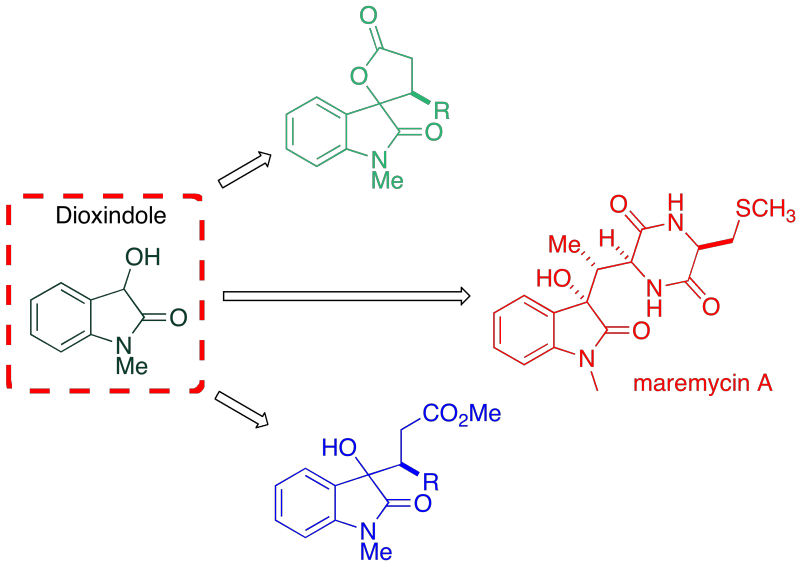
Dioxindole in Asymmetric Catalytic Systems: Routes to Enantioenriched 3-Substituted 3-Hydroxyoxindoles and the Preparation of Maremycin A

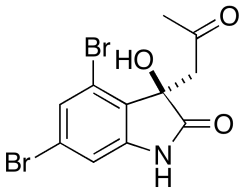


Elisa Farber
Current Literature
01.07.2012

Angew. Chem. Int. Ed. **2011**, *50*, 1-5.
Giulia Bergonzini and Paolo Melchiorre*

3-Substituted 3-Hydroxyoxindole Framework in Biological Active Compounds

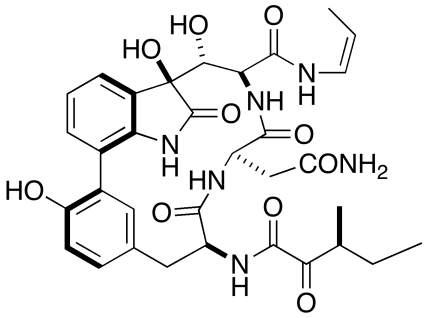
- There are a number of biologically active compounds that have the oxindole framework with a hydroxy-bearing tetrasubstituted stereogenic center at C3



convolutamydine A

- Isolated from marine bryozoan *Amathia convoluta*
- Exhibits potent activity in human promyelocytic leukemia cells.

Jnaneshwar, G. K.; Deshpande, V. H. *J. Chem. Research*, **1999**, 632-633

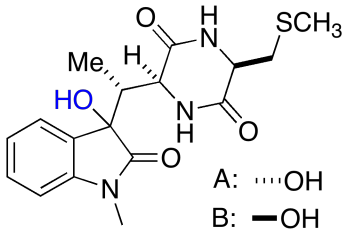


TMC-95A

- Isolated from *Apiospora montagnei Sacc*., from a soil sample
- Anti-tumor activity

Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990-995.

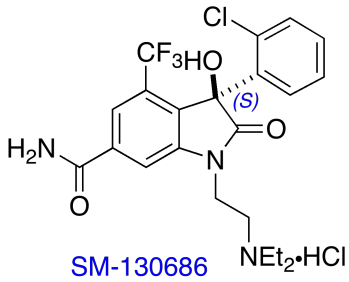
3-Substituted 3-Hydroxyoxindole Framework in Biological Active Compounds



maremycin A and B

- Isolated in 1995 from marine *Streptomyces* strain B 9173
- Both A and B - inactive in antibacterial and antifungal assays
- B: Slightly active human leukemia and Hela human carcinoma

Tang, Y-Q; Sattler, I. Thiericke, R.; Grabley, S.; Feng, X-Z *Eur. J. Org. Chem.* **2001**, 261-267
Balk-Bindseil, E.; Helmke, E.; Weyland, H.; Laatsch, H. *Liebigs Ann.* **1995**, 1291.



