ASAP report

Reporter: Yi Xiao

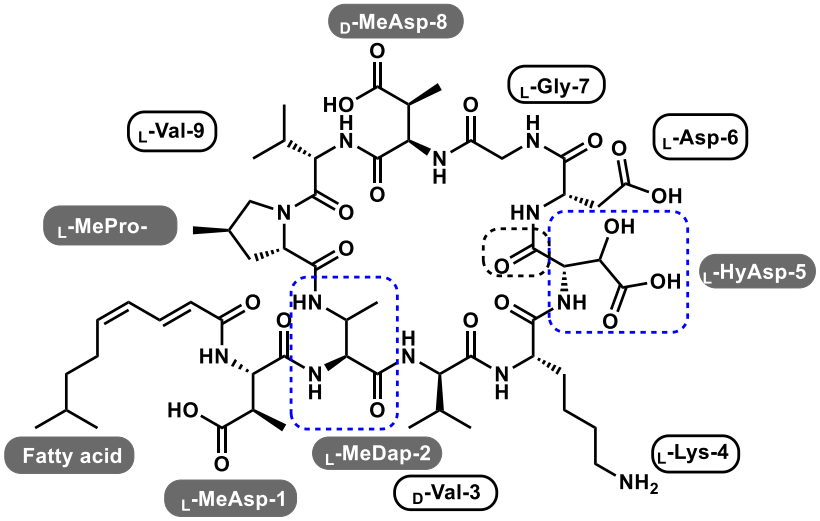
Supervisors: *Prof.* Tao Ye

***Dr.* Yian Guo**

August 10th, 2020

Total Synthesis of Malacidin A by β-Hydroxyaspartic Acid Ligation Mediated Cyclization and Absolute Structure Establishment

Zhenquan Sun[a]+, Zhuo Shang[c]+, Nicholas Forelli[c], Kathy Hiu Laam Po[d], Sheng Chen[d], Sean F. Brady*[c] and Xuechen Li*[a, b]



Malacidin A

1a: L-(3S)-MeDap, L-(3R)-HyAsp
1b: L-(3R)-MeDap, L-(3R)-HyAsp
1c: L-(3S)-MeDap, L-(3S)-HyAsp
1d: L-(3R)-MeDap, L-(3S)-HyAsp

Introduction

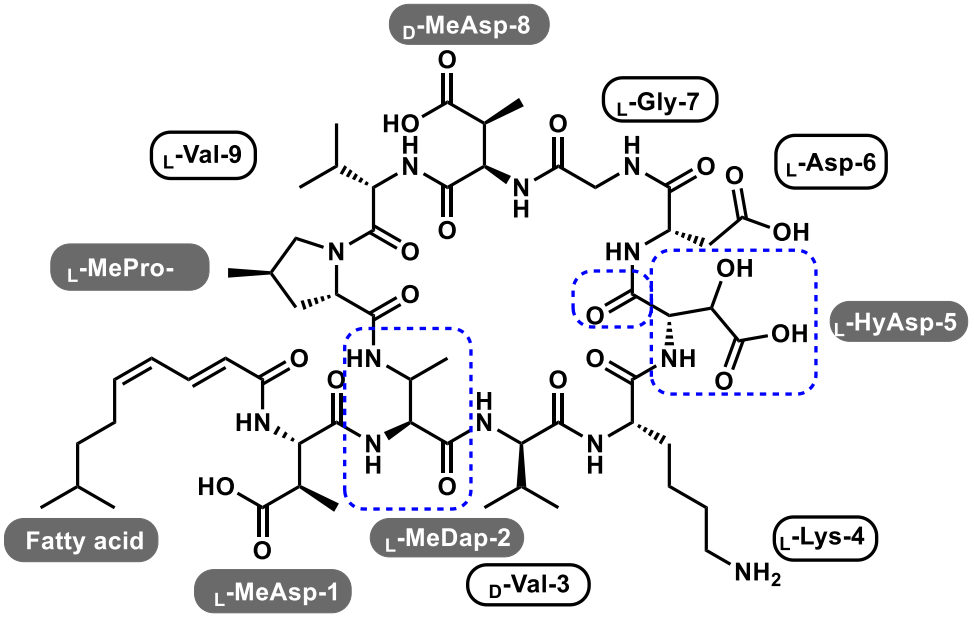
Dr. Xuechen Li
Professor
Department of Chemistry &
State Key Laboratory of Synthetic Chemistry

2018-	Professor, HKU
2014-2018	Associate Professor, HKU
2009-2014	Assistant Professor, HKU
2007-2009	Postdoc, Memorial Sloan Kettering Cancer Center (Professor Samuel Danishefsky)
2004-2007	Ph.D, Harvard University (Professor Dan Kahne)
2000-2003	M.Sc, University of Alberta (Professor Ole Hindsgaul)
1995-1999	B.Sc, Nankai University

Research

I. Method developing for Bio-macromolecules synthesis
II. Medicinal Chemistry of Natural Products
III. Function Definition of Macromolecules and their PTMs
IV. Drug Development

