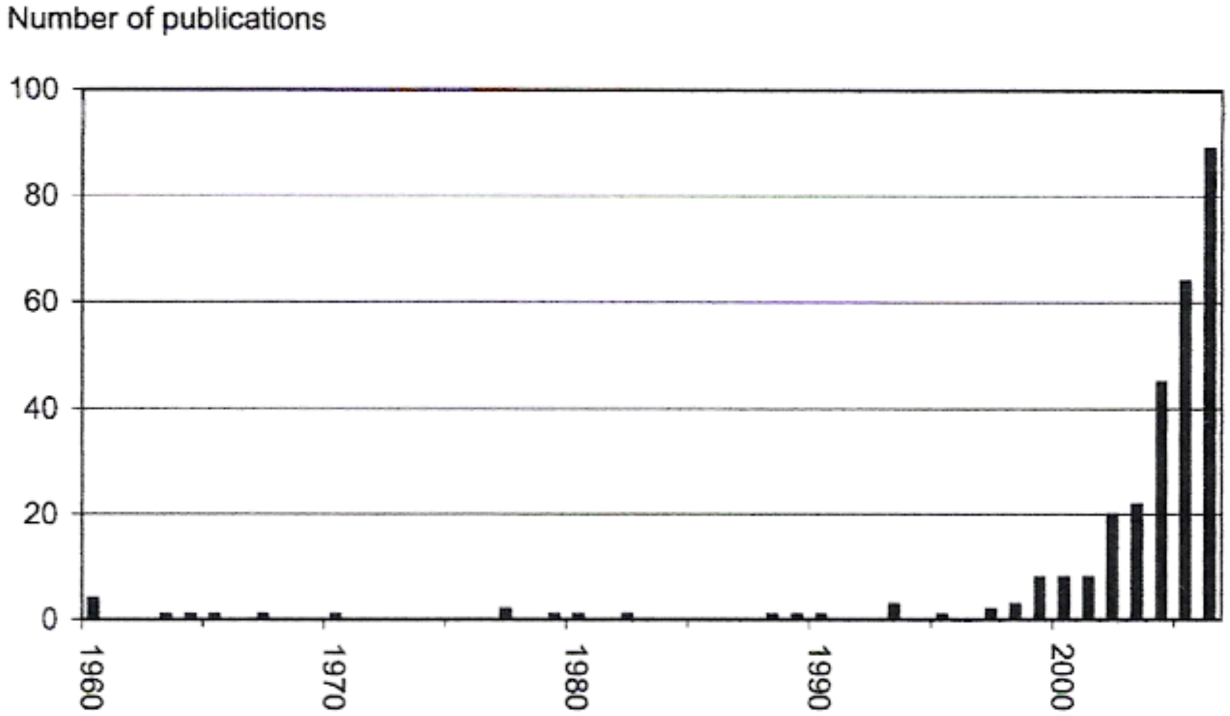
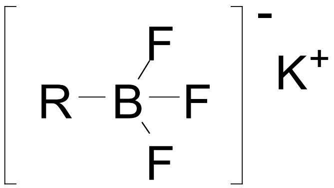
Organotrifluoroborate Salts: Versatile Reagents in Organic Synthesis

Frontiers in Chemistry: May 17, 2008
David Arnold

http://periodictable.com/Elements/005/index.html

Exponential Growth in the Number of Publications Dedicated to Potassium Organotrifluoroborates Over the Last 10 Years





R = alkyl, alkenyl, alkynyl,
allyl, crotonyl, aryl

Chem. Rev. **2008**, *108*, 288

Outline

- A Brief History on the Preparation of Organotrifluoroborate Salts
- General Preparation of Organotrifluoroborate Salts
- Functionalization of Potassium Organotrifluoroborates
- Selected Reactions of Potassium Organotrifluoroborates
- Applications to Natural Product Synthesis
- Conclusions

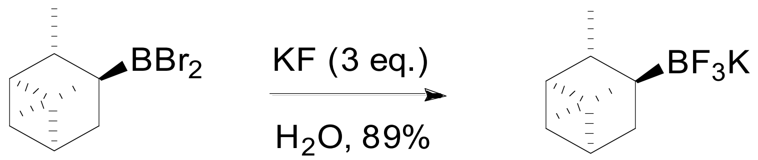
A Brief History on the Preparation of Organotrifluoroborate Salts

- Laboratory curiosities in the 1960: Preparation of the first organotrifluoroborate salt and the first stable compound containing a trifluoromethyl-boron linkage:

$$Me_3Sn{-}SnMe_3 \quad + \quad CF_3I \xrightarrow{h\nu} Me_3SnCF_3 \xrightarrow[CCl_4]{BF_3\text{ gas}} Me_3Sn(CF_3BF_3) \xrightarrow[H_2O]{KF} CF_3BF_3K$$

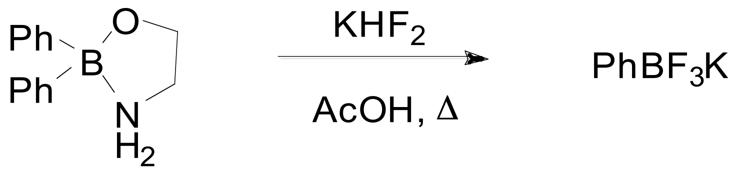
J. Am. Chem. Soc. **1960**, *82*, 5298.

- Preparation from dihaloorganoboranes:



J. Organomet. Chem. **1988**, *340*, 267.

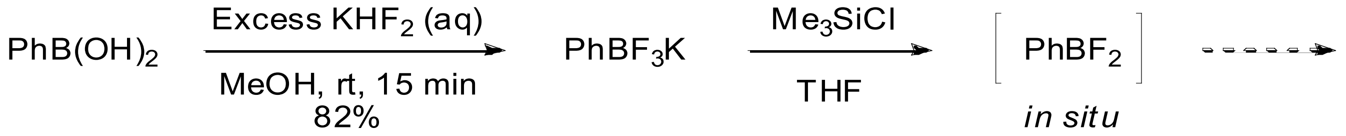
- A breakthrough in the preparation of organotrifluoroborate salts lies dormant:
  Thierig and Umland 1967



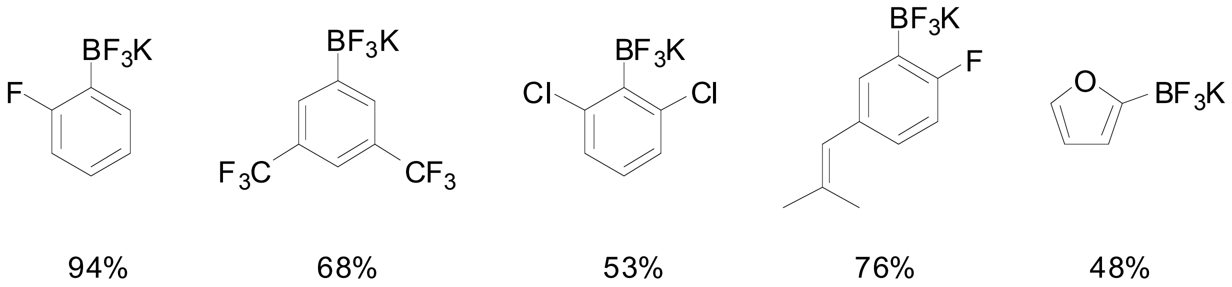
Naturwissenschaften **1967**, *54*, 563.

Revisiting the Past, Vedejs 1995: The Revolution Begins

- Convenient preparation of aryltrifluoroborate salts from boronic acids and in situ conversion to arylboron difluoride Lewis acids



$$PhB(OH)_2 \xrightarrow[\text{MeOH, rt, 15 min}\\ 82\%]{\text{Excess } KHF_2 \text{ (aq)}} PhBF_3K \xrightarrow[\text{THF}]{Me_3SiCl} \left[PhBF_2 \right]_{\textit{in situ}} \dashrightarrow$$



- All salts were found to be air and moisture stable crystalline solids which could be synthesized on a multigram scale and purified by simple recrystallization from acetonitrile or actone/diethyl ether.

- Currently there are 90 commercially available potassium organotrifluoroborates and over 2000 commercially available organoboronic acids.

J. Org. Chem. **1995**, *60*, 3020.

General Preparation of Organotrifluoroborate Salts: Lithium and Magnesium Reagents

- Grignard reagents:

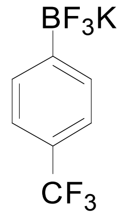
$$\text{R-MgX} \xrightarrow[\text{ii. KHF}_2\text{, H}_2\text{O}]{\text{i. B(OR')}_3\text{, -78 }^{\text{o}}\text{C}} \text{R-BF}_3\text{K}$$

R = alkyl, aryl, vinyl, allyl, alkynyl

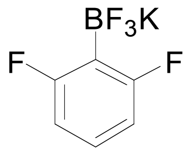
- Notably, potassium vinyltrifluoroborate is stable at room temperature.

- Lithium/halogen exchange:

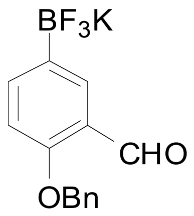
$$\text{Ar-Br} \xrightarrow[\substack{\text{ii. B(OR')}_3 \\ \text{iii. H}_3\text{O}^+}]{\text{i. RLi}} \text{Ar-B(OH)}_2 \xrightarrow{\text{(aq) KHF}_2} \text{Ar-BF}_3\text{K}$$



91%



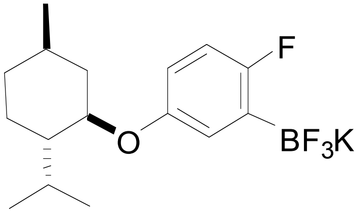
82%



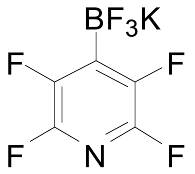
78%

- *Ortho*-lithiation:

$$\text{Ar-H} \xrightarrow[\substack{\text{ii. B(OR')}_3 \\ \text{iii. H}_3\text{O}^+}]{\text{i. RLi}} \text{Ar-B(OH)}_2 \xrightarrow{\text{(aq) KHF}_2} \text{Ar-BF}_3\text{K}$$



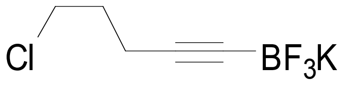
76%



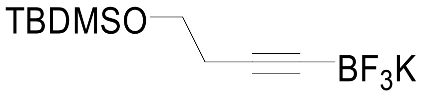
70%

- Deprotonation of alk-1-ynes:

$$\text{R}{-}\text{C}{\equiv}\text{C}{-}\text{H} \xrightarrow[\substack{\text{ii. B(OMe)}_3 \\ \text{iii. (aq) KHF}_2}]{\text{i. } n\text{-BuLi}} \text{R}{-}\text{C}{\equiv}\text{C}{-}\text{BF}_3\text{K}$$



80%

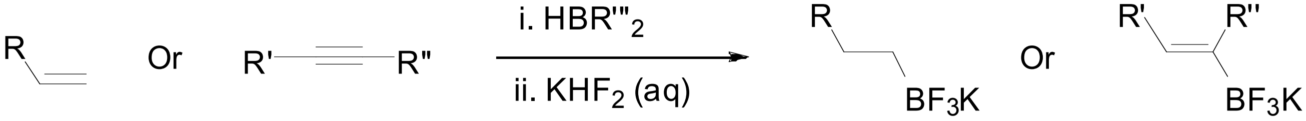


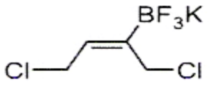
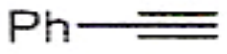
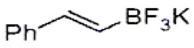
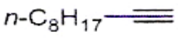
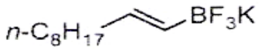
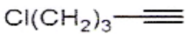
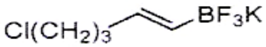
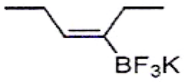
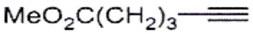
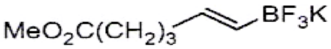
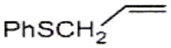
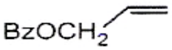
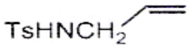
66%

- First air and moisture stable compounds containing an sp-B bond.

