Literature Report IV

Rhodium-Catalyzed Chemo-, Regio-, Diastereo-, and Enantioselective Intermolecular [2+2+2] Cycloaddition of Three Unsymmetric 2π Components

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Checker: Ying-Qi Wang

Shimotsukue, R.; Nagashima, Y.; Tanaka, K.
Angew. *Chem*. *Int*. *Ed*. **2023**, *62*, e202301346

2023-03-27

CV of Prof. Ken Tanaka

Education:

- **1990** B.S., **1993** M.S., **1998** Ph.D., The University of Tokyo
- **1999-2001** Postdoctor, MIT USA, (Prof. Gregory C. Fu)
- **2002-2014** Associate Professor, Professor, Tokyo University of Agriculture and Technology
- **2014-Present** Professor, Tokyo Institute of Technology

Research Interests:

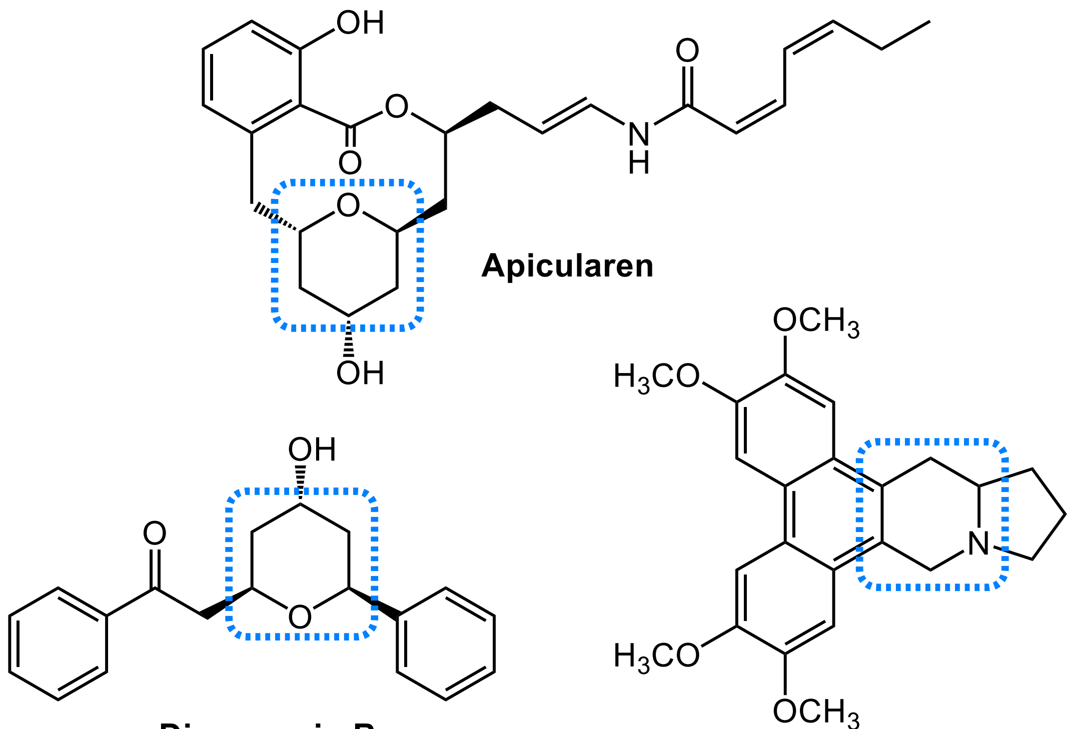
The development of novel transition-metal-catalyzed reactions and their application to organic synthesis

1. Organic synthesis and asymmetric catalysis
2. Physical organic chemistry and bioorganic chemistry

Contents

Introduction

Representative bioactive molecules and natural products containing six-membered cycliccompounds



Apicularen

Diospongin B

Tylophorine

Faustino, H.; Mascare, J. L.; Lopez, F. *Chem. Sci*. **2015**, *6*, 2903-2908.

