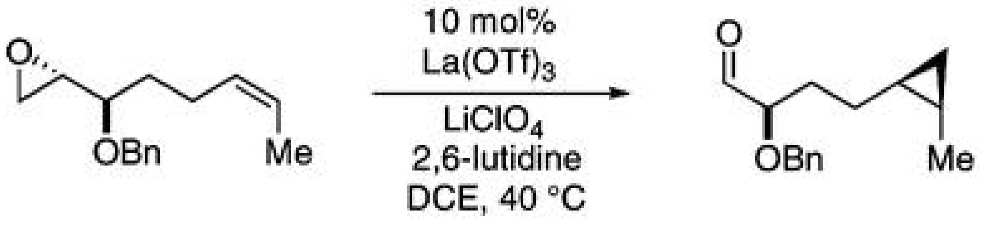
Filip Petronijevic   Current Literature Group Meeting   May 23rd, 2009.



72% yield
>20:1 d.r.

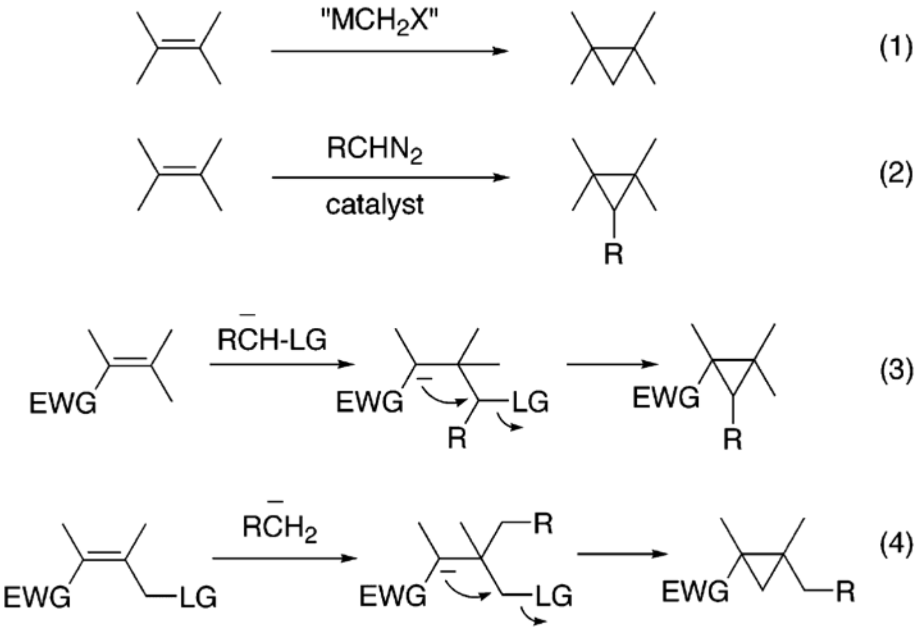
intramolecular methylene transfer

Lanthanum(III) Triflate-Catalyzed Cyclopropanation via Intramolecular Methylene Transfer

David J. Hardee and Tristan H. Lambert

J. Am. Chem. Soc. ASAP

Stereoselective Cycloropanation Reactions



Halomethylmatal (Zn, Sm, Al)-Mediated Cyclopropanation Reactions

Transition Metal-Catalyzed Decomposition of Diazo Compounds

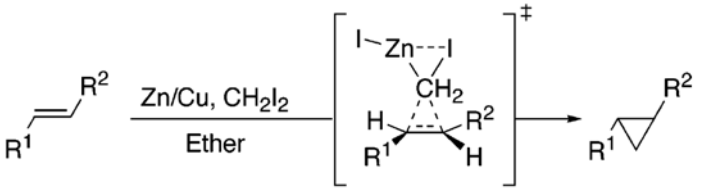
Nucleophilic Addition-Ring Closure

Chem. Rev. **2003**, *103*, 977-1050.
Chem. Rev. **2007**, *107*, 3117-3179.
Synlett **1995**, 1197.

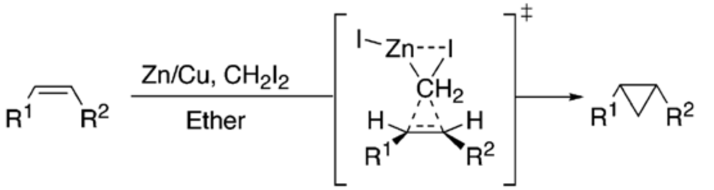
Halomethylmetal-Mediated Cyclopropanation Reactions

- Emschwiller (1929): $CH_2I_2 + Zn \longrightarrow IZnCH_2I$

- Simmons and Smith (1958):



(5)



