Literature Report VI

Ti-Catalyzed Diastereoselective Cyclopropanation of Carboxylic Derivatives with Terminal Olefins

Reporter: Yu-Qing Bai
Checker: Zheng Liu
Date: 2022-06-13

Wang, Z. *et al. J. Am. Chem. Soc.* **2022**, *144*, 7889.

CV of Prof. Zhaobin Wang

Background:

- **2007-2011** B.S., Nanjing University
- **2011-2015** Ph.D., HKUST
- **2016-2019** Postdoc., Caltech
- **2019-Now** Distinguished Researcher, Westlake University

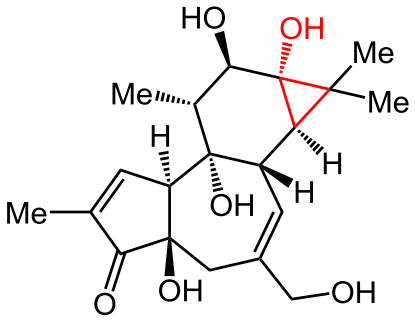
Research:

- Asymmetric catalysis;
- Application of synthetic methodology in the synthesis of biologically active molecules and organic functional molecules.

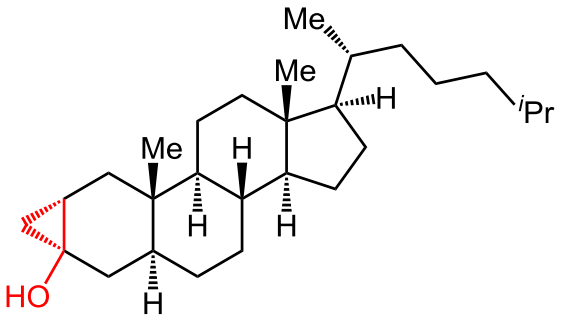
Contents

Introduction

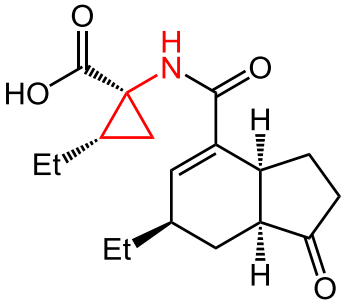
core unit in bioactive compounds



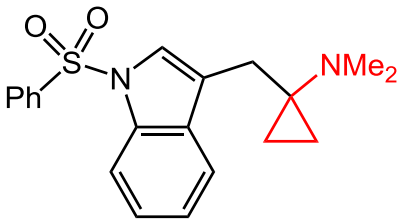
Phorbol



Cholesterol Oxidase Inhibitor



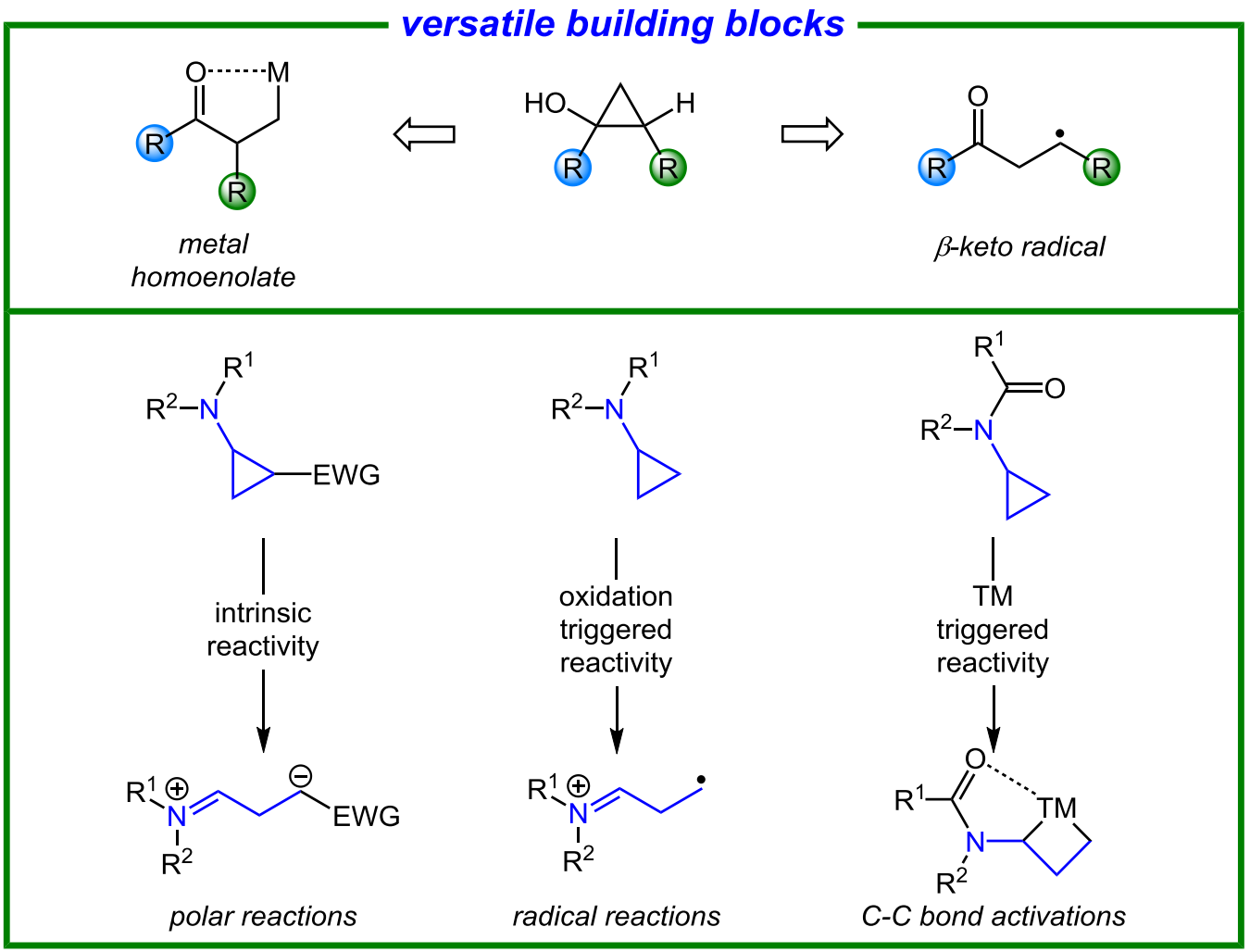
Coronatine



5-HT$_6$ Receptor Ligand

Wang, H.-B. *et al. Chem. Rev.* **2015**, *115*, 2975
Sampson, N. S. *et al. J. Am. Chem. Soc.* **2000**, *122*, 35
Parry, R. J. *et al. J. Am. Chem. Soc.* **1986**, *108*, 4681
Gérard, S. *et al. ChemMedChem* **2013**, *8*, 70

Introduction

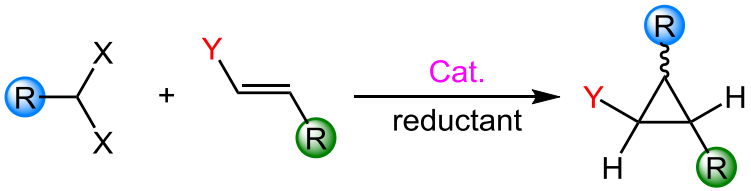


Rousseaux, S. A. L. *et al. Chem. Rev.* **2021**, *121*, 3
Bower, J. F. *et al. Chem. Rev.* **2021**, *121*, 80

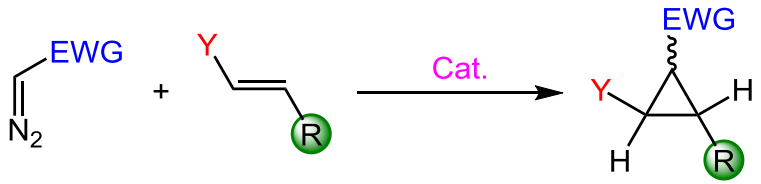
Introduction

Representative Strategies to Access Cyclopropanols & Cyclopropylamines

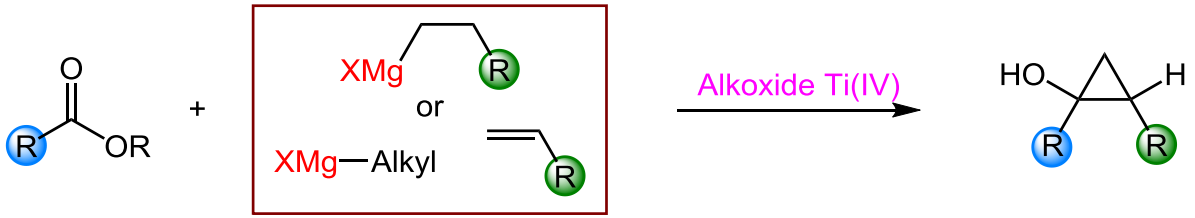
- **Cyclopropanation with Alkyl Dihalides**



