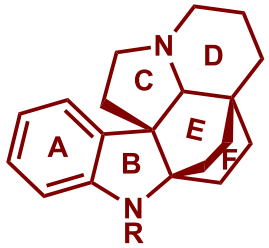
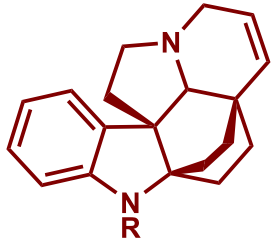
北京大学
PEKING UNIVERSITY

ASAP REPORT



R=H, aspidofractinine
R=Me, N(1)-methyl-aspidofractinine
R=CHO, N(1)-formyl-aspidofractinine



N(1)-methyl-14,15-didehydroaspidofractinine

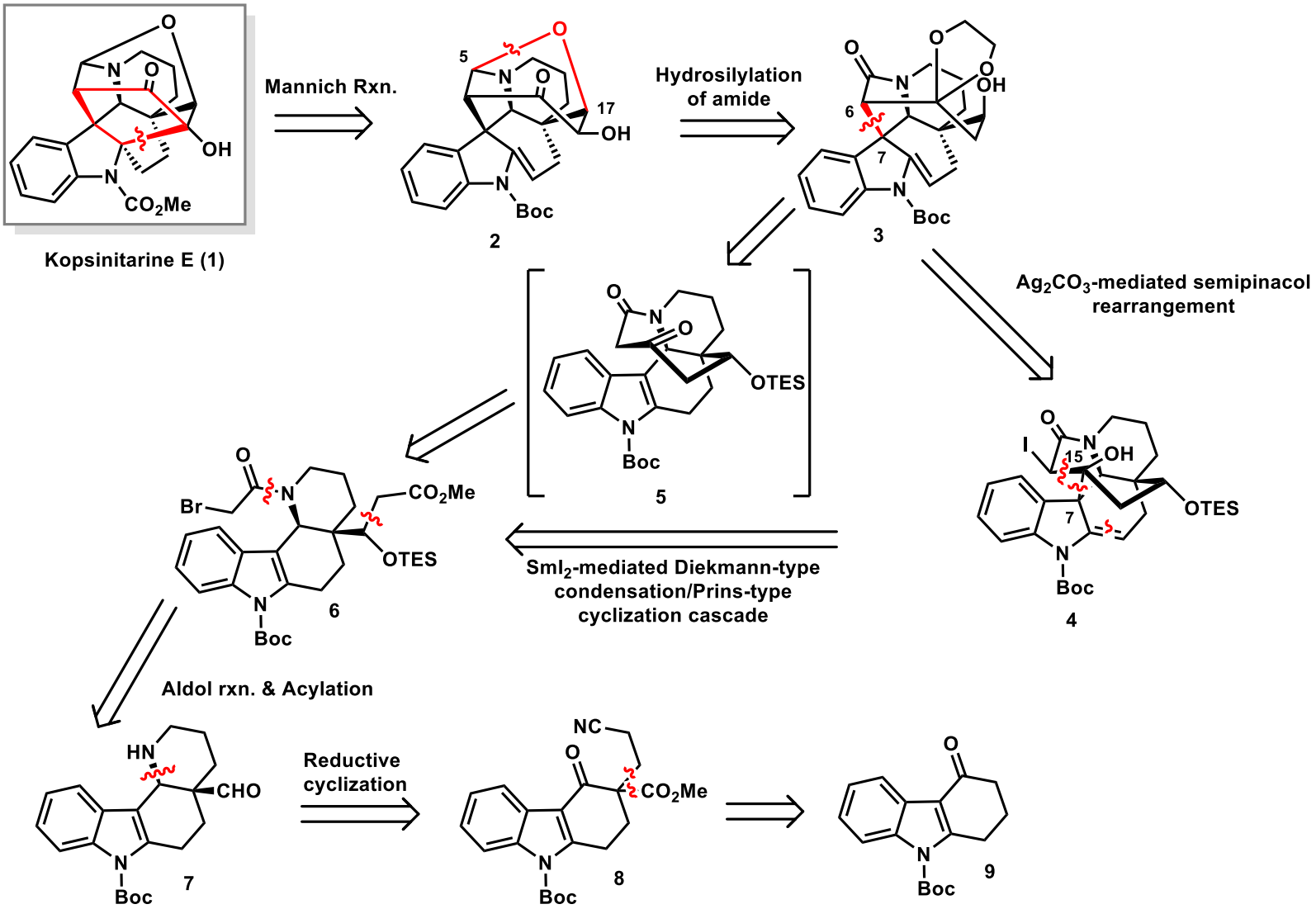
Reporter: Tao Zhang

Supervisors: *Prof.* Tao Ye

***Dr.* Yi-an Guo**

2020.10.12

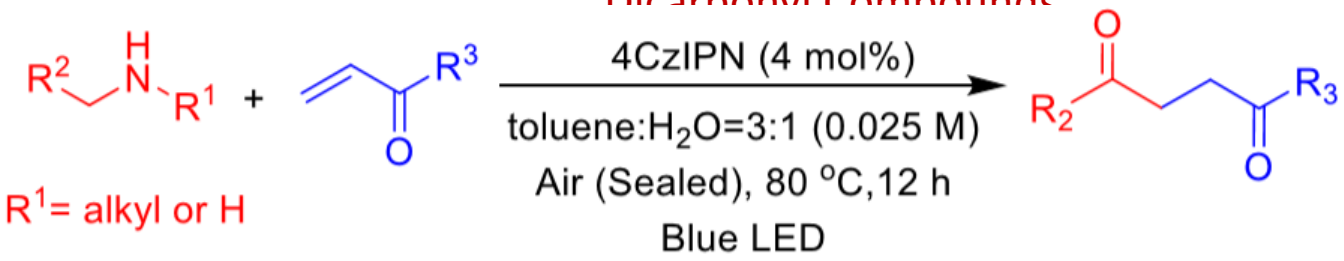
PART I:BRIEF INTRODUCTION TO A TOTAL SYNTHESIS



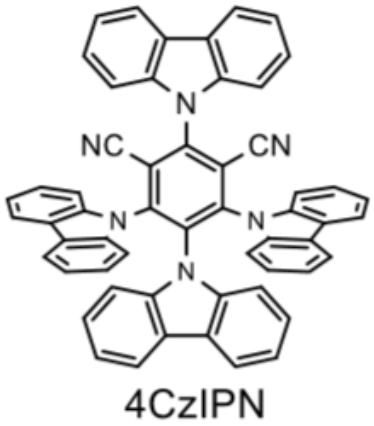
K. Nagaraju, D. Ni, and D. Ma. *Angew. Chem. Int. Ed*. **2020**,asap

PART II: BRIEF INTRODUCTION TO A METHODOLOGY

“ Photoredox-Catalyzed α-C(sp^3)–H Activation of Unprotected ” Secondary Amines: Facile Access to 1,4-Dicarbonyl Compounds



R^1= alkyl or H



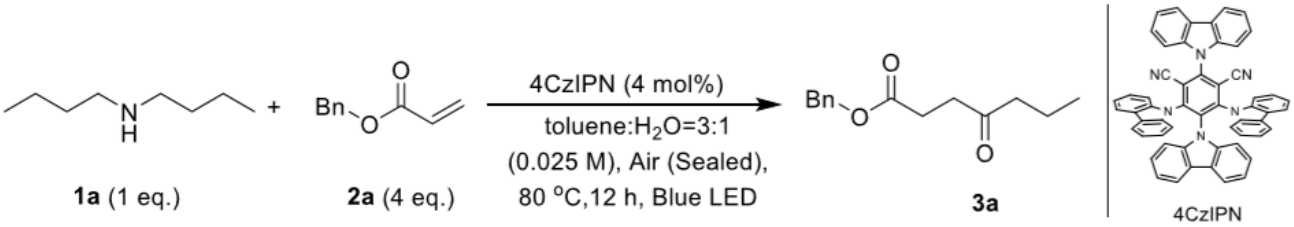
4CzIPN

- Providing a convenient and metal-free method to construct 1,4-dicarbonyl compounds from unprotected secondary and primary amines and electron-deficient alkenes;
- Relatively greenner and having broader substrate scope.

Q. Zhang, *et. al*. *Org. Lett.* **2020**, *22*, 7460−7464

PART II: METHODOLOGY

- Rxn. Optimization

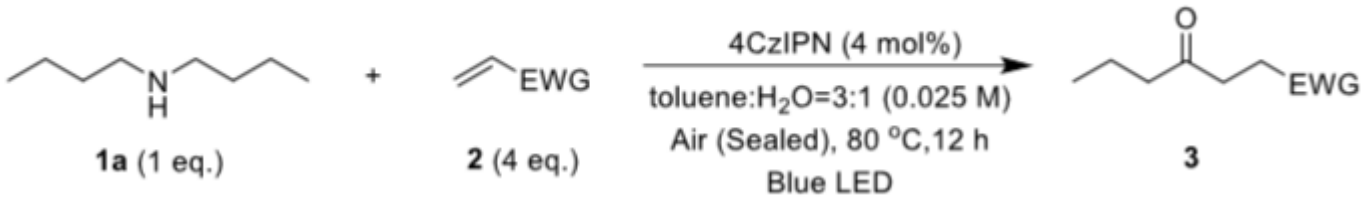


entry	deviation	Yield[b] (%)
1	none	82 (76[c])
2	$Ru(bpy)_3(PF_6)_2$ instead of 4CzIPN	0
3	$Ir[df(CF_3)ppy]_2(dtbbpy)PF_6$ instead of 4CzIPN	26
4	toluene as the solvent	30
5	CH_3CN/H_2O (3:1) as the solvent	66
6	CH_2Cl_2/H_2O (3:1) as the solvent	55
7	0.05 M instead of 0.025 M	10
8	K_2CO_3 as the additive	68
9	Cs_2CO_3 as the additive	46
10	using 2 eq. **2a**	45
11	40 °C instead of 80 °C	56
12	O_2 instead of air	28
13	Without 4CzIPN	0
14	Without light	0

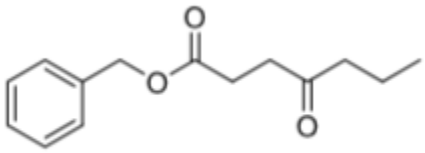
- Main point:
  - 4CzIPN
  - Mixed solvent of toluene and H_2O
  - 0.05 M
  - No additional base
  - Air but not pure O_2

