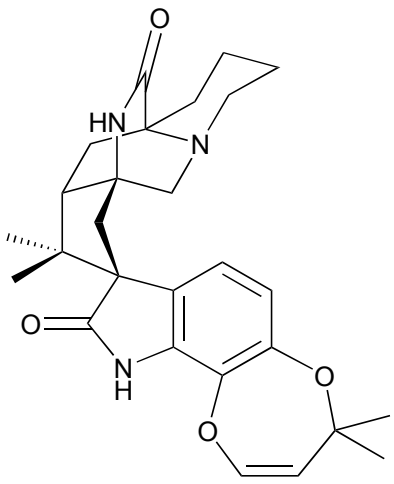
Keita Nagawa (B4)
2008. 01. 16

Total Synthesis of (±)-Marcfortine B

π-Allylpalladium for the assembly of complex cyclic structure



Marcfortine B (**1**)

Isolation: *Penicillium roqueforti*
Structural Elucidation:
J. Polonsky et. al. *J. Chem. Soc., Chem. Commun.* **1980**, 601.
Bioactivity: Potent anthelmintic activity
Total Synthesis: B. M. Trost et. al. *J. Am. Chem. Soc.* **2007**, 3086.

Total synthesis of related alkaloids

Paraherquamide A, B	R. M. Williams et al. *J. Am. Chem. Soc.* **2003**, *125*, 12172. *J. Am. Chem. Soc.* **1996**, *118*, 557.
Stephacidine A, B	P. S. Baran et al. *J. Am. Chem. Soc.* **2006**, *128*, 8678.
Marcfortine C	R. M. Williams et al. *Tetrahedron* **2007**, *63*, 6124

Cotents

1. Strategy of Total Synthesis
2. π-Allylpalladium-Mediated Cycloaddition Reaction
2-1. General Methodology - [3 + 2n] Cycloaddition
2-2. Possible Mechanism
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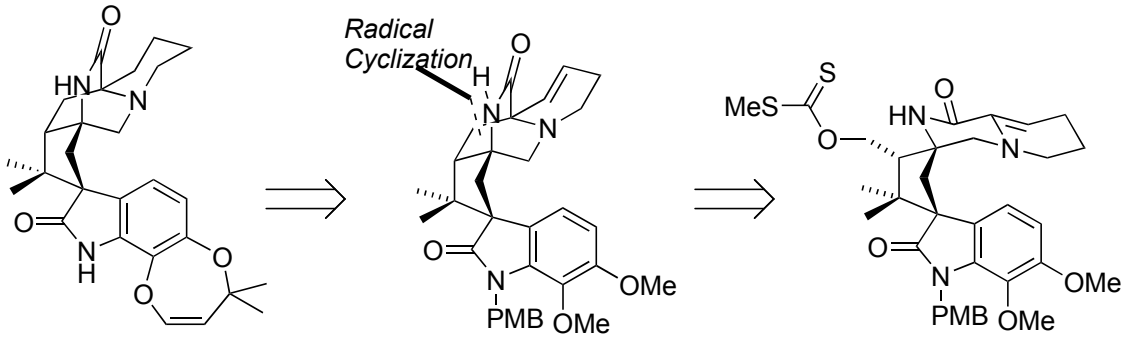
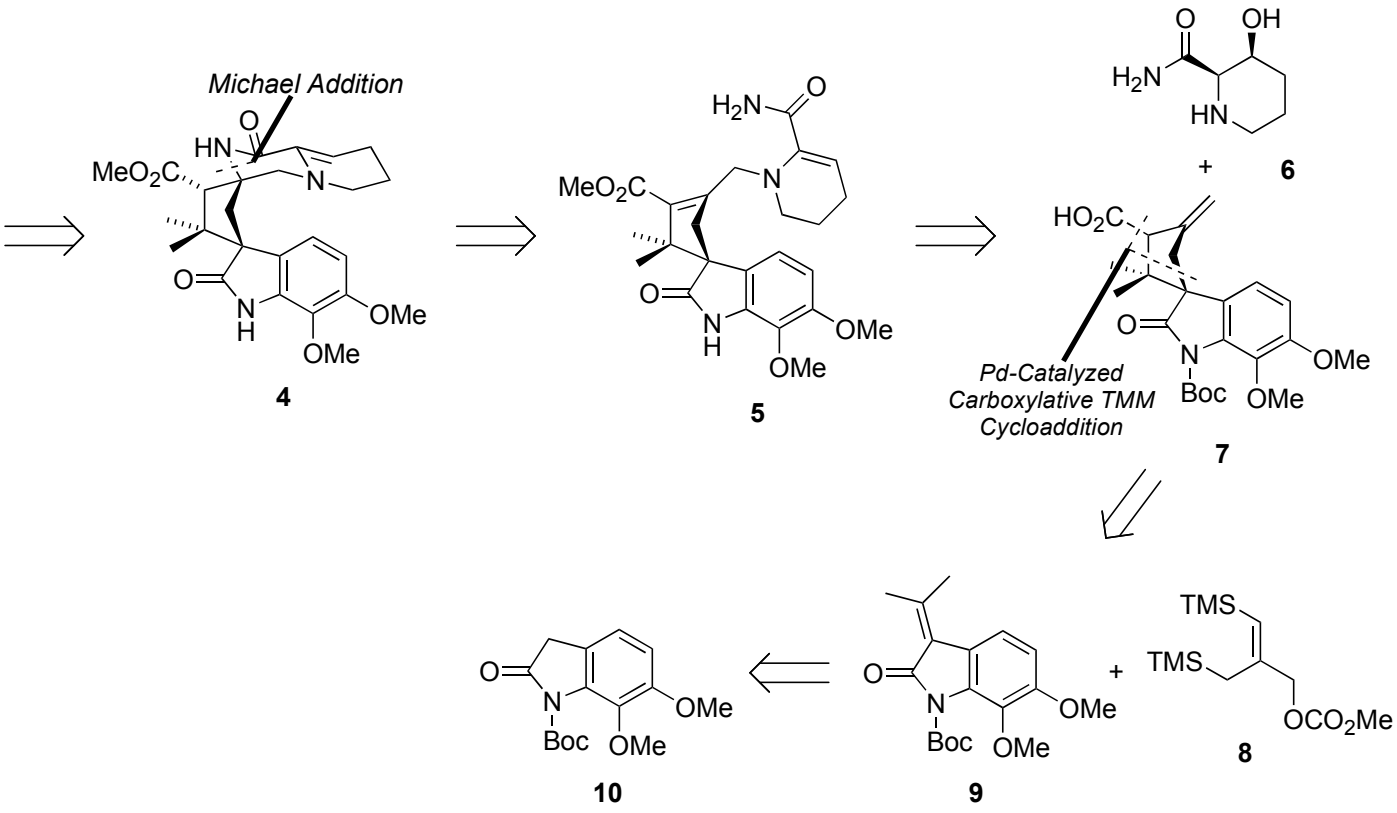
2-4. Recent Development of π-Allylpalladium-Mediated Cycloaddition Reaction
2-5. Pd-Catalyzed Carboxylative [3 + 2] Trimethylenemethane Cycloaddition
3. Total Synthesis of (±)-Marcfortine B
4. Appendix (Total Synthesis of (±)-Marcfortine C)

1. Strategy of Total Synthesis



Marcfortine B (**1**) **2** **3**

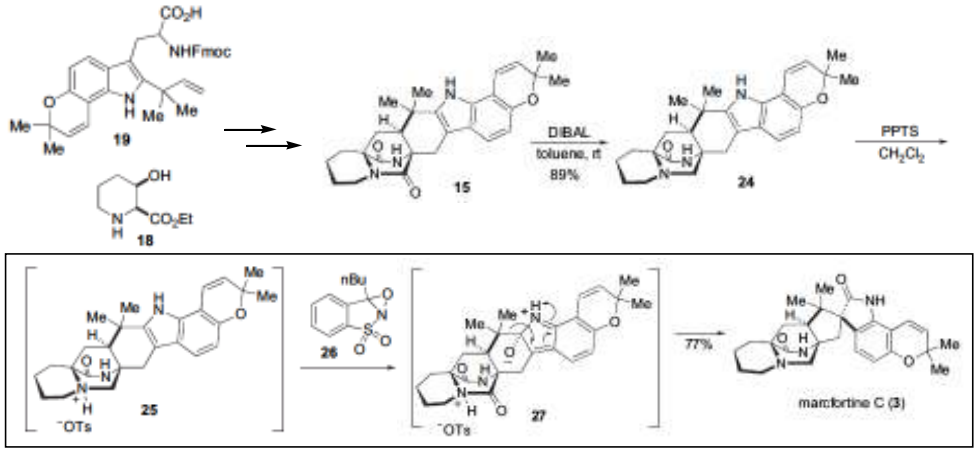


Advantages of Pd-catalyzed carboxylative [3 + 2] TMM cycloaddition

Compared to other *spiro*-oxindole forming reactions
- Oxidative rearrangement (*Figure 1.*), Intramolecular Heck-rxn., etc.