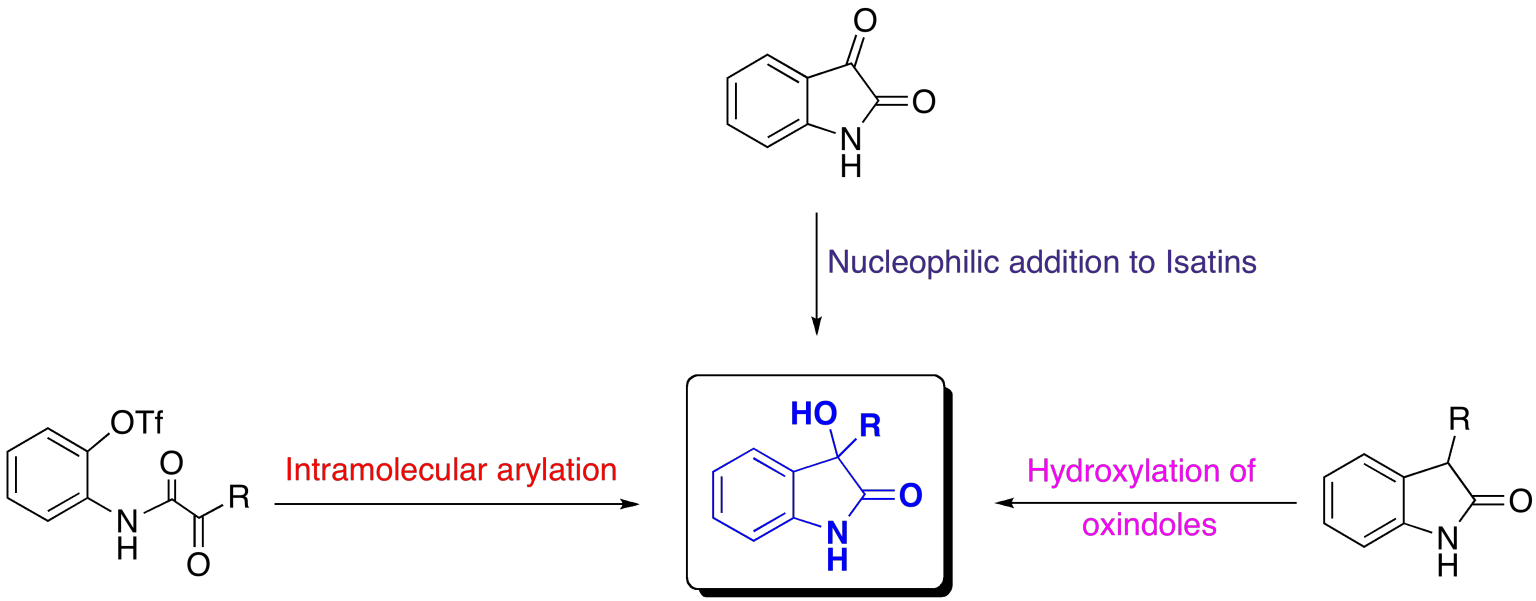
SM-130686

- A synthetic bioactive compound, highly potent growth hormone secretagogue
- The *R*-enantiomer had reduced activity

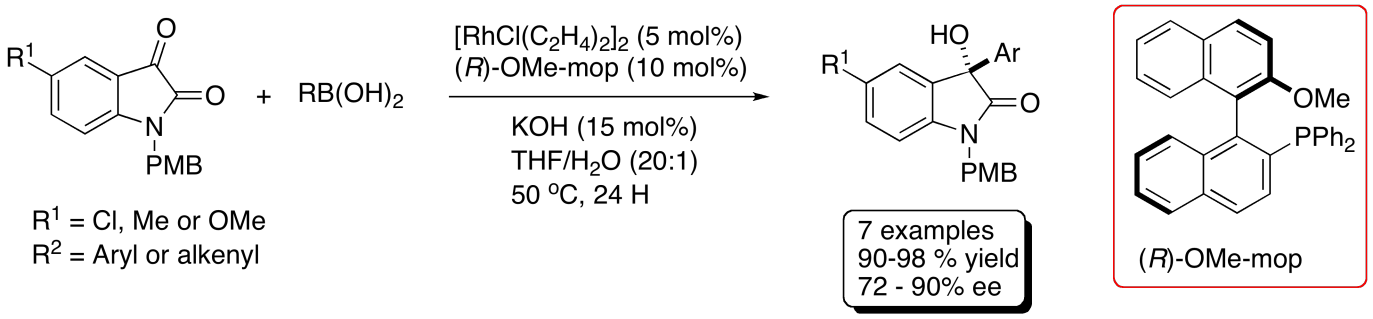
Tokunaga T., Hume W. E., Umezome T., Okazaki K., Ueki Y., Kumagai K., Hourai S., Nagamine J., Seki H., Taiji M., Noguchi H., Nagata R. *J. Med. Chem.* **2001**, 4641.

- SARs showed that stereochemistry at C3 has a considerable influence in the biological activity of these compounds

Previously Reported Strategies



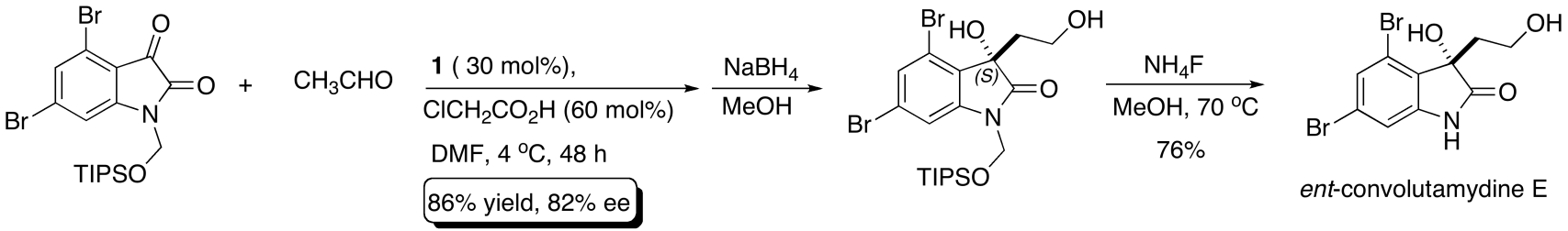
Previously Reported Methods – Addition to Isatin



R^1 = Cl, Me or OMe
R^2 = Aryl or alkenyl

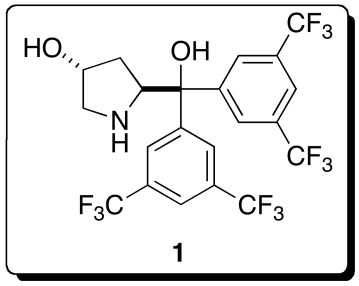
7 examples
90-98 % yield
72 - 90% ee

Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem. Int.* **2006**, *45*, 3353.



