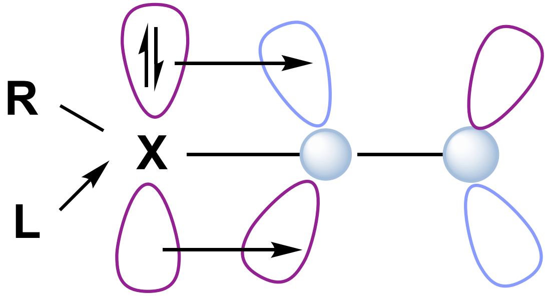
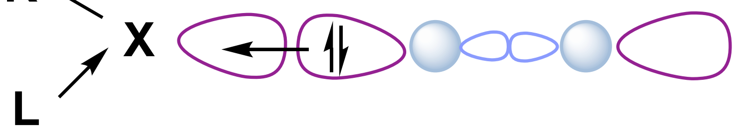
Main-group Elements (Bi) in Catalysis for Organic Synthesis

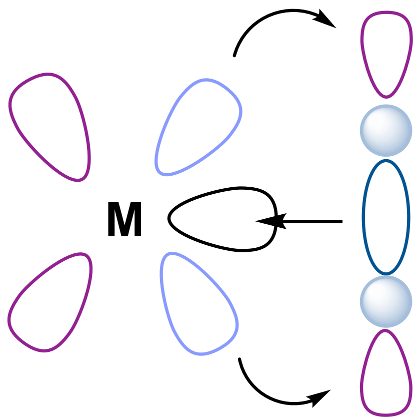




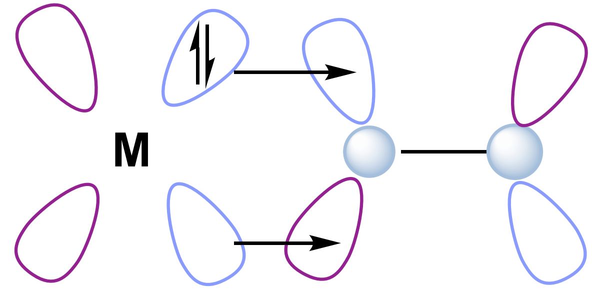
Xiaheng Zhang
MacMillan Group Meeting
March 18th, 2020

Mechanisms of Activation Mode for Main-group Elements

■ Activation mode of transition metal elements

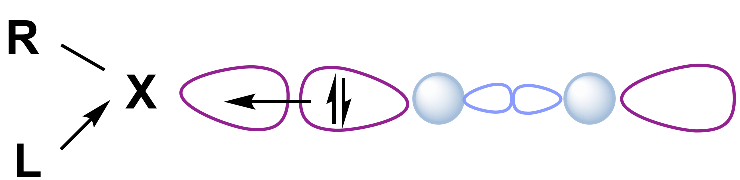


σ donation into empty *d*-orbital

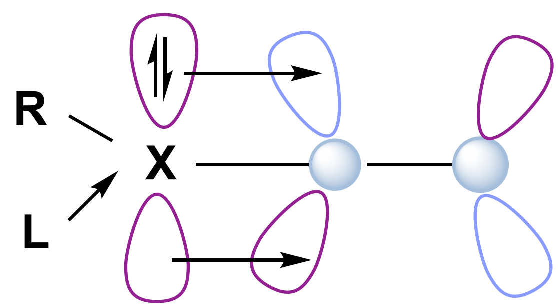


π donation from *d*-orbital into **π***-orbital

■ Activation mode of main-group elements



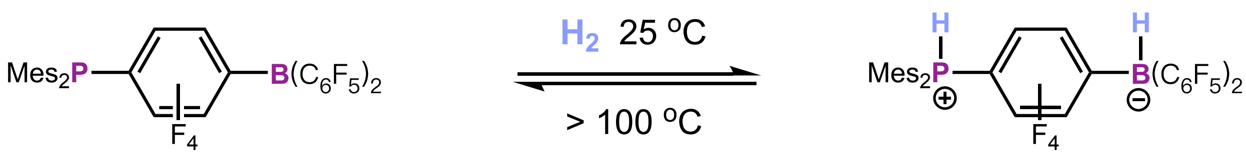
σ donation into empty *p*-orbital



π donation from *p*-orbital into **π***-orbital

Activation of Small Molecules by Main-group Elements

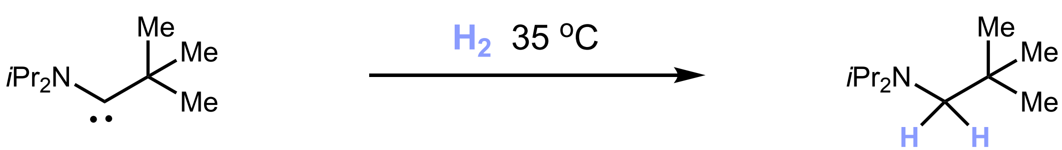
Frustrated Lewis pairs activation



Stephan, D. W. et al. *Science* **2006**, *314*, 1124.

Stephan, D. W. et al. *Science* **2016***, 354*, aaf7229.

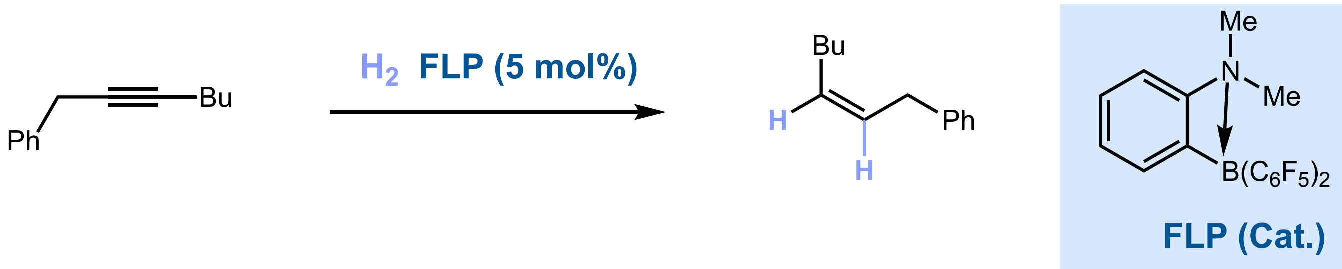
Activation of H_2 by carbenes



Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science* **2007**, *316*, 439.

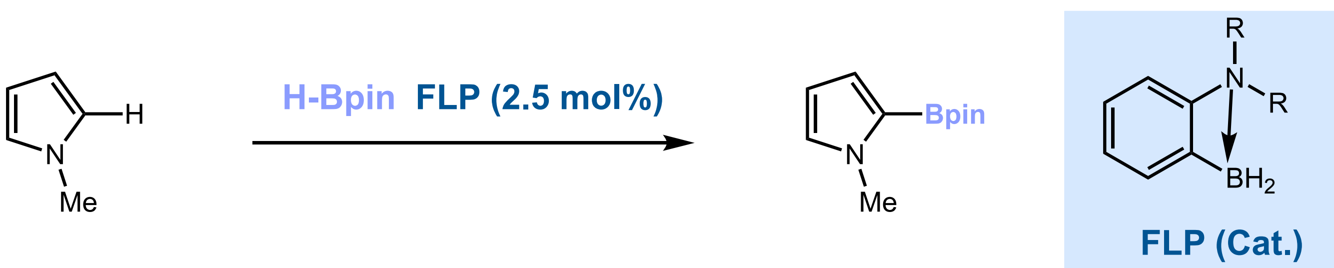
Catalysis Enabled by Main-group Elements

Frustrated Lewis pairs catalyzed hydrogenation



Chernichenko,K.;Madaraśz,A.;Paṕai,I.;Nieger,M.;Leskela, M.;Repo,T. *Nat. Chem.* **2013**, *5*, 718.

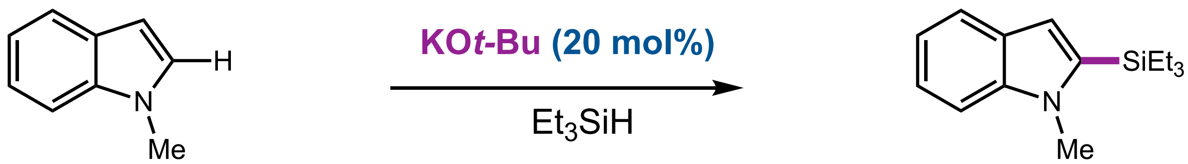
FLP catalyzed C-H activation



Leǵare;M.-A.;Courtemanche,M.-A.;Rochette,É.;Fontaine,F.-G. *Science* **2015**, *349*, 513.

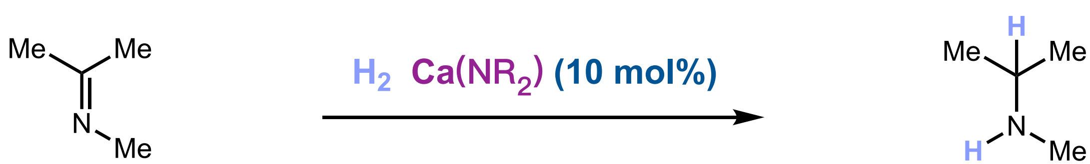
Catalysis Enabled by Main-group Elements

C-H silylation catalyzed by alkali metal catalyst



Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. *Nature* **2015**, *518*, 80.

Imine hydrogenation catalyzed by alkaline earth metal catalyst



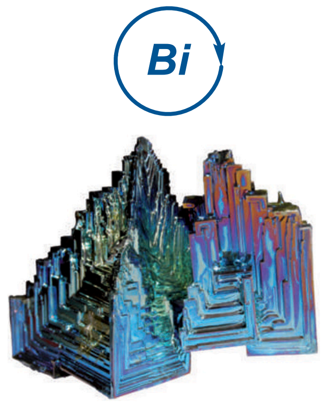
Harder, S. et. al. *Nat. Catal.* **2018,** *1*, 40.

Main-group Elements (Bi) in Catalysis for Organic Synthesis

Outline

- The facts of bismuth
- Synthesis of organobismuthines
- The application of organobismuthines in organic synthesis
- Redox chemistry of bismuth

Why do people care about bismuth catalysis



electron configuration: $4f^{14}5d^{10}6s^{2}6p^{3}$
common oxidation state: +1, +3, +5

Peptobismol OTC

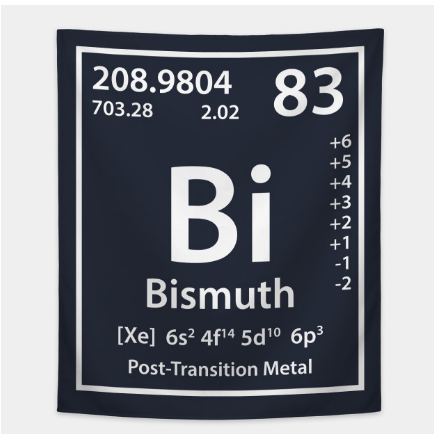
stomach disorders

- **naturally abundant**
- **'green element' even less toxic than NaCl**
- **widely used in industry, antibiotics, radiopaque bone cements, polymers**

Can we discover new reactivity that is unique to bismuth catalysis?

Main-group Elements (Bi) in Catalysis for Organic Synthesis

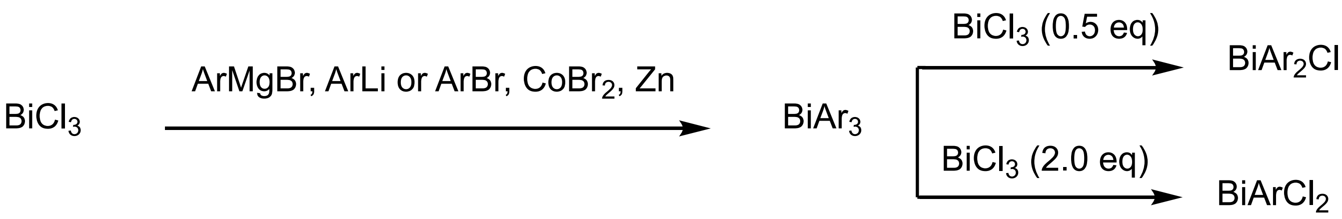
Outline



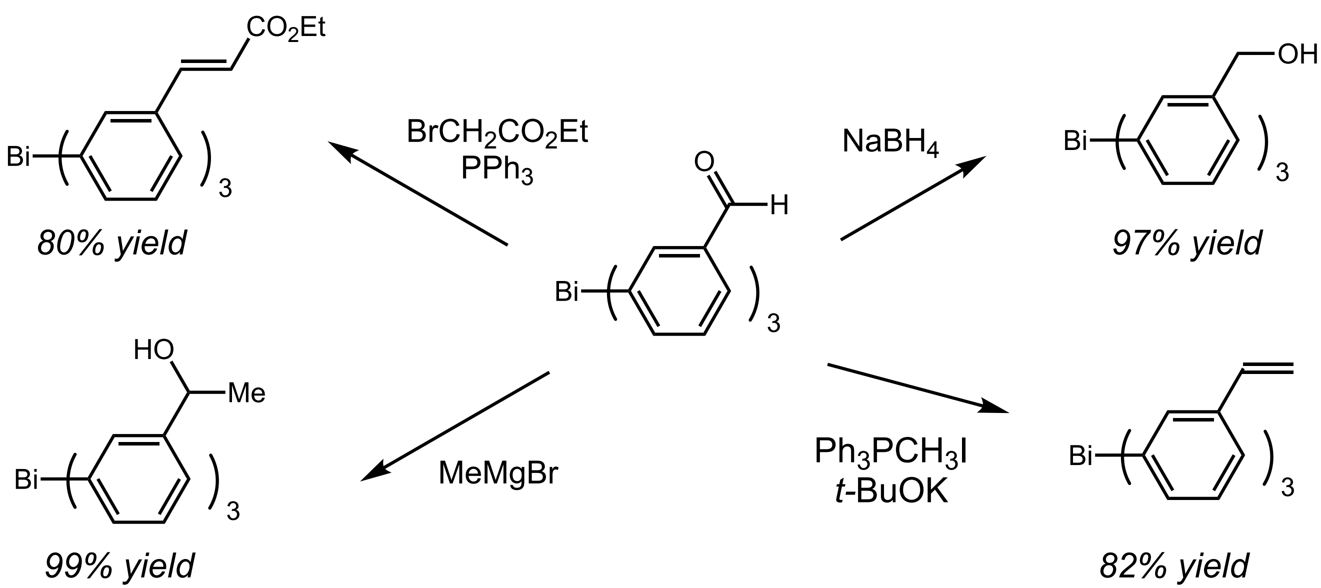
- The facts of bismuth
- Synthesis of organobismuthines
- The application of organobismuthines in organic synthesis
- Redox chemistry of bismuth

Synthesis of organobismuthines

Synthesis of trivalent organobismuthines



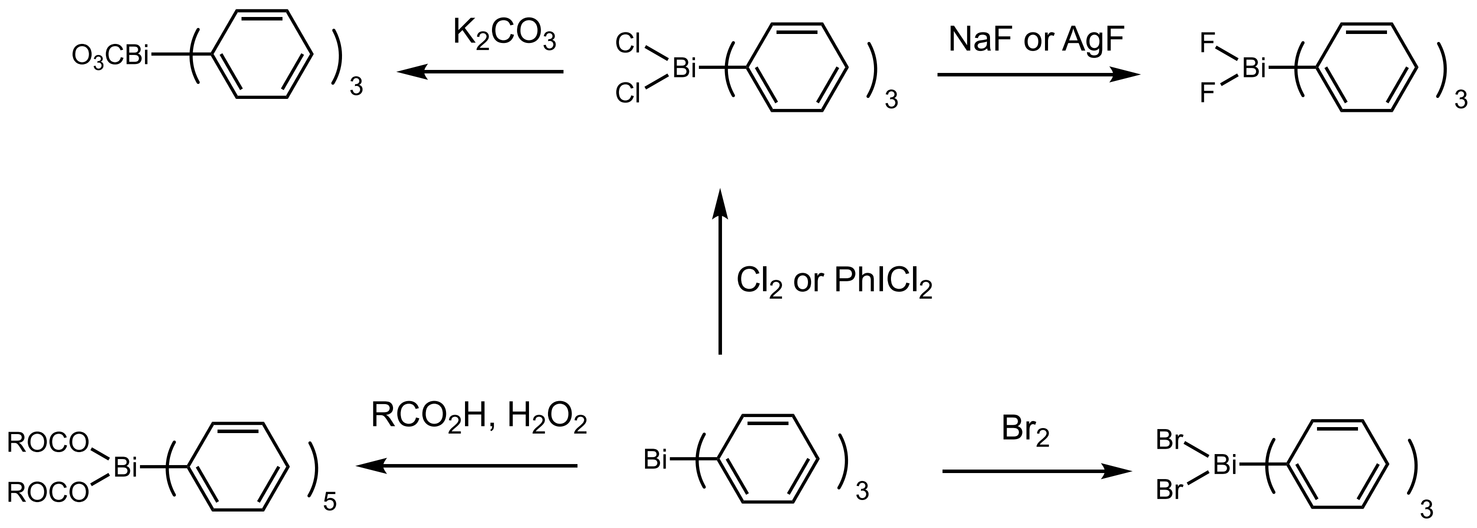
Synthesis of highly functionalized trivalent organobismuthines



Gagnon, A. et. al. *J. Org. Chem.* **2016**, *81*, 5401.