- Construction of a heavily substituted spirocyclic cyclopentane ring at the early stage from simple compounds
  - Short and efficient synthetic route
  - Easy to establish the remaining stereogenic center by using the asymmetry of spirocycle
- Introduction of the requisite carboxylic acid functionality at the same time

Figure 1. Stereoselective oxidation/pinacol rearrangement for another method to construct *spiro*-oxindole moiety (Total synthesis of Marcfortine C)

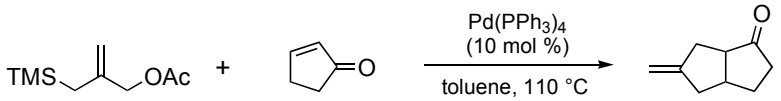


R. M. Williams et al. *Tetrahedron* **2007**, *63*, 6124
(cf. Appendix)

2. π-Allylpalladium-Mediated Cycloaddition Reaction

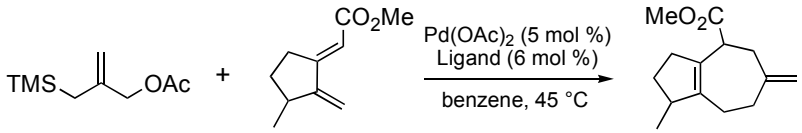
2-1. General Methodology - [3 + 2n] Cycloaddition

[3 + 2] cycloaddition (n = 1)



B. M. Trost et al. *J. Am. Chem. Soc.* **1983**, *105*, 2315.
B. M. Trost et al. *J. Am. Chem. Soc.* **1985**, *107*, 721.

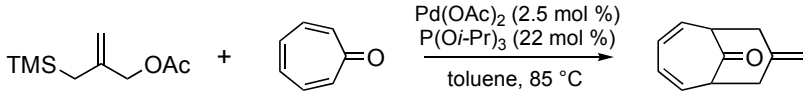
[3 + 4] cycloaddition (n = 2)



B. M. Trost et al. *J. Am. Chem. Soc.* **1987**, *109*, 3483.

Ligand = N,N'-dibenzylideneethylenediamine

[3 + 6] cycloaddition (n = 3)

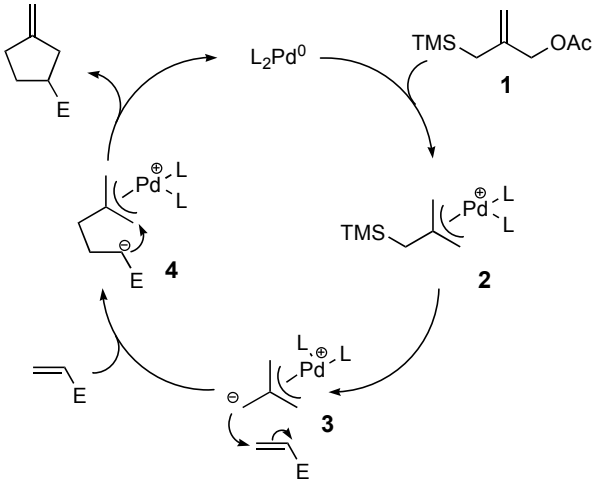


B. M. Trost et al. *J. Am. Chem. Soc.* **1987**, *109*, 615.

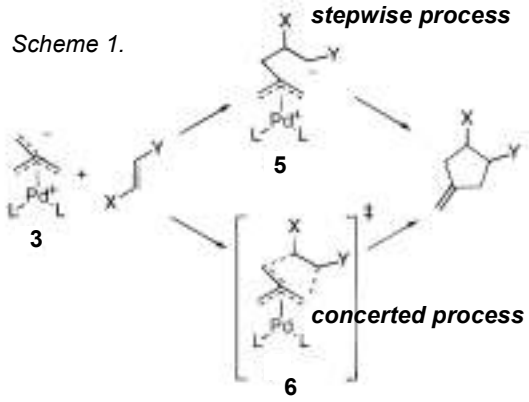
2-2. Possible Mechanism

- Concerted mechanism or stepwise mechanism ? (*Scheme 1.*)

Figure 1. Proposed mechanism (for stepwise process)



Scheme 1.



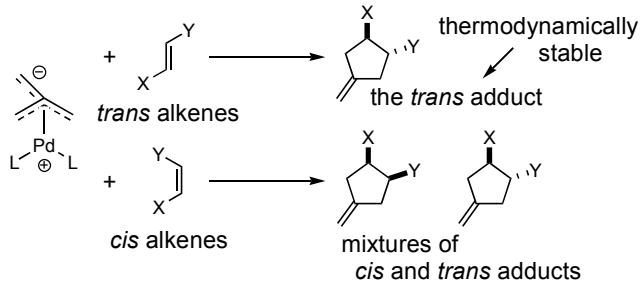
Concerted Mechanism

- Some reactions do exhibit near or complete stereospecificity.
- For certain substrates, several evidences were shown that support for concerted mechanism.
  (D. A. Singleton et al. *J. Am. Chem. Soc.* **1999**, *121*, 9313.)

For now, there is no explanation that can definitively say which process is the most plausible.
(It depends on reaction type and substrates.)

Stepwise Mechanism

- Alkene activation by electron-withdrawing group is necessary.
- No stereospecificity is observed with some substrates.



Diastereomeric ratio from *cis* alkene and *trans* alkene is not completely same.

⇩

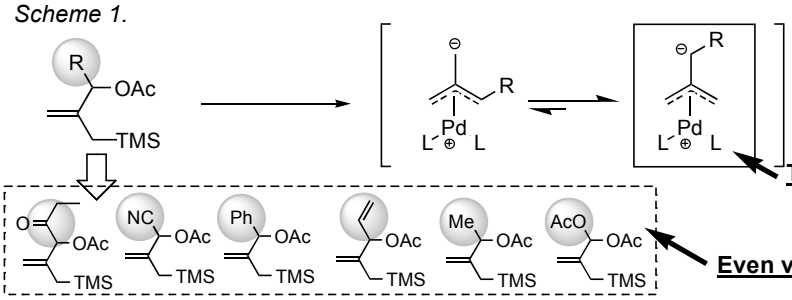
Even if stepwise mechanism is operative, life time of **5** (in *Scheme 1.*) is not so long for the bond rotation.

2-3. Substituents Effect of Trimethylenemethanes

- Various kinds of substituents are possible, and **all reactions afford the same regioselectivity**.

Scheme 1.

