Total Synthesis of Cyclobutane-Containing Natural Products

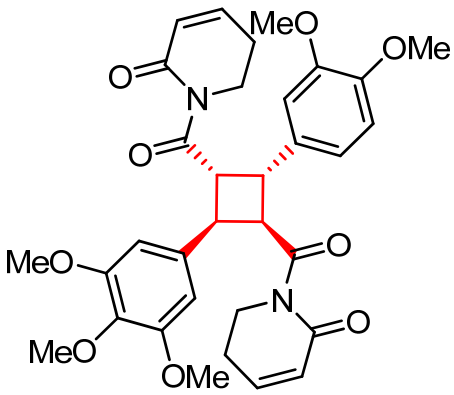
Reporter: Ran-Ning Guo

Checker： Xian-Feng Cai

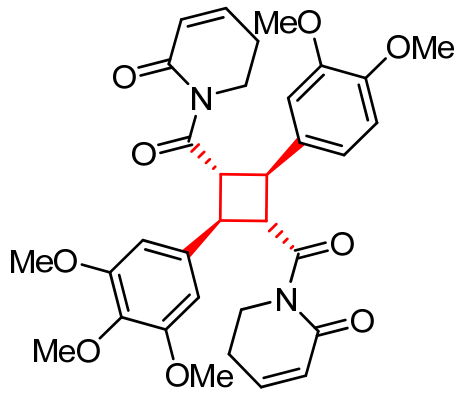
Date: 2012/07/10

Baran, P. S. et al *J. Am. Chem. Soc.* **2011**, *133*, 19076-19079
Angew. Chem. Int. Ed. **2012**, *51*, ASAP
Tang, W. et al *Angew. Chem. Int. Ed*. **2012**, *51*, ASAP

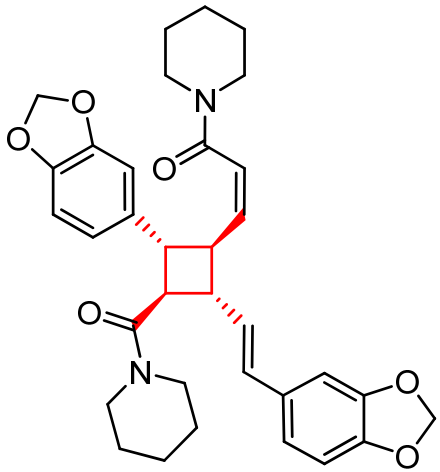
Targets



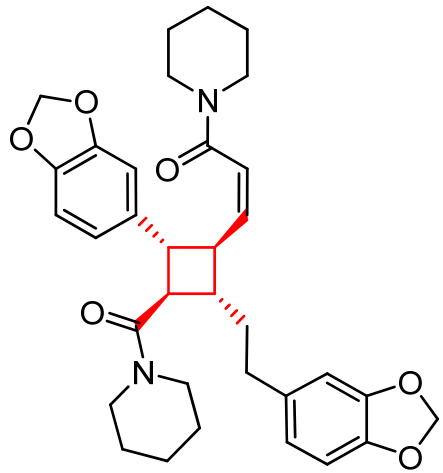
1
piperarborenine B



2
piperarborenine D(proposed)



3
pipercyclobutanamide A(proposed)



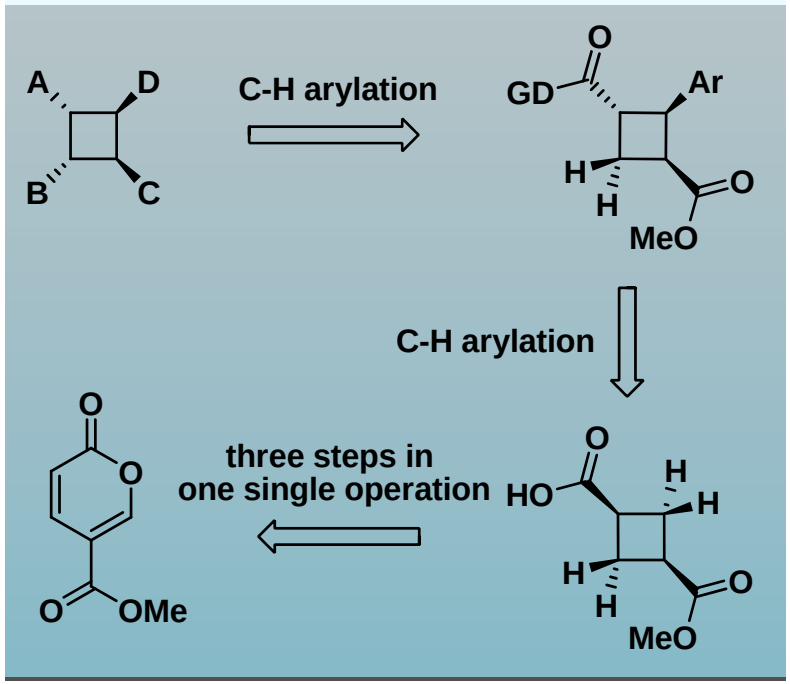
4
piperchabamide G(proposed)

