

# **Development of an effective extension method of carbon chain using new boronates**

**2022.9.24. Literature Seminar  
M1 Hisahiro Morozumi**

# Contents

## 1. Introduction

## 2. Background

## 3. Development of an effective extension method of carbon chain using new boronates

**nature**

Article

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# Automated iterative $Csp^3$ –C bond formation

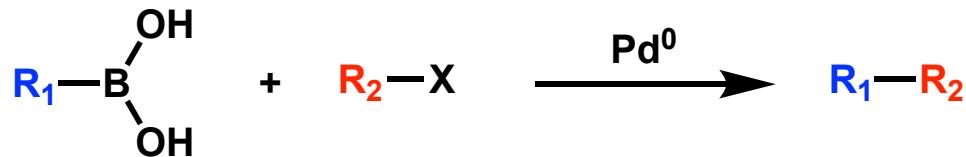
Daniel J. Blair<sup>1✉</sup>, Sriyankari Chitti<sup>1</sup>, Melanie Trobe<sup>1</sup>, David M. Kostyra<sup>1</sup>, Hannah M. S. Haley<sup>1</sup>, Richard L. Hansen<sup>2</sup>, Steve G. Ballmer<sup>2</sup>, Toby J. Woods<sup>3</sup>, Wesley Wang<sup>1</sup>, Vikram Mubayi<sup>1</sup>, Michael J. Schmidt<sup>1</sup>, Robert W. Pipal<sup>1</sup>, Greg. F. Morehouse<sup>1</sup>, Andrea M. E. Palazzolo Ray<sup>1</sup>, Danielle L. Gray<sup>3</sup>, Adrian L. Gill<sup>2</sup> & Martin D. Burke<sup>1,4,5,6✉</sup>

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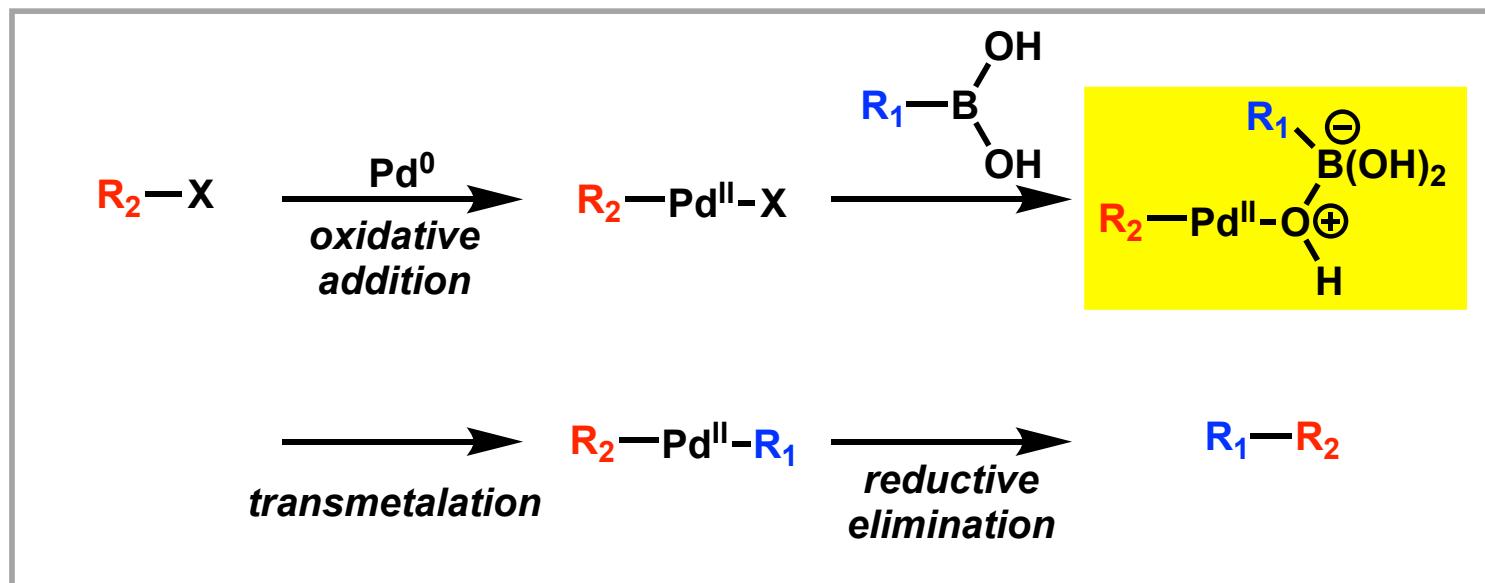
# Suzuki-Miyaura Coupling

Suzuki-Miyaura coupling



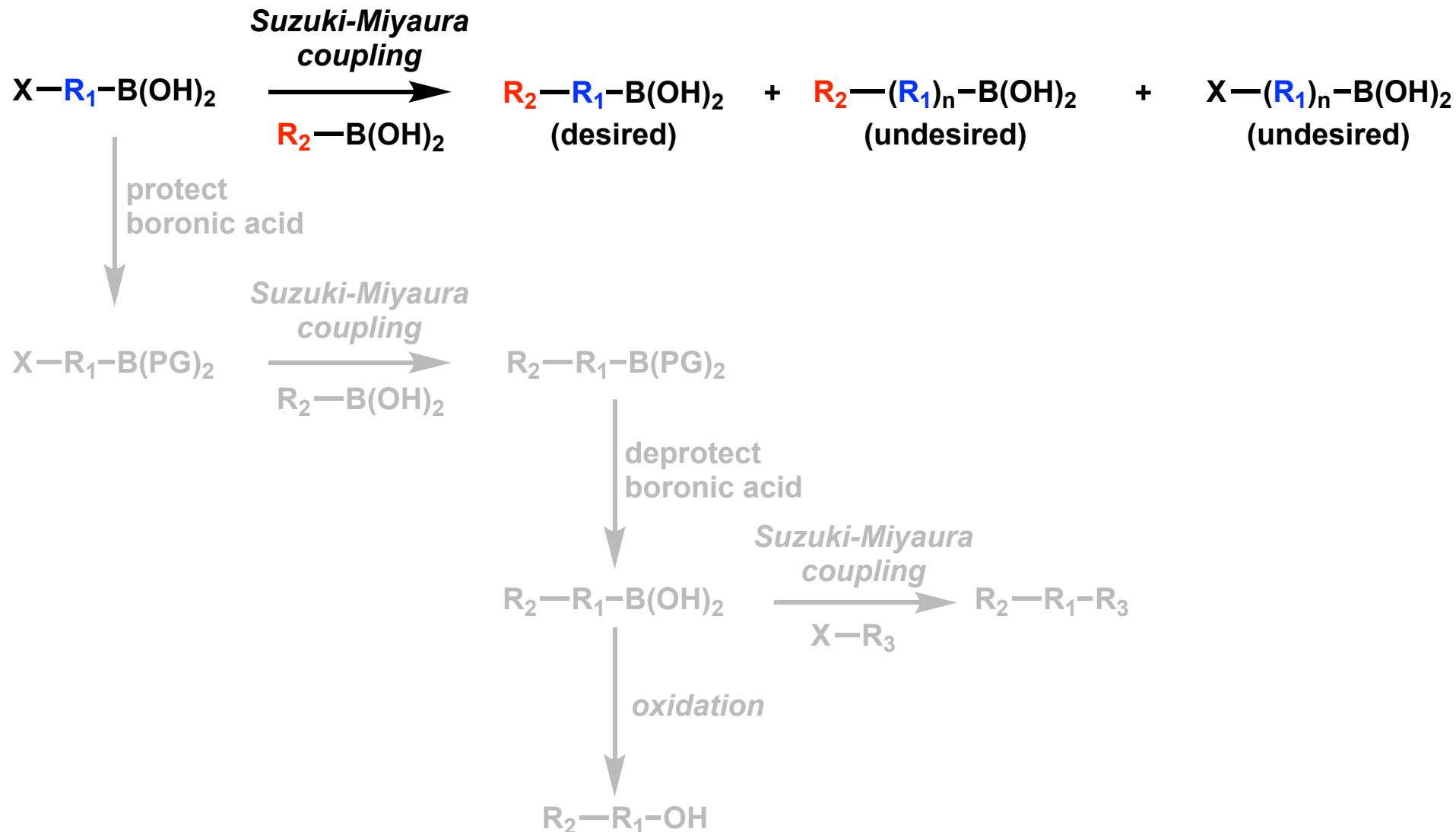
- inexpensive to prepare
- broad functional-group tolerance
- high stability of the organoboron compounds toward air and moisture

Simplified generic mechanism



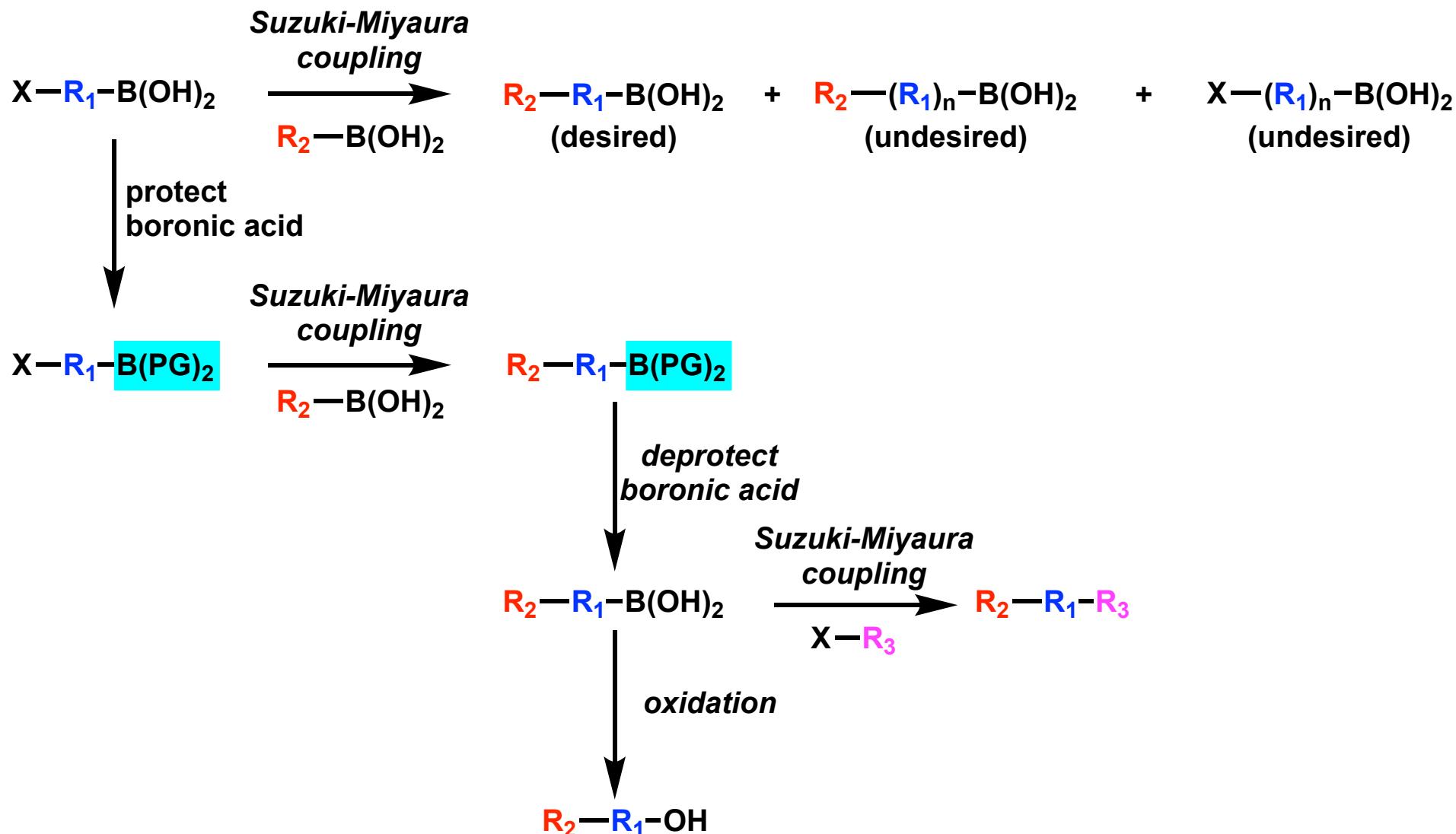
1) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2013**, 52, 7362-7360.