Introduction



Malacidin A

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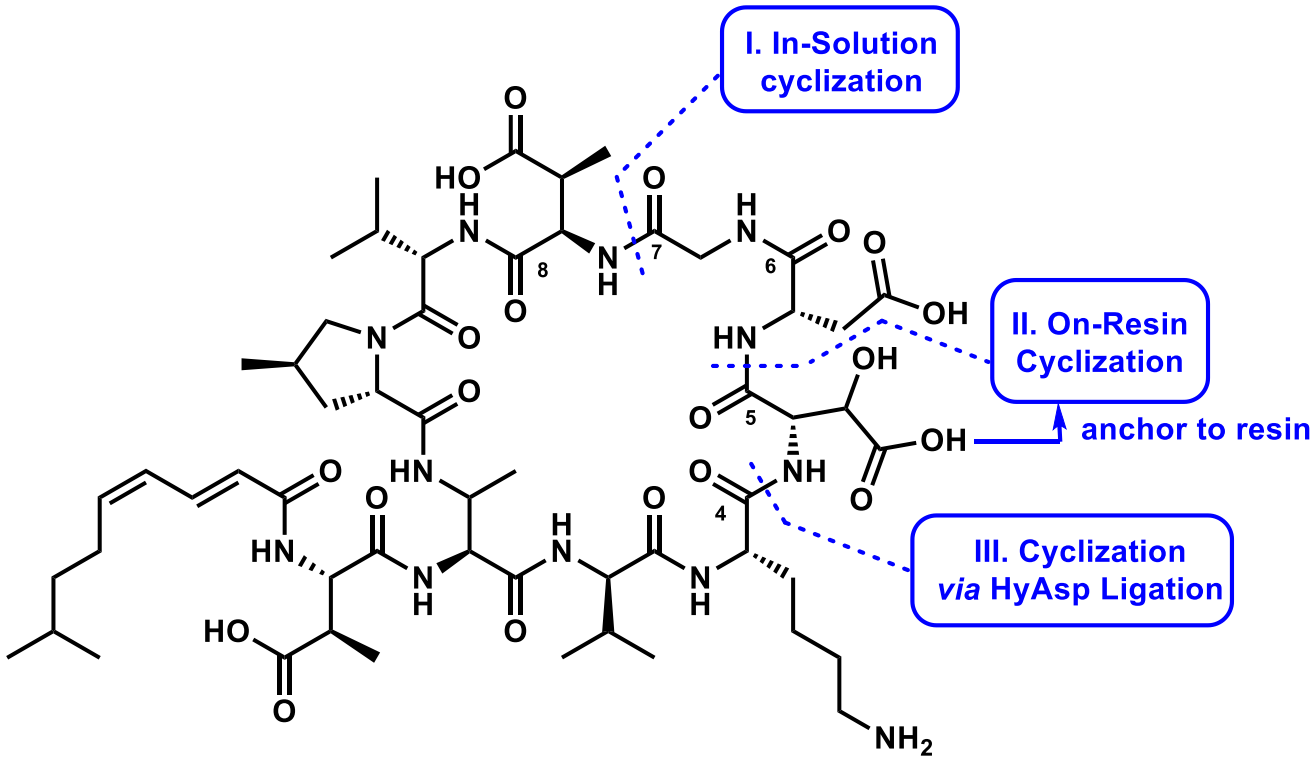
1d: L-(3R)-MeDap, L-(3S)-HyAsp

Biology activity:

Malacidin A exhibits broad activity against Gram-positive bacteria including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE), and has potent MIC values (0.2-2 μg/mL) in the presence of the divalent cation calcium.