PART II: METHODOLOGY

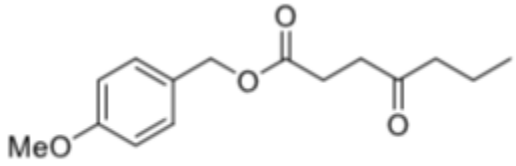
- Substrate Scope of Alkenes



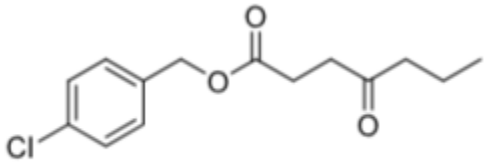
1a (1 eq.) + **2** (4 eq.) → **3**



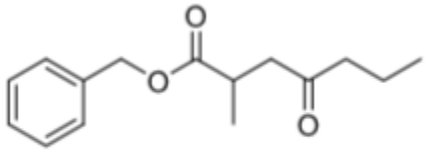
3a, 76%



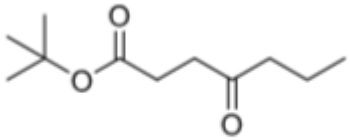
3c, 68%



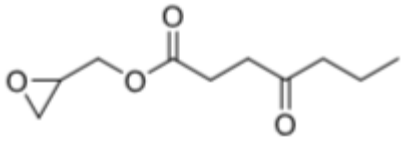
3d, 60%



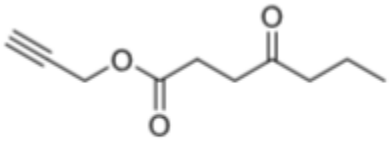
3g, 48%



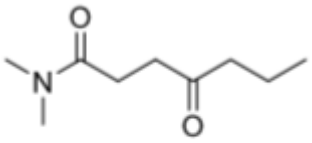
3j, 68%



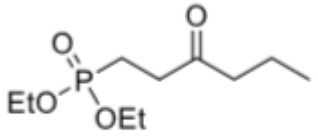
3m, 50%



3o, 45%



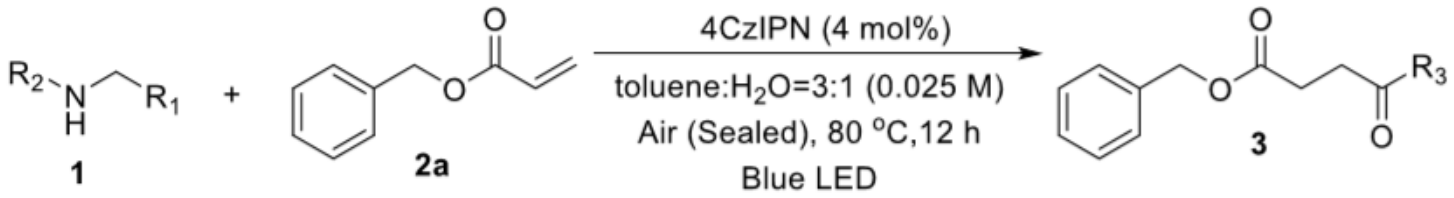
3r, 57%



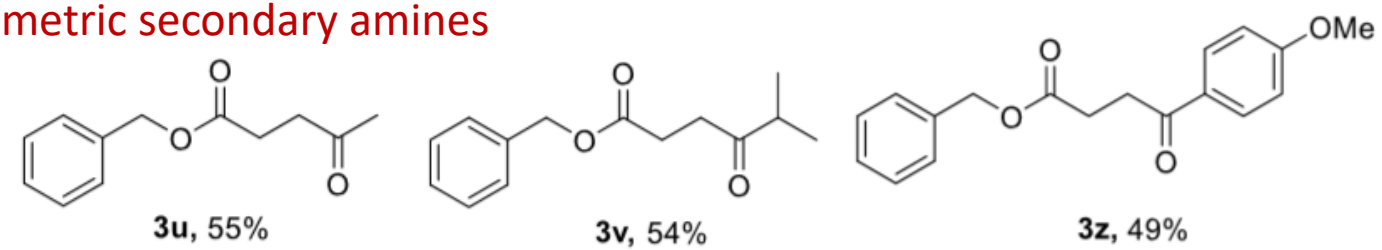
3s, 32%

PART II: METHODOLOGY

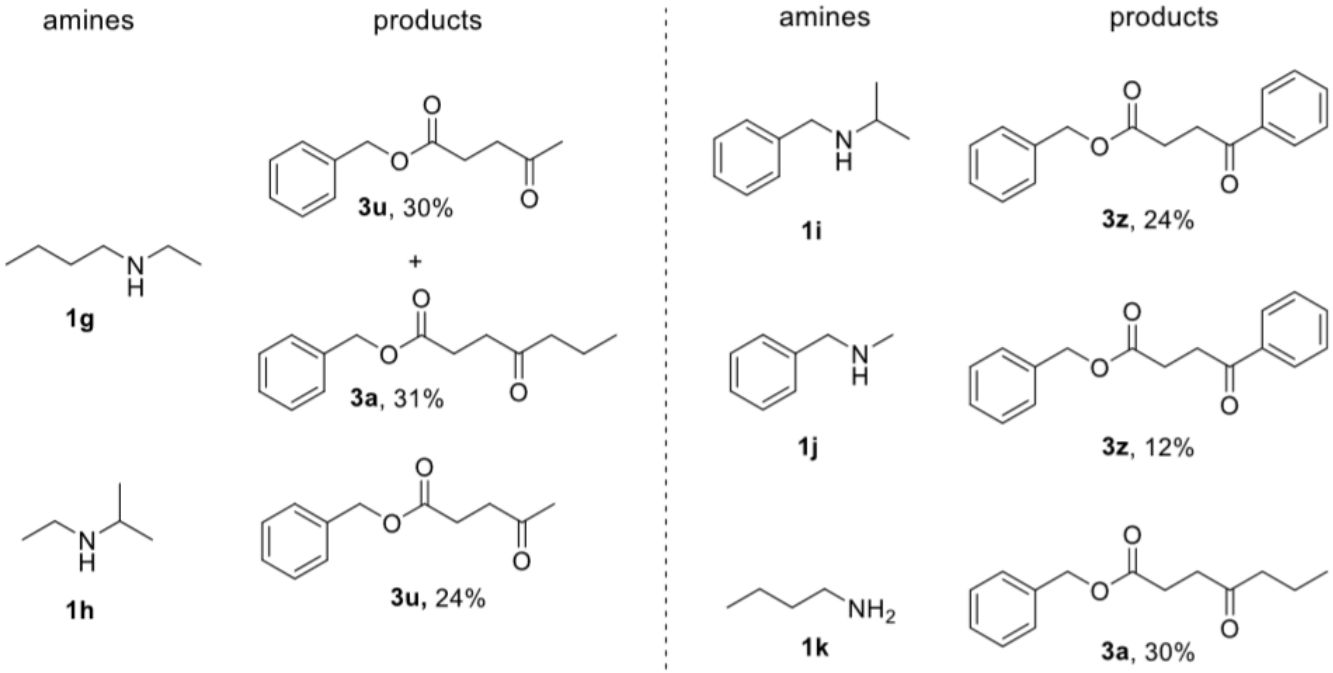
- Substrate Scope of Secondary Amines



a. symmetric secondary amines

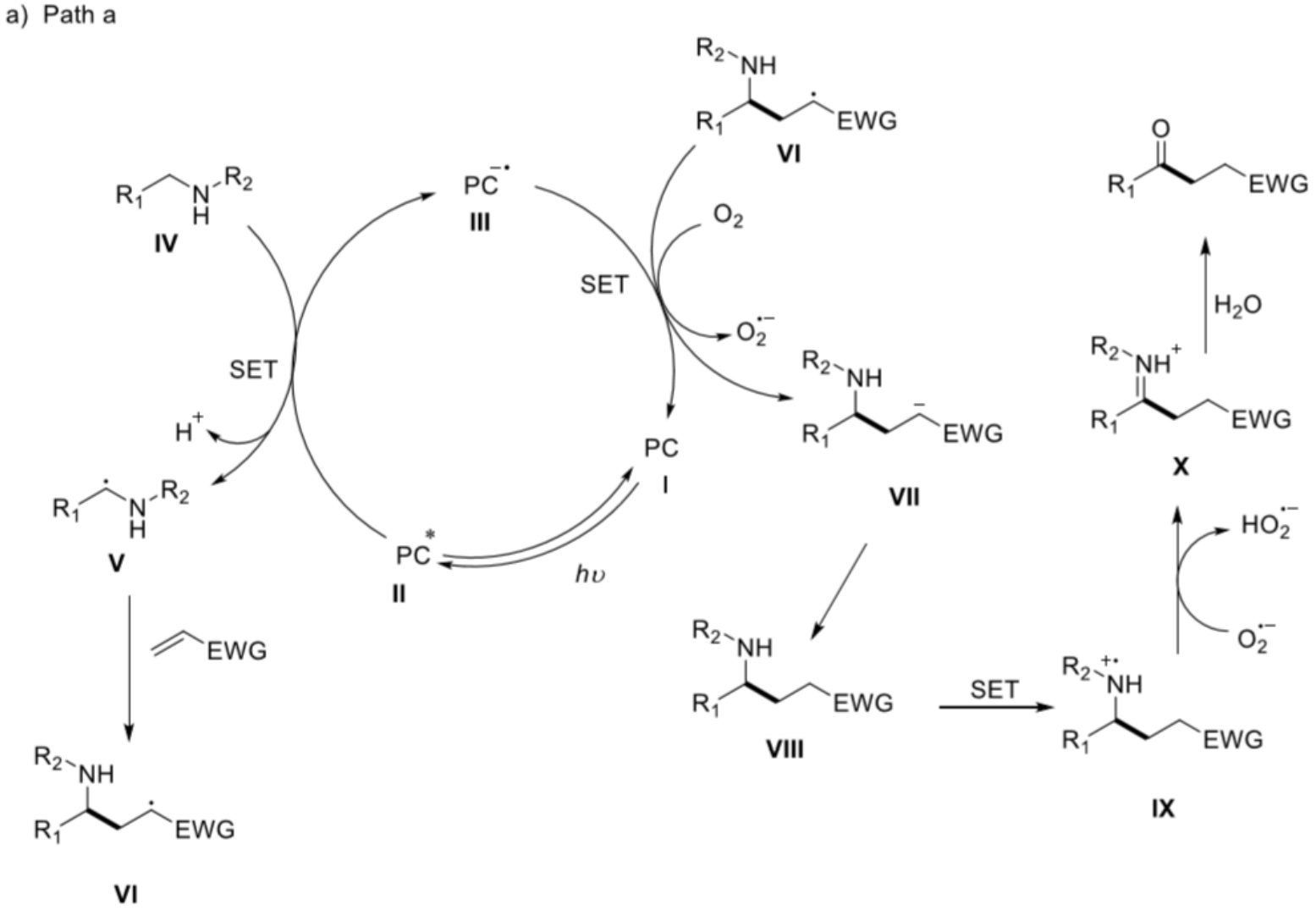


b. asymmetric secondary amines

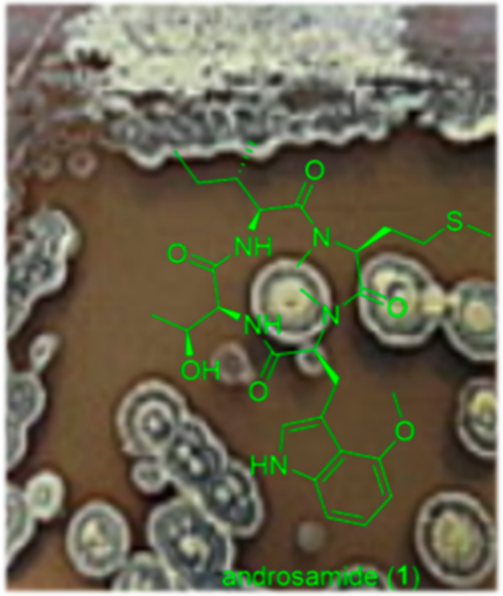


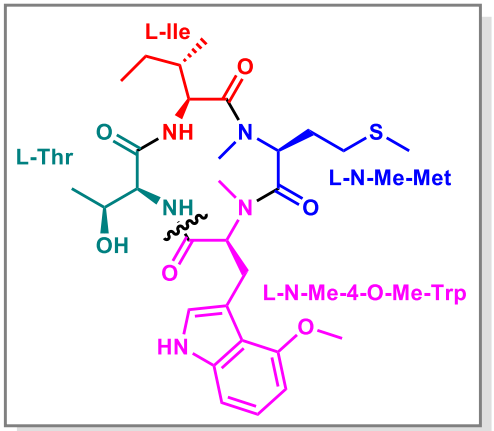
PART II: METHODOLOGY

- Proposed mechanism

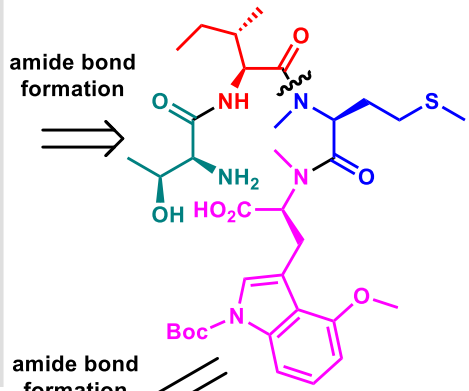


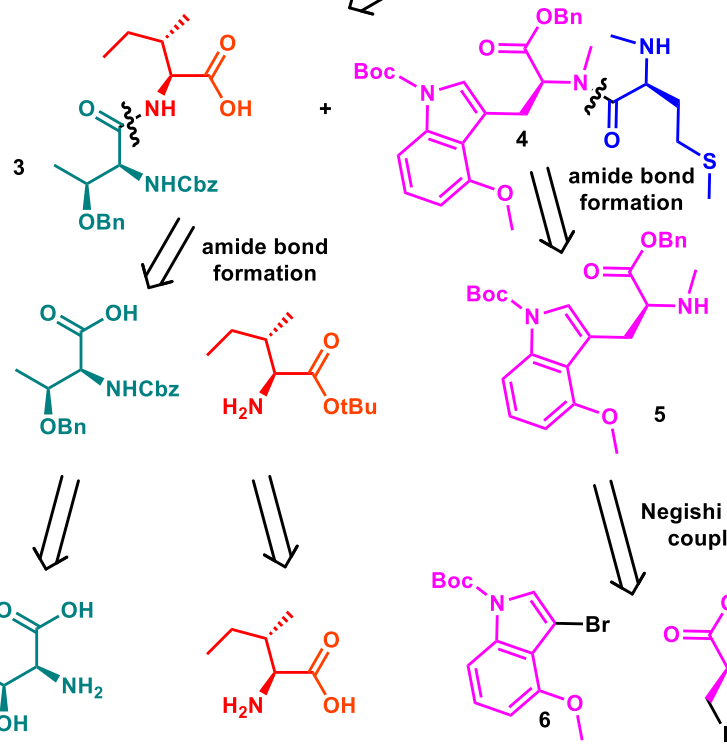
III: BRIEF INTRODUCTION TO A NEW NAT. PROD.