Chem. Rev. **2008**, *108*, 288.

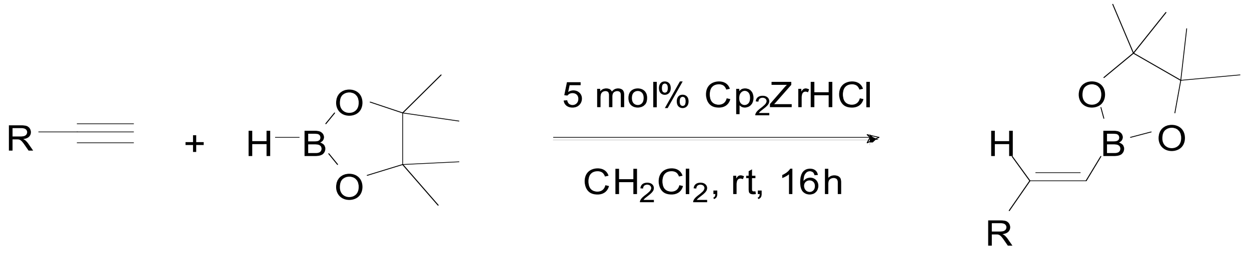
General Preparation of Organotrifluoroborate Salts: Hydroboration of Alkenes and Alkynes



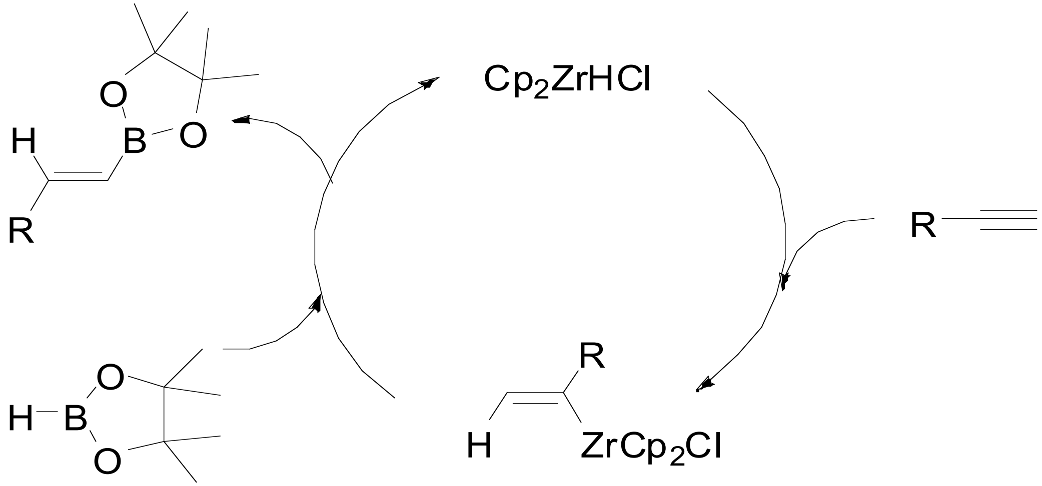
Entry	Substrate	Borane	Product	Yield (%)
1		HB(Ipc)$_2$		45
2		Cathecolborane		81
3		Br$_2$BH·SMe$_2$		83
4		Br$_2$BH·SMe$_2$		68
5		Br$_2$BH·SMe$_2$		63
6		Br$_2$BH·SMe$_2$		47
7		Br$_2$BH·SMe$_2$	PhS(CH$_2$)$_3$BF$_3$K	75
8		Pinacolborane	BzO(CH$_2$)$_3$BF$_3$K	64
9		Pinacolborane	TsHN(CH$_2$)$_3$BF$_3$K	40

Tetrahedron **2007**, *63*, 3623.

General Preparation of Organotrifluoroborate Salts: Zr-Catalyzed Hydroboration of Alkynes

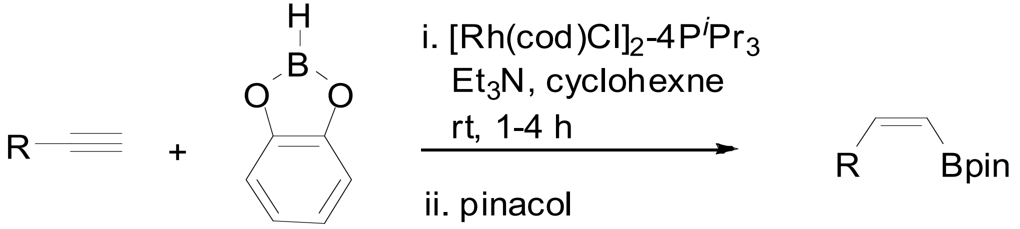


R = $-(CH_2)_3Cl$, $-SiMe_3$, -cyclopentyl, $-CH_2OMe$, -Ph
Yields: 75-94%, *(E)*-selectivities: 90-98%



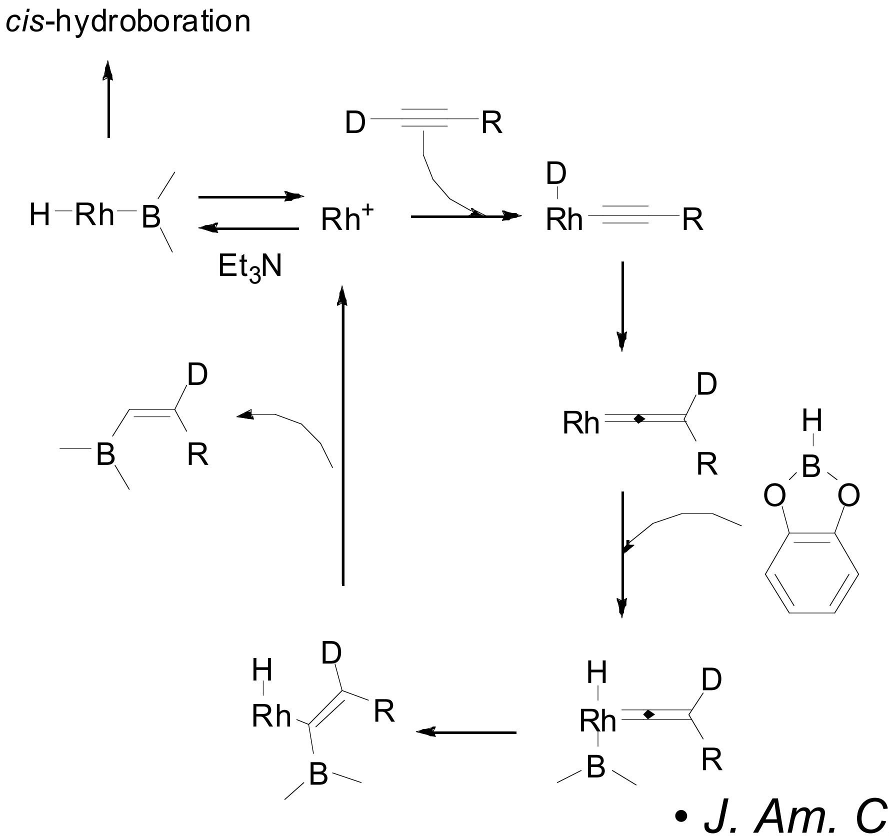
- Organometallics **1995**, *14*, 3127.

General Preparation of Organotrifluoroborate Salts: Rh-Catalyzed *trans*-Hydroboration of Alkynes



R = $-(CH_2)_7CH_3$, $-(CH_2)_3OTBDMS$, -TMS, -Ph
Yields: 60-79%, *(Z)*-selectivities: 98-99%

