Literature Report I

Total Synthesis of (+)-Piperarborenine B

Reporter: Zheng Gu
Checker: Bo Song
Date: 2016-12-12

Hu, J. L.; Xie, Z. W.; Tang, Y. *J. Am. Chem. Soc*. **2016**, *138*, 13151.
Panish, R. A.; Chintala, S. R.; Fox, J. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 4983.

Curriculum Vitae of Zuowei Xie

Education:

1983	B.S.	Hangzhou University
1986	M.S.	Shanghai Institute of Organic Chemistry
1990	Ph.D.	Technische Universität Berlin/ Shanghai Institute of Organic Chemistry

Academic Position:

Since 1995	The Chinese University of Hong Kong

Research Interests:

➢ Organometallic chemistry of transition metal complexes, chemistry of boron clusters, carboranes and metallacarboranes, homogenous catalysis, small molecule activation and polymer synthesis.

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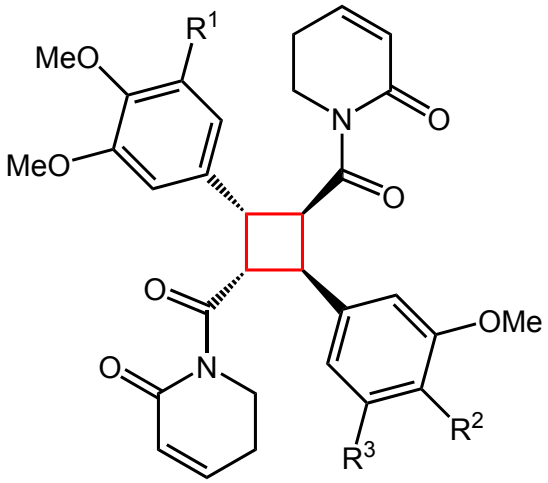
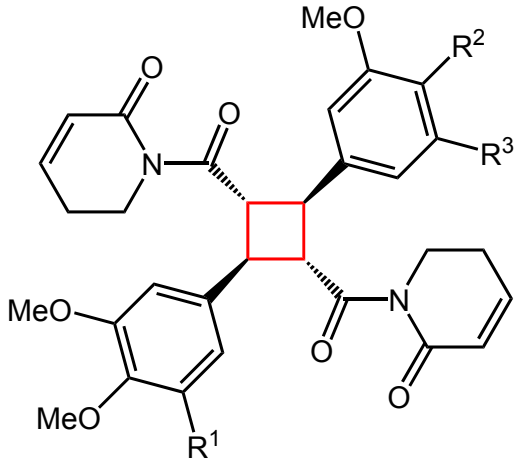
- Introduction
- Total synthesis of (+)-piperarborenine B by Xie and Tang
- Total synthesis of (+)-piperarborenine B by Fox
- Summary

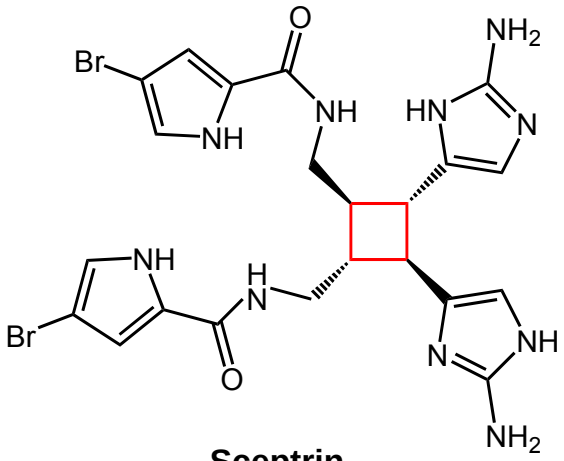
Introduction



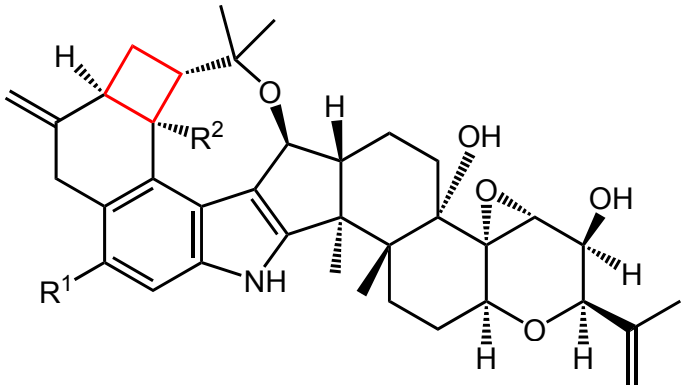
Piperarborenine A $R^1 = R^3 = H$, $R^2 = OMe$
Piperarborenine B $R^1 = R^2 = OMe$, $R^3 = H$



Piperarborenine C $R^1 = OMe$, $R^2 + R^3 = OCH_2O$
Piperarborenine D $R^1 = H$, $R^2 = R^3 = OCH_3$
Piperarborenine E $R^1 = H$, $R^2 + R^3 = OCH_2O$

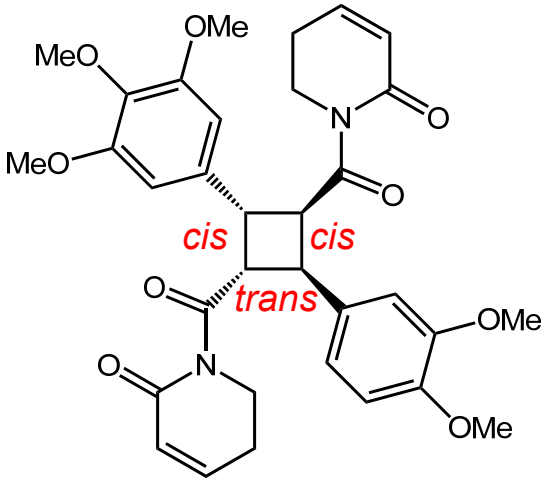


Sceptrin

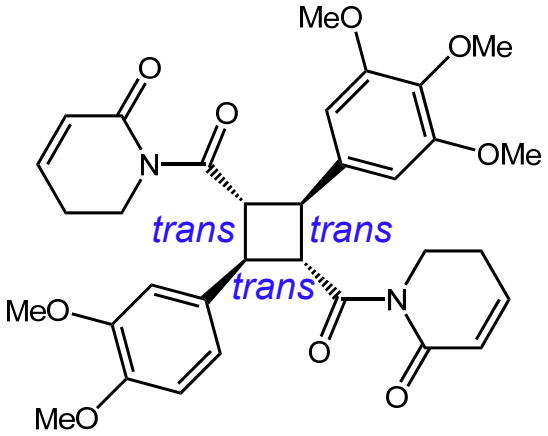


Penitrem A-D

Introduction



Piperarborenine B



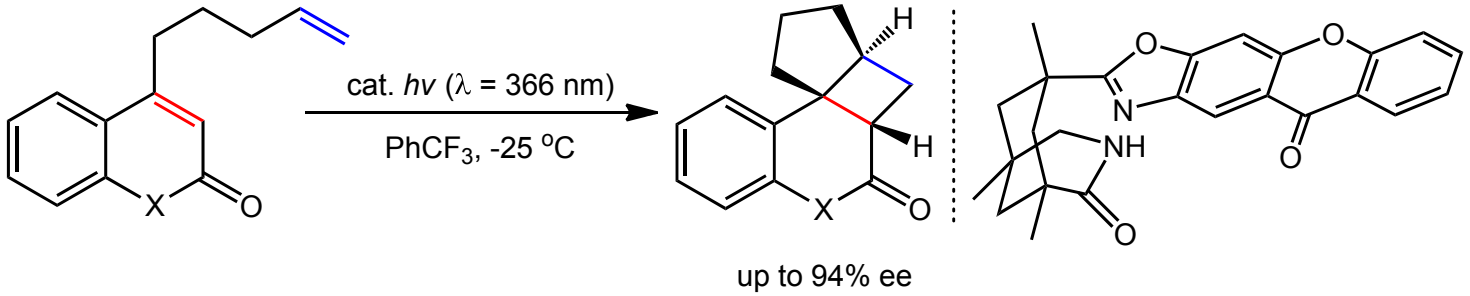
Piperarborenine D

- Isolated from the stems of the creeping shrub *Piper arborescens;*
- Pseudosymmetrical cyclobutane, *cis-trans-cis* and *trans-trans-trans*;
- Exhibiting in *vitro* cytotoxicity against P-388, HT-29, and A549 cancer cell lines (IC_{50} < 4 μg/mL)