# Chain Extension by Suzuki-Miyaura Coupling



It is thought that by lowering the Lewis acidity of the boron atom, the reactivity of organoboronic acid can be suppressed.

# Chain Extension by Suzuki-Miyaura Coupling



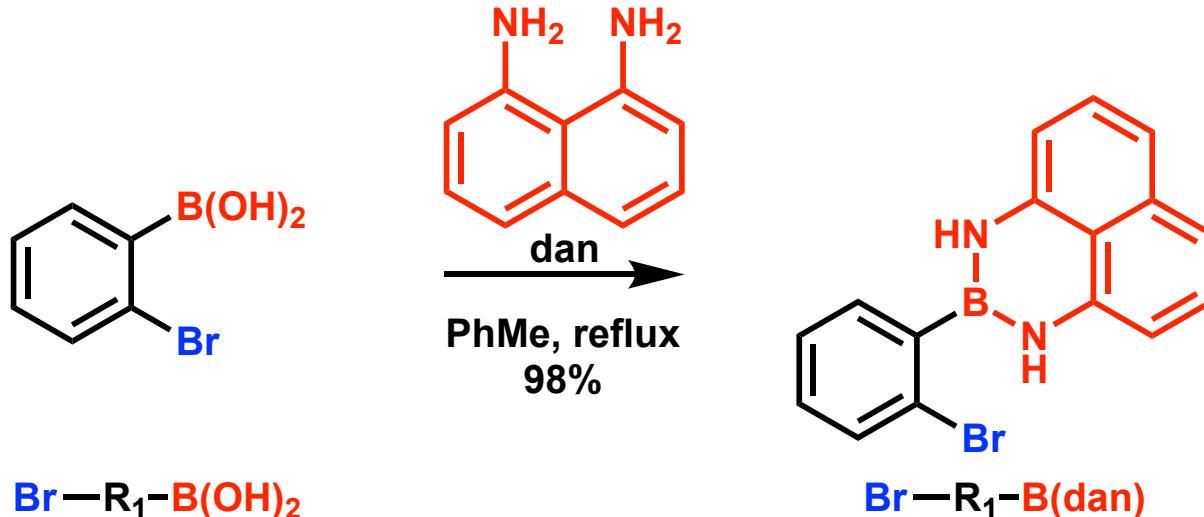
It is thought that by lowering the Lewis acidity of the boron atom, the reactivity of organoboronic acid can be suppressed.

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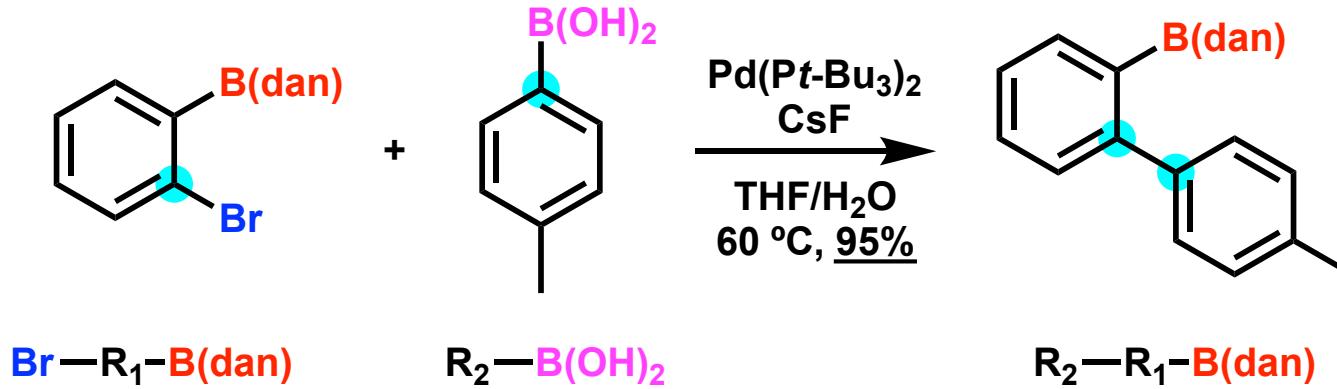
- 1. Introduction**
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# Protect Boronic Acid (1)

1. protecting boronic acid by 1,8-diaminonaphthalene (dan)<sup>1)</sup>



2. Site-selective Suzuki-Miyaura coupling

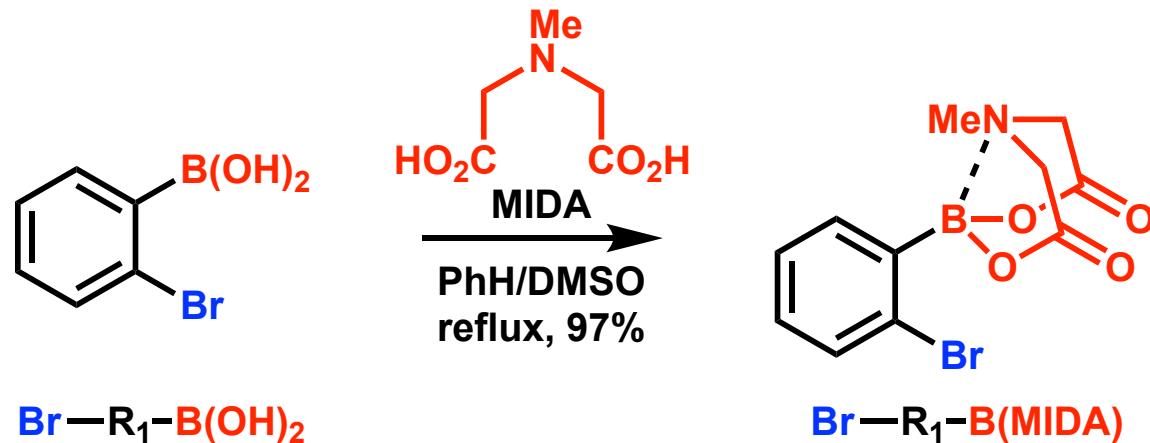


Completely site-selective Suzuki-Miyaura coupling was achieved.

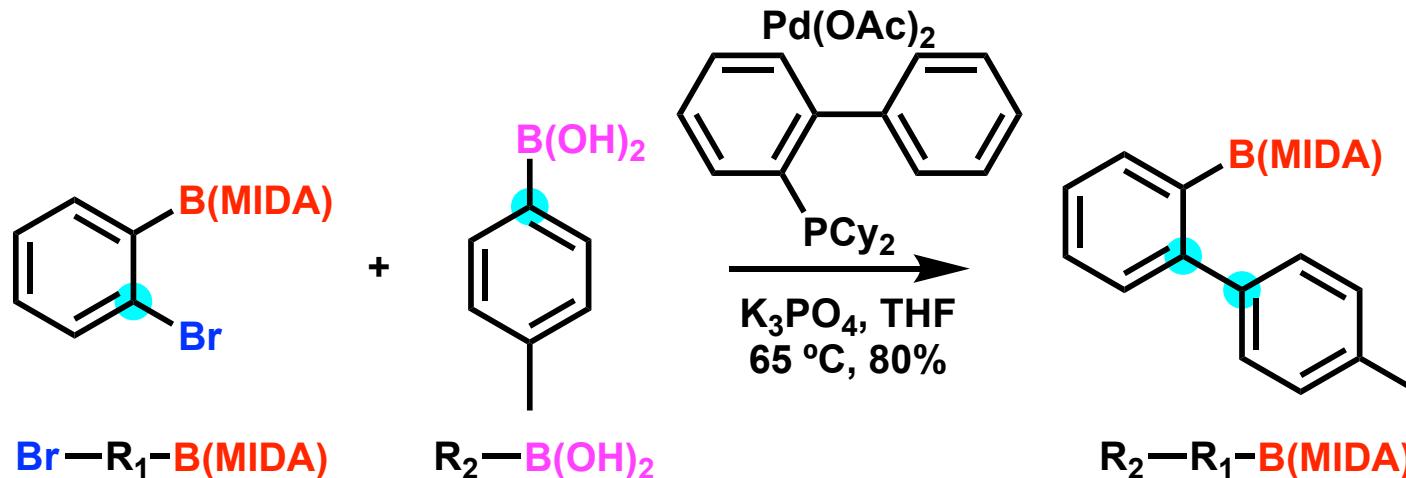
1) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, 129, 758-759