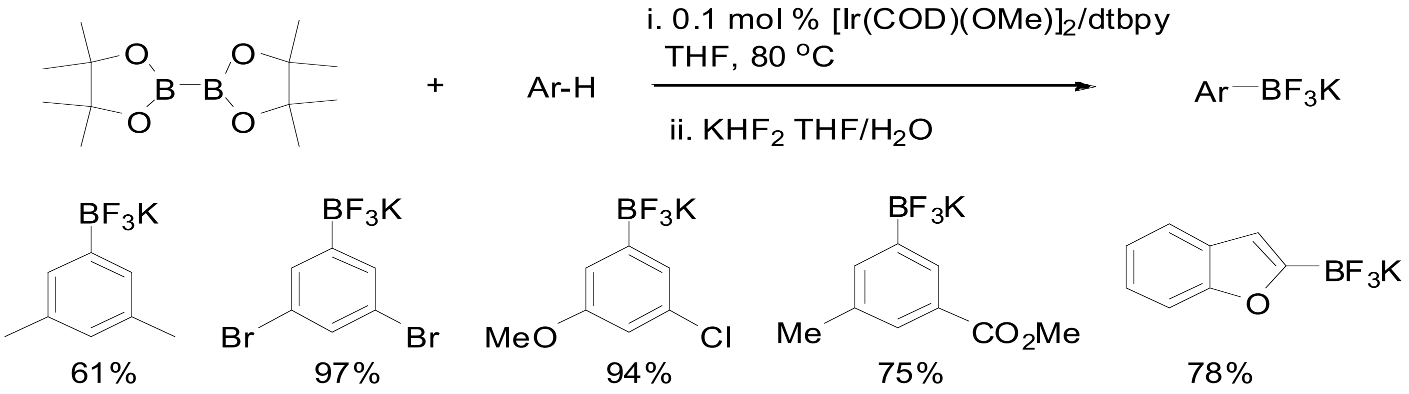
Mechanism



- *J. Am. Chem. Soc.* **2000**, *122*, 49

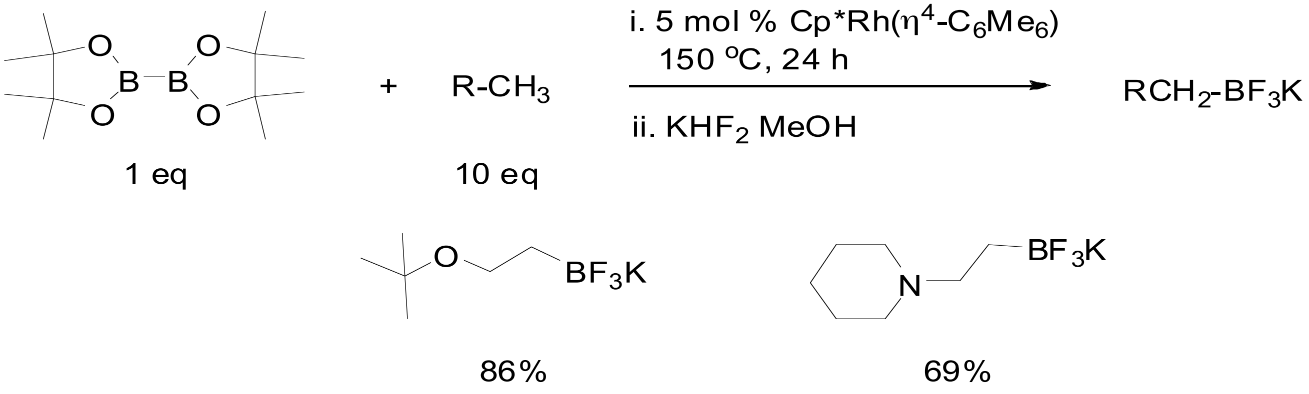
General Preparation of Organotrifluoroborate Salts: C-H Activation, Borylation of Arenes and Alkanes

- Iridium-catalyzed borylation of arenes:



- Generation of 3,5-disubstituted arenes. *Org. Lett.* **2007**, *9*, 757.

- Borylation of methyl C-H bonds in alkyl groups containing heteroatom functionality



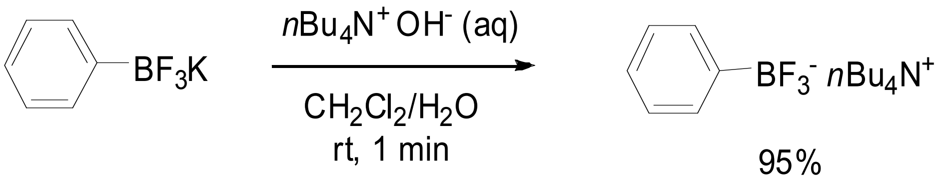
J. Am. Chem. Soc. **2004**, *126*, 15334.

Potassium Organotrifluoroborates

- The salts can be prepared according to the methodologies developed for the preparation of substituted boronic acids and esters followed by reaction with KHF_2

- Potassium organotrifluoroborates:
  - Easily prepared
  - KHF_2 is cheap (~0.07 $/g) vs. pinacol (~0.70 $/g)
  - Generally easily purified by recrystallization
  - Generally air and moisture stable at room temperature
  - Known stoichiometries
  - Reaction byproducts have low toxicities
  - Reagents show good functional group compatibilities
  - Reagents are nucleophilic
  - Can be further elaborated by oxidative processes
  - Soluble in polar solvents: MeOH, CH_3CN, DMF and acetone

- Counter ion exchange: TBA salts soluble in organic solvents such as CH_2Cl_2



Tetrahedron Letters **2001**, *42*, 9099

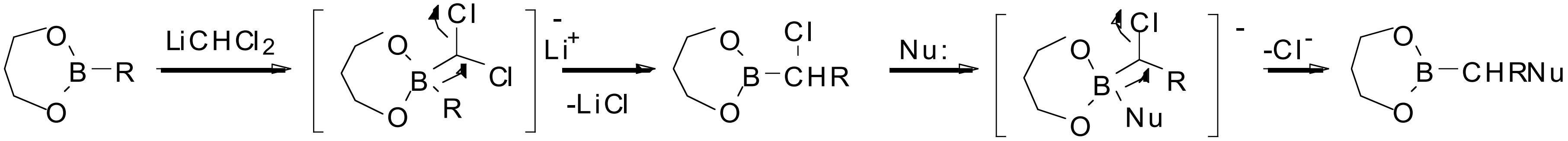
Expanding the Utility: Functionalization of Potassium Organotrifluoroborates

- Halomethyltrifluoroborates
- Lithium-Halogen Exchange
- Oxidation Reactions
- Wittig Reactions
- Horner-Wadsworth-Emmons Olefination
- Click Chemistry
- Reductive Amination

- The functionalization of potassium organotrifluoroborates opens the door to a wide variety of unique and potentially valuable boron containing organic synthons for incorporation into retrosynthetic strategies.

Synthesis and Elaboration of Halomethyltrifluoroborates

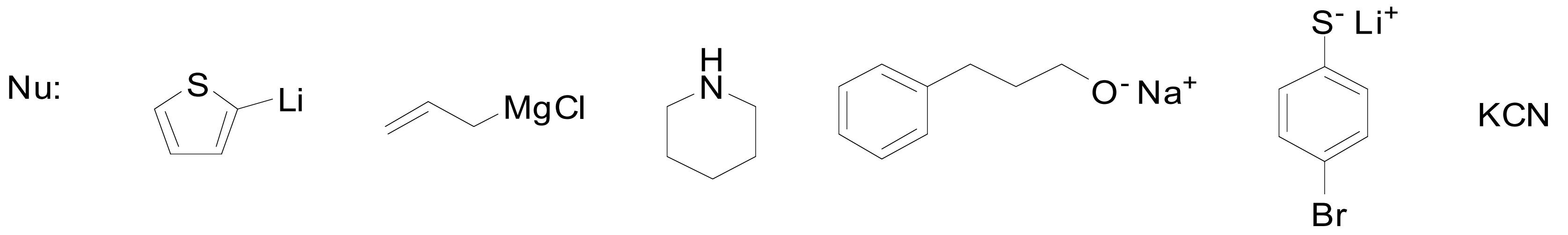
- Similar reaction with boronate esters



Nu: = RLi, RMgX, alkylamines, enamines, enolates...

- Halomethyltrifluoroborates

$$CH_2Br_2 + B(O^iPr)_3 \xrightarrow[\text{ii. }KHF_2/H_2O]{\text{i. THF, }n\text{-BuLi, }-78\ ^oC\text{, 1h}} \underset{88\%}{BrCH_2BF_3K} \xrightarrow[\text{rt, 2h}]{\text{NaI / acetone}} \underset{96\%}{ICH_2BF_3K} \xrightarrow[\text{ii) }KHF_2]{\text{i) Nu:}} NuCH_2BF_3K$$

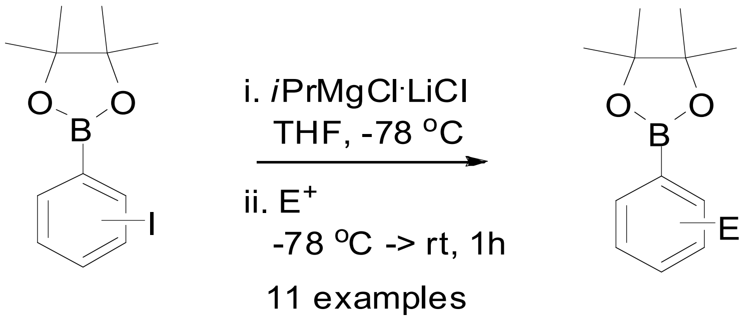


86% 83% 95% 86% 94% 98%

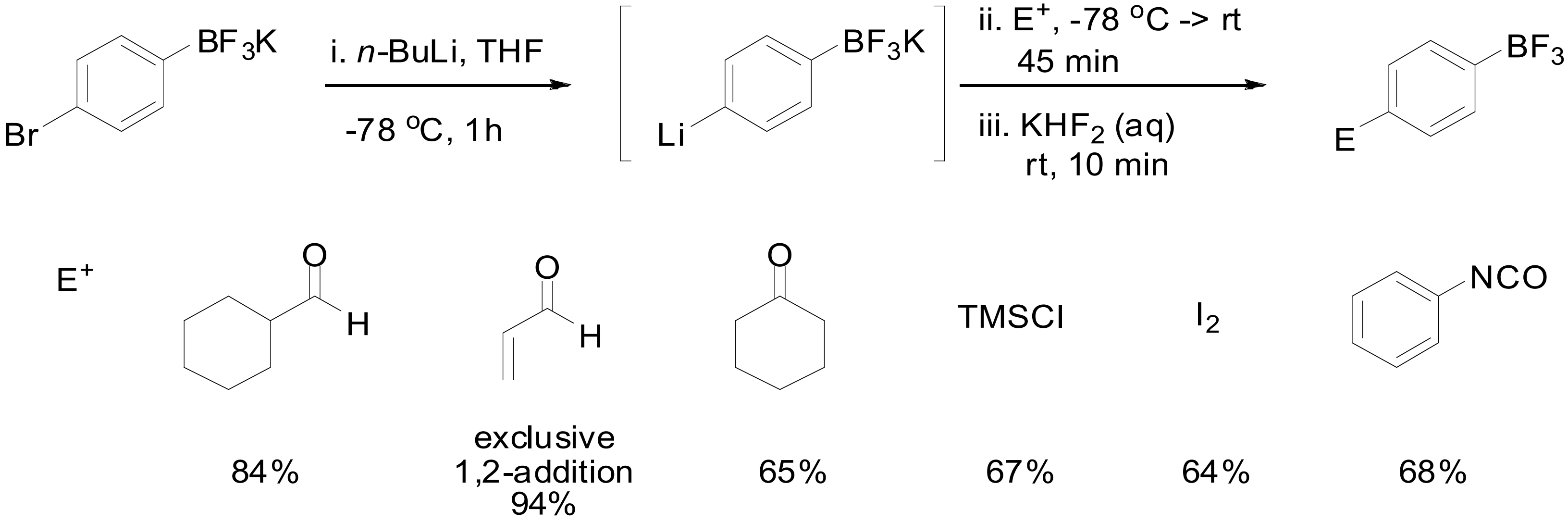
Org. Lett. **2006**, *8*, 2031.

Lithium-Halogen Exchange Reaction of Potassium Aryltrifluoroborates

- One literature reference using magnesium-halogen exchange of arylboronates



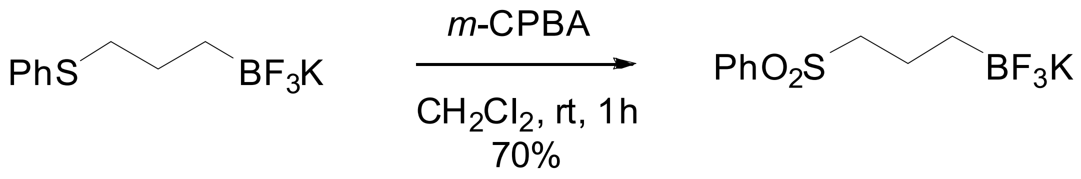
Angew. Chem. Int. Ed. **2005**, *44*, 3133.



