

Total Synthesis of (-)-Haouamine B Pentaacetate and Structural Revision of Haouamine B

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Tokuyama, H. *et al.*
Angew. Chem. Int. Ed. **2014**, 53, 13215-13219.

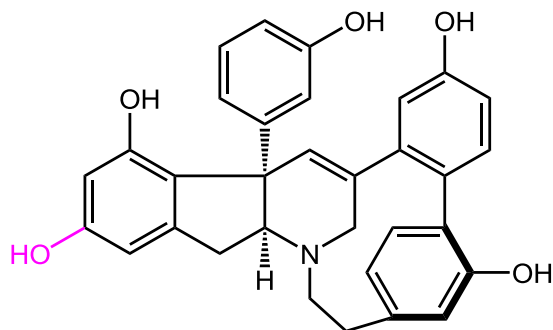


Hidetoshi Tokuyama
Tohoku University

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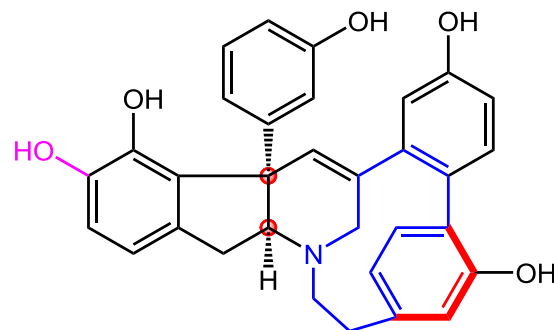
- ✓ **Introduction**
- ✓ **Total Synthesis of Iso-Haouamine B**
- ✓ **Total Synthesis of Haouamine B**
- ✓ **Summary**

Introduction



Iso-Haouamine B
Dirk Trauner, 2012

Structure
revision
→

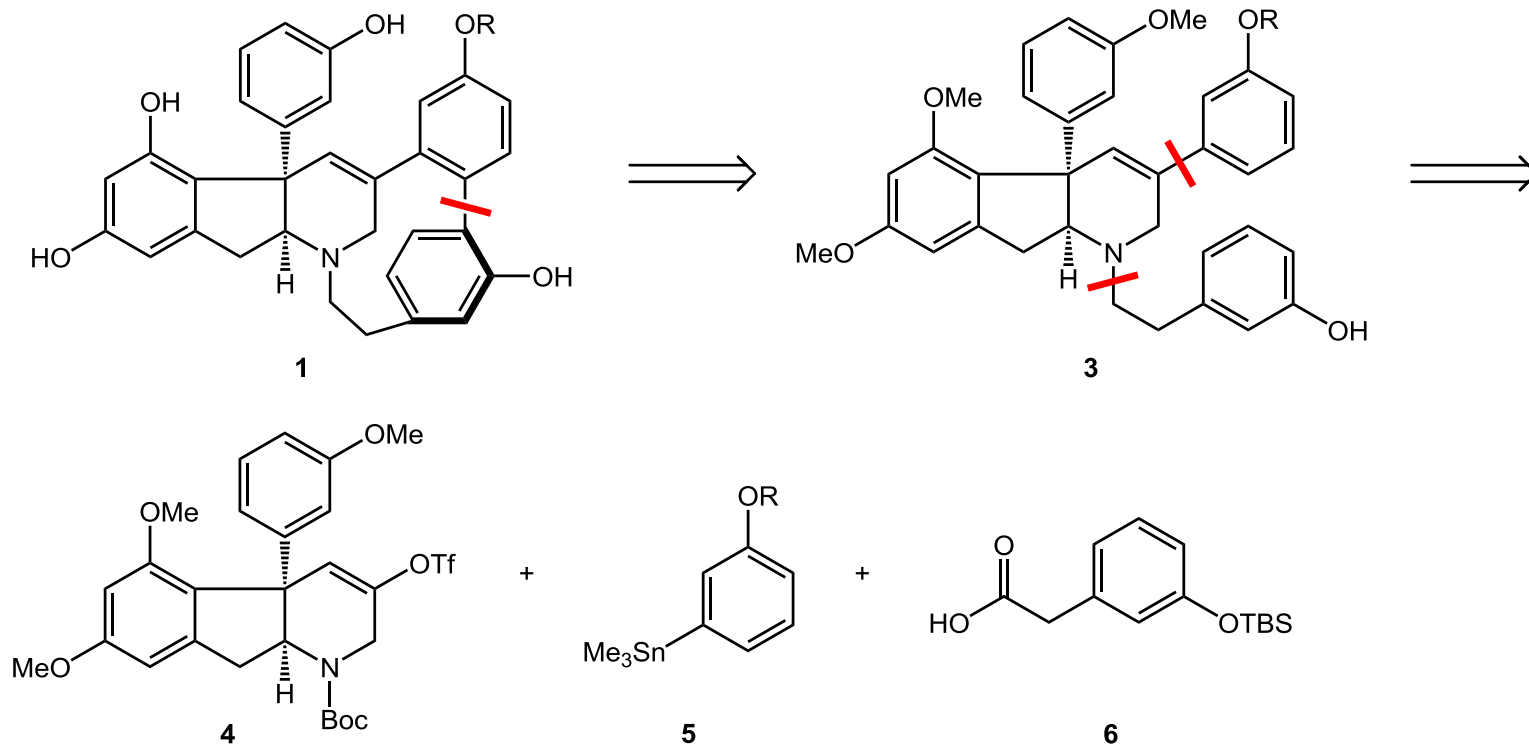


Haouamine B
Hidetoshi Tokuyama, 2014

- ✓ *Cis*-fused indeno-tetrahydropyridine
- ✓ Highly strained 11-membered *p*-paracyclophane containing a stereogenic biaryl axis

Total Synthesis of Iso-Haouamine B

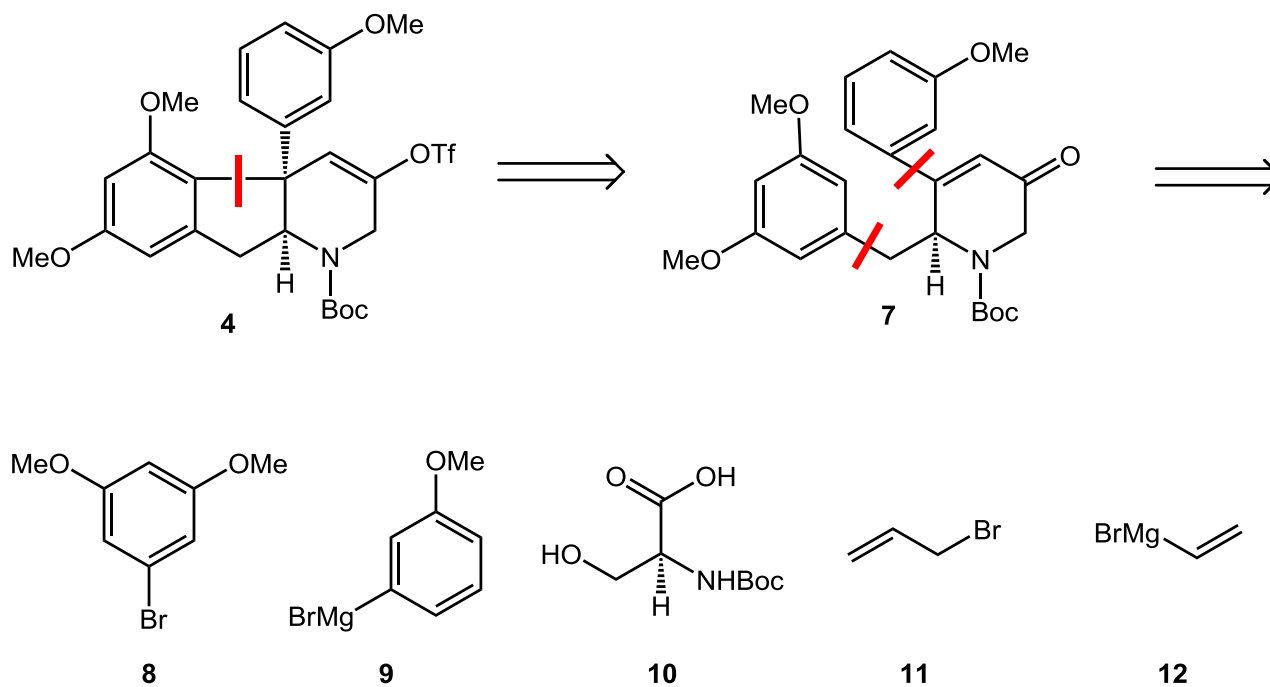
Retrosynthetic Analysis of Iso-Haouamine B



Trauner, D. *et al. J. Am. Chem. Soc.* **2012**, *134*, 9291.