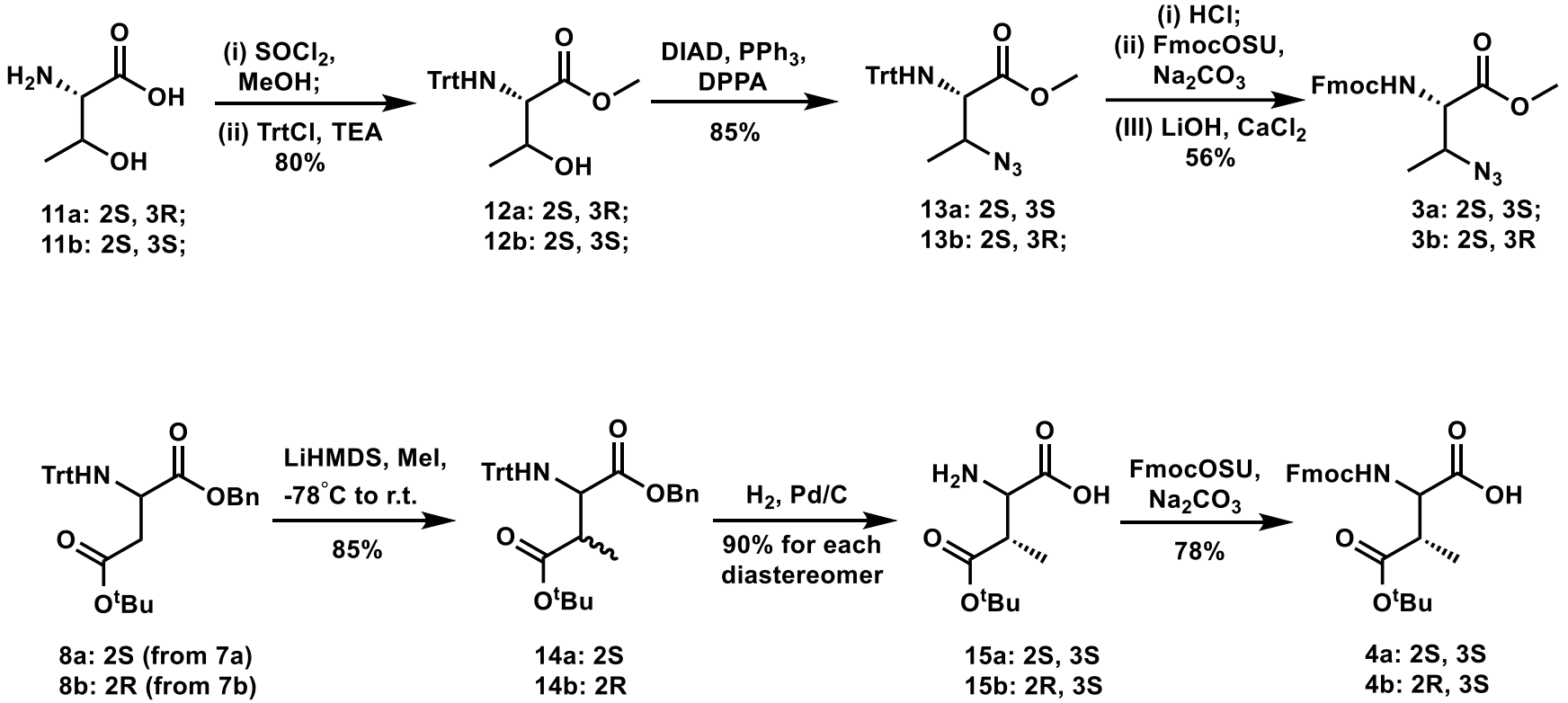
Total Synthesis of Malacidin A

Retrosynthesis



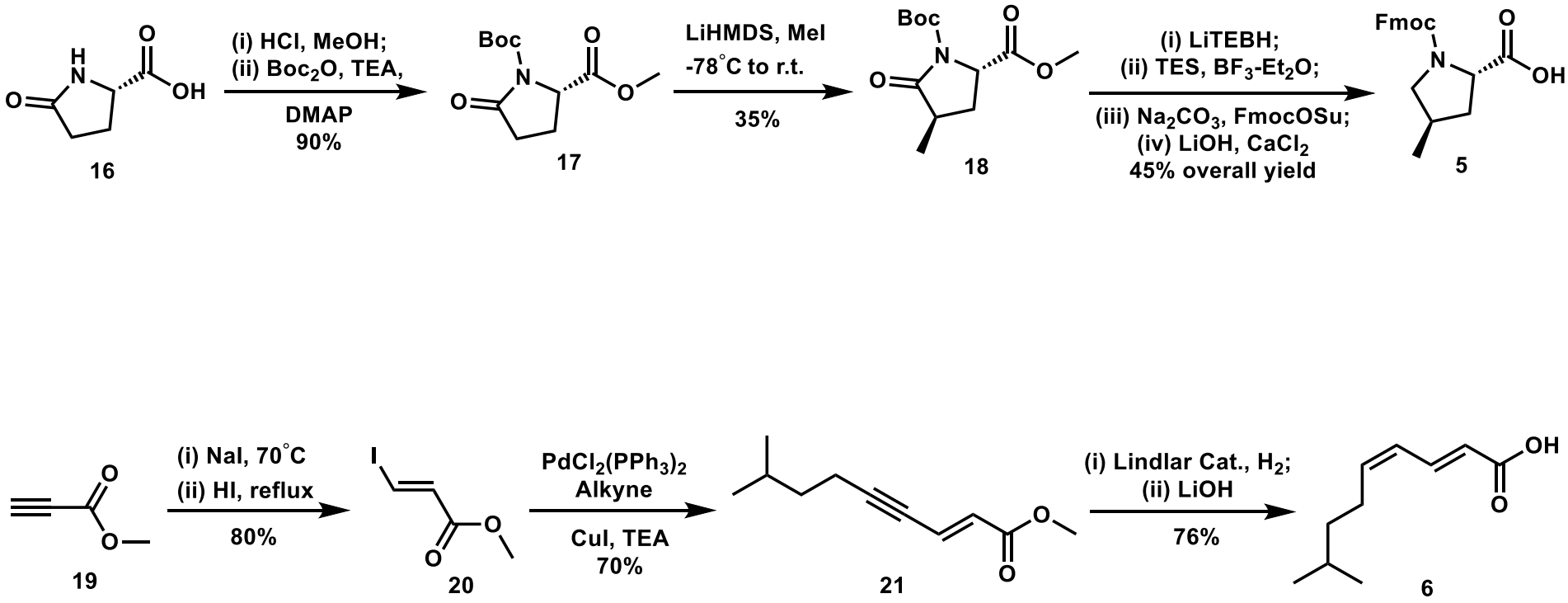
Total Synthesis of Malacidin A

Preparation of 3,4,5,6



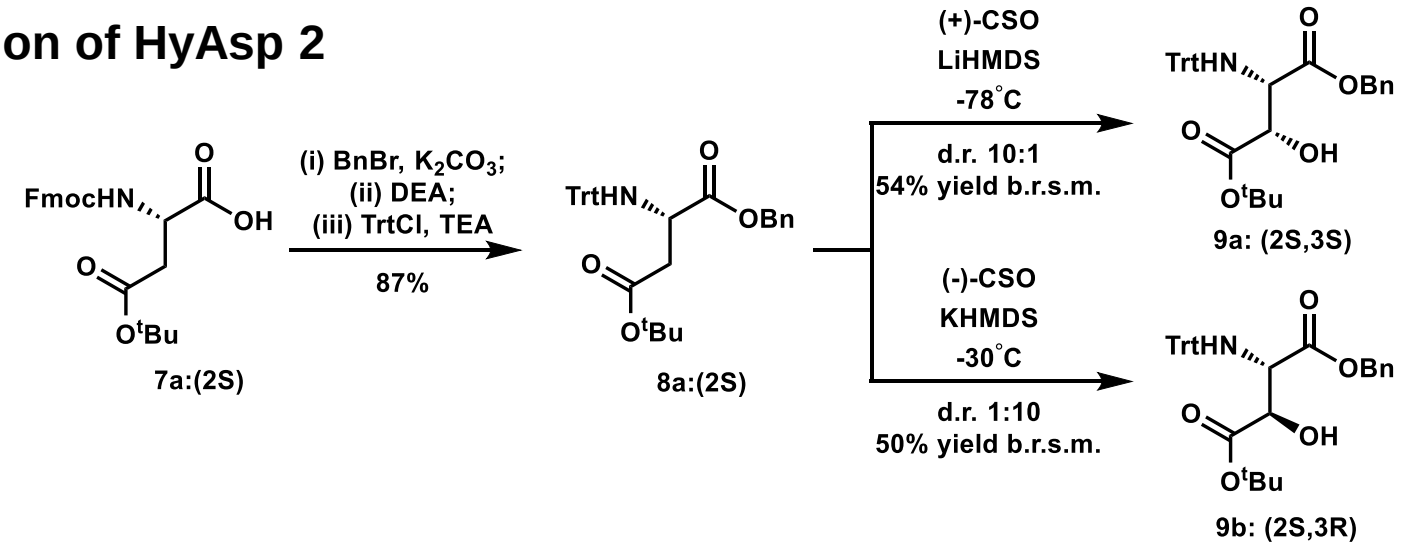