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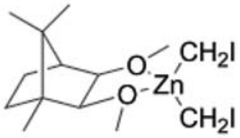
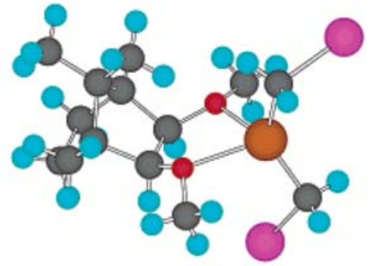
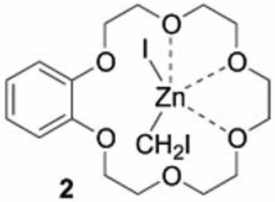


1





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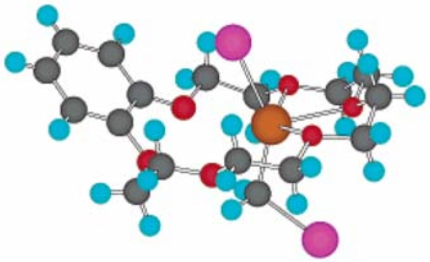

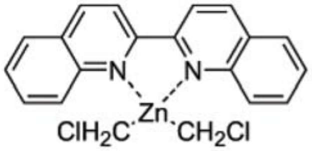

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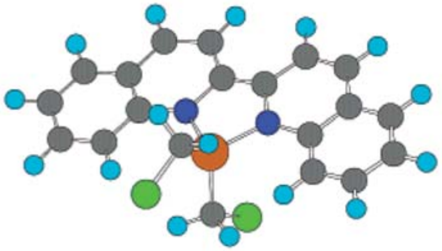


- Wittig (1961): $ZnI_2 + CH_2N_2 \longrightarrow IZnCH_2I$ $(Zn(CH_2I)_2)$

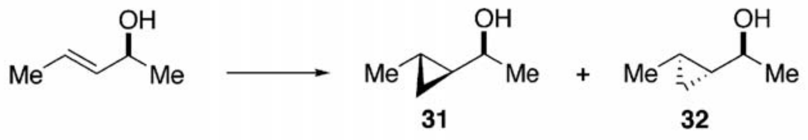
- Furukawa (1966): $ZnI_2 + Et_2Zn \longrightarrow EtZnCH_2I$

- Molander, Yamamoto

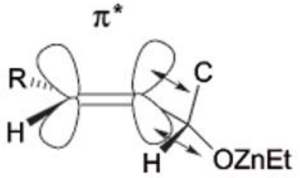
"MCH_2X" $RZnCH_2I$, $RSmCH_2I$
R_2AlCH_2I

Compt. Rend. **1929**, *188*, 1555.
J. Am. Chem. Soc.. **1958**, *80*, 5323.
Justus Liebigs Ann. Chem. **1961**, *650*, 18.
J. Am. Chem. Soc.. **1992**, *114*, 2592.
J. Am. Chem. Soc.. **1996**, *118*, 6792.

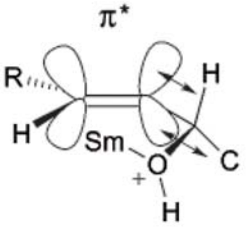
Halomethylmetal-Mediated Cyclopropanation Reactions: Acyclic Alkenes

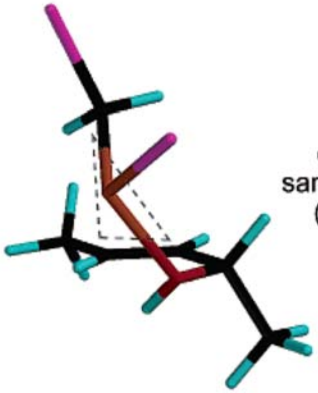


conditions	ratio **31**:**32**
Zn/Cu, CH_2I_2, ether	56:44[46]
Et_2Zn, CH_2I_2 (1:1), CH_2Cl_2	86:14
Et_2Zn, CH_2I_2 (1:1), ether	67:33
$Zn(CH_2I)_2$, CH_2Cl_2	67:33
Sm(Hg), CH_2I_2, THF	25:75

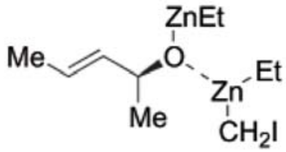


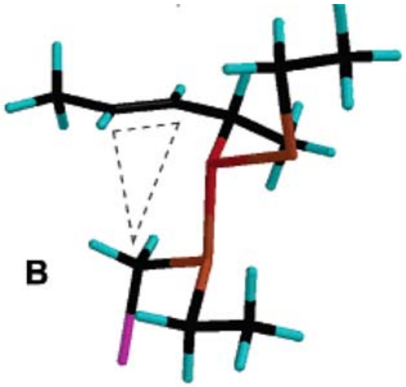
More reactive conformer with zinc alkoxides