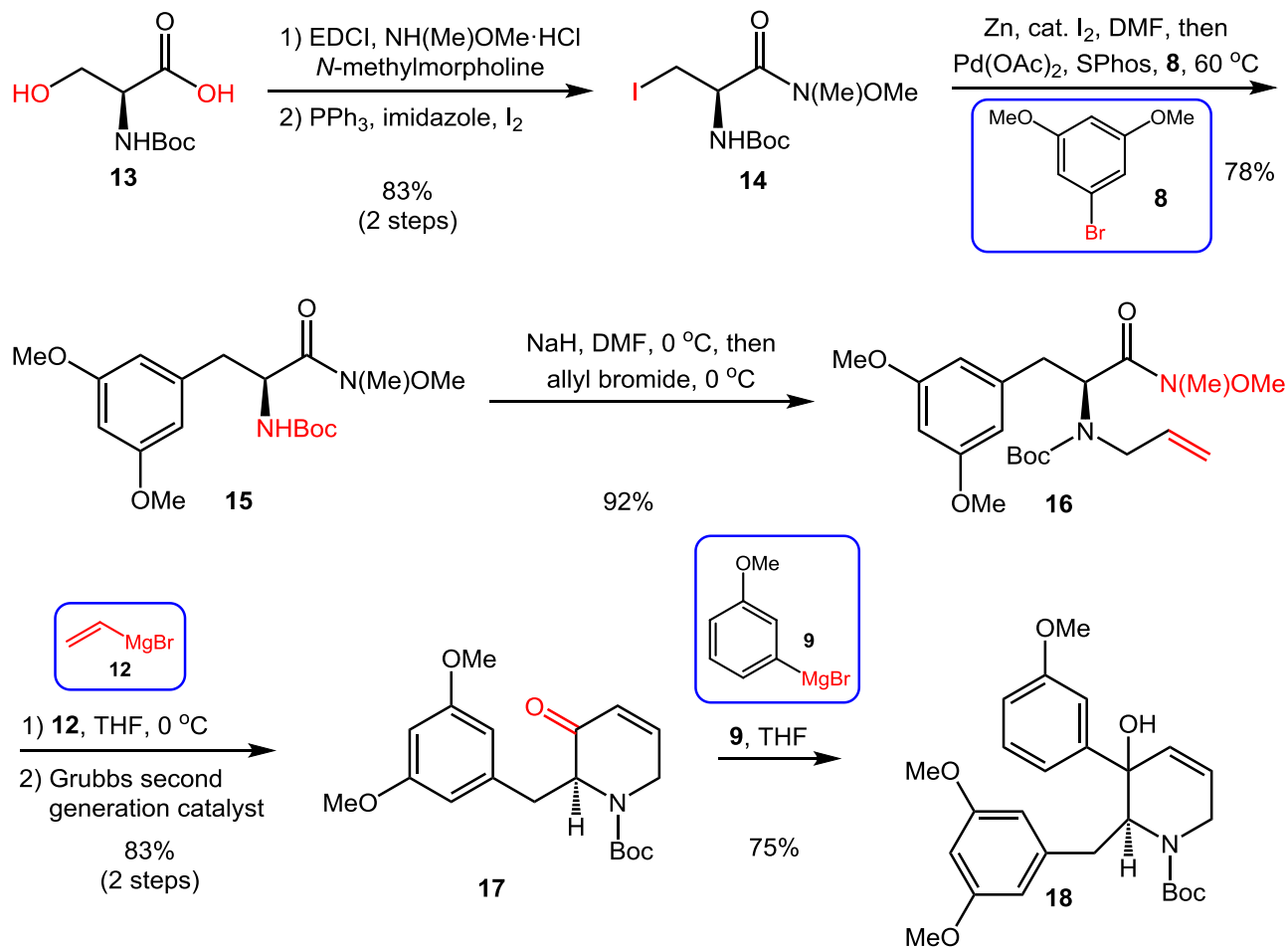
Total synthesis of Iso-Haouamine B

Retrosynthetic Analysis of Iso-Haouamine



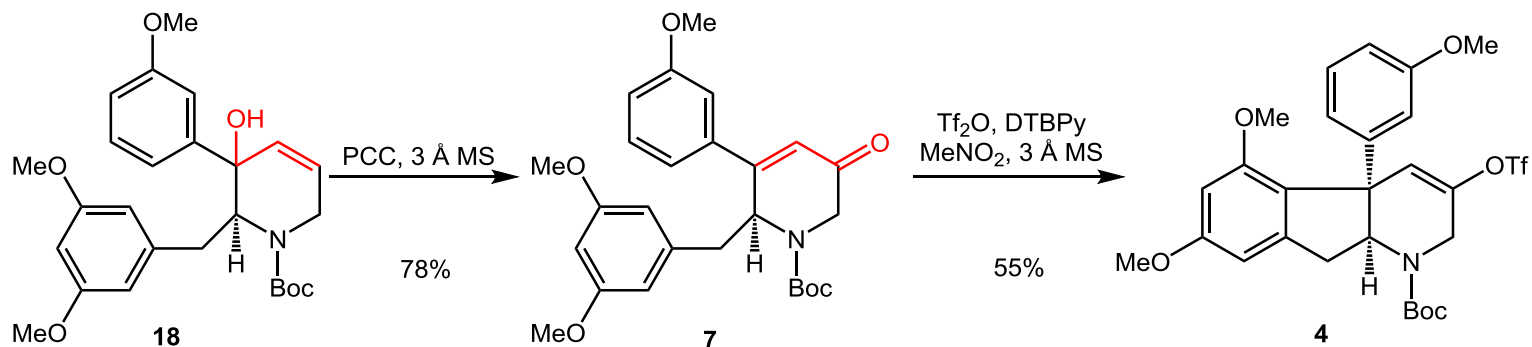
Total synthesis of Iso-Haouamine B

Synthesis of Indeno-tetrahydropyridine Core 4

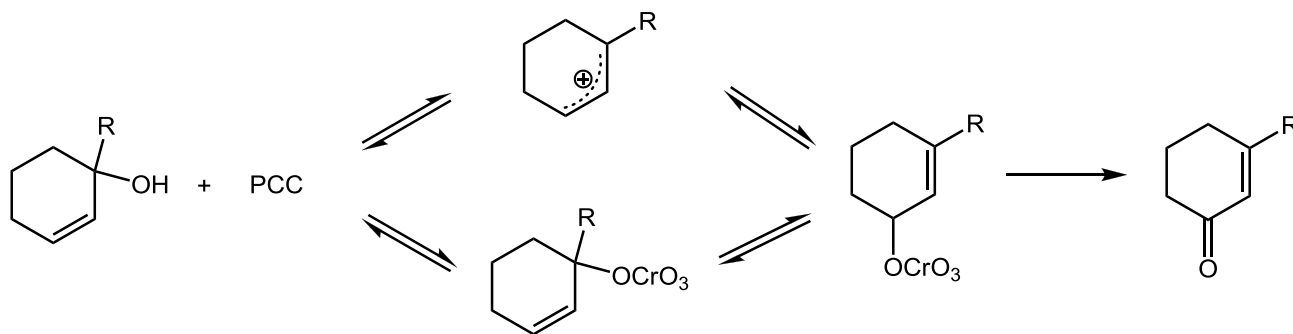


Total synthesis of Iso-Haouamine B

Synthesis of Indeno-tetrahydropyridine Core 4



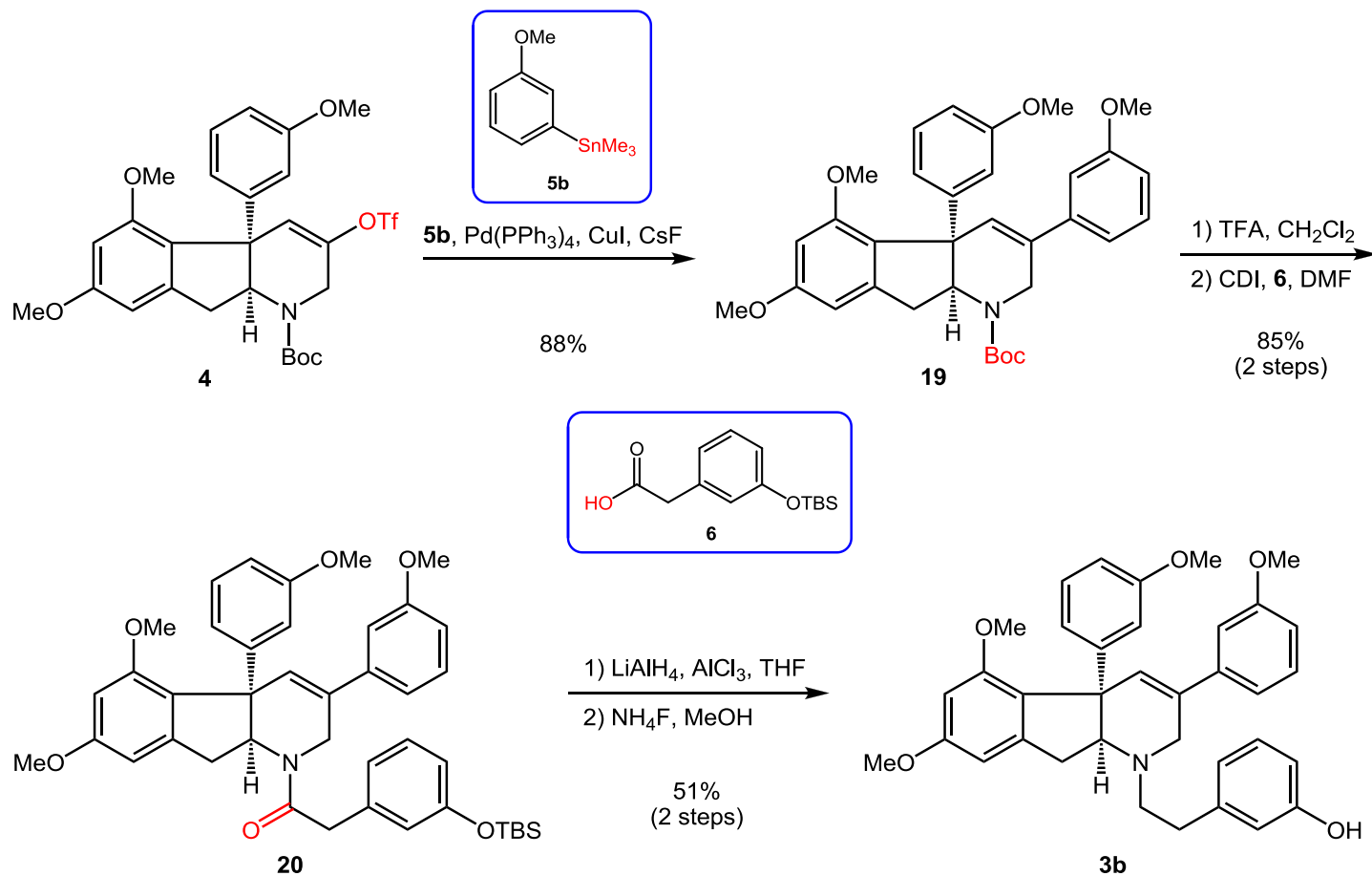
Dauben Oxidation



Dauben, W. G. *et al. J. Org. Chem.* **1977**, *42*, 682.