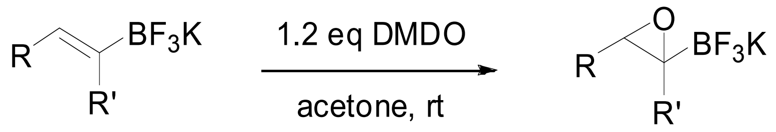
J. Org. Chem. **2006**, *71*, 7491.

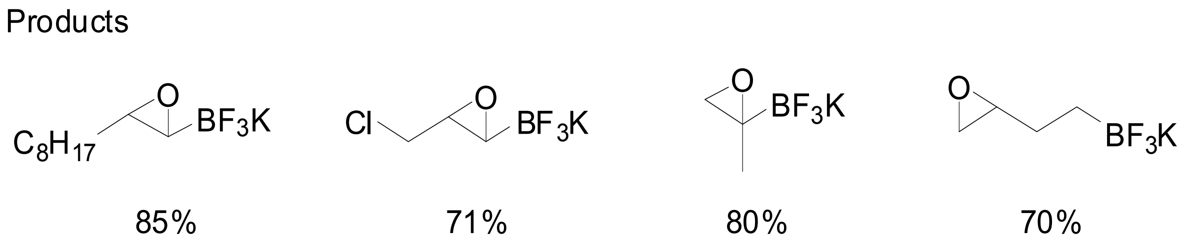
Epoxidation of Potassium Organotrifluoroborates

- In 2003, it was discovered that *m*-CPBA could oxidize a thioether to a sulfone in the presence of a C-BF_3K bond.



- This methodology was then extended to alkene epoxidation

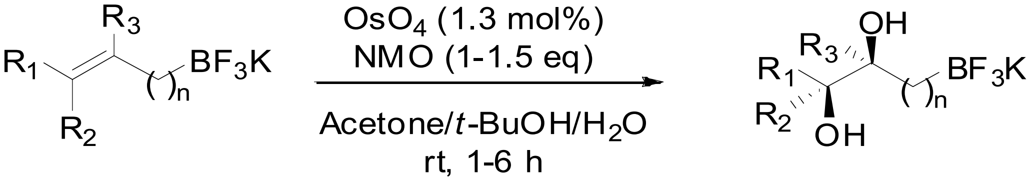


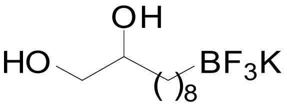


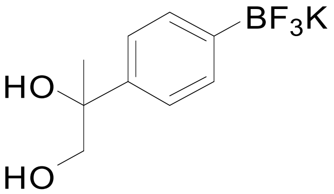
- Potassium organotrifluoroborate epoxides were found to be stable avoiding α -elimination and α-transfer processes

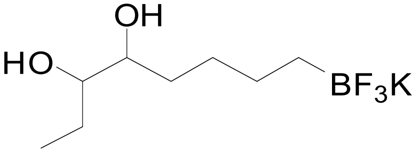
J. Am. Chem. Soc. **2003**, *125*, 11148.

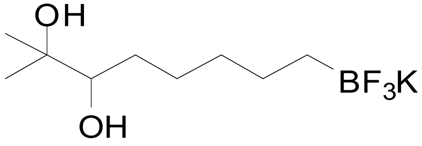
Cis-Dihydroxylation of Potassium Organotrifluoroborates

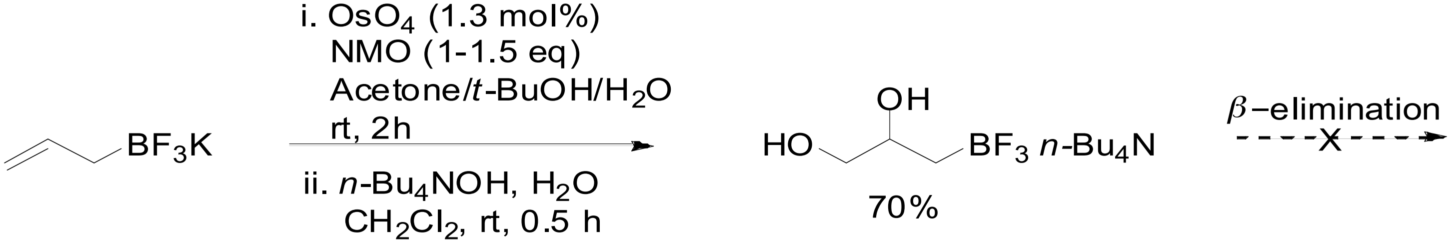

OsO_4 (1.3 mol%)
NMO (1-1.5 eq)
Acetone/*t*-BuOH/H_2O
rt, 1-6 h


75%


56%


71%


69%

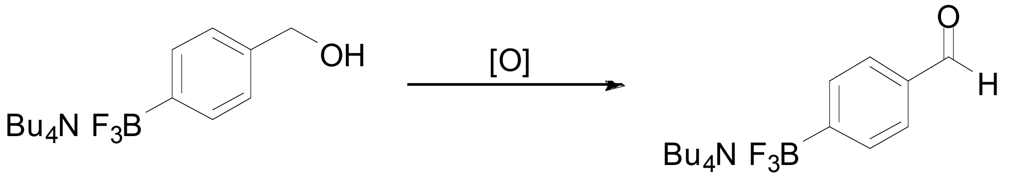

i. OsO_4 (1.3 mol%)
NMO (1-1.5 eq)
Acetone/*t*-BuOH/H_2O
rt, 2h
ii. *n*-Bu_4NOH, H_2O
CH_2Cl_2, rt, 0.5 h

70%

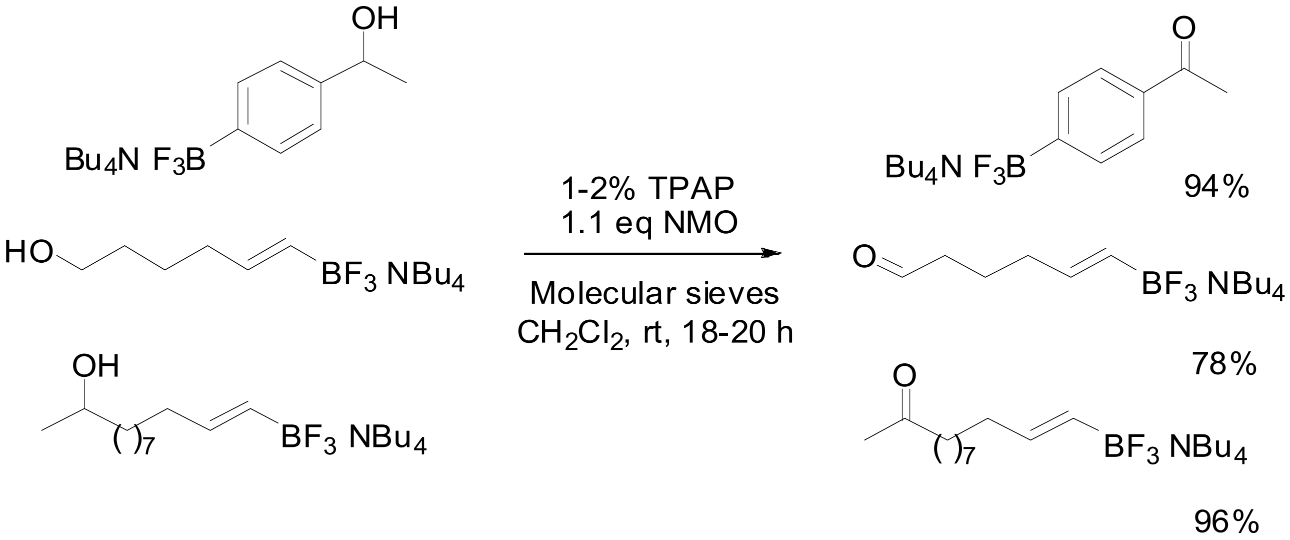
β−elimination

Org. Lett. **2006**, *8*, 75.

Oxidation of Hydroxyl-Substituted Organotrifluoroborates



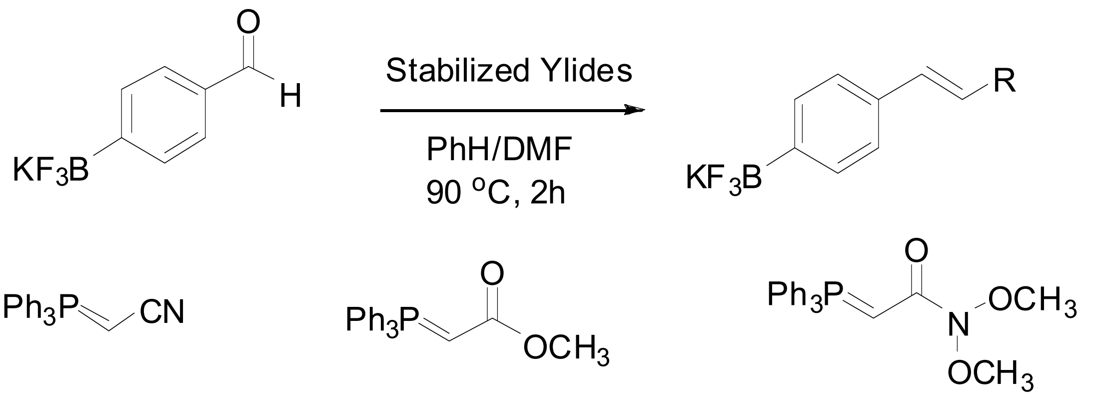
Entry	Conditions	% isolated yield
1	1% TPAP/NMO	91
2	Swern	90
3	Dess-Martin	86



J. Am. Chem. Soc. **128**, *128*, 9634

Wittig Reactions

- Wittig reactions with stabilized ylides gave good yields and *E*-selectivities

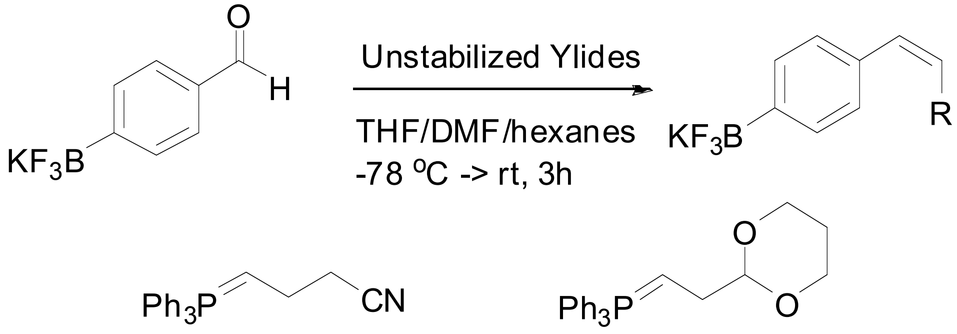


Yield 92%, E:Z 24:1

Yield 78%, E:Z 39:1

Yield 82%, E:Z 76:1

- Wittig reactions with unstabilized ylides gave good yields and good to moderate *z*-selectivities