Background

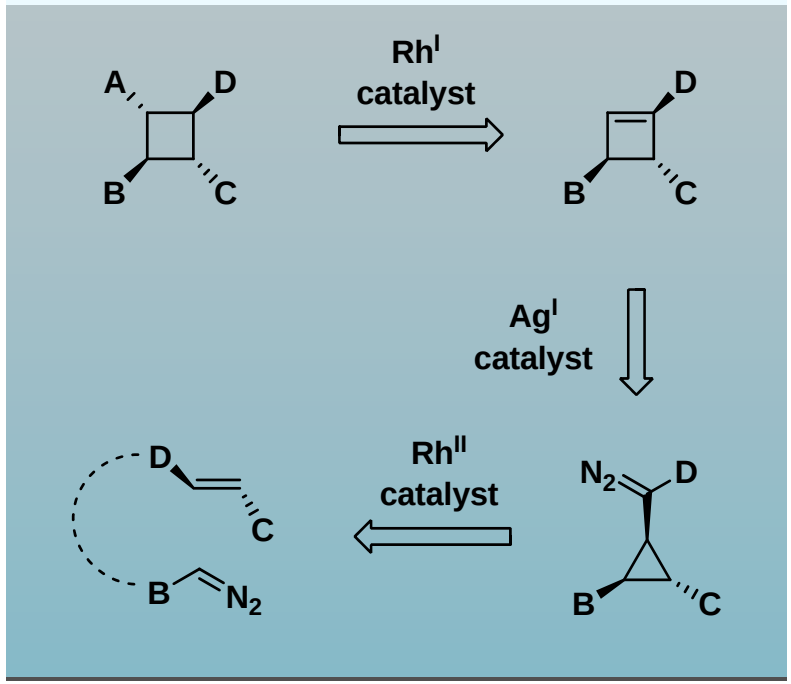
Piperarborenines from *Piper arborescens* In 2005	**Exhibit *in vitro* cytotoxicity against P-388, HT-29, and A549 cancer cell lines (IC50 < 4 μg/mL).**	
Pipercyclobutanamides from *Piper nigrum* In 2001	**Selective inhibition of cytochrome P450 2D6 (CYP2D6).**	
Piperchabamides from *Piper chaba* In 2009	**Inhibits D-GalN/tumor necrosis factor-α-induced death of hepatocytes and has hepatoprotective effect**	

Synthetic Strategies

Baran' work



Tang' s work

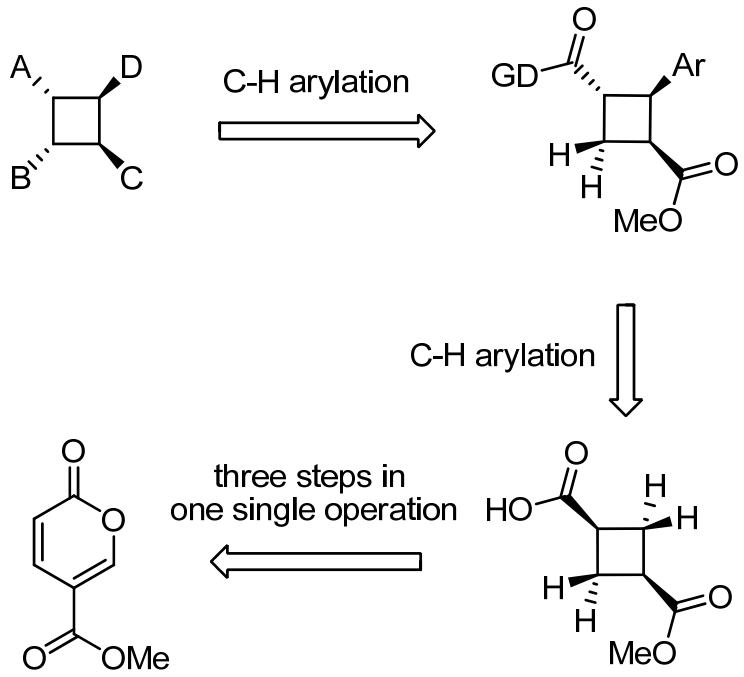


Sequential C-H Functionalization

Ring Expansion Method

Baran's plan

Direct [2+2] photocycloaddition: homodimerization, orientation, E/Z isomerization.



DG Requirements:

Promotes Pd-mediated C-H cleavage

Controls stereochemistry of arylation

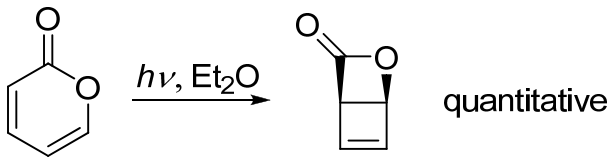
Enables divergent C-1 or C-3 epimerization

Mild installation and removal

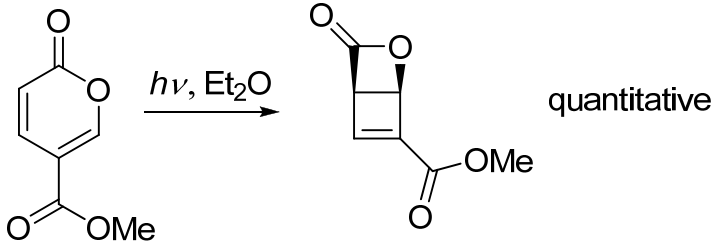
Previous synthesis:

8 steps, 20% overall yield, nonstereocontrolled

Baran's plan- new synthesis

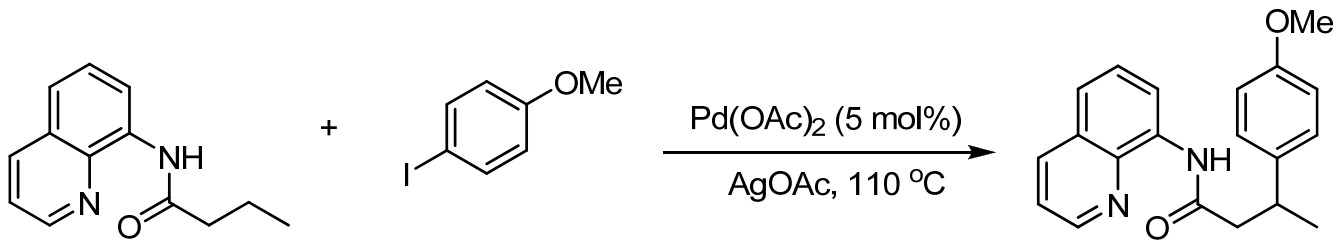


Corey, E. J. et al *J. Am. Chem. Soc*. **1964**, *86*, 959-951

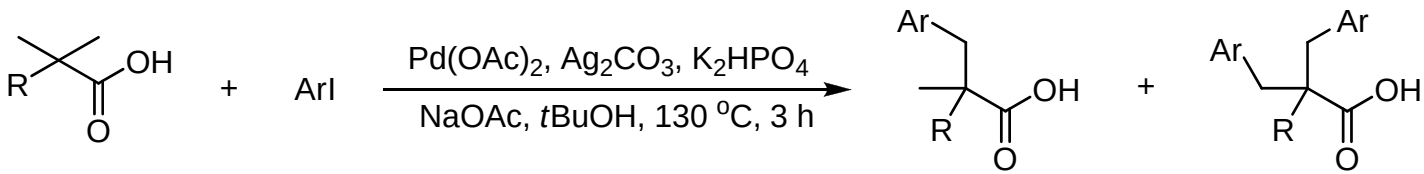


Maulide, N. et al *Angew. Chem., Int. Ed.* **2010**, *49*, 5672-5676

Baran's plan- C-H arylation



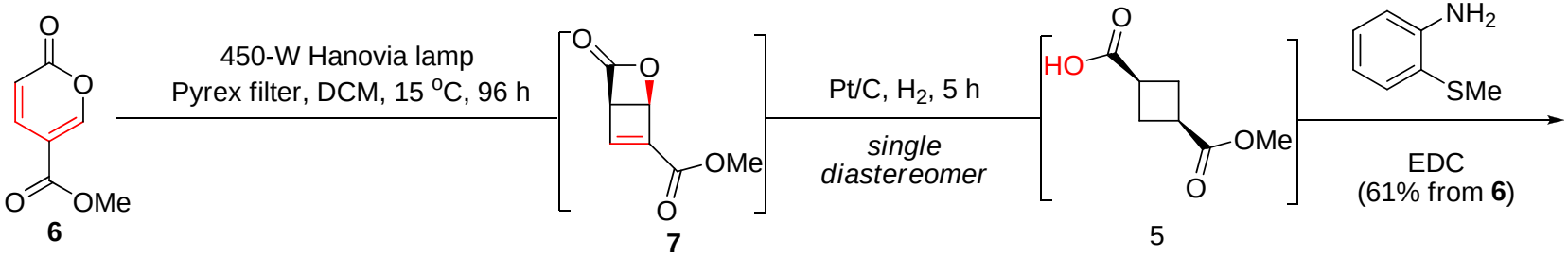
Daugulis, O. J. et al *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155

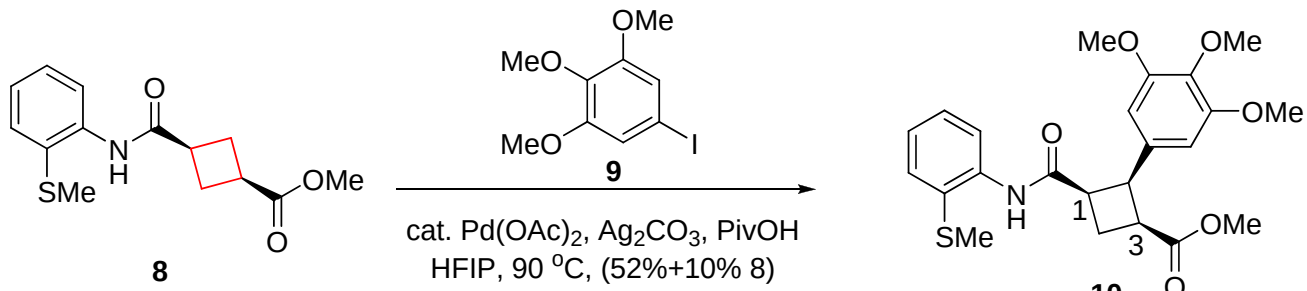


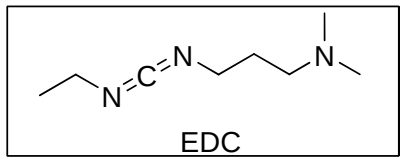
70% (5: 2)

Yu, J.-Q. et al *J. Am. Chem. Soc.* **2007**, *129*, 3510-3511

Synthesis of Piperarborenines



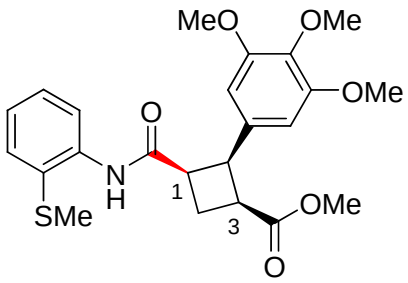




1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

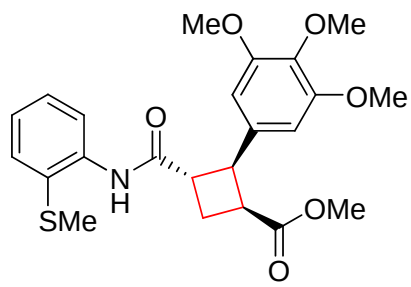
Ashworth, I. W. et al *J. Org. Process Res. Dev*. **2003**, *7*, 74-81

Synthesis of Piperarborenines

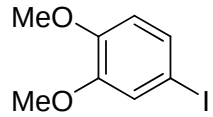


10

LiO^tBu(1.0 eq.), PhMe
50 °C, 36 h
>10:1 d.r. (79%)

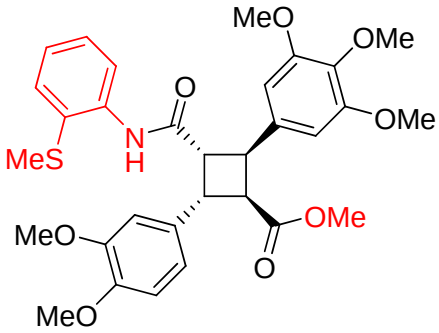


11



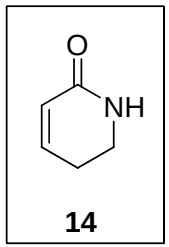
12 (2.0 eq.)

cat. $Pd(OAc)_2$ (0.15 eq.)
Ag_2CO_3 (1.0 eq.)
^{t}BuOH, 75 °C
(46%+20% **11**)

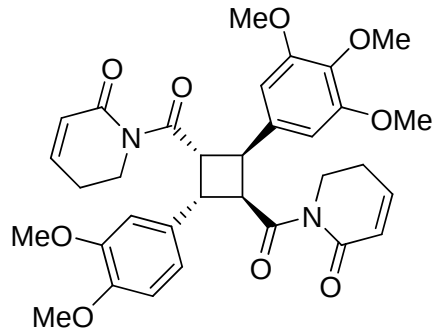


13

1) Boc_2O (*x-ray*), DMAP, MeCN, 5 h, 90%
2) LiOH, H_2O_2, THF/H_2O, 50 °C, 24 h, 83%
3) $(COCl)_2$, DMF, THF, 2 h; **14** (3 eq.), PhMe
4-Å MS, 80 °C, 12 h, 77%

