Scope and Facial Selectivity of the Prins-Pinacol Synthesis of Attached Rings

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Leading Reference"*J. Org. Chem.* **2006**, *71*, 1581-1587

Presented by Zhenyu Zhong
Journal Club Presentation
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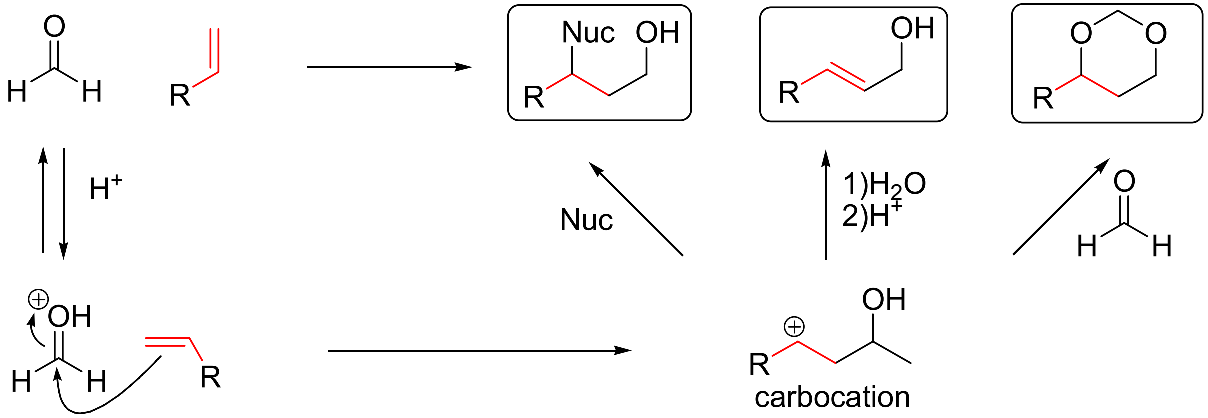
Presentation Outline

- Overview of the Prins-Pinacol Reaction
- Early developments of the acid-promoted Prins-pinacol rearrangement and its potential to be the key strategic element in the total synthesis of heterocyclic and carbocyclic natural products
- Exploration of the scope of the Prins-pinacol reaction for assembling attached rings with various sizes and ring substitutions
- Rationalization of facial stereoselection in the Prins cyclization
- Summary
- Future Work

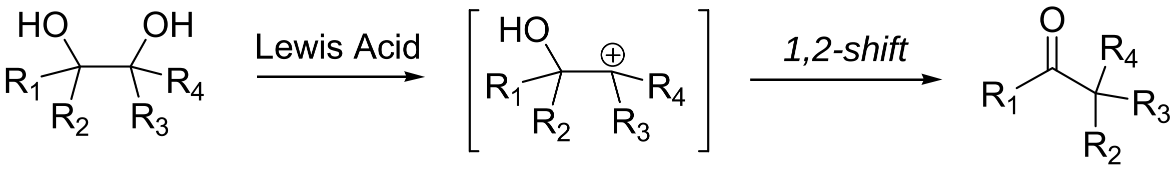
Prins Reaction:

- The acid-catalyzed condensation of alkenes with aldehyde



Condensation of formaldehyde with some unsaturated compounds H. J. Prins, Chemisch Weekblad, 16, 64, 1072, 1510 **1919**