B. M. Trost et al. *J. Am. Chem. Soc.* **1985**, *107*, 721.



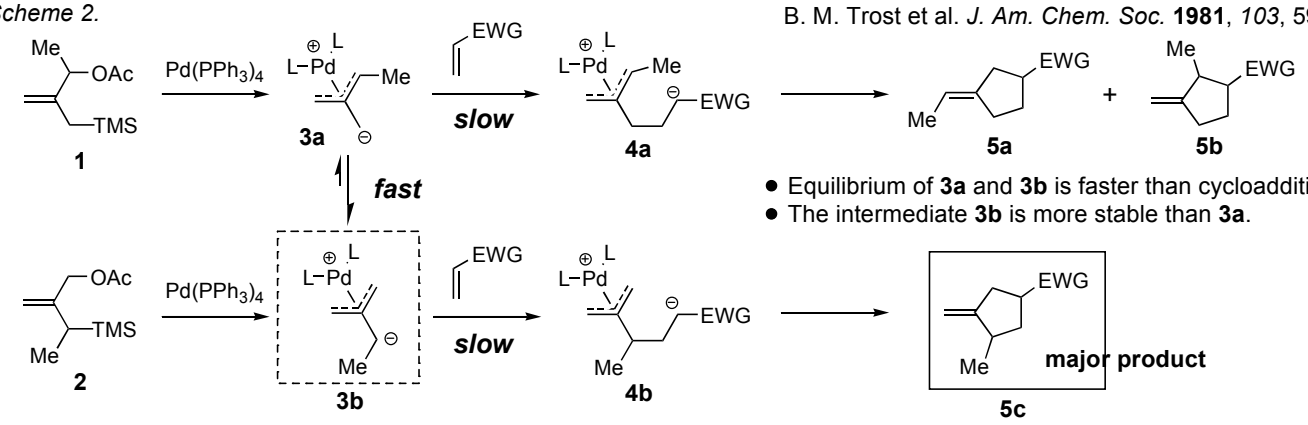
- indicated by the MO calculations (B. M. Trost et al. *JACS* **1981**, *103*, 5974.)

Even vinyl, methyl and acetyl substituents gave same regioselectivity !

- For methyl substituent, two different precursors (**1** and **2**) produce the most stable TMM complex (**3b**) selectively.

Scheme 2.

B. M. Trost et al. *J. Am. Chem. Soc.* **1981**, *103*, 5972.

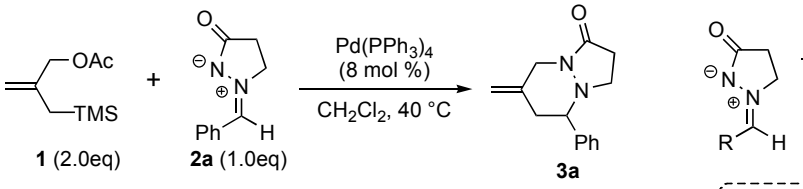


- Equilibrium of **3a** and **3b** is faster than cycloaddition.
- The intermediate **3b** is more stable than **3a**.

2-4. Recent Development of π-Allylpalladium-Mediated Cycloaddition Reaction

(1) Pd-Catalyzed [3 + 3] Cycloaddition of Trimethylenemethane with Azomethine Imines

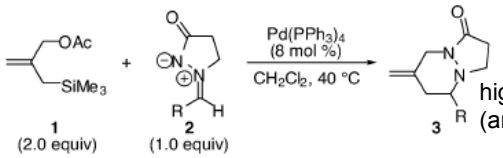
T. Hayashi et al. *J. Am. Chem. Soc.* **2006**, *128*, 6330.



1-Alkylidene-3-oxopyrazolidin-1-ium-2-ides
- Isolable and stable azomethine imines
- Derived from pyrazolidin-3-ones and aldehydes
- 1,3-Dipoles in the context of [3 + 3] cycloadditions

Scope of azomethine imine

Table 2.

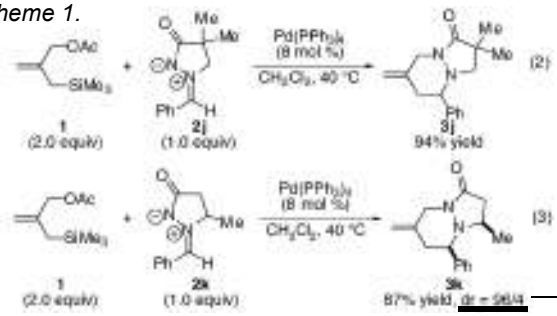


entry	R	product	yield (%)[a]
1	Ph (**2a**)	**3a**	81
2	4-MeC$_6$H$_4$ (**2b**)	**3b**	74
3	4-CF$_3$C$_6$H$_4$ (**2c**)	**3c**	92
4	3-ClC$_6$H$_4$ (**2d**)	**3d**	90
5	2-FC$_6$H$_4$ (**2e**)	**3e**	88
6	2-MeC$_6$H$_4$ (**2f**)	**3f**	70
7	3-pyridyl (**2g**)	**3g**	75
8	1-cyclohexenyl (**2h**)	**3h**	71
9	*t*-Bu (**2i**)	**3i**	20

high yield (aryl, heteroaryl, alkenyl)

less effective (alkyl)

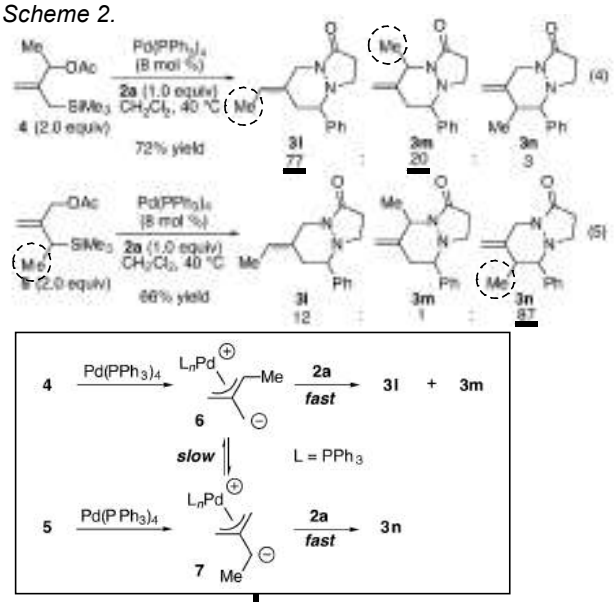
Scheme 1.



→ high diastereoselectivity

The effect of substituents on TMM precursor

Scheme 2.

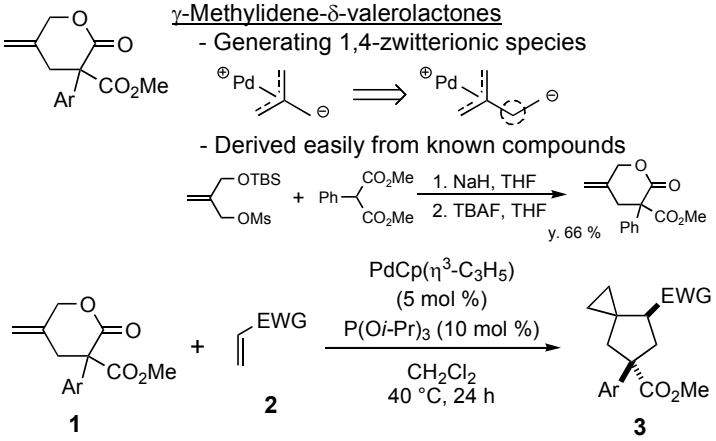


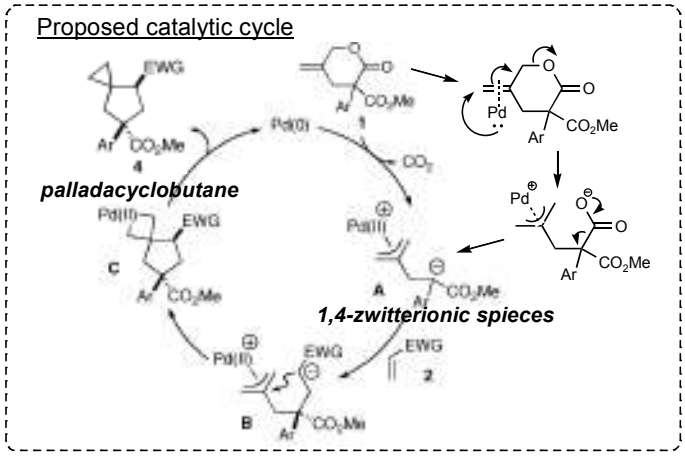
Cycloaddition step is faster than equilibrium between **6** and **7**