Androsamide (1)





- Androsamide (1), a cyclic tetrapeptide, was isolated from a marine actinomycete of the genus Nocardiopsis, strain CNT-189
- Androsamide (1) strongly suppressed the motility of Caco2 cells caused by epithelial–mesenchymal transition

J. Lee, *et. al. J. Nat. Prod*. **2020**, asap

Natural Products Synthesis

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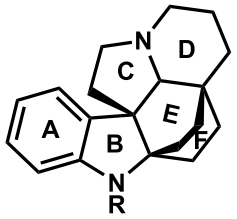
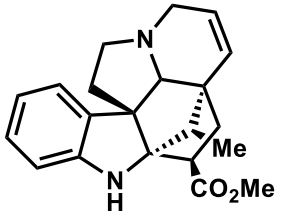
Collective Total Synthesis of Aspidofractinine Alkaloids through the Development of a Bischler–Napieralski/Semipinacol Rearrangement Reaction

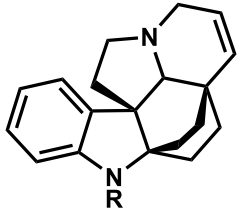
Shuang-Hu Wang, Rui-Qi Si, Qing-Bo Zhuang, Xiang Guo, Tian Ke, Xiao-Ming Zhang, Fu-Min Zhang,* and Yong-Qiang Tu**



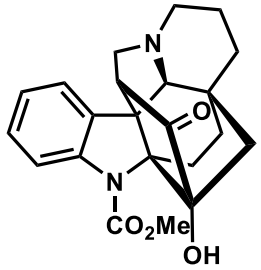
R=H, aspidofractinine **(1)**
R=Me, N(1)-methyl-aspidofractinine **(2)**
R=CHO, N(1)-formyl-aspidofractinine **(3)**



Vindolinene **(6)**



R=Me, N(1)-methyl-14,15-didehydroaspidofractinine **(4)**
R=CHO, N(1)-formyl-14,15-didehydro-aspidofractinine **(5)**



Kopsine **(7)**

BRIEF INTRODUCTION TO THE AUTHOR

Yongqiang Tu

- Educational & working experience
  - -B.S. & Ph.D, Lanzhou University (1982,1989)
  - -Postdoctoral Fellow, The University of Queensland (1993-1995)
  - -Visiting Professor, Bielefeld University, Germany(2004-2005)
  - -P.I., College of Chemistry and Chemical Engineering, Lanzhou University (1995-now)
  - - Academician of Chinese Academy of Sciences (2009-now)

- Research Interests & Areas
  - Synthesis of bioactive natural products and drug
  - Organic synthesis methodology involving C-C bond recombination
  - Asymmetric organic chemical reaction research

CONTENT

BRIEF INTRODUCTION

Isolation:

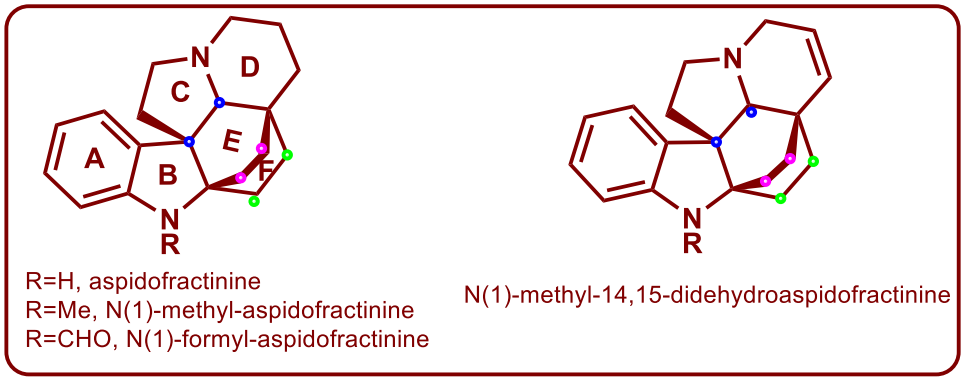
- Isolated from the genus Aspidosperma of Apocynaceae plants

Biological activities of these prd.:

- Antileishmanial, antimanic effects, antitumor, antitussive activities, etc.

Structure features:

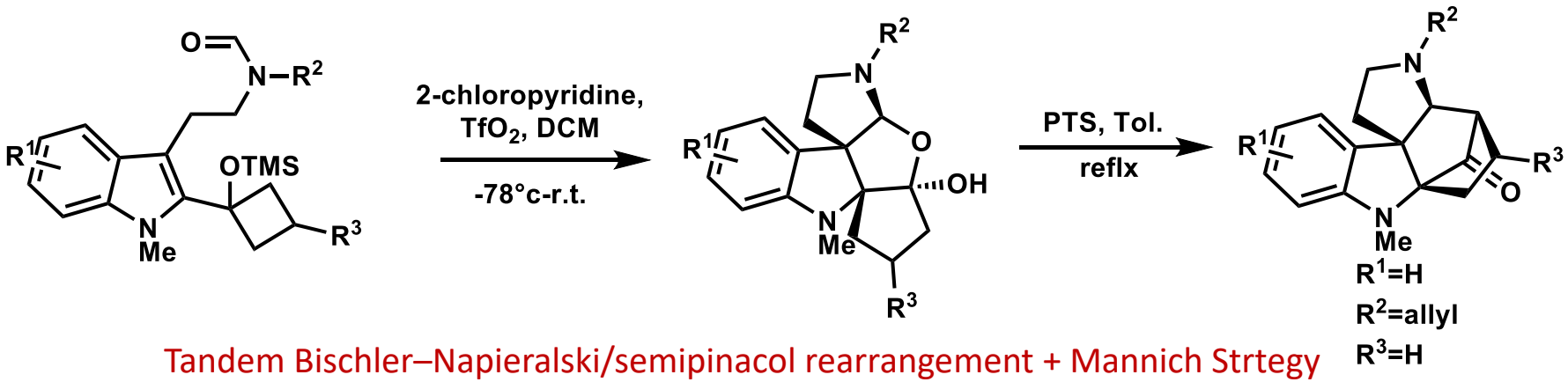
- Having a complex cage-shaped carbon framework (bicyclo[2.2.2] octane nucleus) with incorporation of three highly congested quaternary centers



W. Chi, *et. al*. **Fitoterapia**, *2018*, **130**, 259-264

BRIEF INTRODUCTION

Conduction of condensely substituted bridged-spirofused [2.2.1]cyclic structure:

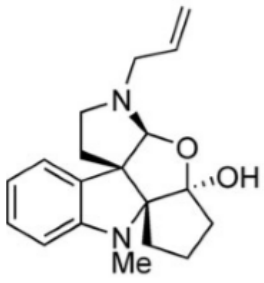


Tandem Bischler–Napieralski/semipinacol rearrangement + Mannich Strtegy

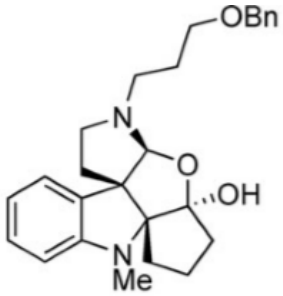
Entry	Conditions	Yield [%][c]
1[b]	2-chloropyridine, $POCl_3$, DCM, −78 °C→RT	0
2	2-chloropyridine, Tf_2O, DCM, −78 °C→RT	67
3	pyridine, Tf_2O, DCM, −78 °C→RT	61
4	2-bromopyridine, Tf_2O, DCM, −78 °C→RT	49
5	DMAP, Tf_2O, DCM, −78 °C→RT	0
6	2-chloropyridine, Tf_2O, THF, −78 °C→RT	0
7	2-chloropyridine, Tf_2O, toluene, −78 °C→RT	0

BRIEF INTRODUCTION

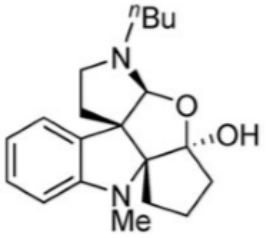
Scope of the Bischler–Napieralski/semipinacol rearrangement cascade