# Protect Boronic Acid (2)

## 1. protecting boronic acid by *N*-methylimino*d*iacetic acid (MIDA)<sup>1</sup>

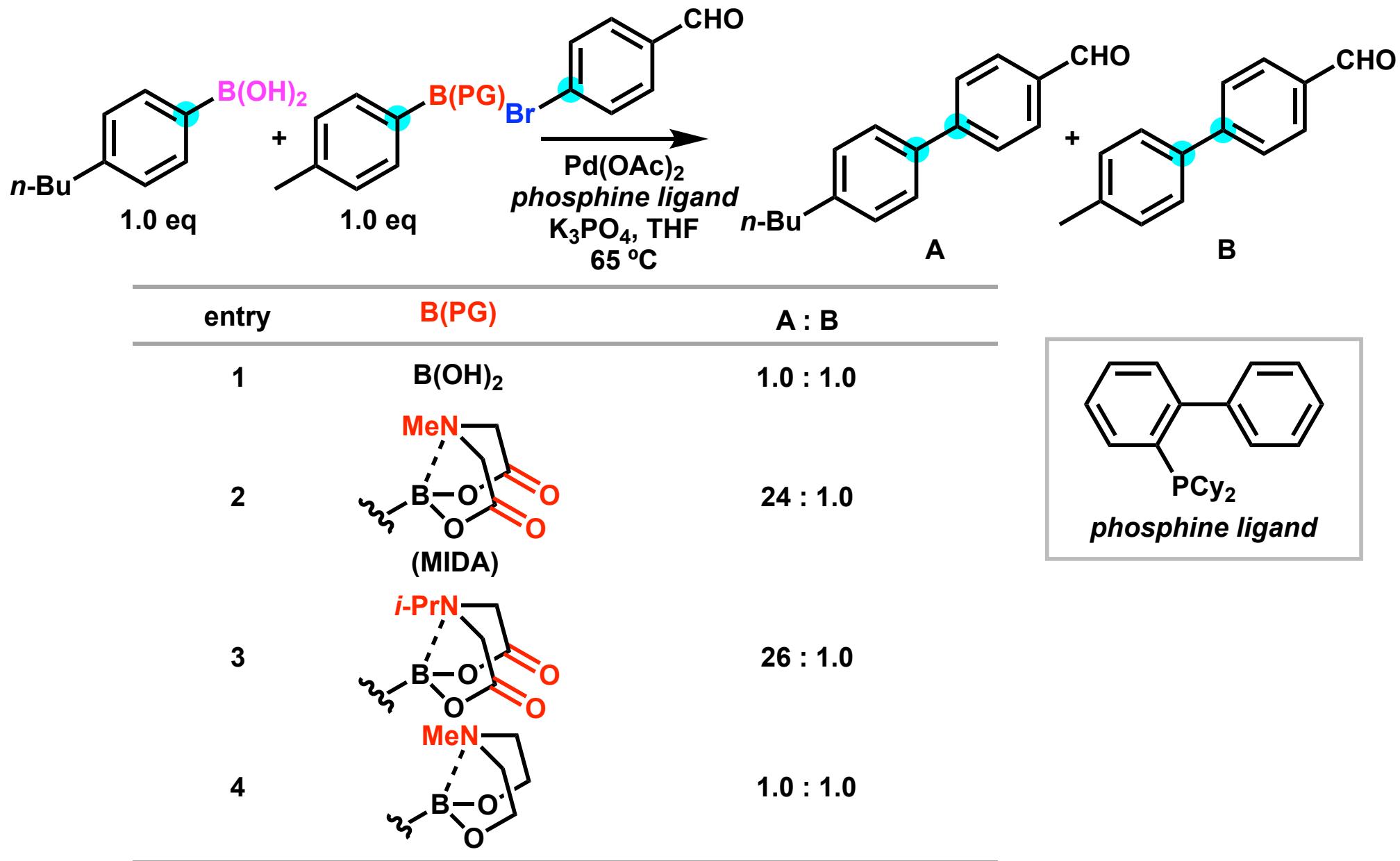


## 2. Site-selective Suzuki-Miyaura coupling



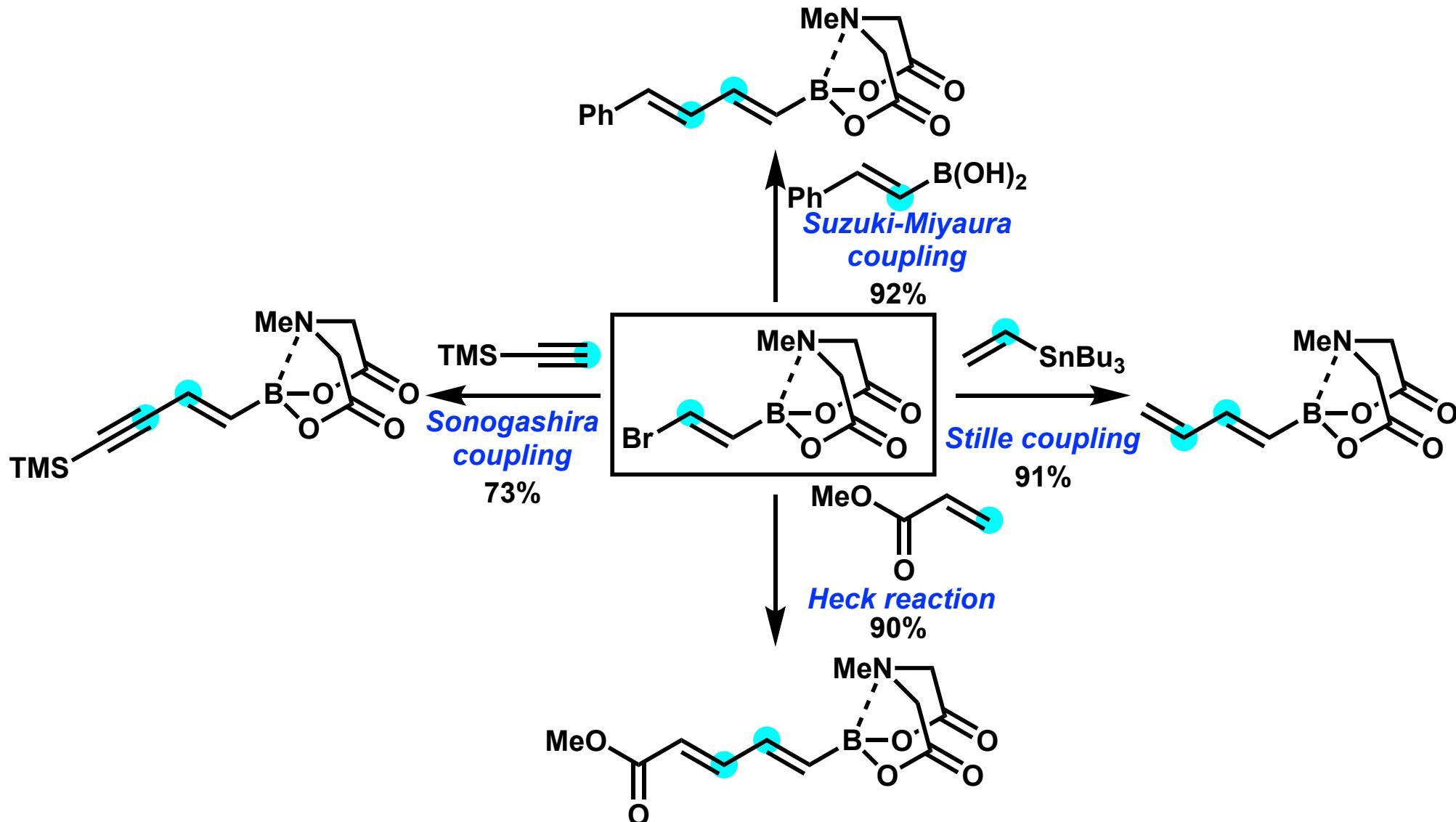
1) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* 2007, 129, 6716-6717

# Optimization



# Tolerance of MIDA (1)

MIDA boronates are compatible with a wide range of common synthetic reagents<sup>1).</sup>

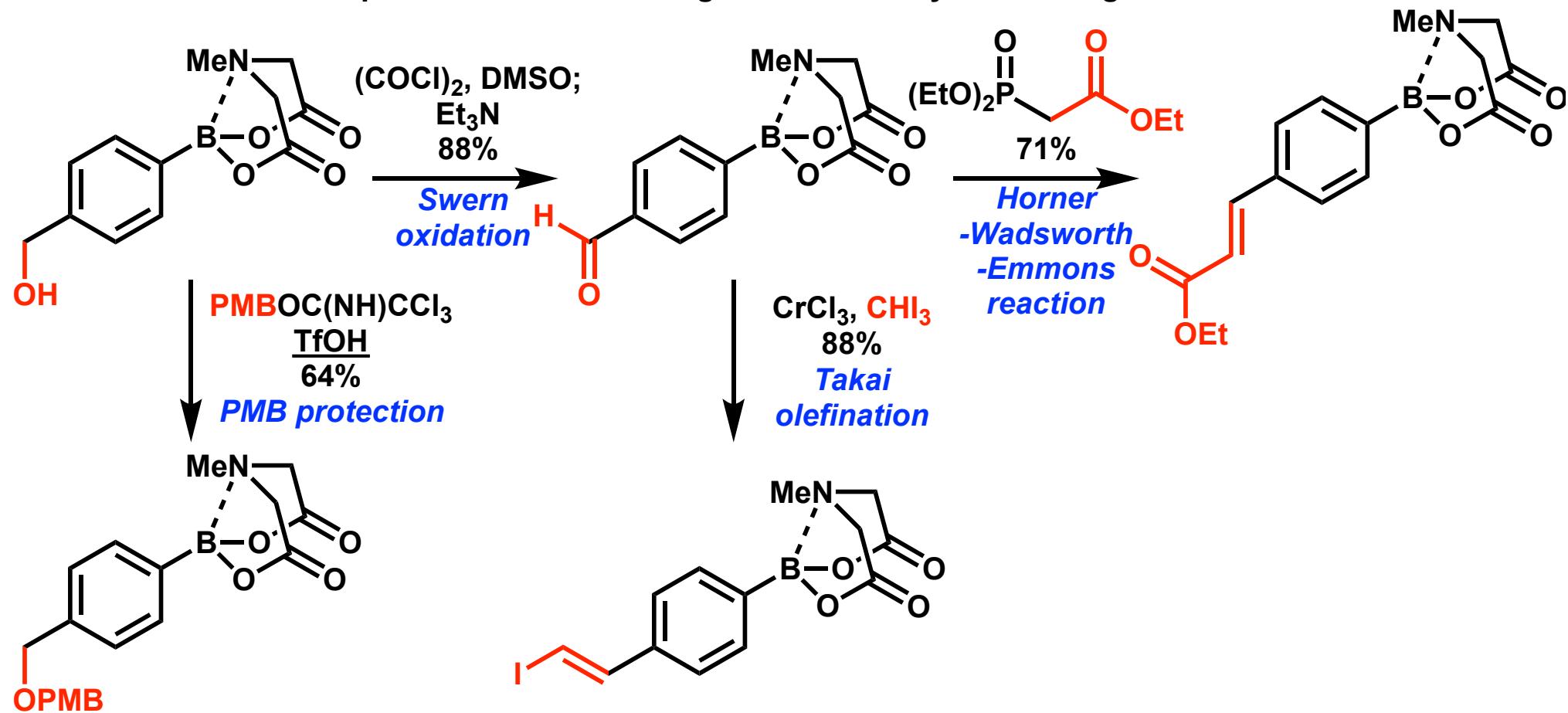


MIDA boronates are stable under various coupling conditions.

1) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* 2008, 130, 466-468

# Tolerance of MIDA (2)

MIDA boronates are compatible with a wide range of common synthetic reagents<sup>1).</sup>



Jones oxidation, oxidation by TPAP and Dess-Martin periodinane were also tolerated.

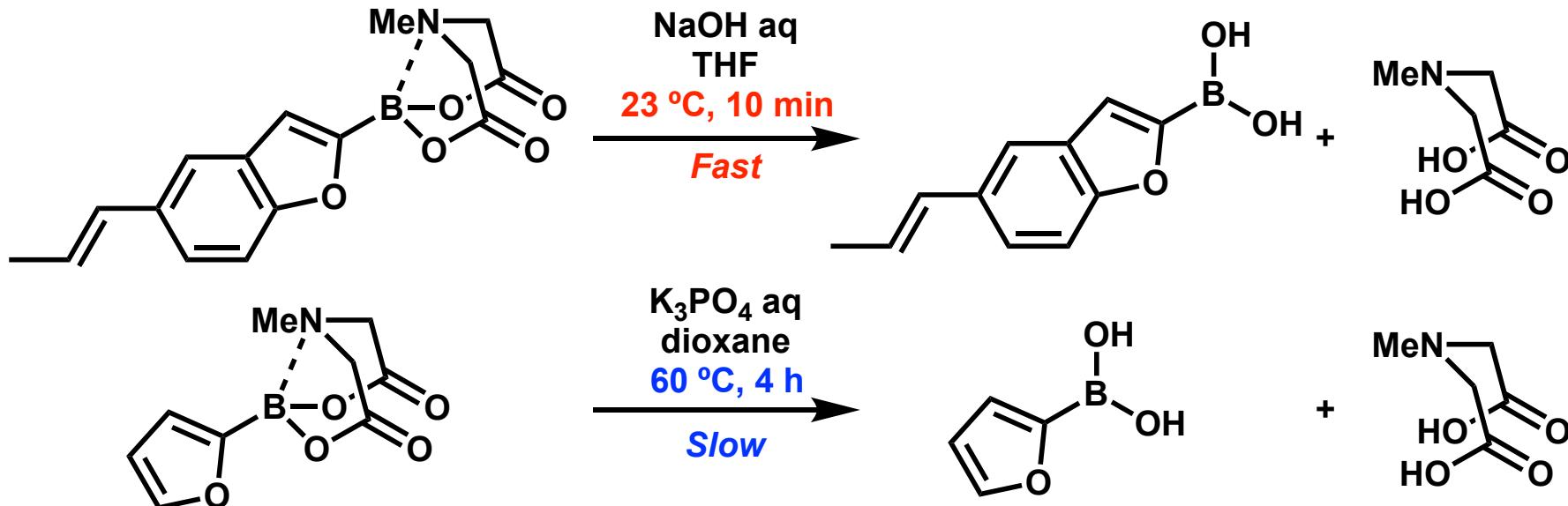
However,

MIDA boronates are hydrolysed under aqueous basic conditions that are commonly used in the Suzuki-Miyaura coupling. Moreover, a variety of carbon nucleophiles react with MIDA protecting group.

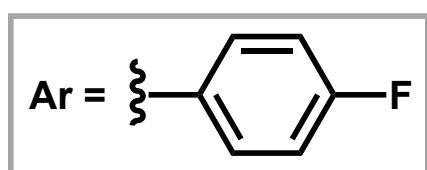
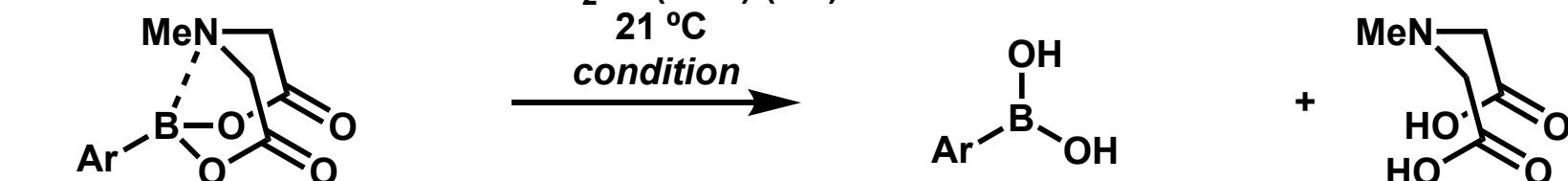
1) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466-468

# Mechanic Study of Hydrolysis (1)

MIDA boronic acid is hydrolyzed at different rates depending on the base<sup>1)2)</sup>.



The rate of boronic acid hydrolysis was verified under various conditions<sup>3)</sup>.