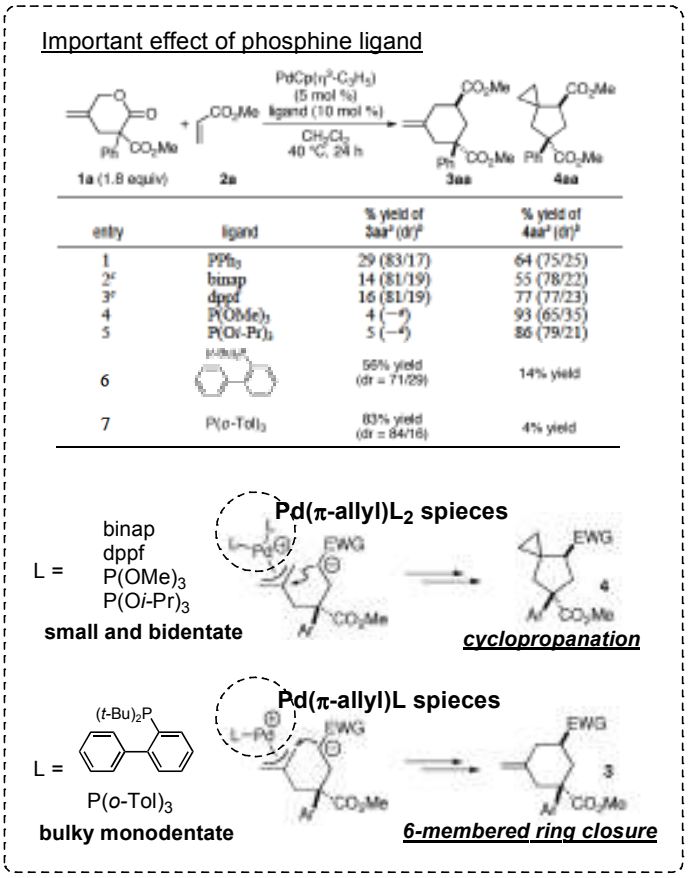
(striking contrast to [3 + 2] cycloaddition Trost reported - cf. 2-3.)

(2) Synthesis of Spiro[2.4]heptanes via π-Allylpalladium Intermediate (Extension of Pd-Catalyzed [4 + 2] Cycloaddition)

T. Hayashi et al. *J. Am. Chem. Soc.* **2007**, *129*, 14866.

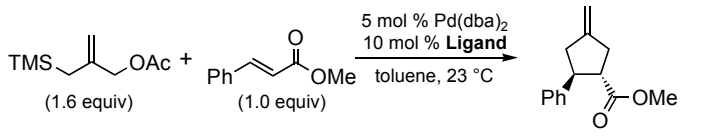


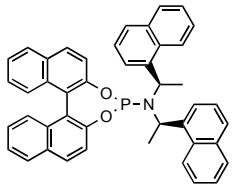




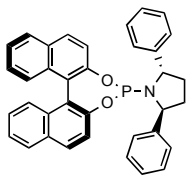
(3) Pd-Catalyzed Asymmetric [3 + 2] Trimethylenemethane Cycloaddition

B. M. Trost et al. *J. Am. Chem. Soc.* **2006**, *128*, 13328



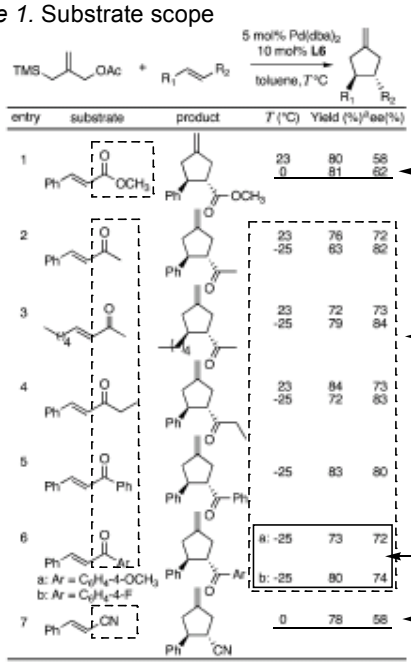


L2-(R,R,R)
y. 78 %
ee. 29 %
L3-(rac,R,R)
y. 77 %
ee. 44 %



L6-(S,S,S)
y. 80 %
ee. 58 %

Table 1. Substrate scope



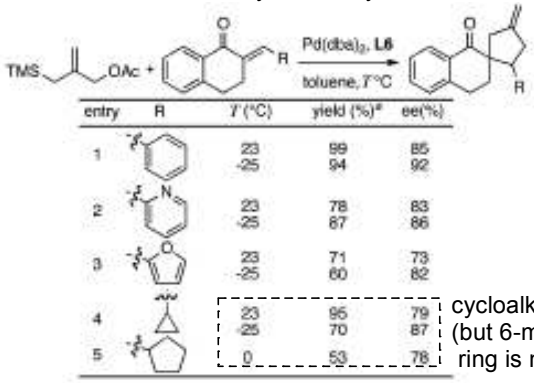
ee. 62 %
(by cooling the rxn.)

ee. 73 - 84 %
at -25 °C

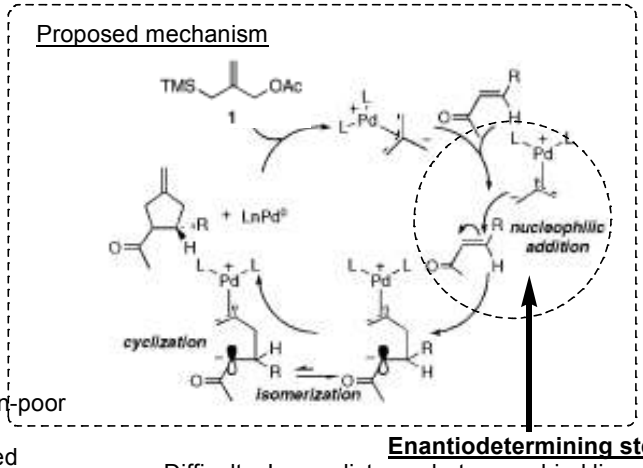
electron-rich or electron-poor
aromatic enones
- ee slightly decreased

modest ee.

Table 2. Reaction with aryl- and alkylidene tetralones

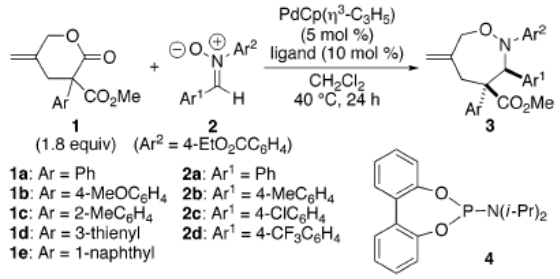


cycloalkyl OK
(but 6-membered
ring is not effective)



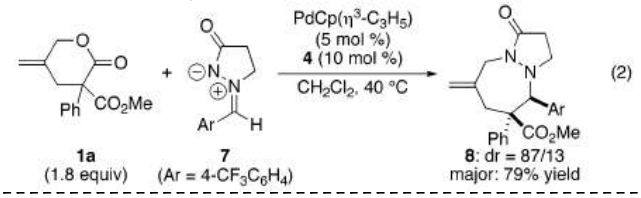
(4) Pd-Catalyzed Asymmetric [4 + 3] Cycloaddition with Nitrones

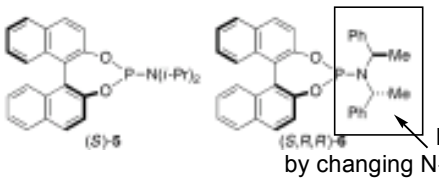
T. Hayashi et al. *J. Am. Chem. Soc.* **2007**, *129*, 12356.