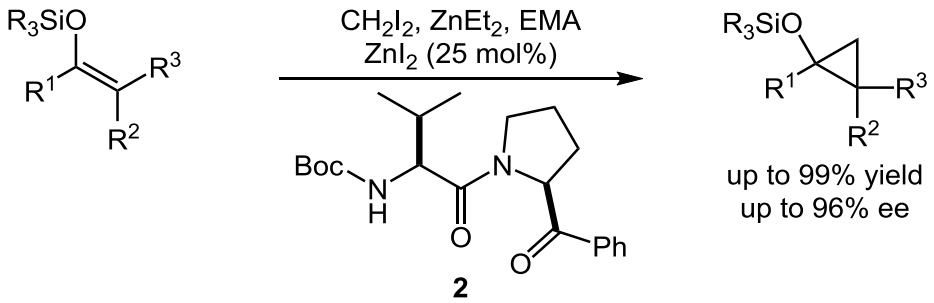
- **Cyclopropanation with Diazo Compounds**

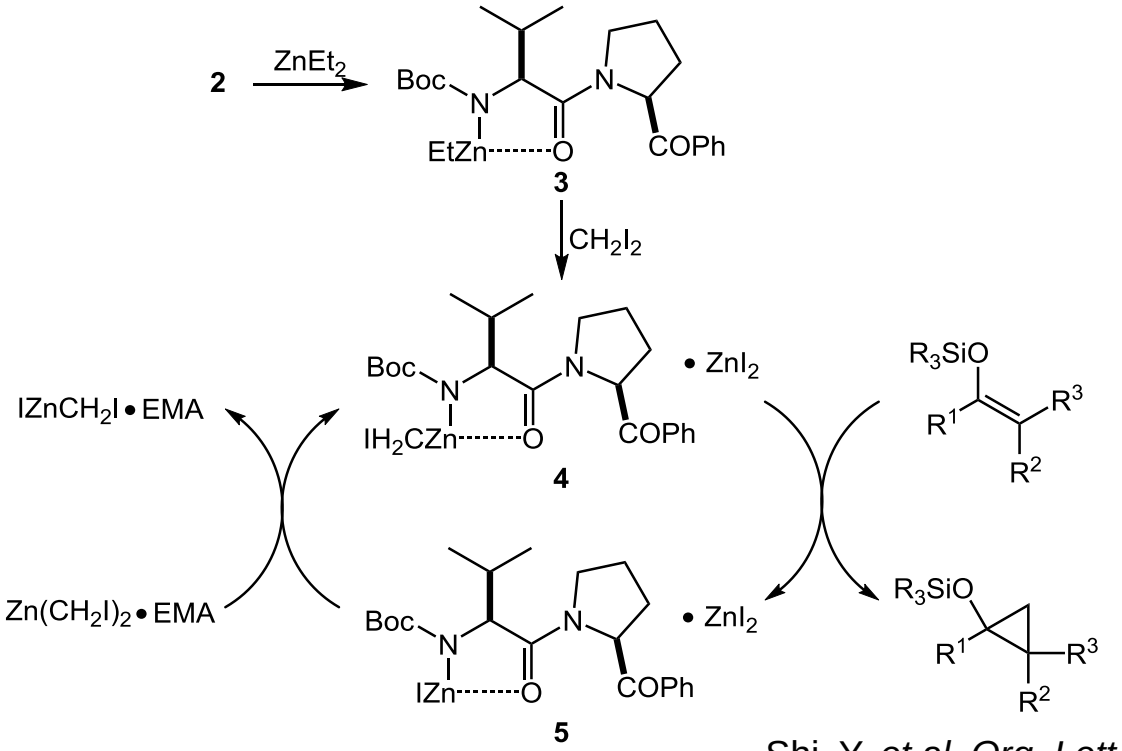


- **Kulinkovich Reaction with Ti Catalysis**



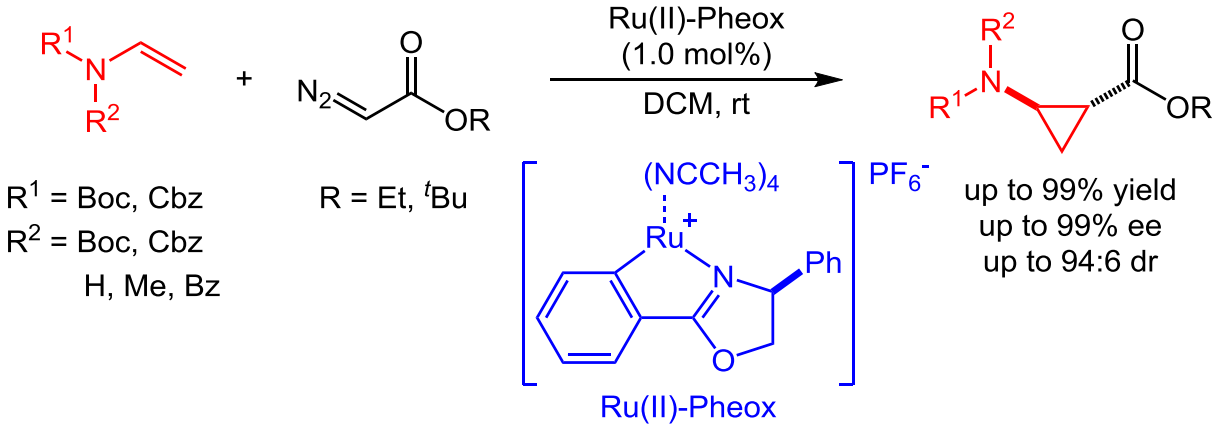
Cyclopropanation with Alkyl Dihalides

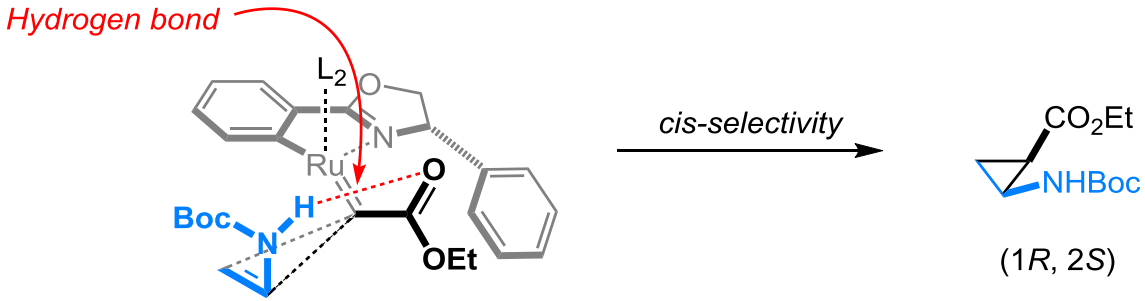




Shi, Y. *et al. Org. Lett.* **2006**, *8*, 2827

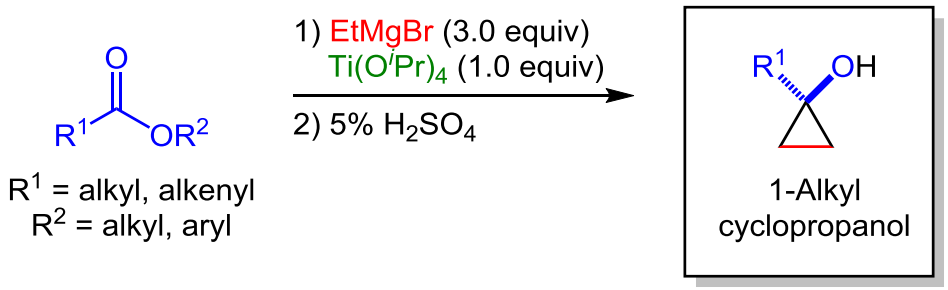
Cyclopropanation with Diazo Compounds



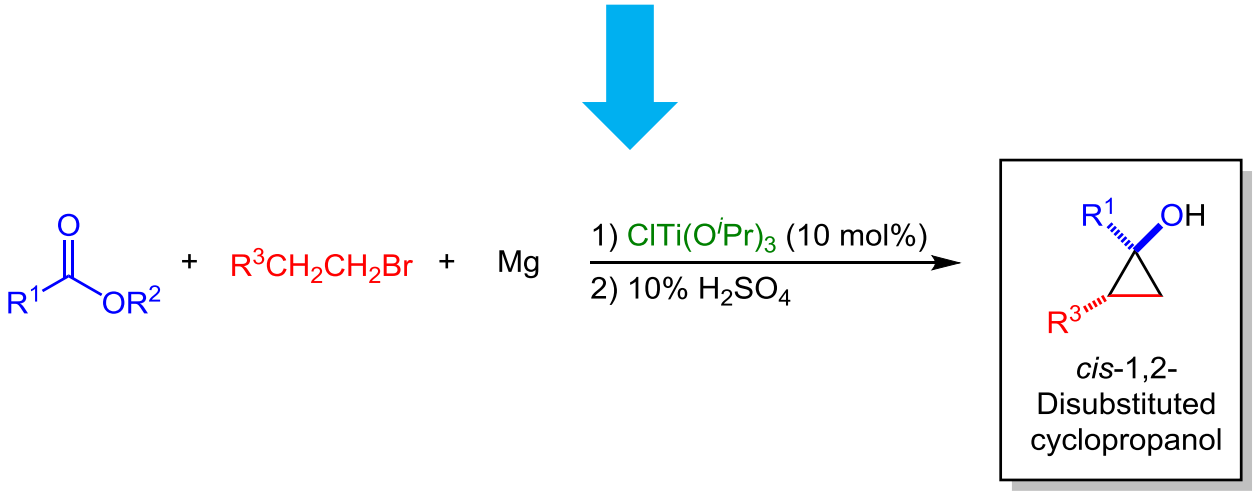


Iwasa, S. *et al. Org. Lett.* **2013**, *15*, 772

