THE SUZUKI-MIYAURA REACTION AND BORON REAGENTS – MECHANISM, SYNTHESIS AND APPLICATION

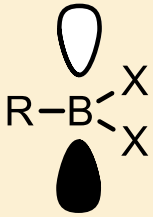
Haraldur Gunnar Guðmundsson

Literature Review – 25.04.14

Outline Of Talk

- Introduction
- Unveiling the role of the base in the Suzuki-Miyaura reaction mechanism
  - *"In vitro"* observations
  - Computational studies and detection of intermediates
  - Kinetic studies
- Selected boron reagents
  - Properties and mechanism
  - Common methods for preparation
  - Selected examples of application

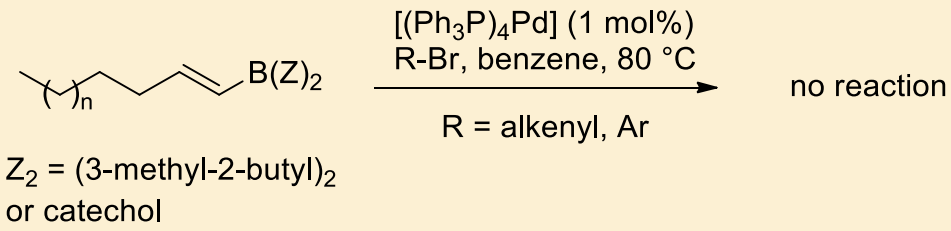
Introduction – Boron Reagents



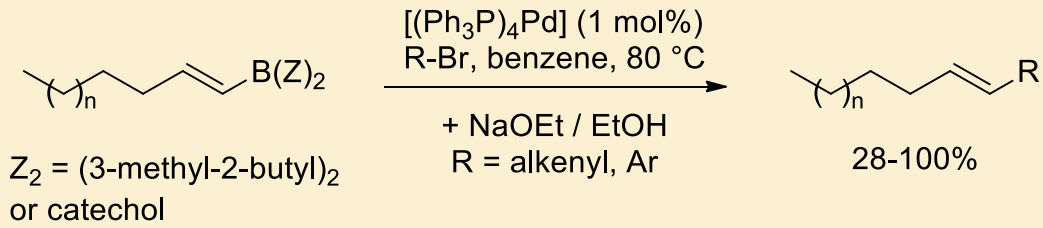
- <u>General properties of boron compounds</u>
  - Boron ($2s^2$, $3p^1$) can engage in three sp^2 hybridised bonds, resulting in a trigonal planar geometry. Boron compounds are highly electrophilic, having an empty p-orbital orthogonal to the plane.
  - <u>Inexpensive</u> and readily prepared.
  - Have a <u>broad functional-group tolerance</u>, are relatively stable and generally environmentally benign.
  - Some are thermally stable and inert to water and oxygen, thus <u>easy to handle</u> (industry).
  - Transmetalate with a variety of metal compounds under exceptionally <u>mild</u> reaction conditions, especially versatile with palladium(II) complexes.
  - This has allowed the Suzuki-Miyaura reaction to develop into the most widely-applied transition metal catalysed C-C bond forming reaction to date.

The Suzuki-Miyaura Coupling reaction

- Attempts by Negishi[1,2] to cross-couple organoboron reagents with organic halides failed because the neutral three-coordinate boron species were not nucleophilic enough to efficiently transmetalate.



- Suzuki and Miyaura[3,4] postulated that activation of the boron using a negatively charged base (alkoxide, acetate or hydroxide ion) might render the organic group on boron nuclephilic enough for transmetalation to take place more readily.



(1) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729. (2) Negishi, E.; Baba, S. *J. Chem. Soc. Chem. Comm.* **1976**, 596b. (3) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (4) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866.

The Suzuki-Miyaura Coupling reaction

- This C-C bond-forming reaction earned Suzuki the Nobel prize in 2010 along with Heck and Negishi for their contribution to palladium-catalysed cross couplings in organic synthesis.

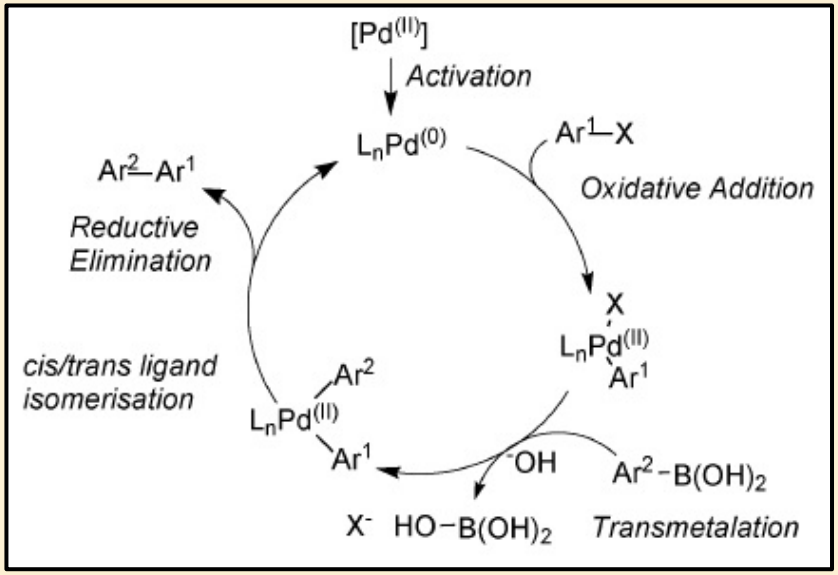
Richard F. Heck

Ei-ichi Negishi

Akira Suzuki

The Suzuki-Miyaura Coupling reaction

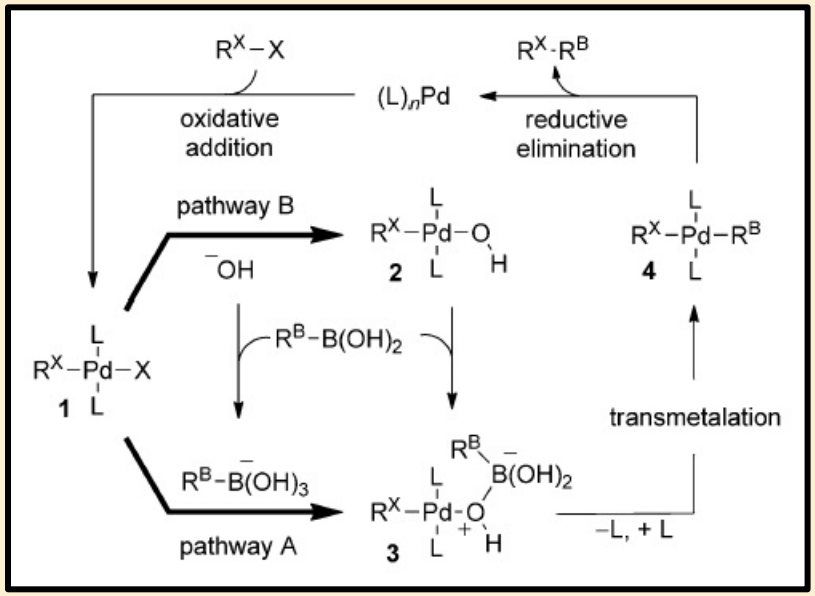
- Follows the generic three-stage “oxidative addition, transmetalation, reductive elimination” sequence.



- Differs from other TMCCCR as it requires a base for activation to proceed.
- OA and RE are well understood, less is known about the transmetalation pathway.
- What is the precise role of the base as an activator in the transmetalation process?
- What are the active transmetalating species?

SM Coupling: The Fork in the Trail

- Ambiguity arises because of two distinct courses of events following the transmetalation pathway.

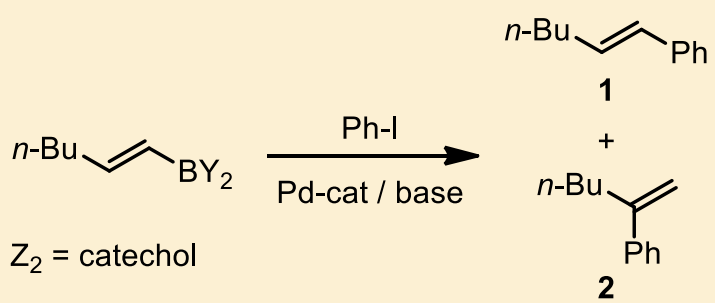


- A) Four-coordinate "active" boron species is preformed and associates with the product of the oxidative addition: <u>The boronate pathway</u>.
- B) Ligand (alkoxy or hydroxy group) on the palladium acts as a Lewis base, generating the four-coordinate species: <u>The oxo-palladium pathway</u>.

SM Coupling: Early Observations

- Initially Suzuki and Miyaura[3,4] proposed that the coupling reaction proceeded through the boronate pathway **A**.
- Detailed study six years later suggested the oxo-palladium pathway **B** was found to be active.[5]
- <u>Findings that led to these conclusions</u>:

1) The type of Lewis base employed matters.[6]

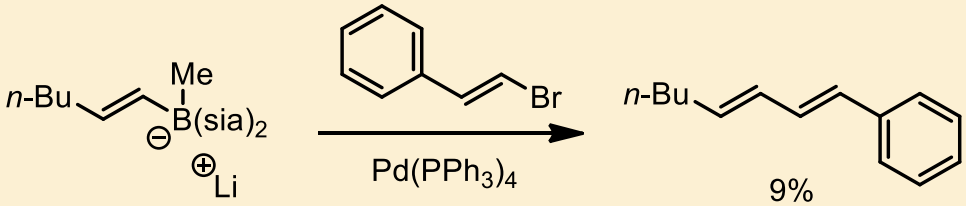


Catalyst	Solvent	Base(eq)	Yield, %(**1**/**2**)
$Pd(PPh_3)_4$	**C_6H_6**	**NaOH (2)**	**99(100/0)**
$Pd(PPh_3)_4$	DMF	Et_3N (5)	54(10/90)
Pd black	**DMF**	**Et_3N (5)**	**94(4/96)**
Pd black	DMF	NaOH (2)	86(56/44)

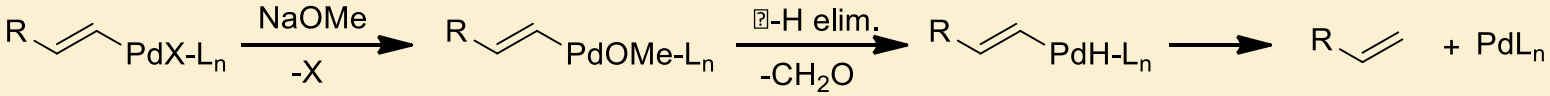
(3) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (4) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866. (5) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972. (6) Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1981**, *213*, C53.

SM Coupling: Early Observation

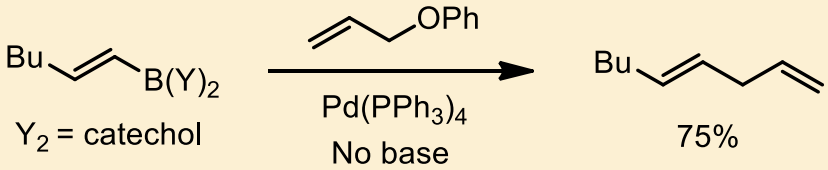
2) Preformed lithium tetra alkylborates couple badly (9%).[5,6]



3) Traces of alkenes (5%), the product of hydro-dehalogenation of the alkenyl halide, was thought to be in support of the oxo-palladium pathway.[5]



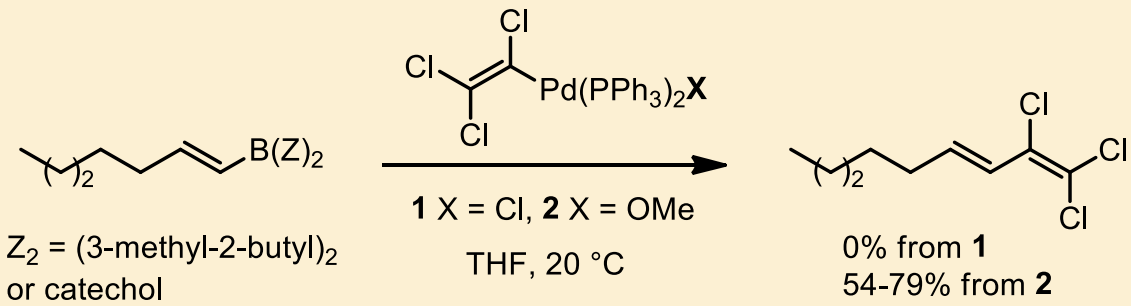
4) Allylic phenoxides and acetates were found to react in the absence of base.[5]



(5) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972. (6) Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1981**, *213*, C53.