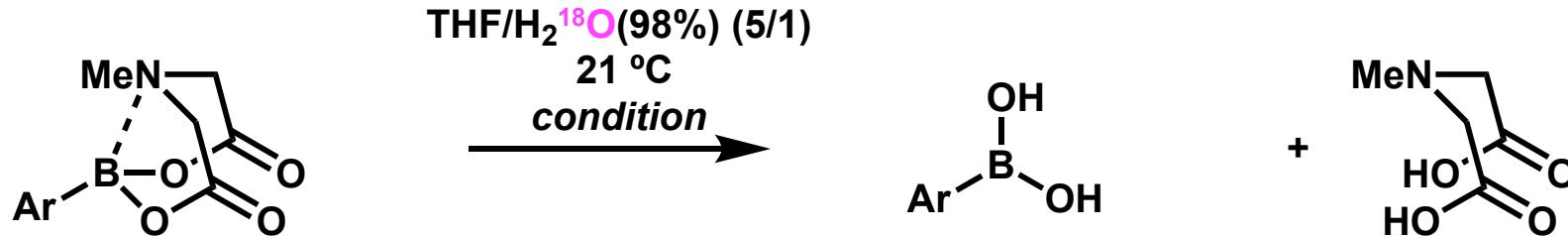
## condition

- A NaOH (2.9 eq, slow addition), 1000 rpm, 10 min
- B NaOH (3.0 eq), sat. NaClaq, 1000 rpm, 24 h
- C NaOH (3.0 eq), sat. NaClaq, 100 rpm, 24 h
- D K<sub>3</sub>PO<sub>4</sub> (5.0 eq), 1000 rpm, 24 h
- E K<sub>3</sub>PO<sub>4</sub> (5.0 eq), 100 rpm, 24 h
- F none, 1000 rpm, 24 h

rpm: rotation per minute

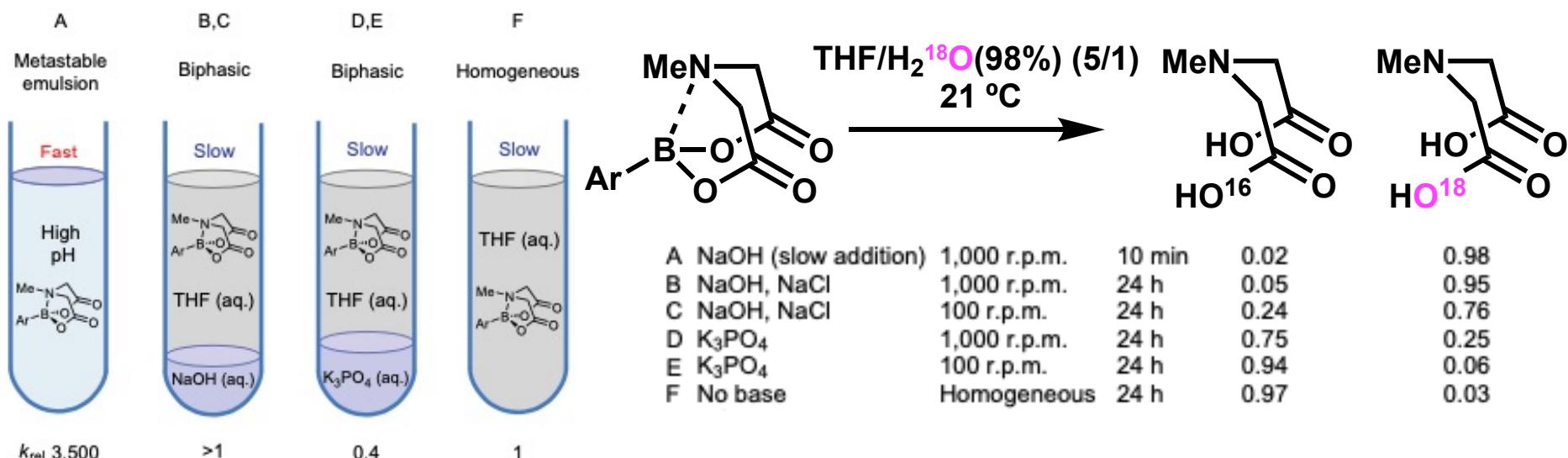
1) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, 129, 6716-6717 2) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, 131, 6961-6963 3) Gonzalez, J. A.; Ogda, O. M.; Morehouse, G. F.; Rosson, N.; Houk, K. N.; Leach, A. G.; Cheong, P. H. Y.; Burke, M. D.; Lloyd-Jones, G. C. *Nat. Chem.* **2016**, 8, 1067-1075

# Mechanic Study of Hydrolysis (2)



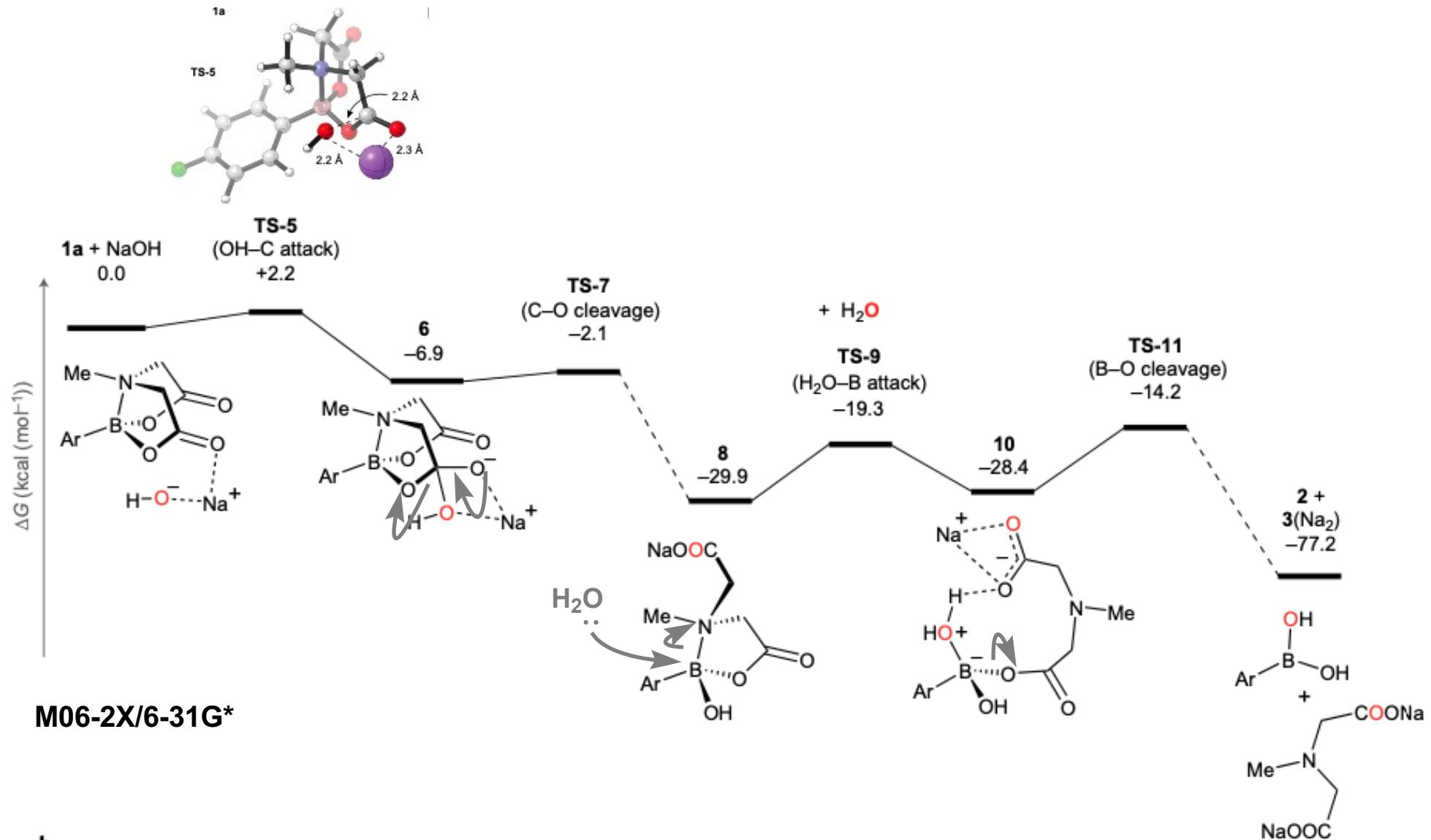
*condition*

- A NaOH (2.9 eq, slow addition), 1000 rpm, 10 min
- B NaOH (3.0 eq), sat. NaClaq, 1000 rpm, 24 h
- C NaOH (3.0 eq), sat. NaClaq, 100 rpm, 24 h
- D K<sub>3</sub>PO<sub>4</sub> (5.0 eq), 1000 rpm, 24 h
- E K<sub>3</sub>PO<sub>4</sub> (5.0 eq), 100 rpm, 24 h
- F no base, 1000 rpm, 24 h

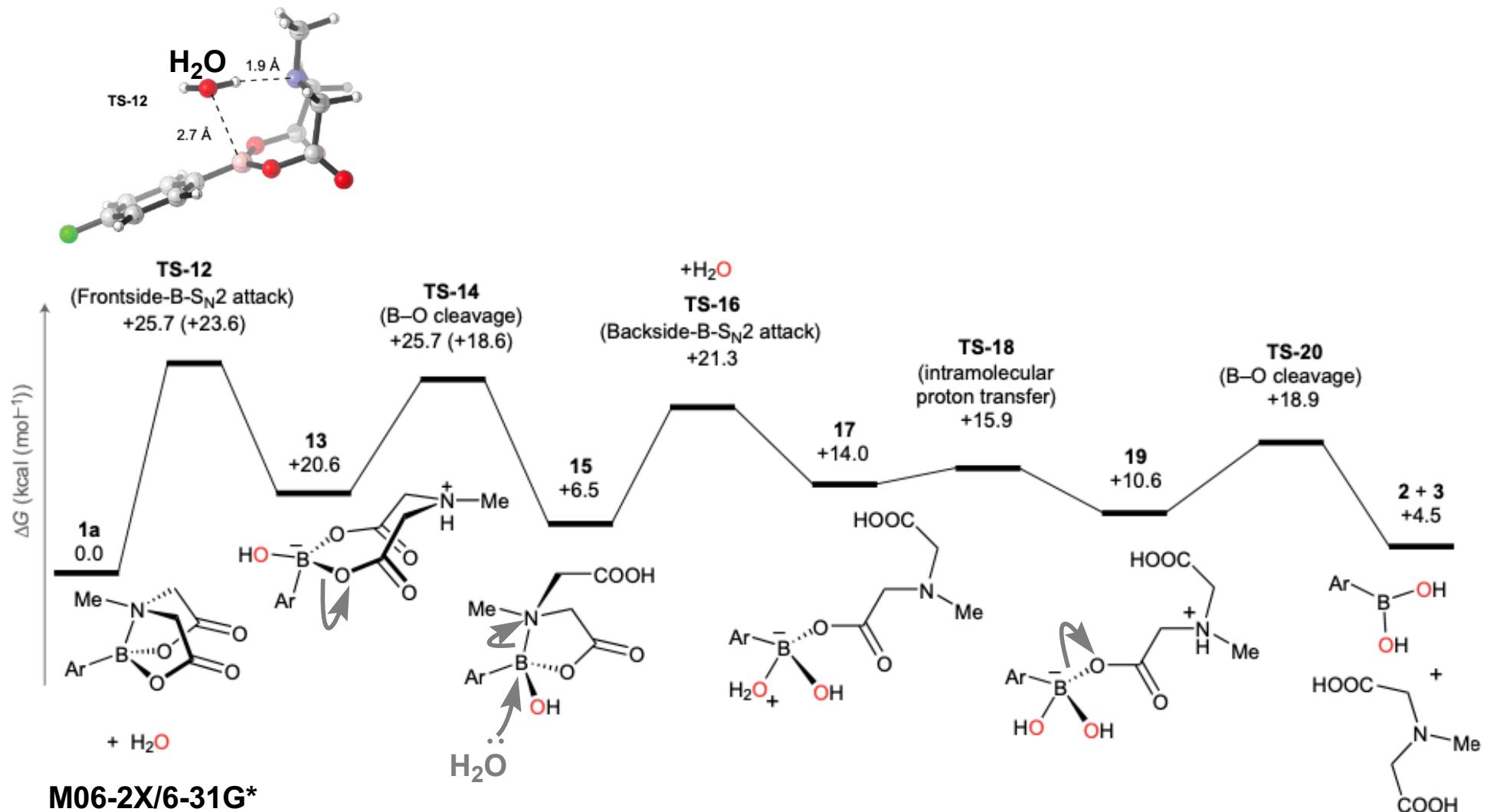


The reaction mechanism is thought to differ between the “fast” hydrolysis with NaOH and the “slow” hydrolysis with K<sub>3</sub>PO<sub>4</sub>.

