Literature Report VIII

Use of Strain-Release for the Diastereoselective Construction of Quaternary Carbon Centers

Reporter: Yi-Xuan Ding
Checker: Zhou-Hao Zhu
Date: 2021-09-13

Glorius, F. *et al. J. Am. Chem. Soc*. **2021**, *143*, 7648.

CV of Prof. Frank Glorius

Frank Glorius

Background:

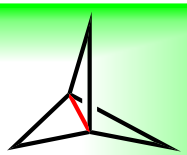
- **1992-1997** Studies of chemistry, the University of Hannover
- **1995-1996** Research studies, Stanford University
- **1996-1997** Diploma thesis, University of Hannover
- **1997-2000** PhD, University of Basel
- **2000-2001** Postdoc., Harvard University
- **2001-2004** Independent research at the Max-Planck-Institut für Kohlenforschung
- **2004-2007** C3-Professor, University of Marburg
- **2007-now** Full Professor, University of Münster

Research Interests:

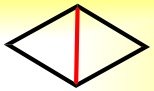
- Arene Hydrogenation
- Photocatalysis
- C–H Activation
- *N*-heterocyclic carbene (NHC) organocatalysis
- Biological membranes

Contents

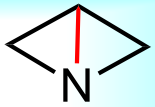
Introduction



[1.1.1]螺桨烷
[1.1.1]propellane



双环[1,1,0]丁烷
bicyclo[1.1.0]buanes
(BCBs)