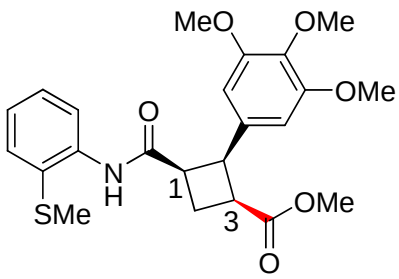


14



1
piperarborenine B

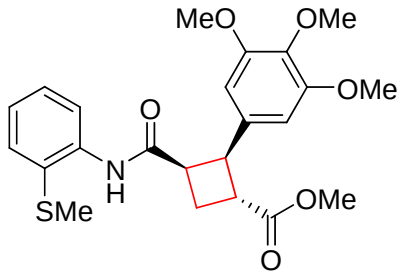
Synthesis of Piperarborenines



10

KHMDS(2.25 eq.), THF, -15 ^{o}C, 3 min;
aq. NH_4Cl

(65-80%) *single diastereomer*



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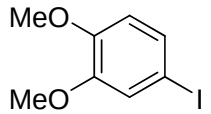
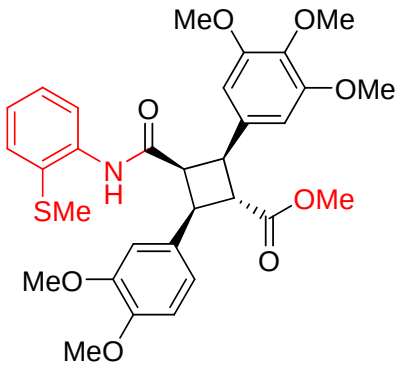


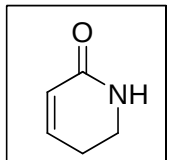
12 (2.0 eq.)

cat. $Pd(OAc)_2$ (0.10 eq.)
Ag_2CO_3 (1.0 eq.)
PivOH (1.0 eq.)
HFIP, 75 ^{o}C, 24 h
81%

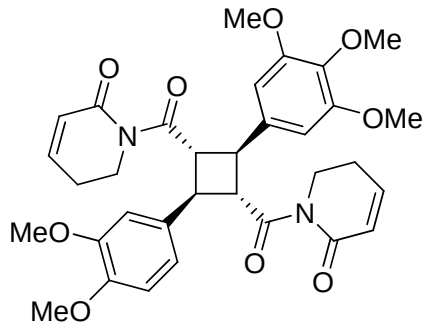


16

1) NaOH, EtOH, 100 ^{o}C, 24 h, 86%
2) $(COCl)_2$, DMF, $CHCl_3$, 2 h;
14(3 eq.), PhMe, 4-Å MS, 80 ^{o}C, 4 h, 78%