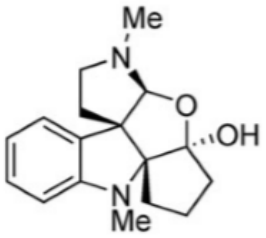
12a, 67%



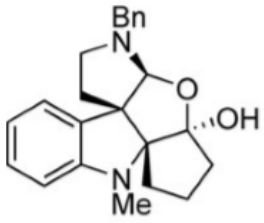
12b, 48%



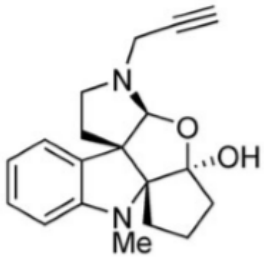
12c, 52%



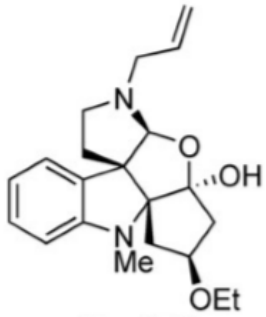
12d, 66%



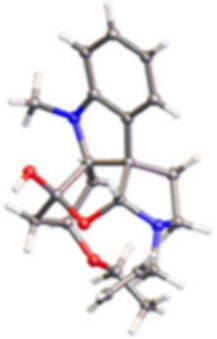
12e, 69%



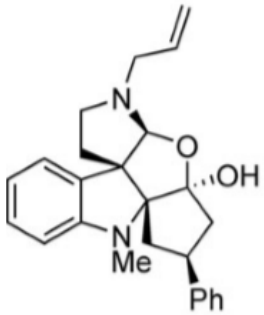
12f, 73%



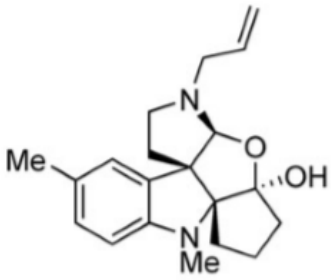
12g, 67%



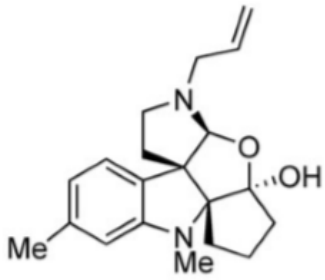
X-ray crystal structure of **12g**



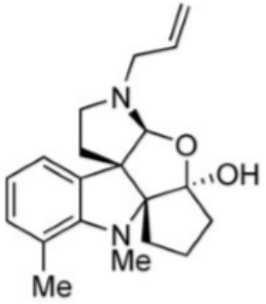
12h, 74%



12i, 64%

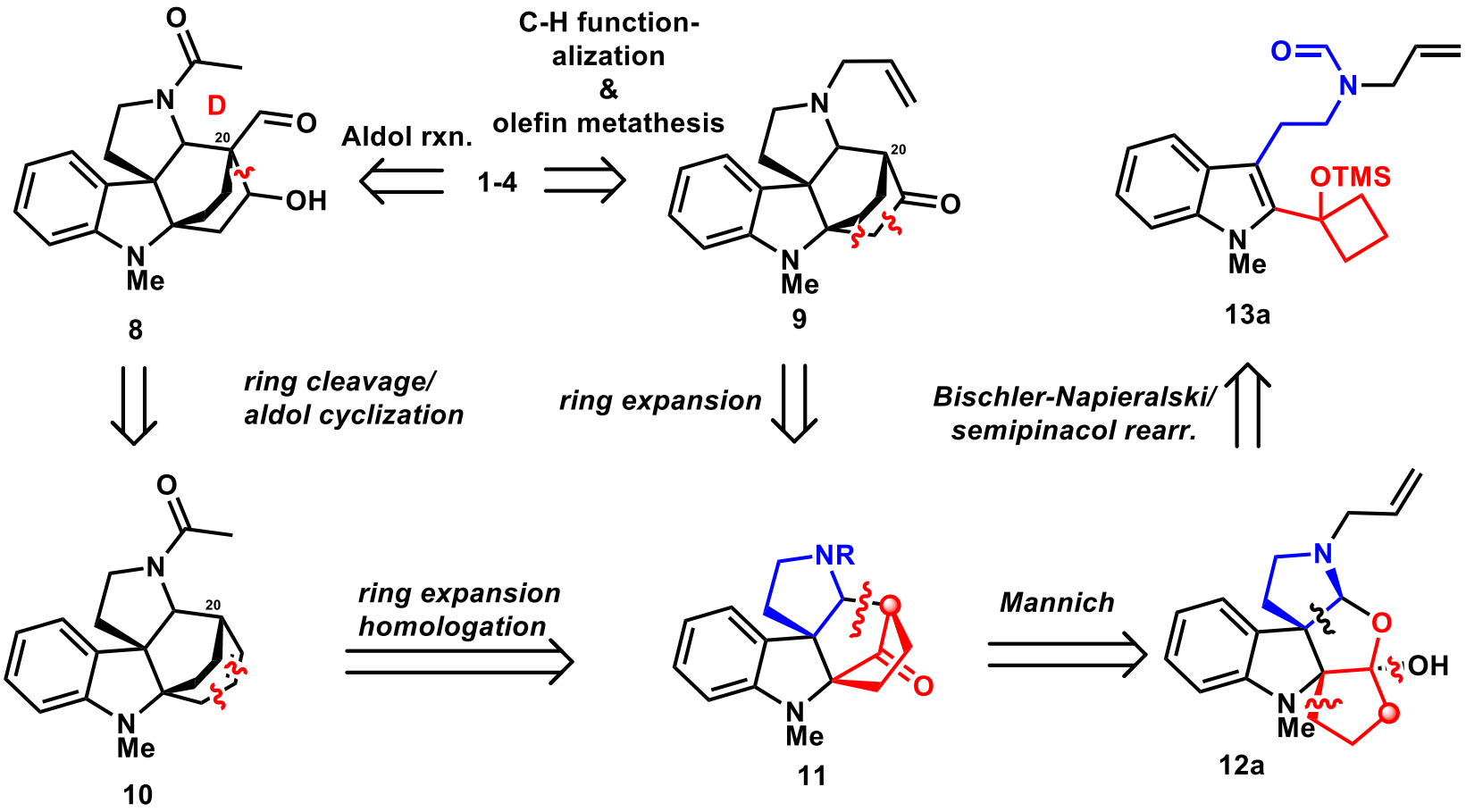


12j, 55%

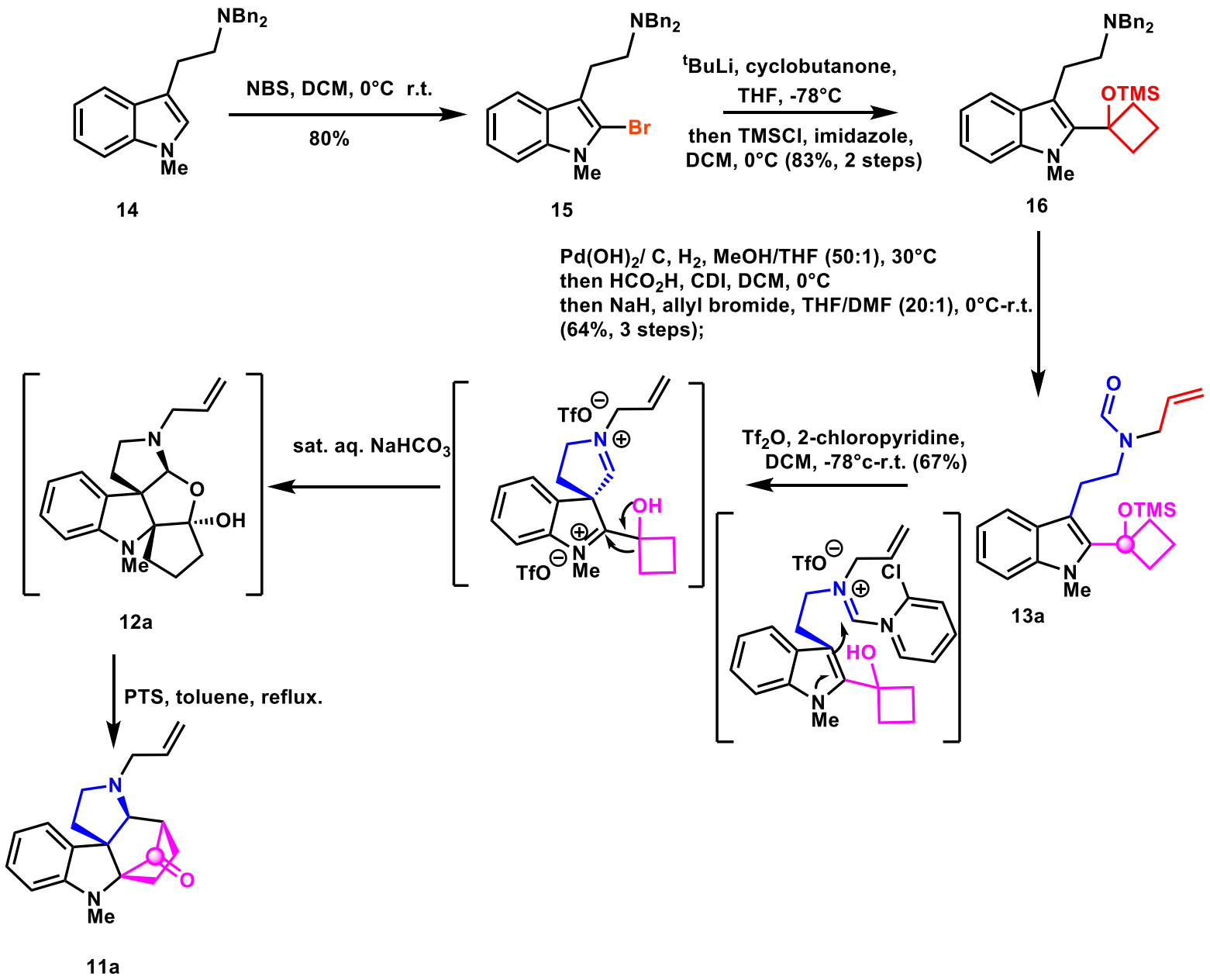


12k, 52%

RETROSYNTHETIC ANALYSIS



SYNTHETIC ROUTE



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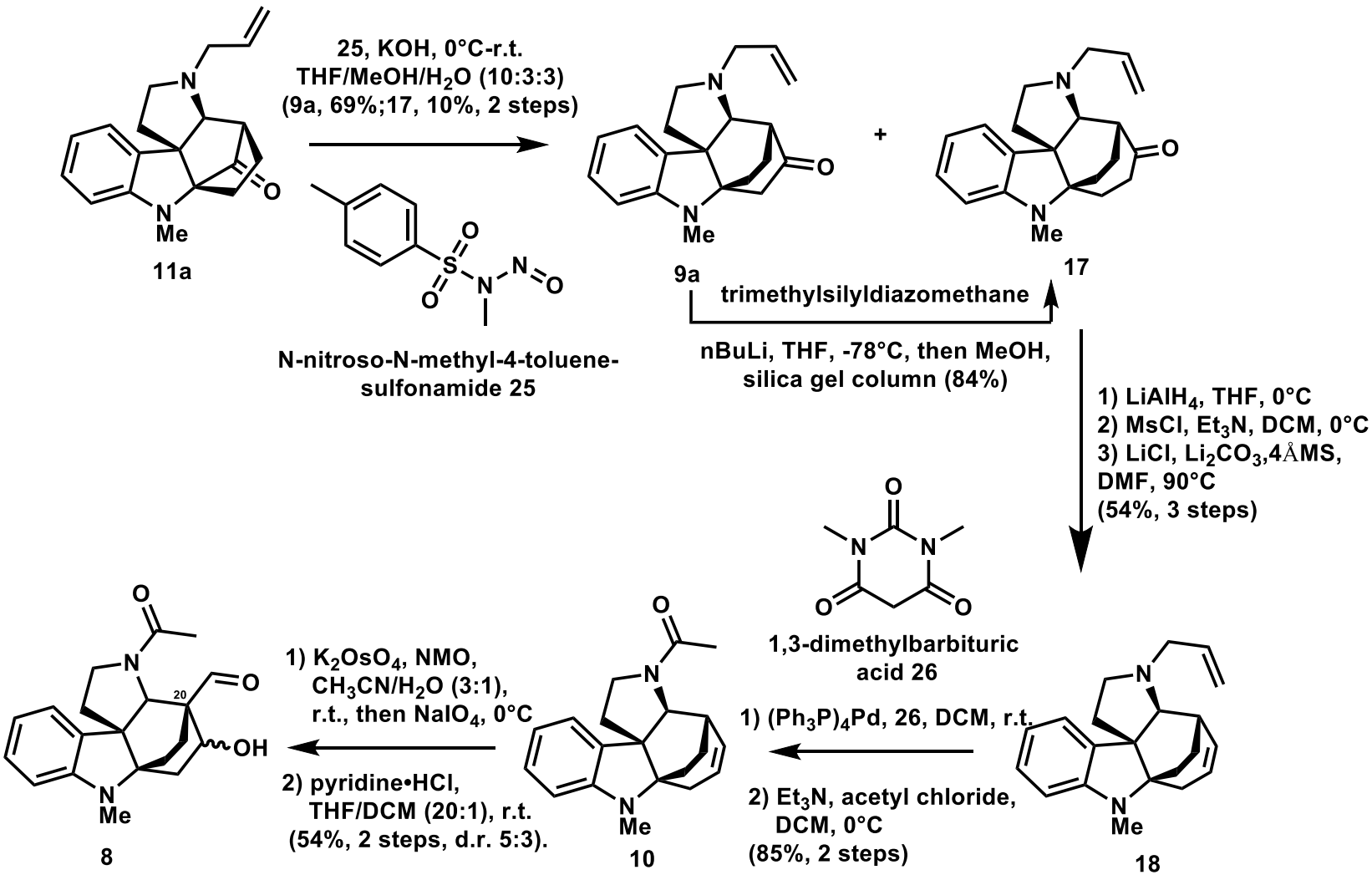
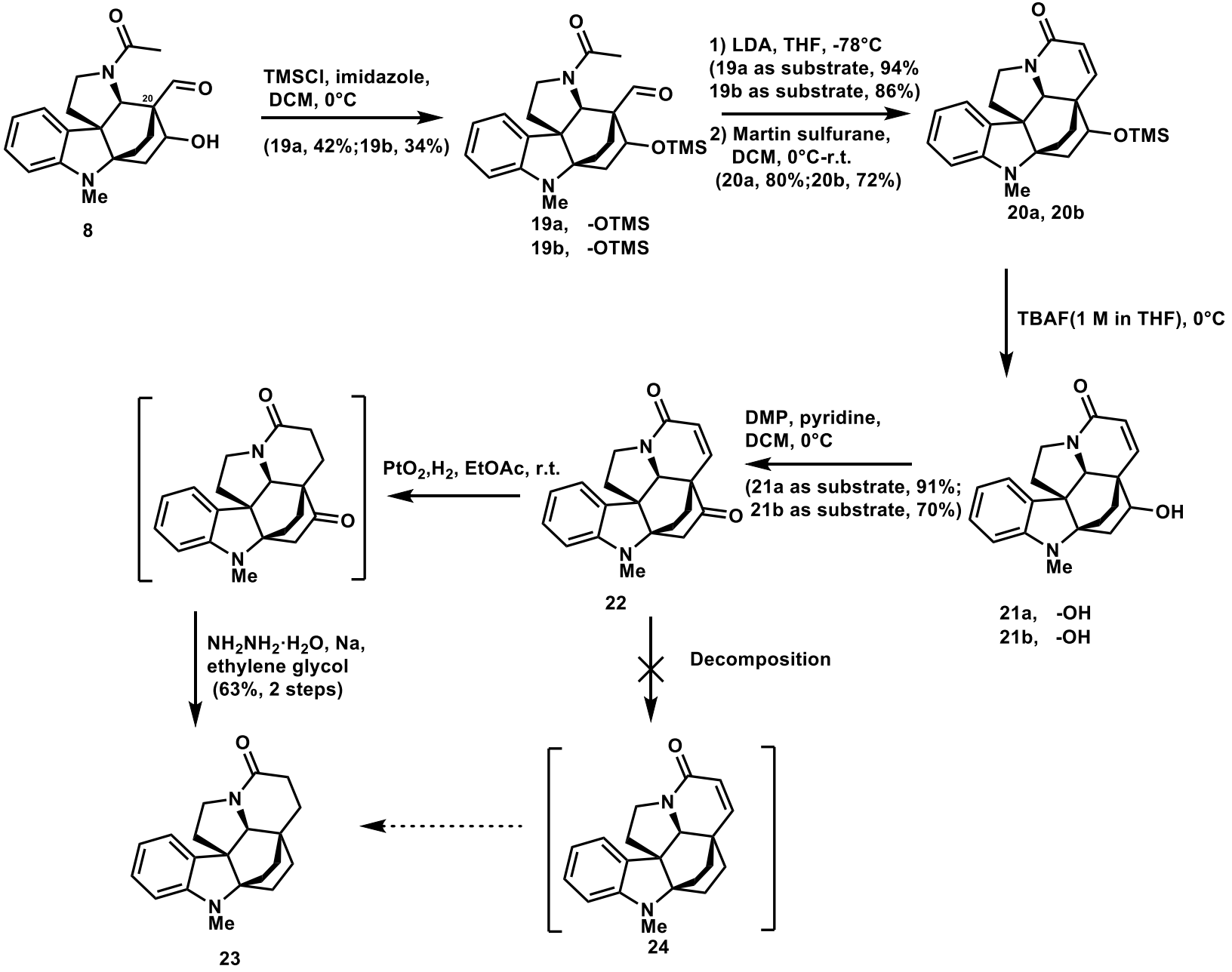
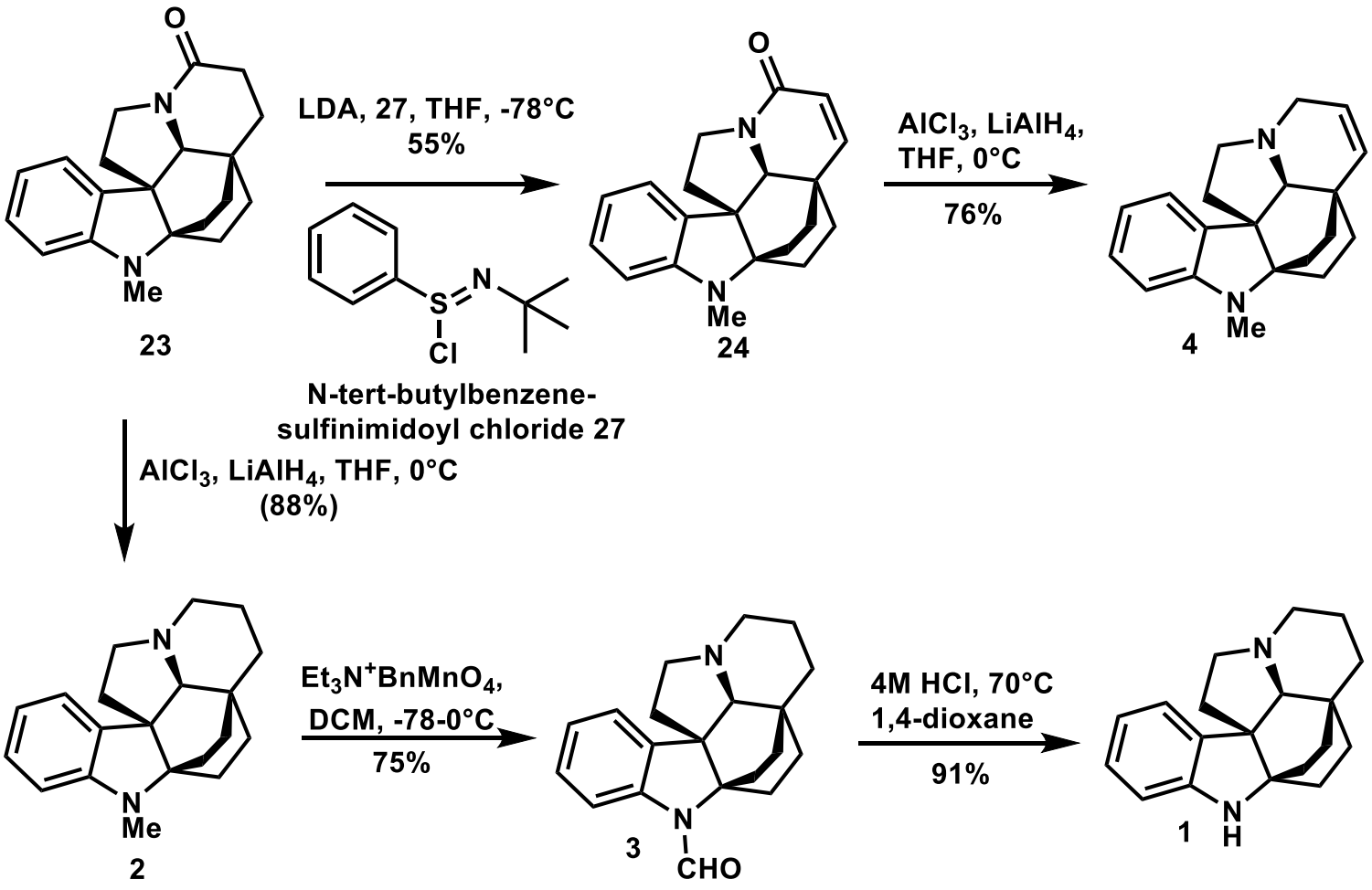