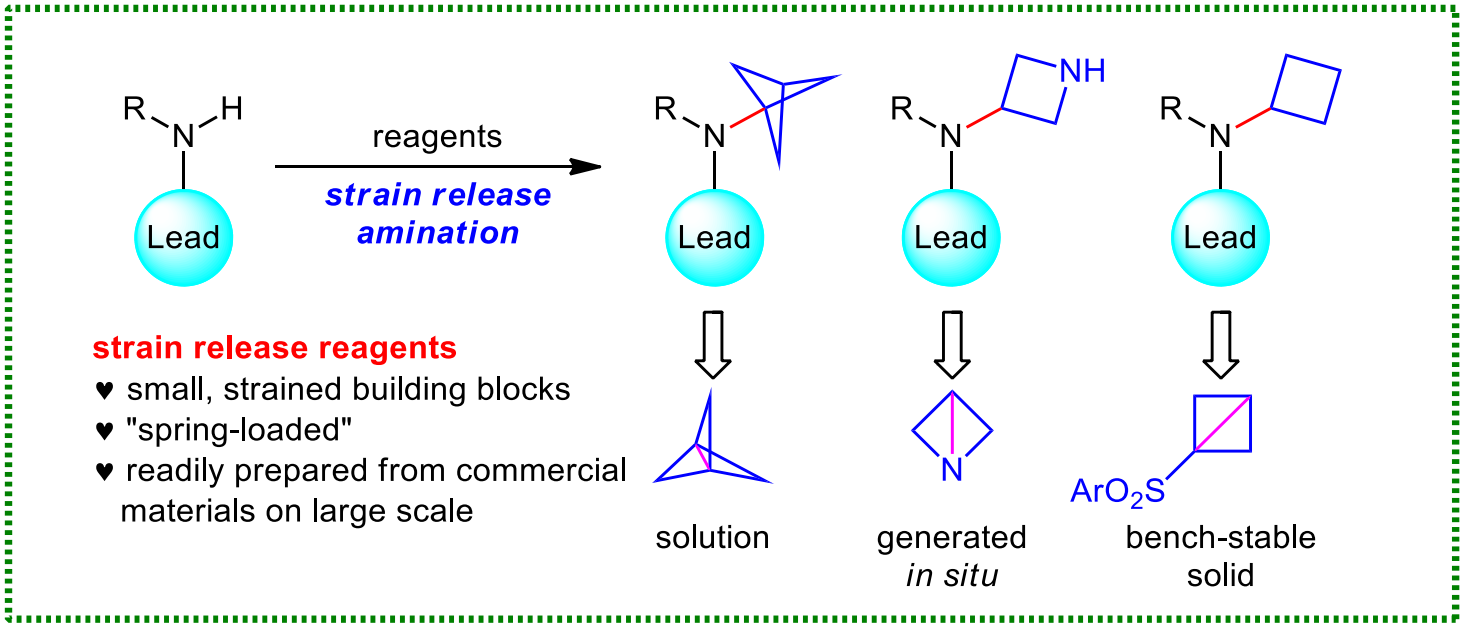


氮杂双环[1,1,0]丁烷
azabicyclo[1.1.0]buanes

Spring-loaded

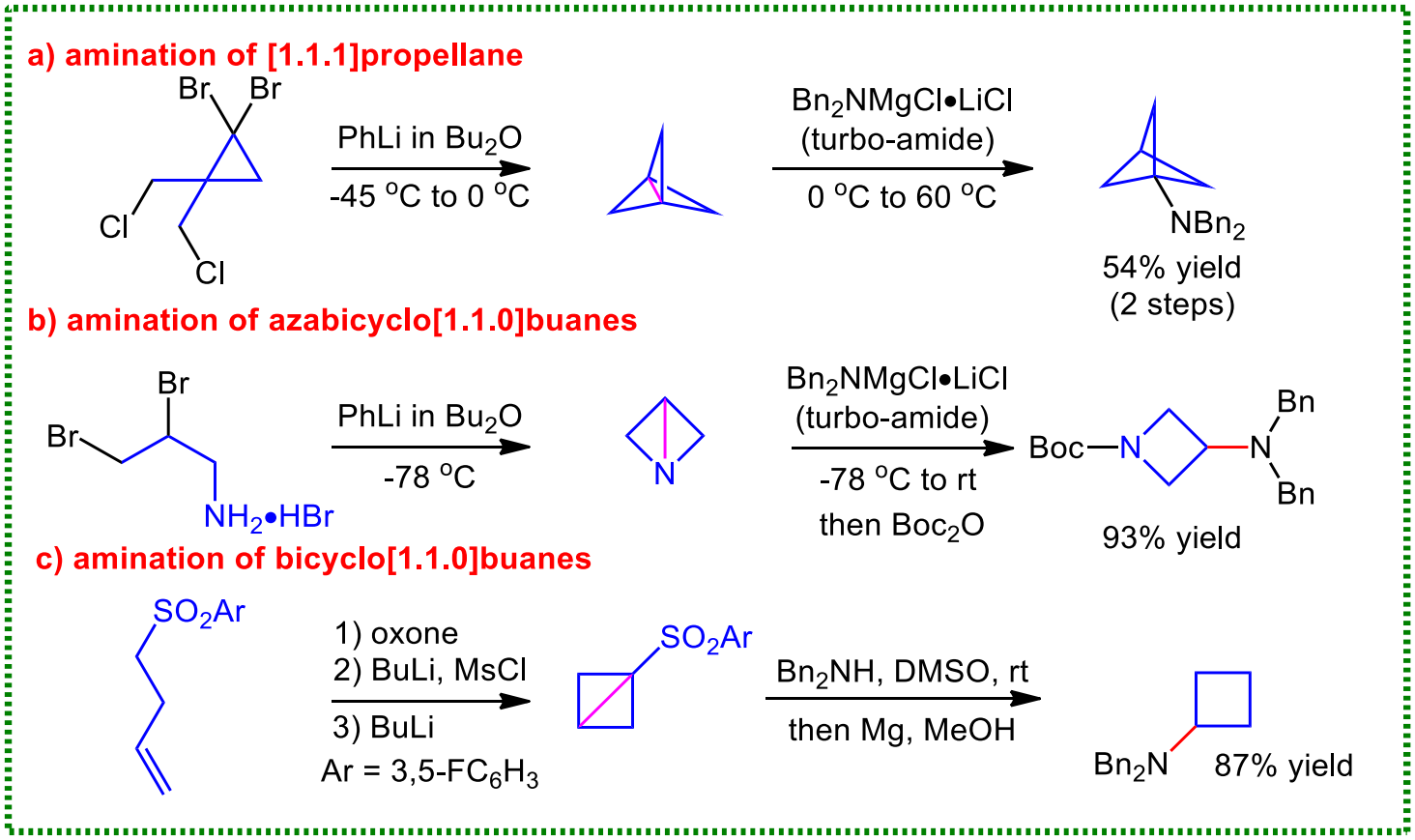
Introduction

Strain release amination



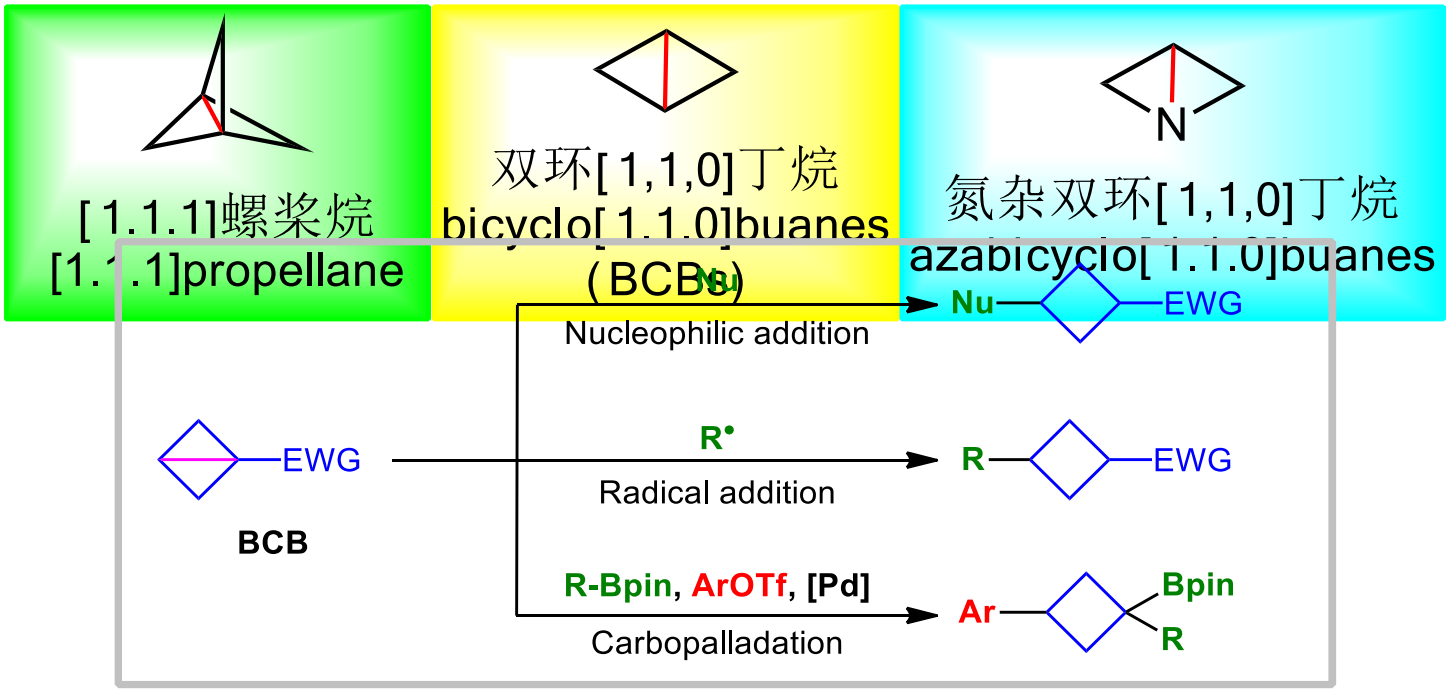
Baran, P. S. *et al*. *Science* **2016**, *351*, 241.

Introduction



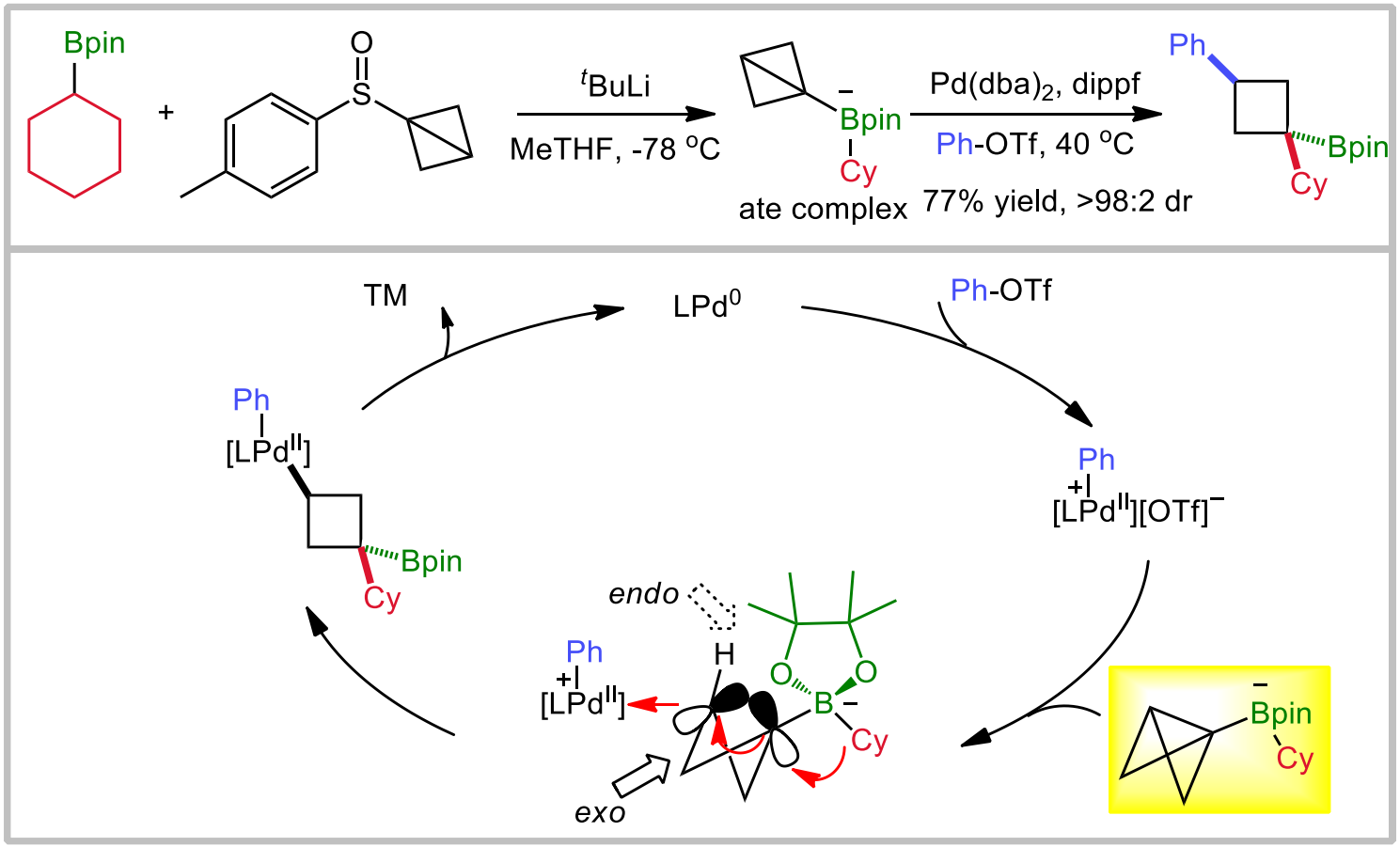
Baran, P. S. *et al*. *Science* **2016**, *351*, 241.