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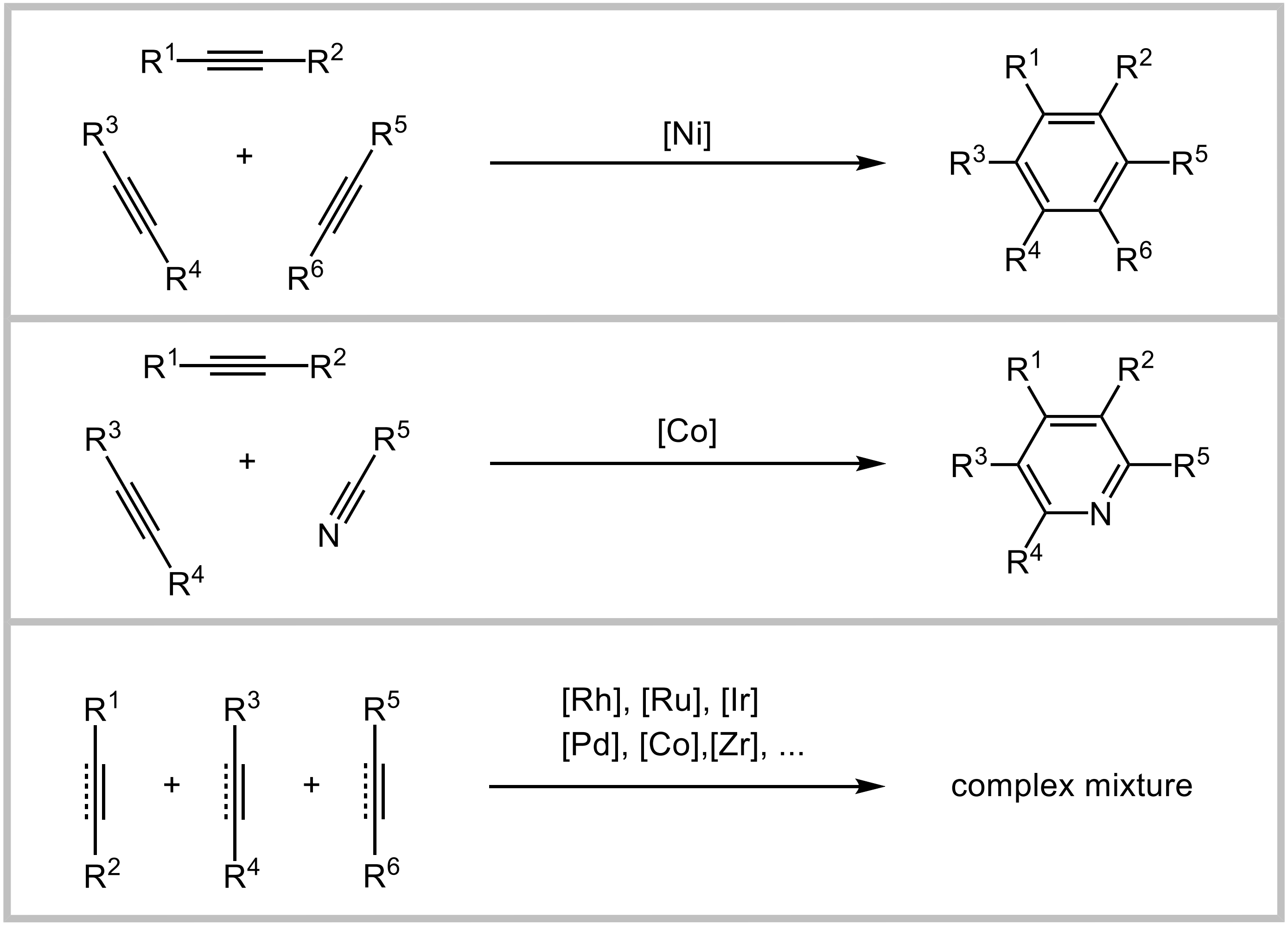
Introduction



