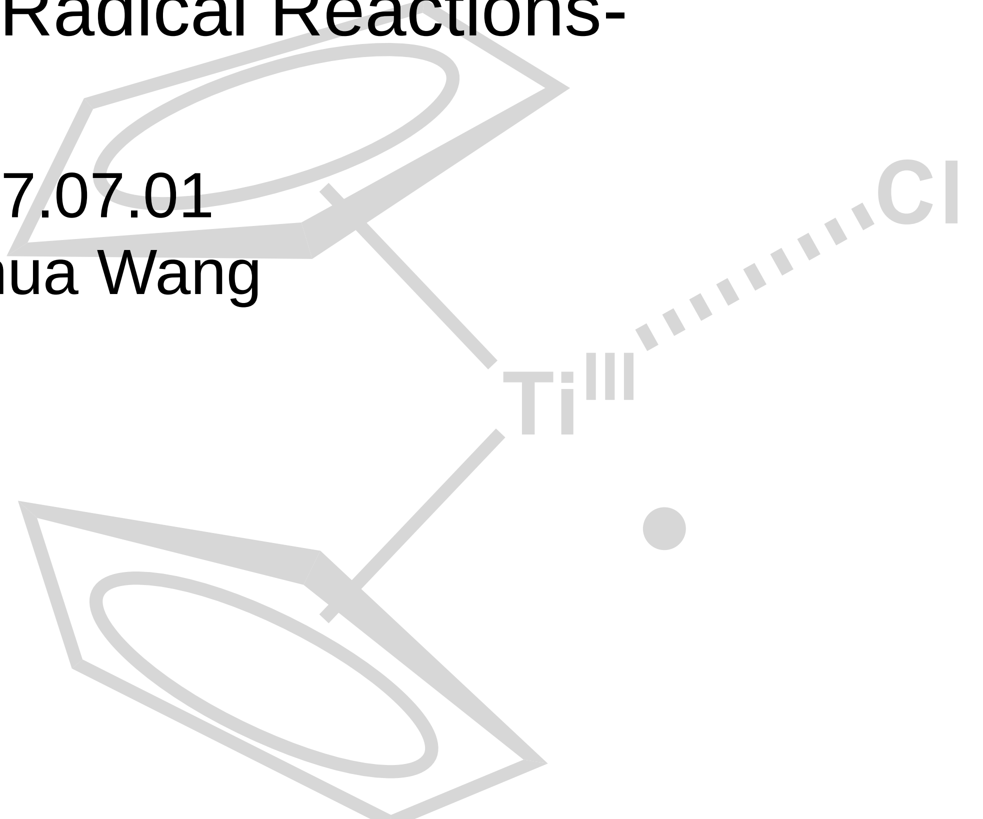
Nugent Reagent

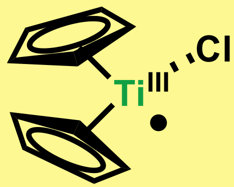
-Application for Radical Reactions-

2017.07.01

Yinghua Wang



Introduction of Nugent Reagent



Nugent reagent
(Cp_2TiCl)

- synthesized for the first time by Wilkinson in 1955

- a mild single-electron-transfer (SET) reagent

- Ti: 7th most abundant metal on Earth

Principal Transformations Mediated by Nugent Reagent are...

- **Radical ring-opening reactions (such as epoxide)**
- **Radical cascade Cyclizations**
- **Coupling reactions (homocoupling, Pinacol coupling, McMurry coupling etc...)**
- **Umpolung reactions**
- **THF-ring formation reactions**
- **Hydrogen-atom transfer**
- **Barbier-type reactions**
- **Deoxygenation of alcohols (see; 131102_LS_Takahiro_KAWAMATA)**
- **Poolymerization reactions**

Rosales, A.; Rodríguez-García, I.; Muñoz-Bascón, J.; Roldan-Molina, E.; Padial, N. M.; Morales, L. P.; García-Ocaña, M.; Oltra, J. E. *Eur. J. Org. Chem.* **2015**, 4567.

Table of Contents

Preparation of Nugent Reagent

Isolation of Cp_2TiCl

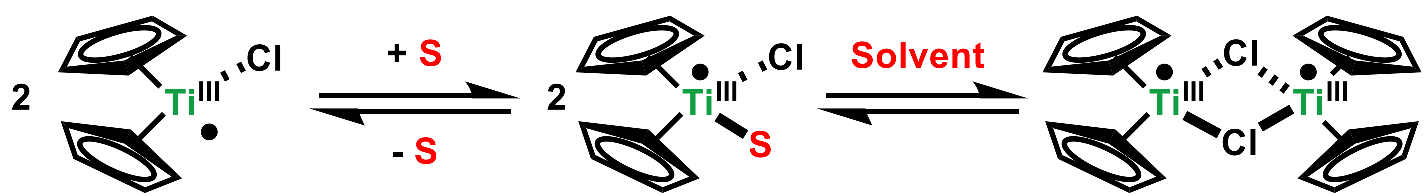
$$TiCl_3 + 2CpTl \xrightarrow[\text{94\%}]{\text{THF, reflux}} Cp_2TiCl + 2TlCl$$

Manzer, L. *Inorg. Synth.* **1982**, *21*, 84.

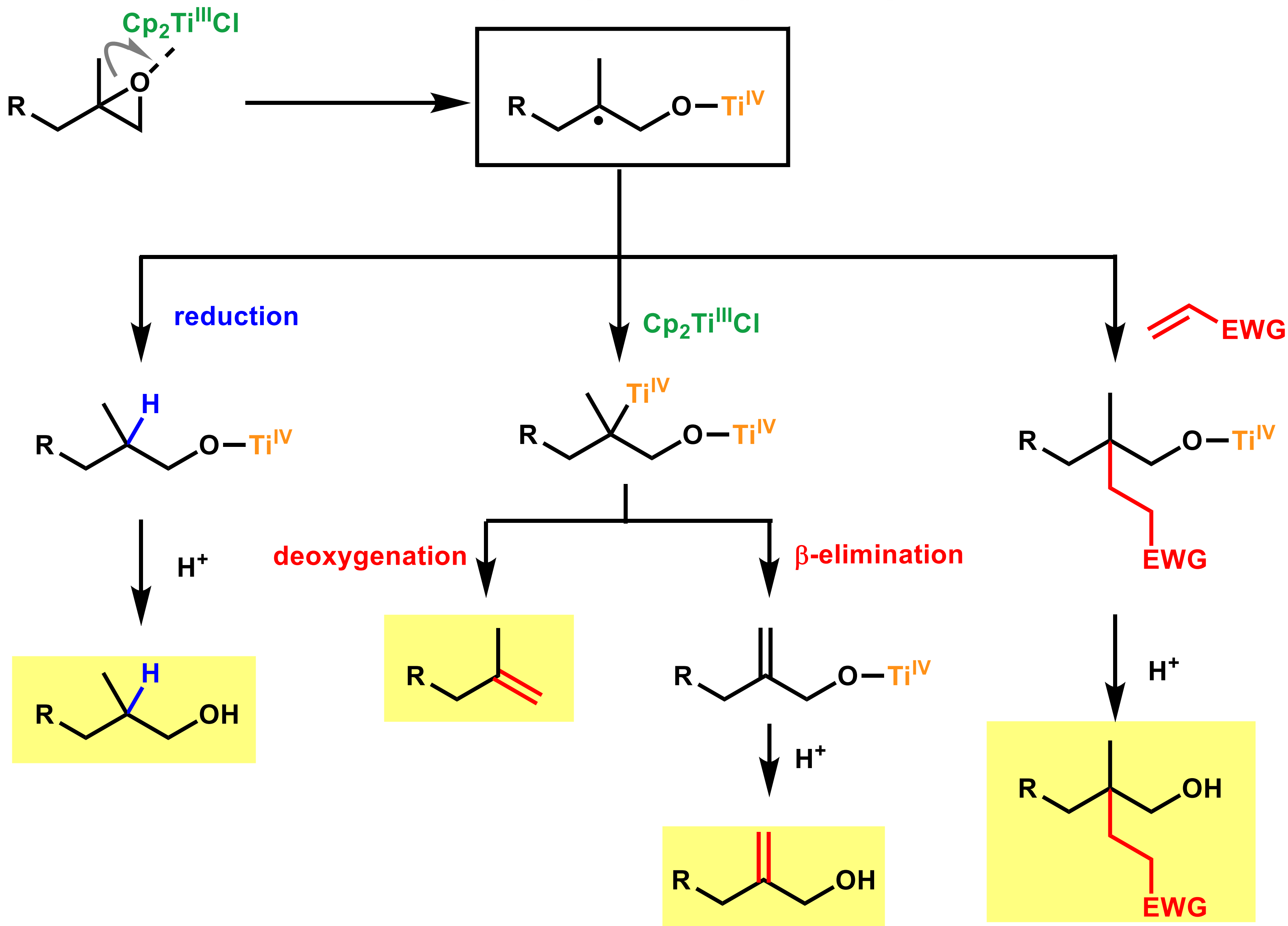
***in situ* preparation of Cp_2TiCl**

$$2Cp_2TiCl_2 + M \xrightarrow[\text{M = Zn or Mn}]{\text{THF}} 2Cp_2TiCl + MCl_2$$

