Boron-catalyzed Amide Formation

2018/03/02

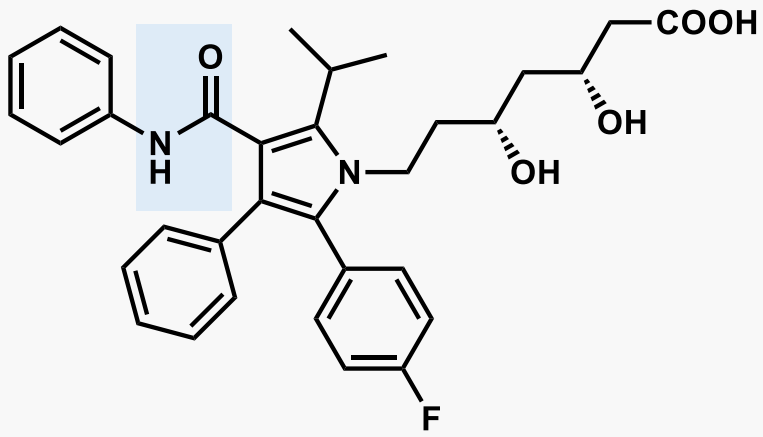
B4 Koki Sasamoto

Contents

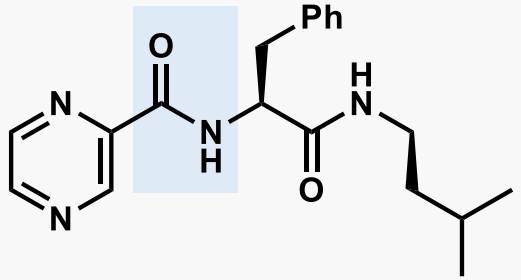
Introduction

Importance of amide bond

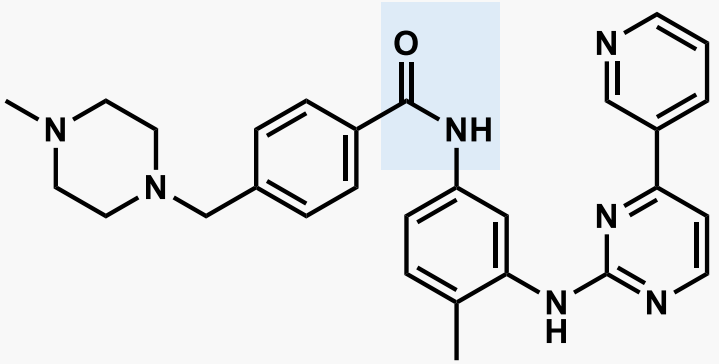
Example of amide-containing drugs



Liptor (Atorvastatin)



Velcade



Gleevec (Imatinib)

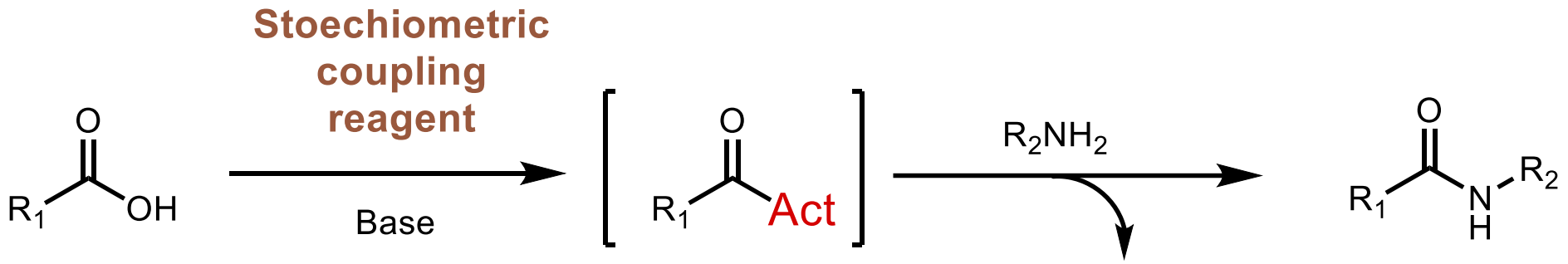
25% of drugs contain amide

16% is amide formation in medchem

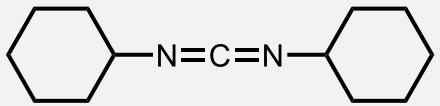
A. K. Ghose *et al. J. Comb. Chem*. **1999**, *1*, 55.; S. D. Roughley *et al*. *J. Med. Chem*. **2011**, *54*, 3451.

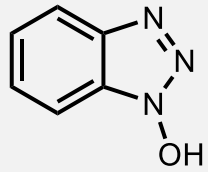
Introduction

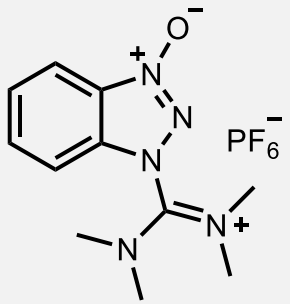
Classical Route

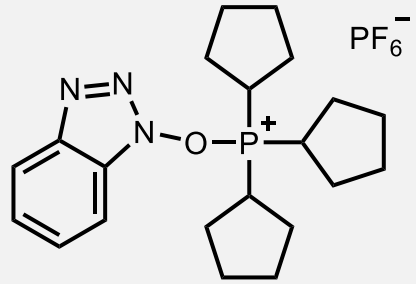


typical coupling reagents and additives


DCC

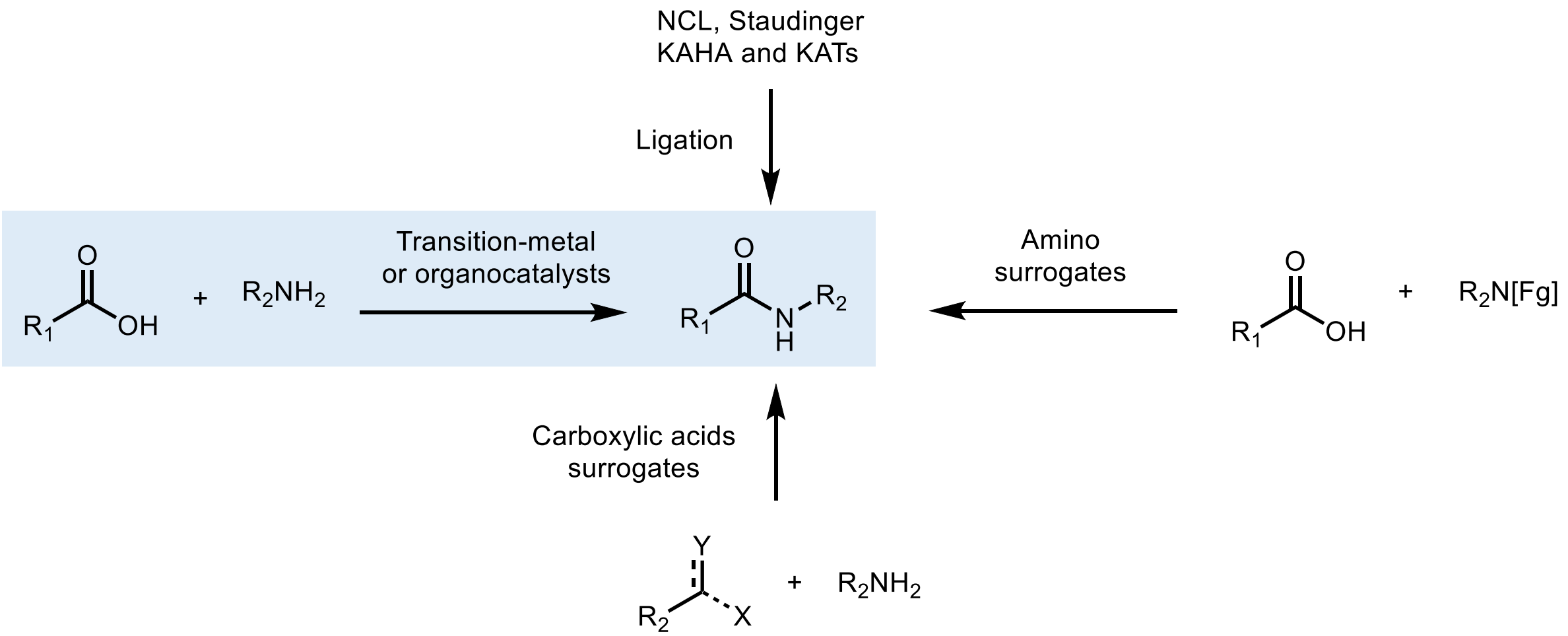

HOBt


HATU


PyBOP

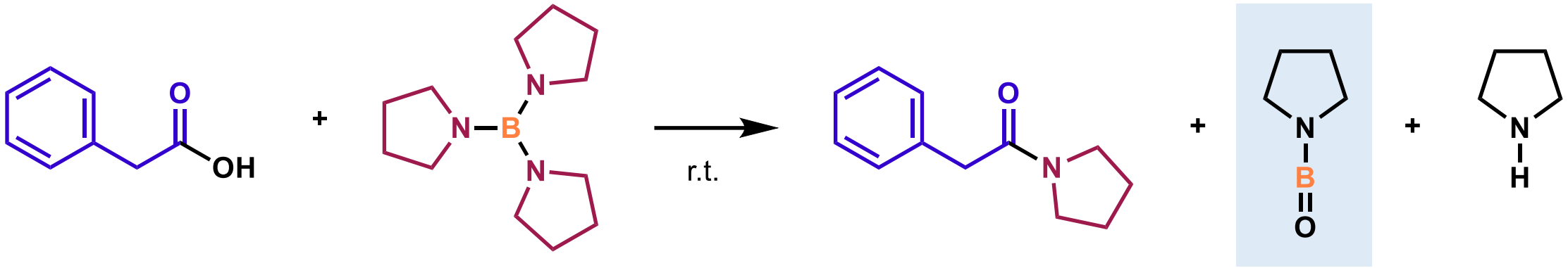
Introduction

Nonclassical routes



Stoichiometric Amidation

Example of amidation using stoichiometric boron reagent



1 eq

1 eq

87%

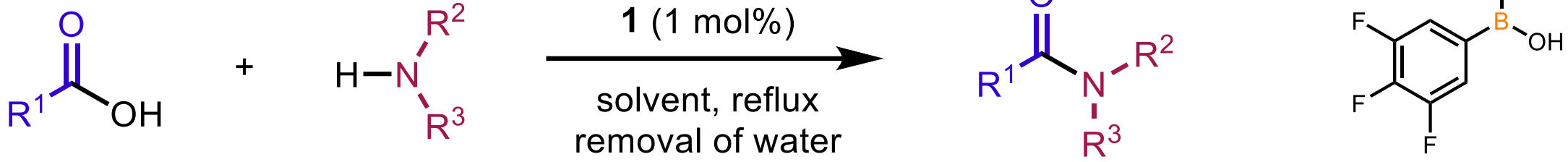
Inactive species

▼

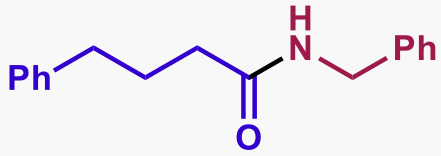
Not proceed catalytically

P. Nelson *et al. J. Chem. Soc.*, **1965**, *5142*.

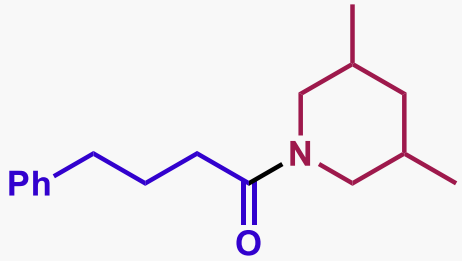
Catalytic Amidation



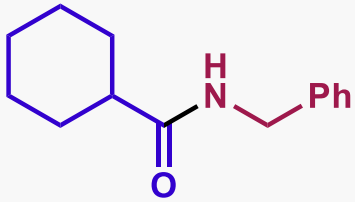
1



96% (toluene)

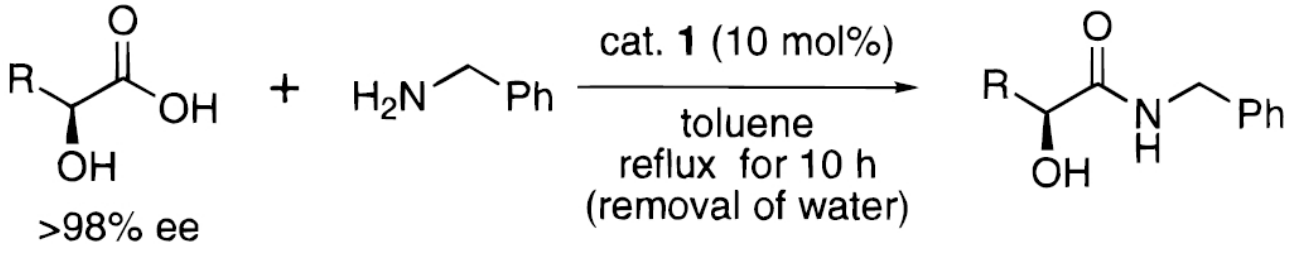


99% (toluene)



96% (xylene)

High yield



>98% ee

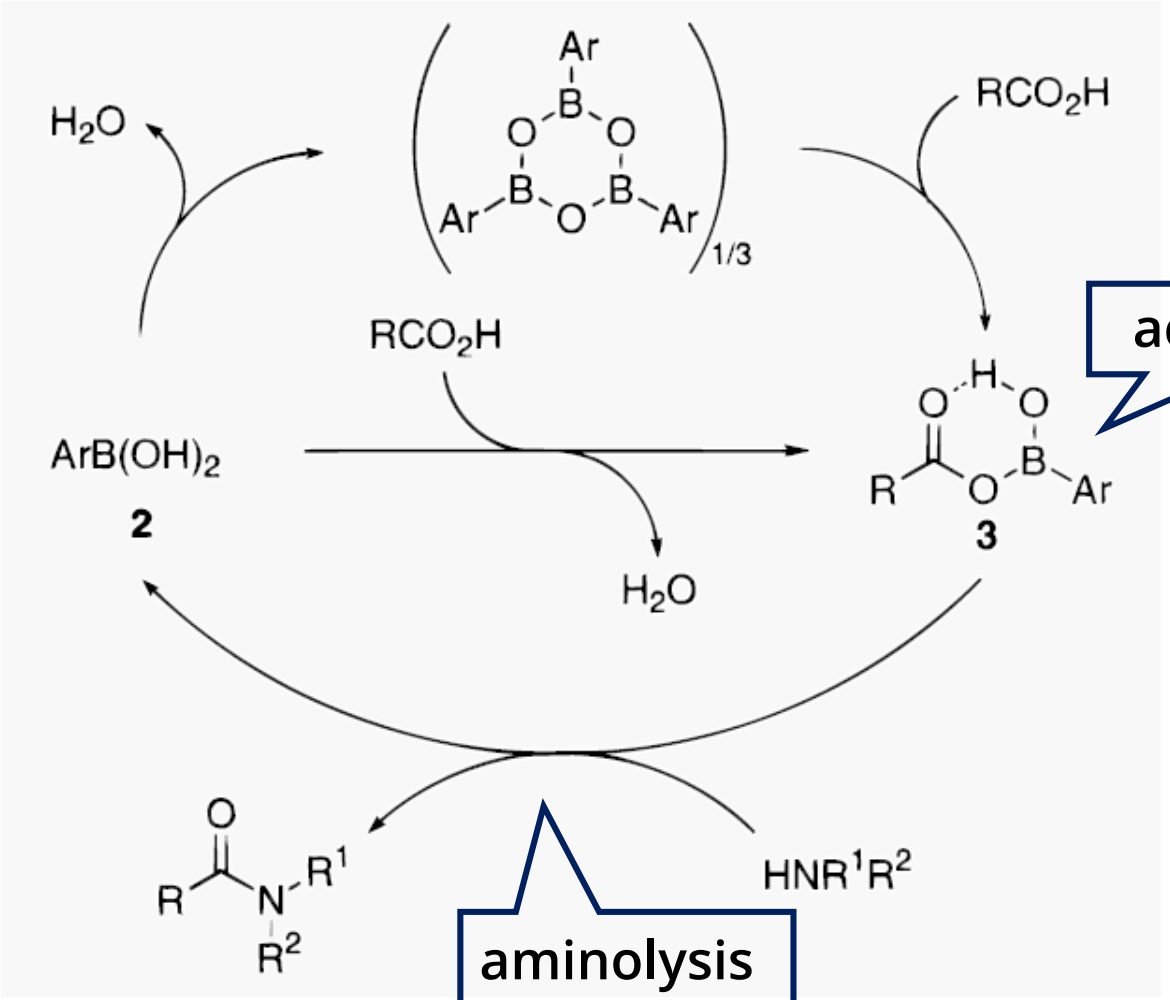
R=Ph: 95% yield, 94% ee
R=*i*-Bu: 87% yield, >98% ee
R=*i*-Pr: 96% yield, >98% ee

