Organobismuth Compounds: Synthesis and Reactivity

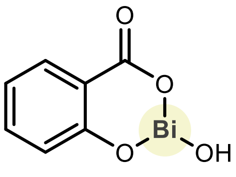
2/22/2018

Ben Boyle

Introduction: Bismuth

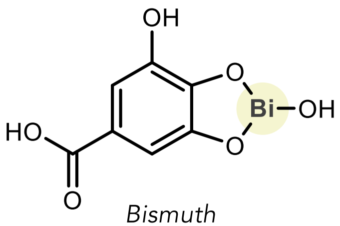
- Elemental Bismuth:
  - heaviest stable element in periodic table (^{209}Bi = only stable isotope)
  - Non-toxic and non-carcinogenic
  - Group 15 p-block element
  - Expands on solidification
  - Configuration: [Xe]$4f^{14}5d^{10}6s^{2}6p^{3}$
- Organobismuth:
  - Most common oxidation states: Bi^{III} and Bi^{V}
  - Range of reactivities
  - Useful in oxidation of alcohols
  - “Green” metal
  - Forms –ate and –onium salts

Pepto-Bismol



Bismuth Subsalicylate

Stomax

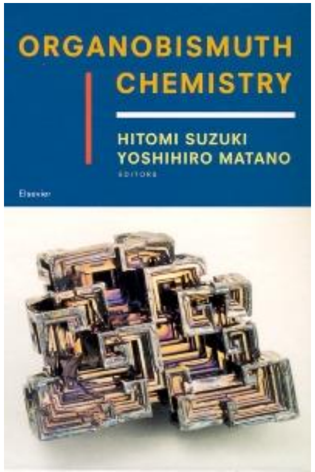


Bismuth Subgallate

Introduction: Bismuth

- Notable Names:
  - Sir Derek Barton (Nobel Laureate: 1969 Conformational Analysis)
  - Dr. Hitomi Suzuki (Organobismuth Chemistry)
  - Dr. Jean-Pierre Finet (Ligand Coupling Reactions with Heteroatomic Compounds)

Sir Derek Barton



ORGANOBISMUTH
CHEMISTRY

HITOMI SUZUKI
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Dr. Hitomi Suzuki

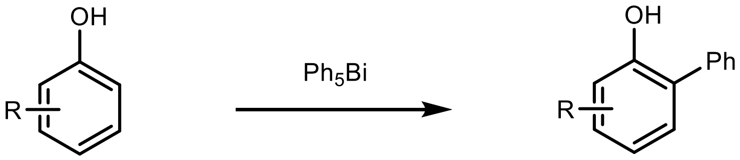
Dr. Jean-Pierre Finet

Introduction: Bismuth

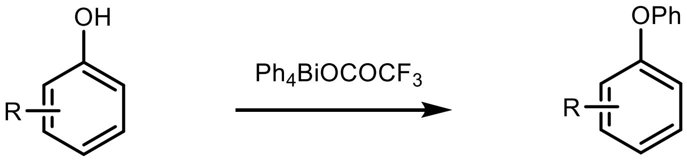
- Reviews:
  - Gilman, H.; Yale, H. L. Organobismuth Compounds. *Chem. Rev.* **1942**, *30* (2), 281–320.
  - Leonard, N. M.; Wieland, L. C.; Mohan, R. S. Applications of Bismuth(III) Compounds in Organic Synthesis. *Tetrahedron* **2002**, *58* (42), 8373–8397.
  - Barton, D. H. R.; Finet, J.-P. Bismuth(V) Reagents in Organic Synthesis. *Pure and Applied Chemistry* **1987**, *59* (8), 937–946.
  - Condon, S.; Pichon, C.; Davi, M. Preparation and Synthetic Applications of Trivalent Arylbismuth Compounds as Arylating Reagents. A Review. *Organic Preparations and Procedures International* **2014**, *46* (2), 89–131.
  - Gagnon, A.; Dansereau, J.; Roch, A. L. Organobismuth Reagents: Synthesis, Properties and Applications in Organic Synthesis. *Synthesis* **2017**, *49* (8), 1707–1745.
  - Elliott, G. I.; Konopelski, J. P. Arylation with Organolead and Organobismuth Reagents. *Tetrahedron* **2001**, *57* (27), 5683–5705.
  - Freedman, L. D.; Doak, G. O. Preparation, Reactions, and Physical Properties of Organobismuth Compounds. *Chem. Rev.* **1982**, *82* (1), 15–57.

Reactivity Overview

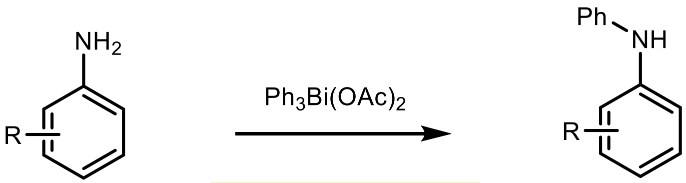
- Powerful arylating reagent with tunable chemoselectivity



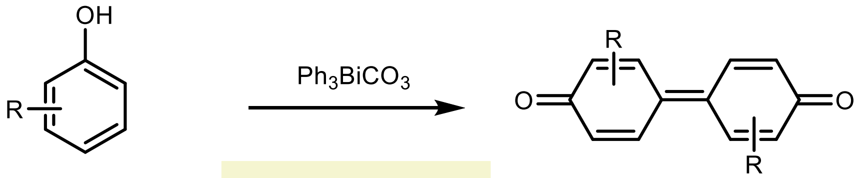
C-C bond formation



C-O bond formation



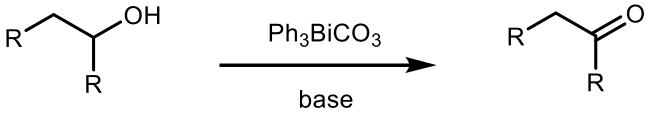
N-C bond formation



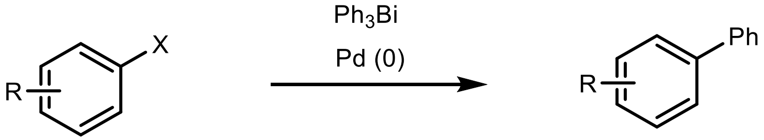
C-C bond formation

- Useful and practical mild oxidants for alcohols

- Nucleophilic Partner in Metal-Catalyzed Cross-Couplings



Mild Oxidant

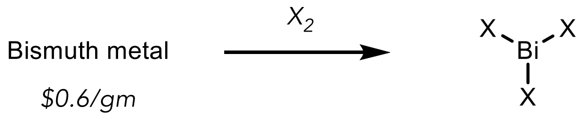


X = Cl, Br, I, OTf

Nucleophilic Coupling Partner

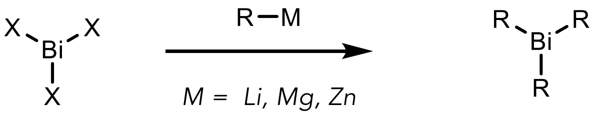
Organobismuth Compounds: Preparation

- Synthesis starts with elemental bismuth, however a number of organobismuth reagents are commercially available



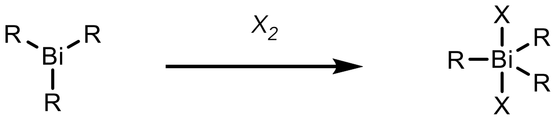
Air and moisture sensitive

$BiCl_3$	$BiOTf_3$	$BiBr_3$
$3.70/gm	*$15.40/gm*	*$2.04/gm*



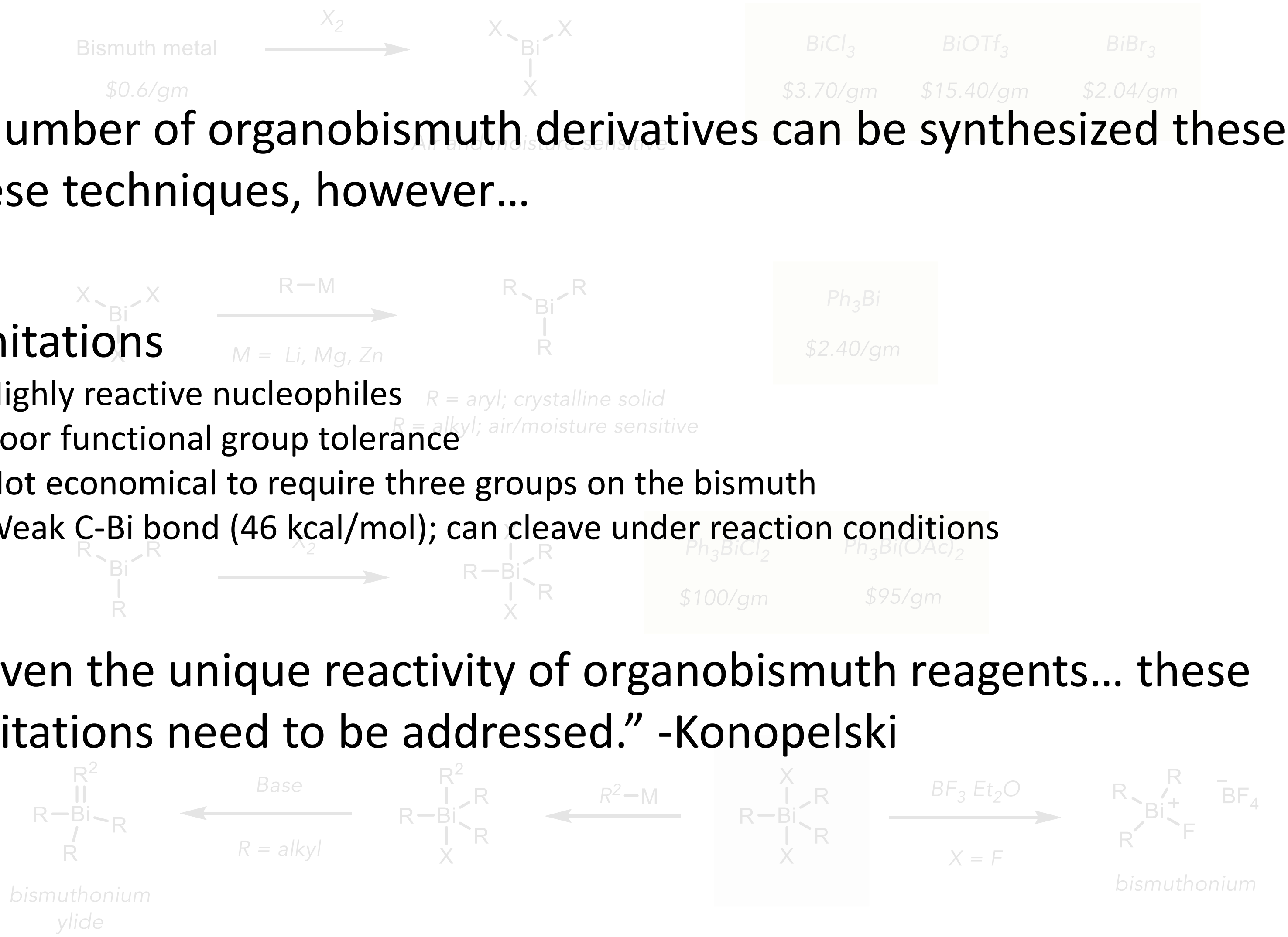
R = aryl; crystalline solid
R = alkyl; air/moisture sensitive

