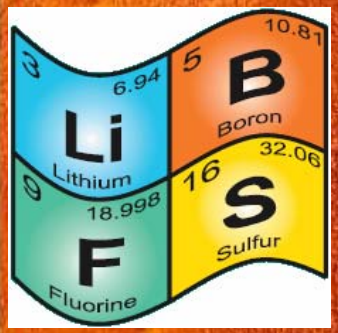


BORONIC ACIDS MANUFACTURE AT INDUSTRIAL SCALE

Dominique DELBRAYELLE, MINAKEM S.A.S.

AGENDA

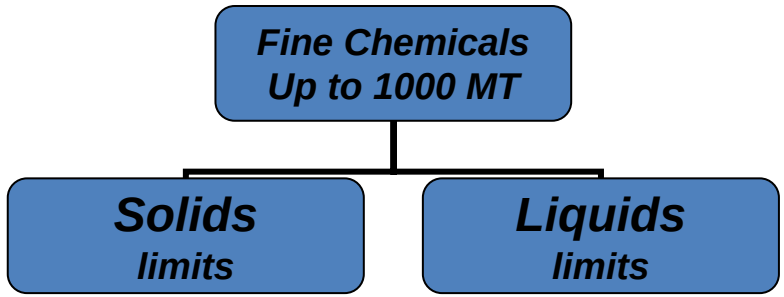
Boronic acids

1. Minakem – overview
2. Boronic acids : a valuable tool for the chemist
3. Boronic acids synthesis
4. Borylation of lithiated species
5. Borylation of organomagnesium species
6. Quality control of boronic acids
7. Diethanolamine esters as boronic acid surrogates
8. Q&A

MINAKEM – overview

- 2005 - acquisition of SEAC's fine chemical business by Minakem, 40 years of experience in custom synthesis. Located near Lille, North of France, FDA approved
- 2006 - acquisition of Chemtec Leuna, Germany, near Leipzig
- 2008 - Chemtec Leuna approved by the FDA for the first time, no 483's
- 2008 - acquisition of Penn Specialties Chemicals, now PennAkem, Memphis, USA
- 2009 - acquisition of the Astra Zeneca's state-of-the-art API site in Dunkirk, North of France
- 2010 - activities in France & Germany unified under the Minakem name

MINAKEM – overview



Lille	***10-20 MT***	***400 MT without distillation 50 MT with distillation***
Leuna	***20-100 MT***	***400 MT without distillation 50 MT with distillation***
Dunkerque	***20-300 MT***	***> 1,000 MT without distillation***
Pennakem	***restricted***	***100 – 10,000 MT***

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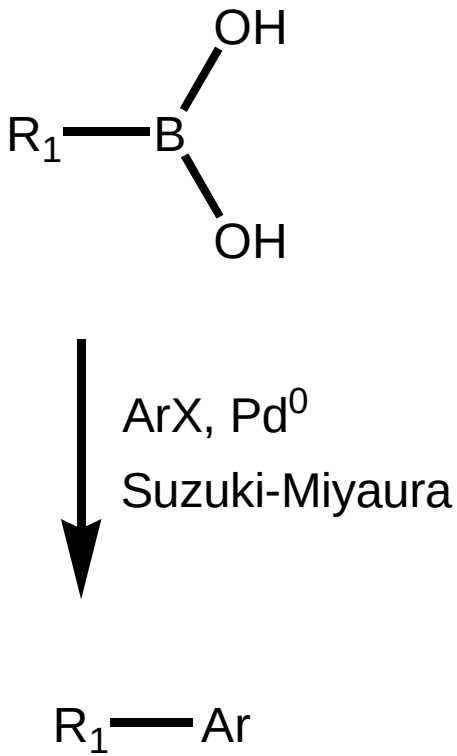
BORONIC ACIDS : A VALUABLE TOOL FOR THE CHEMIST