Kunlinkovich Reaction

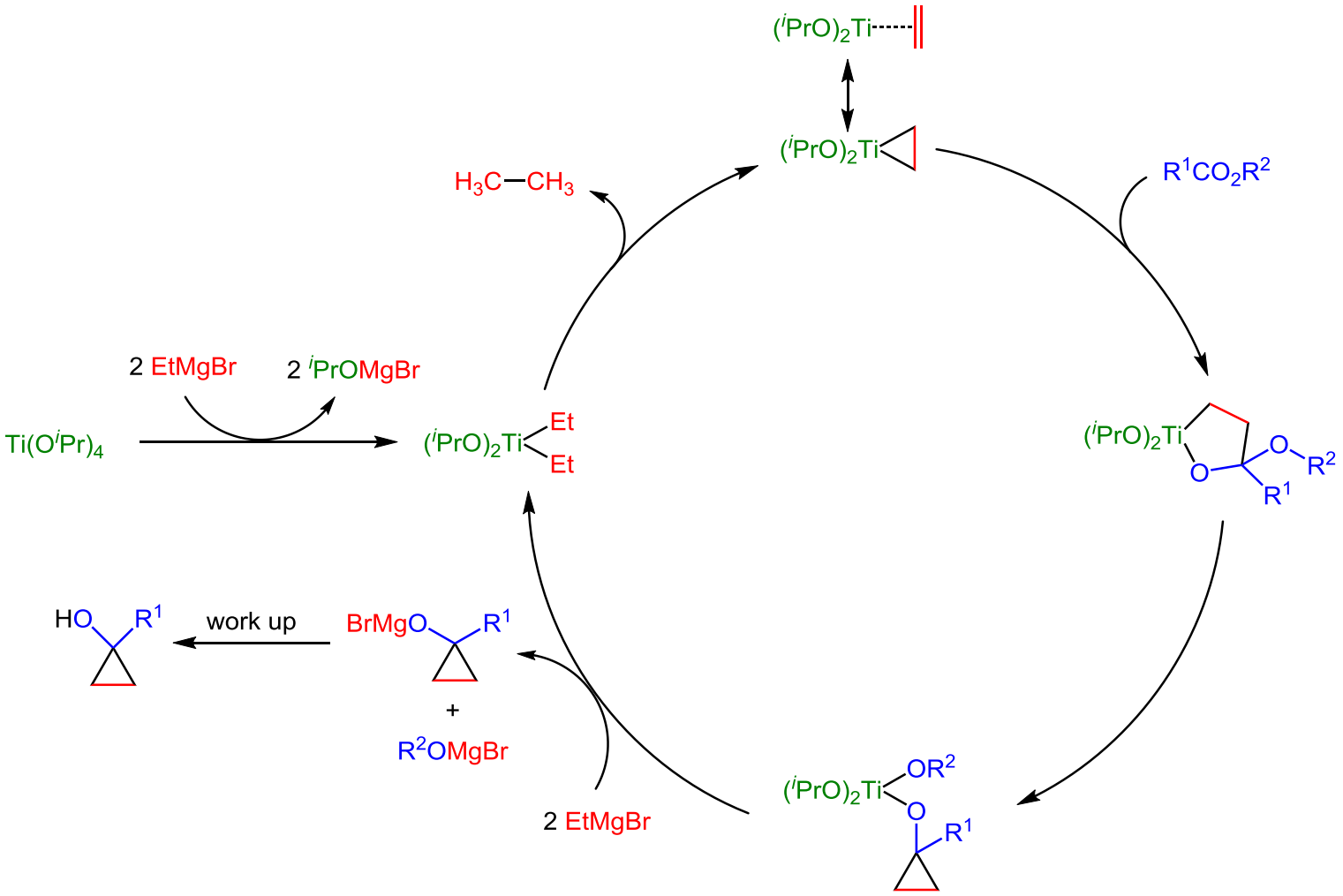


Kulinkovich, O. G. *et al. Zh. Org. Khim.* **1989**, *25*, 2244



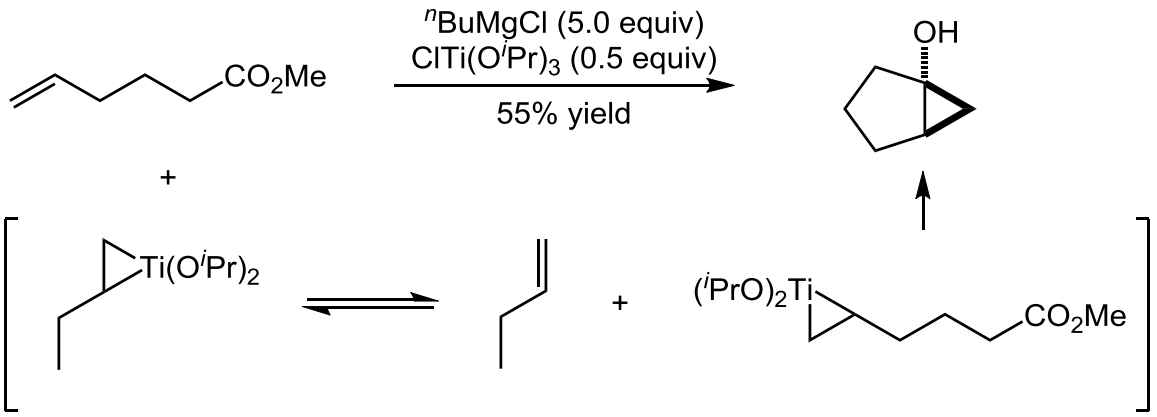
Corey, E. J. *et al. J. Am. Chem. Soc.* **1994**, *116*, 9345

Mechanism of Kunlinkovich Reaction

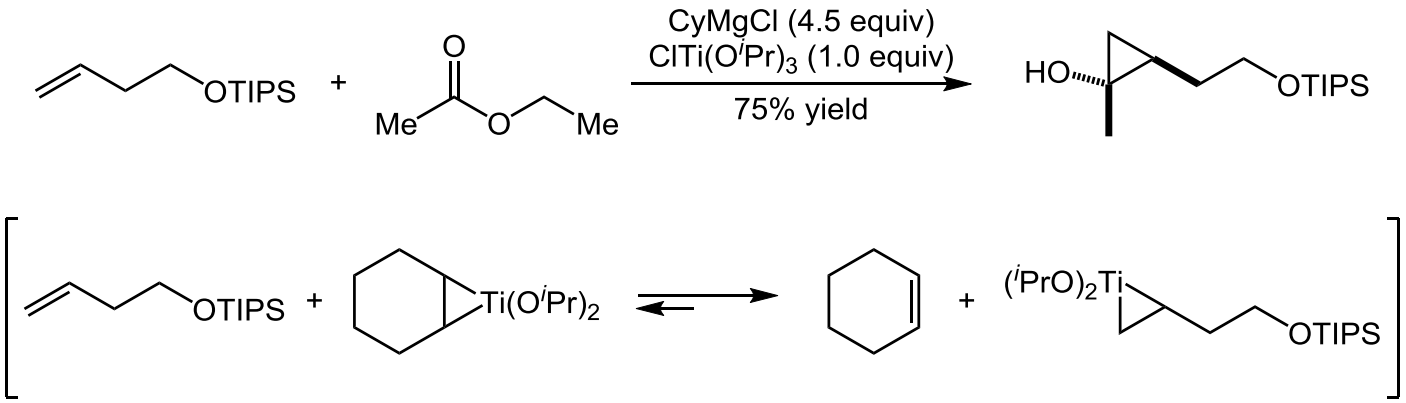


Kulinkovich, O. G. *et al. Synthesis* **1991**, 234

Olefins as Reaction Partners



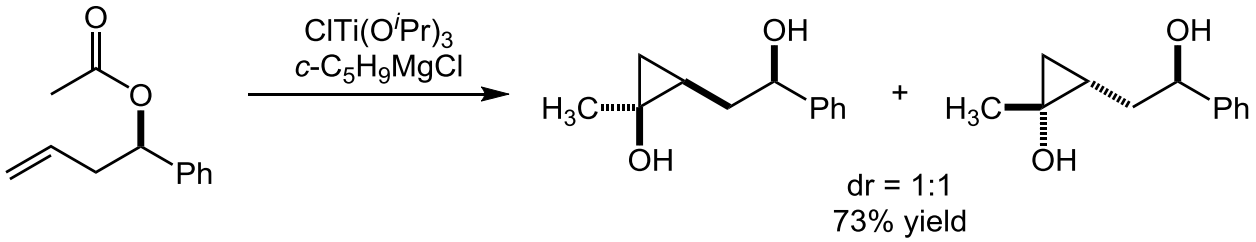
Cha, J. K. *et al. J. Am. Chem. Soc.* **1996**, *118*, 291