Ph_3Bi
$2.40/gm



Ph_3BiCl_2	$Ph_3Bi(OAc)_2$
$100/gm	*$95/gm*

Organobismuth Compounds: Preparation



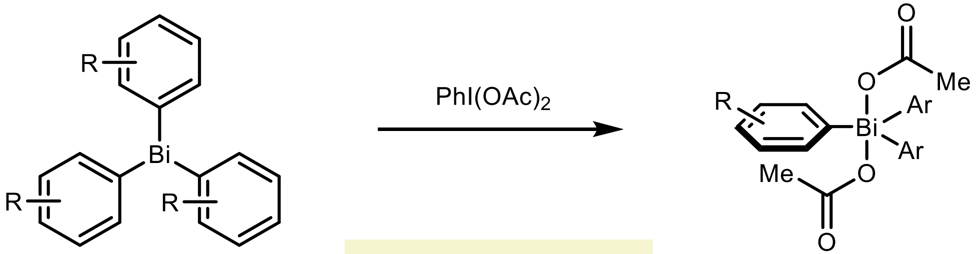
- A number of organobismuth derivatives can be synthesized these these techniques, however…

- Limitations
  - Highly reactive nucleophiles
  - Poor functional group tolerance
  - Not economical to require three groups on the bismuth
  - Weak C-Bi bond (46 kcal/mol); can cleave under reaction conditions

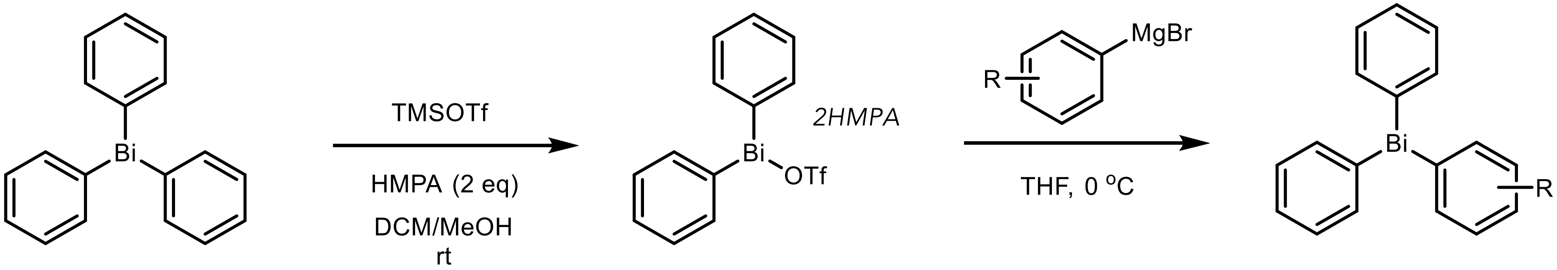
- “Given the unique reactivity of organobismuth reagents… these limitations need to be addressed.” -Konopelski

Organobismuth Compounds: Preparation

- Potentially useful reactions in precusor synthesis



Mild Bi^{III} to Bi^{IV} oxidation

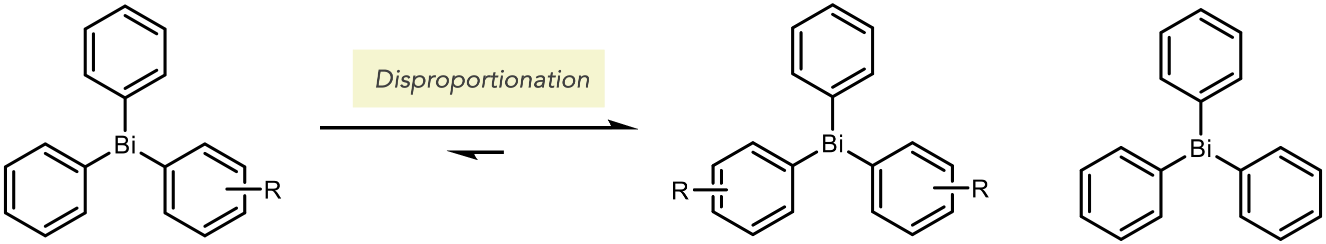


air stable complex

Unsymmetrical bismuthane

Matano, Y.; Miyamatsu, T.; Suzuki, H *Organometallics* **1996**, *15* (7), 1951–1953.

- Caution: Disproportionation reactivity



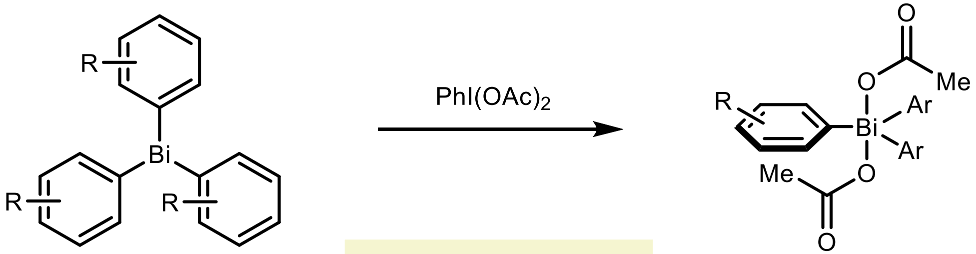
Disproportionation

Unsymmetrical bismuthane

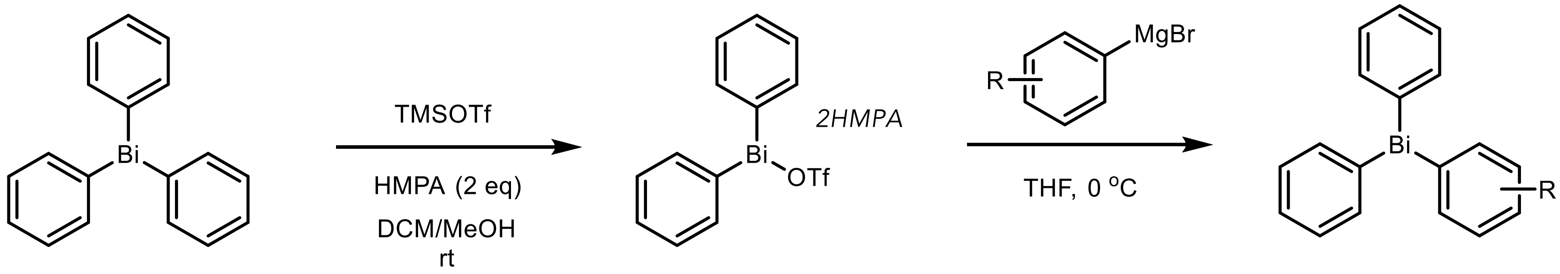
Mixture of bismuthane isomers

Organobismuth Compounds: Preparation

- Potentially useful reactions in precusor synthesis



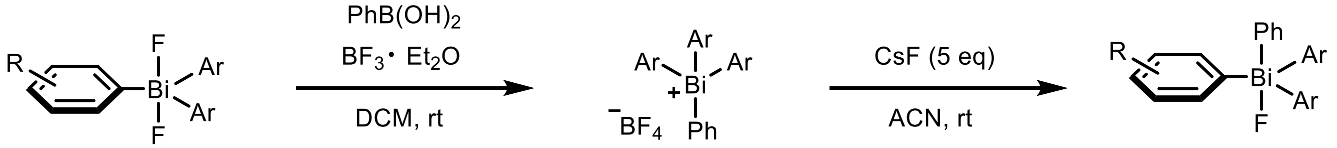
Mild Bi^{III} to Bi^{IV} oxidation



air stable complex

Unsymmetrical bismuthane

Suzuki, H *Organometallics* **1996**, *15* (7), 1951–1953.



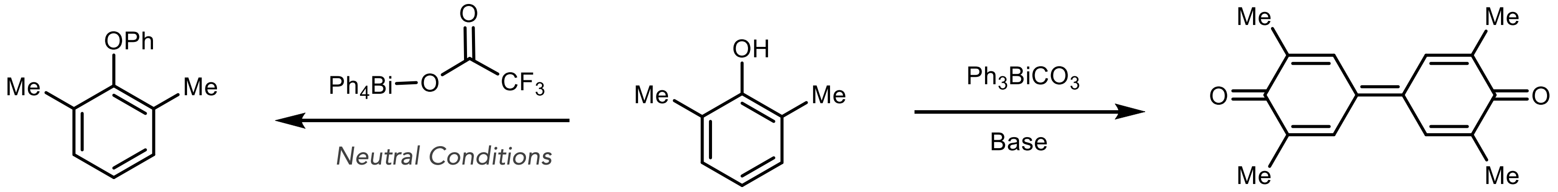
Bismuthonium Salt

Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125* (35), 10494–10495.