Equilibrium of species

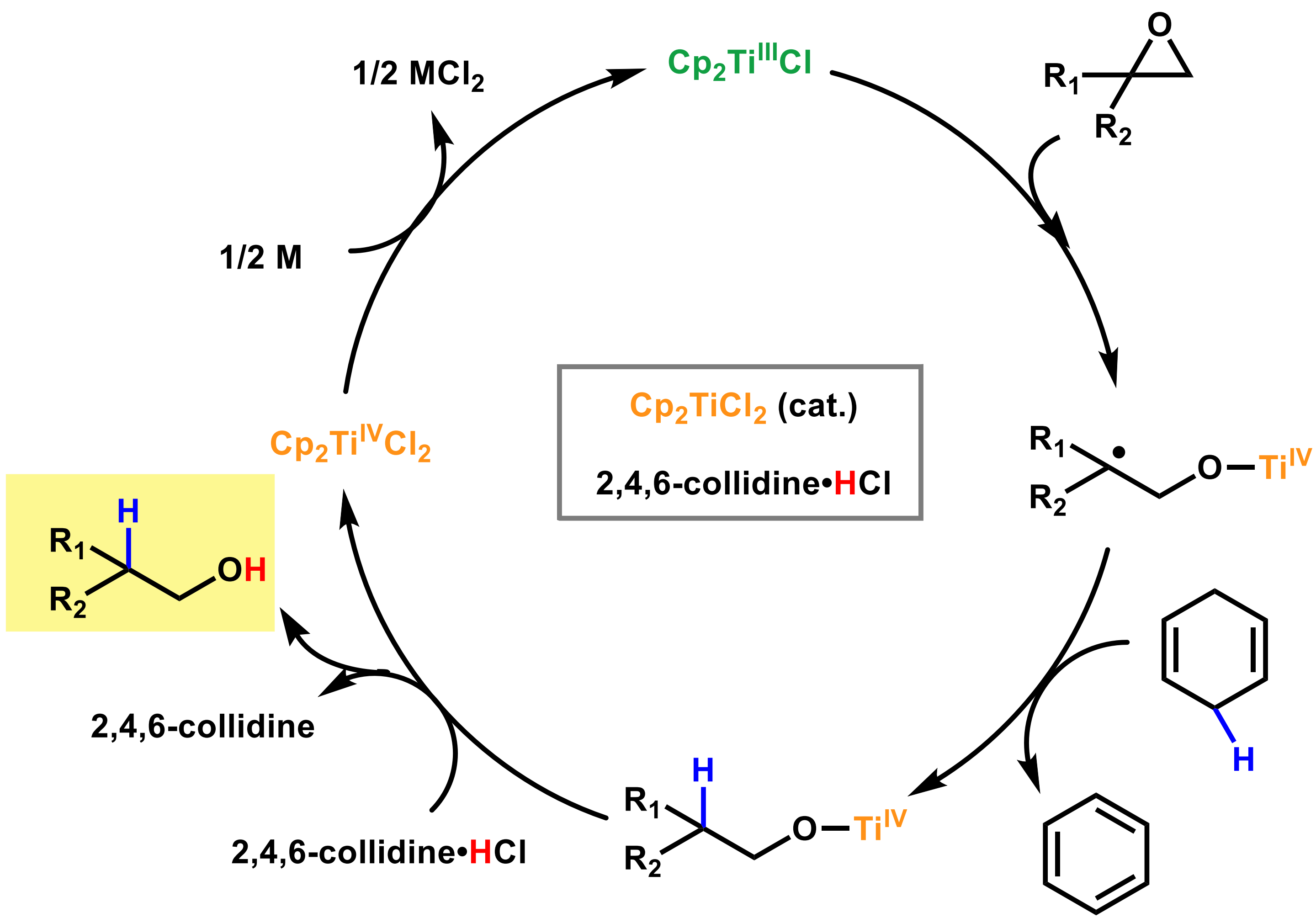


Radical Ring-Opening of Epoxides



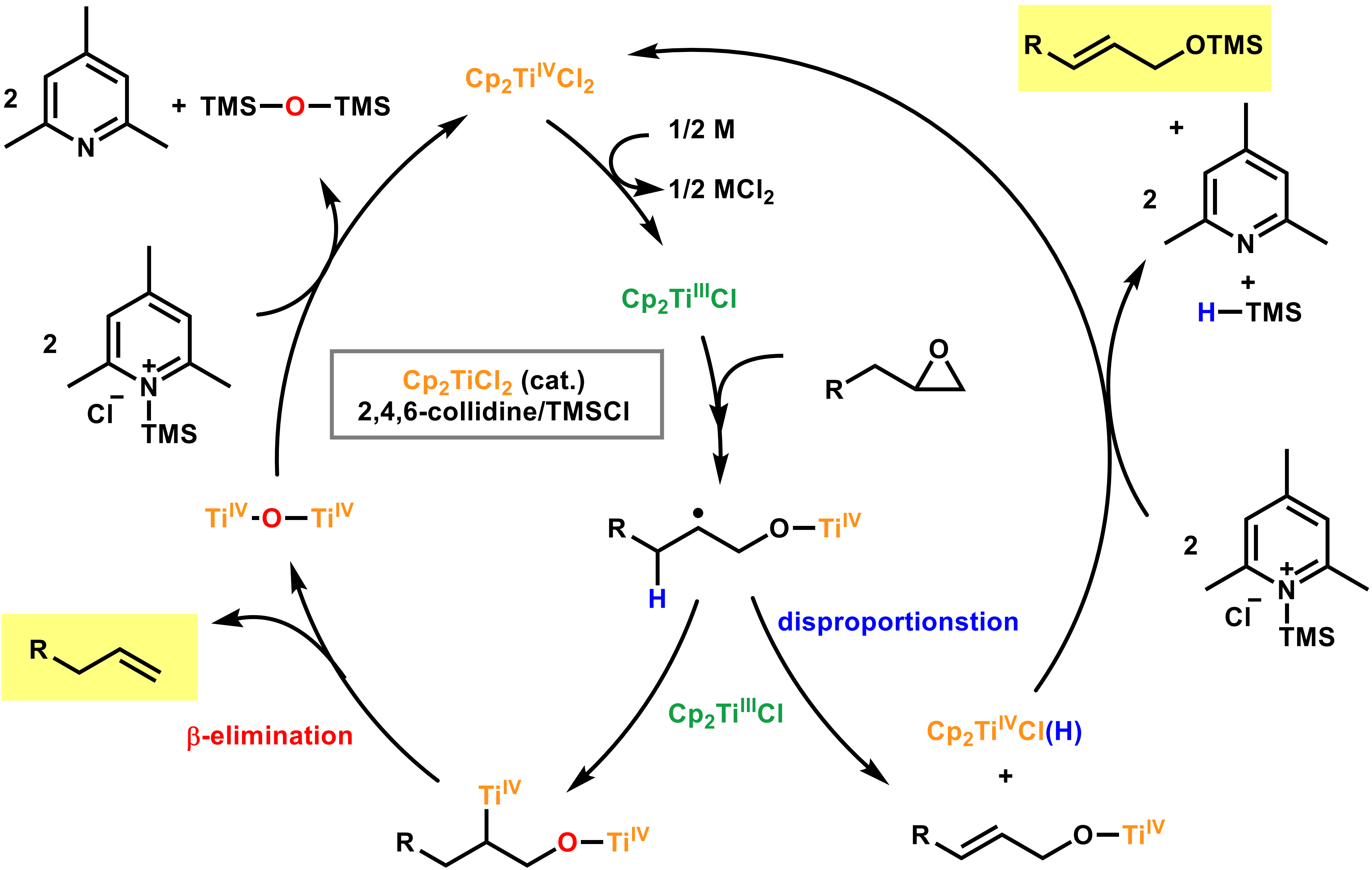
RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

Catalytic Reductive Epoxide Opening Reaction



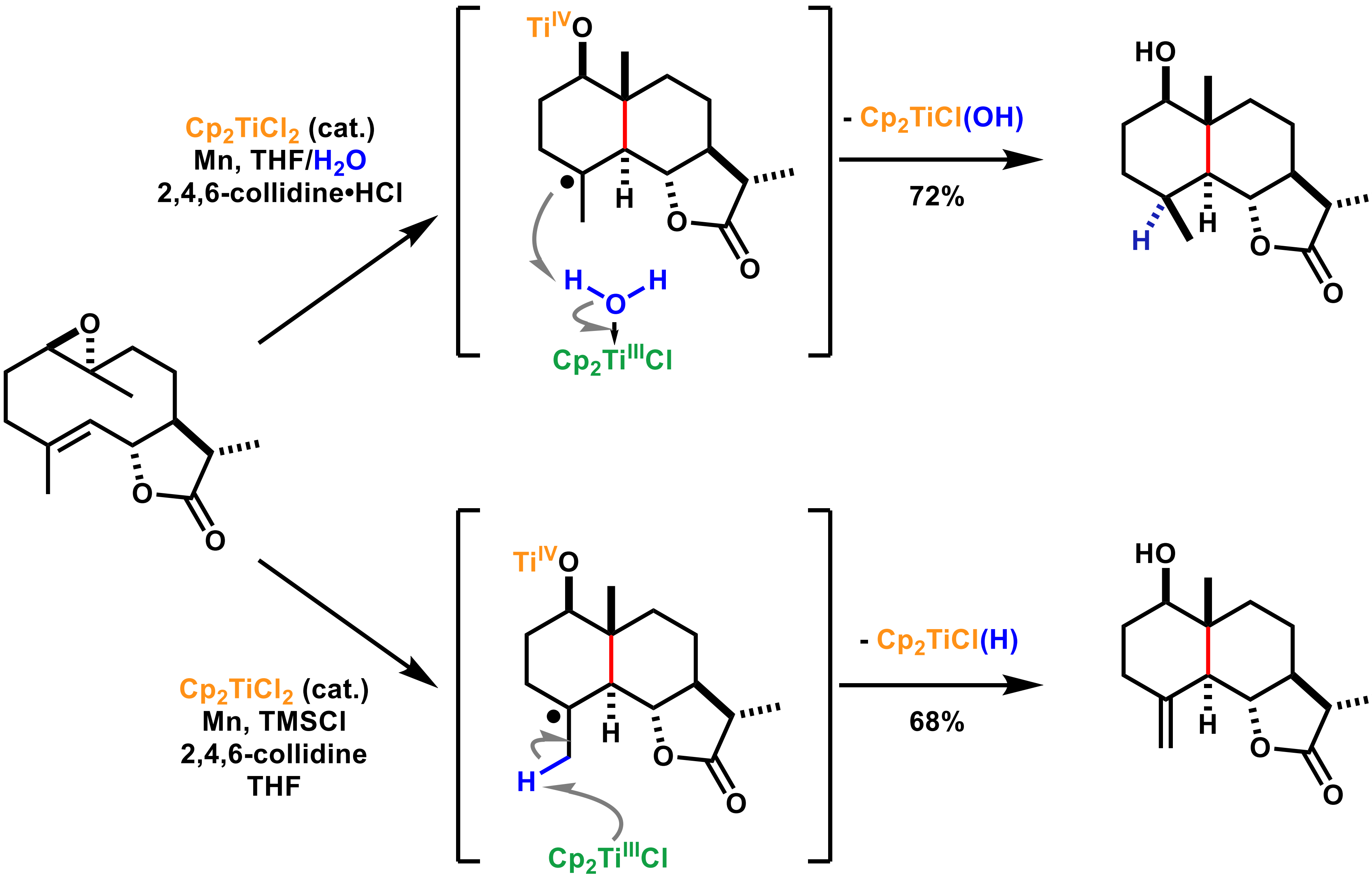
Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 101.

Catalytic Nonreductive Epoxide Opening Reaction



Barrero, A. F.; Rosales, A.; Cuerrva, J. M.; Oltra, J. E. *Org. Lett.* **2003**, *5*, 1935.

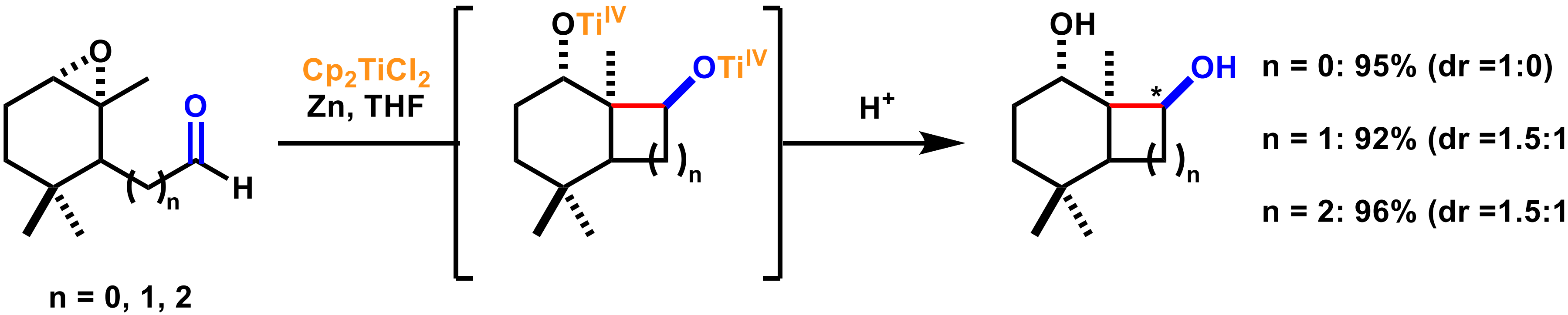
Application of Reductive/Nonreductive Catalytic Cycles



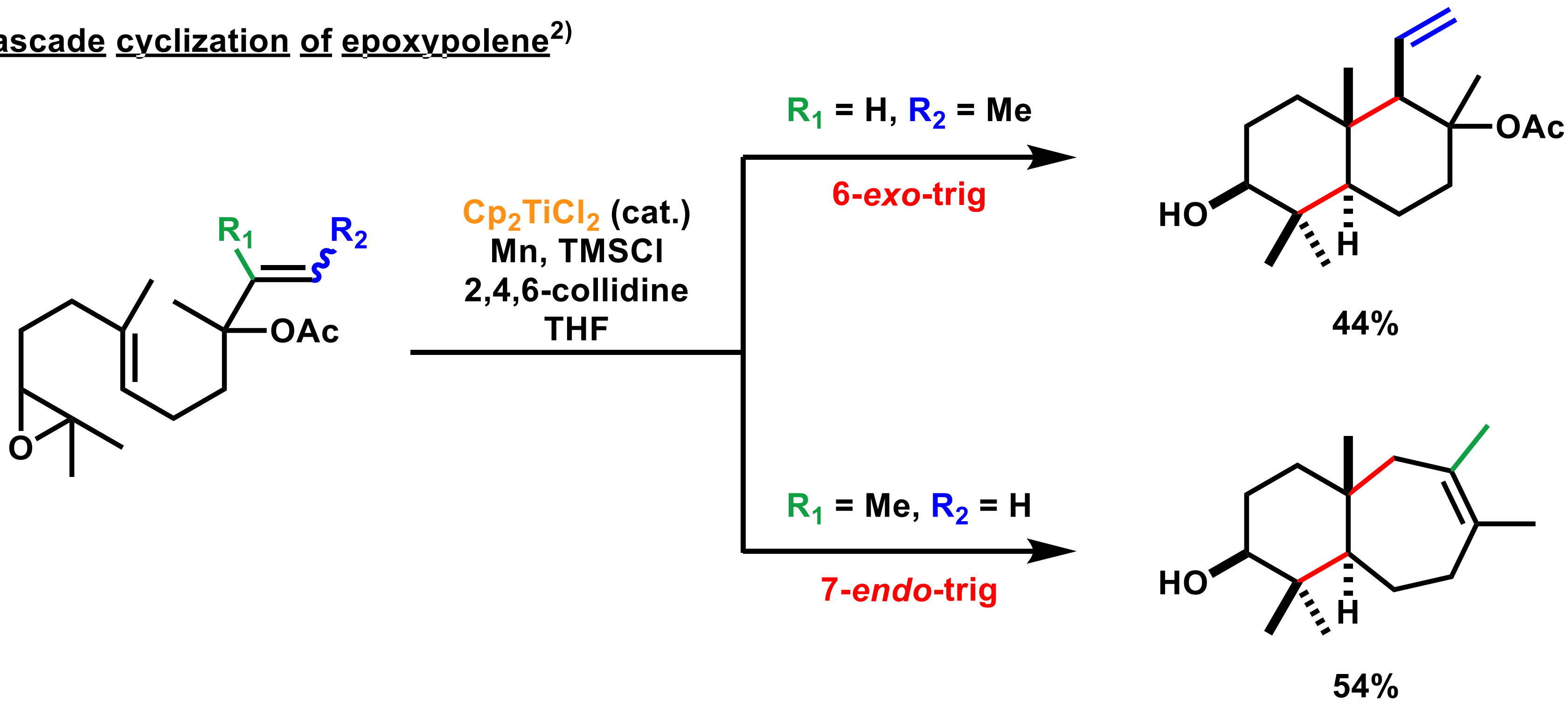
Justicia, J.; Álvarez de Cienfuegos, L.; Estévez, R. E.; Paradas, M.; Lasanta, A. M.; Oller, J. L.; Rosales, A.; Cuerrva, J. M.; Oltra, J. E. *Tetrahedron* **2008**, *64*, 11938.