Cha, J. K. *et al. J. Am. Chem. Soc.* **1996**, *118*, 4198

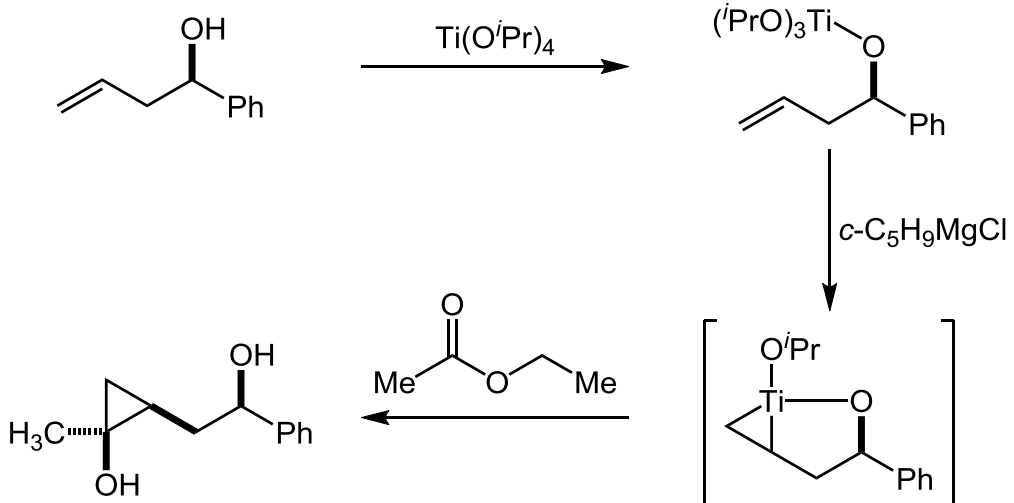
Olefins as Reaction Partners

A) Cyclopropanation of the Esters of Homoallylic Alcohols



dr = 1:1
73% yield

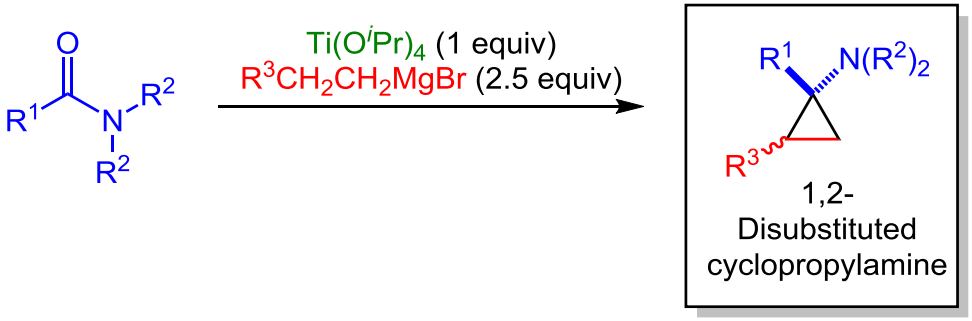
B) Formation of Bicyclic Titanacyclopropanes