Boronic acids

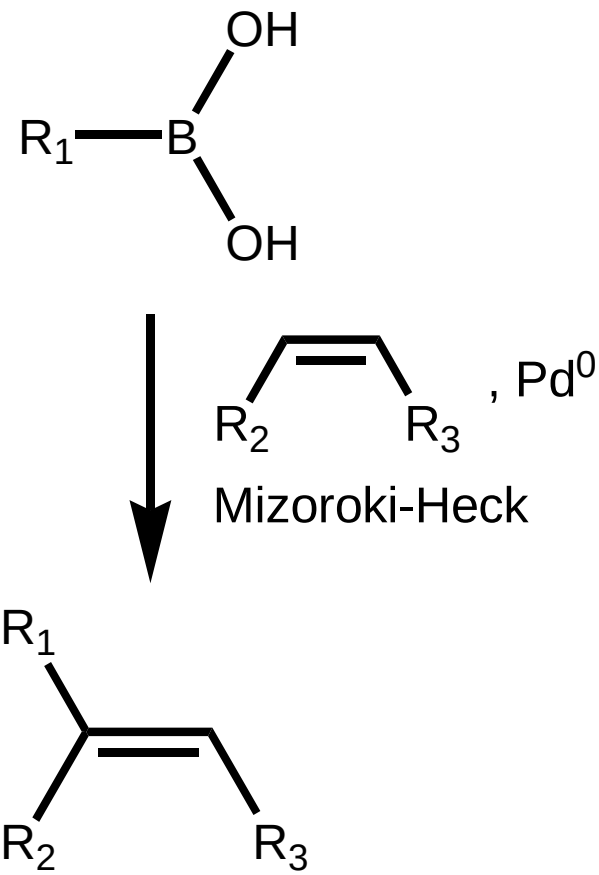
C-C coupling : Suzuki-Miyaura reaction



BORONIC ACIDS : A VALUABLE TOOL FOR THE CHEMIST

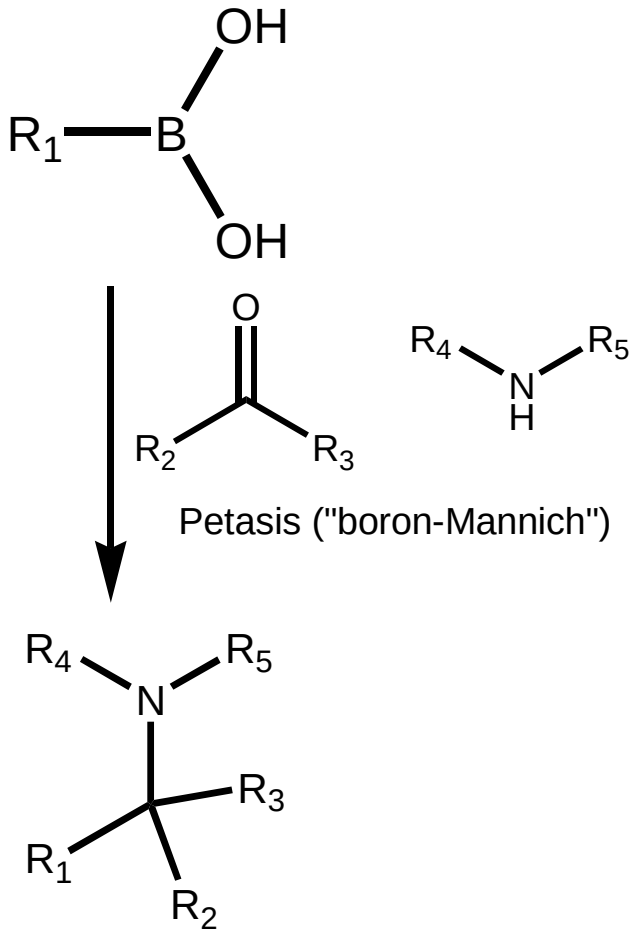
Boronic acids

C-C coupling : Mizoroki-Heck reaction



BORONIC ACIDS : A VALUABLE TOOL FOR THE CHEMIST

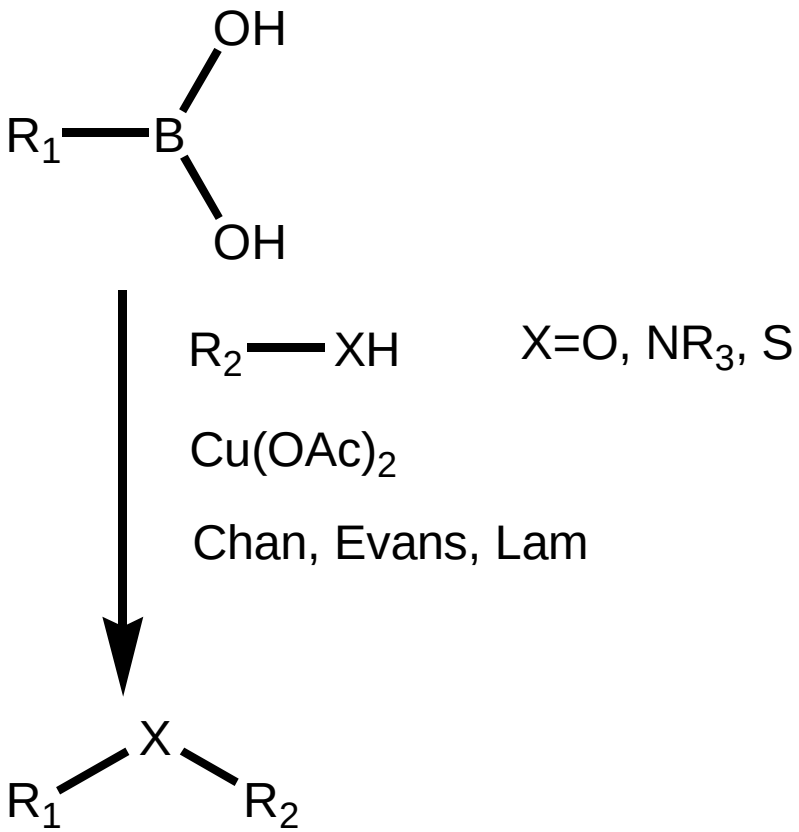
C-C coupling : Petasis reaction



BORONIC ACIDS : A VALUABLE TOOL FOR THE CHEMIST

Boronic acids