Organobismuth: Ligand-Coupling

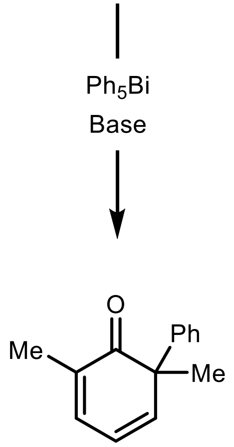
- Distinct Chemoselectivity based on choice in bismuth reagent

What is the origin of the chemoselectivity for bismuth ligand-coupling reactions?



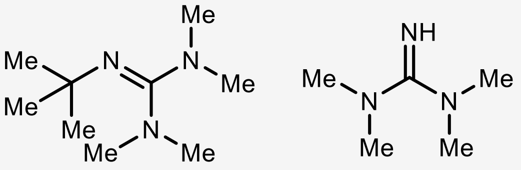
O-C Bond Formation

Dimerization C-C Bond Formation



α-C Phenylation

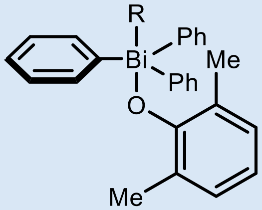
Base = BTMG or TMG



BTMG

TMG

Common Intermediate

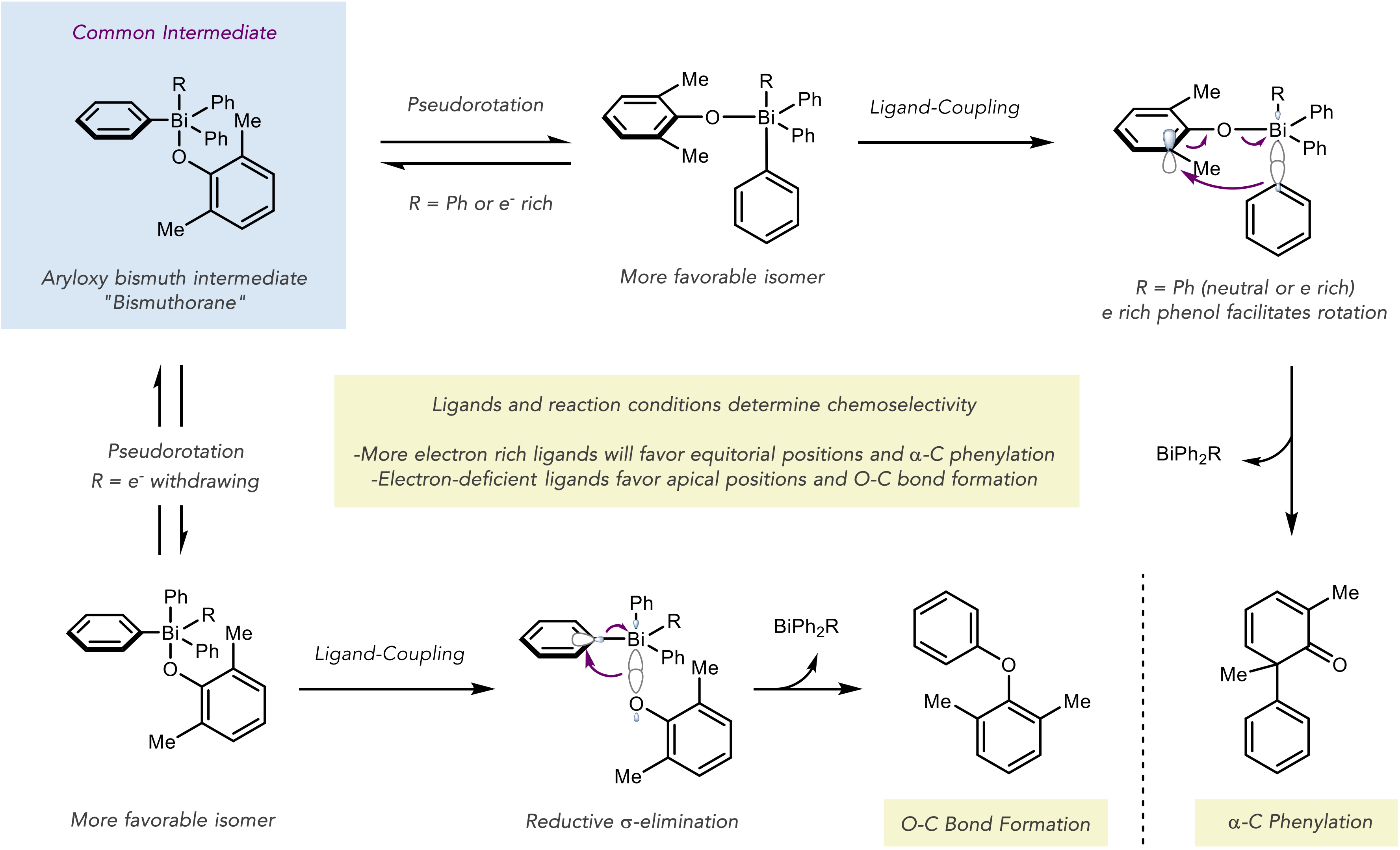


Aryloxy bismuth intermediate "Bismuthorane"

Barton, D. H. R. *Tetrahedron* **1987**, *43* (2), 323–332.

Organobismuth: Ligand-Coupling

- Chemoselectivity dictated by bismuthorane



Common Intermediate

Aryloxy bismuth intermediate "Bismuthorane"

Pseudorotation

R = Ph or e⁻ rich

More favorable isomer

Ligand-Coupling

R = Ph (neutral or e rich)
e rich phenol facilitates rotation

Pseudorotation
R = e⁻ withdrawing

Ligands and reaction conditions determine chemoselectivity

-More electron rich ligands will favor equitorial positions and α-C phenylation
-Electron-deficient ligands favor apical positions and O-C bond formation

More favorable isomer

Ligand-Coupling

Reductive σ-elimination

O-C Bond Formation

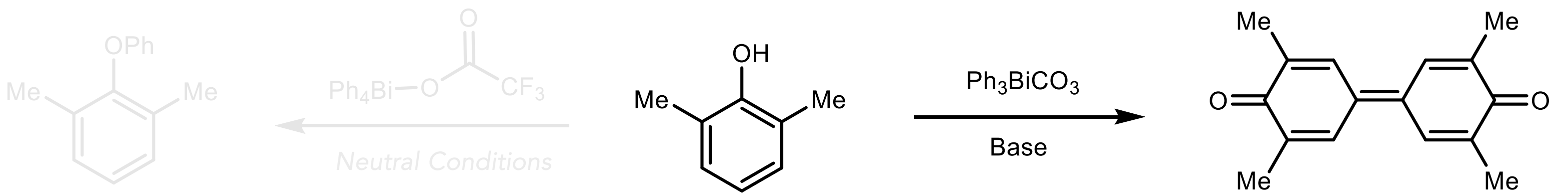
α-C Phenylation

Barton, D. H. R. *Tetrahedron* **1987**, *43* (2), 323–332.

Organobismuth: Ligand-Coupling

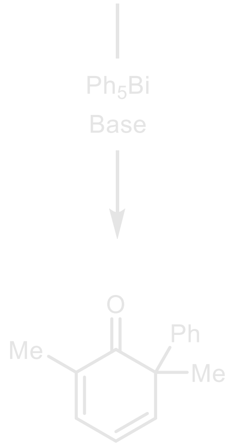
- Distinct Chemoselectivity based on choice in bismuth reagent

What is the origin of the chemoselectivity for bismuth ligand-coupling reactions?



