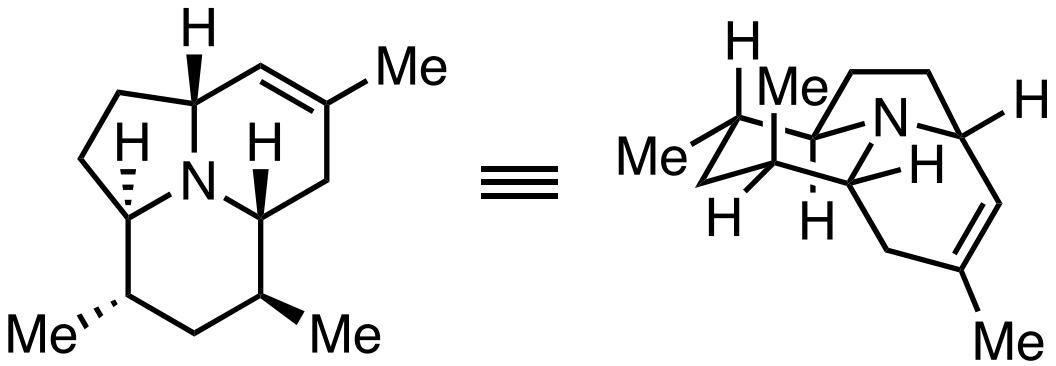
Synthesis of Alkaloid (−)-205B via Stereoselective Reductive Cross-Coupling and Intramolecular [3+2] Cycloaddition

Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15237-15240.



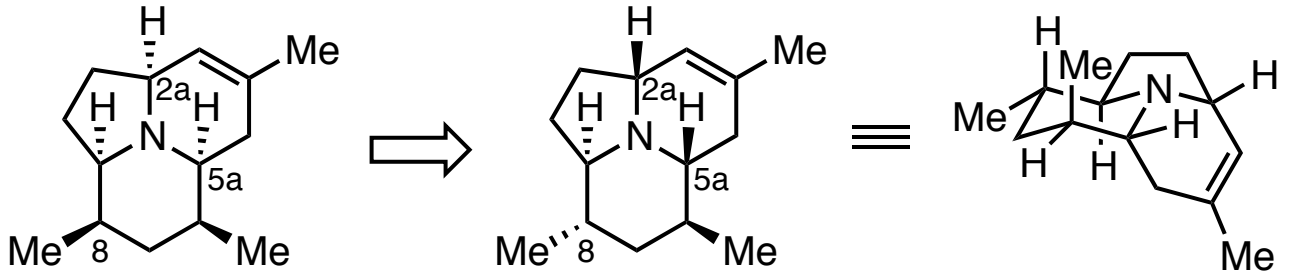
(–)-205B

Kara George Rosenker

Current Literature

6 October 2012

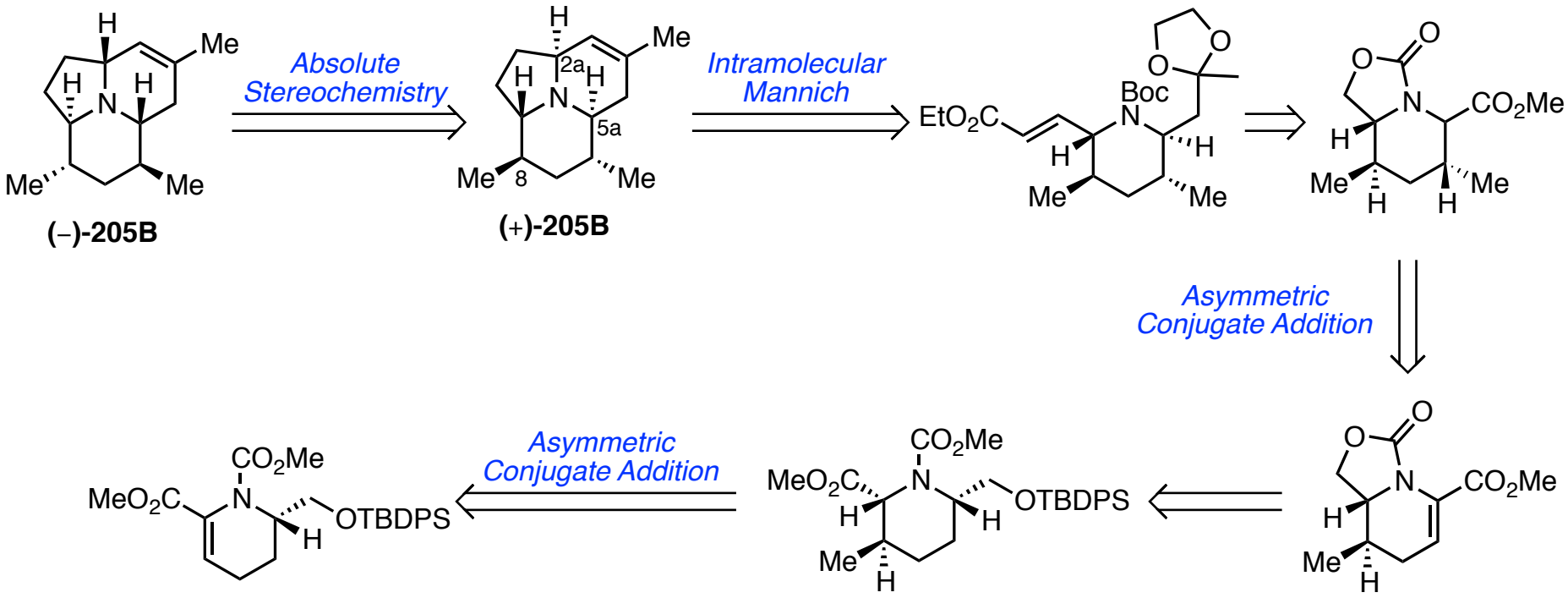
(−)-205B Isolation, Structure, and Biological Activity



- Isolated in 1987 by Daly and co-workers from the skin extracts of the Panamanian frog *Dendrobates pumilio*
- The structure was first reported as **1** and revised in 1998 by Daly and co-workers based on extensive FTIR, NMR, and HRMS
- The absolute sterochemistry was reported in 2003 by Toyooka and co-workers based on their total synthesis of (+)-205B
- (−)-205B possesses an unusual and unique 8b-azaacenaphthylene ring system containing 5 asymmetric centers
- Target of interest due to intriguing structure and the discovery that the unnatural enantiomer, (+)-205B, blocks the 7α nicotinic acetylcholine receptor in a selective fashion

Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M.W.; Daly, J.W. *Tetrahedron* **1987**, *43*, 643.
Tokuyama, T.; Garraffo, H. M.; Spande, T. F.; Daly, J.W. *An. Asoc. Quim. Argent.* **1998**, *86*, 291.
Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 3808.
Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J.A. *Mol. Pharmacol.* **2004**, *66*, 1061.