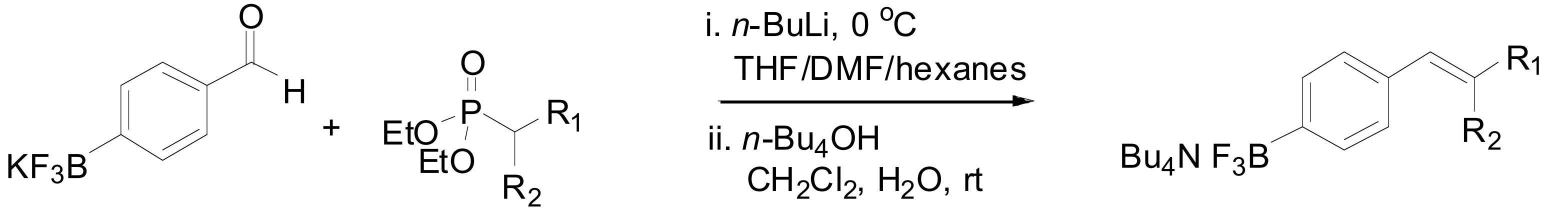


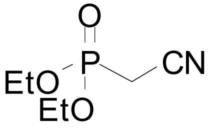
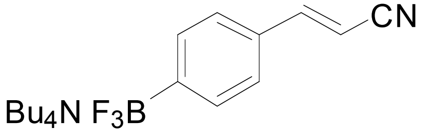
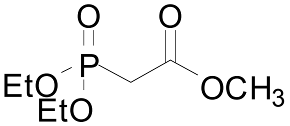
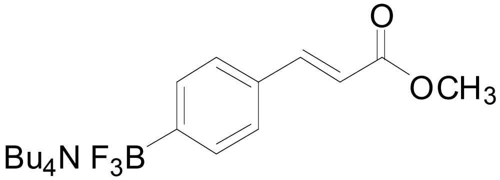
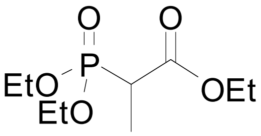
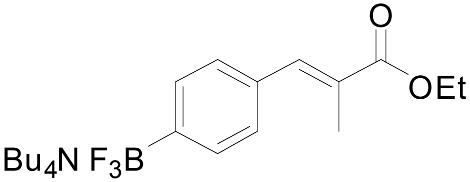
Yield 82%, E:Z 1:28

Yield 65%, E:Z 1:4

J. Org. Chem. **2006**, *71*, 6135.

Horner-Wadsworth-Emmons Olefination



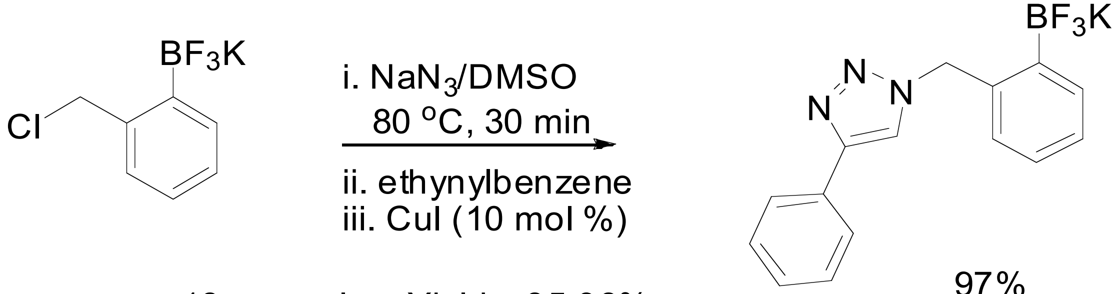
Phosphonate	**Product**
	 Yield 70% E:Z 9:1
	 Yield 91% E:Z 125:1
	 Yield 65% E:Z 20:1

- Good yields and generally high *E*-selectivities

J. Org. Chem. **2006**, *71*, 6135.

Click Chemistry and Reductive Amination

- 1,3-dipolarcycloaddition reactions, synthesis of potassium organotrifluoroborates containing the pharmaceutically important [1,2,3]-triazole subunit

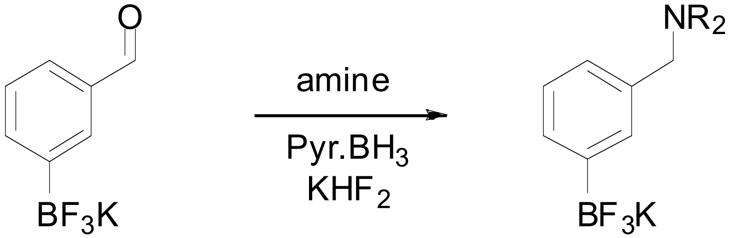


18 examples, Yields: 85-98%

- One Pot Reaction. General for aromatic and alkyl-alkynes containing alcohols, esters, nitriles and ethers.

Org. Lett. **2006**, *8*, 2767.

- Reductive amination, access to amine-substituted organotrifluoroborates



n-butylamine 76%, pyrrolidine 76%, morpholine 89%

J. Org. Chem. **2008**, *73*, 3885.

Selected Reactions of Potassium Organotrifluoroborates

Organodifluoroboranes

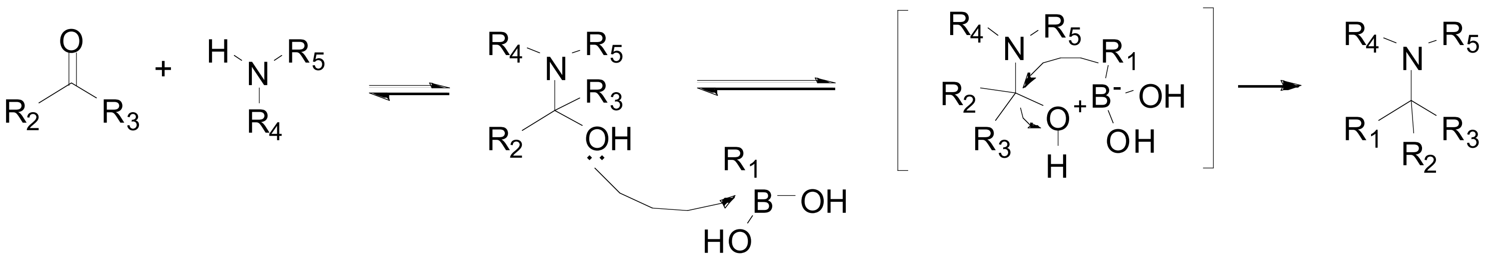
- Petasis Reaction
- Allylation and Crotylation Reactions
- Preparation of Chiral Secondary Amines

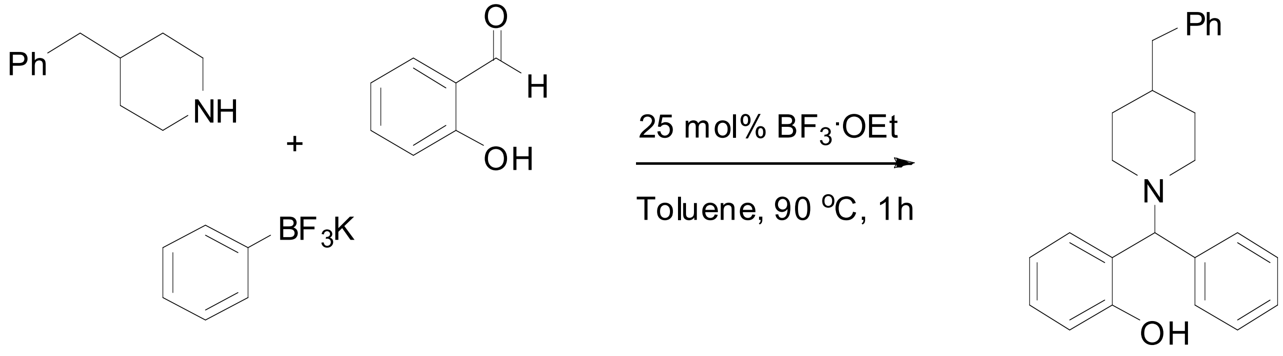
Potassium Organotrifluoroborates

- Rhodium-Catalyzed 1,2- and 1,4-Additions
- Rhodium-Catalyzed Cross-Coupling Reactions
- Diels-Alder/Cross-Coupling Reactions
- Palladium Catalyzed Cross-Coupling Reactions

Petasis Reactions of Difluoroorganoboranes: Three-Component Reactions to Synthesize Heavily Functionalized Amines

Proposed Mechanism





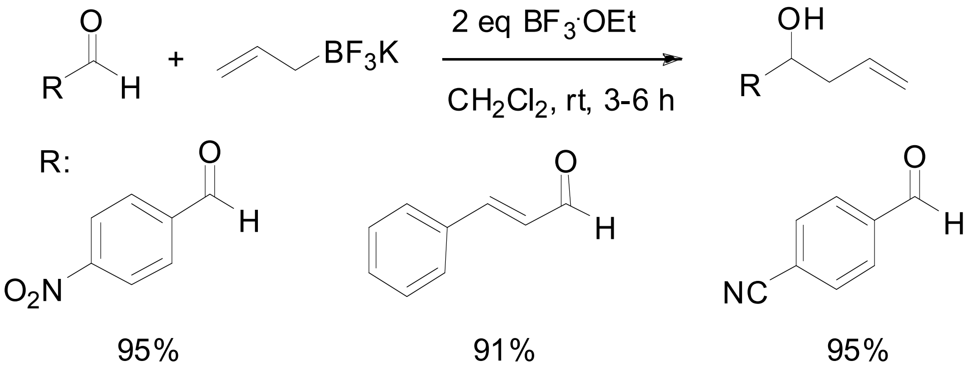
75 %

The reaction can accommodate electron rich aryl-, heteroaryl-, vinyl- and allyltrifluoroborates in moderate to good yields

