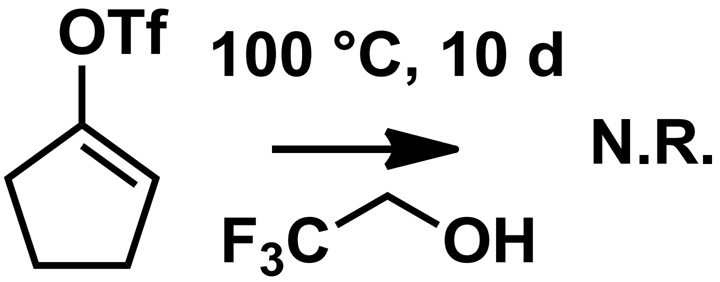


Cyclopentenyl, cyclohexyl vinyl cations were thought to be generated by TfO$^-$. But...

W.D. Pfeifer et. al., *J. Am. Chem. Soc.* **1971**, 93, 1513.

Invulnerable fortress: Cyclopent-1-enylcation

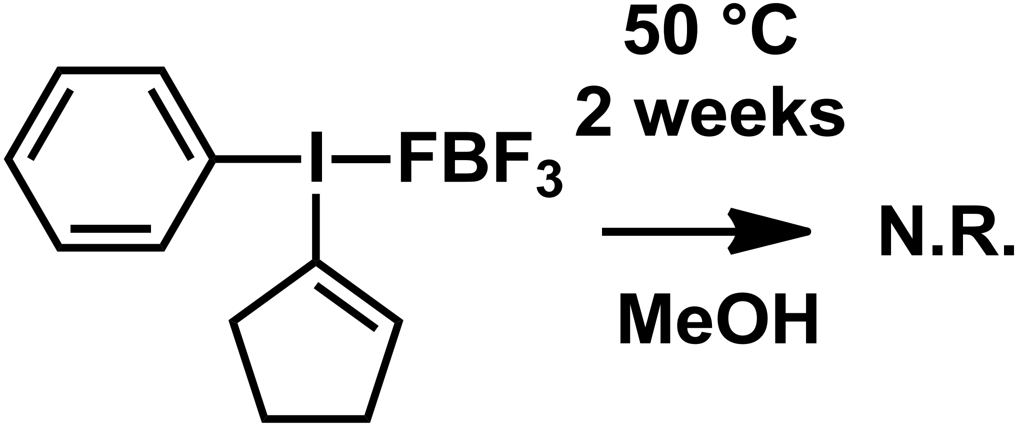




L.R. Subramanian, M.Hanack. *J. Org. Chem.* **1977**, 42, 174.

The leaving ability of triflate anion is not enough to generate cyclopentenyl cation.

Defeat of hyperleaving group I(III)



Despite more than 30 years' investigations, no one could generate the 5-membered cyclic vinyl cation by thermal solvolysis.

M. Slegt et al., *J. Org. Chem.* **2006**, 71, 2227.

Solvolysis of alkenylbromane

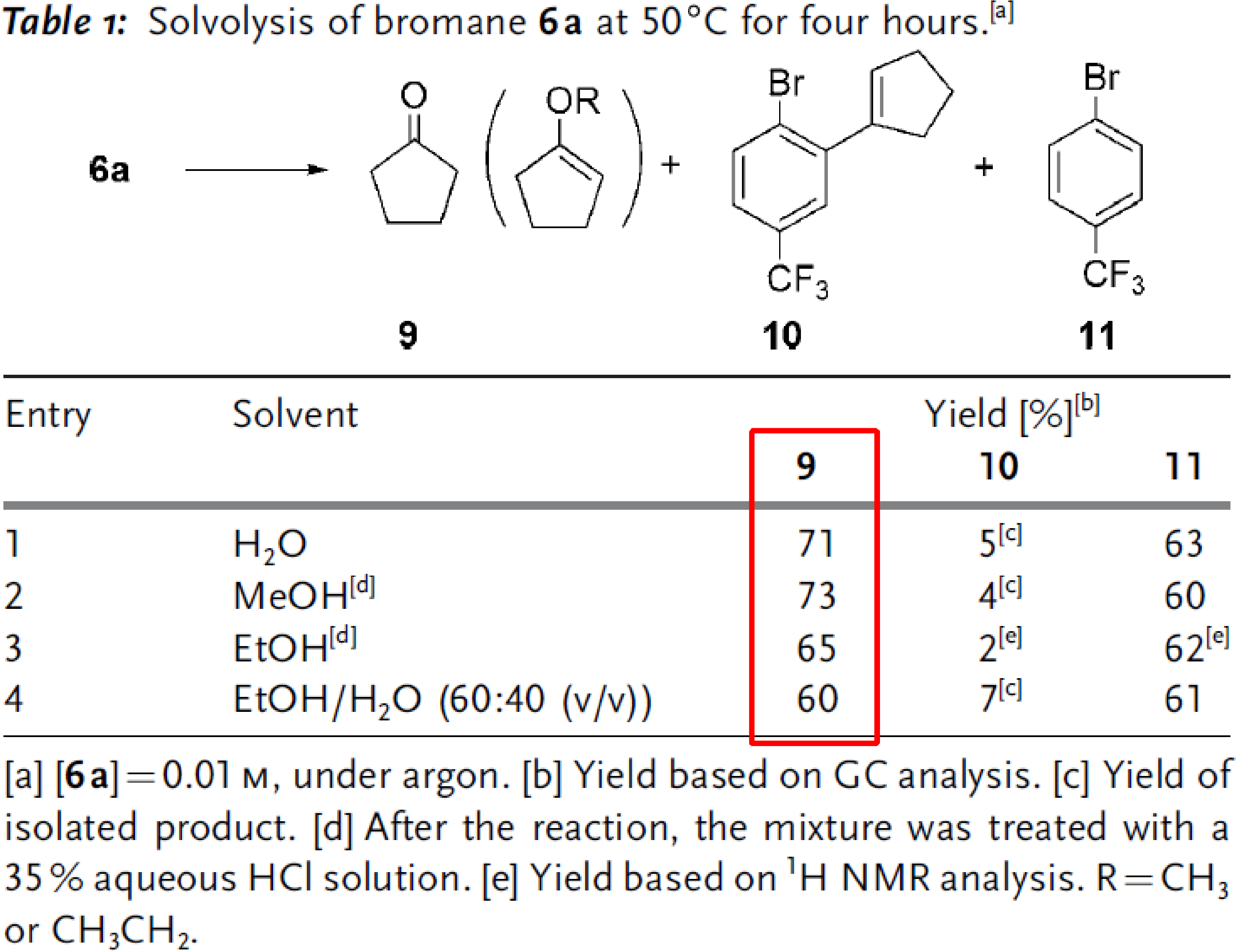


Table 1: Solvolysis of bromane **6a** at 50°C for four hours.[a]