# Mechanic Insight of Hydrolysis (1)



# Mechanic Insight of Hydrolysis (2)



The differing rate and sites of the first-stage attack can be rationalized:

1. hydroxide is much more nucleophilic than water.
2. anionic hydroxide attack more electrophilic carbonyl group.
3. B-N bond can function as a Bronsted base and Lewis acid for water.

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# **Introduction of Prof. Martin D. Burke**



**Prof. Martin D. Burke**

**1998 B.S., @ Johns Hopkins University (Prof. Henry Brem and Gary H. Posner)**

**2003 Ph.D., @ Harvard University (Prof. Stuart L. Shreiber)**

**2005 M.D., @ Harvard University**

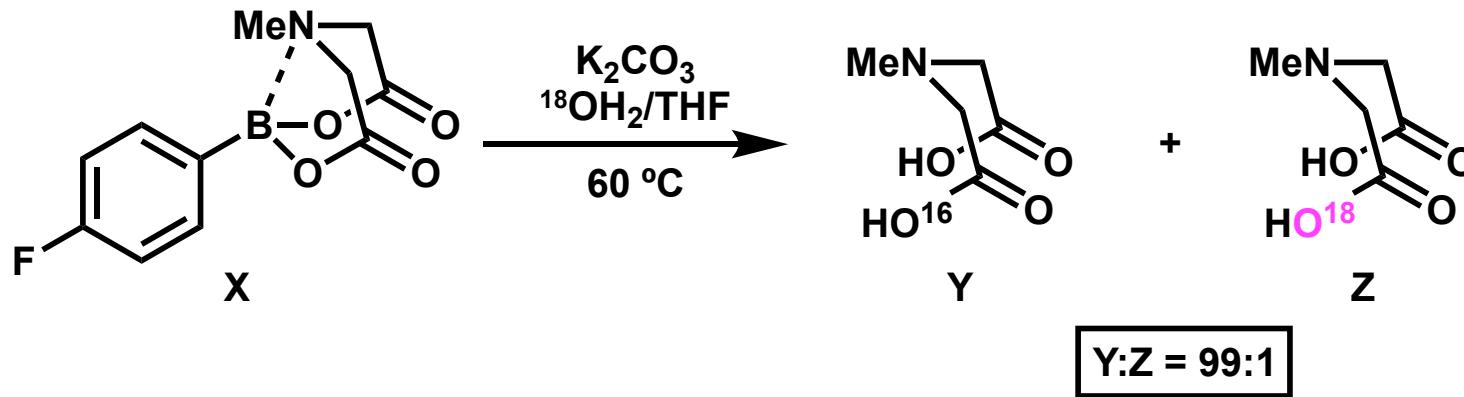
**2005-2011 Assistant professor @ The University of Illinois at Urbana-Champaign**

**2011-2014 Associate professor @ The University of Illinois at Urbana-Champaign**

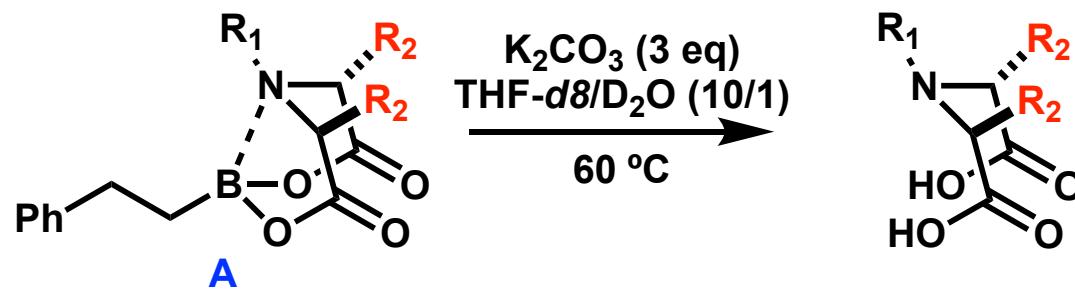
**2014- Professor @ The University of Illinois at Urbana-Champaign**

**Research topic: “Lego Chemistry”(Connecting small molecules),  
Molecular Prosthetics, Antifungal medicine**

# Optimization of Lewis base (1)



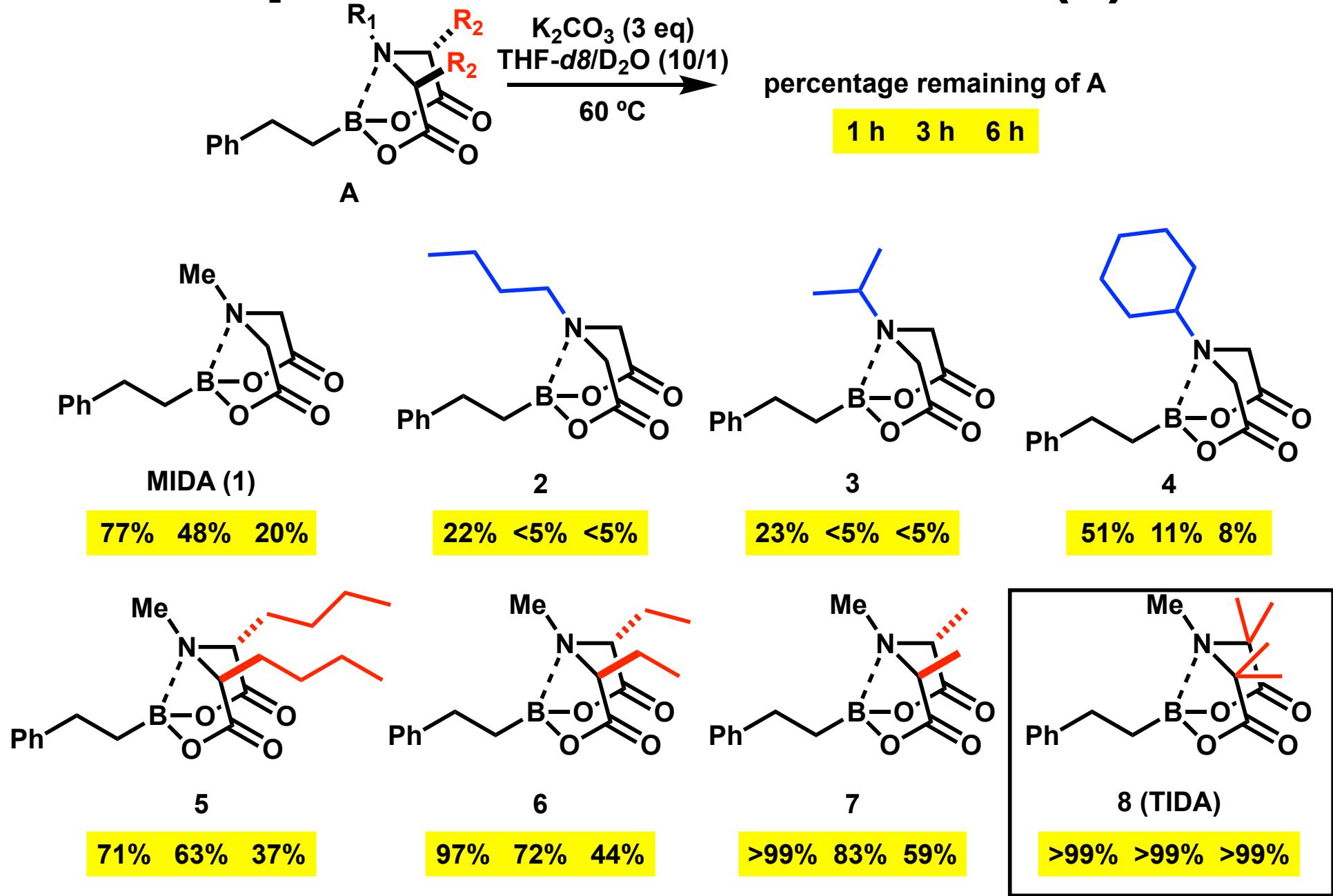
**X** was found to be hydrolyzed with cleavage of the N-B bond.



remaining percentage of **A** was measured after 1 h, 3 h, 6 h

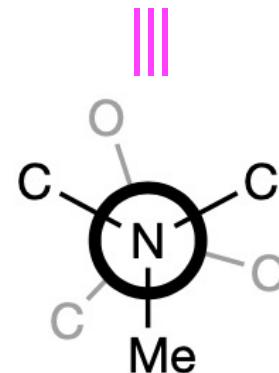
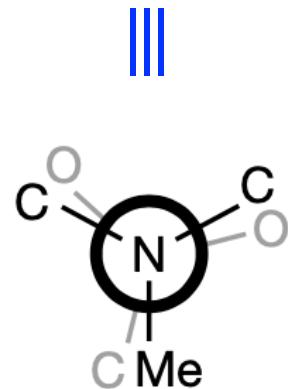
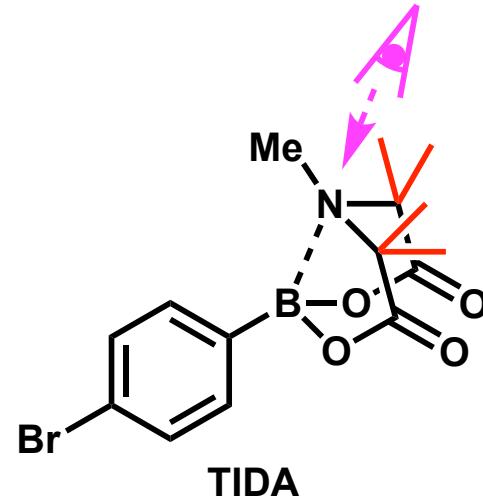
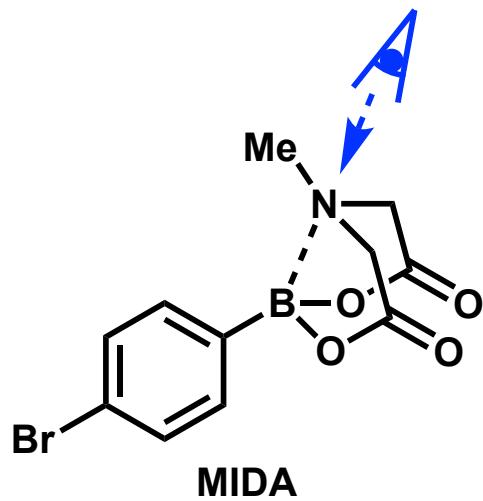
1) Blair, D. J.; Chitti, S.; Trobe, M.; Kostrya, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. *Nature*. **2022**, *604*, 92-97.

# Optimization of Lewis base (2)



1) Blair, D. J.; Chitti, S.; Trobe, M.; Kostrya, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. *Nature*. **2022**, *604*, 92-97.