Total Synthesis of Malacidin A

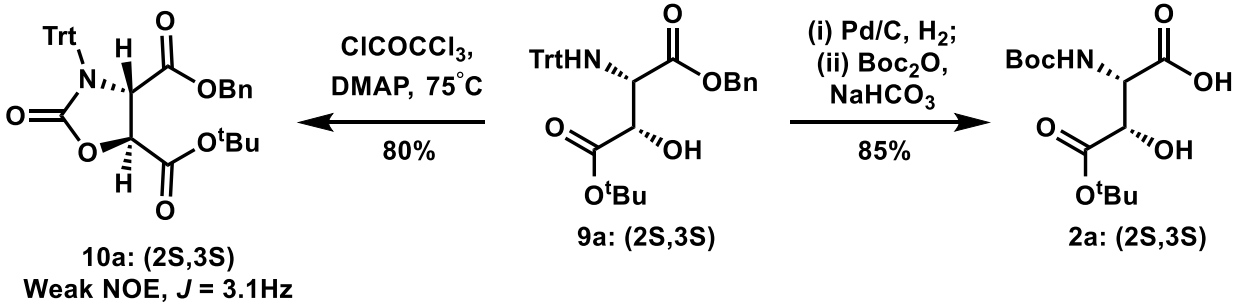
Preparation of 3,4,5,6

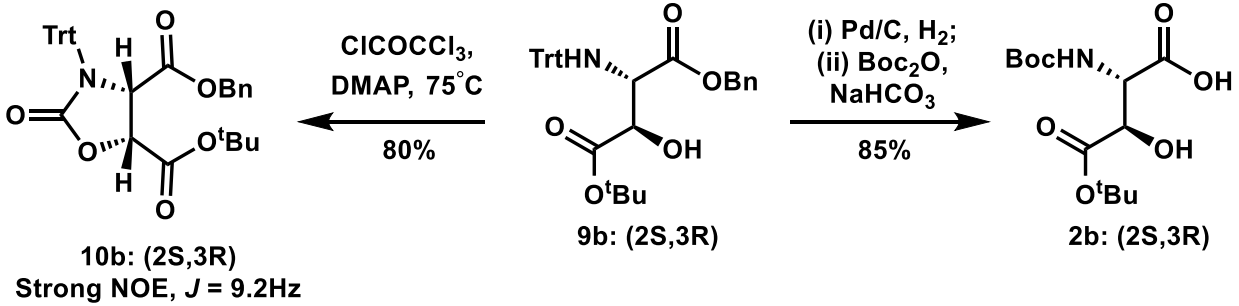


Total Synthesis of Malacidin A

Preparation of HyAsp 2