Introduction



Introduction

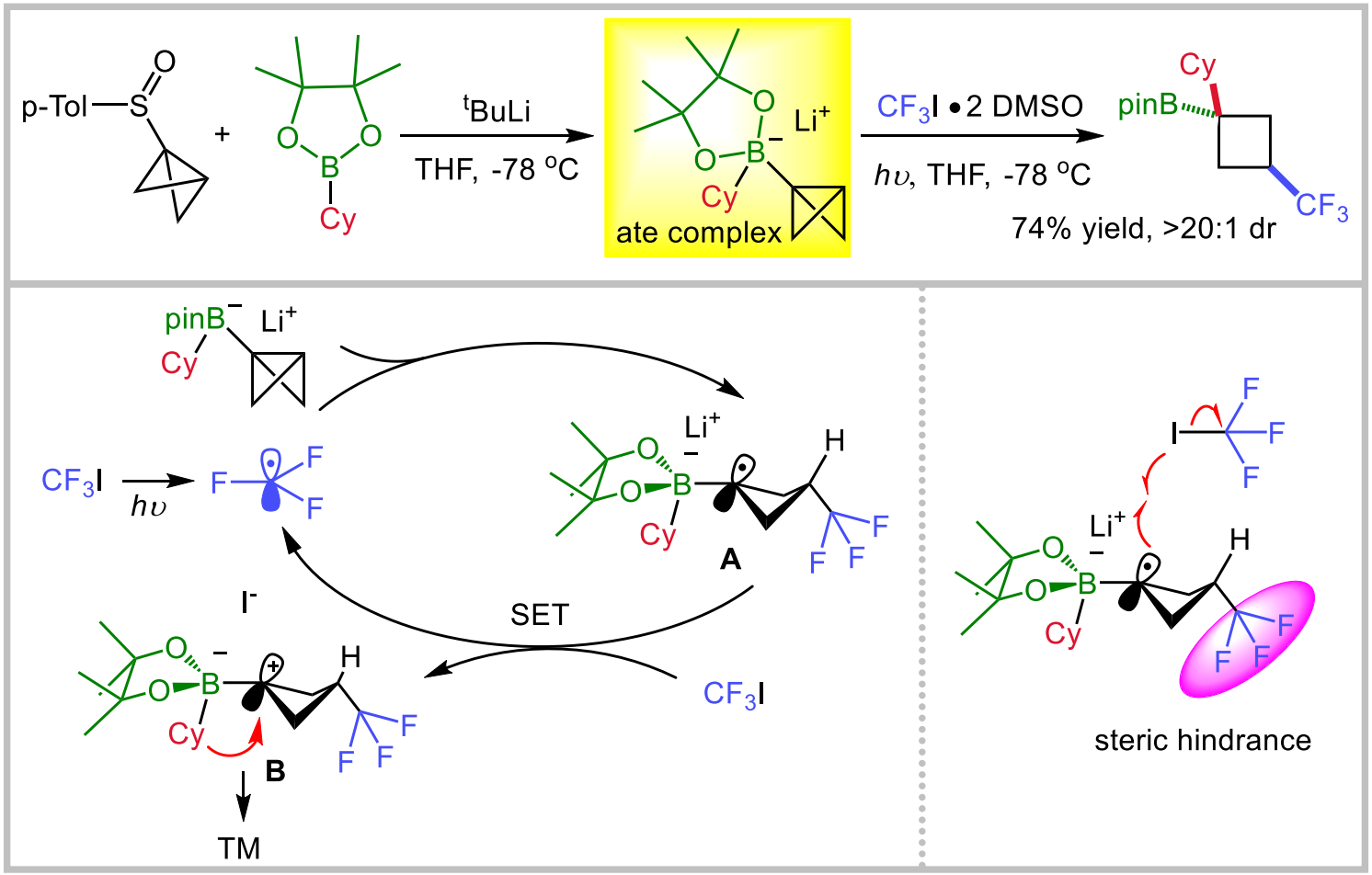
Carbopalladation



Aggarwal, V. K. *et al. Nat. Chem.* **2019**, *11*, 117.

Introduction

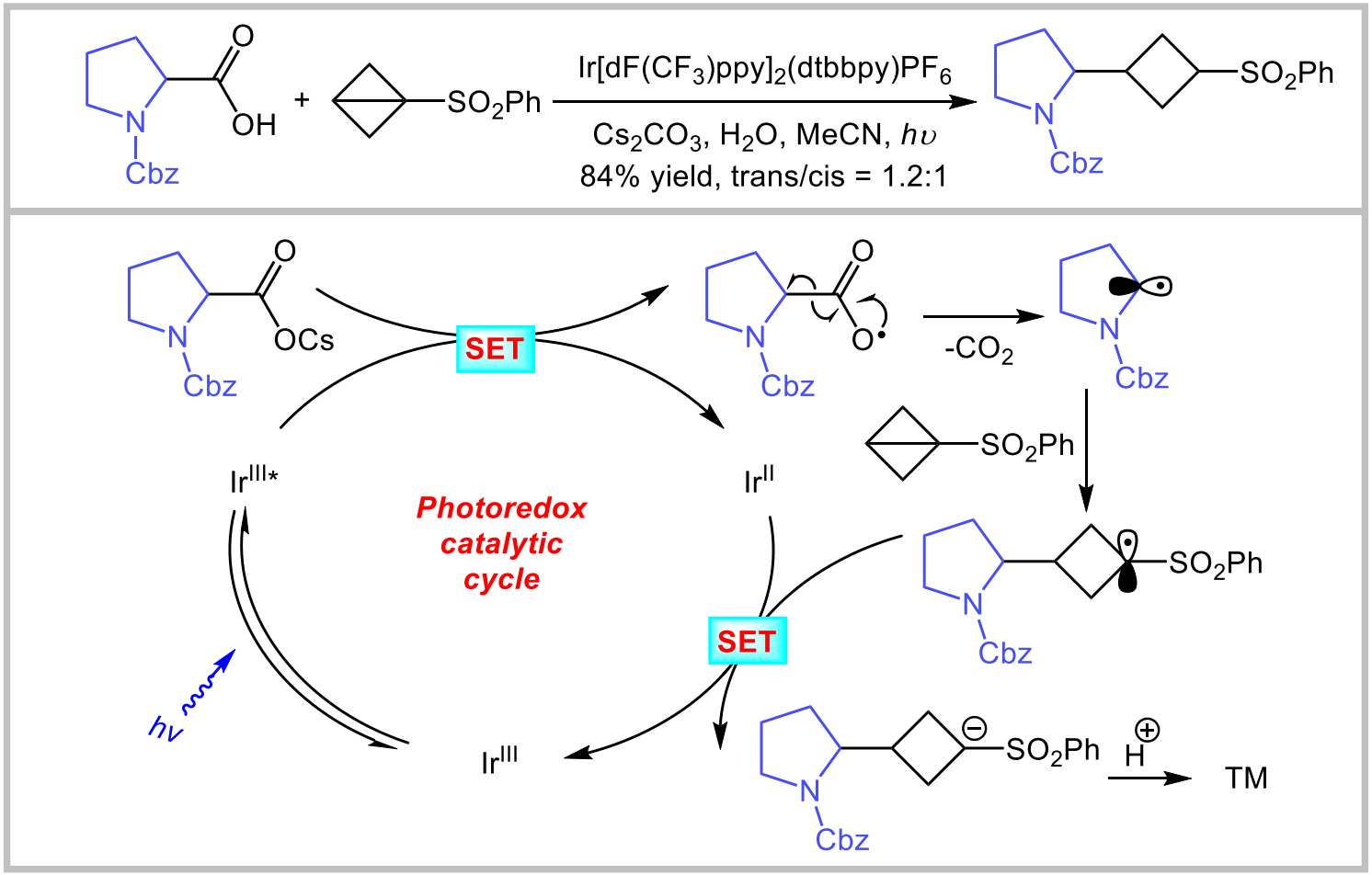
Radical addition



Aggarwal, V. K. *et al. J. Am. Chem. Soc*. **2019**, *141*, 9511.

Introduction

Radical addition



Cintrat, C. *et al*. *Angew. Chem. Int. Ed.* **2020**, *59*, 2618.

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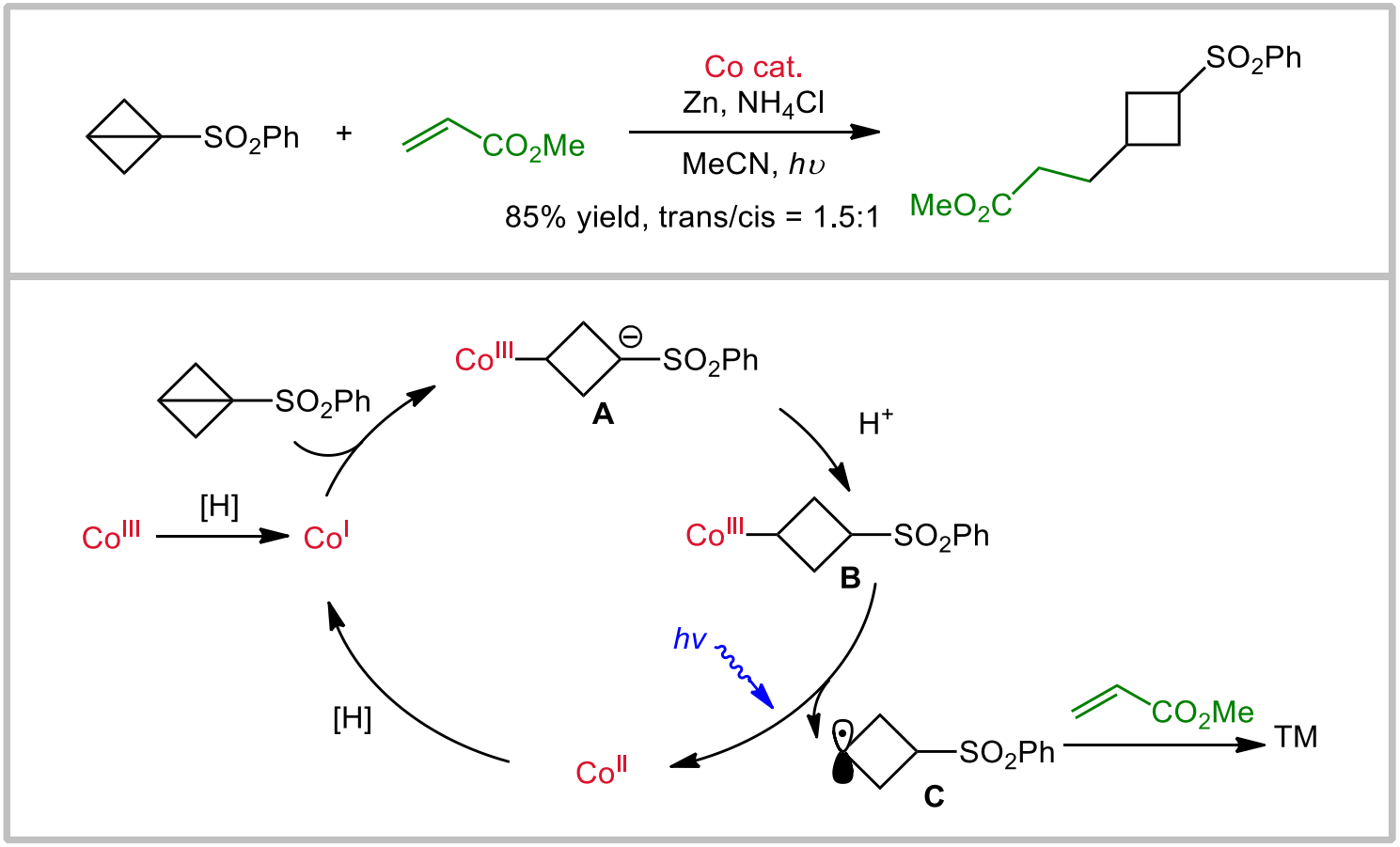
Nucleophilic addition