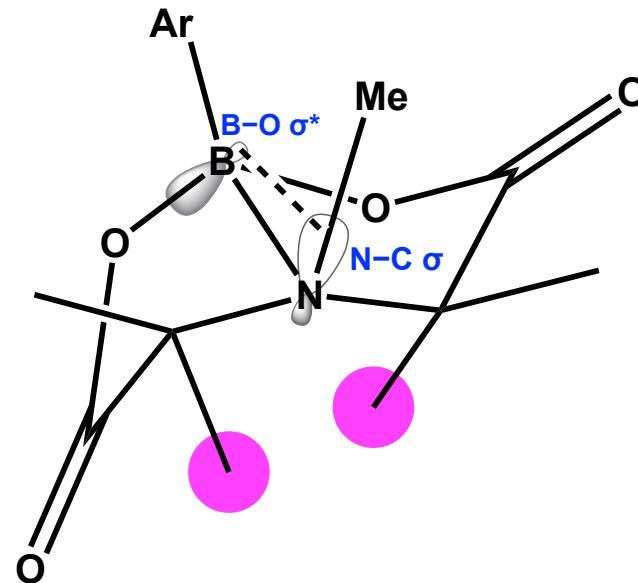
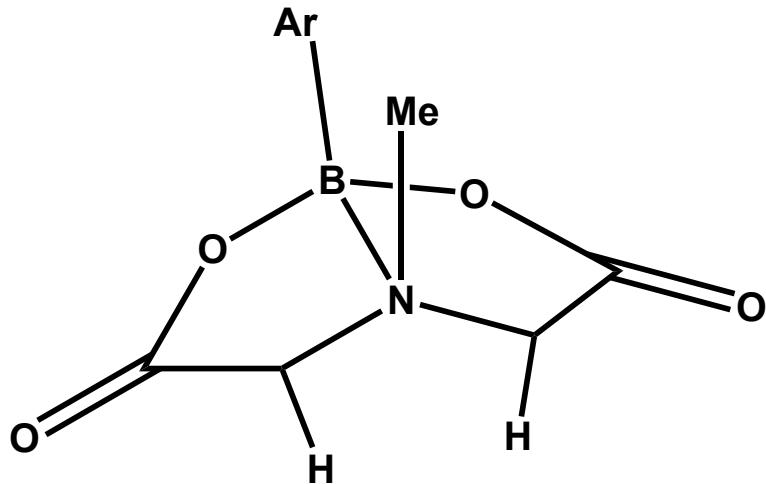
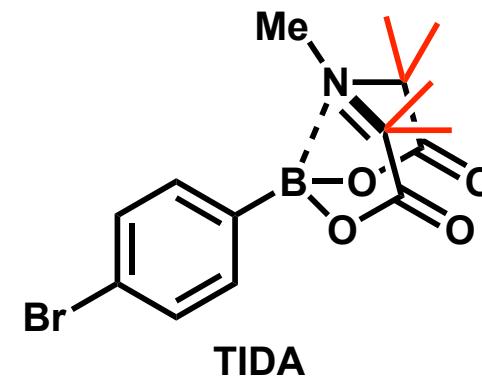
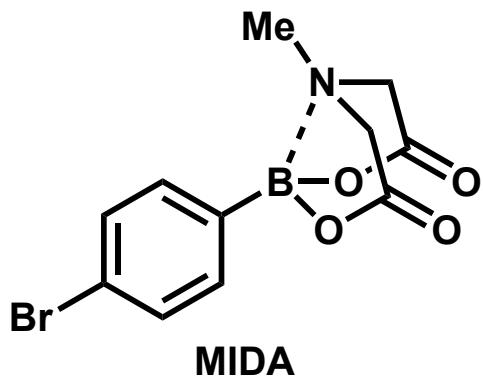
# Stability of TIDA (1)



N-C bonds of TIDA were rotated relative to B-O bonds more than 10 degrees more than those of MIDA.

1) Blair, D. J.; Chitti, S.; Trobe, M.; Kostrya, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. *Nature*. **2022**, *604*, 92-97.

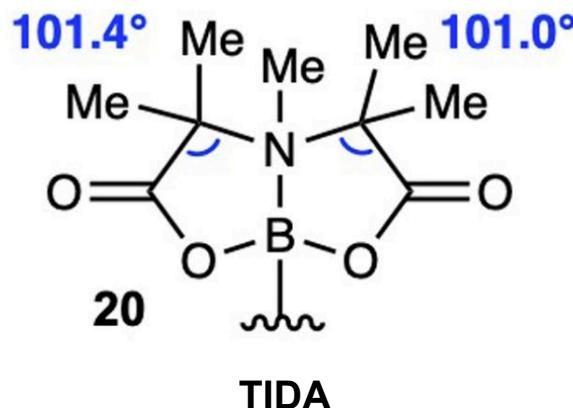
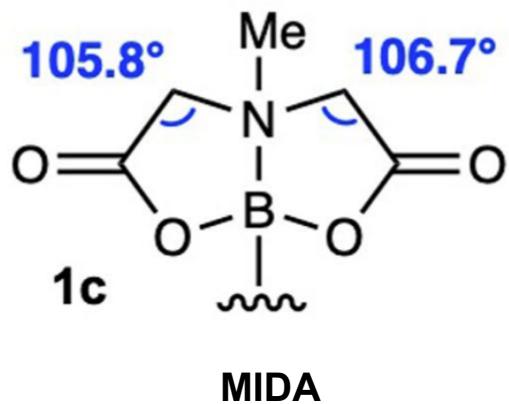
# Stability of TIDA (2)



TIDA is thought to have been twisted to avoid steric hindrance between methyl groups. This results in an interaction between the  $\sigma$  orbital of the N-C bond and the  $\sigma^*$  orbital of the B-O bond. Therefore, N-B bond is expected to be stronger.

1) Blair, D. J.; Chitti, S.; Trobe, M.; Kostrya, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. *Nature*. **2022**, 604, 92-97. 22

# Stability of TIDA (3)



The four methyl groups in TIDA reduce the bond angle.

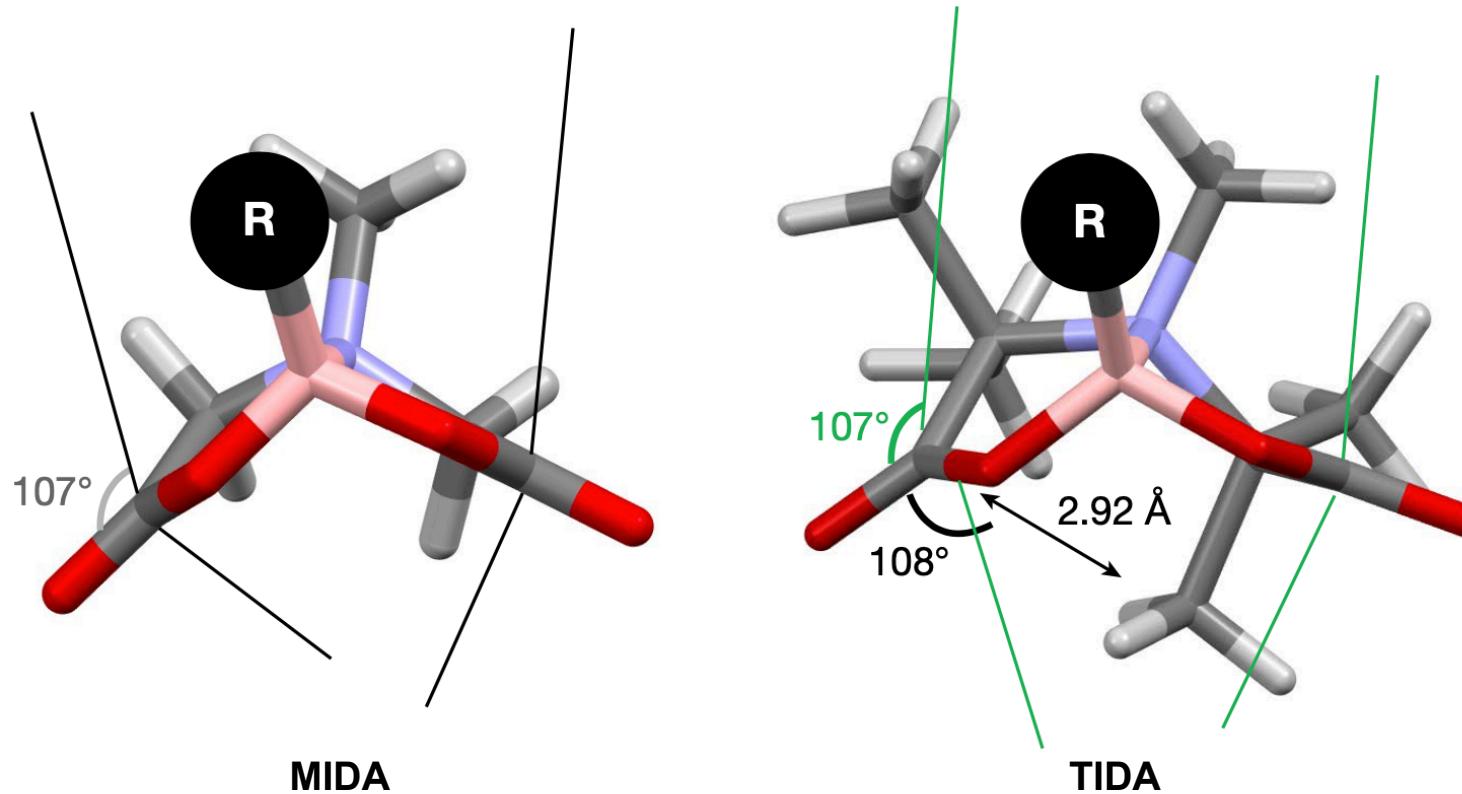
It is also possible that Lewis basicity of the nitrogen is strengthened by electron donation from the methyl groups to the nitrogen.

1) Blair, D. J.; Chitti, S.; Trobe, M.; Kostrya, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. *Nature*. **2022**, *604*, 92-97. 23

# Stability of TIDA (4)

MIDA has the problem of reacting with carbon nucleophiles.

However, TIDA is stable towards carbon nucleophiles (*i*-PrMgCl•LiCl and *t*-BuLi).



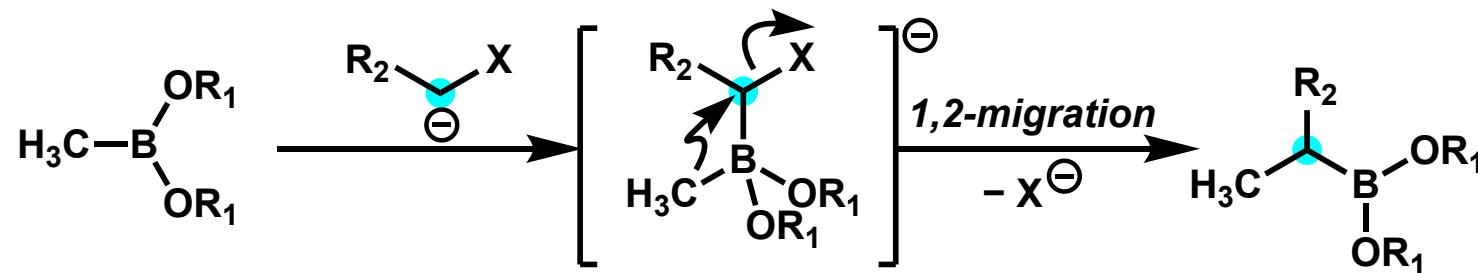
The reason of this stability may be that the four methyl groups prevent the nucleophile from approaching the carbonyl groups from the Burgi-Dunitz angle.

This stability is expected to be utilized in a new synthetic strategy based on the Matteson reaction.

1) Blair, D. J.; Chitti, S.; Trobe, M.; Kostrya, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. *Nature*. **2022**, *604*, 92-97.

