Literature Report 5

Concise Total Syntheses of (–)-Jorunnamycin A and (–)-Jorumycin Enabled by Asymmetric Catalysis

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Checker: Yi-Xuan Ding
Date: 2019-03-11

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Science **2019**, *363*, 270

Contents

CV of Prof. Brian M. Stoltz

Brian M. Stoltz

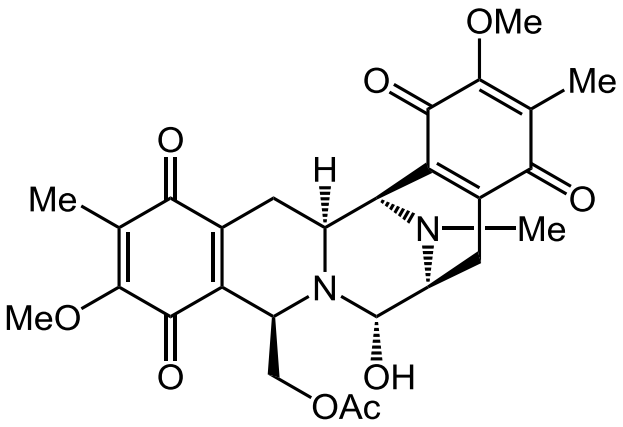
Background:

- **1989-1993** B.S., Indiana University of Pennsylvania
- **1993-1996** M.S., Yale University (John Wood)
- **1996-1997** Ph.D., Yale University (John Wood)
- **1998-2000** NIH Postdoc., Harvard University (E. J. Corey)
- **2000-2005** Assistant professor, Caltech
- **2005-2007** Associate professor, Caltech
- **2007-now** Professor, Caltech

Research Interests:

Development of new strategies for the preparation of complex molecules possessing interesting structural, biological, and physical properties

Introduction



(-)-Jorumycin

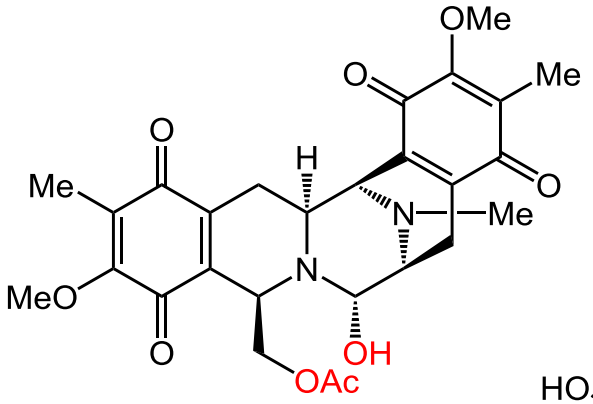
Jorunna funebris

- A bis-tetrahydroisoquinoline natural products isolated from the mantle and mucus of the pacific nudibranch Jorunna funebris;
- Possessing a pentacyclic carbon skeleton, highly oxygenated ring termini, and a central pro-iminium ion;
- The treatment of a variety of drug-resistant and unresectable soft-tissue sarcomas and ovarian cancer.

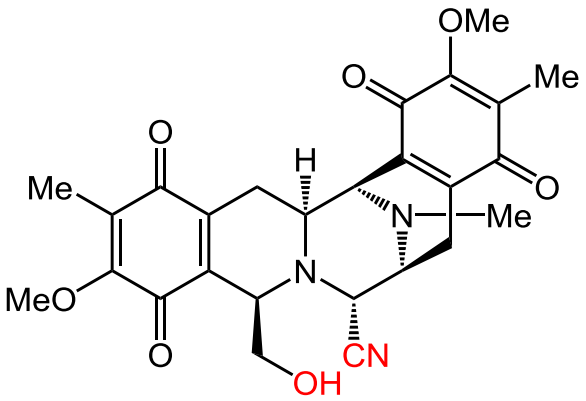
Cimino, G. *et al. Tetrahedron* **2000**, *56*, 7305

Introduction

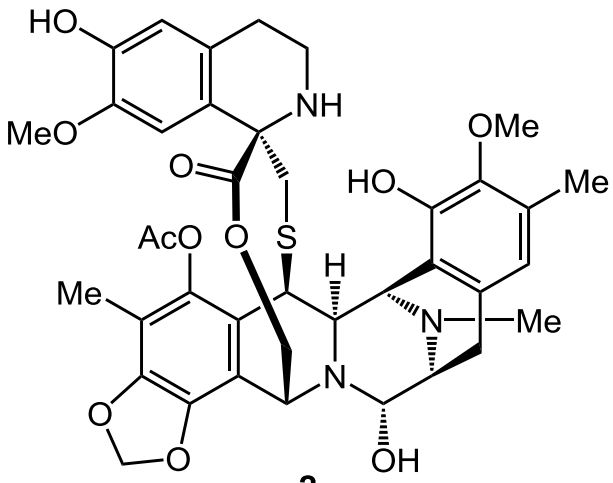
Bis-Tetrahydroisoquinoline (bis-THIQ) natural products
Alaloids that display exceptional anticancer activity



1
(-)-Jorumycin



3
Jorunnamycin A

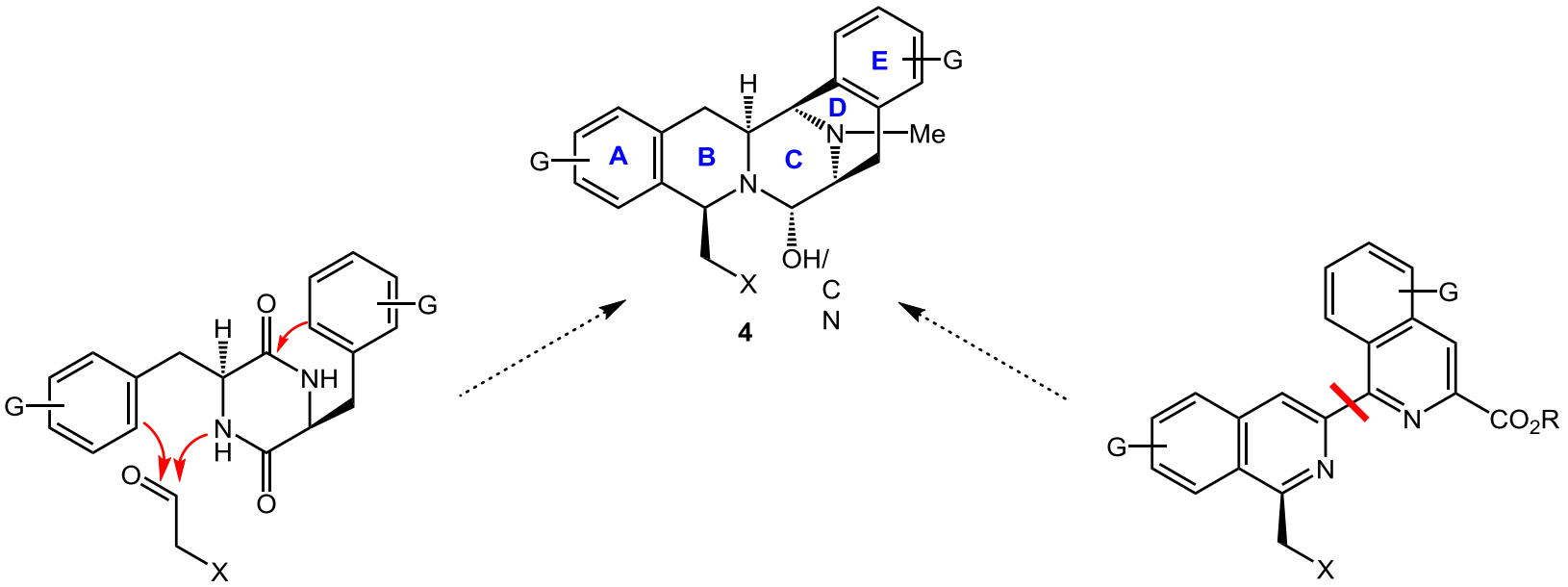


2
Ecteinascidin 743 (Yondelis, trabectidin)

Introduction

A non-biomimetic approach will produce complementary analogs for bioactivity and medicinal chemistry studies

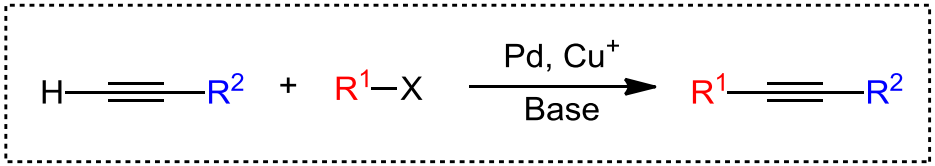
Pentacyclic bis-THIQ Core

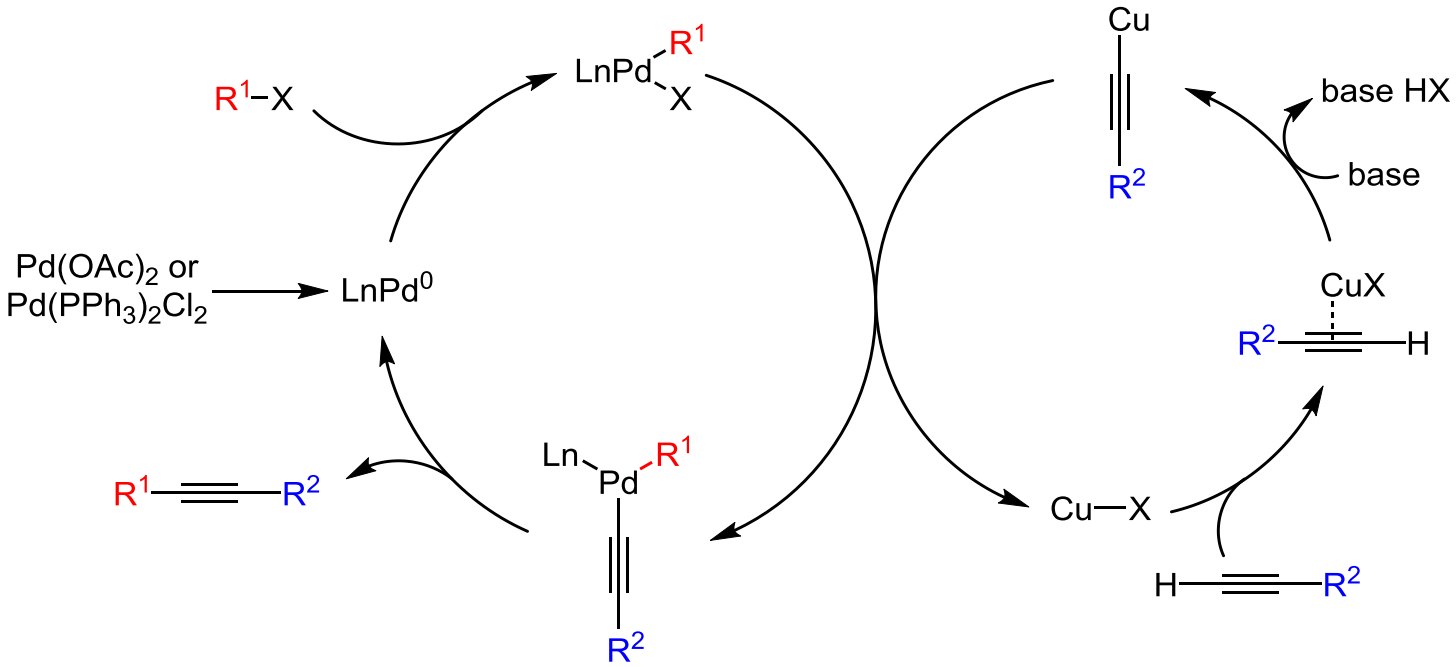


Conventional, Biomimetic Approach: Pictet-Spengler, Bischler-Napieralski

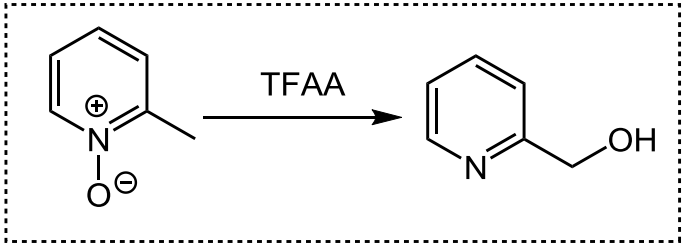
This Research: Cross Coupling/Reductive Cyclization