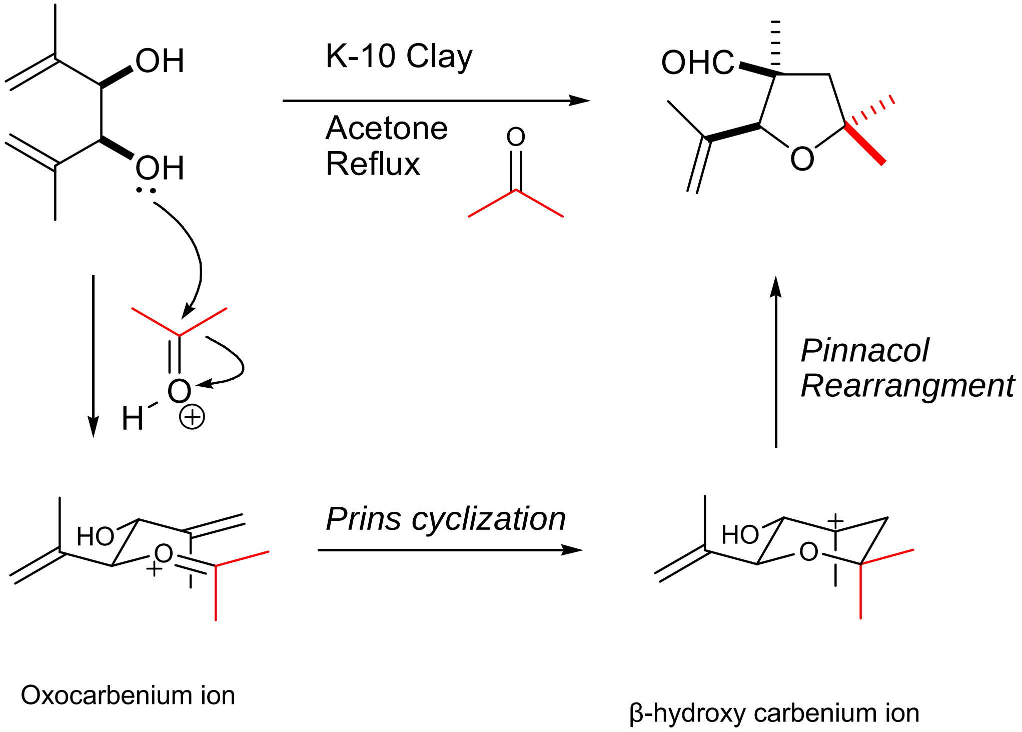
Pinacol Rearrangement



Migratory aptitude: aryl > *t*Bu>> cyclopropyl > 2° alkyl > 1° alkyl

R. Fittig. Justus Liebigs Ann. Chem. 110, 23–45 (**1859**).

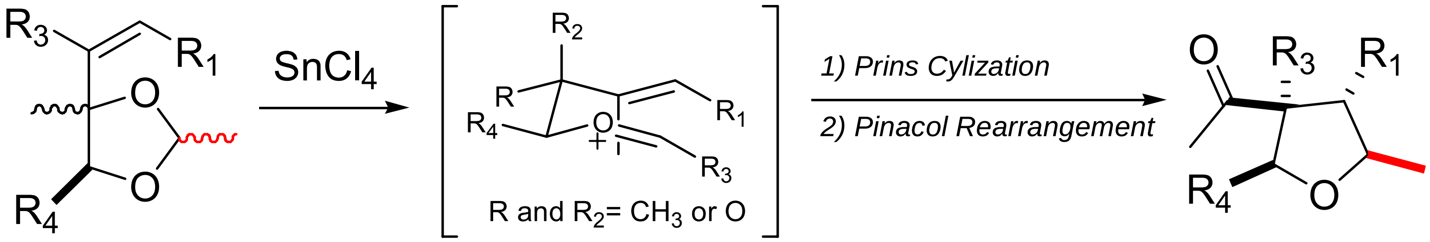
Serendipitous discovery of the Prins-Pinacol Reaction



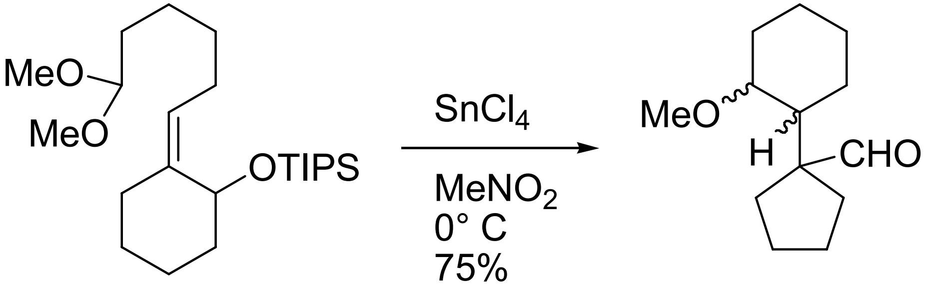
Results two C-C bonds, one C-O bond and two new stereocenters
Completely Stereoselective