H. J. Dauben, Jr., H. J. Ringold, R. H. Wade, D. L. Pearson, A. G. Anderson, *Org. Synth*. **1954**, *34*, 19–22

SYNTHETIC ROUTE



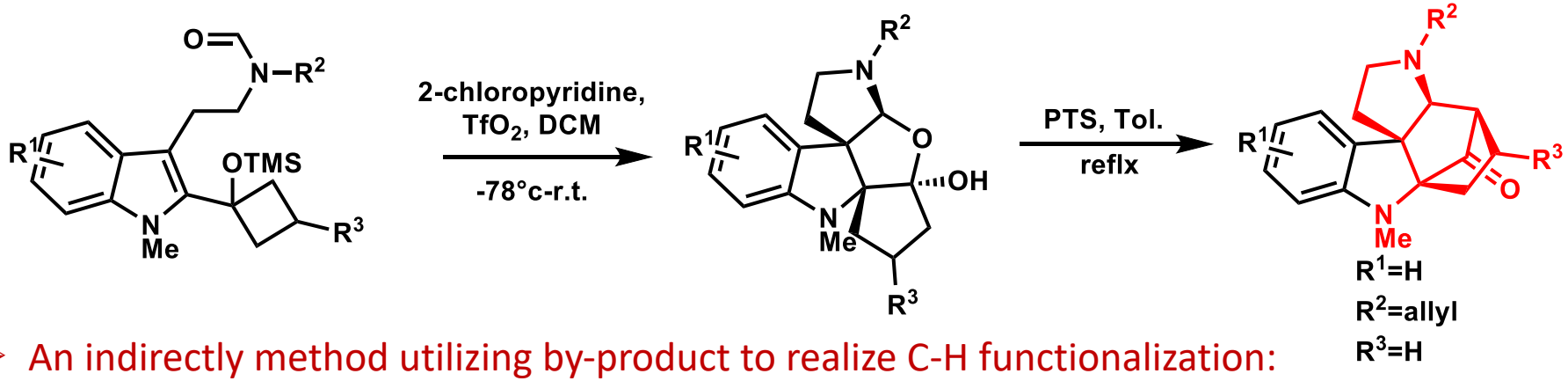
SYNTHETIC ROUTE



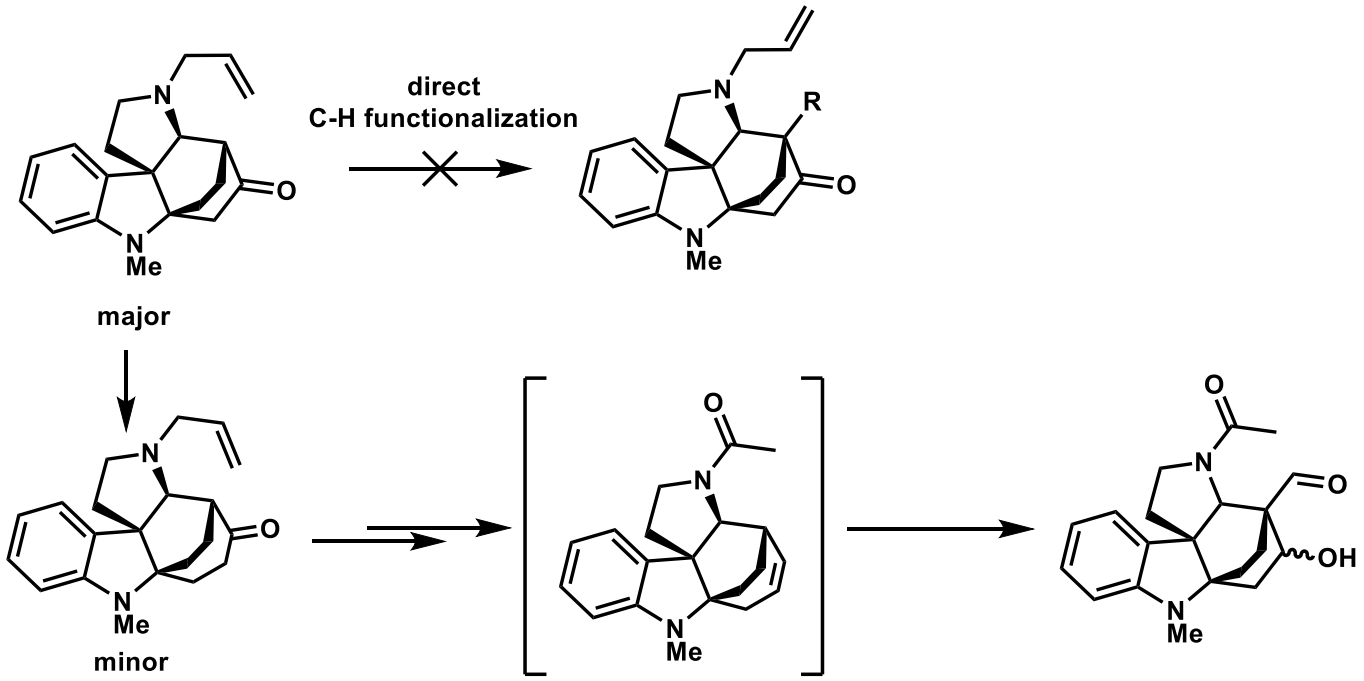
J. I. Matsuo, Y. Aizawa, *Tetrahedron Lett*. **2005**, *46*, 407–410

SUMMARY

- A novel and subtle strategy to form a complex bridge-spirofused core and quaternary centers: Tandem Bischler–Napieralski/semipinacol rearrangement + Mannich Strtegy



- An indirectly method utilizing by-product to realize C-H functionalization:



ACKNOWLEDGEMENT

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- All my labmates in F211;
- All professors and faculties in SCBB;

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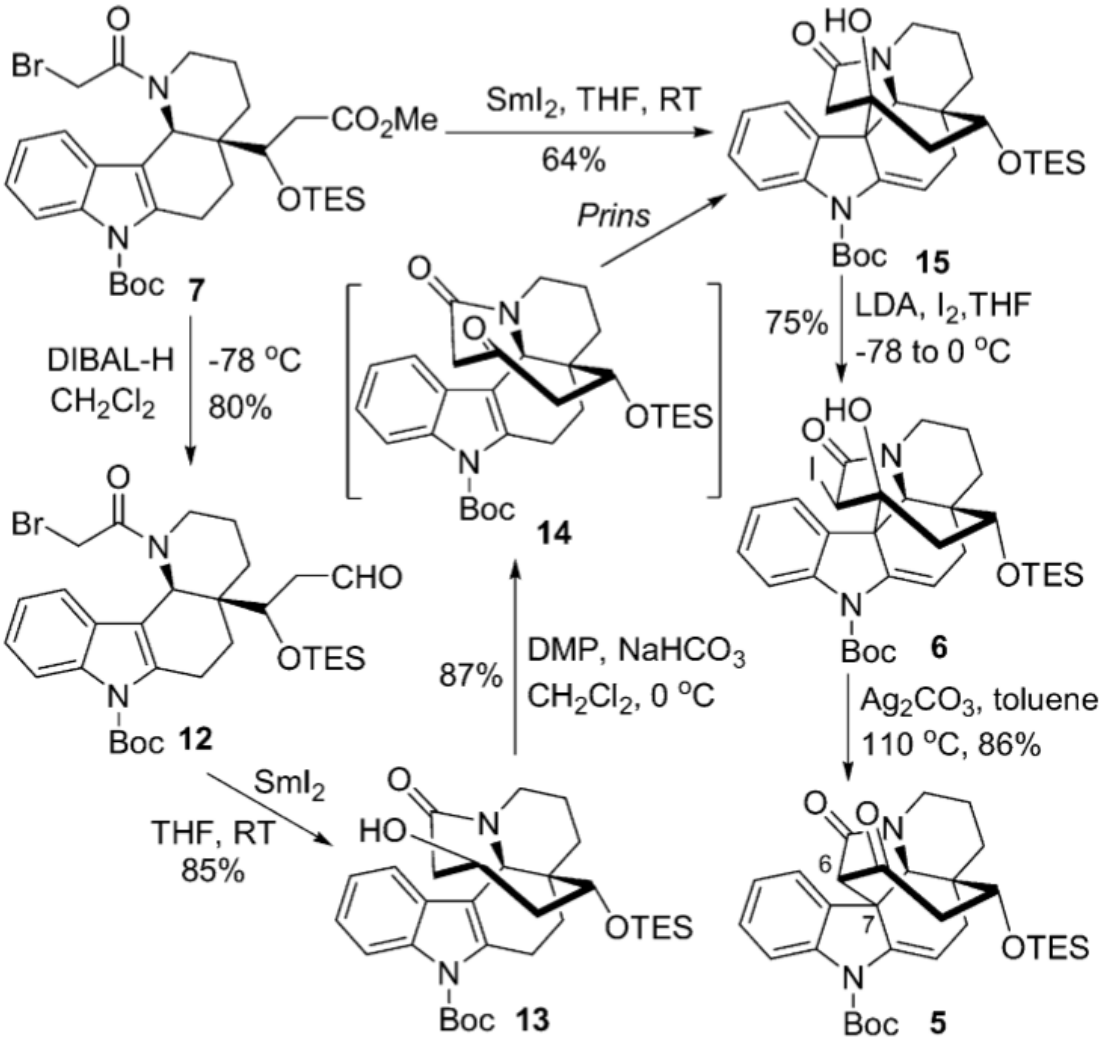
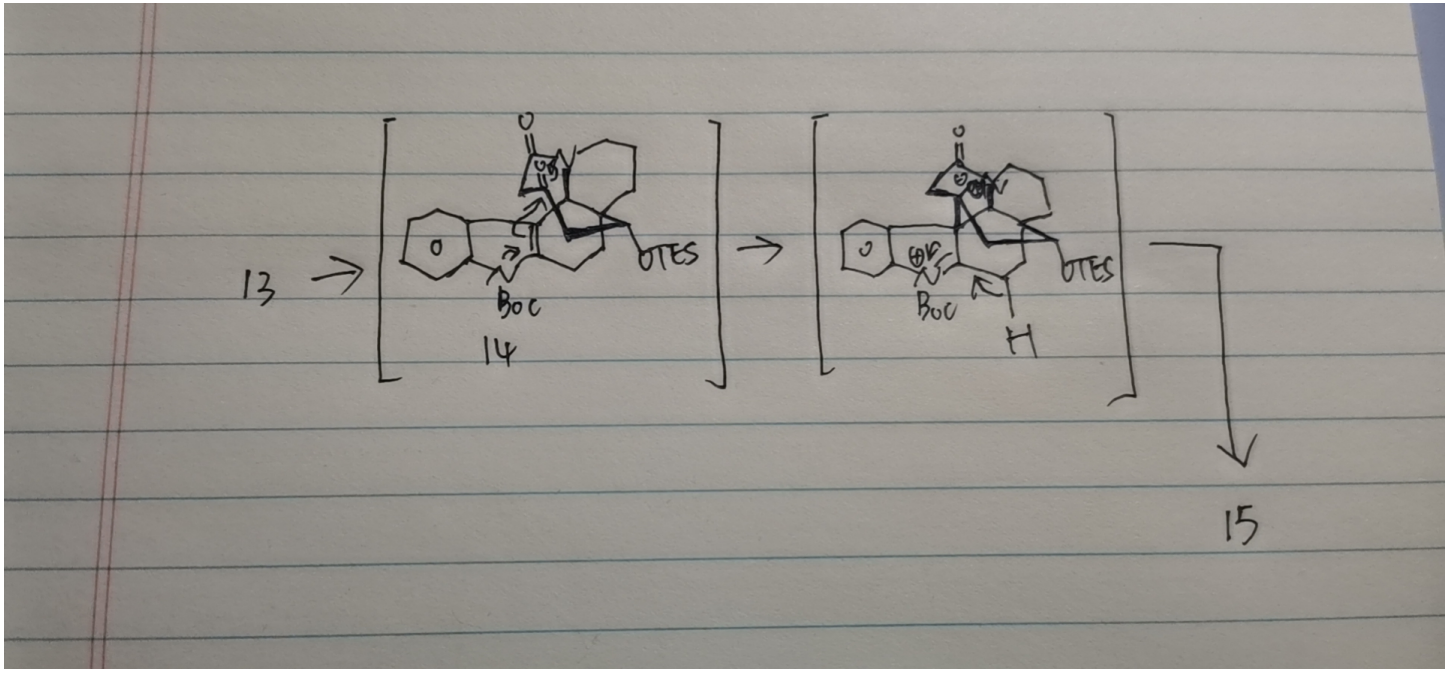
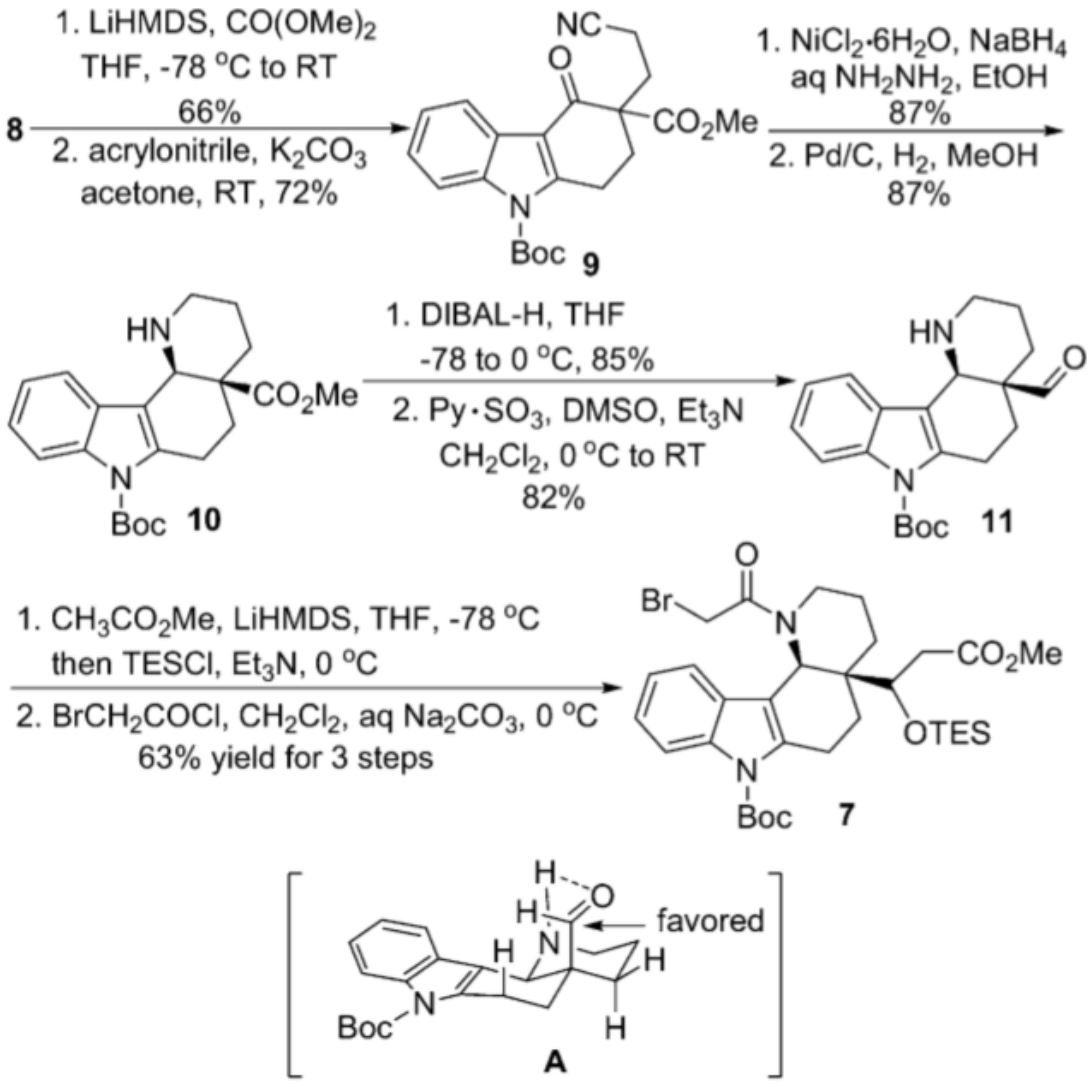
Kopsinitarine E