SM Coupling: Early Observation

5) Stoichiometric reactions of octenyl boron reagent with isolated complexes **1** and **2**.[5]

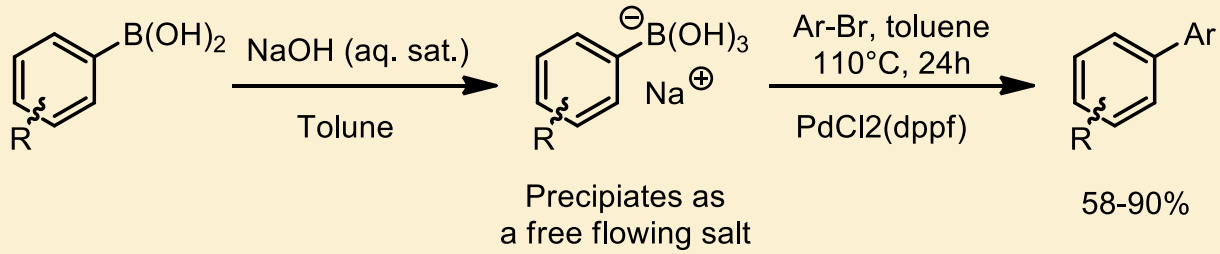


- Overall, it was concluded that after oxidative addition, oxo-palladium intermediates are formed by displacement with base, and <u>this</u> species then captures the neutral organoboron reagent.

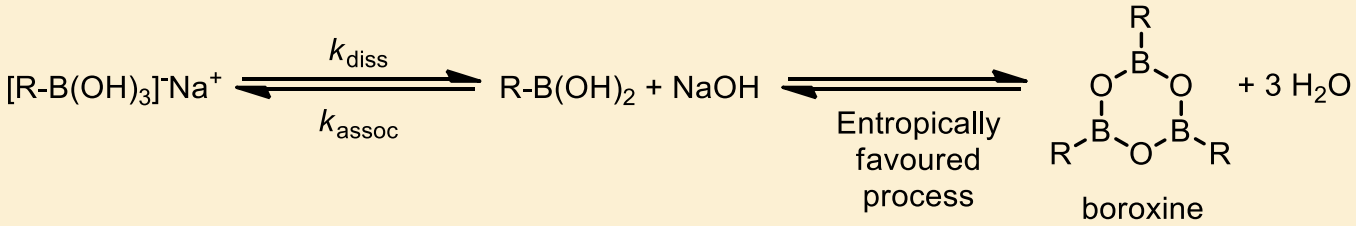
(5) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

SM Coupling: Recent Studies

- Cammidge and co-workers isolated the sodium salt of trihydroxyboronate and used in SM coupling reactions under “no additional” base free conditions.[7]



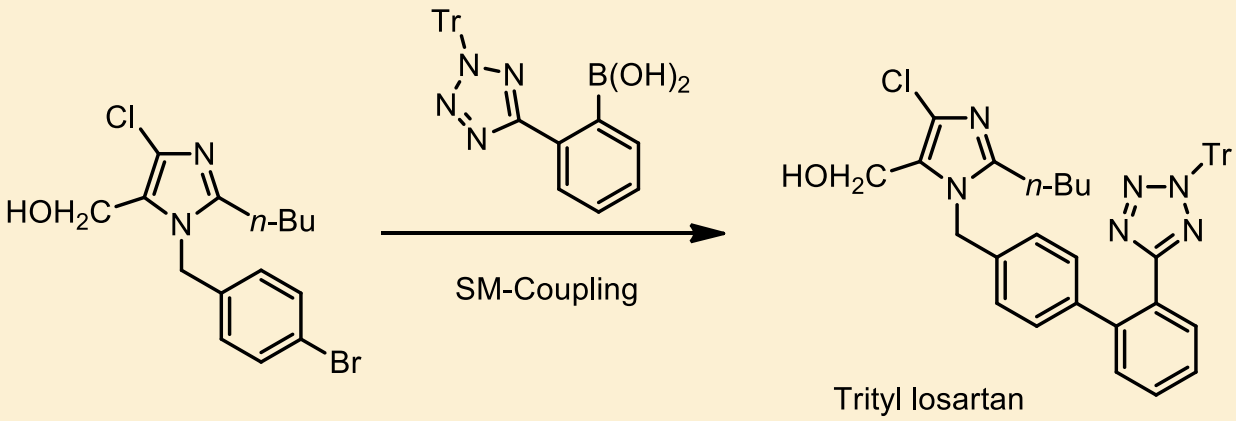
- This result suggests that transmetalation occurs readily through pathway **A**. However, they did not consider the solution-phase associative equilibrium under the reaction conditions.



(7) Cammidge, A. N.; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. J. *Org. Lett.* **2006**, *8*, 4071.

SM Coupling: Recent Studies

- Trityl losartan, a precursor for losartan, is made by a key SM coupling step. Smith and co-workers[8] determined by HPLC data and kinetic modeling that the OA was rate-limiting, concluding that halide dissociative mechanism preceding transmetalation was unlikely.

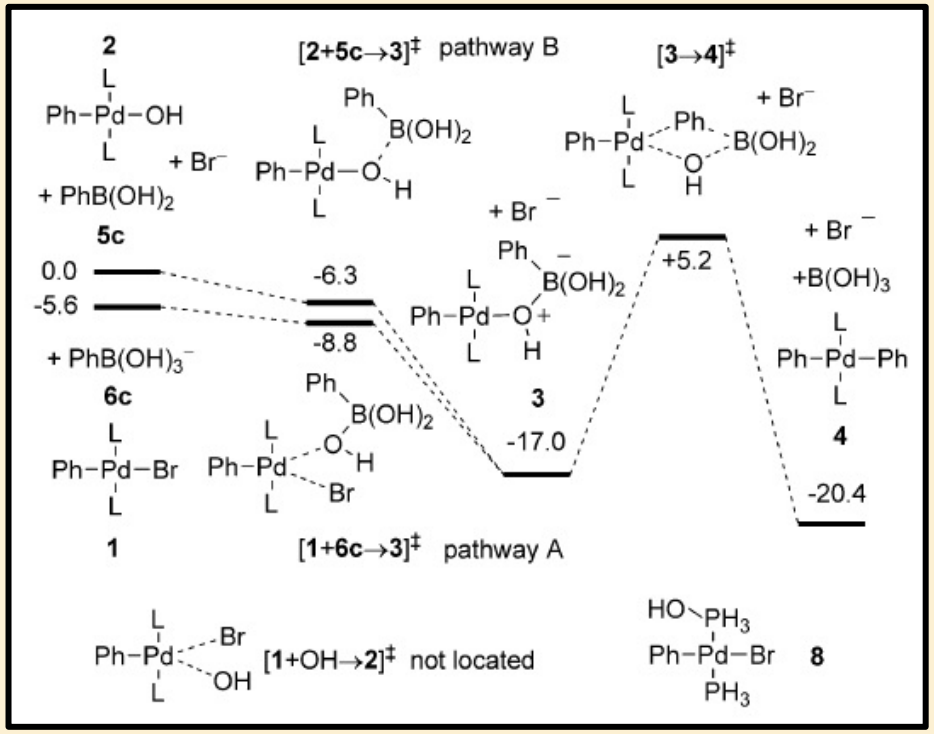


- The reaction failed when bicarbonate was used (pK_a = 6.4) but proceeded smoothly using carbonate (pK_a = 10.3). This was taken as evidence for the generation of trihydroxyboronate ($R\text{-}B(OH)_2$, pK_a = 8.8) as an essential step for coupling *via* the boronate pathway **A**.

(8) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151.

Pathway A or B? Computational Studies

- Maseras and co-workers directly compared pathways **A** and **B** using DFT studies on the transmetalation of vinyl and phenyl boronic acids.[10,11,12]

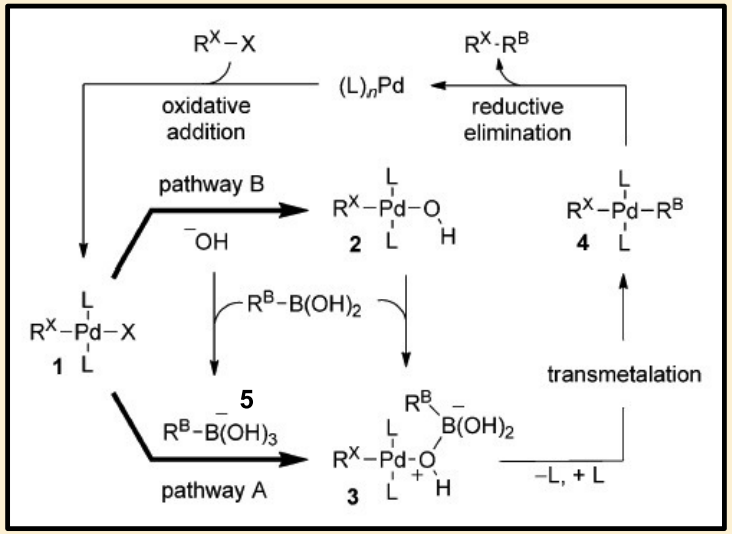


- Without base the reaction does <u>not</u> take place because of high energy barrier.
- Formation of boronate species **6c** almost <u>barrier-less</u> (Pathway **A**).
- **6c** can easily undertake substitution with Br ligand in **1** to form **3** which transmetalates smoothly with Pd to give **4**.
- For pathway **B**, transition state for the direct ligand substitution could <u>not</u> be located (**2**).

(10) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298. (11) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Lledós, A.; Maseras, F. *J. Organomet. Chem.* **2006**, *691*, 4459. (12) Braga, A. A. C.; Ujaque, G.; Maseras, F. *Organometallics* **2006**, *25*, 3647.

SM Coupling: Detection of Intermediates

- ESI-MS was used in a number of studies to analyse transmetalation.[13,14,15]

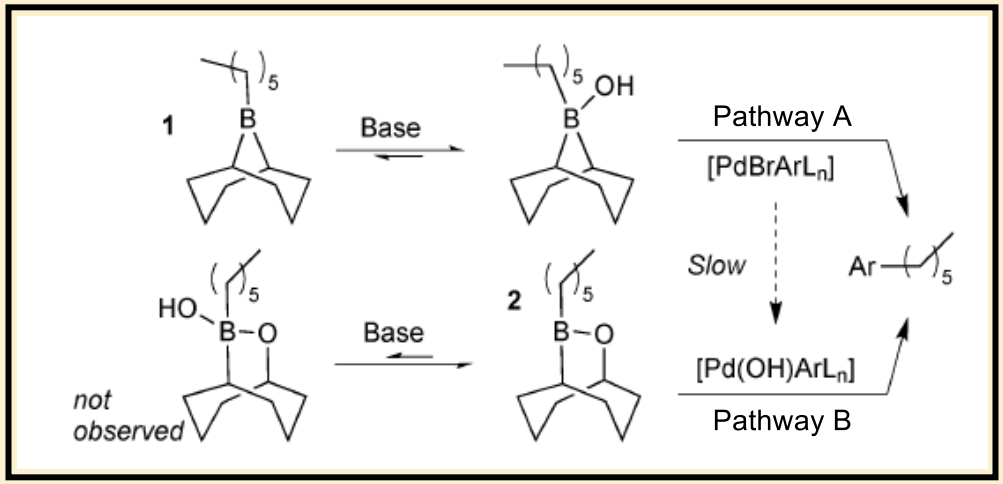


- Boronate species **5** and halide-Pd complex **1**, representing key species of pathway **A**, have both been detected in reaction mixtures.
- Common key intermediate **3** has remained elusive to date.
- No oxo-palladium intermediates have been detected.

(13) Yuen, A. K. L.; Hutton, C. A. *Tetrahedron Lett.* **2005**, *46*, 7899. (14) Nunes, C. M.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2007**, *18*, 1443. (15) Nunes, C. M.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2007**, *18*, 1443.