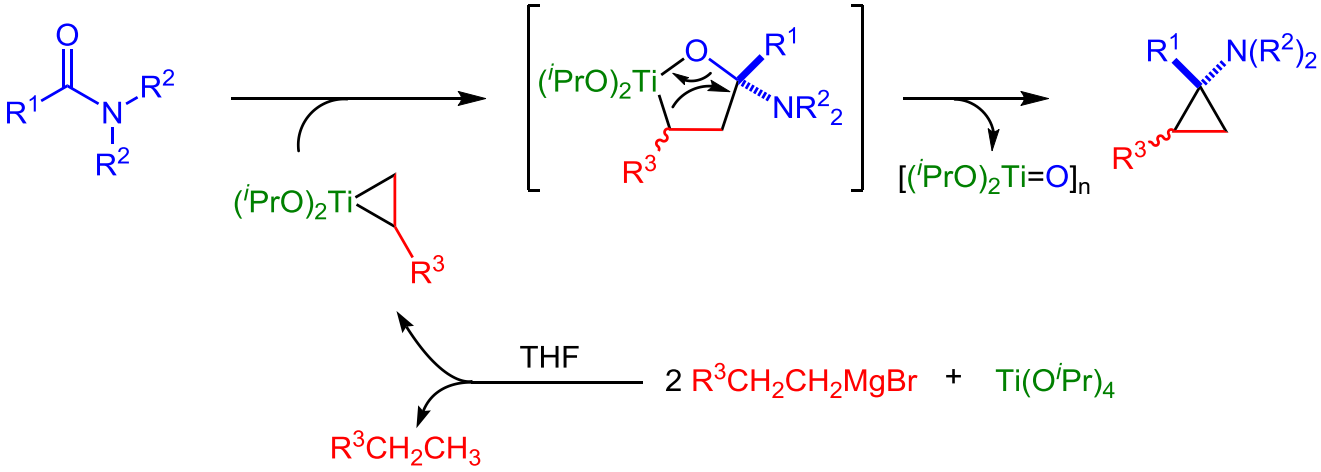


dr = 12:1
68% yield

Cha, J. K. *et al. Angew. Chem. Int. Ed.* **2002**, *41*, 2160

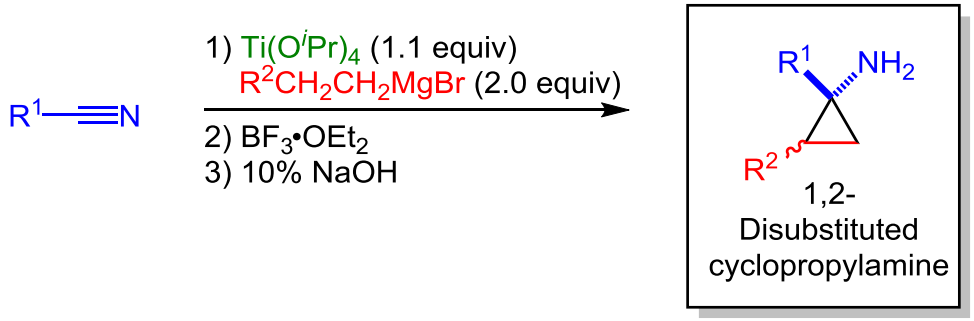
Cyclopropanation of Amides

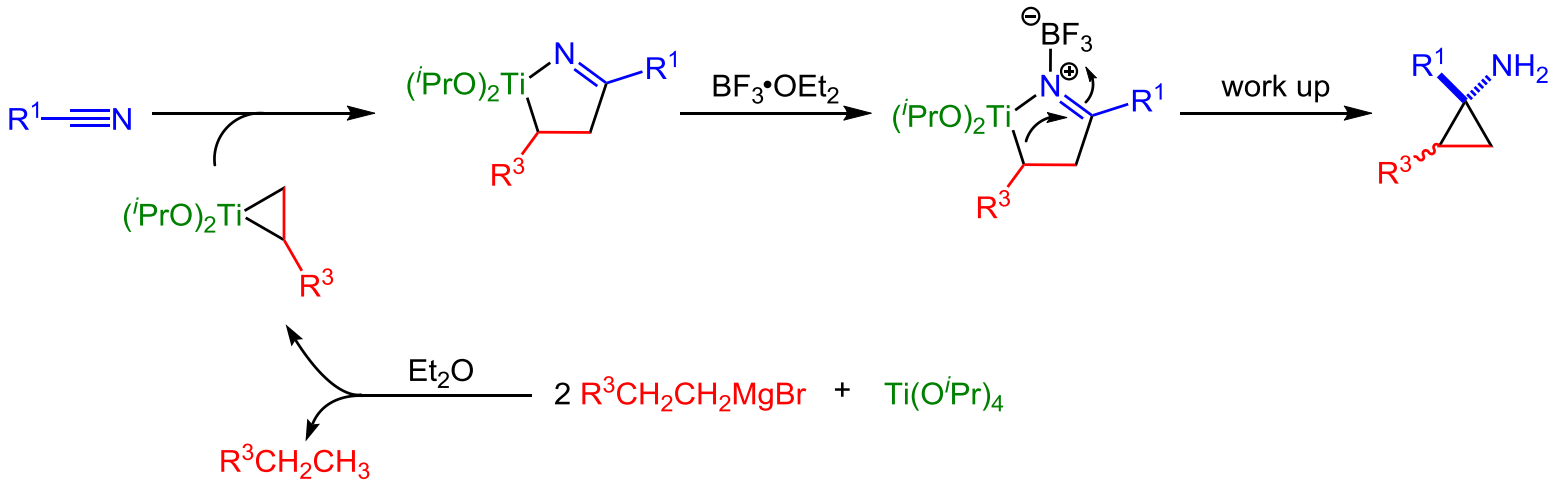




de Meijere, A. *et al. Angew. Chem. Int. Ed.* **1996**, *35*, 413

Cyclopropanation of Nitriles

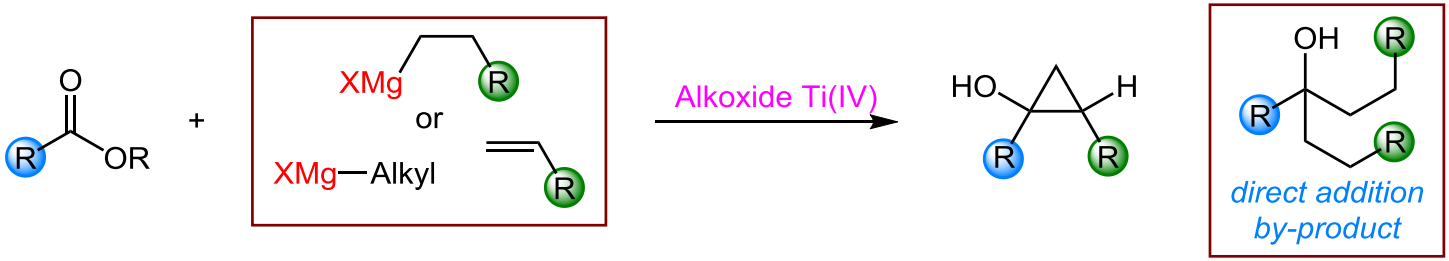




Szymoniak, J. *et al. Chem. Commun.* **2001**, 1792

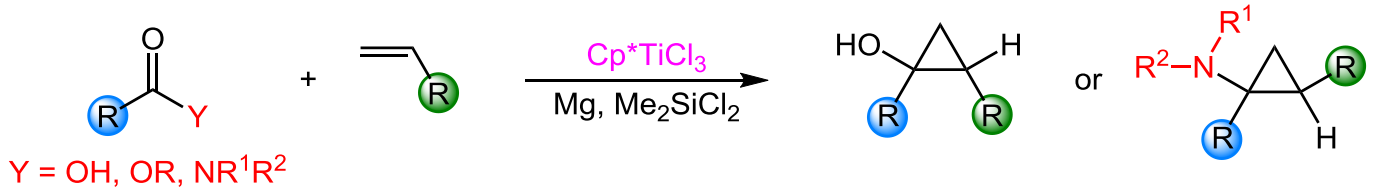
Project Synopsis

Kulinkovich Reaction with Ti Catalysis



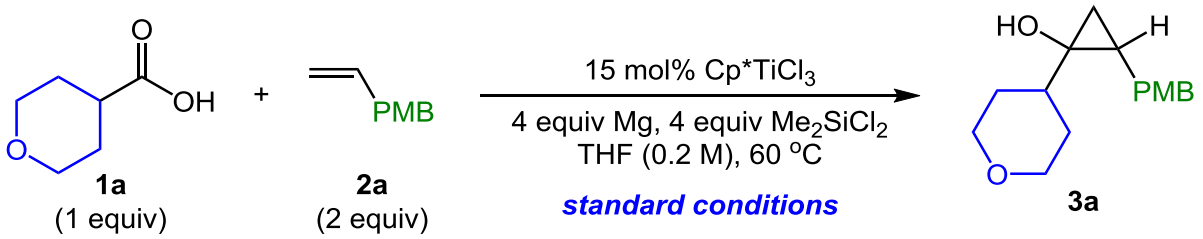
- use of reactive alkyl Grignard reagents
- narrow functional group compatibility

This Work: Ti-Catalyzed Cyclopropanation of Carboxylic Derivatives with Olefins



widely available chemicals

Optimization of Reaction Conditions



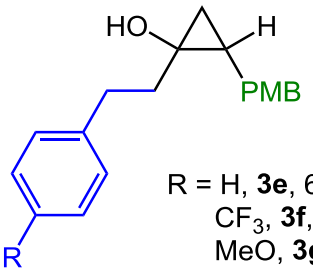
entry	variation from the standard conditions	yield (%)[a]	d.r.[b]
1	none	73	17:1
2	no Cp^*TiCl_3	<2	
3	no Mg	<2	
4	no Me_2SiCl_2	<2	
5	$CpTiCl_3$, instead of Cp^*TiCl_3	6	
6	$Ti(O^iPr)_4$, instead of Cp^*TiCl_3	<2	
7	Me_3SiCl, instead of Me_2SiCl_2	39	13:1
8	$MeSiCl_3$, instead of Me_2SiCl_2	37	18:1
9	2, instead of 4 equiv of Me_2SiCl_2	45	17:1
10	Mn, instead of Mg	<2	
11	rt, instead of 60 °C	36	17:1

[a]Yields were determined via gas chromatography analysis with [n]dodecane as an internal standard. [b]Diastereoselectivity ratio (d.r.) was determined via ^1H NMR analysis of the reaction mixture.

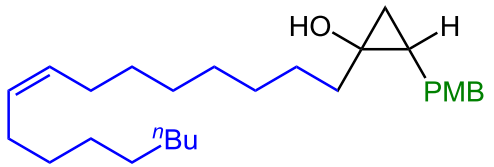
Scope for Cyclopropanol Synthesis

alkyl carboxylic acids

R = Me, **3b**, 46%, 20:1 d.r.
^{i}Pr, **3c**, 83%, 15:1 d.r.
^{t}Bu, **3d**, 39%, 4:1 d.r.

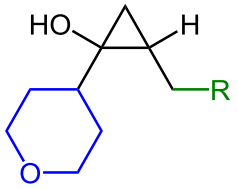


R = H, **3e**, 62%, 15:1 d.r.
CF_3, **3f**, 43%, 17:1 d.r.
MeO, **3g**, 65%, 17:1 d.r.

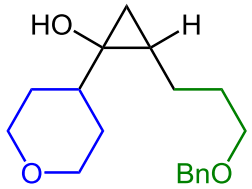


from oleic acid
3h, 50%, 14:1 d.r.

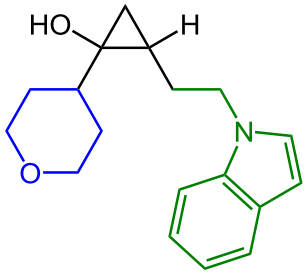
olefins



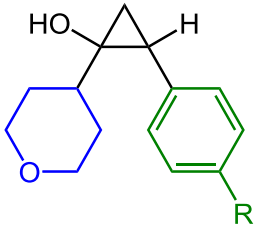
R = Ph, **3i**, 70%, 14:1 d.r.
1-Nap, **3j**, 63%, 16:1 d.r.



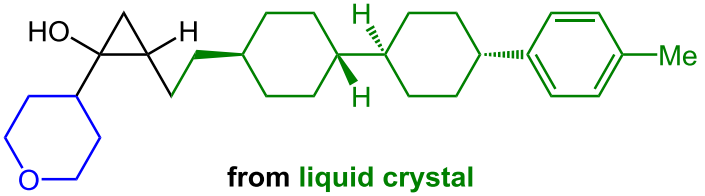
3k, 50%, 4:1 d.r.



3l, 77%, 5:1 d.r.

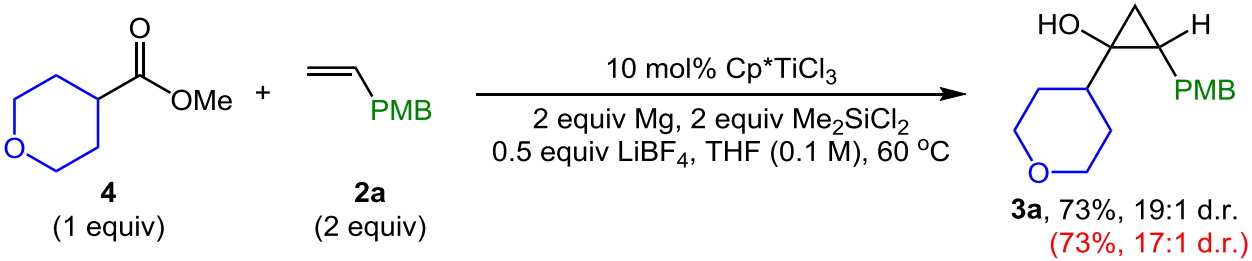


R = H, **3m**, 46%, 20:1 d.r.
F, **3n**, 50%, 20:1 d.r.
OMe, **3o**, 59%, 20:1 d.r.

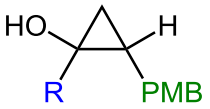


from liquid crystal
3p, 59%, 5:1 d.r.

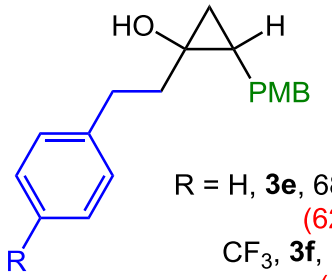
Scope for Cyclopropanol Synthesis



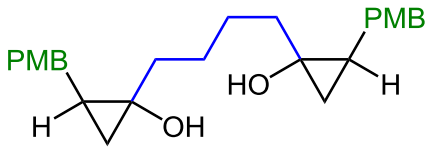
alkyl carboxylic esters



R = Me, **3b**, 66%, 20:1 d.r.
(46%, 20:1 d.r.)
^{i}Pr, **3c**, 74%, 18:1 d.r.
(83%, 15:1 d.r.)