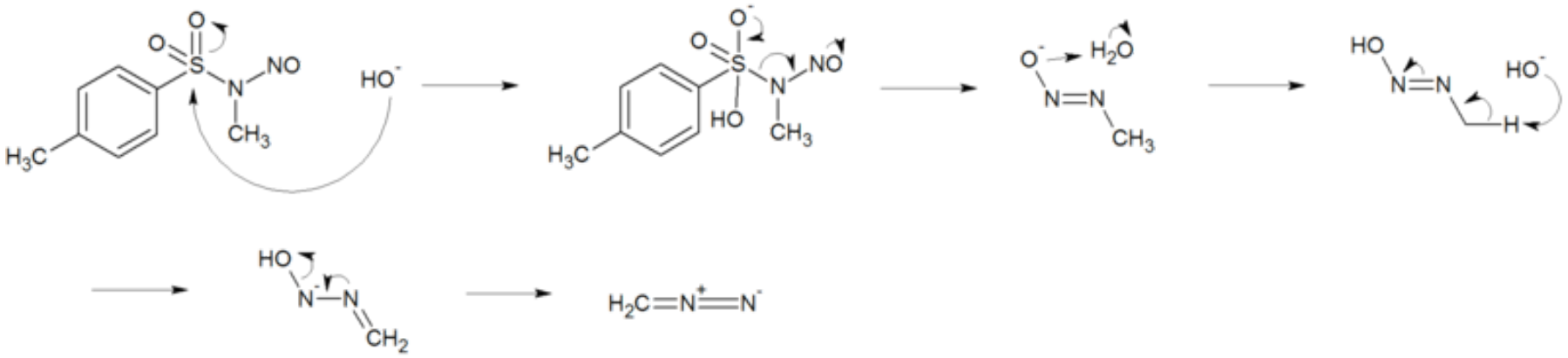
13-15



11-7: Aldol

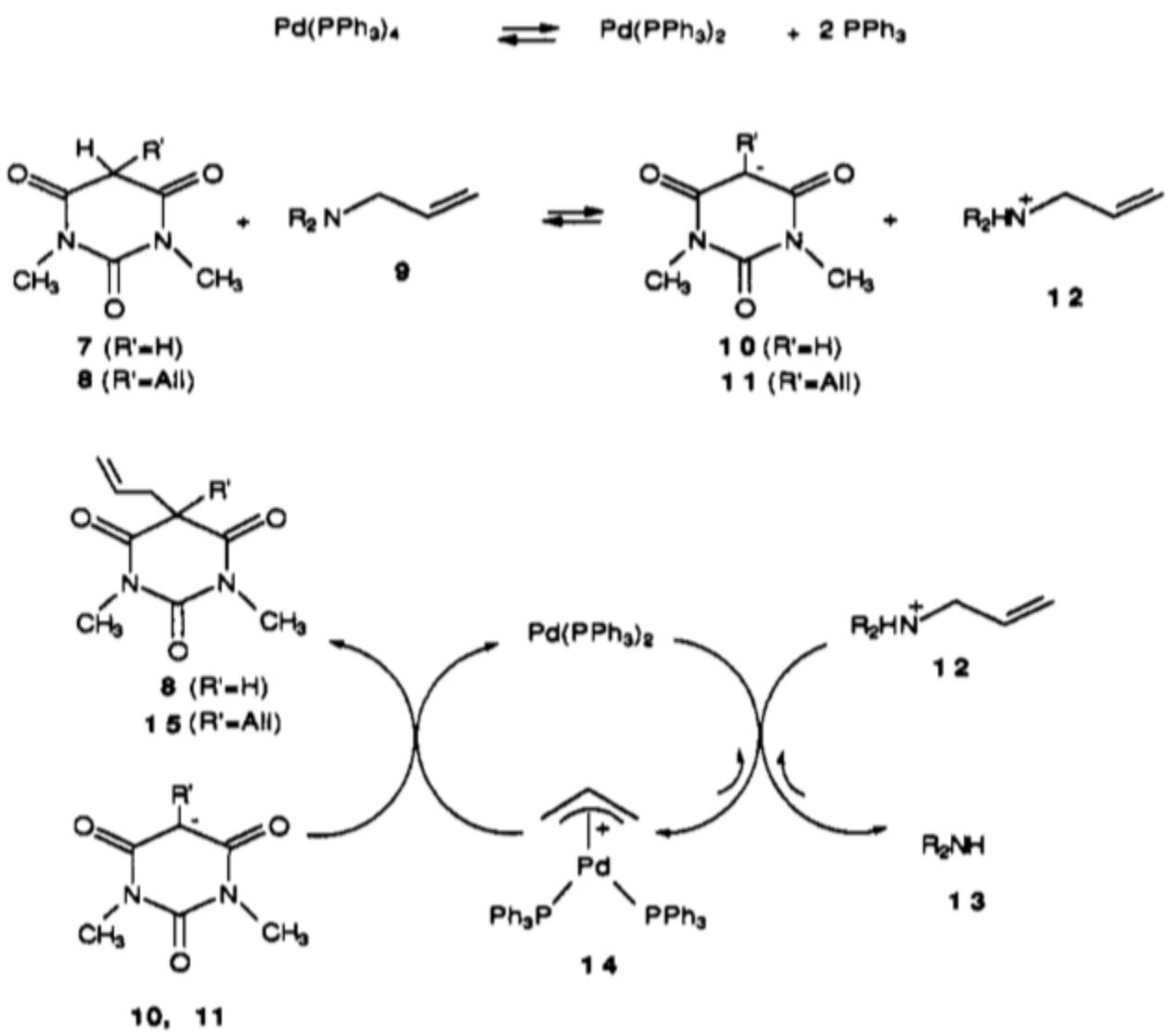

1. LiHMDS, CO(OMe)2
THF, -78 °C to RT
66%
2. acrylonitrile, K2CO3
acetone, RT, 72%
8
NC
O
CO2Me
N
Boc
9
1. NiCl2·6H2O, NaBH4
aq NH2NH2, EtOH
87%
2. Pd/C, H2, MeOH
87%
HN
CO2Me
N
Boc
10
1. DIBAL-H, THF
-78 to 0 °C, 85%
2. Py·SO3, DMSO, Et3N
CH2Cl2, 0 °C to RT
82%
HN
O
N
Boc
11
1. CH3CO2Me, LiHMDS, THF, -78 °C
then TESCl, Et3N, 0 °C
2. BrCH2COCl, CH2Cl2, aq Na2CO3, 0 °C
63% yield for 3 steps
O
Br
N
CO2Me
OTES
N
Boc
7
H
O
H
N
favored
H
H
N
Boc
H
A