Copper-catalyzed C-X coupling



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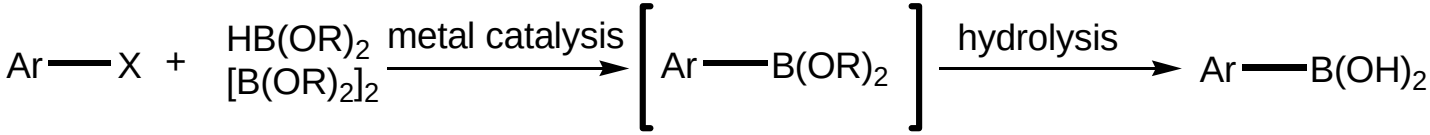
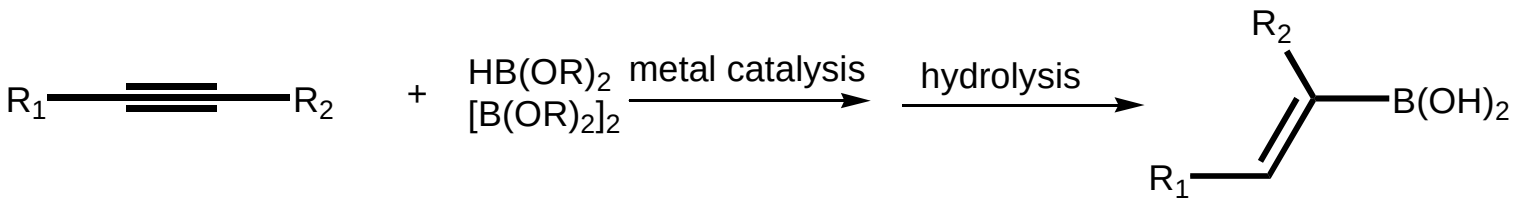
BORONIC ACIDS SYNTHESIS

Synthesis

B-C coupling (for aromatic boronics)



Hydroboration of alkynes (for alkenyl boronics)



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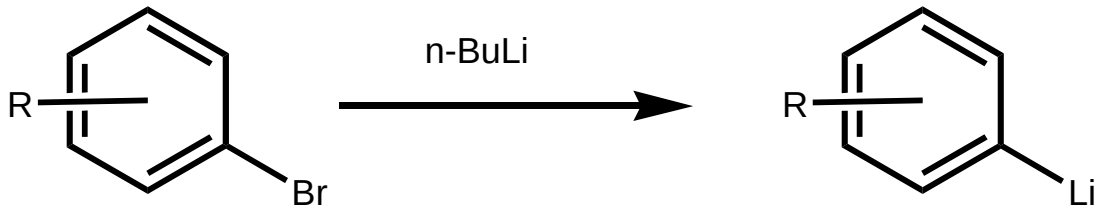
BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