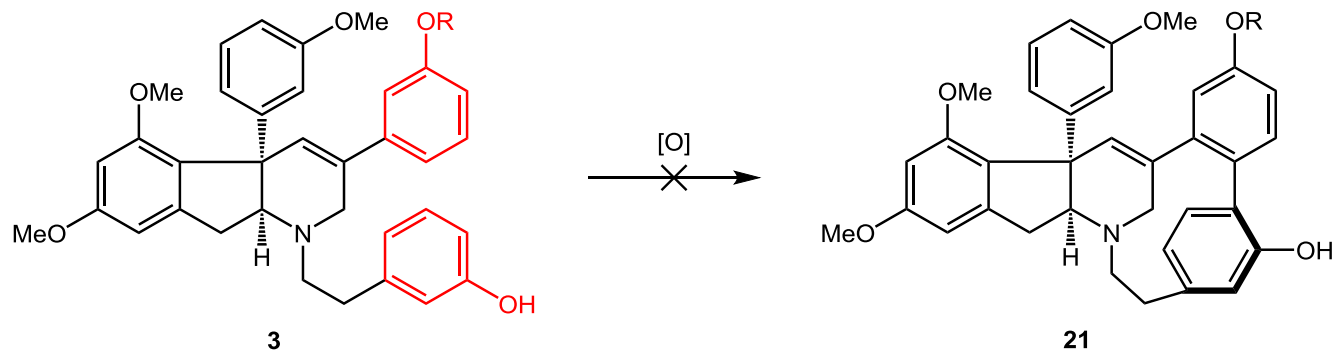
Total synthesis of Iso-Haouamine B

Synthesis of Oxidative Phenol Coupling Substrates

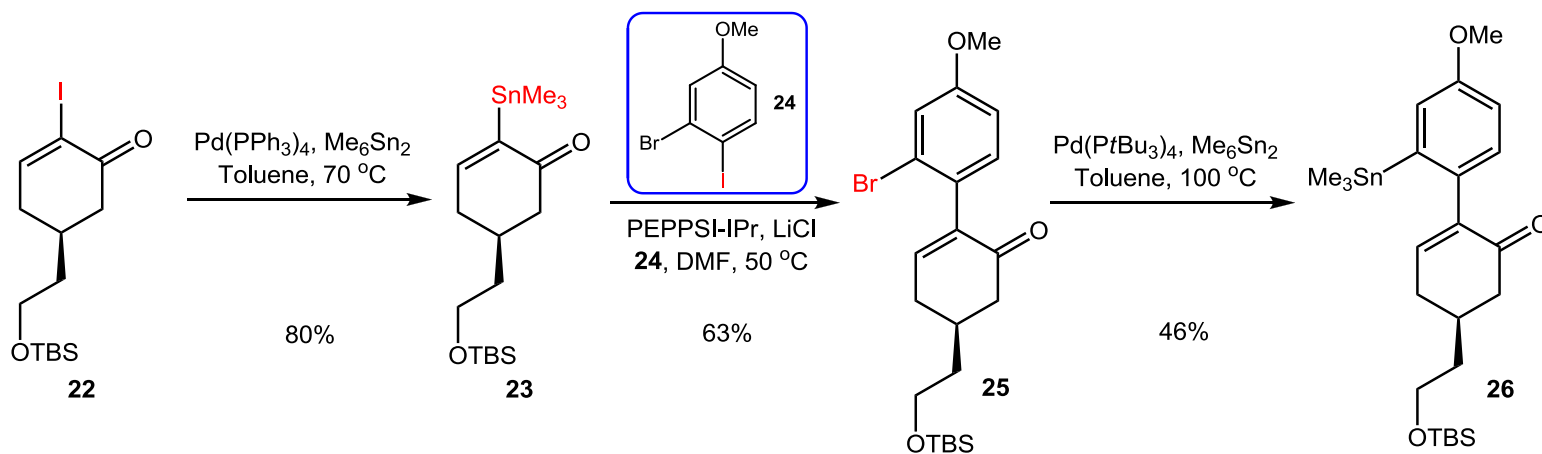


Total synthesis of Iso-Haouamine B

Attempted Oxidative Phenol Couplings

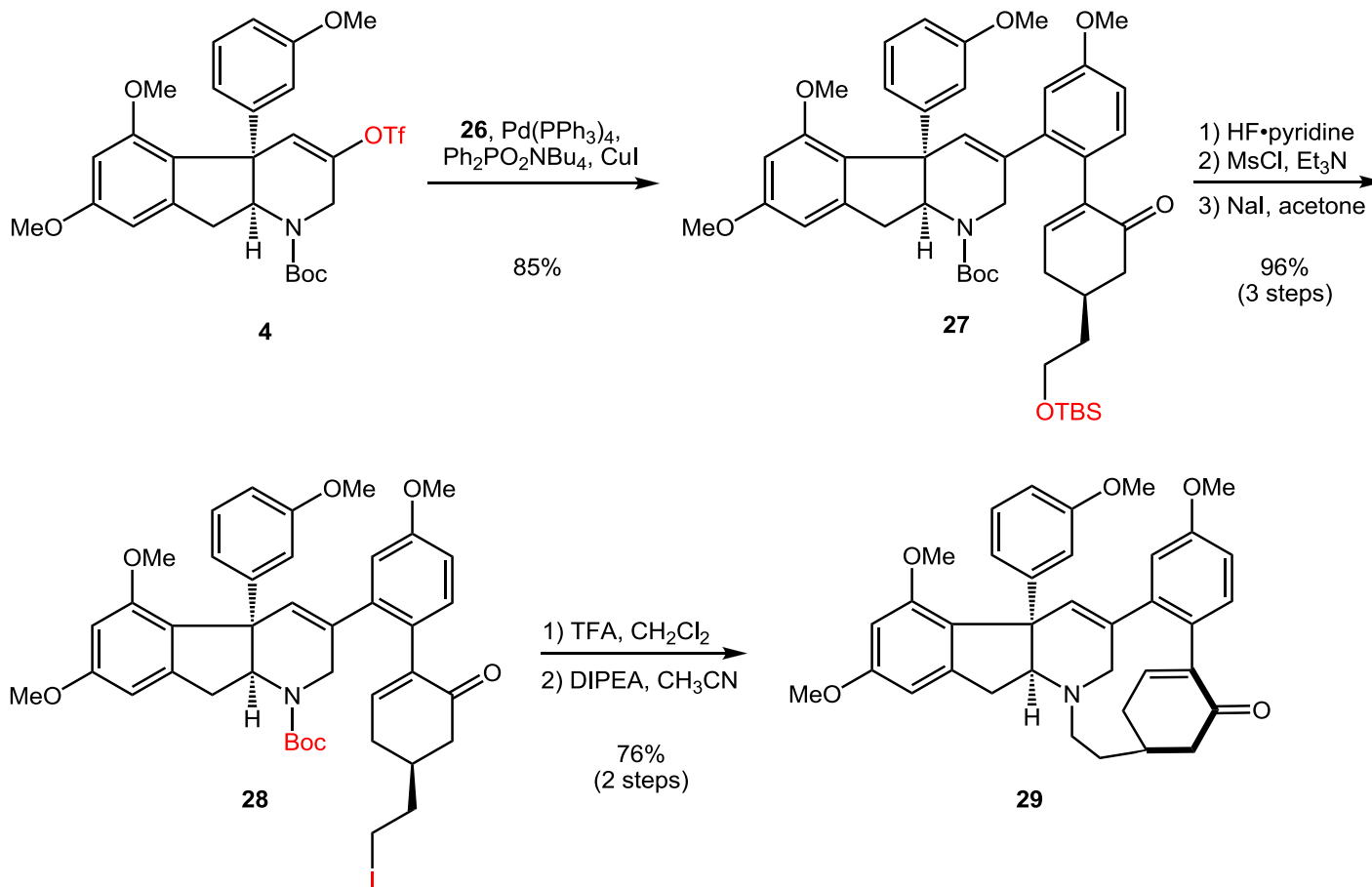