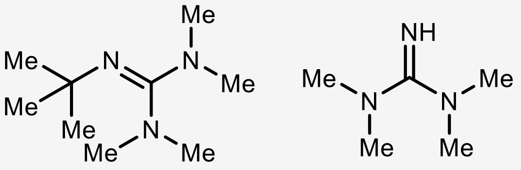
O-C Bond Formation

Dimerization C-C Bond Formation



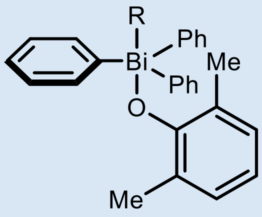
α-C Phenylation

Base = BTMG or TMG



BTMG *TMG*

Common Intermediate

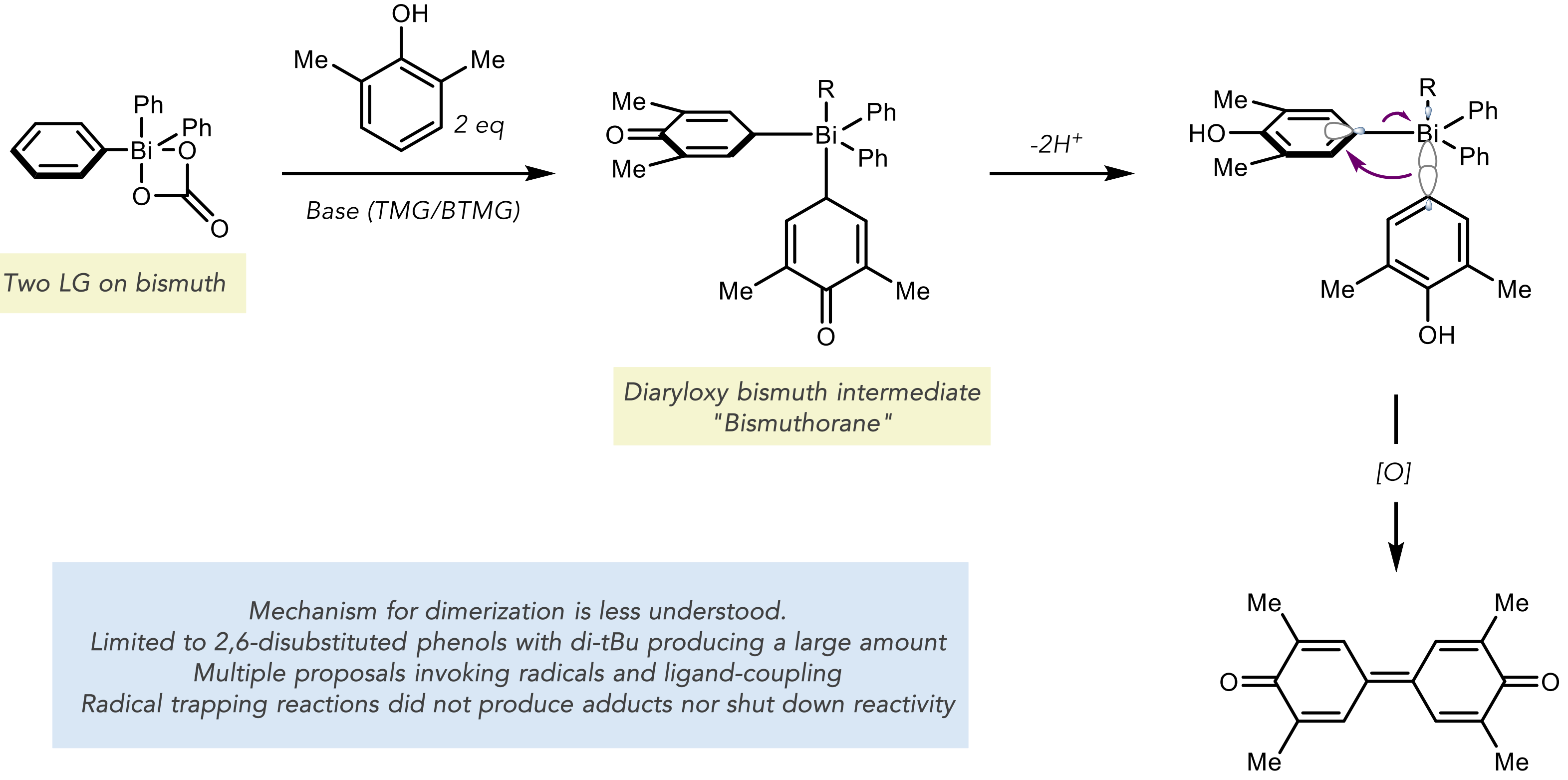


Aryloxy bismuth intermediate "Bismuthorane"

Barton, D. H. R. *Tetrahedron* **1987**, *43* (2), 323–332.

Organobismuth: Ligand-Coupling

- Dimerization goes through a bisaryloxy bismuthorane intermediate



Two LG on bismuth

Diaryloxy bismuth intermediate
"Bismuthorane"

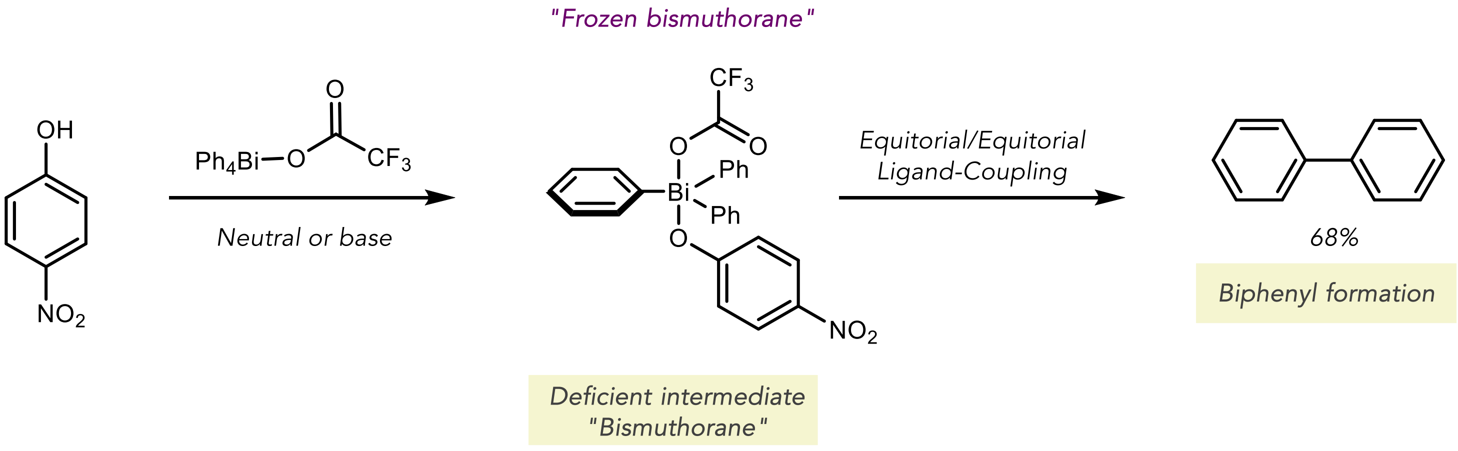
Dimerization C-C Bond Formation

Mechanism for dimerization is less understood.
Limited to 2,6-disubstituted phenols with di-tBu producing a large amount
Multiple proposals invoking radicals and ligand-coupling
Radical trapping reactions did not produce adducts nor shut down reactivity

Barton, D. H. R. *Tetrahedron* **1987**, *43* (2), 323–332.

Organobismuth: Ligand-Coupling

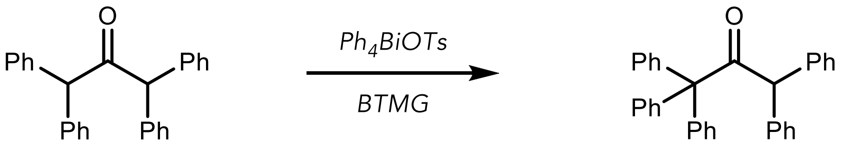
- Chemoselectivity is also impact by phenol substituent when paired with a deficient group on bismuth



Barton, D. H. R. *Tetrahedron* **1987**, *43* (2), 323–332.

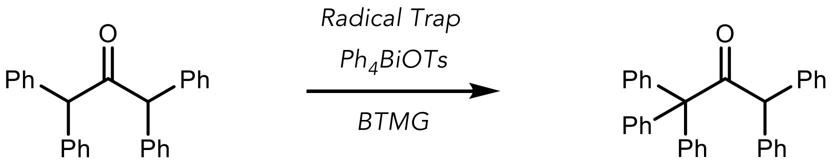
Organobismuth: Is it radicals?

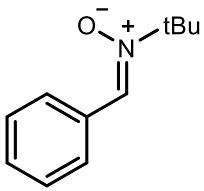
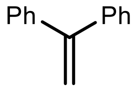
- While ligand-coupling appeared to match the results; a radical mechanism gained attention



Highly hindered product
Pointed towards radical mechanism

ESR indicated the presence/generation of Ph radical under the reaction conditions

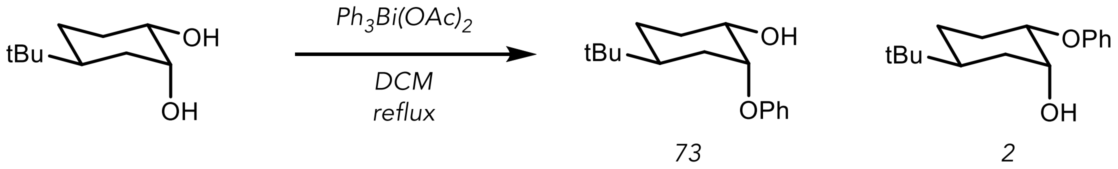


Radical Trap	*Adduct Detected*	*Yield Prd*
None	*N/a*	*88%*
	*Trace*	*83*
	*Trace*	*80*

Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1987**, *0* (0), 241–249

Organobismuth: Aliphatic Alcohols

- While earlier work had focus on phenols and enolizable systems; Bi^V was found to phenylate aliphatic diols as well (David)

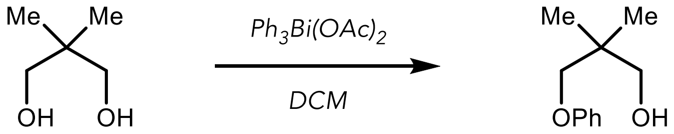


Axial phenylation preference

-Worked well for primary and secondary diols: tertiary resulted in low yields
-Only mono-arylated products were observed
-Axial hydroxyls were phenylated preferencially

-Only worked in DCM
-Required light (no reaction in the dark)
-Induction period prior to reaction progressing

- Barton discovered that the reaction could be catalyzed with copper salts (Co, Ni, and Fe were not effective)



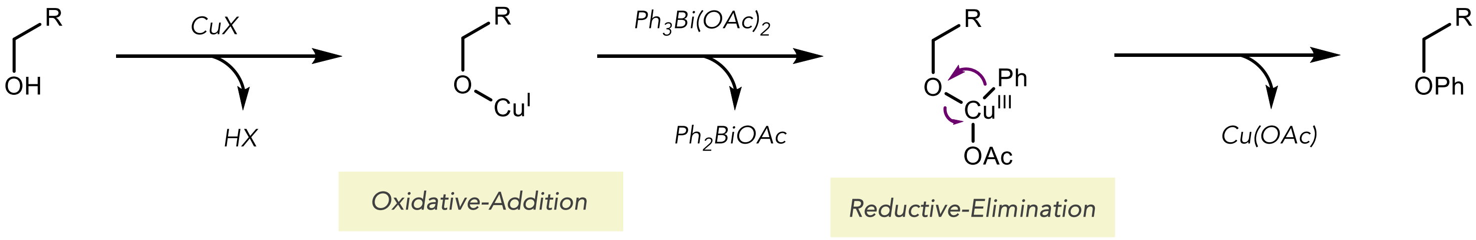
Cu(OAc) mol%	*Temp (°C)*	*Time (h)*	*Yield*
0	*60*	*6**	*91*
0.01	*60*	*0.25*	*82*
10	*60*	*0.25*	*78*
10	*20*	*1*	*82*