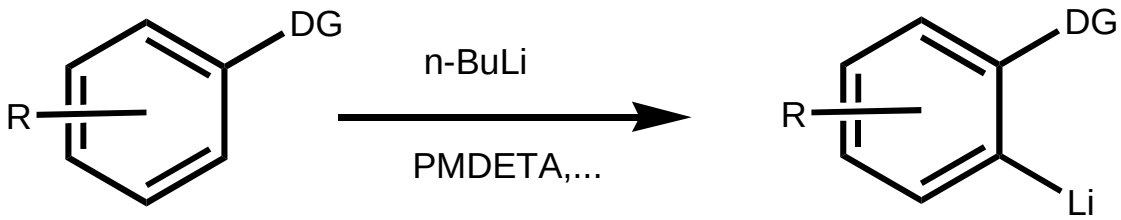
R-Li → R-B(OH)$_2$

Formation of the lithiated species

- by lithium-halogen exchange



- by directed ortho-lithiation

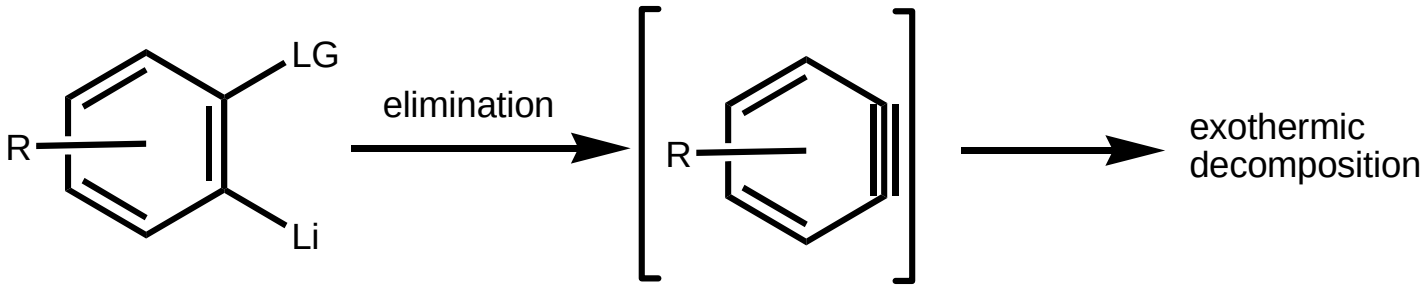


BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)2

Stability of the lithiated species

Leaving groups ortho to the lithium can eliminate to benzyne-type products :



Thermal hazard !

BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)$_2$

Stability of the lithiated species

- decomposition often seen above -50°C
- fast self-heating rate (up to 50°C/min)
- adiabatic temperature rise up to 100°C

BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)$_2$

Stability of the lithiated species

Maximum temperature usually remains below boiling point of solvent
(e.g. THF bp=67°C)

BUT

in ortho-lithiation reactions, sudden butane release is the major hazard !

BUTANE
bp=-1°C
extremely flammable

BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)$_2$

Addressing the stability issues

- determination of the onset temperature by heating experiments
- operating conditions adjustments accordingly
- reactor design for fast quench of the reaction mixture

BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)$_2$

Addressing the stability issues

- use of hexyllithium instead of butyllithium reduces the risk of overpressure in the vessel

- use of 2-methylTHF instead of THF adds 13°C of safety margin

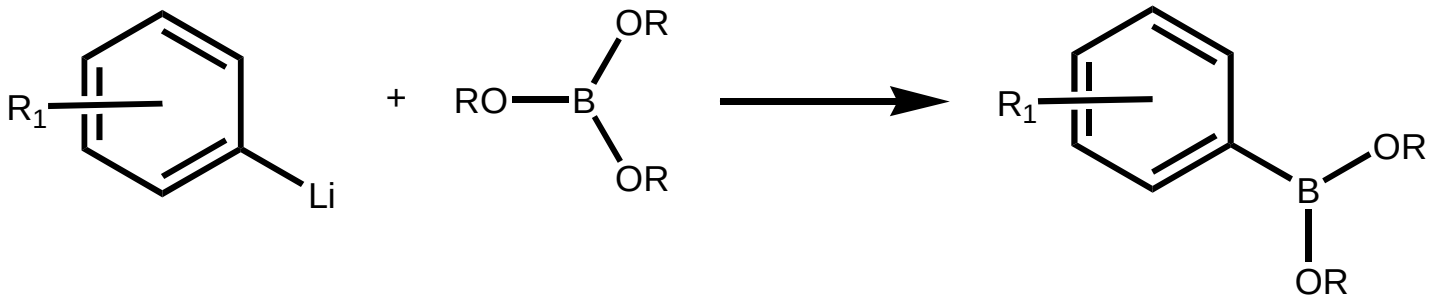
- addition of anhydrous $MgCl_2$ reduces the rate of decomposition