Synthesis of organobismuthines

Synthesis of pentavalent organobismuthines



Michaelis, A. *Ber. Dtsch. Chem. Ges*. **1887**, *20*, 52.
Barton, D. H. R.; Finet, J.-P. *Pure Appl. Chem*. **1987**, *59*, 937.

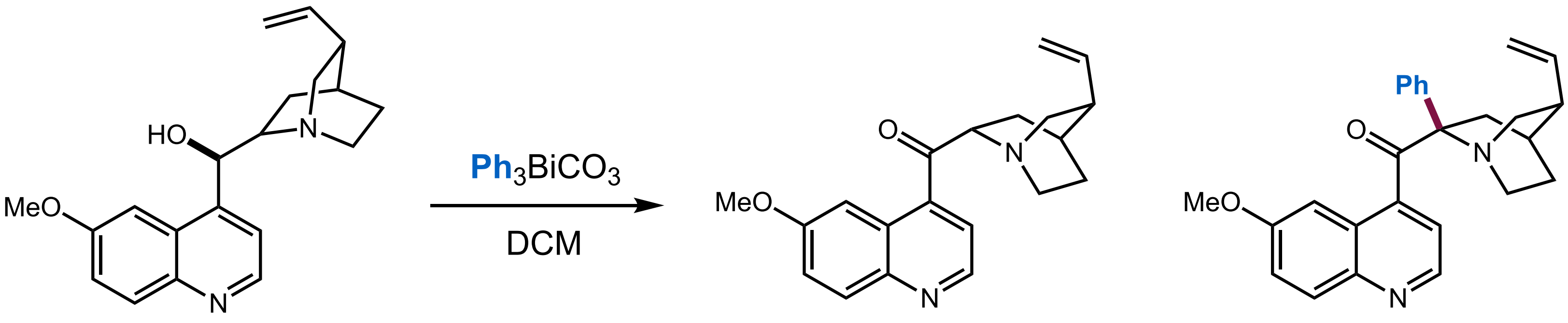
Main-group Elements (Bi) in Catalysis for Organic Synthesis

Outline

- The facts of bismuth
- Synthesis of organobismuthines
- The application of organobismuthines in organic synthesis
- Redox chemistry of bismuth

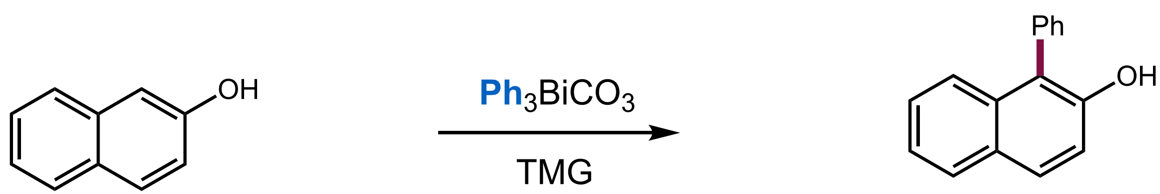
Organobismuth as arylation reagents

The first arylation reaction using organobismuthines



75% yield

The first C-arylation of phenols using organobismuthines

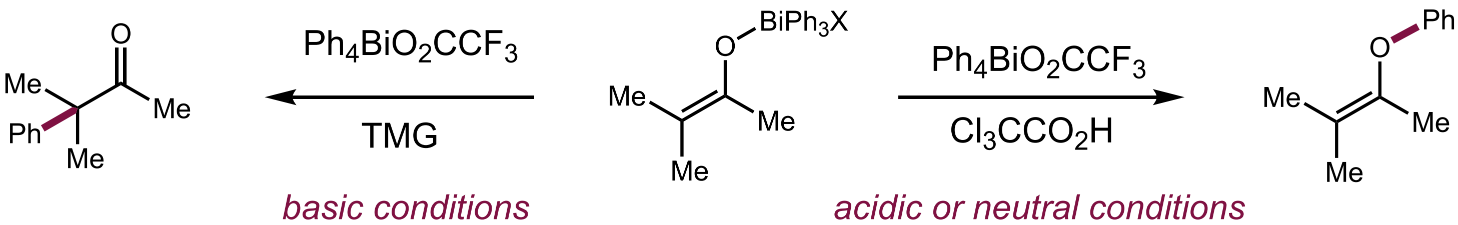


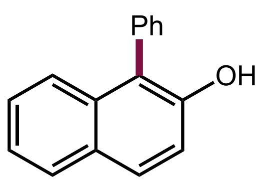
76% yield

Barton, D. H. R.; Lester, D. J.; Motherwell, W. B.; Papoula, M. T. B. *J. Chem. Soc., Chem. Commun*. **1980**, 246.

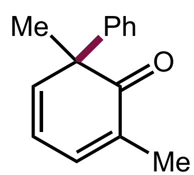
Organobismuth as arylation reagents

O-arylation and *C*-arylation controlled by condition

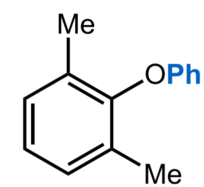




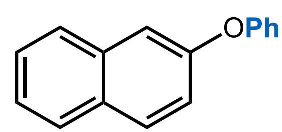
90% yield



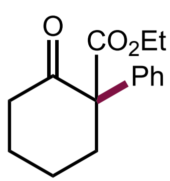
72% yield



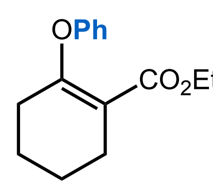
91% yield



90% yield



58% yield

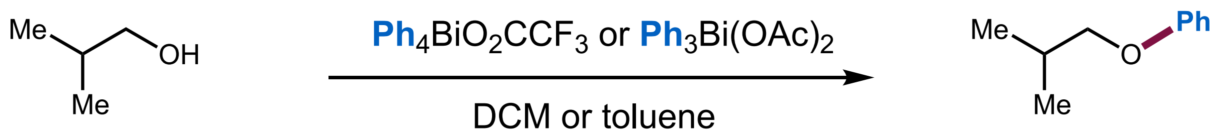


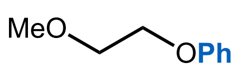
57% yield

Barton, D. H. R. et. al. *J. Chem. Soc., Chem. Commun*. **1980**, 827. Barton, D. H. R. et. al. *J. Chem. Soc., Chem. Commun.* **1981**, 503.

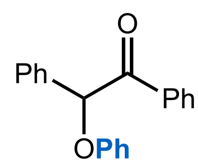
Organobismuth as arylation reagents

O-arylation of alcohols, diols, aminoalcohols

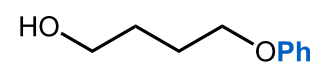




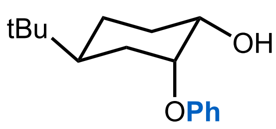
86% yield



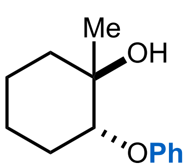
88% yield



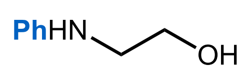
80% yield



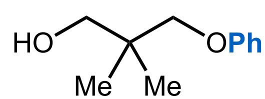
73% yield



88% yield



51% yield

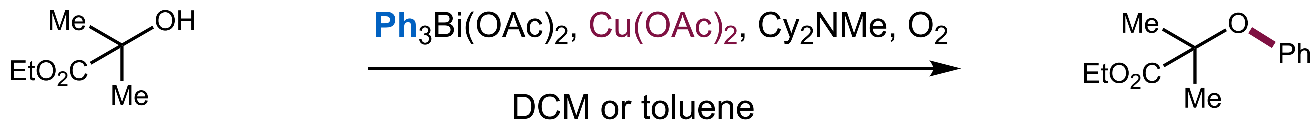


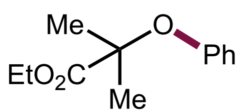
99% yield

David, S.; Thieffry, A. *J. Org. Chem*. **1983**, *48*, 441. Barton, D. H. R. et. al. *J. Chem. Soc., Chem. Commun.* **1986**, 65.

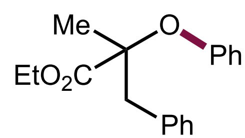
Organobismuth as arylation reagents

O-arylation of tertiary alcohols via Cu catalysis

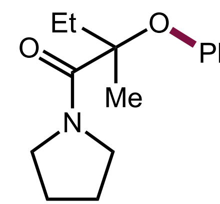




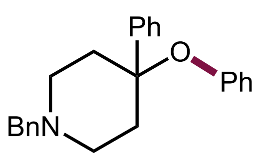
89% yield



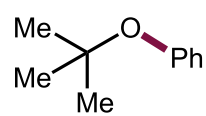
89% yield



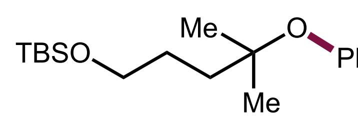
94% yield



88% yield



87% yield

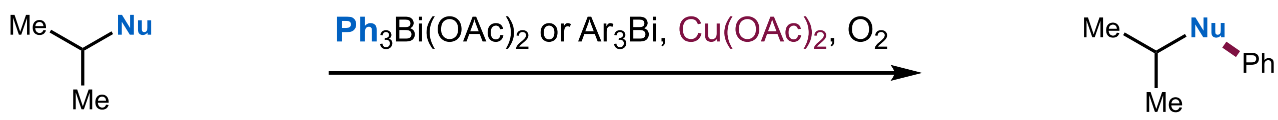


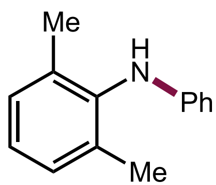
50% yield

Ikegai, K.; Fukumoto, K.; Mukaiyama, T. *Chem. Lett*. **2006**, *35*, 612. Mukaiyama, T.; Sakurai, N.; Ikegai, K. *Chem. Lett*. **2006**, *35*, 1140.

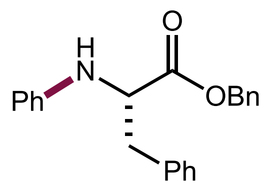
Organobismuth as arylation reagents

Cu catalyzed arylation of *N*, *S*-nucleophiles

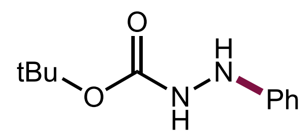




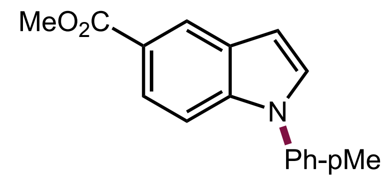
96% yield



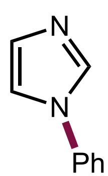
80% yield



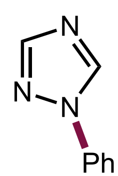
91% yield



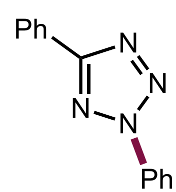
87% yield



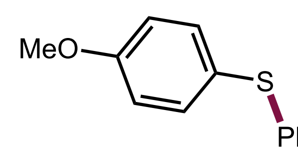
87% yield



60% yield



87% yield

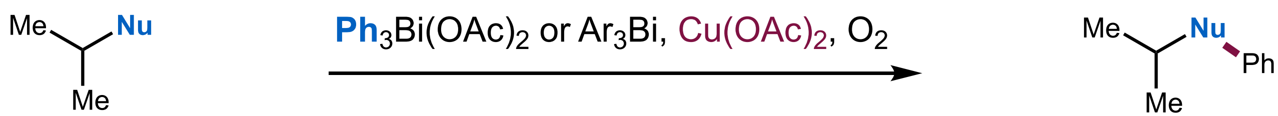


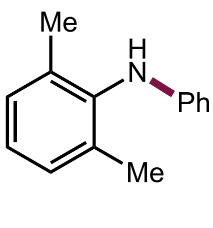
84% yield

Gagnon, A. et. al. *Synthesis* **2017**, *49*, 1707.

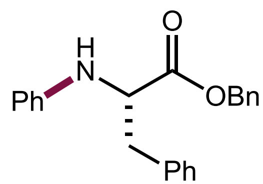
Organobismuth as arylation reagents

Cu catalyzed arylation of *N*, *S*-nucleophiles

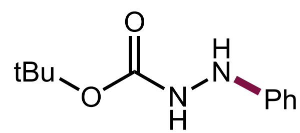




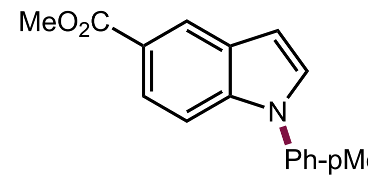
96% yield



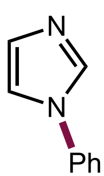
80% yield



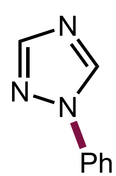
91% yield



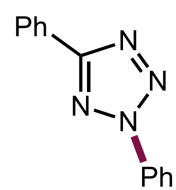
87% yield



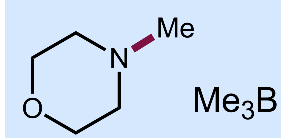
87% yield



60% yield



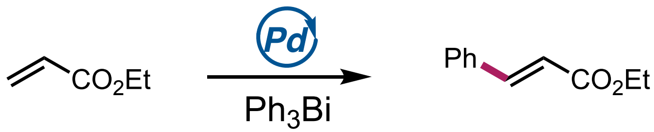
87% yield



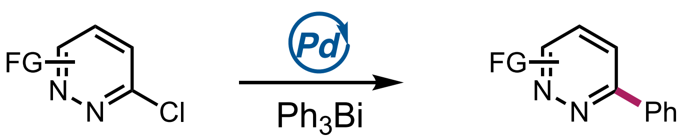
52% yield

Gagnon, A. et. al. *Synthesis* **2017**, *49*, 1707.

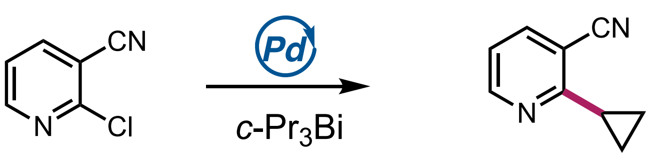
Cross-coupling using organobismuth



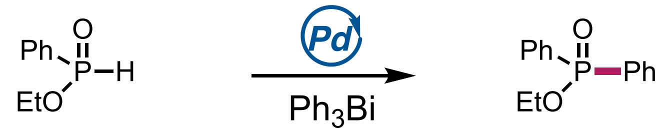
Kawamura, T.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 2021.



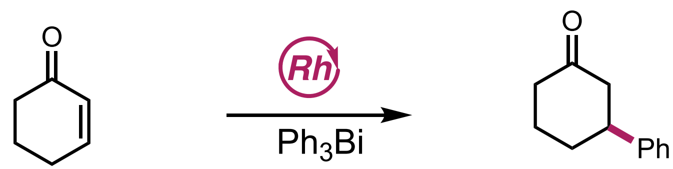
Gagnon, A. *J. Org. Chem.* **2016**, *81*, 5401.



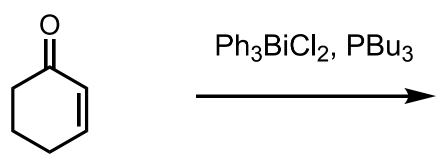
Gagnon, A.; Duplessis, M.; Alsabeh, P.; Barabé, F. *J. Org. Chem.* **2008**, *73*, 3604.



Wang, T.; Sang, S.; Liu, L.; Qiao, H.; Gao, Y.; Zhao, Y. *J. Org. Chem*. **2014**, *79*, 608.



Li, C.-J. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 7451.



Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 5350.

Bi redox chemistry is unclear with rare examples.