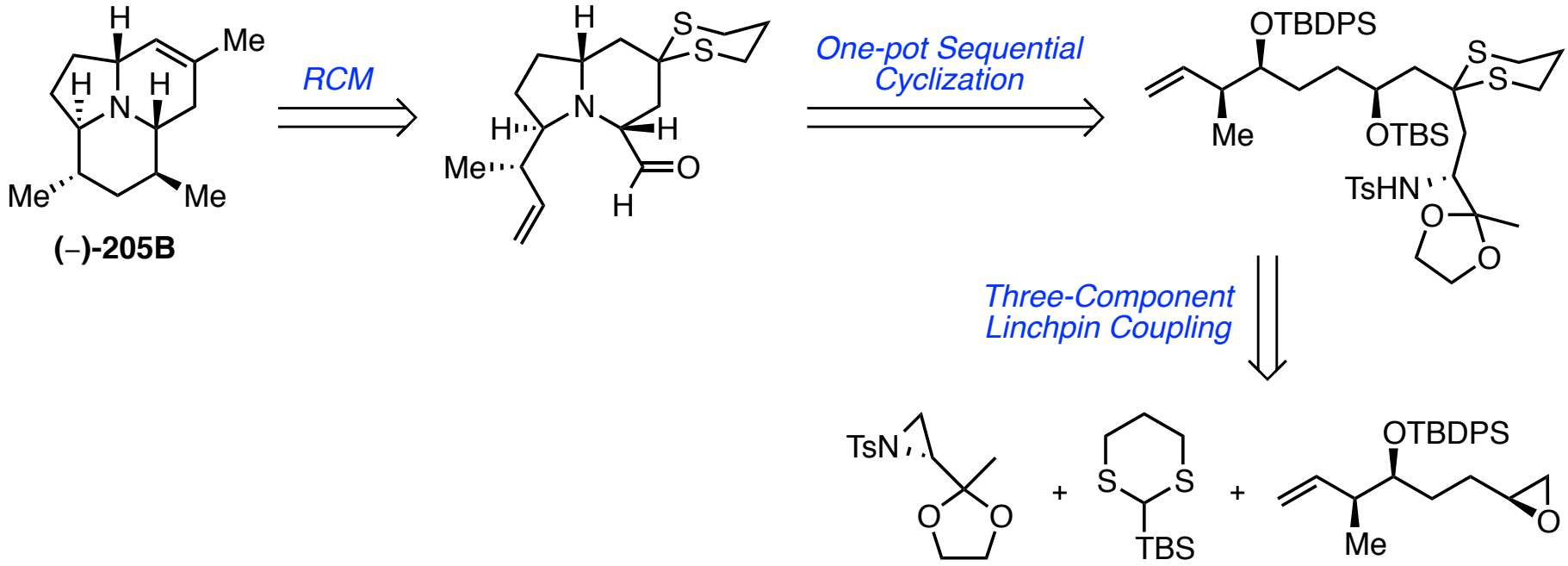
Toyooka and Co-Workers: (+)-205B



- 30 steps (longest linear)
- Determined the absolute stereochemistry of the natural product to be (−)-205B
- Key features:
  - Stereocontrolled Michael-type additions to enaminoesters

Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 3808.
Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol.* **2004**, *66*, 1061.

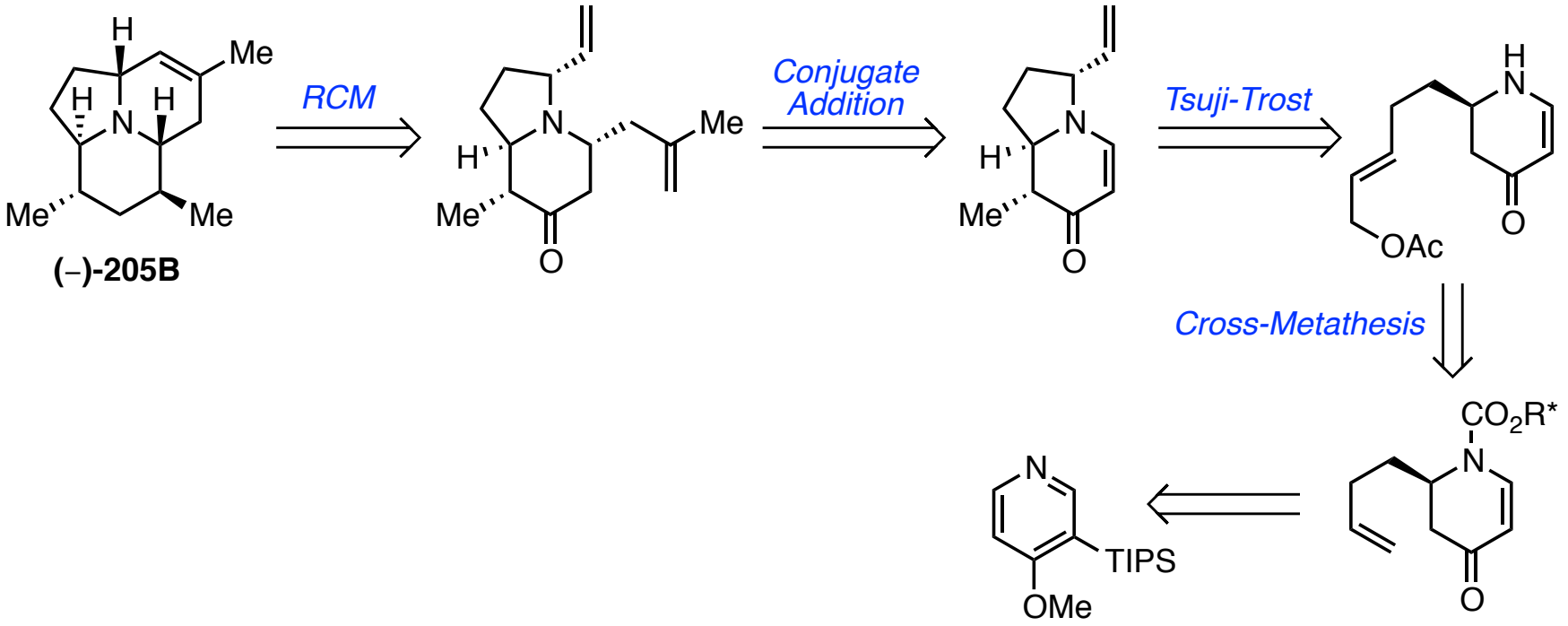
Smith and Co-Workers: (-)-205B



- 19 steps (longest linear)
- 5.6% overall yield
- Key features:
  - Dithiane three-component linchpin coupling
  - One-pot sequential construction of the indolizidine ring

Smith, A. B; Kim, D.-S. *Org. Lett.* **2005**, 7, 3247.