SM Coupling: Kinetic Studies

- Detailed study by Matos and Soderquist revealed that the transmetalation pathway taken depended on the boron species employed.[9]

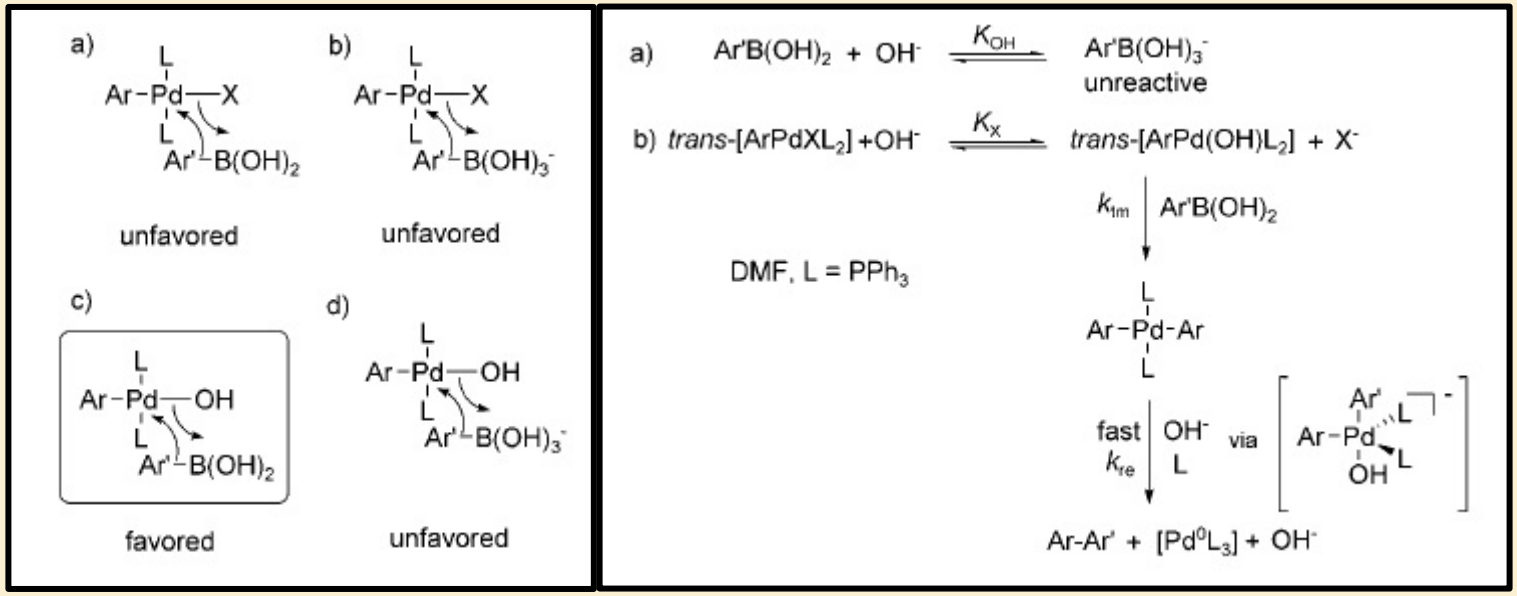


- Lewis acidic alkylborane **1** readily formed boronate complexes (^{11}B NMR) while less acidic boronic ester **2** did not. They also found that OA is rate limiting for **1** while formation of oxo-palladium species is for **2**.

(9) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

SM Coupling: Kinetic Studies

- Amatore and Jutand[16,17,18] employed <u>electrochemical techniques</u> to probe the mechanism and clarify the role of the base. Catalytic conditions were imitated and four transmetalation scenarios were considered.

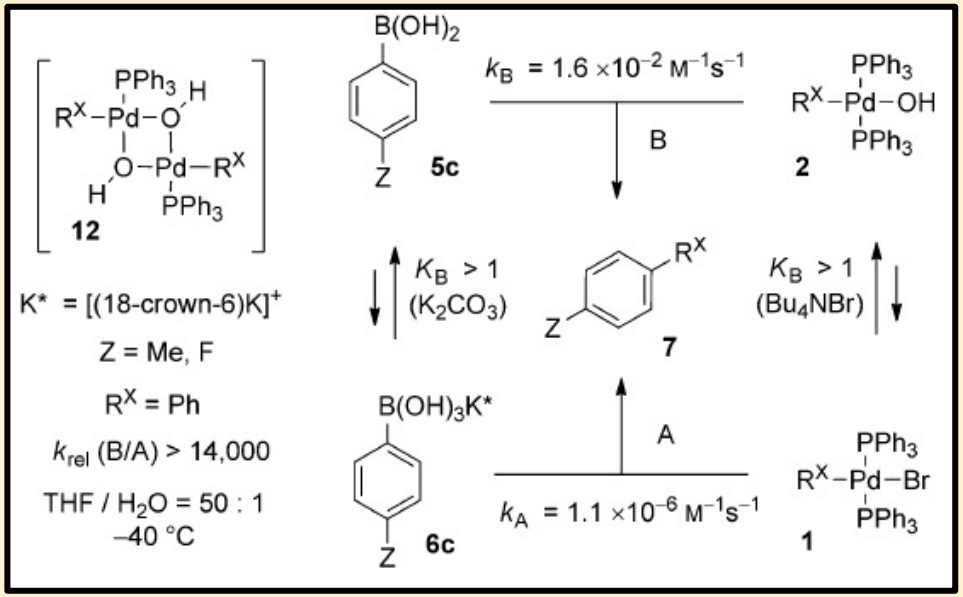


- The base was found to play three roles. **1.** Formation of active oxo-palladium catalyst. **2.** Promotion of reductive elimination. **3.** Formation of poorly reactive hydroxy boronate, retarding the reaction.

(16) Amatore, C.; Jutand, A.; Le Duc, G. *Chemistry* **2011**, *17*, 2492. (17) Amatore, C.; Jutand, A.; Le Duc, G. *Chemistry* **2012**, *18*, 6616. (18) Amatore, C.; Le Duc, G.; Jutand, A. *Chemistry* **2013**, *19*, 10082.

SM Coupling: Kinetic Studies

- Hartwig[19] conducted similar mechanistic studies but employed ^{31}P NMR to measure the decay of palladium species at low temperatures.

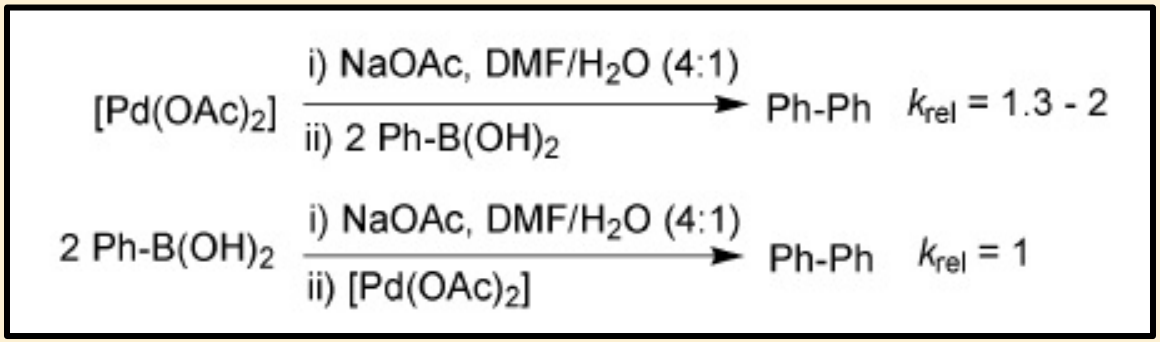


- Transmetalation between **6c** and **1** was found to be much slower than between **5c** and **2** concluding that the oxo-palladium pathway **B** is kinetically more favoured.

(19) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116.

SM Coupling: Kinetic Studies

- Schmidt[1] measured the rates of reaction between boronic acid and an equilibrium mixture of $Pd(OAc)_2$ and NaOAc using UV spectroscopy. This was compared to the rate between $Pd(OAc)_2$ and an eql. mixture of boronic acid and NaOAc.



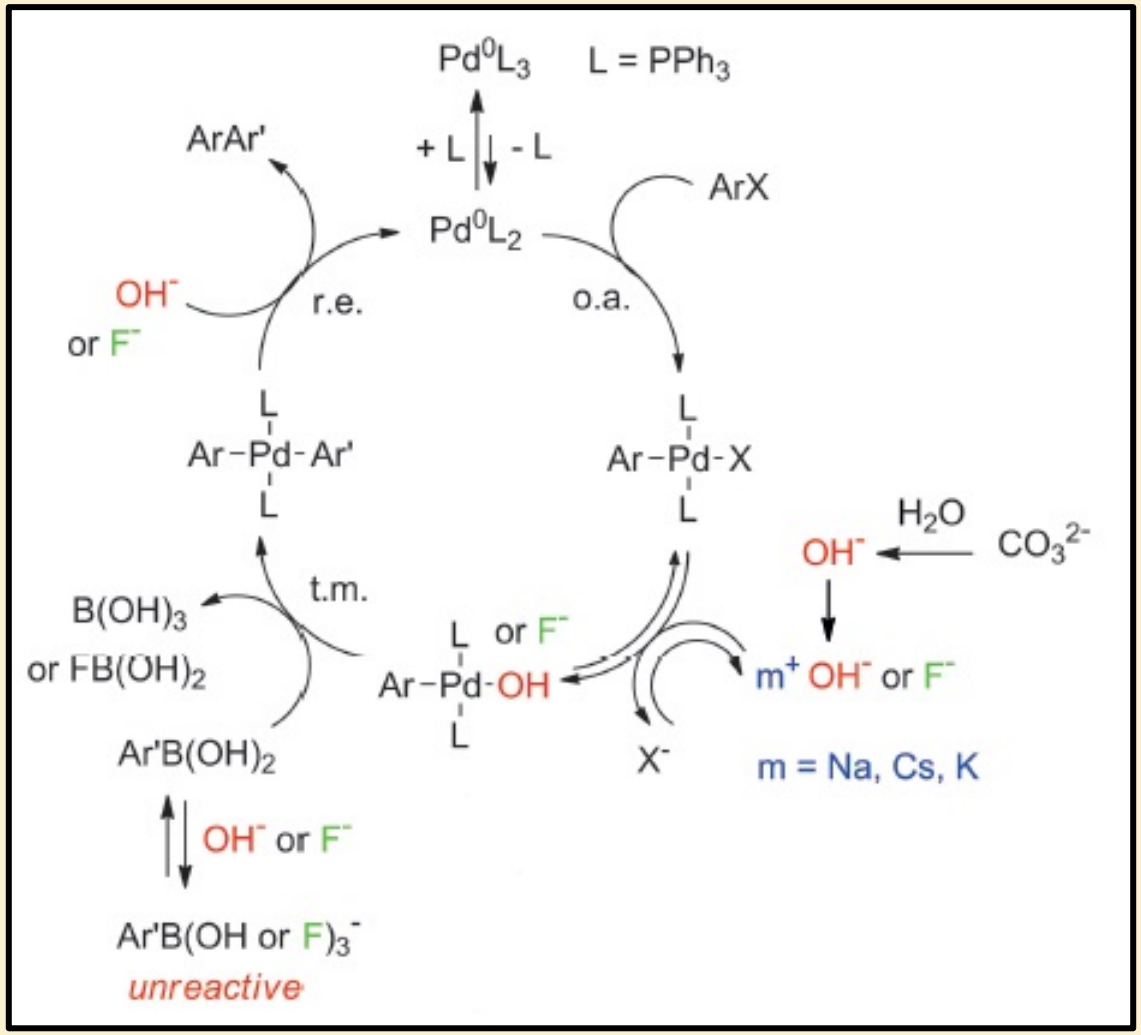
- Formation of biphenyl was 1.3-2 times faster when neutral boronic acid was added, indicating that the oxo-palladium pathway **B** is kinetically favoured.

(20) Schmidt, A. F.; Kurokhtina, A. A.; Larina, E. V. *Russ. J. Gen. Chem.* **2011**, *81*, 1573..

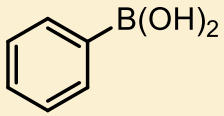
SM Coupling - Conclusion

- The mechanism and the role of the base in the transmetalation step has been of much debate.
- The work of Amatore and Jutand, Hartwig, and Schmidt provide compelling evidence for the catalytic transit through oxo-palladium pathway **B**.
- However, this only applies with some certainty to the coupling of aryl boronic acids.
- There is little or no compelling evidence for boronate pathway **A** except for the work of Matos and Soderquist using the 9-BBN derivatives.
- However, Pathway **A** should not be ruled out.