Gryko, D. *et al. J. Am. Chem. Soc*. **2020**, *142*, 5355.

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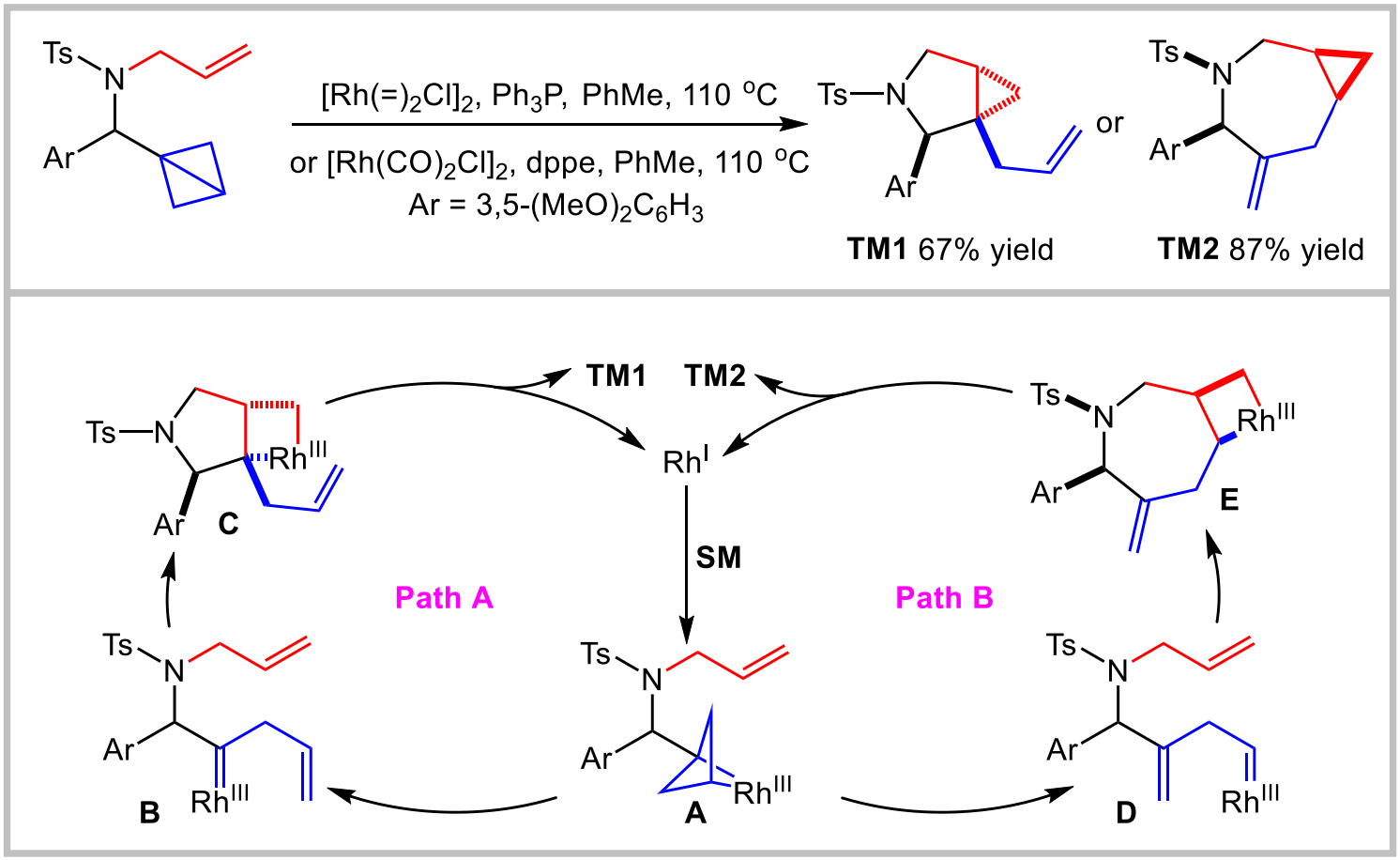
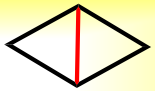
Cycloisomerization



Wipf, P. *et al. J. Am. Chem. Soc*. **2008**, *130*, 6924.

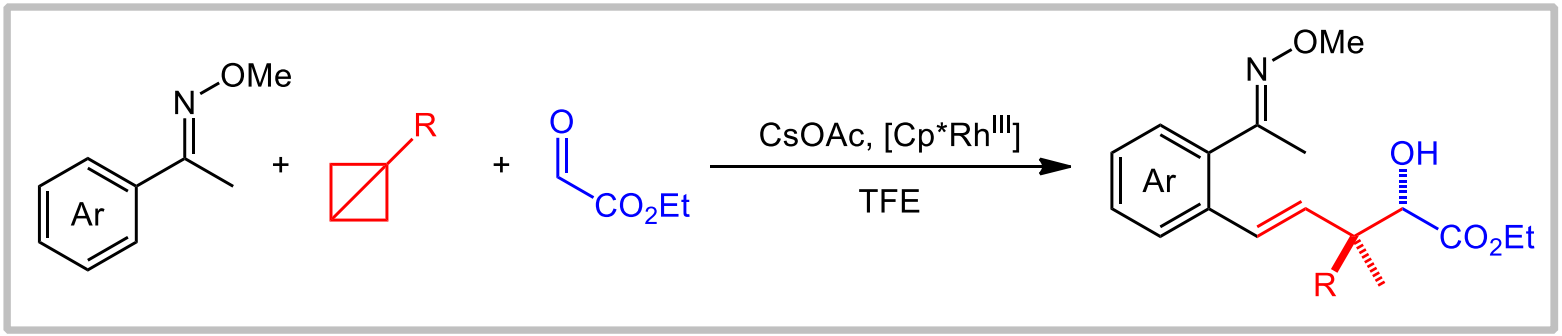
Project Synopsis



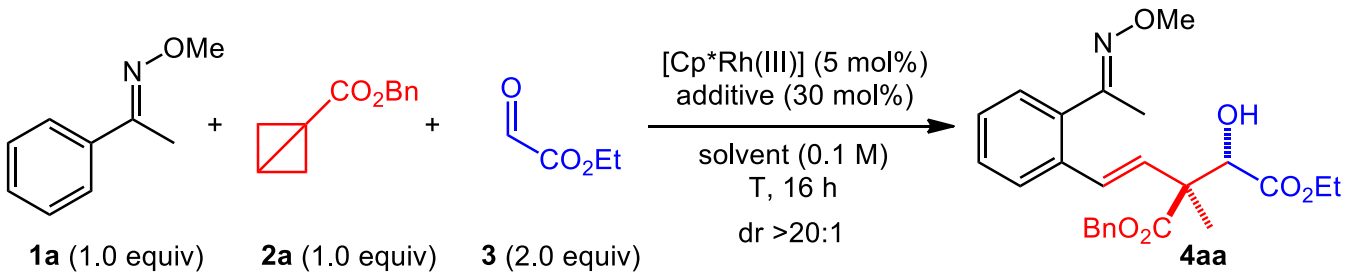
双环[1,1,0]丁烷
bicyclo[1.1.0]buanes
(BCBs)