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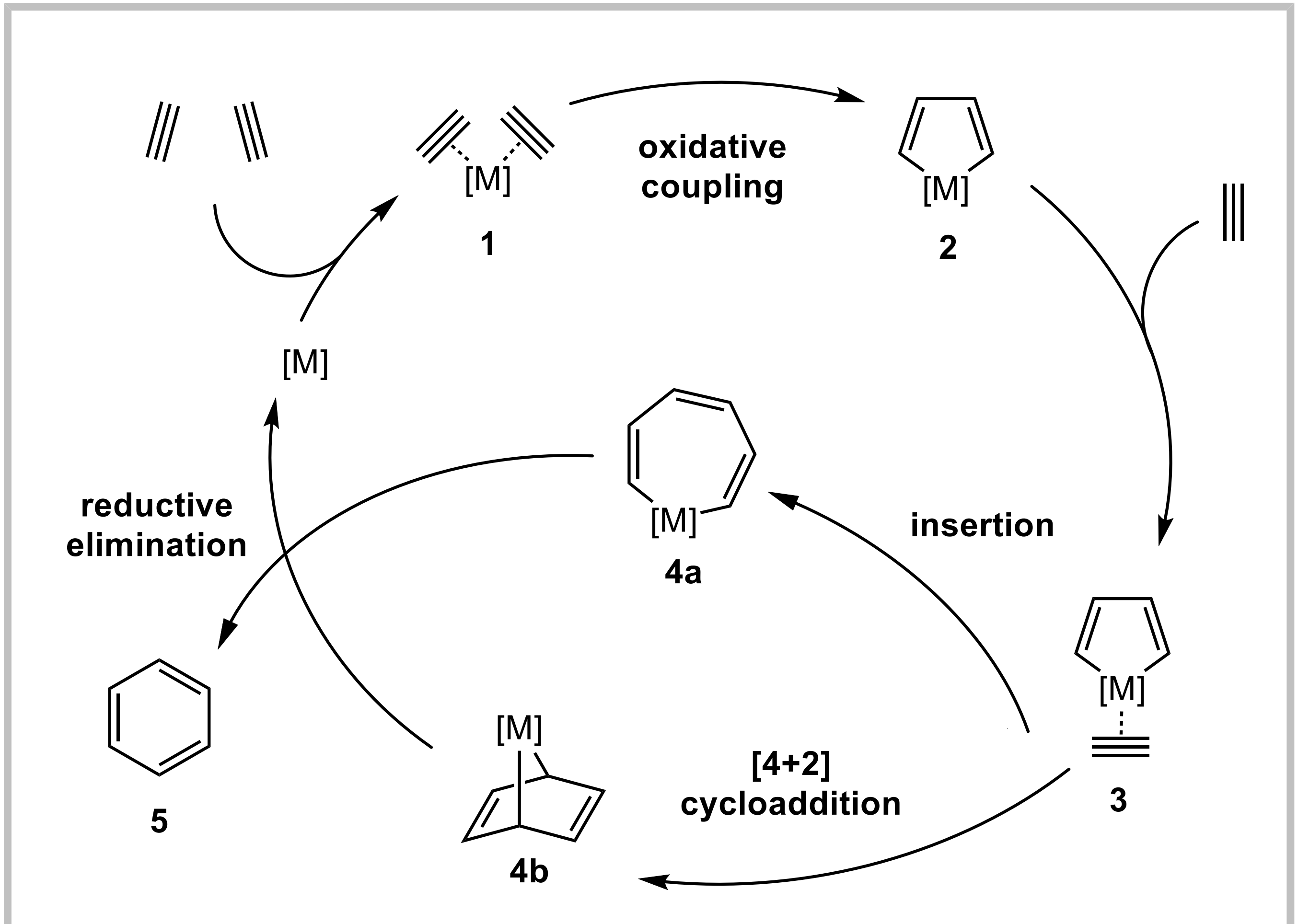
Introduction