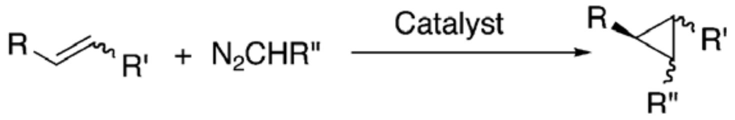
More reactive conformer with samarium "oxonium" (small C group)

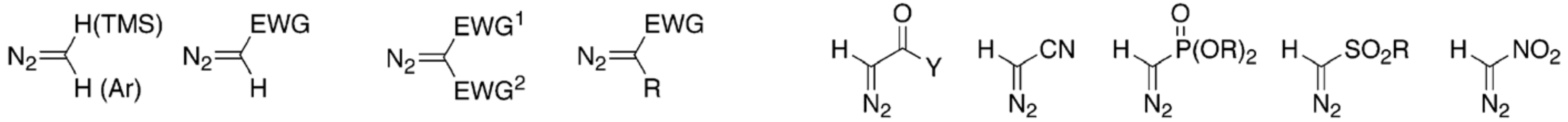




Chem. Rev. **1993**, *93*, 1307.
Chem. Rev. **1989**, *89*, 1841.

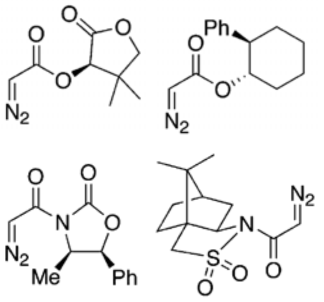
Transition Metal-Catalyzed Decomposition of Diazoalkanes

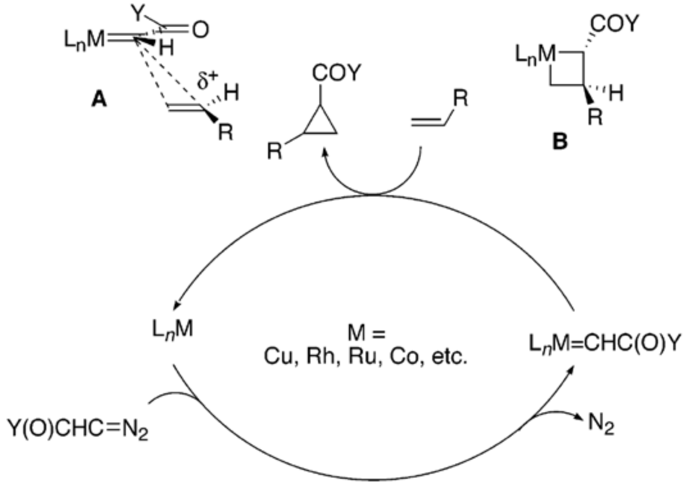




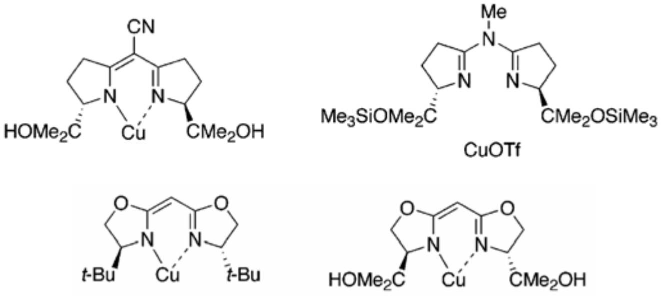
Metals: Cu, Rh, Ru, Os, Co, Fe, Pd, Pt, Cr

chiral auxilaries



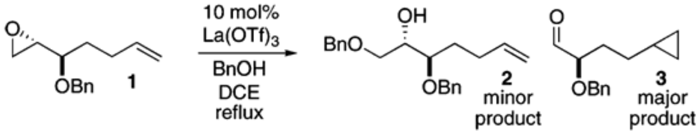


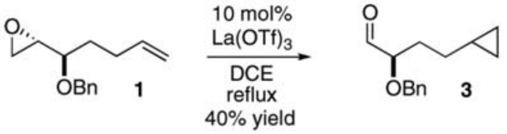
chiral catalysts



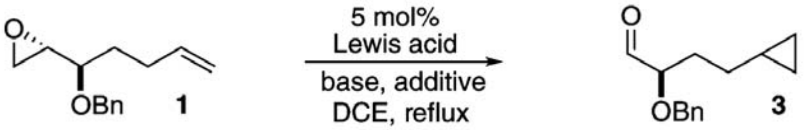
Chem. Rev. **2003**, *103*, 977.
J. Am. Chem. Soc. **2001**, *123*, 7616.
Chem. Eur. J. **2002**, *8*, 177.