Synthesis of the Reduced Eastern Half



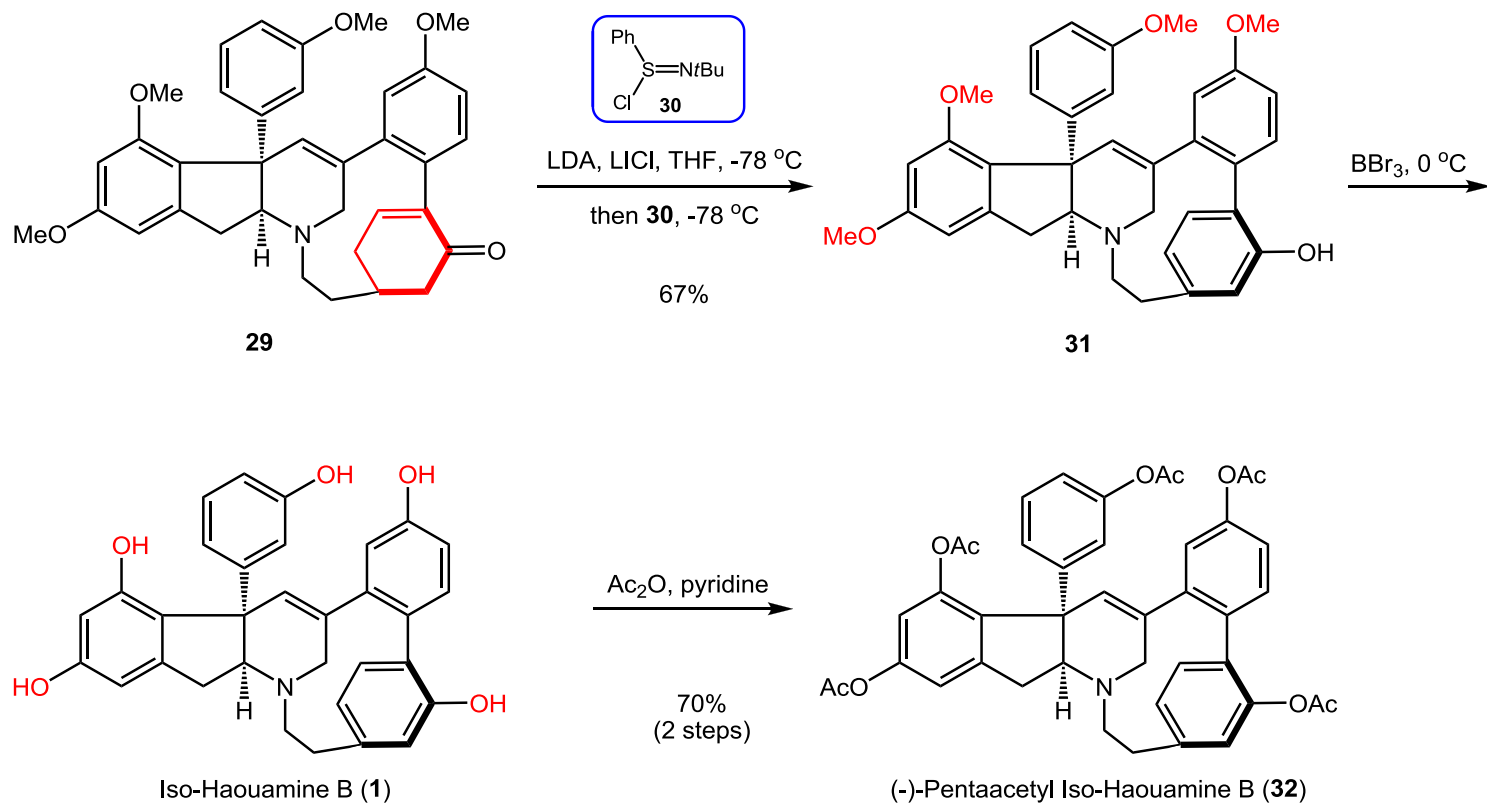
Total synthesis of Iso-Haouamine B

Total Synthesis of Iso-Haouamine



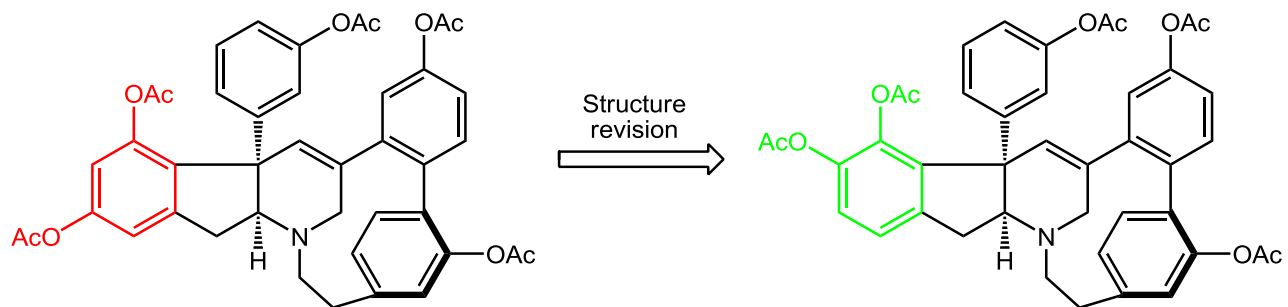
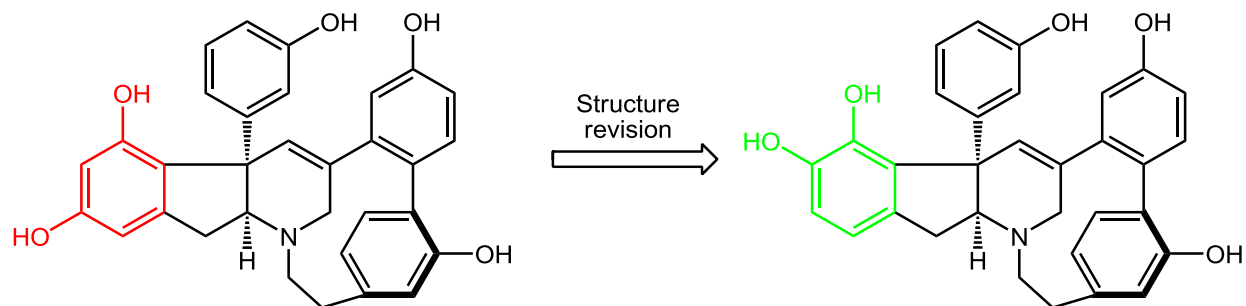
Total synthesis of Iso-Haouamine B