**2 hour induction period*

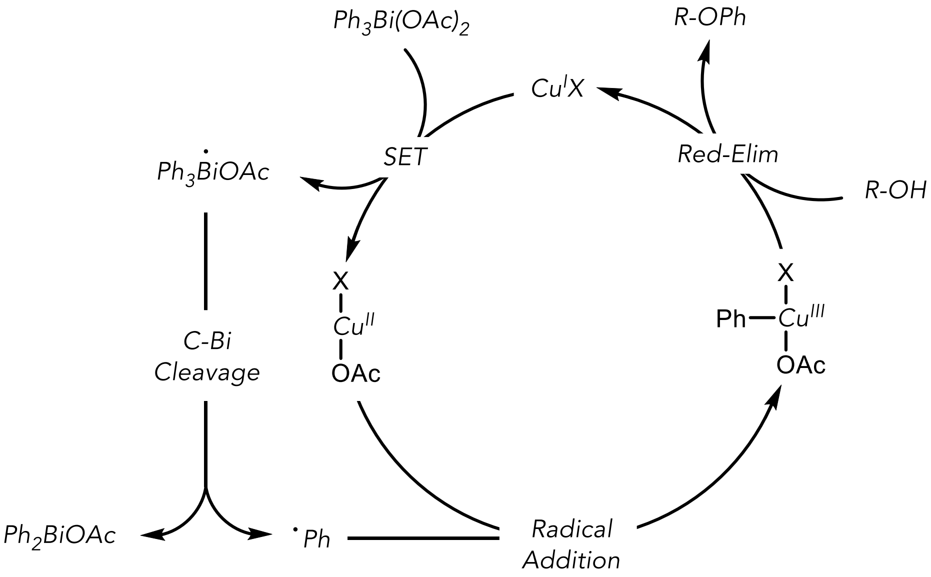
David, S. *J. Org. Chem.* **1983**, *48* (4), 441–447. (1)
Barton, D. H. R.; *J. Chem. Soc., Chem. Commun.* **1986**, *0* (1), 65–66.

Organobismuth: Copper Reaction Mechanism

- Mechanistic debate regarding the copper catalyzed mechanism: Oxidative addition/elimination vs radical
- Barton: Proposed a Cu^I to Cu^{III} cycle with oxidative addition by the Cu^I species



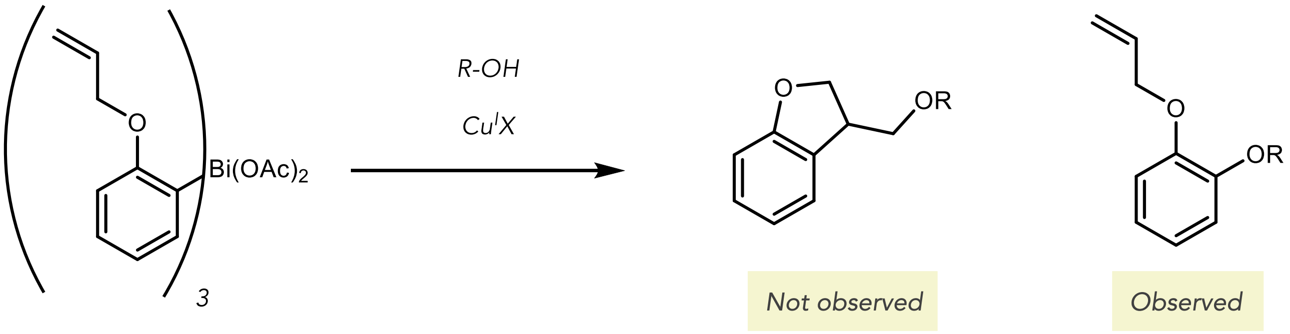
- ESR studies indicated presence of Ph radical
- Dodonov: Proposed a Cu^I to Cu^{II} cycle with SET to reduce the Bi^V and generate Ph radical



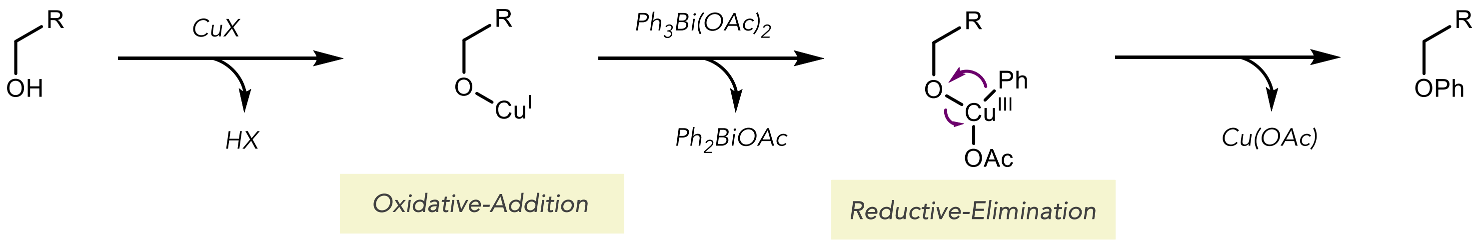
Barton, D. H. R. *Tett. Lett.* **1987**, 28 (8), 887-890.
Dodonov, V. A. *Metaloorg. Khim.* **1990**, 56, 2714-2721

Organobismuth: Copper Reaction Mechanism

- Mechanistic debate regarding the copper catalyzed mechanism: Oxidative addition/elimination vs radical
- Finet: Radical trapping studies on both copper catalyzed and non-copper catalyzed bismuth reactions



- Trapping experiment supports radical-free mechanism



Finet, J.-P. *Tetrahedron* **1999**, *55* (11), 3377–3386

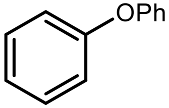
Organobismuth: Copper Phenylation

- Impact of copper catalyzed reaction: allowed for a larger range of alcohols
- No longer required high temperature and long reaction times
- Expanded heteroatoms to nitrogen as well

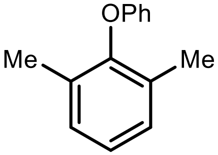
$$Ph_3Bi(OAc)_2 \xrightarrow[\text{DCM, rt}]{\text{Cu (cat). RXH}} R\text{-}XPh$$

$X = O$ or N

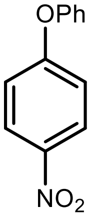
Oxygen Copper-catalyzed phenylation



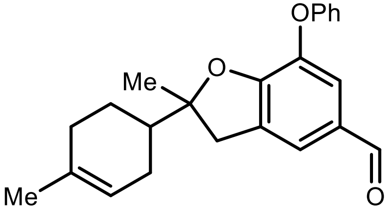
88%



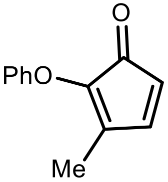
67%



73%

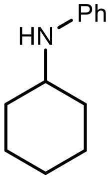


76%

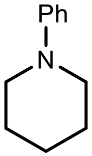


70%

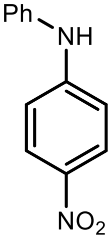
Nitrogen Copper-catalyzed phenylation



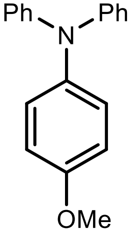
90%



58%



90%



78%

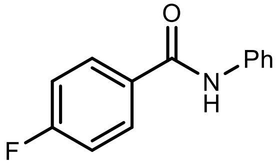
Dodonov, V. A. *Metaloorg. Khim.* **1990**, 56, 2714-272.
Dodonov, V.A. *Obshch. Khim.* **1985**, 55, 2514-2519

Organobismuth: Copper Phenylation

- Stoichiometric copper was found to enable deficient functional groups and allow the use of $\mathrm{Bi^{III}}$

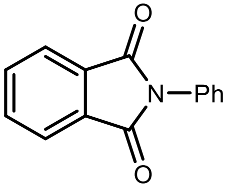
$$\mathrm{Ph_3Bi} \xrightarrow[\text{DCM, rt}]{\mathrm{Cu(OAc)_2},\ \mathrm{R_2NH}} \mathrm{R_2\text{-}NPh}$$

Amides



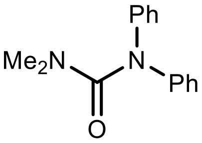
83% (4.4:1:Mono:Di)