Introduction

Photopromoted enantioselective [2+2] reactions

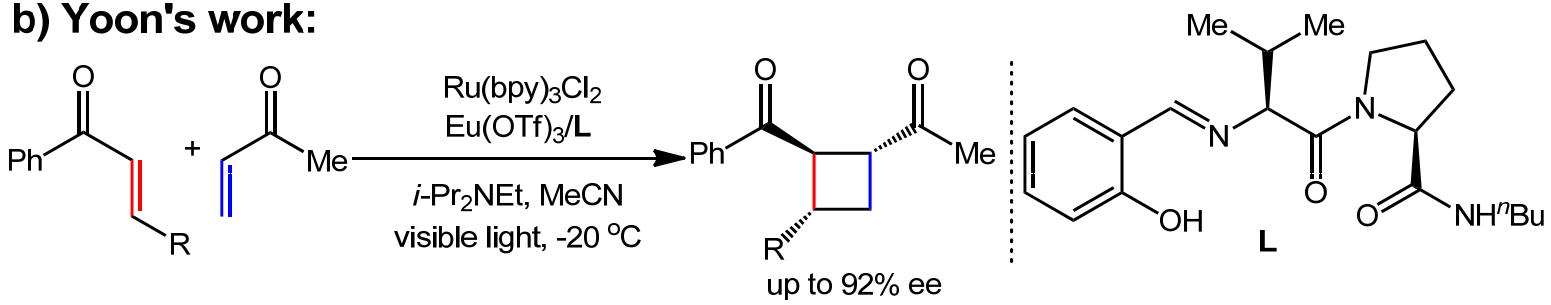
a) Bach's work:



up to 94% ee

Müller, C.; Miranda, M. A.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 16689.

b) Yoon's work:



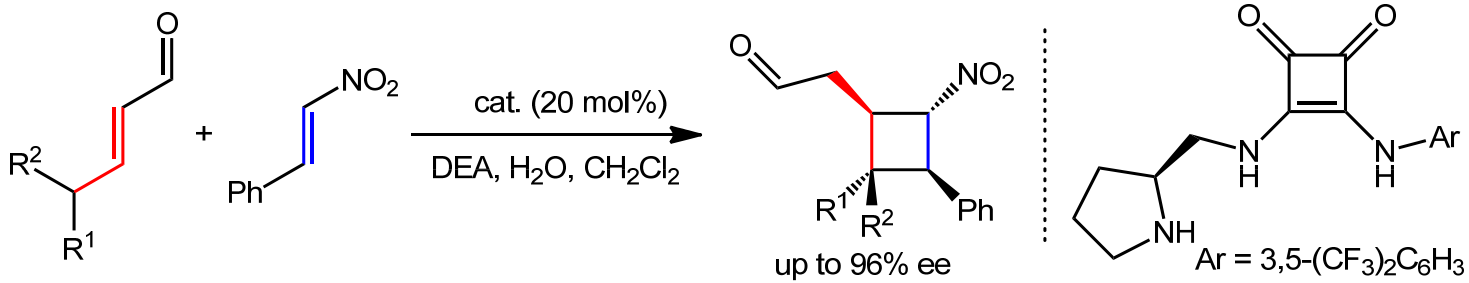
up to 92% ee

Du, J.; Skubi, K. L.; Yoon, T. P. *Science* **2014**, *344*, 392.

Introduction

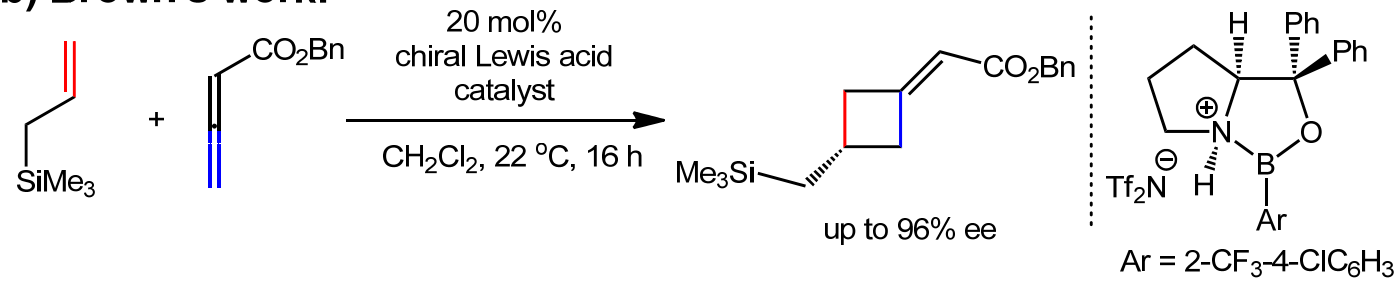
Organocatalytic enantioselective [2+2] reactions

a) Jørgensen's work:



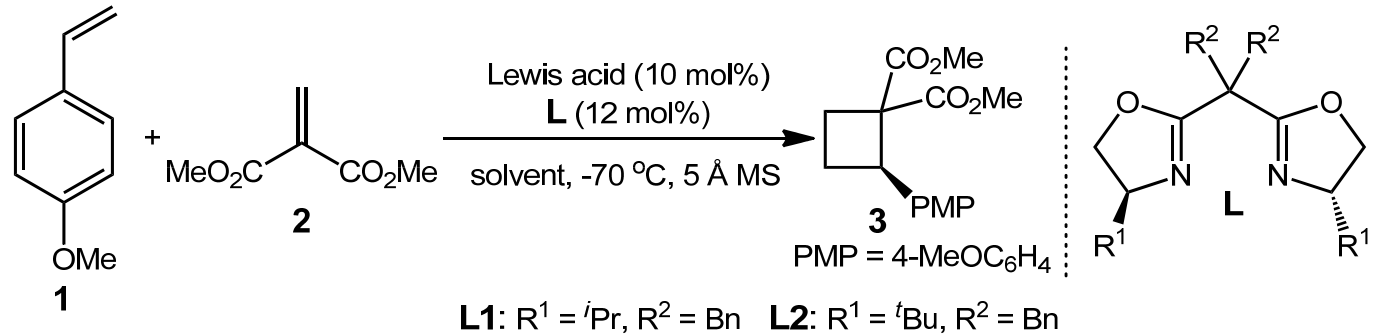
Albrecht, Ł.; Dickmeiss, G.; Jørgensen, K. A. *J. Am. Chem.Soc.* **2012**, *134*, 2543.

b) Brown's work:



Conner, M. L.; Xu, Y.; Brown, M. K. *J. Am. Chem. Soc.* **2015**, *137*, 3482.