- ♥ Strain-release Protocol
- ♥ C-H Activation
- ♥ Three-component Reaction

This work



Optimization of Reaction Conditions

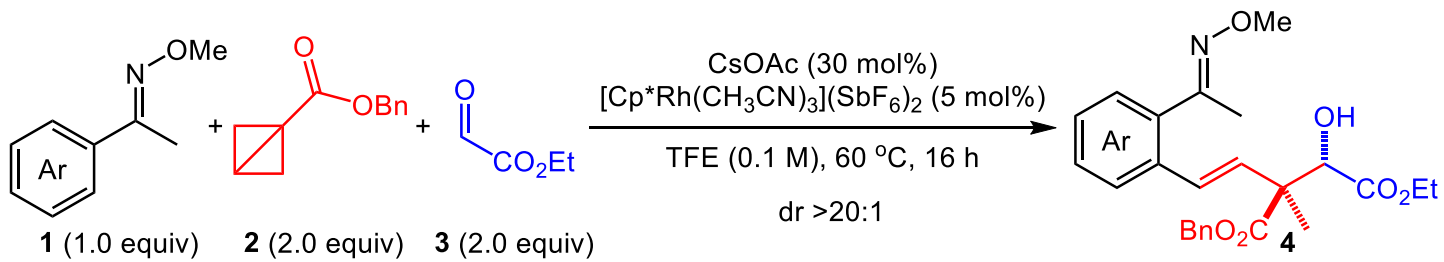


1a (1.0 equiv) **2a** (1.0 equiv) **3** (2.0 equiv) **4aa**

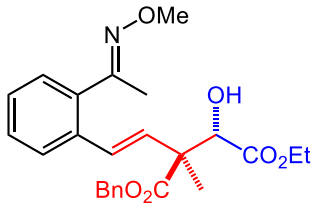
Entry[a]	Solvent	Additive	T (°C)	Yield (%)
1	**TFE**	CsOAc	60	60
2	DCE	CsOAc	60	traces
3	1,4-dioxane	CsOAc	60	-
4	HFIP	CsOAc	**60**	8
5	TFE	CsOAc	rt	9
6	TFE	CsOAc	40	40
7	TFE	**CsOAc**	80	47
8	TFE	Na_2CO_3	60	28
9	TFE	KOAc	60	55
10	TFE	NaOAc	60	49
11	TFE	K_3PO_4	60	30
12[b]	**TFE**	**CsOAc**	**60**	**82**

[a]Reactions were performed on a 0.10 mmol scale with $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ as the catalyst. [b]2.0 equiv of **2a**.

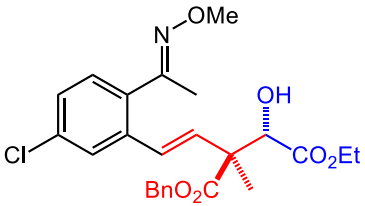
Substrate Scope



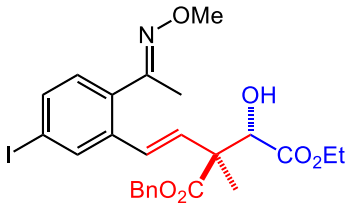
1 (1.0 equiv) **2** (2.0 equiv) **3** (2.0 equiv) **4**



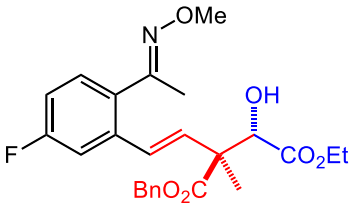
4aa, 74%



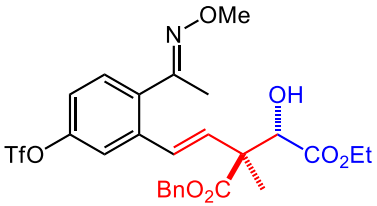
4ba, 69%



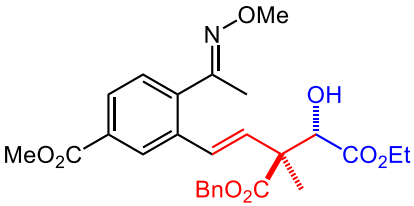
4ca, 66%



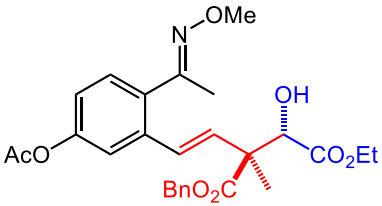
4da, 69%



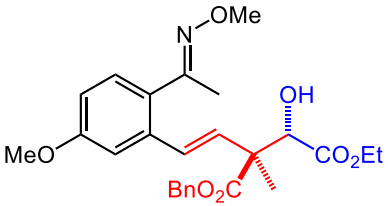
4ea, 67%



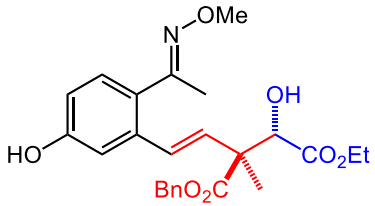
4fa, 74%



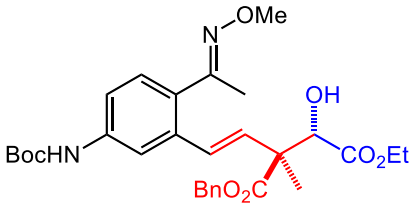
4ga, 54%



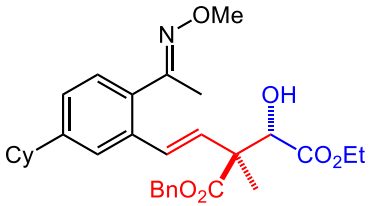
4ha, 80%



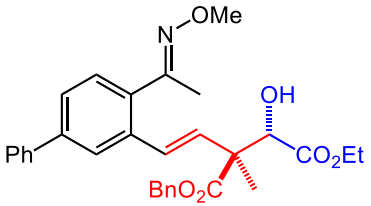
4ia, 57%



4ja, 62%

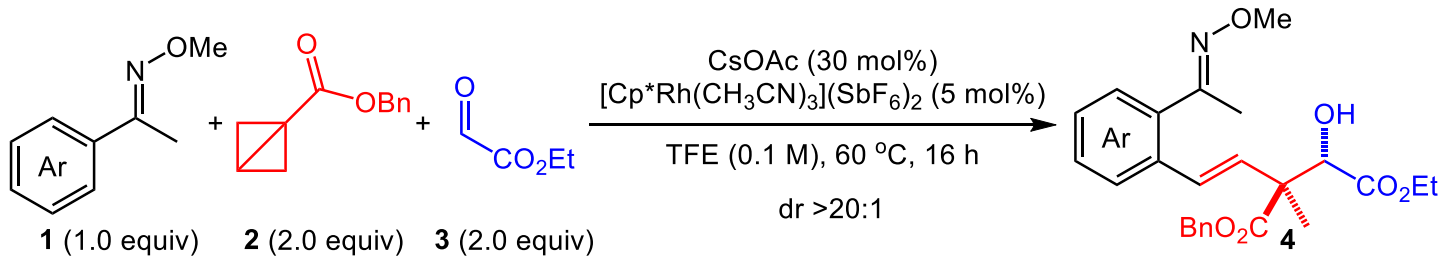


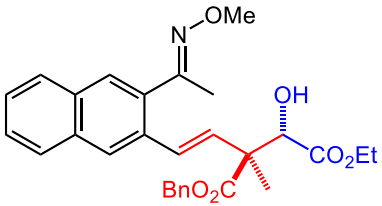
4ka, 62%



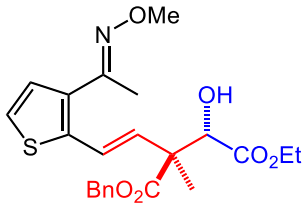
4la, 76%

Substrate Scope

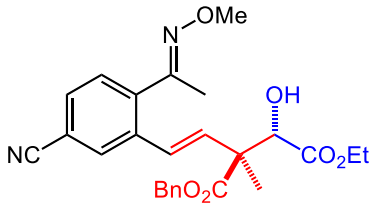




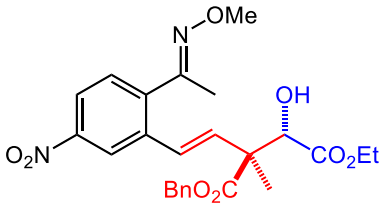
4ma, 56%



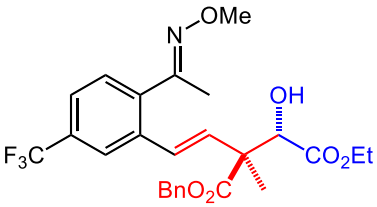
4na, 62%



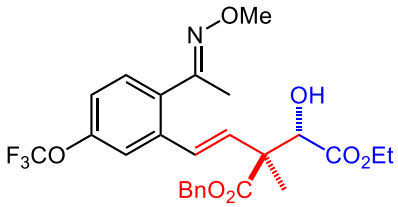
4oa, 69%



4pa, 53%



4qa, 59%



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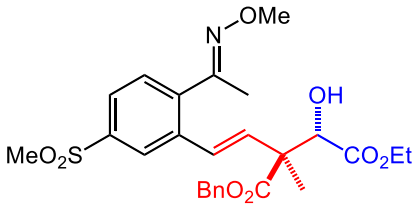
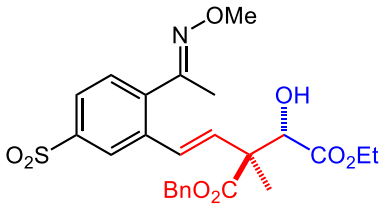
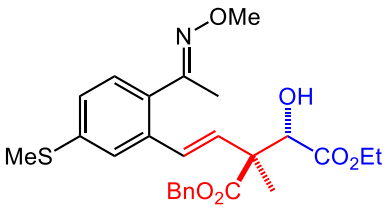