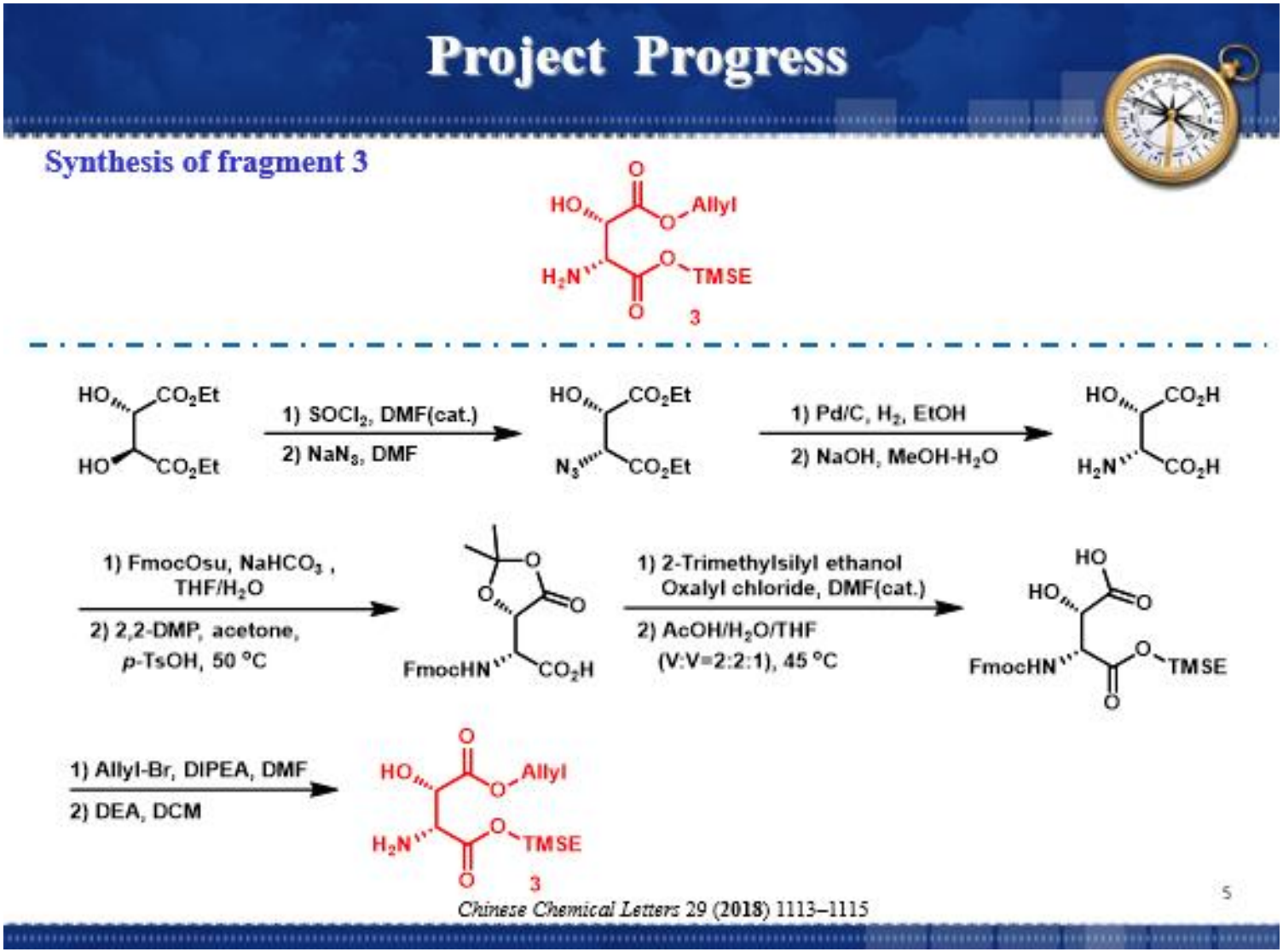






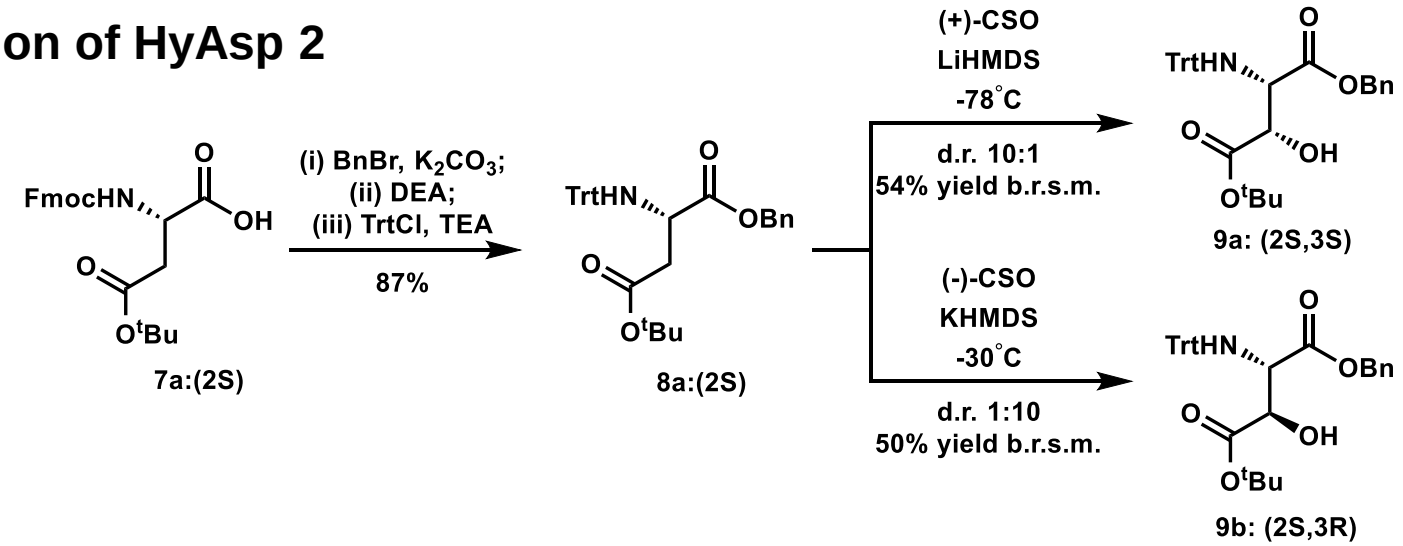
Total Synthesis of Malacidin A

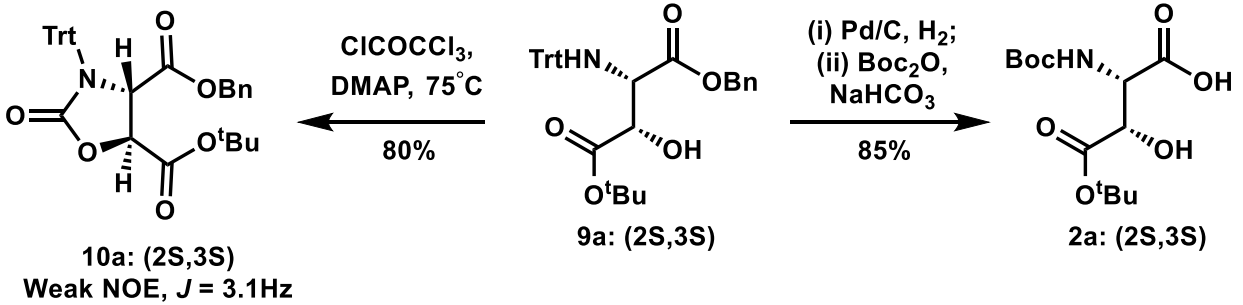
Preparation of HyAsp 2

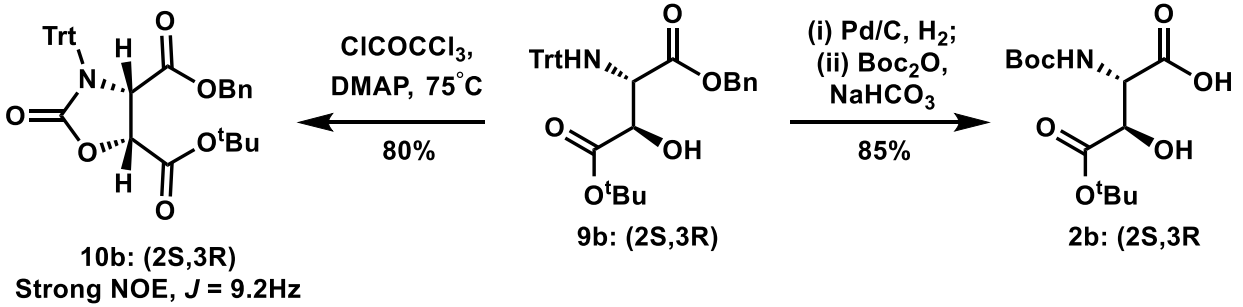