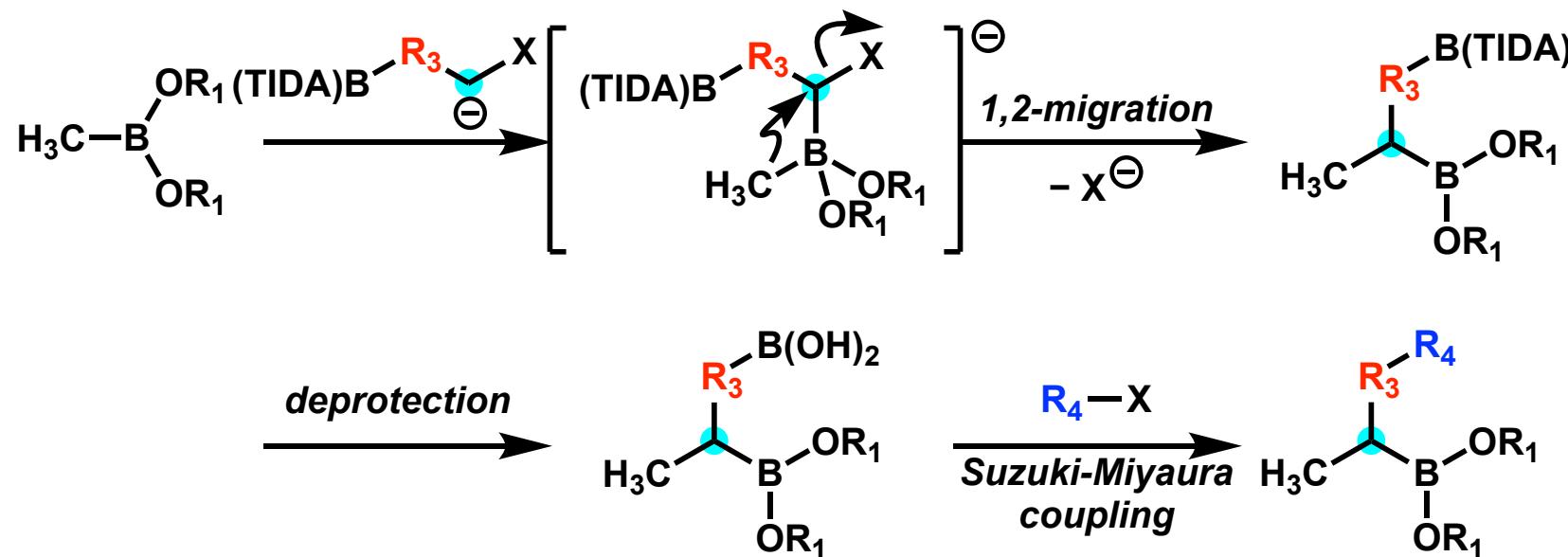
# Application to Matteson Reaction

Matteson reaction

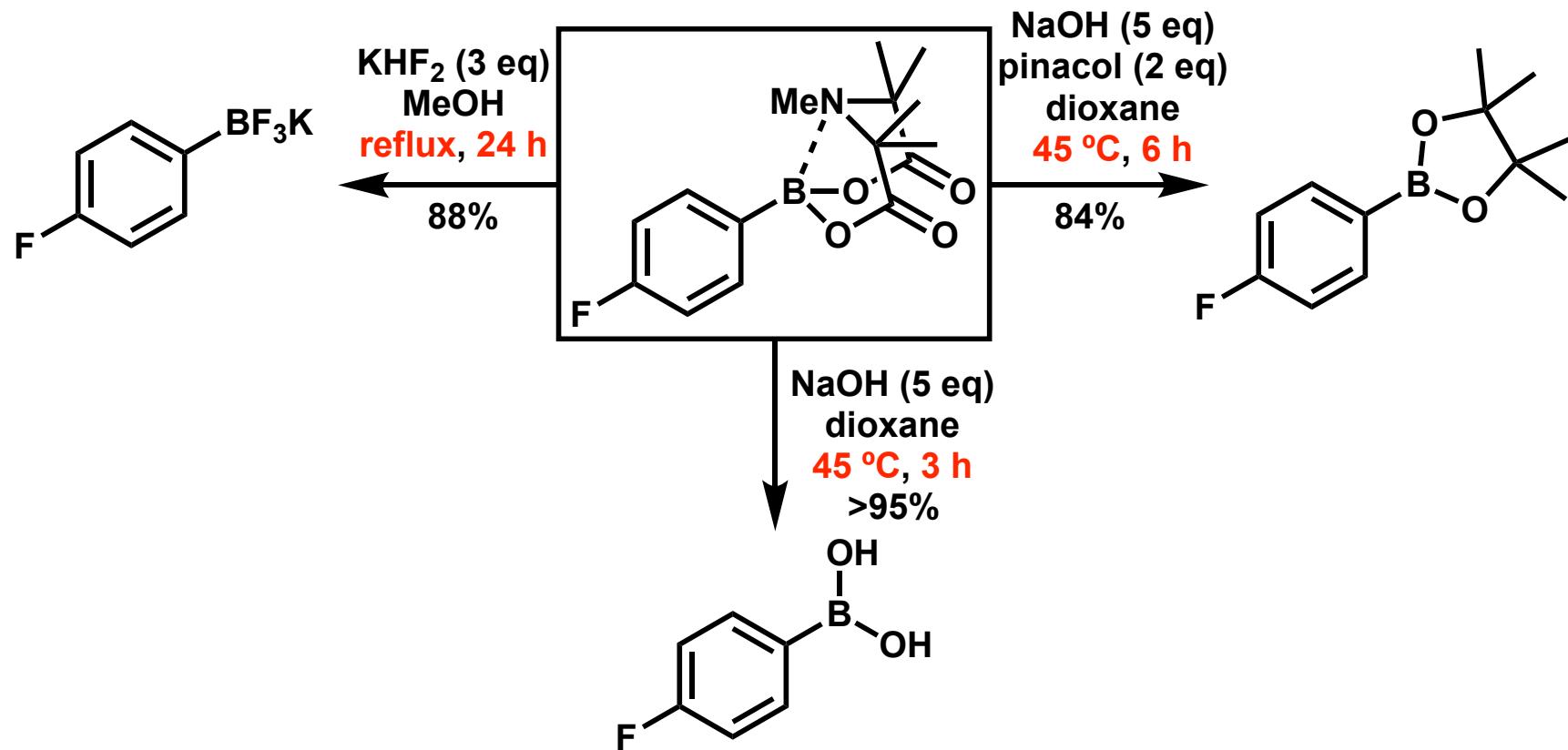


Since the Matteson reaction uses a carbanion formed by a carbon nucleophile, MIDA could not be used.

new strategy



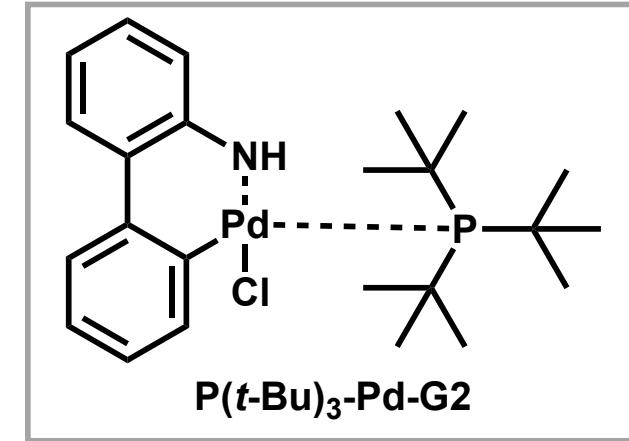
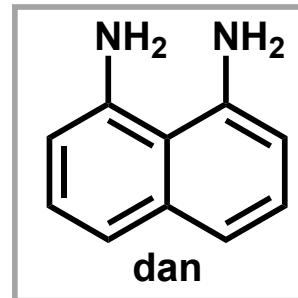
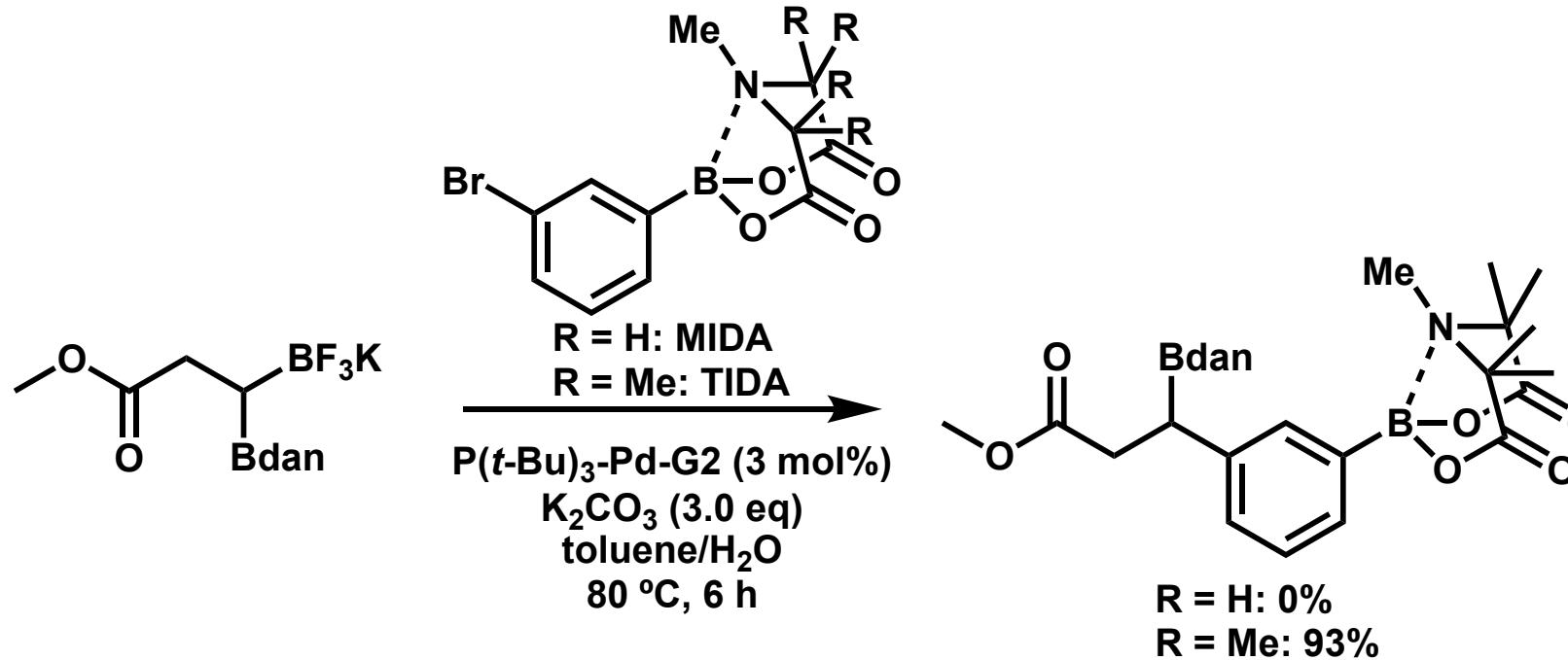
# Deprotection of TIDA



MIDA is hydrolyzed in a few minutes at room temperature, whereas TIDA requires more time under heating conditions for hydrolysis.

1) Blair, D. J.; Chitti, S.; Trobe, M.; Kostrya, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. *Nature*. **2022**, *604*, 92-97.

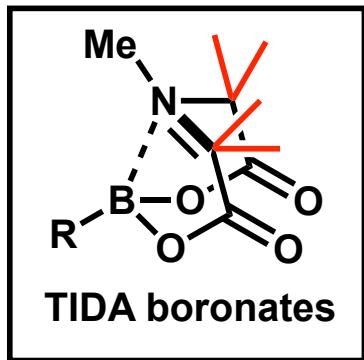
# Reaction Efficiency of TIDA



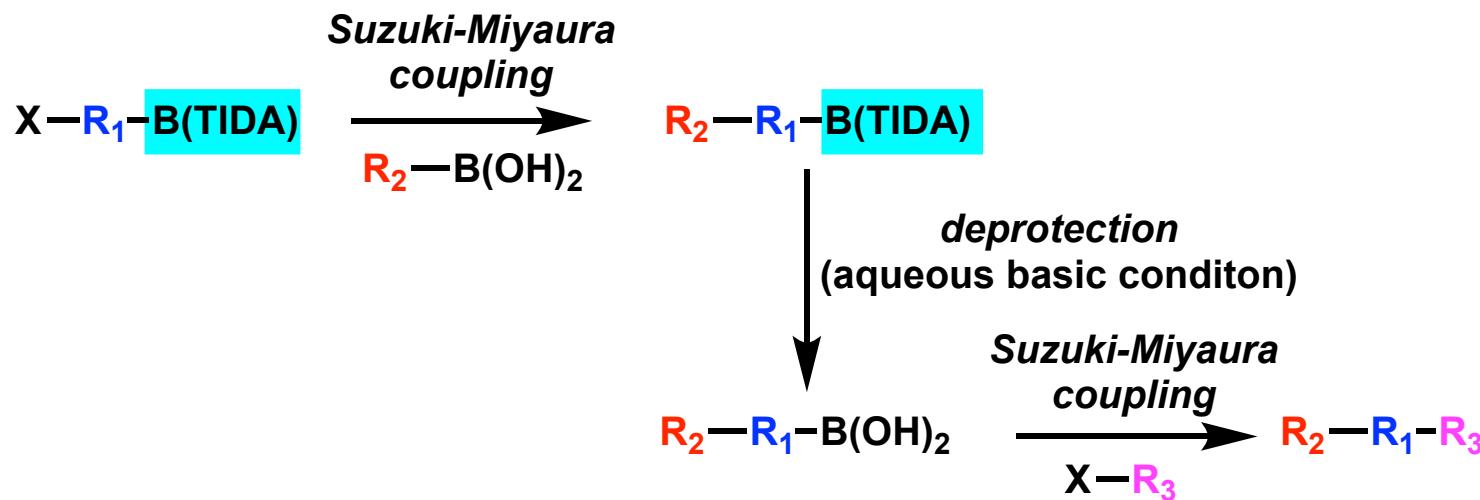
- Possible to synthesize substrates with TIDA on a **kg scale**.
- Stable to a wide range of common cross-coupling reactions.
- Stable to a wide range of chemical transformations (oxidation, reduction, borylation, olefination)

1) Blair, D. J.; Chitti, S.; Trobe, M.; Kostrya, D. M.; Haley, H. M. S.; Hansen, R. L.; Ballmer, S. G.; Woods, T. J.; Wang, W.; Mubayi, V.; Schmidt, M. J.; Pipal, R. W.; Morehouse, G. F.; Palazzolo Ray, A. M. E.; Gray, D. L.; Gill, A. L.; Burke, M. D. *Nature*. **2022**, *604*, 92-97.