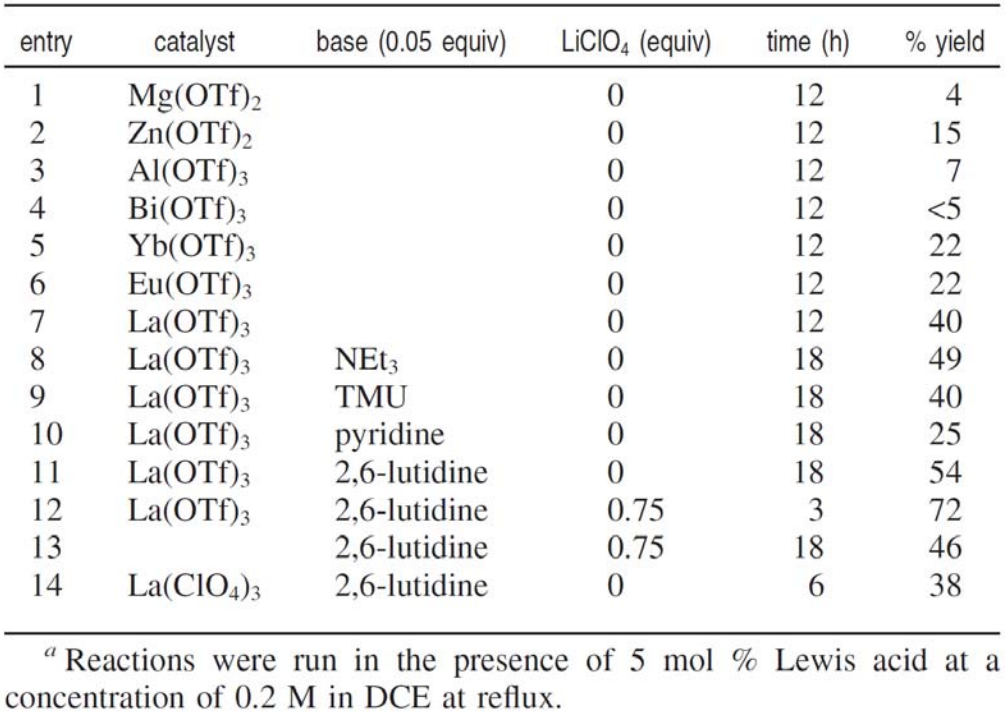
Title Paper: Cyclopropanation via Intramolecular Methylene Transfer