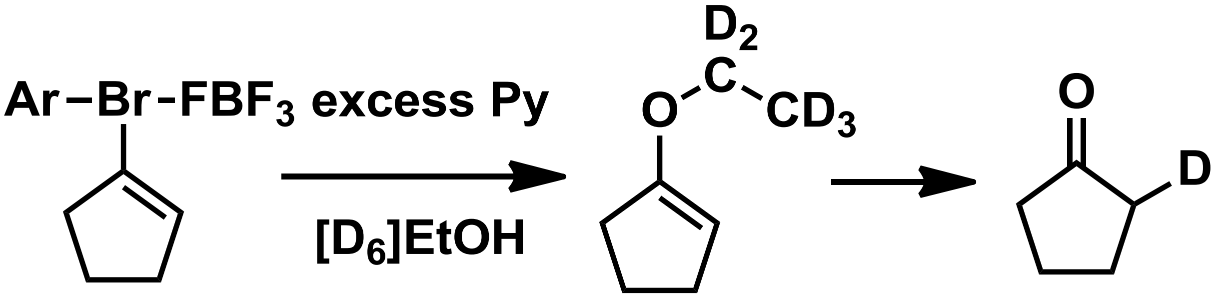
Entry	Solvent	Yield [%][b]		
		9	**10**	**11**
1	H_2O	71	5[c]	63
2	MeOH[d]	73	4[c]	60
3	EtOH[d]	65	2[e]	62[e]
4	EtOH/H_2O (60:40 (v/v))	60	7[c]	61

[a] [**6a**] = 0.01 M, under argon. [b] Yield based on GC analysis. [c] Yield of isolated product. [d] After the reaction, the mixture was treated with a 35% aqueous HCl solution. [e] Yield based on ^1H NMR analysis. R = CH_3 or CH_3CH_2.

K. Miyamoto et. al., *Angew. Chem. Int. Ed.*, **2009**, 48, 8931.

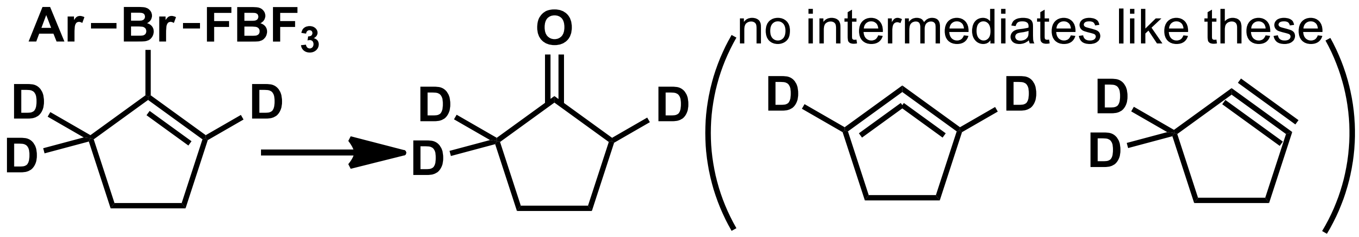
Evidences of last cyclic vinyl cation

- **Time-course analysis by NMR**



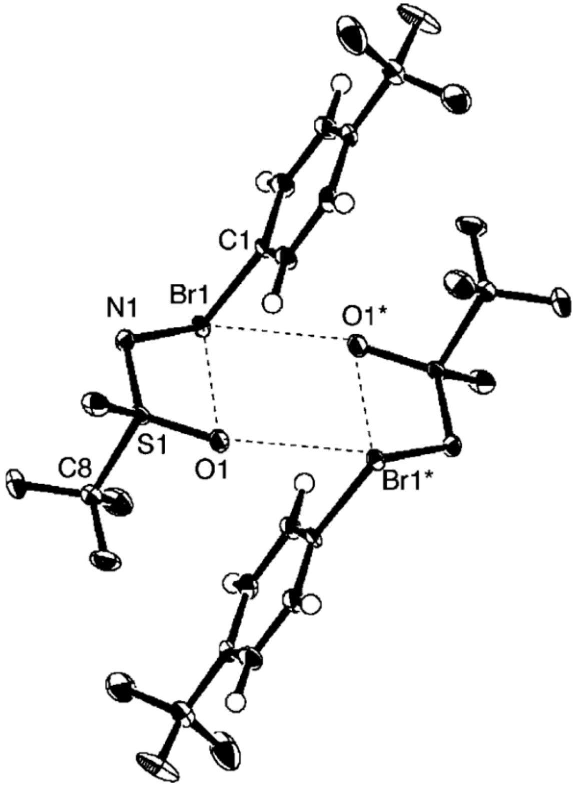
- **Large activation entropy**: 9.13 cal/(mol•K)
--->Good agreement with SN$_1$ solvolysis

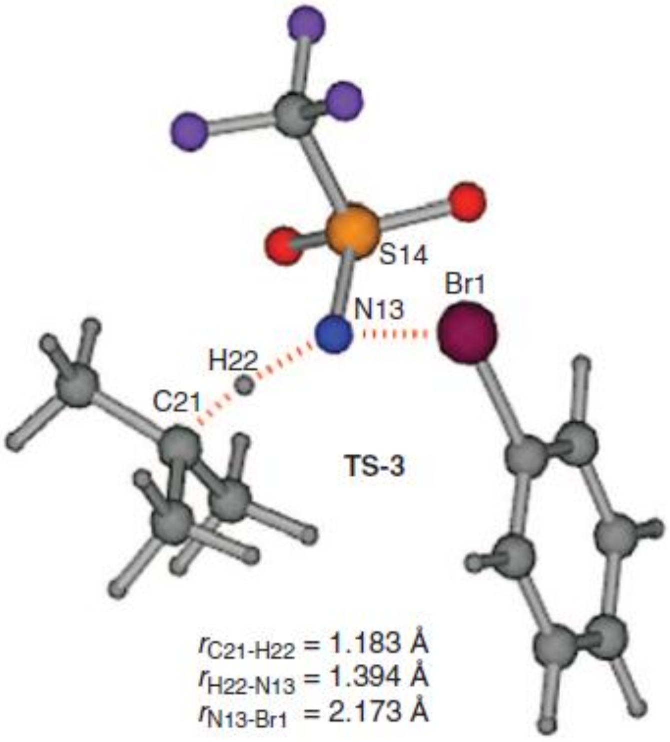
- **Retrained D labels**



Finally in 2009, last cyclic vinyl cation generation was achieved by the hypernucleofuge: trivalent bromine group.