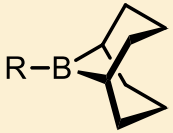
Suzuki-Miyaura Reaction Mechanism Unveiled



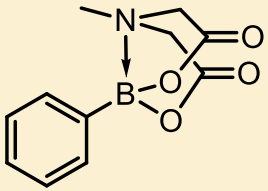
Boron Reagents for SM reaction



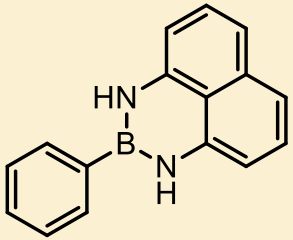
Boronic acid



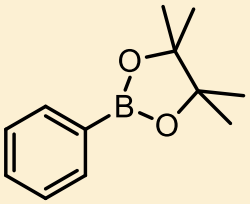
9-BBN borane



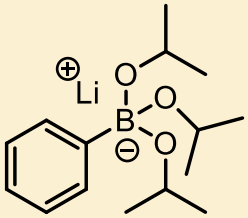
MIDA boronate



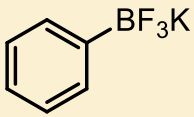
1,8-diaminonaphthyl boronamide



Pinacol boronic ester

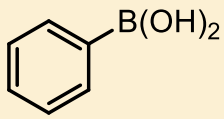


Triisopropyl-boronate

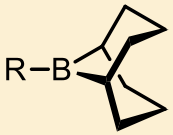


Organotrifluoroborate

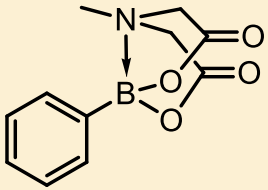
Boron Reagent – Closer Look



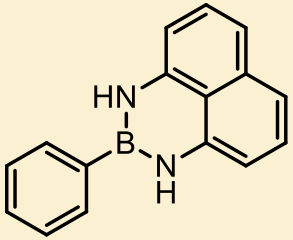
Boronic acid



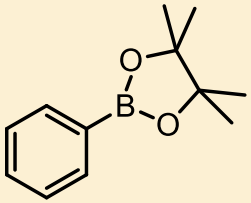
9-BBN borane



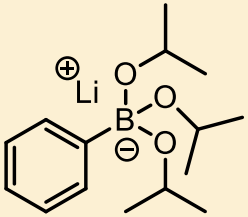
MIDA boronate



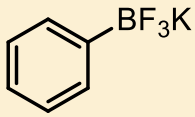
1,8-diaminonaphthyl boronamide



Pinacol boronic ester

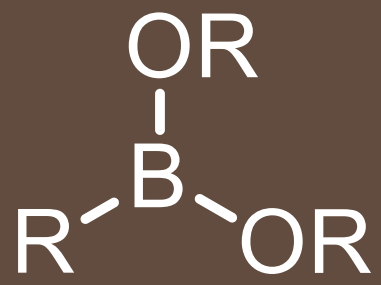


Triisopropyl-boronate



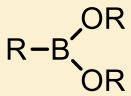
Organotrifluoroborate

BORONIC ESTERS – PROPERTIES, MECHANISM, SYNTHESIS AND APPLICATION

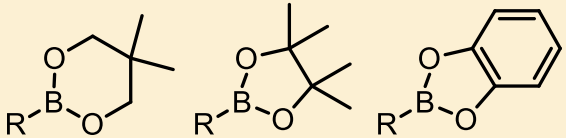


Properties and Mechanism – Boronic Esters

- <u>Properties of boronic esters.</u>
  - <u>Less reactive</u> than boronic acids.
  - Loss of hydrogen bonding makes them less polar and easier to handle.
  - In most cases, boronic esters are <u>stable</u> towards column chromatography.



Boronic Ester

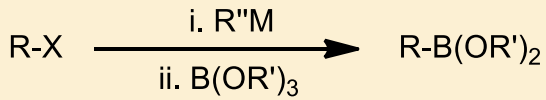


Neopentyl- **Pinacol-** **Catechol**

  - Acyclic boronic esters readily hydrolysed, while cyclic are more robust and are <u>stable</u> to aqueous work-up.
  - Can withstand a wide variety of reaction conditions.
  - Dissolves readily in apolar solvents and are monomeric in nature.
- <u>Mechanism of boronic esters.</u>
  - Not clear what the active transmetalating species is during the Suzuki-Miyaura coupling.
  - Either boronic ester react directly with an oxo-palladium species or it undergoes complete or partial hydrolysis to react *via* the <u>oxo-palladium</u> or <u>boronate pathways</u>.

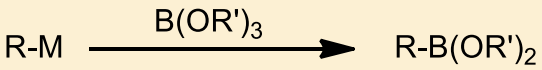
Preperation of Boronic Esters

Electrophilic trapping of alkenyl/aryl-metal intermediates



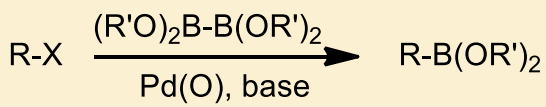
R = aryl, vinyl
X = Br, I
M = Li or Grignard

Transmetalation methods



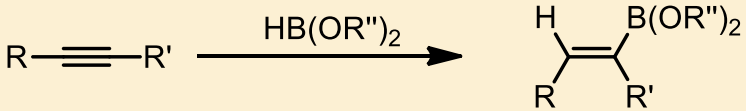
R = aryl, vinyl
M = $ZrCp_2$, $SiMe_3$, $SnMe_3$

Transition metal-catalysed coupling

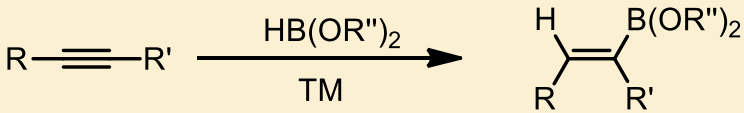


R = aryl, vinyl
X = Br, I, triflates

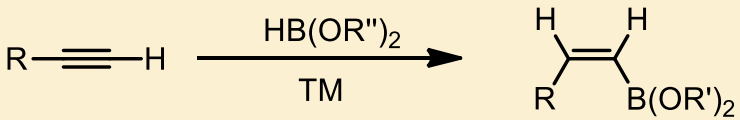
Direct *cis*-hydroboration of alkenes/alkynes



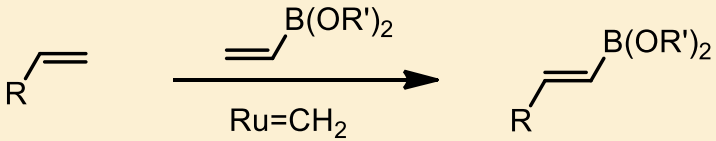
TM catalysed *cis*-hydroboration of alkenes/alkynes



TM catalysed *trans*-hydroboration of alkenes/alkynes

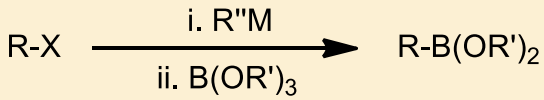


Alkene methathesis



Preperation of Boronic Esters

Electrophilic trapping of alkenyl/aryl-metal intermediates



R = aryl, vinyl
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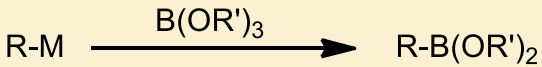
M = Li or Grignard

Transmetalation methods



R = aryl, vinyl
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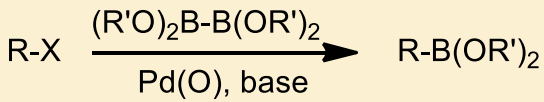
Transition metal-catalysed coupling



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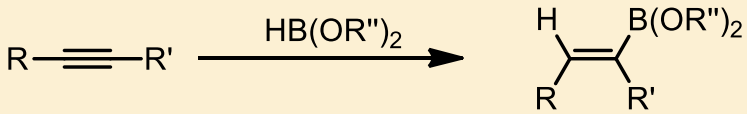
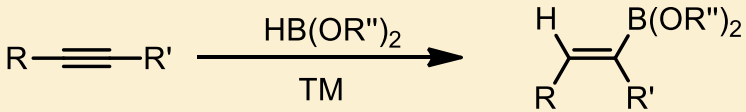
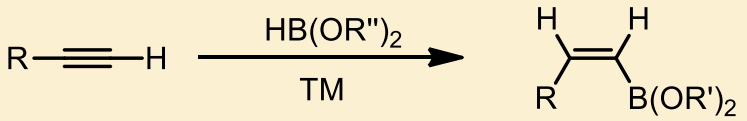
Direct *cis*-hydroboration of alkenes/alkynes



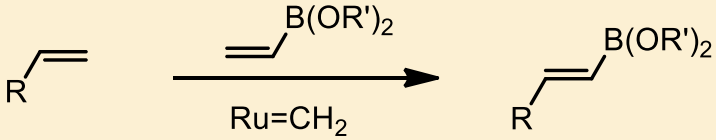
TM catalysed *cis*-hydroboration of alkenes/alkynes



TM catalysed *trans*-hydroboration of alkenes/alkynes

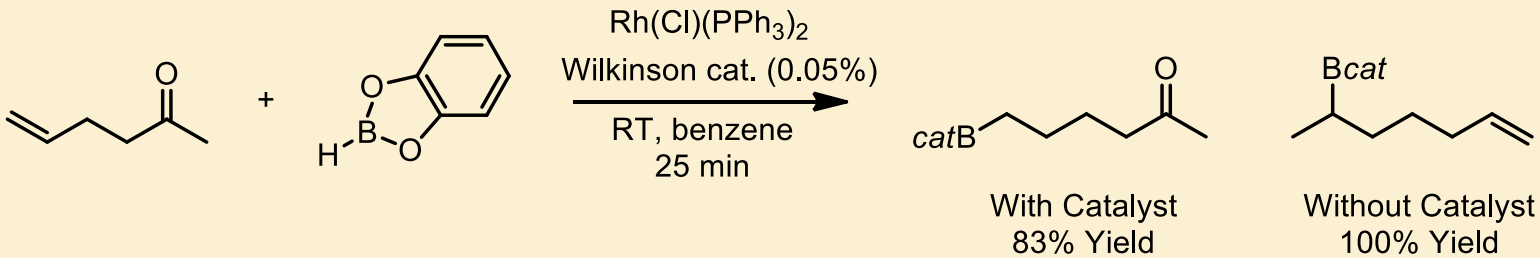


Alkene methathesis



Preperation of Boronic Esters

- <u>Hydroboration of alkenes/alkynes</u>.
  - Direct hydroboration of alkynes, first descriped by Brown[21,22], requires harsh reaction conditions and is functional group sensitive.
  - Nöth reported the first rhodium catalysed selective addition of catecholborane to alkenes[23].

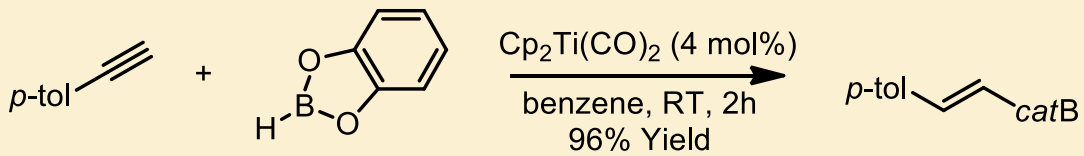


  - Additionally, enantioselectivity can be achieved through use of chiral ligands on rhodium[24,25].
  - Generally does not give satisfactory results with alkynes, because of decomposition observed under rhodium catalysis.

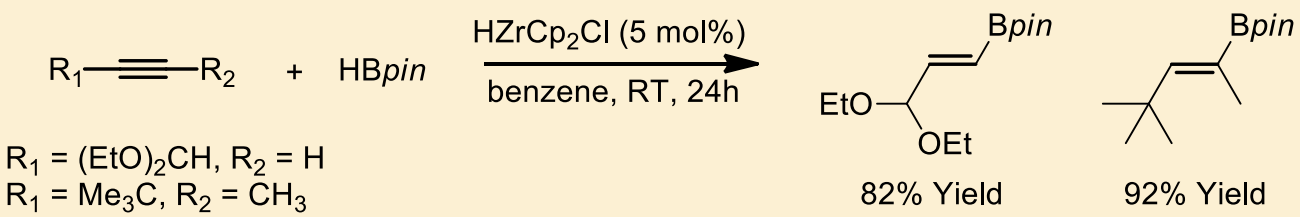
(21) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 1816. (22) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370. (23) Mannig, D.; Nöth, H. *Angew. Chemie Int. Ed. English* **1985**, *24*, 878. (24) Crudden, C. M.; Edwards, D. *European J. Org. Chem.* **2003**, *2003*, 4695. (25) Carroll, A.-M.; O'Sullivan, T.; Guiry, P. *Adv. Synth. Catal.* **2005**, *347*, 609.