86% yield, 82% ee

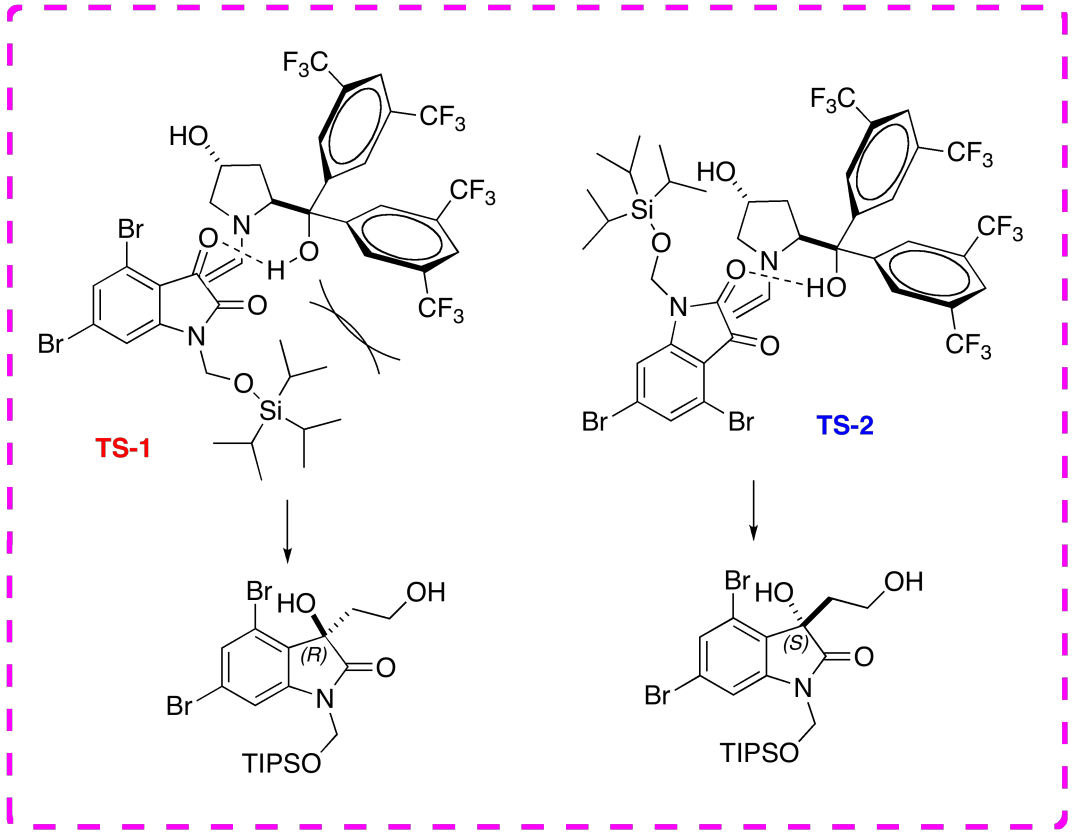
ent-convolutamydine E



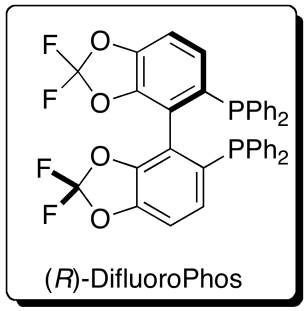
1

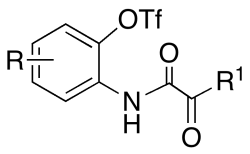
Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854.

Previously Reported Methods – Addition to Isatin



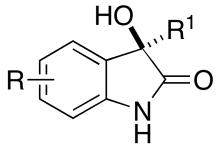
Previously Reported Methods – Intramolecular Arylation





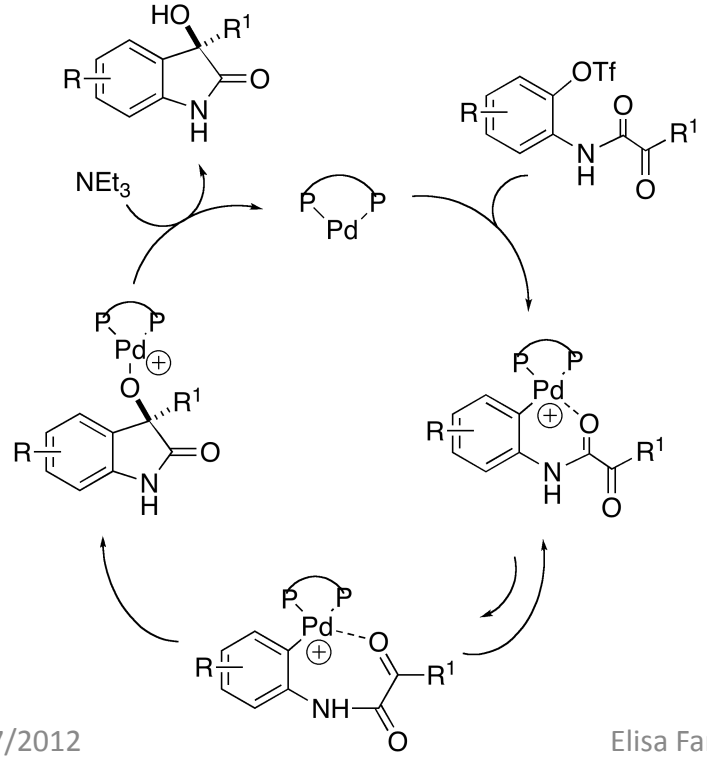
R = H, Me, Cl, OMe
R^1 = alkyl and aryl

$[Pd(CH_3CN)_4(BF_4)_2$ (5 mol%)
(*R*)-DifluoroPhos (6 mol%)
Et_3N (250 mol%)
toluene, 100 °C, 24 h
53-92% yield
82-99% ee

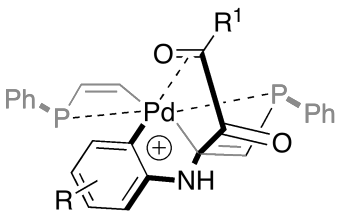


Yin, L.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7620.