Total Synthesis of Iso-Haouamine



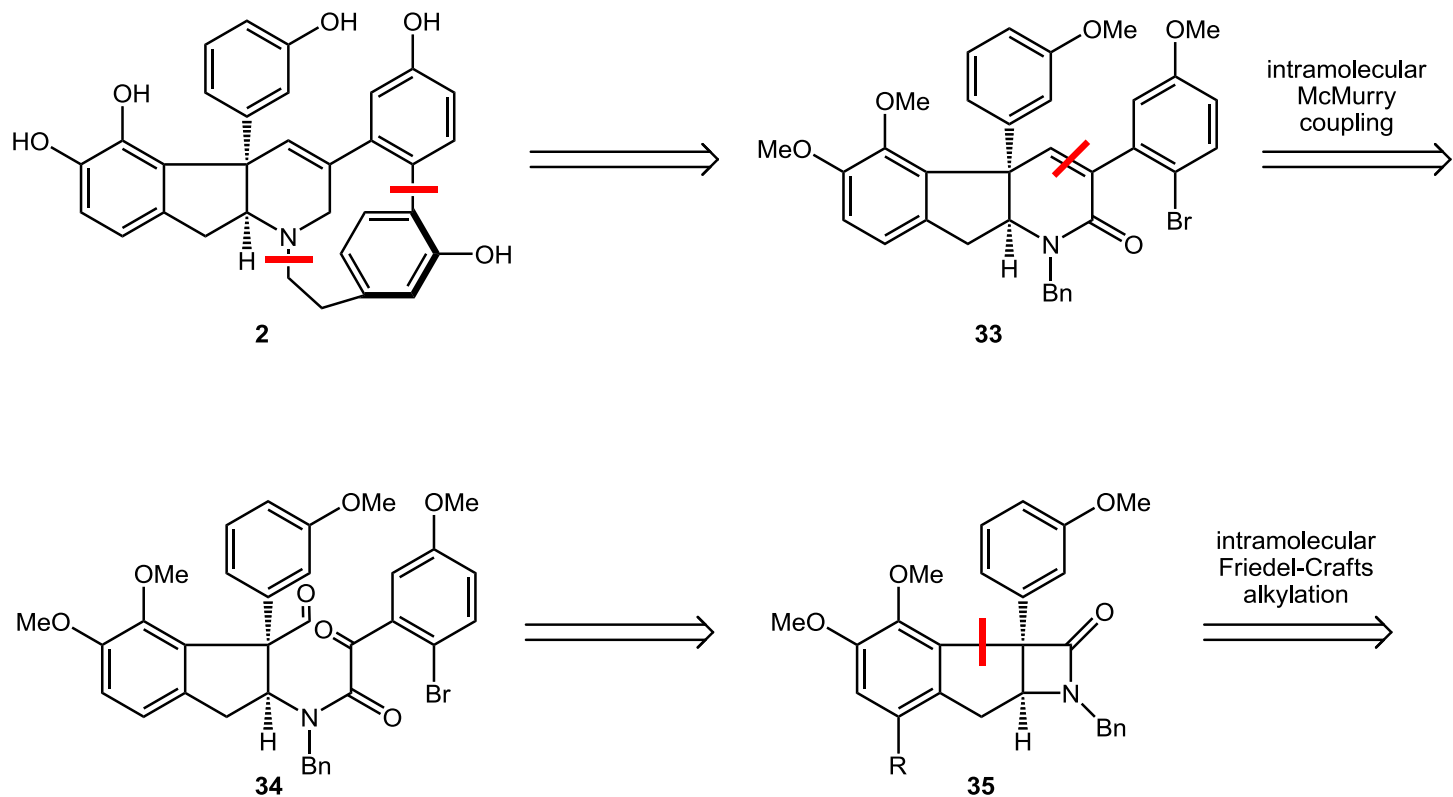
Total Synthesis of Iso-Haouamine B

Revised Structures of Haouamine B and Its Pentaacetate



Total Synthesis of Haouamine B

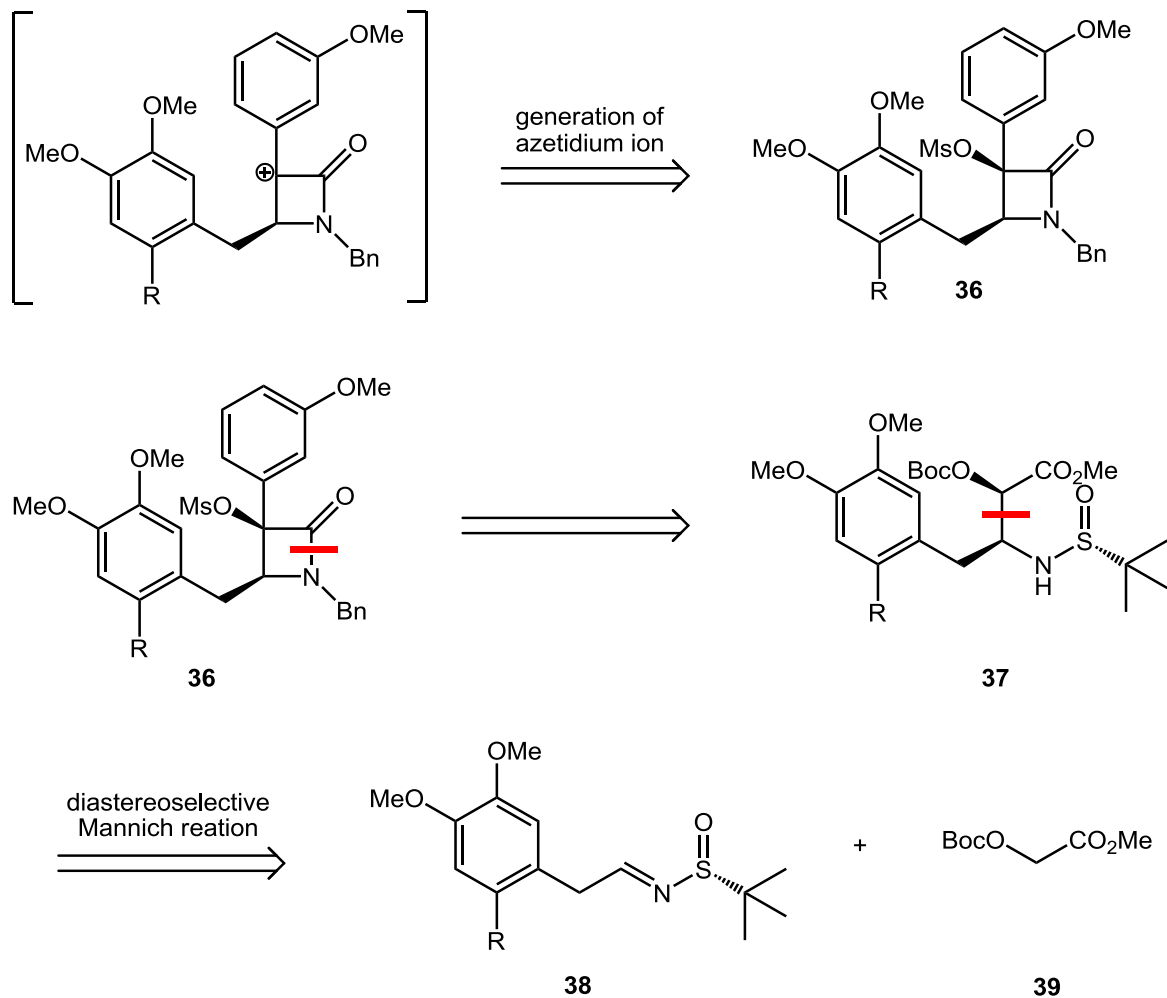
Retrosynthetic Analysis of Haouamine B



Tokuyama, H. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 13215.