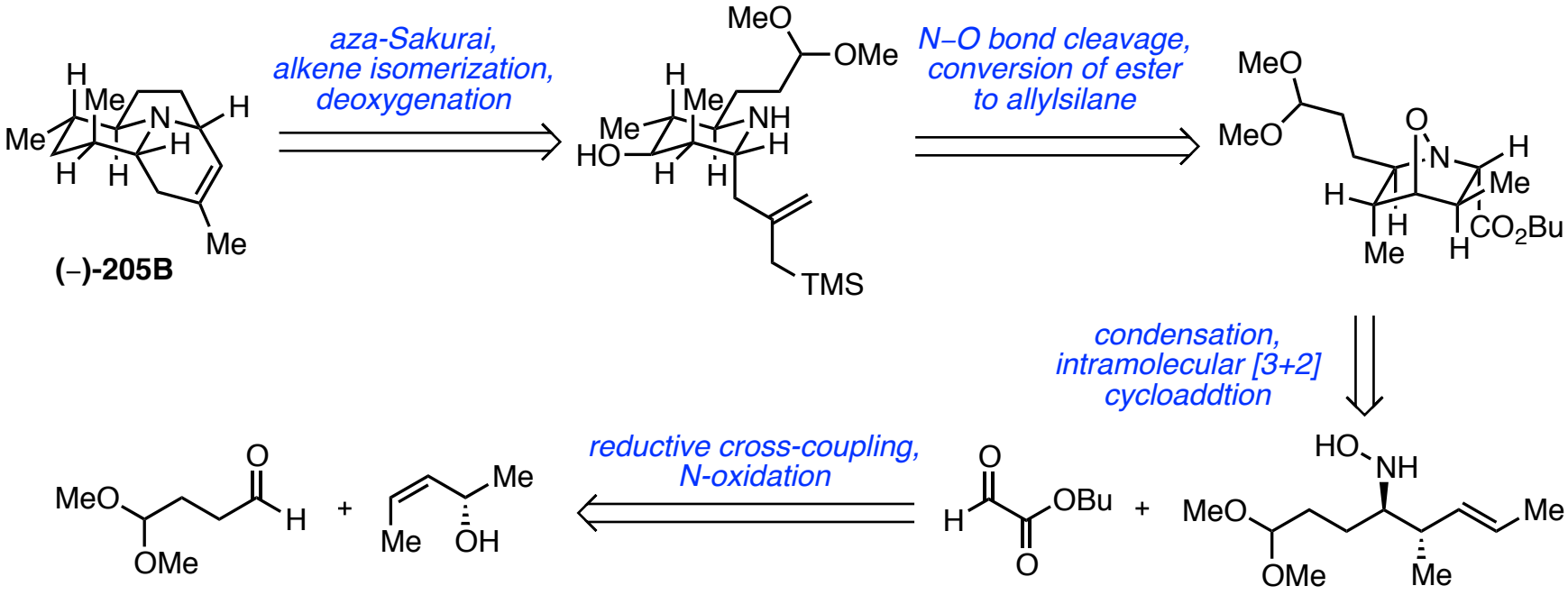
Comins and Co-Workers: (-)-205B

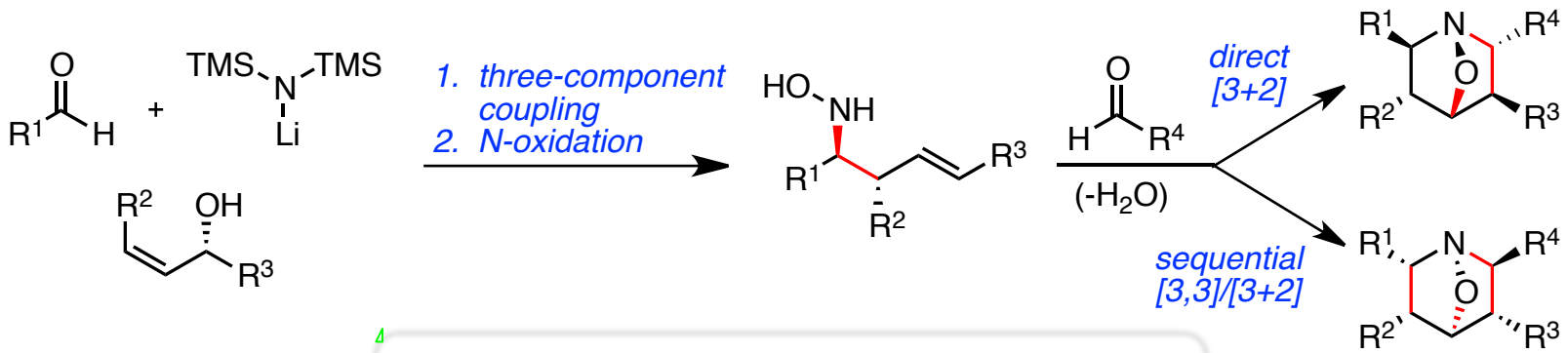


- 11 steps (longest linear)
- 8% overall yield
- Key features:
  - Asymmetric *N*-acylpyridinium reaction
  - Tsuji-Trost allylic amination of a vinylogous amide

Tsukanov, S.V.; Comins, D. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8626.