Low Racemization

H. Yamamoto *et al*. *J. Org. Chem*. **1996**, *61*, 4196.

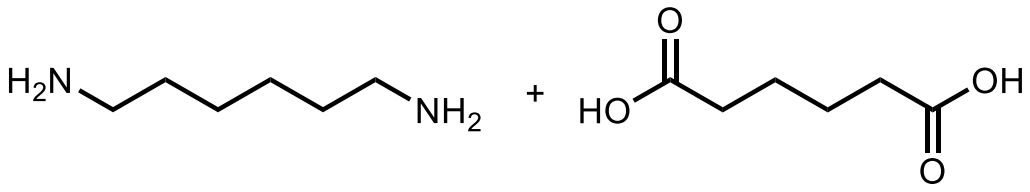
Catalytic Amidation

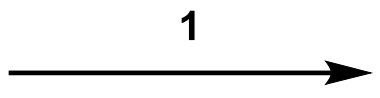
Plausible reaction mechanism



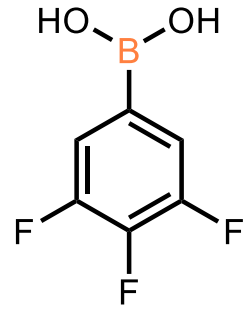
H. Yamamoto *et al*. *J. Org. Chem.* **1996,** *61,* 4196.

Direct polycondensation





Nylon 6,6



1

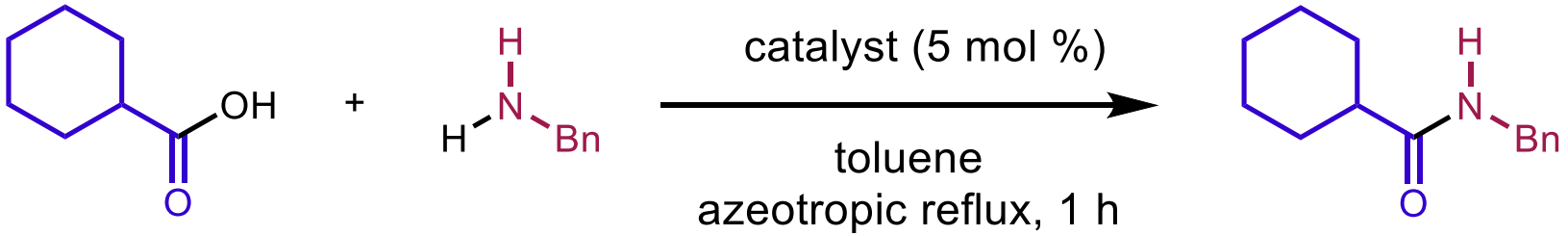
entry	cat. **1** (mol %)	solvent	yield (%)	M_n	M_w
1	10	*o* -xylene/*m* -cresol	85	4690	22400
2	10	*o*- xylene	89	2680	8330
3	10	toluene/*m* -cresol	83	-	-
4	0	toluene/*m* -cresol	0	-	-

M_n the number-average molecular weight, *Mw* the weight-average molecular weight

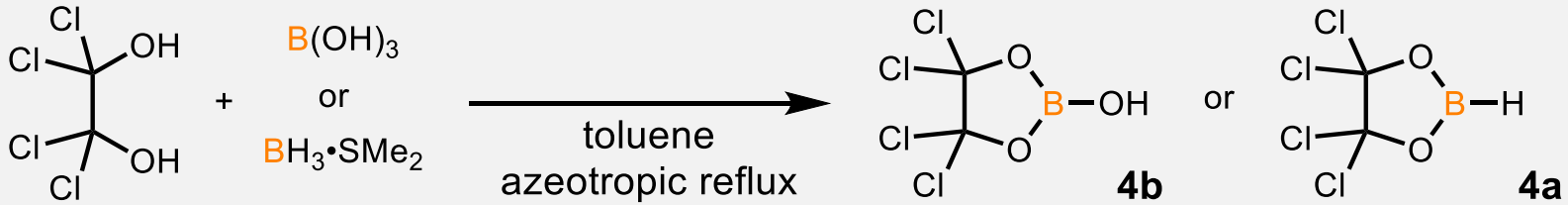
H. Yamamoto *et al*. *Macromolecules*, **2000**, *33*, 3511.

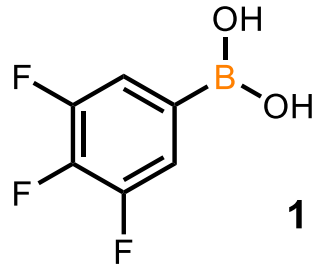
Catalytic Amidation

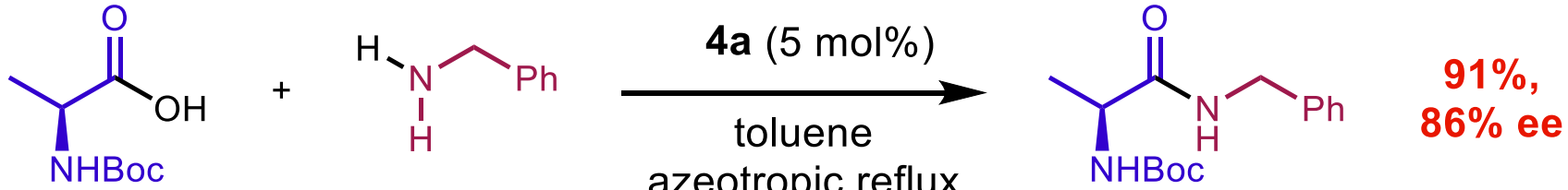
Amidation for sterically demanding carboxylic acid



entry	catalyst	yield (%)
1	**4a**	**62**
2	**4b**	**52**
3	**1**	32
4	$B(OH)_3$	2



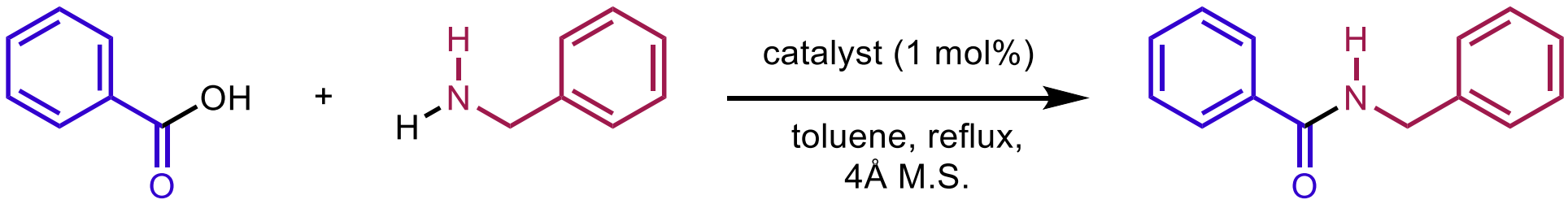




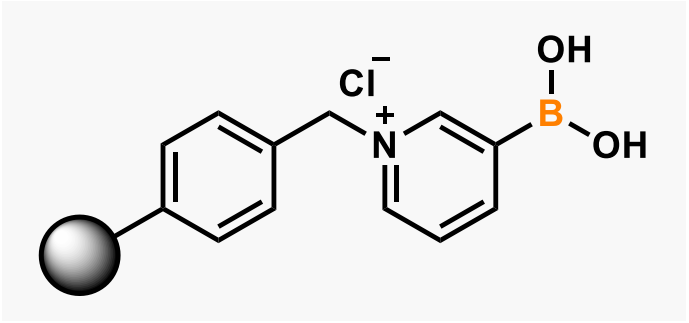
91%,
86% ee

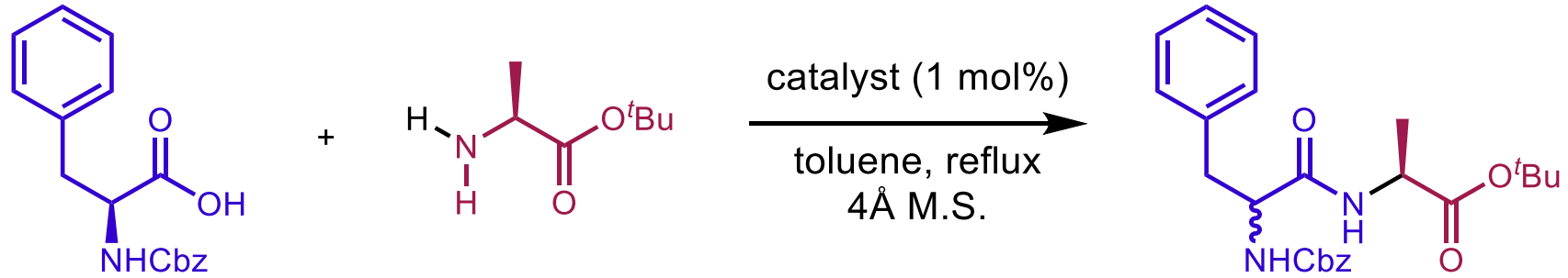
H. Yamamoto *et al*. *Org. Lett*., **2006**, *8*, 1431.

Solid Phase Amidation



run	time (h)	yield (%)
1	16	95
2	20	95
3	21	**97**



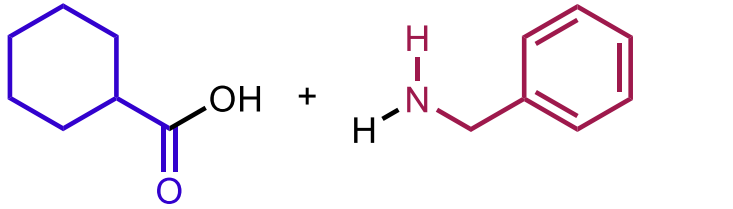


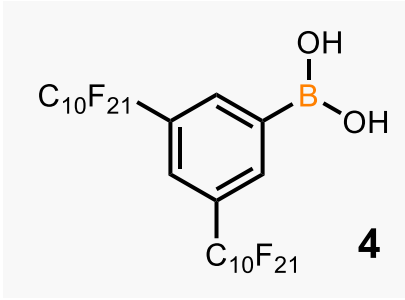
85%, complete epimerization

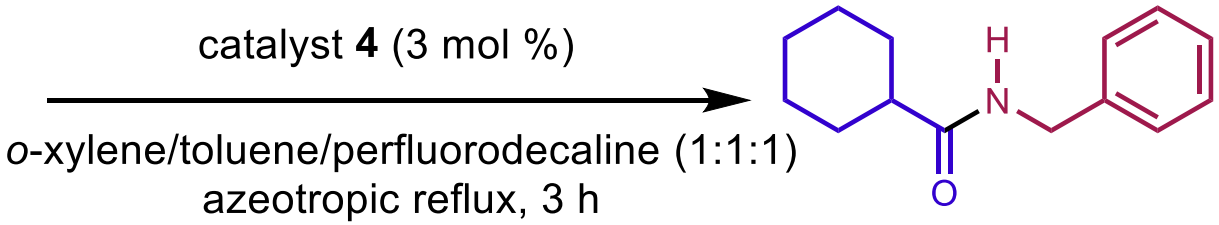
B. Wang *et al. Synthesis*, **2001**, *11*, 1611.

Solid Phase Amidation

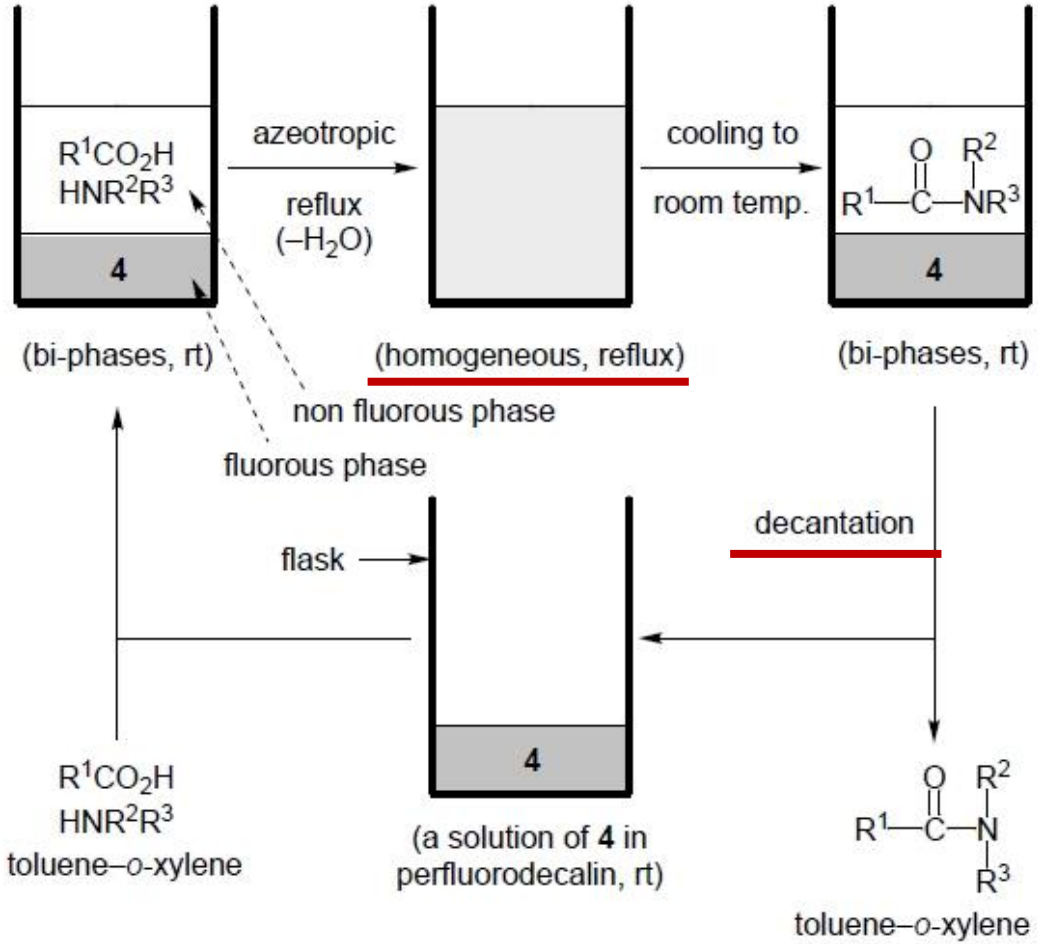
Amidation using fluorous bi-phasic catalyst