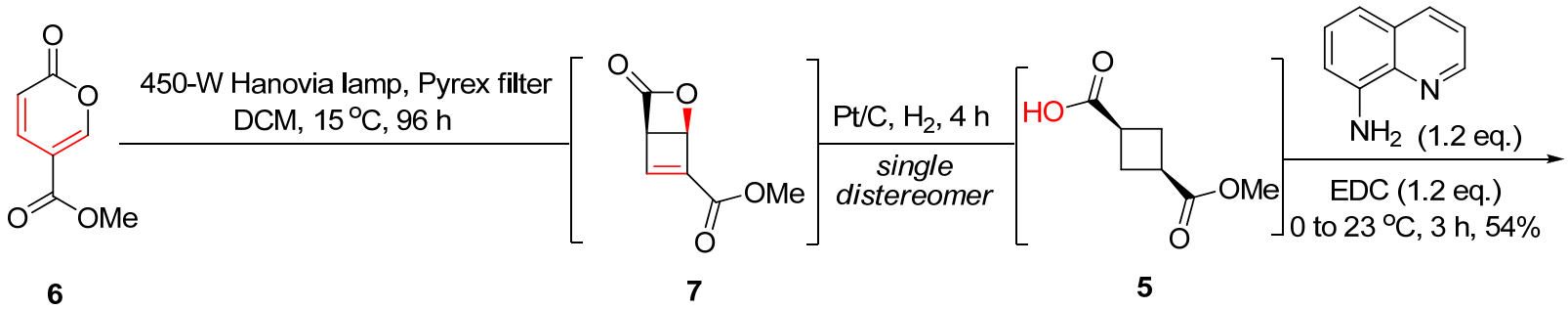


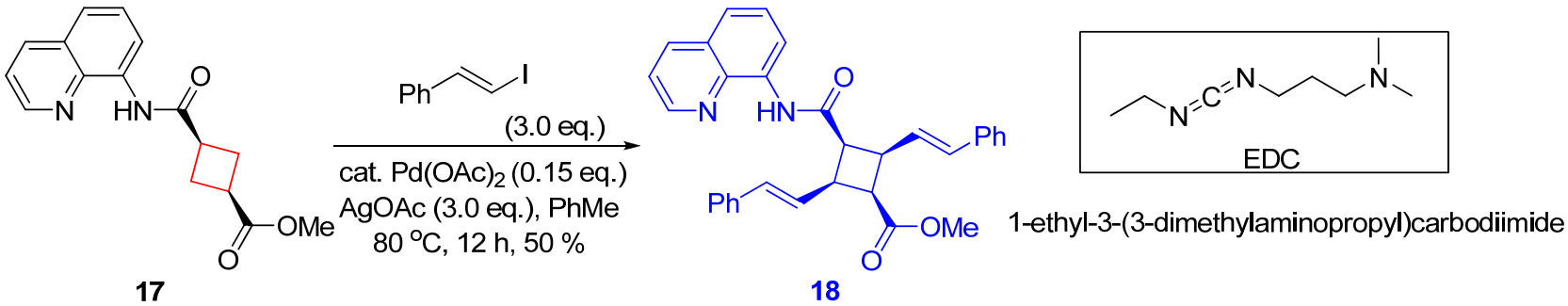
14



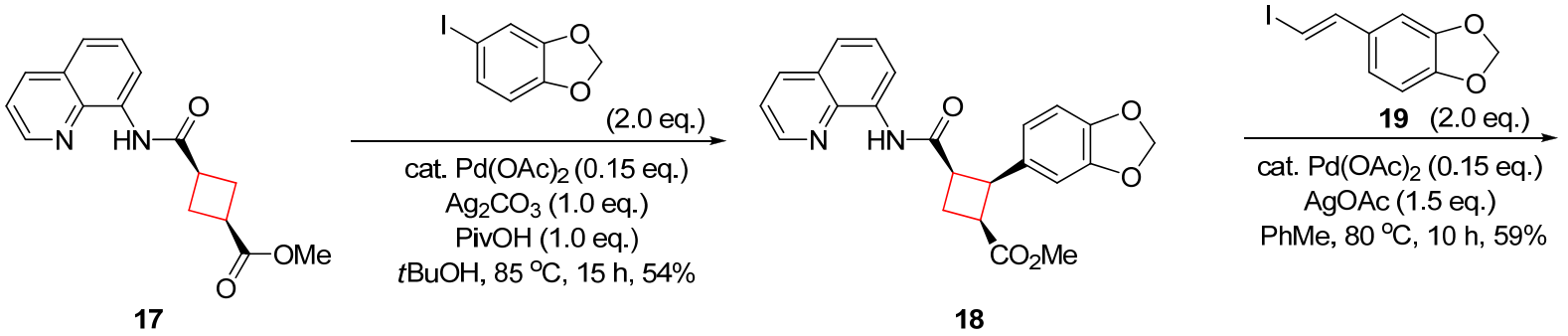
2
piperarborenine D)
(proposed)