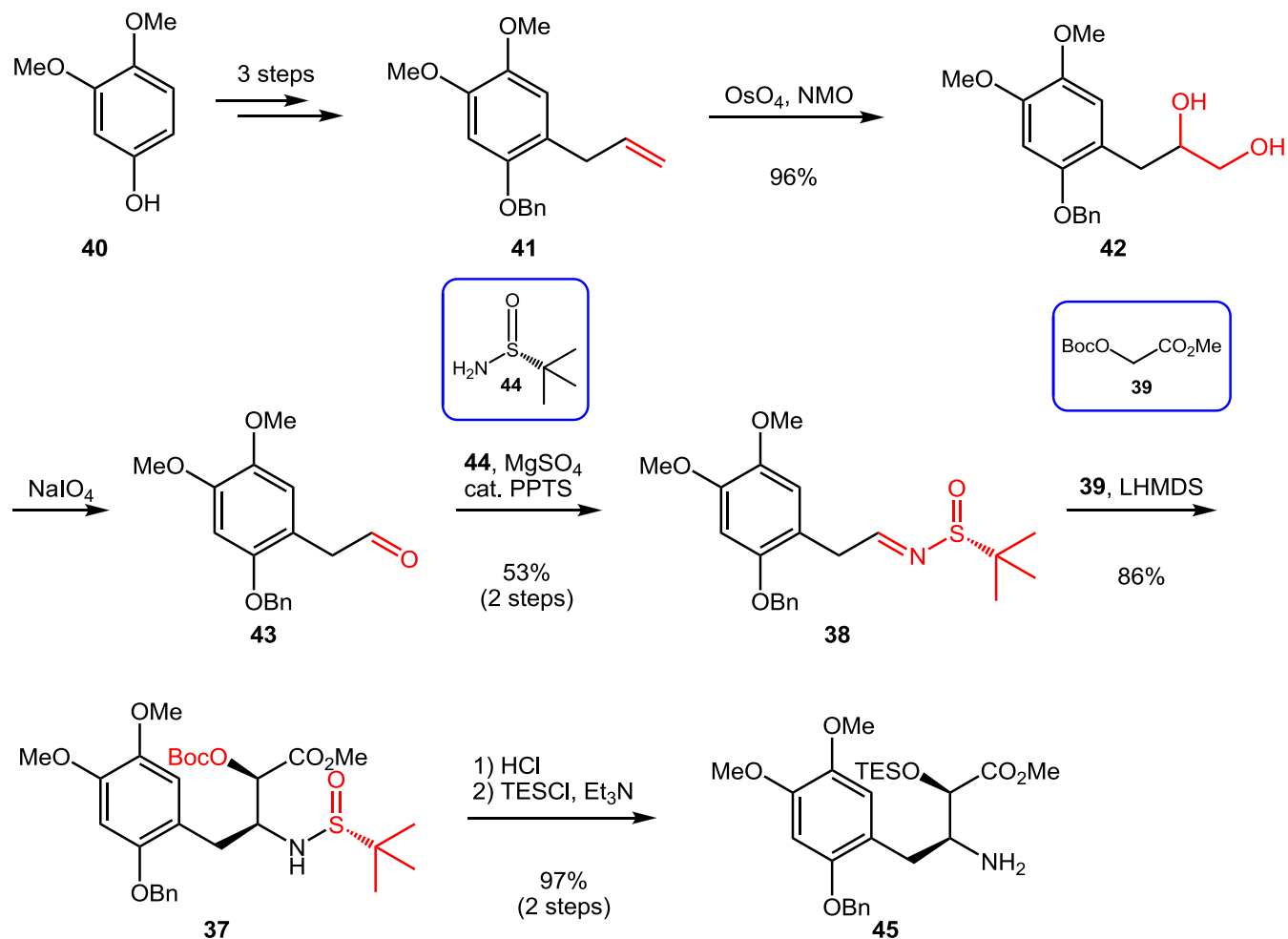
Total Synthesis of Haouamine B

Retrosynthetic Analysis of Haouamine B



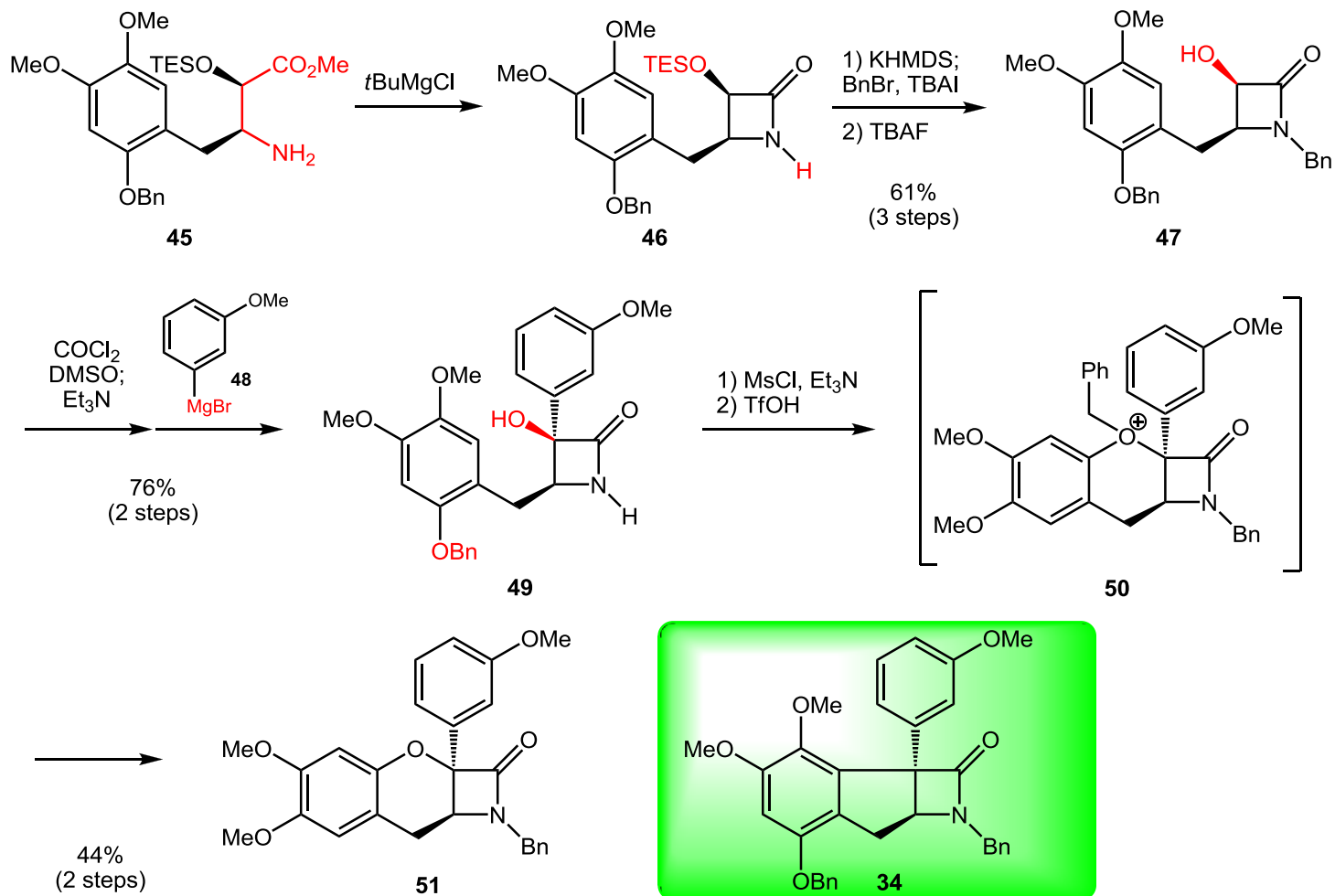
Total Synthesis of Haouamine B

Synthesis of building block 45



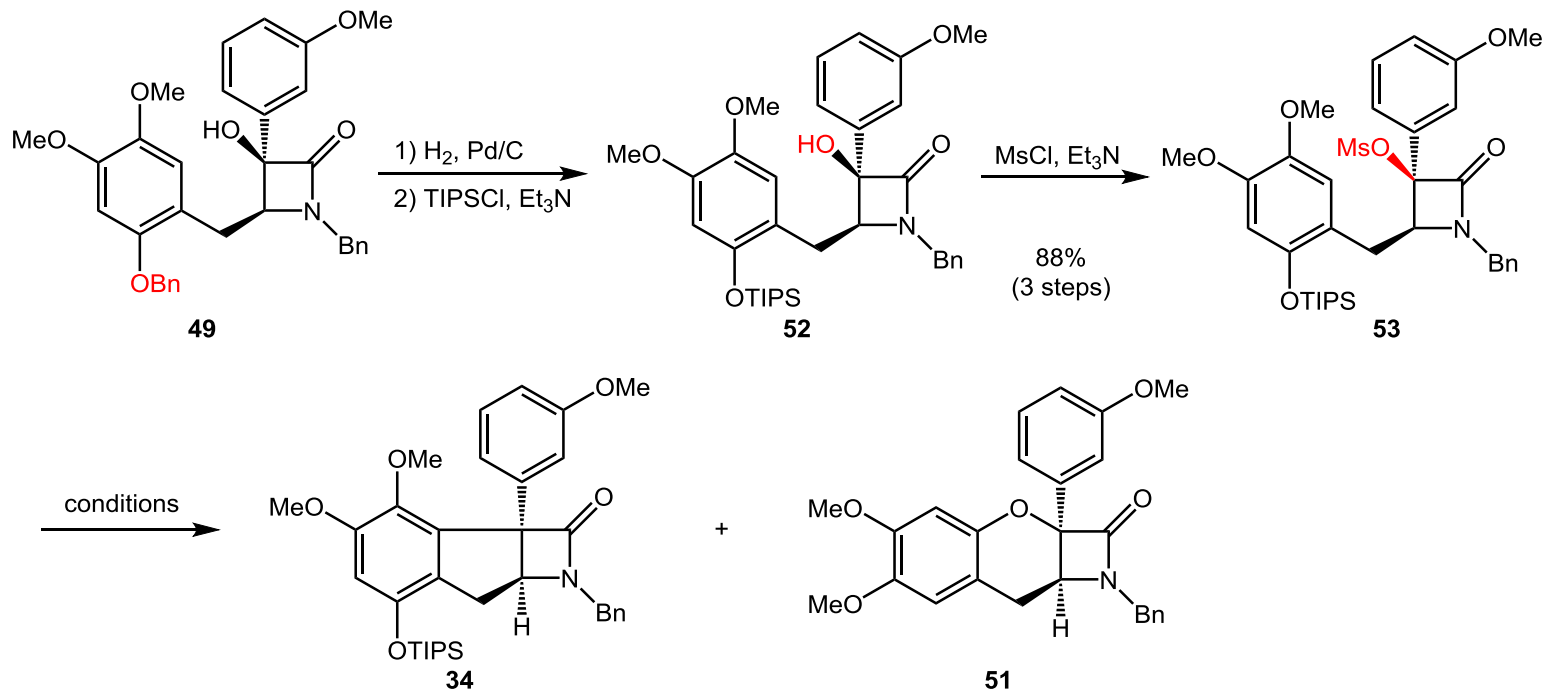
Total Synthesis of Haouamine B

Synthesis of Building Block 34