only product
intramolecular methylene transfer



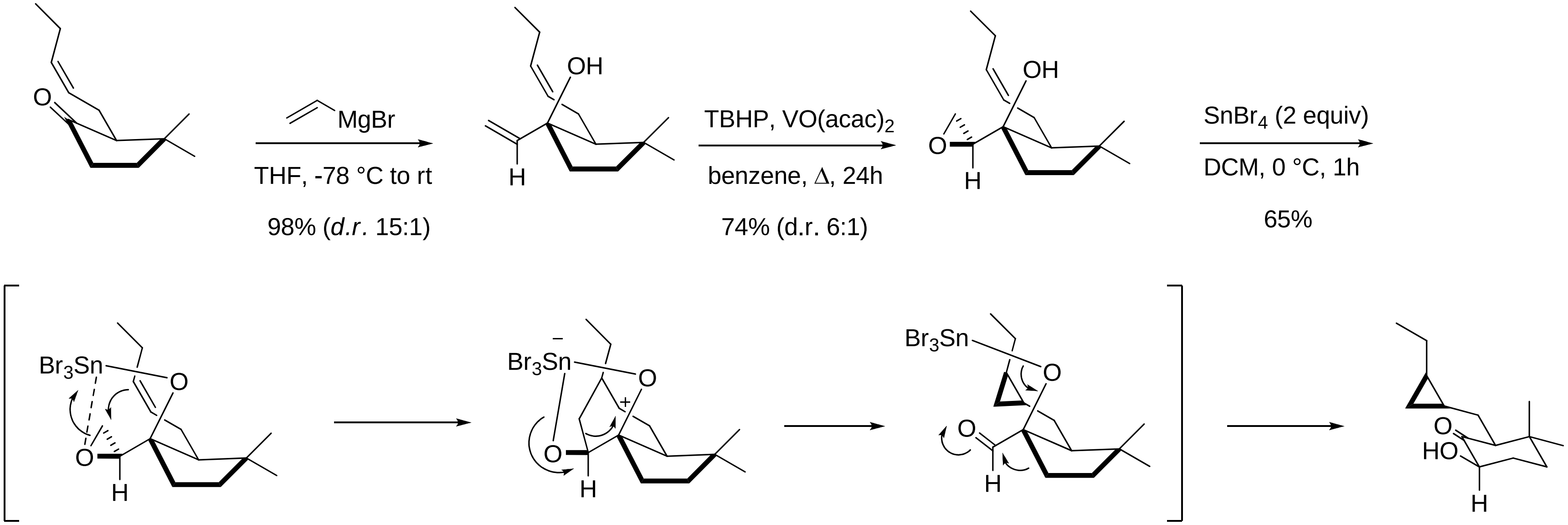


entry	catalyst	base (0.05 equiv)	$LiClO_4$ (equiv)	time (h)	% yield
1	$Mg(OTf)_2$		0	12	4
2	$Zn(OTf)_2$		0	12	15
3	$Al(OTf)_3$		0	12	7
4	$Bi(OTf)_3$		0	12	<5
5	$Yb(OTf)_3$		0	12	22
6	$Eu(OTf)_3$		0	12	22
7	$La(OTf)_3$		0	12	40
8	$La(OTf)_3$	NEt_3	0	18	49
9	$La(OTf)_3$	TMU	0	18	40
10	$La(OTf)_3$	pyridine	0	18	25
11	$La(OTf)_3$	2,6-lutidine	0	18	54
12	$La(OTf)_3$	2,6-lutidine	0.75	3	72
13		2,6-lutidine	0.75	18	46
14	$La(ClO_4)_3$	2,6-lutidine	0	6	38

[a] Reactions were run in the presence of 5 mol % Lewis acid at a concentration of 0.2 M in DCE at reflux.

J. Am. Chem. Soc. **2009**, ASAP.

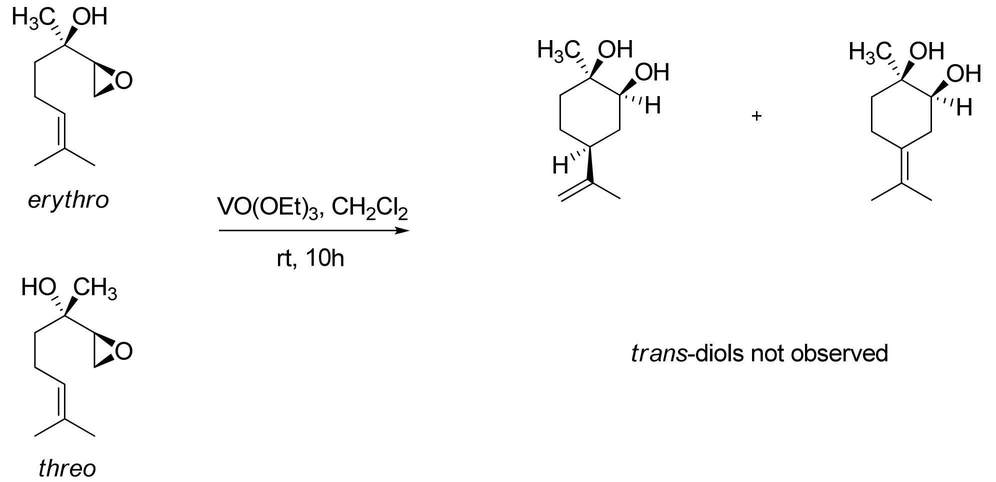
Sequential Stereocontrolled Cyclopropane formation – Semi-pinacol Rearrangement



- multiple equivalents of Lewis acid promoter were used
- methylene is transferred in a constrained system

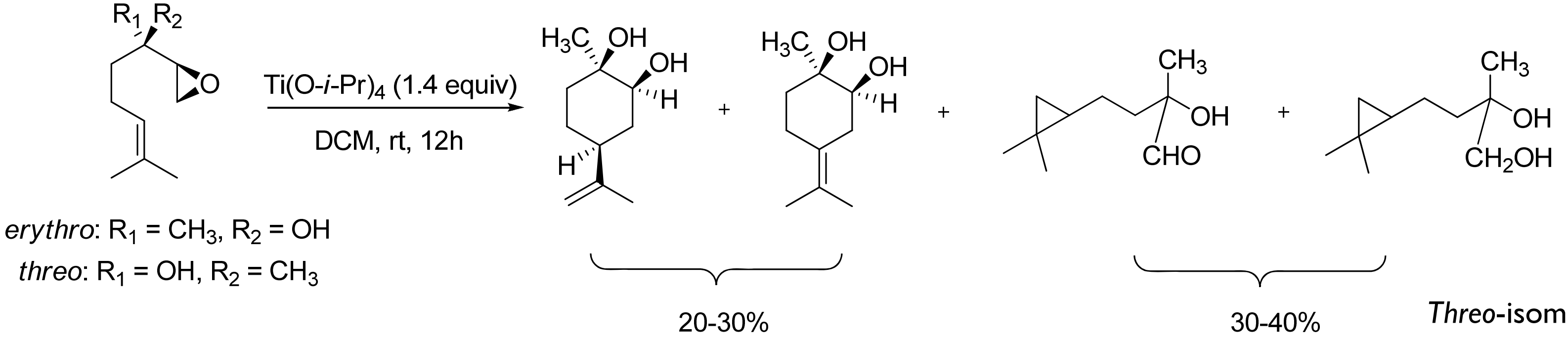
Marson, C. M. et al. *Tetrahedron Lett.* **2003**, *44*, 141.