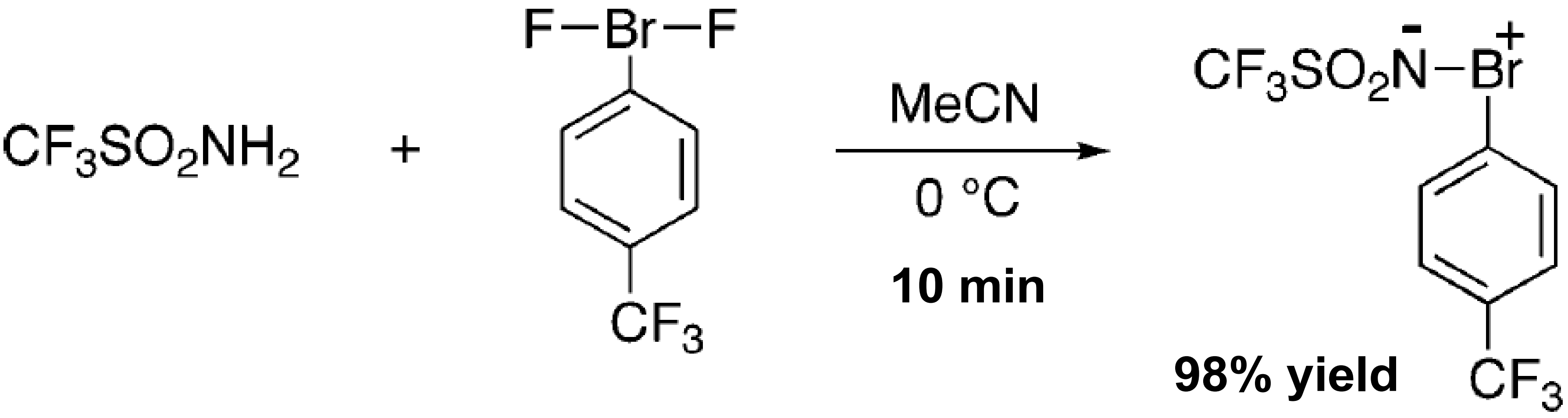
3. *S*ulfonylimino-λ^3-bromanes

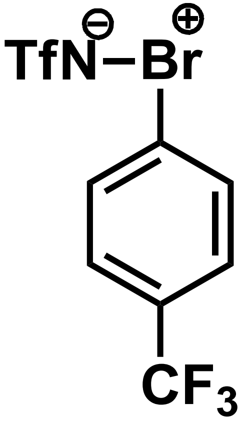




Synthesis

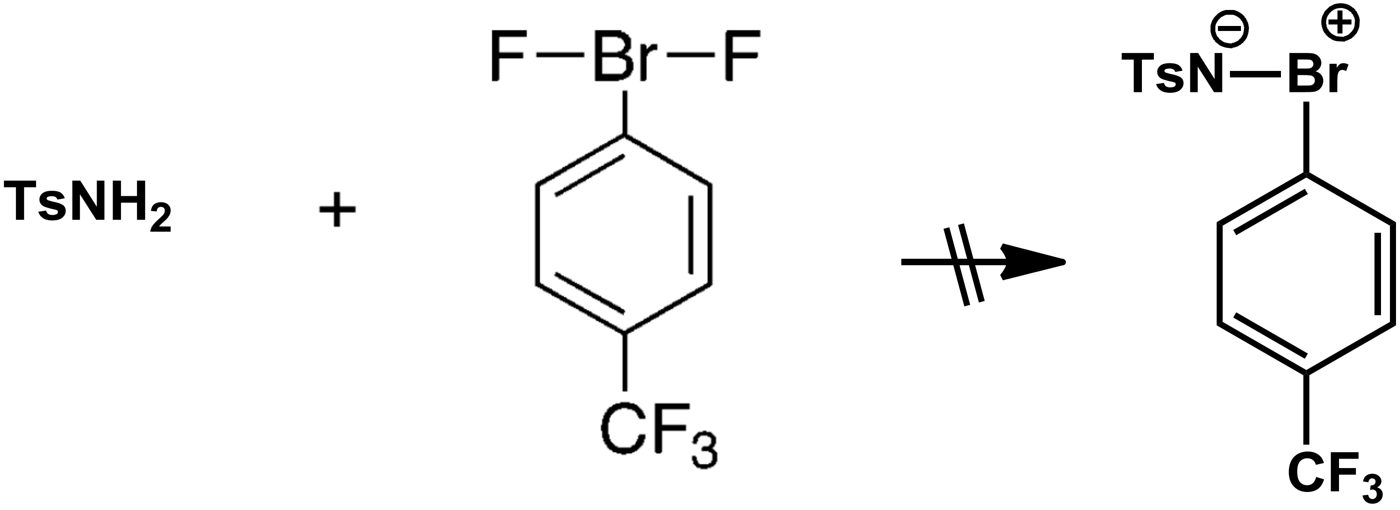
Ligand exchange on Br(III)





- **White solid**
- **Soluble in DCM, MeCN, acetone**
- **Storable in refrigerator under Ar over 2 months!**