Total Synthesis of Malacidin A

Preparation of HyAsp 2

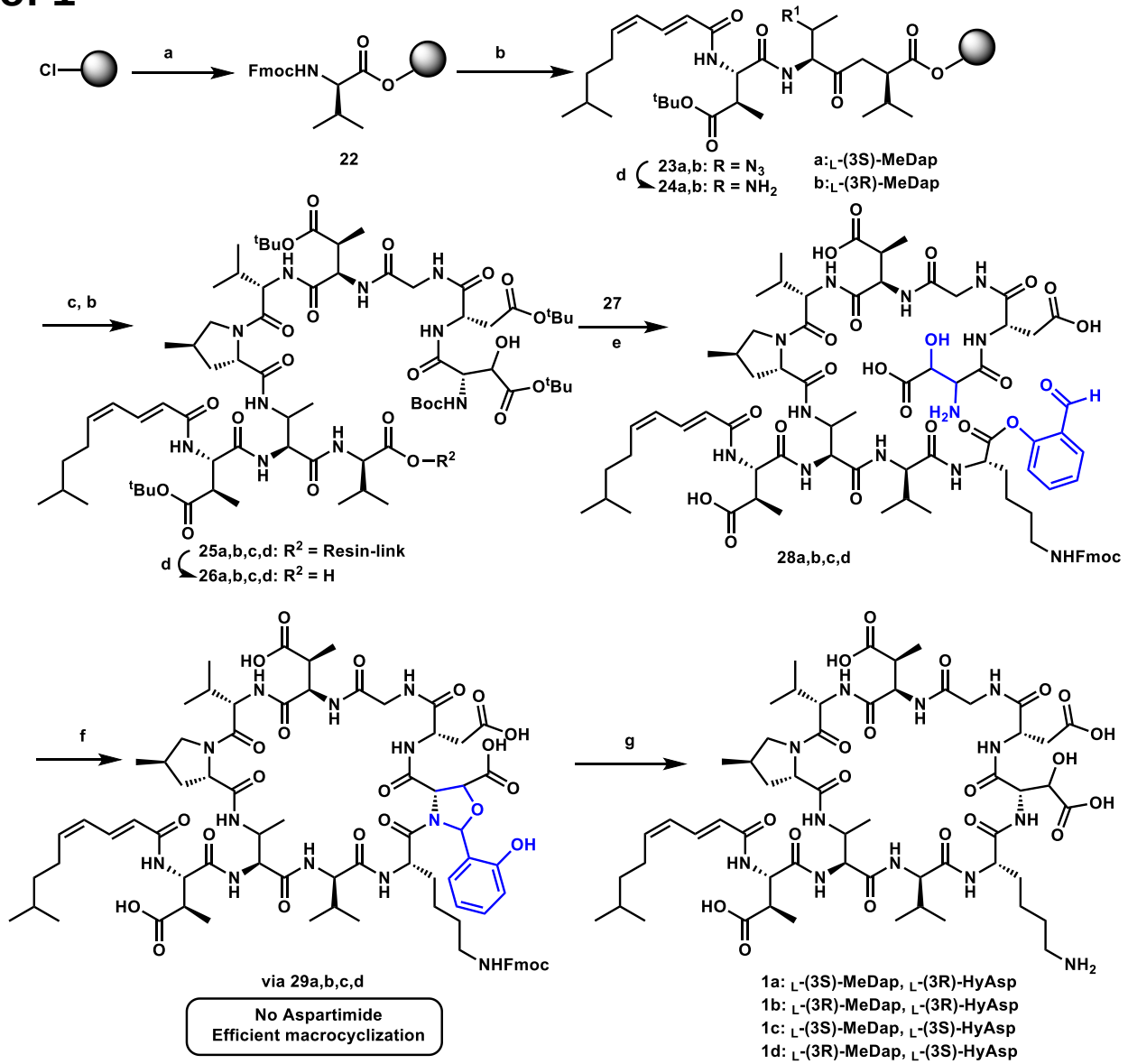






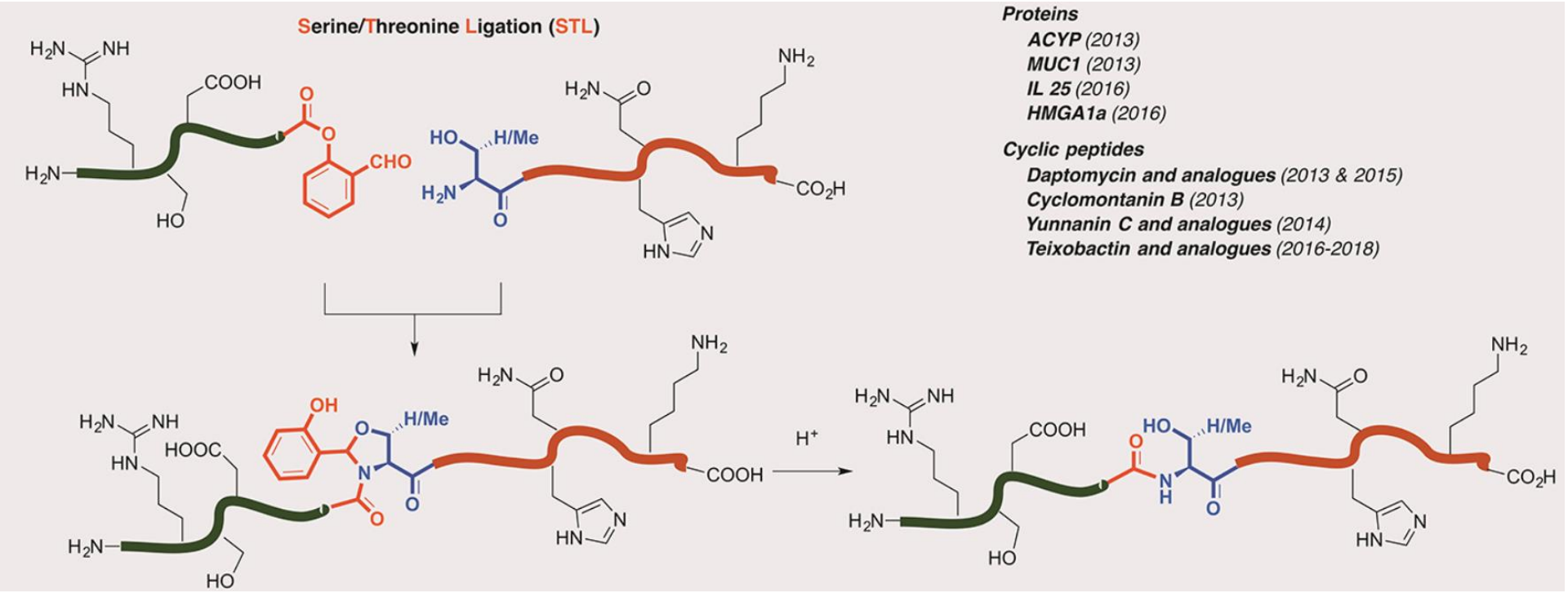
Total Synthesis of Malacidin A

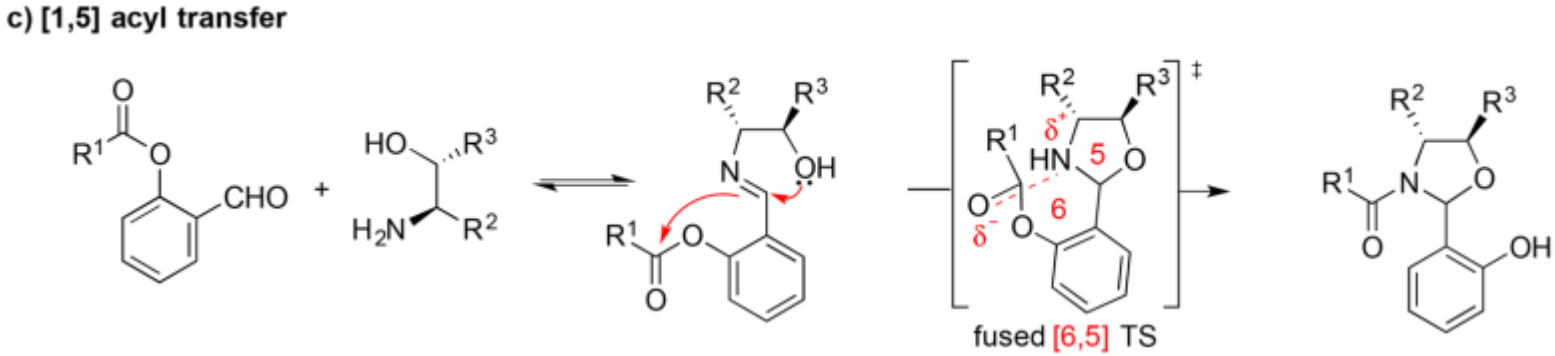
Preparation of 1