Preperation of Boronic Esters

- Hartwig[26] showed that titanocene complexes led to *cis*-hydroboration of <u>terminal</u> alkenes and alkynes without decomposition.



- Pinacol boronic esters can be prepared *via* a highly regio- and stereoselective zirconocene hydroboration of terminal and <u>internal</u> alkynes[27].

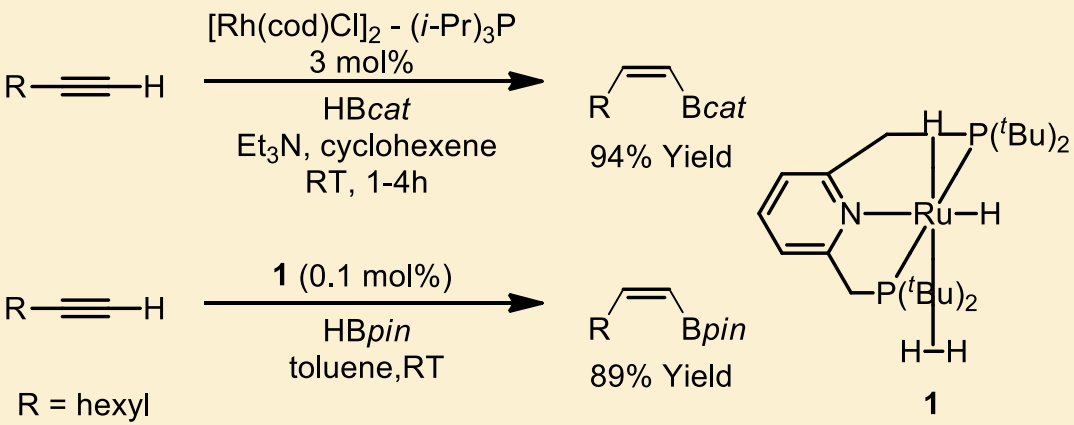


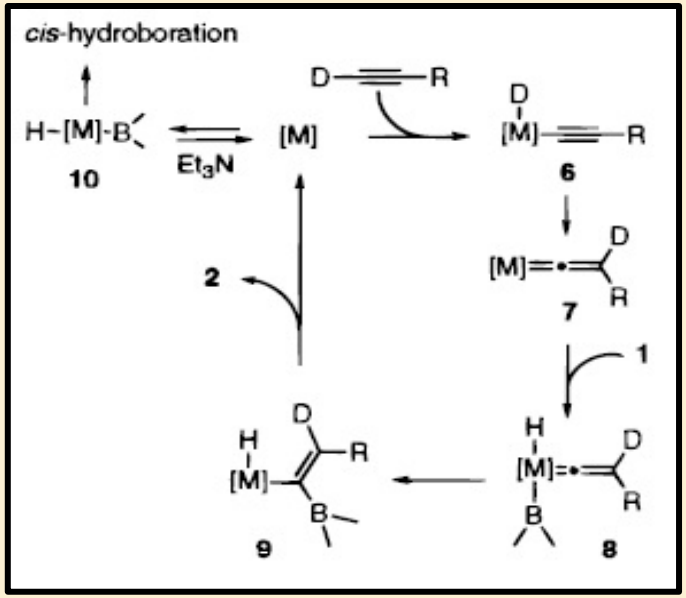
- Plethora of none-precious metal catalyst systems (e.g. Iron and copper) exist, as well as transition metal-free procedures.

(26) He, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 1696. (27) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.

Preperation of Boronic Esters

- Majority of alkyne hydroboration reactions proceed with *syn* addition to give the *trans* alkene. Preparation of the *cis* isomer considerably more challenging.
- Miyaura[27] developed conditions using an *in-situ* generated catalyst from $[Rh(cod)Cl]_2$ and $P(i\text{-}Pr)_3$ as well as employing Et_3N as base. Leitner[28] developed a ruthenium pincer complex without the need for base.

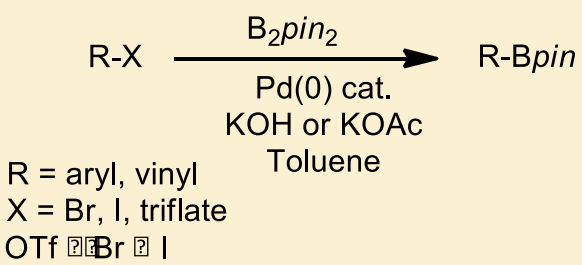




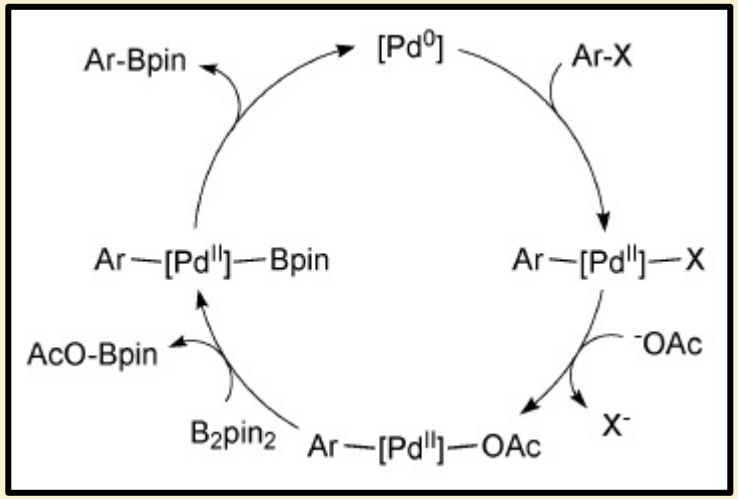
(27) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990. (28) Gunanathan, C.; Hölscher, M.; Pan, F.; Leitner, W. *J. Am. Chem. Soc.* **2012**, *134*, 14349.

Preperation of Boronic Esters

- <u>TM catalysed coupling reactions</u>.
  - Boronic esters can be prepared *via* the <u>Miyaura</u> borylation[28,29].



  - The mildness and high functional group tolerance (e.g. siloxy, chloro, cyano, ester groups) of this tranformation allows access to a wide variety of substrates.
  - Mechanisticly it is closely related to the SM reaction.



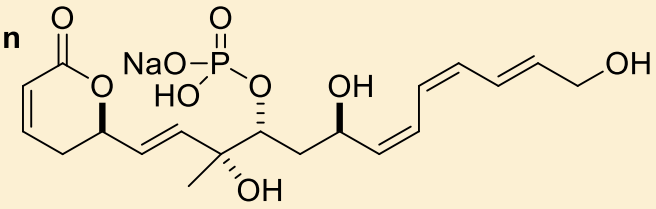
  - Choice of base is crucial to suppress competing SM coupling.
  - Stoichiometric studies established that the oxo-palladium pathway is active.
  - Only half the diboron reagent used.

(28) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (28) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.

Application of Boronic Esters in SM Coupling

- Total synthesis of the natural product fostriecin[30] deploys at least four methodologies derived from Nobel prizes.

Fostriecin



(30) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752.

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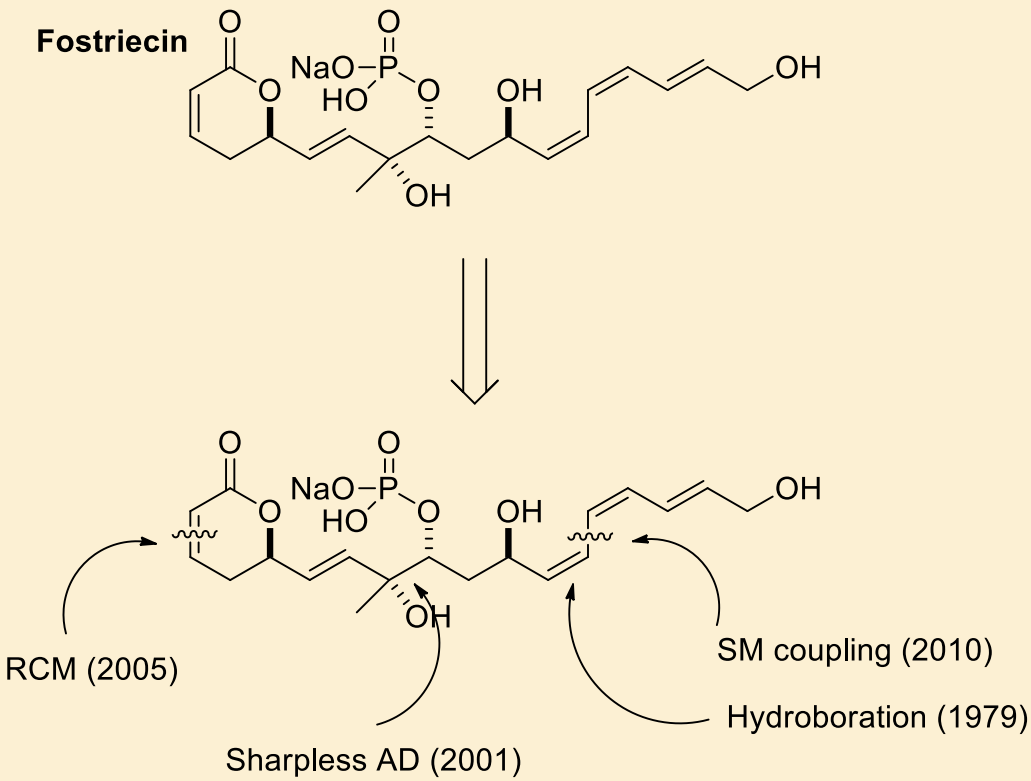
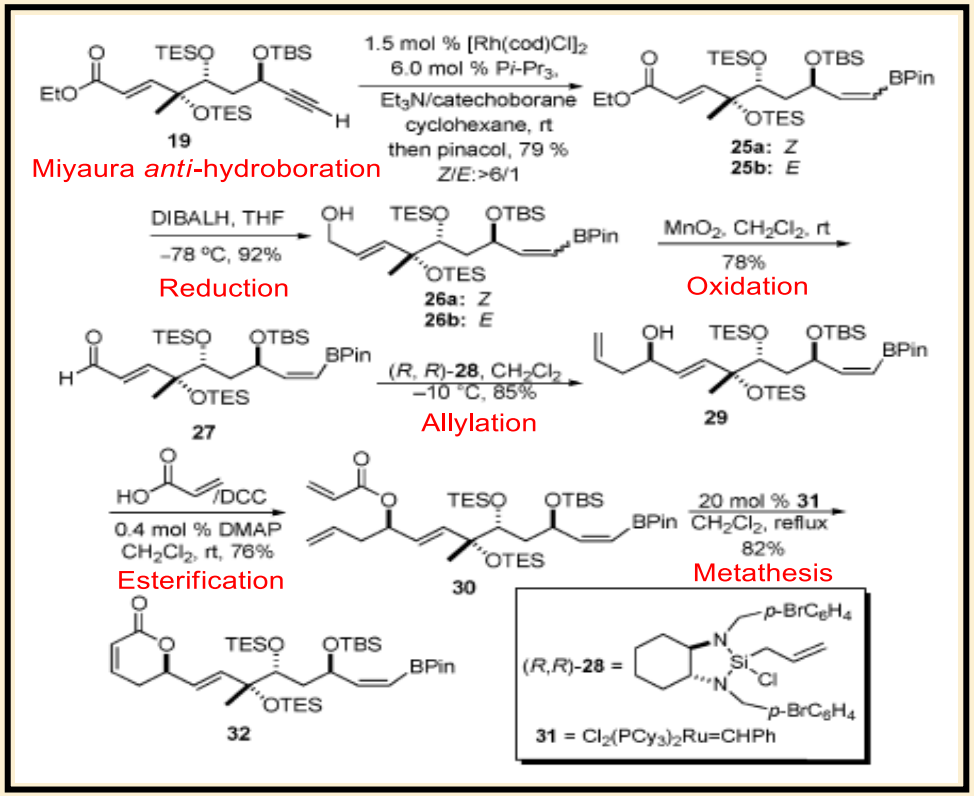


(30) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752.