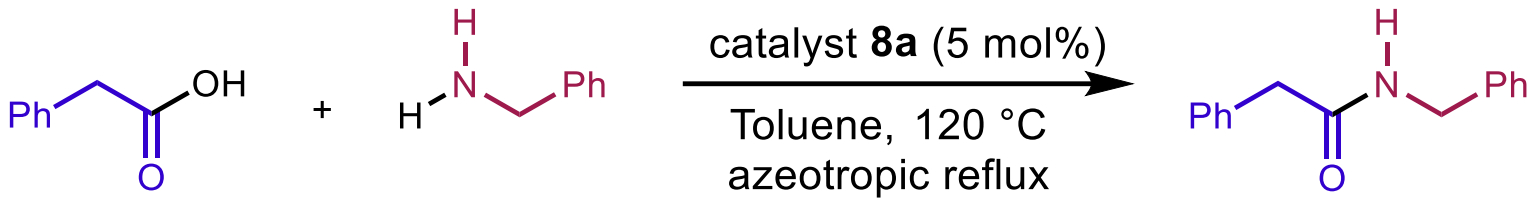
run	1	2	3	4	5
conversion (%)	>99	>99	>99	>99	>99



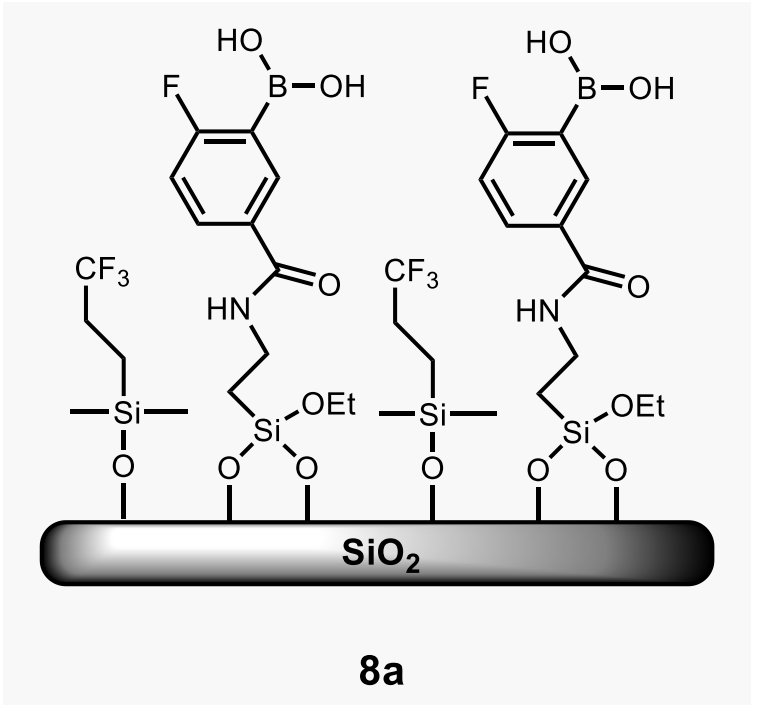
H. Yamamoto *et al*. *Synlett*, **2001**, *9*, 1371.

Solid Phase Amidation

MCF-supported boronic acids



Use of **8a**	1	2	3	4	5	6
Yield (%)	91	94	>98	>98	>98	>98



8a

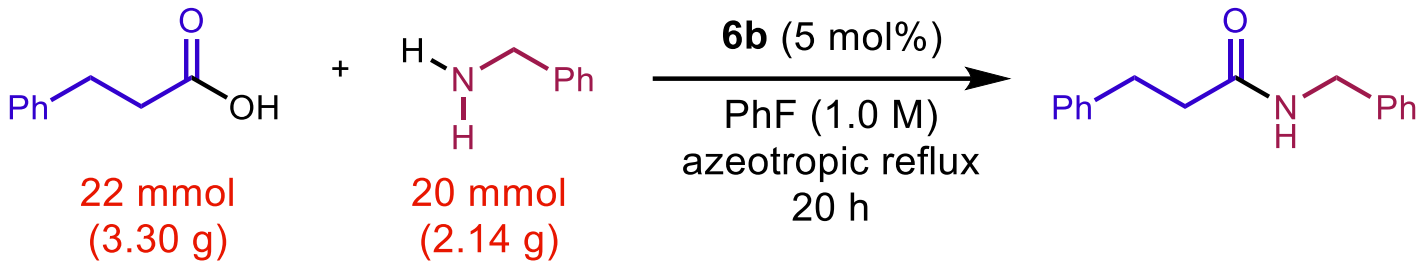
<u>MCF (mesocellular siliceous form)</u>

- large and interconnected pores
- controlled micro-environments

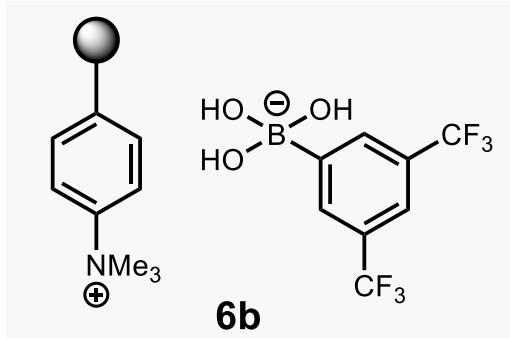
L. Gu *et al*. *Chem. Commun*., **2014**, *50*, 7017.

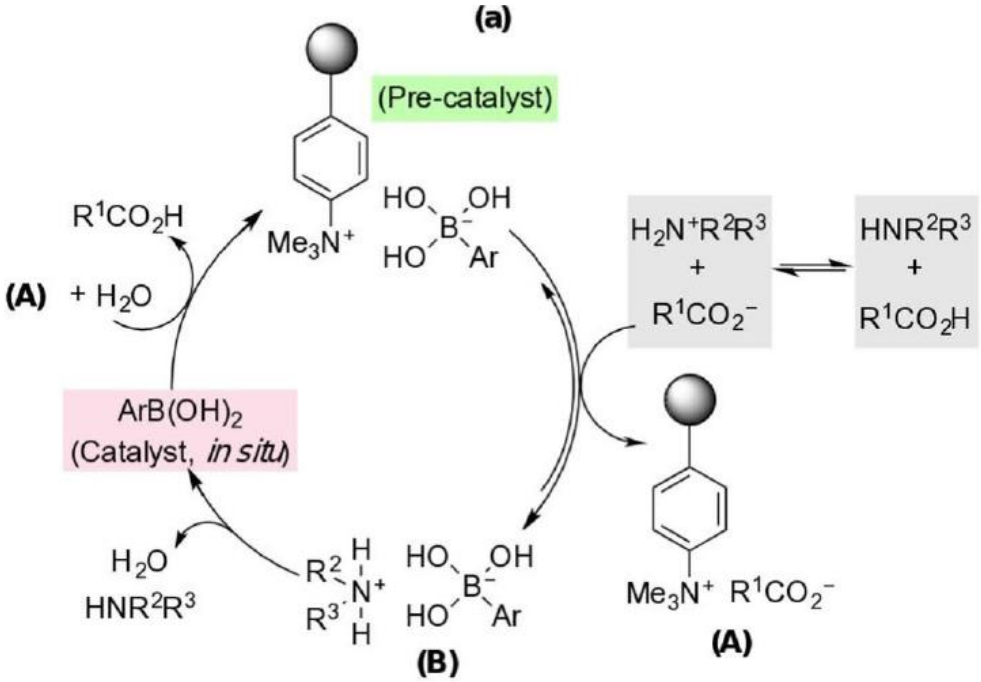
Solid Phase Amidation

DOWEX-bound boronic acid



Run	Yield (%)	Recovery rate (%)	Run	Yield (%)	Recovery rate (%)
1	>99	>95	6	>99	>95
2	>99	>95	7	>99	>95
3	>99	>95	8	>99	>95
4	>99	>95	9	>99	>95
5	>99	>95	10	>99	>95

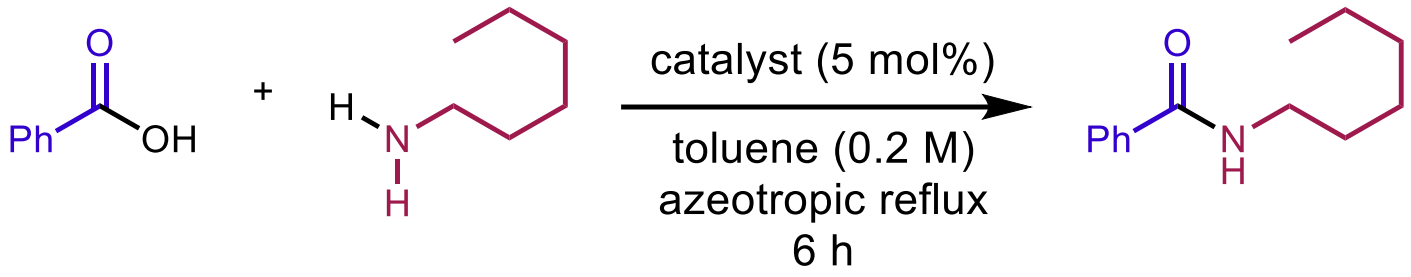




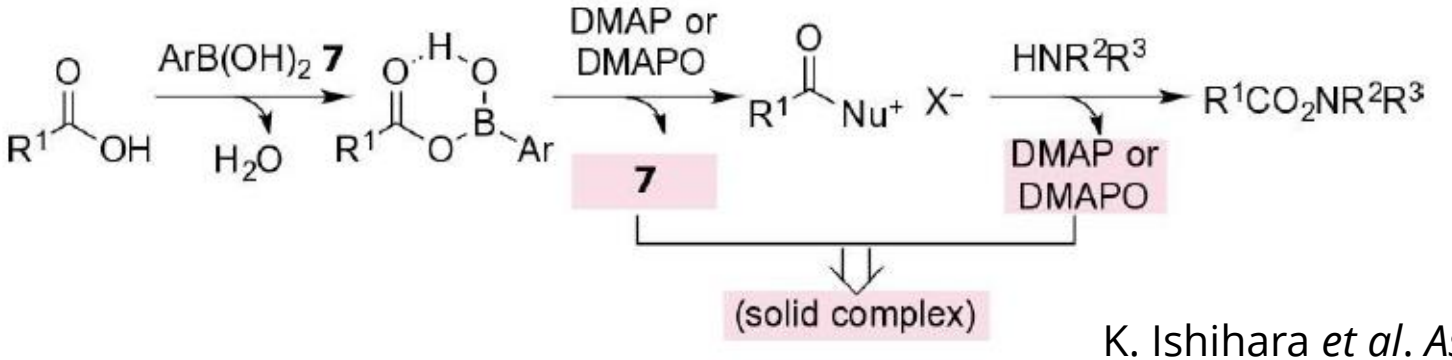
K. Ishihara *et al*. *Asian J. Org. Chem*., **2017**, *6*, 1191.

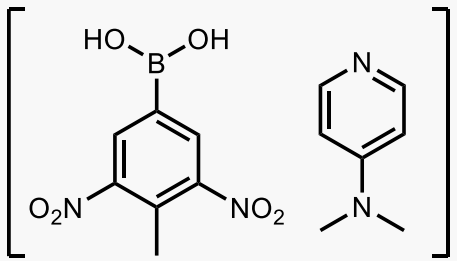
Solid Phase Amidation

Boronic acid-DMAPO or DMAP complex

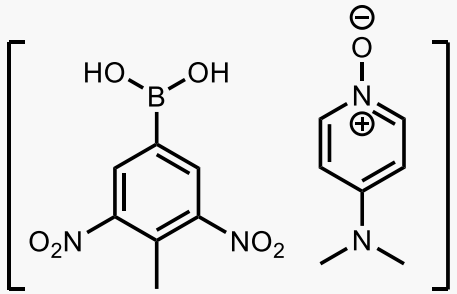


entry	catalyst	yield (%)	Recovery rate (%)
1	7a	<5	-
2	7a･DMAP	92	95
3	7a･DMAPO	99	85