Total Synthesis of Malacidin A

Take-home message - Serine/Threonine Ligation





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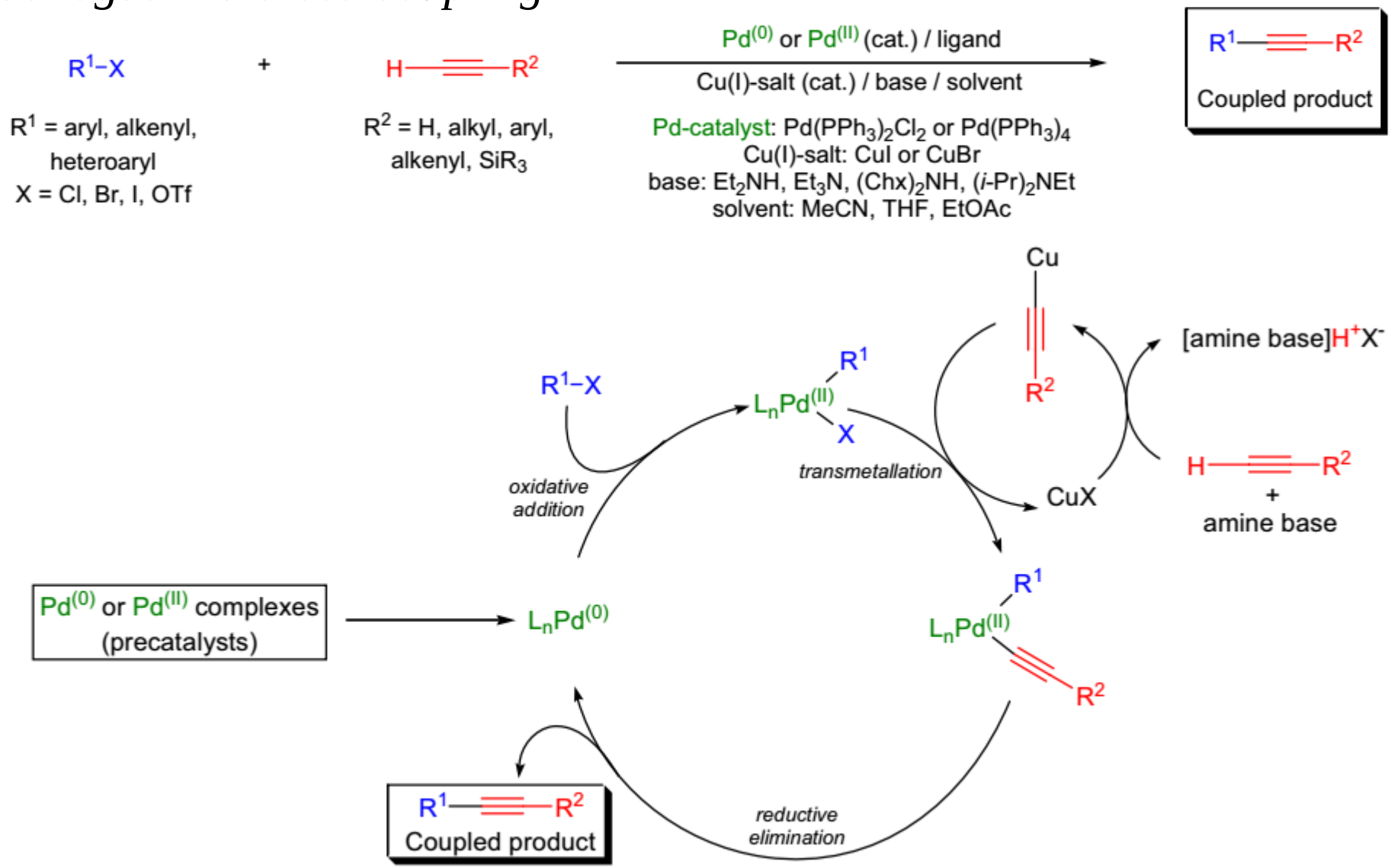
Acknowledgement

THANKS
FOR YOUR ATTENTION!