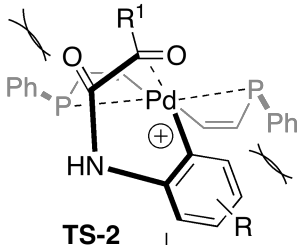
catalytic cycle



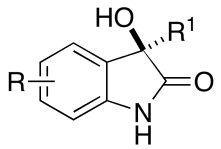
enantio-differentiation

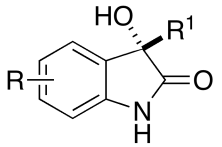


TS 1

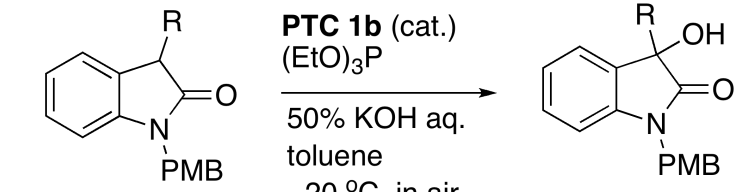


TS-2



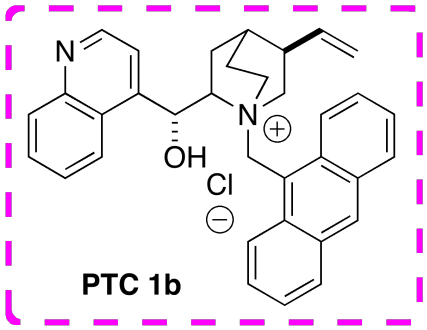


Previously Reported Methods – Hydroxylation

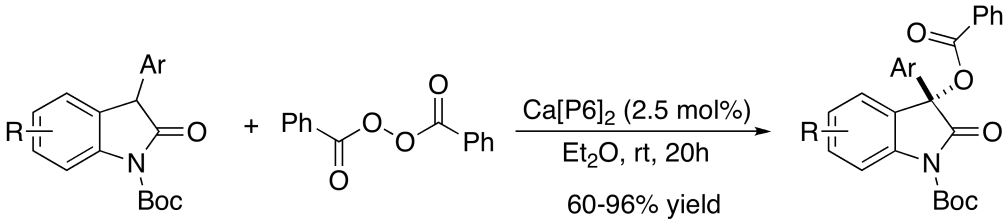


R = allyl, propargyl, alkyl, ester, benzyl

91%-quant.
67-93% ee

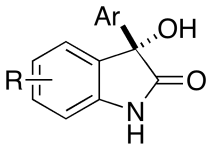


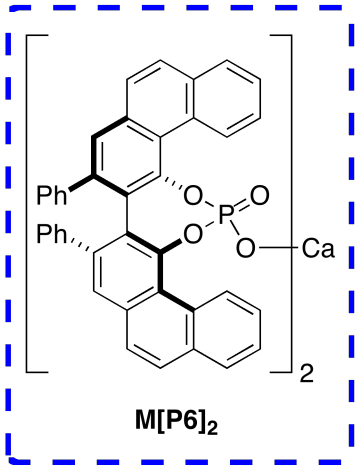
Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593.

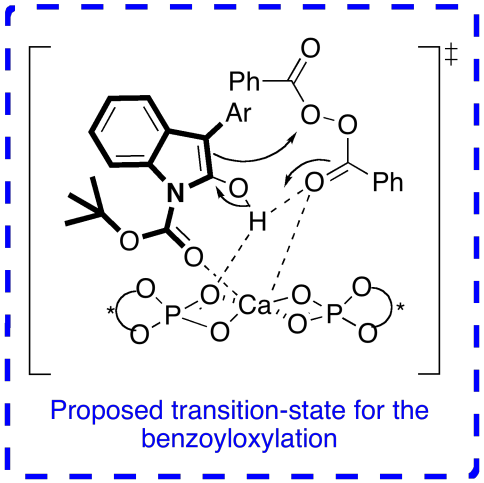


Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 1135.

1) TFA, DCM
2)DIBAL-H
toluene



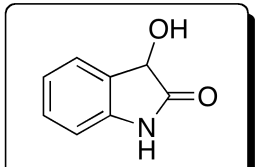




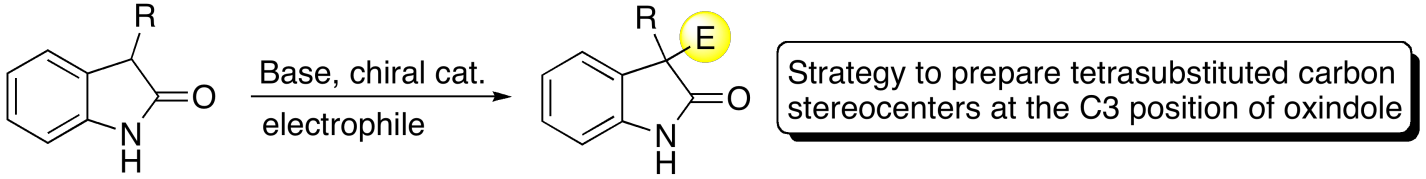
Proposed transition-state for the benzoyloxylation

Title Paper - Introduction

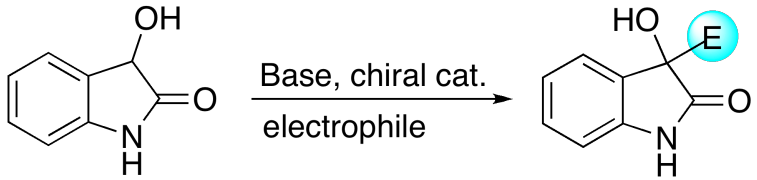
- Unprecedented strategy to access 3-substituted-3-hydroxyoxindoles in excellent enantioselectivities
- Use of 3-hydroxyoxindole to explore its nucleophilicity