Synthesis of Pipercyclobutanamide A

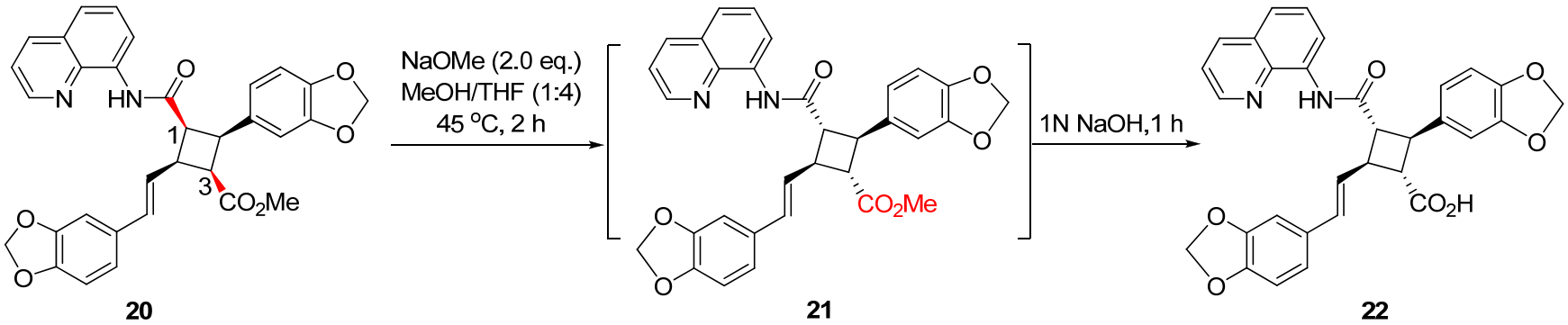




Synthesis of Pipercyclobutanamide A

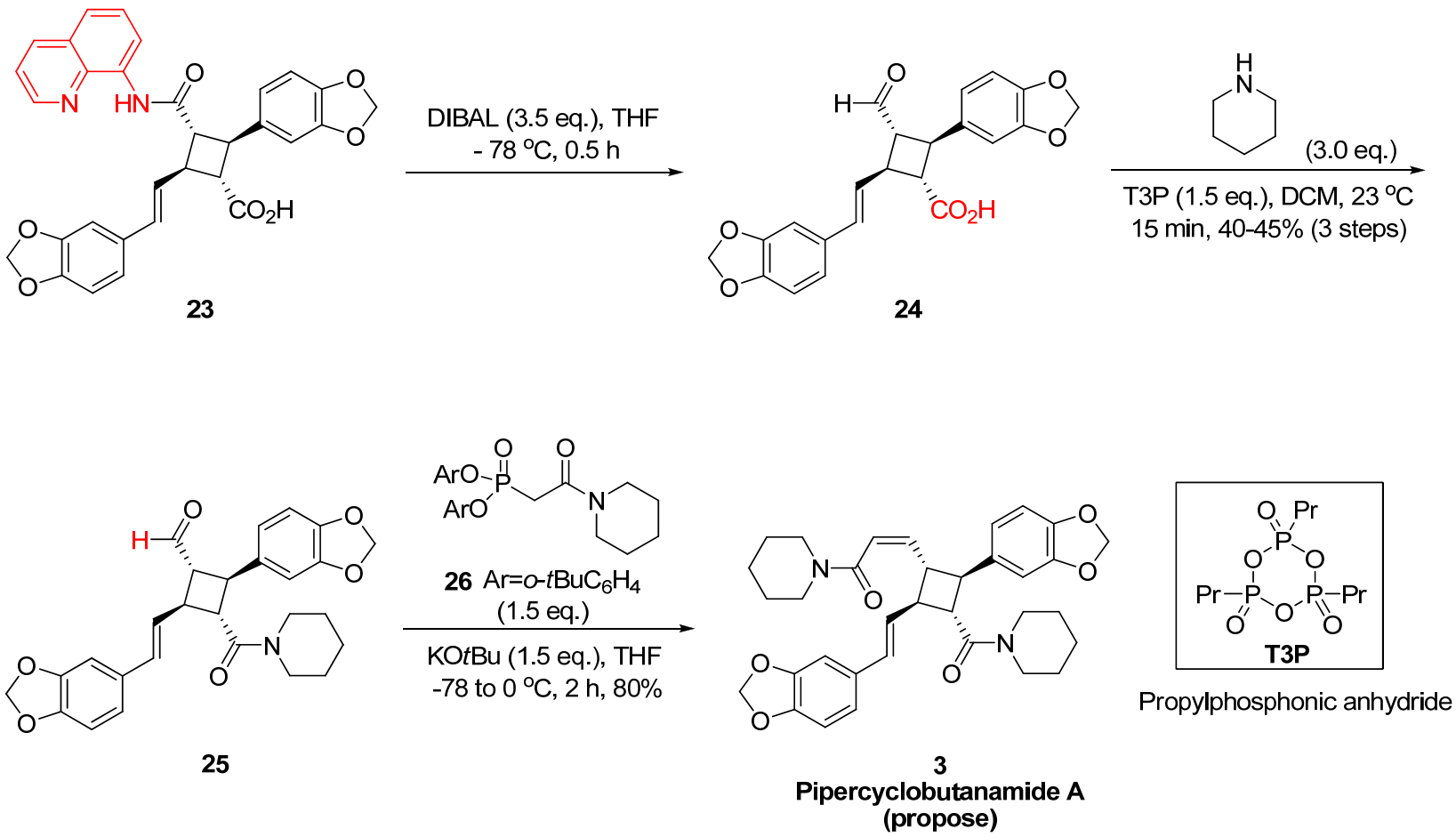


17 **18**

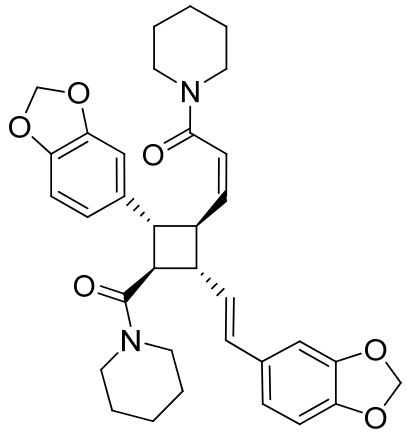


20 **21** **22**

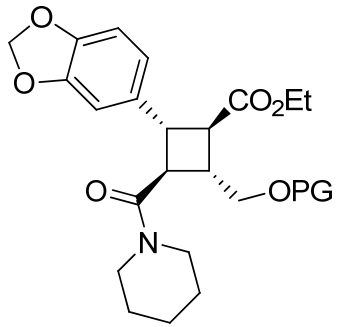
Synthesis of Pipercyclobutanamide A

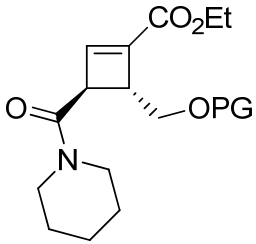


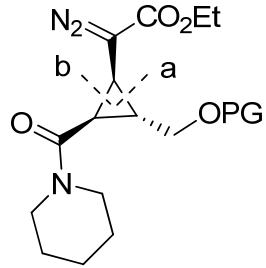
Retrosynthesis by Tang



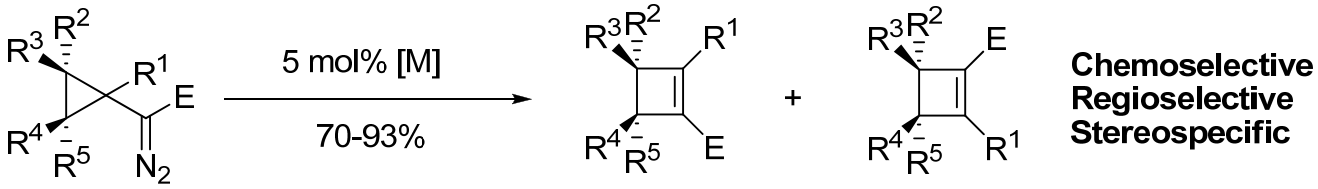
3
pipercyclobutanamide A
(proposed)