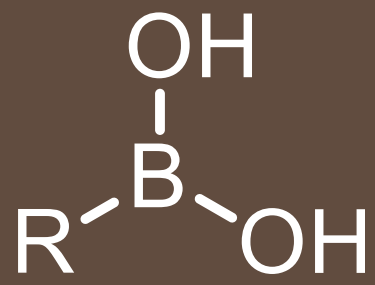
Application of Boronic Esters in SM Coupling

- The pinacol boronic ester formed withstands a number of distal manipulations[30].



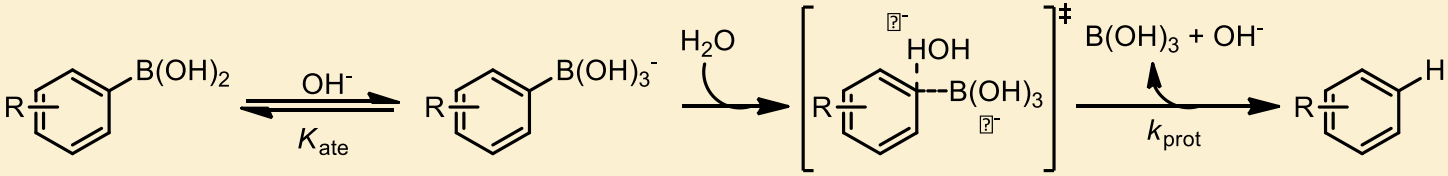
(30) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752.

BORONIC ACIDS – PROPERTIES, MECHANISM, SYNTHESIS AND APPLICATION

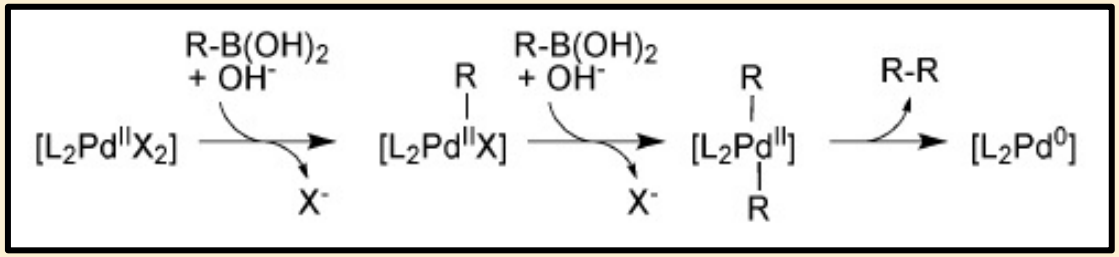


Properties and Mechanism – Boronic Acids

- <u>Properties of boronic acids</u>.
  - Are highly reactive towards transmetalation and are atom efficient.
  - Can be difficult to handle as well as purify, many decompose in air.
  - Are susceptible to side reactions in the SM coupling.
    - Under SM conditions base-catalysed protodeboronation is common[31].



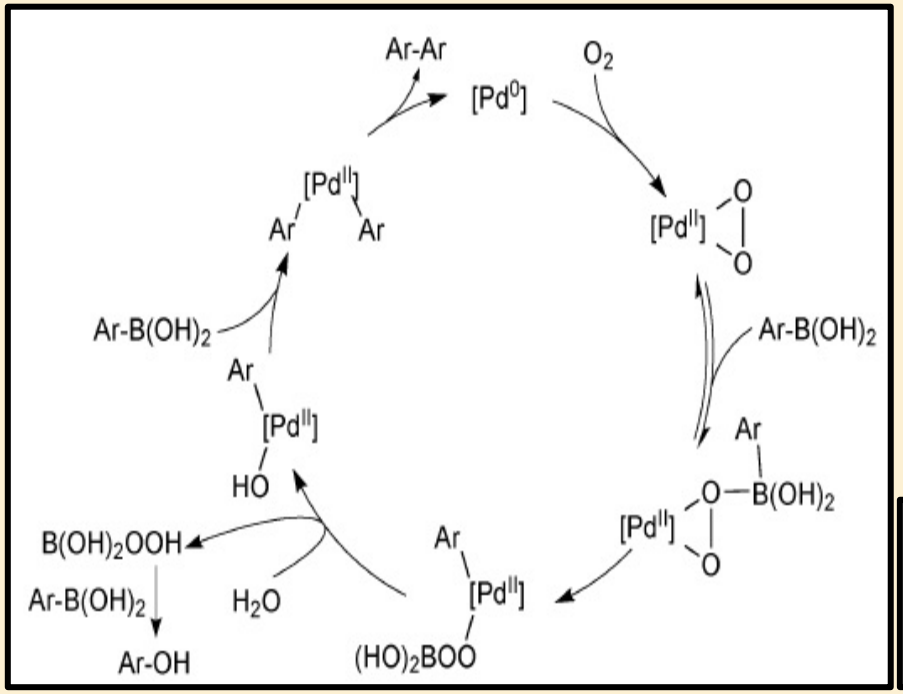
    - Pd(II) can mediate boronic acid homocoupling[32]:
      - Firstly by reductive activation of a Pd(II) precatalyst.



(31) Kuivila, H. G.; Reuwer Jr., J. F.; Mangravite, J. A. *Can. J. Chem.* **1963**, *41*, 3081. (32) Lennox, A.; Lloyd-Jones, G. *Chem. Soc. Rev.* **2014**.

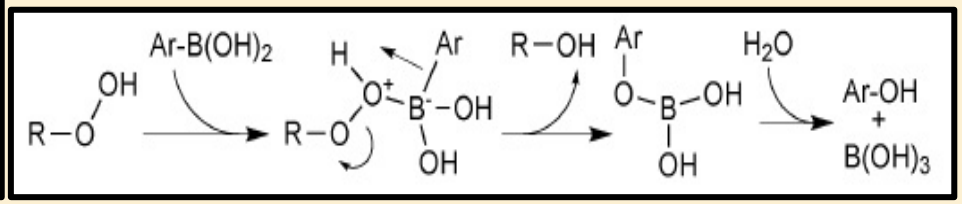
Properties and Mechanism – Boronic Acids

- Secondly, when oxygen enters the system. The mechanism for this catalytic side reaction was investigated by Amatore and Jutand by electrochemical techniques[33].



- The peroxide formed, or aerobically generated, can oxidise the boronic acid giving rise to the third type of side reaction.

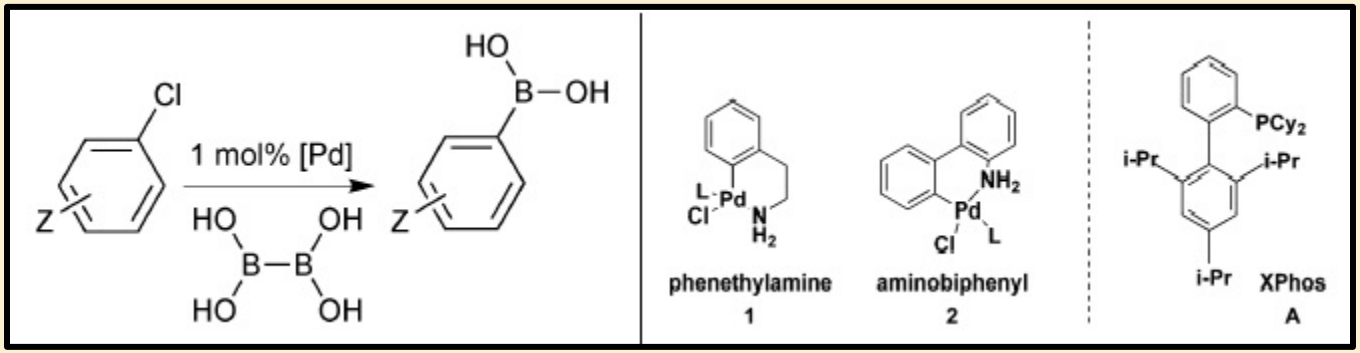
- <u>Mechanism of boronic acids</u>.
  - The *oxo*–palladium pathway is the most likely.



(33) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

Preperation of Boronic Acids

- Generally, boronic acids are generated by hydrolysis of boronic esters.
- For direct preparation, similar methodology to the Miyaura borylation has been developed. Buchwald preformed X-Phos complexes (1 first and 2 second generation) were used in combination with BBA (bisboronic acid)[34,35].

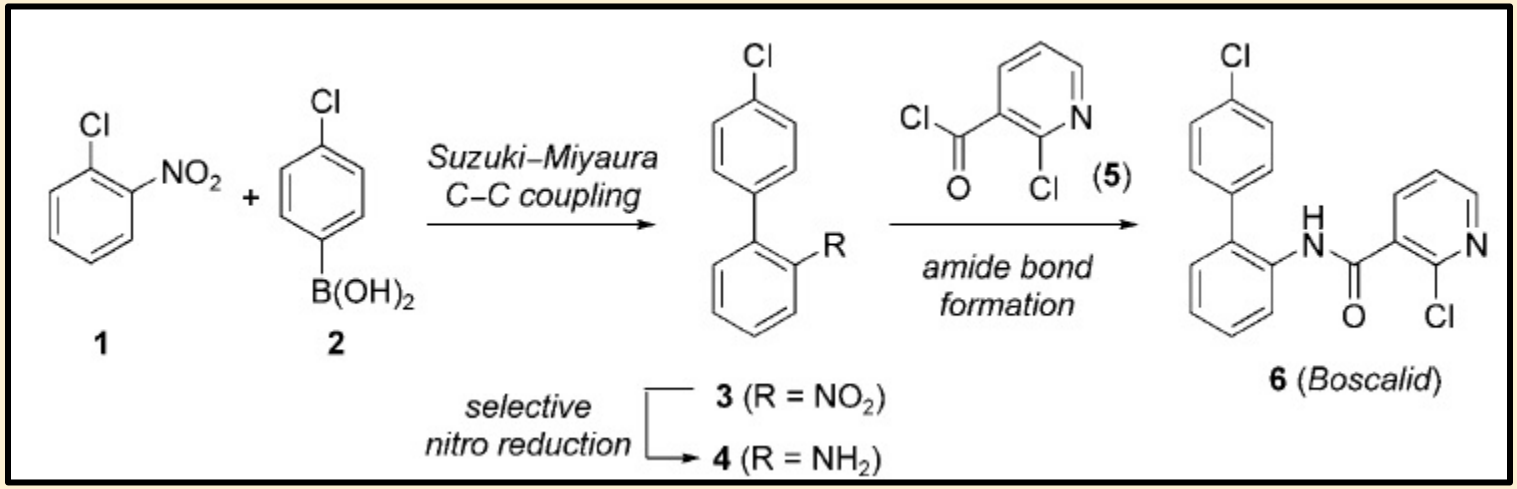


- Good range of functional groups tolerated (major exceptions are aldehydes or nitro groups) and gives moderate to excellent yields.

(34) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701. (35) Molander, G. A.; Trice, S. L. J.; Kennedy, S. M.; Dreher, S. D.; Tudge, M. T. *J. Am. Chem. Soc.* **2012**, *134*, 11667.

Application of Boronic Acids in SM Coupling

- Boronic acids are employed in the industrial preparation of Boscalid, a multipurpose fungicide[32,35].
- Undoubtedly the largest scale SM coupling reaction currently performed.
- More than 1000 tonnes are manufactured per year.



(32) Lennox, A.; Lloyd-Jones, G. *Chem. Soc. Rev.* **2014**. (35) Glasnov, T. N.; Kappe, C. O. *Adv. Synth. Catal.* **2010**, *352*, 3089.