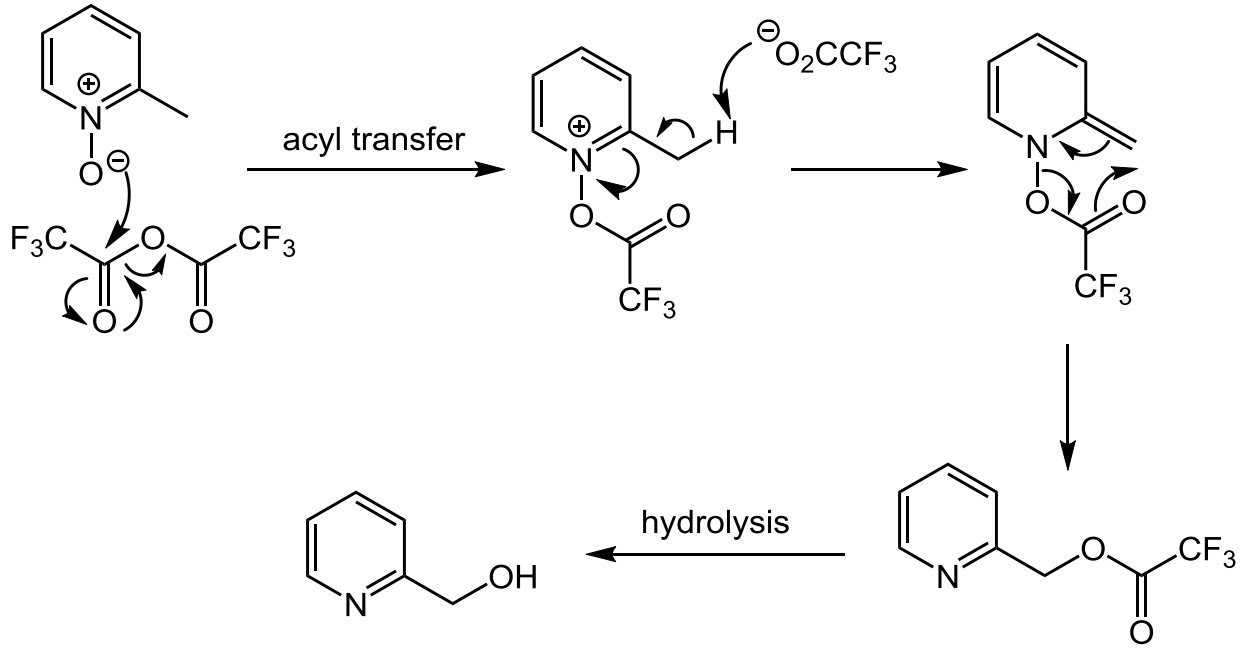
Sonogashira Coupling



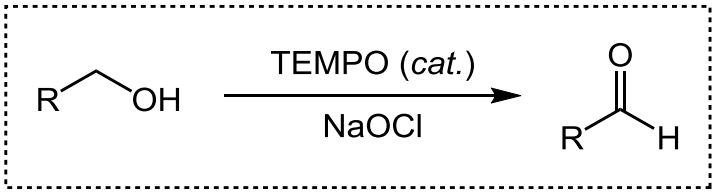


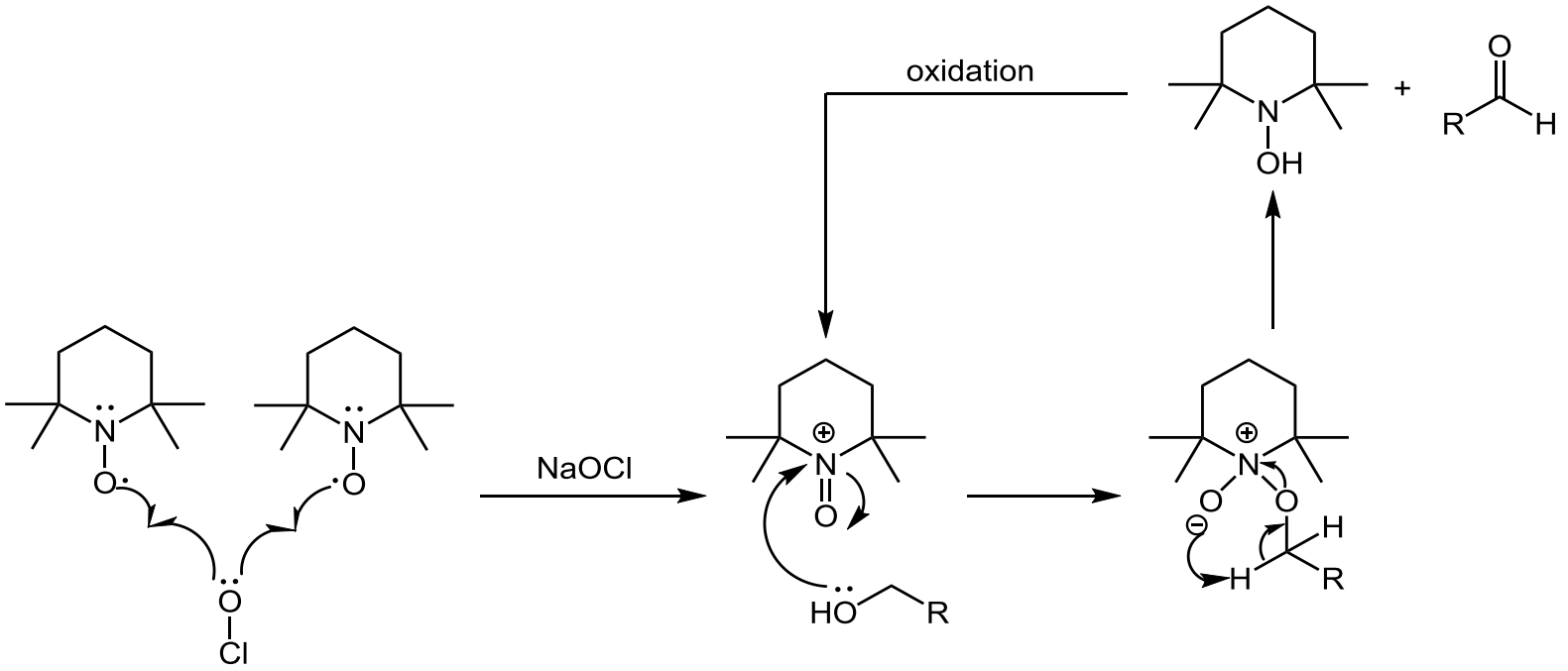
Boekelheide Reaction



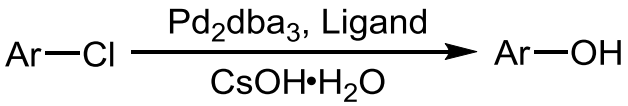


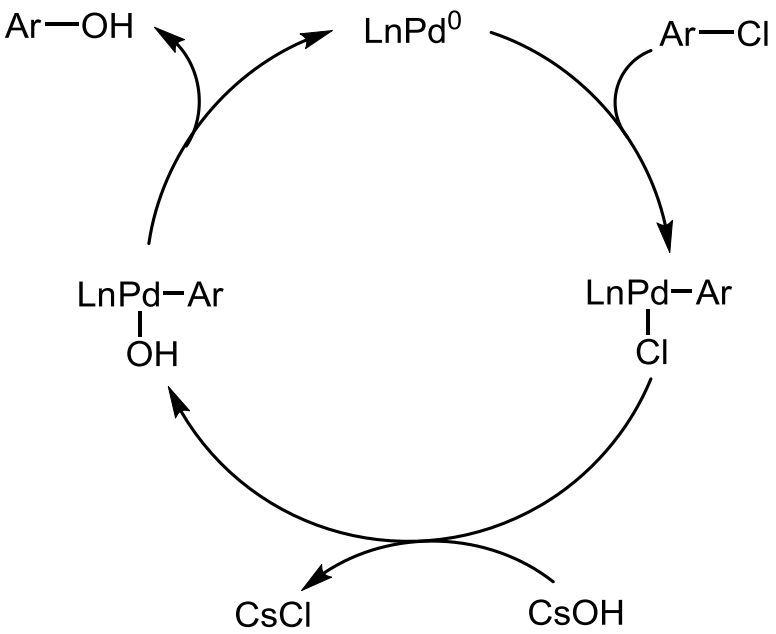
TEMPO Oxidation





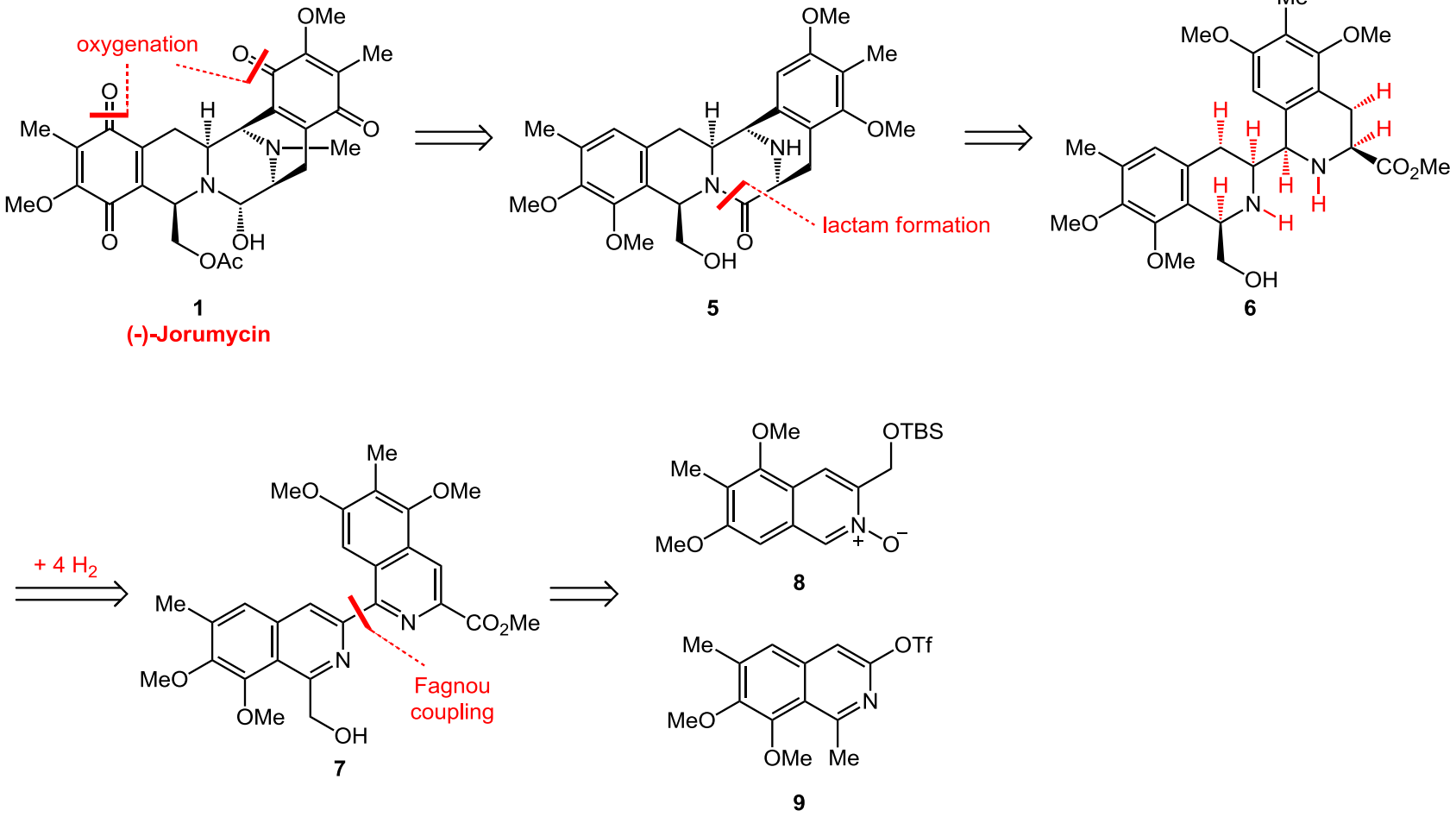
Hydroxylation of Aryl Halides by Stradiotto



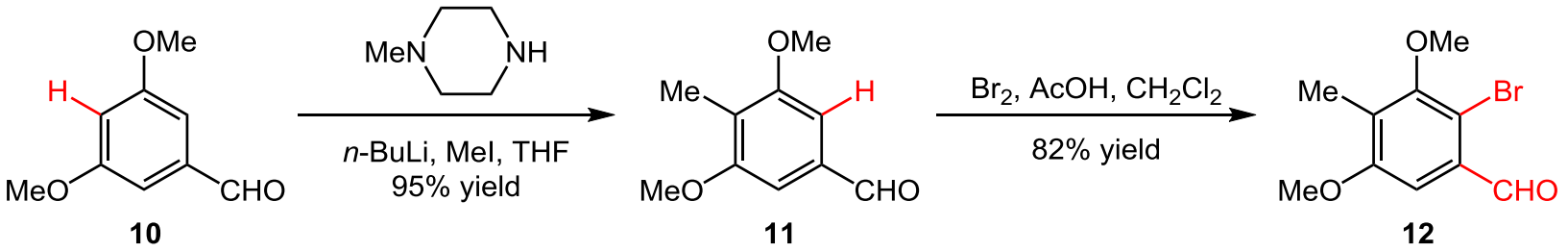


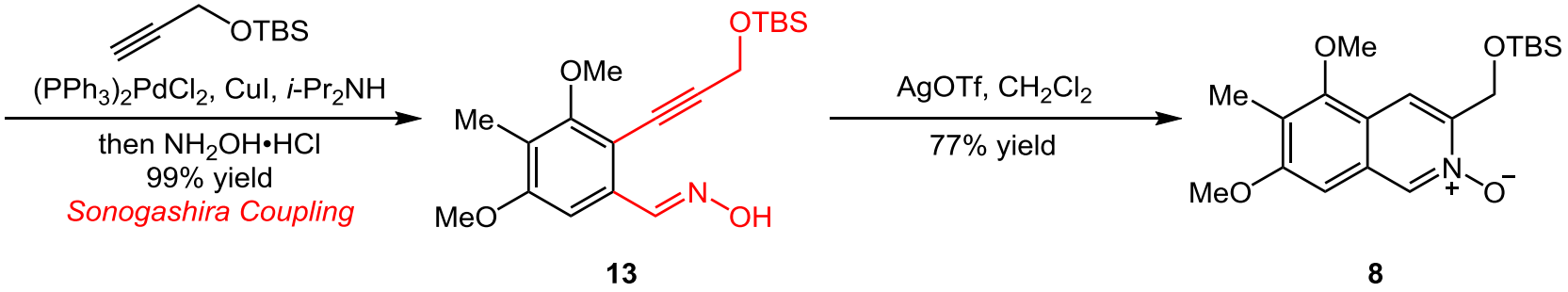
Stradiotto, M. *et al. Adv. Synth. Catal.* **2013**, *355*, 981