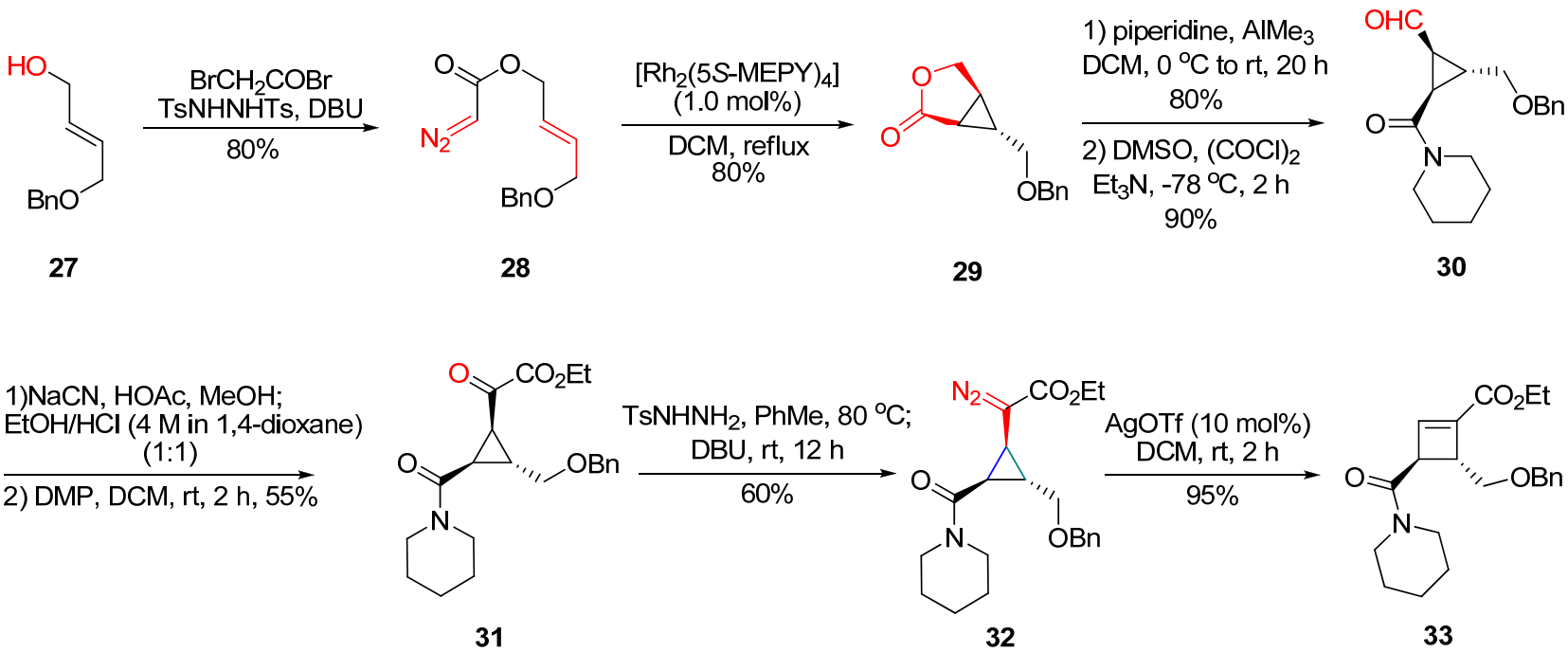
Tang's method

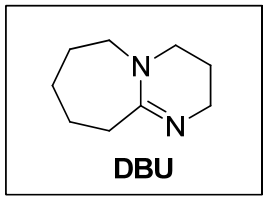


[M] = [Rh], [Cu], or [Ag]

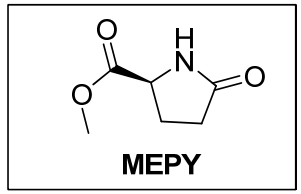
Tang, W. et al *Angew. Chem*. **2008**, *120*, 9065-9068
Angew. Chem. Int. Ed. **2008**, *47*, 8933-8936