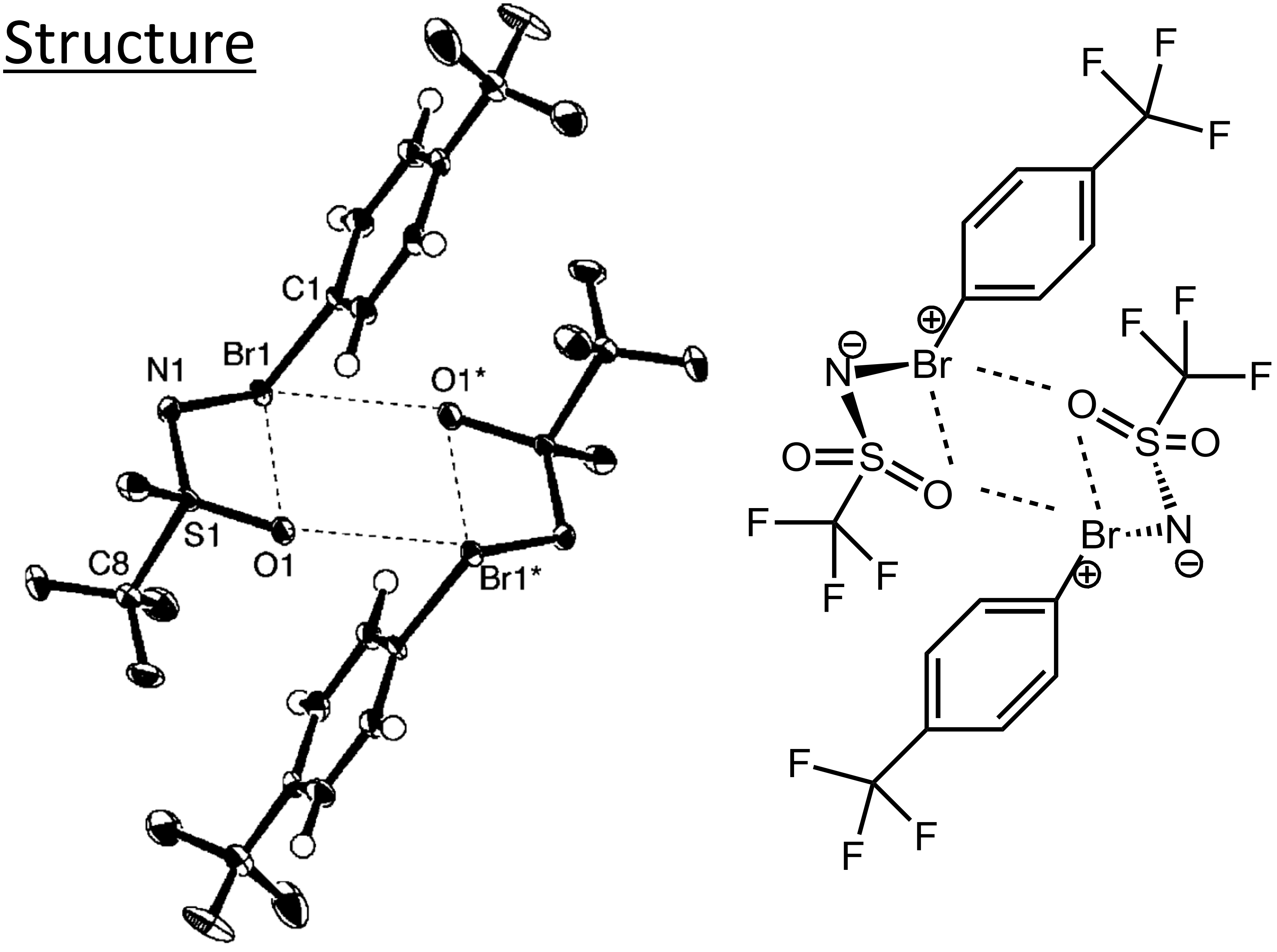
Report of *unsuccessful* synthesis



Iminobromane formation requires strong EWG on N atom.