ORGANOTRIFLUOROBORATE SALTS– PROPERTIES, MECHANISM, SYNTHESIS AND APPLICATION

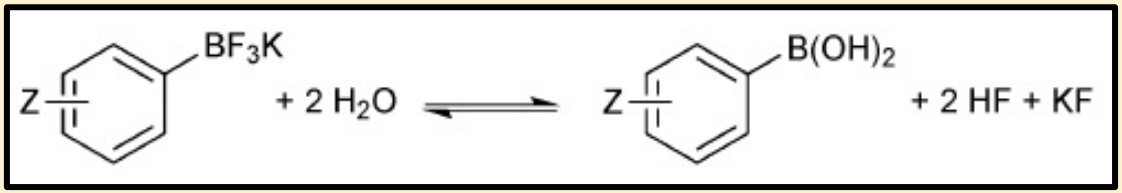
Properties and Mechanism – Organotrifluoroborate Salts

- Properties of organotrifluoroborate salts.
  - Were first reported by Chambers in 1960[36].
  - Have had a resurgence since the mid-1990s and have become a very widely used class of organoboron reagent[32].
  - Contrast to boronic acids and esters are not Lewis acidic.
  - Free-flowing crystalline solids, which are stable to air and moisture thus easy to handle.
  - Chemically robust, withstand many synthetic transformations e.g. Swern and DM oxidations, ozonolysis, Wittig and HWE, condensation reactions and click chemistry.
  - Are unstable to silica-gel and are insoluble in many apolar solvents.
  - Easily purified through crystallisation.

(36) Chambers, R. D.; Clark, H. C.; Willis, C. J. *J. Am. Chem. Soc.* **1960**, *82*, 5298. (32) Lennox, A.; Lloyd-Jones, G. *Chem. Soc. Rev.* **2014**.

Properties and Mechanism – Organotrifluoroborate Salts

- <u>Mechanism of organotrifluoroborate salts</u>.
  - <u>Superior</u> reaction outcome in SM coupling have been reported when OTFB salts have been employed[37].
  - The OTFB <u>not</u> the active transmetalating species[38]. When subjected to aqueous/protic media they hydrolyse to form the boronic acid suggesting the *oxo*-palladium pathway is active.

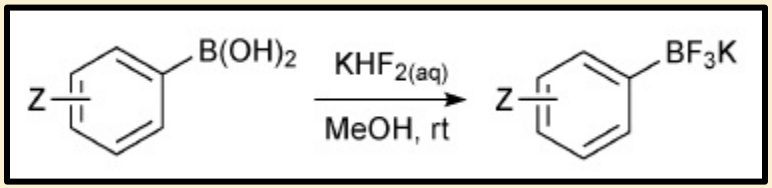


  - This "slow release" mechanism <u>suppresses side reactions</u> commonly involved when boronic acids are used (protodeboration, Pd precatalyst activation, oxidative homocoupling and oxidation).
  - Fluorophiles commonly used to "mop-up" fluoride liberated by hydrolysis or else sacrificing glassware.

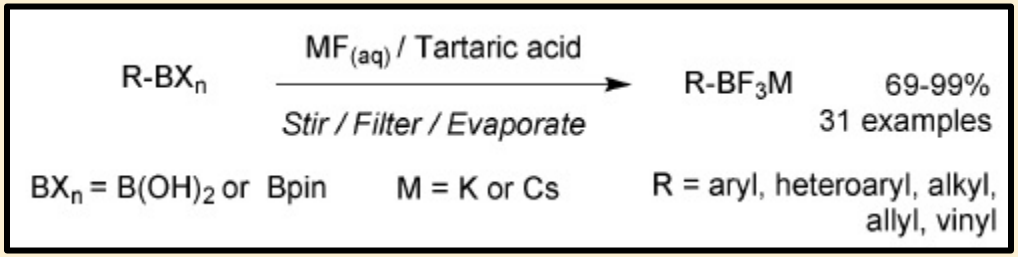
(37) Molander, G. A.; Canturk, B. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 9240. (38) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

Preperation of Organotrifluoroborate salts

- OTFB salts are generated from the corresponding boronic acid or ester.
- Vadejs reported that sat. aqueous KHF_2 converted organoboronic acids to the corresponding OTFB salt. The scope is wide and isolation is achieved by precipitation[39].



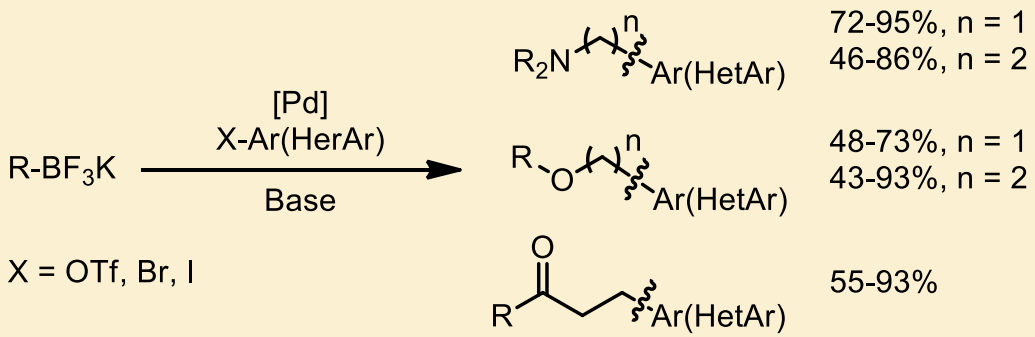
- An alternative method employs KF/tartaric acid, avoiding the use of glass etching KHF_2. Co-products precipitate out of solution and simple filtration, concentration affords the OTFB in good yield[40].



(39) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020. (40) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 9385.

Application of OTFB salts in SM Couplings

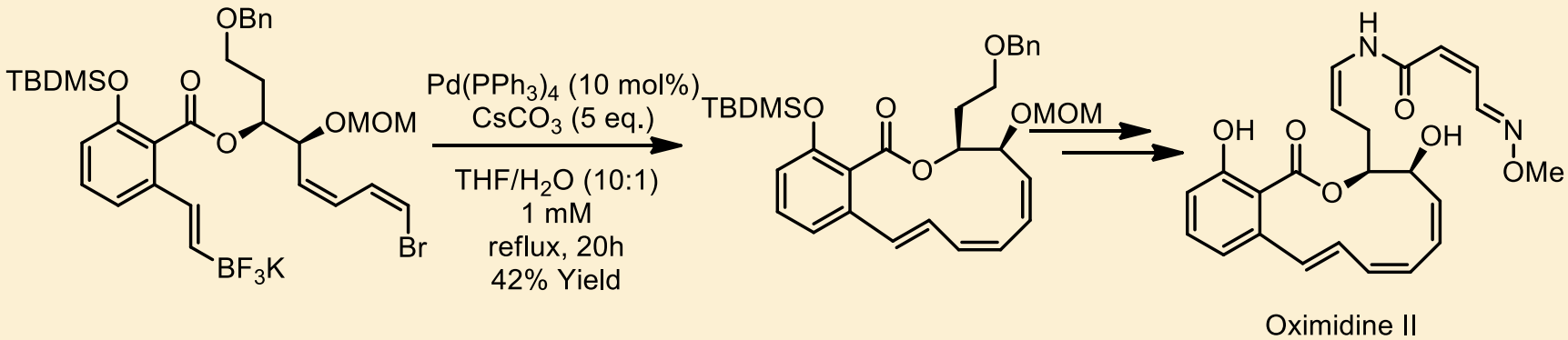
- Cross-coupling of sp_3 systems is <u>challenging</u> due to slow transmetalation, instability towards protodeboronation and competitive β-hydride elimination with reductive elimination.
- Molander has had great success employing OTFB substrates to minimise these side reactions[41,42,43,44,45].



(41) Molander, G. A.; Gormisky, P. E.; Sandrock, D. L. *J. Org. Chem.* **2008**, *73*, 2052. (42) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2007**, *72*, 8422. (43) Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, *10*, 2135. (44) Fleury-Brégeot, N.; Presset, M.; Beaumard, F.; Colombel, V.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2012**, *77*, 10399. (45)Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2009**, *74*, 1297.

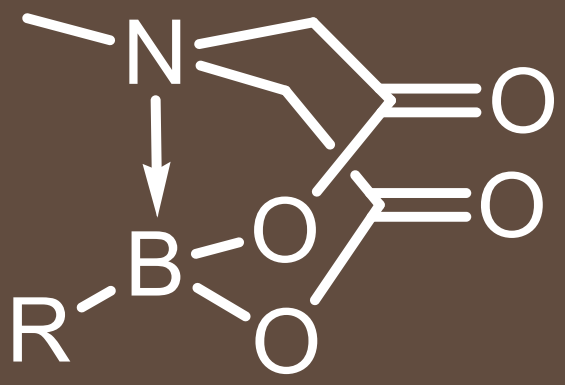
Application of OTFB salts in SM Couplings

- In the formal synthesis of the natural product oximidine II, Molander demonstrated the use of OTFB in the construction of the highly strained, polyunsaturated 12-membered macrolactone.
- The OTFB salt formed was stable for weeks at ambient temperature in air, allowing the development of reaction conditions[46].



(46) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313.

N-COORDINATED BORONATES– PROPERTIES, MECHANISM, SYNTHESIS AND APPLICATION



Properties and Mechanism – N-Coordinated Boronates

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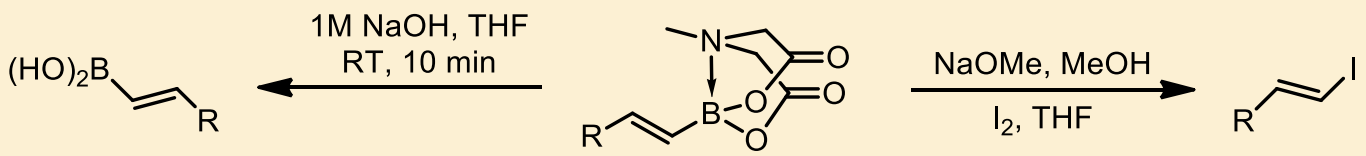
- <u>Properties of N-coordinated Boronates</u>.
  - First prepared and characterised by Contreras in the 1980s[47].
  - Characterised by a nitrogen atom contained in a cyclic boronic ester backbone.
  - Like the OTFB salts, they are free-flowing crystalline solids and can be easily purified by crystallisation.
  - Indefinitely stable to air and moisture and unlike the OTFB salts are <u>stable to silca-gel chromatography,</u> and are soluble in many organic solvents.
  - Chemically robust but incompatible with hard nucleophiles e.g. $LiAlH_4$, DIBALH, TBAF and metal alkoxides.

(47) Contreras, R.; García, C.; Mancilla, T.; Wrackmeyer, B. *J. Organomet. Chem.* **1983**, *246*, 213.

Properties and Mechanism – N-Coordinated Boronates

- Are stable under "anhydrous" SM conditions but can be efficiently hydrolysed to give the boronic acid by aqueous NaOH.
- Not only can they act as masked boronic acids but elelctrophilic organo-halides as well[48].

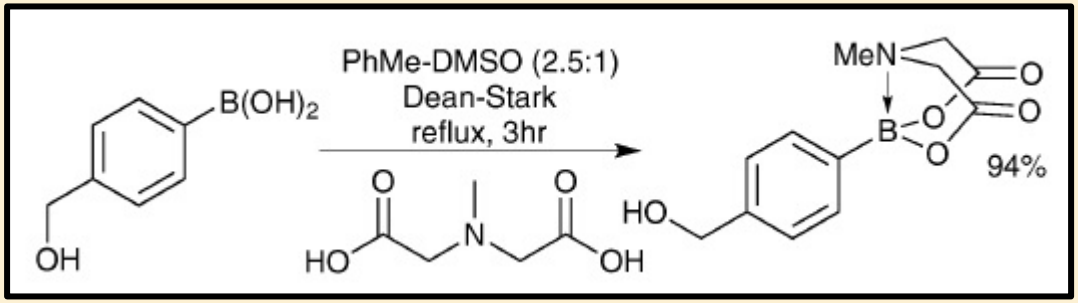


- Mechansim of N-coordinated Boronates.
  - *Oxo*-palladium pathway most likely pathway for transmetalation.

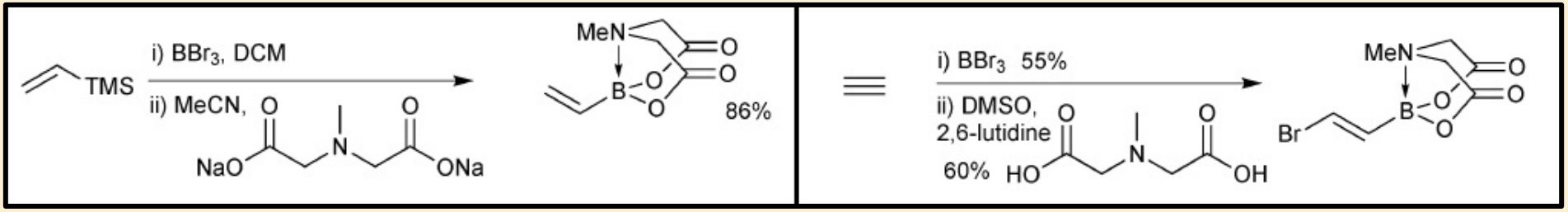
(48) Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17.