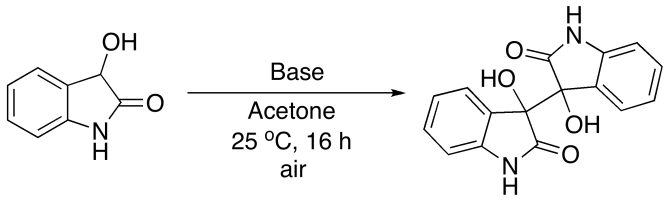
3-hydroxyoxindole



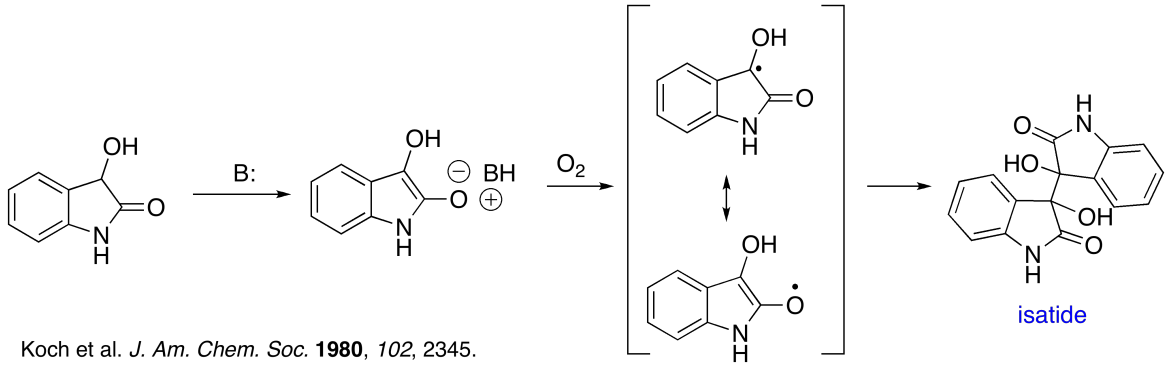
Strategy to prepare tetrasubstituted carbon stereocenters at the C3 position of oxindole



Understanding the Reactivity of Dioxindole

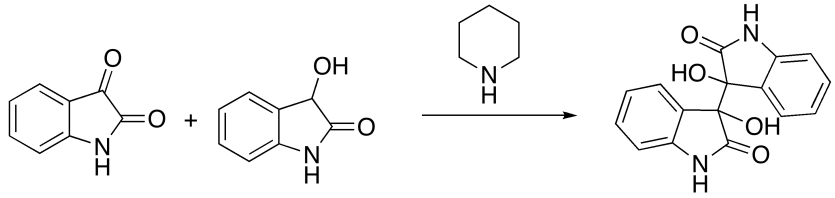


Entry	Base	Yield (%) (isatide)
1	DABCO	39
2	quinine	37



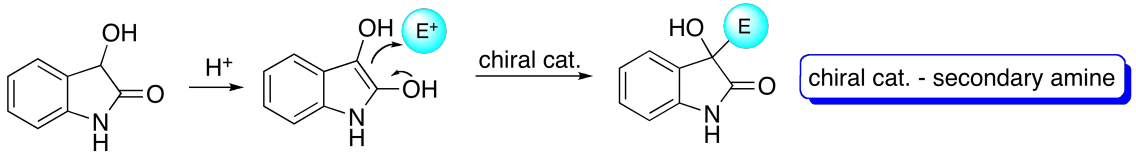
isatide

Koch et al. *J. Am. Chem. Soc.* **1980**, *102*, 2345.



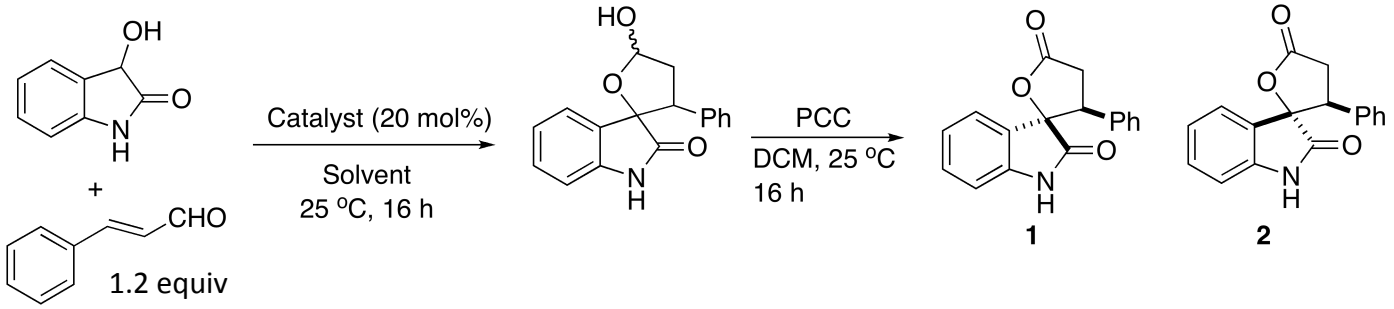
isatide

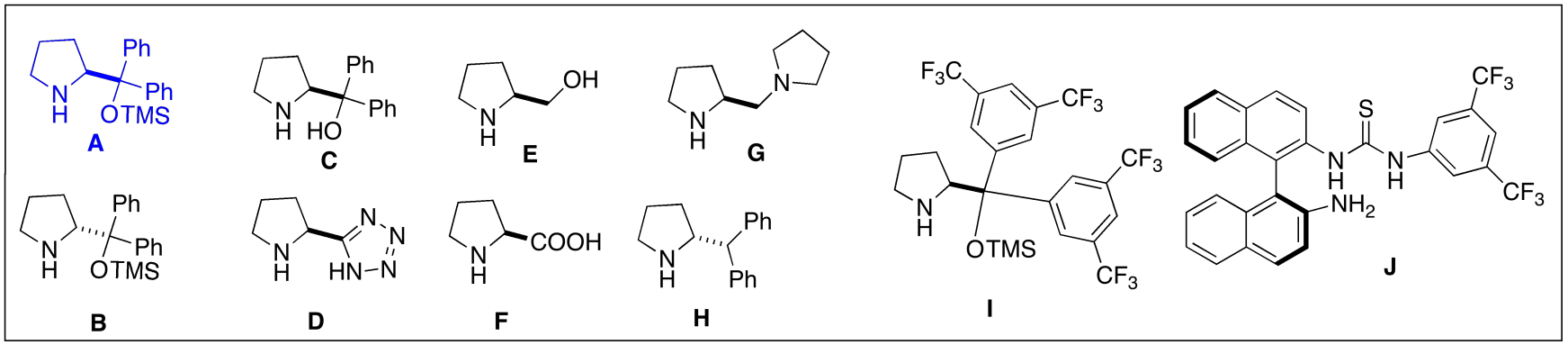
Bergmann, E. D. *J. Am. Chem. Soc.* **1955**, *77*, 1549.
Hansen, W. *Ann. Chim.* **1924**, *1*, 119.
Heller, G. *Ber.* **1904**, *37*, 943.