M. Ochiai et al., *J. Am. Chem. Soc.* **2007**, 129, 12938.

Structure

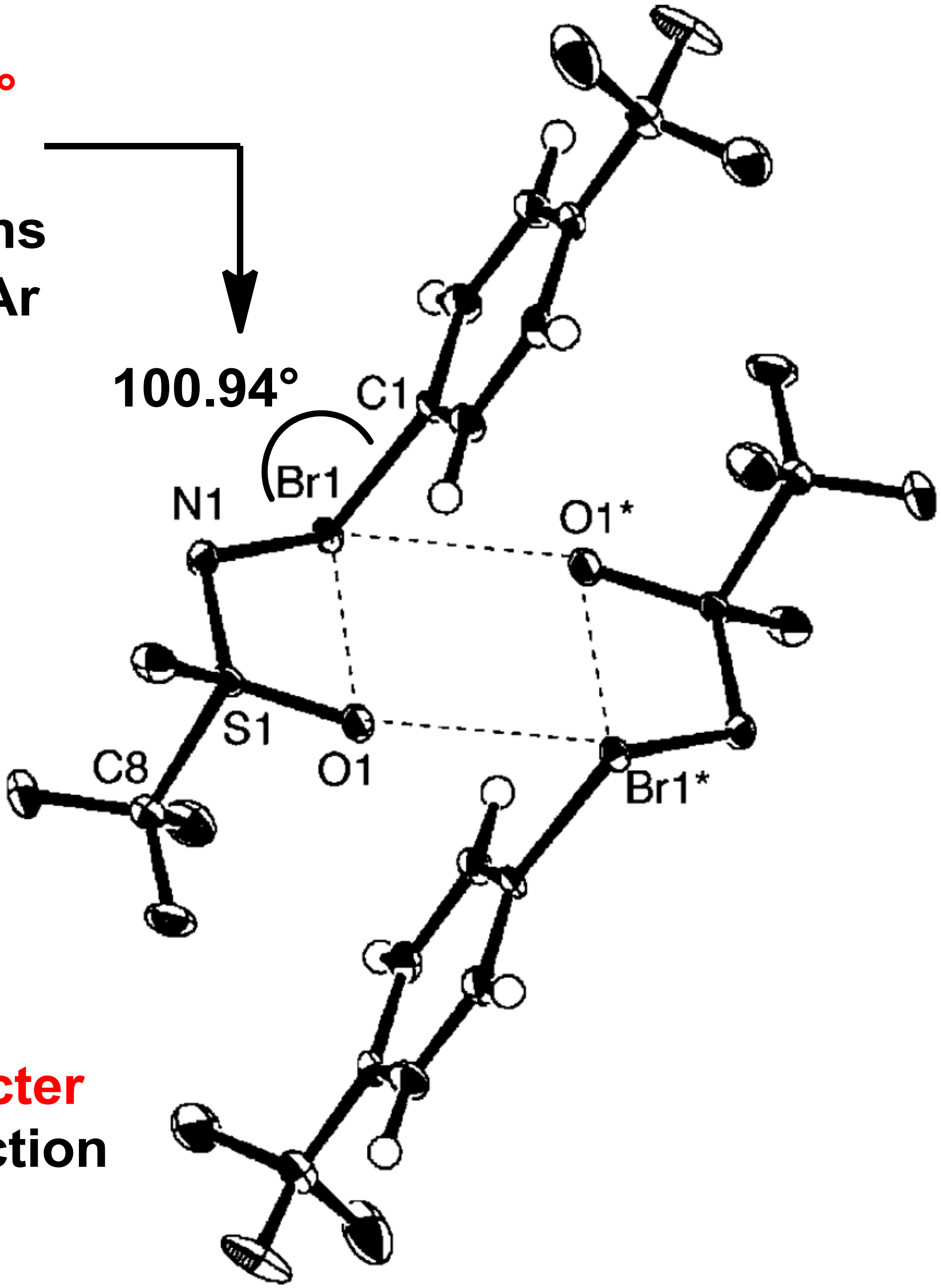


A centrosymmetric dimer with Br_2O_2 rhomboid structure

Angle larger than 90°

↓

nonbonding repulsions between NSO_2 and Ar



Distance

N_1-Br_1: 1.846 Å

Covalent radius

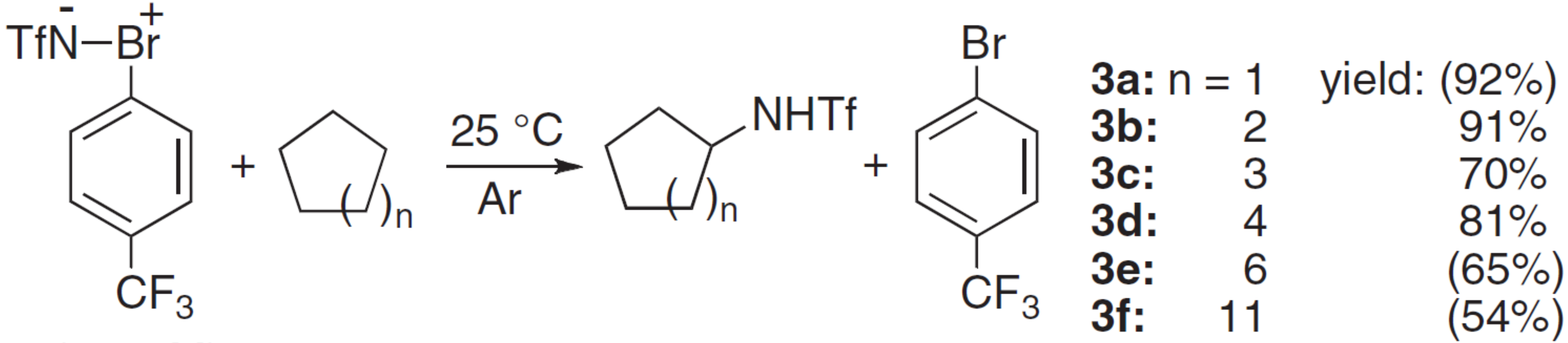
N: 0.70 Å

Br: 1.14 Å

N_1-Br_1 bond posesses

- **little double bond character**
- **small electrostatic attraction**

Reactions: Direct C-H amination



1 (0.01 M) **2** **3**

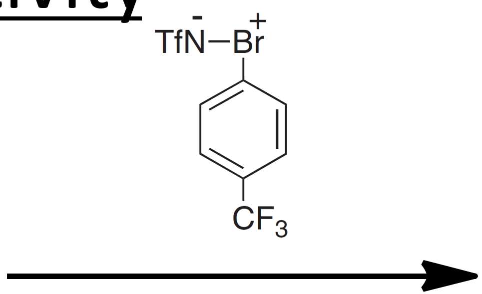
	n	yield
3a:	1	(92%)
3b:	2	91%
3c:	3	70%
3d:	4	81%
3e:	6	(65%)
3f:	11	(54%)

Direct sp^3 C-H amination on unactivated alkanes.

M. Ochiai et al., *Science.* **2011**, 332, 448.

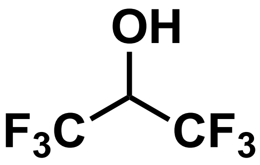
Regioselectivity

alkanes 2

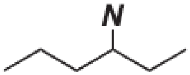
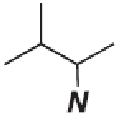
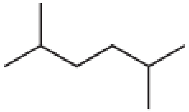
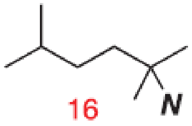
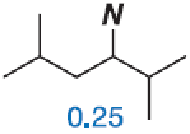
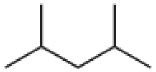
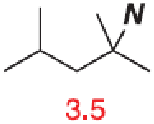
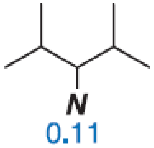


+/- HFIP(20 eq)
neat

Product 3

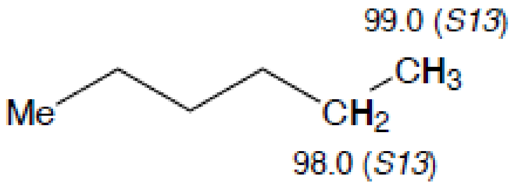


HFIP
supresses decomposition of iminobromane

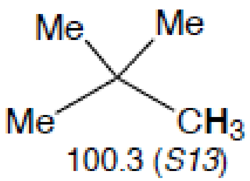
Entry	Alkane 2		Additive (equiv)	Product 3		Yield (%)	Ratio
1		**2g**	-			51	57:43
2			HFIP			55 (55)*	57:43
3		**2h**	-			42	95:5
4			HFIP			72 (47)	94:6
5		**2i**	-	 16	 0.25	46	97:3
6			HFIP			91 (79)	97:3
7		**2j**	-	 3.5	 0.11	34	97:3
8			HFIP			64 (51)	97:3

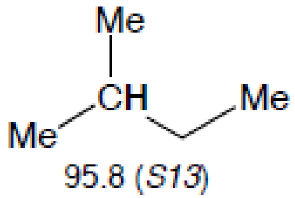
High 3° selectivity was confirmed. Why??