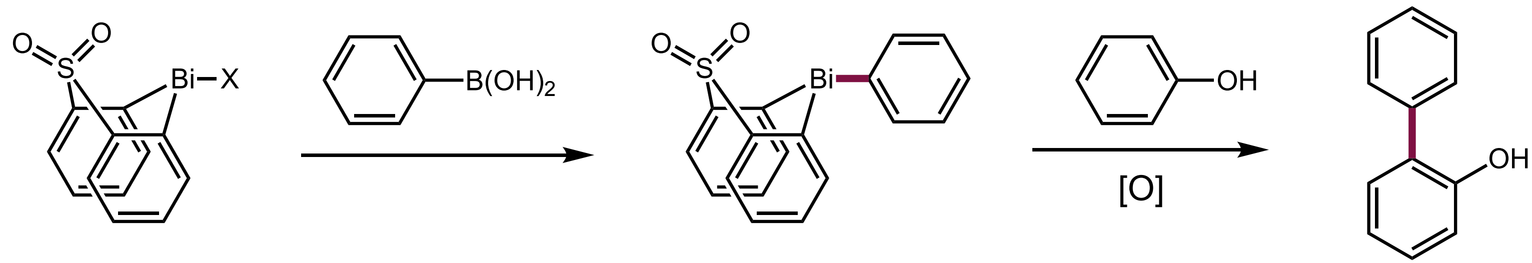
Main-group Elements (Bi) in Catalysis for Organic Synthesis

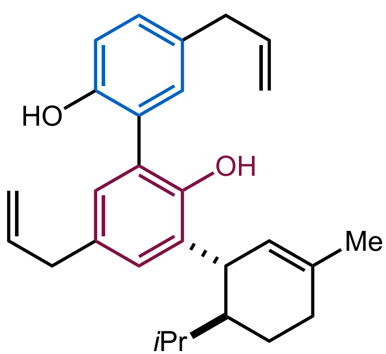
Outline

- The facts of bismuth
- Synthesis of organobismuthines
- The application of organobismuthines in organic synthesis
- Redox chemistry of bismuth

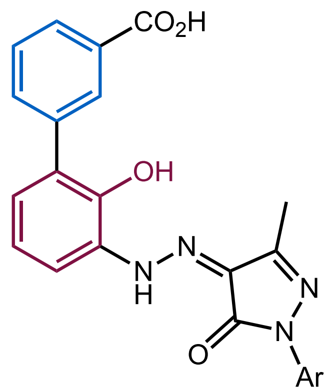
Bi(III)/Bi(V) redox activation

ortho-Arylation of phenols via Bi(III)/Bi(V) redox activation

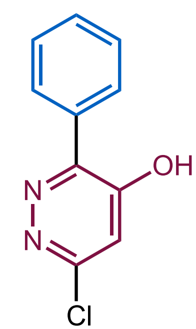




Liganas
antibacterial, cyctotoxic



Pharmaceuticals
aplastic anemia

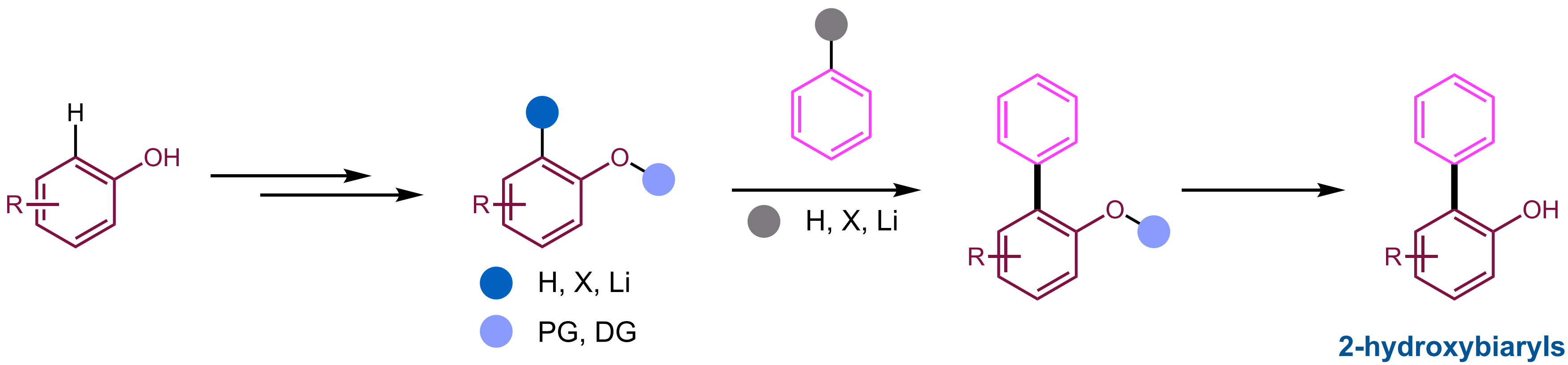


Agrochemicals
herbicide

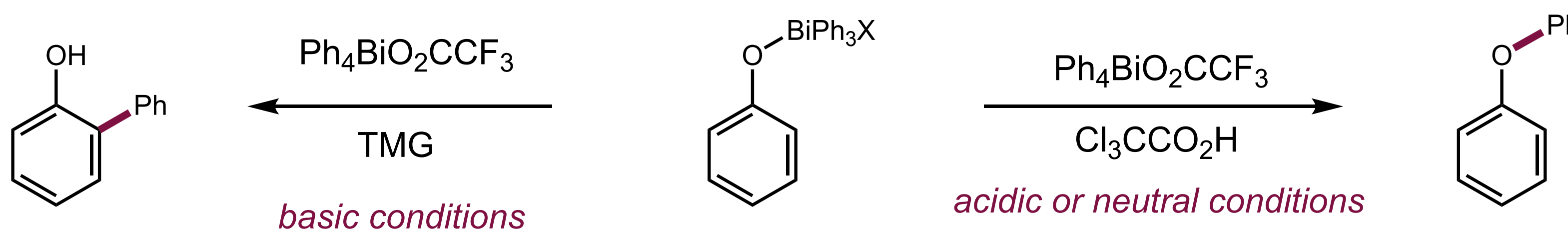
Jurrat, M.;Maggi, L.;Papai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

Bi(III)/Bi(V) redox activation

Current approaches for the preparation of 2-hydroxybiaryls



Barton's pioneer discovery

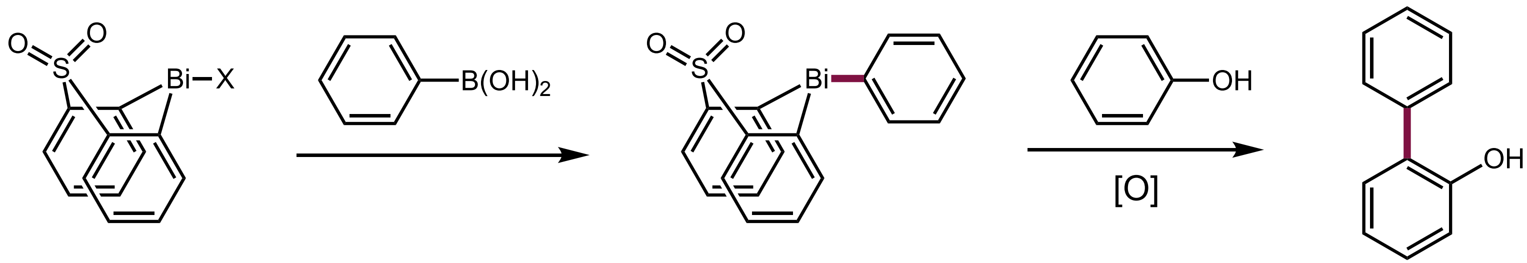


- **O or C arylation is highly dependent on the nature of the organobismuth and reaction conditions**
- **multistep synthesis of arylbismuth reagents, transfer one of the aryl groups in the organobismuth**
- **lack of systematic studies of mechanism which impedes practical exploration of the method**

Jurrat, M.;Maggi, L.;Paṕai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

Bi(III)/Bi(V) redox activation

ortho-Arylation of phenols via Bi(III)/Bi(V) redox activation

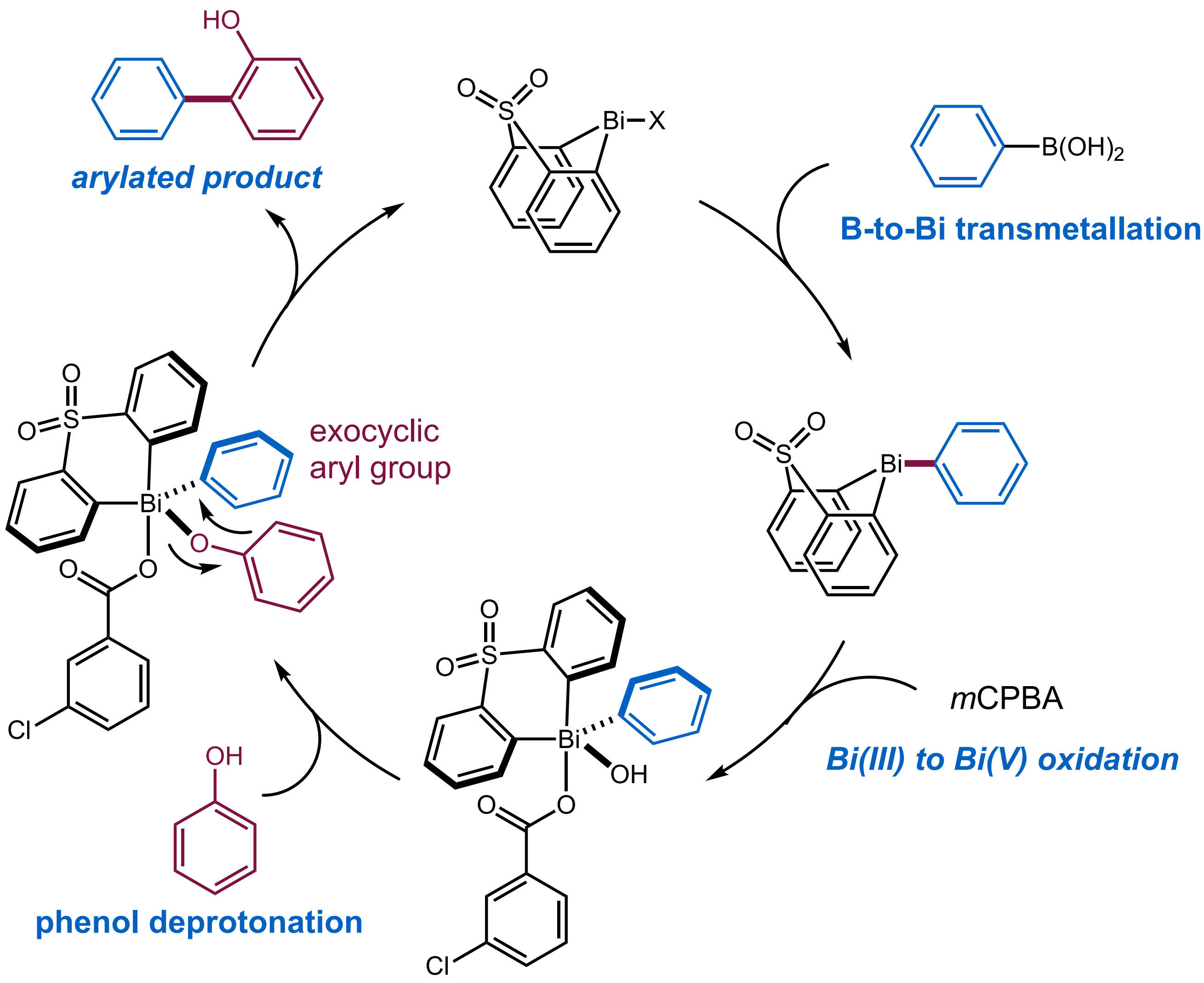


- ***one-pot boron-to-bismuth transmetallation***
- ***commercially available starting materials***
- ***completely prevents the formation of O-arylated products***
- ***operates under air in non-anhydrous conditions***

Jurrat, M.;Maggi, L.;Paṕai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

Bi(III)/Bi(V) redox activation for ortho-Arylation of phenols

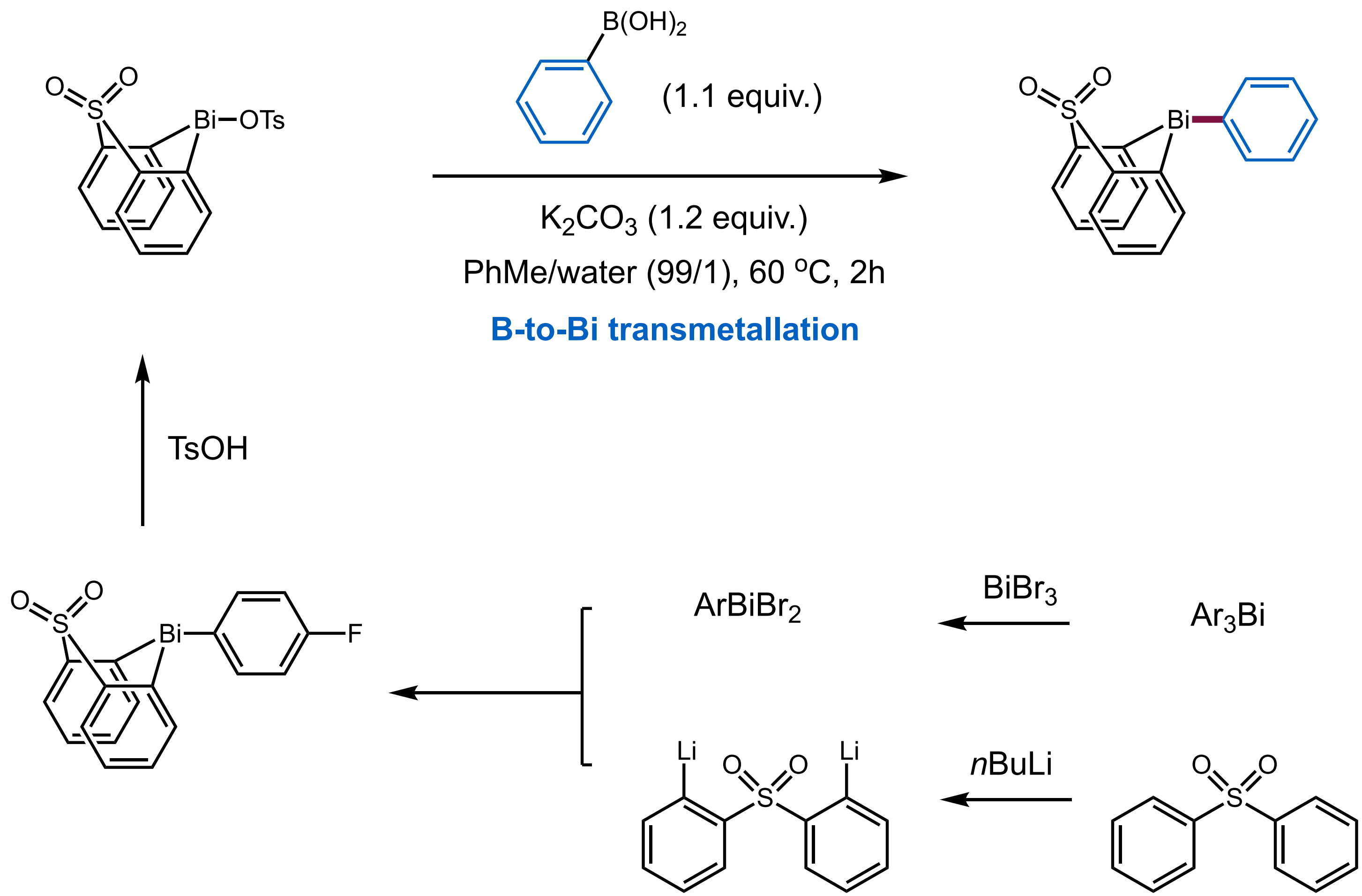
■ Reaction design



Jurrat, M.;Maggi, L.;Papai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

Bi(III)/Bi(V) redox activation for ortho-Arylation of phenols

Transmetallation to universal bismacyclic precursor



Jurrat, M.;Maggi, L.;Paṕai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

Bi(III)/Bi(V) redox activation for ortho-Arylation of phenols

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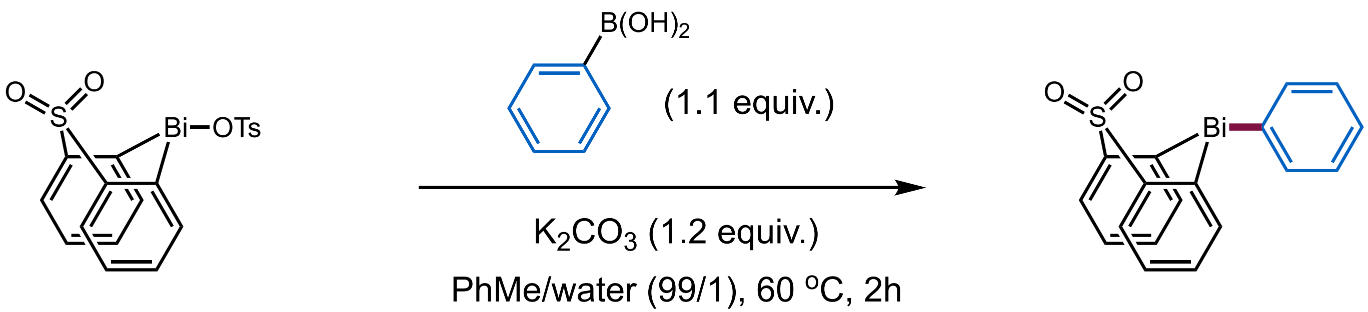
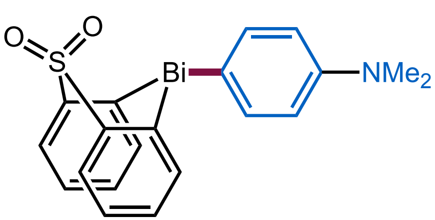
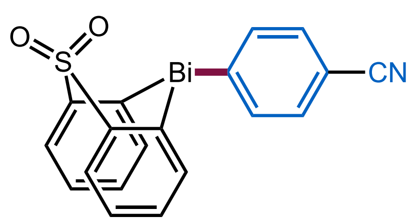
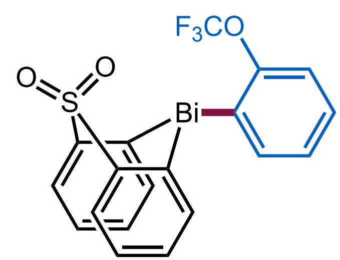