(Rawalpally & al., Org. Proc. Res. Dev. 2008, 12, 1293-1298)

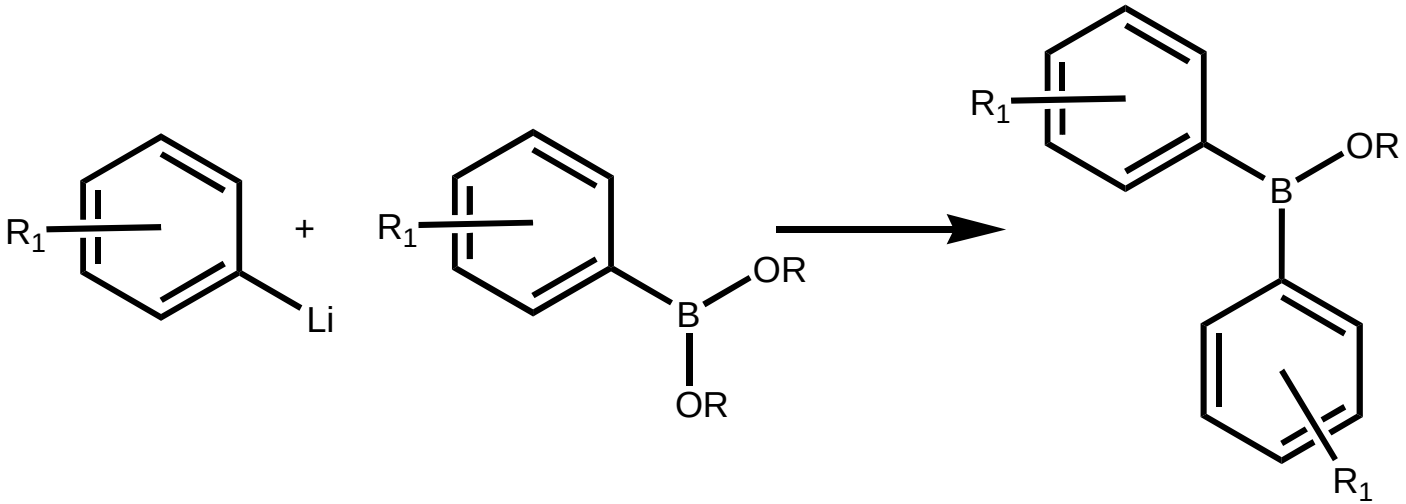
BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)$_2$

Borylation reaction



Side reaction gives borinic acid



BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)$_2$

Borinic acid side-product

- the amount of borinic acid formed is very variable depending on the substrate

- borinic acid behaves like boronic acid in coupling reactions

BUT

is lost on boronic acid isolation : yield loss

or not : purity loss

BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)$_2$

Borinic acid side-product:
how to minimize it ?

- excess borate reduces the borinic acid formation (but gives boric acid on hydrolysis)
- low temperature reduces second addition
- triisopropyl borate vs. trimethyl borate
- order of addition of the reagents

BORYLATION OF ALKYL- OR ARYLLITHIUM SPECIES

R-Li → R-B(OH)$_2$

Order of addition of the reagents

- lithiated species onto cold borate
  OK if no stability issues

- usually borate onto lithiated species with controlled addition rate

- for reactive lithiated species : butyllithium onto mixture of starting material and borate

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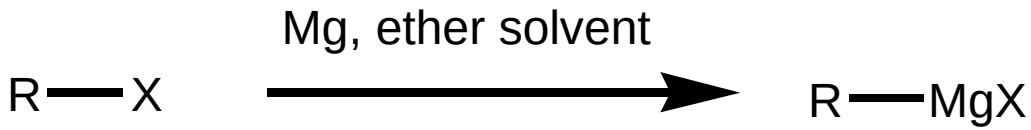
BORYLATION OF ORGANOMAGNESIUM SPECIES