Examples of Radical Cyclization

Radical cyclization; Addition to carbonyl group[1)]

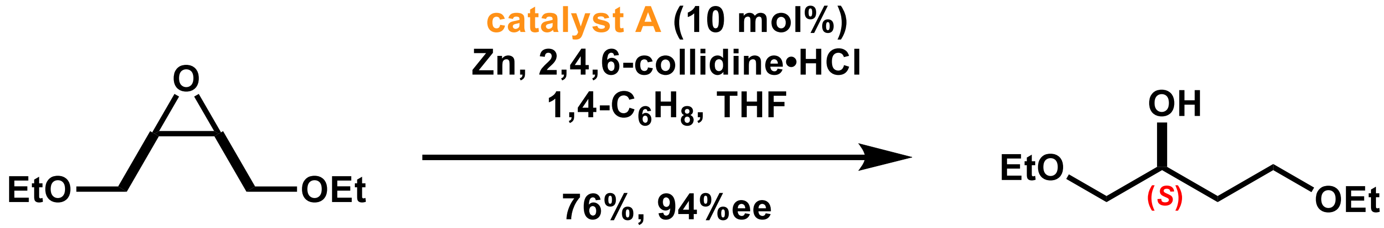


Cascade cyclization of epoxypolene[2)]

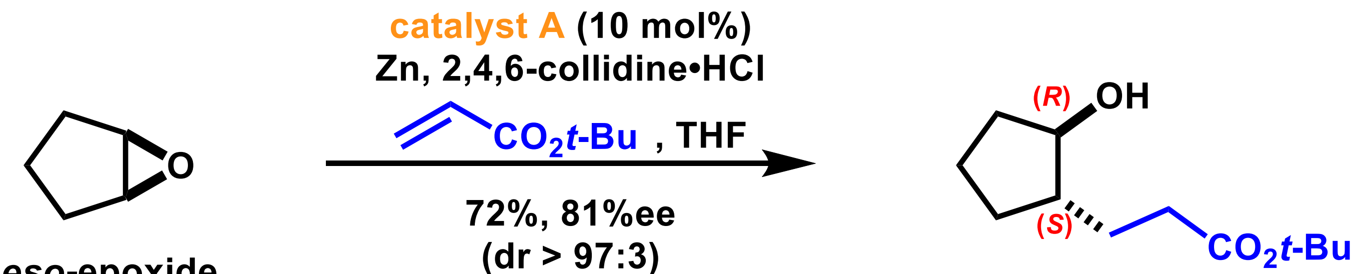


1) Fernandez-Mateos, A.; Martin de la Nava, E.; Coca, G. P.; Silvo, A. R.; Gonzalez, R. R. *Org. Lett*. **1999**, *1*, 607. 2) Justica, J.; Jimenez, T.; Miguel, D.; Contreras-Montoya, R.; Chanboun, R.; Alvarez-Manzaneda, E.; Collado-Sanz, D.; Cardenas, D. J.; Cuerva, J. M. *Chem.-Eur. J.* **2013**, *19*, 14484.

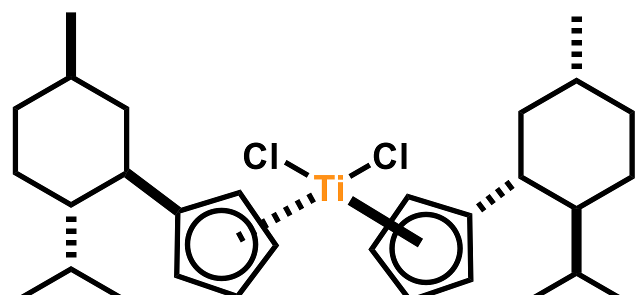
Enantioselective Opening of Epoxide



***meso*-epoxide**



***meso*-epoxide**

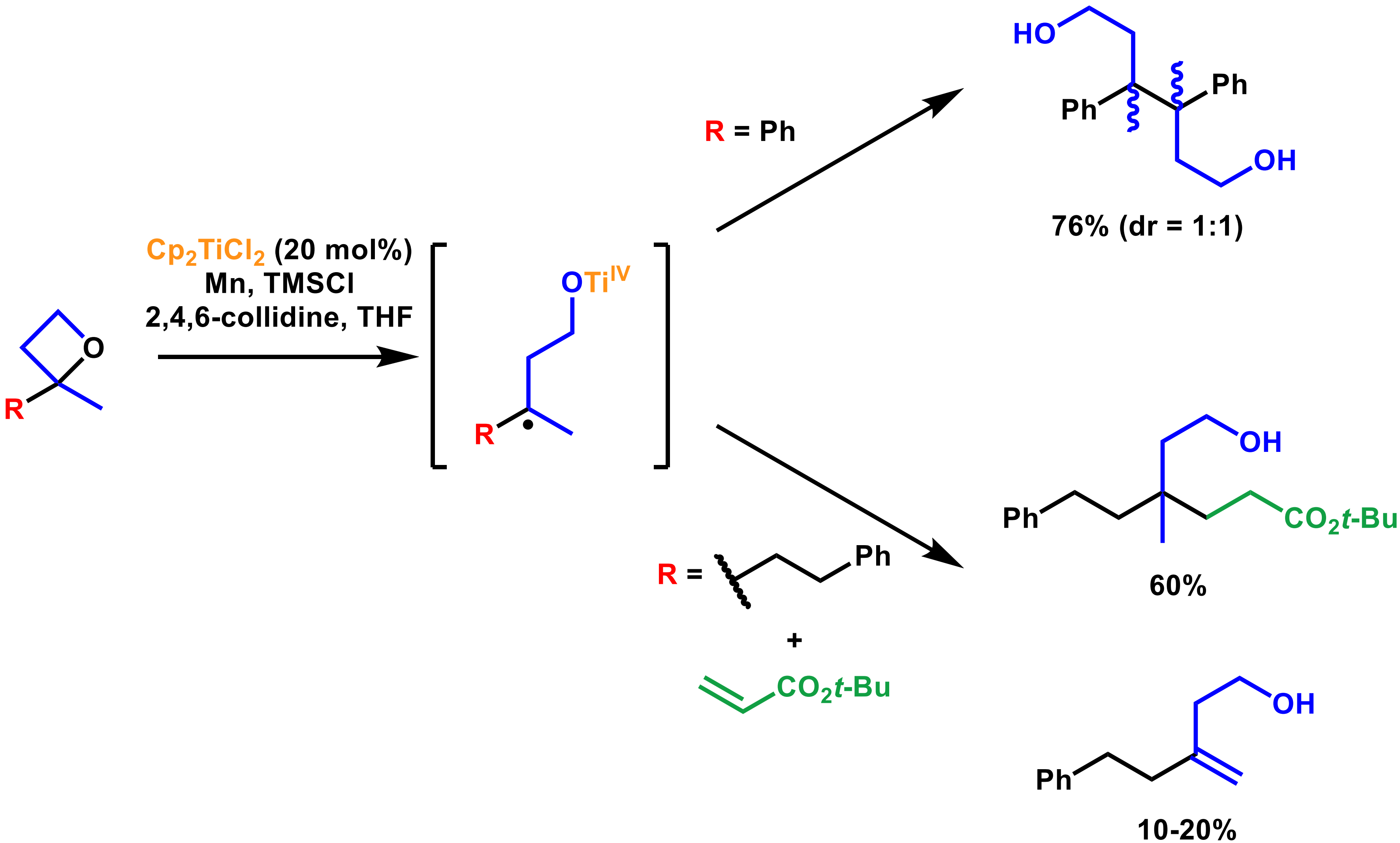


catalyst A

Gansäuer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem. Eur. J.* **2003**, *9*, 531.

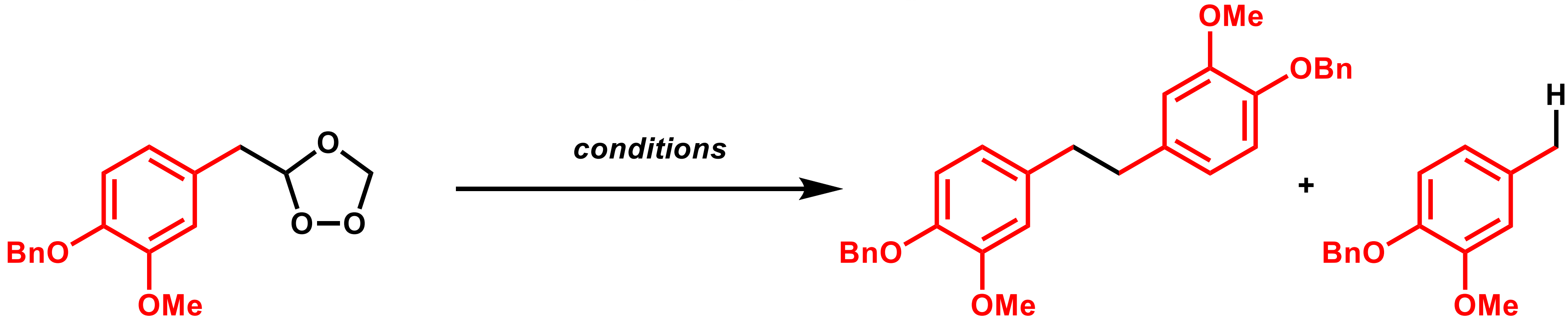
Table of Contents

Radical Ring-Opening of Oxetanes

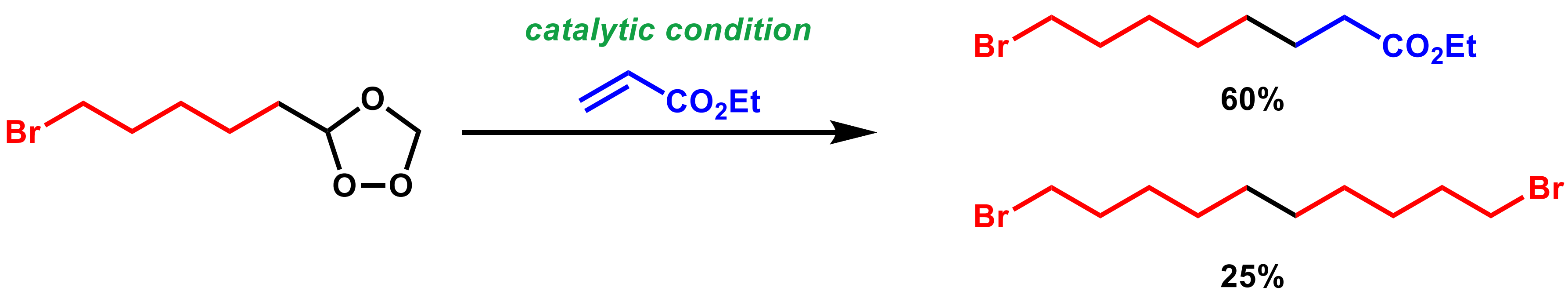


Gansäuer, A.; Ndene, A.; Lauterbach, T.; Justicia, J.; Winkler, I.; Mück-Lichtenfeld, C.; Grimme, S. *Tetrahedron* **2008**, *64*, 11839.

Radical Ring-Opening of Ozonide



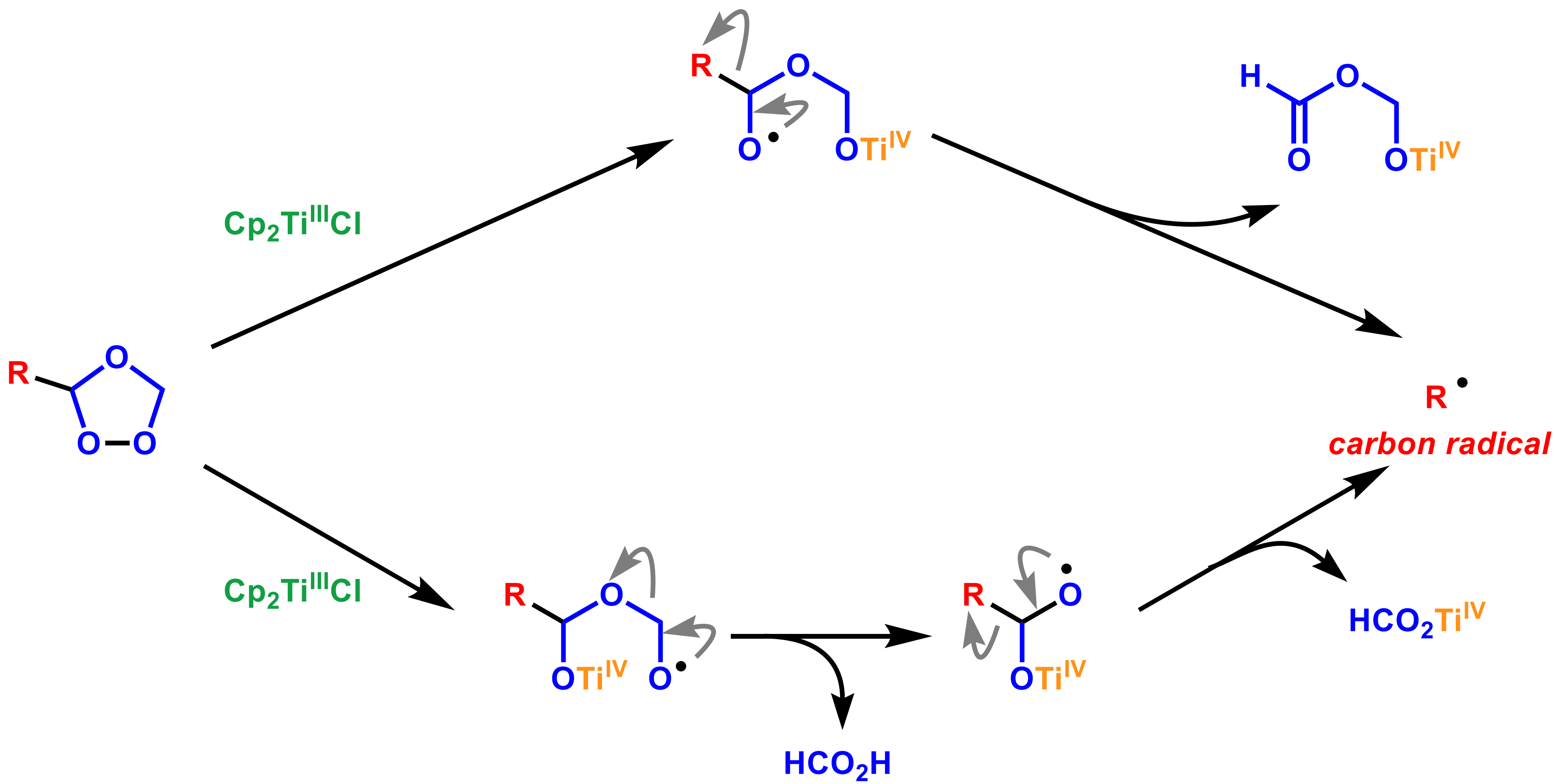
stoichiometric condition	61%	37%
catalytic condition	99%	0%