entry	1	2	ligand	product	yield (%)[a]	dr[b]
1	1a	2a	PPh_3	3aa	95	72/28
2	1a	2a	$P(Oi\text{-}Pr)_3$	3aa	97	78/22
3	1a	2a	4	3aa	99	90/10
4	1b	2a	4	3ba	95	93/7
5	1c	2a	4	3ca	62	87/13
6	1d	2a	4	3da	92	91/9
7	1e	2a	4	3ea	96	94/6
8	1e	2b	4	3eb	77	92/8
9	1e	2c	4	3ec	98	93/7
10	1e	2d	4	3ed	98	94/6

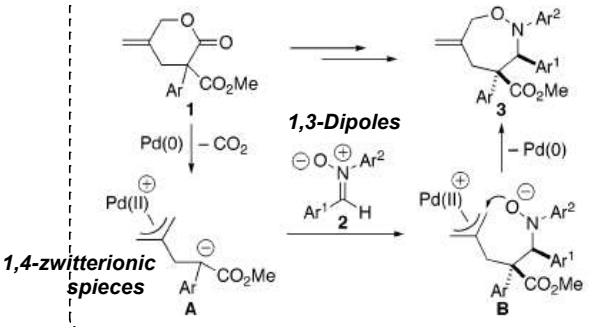
Another possibility - azomethine imine





entry	1	2	ligand	product	yield (%)[a]	dr[b]	ee (%)[c]
1	1a	2d	(S)-5	3ad	98	85/15	71
2	1a	2d	(S,R,R)-6	3ad	98	81/19	83
3	1b	2d	(S,R,R)-6	3bd	99	86/14	84
4	1e	2d	(S,R,R)-6	3ed	98	80/20	96
5[d]	1e	2b	(S,R,R)-6	3eb	99	70/30	89[e]
6	1e	2c	(S,R,R)-6	3ec	89	72/28	88[f]

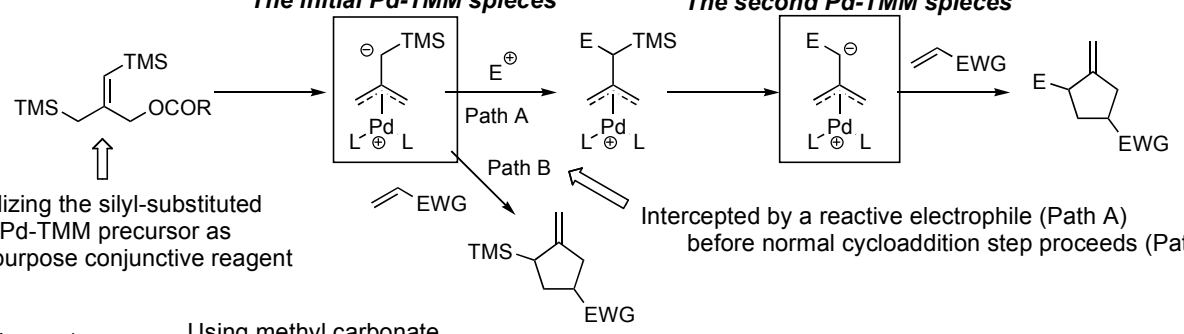
Proposed catalytic cycle



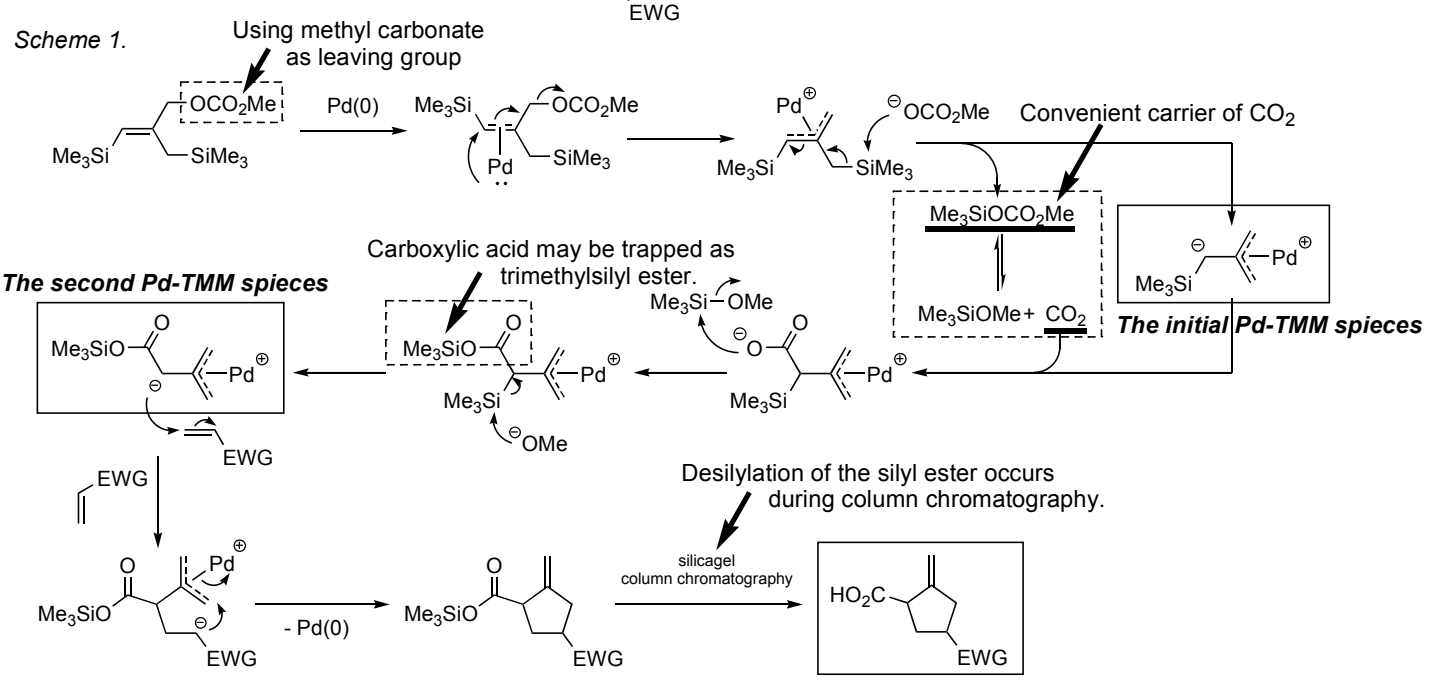
2-5. Pd-Catalyzed Carboxylative Trimethylenemethane [3 + 2] Cycloaddition

B. M. Trost et al. *J. Am. Chem. Soc.* **1986**, *108*, 6051.

Background concept

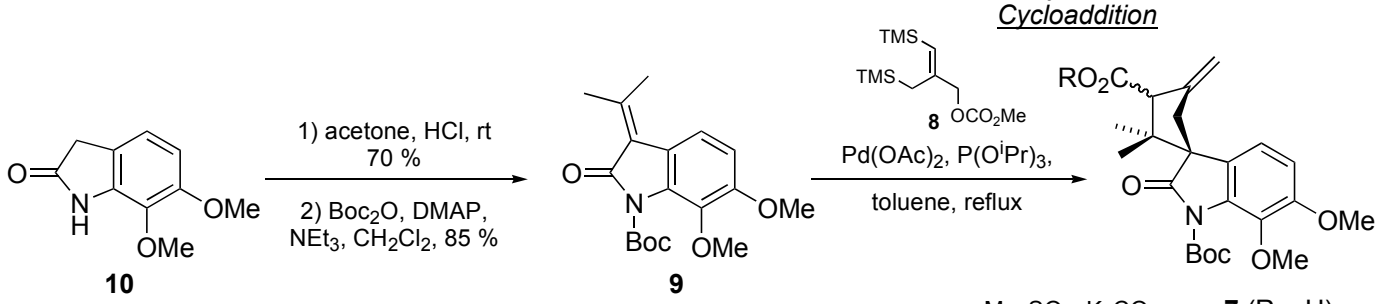


Scheme 1.