Enantioselective construction of cyclobutanes



L1: $R^1 = {}^{i}Pr$, R^2 = Bn **L2**: $R^1 = {}^{t}Bu$, R^2 = Bn
L3: $R^1 = {}^{i}Pr$, R^2 = H **L4**: $R^1 = {}^{i}Pr$, R^2 = 2-$BrC_6H_4CH_2$

entry	Lewis acid	solvent	L	yield (%)	ee (%)
1[a]	$Cu(OTf)_2$	CH_2Cl_2	**L1**	41	63-69
2	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	**L1**	29	0
3	$Cu(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	**L1**	45	72
4	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L1**	41	93
5	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L2**	7	56
6	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L3**	48	83
7	**$Cu(ClO_4)_2{\cdot}6H_2O$**	**THF**	**L4**	**82**	**97**

[a] 4 Å MS; Without Et_3N quench.

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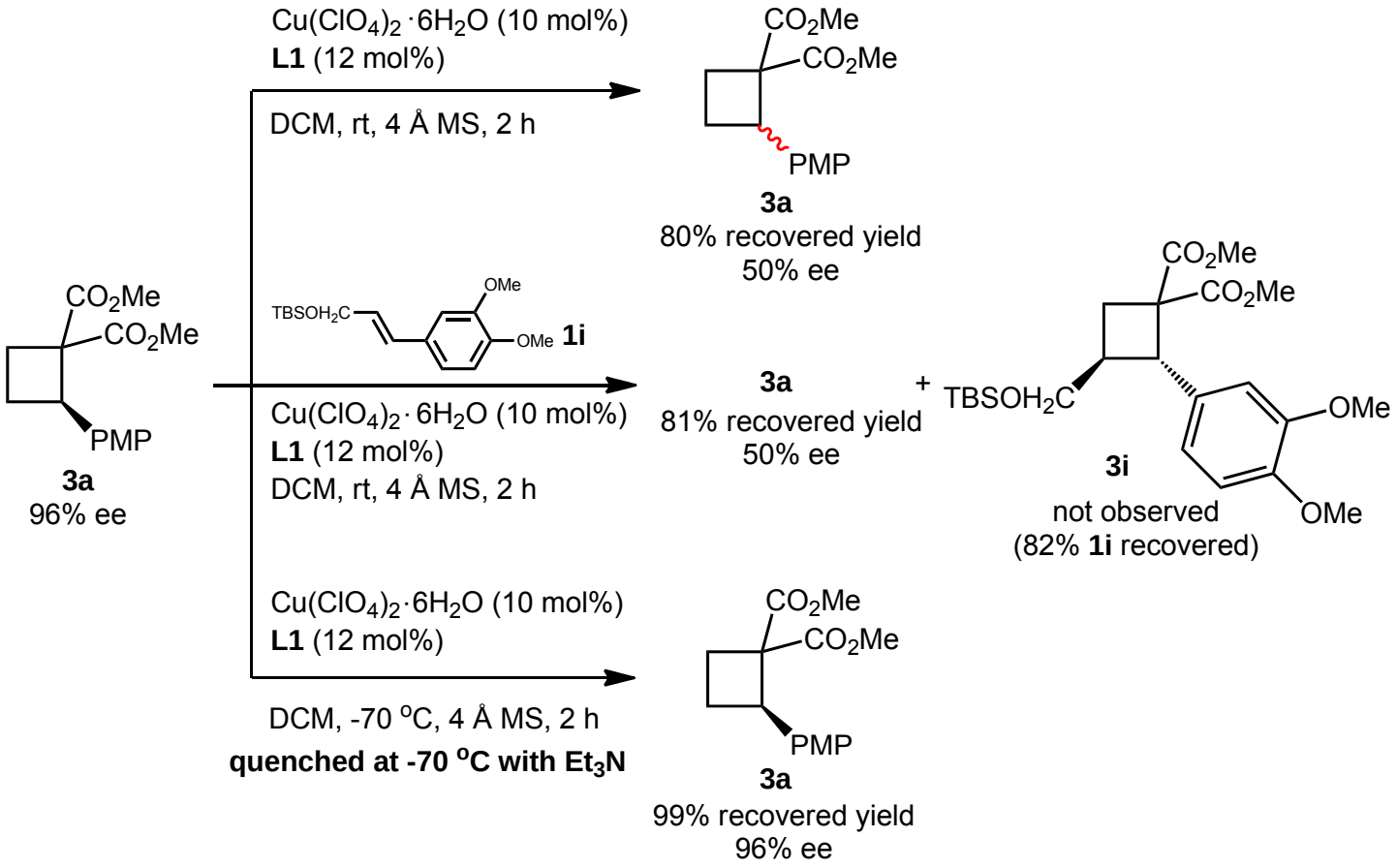
Mechanistic studies



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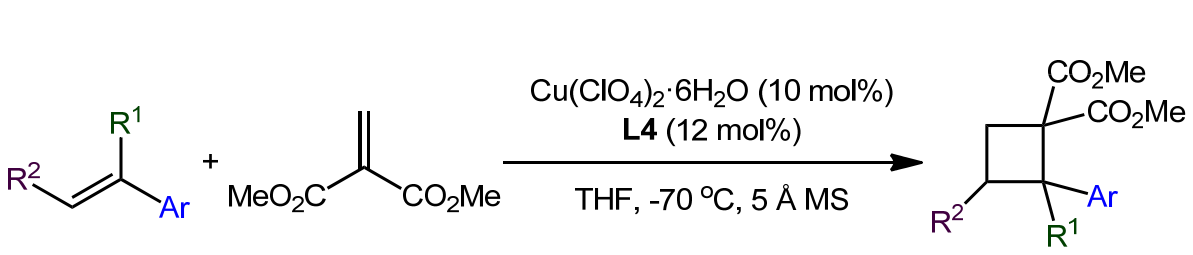
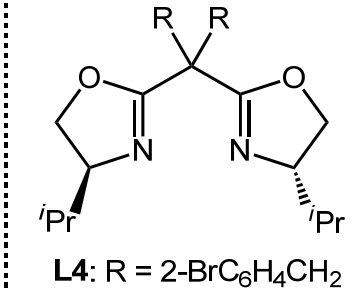
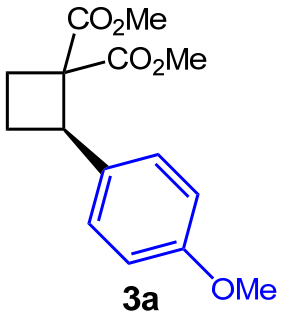
Substrate scope

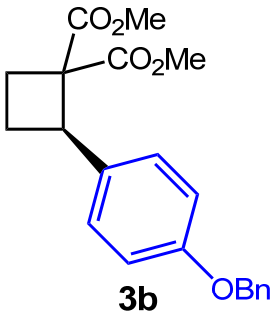




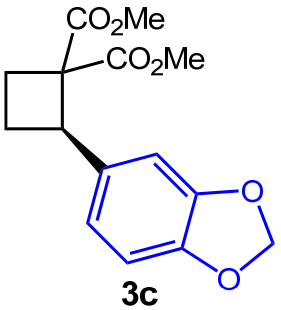
L4: R = 2-$BrC_6H_4CH_2$



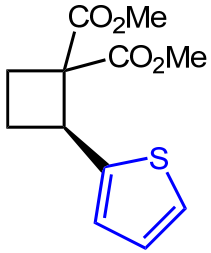
3a
82% yield, 97% ee



3b
91% yield, 96% ee



3c
60% yield, 96% ee



3d
25% yield, 95% ee

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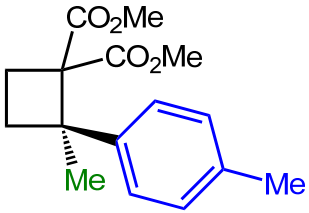
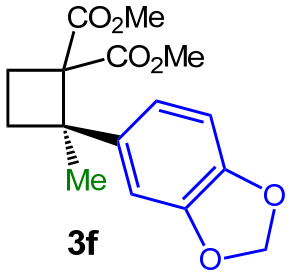
Substrate scope