Retrosynthetic Analysis

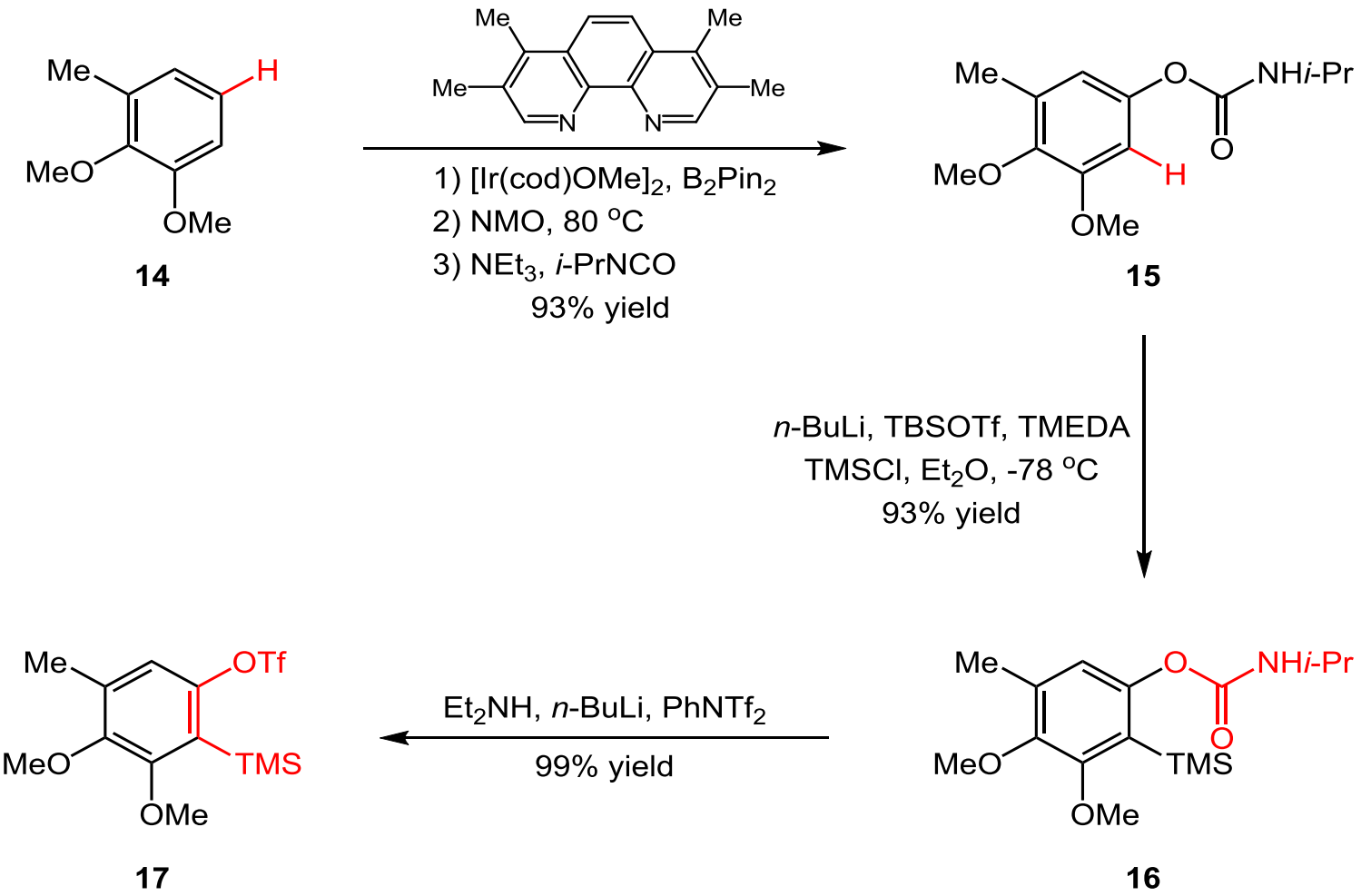


Synthesis of Isoquinoline Monomer 8

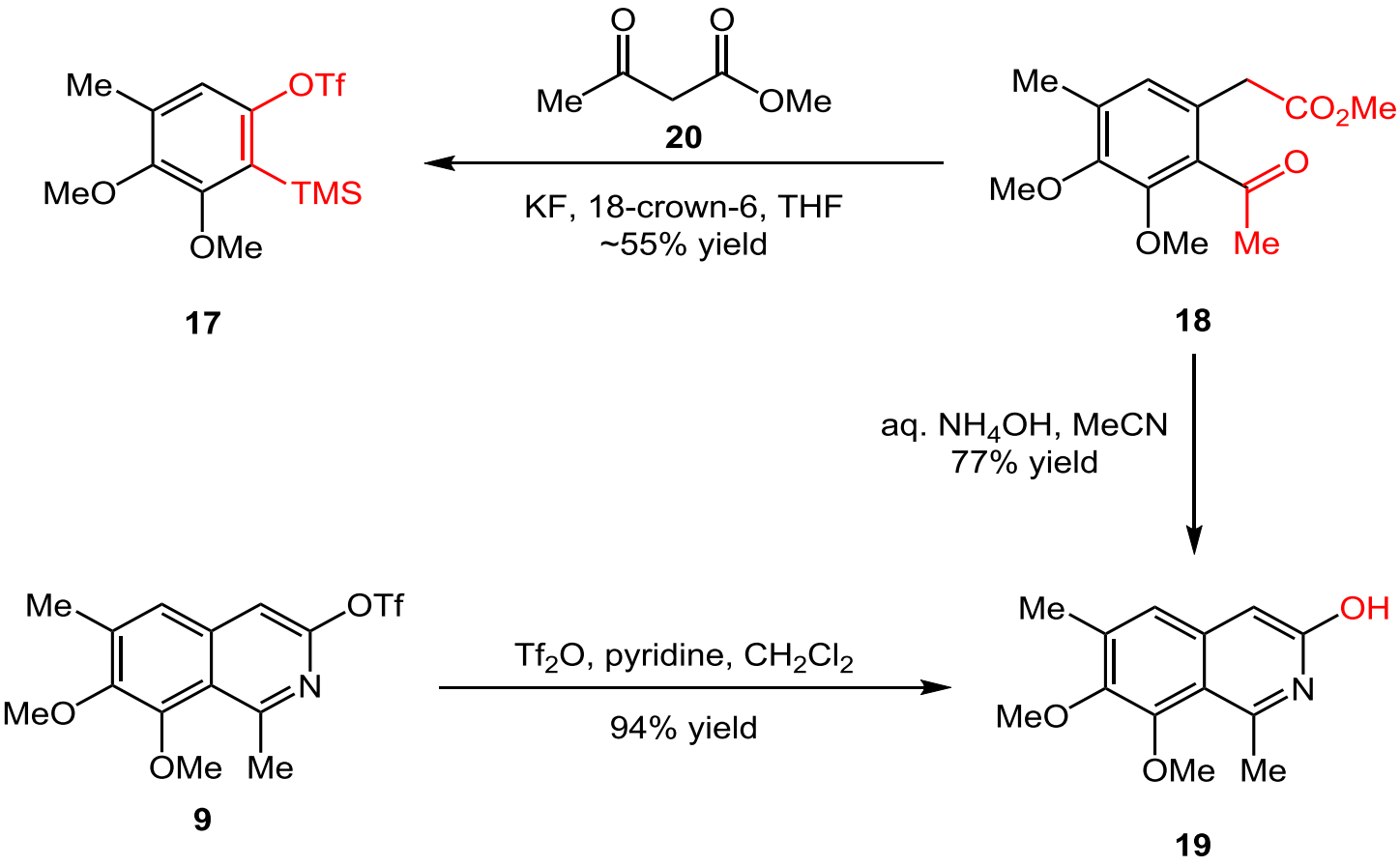




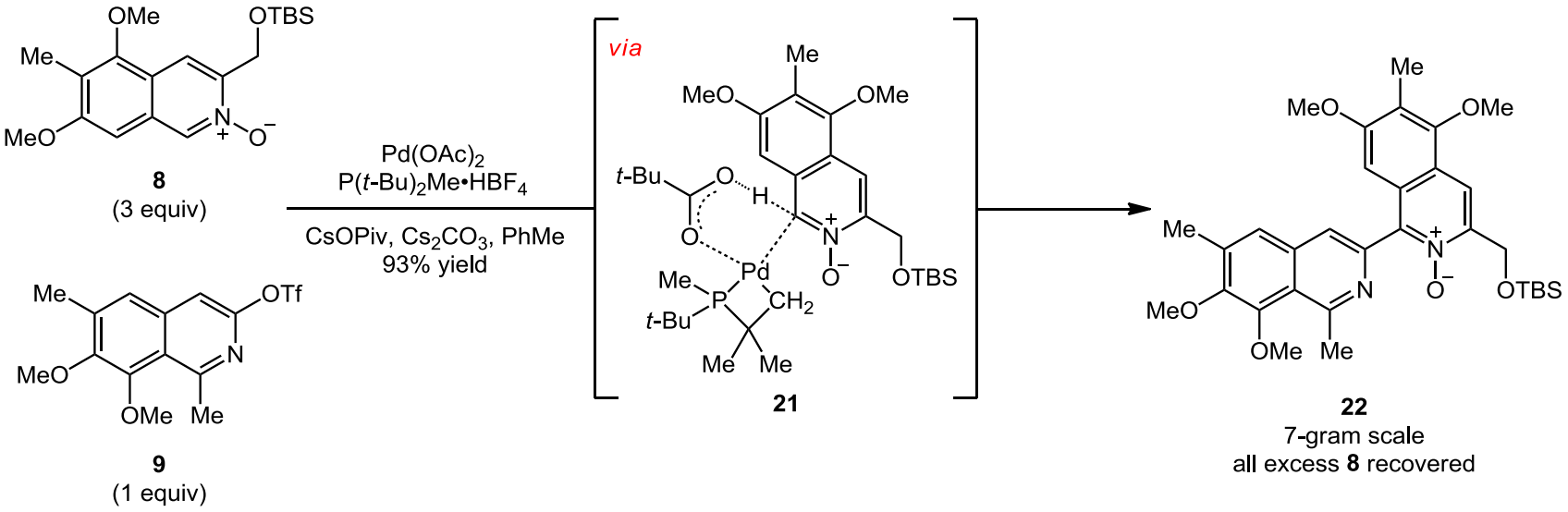
Synthesis of Isoquinoline Monomer 9



Synthesis of Isoquinoline Monomer 9



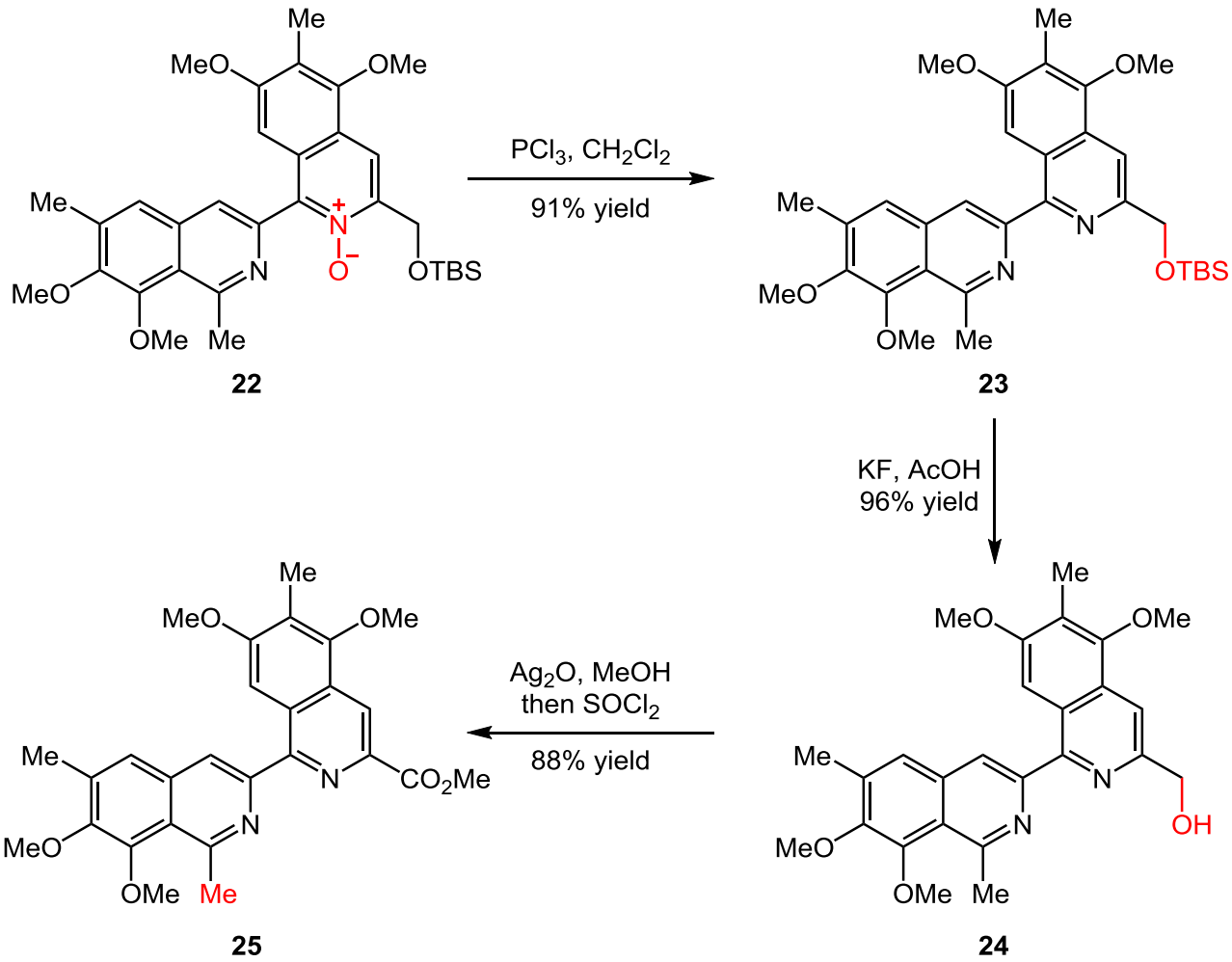
Fagnou Coupling



Fagnou, K. *et al. J. Am. Chem. Soc.* **2008**, *130*, 3266

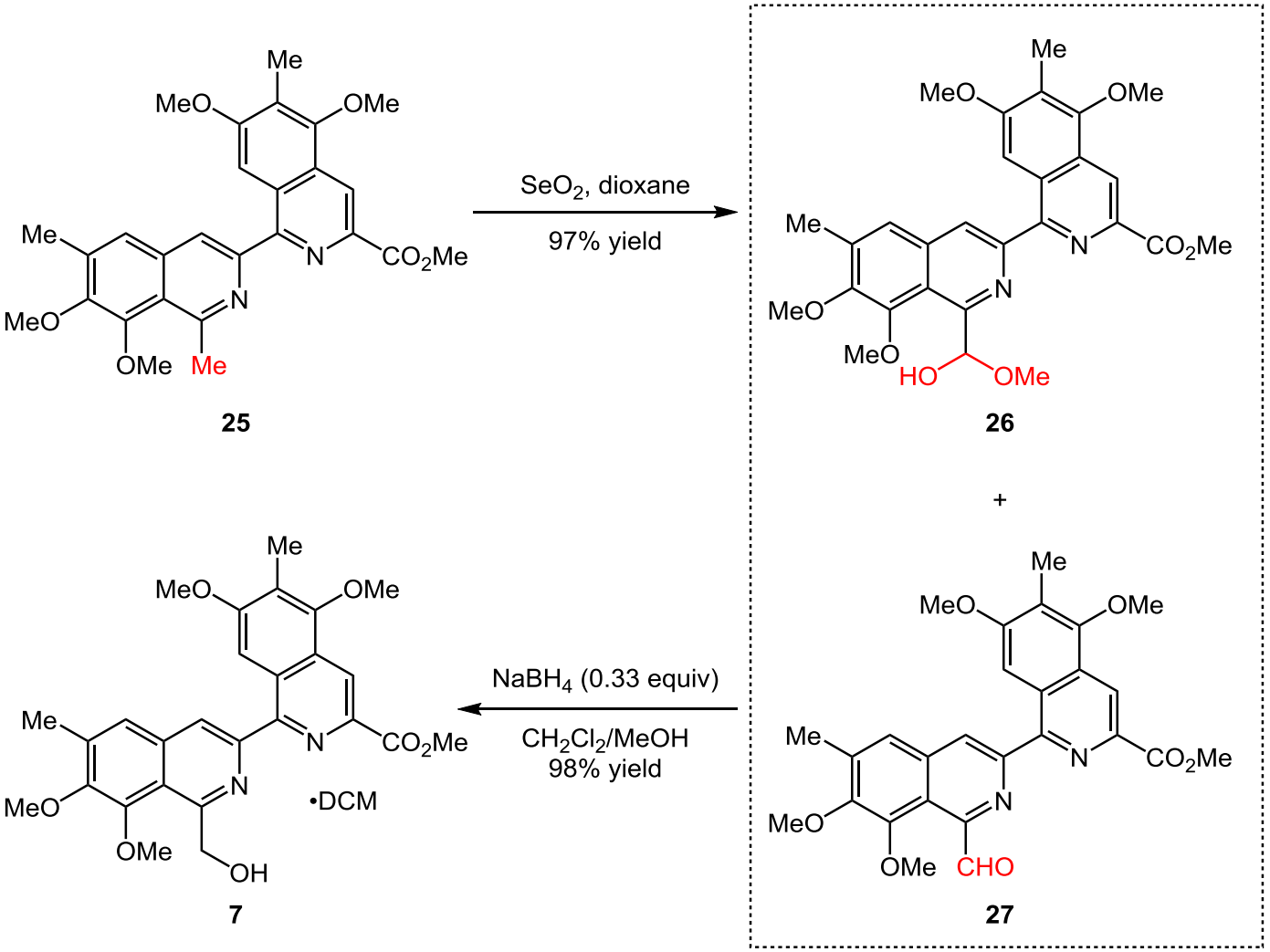
Synthesis of Hydrogenation Precursor 7

First Generation



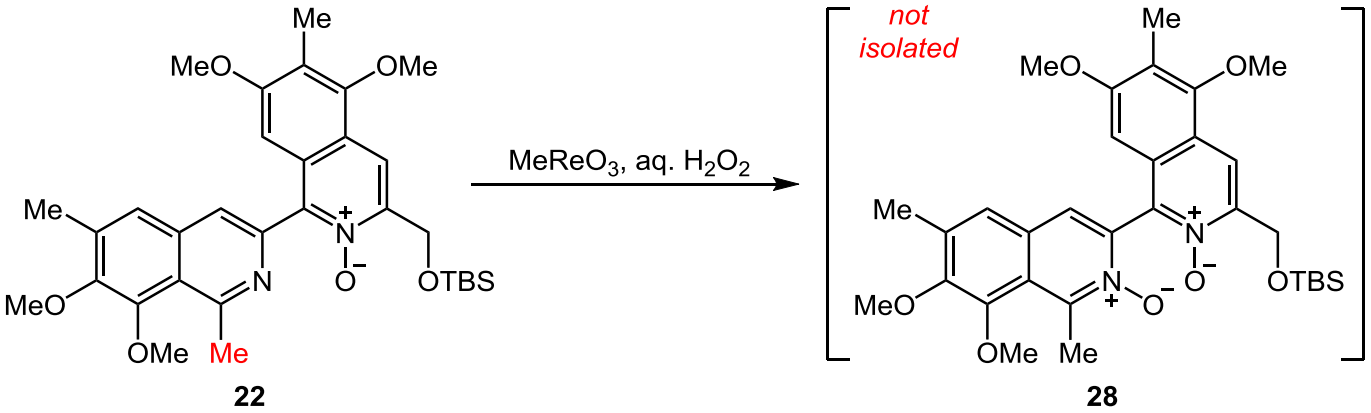
Synthesis of Hydrogenation Precursor 7

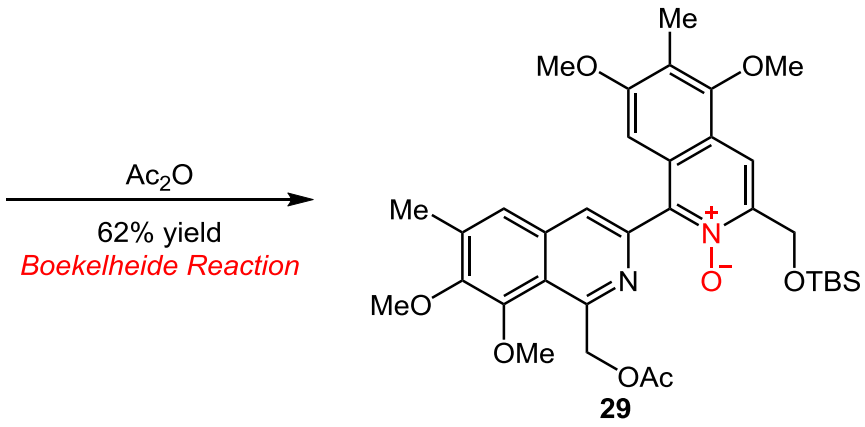