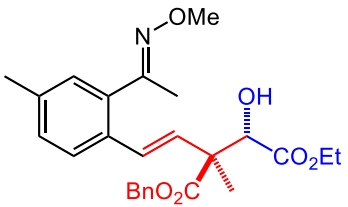
4sa, 78%,



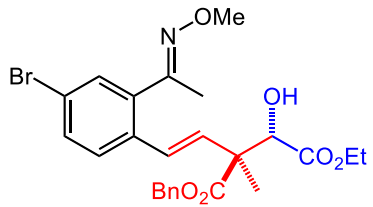
4ta, 81%



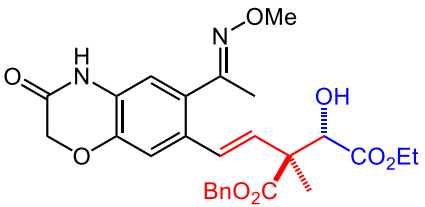
4ua, 44%



4va, 64%

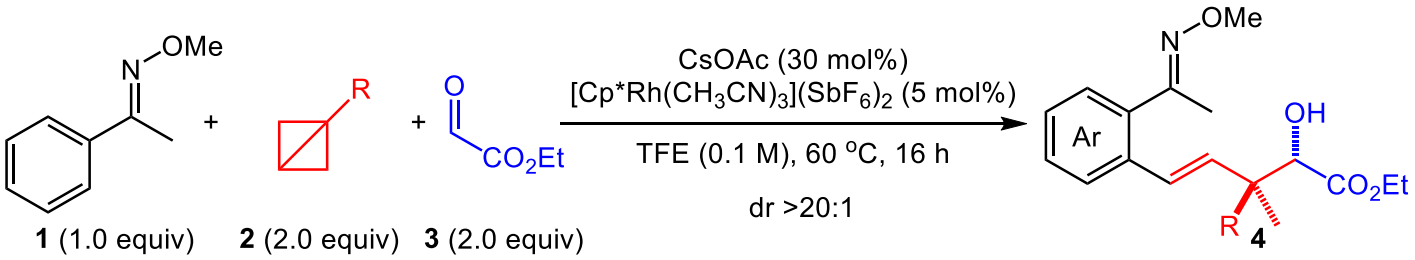


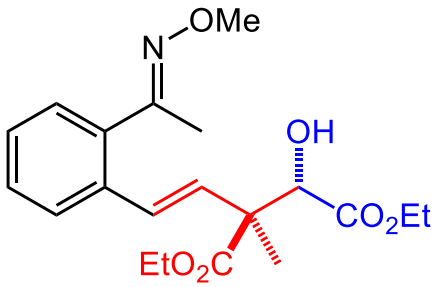
4wa, 63%



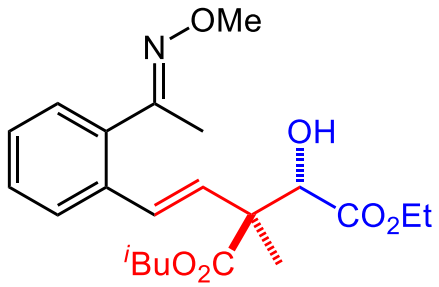
4xa, 72%

Substrate Scope

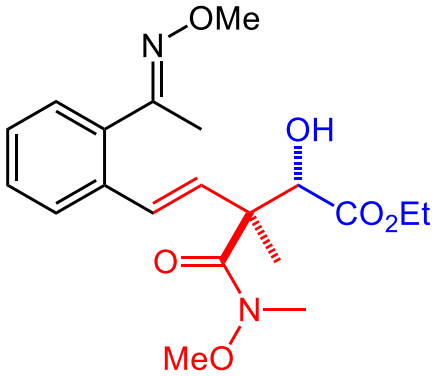




4ab, 72%

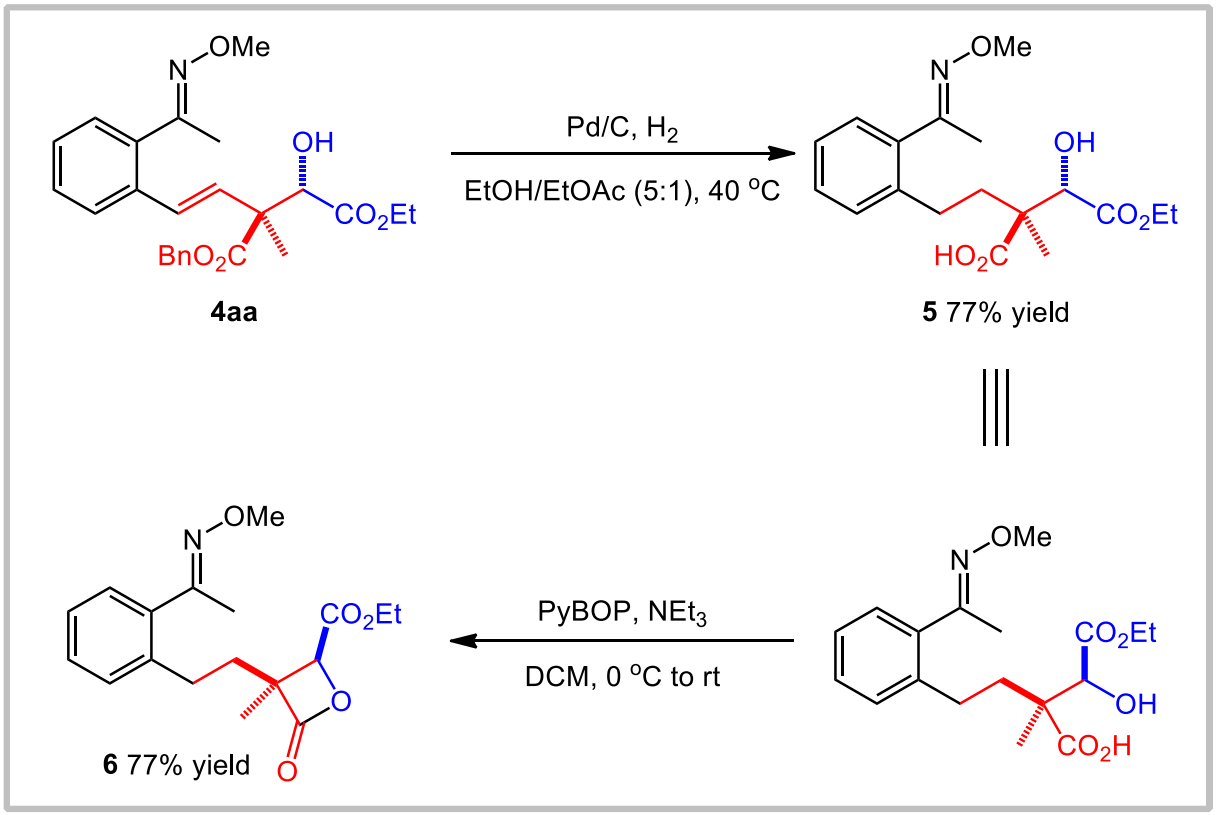


4ac, 69%