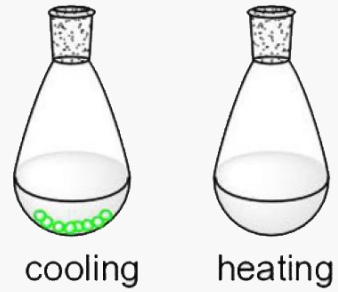




7a•DMAP

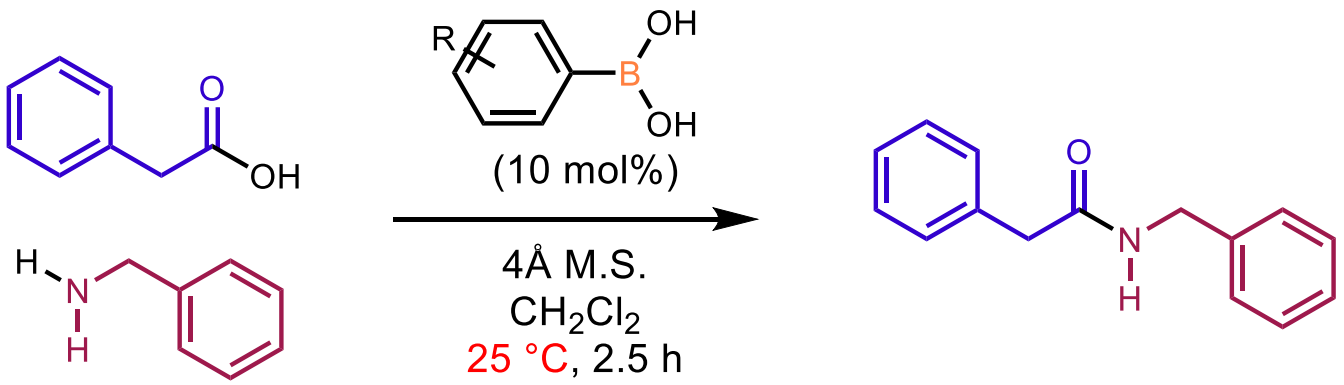


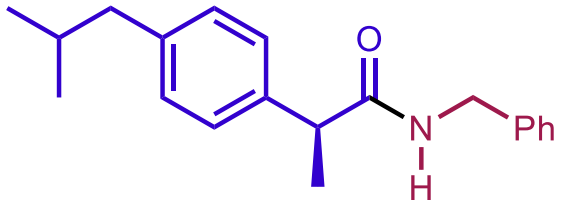
7a•DMAPO

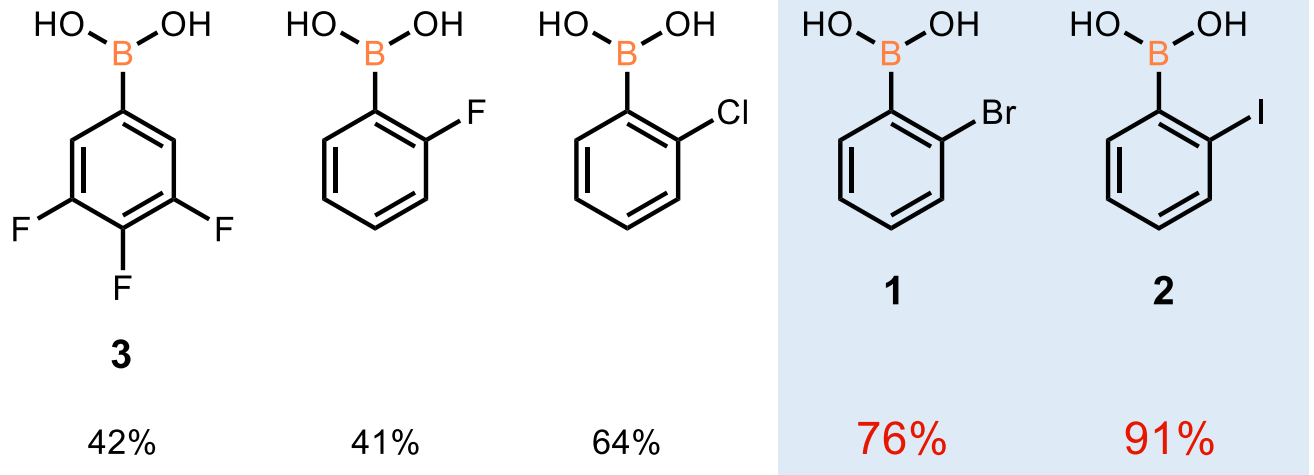


K. Ishihara *et al*. *Asian J. Org. Chem*. **2017**, *6*, 1191.

Amidation at Room Temperature







3 42%

41%

64%

1 76%

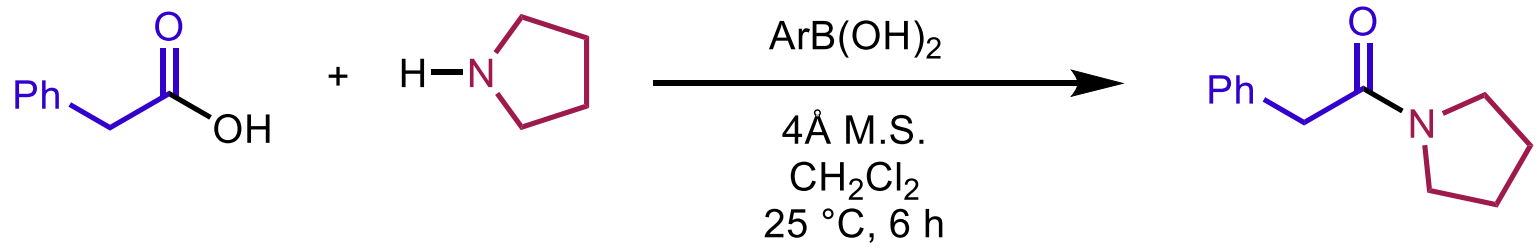
2 91%

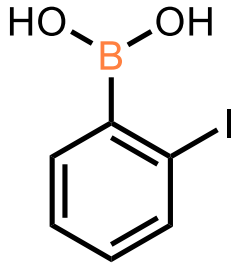
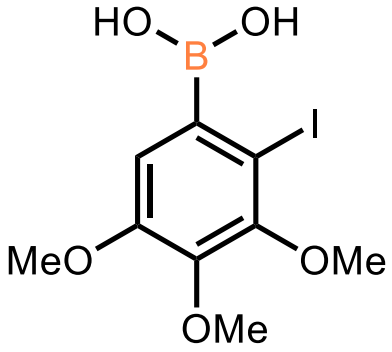
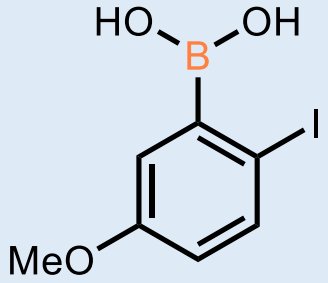
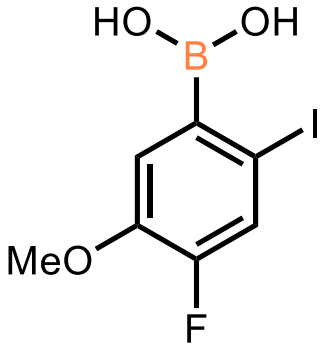
Conditons	Reaction outcomes
2, 4Å M.S, THF, 25 °C	70 %, < 5% racemization
3, toluene, reflux	30% < racemization

D. G. Hall *et al*. *Angew. Chem. Int. Ed*., **2008**, *47*, 2876.

Amidation at Room Temperature

Electron-donating group effects

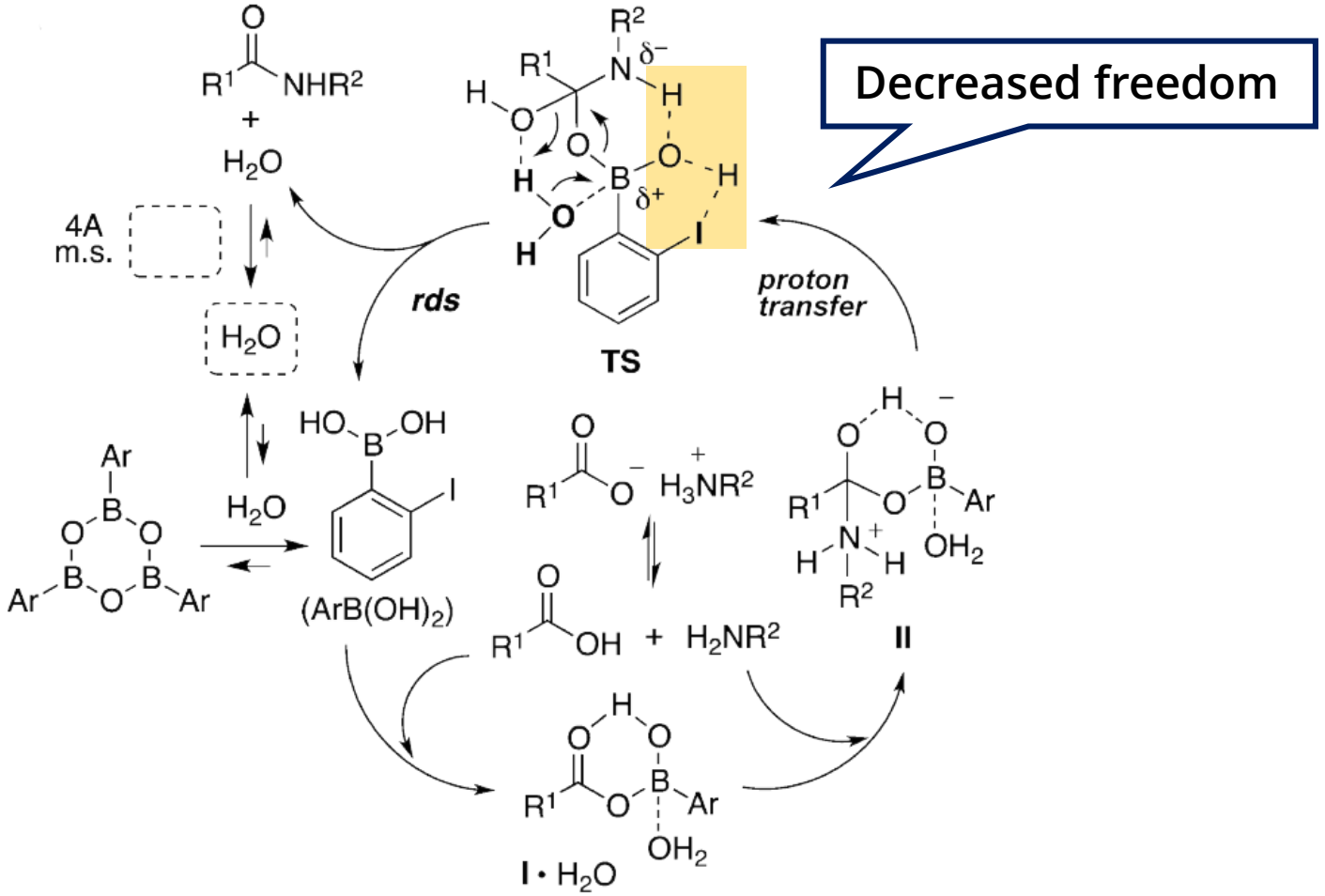


ArB(OH)$_2$				
	4a	**4b**	**4f**	**4h**
	38%	52%	72%	60%

D. G. Hall *et al. J. Org. Chem.*, **2012**, *77*, 8386.

Amidation at Room Temperature

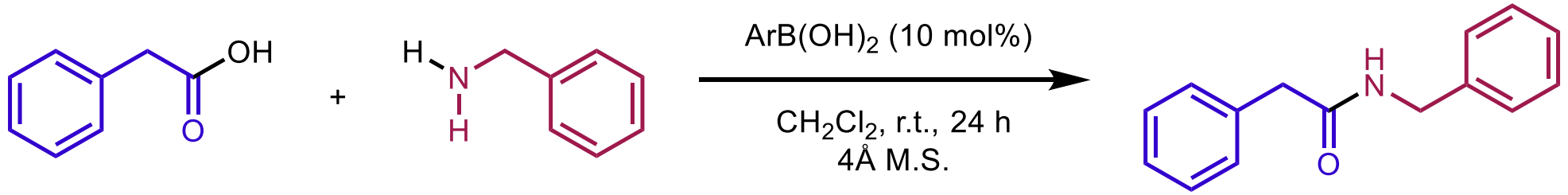
Plausible reaction mechanism



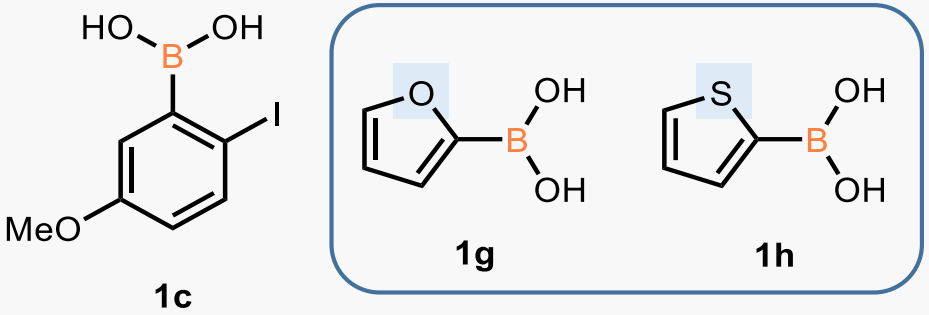
D. G. Hall *et al*. *J. Org. Chem*., **2012**, *77*, 8386.

Amidation at Room Temperature

Commercially available boronic acid



entry	Ar	yield (%)
1c	2-I, 5-MeOC_6H_3	99
1g	**2-furanyl**	**99**
1h	2-thiophenyl	92



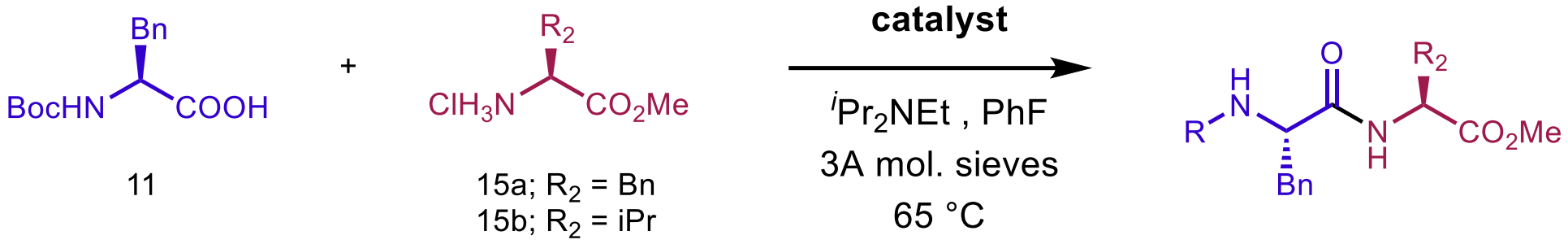
synthesized with Ag_2SO_4

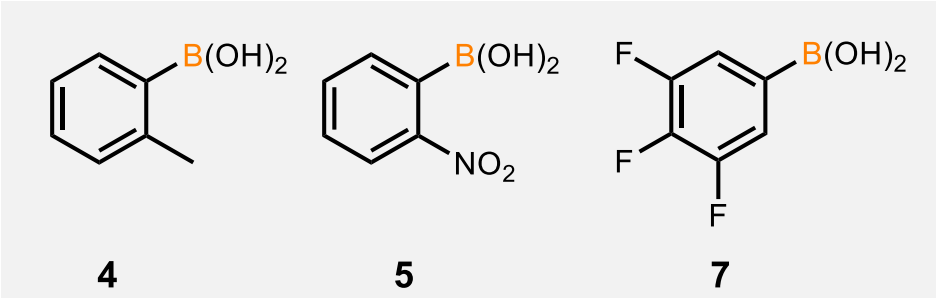
commercially available

E. K. W. Tam and A. Chen *et al*. *Eur. J. Org. Chem*., **2015**, 1100.

Dipeptide synthesis

Dual boronic acid catalysts



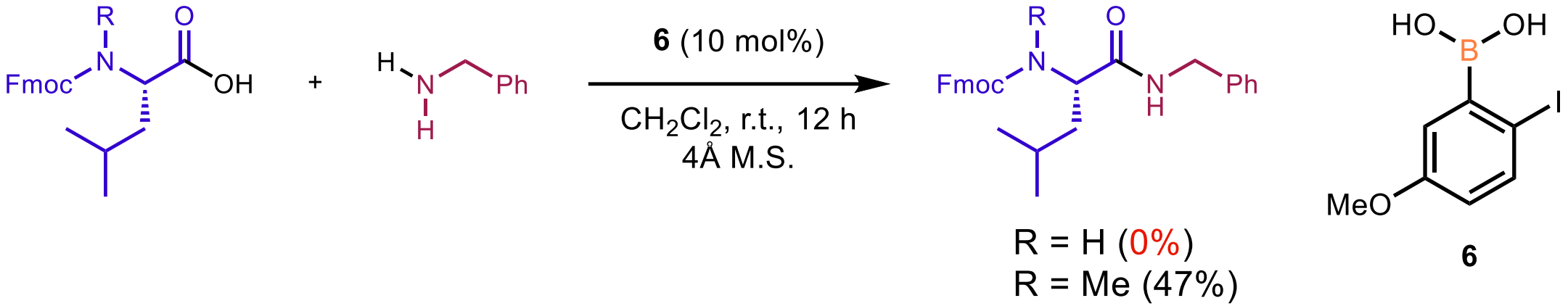


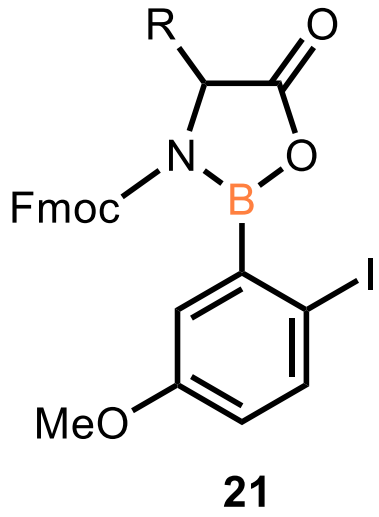
Entry	Carboxylic acid	Ammonium salt	cat	cat. Loading (X mol%)	Yield (%)
1	11	15a	7	25	13
2	11	15a	5	100	58
3	11	15b	**5**	**100**	**< 2**
4	11	15b	**5 + 4**	**50 + 50**	**55**