stoichiometric condition: Cp_2TiCl_2 (3 eq.), Mn, THF
catalytic condition: Cp_2TiCl_2 (10 mol%), Mn, TMSCl, 2,4,6-collidine, THF

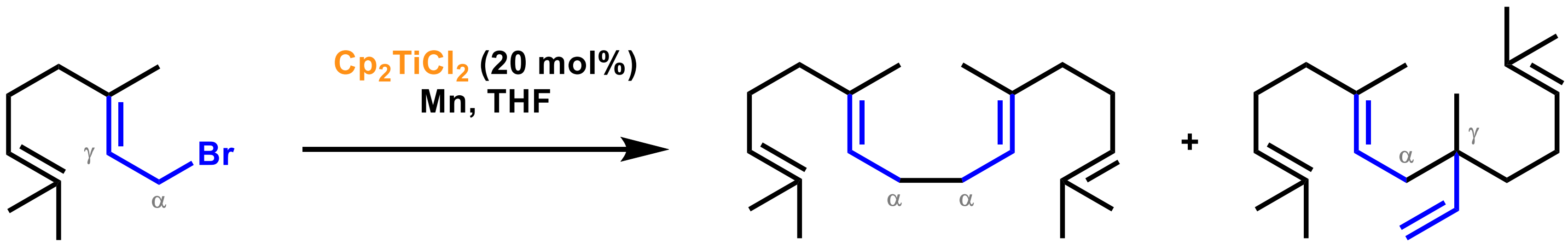
Rosales, A.; Muñoz-Bascón, J.; López-Sánchez, C.; Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I.; Oltra, J. E. *J. Org. Chem.* **2012**, *77*, 4171.

Proposed Mechanism of Homolytic Ozonide Opening

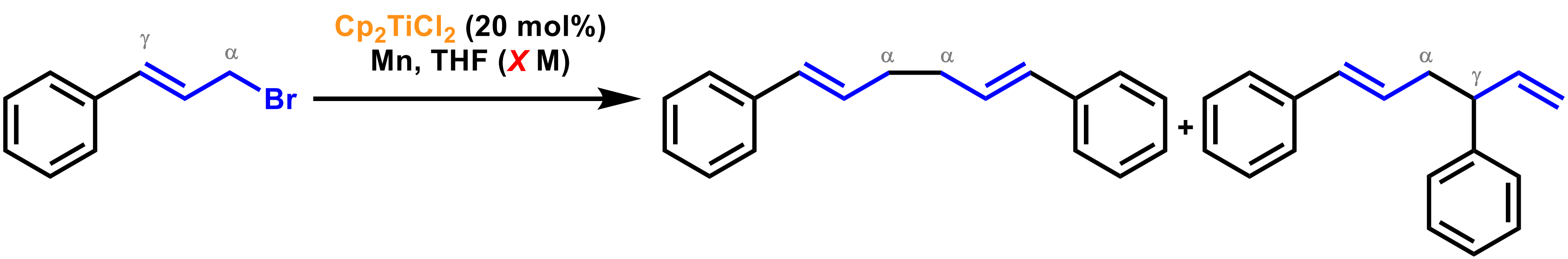


Rosales, A.; Muñoz-Bascón, J.; López-Sánchez, C.; Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I.; Oltra, J. E.
J. Org. Chem. **2012**, *77*, 4171.

Homocoupling of Allylic Halides



89% (αα:αγ = 64:36)

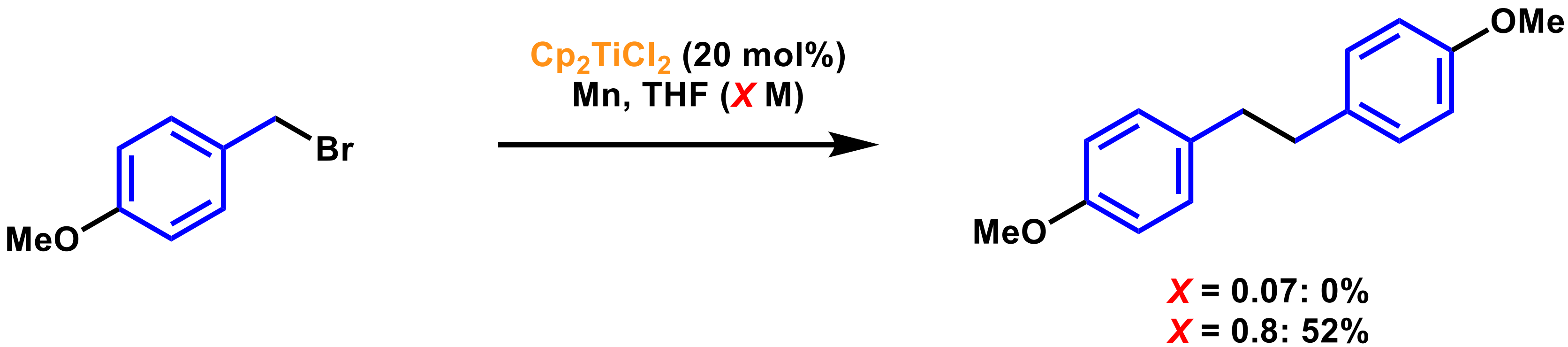


X **= 0.07: 0%**
X **= 0.8: 85% (αα:αγ = 45:55)**

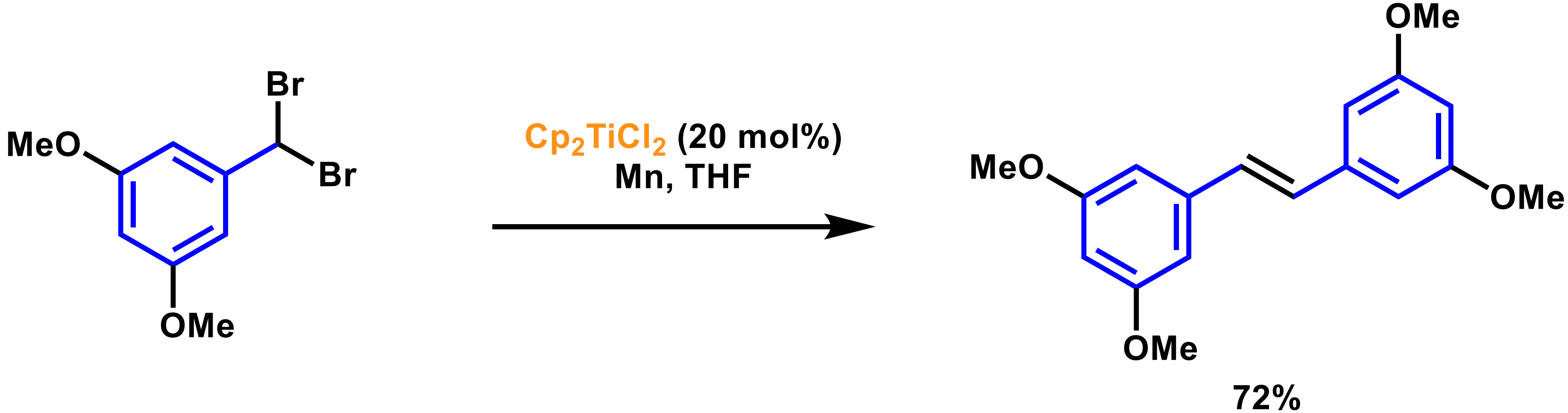
Barrero, A. F.; Herrador, M. M.; Quilez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Dieguez, H. R.; Sanchez, E. M. *J. Org. Chem.* **2007**, *72*, 2988.

Homocoupling of Benzylic Halides

Homocoupling of Benzylic Bromide

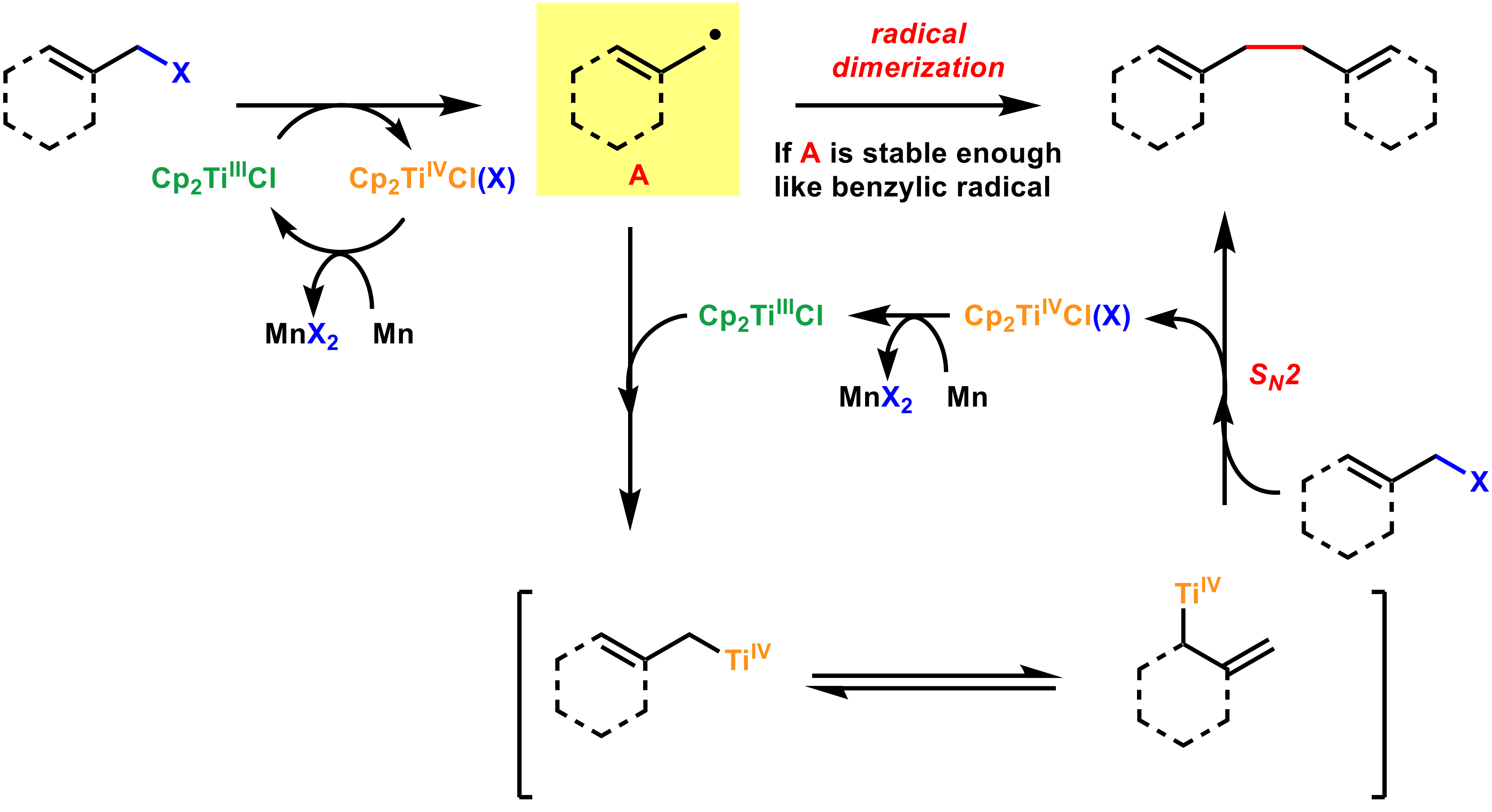


Homocoupling of Benzylic gem-Dibromide



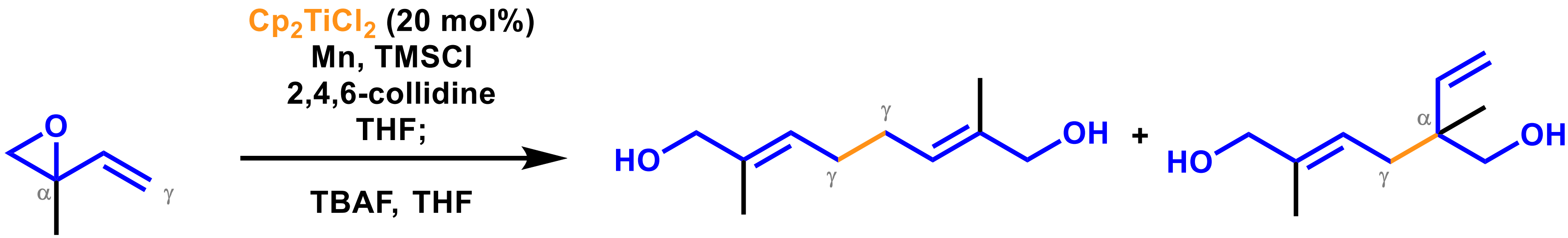
Barrero, A. F.; Herrador, M. M.; Quilez del Moral, J. F.; Arteaga, P.; Akssira, M.; Hanbali, F. E.; Arteaga, J. F.; Dieguez, H. R.; Sanchez, E. M. *J. Org. Chem.* **2007**, *72*, 2251.