SI



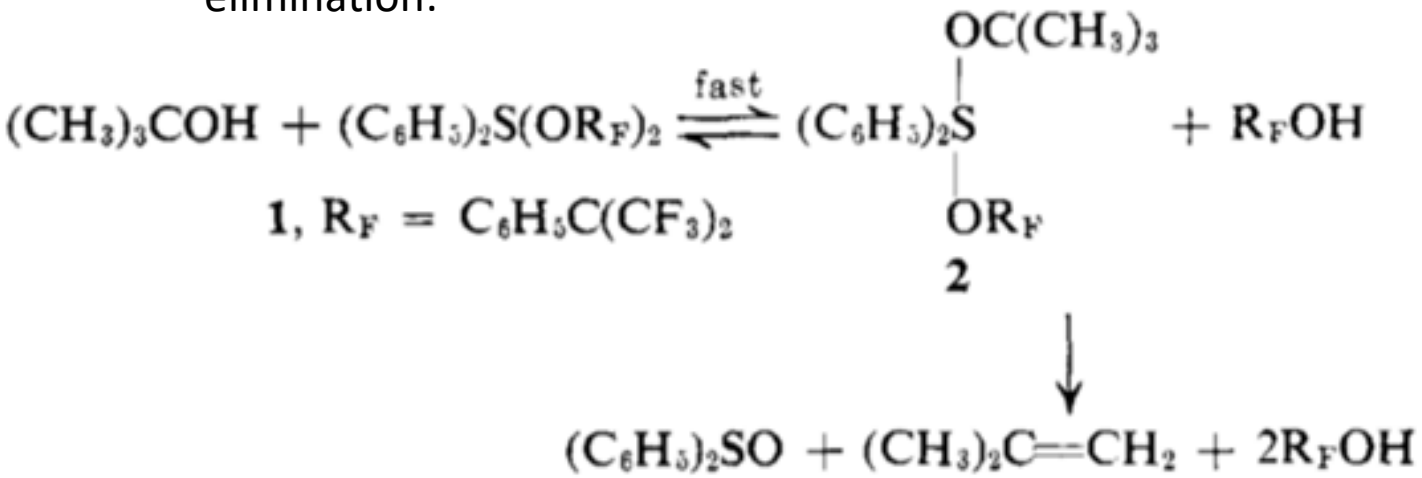
SI

Scheme I

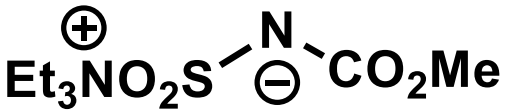


F. Garro-Helion, *et. al. J. Org. Chem.*, **58**(22), 6109-6113

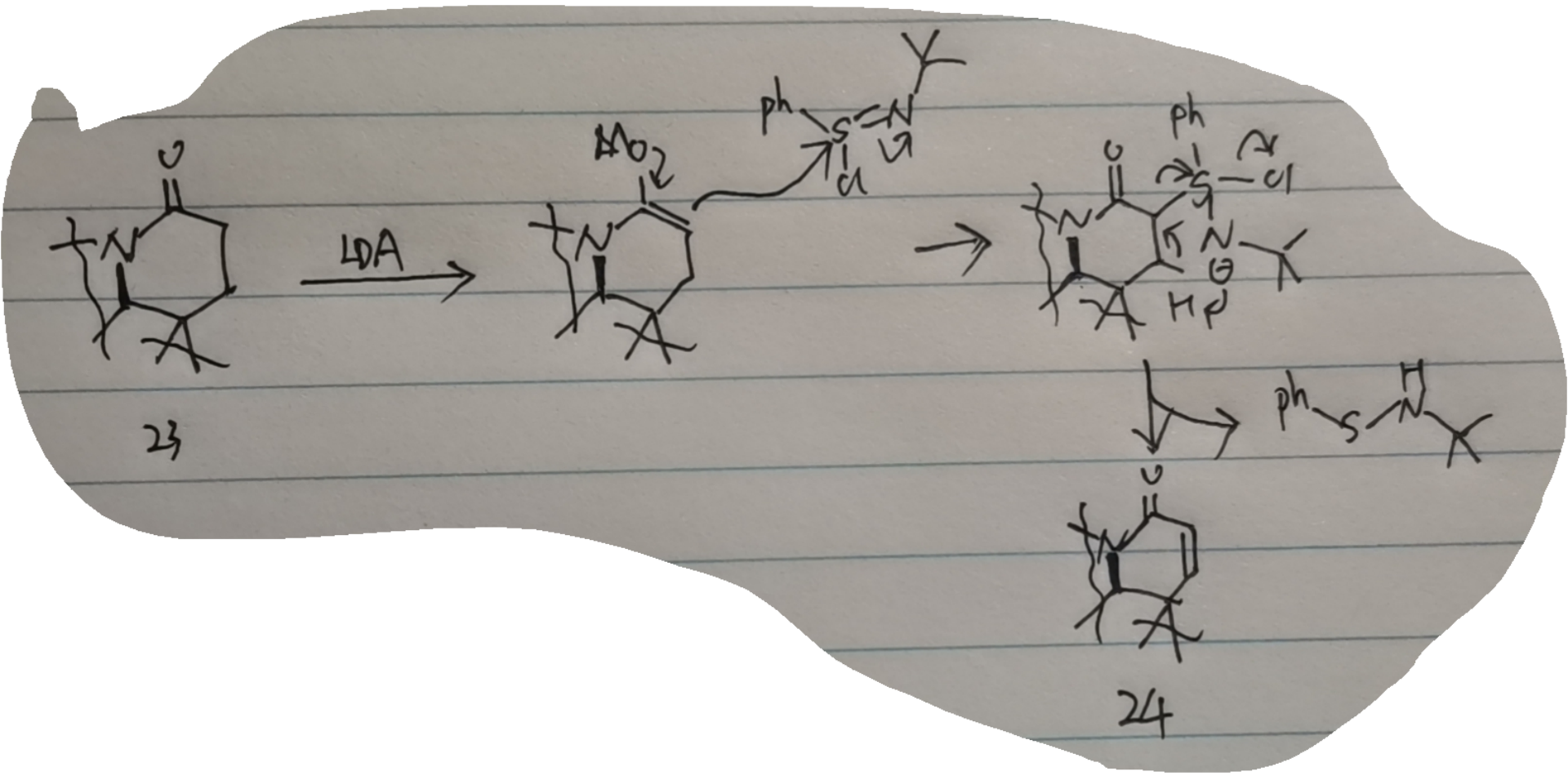
Dehydration with martin's reagent （anti elimination:



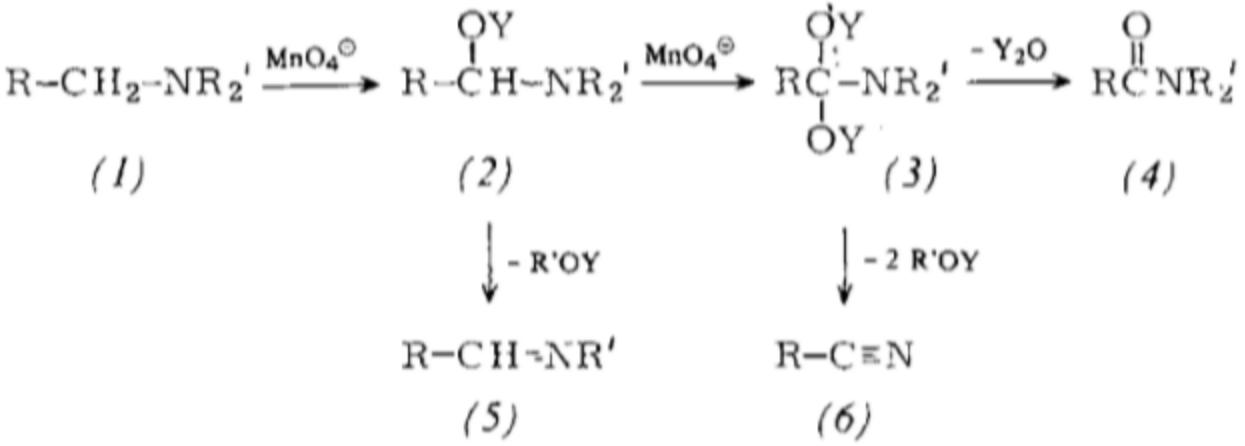
Burgess reagent-syn elimination



SI



SI



R = Phenyl, Alkyl; R' = H, Alkyl; Y = H, $MnO_3H^{\ominus}$

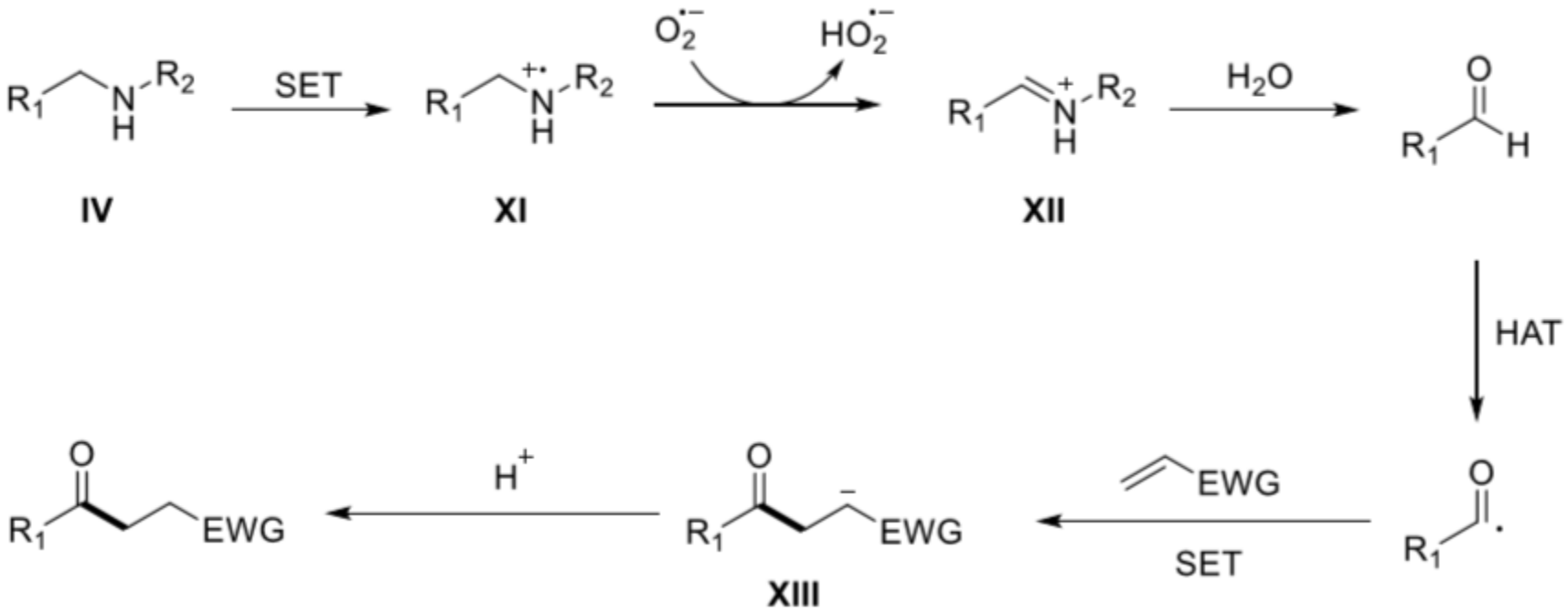
ylic acids and esters, presumably by oxidation of the imine *(5)*. Tertiary amines afford the amides *(4)* in 75—98% yield, practically without formation of byproducts. The different CH bonds react with about the following chemoselectivities: benzyl: CH_2: CH_3 = 24:2:1.