chiral cat. - secondary amine

Understanding the Reactivity of Dioxindole

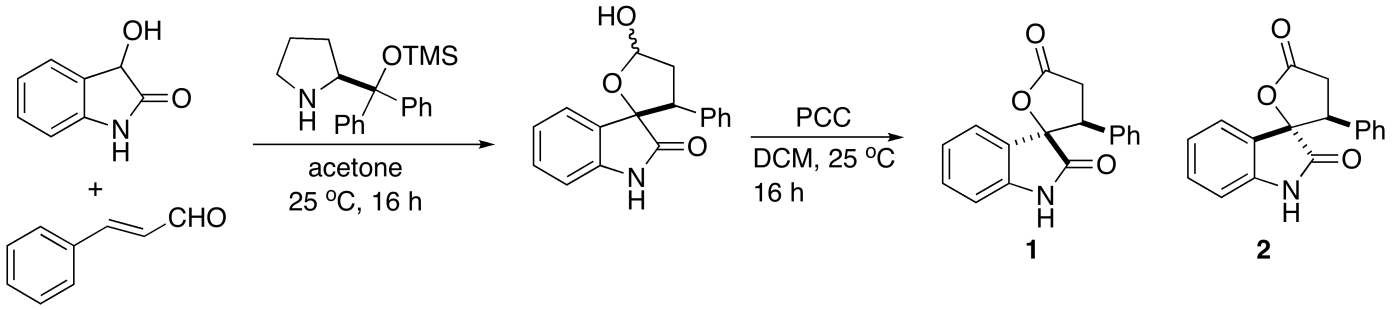


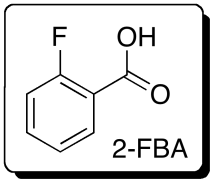


Catalyst	Solvent	Conversion (%) or yield (%) (1 +2)	dr (1:2)	ee (1/2)
A	THF	82[a]	1:1	90/90
A	Acetone	87[b]	1:1	97/97

[a] Reaction with 20 mol% of benzoic acid
[b] Yield of **1** and **2**

Understanding the Reactivity of Dioxindole



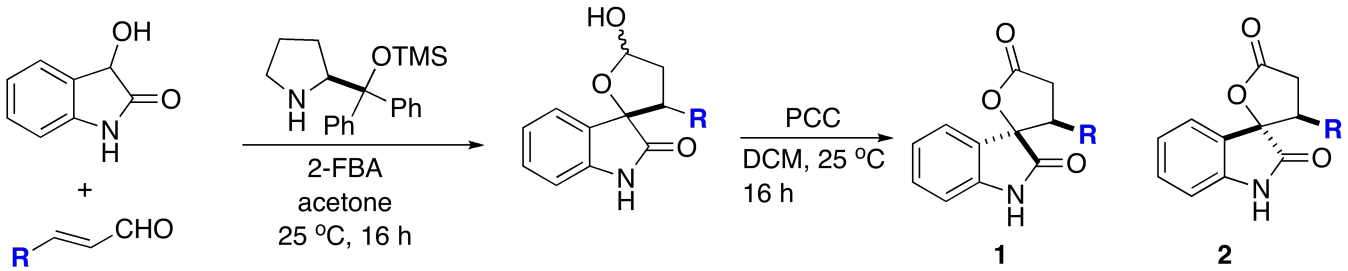


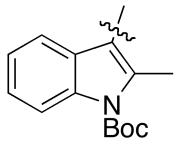
Entry	Catalyst (mol%)	Additive [(mol%)]	Aldehyde (equiv)	Yield (%) (isatide)	Yield (%) (1 +2)	ee (1/2)
1	5	-	-	11	-	-
2	5	-	1.2	6	24	96/97
3	5	2-FBA (5)	1.2	<5	85	97/97
4	1	2-FBA (1)	1.2	12	<5	n.d.
5	1	2-FBA (50)	1.2	-	99	97/97
6	0.5	2-FBA (50)	1.2	-	81	97/97