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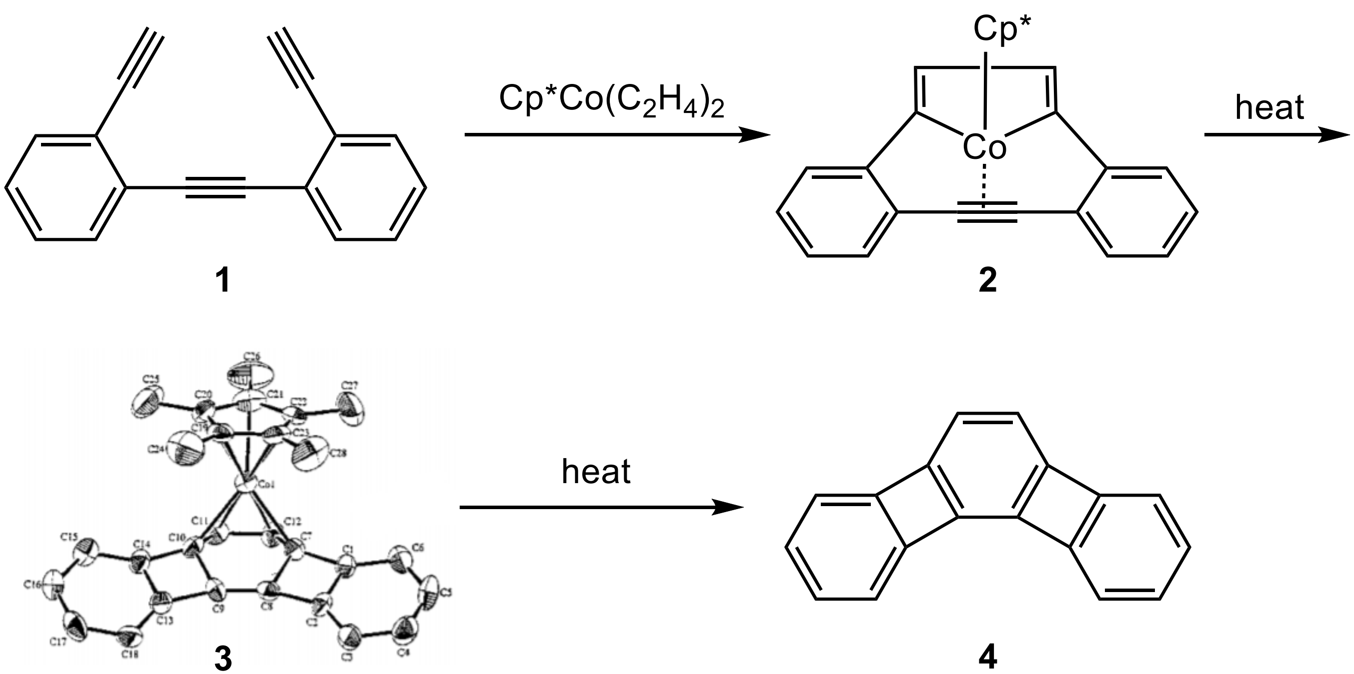
Introduction

The first metallacyclopentadiene(Alkyne) complexes



Diercks, R.; Eaton, B.; Vollhardt, K. P. *J. Am. Chem. Soc.* **1998**, *120*, 8247-8248.