First Generation



Synthesis of Hydrogenation Precursor 7

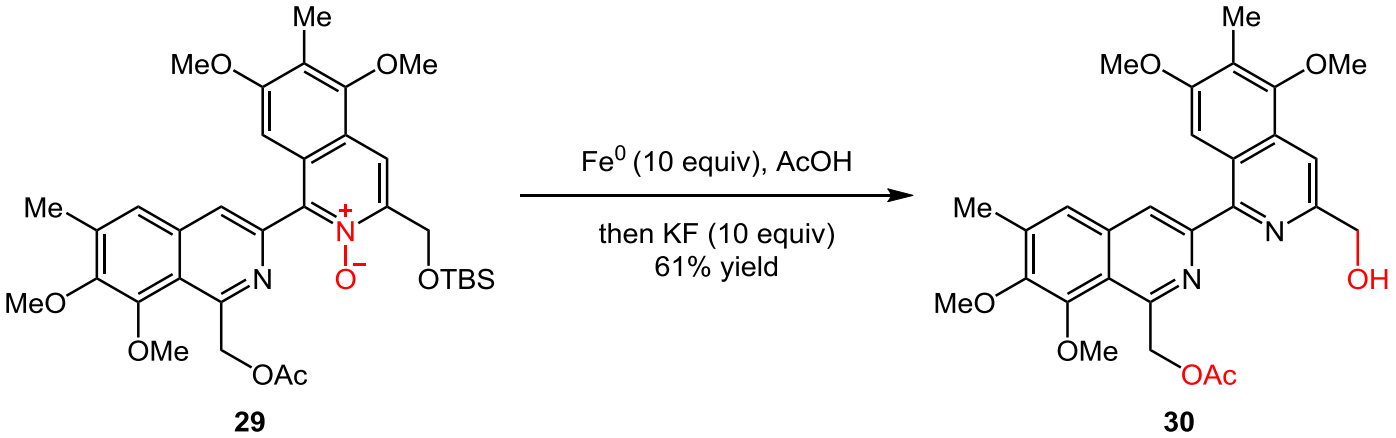
Second Generation

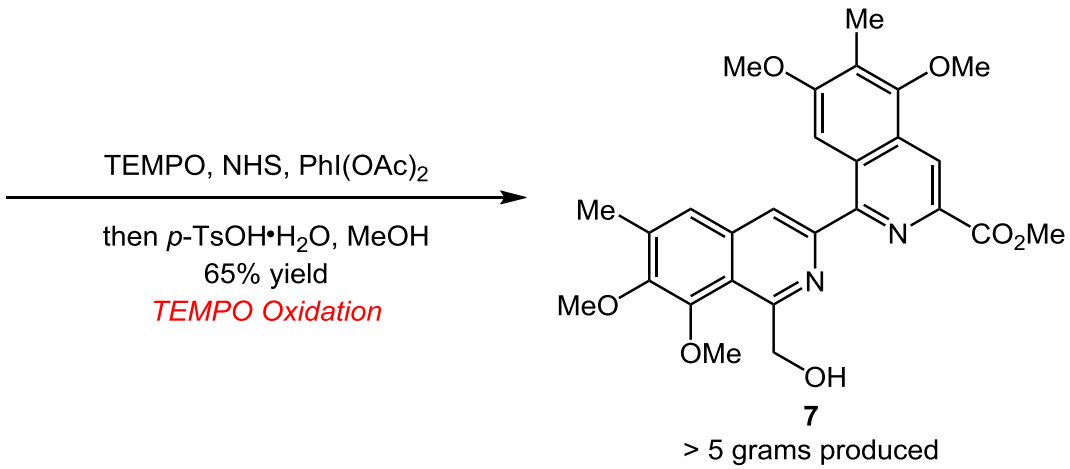




Synthesis of Hydrogenation Precursor 7

Second Generation

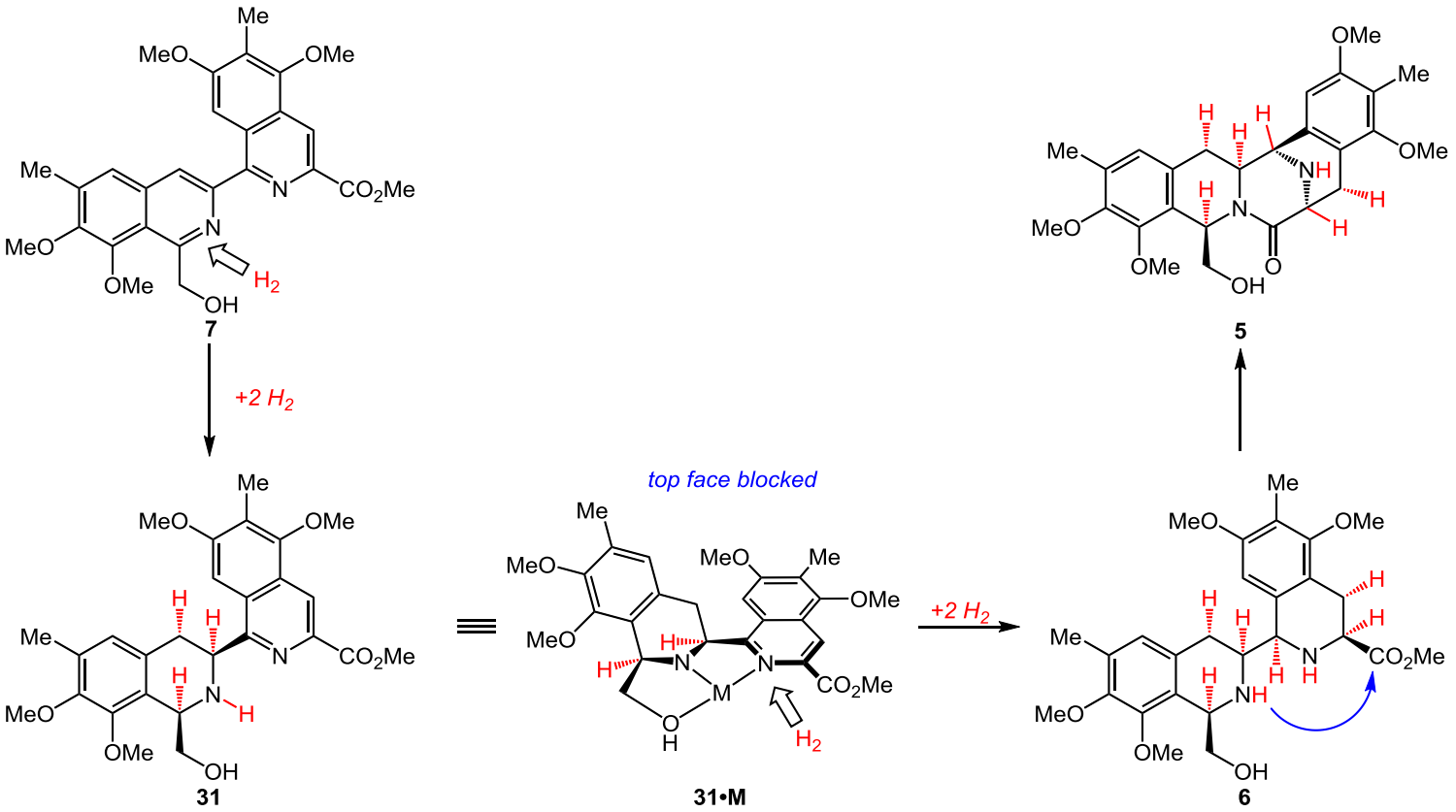




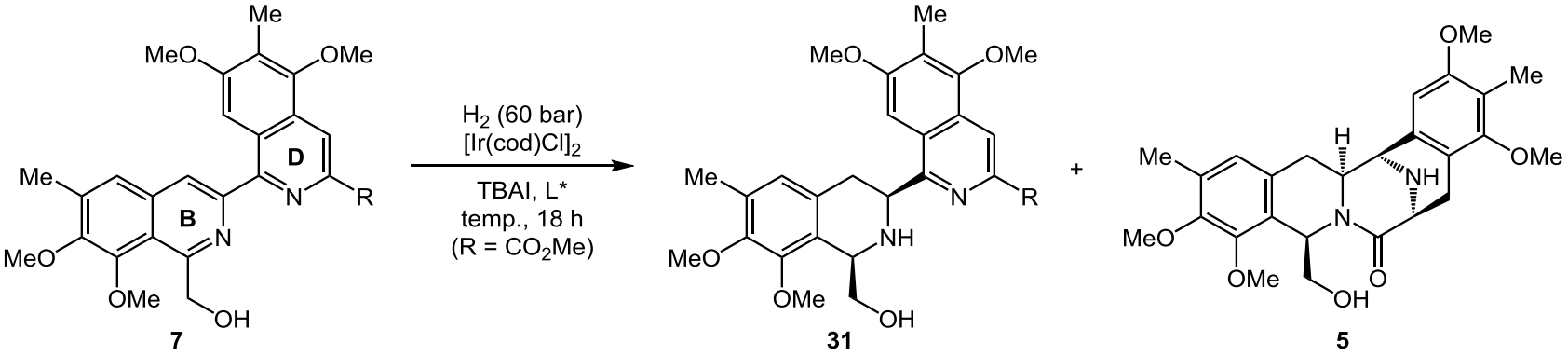
Lactam Formation

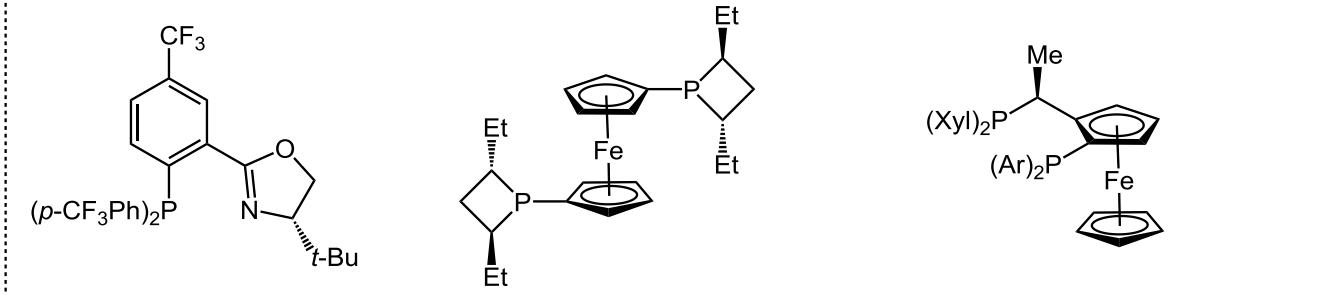
Directed Si-face reduction of **7** leads to enantioenriched generation of intermediate **31**

Three-dimensional structure of **31·M** leads to substrate-reinforced diastereoselectivity



Reduction Optimization Studies





32
(*S*)-(CF$_3$)-*t*-BuPHOX