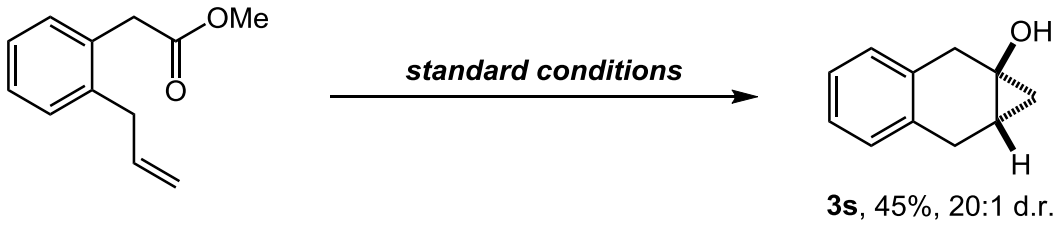


R = H, **3e**, 68%, 16:1 d.r.
(62%, 15:1 d.r.)
CF_3, **3f**, 58%, 20:1 d.r.
(43%, 17:1 d.r.)



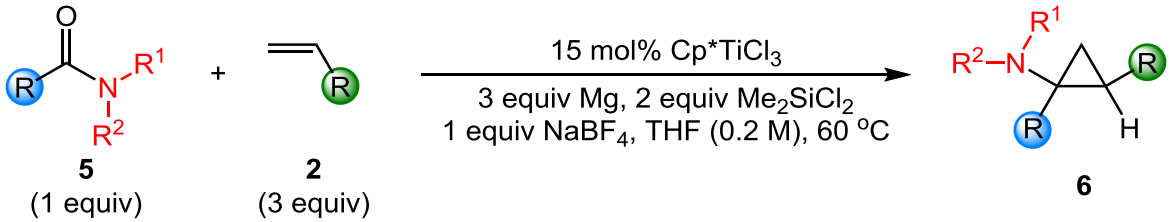
from adipic acid
3r, 71%, 16:1 d.r.

intramolecular cyclopropanation



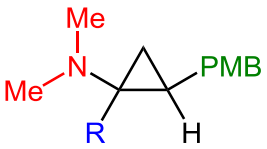
3s, 45%, 20:1 d.r.

Scope for Cyclopropylamine Synthesis

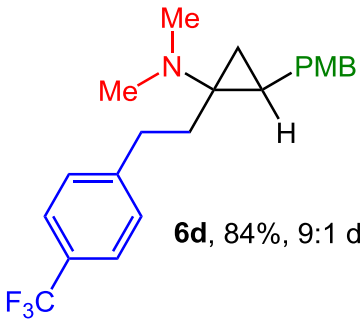


5 (1 equiv) + **2** (3 equiv) → **6**

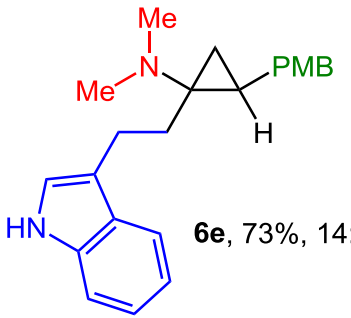
amides



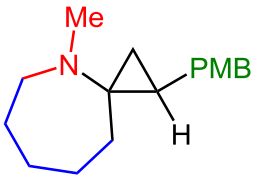
R = Me, **6a**, 60%, 8:1 d.r.
Et, **6b**, 82%, 14:1 d.r.
^{i}Bu, **6c**, 86%, 12:1 d.r.



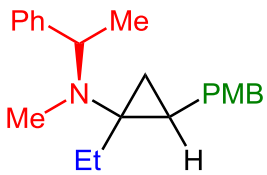
6d, 84%, 9:1 d.r.



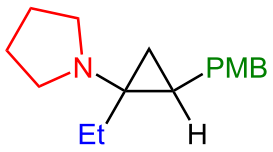
6e, 73%, 14:1 d.r.



6f, 60%, 10:1 d.r.



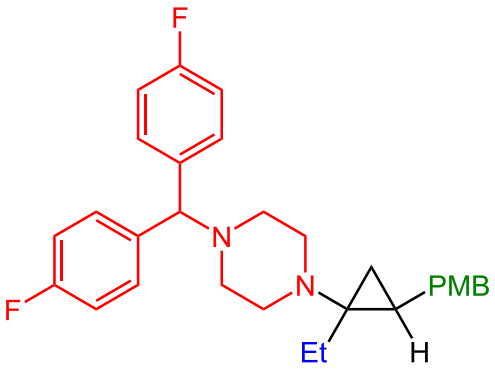
6g, 70%, 4:1 d.r.



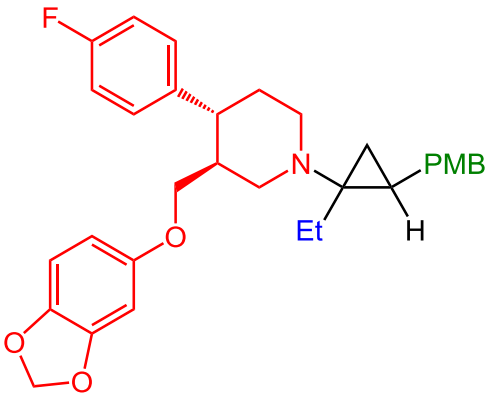
6h, 78%, 13:1 d.r.

Scope for Cyclopropylamine Synthesis

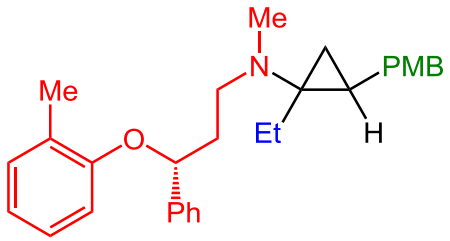
amides



from iomerizine
6i, 81%, 4:1 d.r.

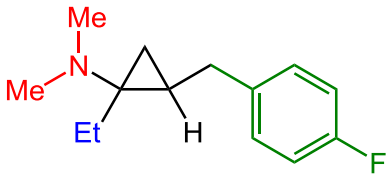


from paroxetine
6j, 69%, 8:1 d.r.

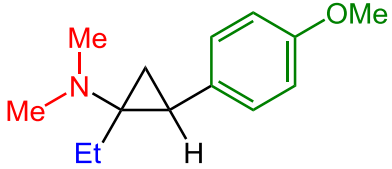


from atomoxetine
6k, 72%, 5:1 d.r.

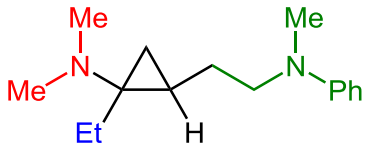
olefins



6l, 79%, 15:1 d.r.

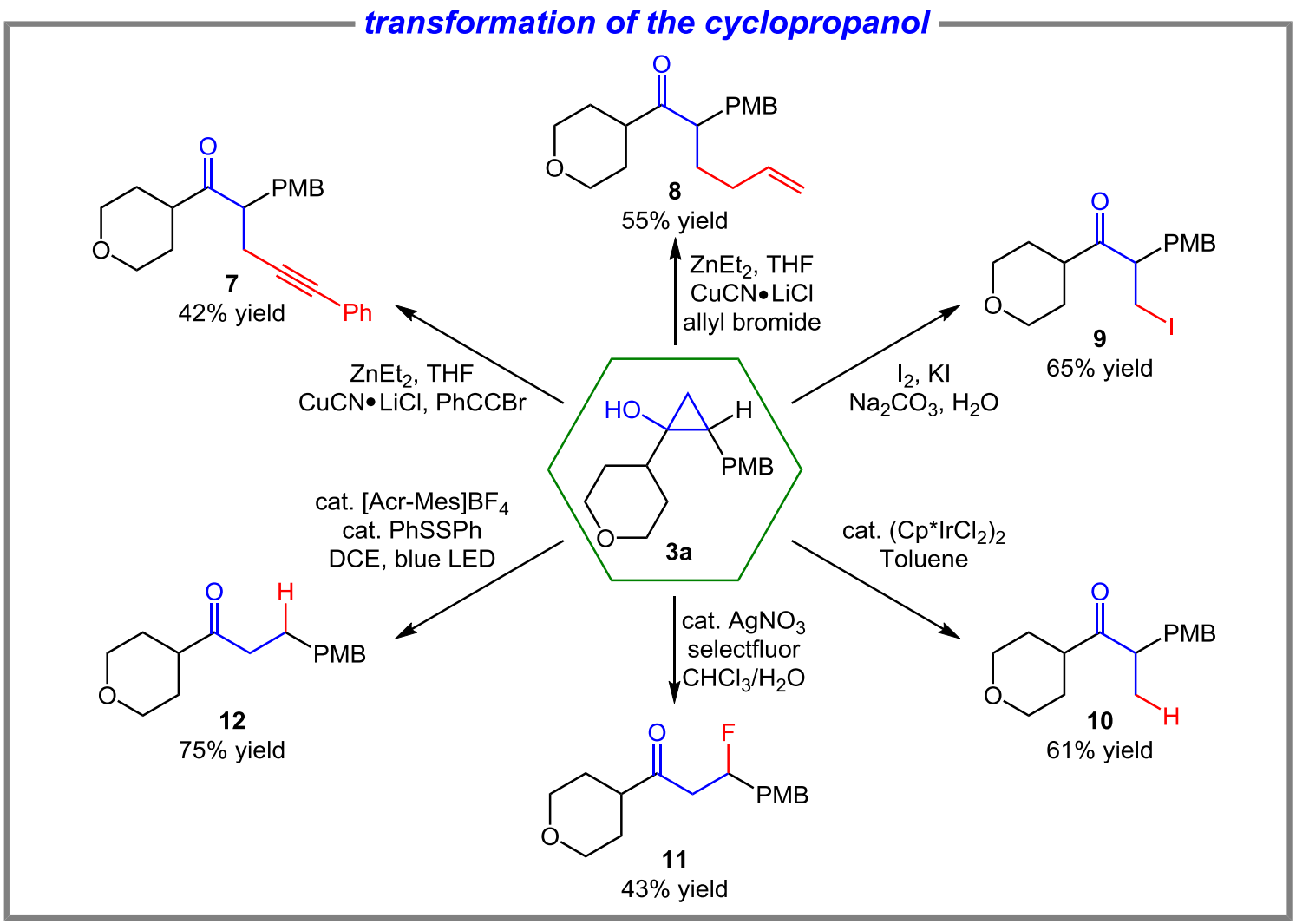


6m, 77%, 1.5:1 d.r.