A. Whiting *et al*., *Eur. J. Org. Chem.* **2013**, 5692–5700.

Dipeptide synthesis

Failure of coupling with amino acid



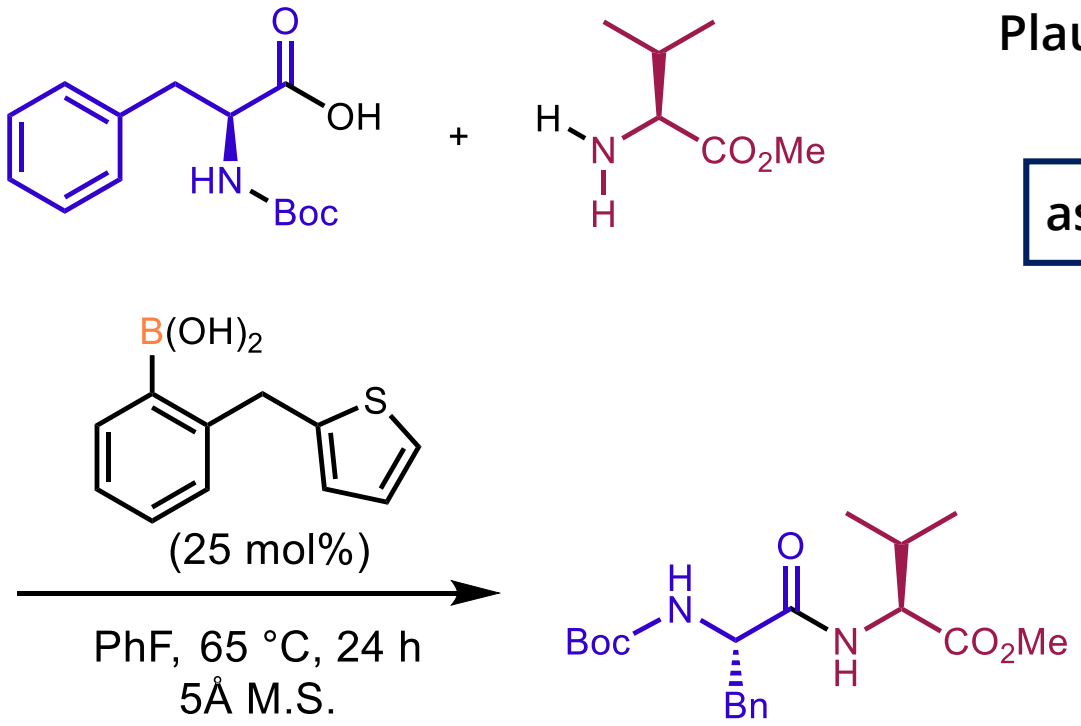


Complex was formed?

D. G. Hall *et al*., *Green Chem*, **2015**, *17*, 4016 .

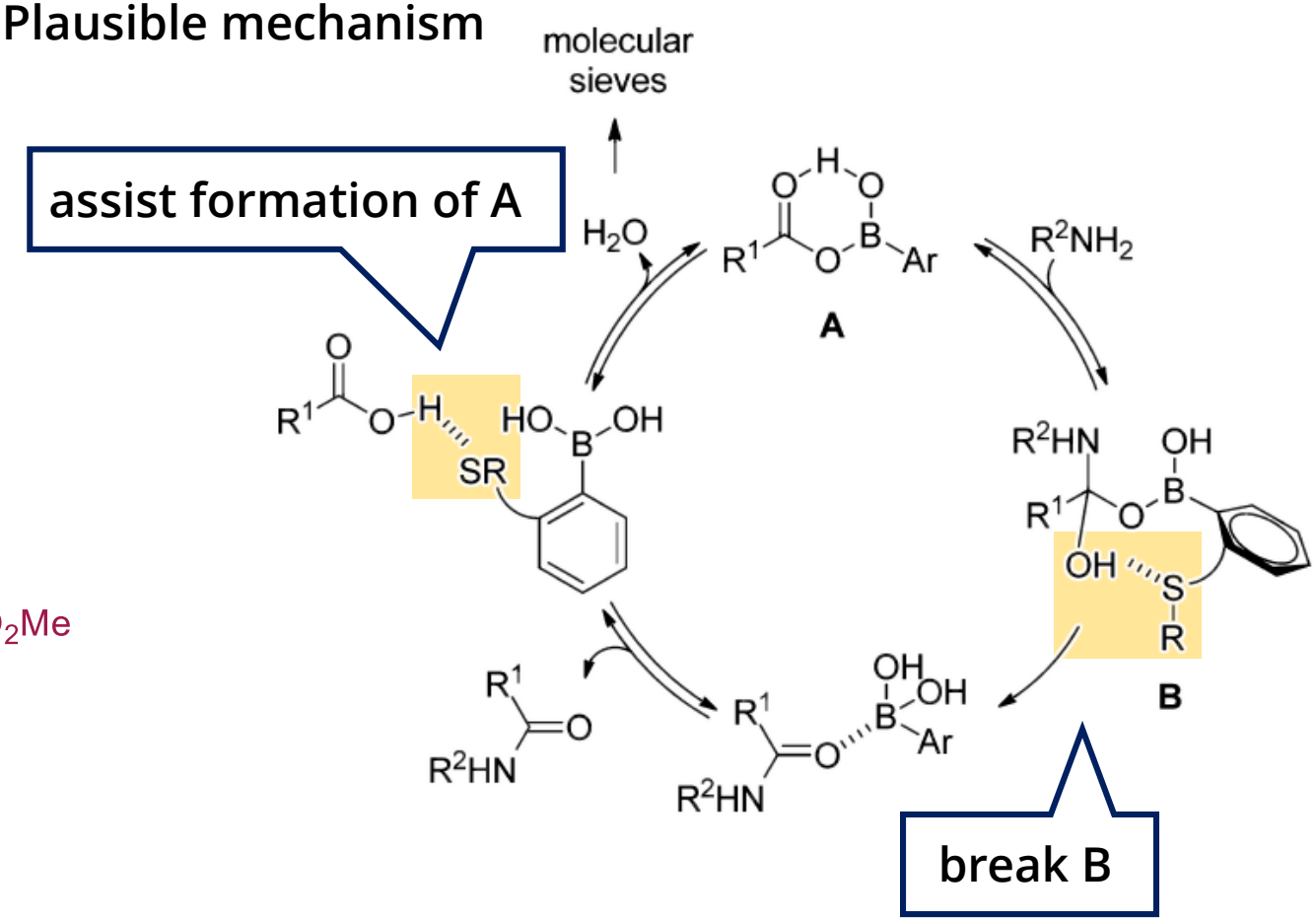
Dipeptide synthesis

Boronic acid containing thiophene



y. 50%
dr > 98:2

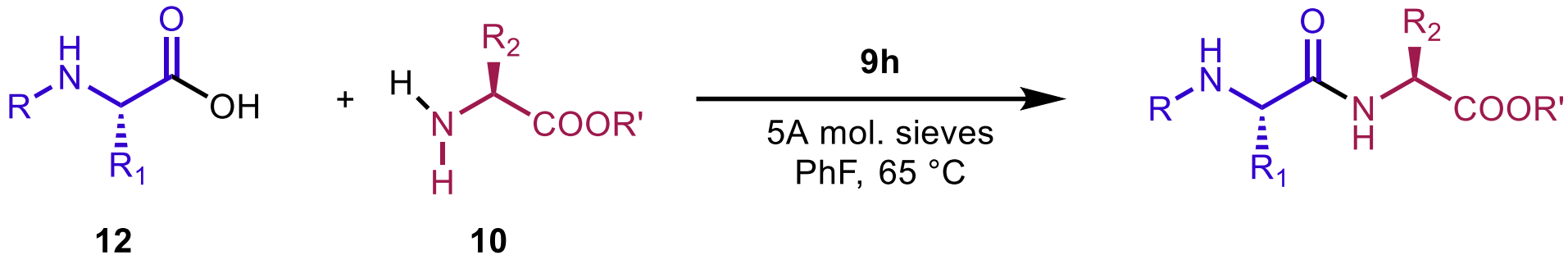
Plausible mechanism



J. Blanchet *et al.*, *J. Org. Chem*, **2015**, *80*, 4532.

Dipeptide synthesis

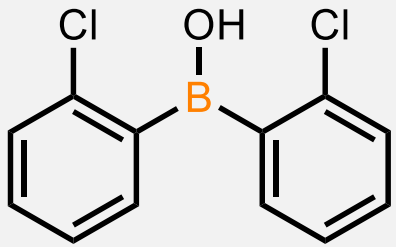
Ortho-substituted borinic acid



12 **10**

Selected Example of Peptide Synthesis

Entry	Amino acid **12**	Amino ester **10**	Yields (%)
1	Boc-Phe-OH	H_2N-Val-OMe	51
2	Boc-Phe-OH	H_2N-Phe-OMe	61
3	Z-Pro-OH	H_2N-Phe-OMe	60
4	Z-Pro-OH	H_2N-Val-OBn	59