33
(*S,S*)-Et-FerroTANE

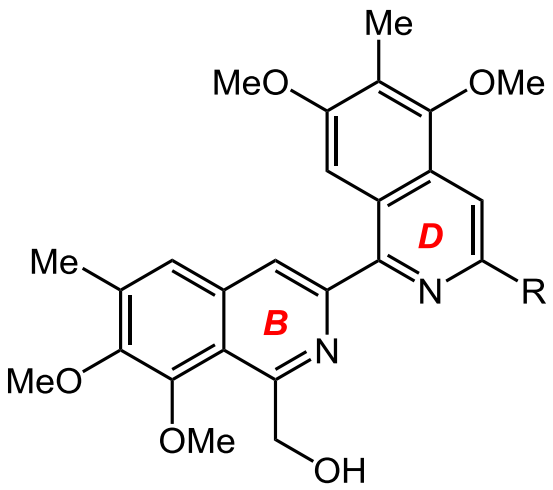
34: (*S,R$_p$*)-Xyliphos (Ar = Ph)
35: (*S,R$_p$*)-BTFM-Xyliphos [Ar = 3,5-(CF$_3$)$_2$Ph]

Reduction Optimization Studies

entry	catalyst loading	ligand	temperature	yield 31[a]	ee 31[b]	yield 5[a]	dr 5[c]	ee 5[b]
1	5 mol%	**34**	23 °C	2%	ND	0%	--	--
2	5 mol%	**32**	60 °C	22%	-82%	0%	--	--
3	5 mol%	**33**	60 °C	26%	-87%	0%	--	--
4	5 mol%	**34**	60 °C	30%	80%	0%	--	--
5	5 mol%	**35**	60 °C	83%	94%	10%	> 20:1	ND
6	5 mol%	**35**	80 °C	31%	87%	43%	> 20:1	ND
7	5 mol%	**35**	60 °C to 80 °C[d]	7%	94%	59%	> 20:1	88%
8	10 mol%	**35**	60 °C to 80 °C[d]	3%	94%	83%	> 20:1	88% (>99%)[e]