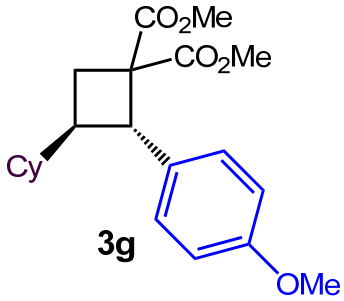
3e

52% yield, 94% ee



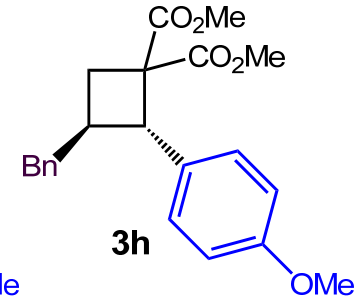
3f

72% yield, 96% ee



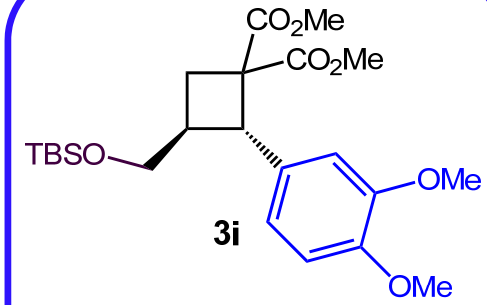
3g

50% yield, 99% ee
dr: 93/7



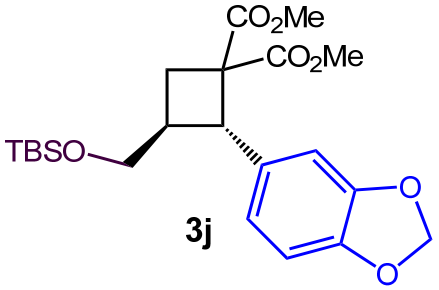
3h

87% yield, >99% ee
dr: >99/1



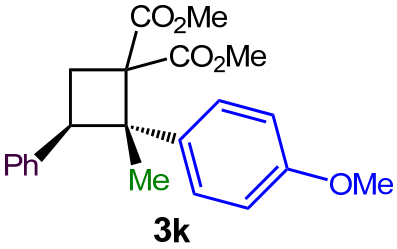
3i

68% yield, 99% ee
dr: >99/1



3j

92% yield, 96% ee
dr: >99/1



3k

74% yield, 95% ee
dr: >99/1

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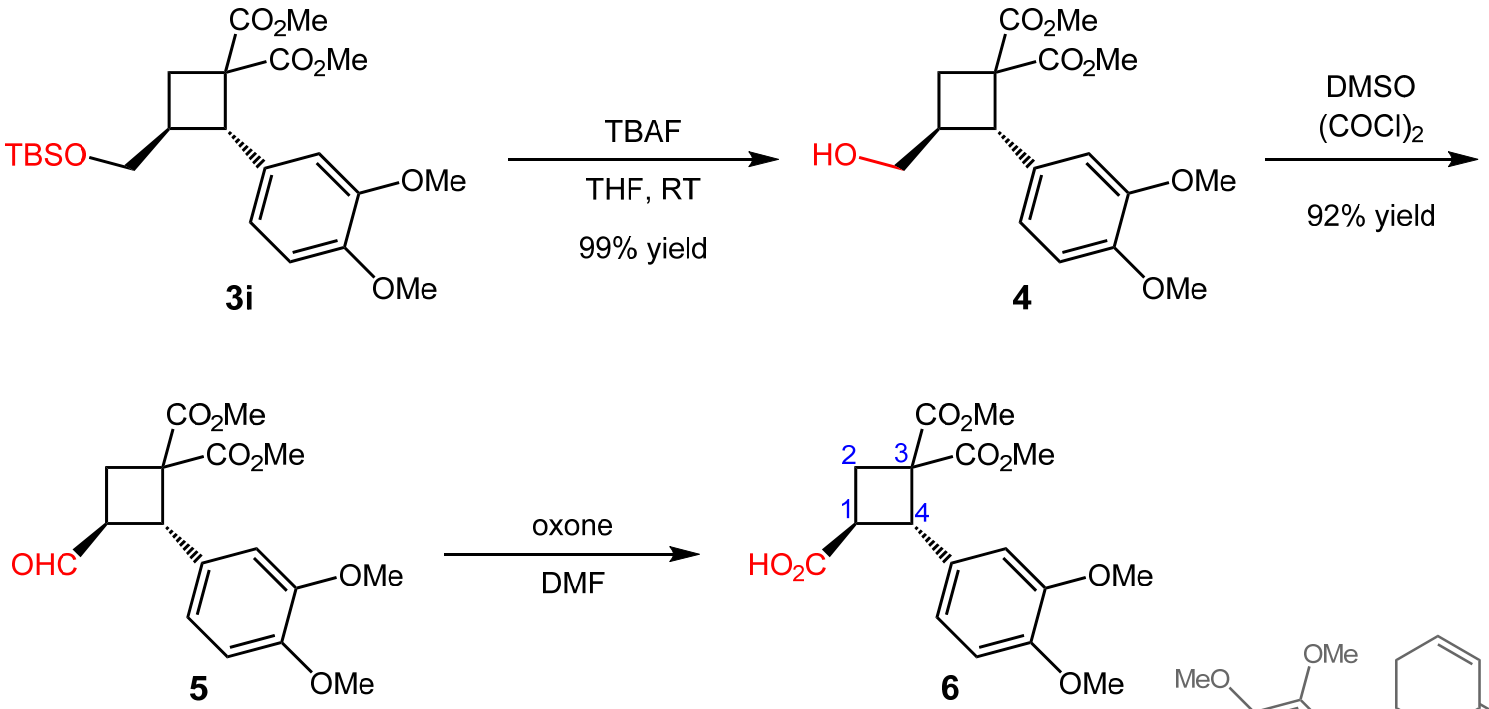
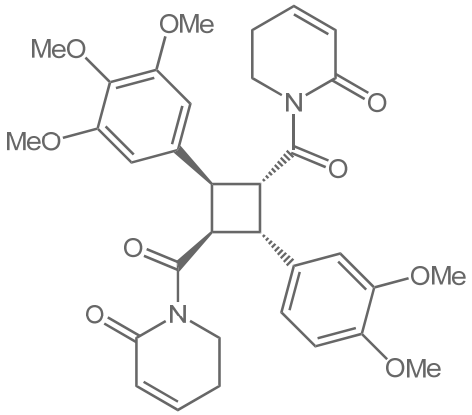
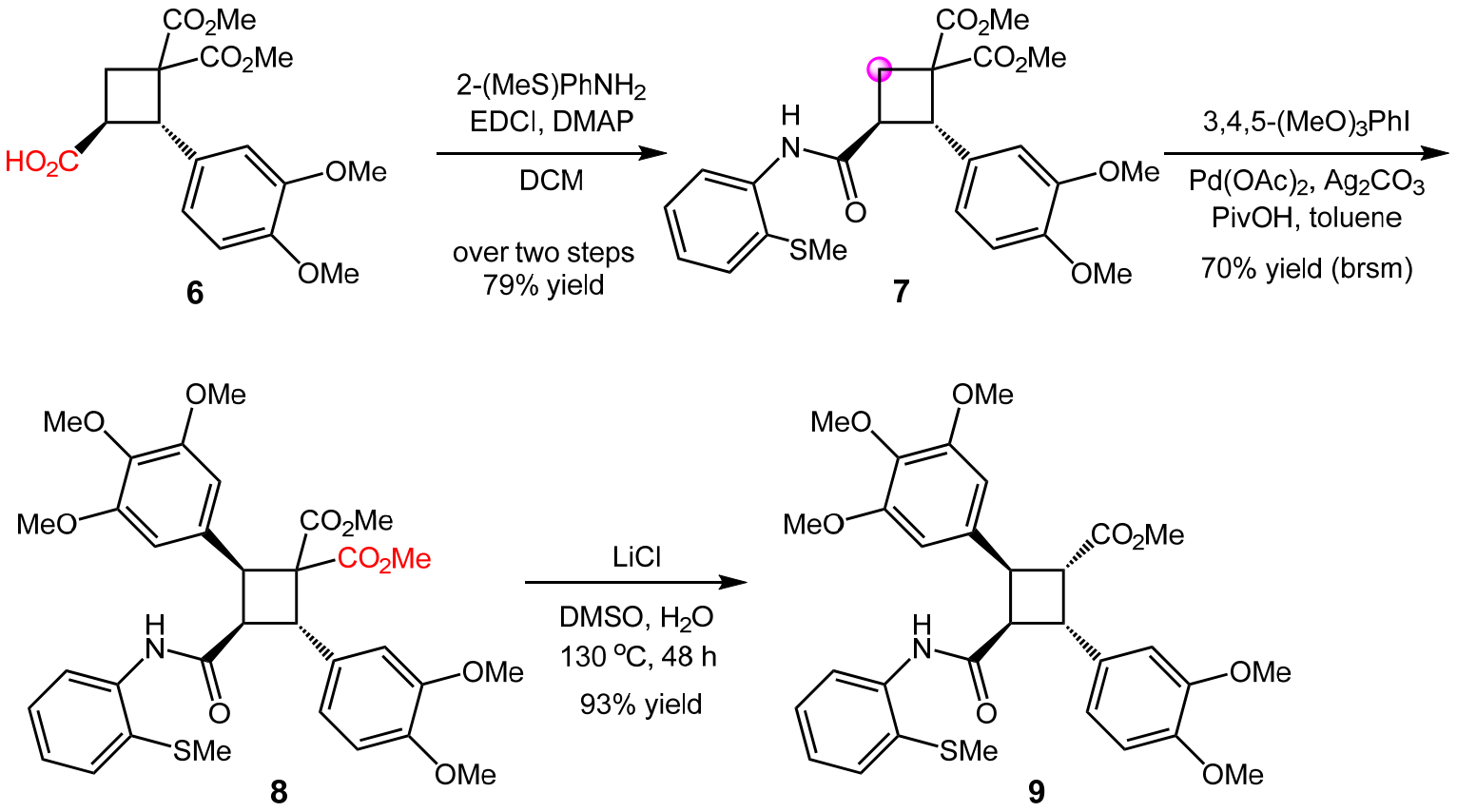
Total synthesis of (+)-piperarborenine B