Martinet, P.; Mousset, G.; Michel, M. *C. R. Acad. Sci. Paris, Ser. C* **1969**, *268*, 1303-1306

Other Examples of Prins-Pinacol Reaction

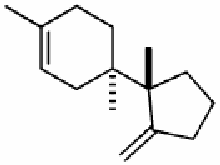


Overman et al. *J.* Am. Chem. Soc. **1987,** *109,* 4748-4749

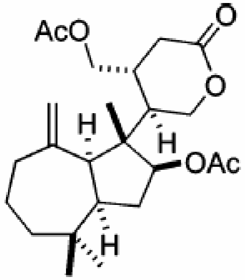


Overman et al *Can. J. Chem.* **2000**, *78*, 732

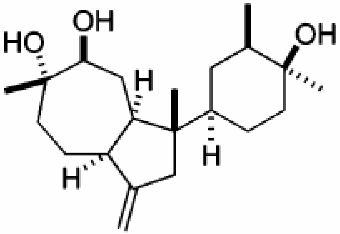
Natural Products Containing Attached Rings



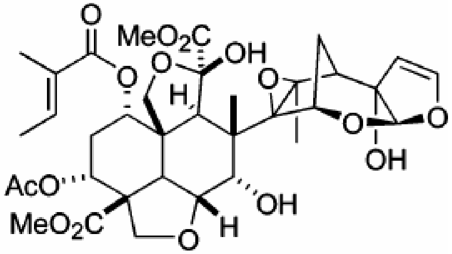
trichodiene



shahamin K



prevezol E

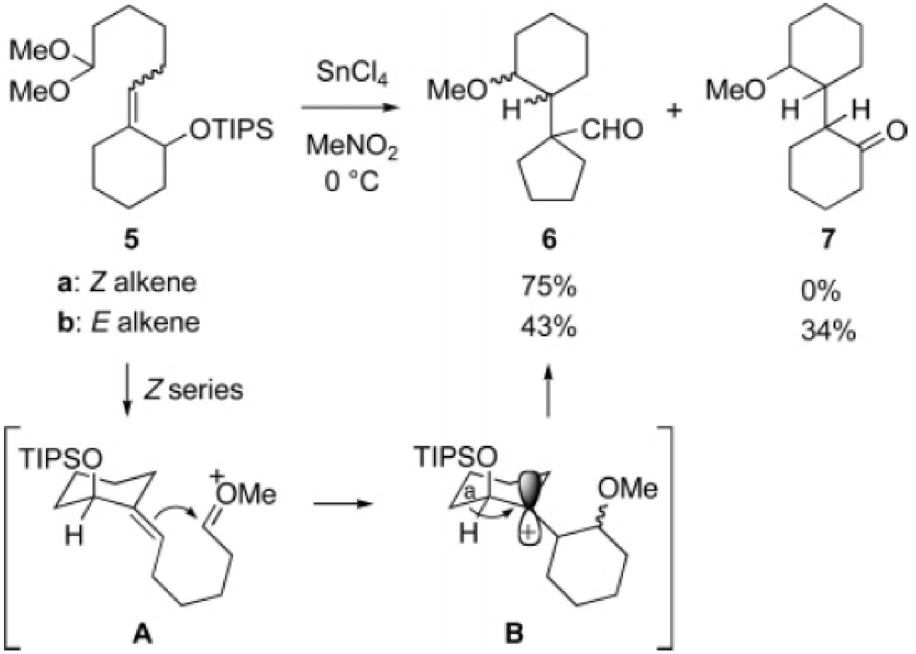


azadirachtin

- Rings joined by a C-C σ bond are prevalent in many oxacyclic and carbocyclic natural products.
- Prins-Pinacol reaction, like many sequential, tandem, cascade, or domino reactions, allows the construction of such rings with high stereoselective from relatively simple starting materials.