Proposed Mechanism of Homocoupling of Allylic and Benzylic Halides

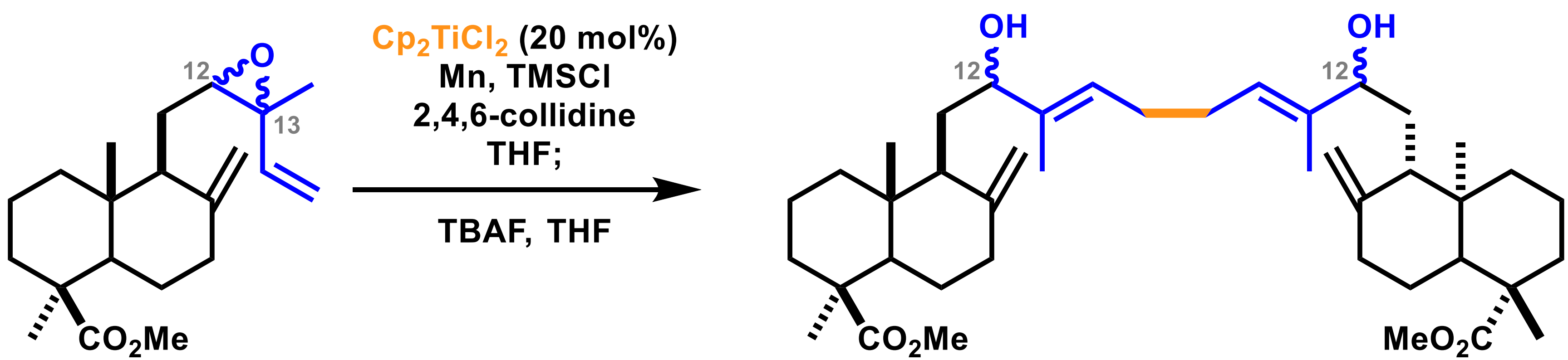


Barrero, A. F.; Herrador, M. M.; Quilez del Moral, J. F.; Arteaga, P.; Akssira, M.; Hanbali, F. E.; Arteaga, J. F.; Dieguez, H. R.; Sanchez, E. M.
J. Org. Chem. **2007**, *72*, 2251.

Homocoupling of Vinyl Epoxides



92% (γγ : γα = 6 : 1)

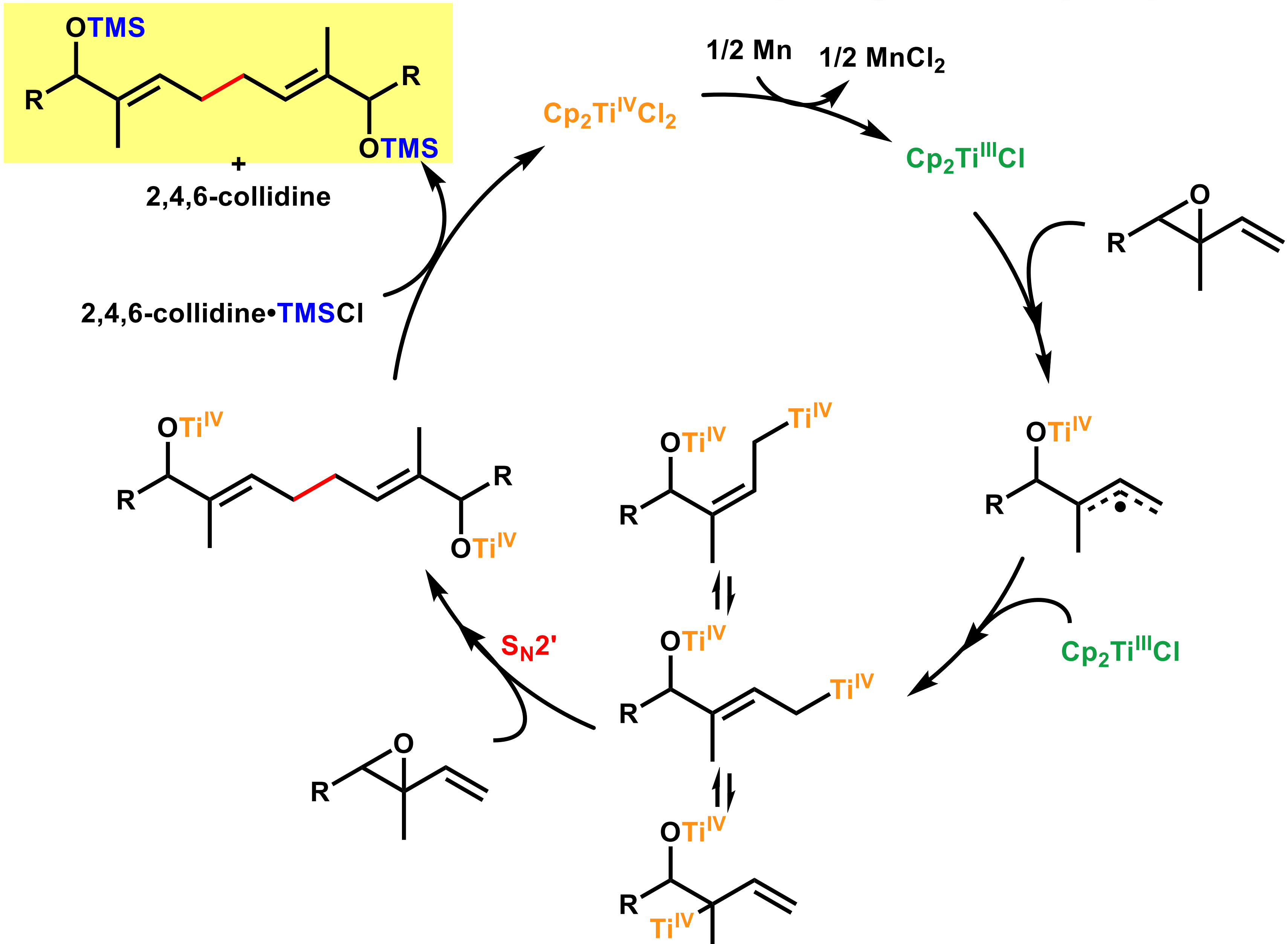


(12*R*,13*R*):(12*S*, 13*S*) = 60:40

75%
(*RR*:*RS*:*SS* = 26:32:17)

Barrero, A. F.; Quilez del Moral, J. F.; Sanchez, E. M.; Arteaga, J. F. *Org. Lett.* **2006**, *8*, 669.

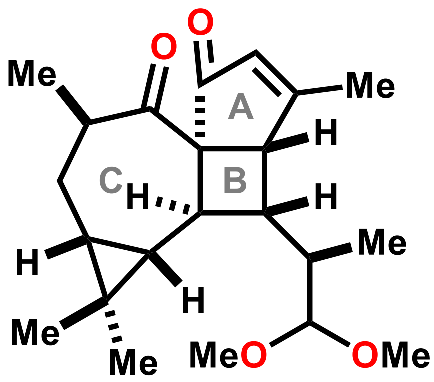
Proposed Mechanism of Homocoupling of Vinyl Epoxides



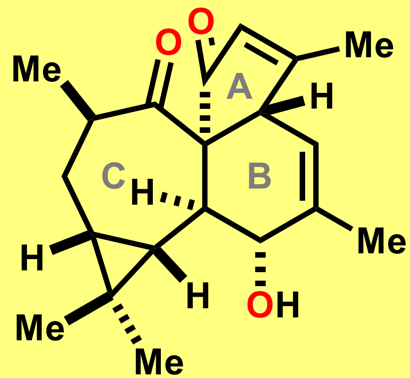
Barrero, A. F.; Quilez del Moral, J. F.; Sanchez, E. M.; Arteaga, J. F. *Org. Lett.* **2006**, *8*, 669.

Table of Contents

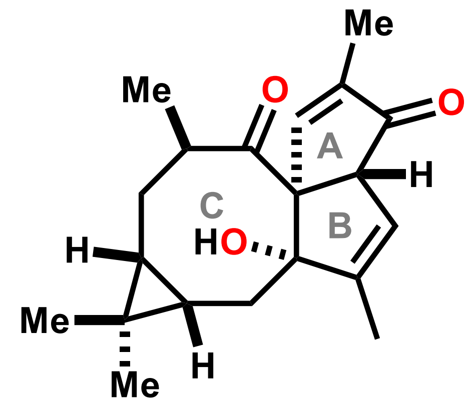
Introduction of Pepluanol A



pepluacetal



pepluanol A



pepluanol B

Isolation:

from *Euphorbia peplus*

Wan, L.-S.; Nian, Y.; Ye, C.-J.; Shao, L.-D.; Peng, X.-R.; Geng, C.-A.; Zuo, Z.-L.; Li, X.-N.; Yang, J.; Zhou, M.; Qiu, M.-H. *Org. Lett.* **2016**, *18*, 2166.

Biological activity:

Kv1.3. pottasium channel inhibitor

Structual feature:

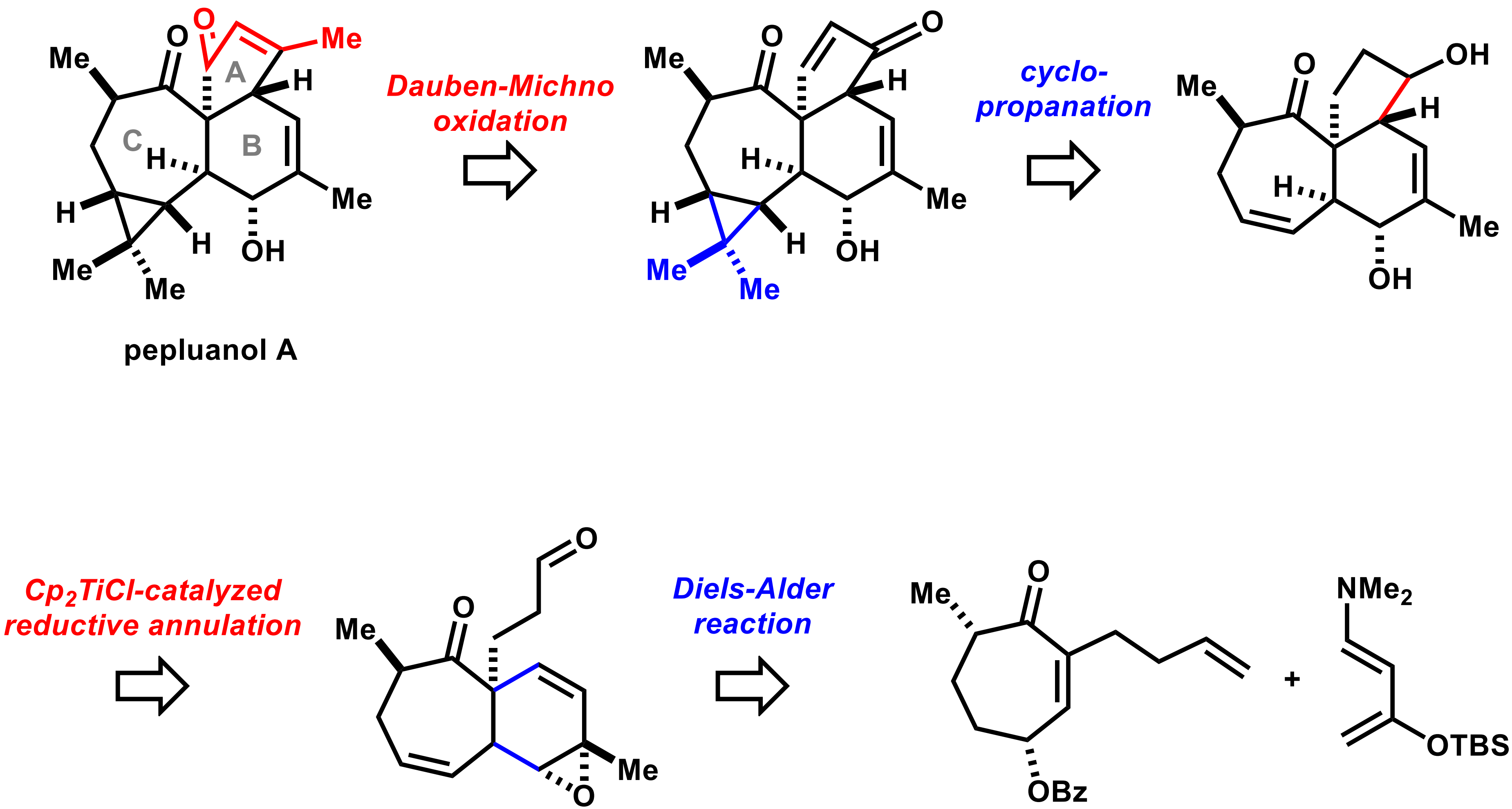
Euphorbia diterpenoid

novel 5/4/7/3, 5/6/7/3, and 5/5/8/3 fused-ring skeletons, including 6-8 stereogenic centers