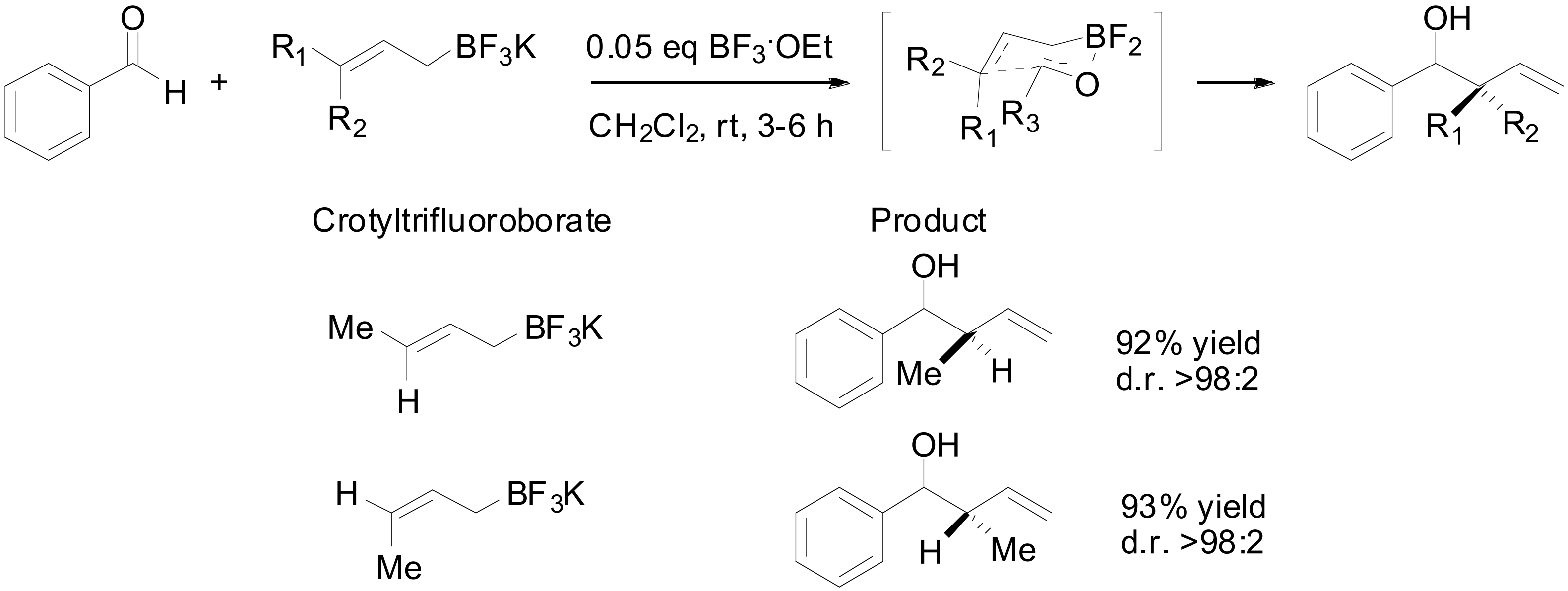
Tetrahedron. Lett. **2004**, *45*, 3471.

Difluoroorganoboranes: Allylation and Crotylation Reactions

- Allylation of aldehydes

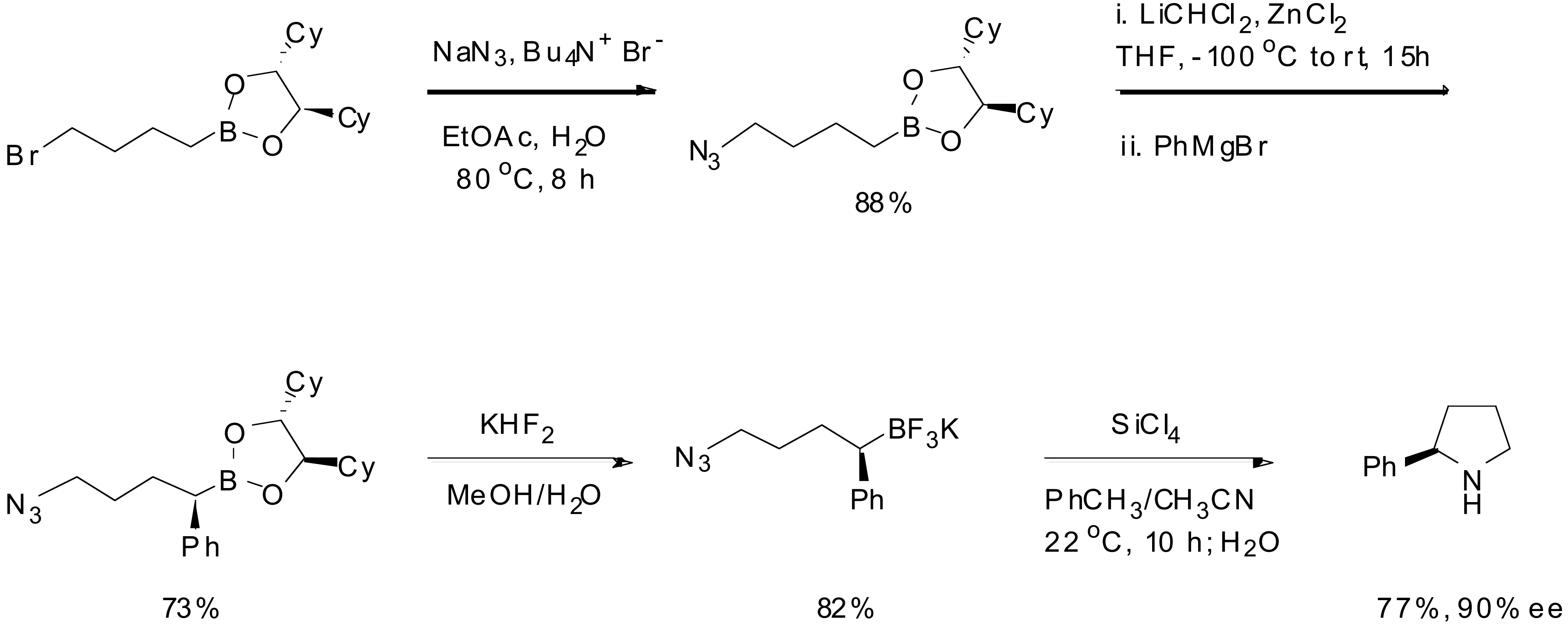


- Crotylation of aldehydes



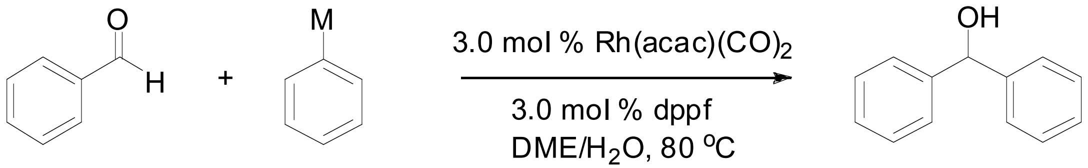
Synthesis **2000**, *7*, 990.

Difluoroorganoboranes: Preparation of Chiral Secondary Amines



Org. Lett. **2002**, *4*, 2153.

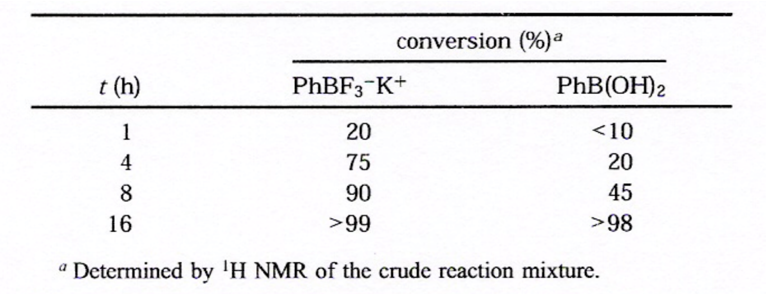
Reactions of Potassium Organotrifluoroborates: Rh-Catalyzed Addition to Aldehydes and Enones



3.0 mol % $Rh(acac)(CO)_2$

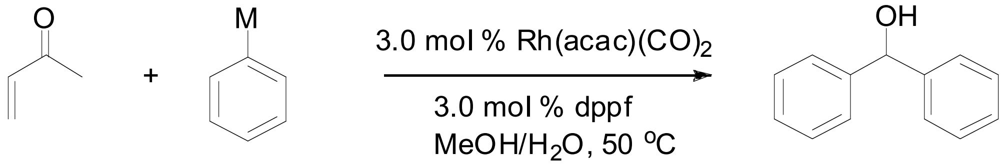
3.0 mol % dppf
DME/H_2O, 80 °C

M = $-B(OH)_2$ or $-BF_3K$



t (h)	conversion (%)[a]	
	$PhBF_3^-K^+$	$PhB(OH)_2$
1	20	<10
4	75	20
8	90	45
16	>99	>98

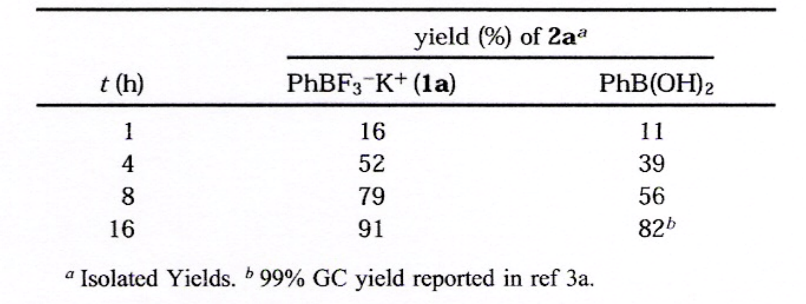
[a] Determined by ^1H NMR of the crude reaction mixture.



3.0 mol % $Rh(acac)(CO)_2$

3.0 mol % dppf
$MeOH/H_2O$, 50 °C

M = $-B(OH)_2$ or $-BF_3K$

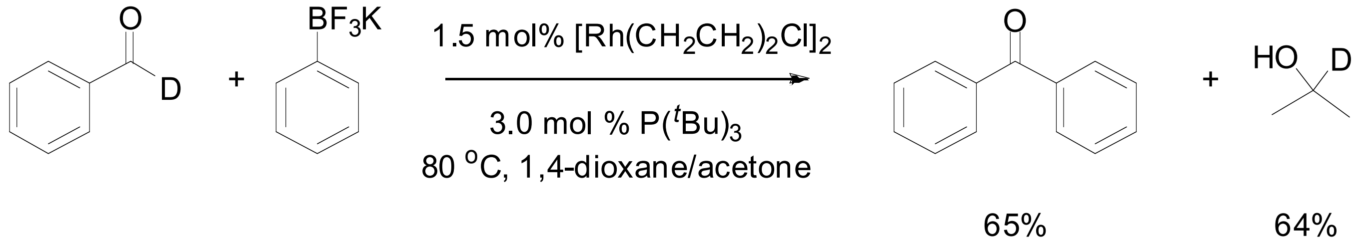


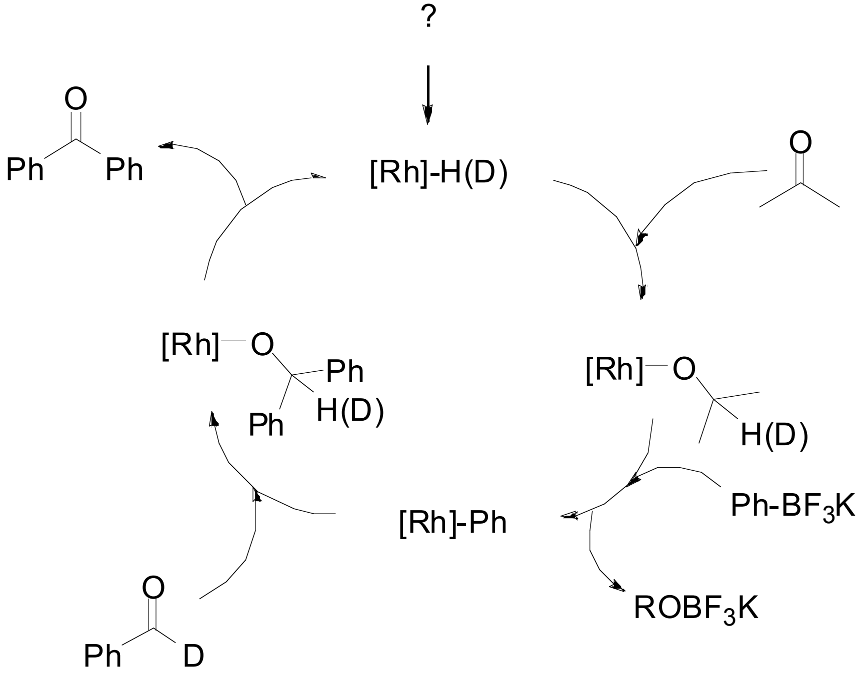
t (h)	yield (%) of **2a**[a]	
	$PhBF_3^-K^+$ (**1a**)	$PhB(OH)_2$
1	16	11
4	52	39
8	79	56
16	91	82[b]

[a] Isolated Yields. [b] 99% GC yield reported in ref 3a.