R-MgX → R-B(OH)$_2$

Formation of the Grignard reagent

- by direct reaction with magnesium metal



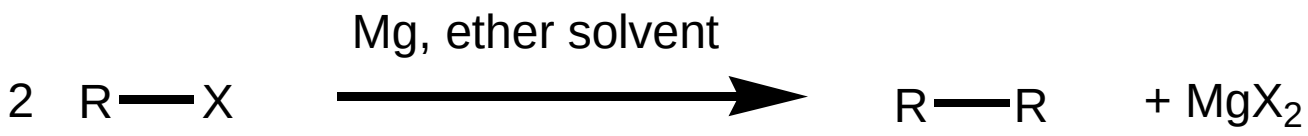
- by halogen-magnesium exchange

BORYLATION OF ORGANOMAGNESIUM SPECIES

R-MgX → R-B(OH)$_2$

Formation of the Grignard reagent

Side reaction : Wurtz-type coupling



- Yield loss
- Excess borate reagent in the borylation step
- Potential impurity in final product, especially if telescoped process with Suzuki coupling

BORYLATION OF ORGANOMAGNESIUM SPECIES

R-MgX → R-B(OH)$_2$

Minimizing by-product : Methyl THF

#	Reagent	Solvent	Organomagnesium Yield	MeTHF Yield Improvement
1	benzyl chloride	THF	85%	**14%**
		MeTHF	99%	
2	benzyl bromide	THF	83%	**15%**
		MeTHF	98%	
3	o-methylbenzyl chloride	THF	78%	**19%**
		MeTHF	97%	
4	o-chlorobenzyl chloride	THF	20%	**66%**
		MeTHF	86%	
5	allyl chloride	THF	73%	**16%**
		MeTHF	89%	

P. Rittmeyer et al., Chemetall DE 19808570

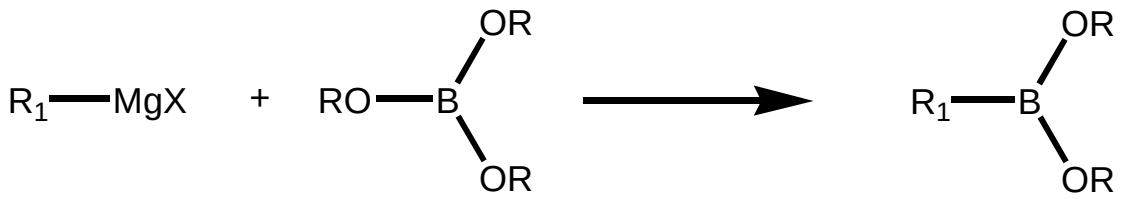
Suppression of dimerization for benzyl and allyl substrates is general

MINAKEM

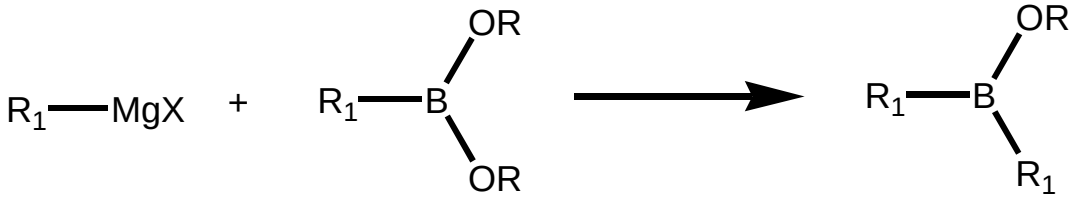
BORYLATION OF ORGANOMAGNESIUM SPECIES

R-MgX → R-B(OH)$_2$

Borylation reaction



Side reaction gives borinic acid



- Same issues as with lithiated species

BORYLATION OF ORGANOMAGNESIUM SPECIES

$R\text{-}MgX \rightarrow R\text{-}B(OH)_2$

Borylation reaction

Low solubility of the Grignard reagent can be problematic

- RM thick or not stirrable at low temp, dilution required
- reagent precipitation during transfer

Here again, Methyl THF is a solution !