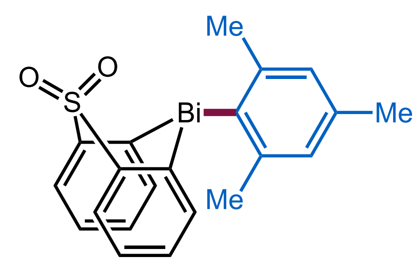
>99% yield



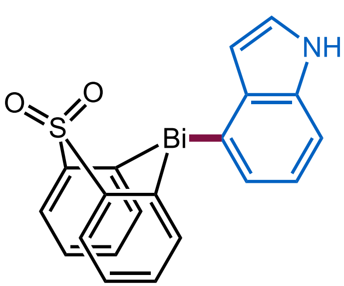
>99% yield



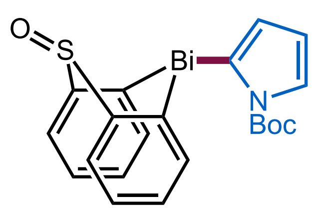
>99% yield



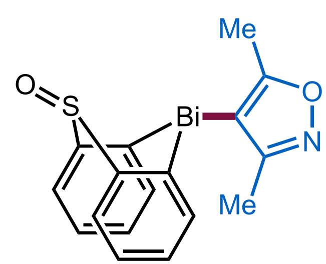
>99% yield



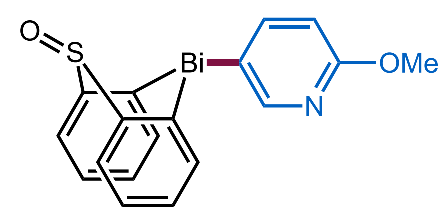
>99% yield



>99% yield



>99% yield

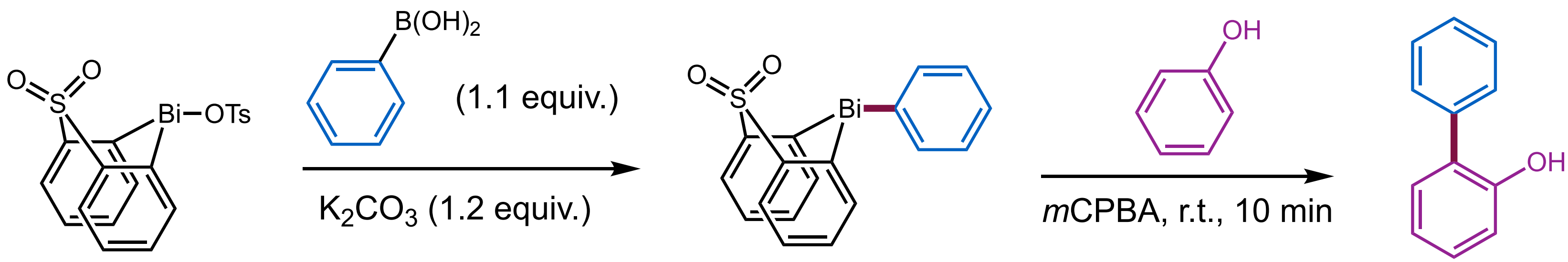


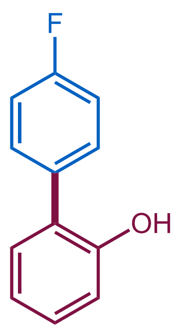
>99% yield

Jurrat, M.;Maggi, L.;Papai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

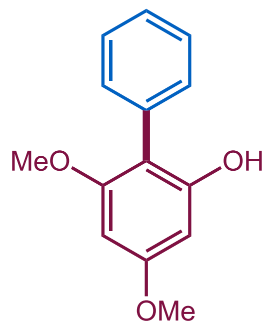
Bi(III)/Bi(V) redox activation for ortho-Arylation of phenols

One-pot, Bi(V)-mediated arylation of phenols and naphthols

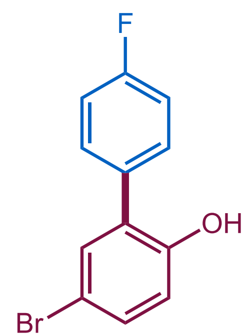




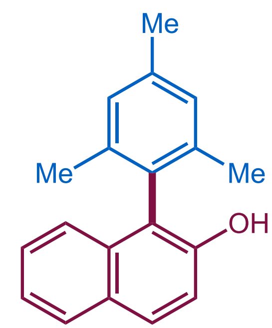
69% yield



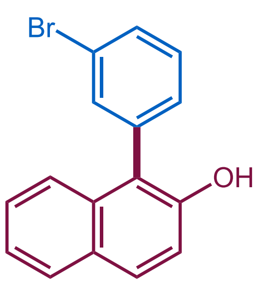
77% yield



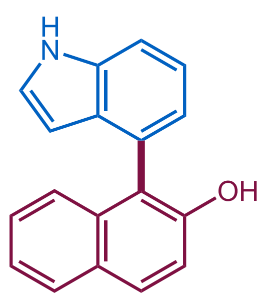
59% yield



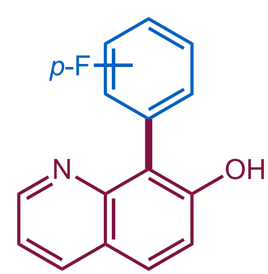
89% yield



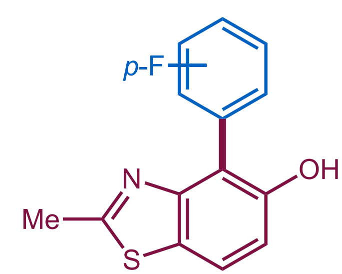
87% yield



59% yield



93% yield

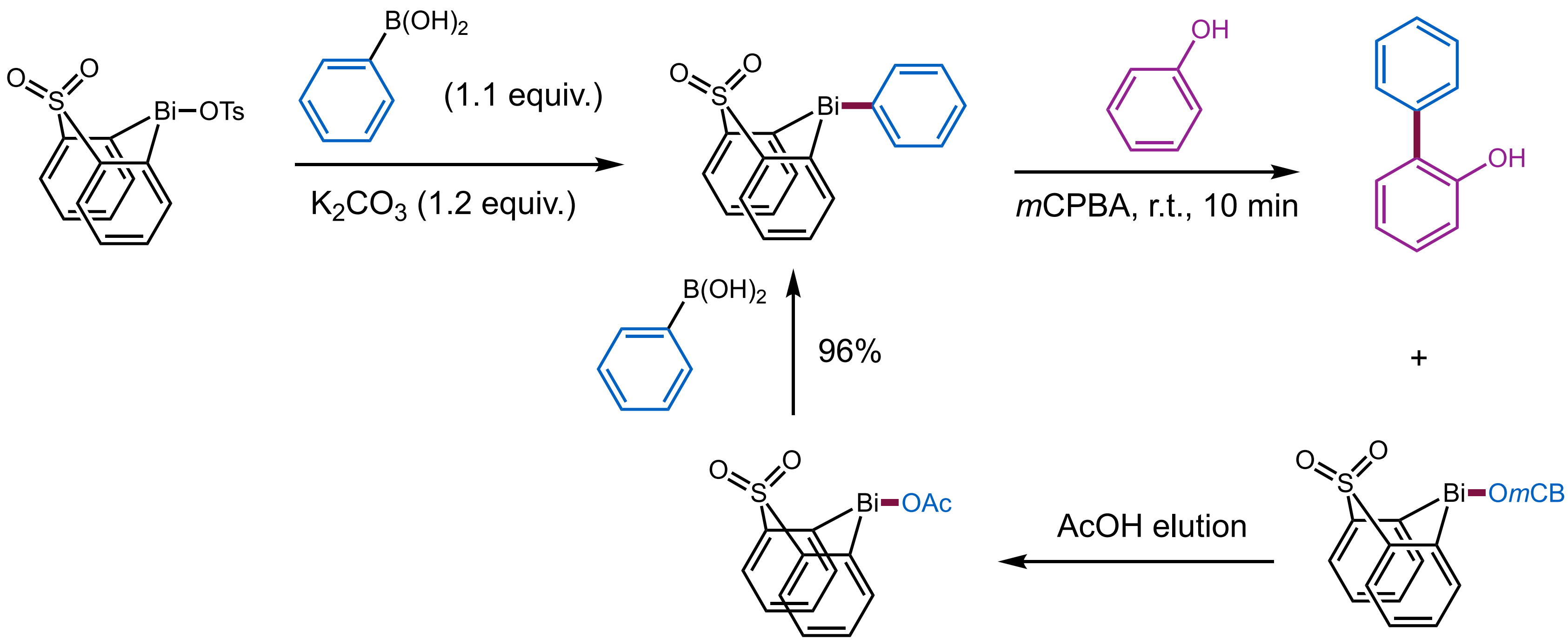


90% yield

Jurrat, M.;Maggi, L.;Paṕai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

Bi(III)/Bi(V) redox activation for ortho-Arylation of phenols

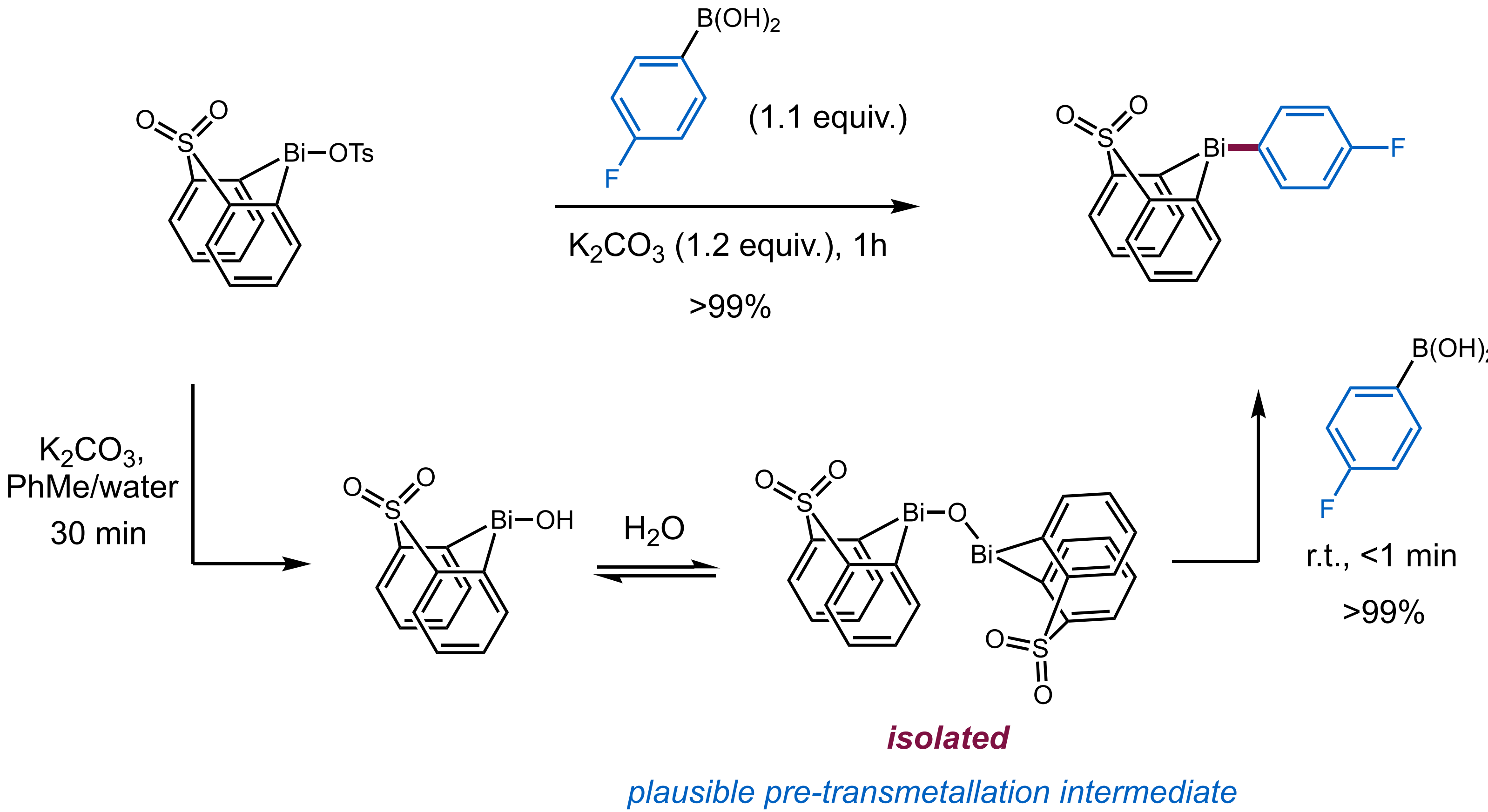
■ One-pot, Bi(V)-mediated arylation of phenols and naphthols