[a] Measured by UHPLC-MS UV absorption vs. 1,3,5-trimethoxybenzene internal standard unless otherwise noted. [b] Measured by chiral HPLC analysis. [c] Measured by 1H-NMR analysis of the crude reaction mixture. [d] Reaction performed at 60° C for 18 hours, then the temperature was raised to 80 °C and maintained at that temperature for 24 hours. [e] After one recrystallization.

Explanation of Selectivity Differences



7

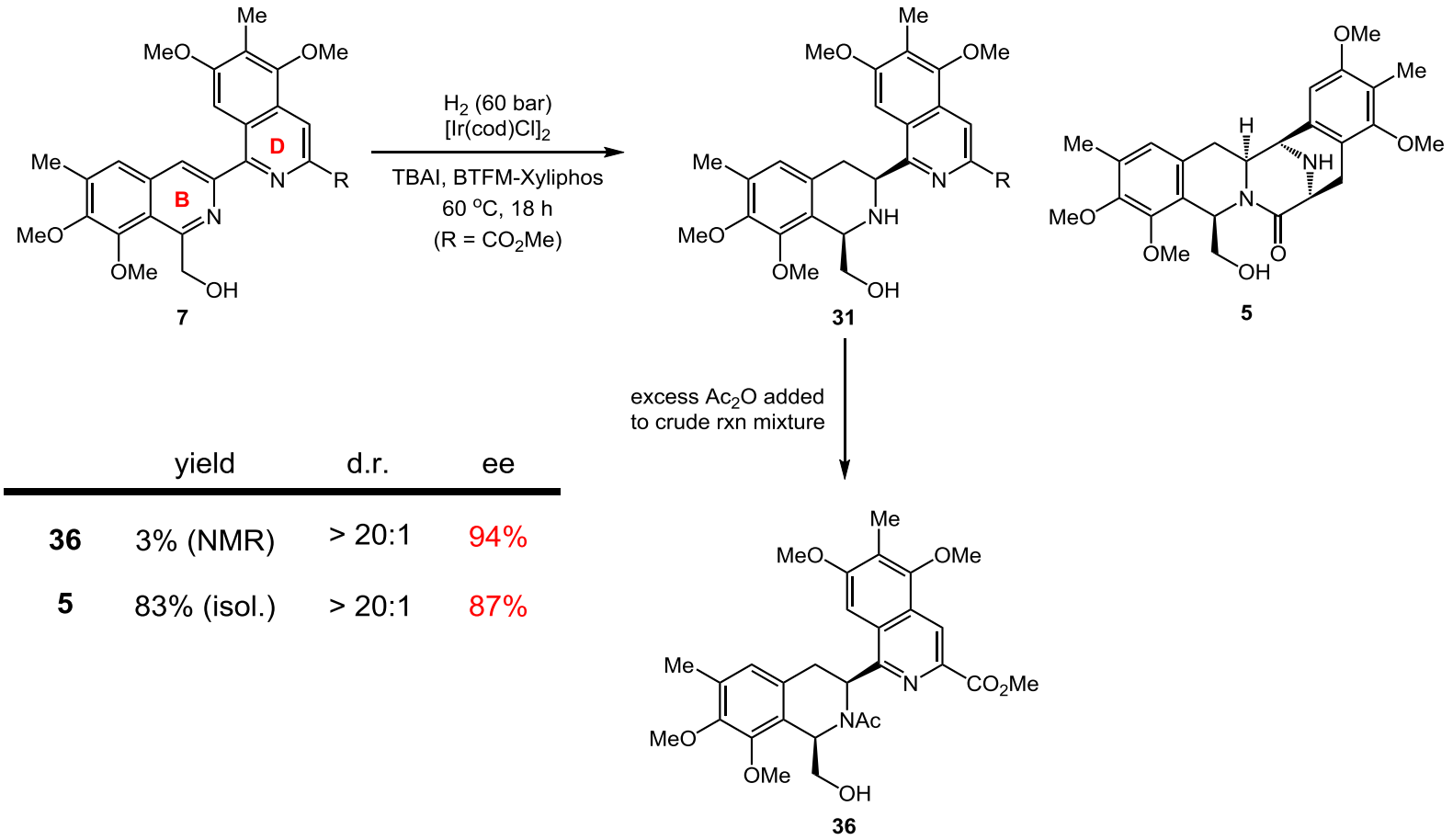
B-ring: Activated by proximity to hydroxyl directing group
D-ring: Electronically activated by ester for hydritic reduction