Total Synthesis:

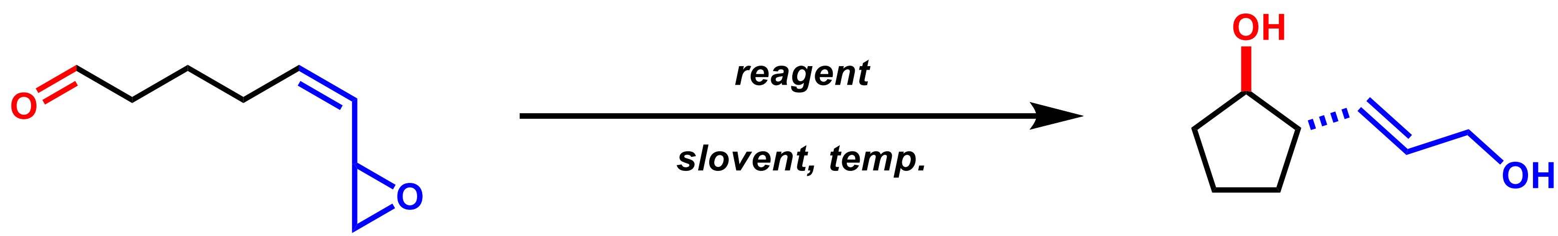
Xuan, J.; Liu, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H. *Angew. Chem. Int. Ed.* in press

Retrosynthetic Analysis of Pepluanol A



Xuan, J.; Liu, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H. *Angew. Chem. Int. Ed.* in press

Reductive Annulation of Vinyl Epoxide-Aldehyde

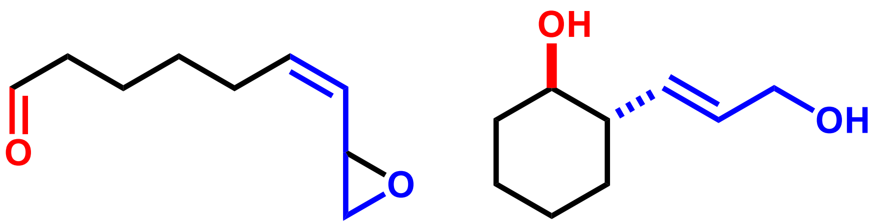


entry	*reagent*	*solvent*	*temp.*	*yield* (dr)
1	SmI_2, HMPA	THF	25 °C	52% (>20:1)
2	*n*-Bu_3SnH, AIBN	benzene	80 °C	33% (1.3:1)
3	LiDBB	THF	0 °C	78% (1.6:1)
4	Cp_2TiCl_2, Zn	THF	25 °C	88% (1.5:1)
5	Cp_2TiCl_2 (20 mol%), Zn 2,4,6-collidine•HCl	THF	25 °C	95% (1.5:1)

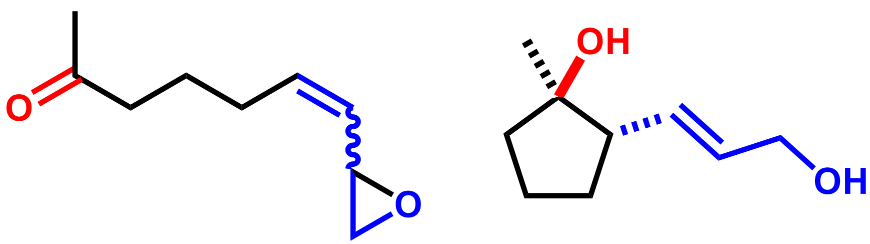
Xuan, J.; Liu, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H. *Angew. Chem. Int. Ed*. in press

Substrate Scope

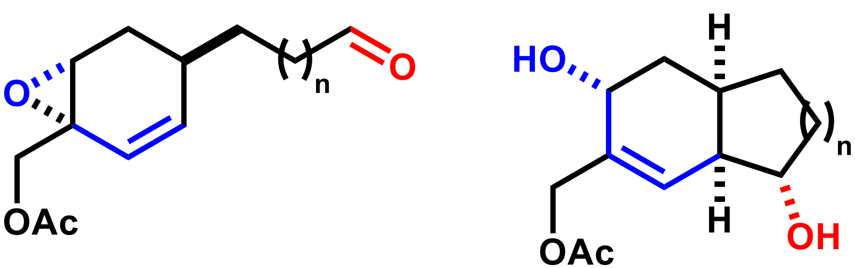
substrates	products	substrates	products



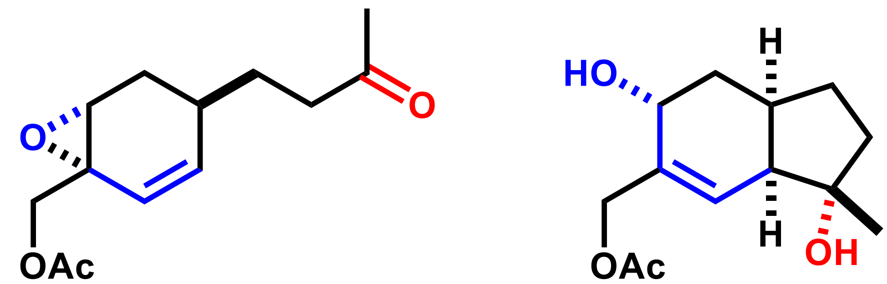
88% (dr = 1.8:1)



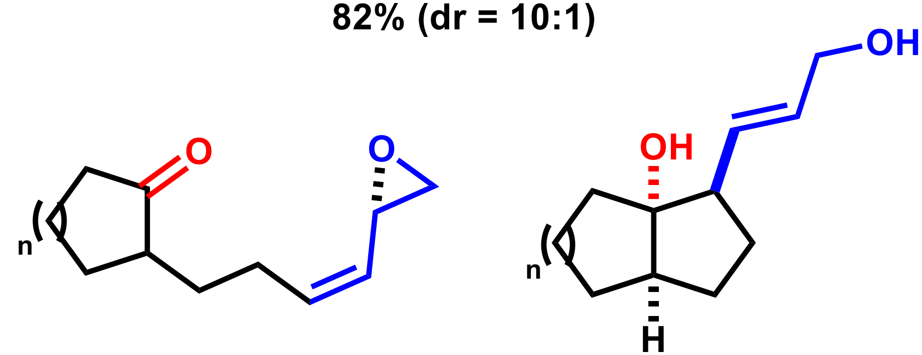
E-isomer: 84% (dr = 8:1)
Z-isomer: 83% (dr = 8:1)



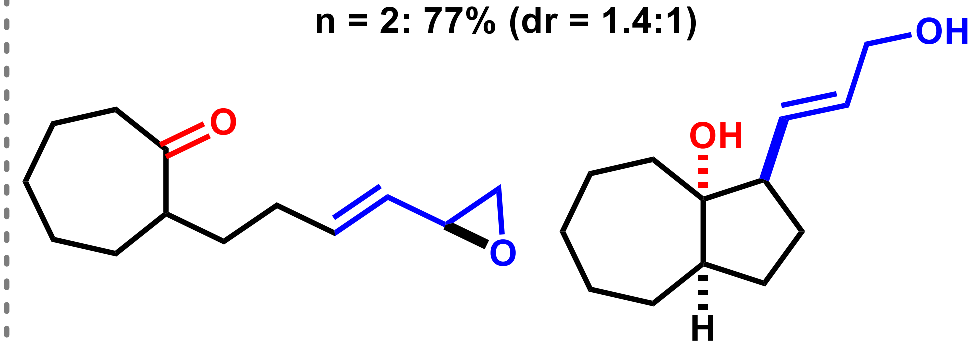
n = 1: 93% (dr = 2:1)
n = 2: 86% (dr = 1:1)



82% (dr = 10:1)



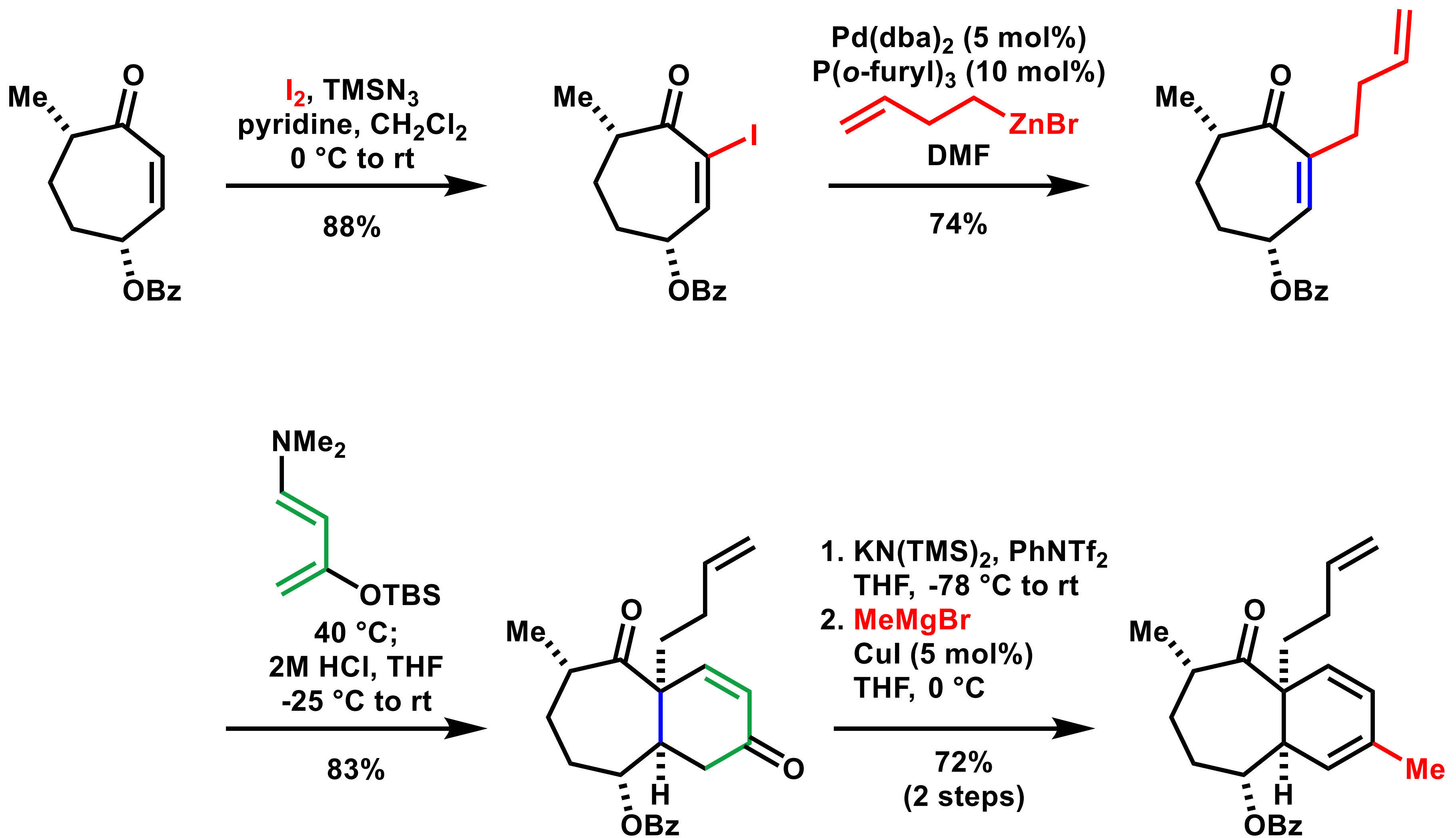
n = 1: 82% (dr = 5:1)
n = 2: 77% (dr = 1.4:1)



73% (dr = 1:1)