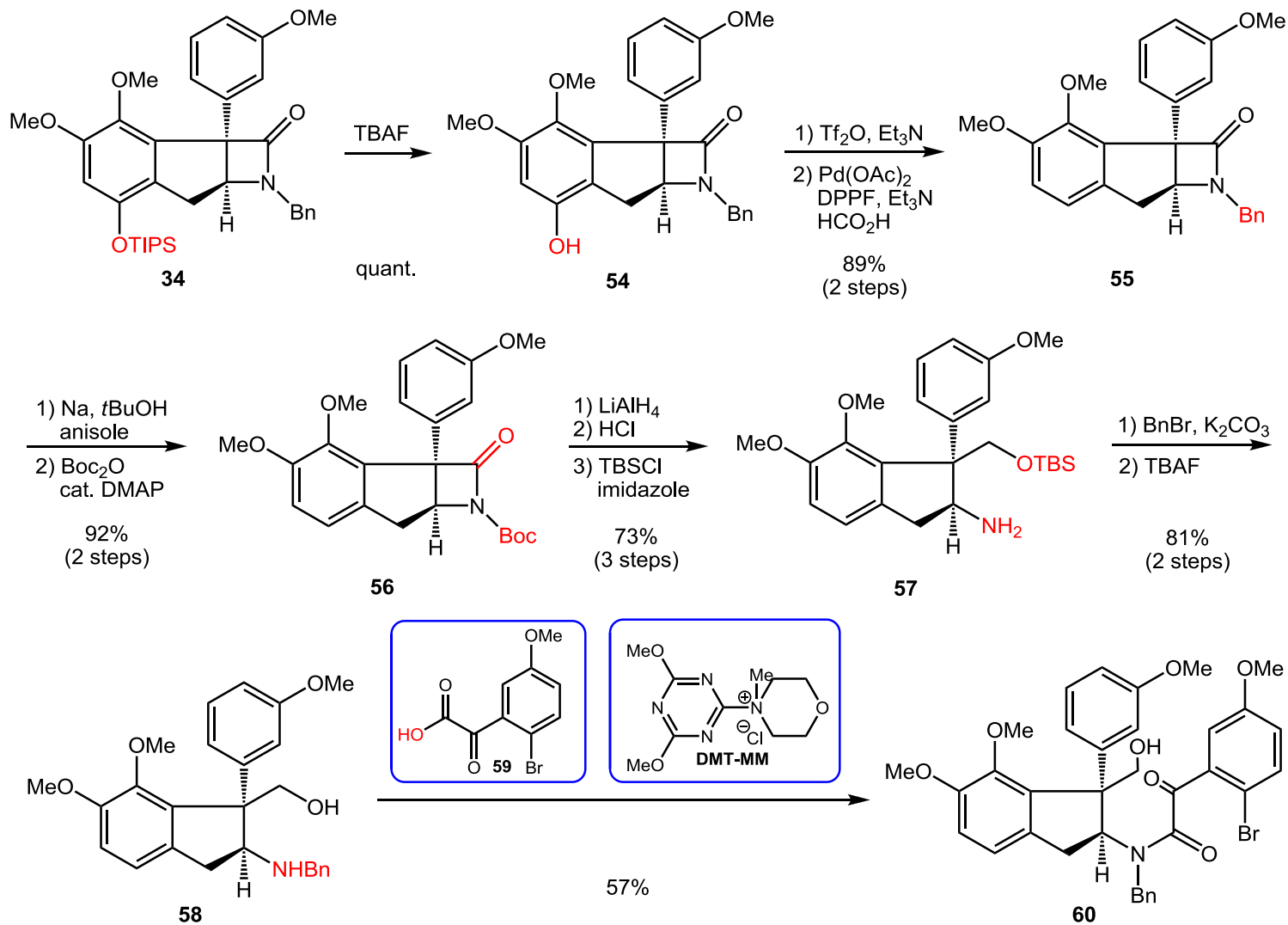
Total Synthesis of Haouamine B

Intramolecular Friedel–Crafts Alkylation.

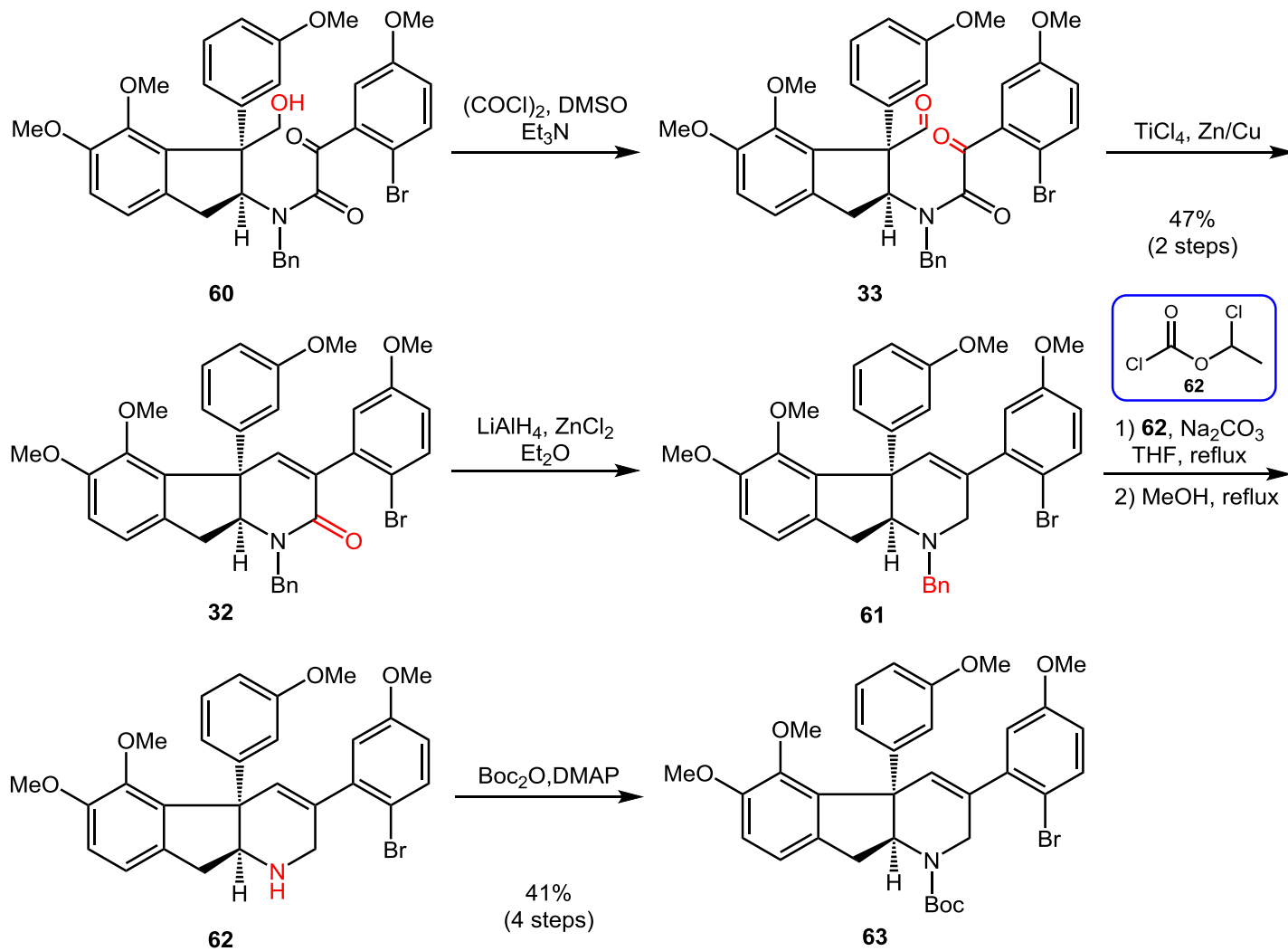


Entry	Solvent	Reagents	T (°C)	34 (%)	51 (%)
1	CH ₃ CN	TfOH	-40 to RT	--	36
2	CH ₂ Cl ₂	Sc(OTf) ₃	0 to RT	14	trace
3	CH₂Cl₂	Sc(OTf)₃ DTBPY	0 to RT	80	--