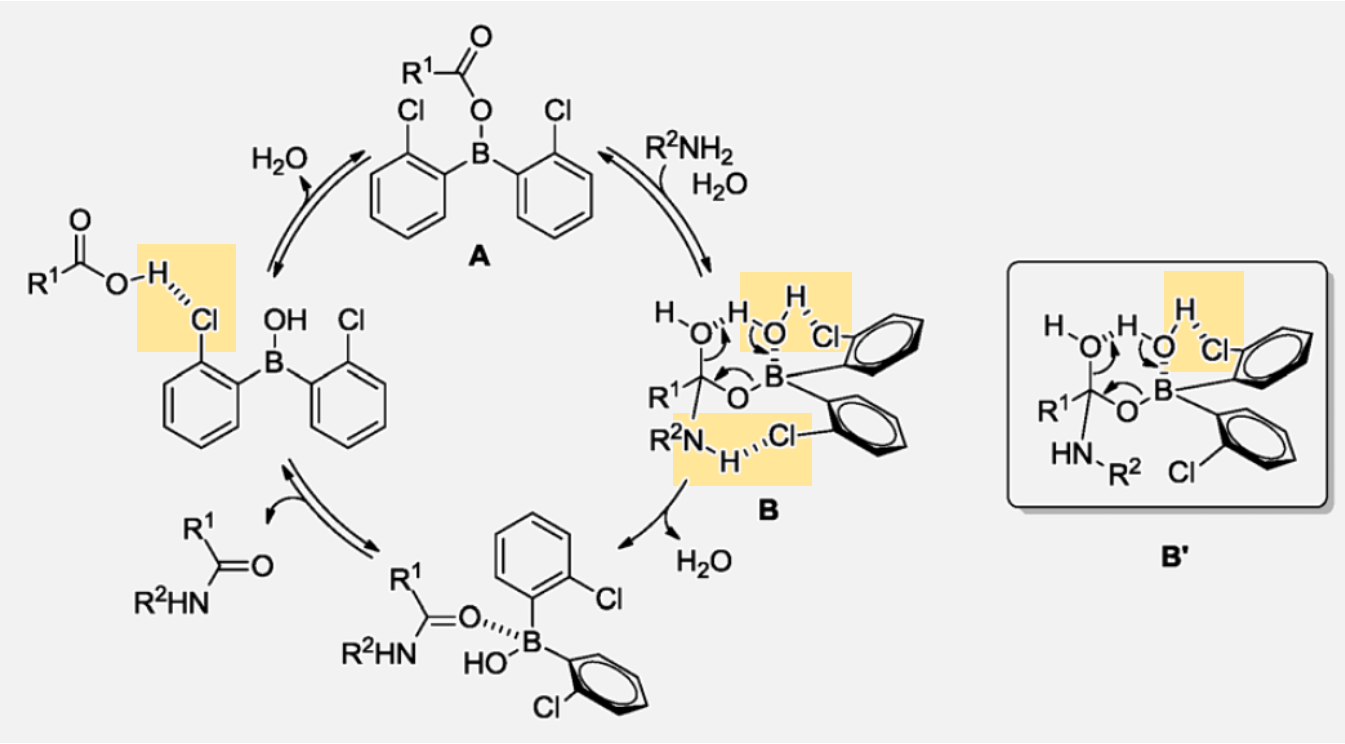
9h

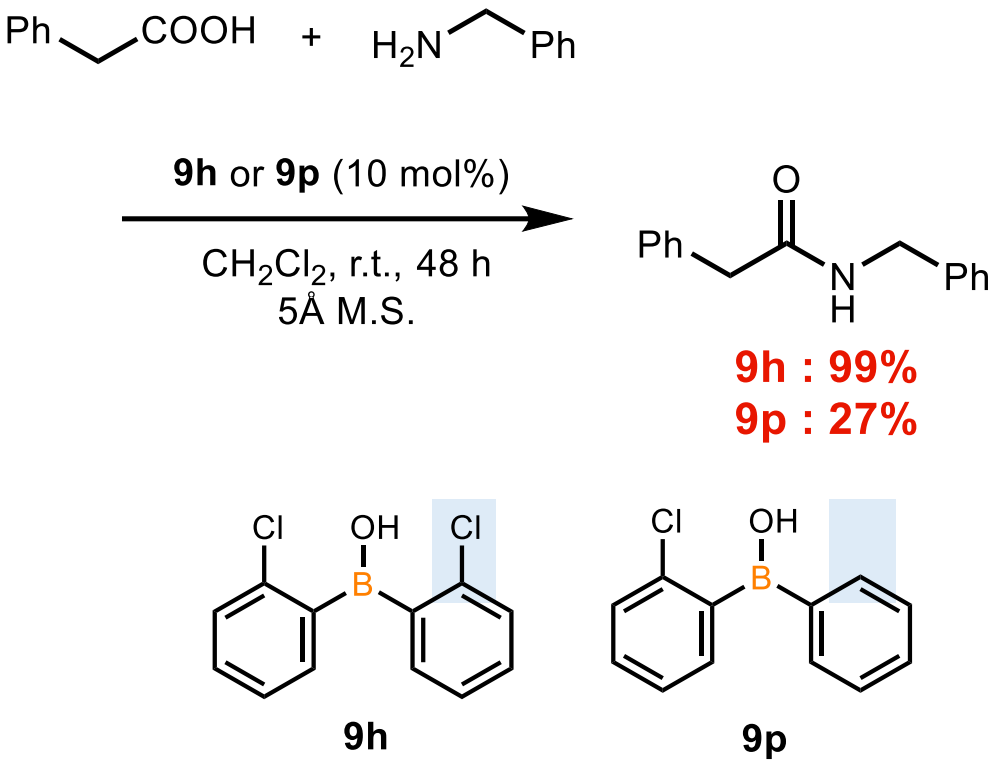
No detective epimerization

J. Blanchet *et al*., *Chem. Commun.*, **2015**, *51*, 16084.

Dipeptide synthesis

Plausible mechanism



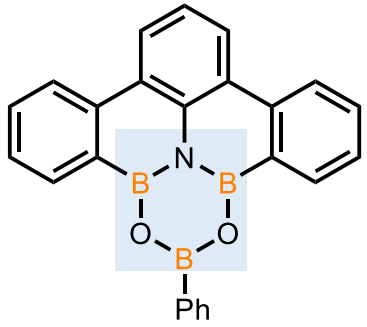


J. Blanchet *et al.*, *Chem. Commun.*, **2015**, *51*, 16084.

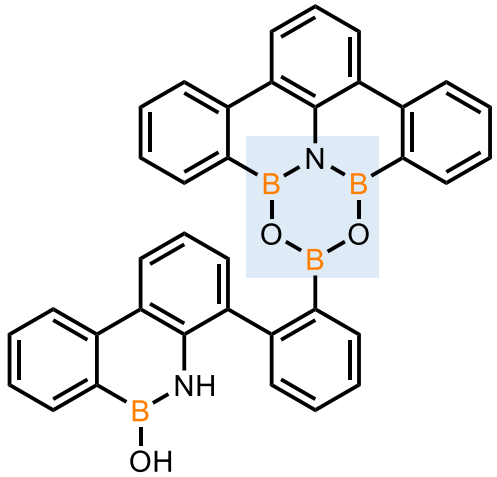
Dipeptide synthesis

DATB (B_3NO_2) system

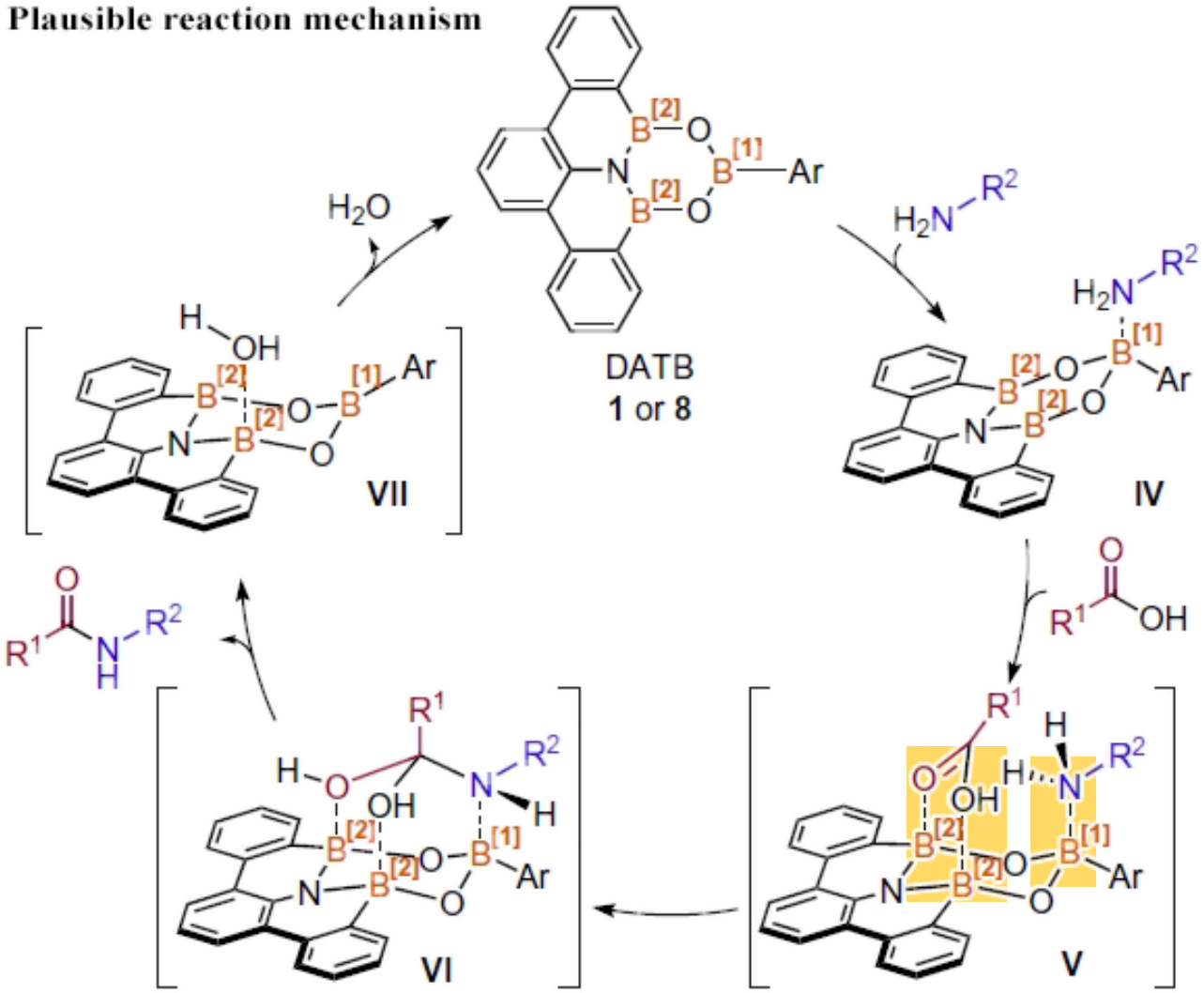
DATB



DATB **1a**



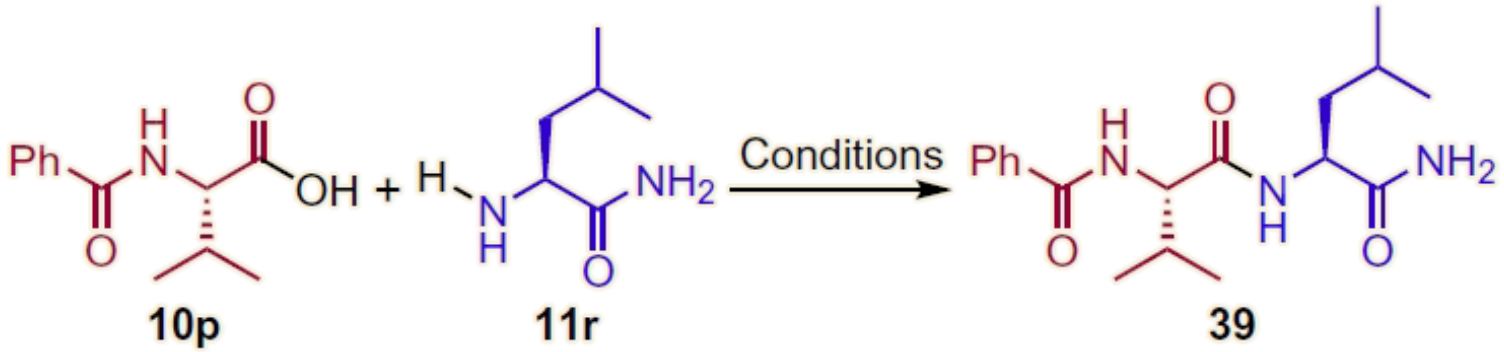
DATB **8a**



M. Shibasaki and N. Kumagai *et al.*, *Nat. Chem.*, **2017**, *9*, 571.

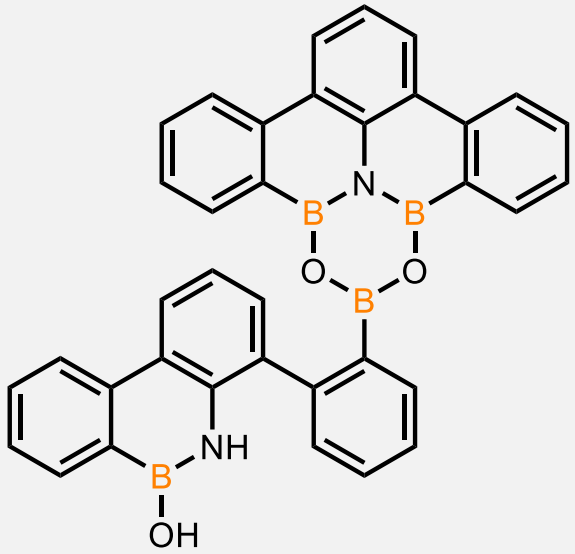
Dipeptide synthesis

Dipeptide coupling using DATB

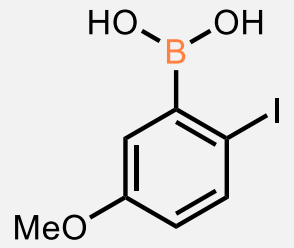


10p **11r** **39**

Conditions	Reaction outcome
8a: 5 mol%, toluene, 50 °C, 14 h*	75% yield, stereochemically pure†
EDCI: 1.0 equiv, CH_2Cl_2, RT, 4 h	89% yield, diastereomixture (53/47)†
Catalyst **14** or **15** (10 mol%) Toluene or CH_2Cl_2 50 °C (bath temperature), 24 h*	No conversion



8a



14

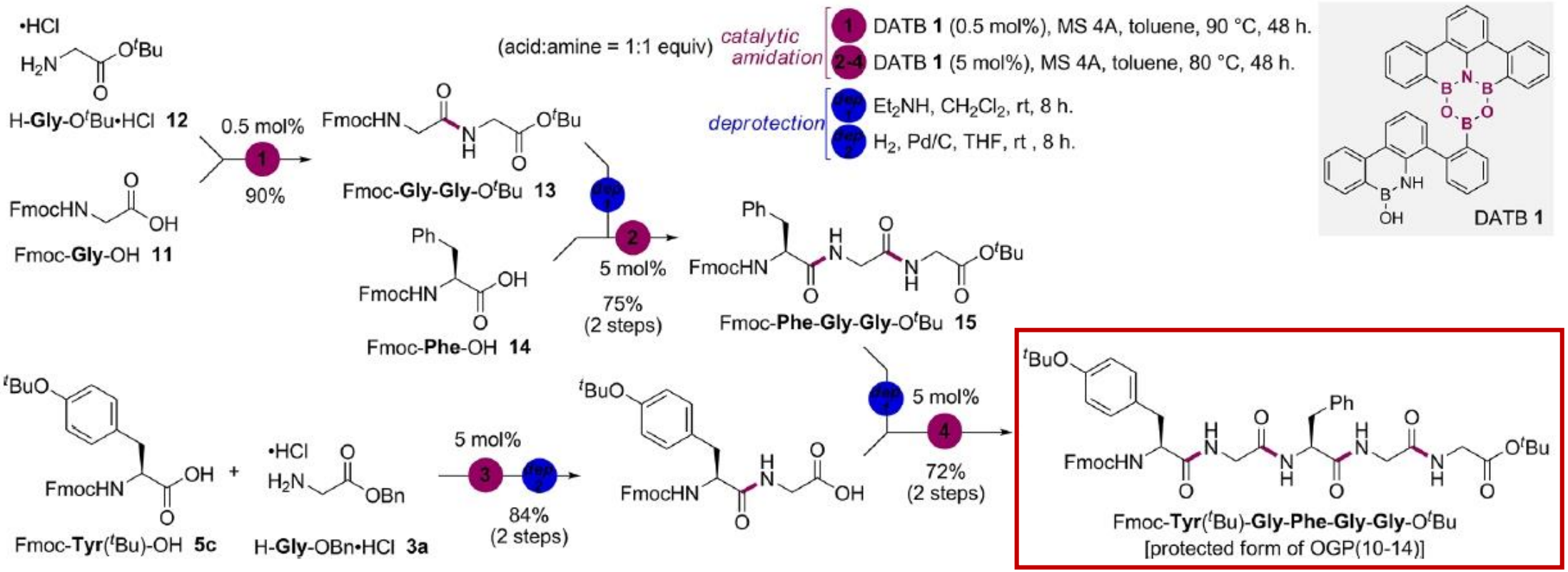
Cp_2HfCl_2

15

M. Shibasaki and N. Kumagai *et al*., *Nat. Chem.*, **2017**, *9*, 571.

Olygopeptide synthesis

Olygopeptide OGP(10-14) synthesis by using DATB



M. Shibasaki, N. Kumagai *et al*., *Org. Lett*. **2018**, *20*, 612.

Summary of Section 2

- Boronic acid catalyzed amide condensation.

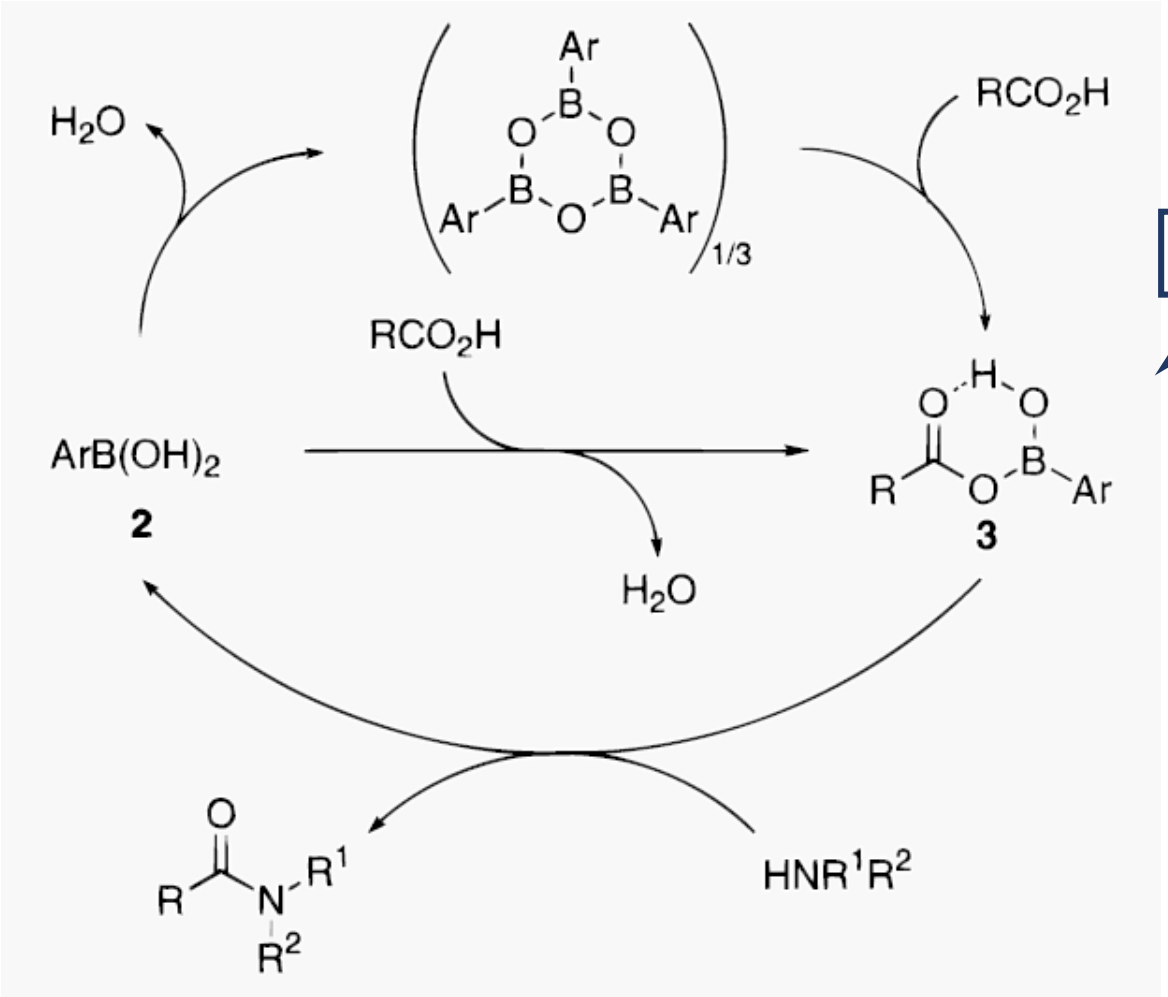
  Hall first developed reactions at room temperature.

- Recently, useful boronic acid catalysts developed for peptide synthesis.

- Catalysts such as DATB, which makes the reactions proceed with a new mechanism attracted attentions.