Answer ~Bond dissociation energy~

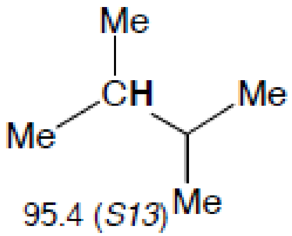


2g

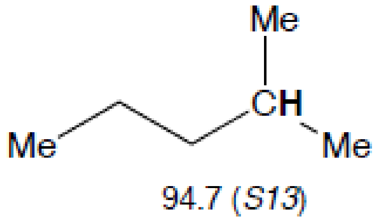


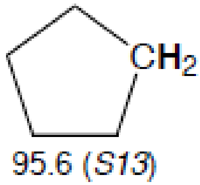


2h

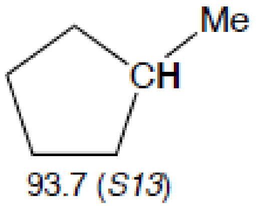


2l

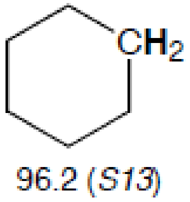




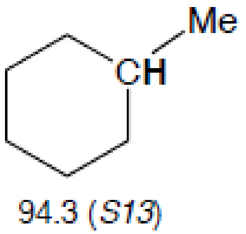
2a



2n



2b

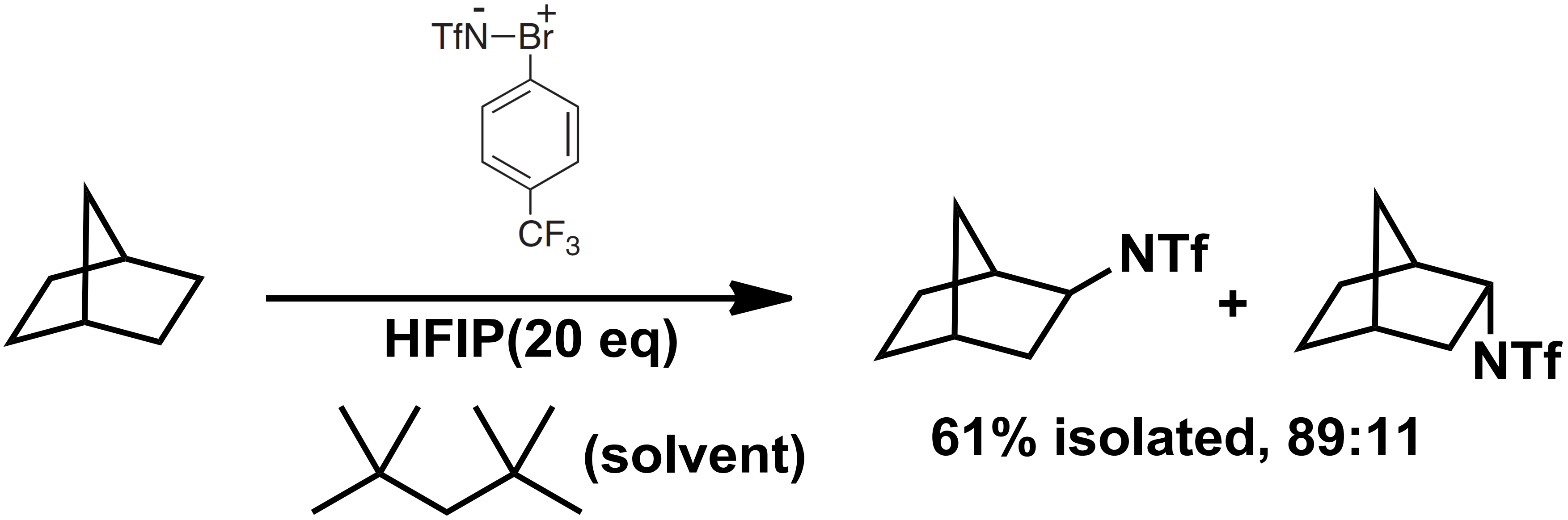


(kcal/mol for each)

Br(III) recognizes subtle differences in bond dissociation energy.

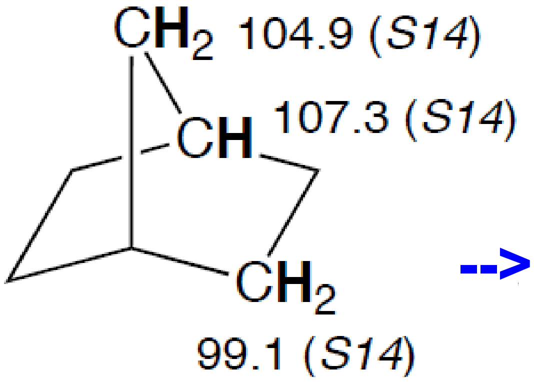
Y.-R. Luo, Handbook of Bond Dissociation Energies in Organic Compounds (CRC Press, Boca Raton, 2003).

Typical example: Norbornane



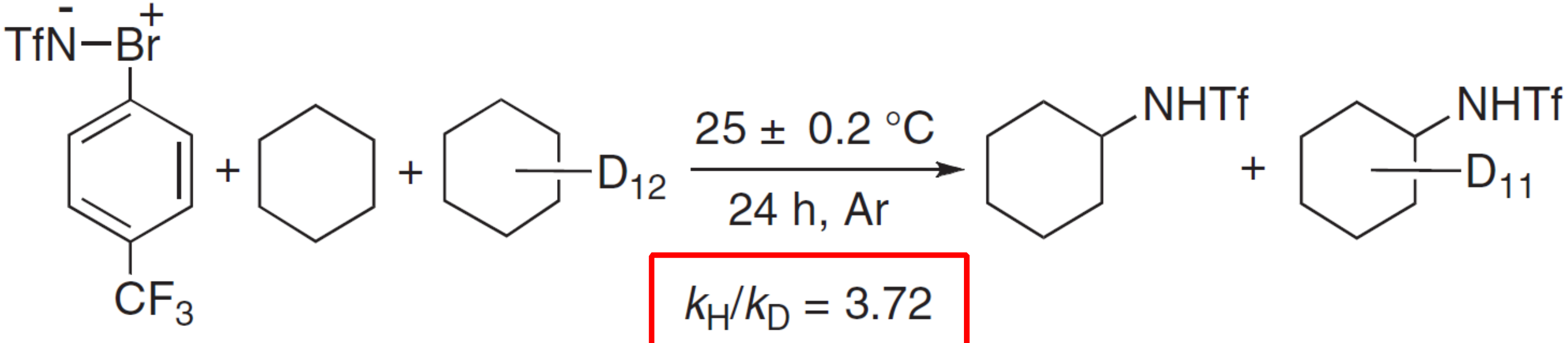
61% isolated, 89:11

Exclusive 2° CH amination



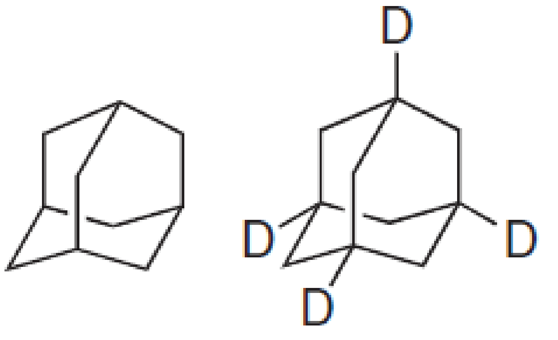
--> 3° CH bond is stronger in norbornane

Reaction mechanism study: *KIE*



$k_H/k_D = 3.72$

1 (0.01 M) **2b** **2b**-d_{12} 99.6% D **3b** yield 68% **3b**-d_{11} yield 18%



2v **2v**-d_4 94% D

kinetics:
2,2,4,4-tetramethylpentane (**2m**)/30 ± 0.1 °C/Ar

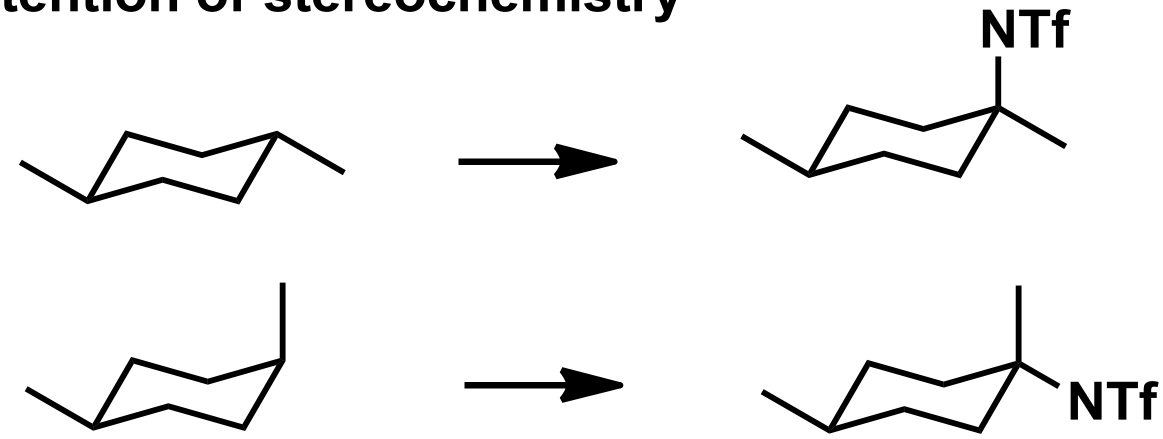
$k_H/k_D = 1.49$

Moderate KIE suggests only partial C-H bond cleavage in TS.