Org. Lett. **1999**, *1*, 1683

Rhodium-Catalyzed Cross-Coupling Reaction with Potassium Organotrifluoroborates: Conversion of Aldehydes to Ketones

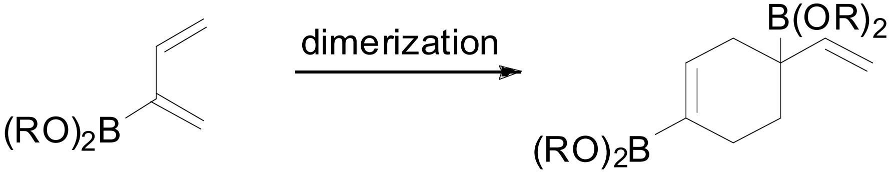




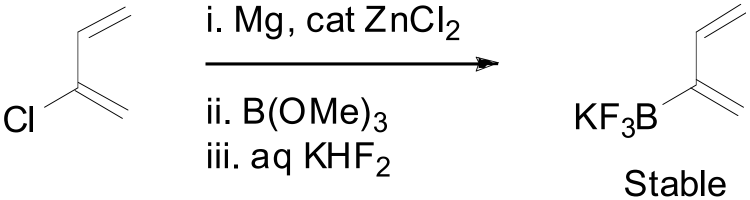
J. Am. Chem. Soc. **2004**, *126*, 15356.

Diels-Alder/Cross-Coupling Reactions of 2-BF_3-Substituted 1,3-Dienes

- Limitations to the use of 1,3-dienyl-2-boronates

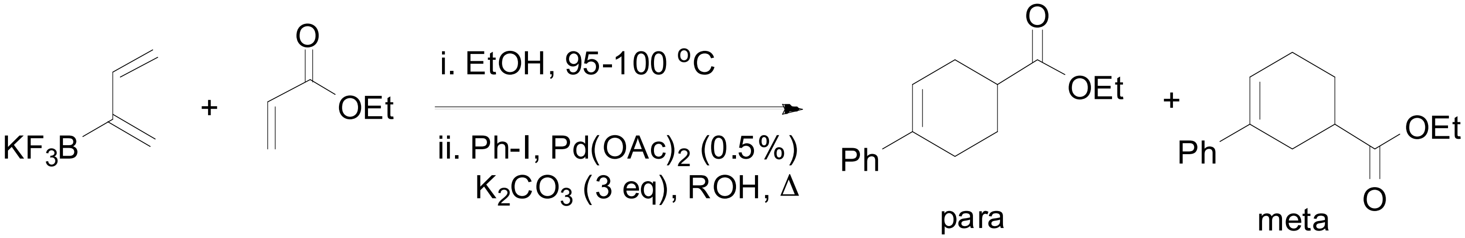


- Preparation of stable 2-potassium trifluoroborate 1,3-dienes



Stable

- Diels-Alder/Cross-Coupling Reactions



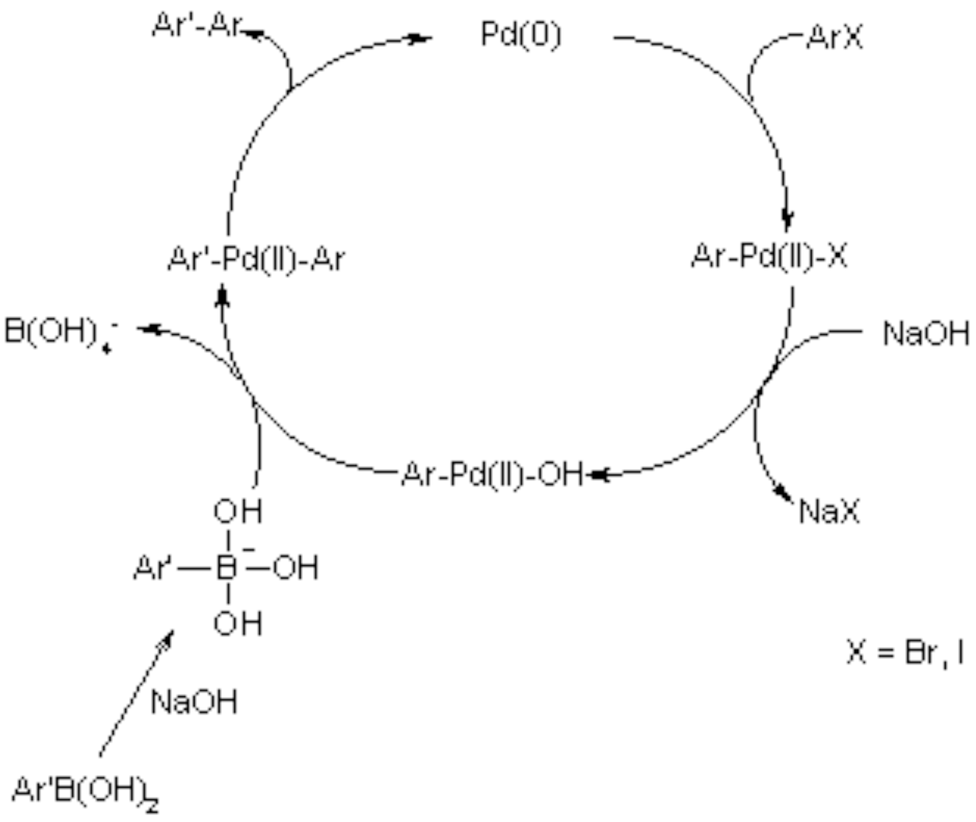
60% yield, para:meta 2.5:1

- 13 examples, moderate yields and regioselectivities

Org. Lett. **2005**, *7*, 2481

Palladium Catalyzed Cross-Coupling Reactions of Organotrifluoroborates

- Mechanism of the Suzuki Reaction



Palladium Catalyzed Cross-Coupling Reactions of Organotrifluoroborates

- General overall transformation:

$$R{-}X \quad + \quad R'{-}BF_3K \xrightarrow[\text{Base, } H_2O]{\text{Pd(0)}} R{-}R'$$

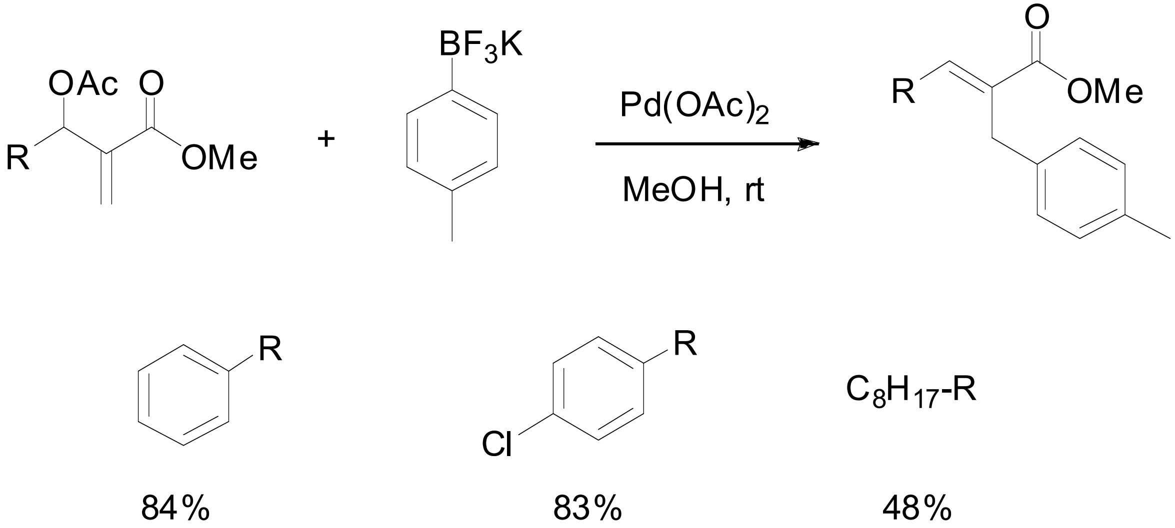
X = I, Br, OTf

R = Aryl, alkenyl, allyl
R' = Alkyl, alkenyl, alkynyl, Aryl

- Palladium catalyzed cross-coupling reactions have been one of the most highly investigated areas involving reactions of potassium organotrifluoroborates

- For recent reviews see: *Chem. Rev.* **2008**, *108*, 288.
  Tetrahedron **2007**, *63*, 3623.