Catalytic Amidation

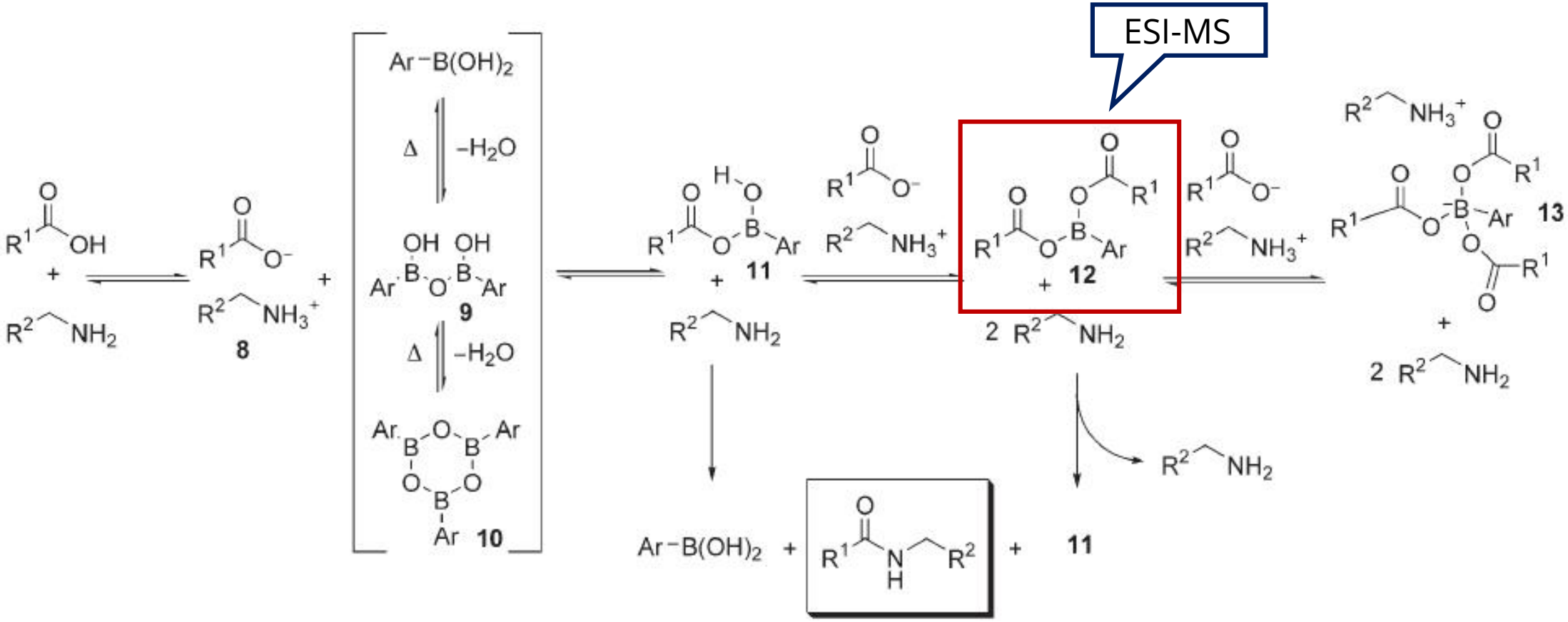
Plausible reaction mechanism



H. Yamamoto *et al*. *J. Org. Chem.* **1996,** *61,* 4196.

Reaction mechanism analysis

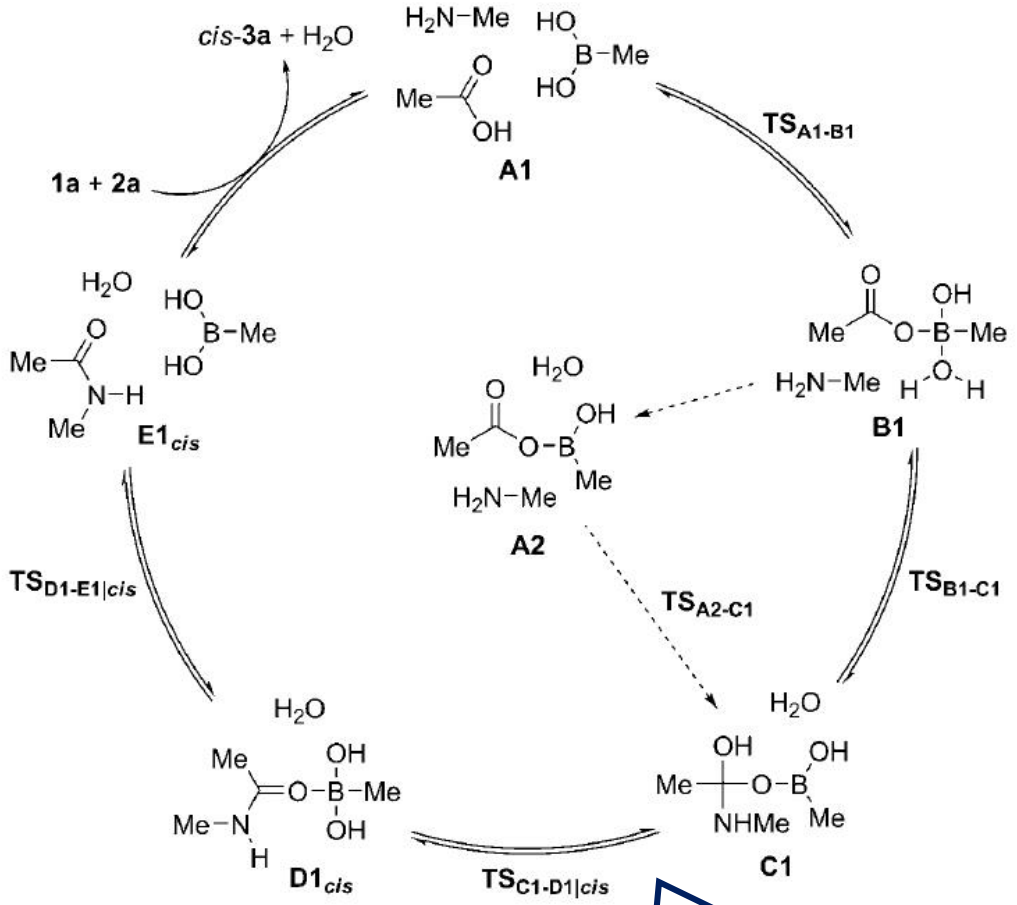
Possibility of involving bis(acyloxy)boronate

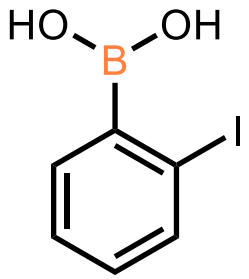


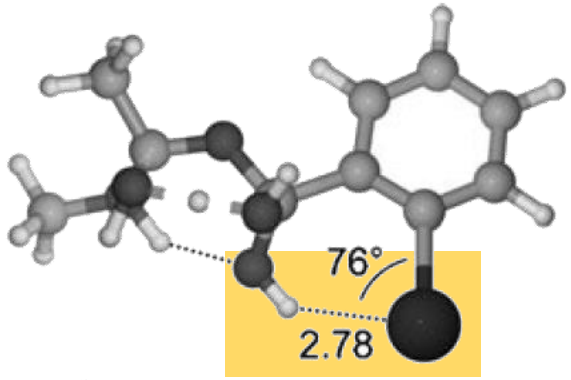
A. Whiting *et al., Adv. Synth. Catal.*, **2006**, *348*, 813.

Reaction mechanism analysis

Overall mechanism of catalytic cycle







$TS_{iodo1|cis}$

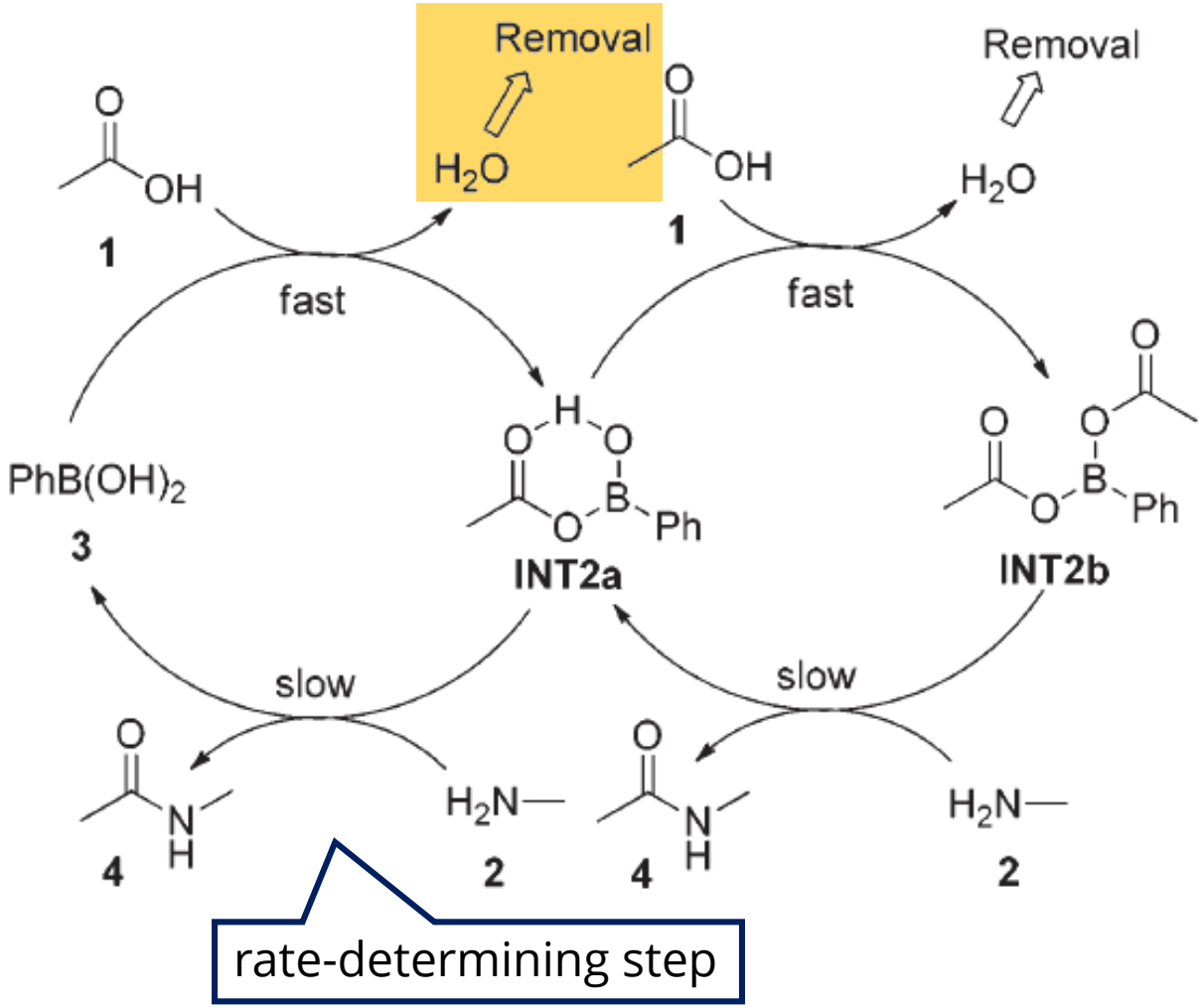
O-H···X bond

rate-determining step

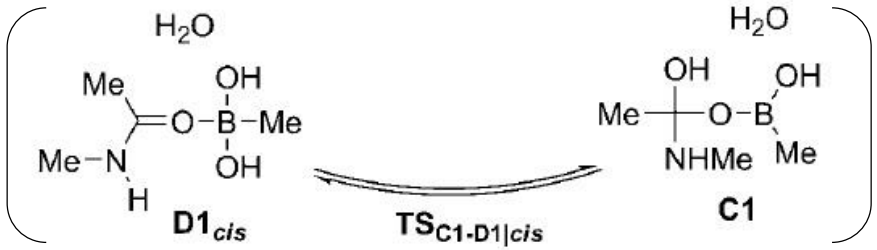
T. Marcelli, *Angew. Chem. Int. Ed.*, **2010**, *49*, 6840.

Reaction mechanism analysis

Overall mechanism of catalytic cycle



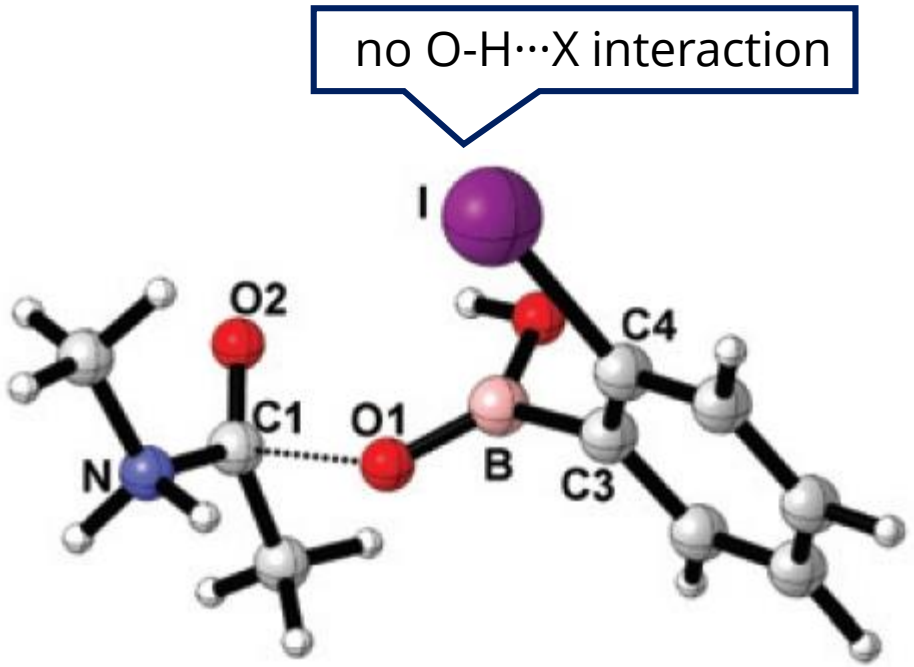
Marcelli



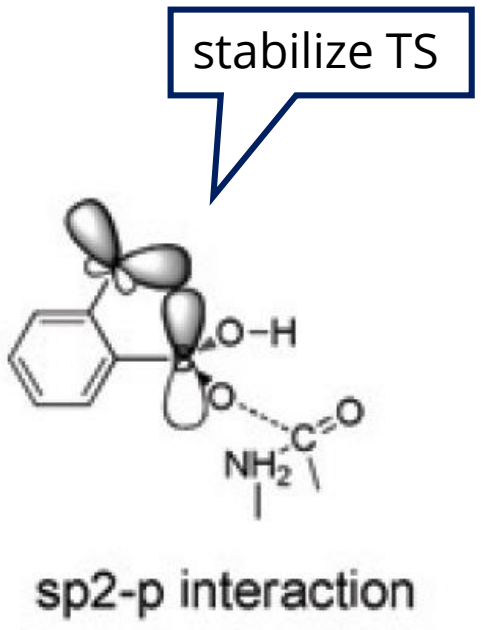
Y. Fu *et al*., *Org. Biomol. Chem*., **2013**, *49*, 6840.