Title Paper: Retrosynthesis of (−)-205B





Control of reaction pathway dictates stereochemistry of the heterocyclic product

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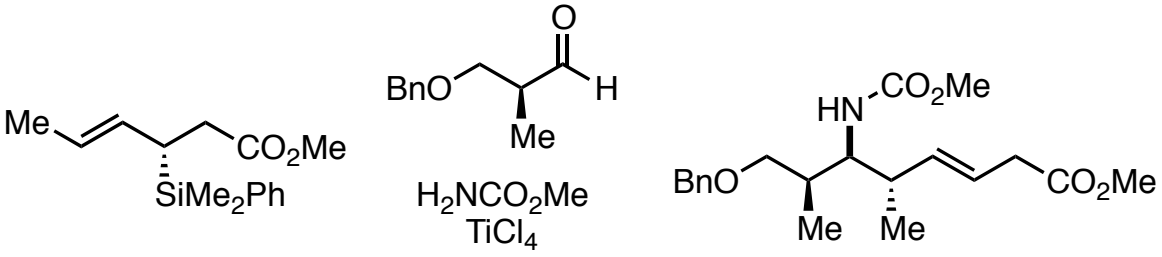
(*E*)-*anti*-Homoallylic Primary Amines

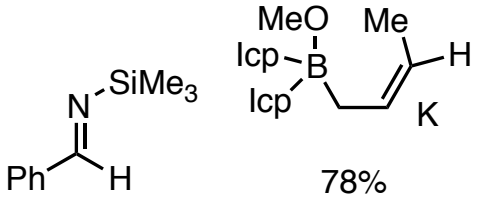
- Chelation-controlled addition reactions of chiral crotylsilanes for the synthesis of *(E)-anti*-homoallylic carbamates



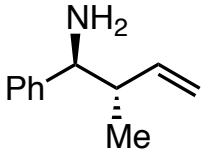
50%, 30:1 dr

Schaus, J.V.; Jain, B.; Panek, J. S. *Tetrahedron* **2000**, *56*, 10263.

- Asymmetric crotylation and allylation reactions of imines and oximes

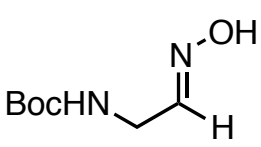


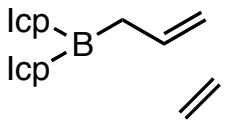
78%

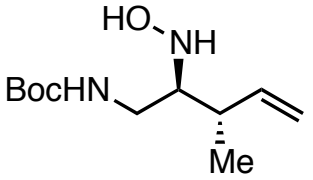


92% ee, 96% de

Ramachandran, P.V.; Burghardt, T. E. *Chem. – Eur. J.* **2005**, *11*, 4387.

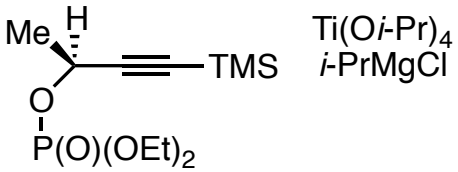




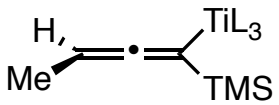


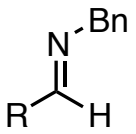
White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963.

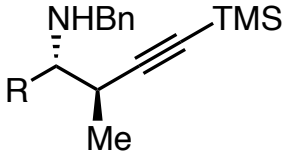
- Iminine propargylation



Ti(O*i*-Pr)$_4$
i-PrMgCl



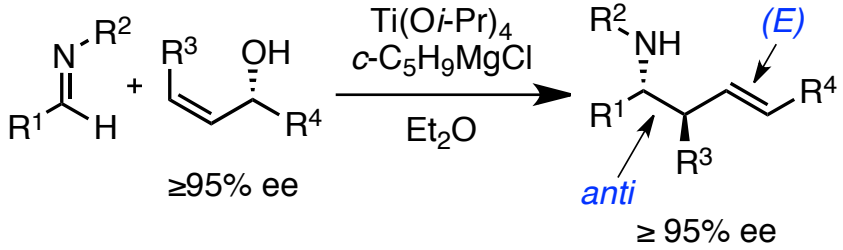


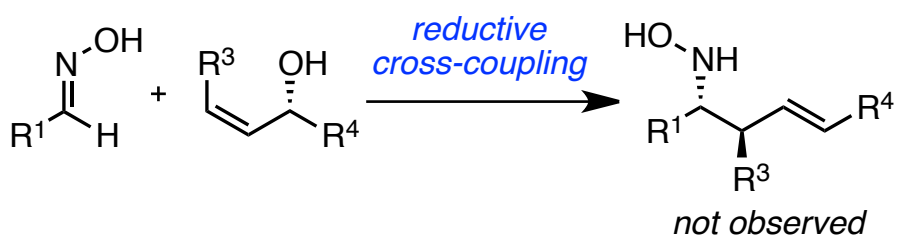


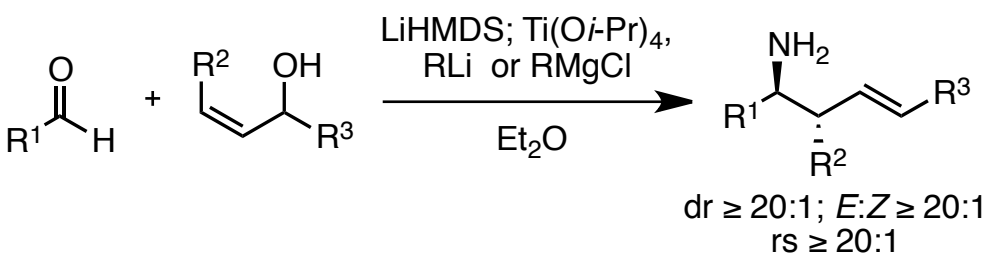
87% (9:1 dr)

Song, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **2002**, *43*, 8653.