In case of Ru, Cu nitrenoid, KIE = 6.1~6.6.
(in which TS involves H abstraction / radical rebound processes)

Reaction mechanism study: *other aspects*

•Retention of stereochemistry



No long-lived free radical or carbocation intermediates

•Rate constants: *kobs* are proportional to alkane concentration.
--> Bimolecular TS
--> Rate determining step is not "free nitrene formation"

•Calculations suggests positively charged alkane moiety in TS.

Optimized TS structures by calculation

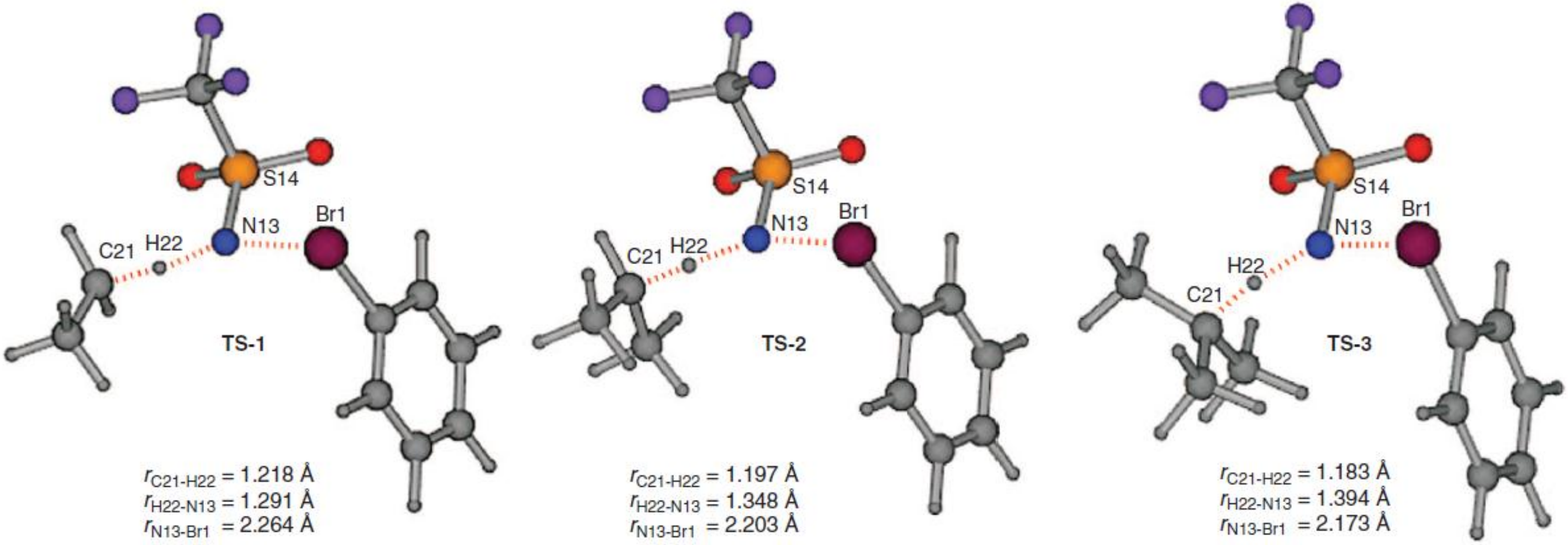
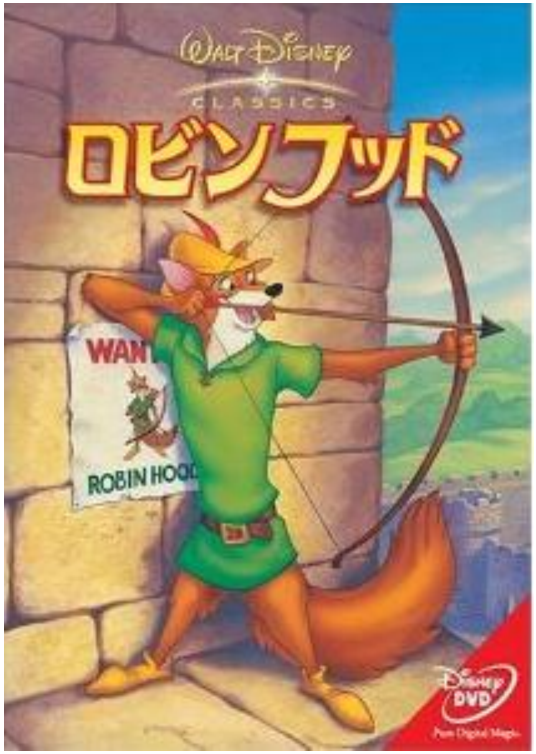


Fig. 2. Transition state structures for C–H aminations of ethane (**TS-1**), propane (**TS-2**), and isobutane (**TS-3**) with PhBr=NTf **4** optimized at the MP2/6-311+G (d) (Br, S, N) and 6-31G(d,p) (F, O, C, H) levels. *r*, bond length.