⇩

B-ring reduction: fast with all successful ligands
D-ring reduction: only observed with BTFM-Xyliphos ligand

Conclusion: Hydroxyl direction lowers activation energy more than electronic activation

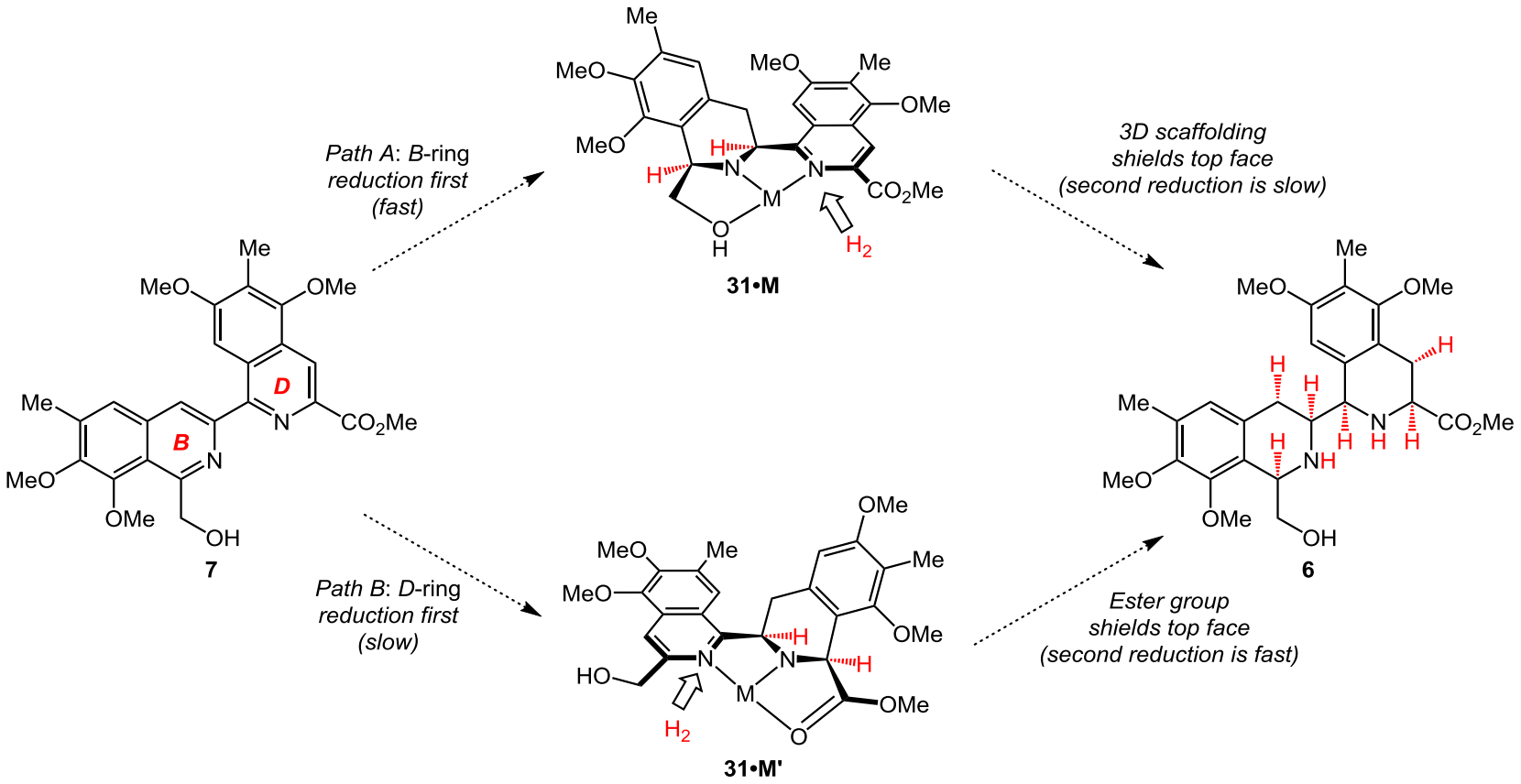
Explanation of Selectivity Differences



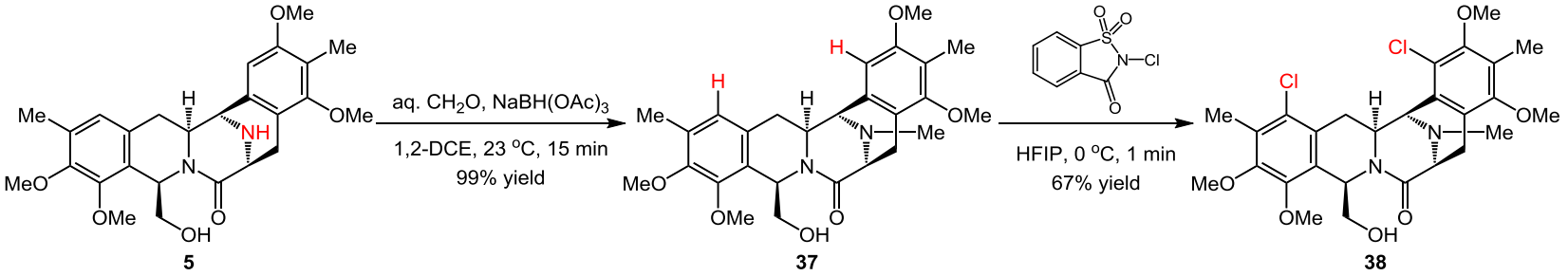
	yield	d.r.	ee
36	3% (NMR)	> 20:1	94%
5	83% (isol.)	> 20:1	87%

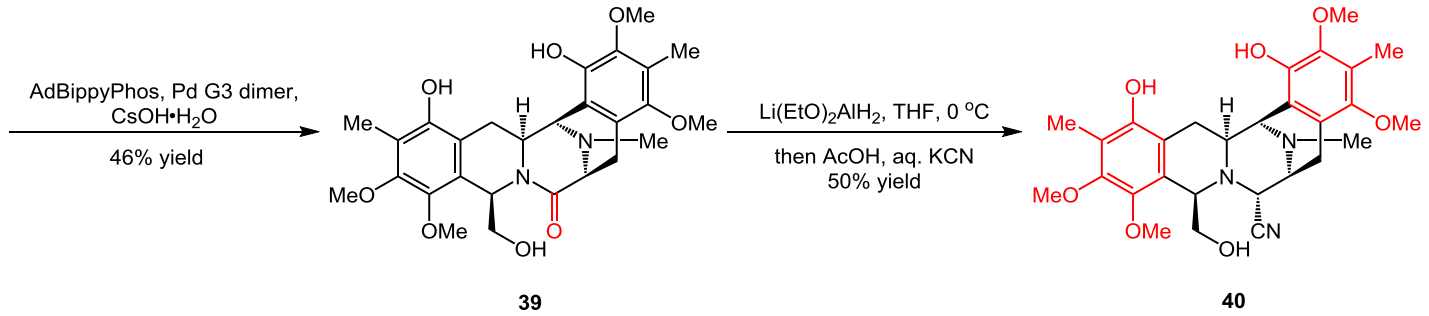
31 was found to be unstable to isolation,
presumably due to reaction between amine and ester