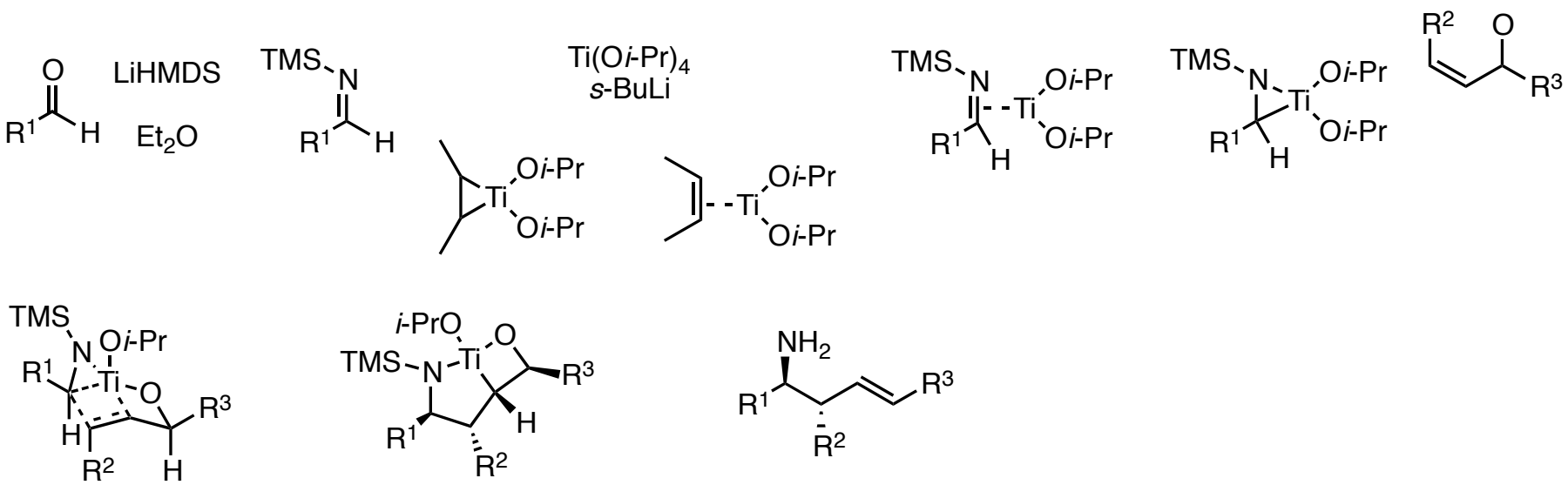
Methodology: Stereodefined Homoallylic Hydroxylamines





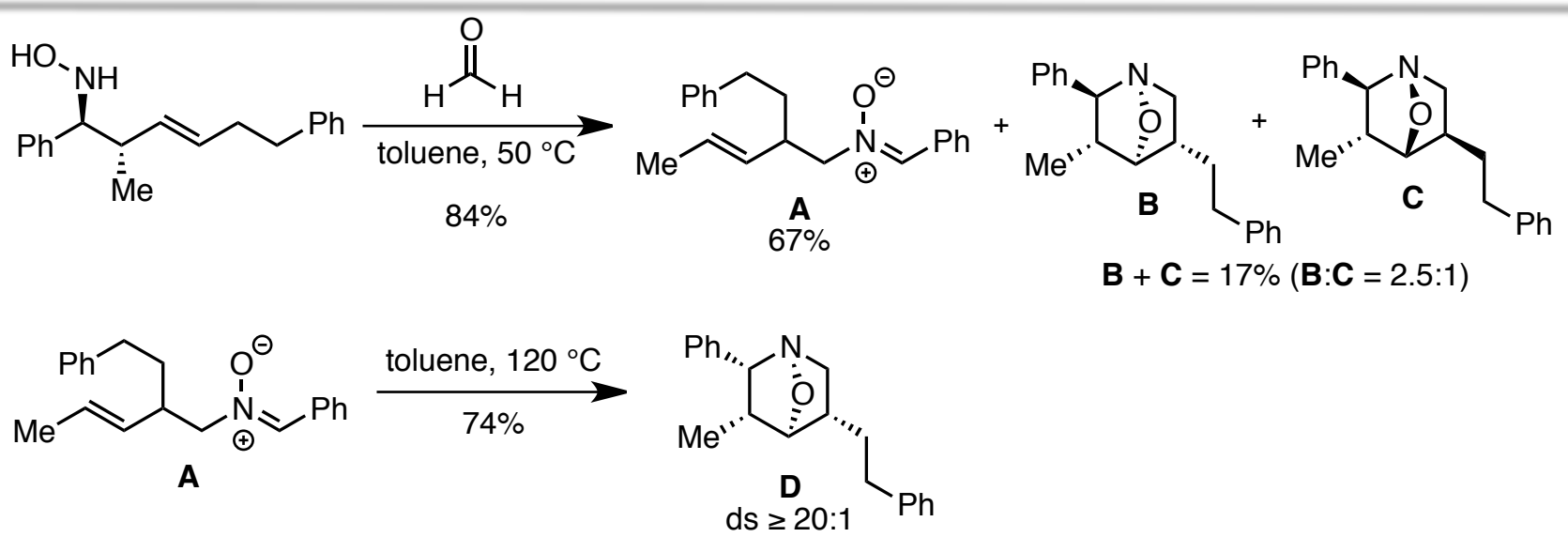


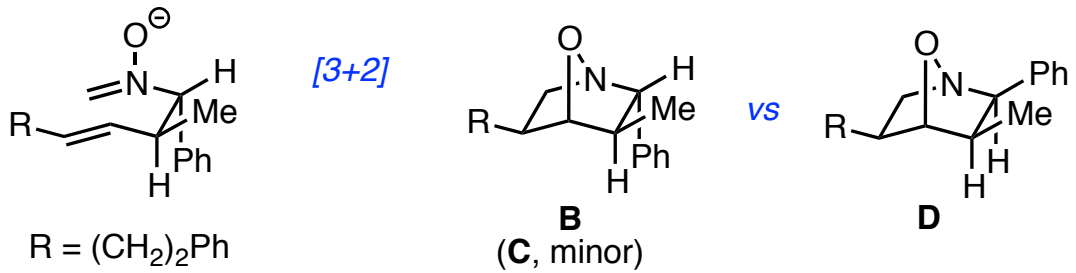
- Reaction proceeds with aromatic and aliphatic aldehydes
- Delivers stereodefined (*E*)-*anti*-homoallylic amines as single diastereomers

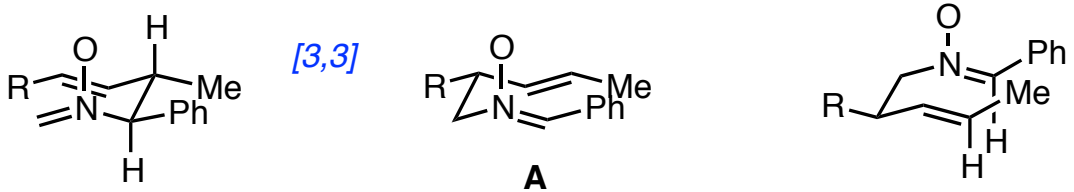


Angew. Chem. Int. Ed. **2009**, *48*, 3648; *Org. Lett.* **2009**, *11*, 5402; *J. Am. Chem. Soc.* **2009**, *131*, 17548.; *J. Org. Chem.* **2010**, *75*, 8048; . *J. Am. Chem. Soc.* **2011**, *133*, 9216.