Highly concerted, but asynchronous pathway

N13-H22 bond formation, followed by N13-C21 bond formation

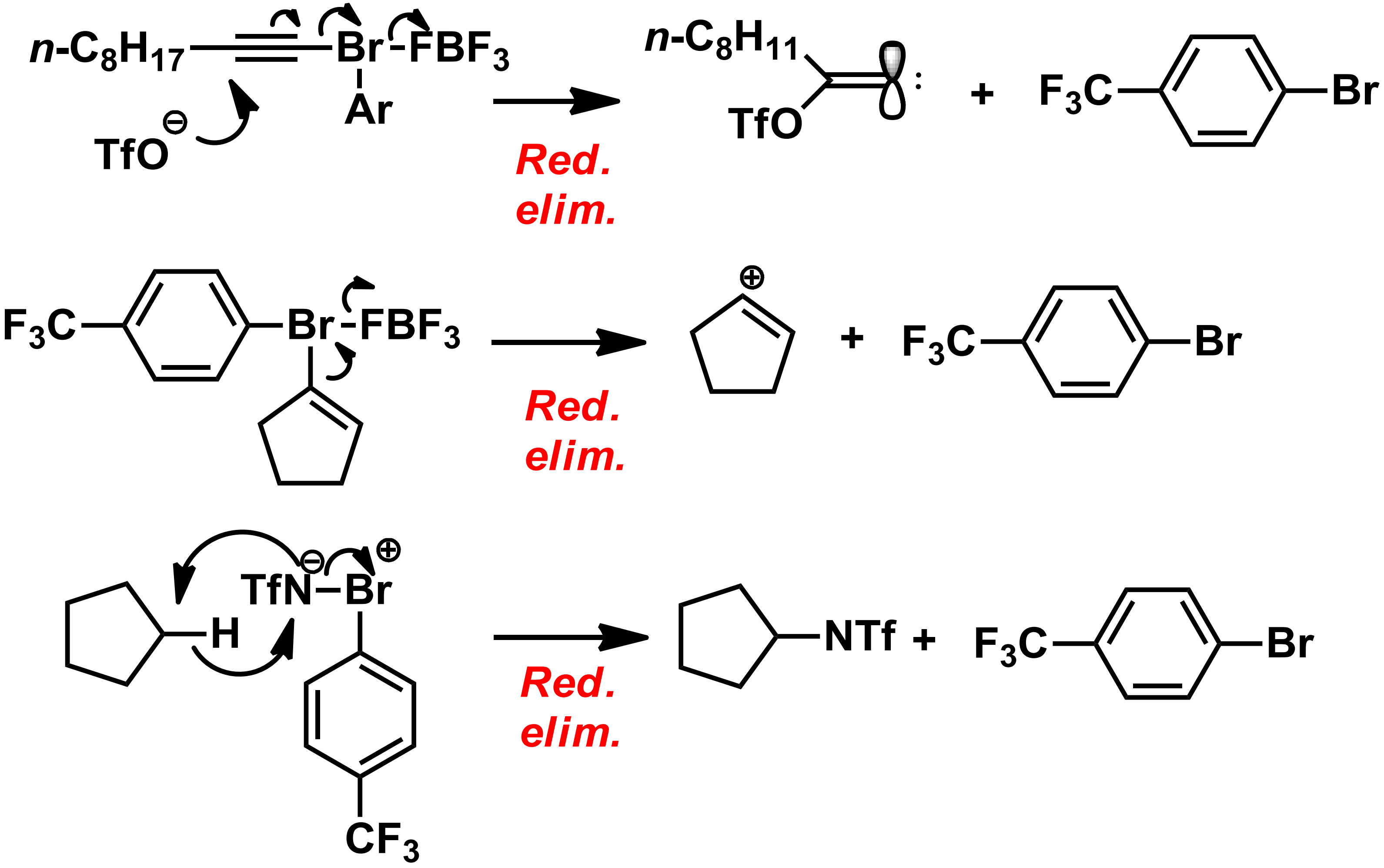
5. Perspectives



The 14C outlaw is now a movie star!

What about…?

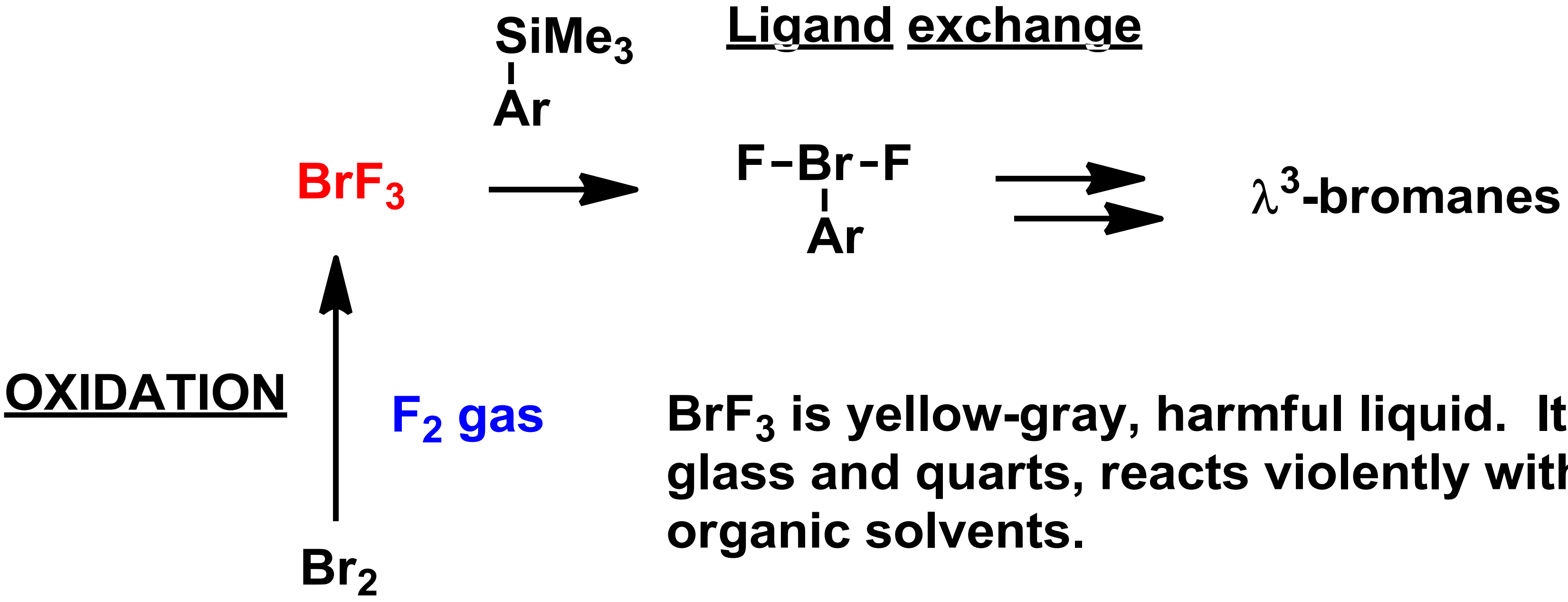
Key word ~Reductive elimination~



Hypervalent bromines undergo various kinds of unexpected reactions, but much of their behavior derive from their outstanding *nucleofugality*.

Problem: OXIDATION of Br(I)

In most of the articles, BrF_3 is used as Br(III) source.



Ligand exchange

$BrF_3 \xrightarrow{Ar-SiMe_3} F-Br(Ar)-F \rightleftharpoons \lambda^3$-bromanes

OXIDATION

$Br_2 \xrightarrow{F_2\ gas} BrF_3$

BrF_3 is yellow-gray, harmful liquid. It etches glass and quarts, reacts violently with most organic solvents.

New methodology for facile preparation of Br(III) compounds (especially oxidizing measures of Br(I)!!) are highly demanded for the further development of this area.