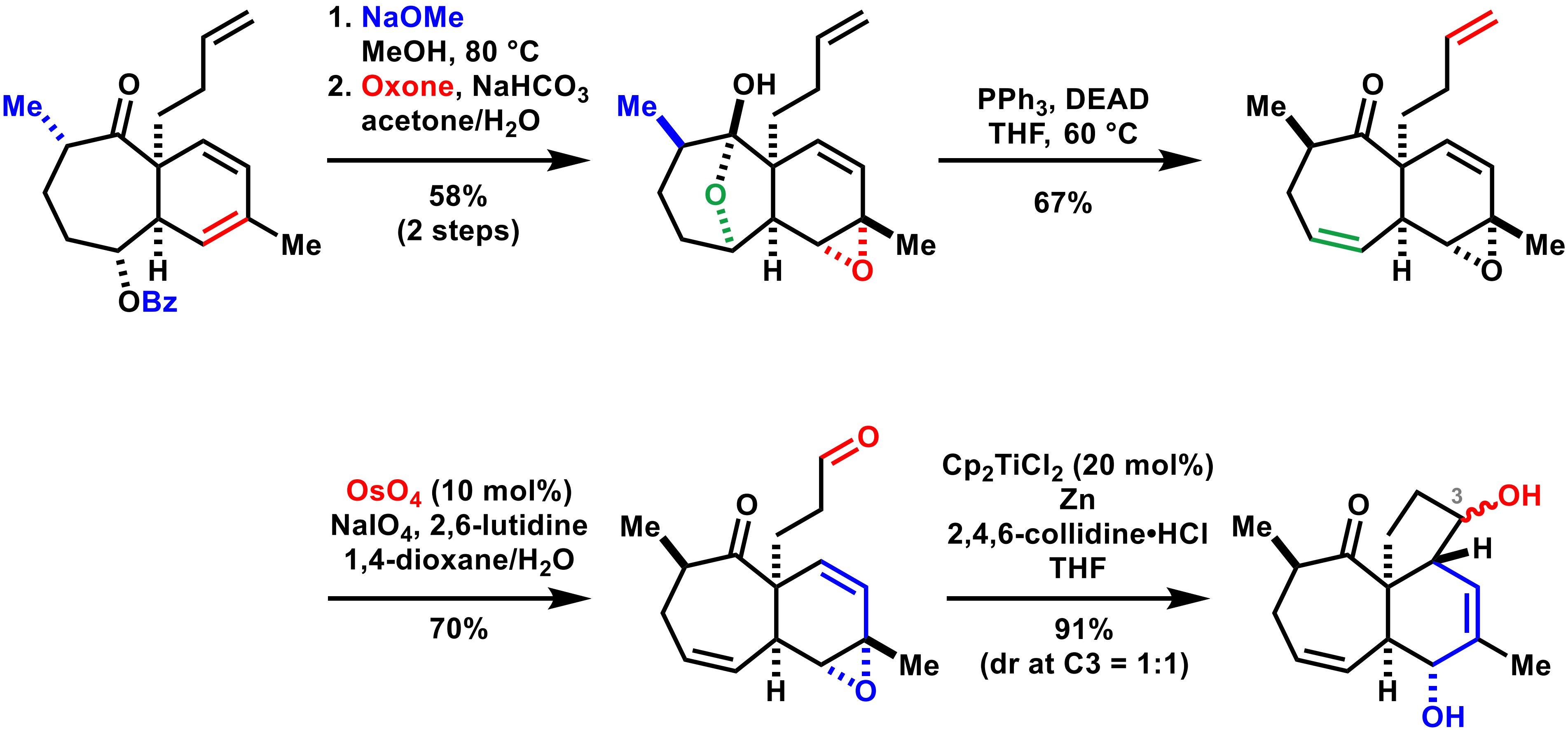
Xuan, J.; Liu, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H. *Angew. Chem. Int. Ed.* in press

Total Synthesis of Pepluanol A (1)



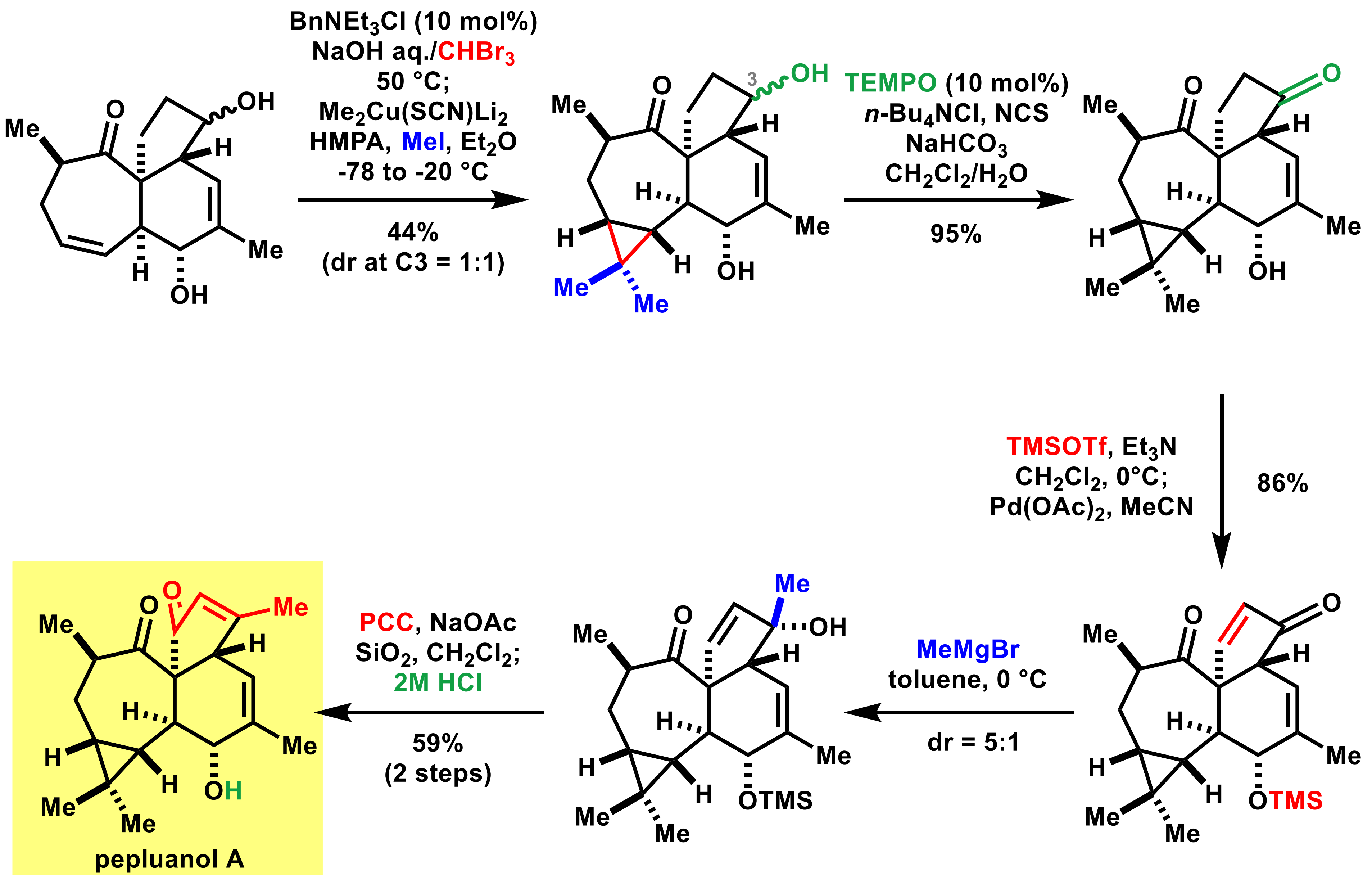
Xuan, J.; Liu, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H. *Angew. Chem. Int. Ed.* in press

Total Synthesis of Pepluanol A (2)



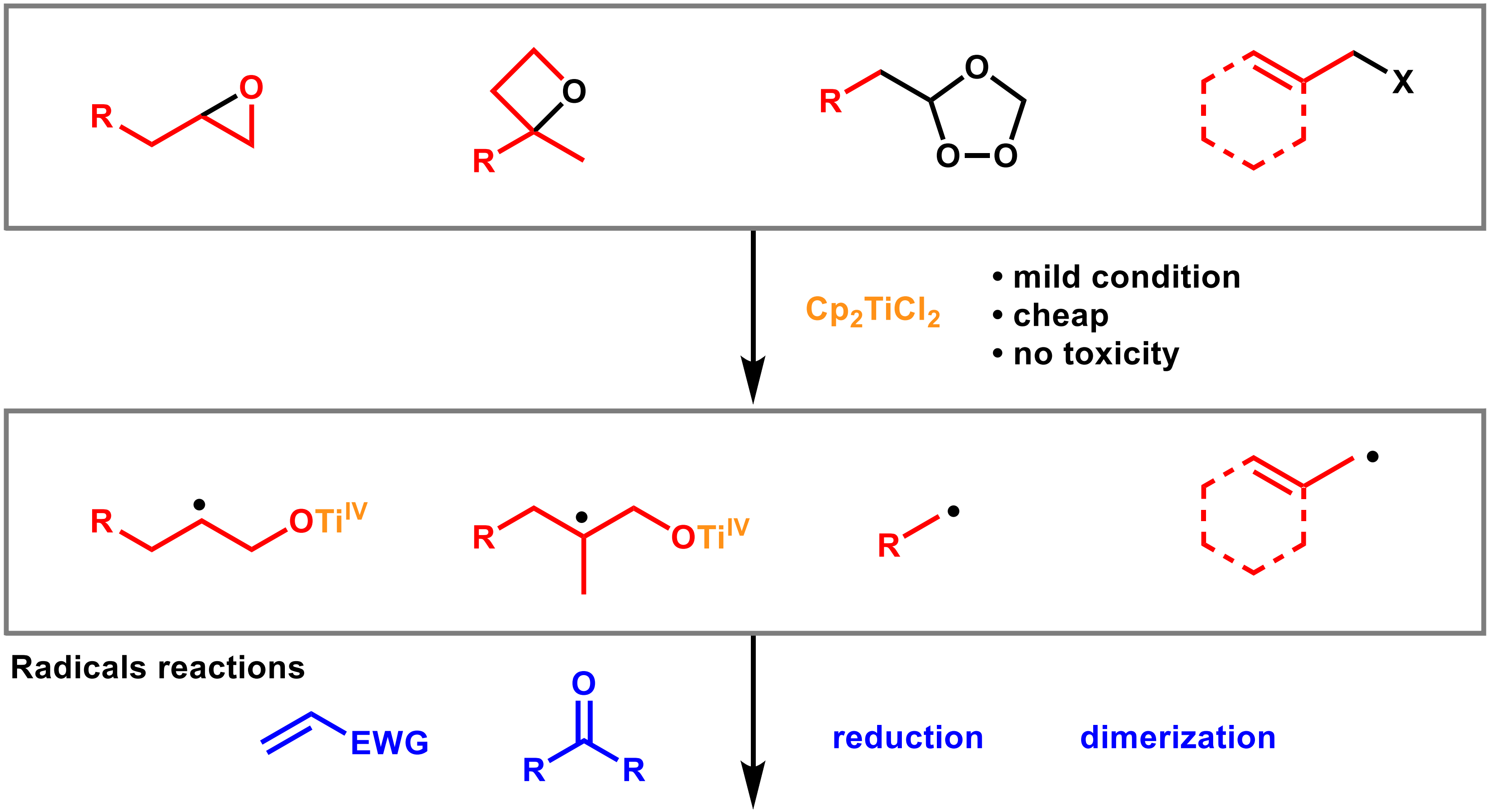
Xuan, J.; Liu, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H. *Angew. Chem. Int. Ed.* in press

Total Synthesis of Pepluanol A (3)



Xuan, J.; Liu, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H. *Angew. Chem. Int. Ed.* in press

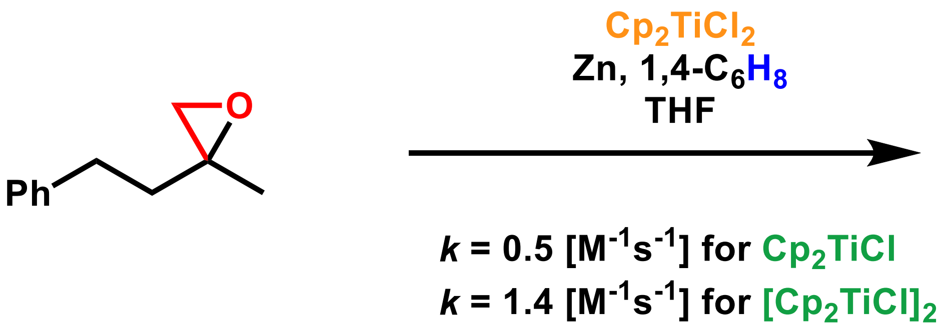
Summary

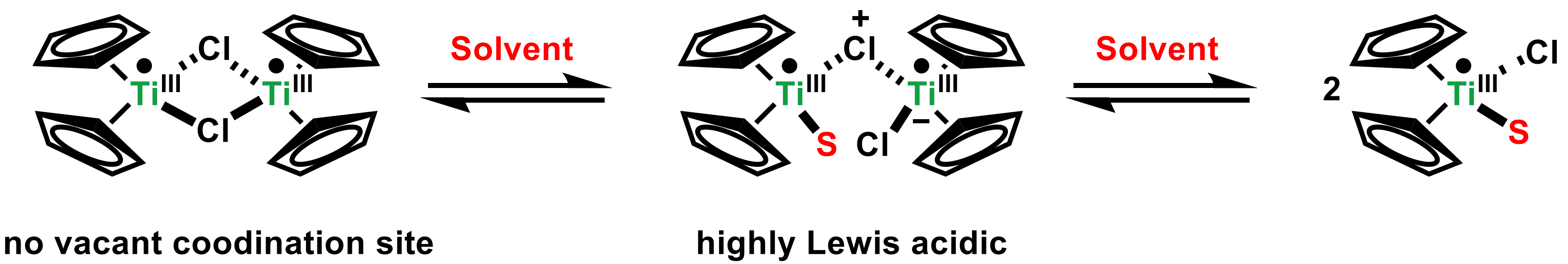


Various Natural Products Syntheses!