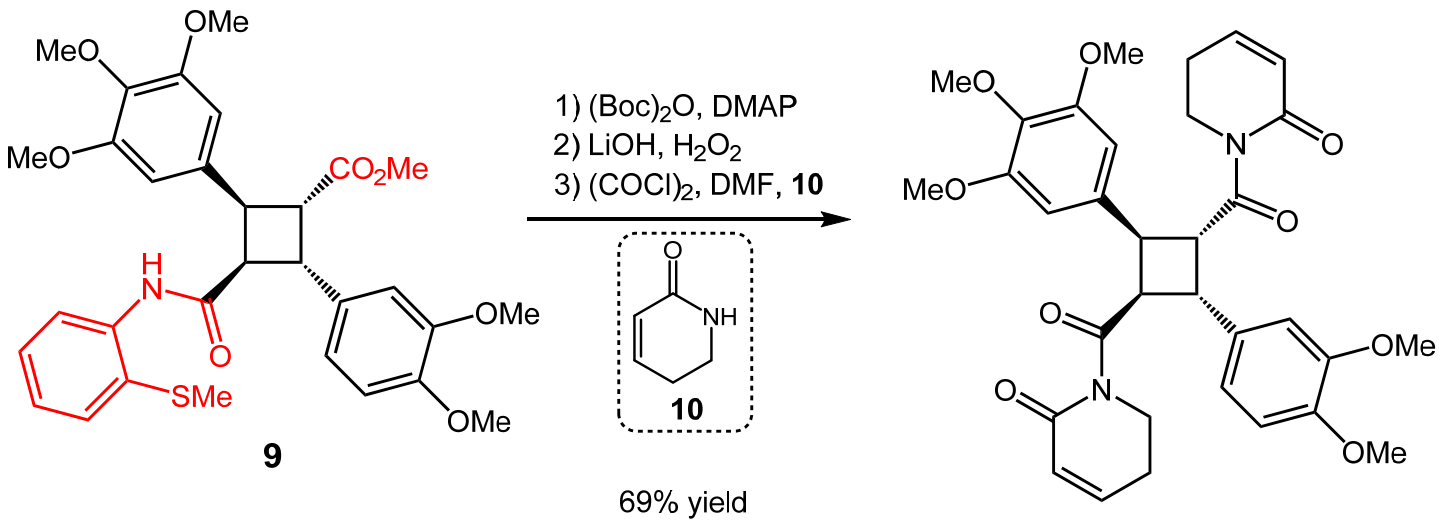


Total synthesis of (+)-piperarborenine B

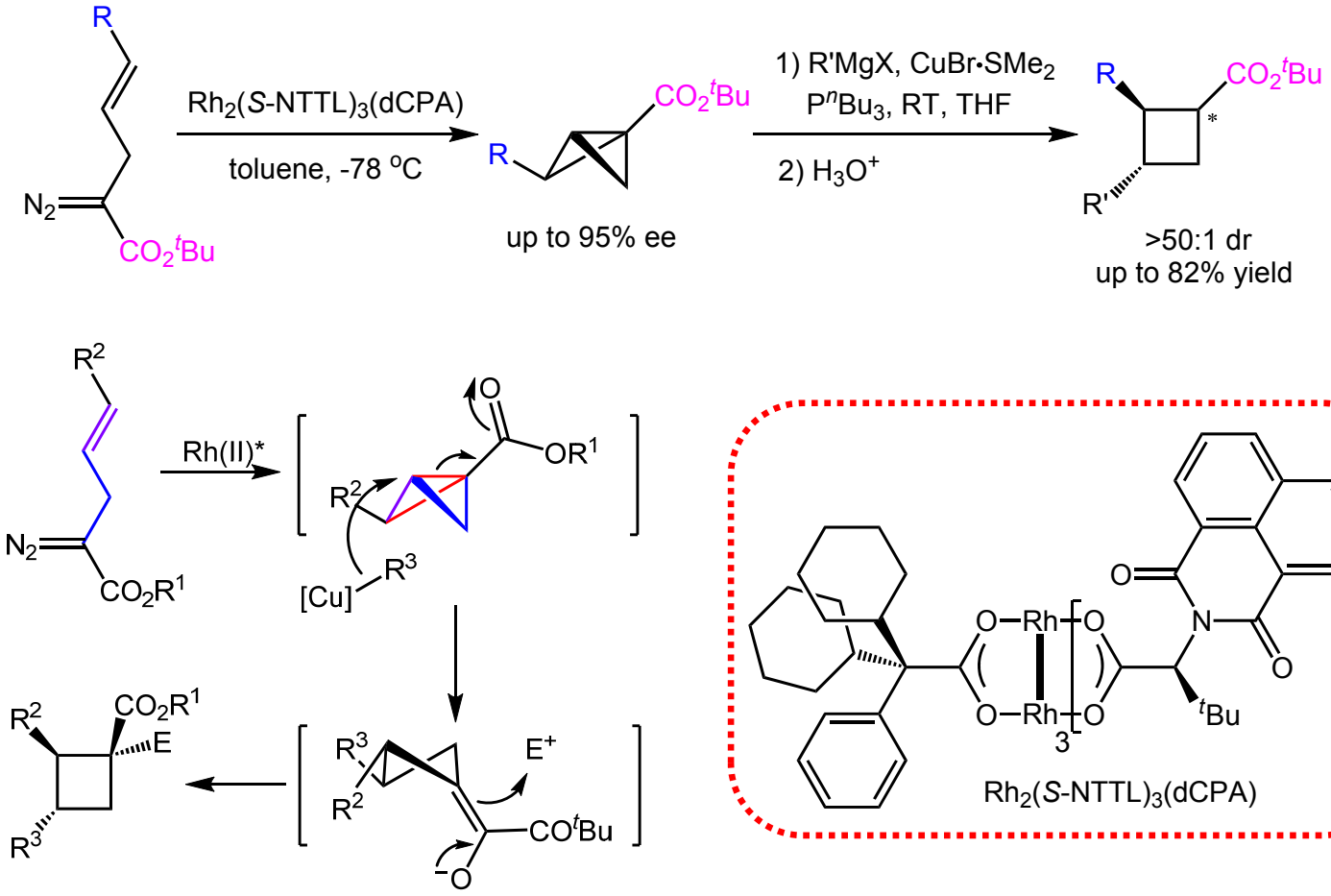


Gutekunst. W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076.

Total synthesis of (+)-piperarborenine B

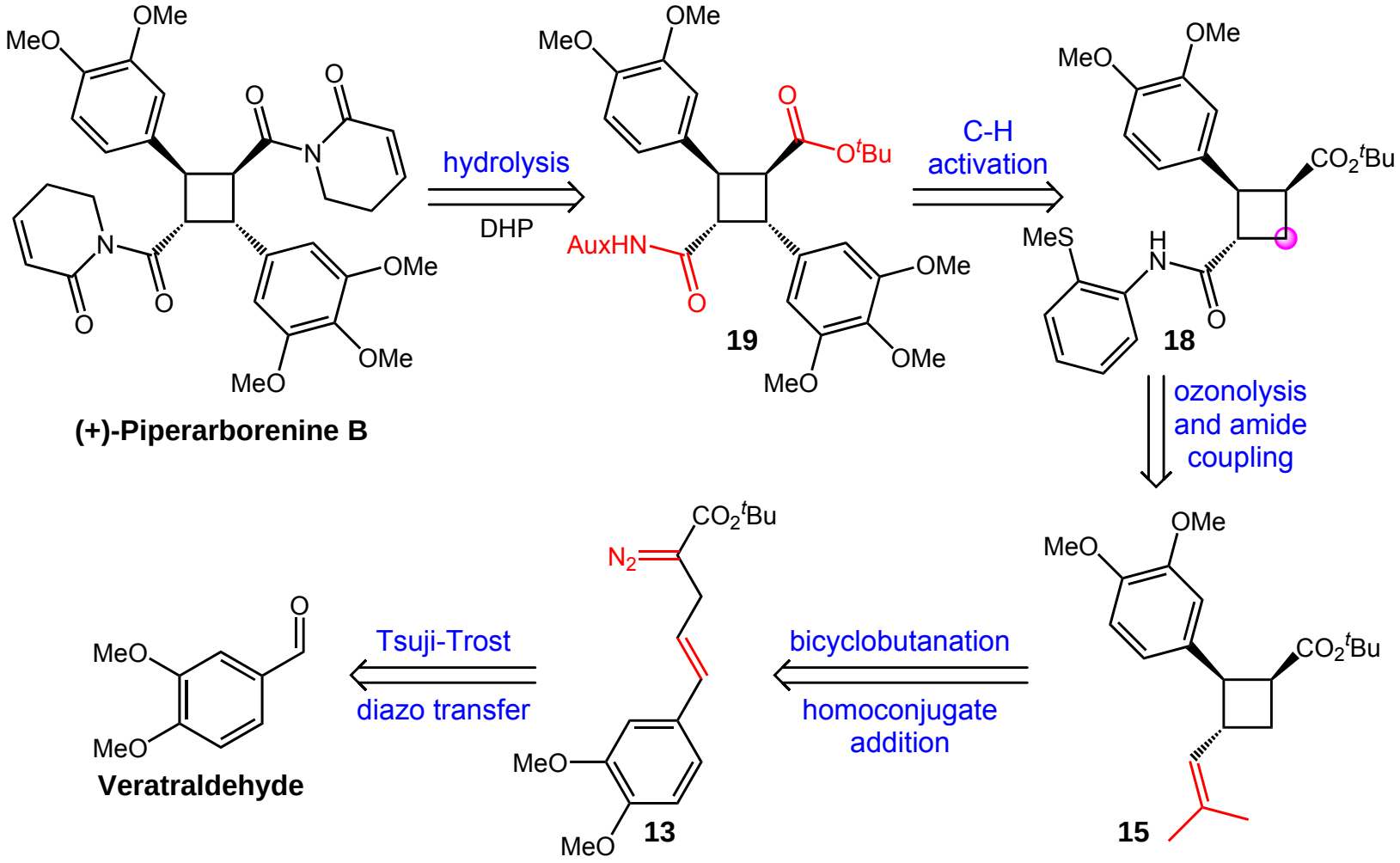


Bicyclobutanation/homoconjugate addition



Panish, R.; Chintala, S. R.; Fox, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 9283.