Imides



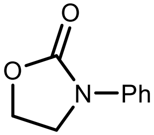
99%

Ureas



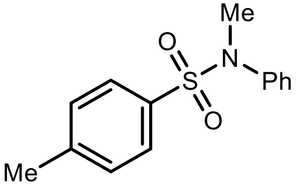
77%

Carbamates



94%

Sulfonamides

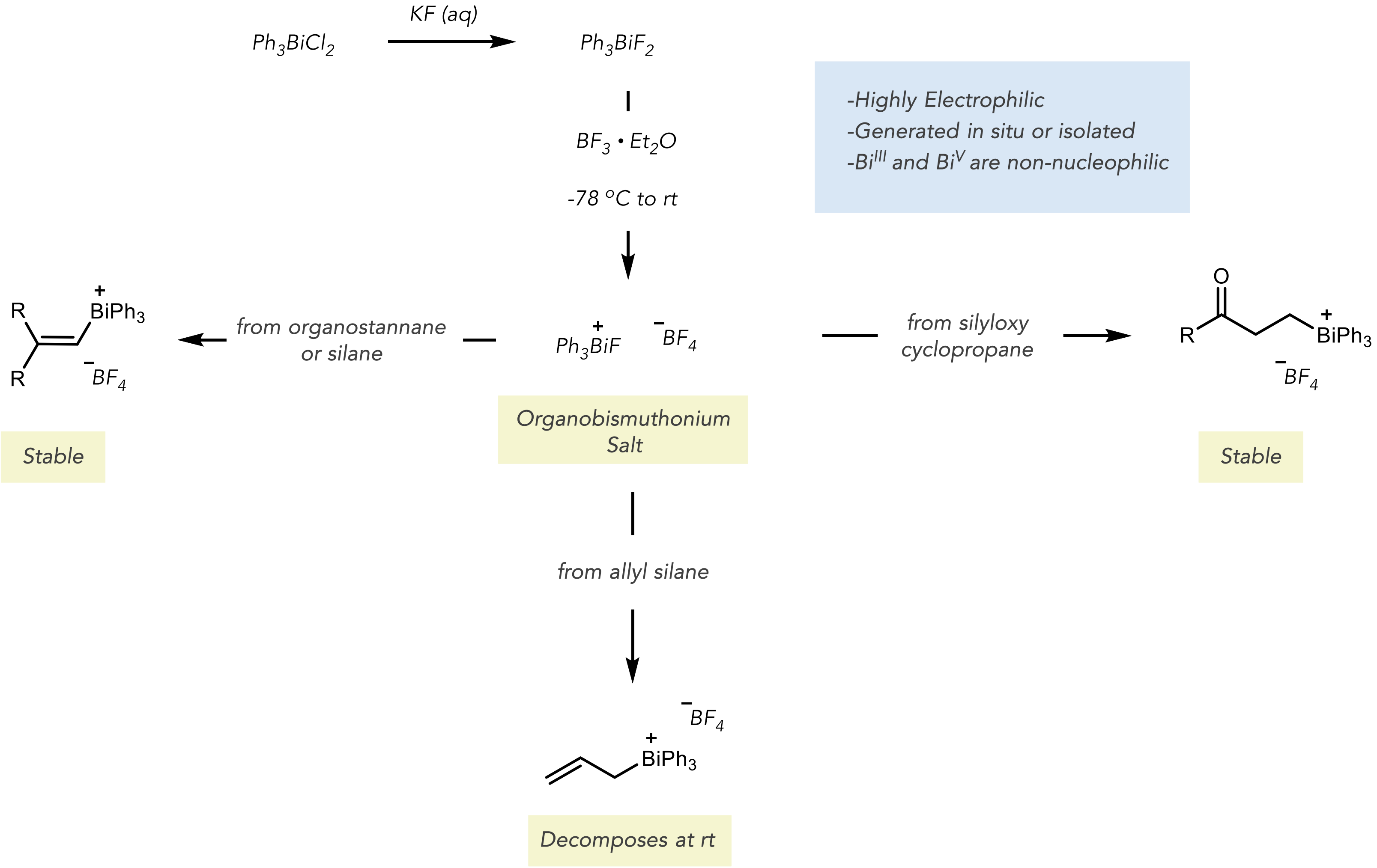


99%

Chan, D.M.T. *Tetrahedron Lett.* **1996**, 37, 9013-9016

Organobismuth: Bismuthonium Salts

- Most work in the area was focused on Bi^{V} species and using the nucleofugality of Bi to drive reactions
- Hitomi Suzuki developed conditions for synthesis of a range of organobismuthonium salts



$Ph_3BiCl_2 \xrightarrow{KF\ (aq)} Ph_3BiF_2$

$BF_3 \cdot Et_2O$

-78 °C to rt

$Ph_3BiF^{+}\ {}^{-}BF_4$

Organobismuthonium Salt

-Highly Electrophilic
-Generated in situ or isolated
-Bi^{III} and Bi^{V} are non-nucleophilic

from organostannane or silane

Stable

from silyloxy cyclopropane

Stable

from allyl silane

Decomposes at rt

Suzuki, H. *J. Chem. Soc. Perkins Trans. 1*. **1995**, 2543-2549

Organobismuth: Bismuthonium Salts

- Most work in the area was focused on Bi^V species and using the nucleofugality of Bi to drive reactions
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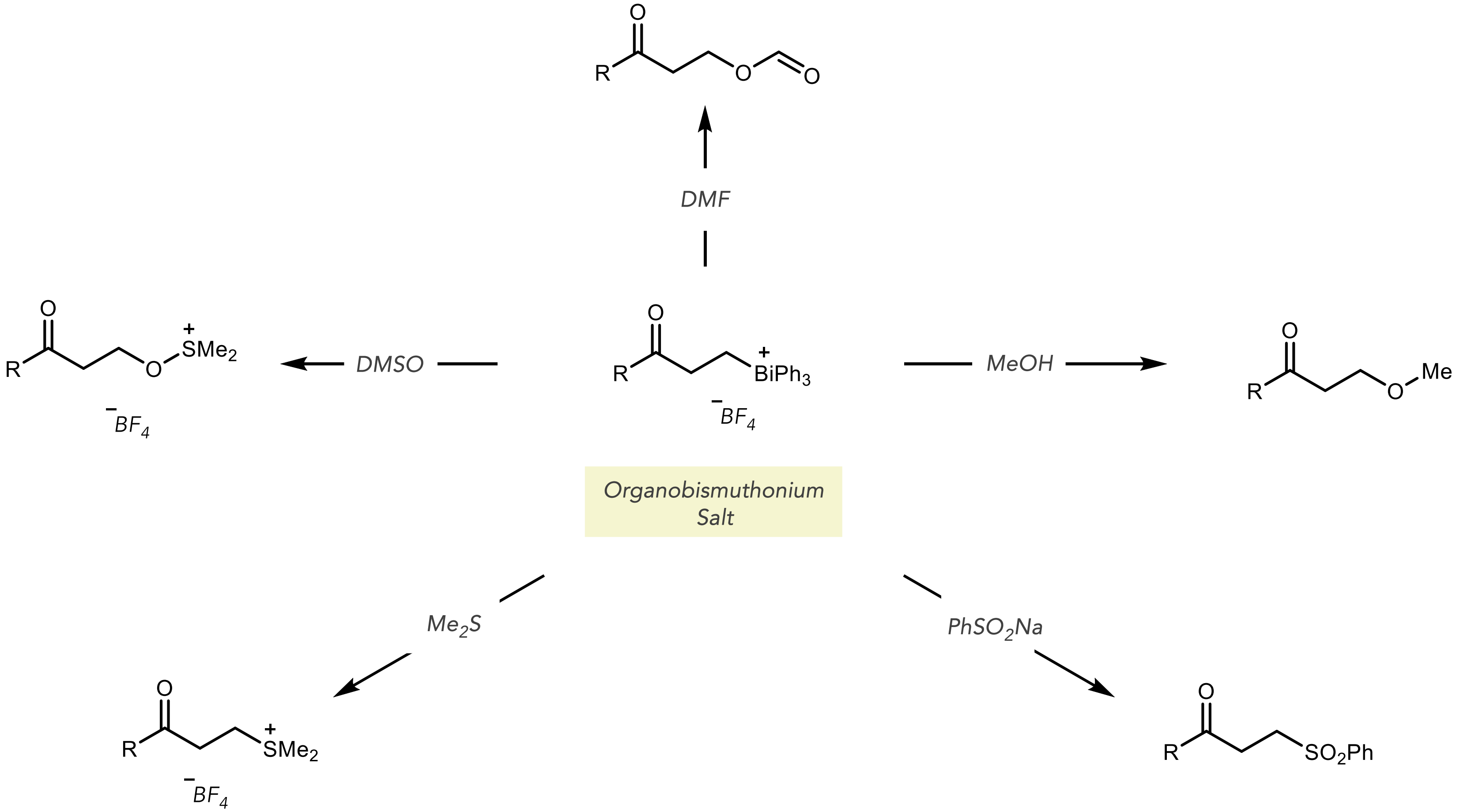
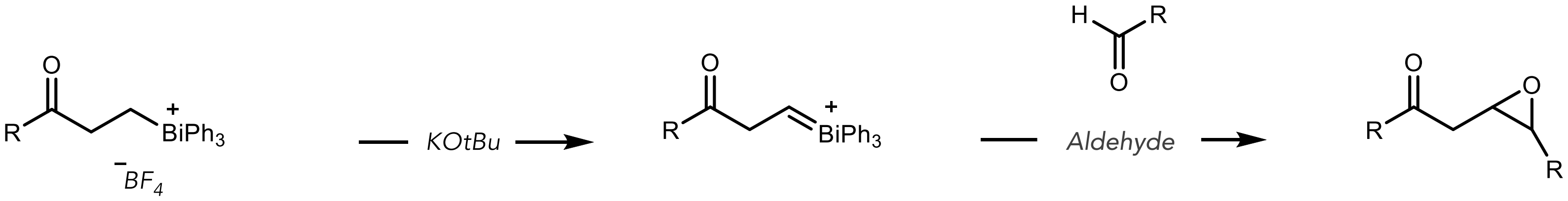


Suzuki, H. *J. Chem. Soc. Perkins Trans. 1*. **1995**, 2543-2549

Organobismuth: Bismuthonium Salts

- Bismuthonium ylides react with aldehydes to give epoxide products (distinct from the Wittig reaction)



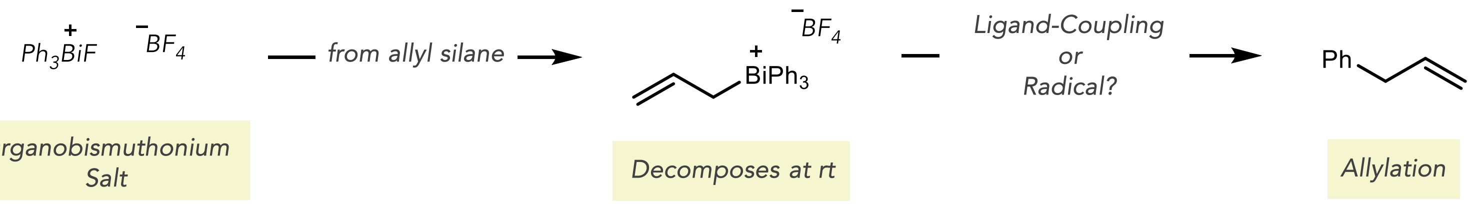
Organobismuthonium Salt

Organobismuthonium ylide

Epoxide formation

Organobismuth: Allyl Bismuthonium Salts

- While unstable at room temperature, allyl bismuthonium salts display unusual reactivity