Methodology: 1-Aza-7-oxabicyclo[2.2.1]heptanes







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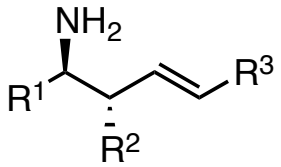
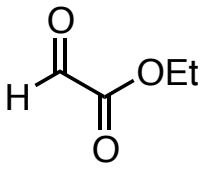
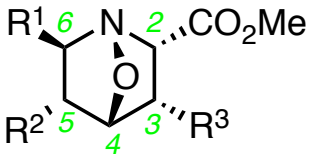
Methodology: 1-Aza-7-oxabicyclo[2.2.1]heptanes



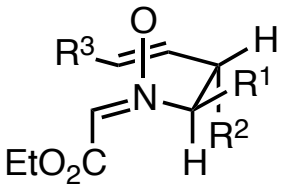


toluene
4Å mol. sieves

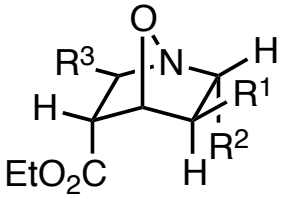
rt to 120 °C
2-12 h



2,3-*anti*; 3,4-*syn*;
4,5-*anti*; 5,6-*anti*

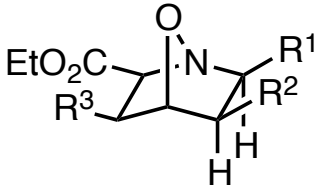


[3+2]



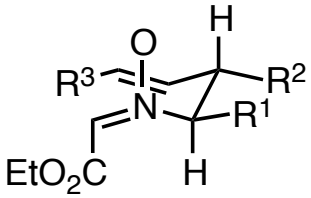
major product

vs

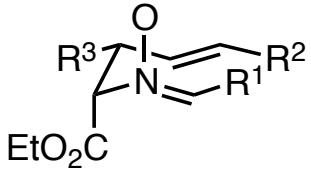


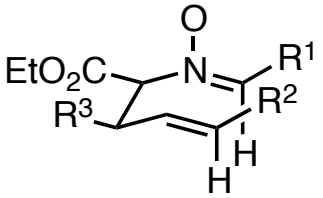
not observed

[3+2]



[3,3]





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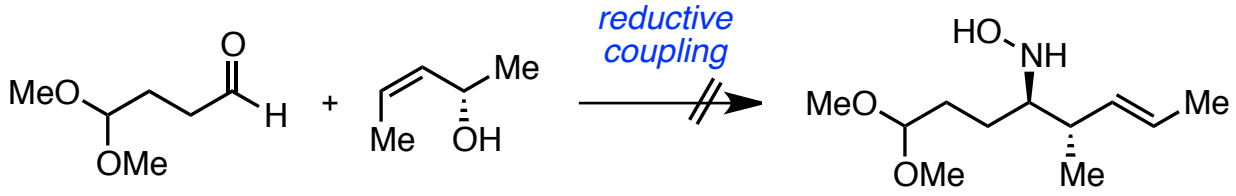
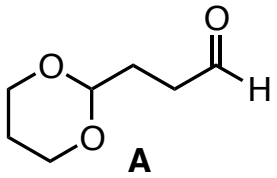
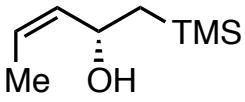
Ti-Mediated Reductive Cross-Coupling



low conversion
poor steroselection



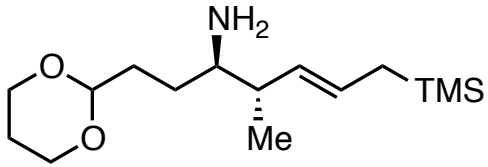
A



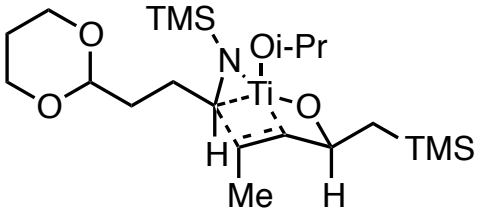
B
(91% ee)

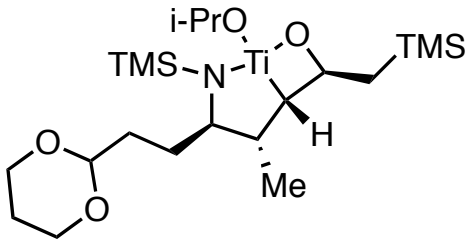
A, LiHMDS, Et_2O;
then $Ti(O\textit{i}\text{-}Pr)_4$, *s*-BuLi;
then **B**

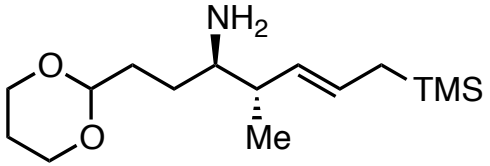
57%



(91% ee)







(91% ee)

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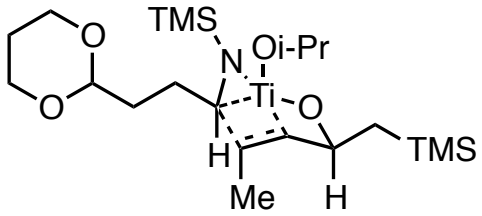
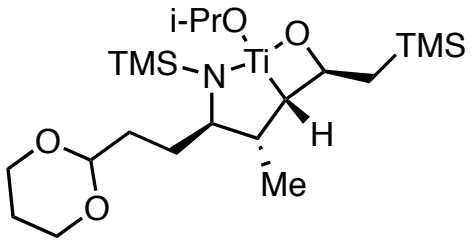
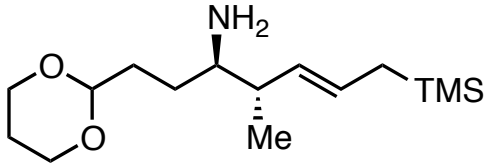
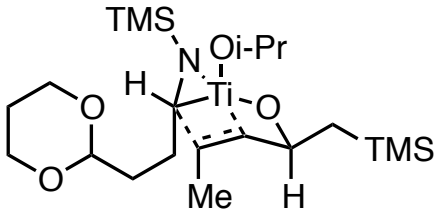
Stereochemical Analysis of Reductive Cross-Coupling