Epoxy Alcohol Rearrangements: Hydroxyl-Mediated Delivery of Lewis Acid Promoters



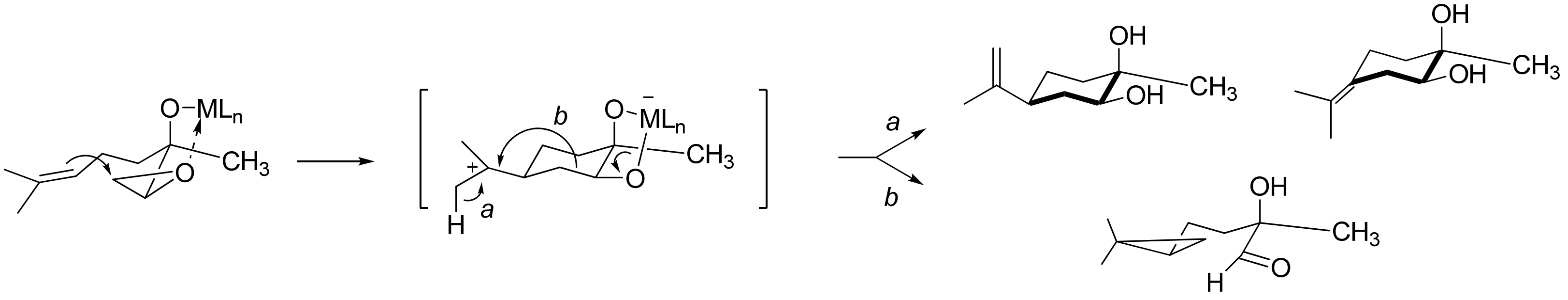
trans-diols not observed

Threo-isomer decomposed



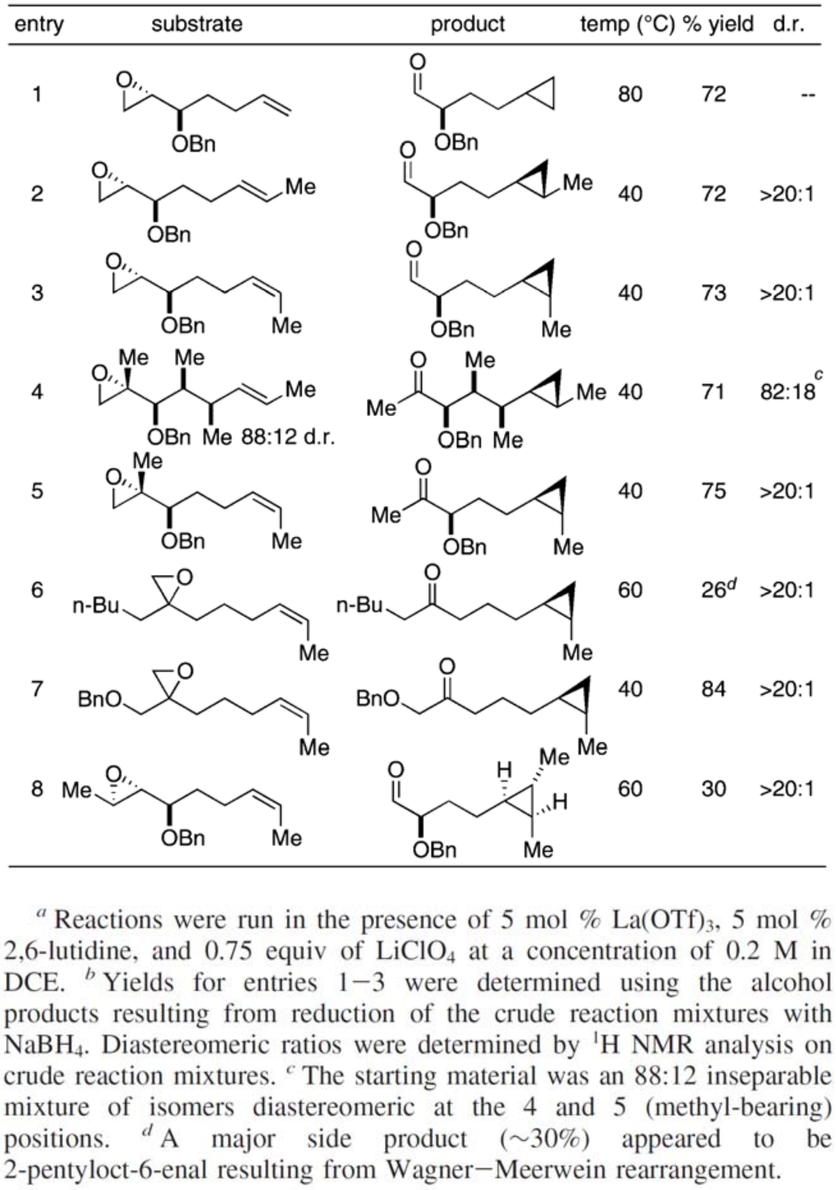
erythro: $R_1 = CH_3$, $R_2 = OH$
threo: $R_1 = OH$, $R_2 = CH_3$