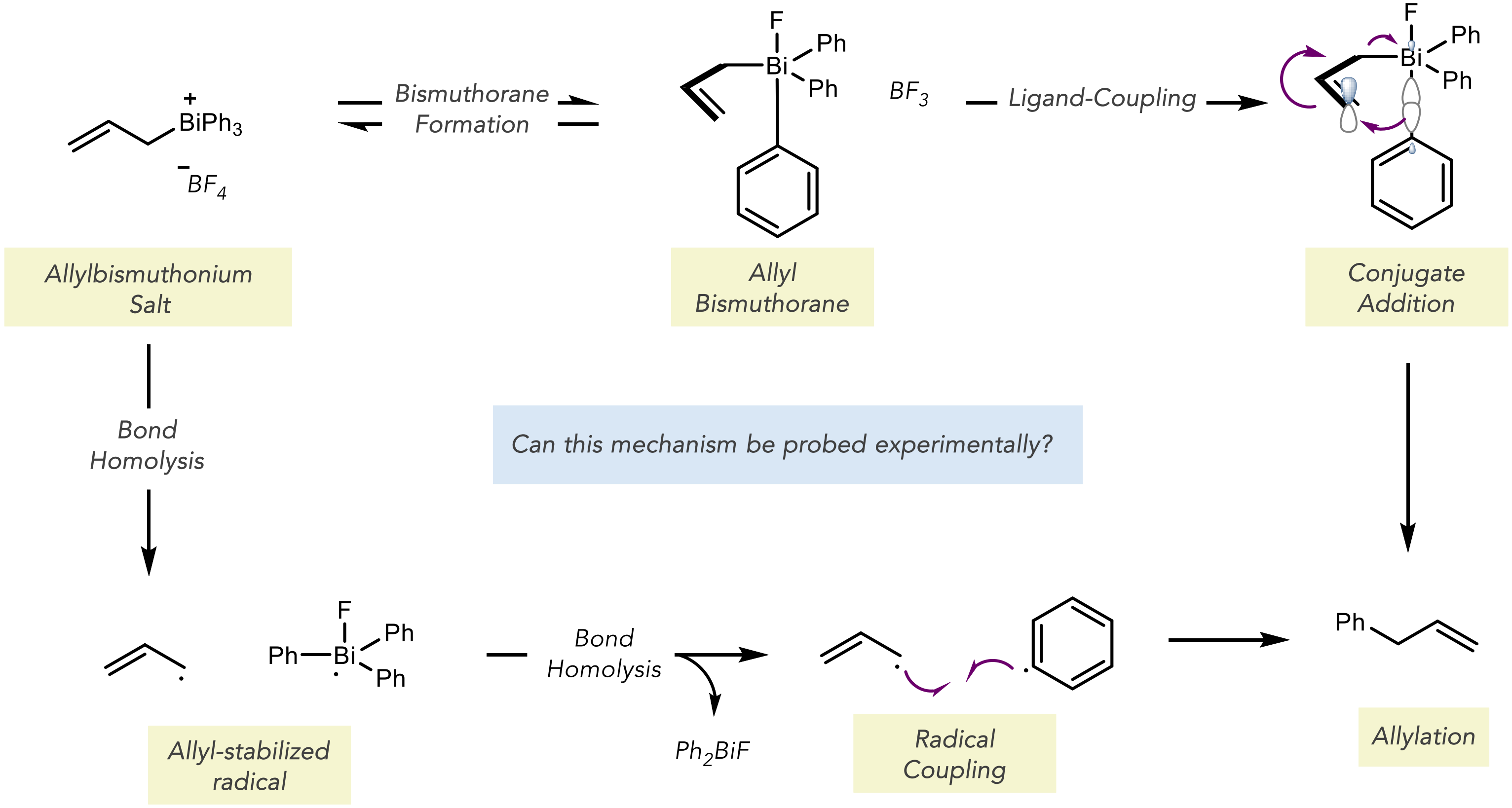


$Ph_3\overset{+}{Bi}F$ $^{-}BF_4$ — from allyl silane → allyl–$\overset{+}{Bi}Ph_3$ $^{-}BF_4$ — Ligand-Coupling or Radical? → Ph–allyl

Organobismuthonium Salt

Decomposes at rt

Allylation



Allyl–$\overset{+}{Bi}Ph_3$ $^{-}BF_4$ ⇌ Bismuthorane Formation ⇌ allyl–BiFPh_3 BF_3 — Ligand-Coupling →

Allylbismuthonium Salt

Allyl Bismuthorane

Conjugate Addition

Bond Homolysis

Can this mechanism be probed experimentally?

Ph–$\dot{Bi}$F–Ph$_2$ — Bond Homolysis → Ph_2BiF

Allyl-stabilized radical

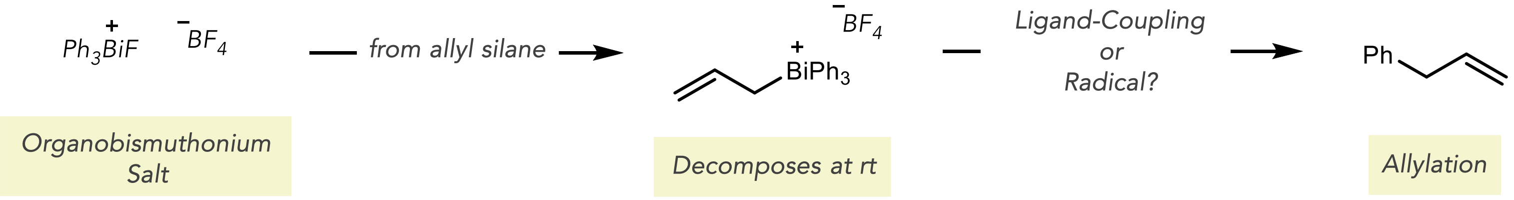
Radical Coupling

Allylation

Suzuki, H. *Tetrahedron Lett.* **1995**, **(36)**, 41, 7475-7478

Organobismuth: Allyl Bismuthonium Salts

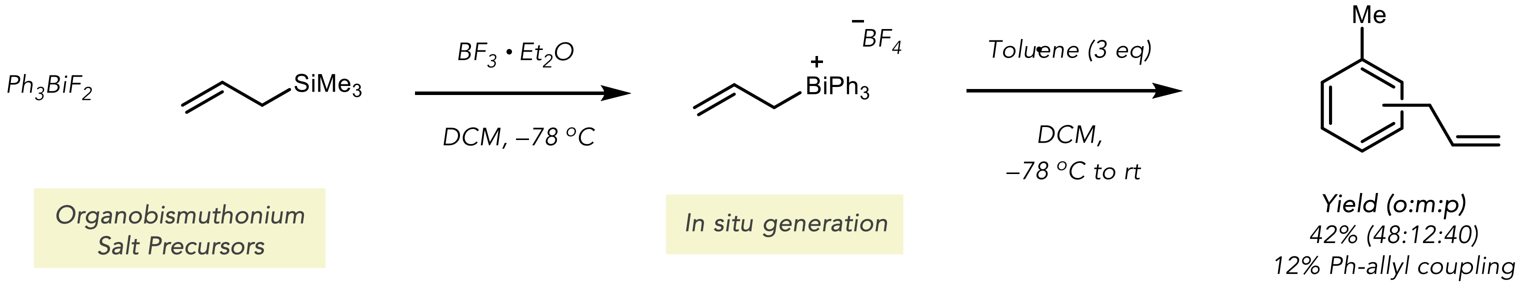
- Allyl bismuthonium salt decomposition: mechanistic probe



Organobismuthonium Salt

Decomposes at rt

Allylation



Organobismuthonium Salt Precursors

In situ generation

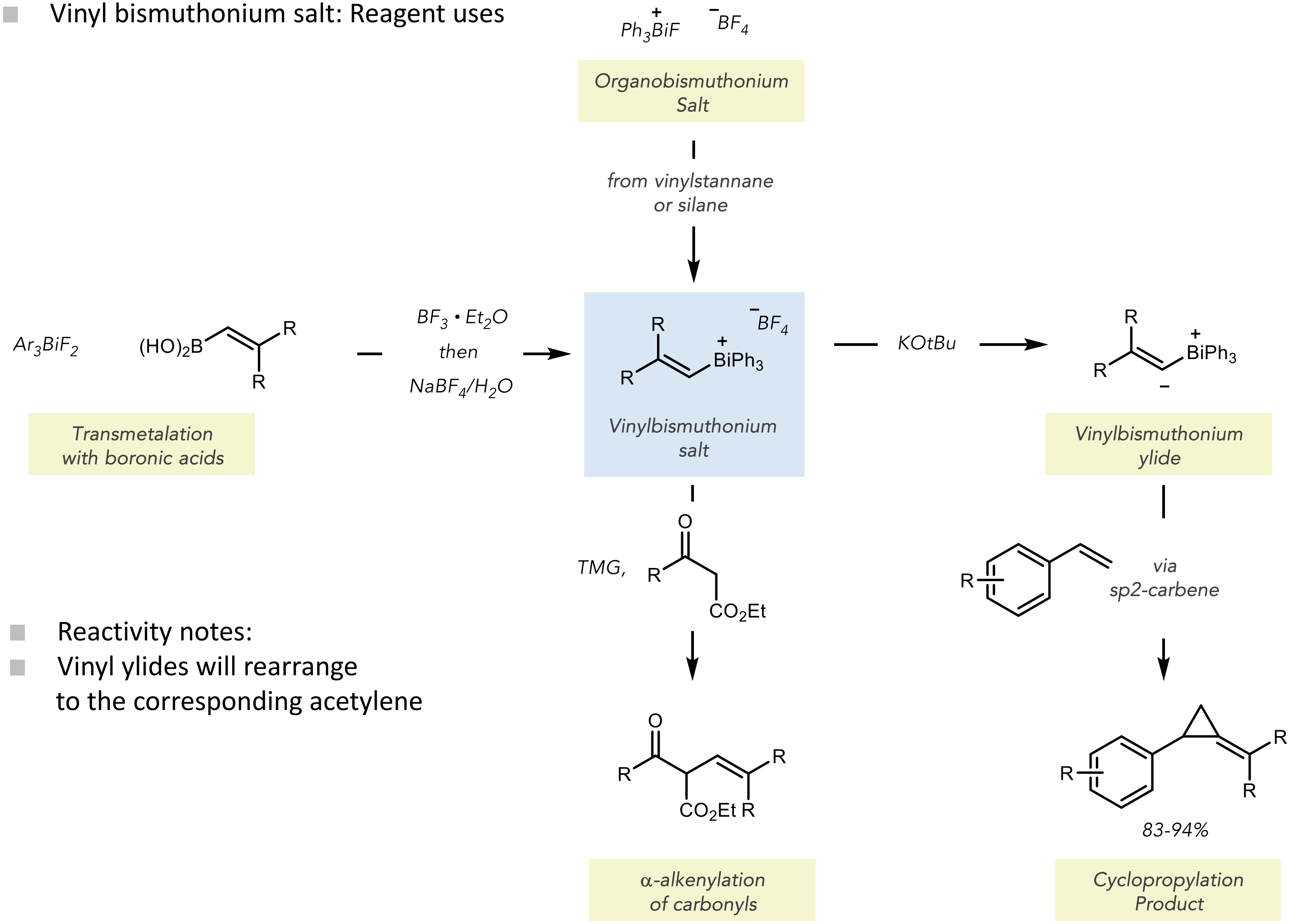
Yield (o:m:p)
42% (48:12:40)
12% Ph-allyl coupling