Jurrat, M.;Maggi, L.;Papai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

Bi(III)/Bi(V) redox activation for ortho-Arylation of phenols

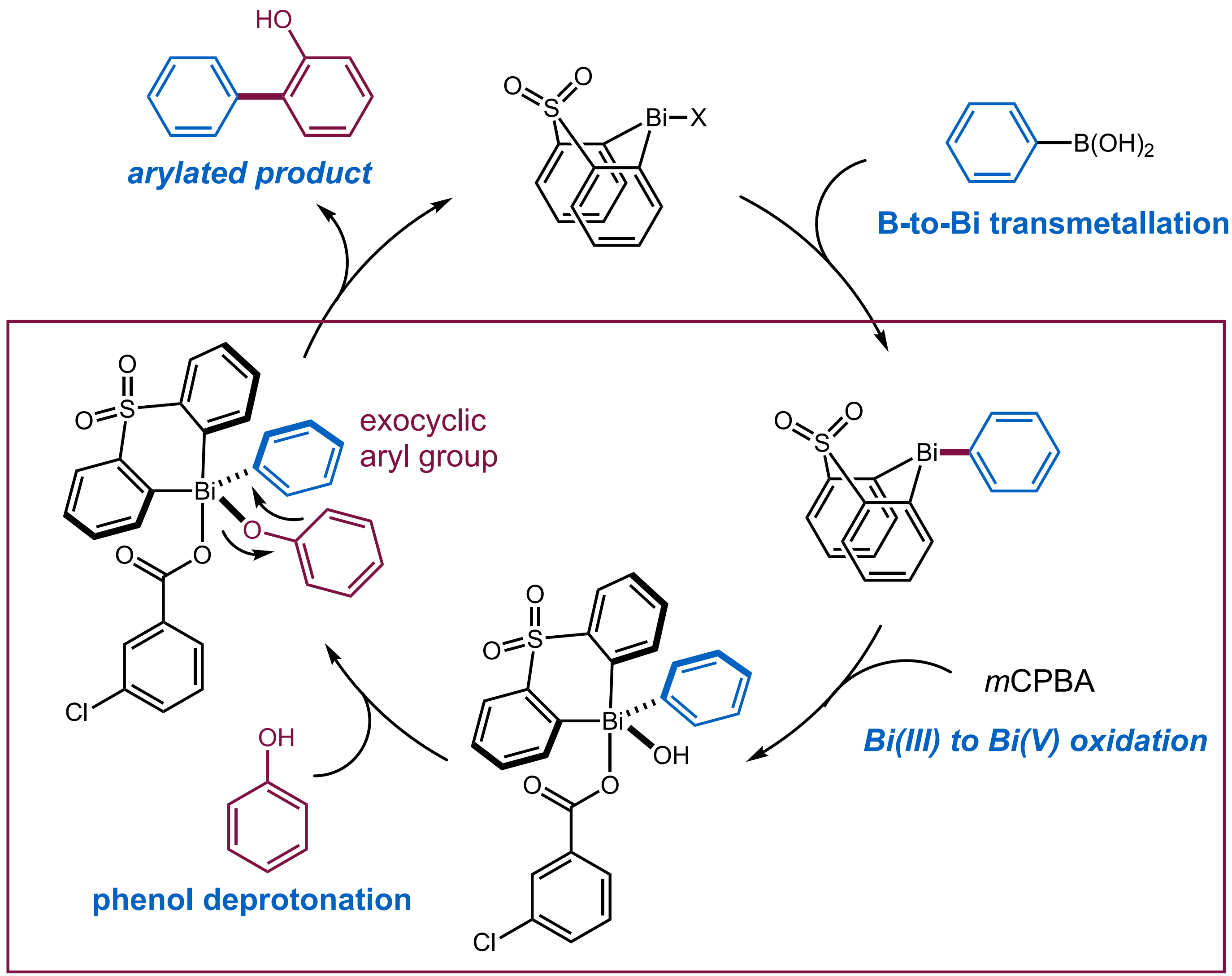
Mechanistic studies for the reaction



Jurrat, M.;Maggi, L.;Paṕai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

Bi(III)/Bi(V) redox activation for ortho-Arylation of phenols

■ Reaction design



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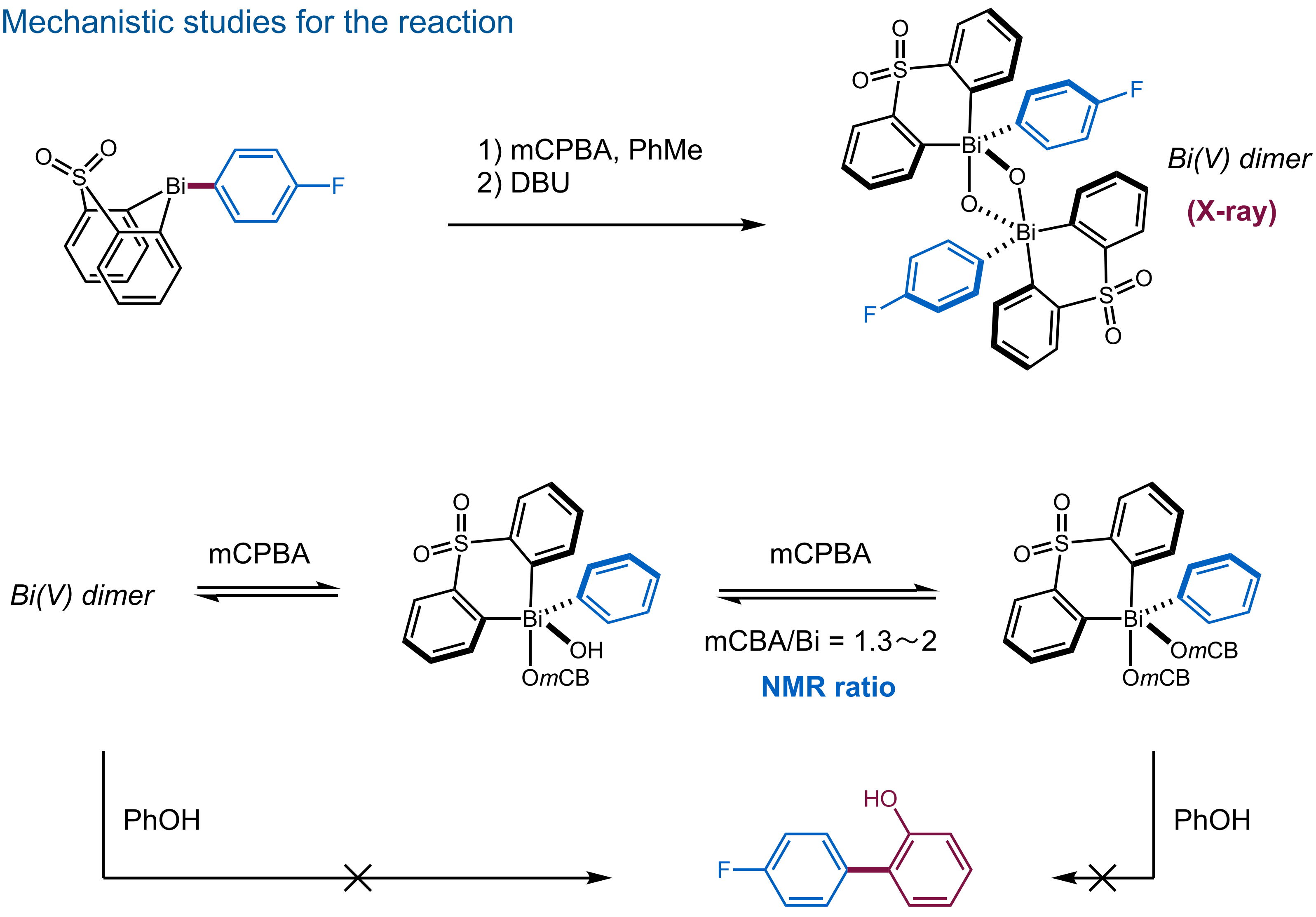

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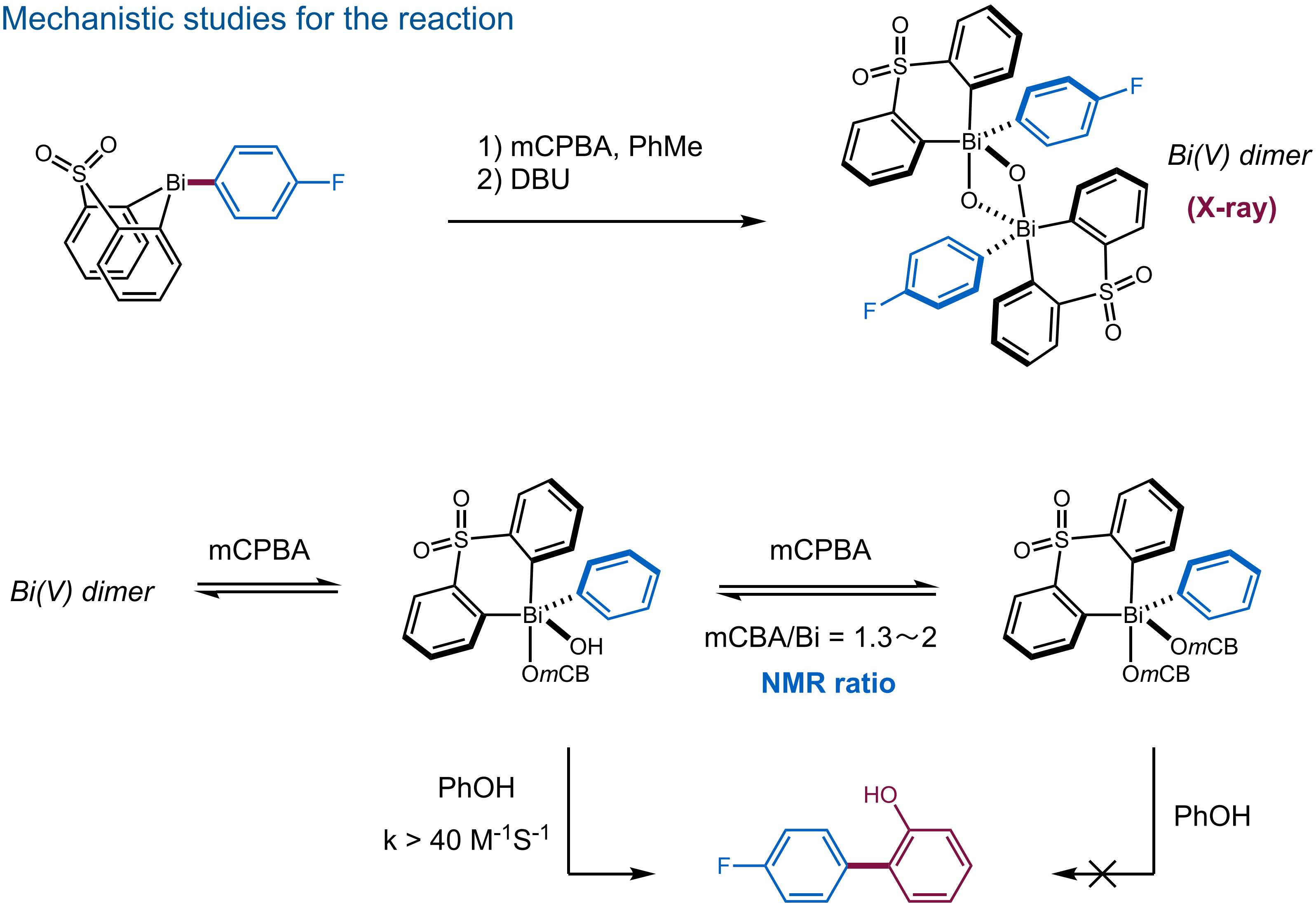

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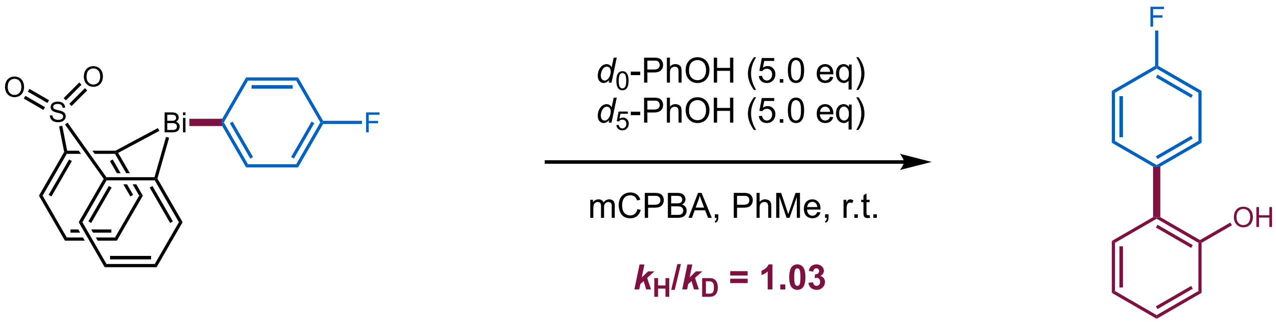

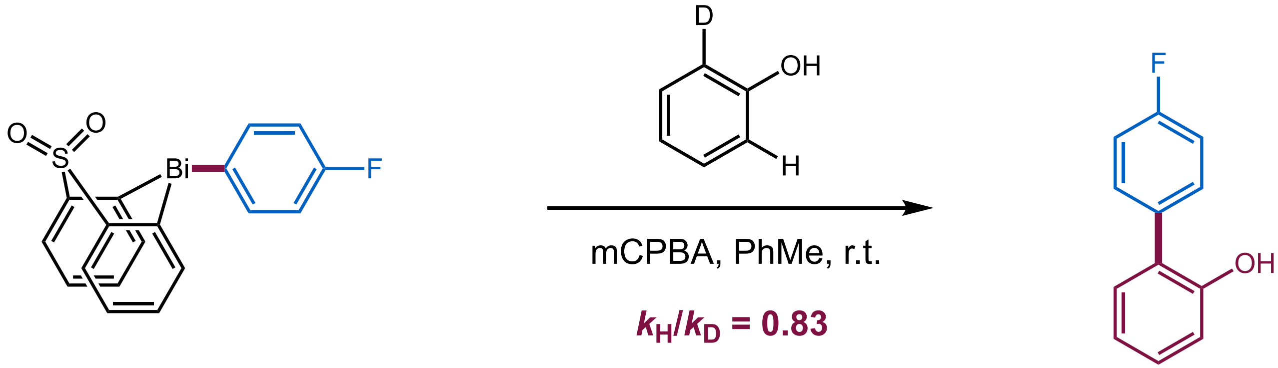

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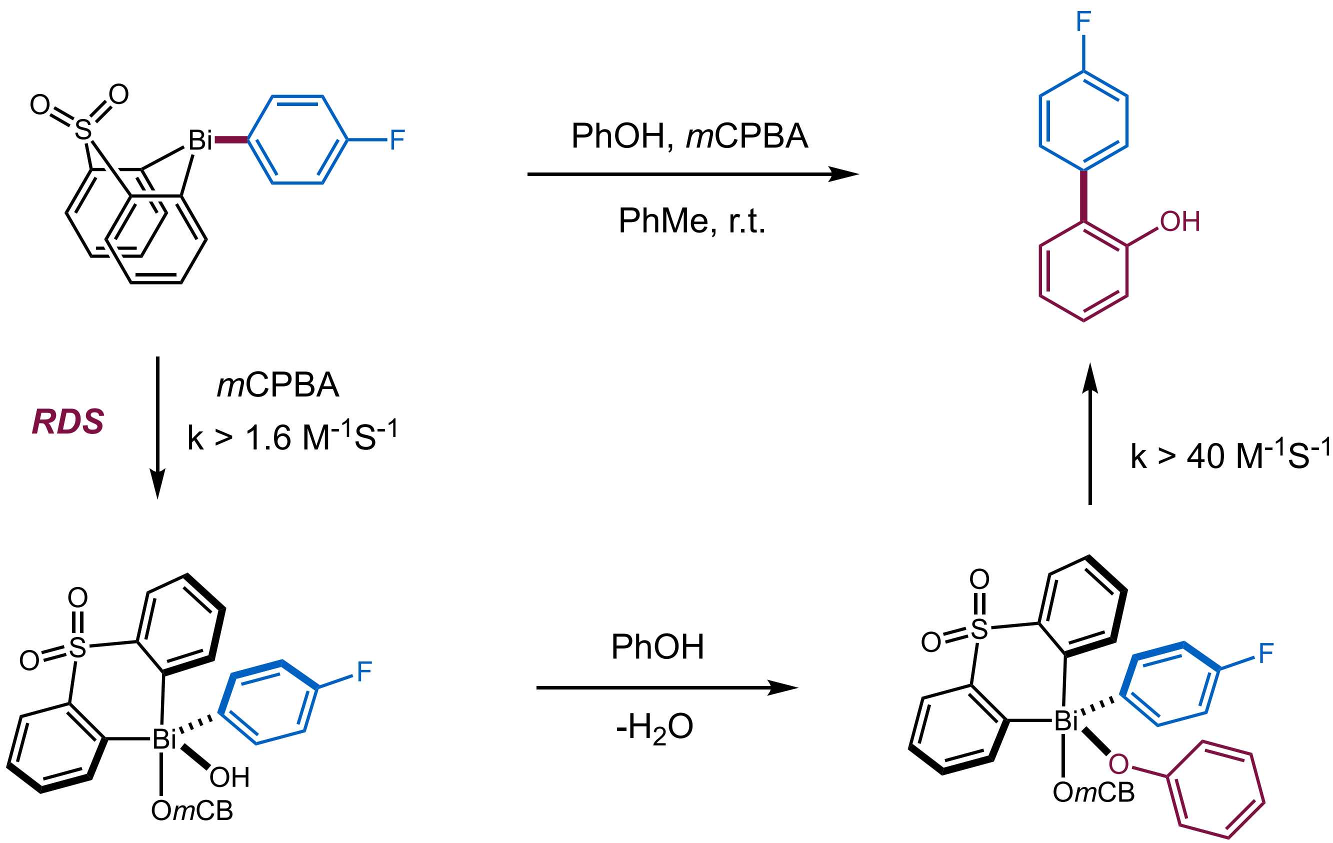
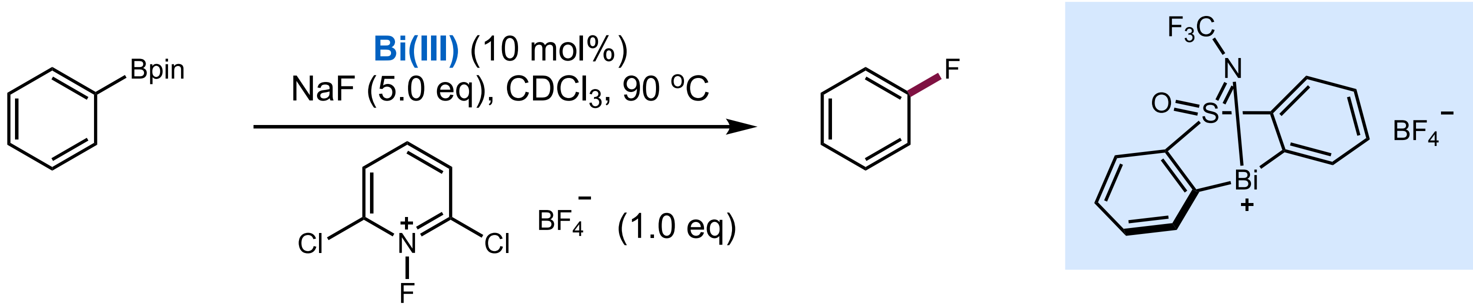
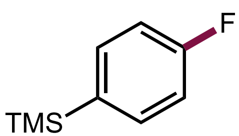


Jurrat, M.;Maggi, L.;Paṕai,I.;Lewis, W.;Ball, L. T. *Nat. Chem.* **2020**, *12*, 260.

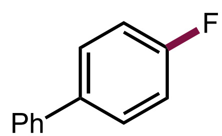
What about Bi(III)/Bi(V) redox catalysis?