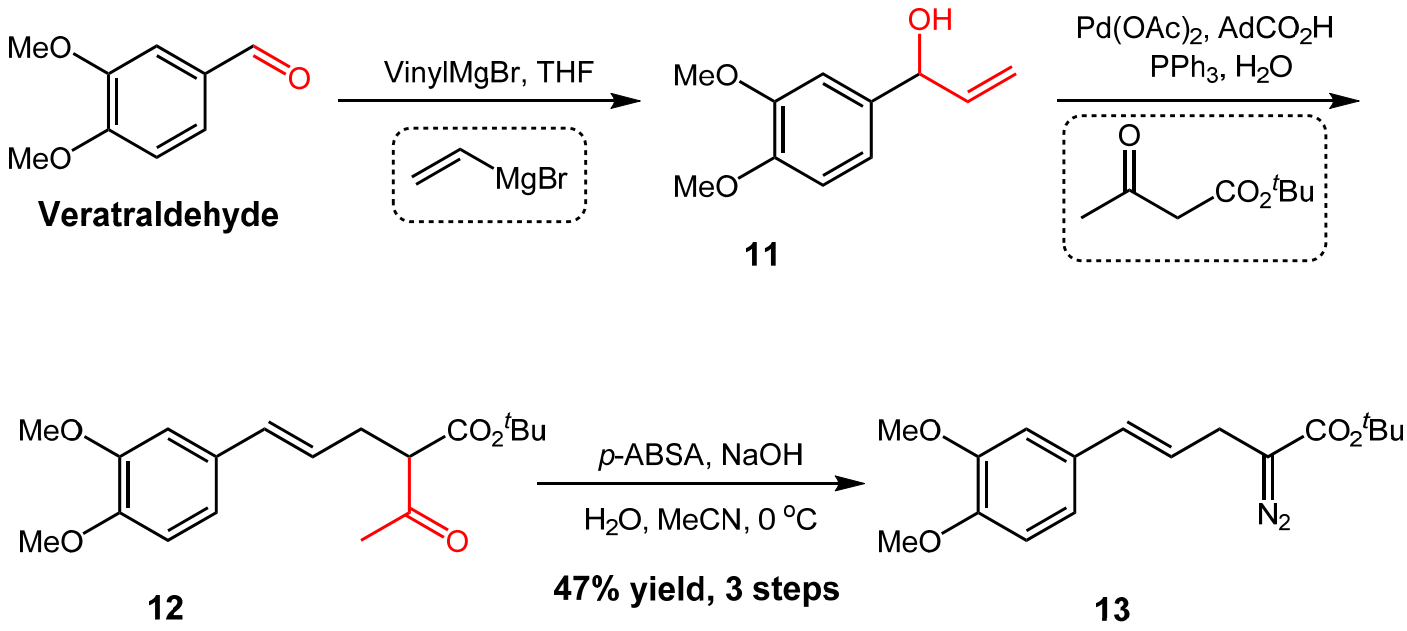
Retrosynthetic analysis



Panish, R. A.; Chintala, S. R.; Fox, J. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 4983.