Reaction mechanism analysis

Performance of the *ortho*-halo-phenylboronic acids



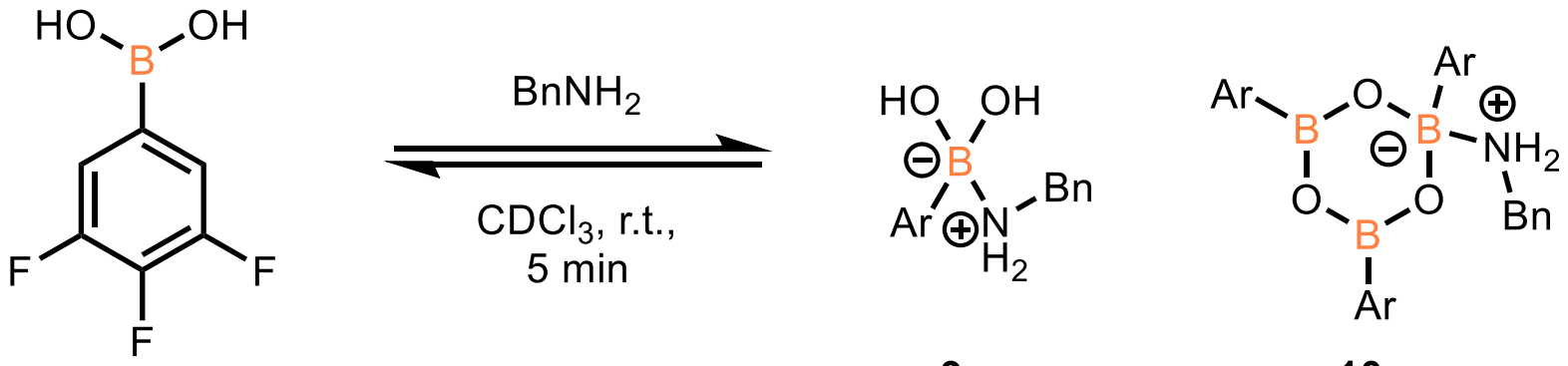
Key Transition State

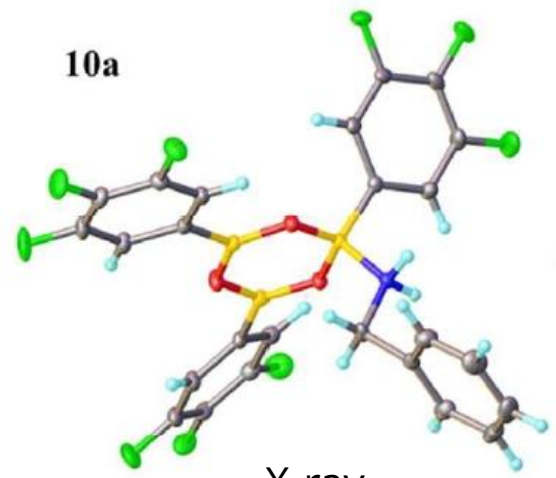


Y. Fu *et al*., *Org. Biomol. Chem*., **2013**, *49*, 6840.

Reaction mechanism analysis

Boronic acids with amines





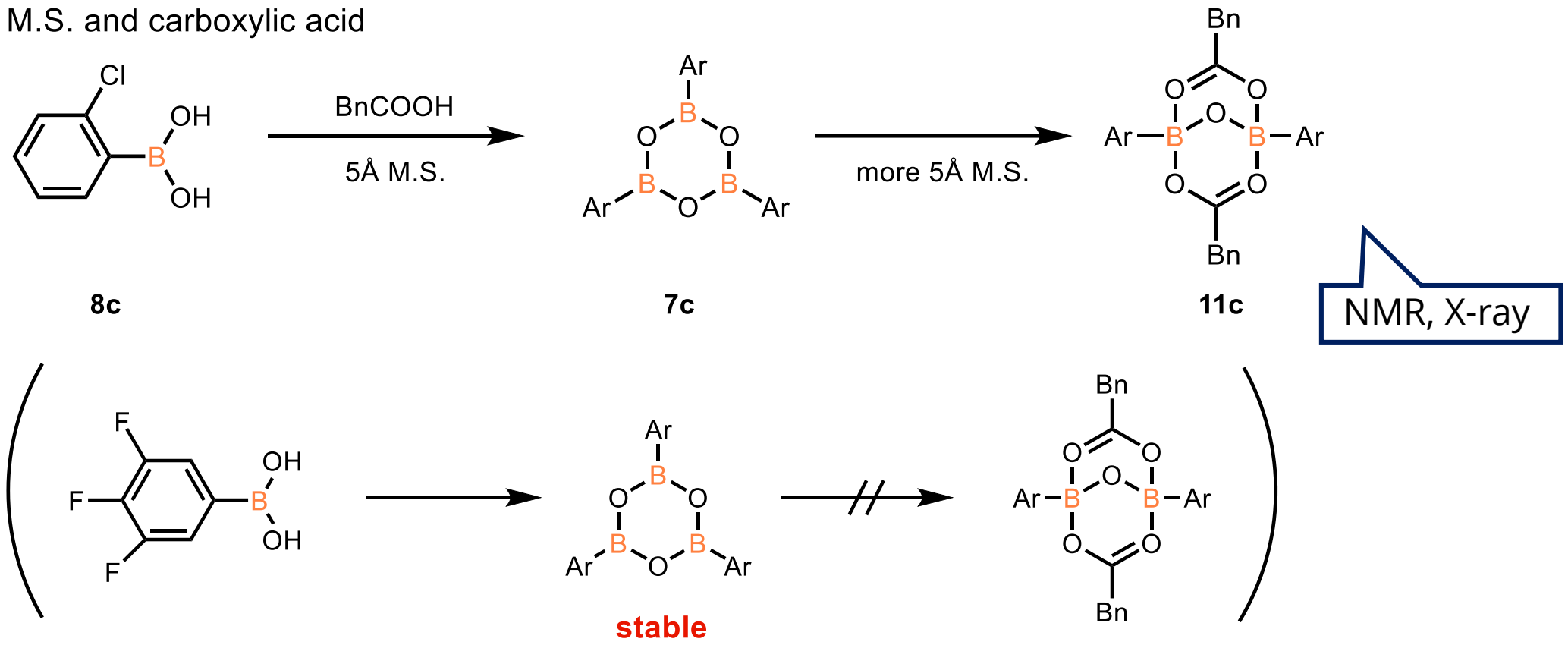
X-ray

ESI, X-ray

A. Whiting *et al*., *Chem. Sci*., **2018**, *9*, 1058.

Reaction mechanism analysis

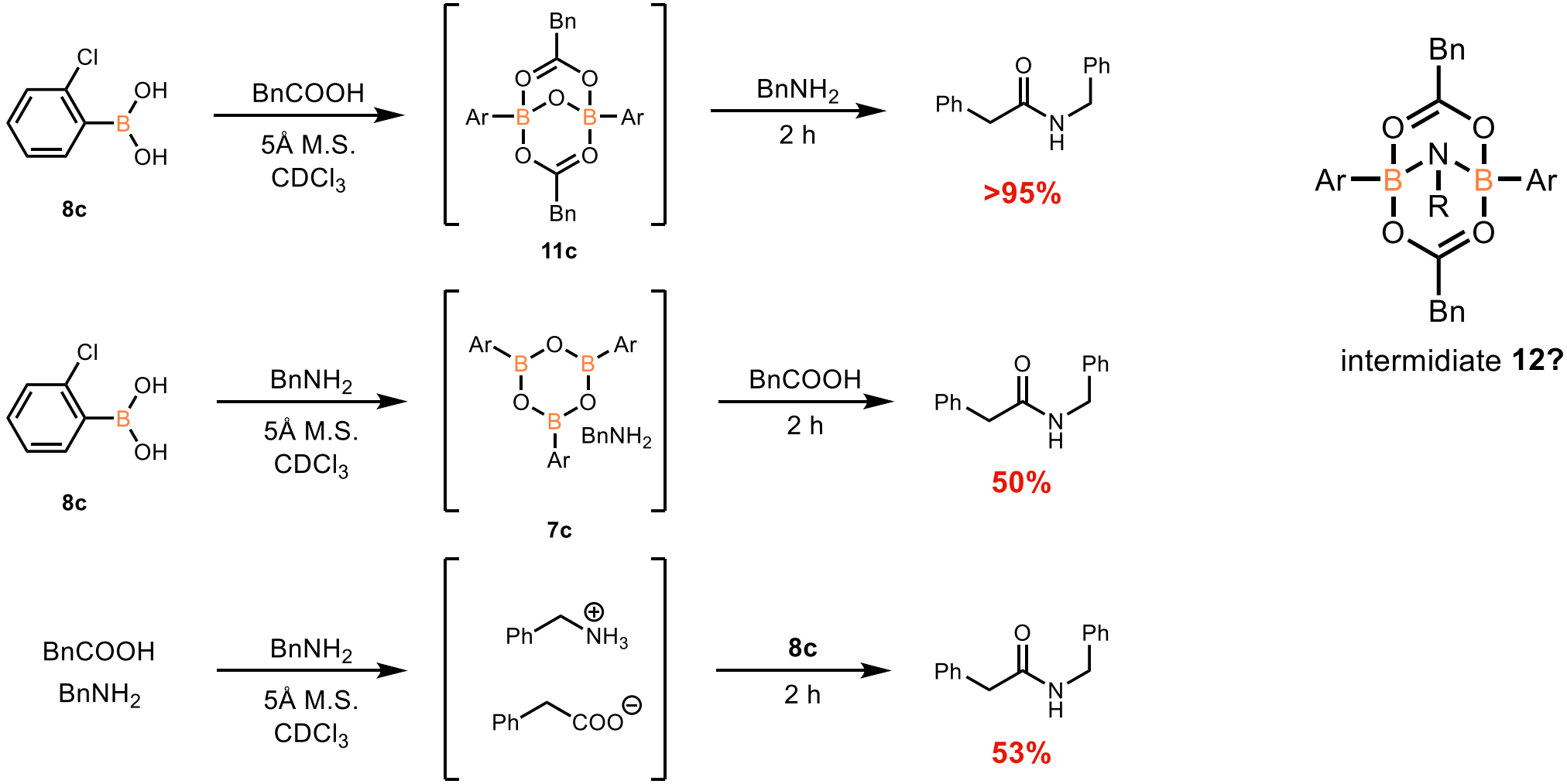
Boronic acids with carboxylic acids



A. Whiting *et al*., *Chem. Sci*., **2018**, *9*, 1058.

Reaction mechanism analysis

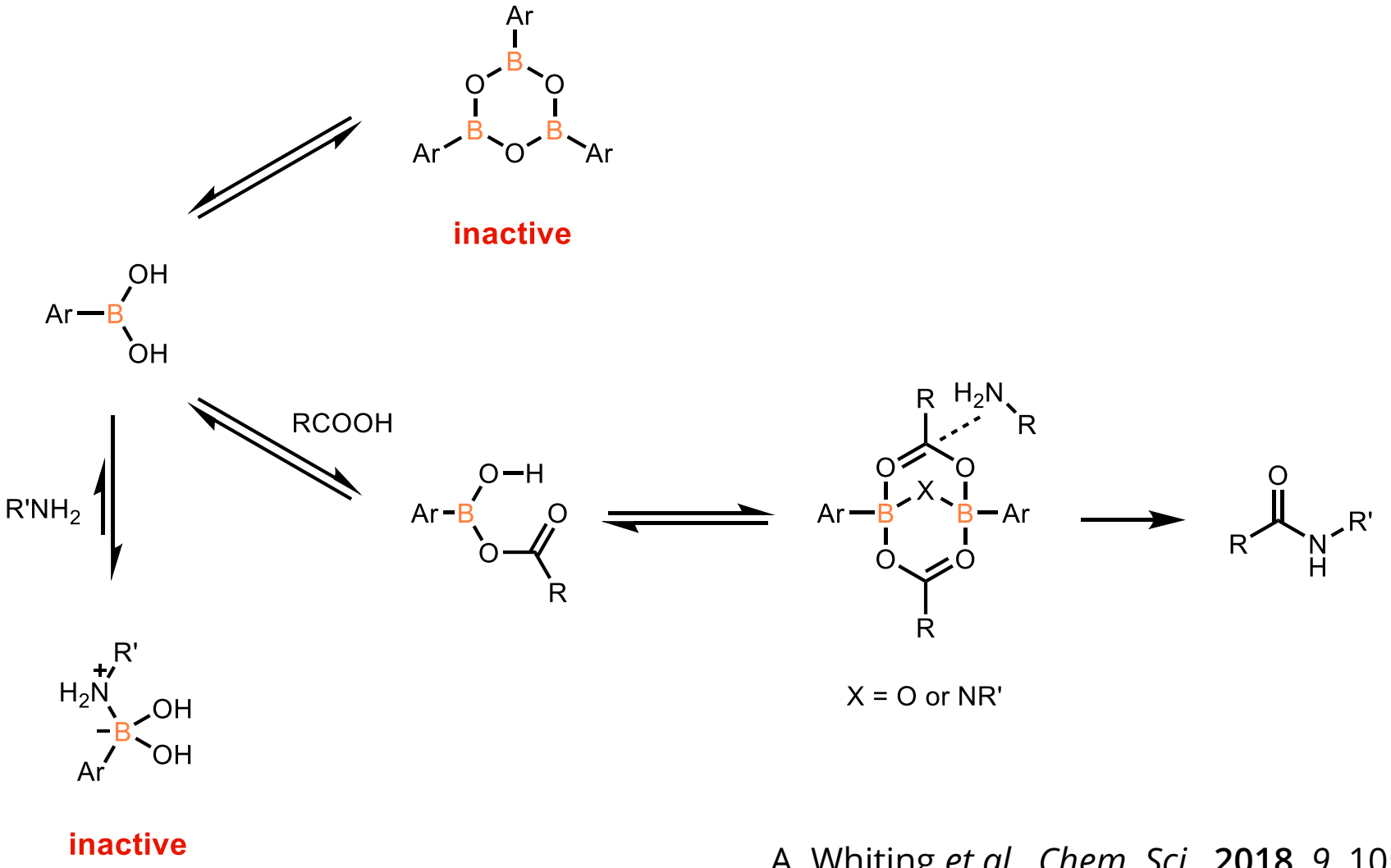
Boronic acid / carboxylic acid / amine system → **depend on order of addition**



A. Whiting *et al.*, *Chem. Sci.*, **2018**, *9*, 1058.

Reaction mechanism analysis

Boronic acid / carboxylic acid / amine system

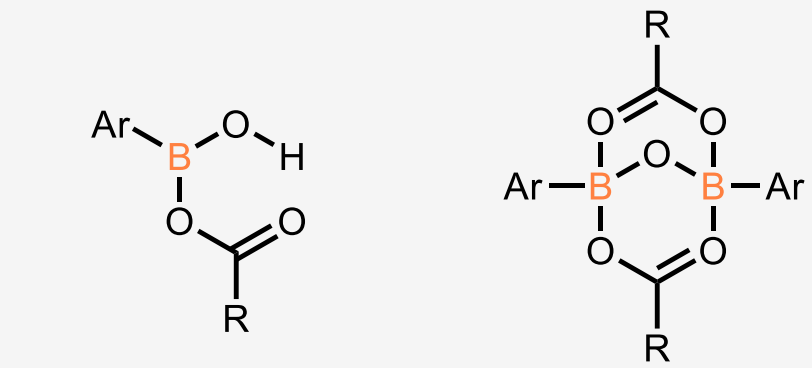


A. Whiting *et al.*, *Chem. Sci.*, **2018**, *9*, 1058.

Summary of Section 3

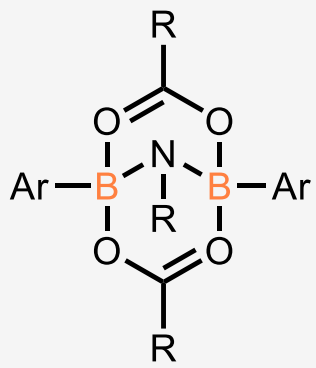
- The reaction intermediates of amide coupling by boronic acids have been thought to be mono(acyloxy)boronate or bis(acyloxy)boronate.

- If dimers of boronic acid such as 11 and 12 are intermediates, boronic acids which are easy to dimerize can be potential candidates.



mono(acyloxy)boronate

11



12?

Summary

- Peptide synthesis achieved in recent years using boronic acids derivatives.

- Further mechanistic insights will provide valuable assistance for the design of more active boronic acids.