MINAKEM

BORYLATION OF ORGANOMAGNESIUM SPECIES

R-MgX → R-B(OH)$_2$

Grignard reagents in Methyl THF

Reagents	% Sol. In MeTHF	% Sol. In THF
MeMgBr	35%	15%
EtMgBr	40%	10%
PhMgBr	45%	15%
EtMgCl	30%	25%

Easier handling, better productivity
Easier workup (not miscible with water)

BORYLATION OF ORGANOMETALLICS

Reaction workup

1) Acidic quench
   - boronic ester hydrolyzed to boronic acid
   - excess borate gives boric acid
2) Extraction
3) Crystallization
   - dehydrating conditions give boroxine (cyclic anhydride)

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QUALITY CONTROL OF BORONIC ACIDS

Quality control

Quality control: what is really in there?

A “classical” organic product contains the desired product + impurities and solvents

- Purity by HPLC or GC
- Assay with a standard by HPLC or GC

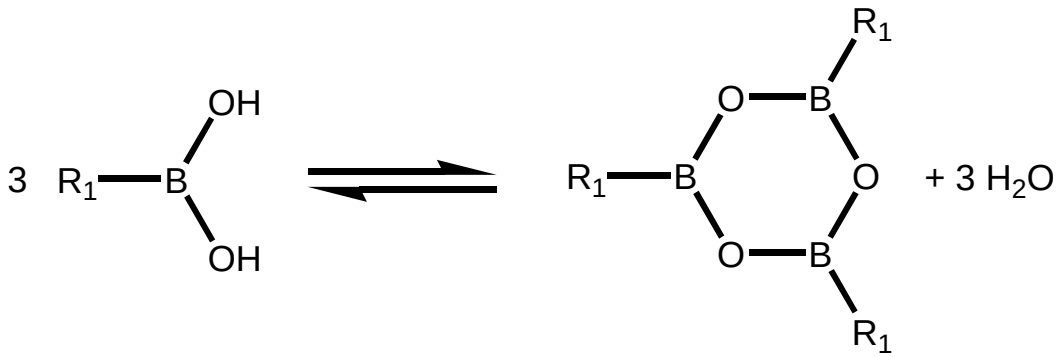
A boronic acid product contains the boronic acid, but also possibly water, the boroxine (anhydride), and some boric acid !

➢w/w analysis is a nightmare !

QUALITY CONTROL OF BORONIC ACIDS

Boroxine: an inevitable companion

A boronic acid is in equilibrium with its cyclic anhydride (boroxine)

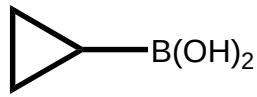
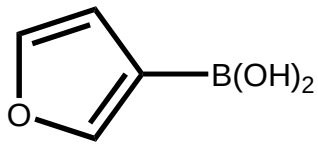
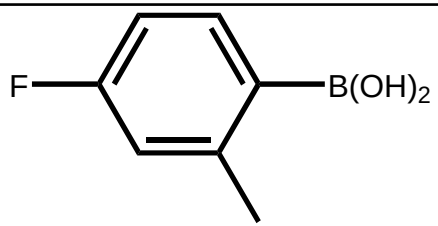


Even at room temperature, %boroxine varies between 0% and 100% depending on R_1, crystallization conditions, drying conditions…

QUALITY CONTROL OF BORONIC ACIDS

Quality control

Boroxine: an inevitable companion

Boronic acid	% boroxine
	<10%
	~20%
	>90%

QUALITY CONTROL OF BORONIC ACIDS

Quality control

<u>w/w assay by titration with NaOH:</u>

routine… but meaningless

- Does not differentiate boronic acid and boric acid

- Boroxine readily reverts to boronic acid during the titration, thus increasing the assay results

➢ Assay is often >100% (up to 120%)

➢ Low quality material can assay >100% !

QUALITY CONTROL OF BORONIC ACIDS

Quality control

w/w assay by titration with NaOH:

routine… but meaningless

For a boronic acid with MW=150g/mol

Composition	NaOH titration result
100% boroxine	113.6%
90.5% boronic acid 9.5% boric acid	113.6%
70.7% boronic acid 17.7% boric acid 11.6% water	113.6%

QUALITY CONTROL OF BORONIC ACIDS

Other analytical difficulties

- KF titration does not work (drives dehydration, boronic acid can oxidize)
- Melting point is unreliable (usually only mp of the boroxine is observed)

QUALITY CONTROL OF BORONIC ACIDS

Quality control

Consequences

- Poor quality control unacceptable for critical raw materials
- Potential variability between suppliers
- Misadjustment of stoichiometry in the subsequent reactions ➔ impurities, extra costs

What is the solution ?