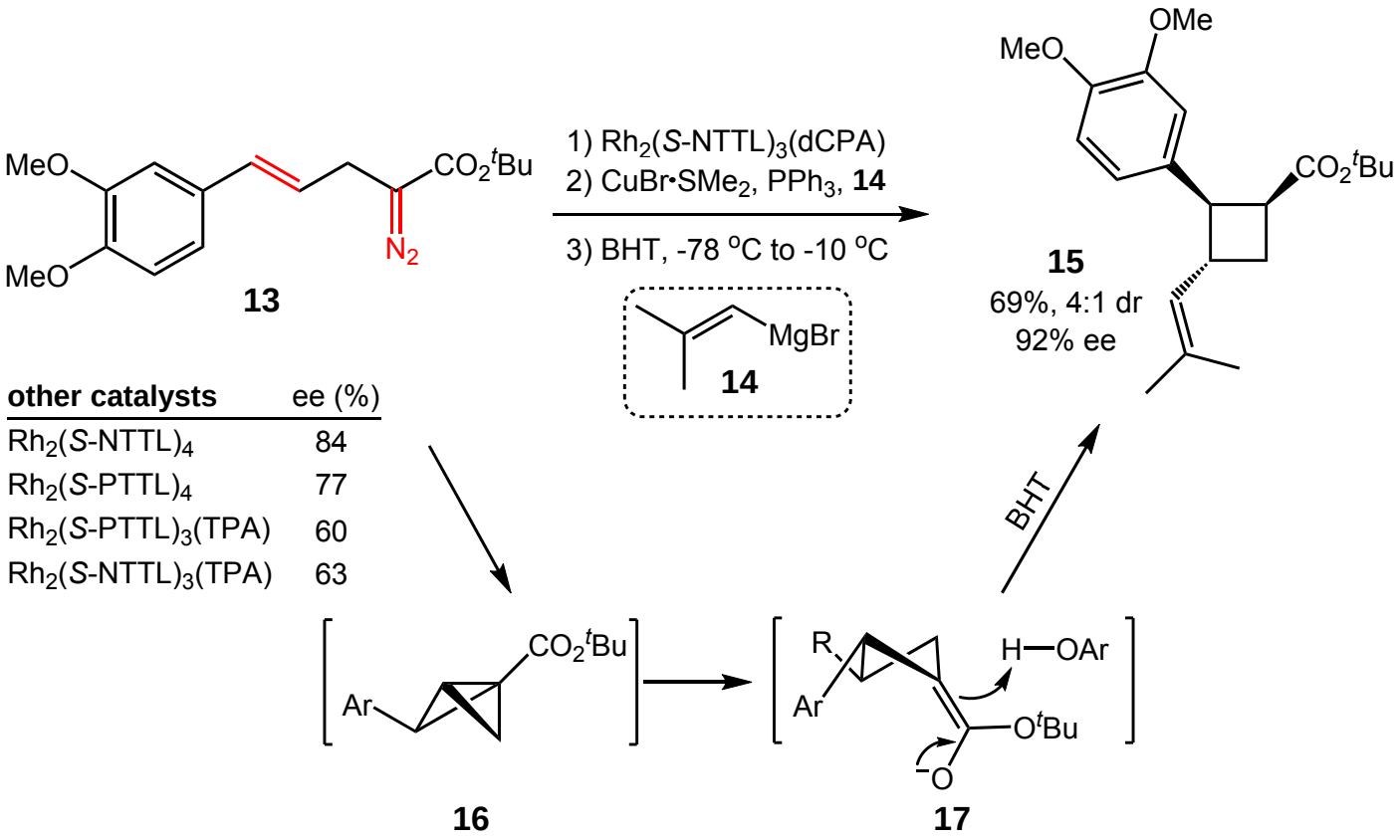
Total synthesis of (+)-piperarborenine B

Synthesis of the substituted diazoester



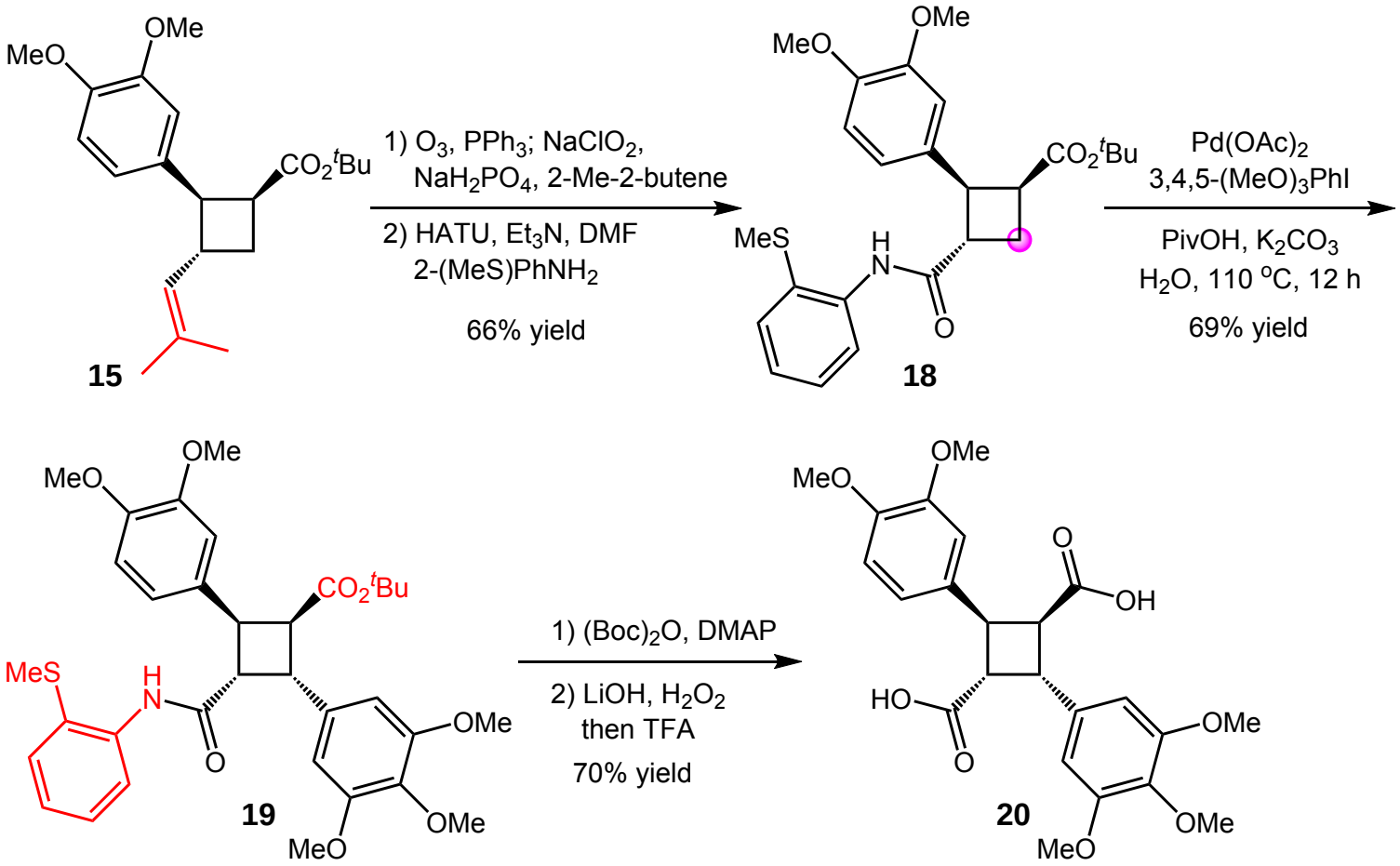
Total synthesis of (+)-piperarborenine B