Threo-isomer recovered



Morgans, D. J. ; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 462.

Title Paper: Substrate Scope Studies for La(OTf)$_3$-Catalyzed Intramolecular Methylene-Transfer Cyclopropanation



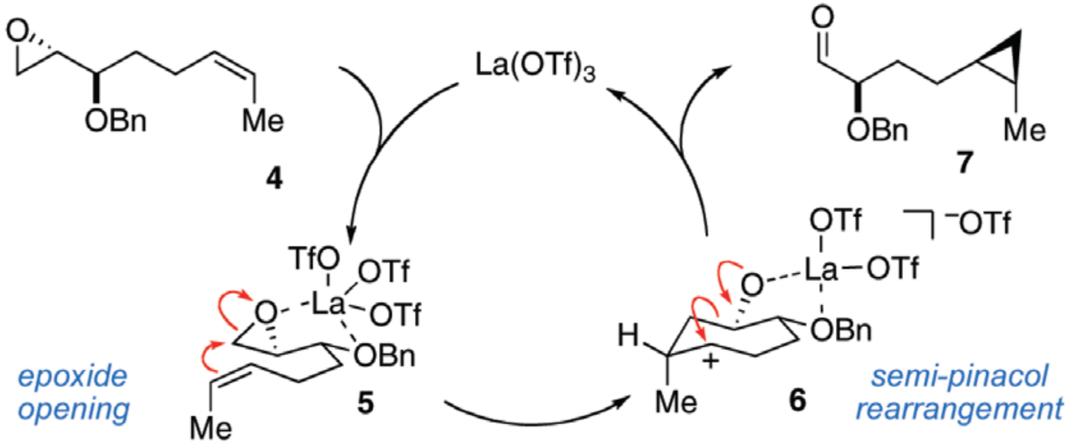
entry	substrate	product	temp (°C)	% yield	d.r.
1			80	72	--
2			40	72	>20:1
3			40	73	>20:1
4	88:12 d.r.		40	71	82:18[c]
5			40	75	>20:1
6			60	26[d]	>20:1
7			40	84	>20:1
8			60	30	>20:1

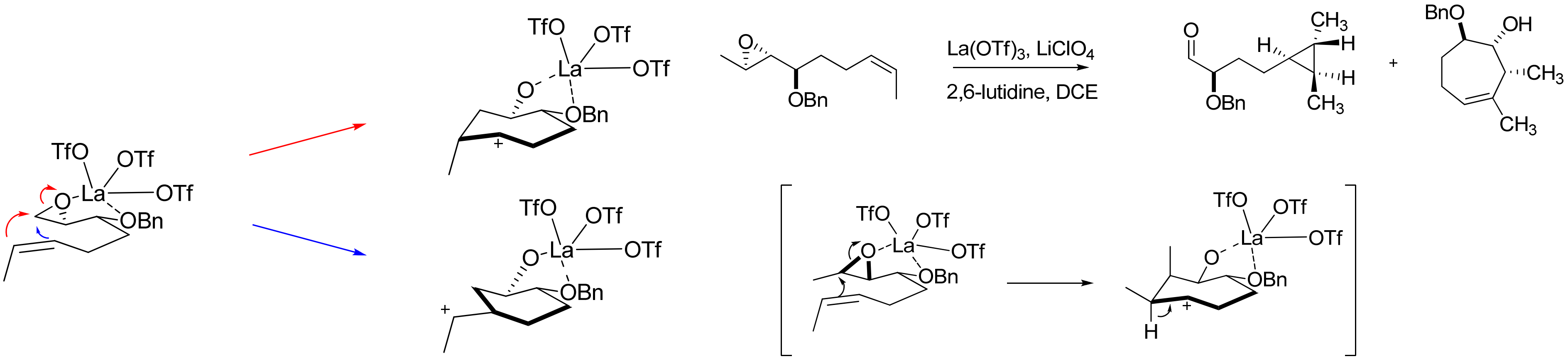
[a] Reactions were run in the presence of 5 mol % La(OTf)$_3$, 5 mol % 2,6-lutidine, and 0.75 equiv of LiClO$_4$ at a concentration of 0.2 M in DCE. [b] Yields for entries 1−3 were determined using the alcohol products resulting from reduction of the crude reaction mixtures with NaBH$_4$. Diastereomeric ratios were determined by ^{1}H NMR analysis on crude reaction mixtures. [c] The starting material was an 88:12 inseparable mixture of isomers diastereomeric at the 4 and 5 (methyl-bearing) positions. [d] A major side product (~30%) appeared to be 2-pentyloct-6-enal resulting from Wagner−Meerwein rearrangement.