Explanation of Selectivity Differences

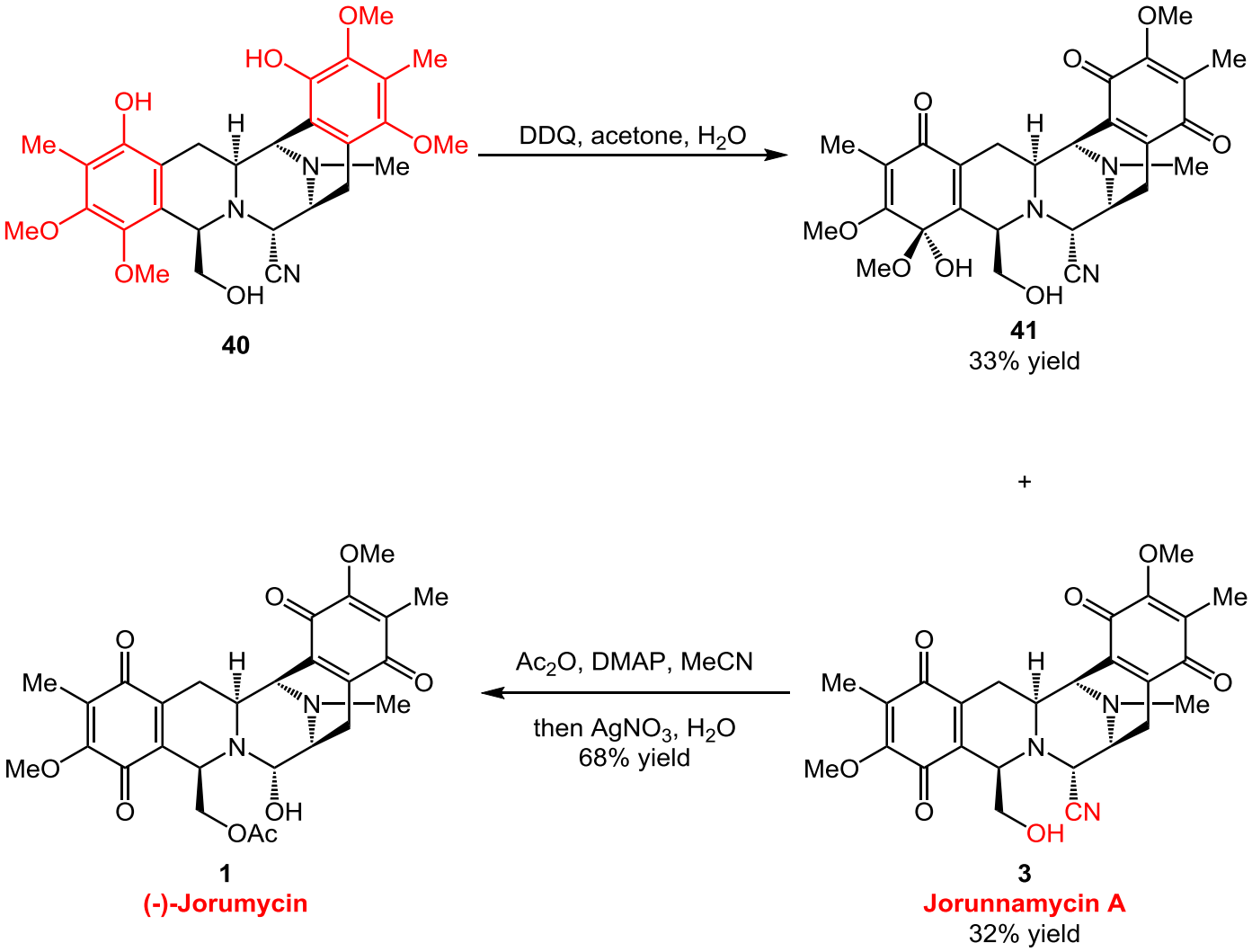


Endgame Synthesis of Jorumycin





Endgame Synthesis of Jorumycin



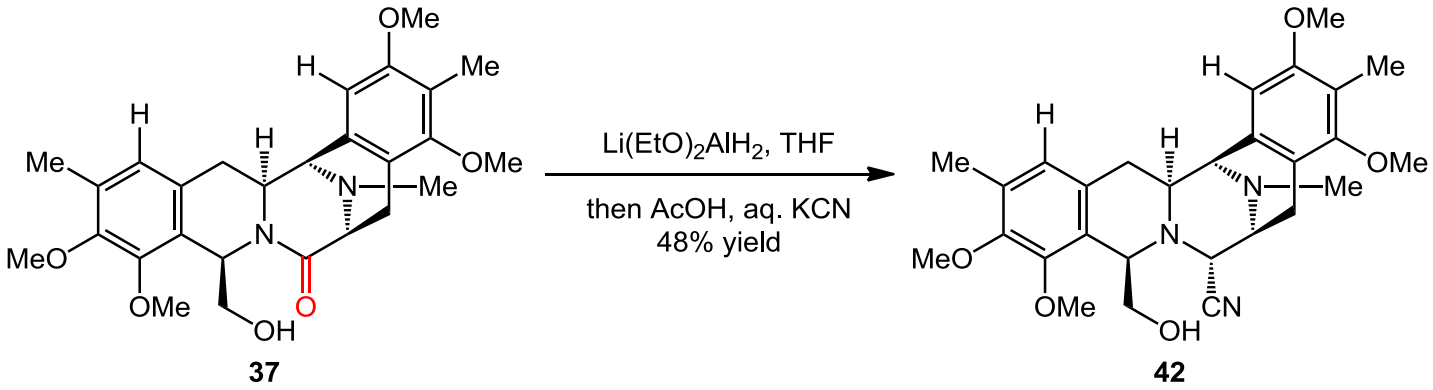
40

41
33% yield

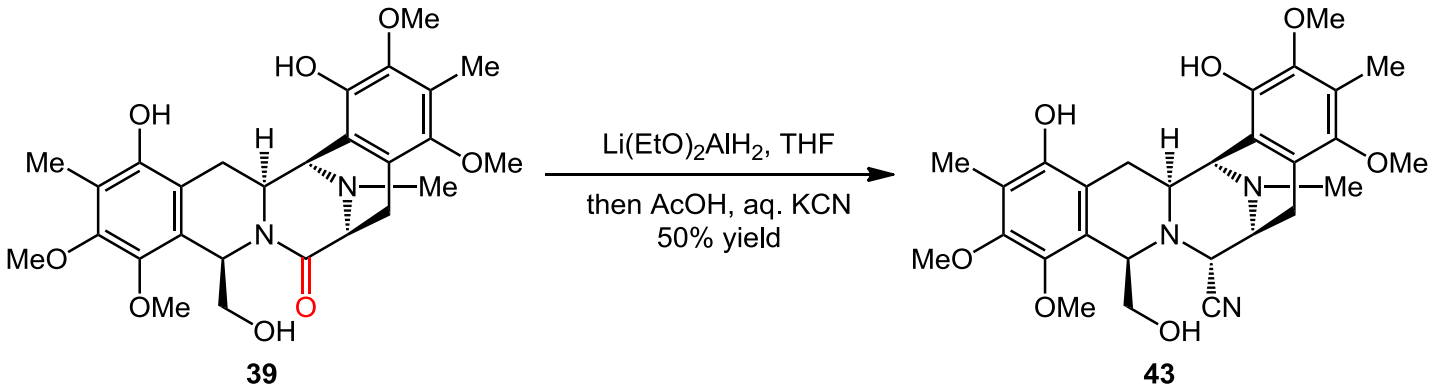
1
(-)-Jorumycin

3
Jorunnamycin A
32% yield

Synthesis of Derivatives

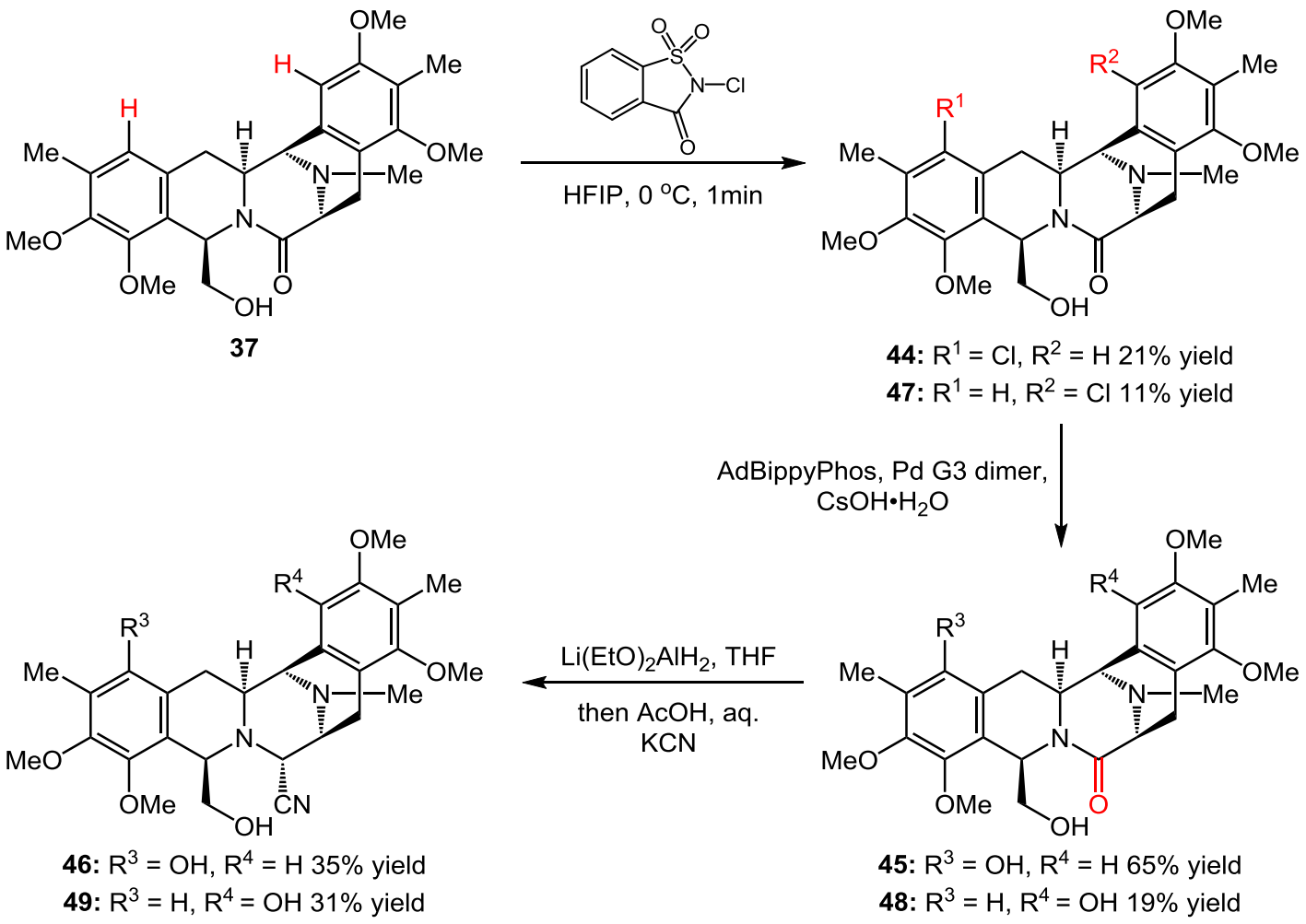


37 42

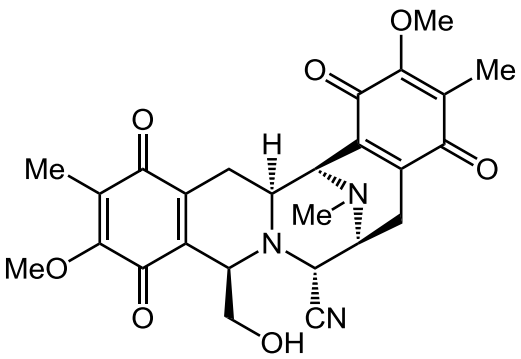


39 43

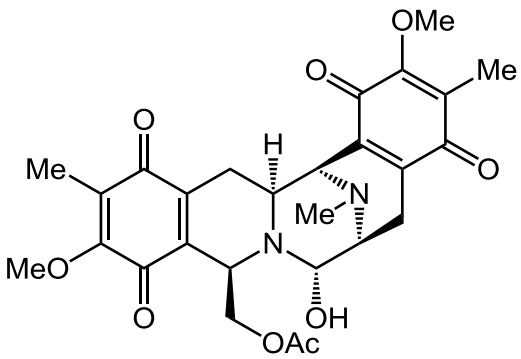
Synthesis of Derivatives



Summary



Jorunnamycin A



(-)-Jorumycin

- 15 and 16 steps, 0.24% and 0.17% overall yield respectively;
- Harnesses the power of modern transition-metal catalysis for the three major bond-forming events;
- Proceeds with high efficiency ;
- By breaking from biomimicry, this strategy allows for the preparation of a more diverse set of non-natural analogs.

The First Paragraph

The bis-tetrahydroisoquinoline natural products have been studied intensively by chemists and biologists alike during the 40+ years since their initial discovery due to their intriguing chemical structures, potent biological activities, and unique mechanisms of action. Jorumycin and its congeners ecteinascidin 743 and jorunnamycin A possess a pentacyclic carbon skeleton, highly oxygenated ring termini, and a central pro-iminium ion. This latter functionality serves as an alkylating agent in vivo, resulting in covalent modification of DNA in a process that ultimately leads to cell death. The promise of these natural products as anticancer agents has been realized in the case of Et 743 (Yondelis®, trabectedin), which has been approved in the US, Europe, and else-where for the treatment of a variety of drug-resistant and unresectable soft-tissue sarcomas and ovarian cancer. Unfortunately, although **2** is available from nature, isolation of one gram of the drug would require more than one ton of biological material.

The First Paragraph

For this reason, the successful application of 2 as an antitumor agent has necessitated its large-scale chemical synthesis, a 21-step process that begins with cyanosafracin A, a fermentable and fully functionalized bis-THIQ natural product. This has restricted medicinal chemistry endeavors via this route to the production of only compounds with a high degree of similarity to the natural products themselves.

The Last Paragraph

The use of catalysis, rather than native reactivity, is a key advantage to our synthesis, allowing us to expedite access to both the natural products themselves, and also biologically relevant derivatives.

Thanks for your attention