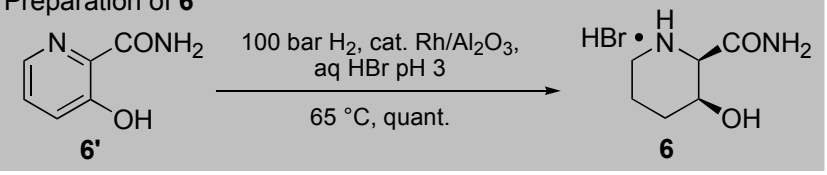
3. Total Synthesis of (±)-Marcfortine B

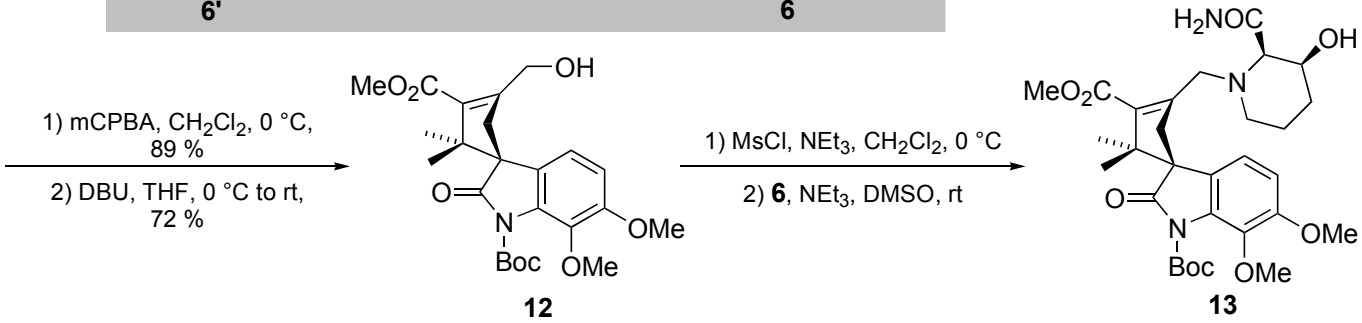
Pd-Catalyzed Carboxylative TMM Cycloaddition

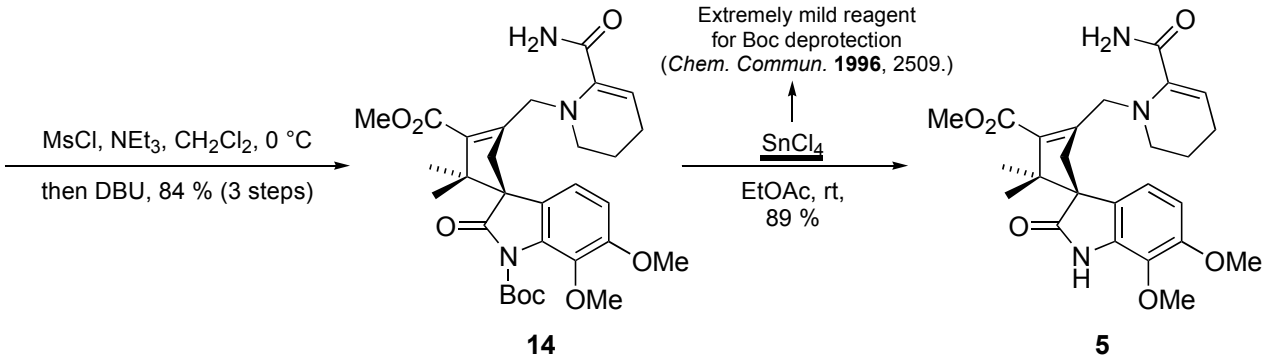


Me$_2$SO$_4$, K$_2$CO$_3$, acetone, reflux, 93 % (2 steps) → **7** (R = H), **11** (R = Me)