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

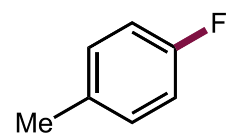




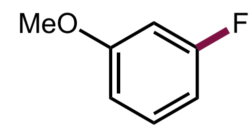
90% yield



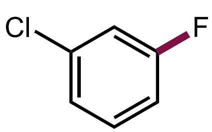
71% yield



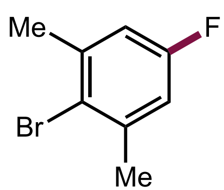
77% yield



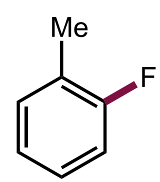
55% yield



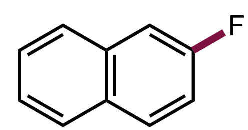
36% yield



84% yield



45% yield

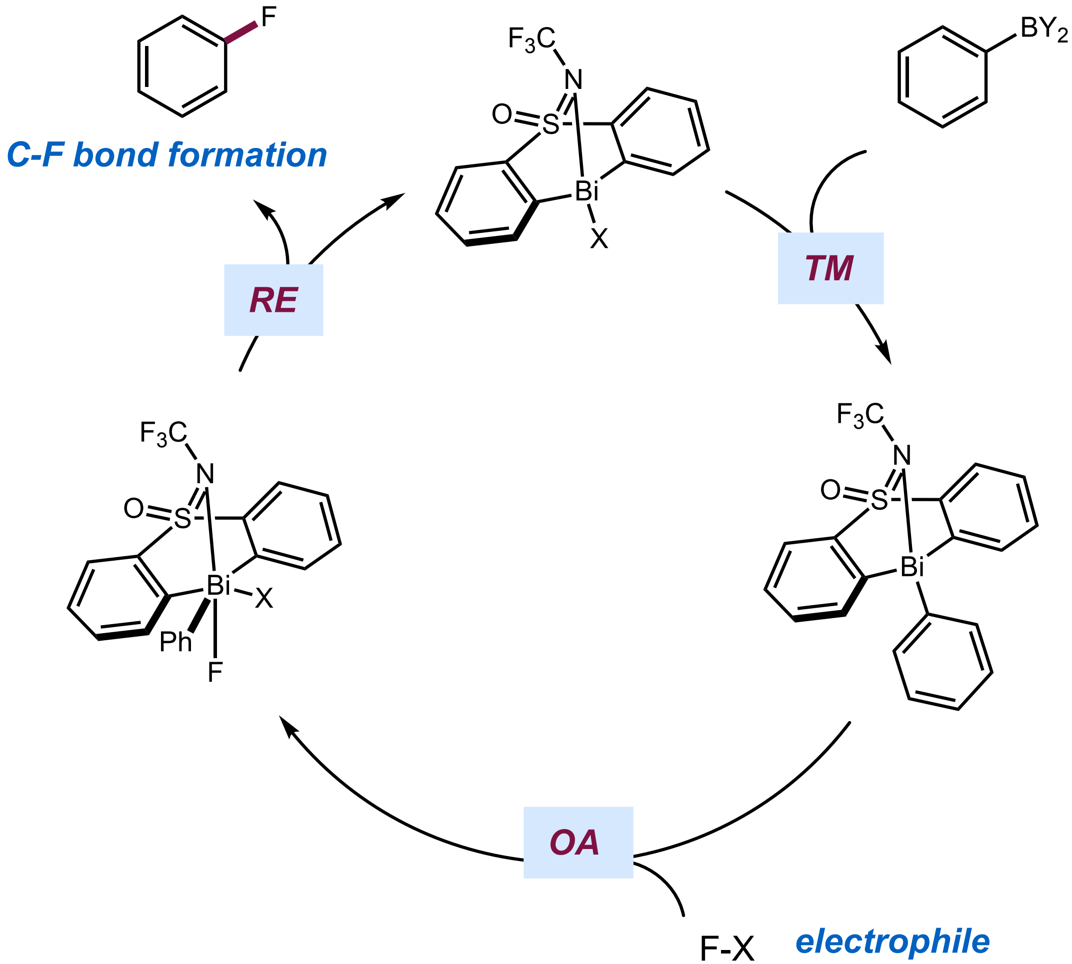


49% yield

Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

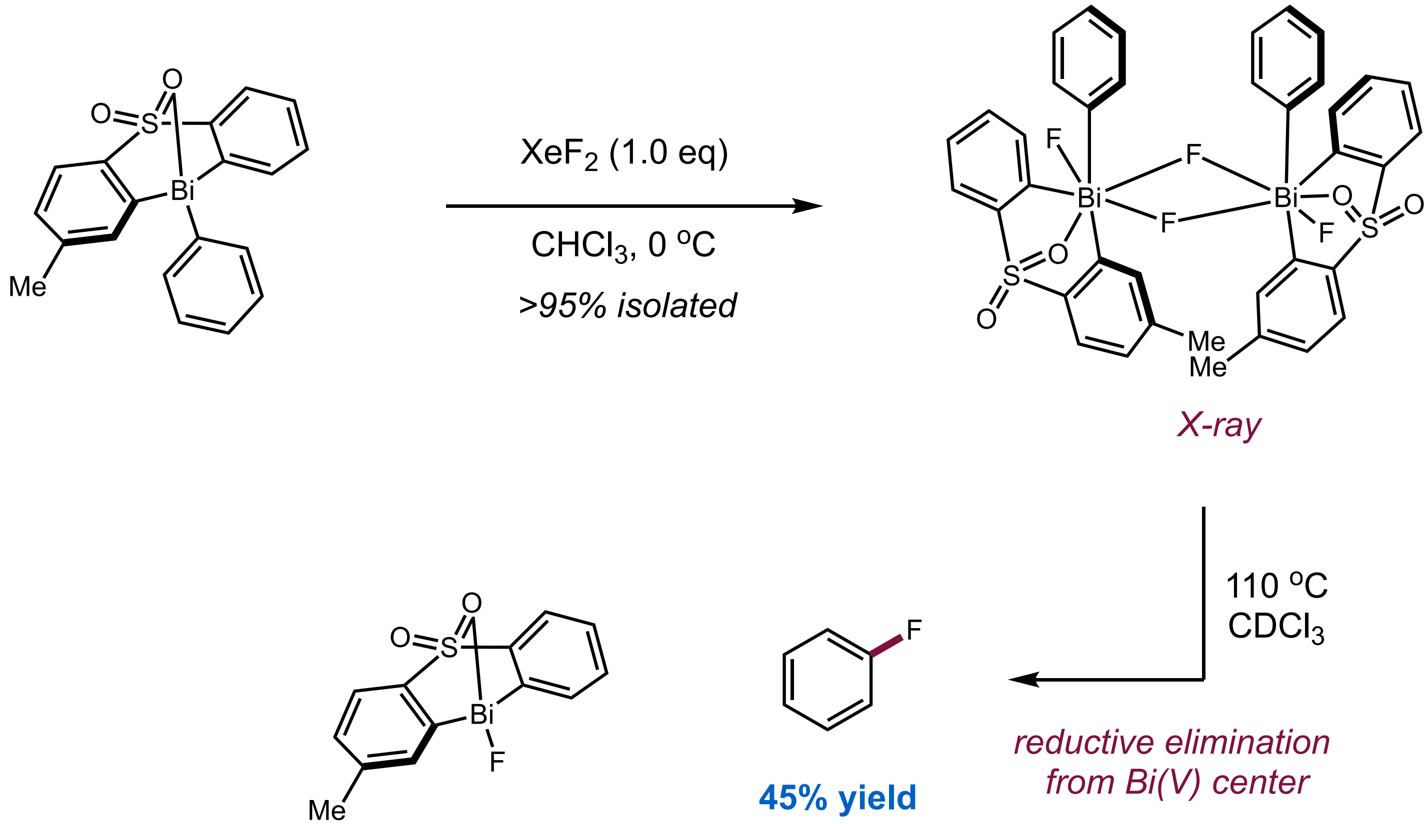
Proposed mechanism for Bi(III)/Bi(V) redox catalysis



Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

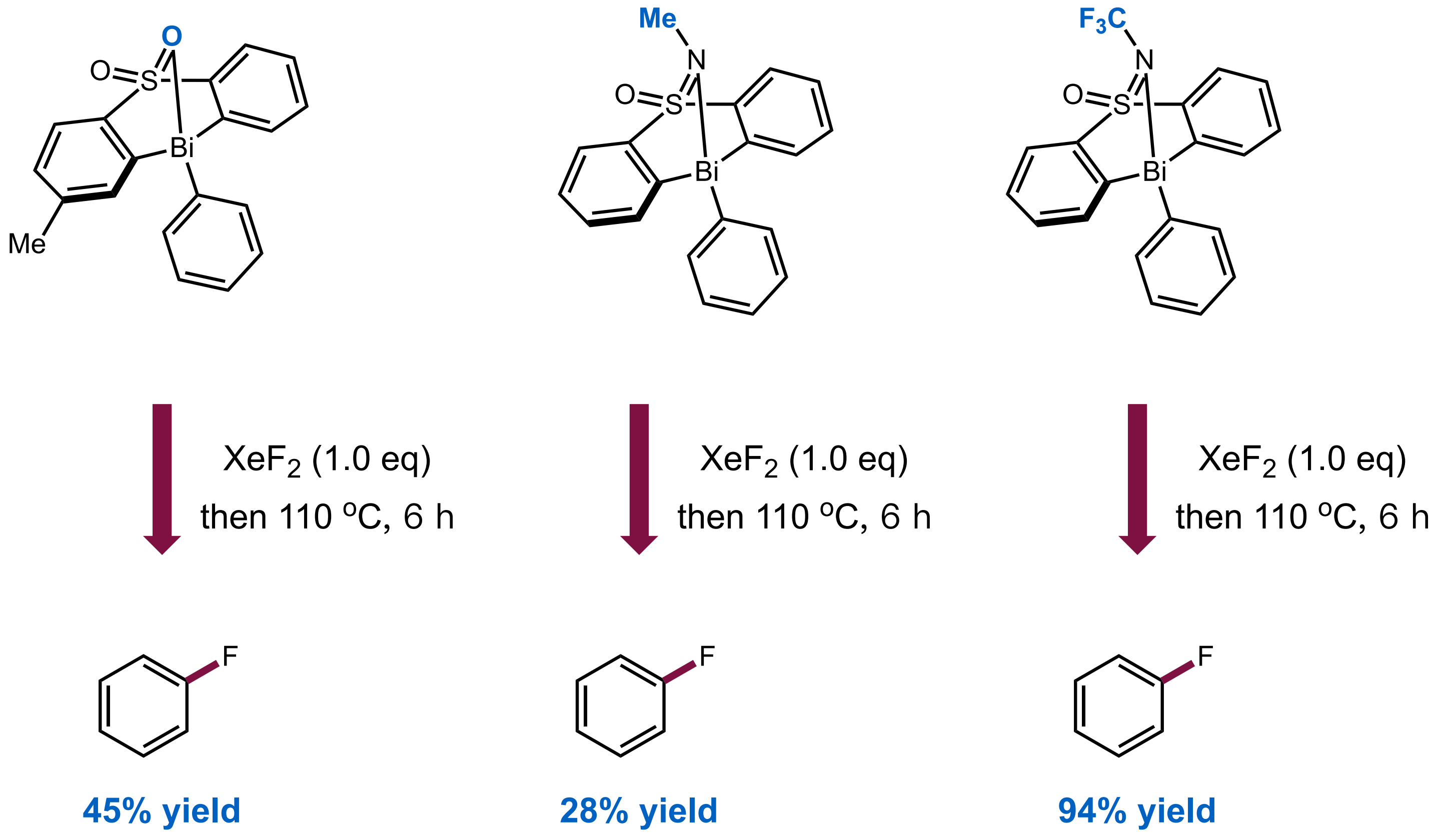
Proof of concept study



Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

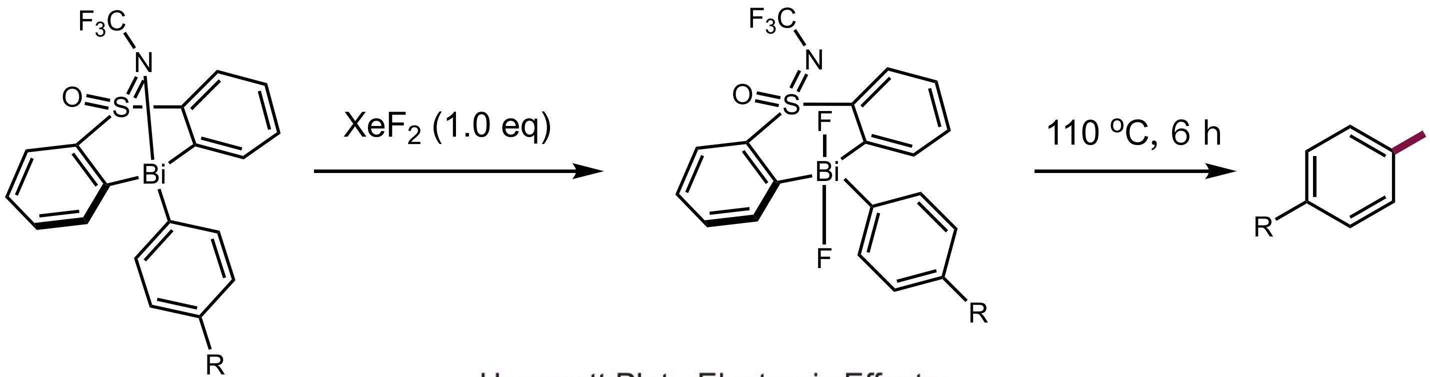
Ligand effect for the reductive elimination