Enantioselective synthesis of vinylcyclobutane



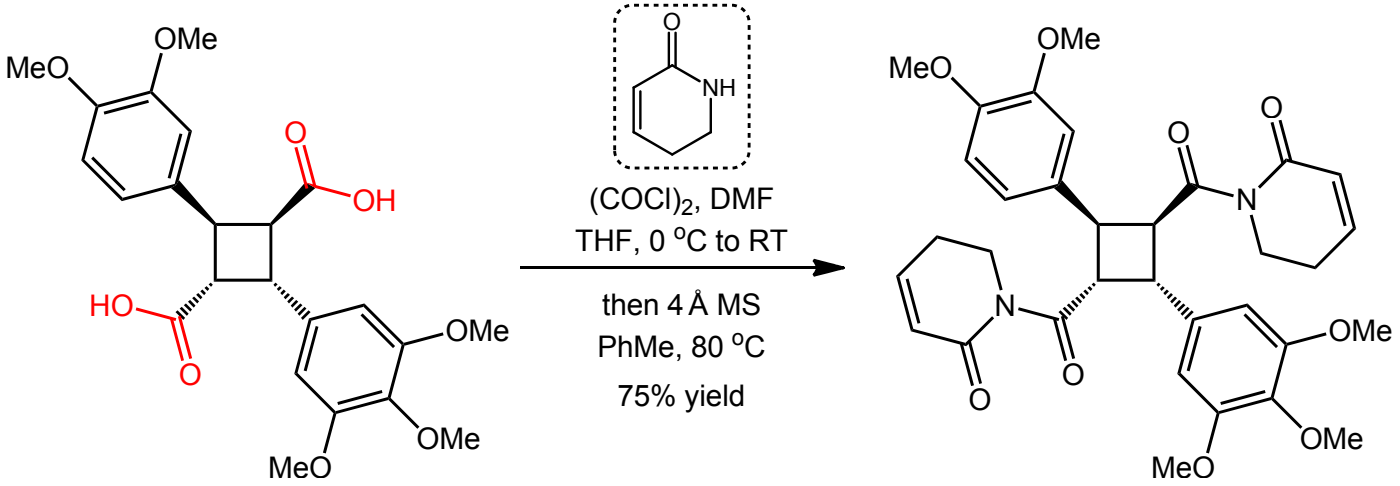
other catalysts	ee (%)
Rh_2(S-NTTL)$_4$	84
Rh_2(S-PTTL)$_4$	77
Rh_2(S-PTTL)$_3$(TPA)	60
Rh_2(S-NTTL)$_3$(TPA)	63

Total synthesis of (+)-piperarborenine B



Gutekunst. W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076.

Total synthesis of (+)-piperarborenine B

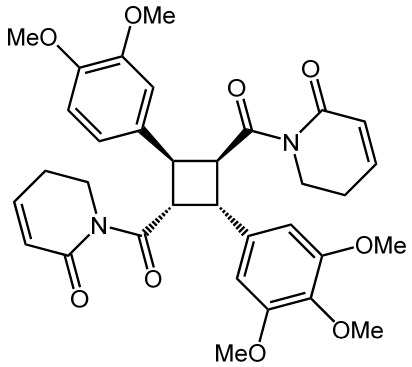


20

(+)-Piperarborenine B

1 week, 10 steps
8% overall yield
>400 mg prepared

Summary



(+)-Piperarborenine B

- 8 Steps, 17% overall yield;
- Cu(II)/SaBOX catalyzed [2+2] cycloaddition;
- Late stage sp^3 C-H activation.

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- 10 Steps, 8% overall yield;
- Bicyclobutanation/homoconjugate addition;
- Late stage sp^3 C-H activation.

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The first paragraph

The occurrence of cyclobutane frameworks in many natural products and biologically active compounds has aroused great interest in building these fascinating structures. Although enantioselective protocols have achieved remarkable breakthroughs, successful examples of asymmetric cyclobutanation are still limited. Accordingly, the appeal of developing new and effective enantioselective methods for the construction of new-fashioned cyclobutanes is urgent and necessary. Methylidenemalonate, which was first prepared by Perkin in 1886, has been found to be a very reactive candidate in [2+2] cycloadditions with electron-rich alkenes to form donor−acceptor (D−A) cyclobutanes in the presence of Lewis acid catalysts since 1983. However, to the best of our knowledge, an enantioselective version of this reaction has not been realized yet.

The first paragraph

This can probably be ascribed to the high symmetry of the methylidene-malonate molecule, the remote chiral delivery to the prostereogenic olefin, and the fact that the resulting optically active D−A cyclobutanes are likely to decompose into the racemic zwitterions promoted by Lewis acids, which makes the enantioselective cyclobutanation reaction a challenging problem. In this work, we have developed a Cu(II)/bisoxazoline (BOX)-catalyzed [2+2] cycloaddition of methylidenemalonate with multi-substituted alkenes that furnishes tri- and tetrasubstituted cyclobutanes with high diastereoselectivities and excellent ee's. In addition, optically active (+)-piperarborenine B was synthesized with this newly developed method in eight steps from methylidenemalonate and olefin in 17% overall yield with >99/1 dr and 99% ee. Herein we report these preliminary results.

The last paragraph

In summary, the first asymmetric [2+2] cycloaddition of dimethyl methylidenemalonate with polysubstituted olefins has been developed using Cu(II)/SaBOX as the catalyst, giving optically active cyclobutanes in high yields with >99/1 dr and up to >99% ee. The reaction has a broad substrate scope, in which mono-, di-, and trisubstituted alkenes all work well. This newly developed method has been applied to the enantioselective total synthesis of (+)-piperarborenine B, which was completed in eight steps from methylidenemalonate and **2m** in 17% overall yield with 99% ee. Further application of this reaction is an ongoing project in our laboratory.

Acknowledgment

Thanks for your attention !