- Resulting product indicates radical mechanism for decomposition

Suzuki, H. *Tetrahedron Lett.* **1995**, 36 (41), 7475-7478

Organobismuth: Vinyl Bismuthonium Salts

- Vinyl bismuthonium salt: Reagent uses

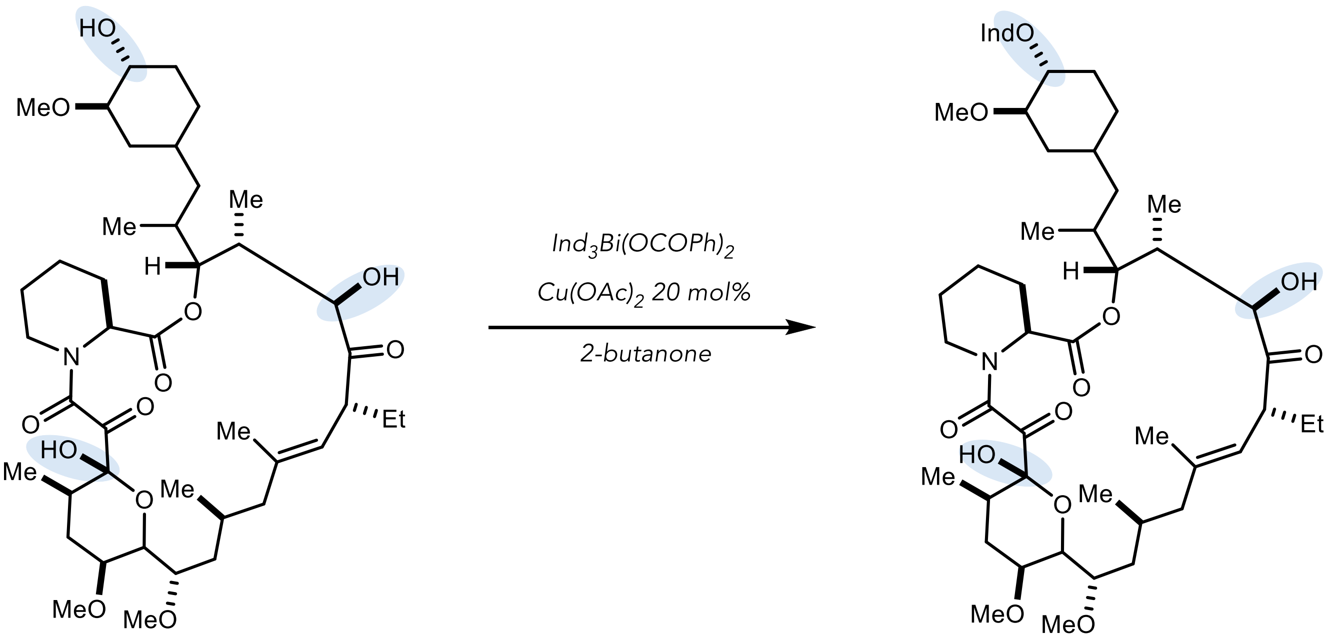


- Reactivity notes:
- Vinyl ylides will rearrange to the corresponding acetylene

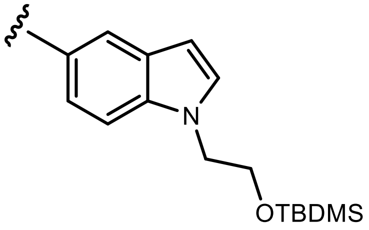
Suzuki, H. *J. Chem. Soc. Perkins Trans 1*, **1996**, 1971-1977
Matano, Y. *J. Org. Chem*. **2004**, 69, 5505-5508

Organobismuth: Examples from literature

- Vinyl Merck Process: L-732531 synthesis: Selective arylation



Ind =

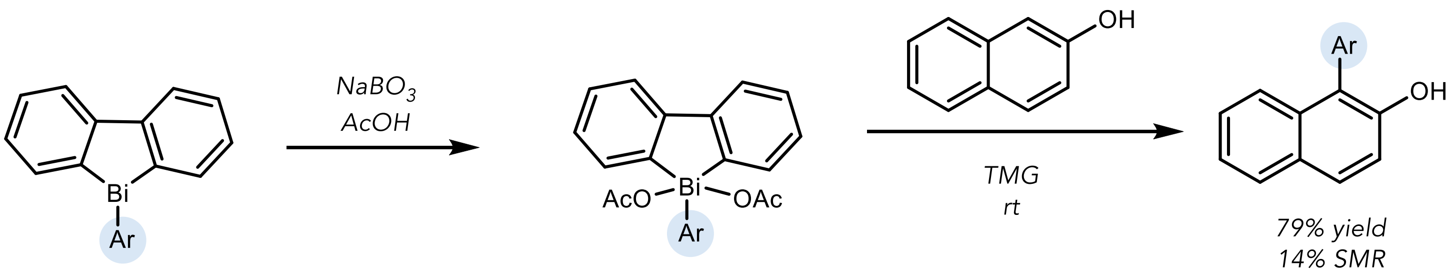


Eq [Bi]	Yield	Double addition
1.26	83	8
1.47	86	12

Williams, J. M. *J. Org. Chem*, **1998**, 63 (19), 6721-6726

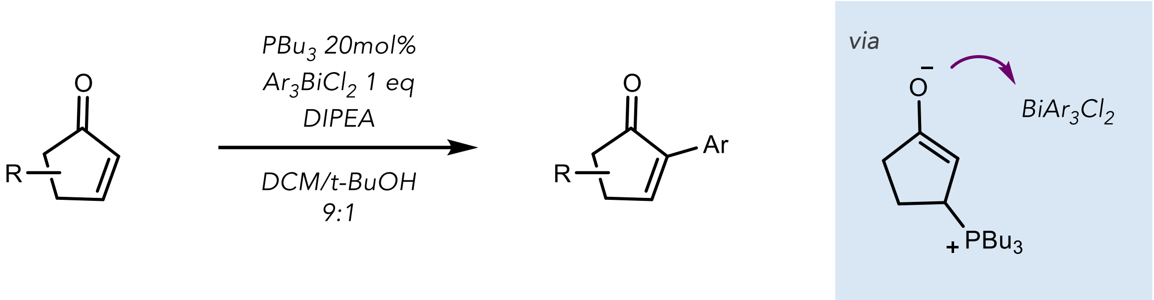
Organobismuth: Examples from literature

- Controlling aryl group transfer: Solving the 3x requirement of arene (Finet)

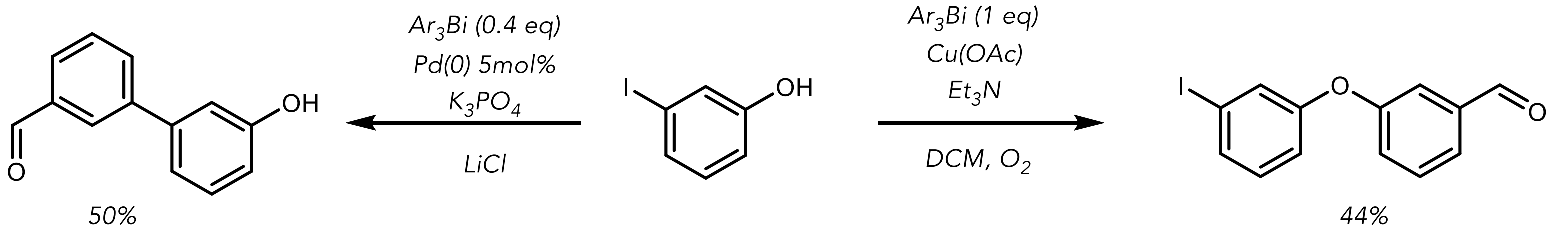


Selective Transfer
of non-bridged Arene

- α-phenylation of α,β-unsaturated ketones (Krische)



- Distinct chemoselectivity can be exploited (Gagnon)



Finet, J.-P. *J. Chem. Soc., Perkin Trans. 1* **2000**, *0* (22), 3775–3778.
Krische, M. J *J. Am. Chem. Soc.* **2004**, *126* (17), 5350–5351.
Gagnon, A. *J. Org. Chem.* **2016**, *81* (13), 5401–5416