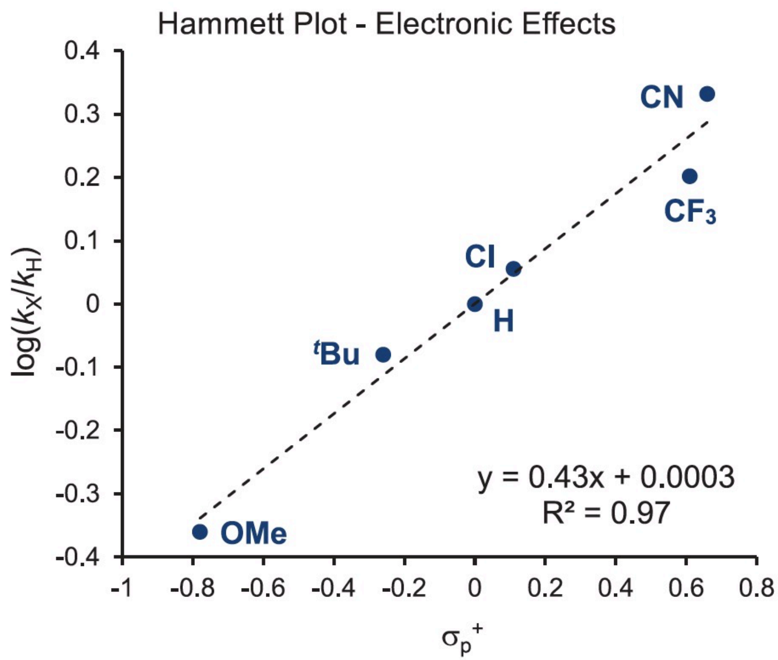


Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

Kinetic analysis of the reductive elimination

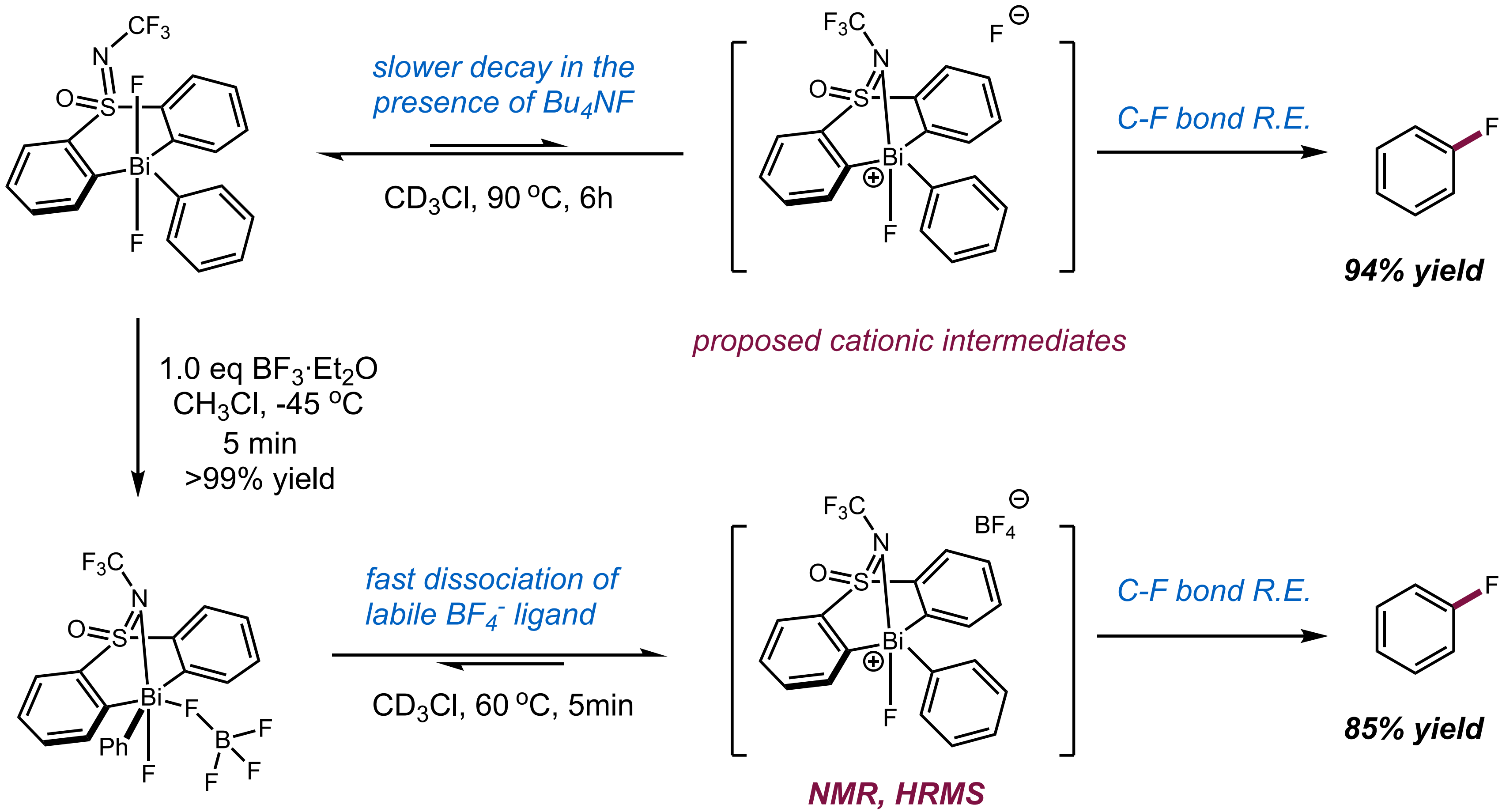




Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

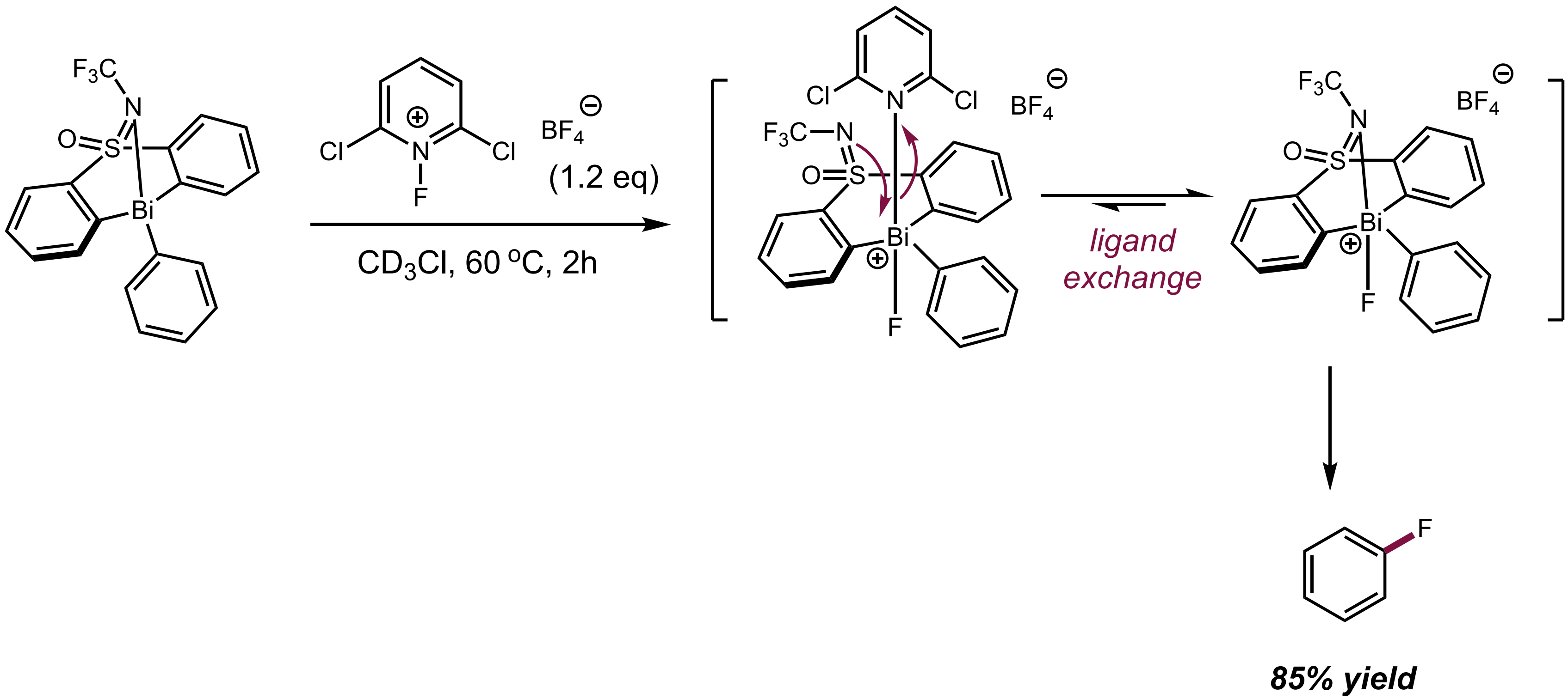
Mechanism study of the reductive elimination



Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

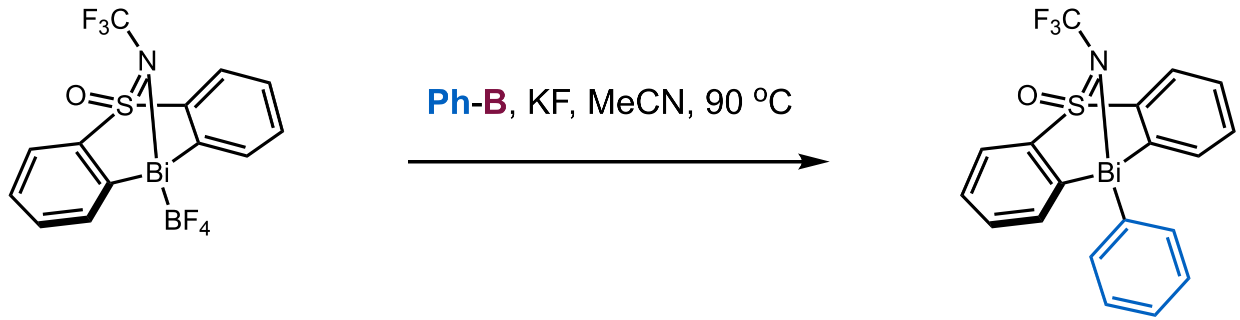
Fluoropyridinium as fluorinating reagent

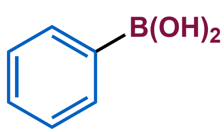


Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

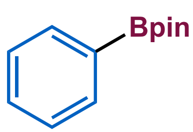
Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

■ Transmetallation of arylborone to Bi(III) complex

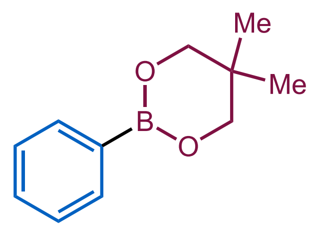




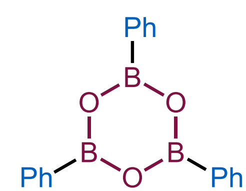
95% yield



67% yield



72% yield

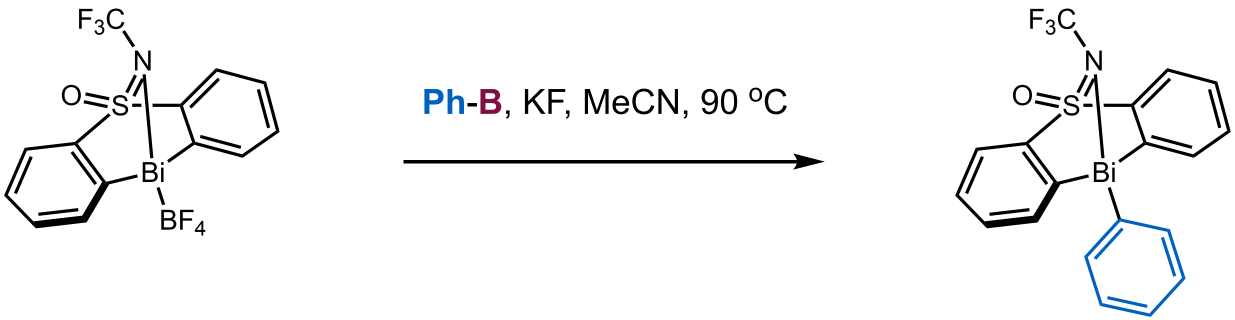


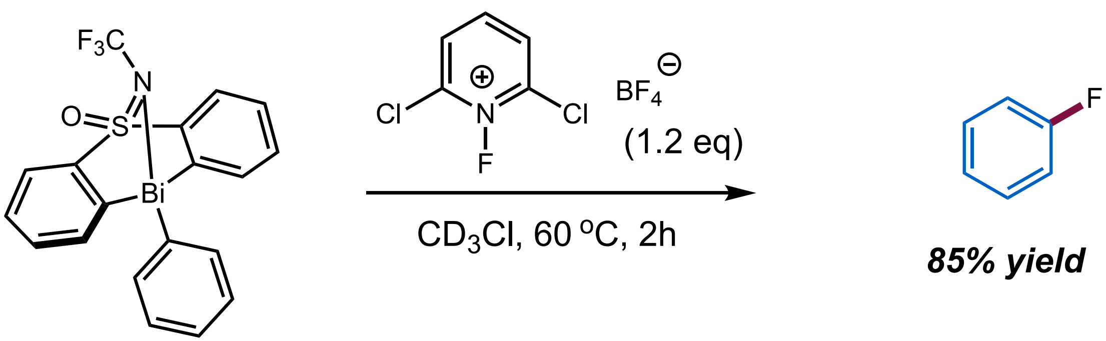
80% yield

Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

■ Merging element steps together for Bi(III)/Bi(V) redox catalysis

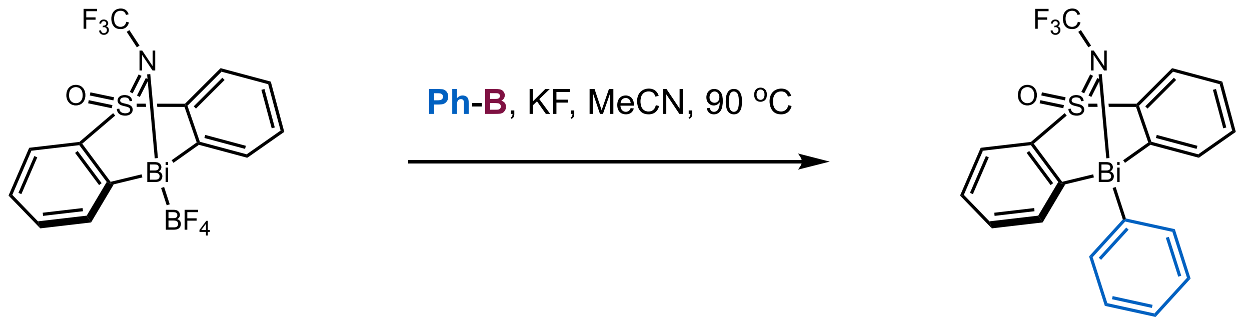




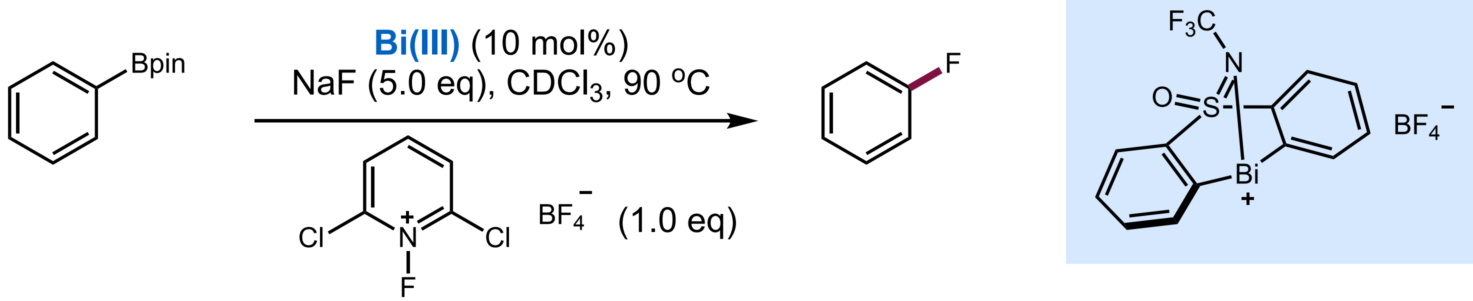
Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

Fluorination of arylboron via Bi(III)/Bi(V) redox catalysis

Merging element steps together for Bi(III)/Bi(V) redox catalysis



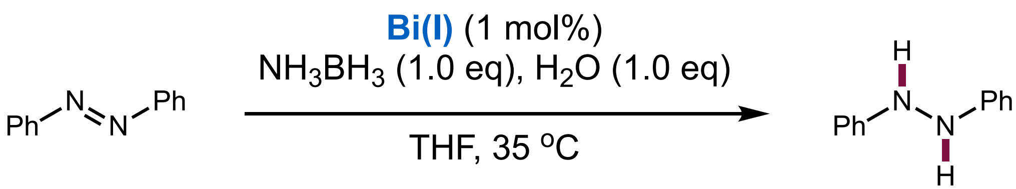
First Bi(III)/Bi(V) redox catalysis

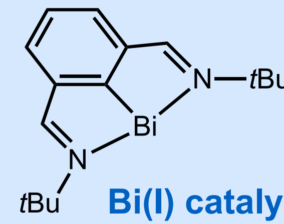


Planas, O.; Wang, F.; Leutzsch, M.; Cornella, J. *Science.* **2020**, *367*, 313.

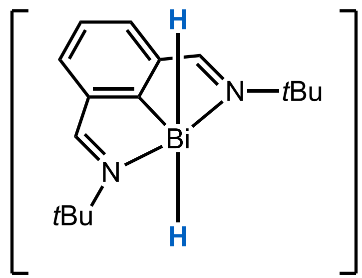
What about Bi(I)/Bi(III) redox catalysis?

Bi(I) catalyzed transfer hydrogenation





Bi(I) catalyst



via Bi(III) hydride

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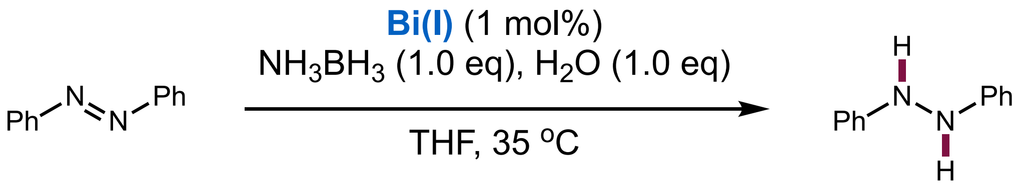
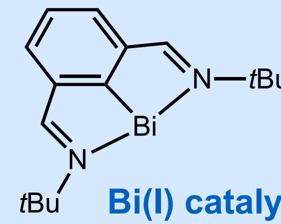
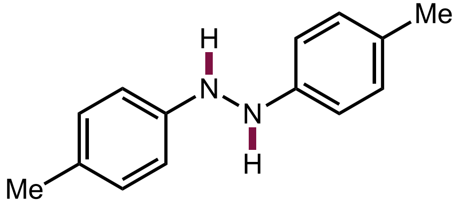
What about Bi(I)/Bi(III) redox catalysis?