# Summary



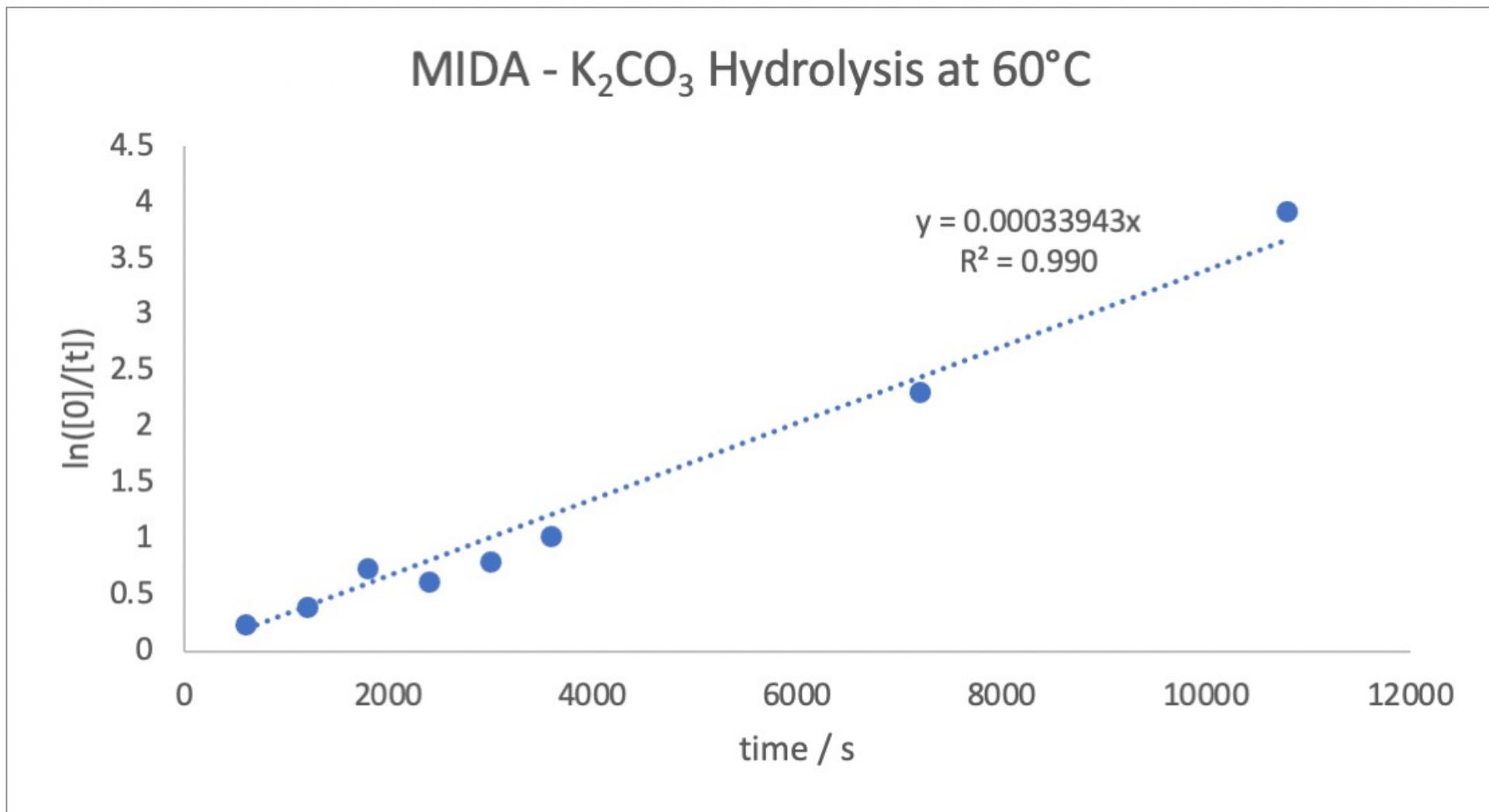
- Resistant to hydrolysis under mild aqueous basic conditions
- Stable towards carbon nucleophiles.
- Tolerable against various coupling conditions and chemical formation



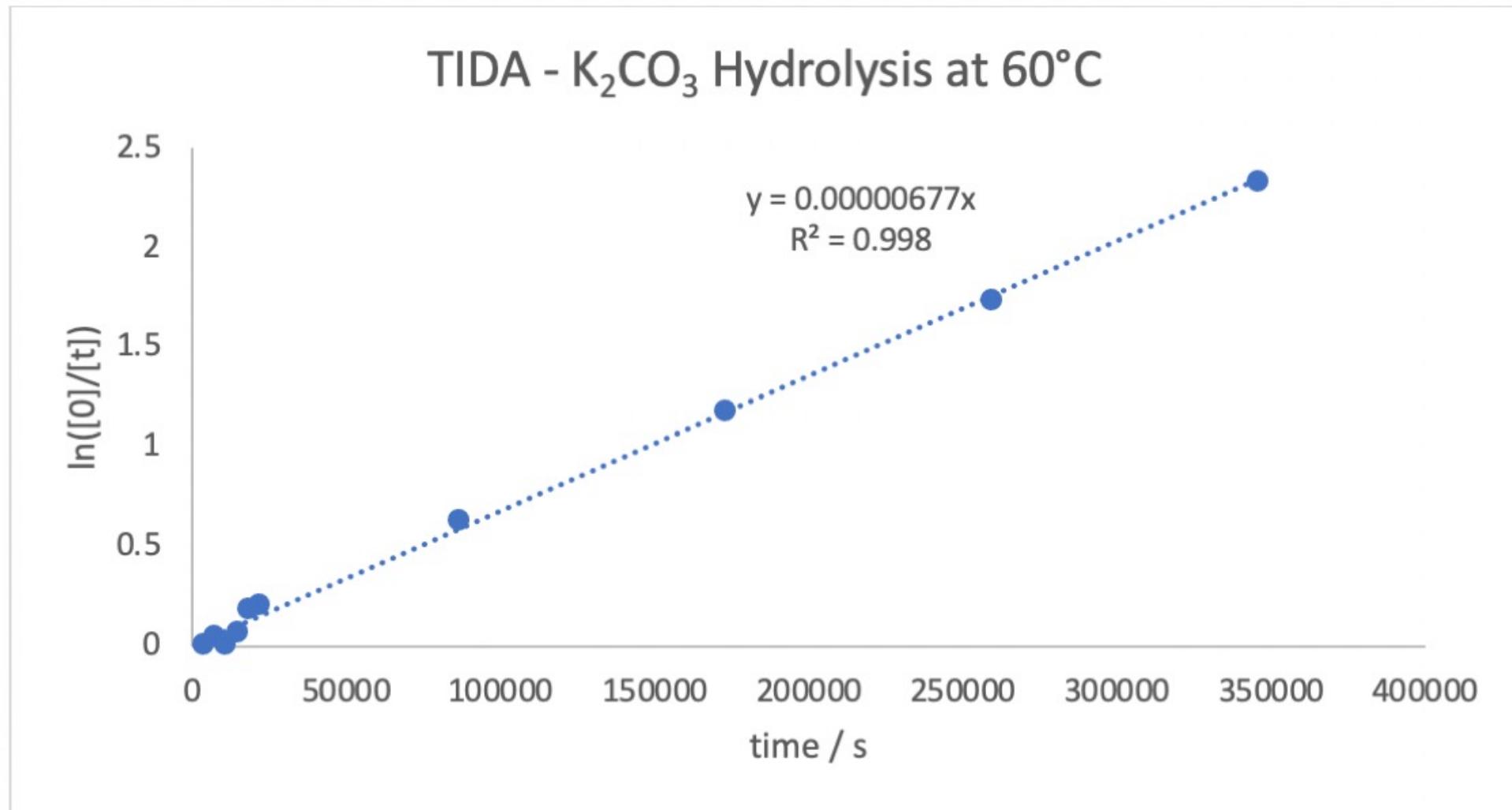
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# **Appendix**

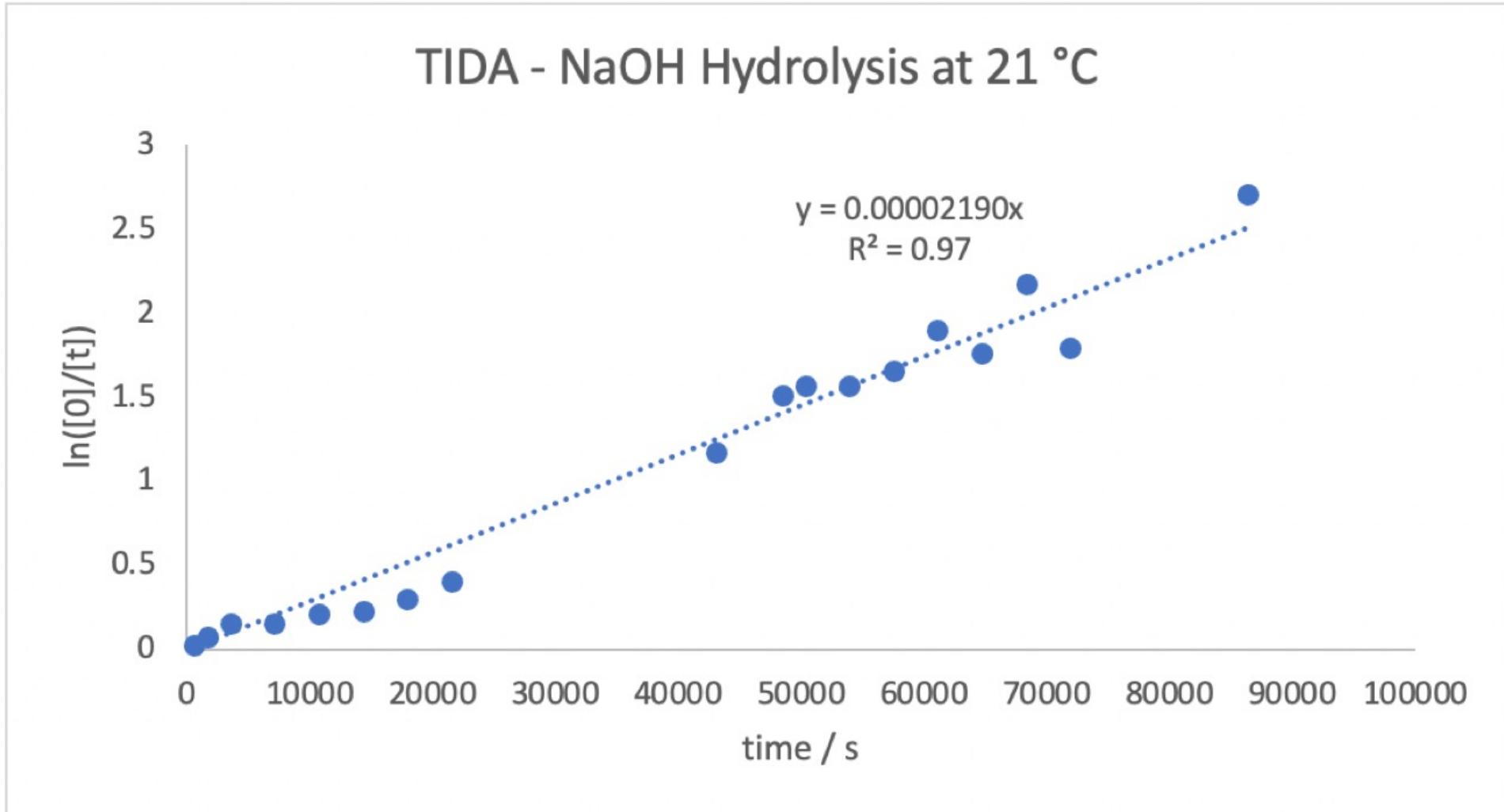
# Hydrolysis of MIDA using $K_2CO_3$ at 60 °C



# Hydrolysis of TIDA using $\text{K}_2\text{CO}_3$ at 60 °C



# Hydrolysis of TIDA using NaOH at 21 °C



# **Mechanism of B-ring construction**