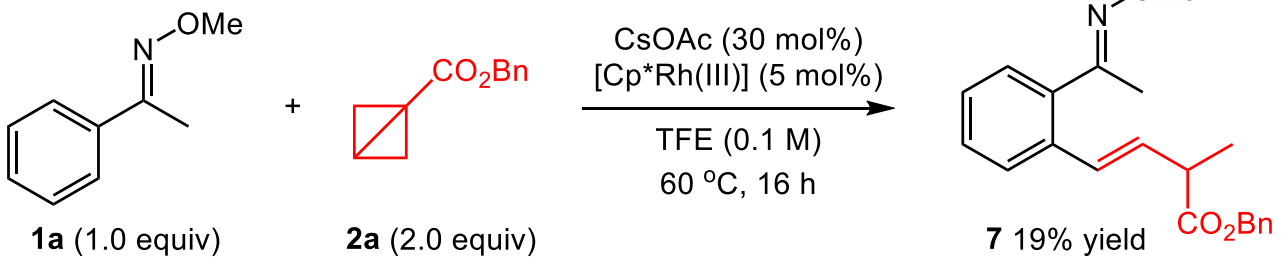
4ad, 51%

β-Lactone Formation

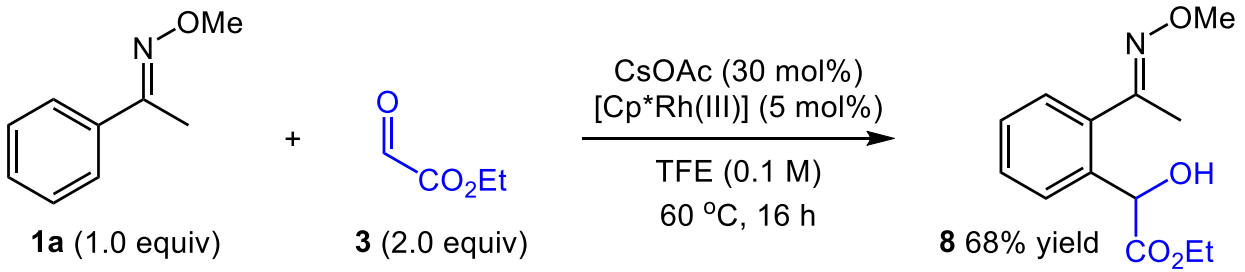


Mechanistic Investigations

a) Two-Component Experiments

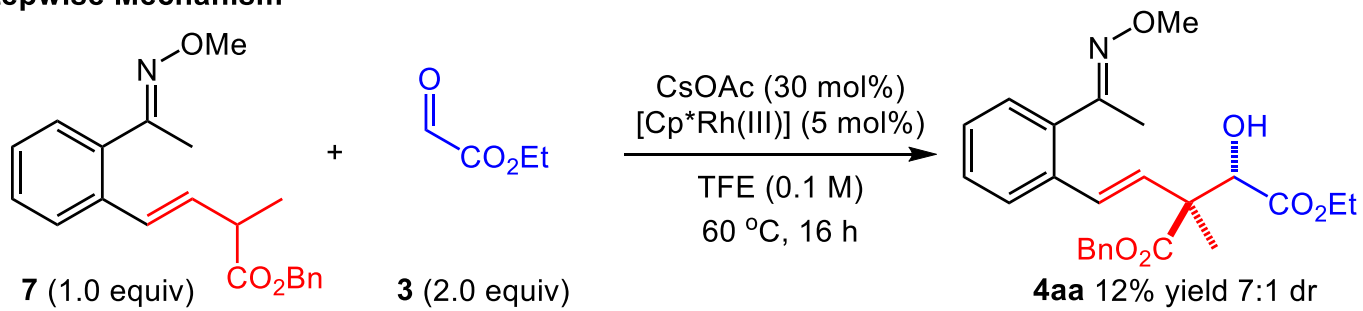


1a (1.0 equiv) **2a** (2.0 equiv) **7** 19% yield



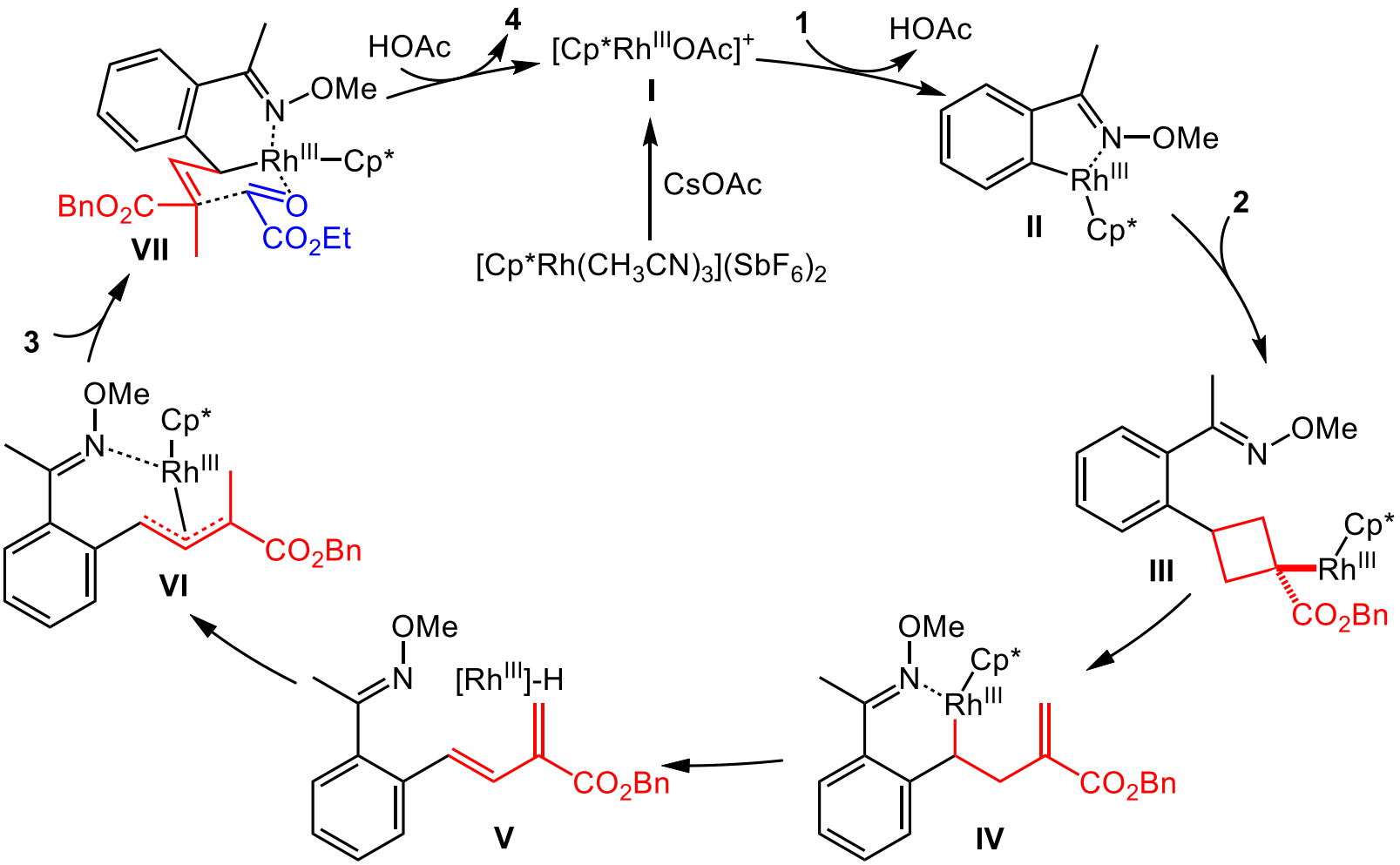
1a (1.0 equiv) **3** (2.0 equiv) **8** 68% yield

b) Stepwise Mechanism



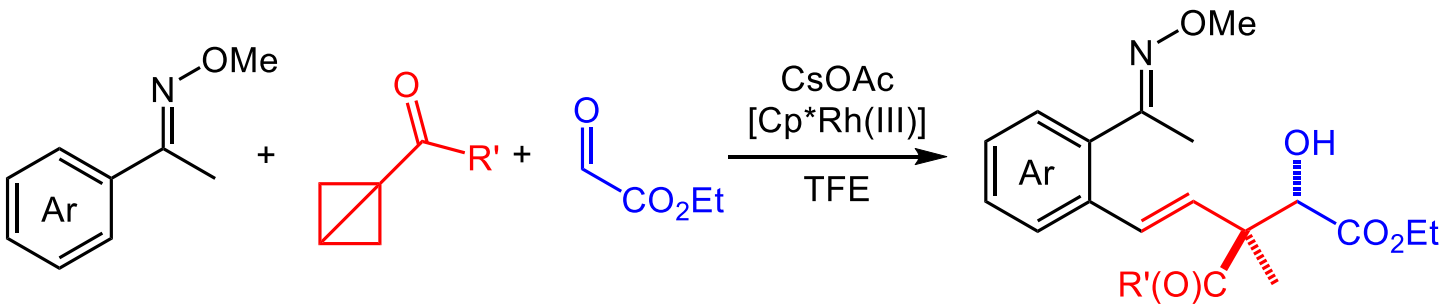
7 (1.0 equiv) **3** (2.0 equiv) **4aa** 12% yield 7:1 dr