Bi(I) catalyzed transfer hydrogenation

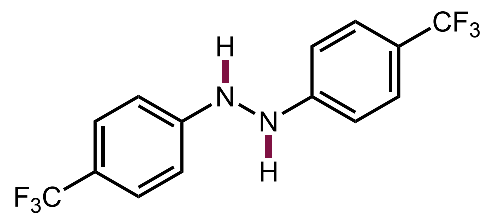




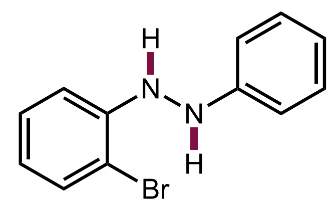
Bi(I) catalyst



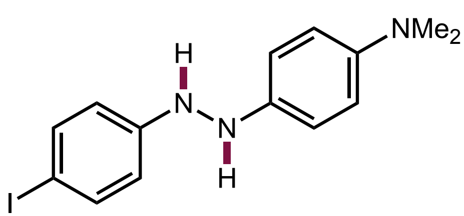
97% yield



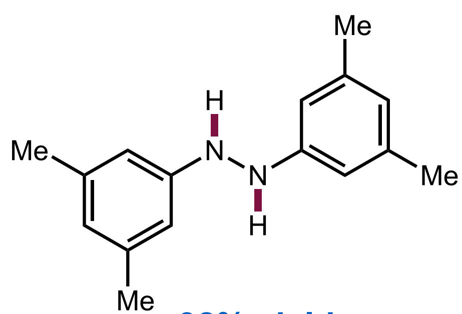
99% yield



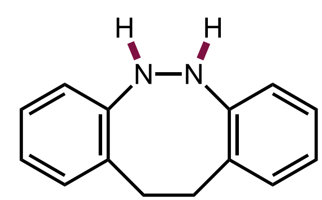
98% yield



99% yield



98% yield



99% yield

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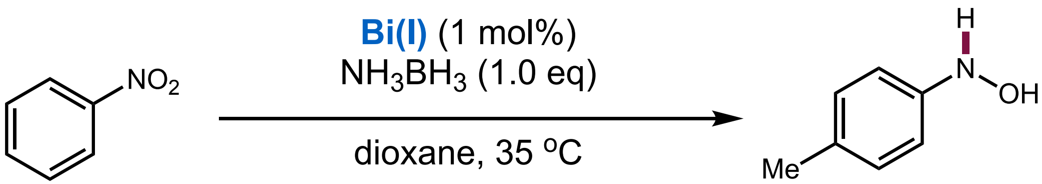
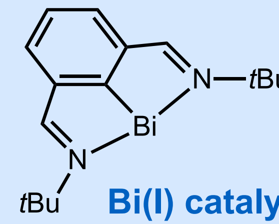
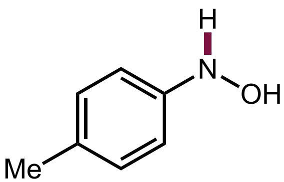
Transfer hydrogenation via Bi(I)/Bi(III) redox catalysis

Bi(I) catalyzed transfer hydrogenation of nitroarenes

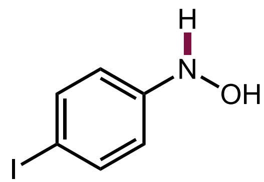




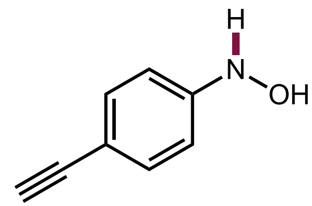
Bi(I) catalyst



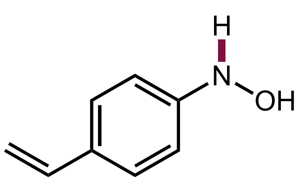
97% yield



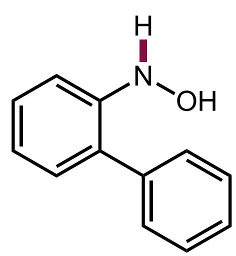
88% yield



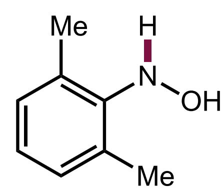
67% yield



82% yield



75% yield



22% yield

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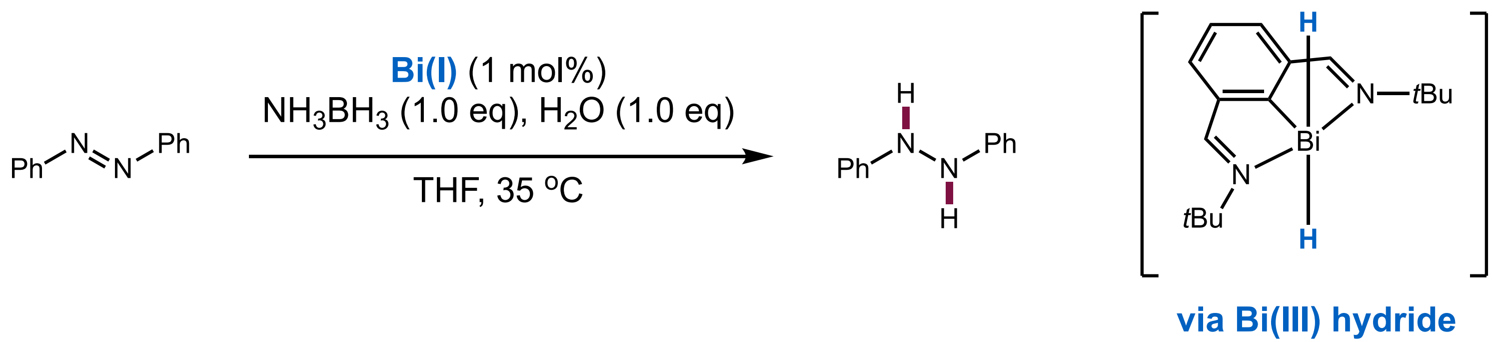
Transfer hydrogenation via Bi(I)/Bi(III) redox catalysis

Effect of water



	NH_3BH_3	NH_2**Me**BH_3	NH**Me$_2$**BH_3	N**Me$_3$**BH_3	NH_3B**Et$_3$**
without H_2O	57% (16h)	55% (16h)	36% (16h)	10% (16h)	- (16h)
with 1.0 equiv. H_2O	99% (2h)	97% (7h)	90% (16h)	31% (16h)	- (16h)

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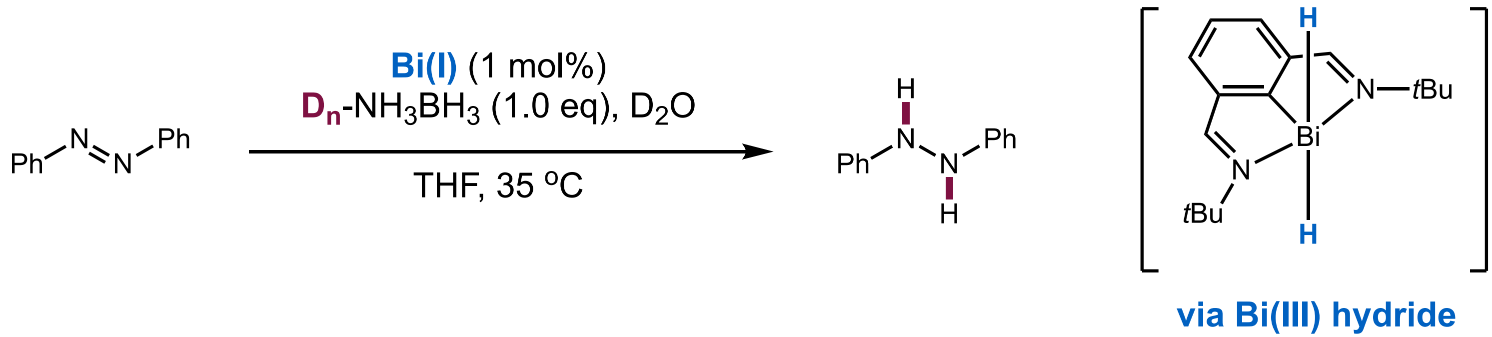
Transfer hydrogenation via Bi(I)/Bi(III) redox catalysis

KIE experiments



	ND_3BH_3	NH_3BD_3	ND_3BD_3
Kinetic Isotope Effect	1.63	3.94	7.05

Both N-H and B-H bonds are cleaved in the rate-determining step

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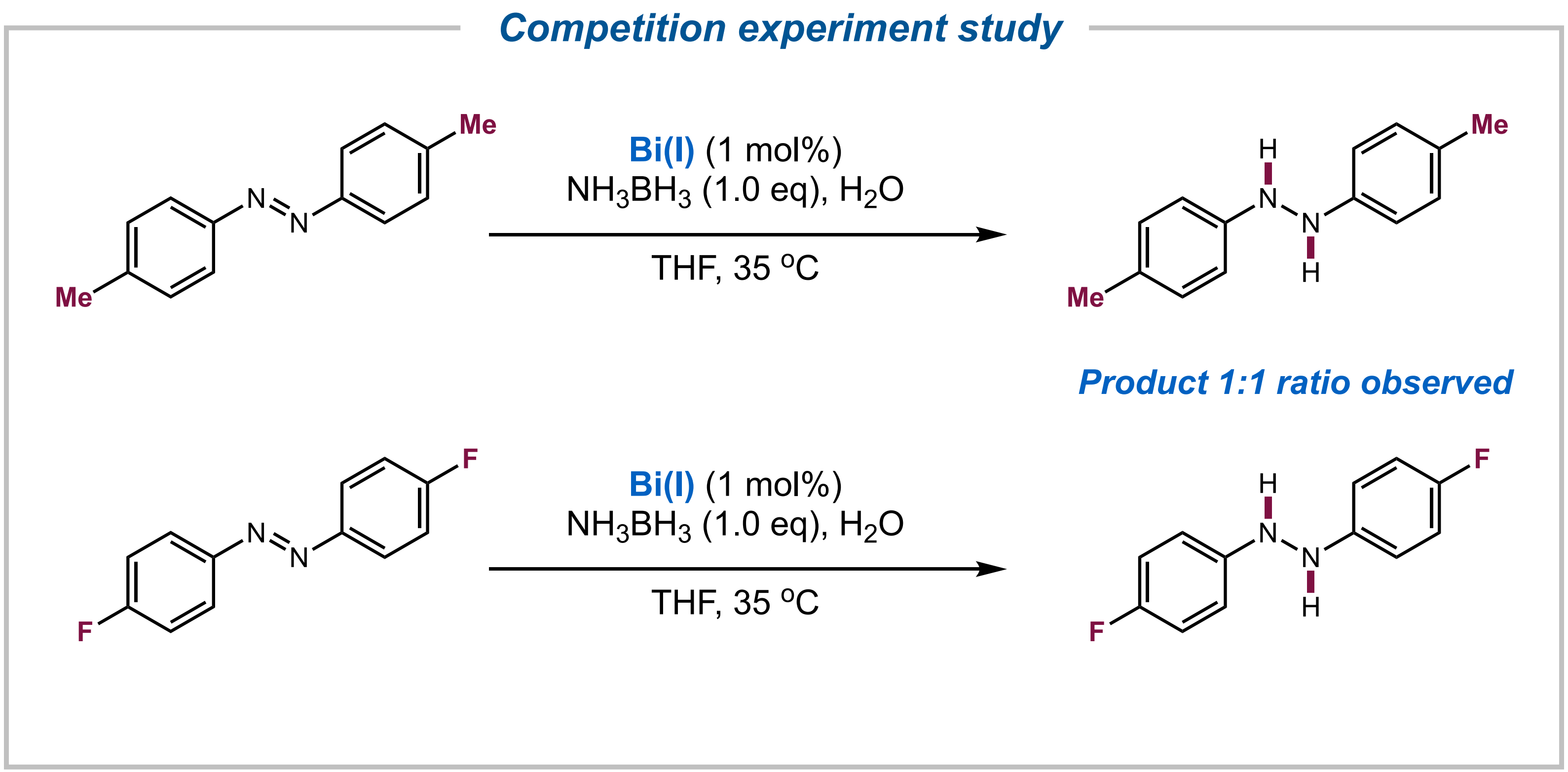
Transfer hydrogenation via Bi(I)/Bi(III) redox catalysis



- *azoarenes are not participating in the RDS of this transformation*
- *Bi(I) and AB are both involved in the RDS*

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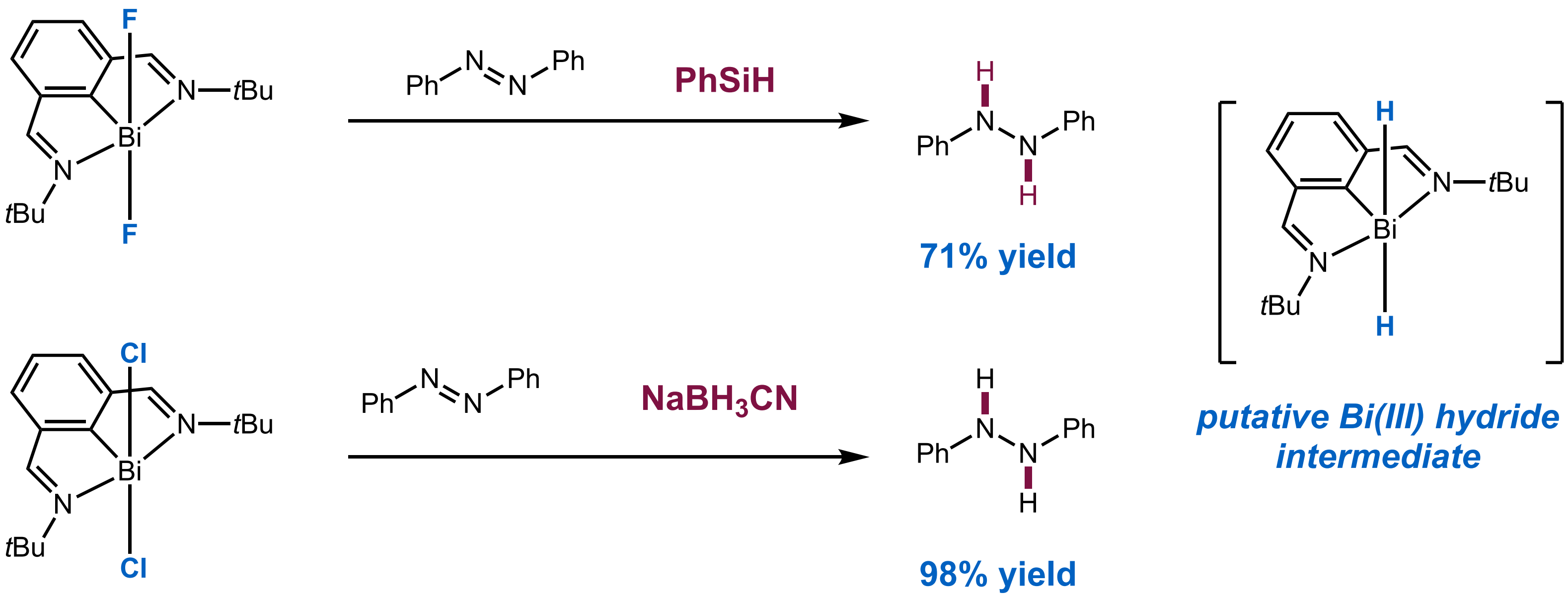
Transfer hydrogenation via Bi(I)/Bi(III) redox catalysis

Stoichiometric study for Bi(III)—H species



putative Bi(III) hydride intermediate

- *Bi(I) and H_2 was detected during the reaction*
- *proton is from hydridic sources*

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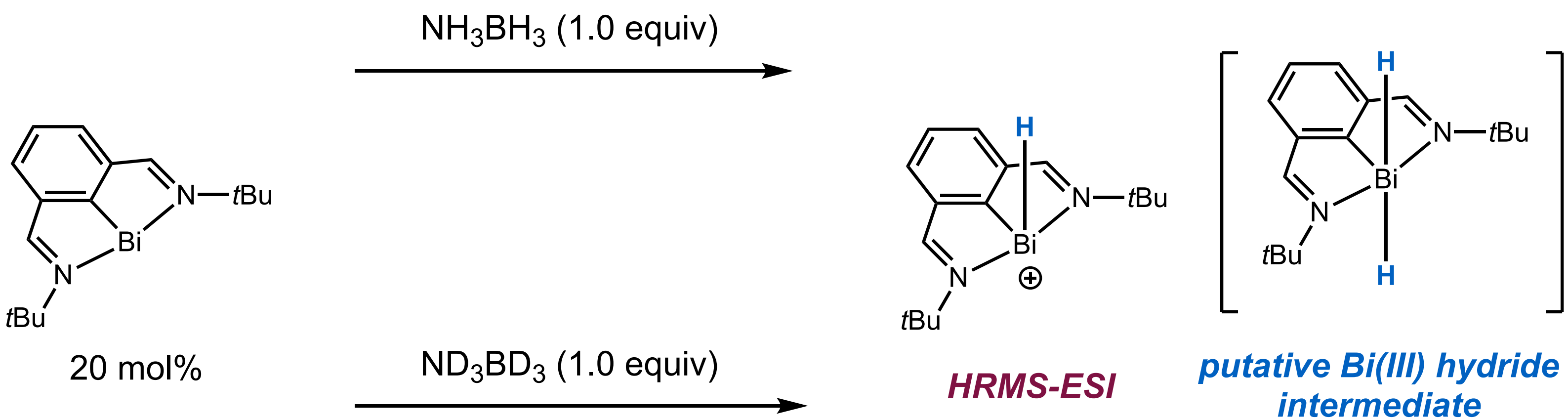
Transfer hydrogenation via Bi(I)/Bi(III) redox catalysis

Mass-spectrometry study for Bi(III)—H species



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