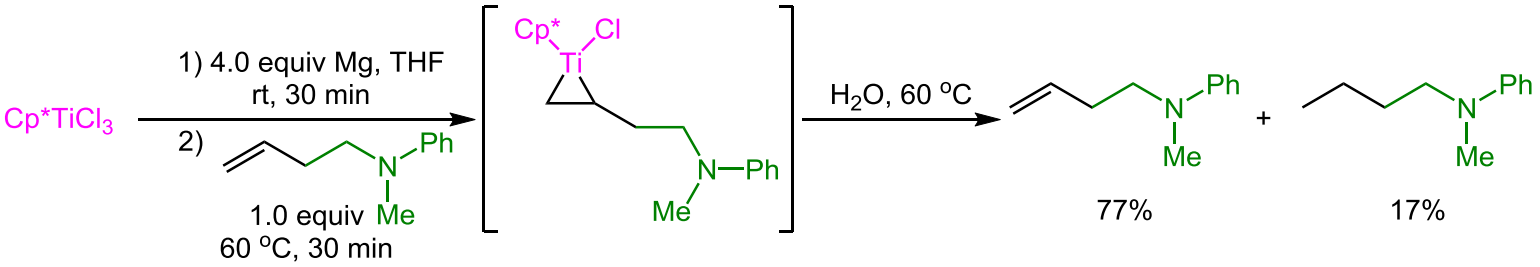
6n, 80%, 8:1 d.r.

Synthetic Applications

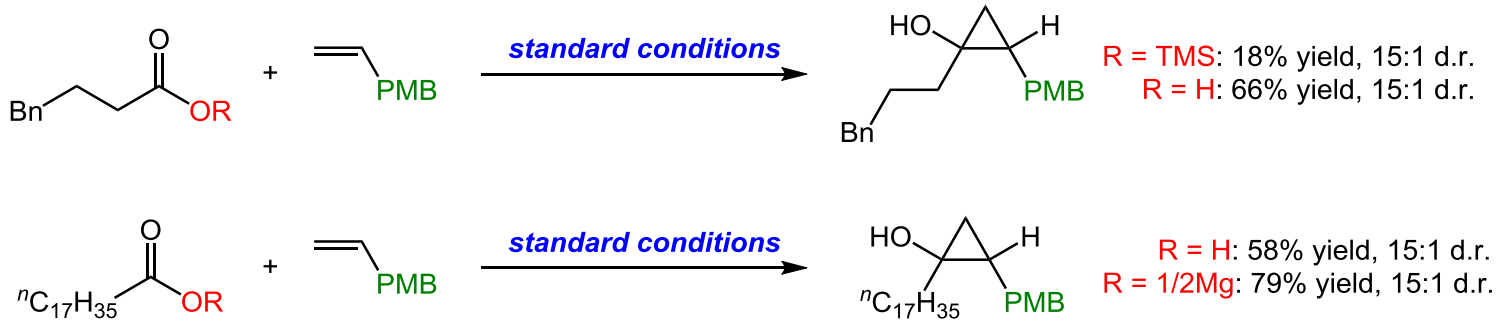


Mechanistic Investigation

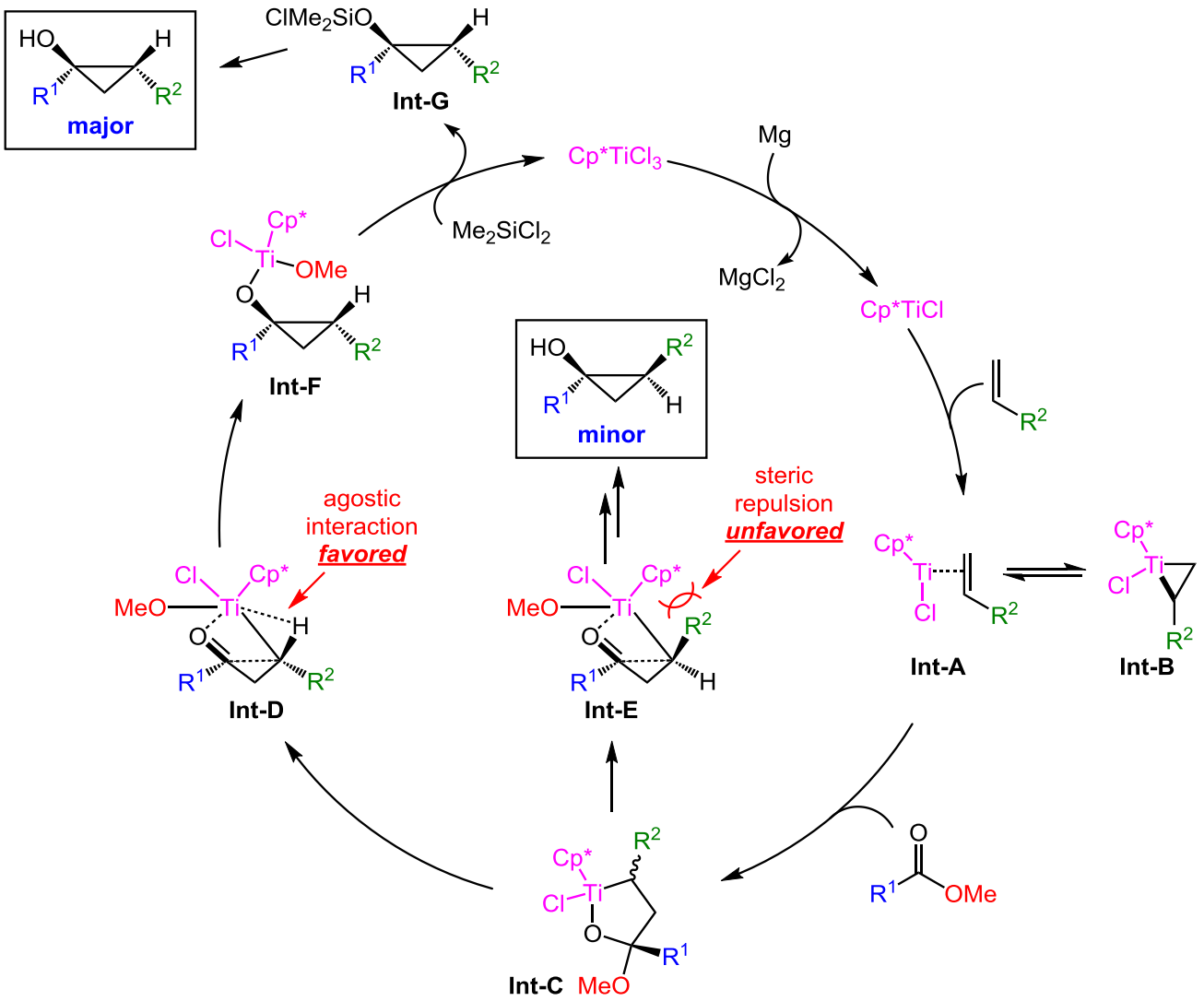
(a) Evidence on the titanacyclopropane intermediate