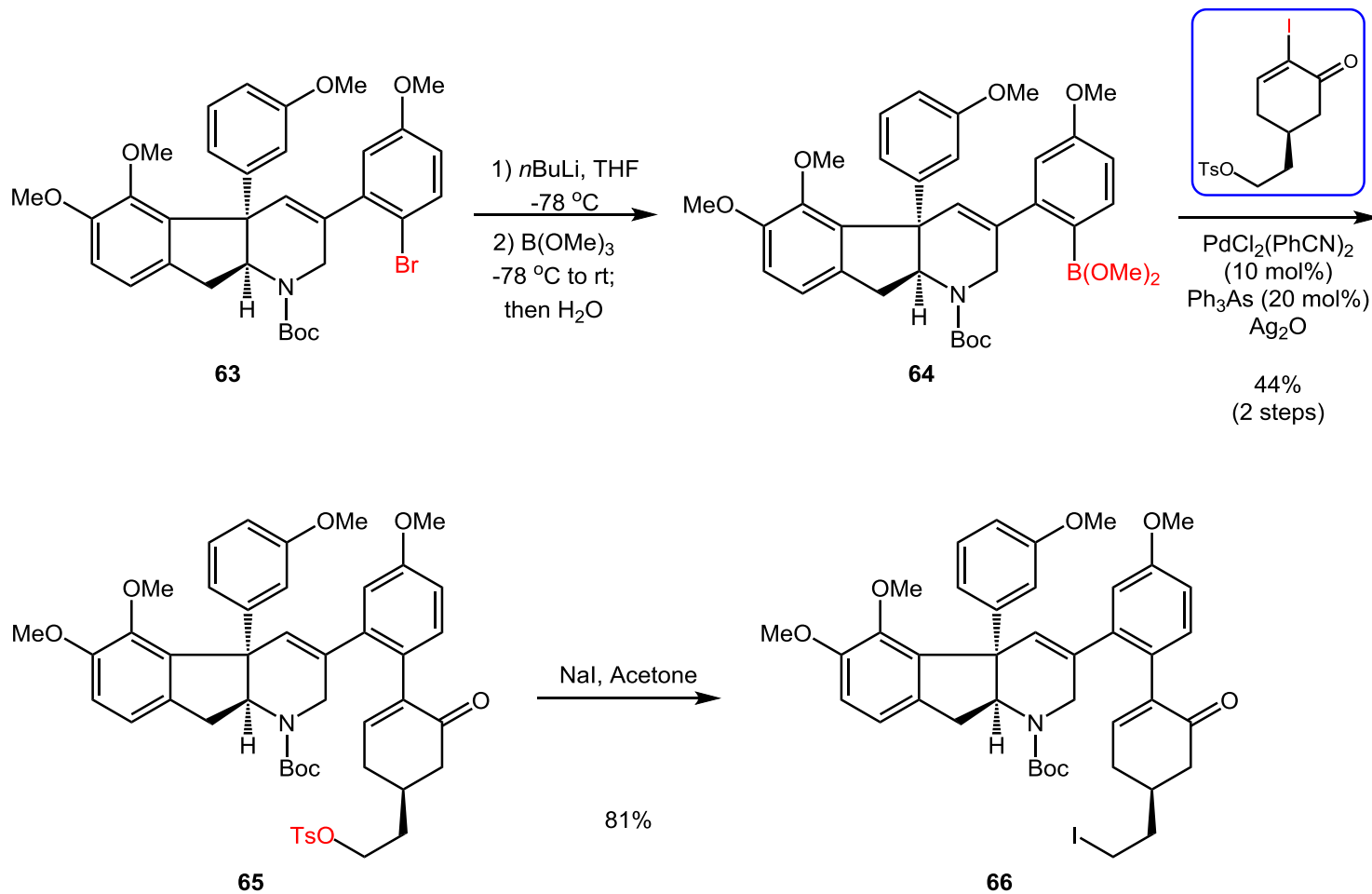
Total Synthesis of Haouamine B



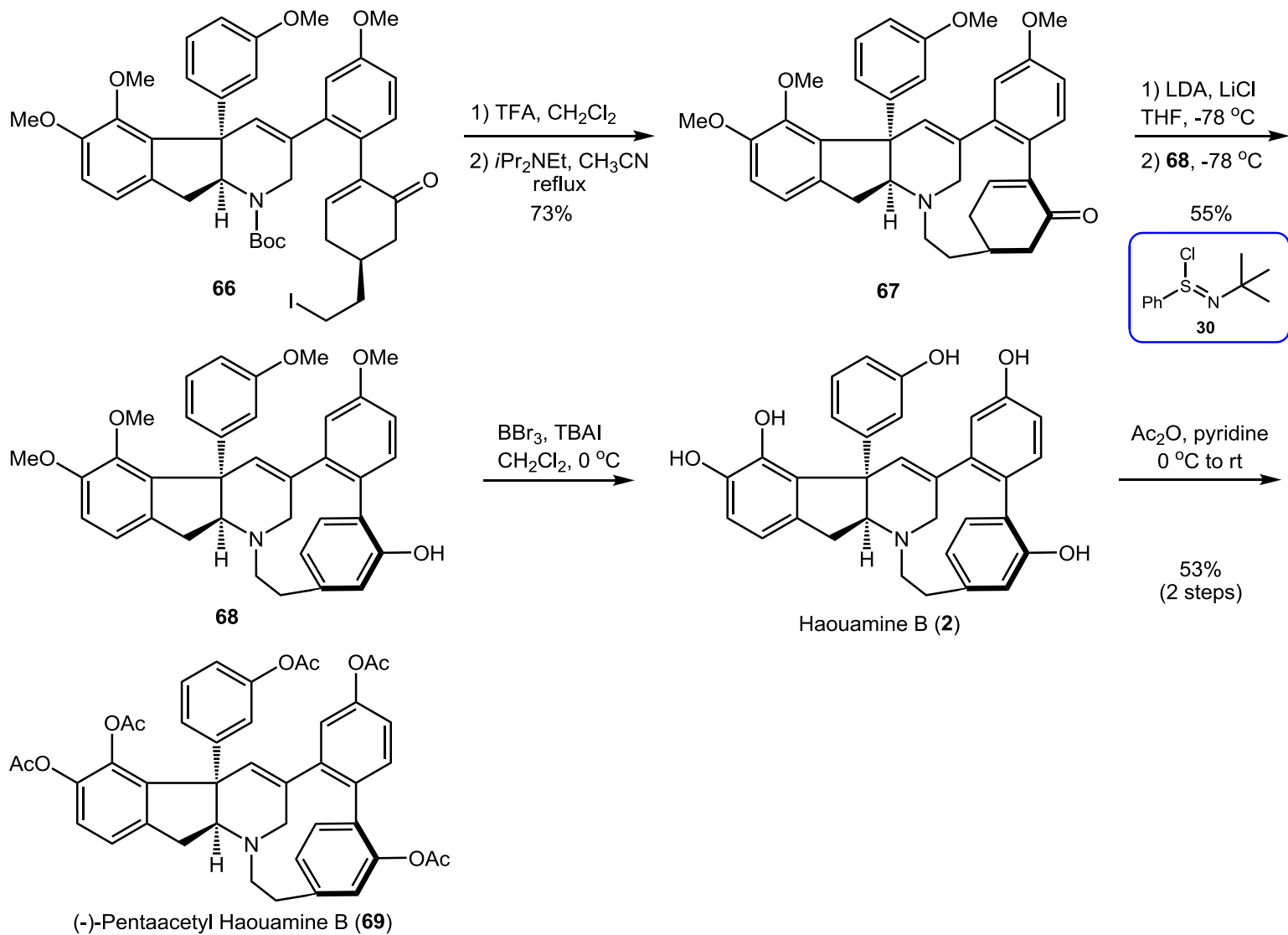
Total synthesis of Haouamine B



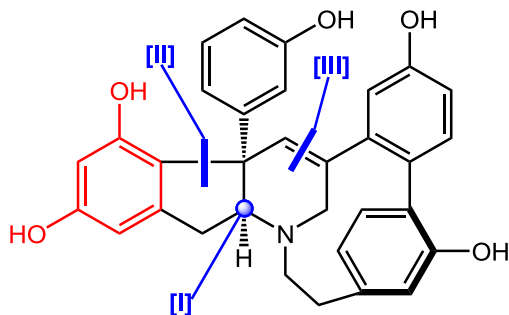
Total synthesis of Haouamine B



Total synthesis of Haouamine B

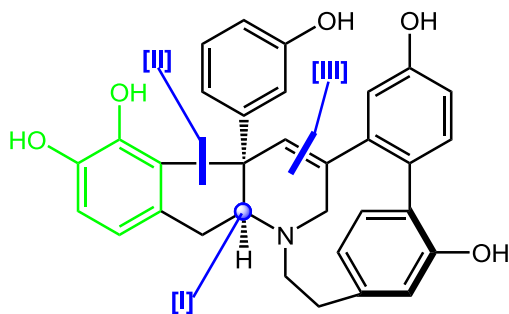


Summary



Iso-Haouamine B

- [I] Chirality came from *N*-Boc serine
- [III] Tf_2O mediated Friedel-Crafts triflation reaction
- [III] Olefin cross metathesis



Haouamine B

- [I] Chirality induced by optically active sulfinamide
- [III] $\text{Sc}(\text{OTf})_3$ mediated Friedel-Crafts reaction
- [III] Intramolecular McMurry coupling

Alkaloids continue to surprise with unusual and unexpected structures that have motivated advances in synthetic methodology and strategy. A case in point are the haouamines, a pair of intriguing alkaloids from the ascidian *Aplidium haouarianum* that display cytotoxic effects. Structurally, these alkaloids feature an indeno-tetrahydropyridine moiety that contains a diaryl quaternary center and an anti-Bredt double bond.

The tetrahydropyridine ring is fused to a highly strained 11-membered *p*-cyclophane ring system, which contains a stereogenic biaryl axis. The complexity of the NMR spectra of the haouamines, however, does not arise from two interconverting biaryl atropisomers but rather from an equilibrating mixture of two isomers formed through nitrogen inversion coupled with a conformational reorganization around the tetrahydropyridine ring.

In summary, we have developed a concise, total synthesis of the structure originally assigned to haouamine B. Our fast approach to the core of the molecule allowed for the detailed investigation of a hypothesized oxidative phenol coupling and eventually led to the proposed structure of the alkaloid. The true structure of haouamine B was revised in accord with our findings and has been reassigned to the catechol **34**.

In principle, our total synthesis could be adapted to reach **34**, but with limited time and resources we have decided to resist this temptation and focus on the further evaluation of iso-haouamine B. The biological activity of **2** and a number of synthetic intermediates and derivatives is currently under investigation and will be reported in due course.