dr: 1.4:1 to 1:1

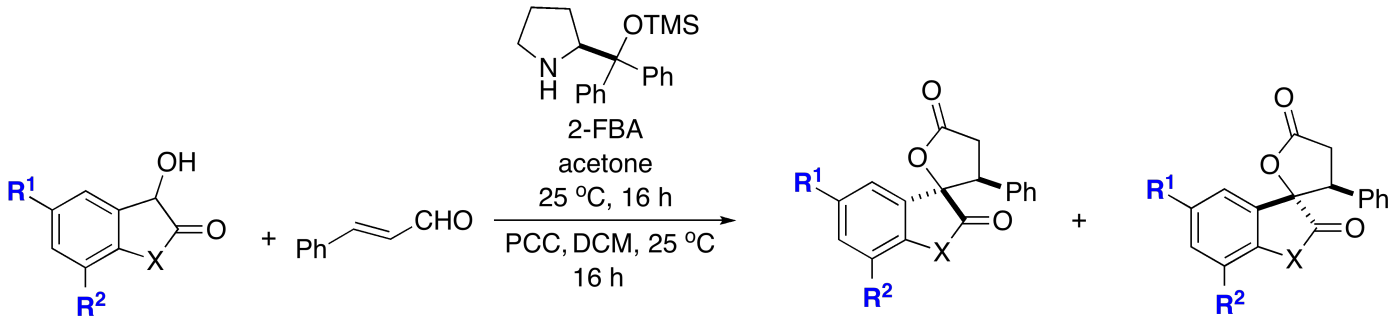
concentration: 0.6 M in acetone

Aldehyde Scope



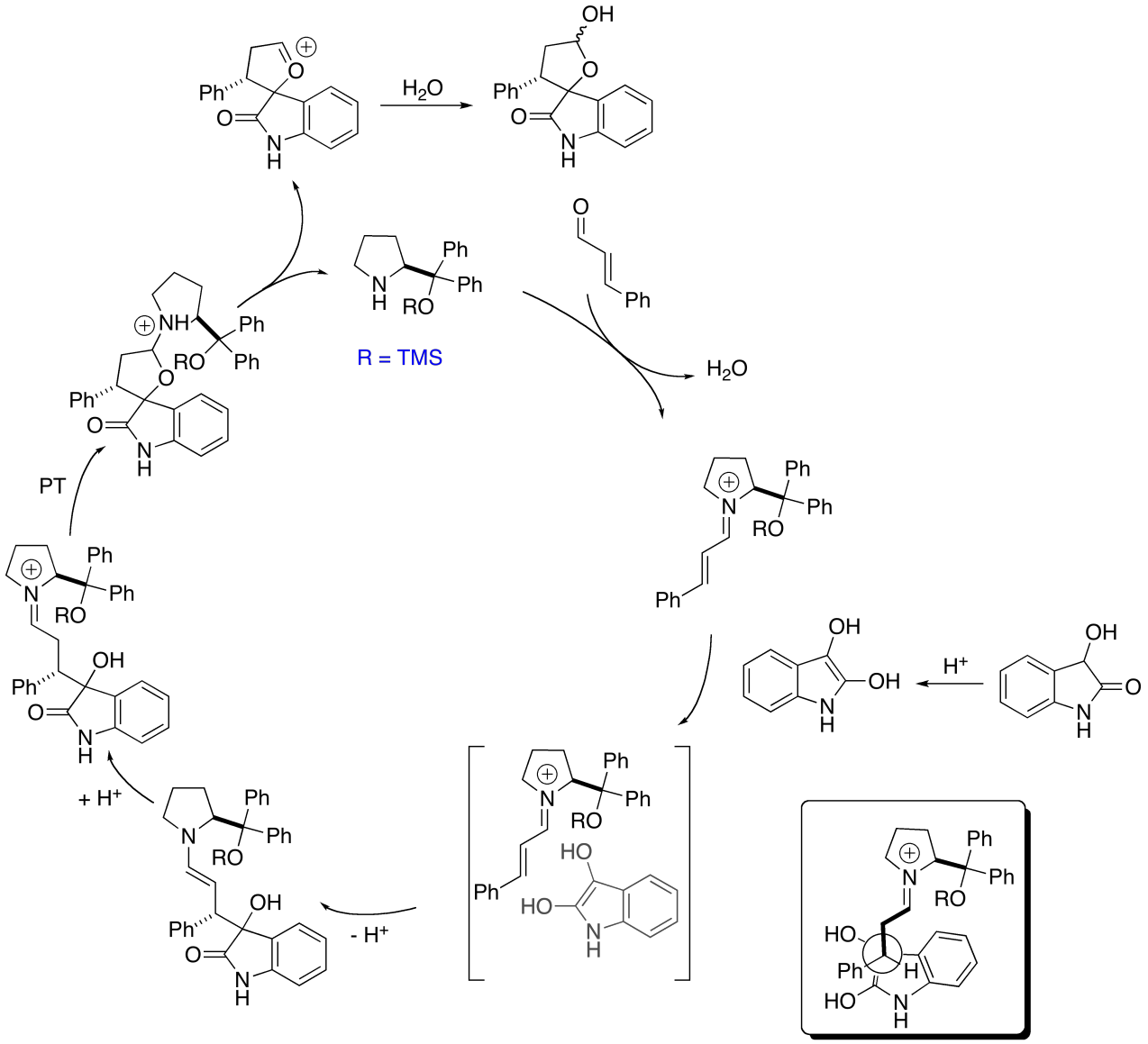
Entry	R	Yield (%) (1 +2)	ee (1/2)
1	Ph	98 (43/55)	97/97
2	4-MeOPh	63 (24/39)	97/98
3	4-NO_2Ph	89 (47/42)	88/92
4	2-NO_2Ph	92 (43/49)	94/98
5	4-ClPh	93 (39/54)	97/98
6	2-furanyl	65 (30/35)	96/97
7	3-thiophenyl	91 (38/53)	99/99
8		74 (39/35)	96/97
9	CH=CHCH$_3$	79 (29/50)	89/97
10	pentyl	63 (73/27)	98/86
11	CO_2Et	72 (50/50)	66/70