H. Jiirgen Schmidt, et. al. *Angew. Chem. Inf. Ed. Engl.* **1981**,*20,* 109

SI

4a + **2a** → **3a**, Not detected

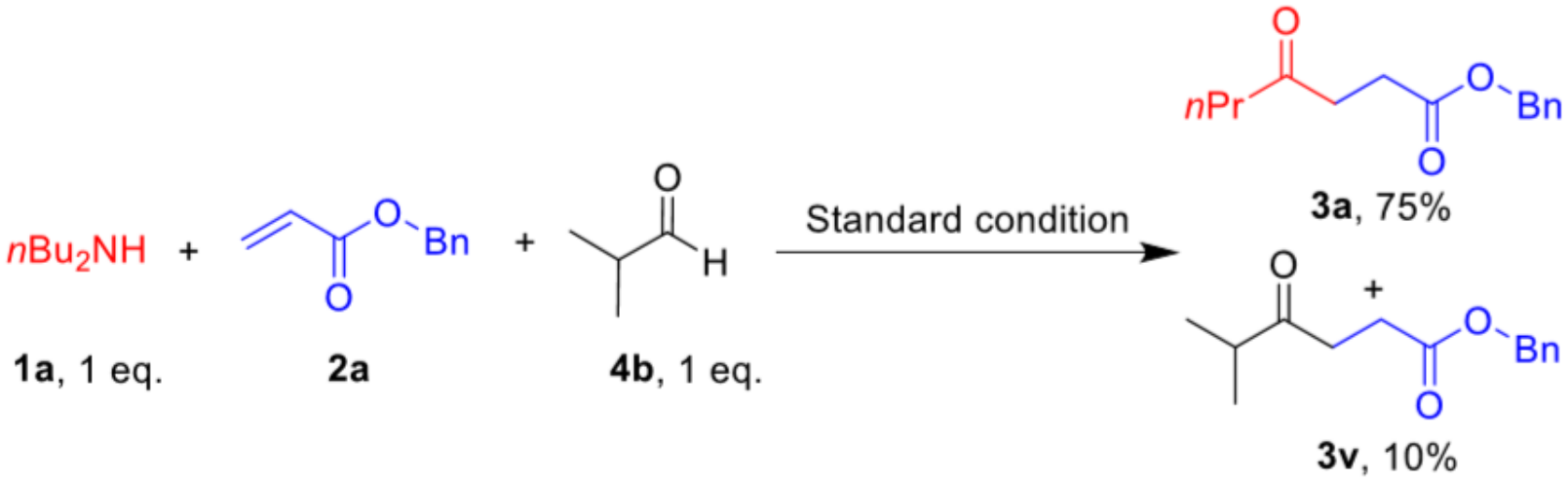
b) Path b

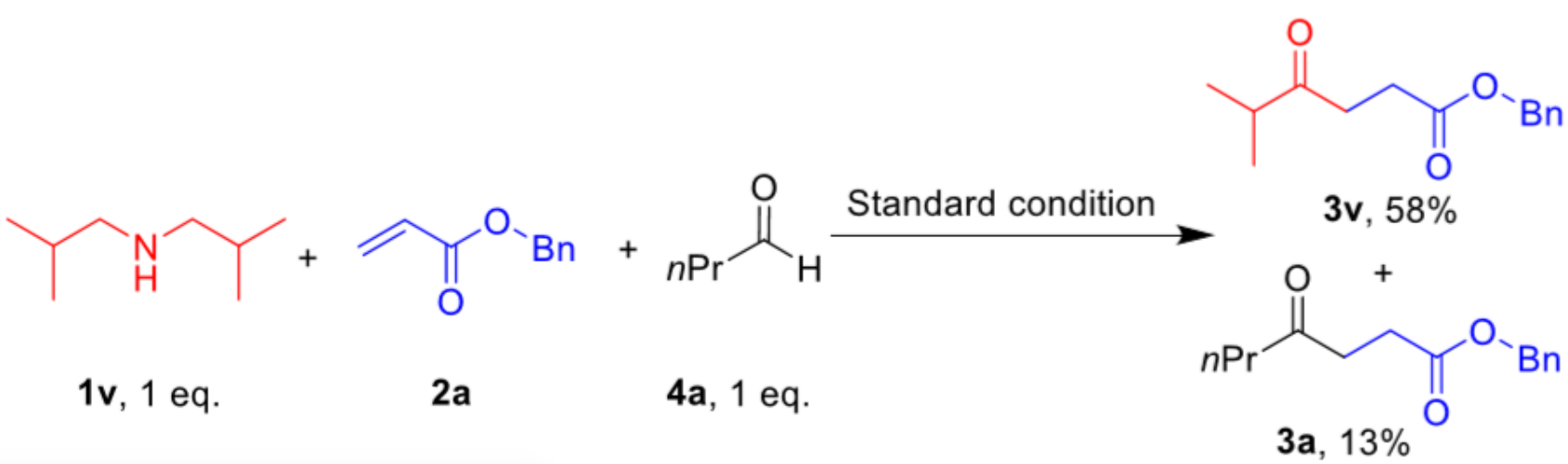


IV **XI** **XII** **XIII**

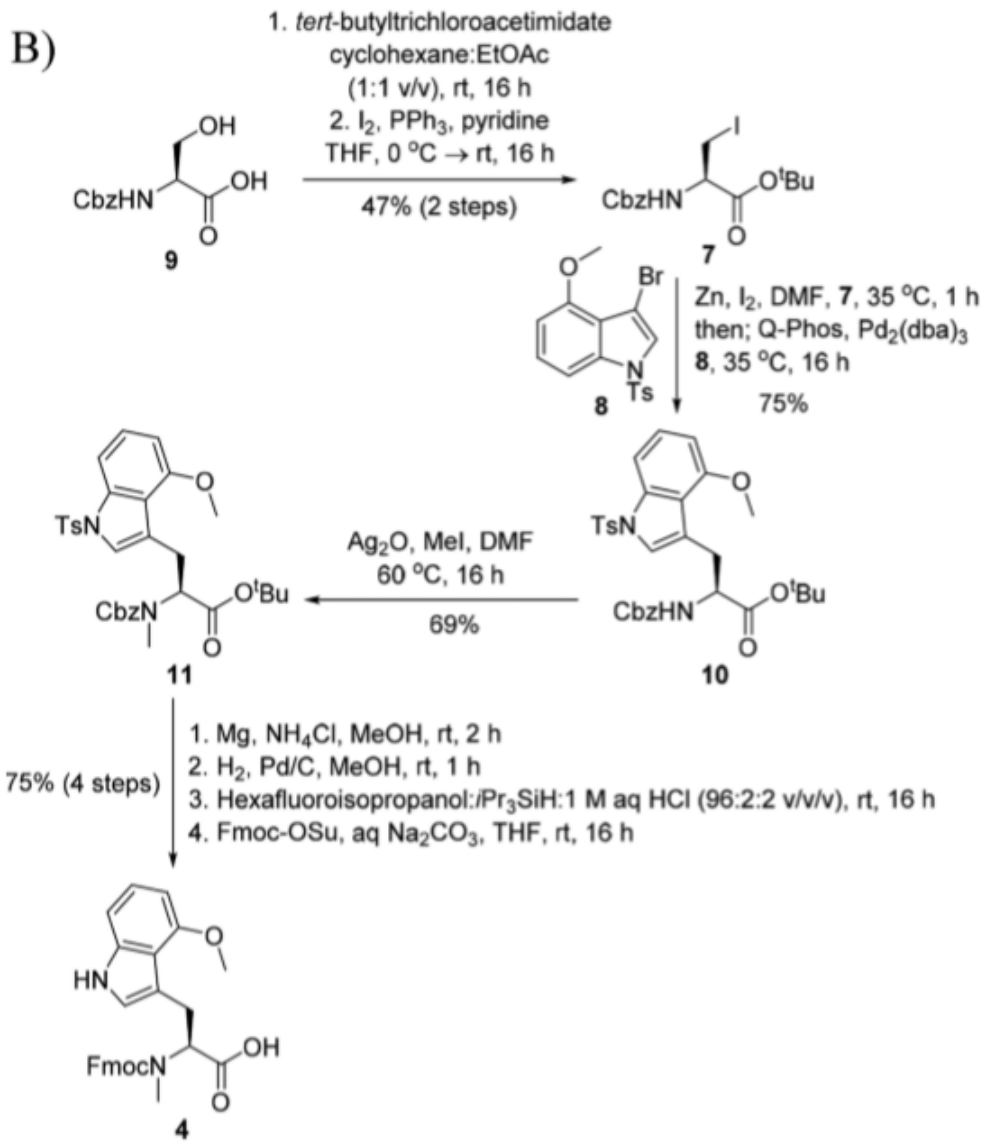
c)


Standard condition
nPr
Bn
4a
2a
3a, Not detected


nBu2NH
Standard condition
nPr
Bn
3a, 75%
1a, 1 eq.
2a
4b, 1 eq.
3v, 10%


Standard condition
Bn
3v, 58%
nPr
3a, 13%
1v, 1 eq.
2a
4a, 1 eq.

SI



Paige M. E. Hawkins, *et. al. Org. Lett*. **2018**, *20*, 1019−1022

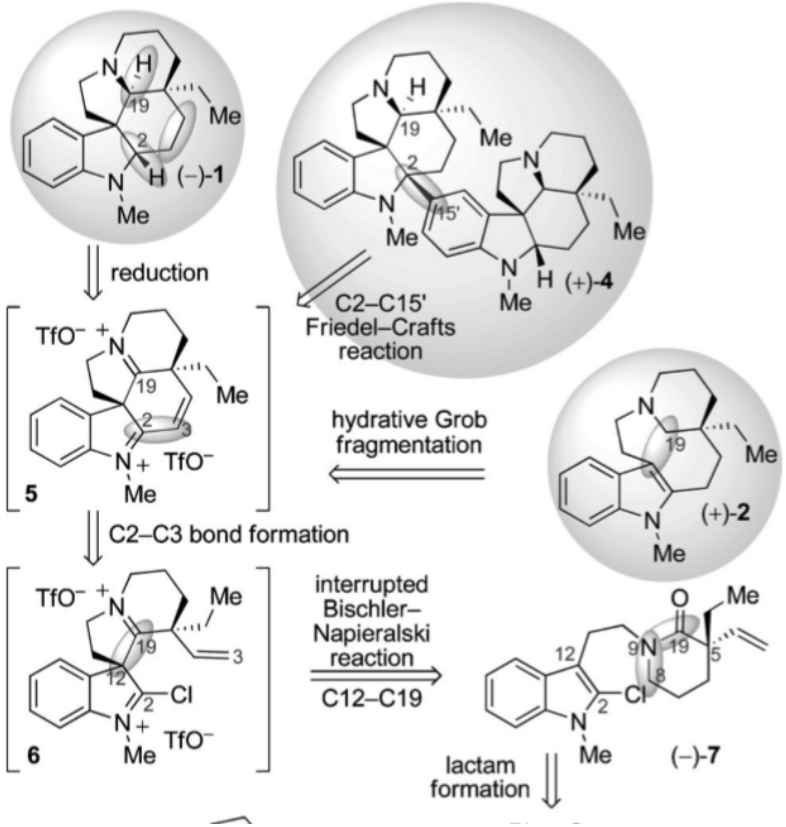
Angewandte
Communications

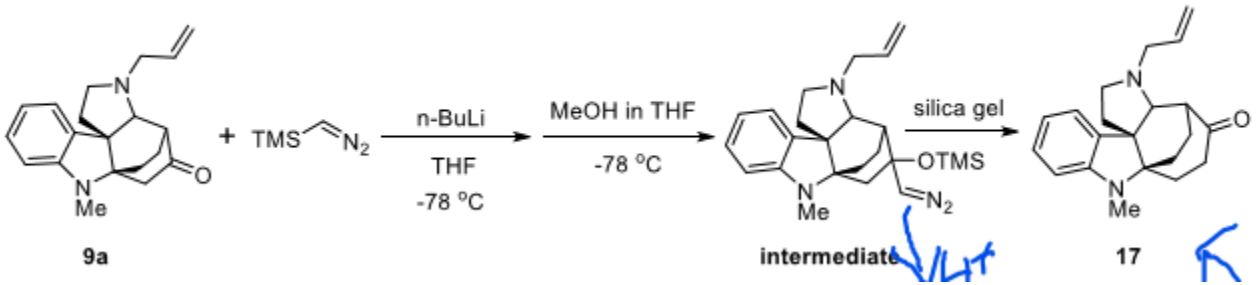
VIP Alkaloid Synthesis

DOI: 10.1002/anie.201200387

A Concise and Versatile Double-Cyclization Strategy for the Highly Stereoselective Synthesis and Arylative Dimerization of Aspidosperma Alkaloids**

*Jonathan William Medley and Mohammad Movassaghi**




TMS
N2
n-BuLi
THF
-78 °C
MeOH in THF
-78 °C
silica gel
OTMS
N2
N
Me
O
9a
intermediate
17

4.1 Radical trapping experiment

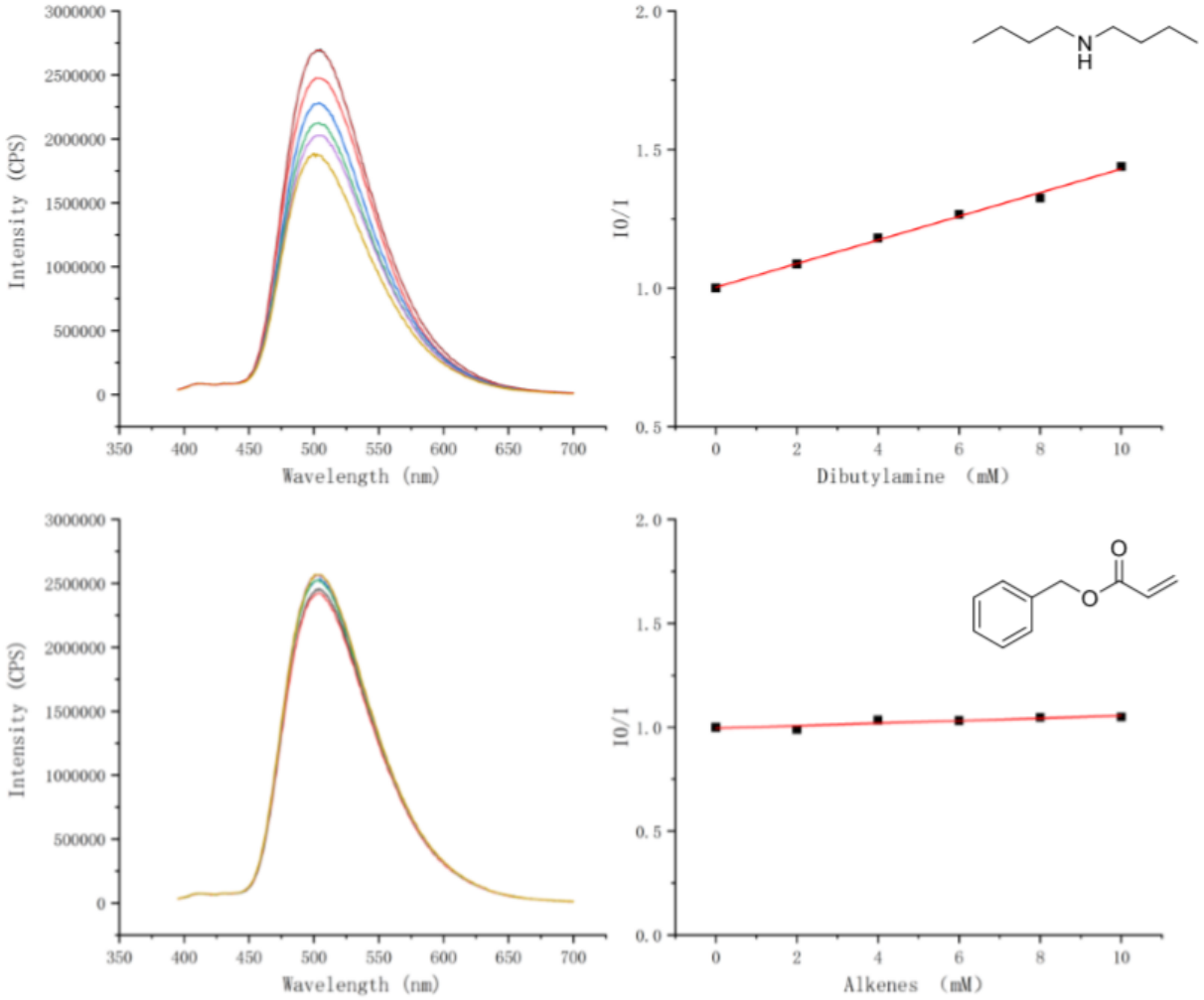


Figure S2 Stern-Volmer quenching of 4CzIPN by dibutylamine and alkenes

4.3 Cyclic voltammetry measurements

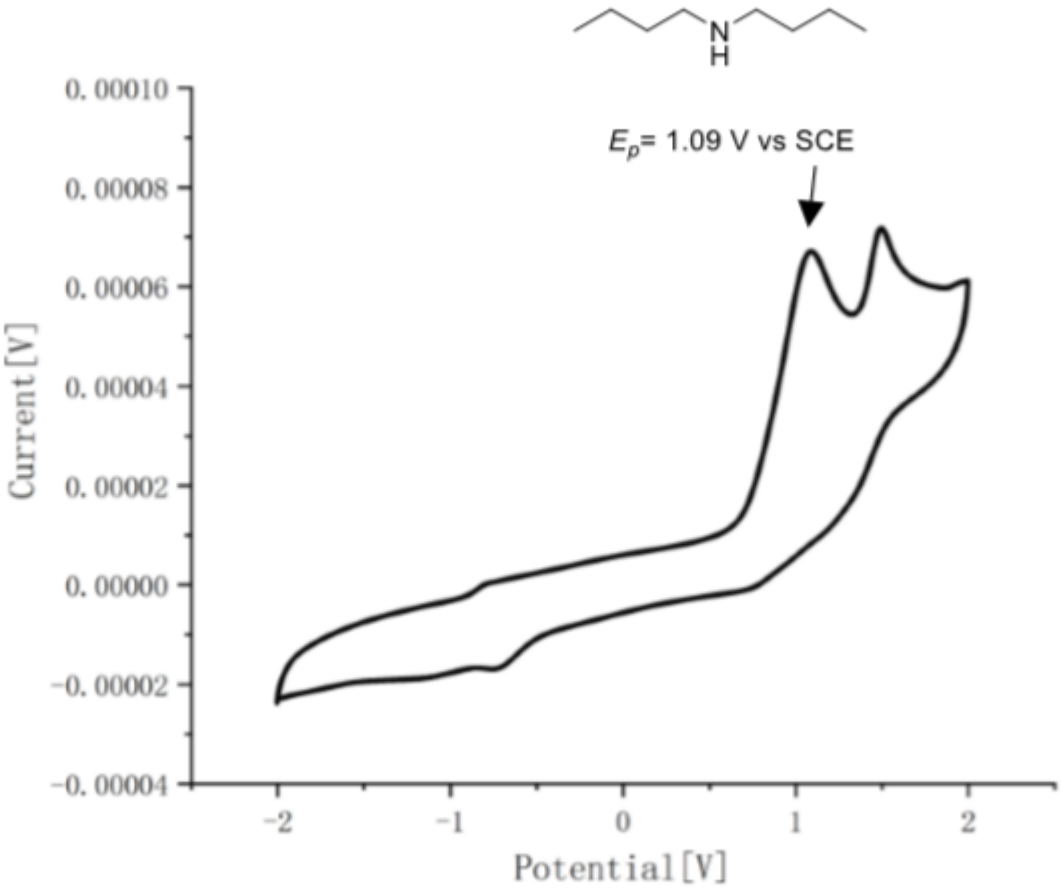


Figure S3. Cyclic Voltammetry of dibutylamine in CH_3CN