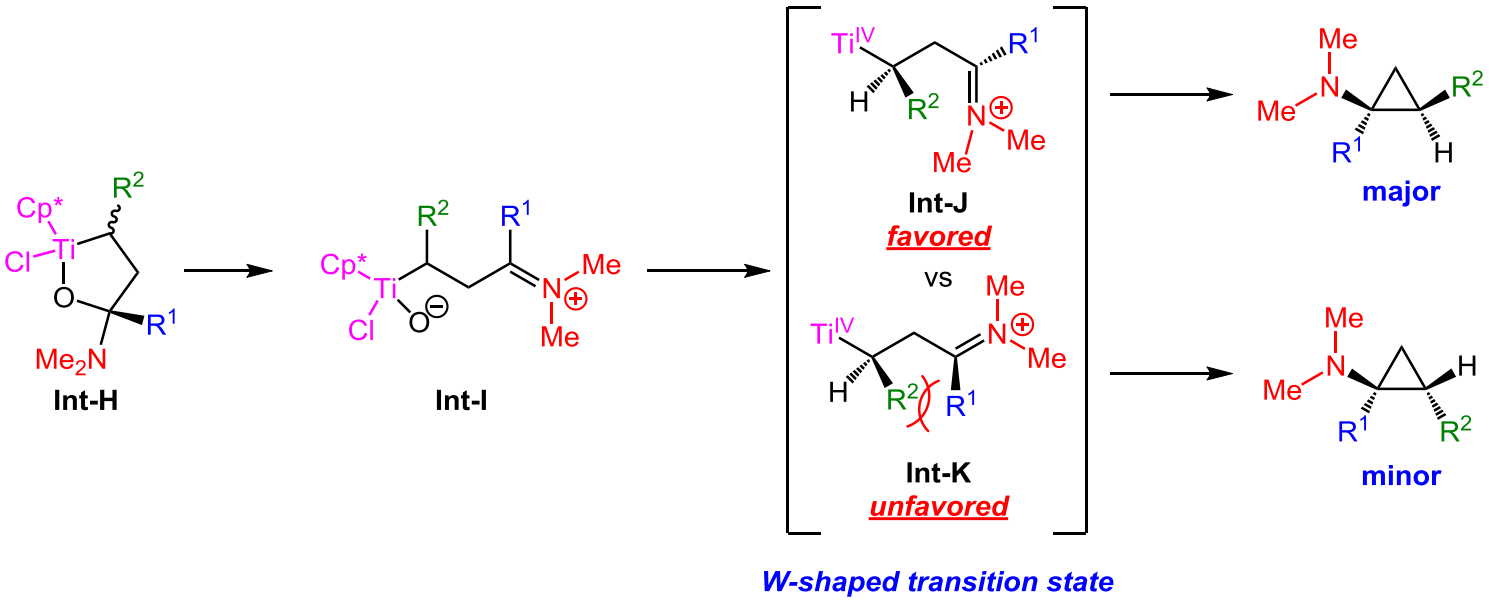
(b) Activation of carboxylic acid



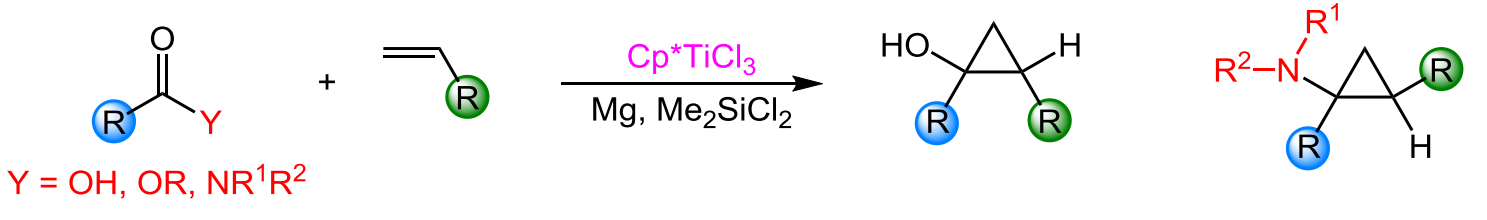
Mechanism for Cyclopropanol Synthesis



Stereochemistry for Cyclopropylamine



Summary



widely available chemicals *cyclopropanol* *cyclopropylamine*

- **Indentify Cp^*TiCl_3 as an effective catalyst**
- **Direct cyclopropanation of carboxylic acid**
- **Both reaction partners widely available**
- **Mild condition & broad substrate scope**
- **Good diastereoselectivity**
- **Diverse applications in organic synthesis**

The First Paragraph

Writing strategy

Introduction of structural properties and synthetic methods for cyclopropanes

↓

Lack of diastereoselective preparation of heteroatom-substituted cyclopropane derivatives

↓

Specific activities for cyclopropanols and cyclopropylamines

The First Paragraph

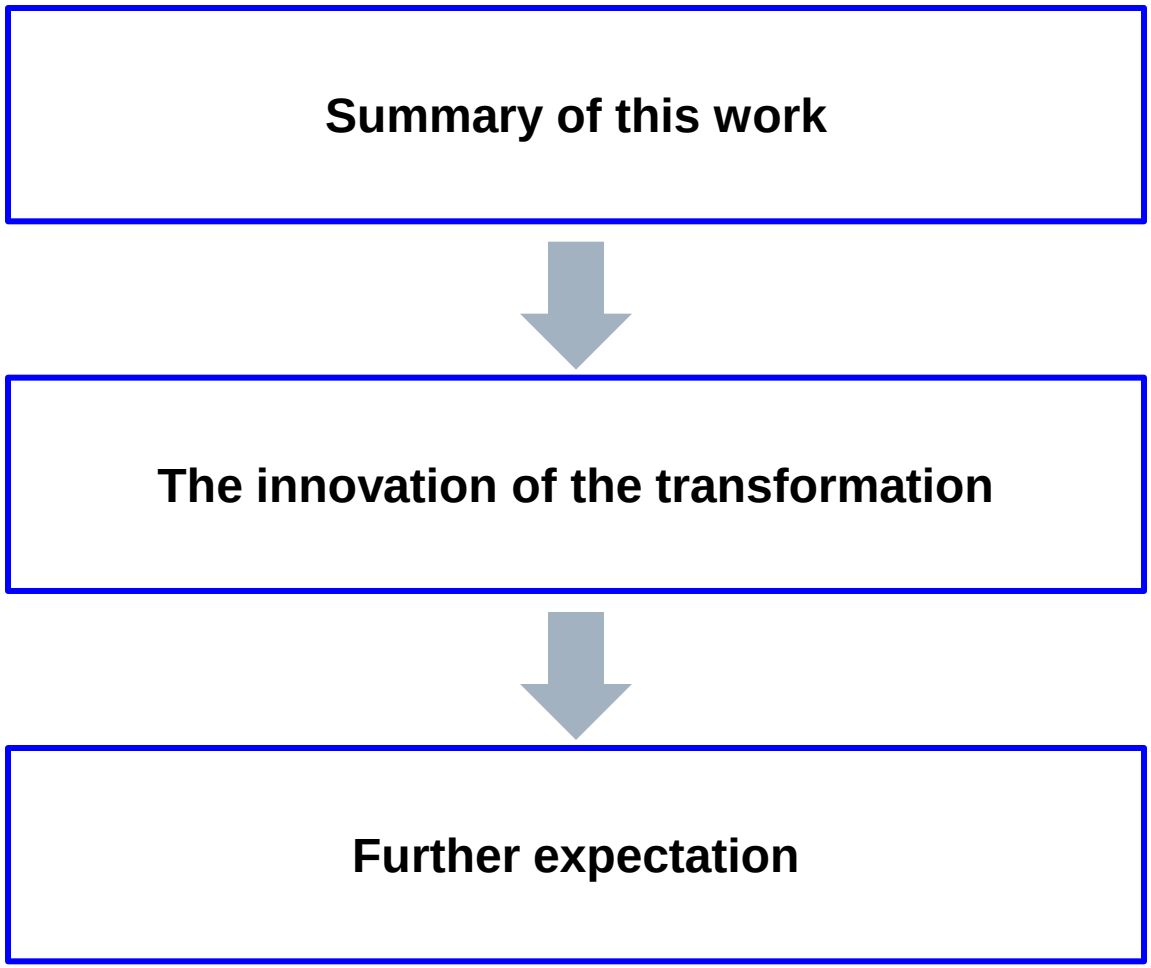
Cyclopropanes, structurally featuring high ring strain and unusual bonding properties, represent a versatile building block in a diverse array of bond-forming reactions. Great efforts have been devoted to synthesizing these small carbocycles in the past several decades, including the Simmons-Smith reaction, transition-metal catalysis with diazo-derived carbenoids, metalloradical catalysis, nucleophilic displacement reactions, and enzymatic methods. However, much less attention has been dedicated to the diastereoselective preparation of heteroatom-substituted cyclopropane derivatives, such as cyclopropanols and cyclopropylamines, despite the fact that they also exhibit manifold reactivities and are encountered in many biologically active compounds.

The First Paragraph

Particularly, the heteroatom substituent proves to endow the cyclopropane ring with novel activities. For instance, the ring opening of cyclopropanols could generate metal homoenolate or *β*-keto radical, while the transformation of cyclopropylamines could proceed via the C-C bond activation chemistry, radical-type chemistry, or polar-type chemistry. These fabulous reaction patterns resulted in the broad utility of cyclopropanols and cyclopropylamines in organic synthesis.

The Last Paragraph

Writing strategy



The Last Paragraph

In summary, we have demonstrated that a Ti-based catalyst can effectively promote the diastereoselective cyclopropanation of widely available carboxylic acids and their derivatives with terminal olefins. Notably, the use of Mg dust as the reductant and Me_2SiCl_2 as the dissociation reagent efficiently turns over the Ti-based catalytic cycle, thus overcoming the requirement for reactive alkyl Grignard reagent in previous reports.

The Last Paragraph

The present method exhibits a broad substrate scope with good functional group compatibility and is amenable to late-stage synthetic manipulations of natural products and biologically active molecules. Given the synthetic importance of cyclopropane derivatives as well as the growing interest in low-valent early transition-metal catalysis, we anticipate that our protocol will find broad utility in synthetic chemistry and facilitate current endeavors in accessing valuable building blocks from stable and readily available starting materials.

Representative Examples

Our method exhibits broad substrate scope with good functional group compatibility and is amenable to late-stage synthetic manipulations of natural products and biologically active molecules. (适用于)

The use of sterically hindered amides is detrimental to the diastereoselectivity. (对…是不利的)

They also exhibit manifold reactivities and are encountered in many biologically active compounds. (多种多样的)

Thanks for your attention