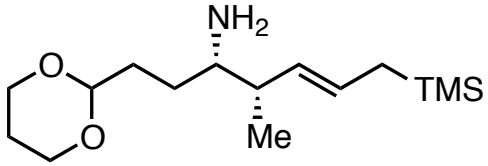


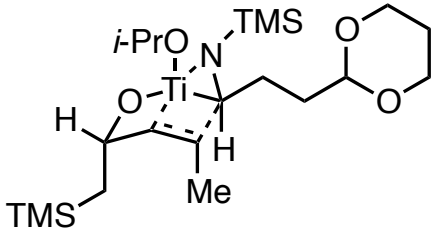


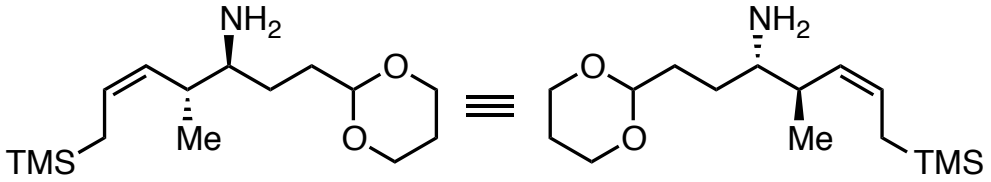


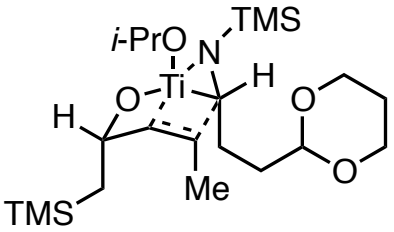
(91% ee)