- terminal olefins require reflux; internal olefins react at lower temperatures
- process is stereospecific
- substitution along the carbon chain is well tolerated
- chelating motif is necessary
- internal epoxides react in lower yield

Hardee, D. J.; Lambert, T. H. J. Am. Chem. Soc. **2009**, ASAP.

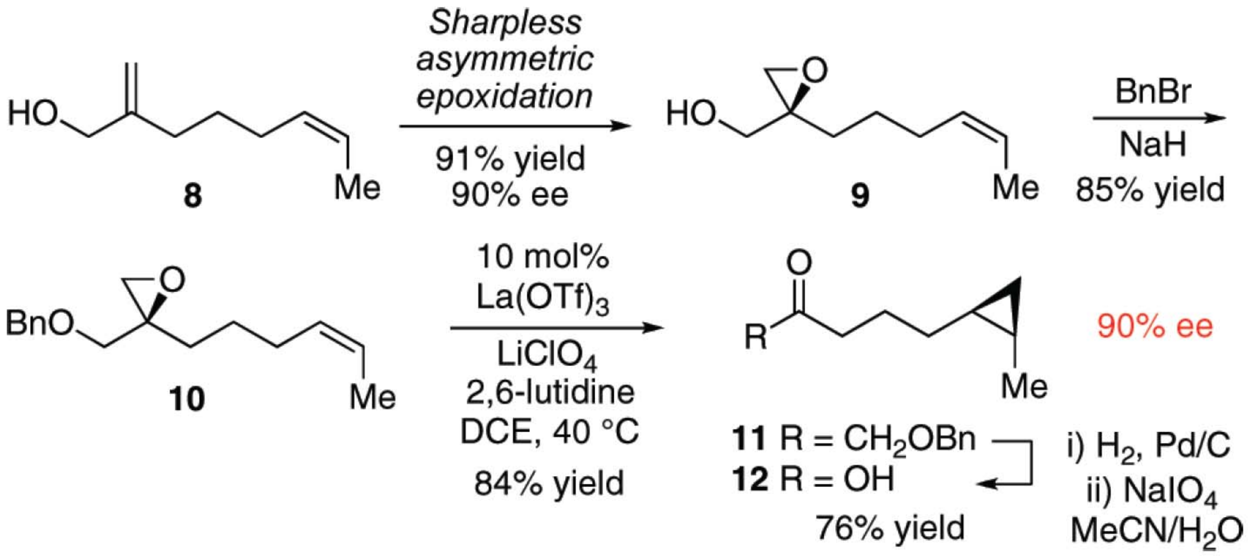
Title Paper: Proposed Mechanism for Methylene-Transfer Reaction





J. Am. Chem. Soc. **2009**, ASAP.

Title Paper: Synthesis of an Enantioenriched Cyclopropane via Asymmetric Epoxydation/Methylene Transfer



J. Am. Chem. Soc. **2009**, ASAP.

Conclusions

- New cyclopropanation strategy based on intramolecular methylene transfer from epoxydes to olefines

- Optimal yields were obtained with $LiClO_4$ as an additive, though its role is not clear

- Both internal and terminal olefins react (internal olefins reacts faster at lower temperatures)

- The reaction is stereospecific

- Chelating group is necessary, but need not reside along the carbon backbone between the epoxide and olefin moieties

- The mechanism involves Lewis acid activation of the substrate followed by semi-pinacol rearrangement

- The methylene transfer reaction can be used for the synthesis of enantioenriched cyclopropanes