Proposed Mechanism



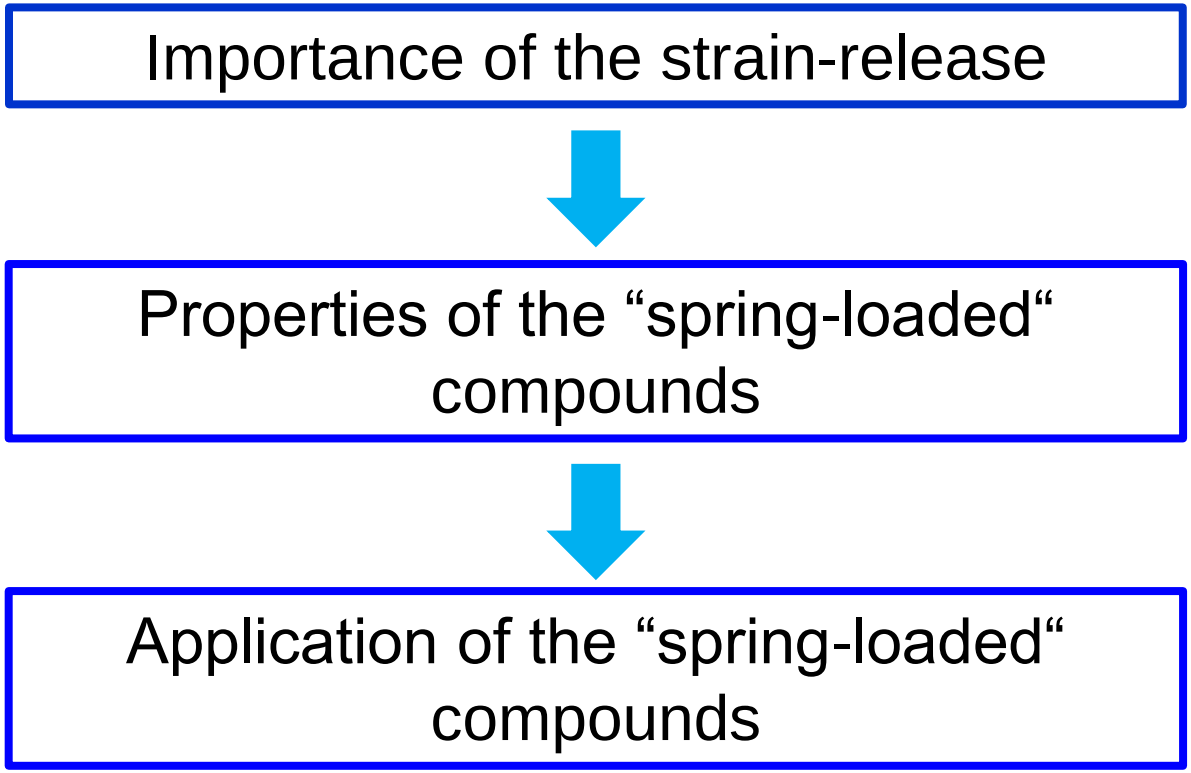
Summary

Strain-Release Construction of Quaternary Carbon Centers



♥ **quaternary carbon centers** ♥**diastereoselectivity**
♥***E*-selectivity** ♥**broad FG tolerance** ♥**three-component**
♥**twofold C-C bond cleavage** ♥**mild conditions**

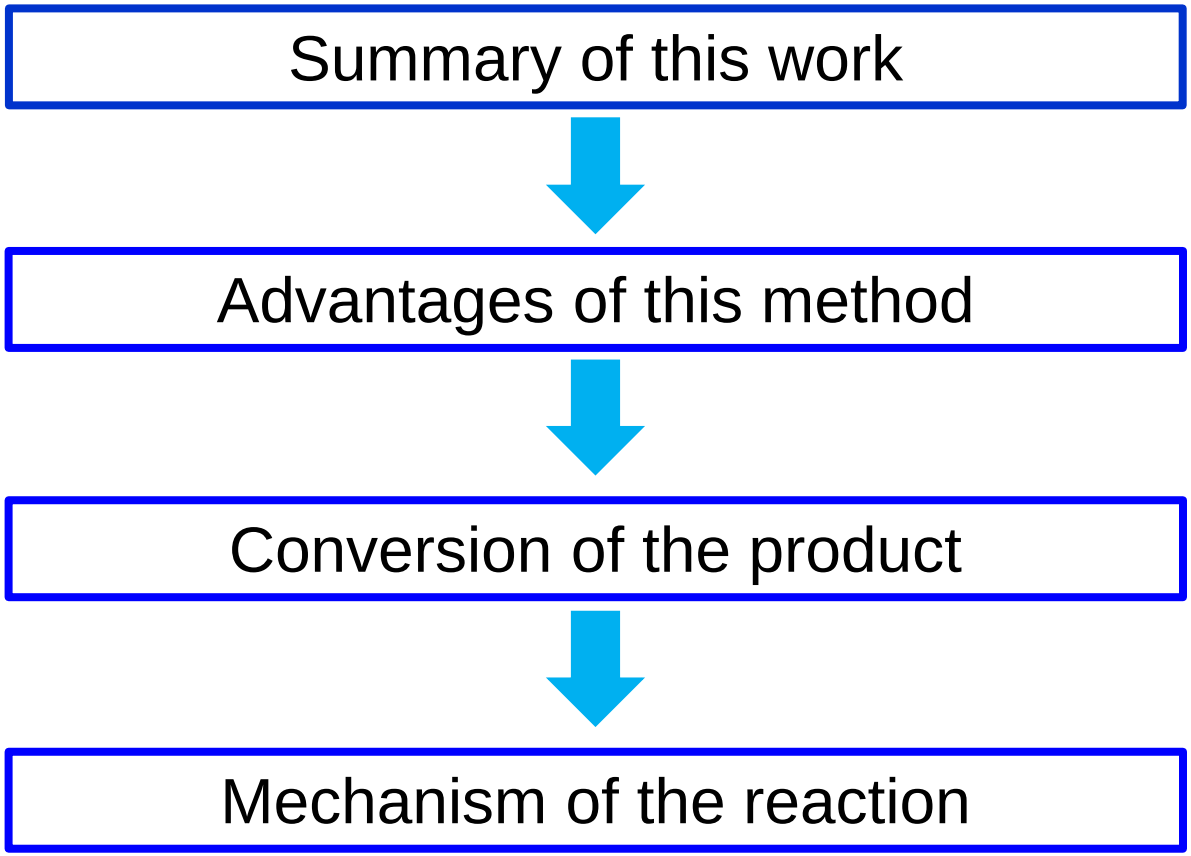
Writing Strategy



The First Paragraph

During the past decades strain-release driven transformations have gathered significant attention in synthetic organic chemistry, materials science, and bioconjugation. Accordingly, molecules that bear a bridging bond between opposite carbon or nitrogen atoms such as [1.1.1]propellane, bicyclo[1.1.0]butanes (BCBs), or 1-azabicyclo[1.1.0]butanes have emerged as a privileged class of compounds. Owing to their relative destabilization, arising from bond length and bond angle distortions, torsional strain, and nonbonded as well as transannular steric interactions, these “spring-loaded“ compounds display π-bond-type behavior towards nucleophiles, electrophiles, and radicals. Such versatile reactivity is especially desirable in the field of medicinal chemistry where they are commonly used to install the bicyclo[1.1.1]pentane, cyclobutane, and azetidine moieties, motifs which serve as bioisosteres in the development and modification of pharmaceuticals.

Writing Strategy



The Last Paragraph

In conclusion, we have developed a highly diastereoselective and E-selective three-component protocol for the construction of quaternary carbon centers via strain-release from BCB esters by twofold C−C bond cleavage. The reaction proceeds under mild conditions and tolerates a wide range of common functional groups. The products could be further transformed into valuable *α*-quaternary *β*-lactones. The high diastereoselectivity was rationalized by mechanistic investigations that suggest a catalytic cycle proceeding through a key C−C σ-bond insertion, followed by a *β*-carbon elimination and a subsequent allylation via a six-membered transition state.

Representative Examples

We were **intrigued** when we observed the anti-product 4aa in 60% yield with excellent E-selectivity and diastereoselectivity that was formed upon twofold C−C bond cleavage of the BCB moiety and subsequent addition to aldehyde 3 . **(*adj.* 好奇的)**.

The relative configuration of the stereocenters was **unambiguously** assigned by X-ray crystallographic analysis of a derivative of sulfone 4sa that was obtained after esterification and subsequent debenzylation. **(*adv.* 不含糊地)**.

In order to get insight into the **underlying** reaction mechanism a preliminary series of mechanistic experiments was conducted (Figure 3).(***adj.*** 潜在的).

Thanks
for your attention