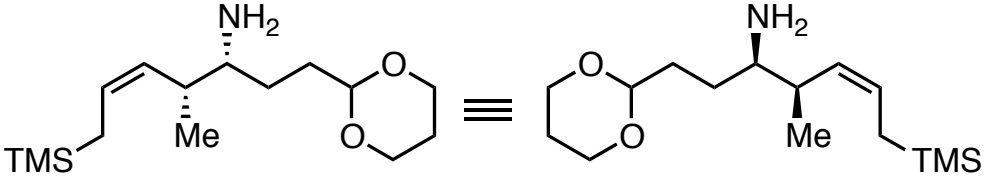






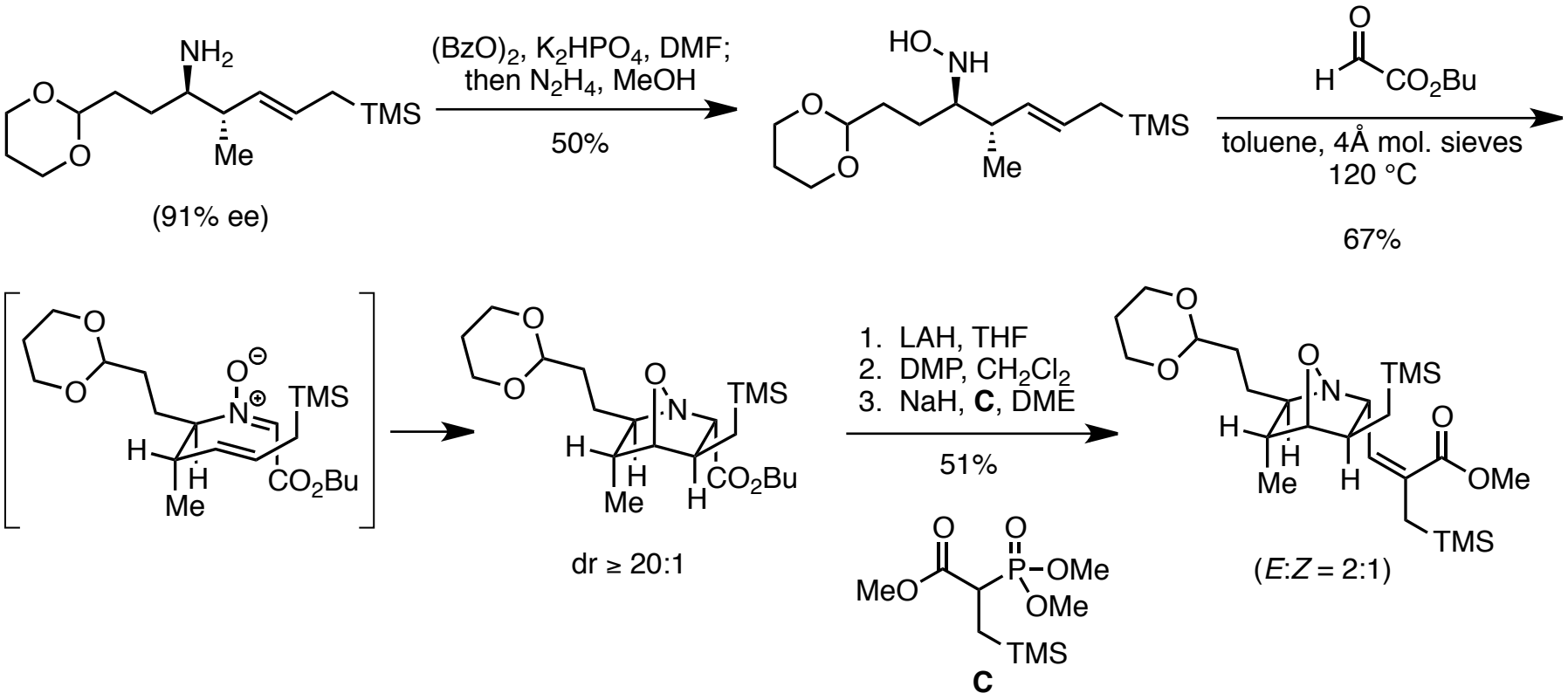






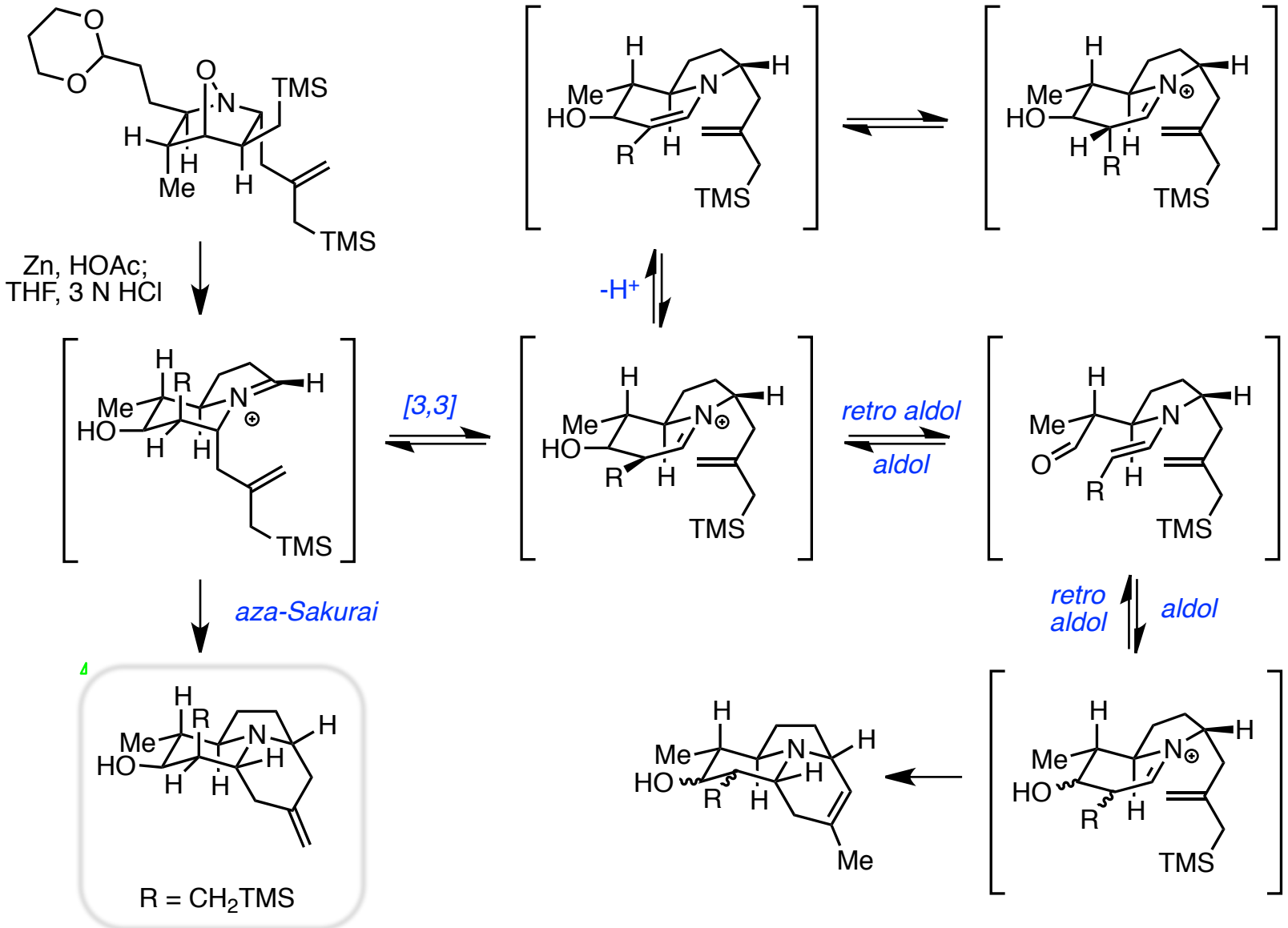
Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15237-15240.

Asymmetric Synthesis of (−)-205B



Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15237-15240.

Cationic Annulation: Aza-Sakakurai vs Aza-Cope



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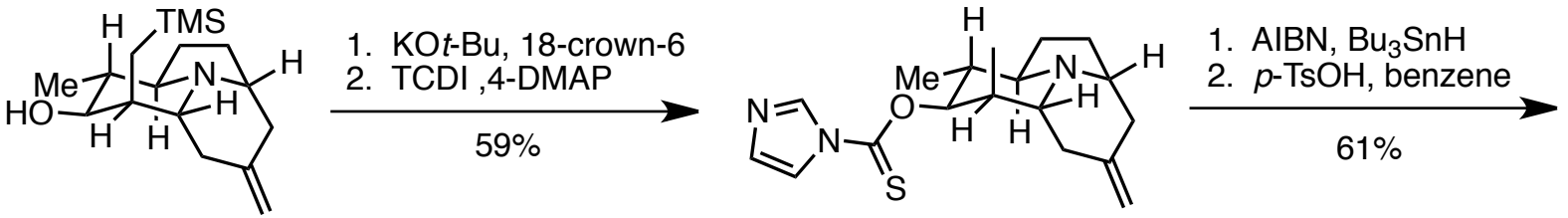
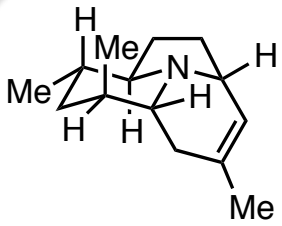
Completion of (−)-205B





(–)-205B

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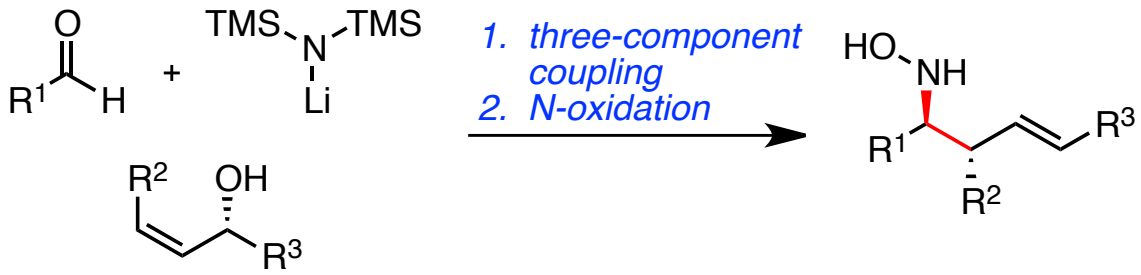
Conclusion

- Completed the asymmetric total synthesis of (−)-205B in 17 steps
- Successfully employed two stereoselective synthetic methods developed in their laboratories
  - Ti-mediated reductive cross-coupling of allylic alcohols with aldehydes



  - Path-selective intramolecular [3+2] cycloaddition of glyoxylate-based homoallylic nitrones