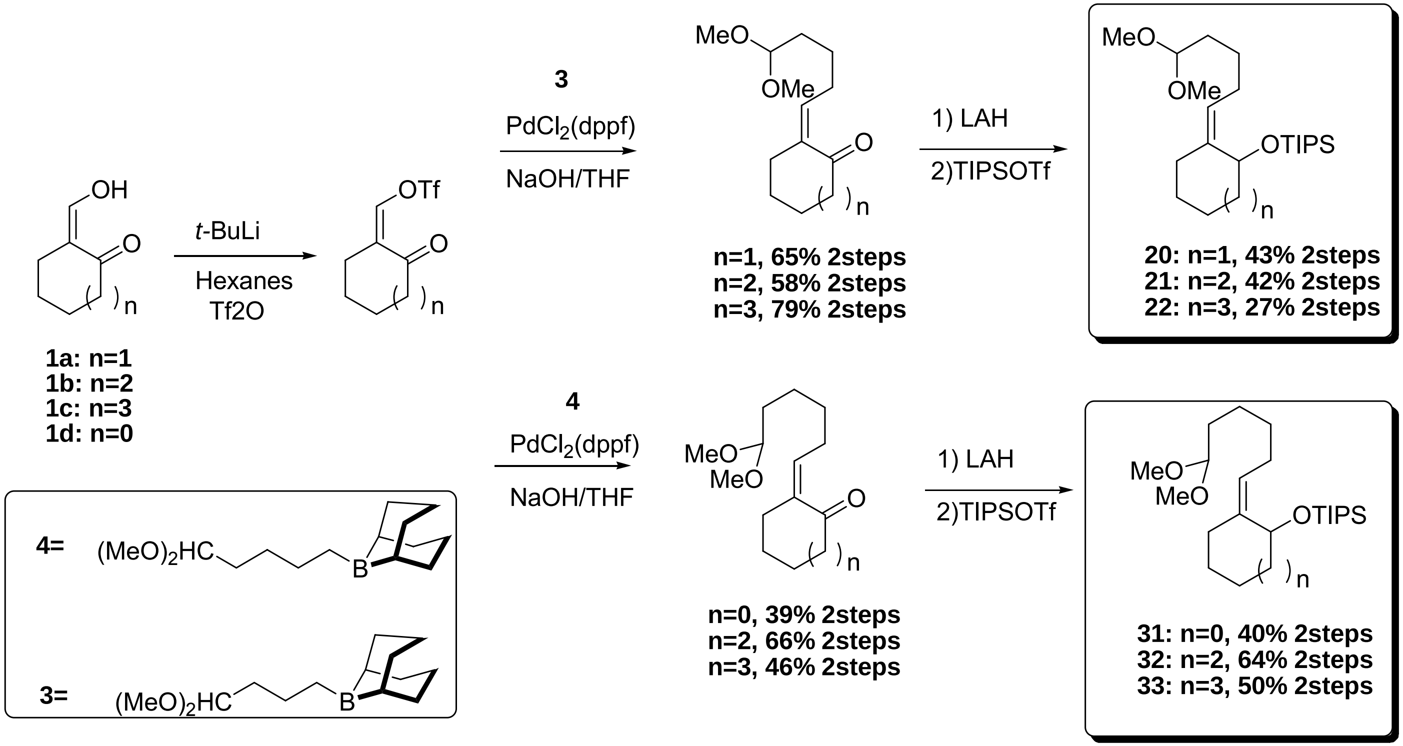
Early Study on Prins-Pinacol Reaction

SCHEME 1



- Due to $A^{1,3}$ minimized chair conformer of the *Z*-alkene, a greater regio-selectivity can be achieved to form the desired Prins-Pinacol products as a mixture of methoxy epimers.
- Prins-Pinacol reaction on *E*-alkene shows less regio-selectivity.

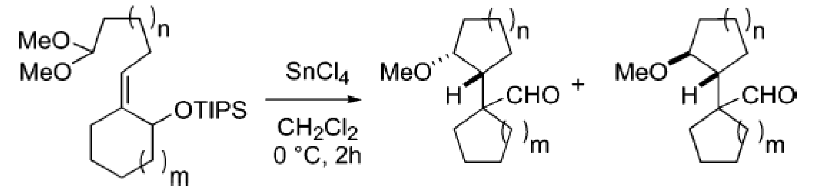
Preparation of the *Prins-Pinacol* Precursors