Palladium-Catalyzed Cross-Coupling of Acetates of Baylis-Hillman Adducts

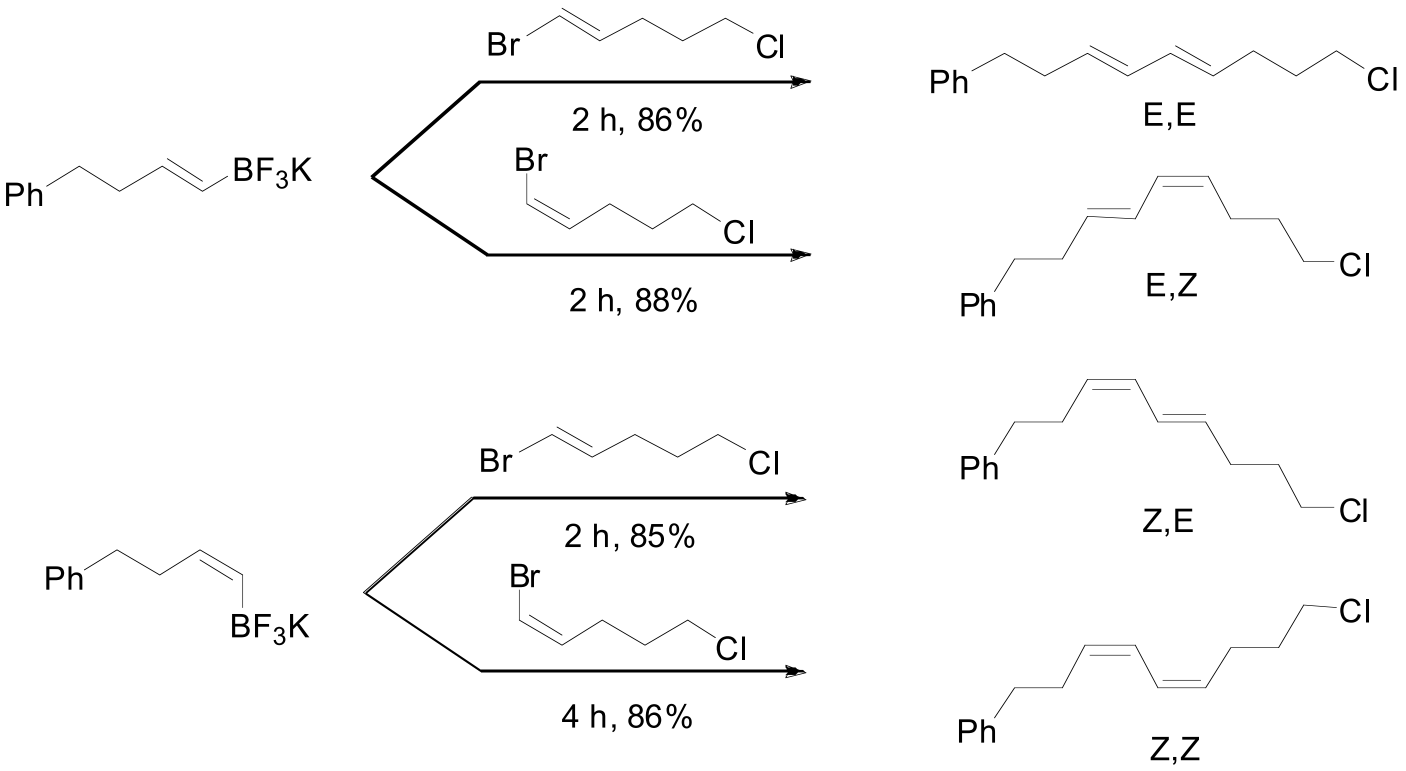


- This cross-coupling reaction has been used to generate densely functionalized molecules in moderate to good yields with high stereoselectivity

Org. Lett. **2003**, *5*, 3803

Setreoselective Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates with Alkenyl Bromides

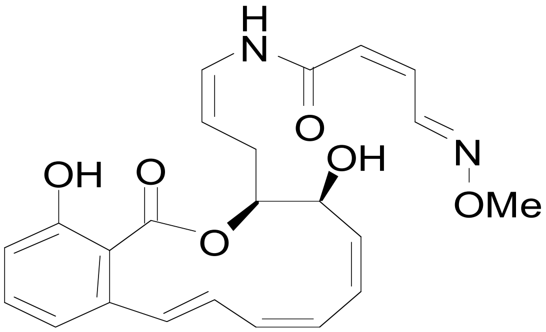
Reaction Conditions:
5 mol% $Pd(OAc)_2/2PPh_3$, 3 eq Cs_2CO_3, THF-H_2O (10:1)



- Stereospecific synthesis (>99%) of the four geometrical isomers of 9-chloronona-3,5-dienylbenzene

J. Org. Chem. **2005**, *70*, 3950.

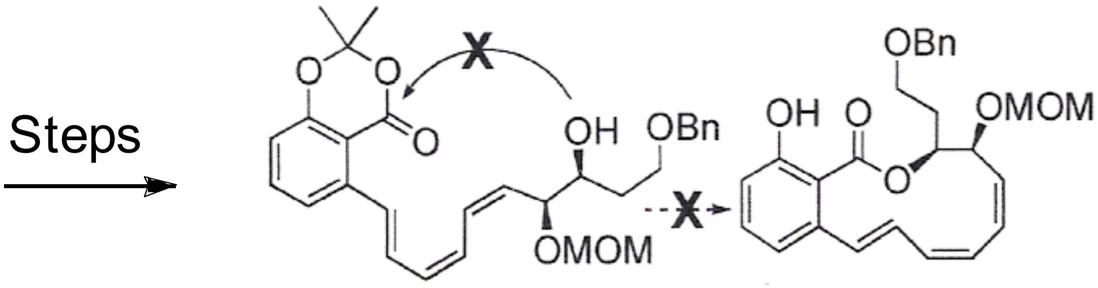
From Methodology to Utility: Potassium Organotrifluoroborates in Natural Product Synthesis: Oximidine II



Oximidine II

- First isolated in 1999 from Pseudomonas sp. Potential cancer therapeutics

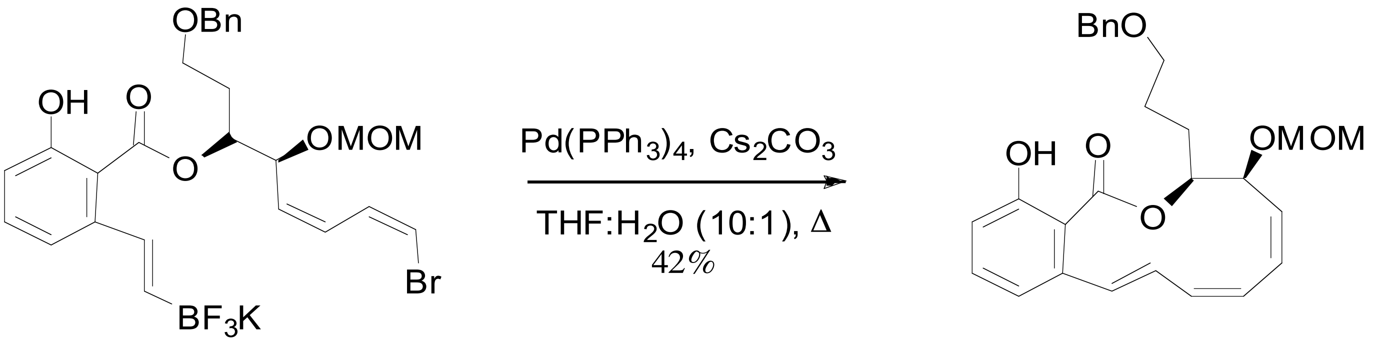
- Key step: macrolactonization via esterification did not succeed



J. Am. Chem. Soc. **2004**, *126*, 10317.

Oximidine II

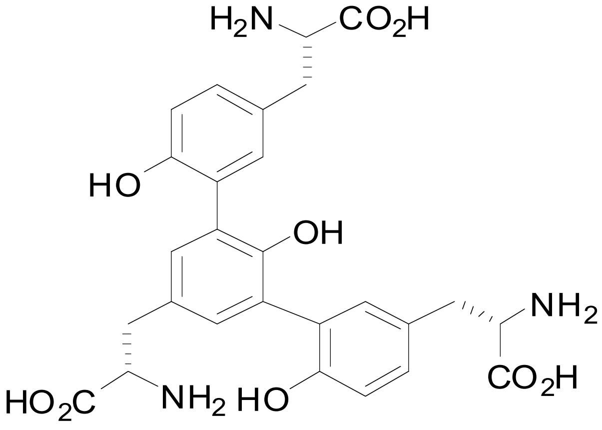
- Palladium catalyzed cross-coupling of the organotrifluoroborate furnished the macrolactone portion of Oximidine II



J. Am. Chem. Soc. **2004**, *126*, 10317.

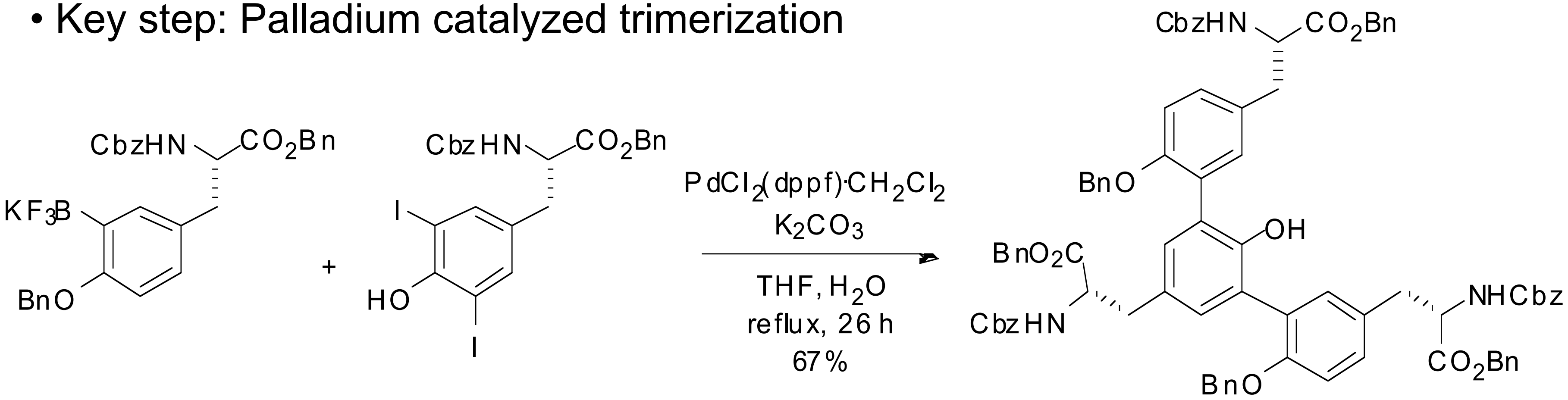
Trityrosine

- Isolated from bacteria, plants and yeast. Target of interest for biological studies.



trityrosine

- Key step: Palladium catalyzed trimerization



- The corresponding Suzuki Reaction using the pinacoleboronate ester gave none of the desired product, highlighting the higher reactivity of organotrifluoroboranes

J. Org. Chem. **2005**, *18*, 7353

Conclusion

- Potassium organotrifluoroborates have been demonstrated to be viable reagents in contemporary organic synthesis. Their ease of preparation coupled with their often higher reactivities vs. other organoborane reagents has highlighted their use in a number of transition metal catalyzed reactions.

- This class of organoboron reagents has a high utility due to the overall stability of the C-B bond towards oxidation, proteodeboronation and nucleophilic attack allowing the organic portions of the reagent to be further elaborated. Thus expanding their use as valuable organic synthons in retrosynthetic strategies.

- While there are a host of transition metal catalyzed reactions known for potassium organotrifluoroborates, in many cases the specific mechanisms by which these reagents participate are not fully understood. Further knowledge of the reactive organoboron species in these reactions may lead to the development of new transition metal catalyzed reactions.