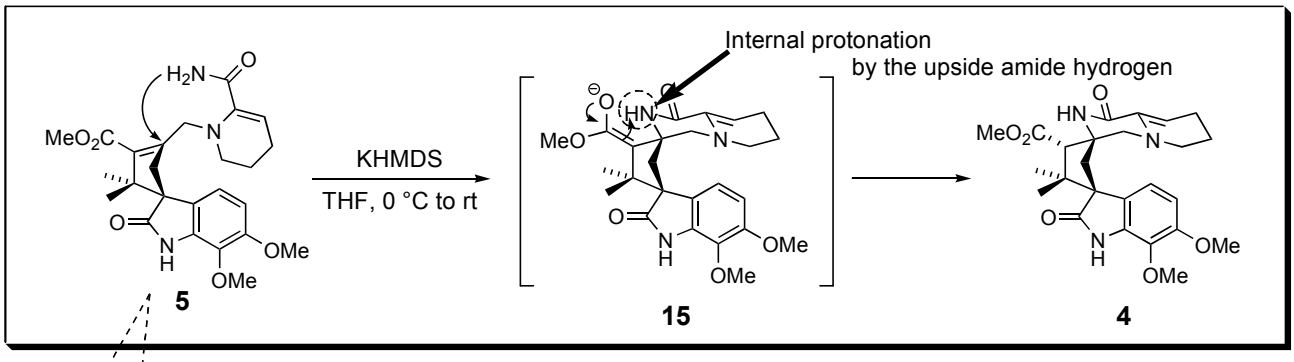
Preparation of **6**

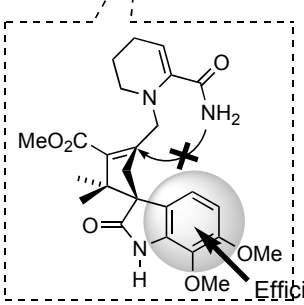






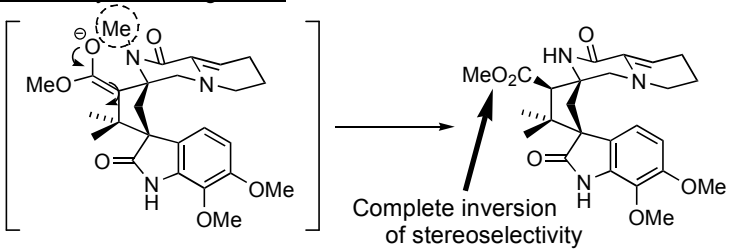
- *Michael Addition*

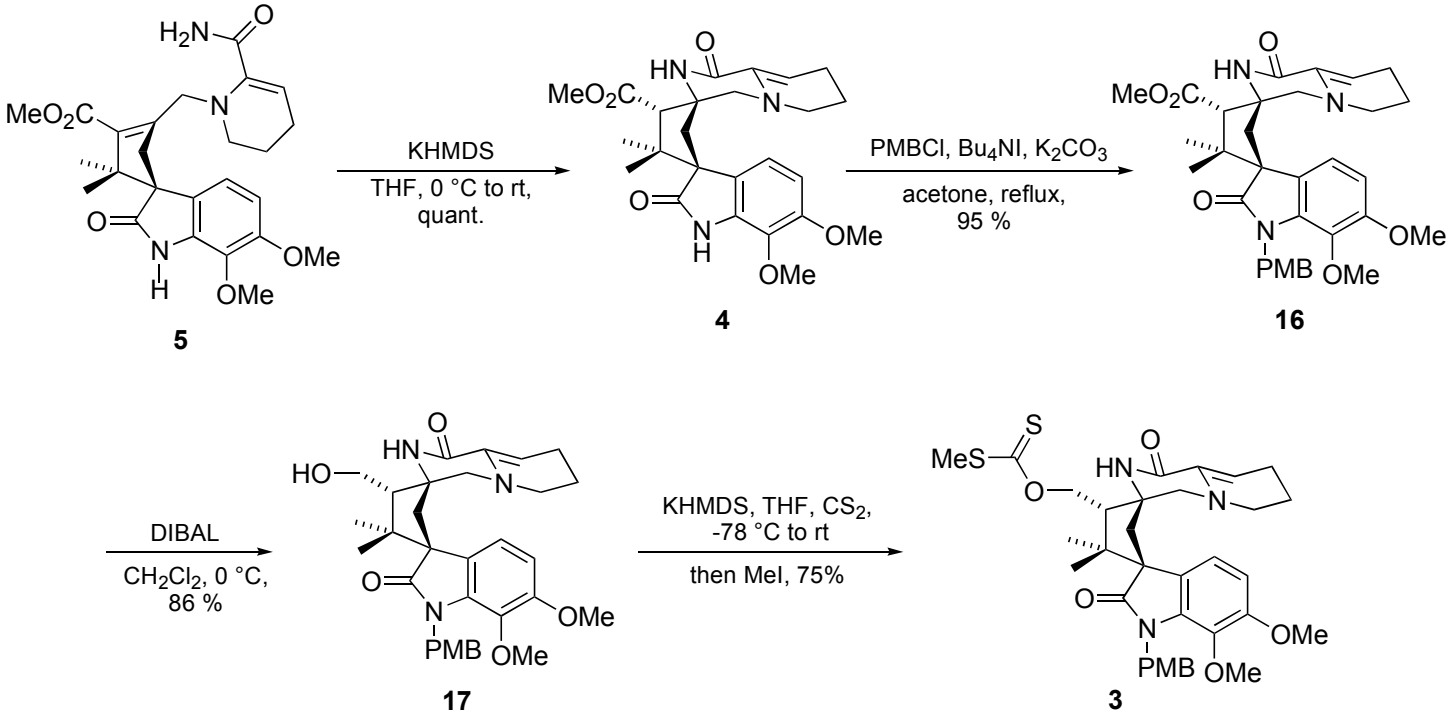




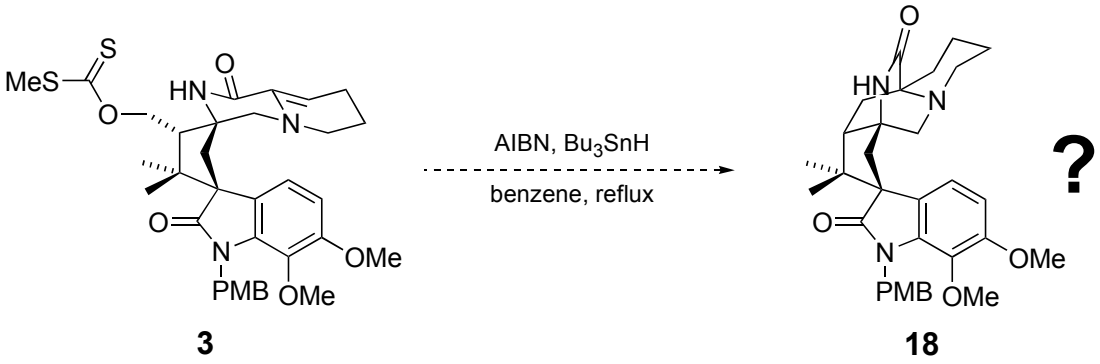
Efficient shielding of the *re*-face of the Michael-acceptor by the aromatic portion of the molecule

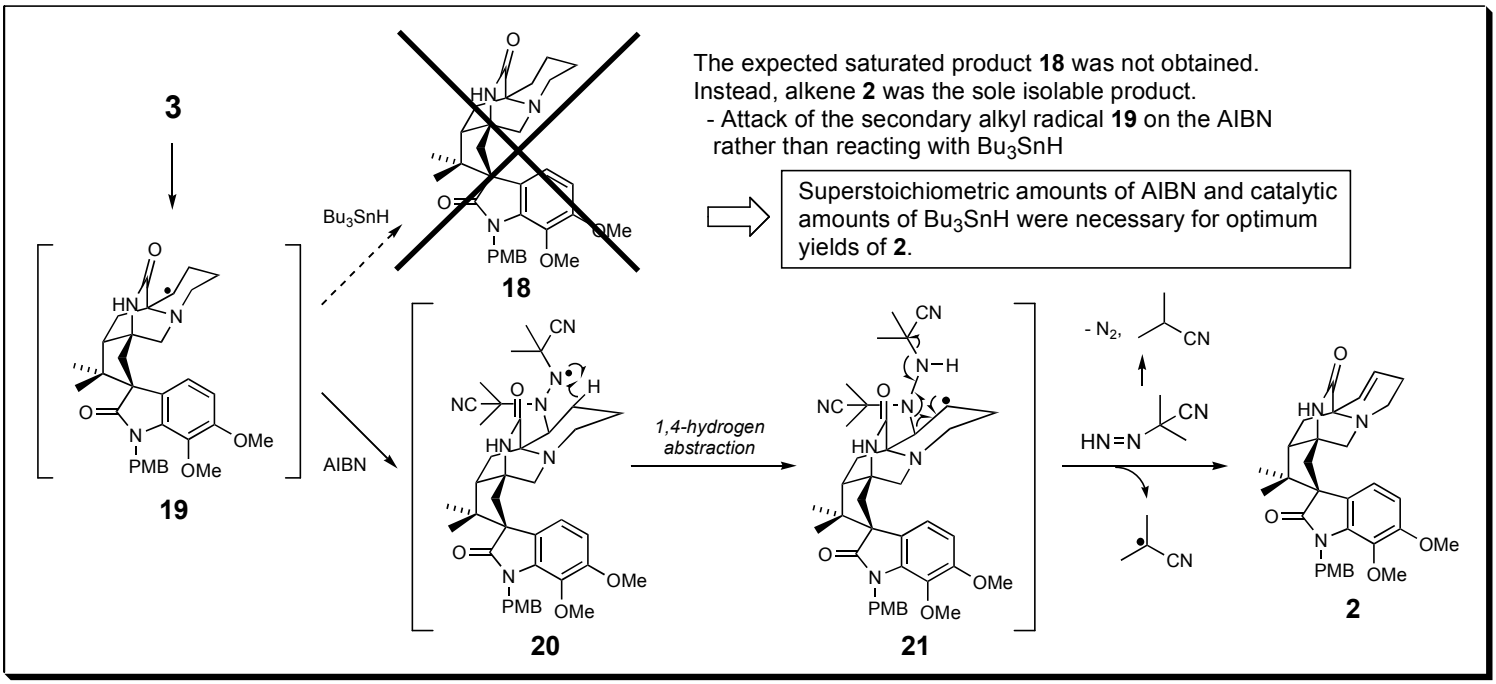
What if N-methylated congener ?