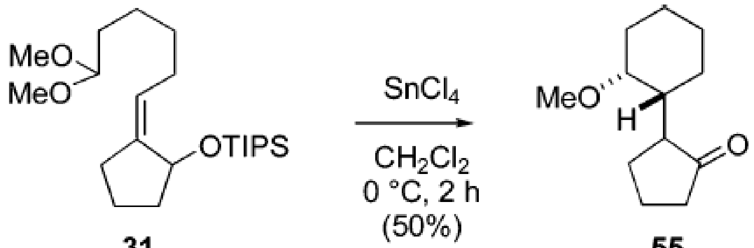
- Relatively short sequence to prepare the (*Z*)alkylidenecycloalkylnols
- Low overall yield

Results for Various Attached Rings systems

TABLE 1. Prins-Pinacol Reactions To Form Various Attached Ring Systems



entry	substrate	*n*	*m*	yield, %	*cis*/*trans* (product)
1	**20**	1	1	69	1.0:3.4 (**50a** + **50b**)
2	**21**	1	2	75	1.0:1.0 (**51a** + **51b**)
3	**22**	1	3	71	1.2:1.0 (**52a** + **52b**)
4	**32**	2	2	82	1.5:1.0 (**53a** + **53b**)
5	**33**	2	3	68	2.4:1.0 (**54a** + **54b**)