Appendix

A1. Reaction Mechanism of Epoxide Opening (1)

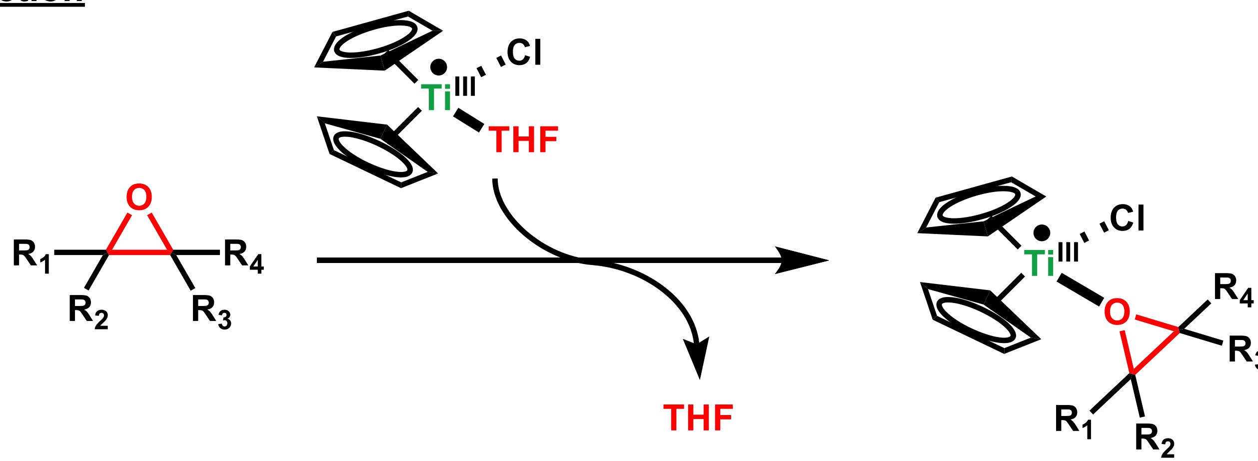




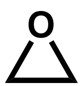
Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 2041.

A2. Reaction Mechanism of Epoxide Opening (2)

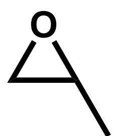
Initiation of the reaction



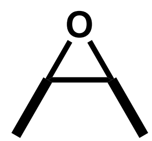
Binding enthaplies of epoxides relative to those of THF-complex



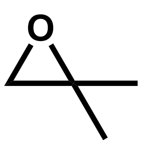
-2.1



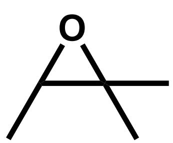
-2.2



-2.3



+2.2



+0.4

THF

0

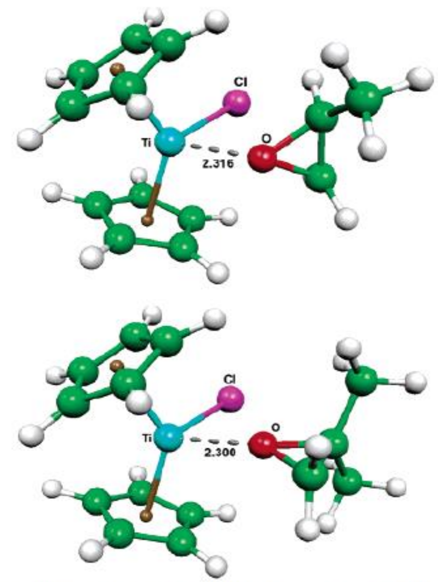
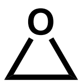
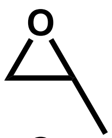
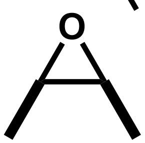
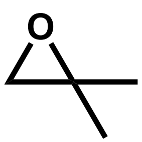
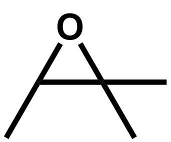


Figure 5. Structure (BP86/TZVP) of the 5a complexes of 8 (top) and 10 (bottom). Distances in angstrom.

Gansäuer, A.; Barchuk, A.; Keller, F. Shmitt, M.; Grimme, S.; Gerenkamp, Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359.

A3. Reaction Mechanism of Epoxide Opening (3)

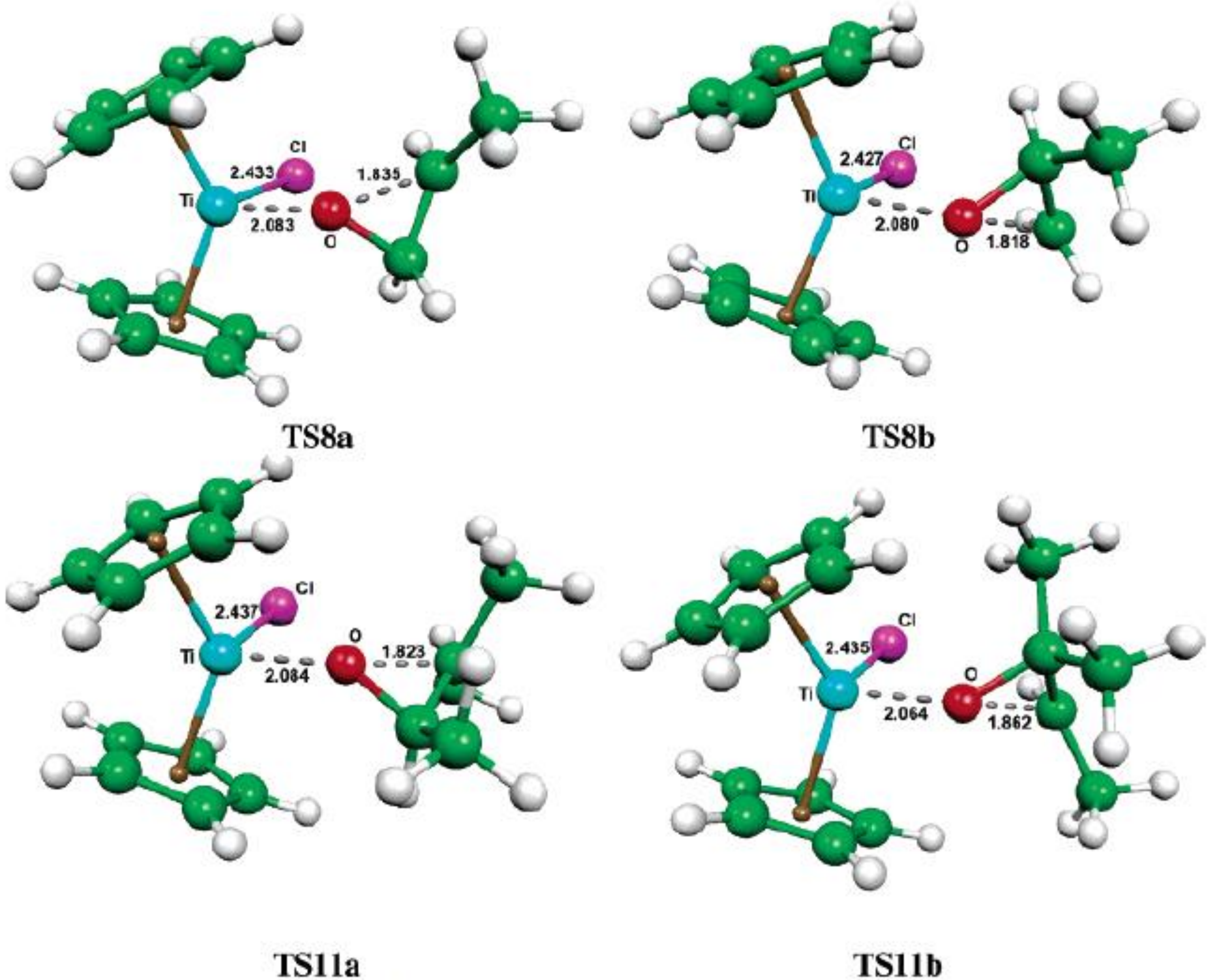
Table 3. Activation and Reaction Energies of the Epoxide Complexes **5a*7−5a*11** in kcal mol^{-1}

	Product	ΔE	$\Delta E^{\ddagger}$	Substrate	$\Delta E^{\ddagger}$	ΔE	Product
	 **7a**	-4.1	8.7	**5a*7**	-	-	-
	 **8a**	-4.0	8.2	**5a*8**	9.4	-1.8	 **8b**
	 **9a**	-1.8	8.8	**5a*9**	-	-	-
	 **10a**	-8.5	7.0	**5a*10**	9.0	-1.3	 **10b**
	 **11a**	-4.9	8.7	**5a*11**	10.3	+0.7	 **11b**

by DFT calculation with the BP functional and a TZVP basis set

Gansäuer, A.; Barchuk, A.; Keller, F. Shmitt, M.; Grimme, S.; Gerenkamp, Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359.

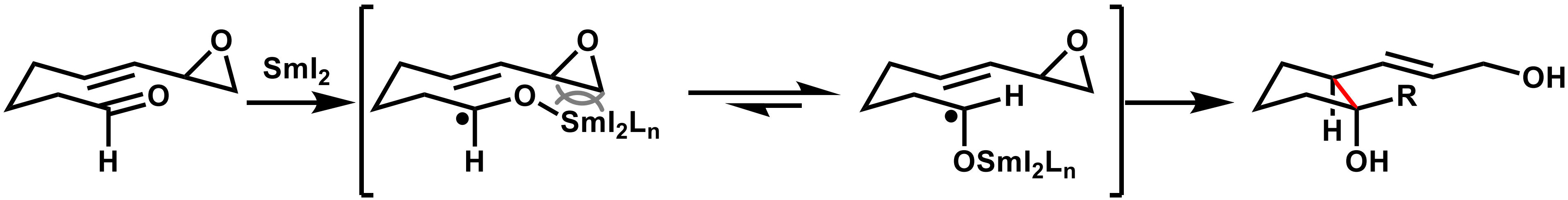
A4. Reaction Mechanism of Epoxide Opening (4)

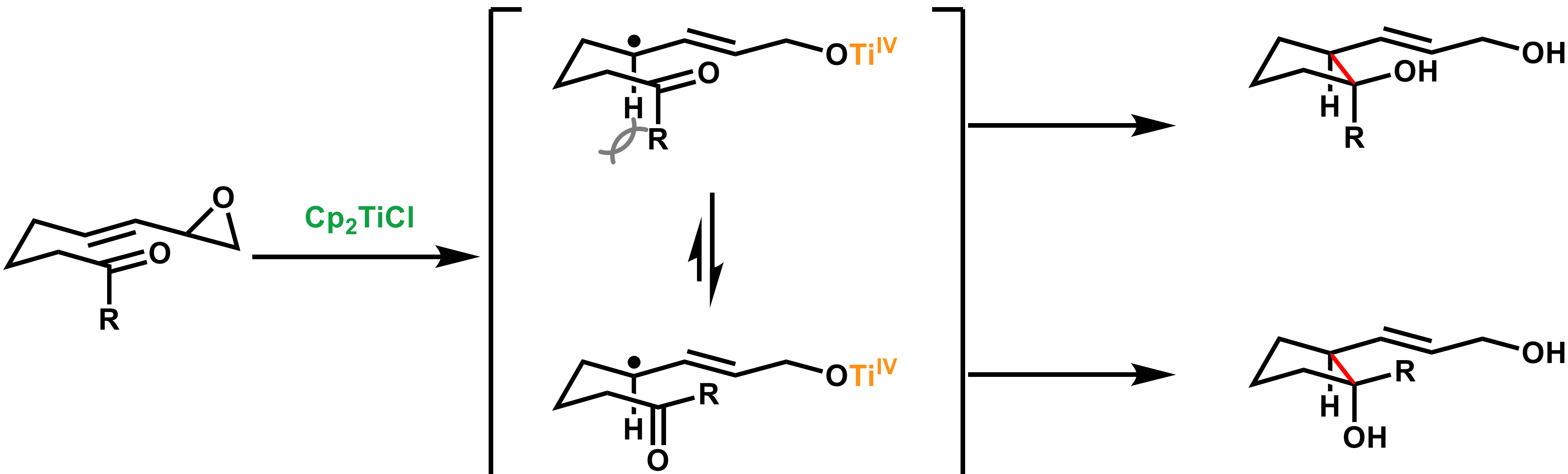


: Transition structures of the opening of 8 and 11.

Gansäuer, A.; Barchuk, A.; Keller, F. Shmitt, M.; Grimme, S.; Gerenkamp, Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359.

A5. Proposed Difference between Sm and Ti





major