Preperation of N-Coordinated Boronates

- Generally prepared by condensation of boronic acids with diethanolamine based ligands[48].



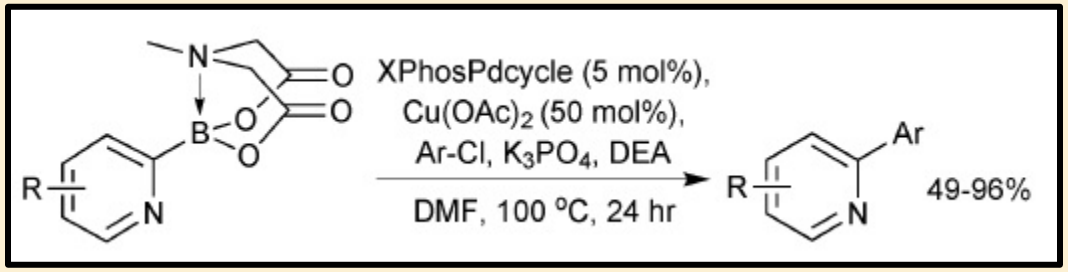
- Alternative methods include trapping of bromoborane species[48].



(48) Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17.

Application of N-Coordinated Boronates

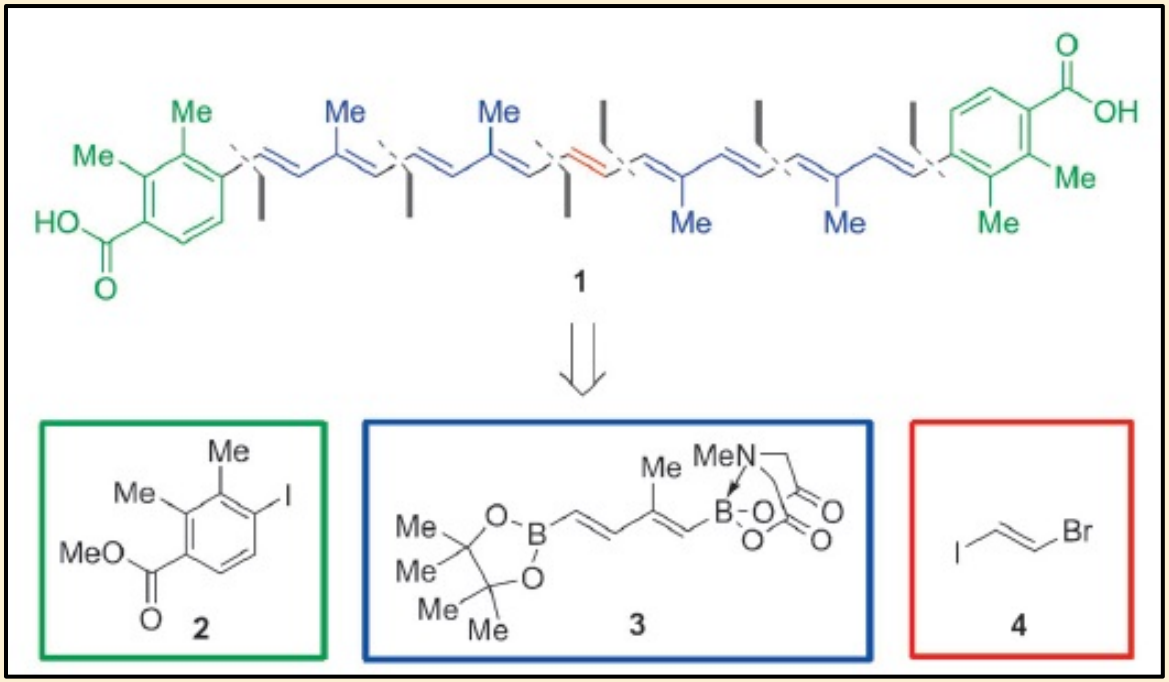
- Although they are stable under SM reaction condition the MIDA boronates are slowly hydrolysed releasing the boronic acid.
- This feature has been exploited for cross-coupling of 2-pyridyl substrates which are notoriously unstable towards protodeboronation[49].



(49) Dick, G. R.; Woerly, E. M.; Burke, M. D. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 2667.

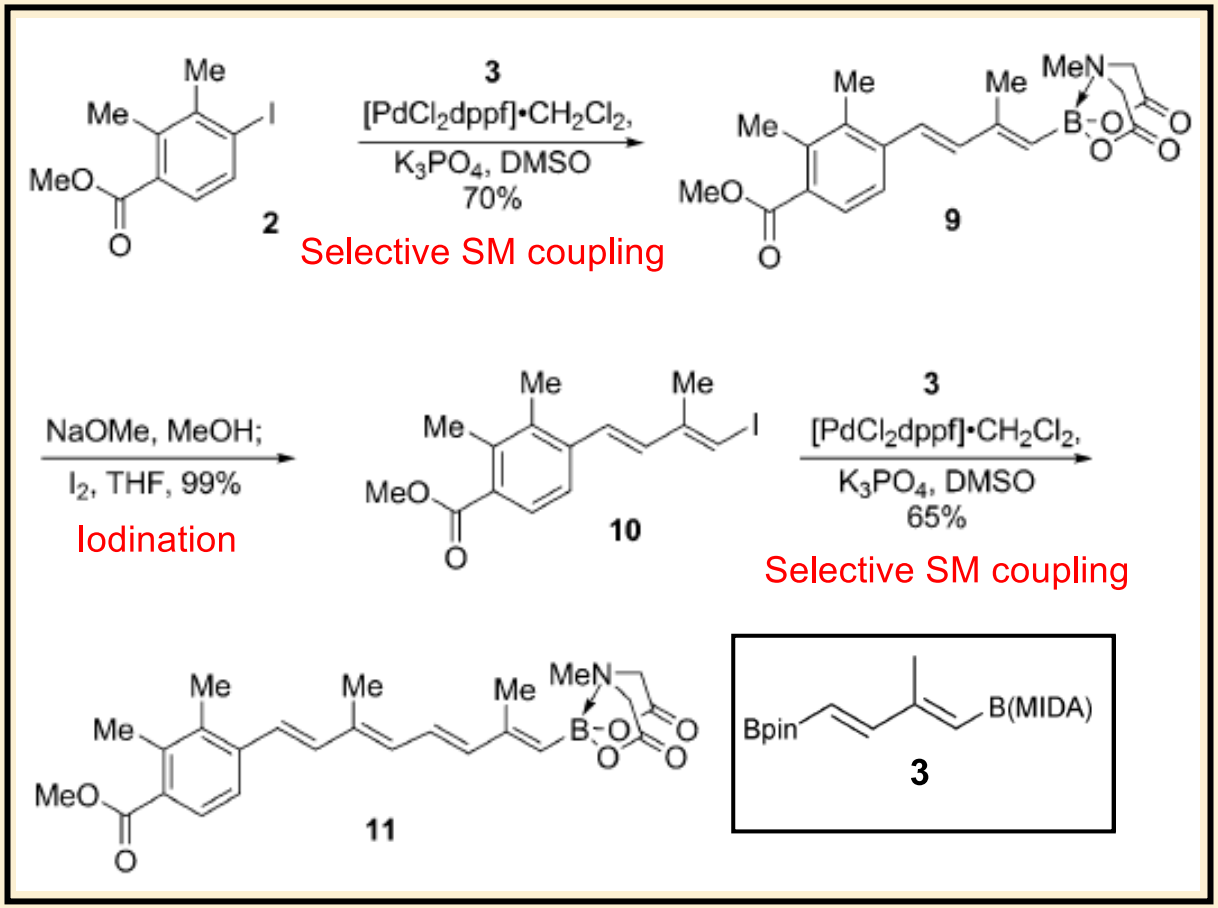
Application of N-Coordinated Boronates

- The stability of MIDA boronates towards SM reaction conditions, their selective hydrolyses as well as the ability to act as masked electrophilic organic halides was exploited beautifully by Burke for the synthesis of synechoxanthin[50].

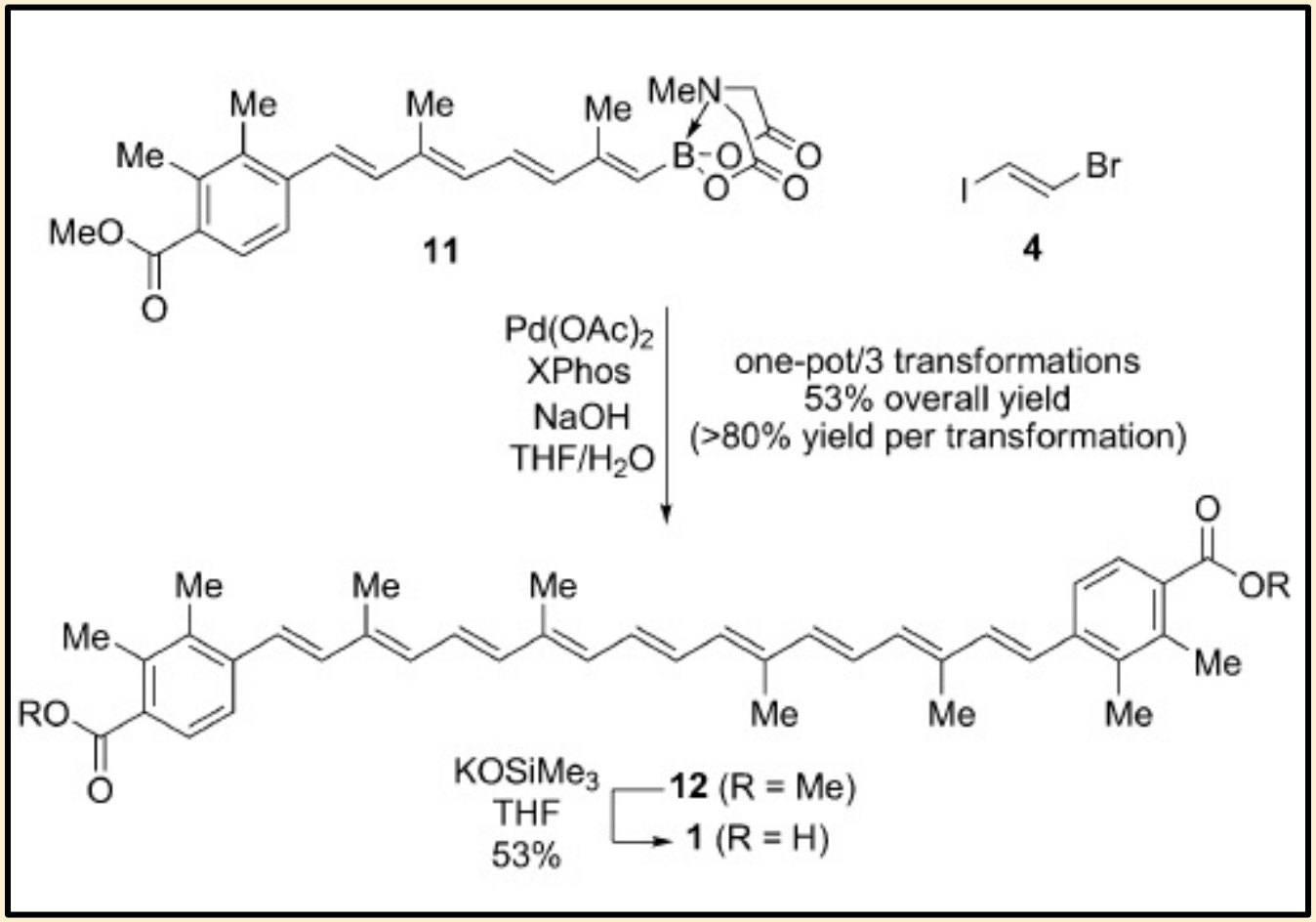


(50) Fujii, S.; Chang, S. Y.; Burke, M. D. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 7862..

Application of N-Coordinated Boronates



Application of N-Coordinated Boronates



Finally....