Sonogashira cross-coupling



Scheme 1

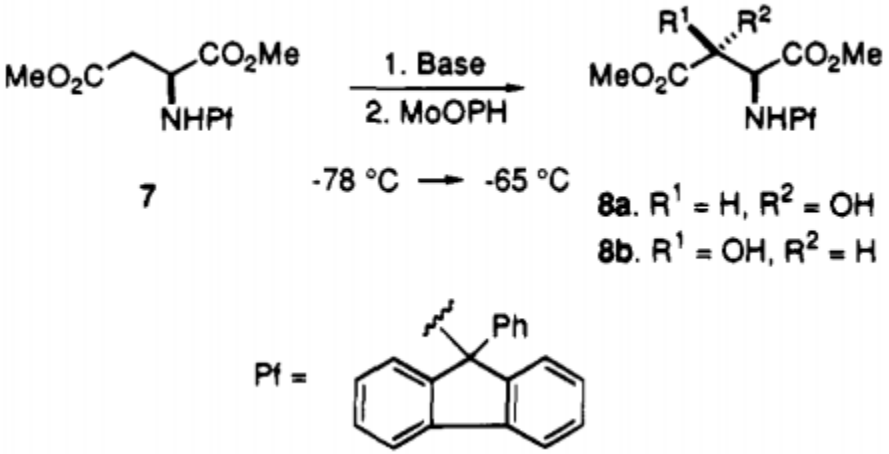
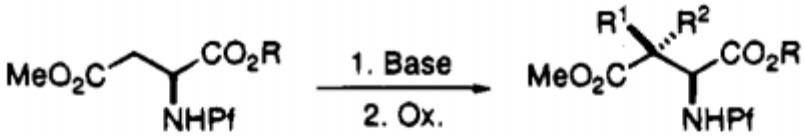


Table 1

entry	base (mol %)	cosolvent	**8b/8a**	yield (%)
1	KHMDS (180)	none	3/1	90[a]
2	LHMDS (300)	none	1/8	65[a]
3	LDA (300)	none	2/1	45[a]
4	LTMP (180)	none	1/2	22[a]
5	LHMDS (300)	DMPU	8/1	92[a]
6	LHMDS (300)	HMPA	11/1	74[b]
7	LHMDS (300)	DME	1/2.5	70[a]
8	LHMDS (300)	TMEDA	1/8	80[a]
9	LHMDS (300)	PMDET[c]	1/5	75[a]
10	KHMDS (180)	18-crown-6	*d*	
11	LHMDS (300)	12-crown-4	*d*	
12	n-BuLi (100)/LHMDS (300)	none	1/20	60 (83)[b]
13	n-BuLi (100)/LHMDS (300)	HMPA	2/1	95[a]

Scheme 3



12a. R = *t*-Bu
12b. R = H

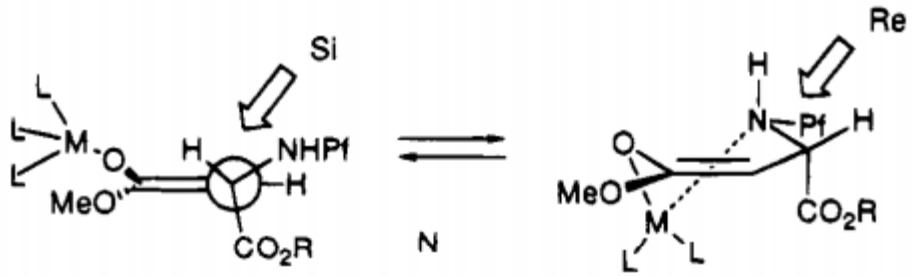
13. R = *t*-Bu
14. R = H
a. R^1 = H, R^2 = OH
b. R^1 = OH, R^2 = H

12a → 13

Base (cosolv.)	Oxidant	13b/13a	Yield [a]
KHMDS	MoOPH	7/1	95% (65%) [b]
LHMDS	MoOPH	-	-
LHMDS (HMPA)	MoOPH	4/1	70%
KHMDS	Davis' oxaz.	1/2	98%

12b → 14

Base (cosolv.)	Oxidant	14b/14a	Yield [a]
KHMDS	MoOPH	2/1	30%
LHMDS or LDA	MoOPH	-	-
LHMDS (HMPA)	MoOPH	-	-
KHMDS	Davis' oxaz.	7/1	86%
LHMDS	Davis' oxaz.	1/4	80%



24 **25**

Favored by good ligands of M (M = Li^+) or M = K^+

Favored by poor ligands of M and M = Li^+

proach of an electrophile which cannot complex to the metal cation (MoOPH) to the less hindered face of the predominant nucleophilic species in the reaction medium should yield the observed results (Table 1, Scheme 3). The K_{eq} of the aforementioned equilibrium should be strongly dependent on the nature of the enolate counterion (M) and its ligands (L): the open form **24** would be favored by strongly coordinating ligands (DMPU or HMPA, Table 1, entries 5 and 6), or by the use of K^+ as the enolate counterion. Poorly coordinating ligands (HMDS or THF) and/or deprotonation of the Pf-amino group (by addition of 100 mol % of n-BuLi, entry 12) would favor the chelated form **25**.