Synthesis of Pipercyclobutanamide A and Piperchabamide G



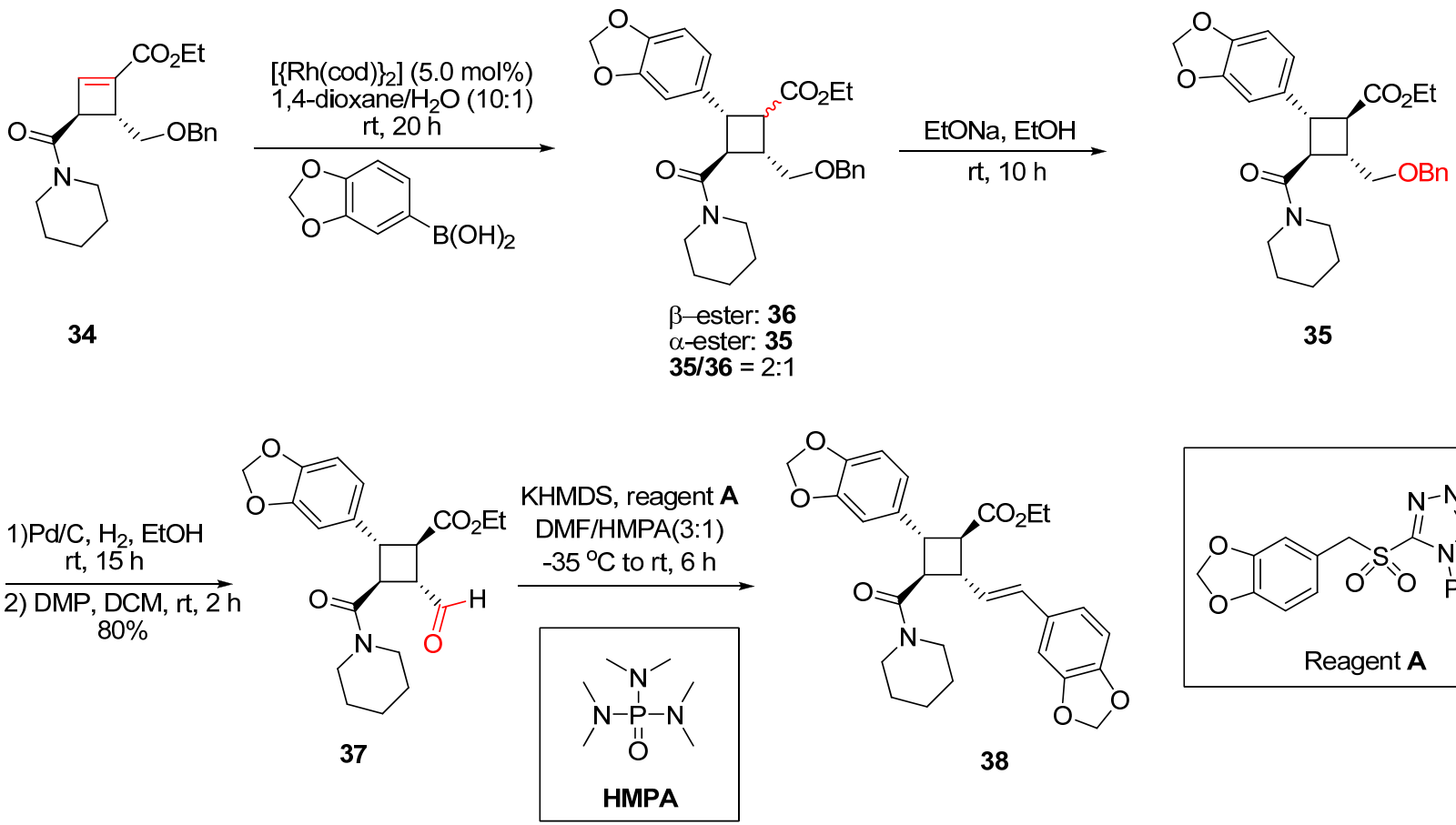


1,8-diazabicyclo[5.4.0]undec-7-ene



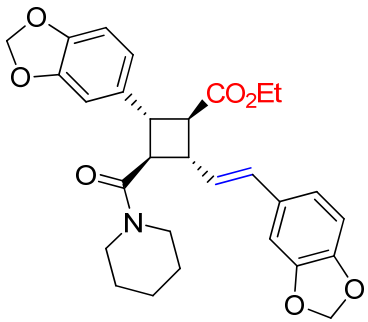
methyl 2-pyrrolidone-5(*S*)-carboxylate

Synthesis of Pipercyclobutanamide A and Piperchabamide G



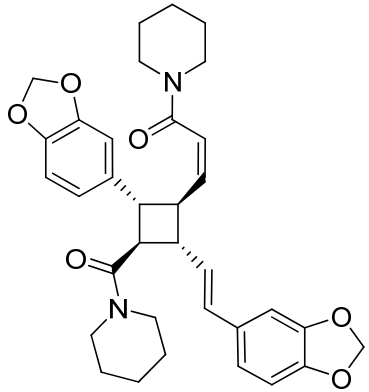
hexamethylphosphoric acid triamide

Synthesis of Pipercyclobutanamide A and Piperchabamide G



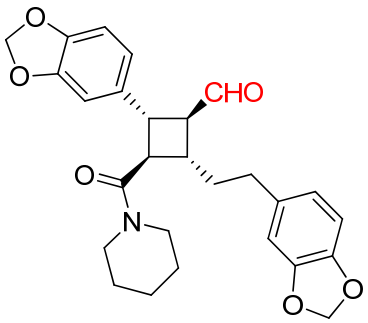
38

1) DIBAL, PhMe, -78 °C, 30 min
2) KHMDS, Reagent **B**, THF
- 78 to 0 °C, 2 h
50%



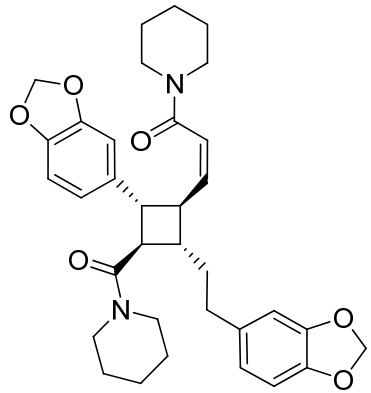
3
pipercyclobutanamide A
(proposed)

1) Pd/C, H_2, MeOH, rt, 15 h
2) DIBAL, PhMe, -78 °C, 30 min
61%

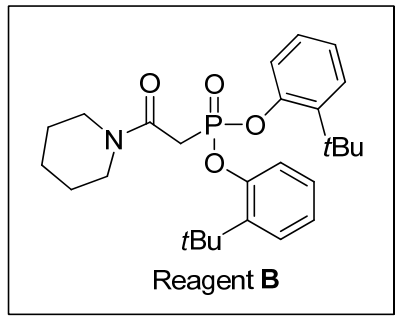


39

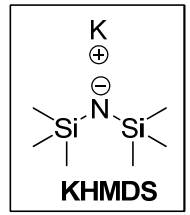
KHMDS, Reagent **B**, THF
-78 °C to 0 °C, 2 h
62%



4
piperchabamide G
(proposed)



Reagent **B**



KHMDS

potassium bis(trimethylsilyl)amide

Conclusion

Baran (2011):

Piperarborenine B was synthesized in 7 steps, 7% overall yield;
Piperarborenine D (proposed) was synthesized in 6 steps, 12% overall yield;
The first example of catalytic transition metal mediated C-H activation of cyclobutane ring;
Divergent epimerization and sequential Sp3 arylation strategy were employed;
Synthesis of desired cyclobutane SM in a stereocontrolled fashion.

Baran (2012):

Pipercyclobutanamide A (proposed) was synthesizd in 7 steps, 5 % overall yield;
The sequence features mostly skeleton-forming transformations, protecting-group-free, has only one concession step (DIBAL reduction) leading to an ideality of 85 %;
The first example of C-H olefination on an unactivated cyclobutane ring ;
Stereocontrolled access to highly strained all-cis cyclobutanes;
Direct conversion of aminoquinoline amides directly to aldehydes;
The use of a carboxylate anion as an innate protecting group in an amide reduction.

Tang (2012):

Pipercyclobutanamide A (proposed) and **Piperchabamide G** (proposed) was synthesized in 15 steps, 4% overall yield and 16 steps, 3% overall yield;
Ring expansion of a cyclopropylsilver(I) carbene derived from the diazocompound occurred regioselectively and stereospecifically to afford the cyclobutenoate;
A rhodium(I)-catalyzed conjugate addition of aryl boronic acid to cyclobutenoate;
Stereoselective synthesis of the trans and cis alkenes in the proposed structure of **pipercyclobutanamide A**.

Dimeric, cyclobutane-containing natural products comprise a small yet diverse family with a variety of biological activities. Although no "[2+2]-ase" has been identified, it is generally presumed that such compounds originate from the direct coupling of the parent monomeric olefins in Nature. From the vantage point of synthetic strategy, cyclobutanes derived from such a heterodimerization are quite difficult to prepare in a controlled fashion. For example, dictazole A and the piperarborenines are pseudosymmetrical cyclobutane natural products that are only differentiated by remote substituents. While a direct [2+2] photocycloaddition is an appealing route for coupling two similar yet distinct olefins, this strategy is problematic for several reasons, including homodimerization, orientation (head-to-head versus head-to-tail), and E/Z isomerization, leading to a variety of possible structural and stereochemical outcomes. While crystal engineering and solid-state photochemistry techniques have provided stereodefined access to some cyclobutane classes, examples of direct heterodimerization of isolated olefins to form cyclobutanes are rare and are generally limited in scope. In this communication, the first catalytic, transition metal-mediated C-H functionalization of cyclobutanes is reported as an alternative to [2+2] cycloaddition for the preparation of pseudosymmetrical cyclobutane structures. It is further shown for the first time that sp3 C-H arylation reactions can be conducted sequentially to access a set of stereoisomeric natural products in a practical and divergent fashion.

The short routes (7 steps, 7% overall yield; 6 steps, 12% overall) demonstrate the power of guided C-H functionalization logic to enable a fundamentally new approach to cyclobutane natural product synthesis. Notable elements of the synthesis include the following: (1) a one-step, stereocontrolled preparation of 8 from methyl coumalate; (2) the first example of catalytic transition metal-mediated C-H activation on a cyclobutane ring; (3) the first example of sequential sp^3 C-H arylation reactions performed in natural product synthesis; (4) divergent epimerization of 10 to access both proposed piperarborenine stereoisomers.

Thanks!