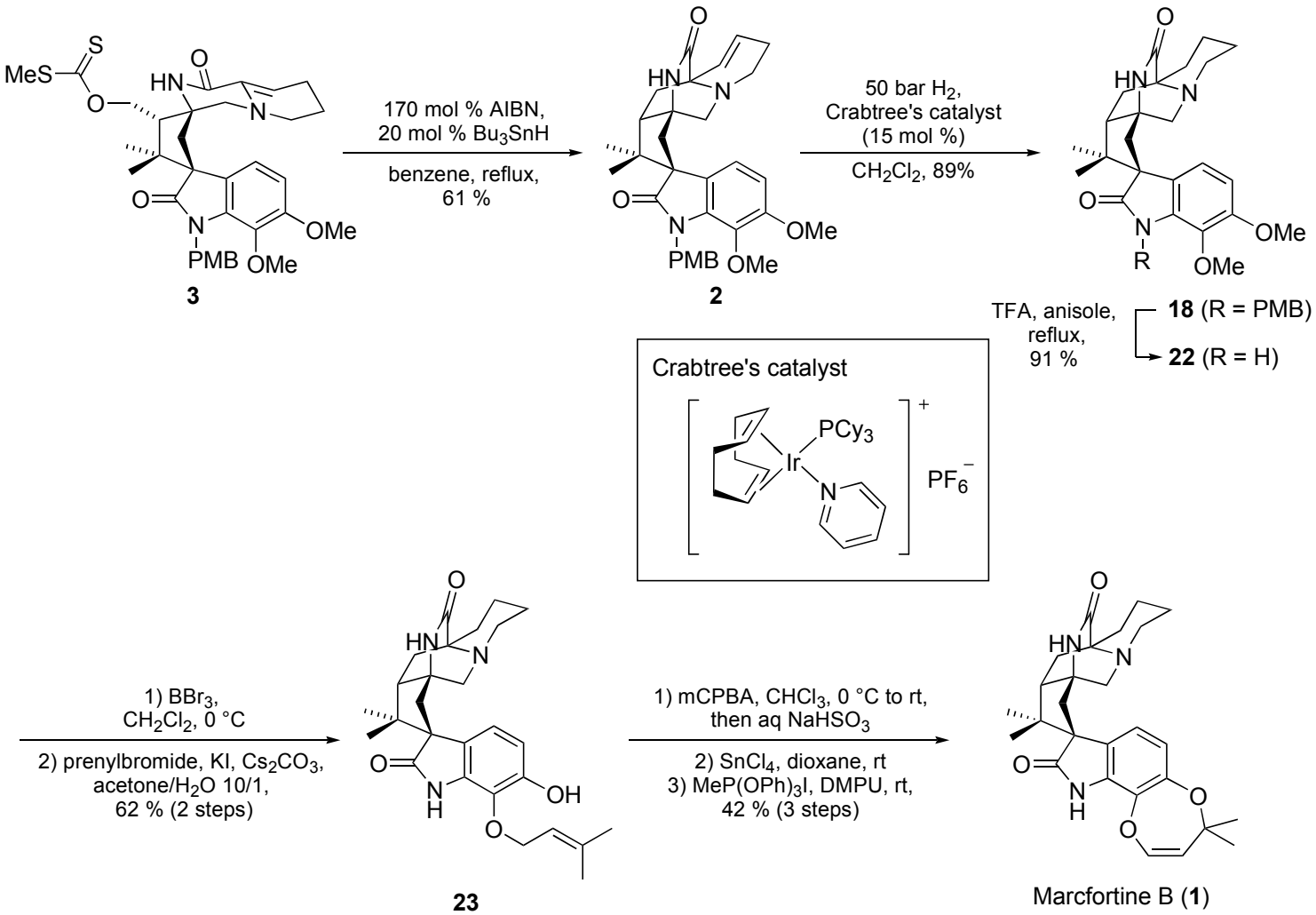




- ***Radical Cyclization***

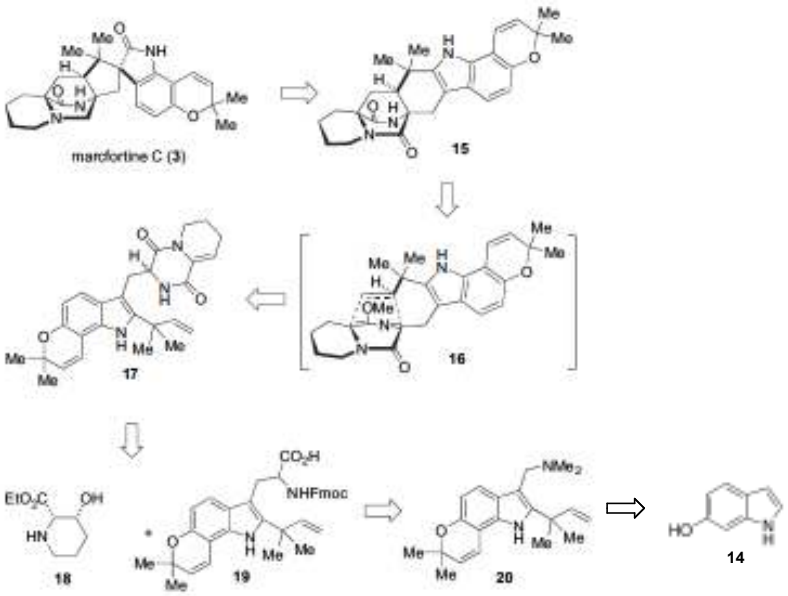





MeS
S
O
HN
O
N
O
N
PMB
OMe
OMe
3
170 mol % AIBN,
20 mol % Bu3SnH
benzene, reflux,
61 %
2
50 bar H2,
Crabtree's catalyst
(15 mol %)
CH2Cl2, 89%
R
18 (R = PMB)
22 (R = H)
TFA, anisole,
reflux,
91 %
Crabtree's catalyst
PCy3
Ir
PF6
1) BBr3,
CH2Cl2, 0 °C
2) prenylbromide, KI, Cs2CO3,
acetone/H2O 10/1,
62 % (2 steps)
OH
23
1) mCPBA, CHCl3, 0 °C to rt,
then aq NaHSO3
2) SnCl4, dioxane, rt
3) MeP(OPh)3I, DMPU, rt,
42 % (3 steps)
Marcfortine B (1)

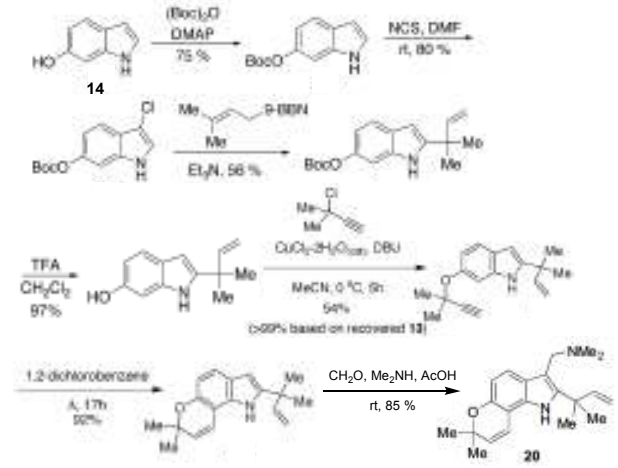
4. Appendix (Total Synthesis of (±)-Marcfortine C)

Retrosynthetic Analysis

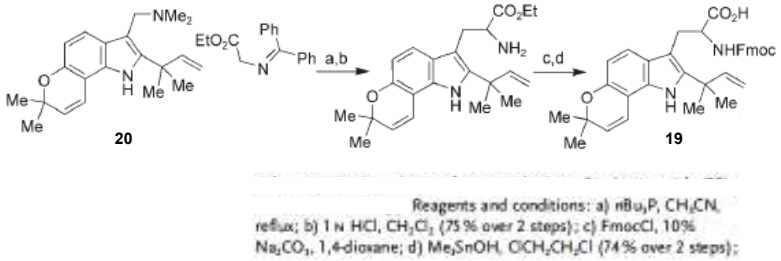


R. M. Williams et al. *Tetrahedron Lett.* **2007**, *63*, 6124.;
R. M. Williams et al. *Angew. Chem., Int. Ed.* **2007**, *46*, 2257.
A. W. Grubbs et al. *Tetrahedron Lett.* **2005**, *46*, 9013.;
R. M. Williams et al. *Tetrahedron Lett.* **2002**, *43*, 2149.;

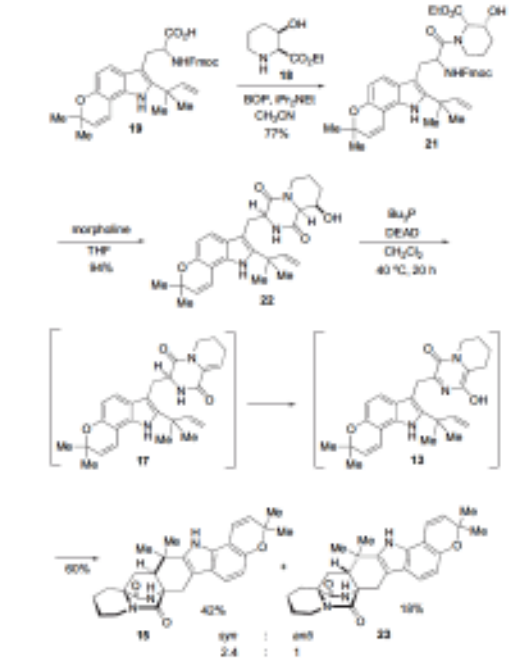
● **14 ➡ 20**



● **20 ➡ 19**



● **19 ➡ 15**



● **15 ➡ Marcfortine C(3)**