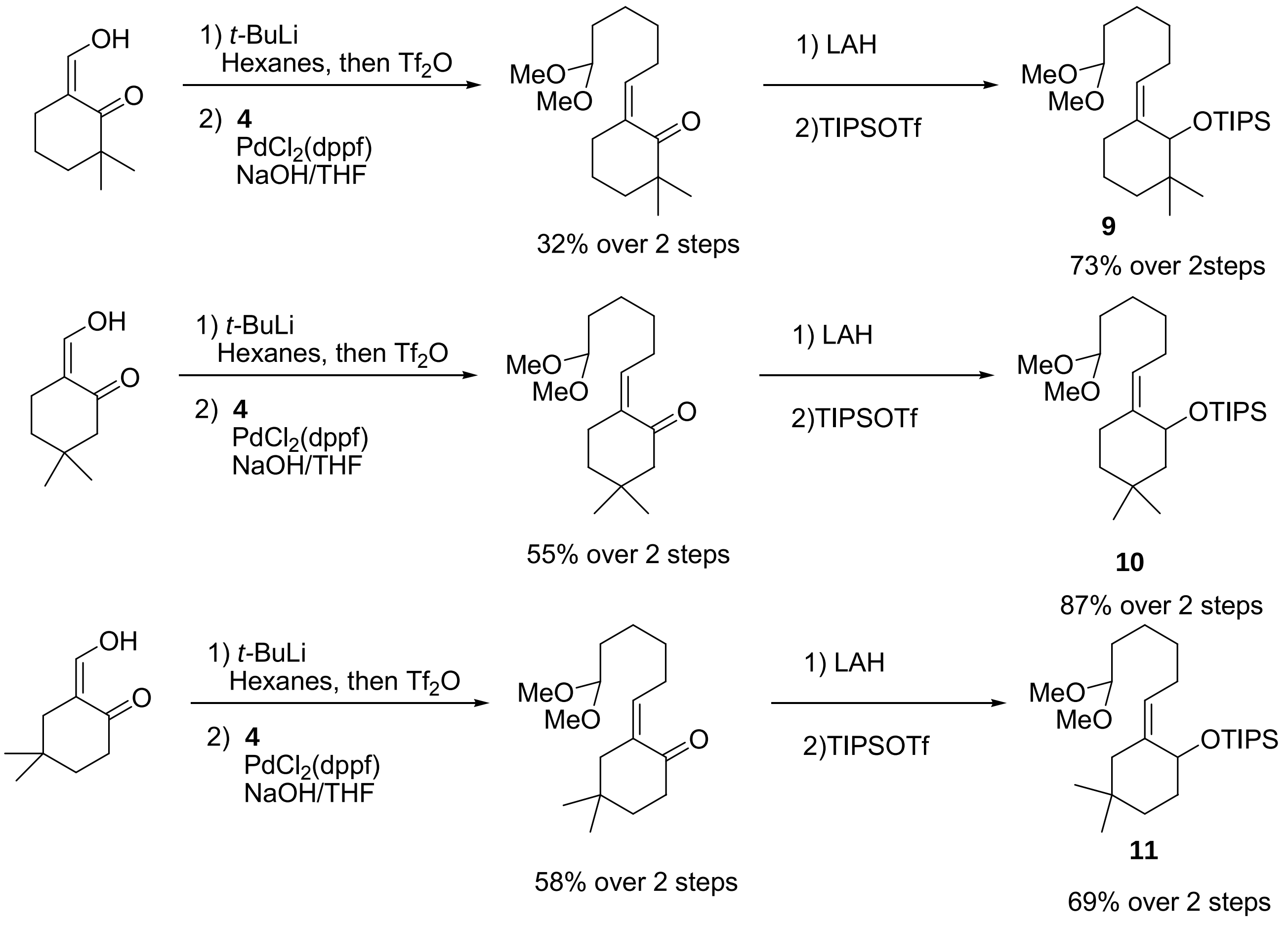


31 **55**

Scope and limitations:

When the starting ring is Five membered, the cation produced upon Prins cyclization would not undergo Pinacol ring contraction, due to high ring constrain associated with forming of cyclobutane ring.

Effect of Ring substitution upon Prins-Pinacol reaction
Preparation of the Precursors



1) *t*-BuLi Hexanes, then Tf_2O

2) **4** $PdCl_2(dppf)$ NaOH/THF

32% over 2 steps

1) LAH

2)TIPSOTf

9

73% over 2steps

1) *t*-BuLi Hexanes, then Tf_2O

2) **4** $PdCl_2(dppf)$ NaOH/THF

55% over 2 steps

1) LAH

2)TIPSOTf

10

87% over 2 steps

1) *t*-BuLi Hexanes, then Tf_2O

2) **4** $PdCl_2(dppf)$ NaOH/THF

58% over 2 steps

1) LAH

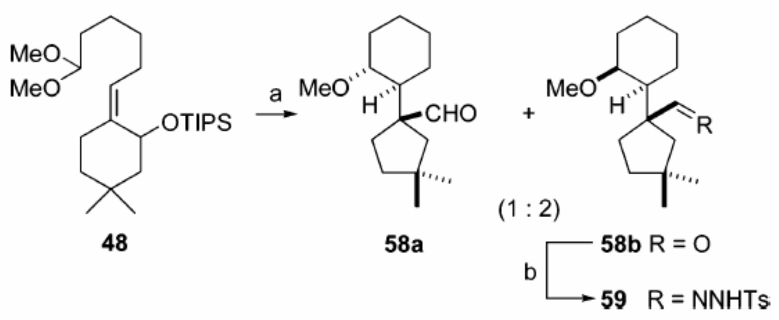
2)TIPSOTf

11

69% over 2 steps

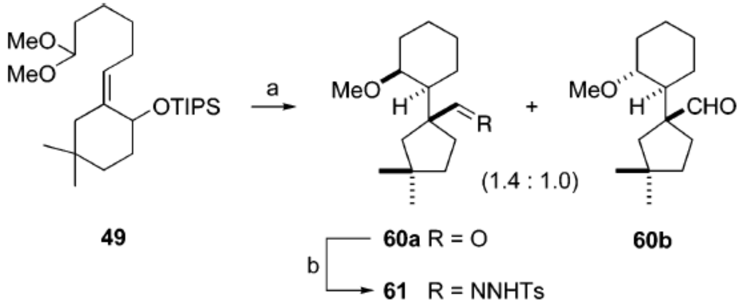
Effect of Ring substitution upon Prins-Pinacol reaction cont'd

SCHEME 5[a]



[a] Reagents and conditions: (a) $SnCl_4$, $MeNO_2$, 0 °C (48%); (b) NH_2NHTs, AcOH (50%).