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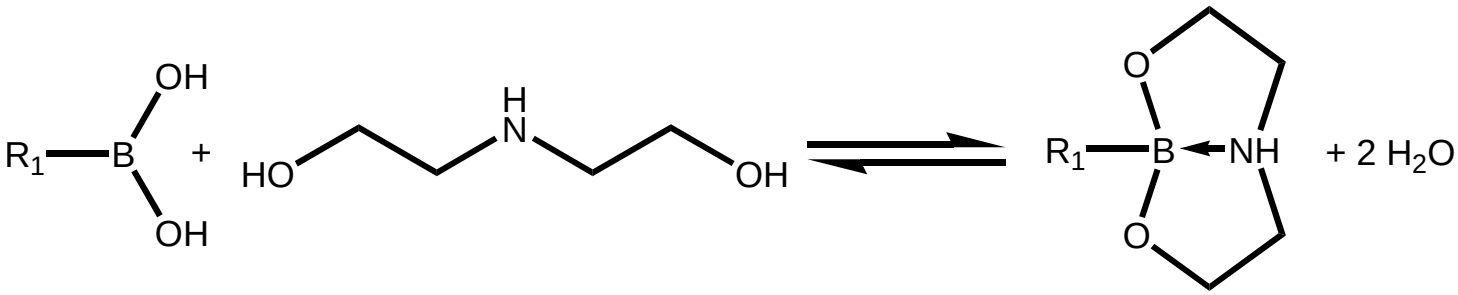
QUALITY CONTROL OF BORONIC ACIDS

Diethanolamine ester as boronic acid surrogate



- Stable solid, does not oxidize or hydrate
- Readily reverts to boronic acid in acidic aqueous solution
- Can be used as HPLC standard

DIETHANOLAMINE ESTERS AS BORONIC ACID SURROGATES

Diethanolamine esters

Use as “hidden” boronic acid

Convenient procedure :

1. Dissolve in aqueous HCl ➔ reverts to boronic acid
2. Extract with organic solvent (MTBE, MeTHF, …)
3. Proceed with coupling reaction

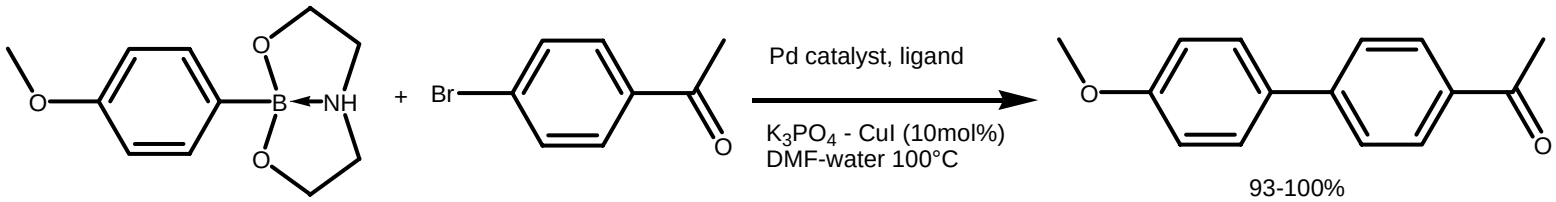
Perfect control of stoechiometry !

DIETHANOLAMINE ESTERS AS BORONIC ACID SURROGATES

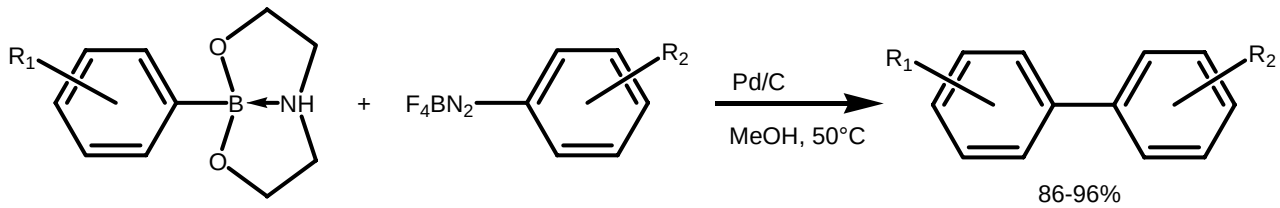
Diethanolamine esters

Direct use in cross-coupling reactions

With aryl bromides :



With diazonium tetrafluoroborates, using Pd/C, and no base :



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