Nucleophile Scope

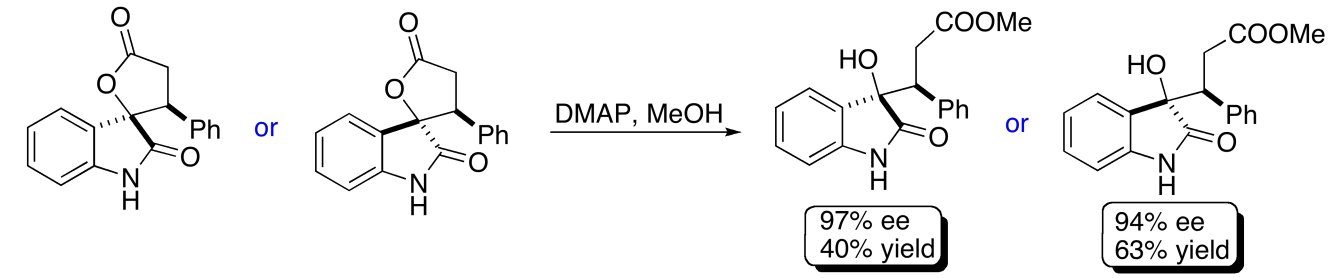


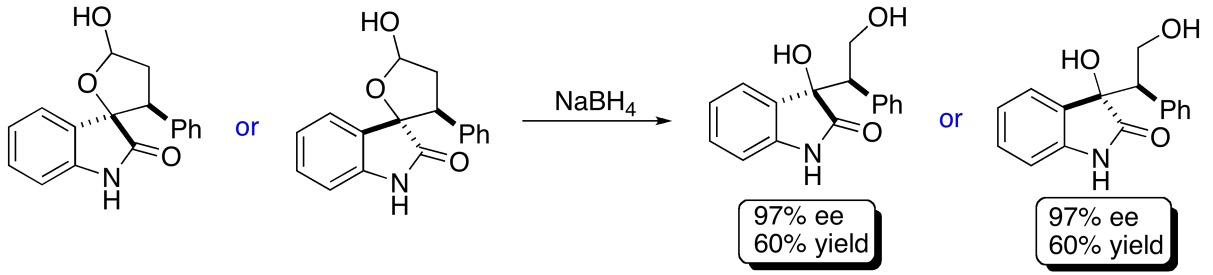
Entry	R^1	R^2	X	Yield (%) (1 + 2)	ee (1/2)
1	Me	H	NH	89 (32/57)	97/97
2	CF_3O	H	NH	92 (44/48)	97/93
3	Br	H	NH	64 (24/40)	96/96
4	H	Br	NH	93 (60/40)	95/95
5	H	H	NMe	67 (39/28)	90/94
6	H	H	NBn	92 (52/48)	95/95
7	*t*-Bu	*t*-Bu	O	72 (30/42)	96/97

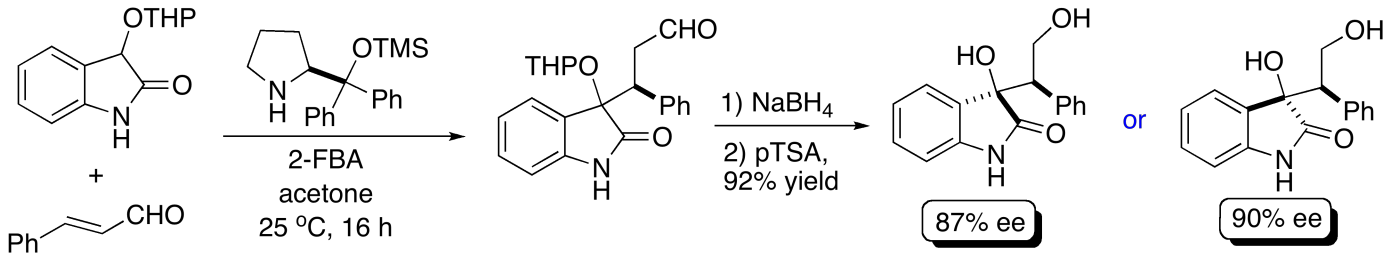
Proposed Catalytic Cycle



Spiro Oxindole γ-Butyrolactones to 3-Hydroxyoxindoles

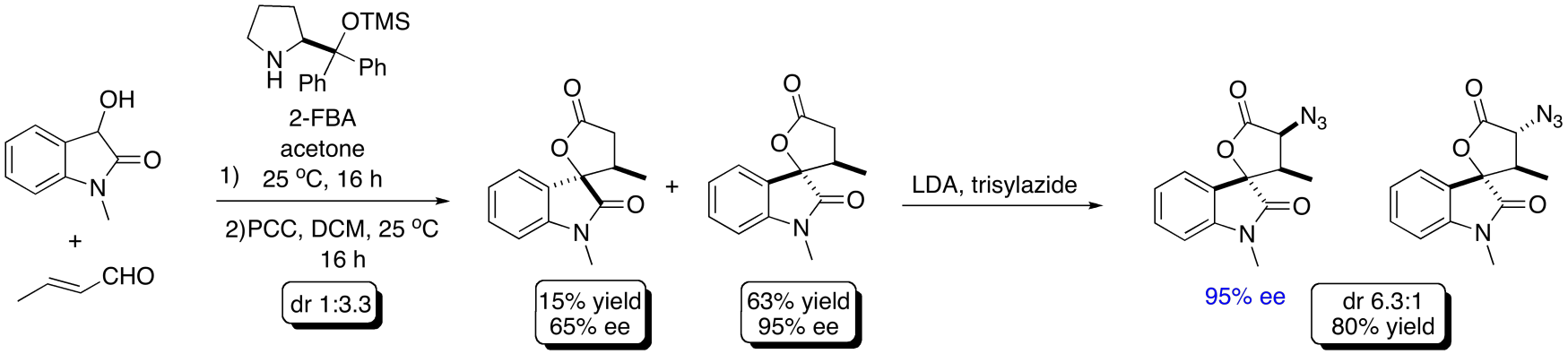


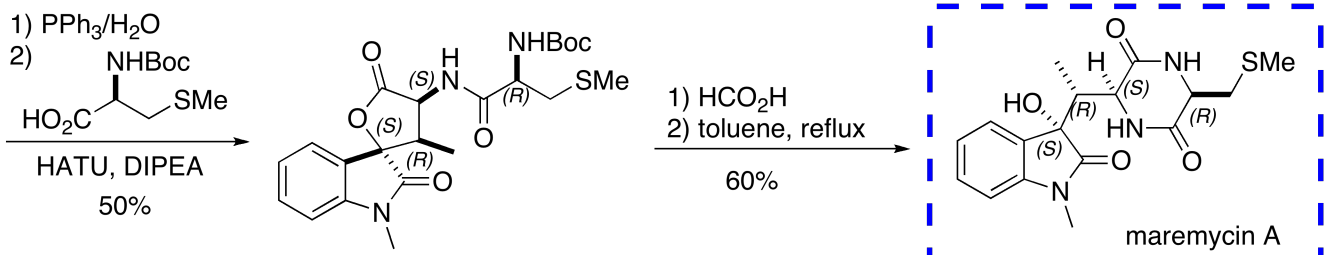




Application of the New Synthetic Method

Synthesis of maremycin A





Overall yield: 15%

Conclusion

- Better understand the reactivity of dioxindole – exploring its nucleophilicity

- The synthetic method was utilized to prepare 3-substituted-3-hydroxyoxindoles with high enantiomeric excess and maremycin A

- Future Work:

✧ Applications in other catalytic asymmetric transformations including the syntheses of other enantioenriched 3-substituted-3-hydroxyoxindoles