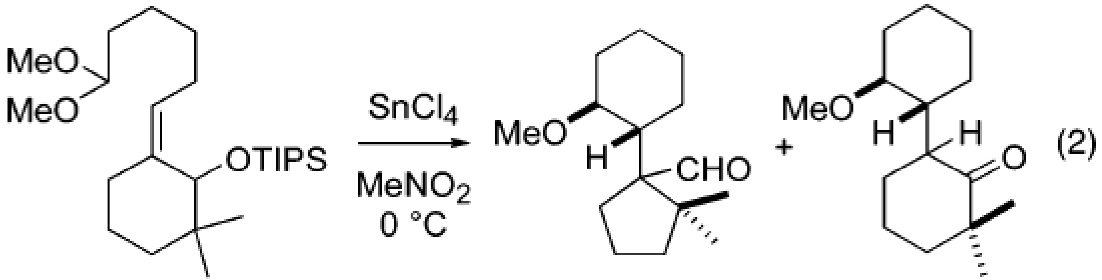
SCHEME 6[a]



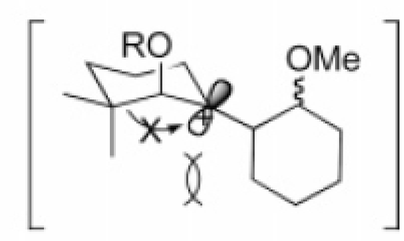
[a] Reagents and conditions: (a) $SnCl_4$, $MeNO_2$, 0 °C (84%); (b) NH_2NHTs, AcOH (84%).

Geminally disubstituted precursor (48) give desire Prins-Pinacol products in moderate yield. Whereas the precursor (49) affords the Prins-Pinacol in a higher yield.

Effect of Ring Substitution upon Prins-Pinacol reaction cont’d



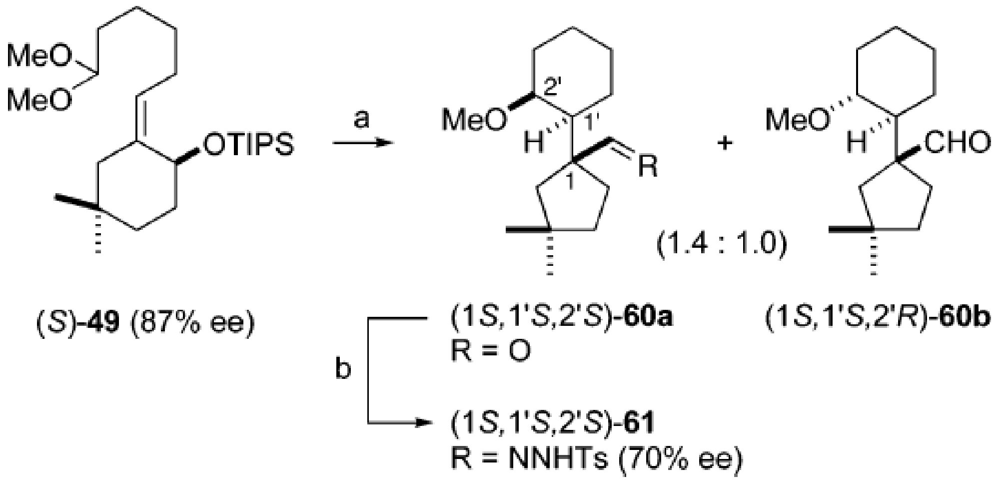
47 **56** (8%) **57** (21%)



Disfavoring ring contraction of carbocation was due to the developing steric interactions between the axial methyl and pseudoaxial cyclohexyl subsitituent, thus, resulting lower yield for the desired Prins-Pinacol product.

Prins-Pinacol Reaction on Enatiomerically Riched Precursor

SCHEME 9 [a]



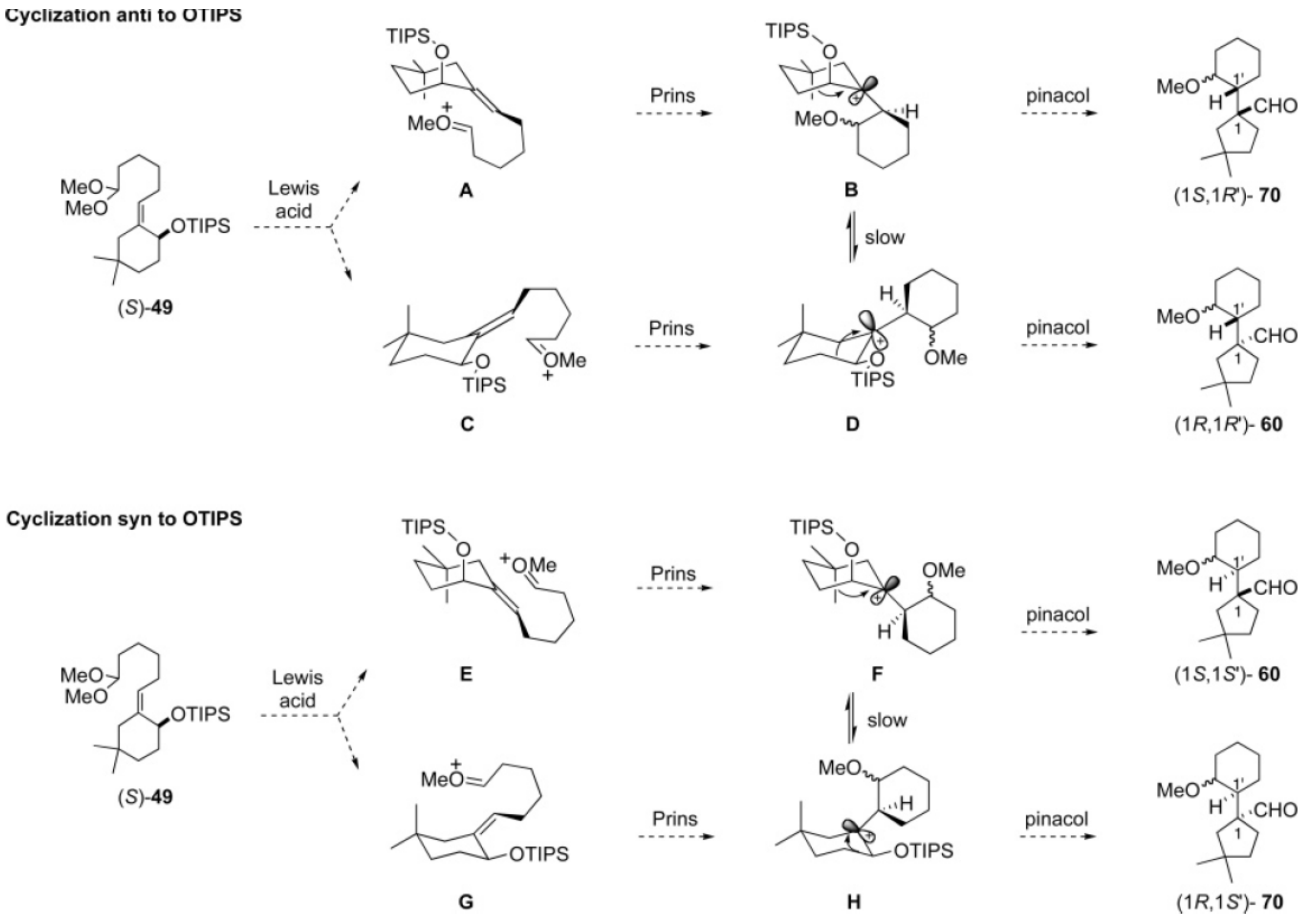
(*S*)-**49** (87% ee)

(1*S*,1'*S*,2'*S*)-**60a**
R = O

(1*S*,1'*S*,2'*R*)-**60b**

(1*S*,1'*S*,2'*S*)-**61**
R = NNHTs (70% ee)

Analysis of stereochemical outcome



Summary

- A variety of attached ring systems were prepared using Prins-pinacol reaction on simple precursors, cyclohexyl- and cyclopentyl triisopropylsiloxy ethers bearing (2*Z*)-(6,6-dimethoxyhexylidene) or (2*Z*)-(6,6-dimethoxyhexylidene) side chains.

- The facial selectivity of Prins reaction was rationalized by the through-space electrostatic stabilizing interactions between the α-alkyloxycarbenium ion and an axially positioned oxygen subsituent.

Future Work

- Improve the efficiency for preparation of precurors of Prins-pinacol reaction.

Acknowledgements

- Dr. Wipf
- All members of Chem 2320

Thank you!