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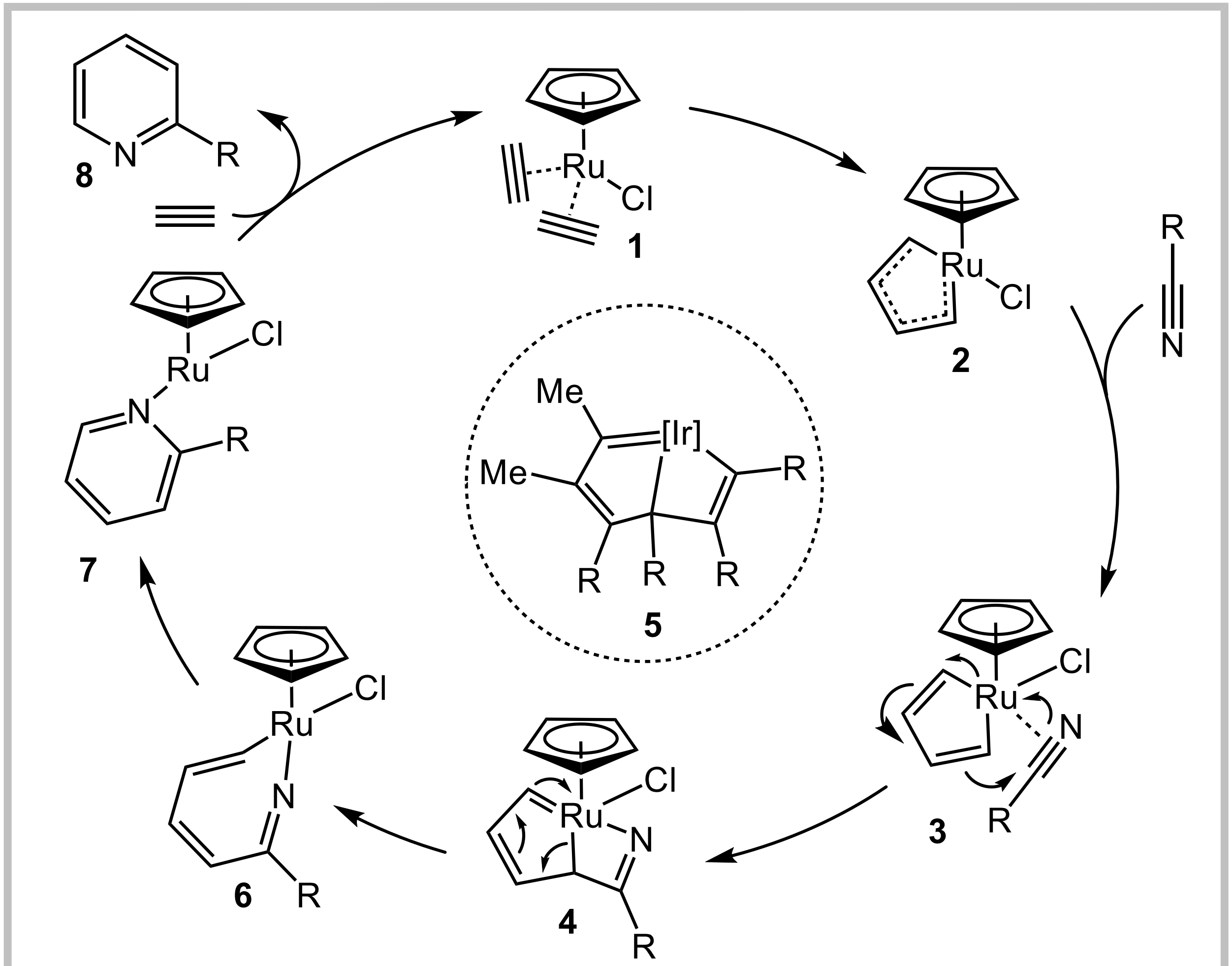
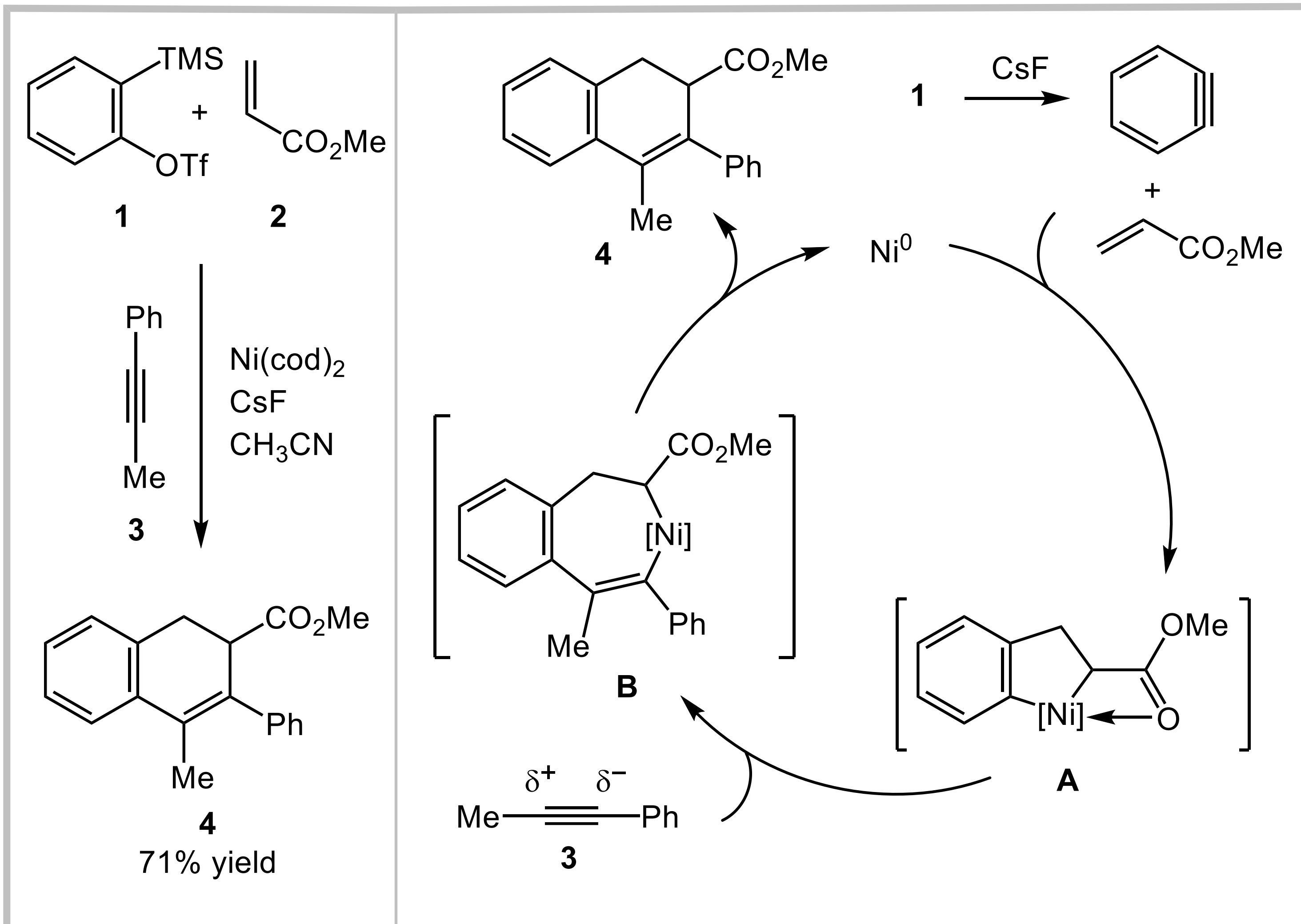
Introduction



Dazinger, G.; Torres, M.; Kirchner, K. *J. Organomet. Chem.* **2006**, *691*, 4434-4445.
Yamamoto, Y.; Kinpara, K.; Saigoku, T. *J. Am. Chem. Soc.* **2005**, *127*, 605-613.

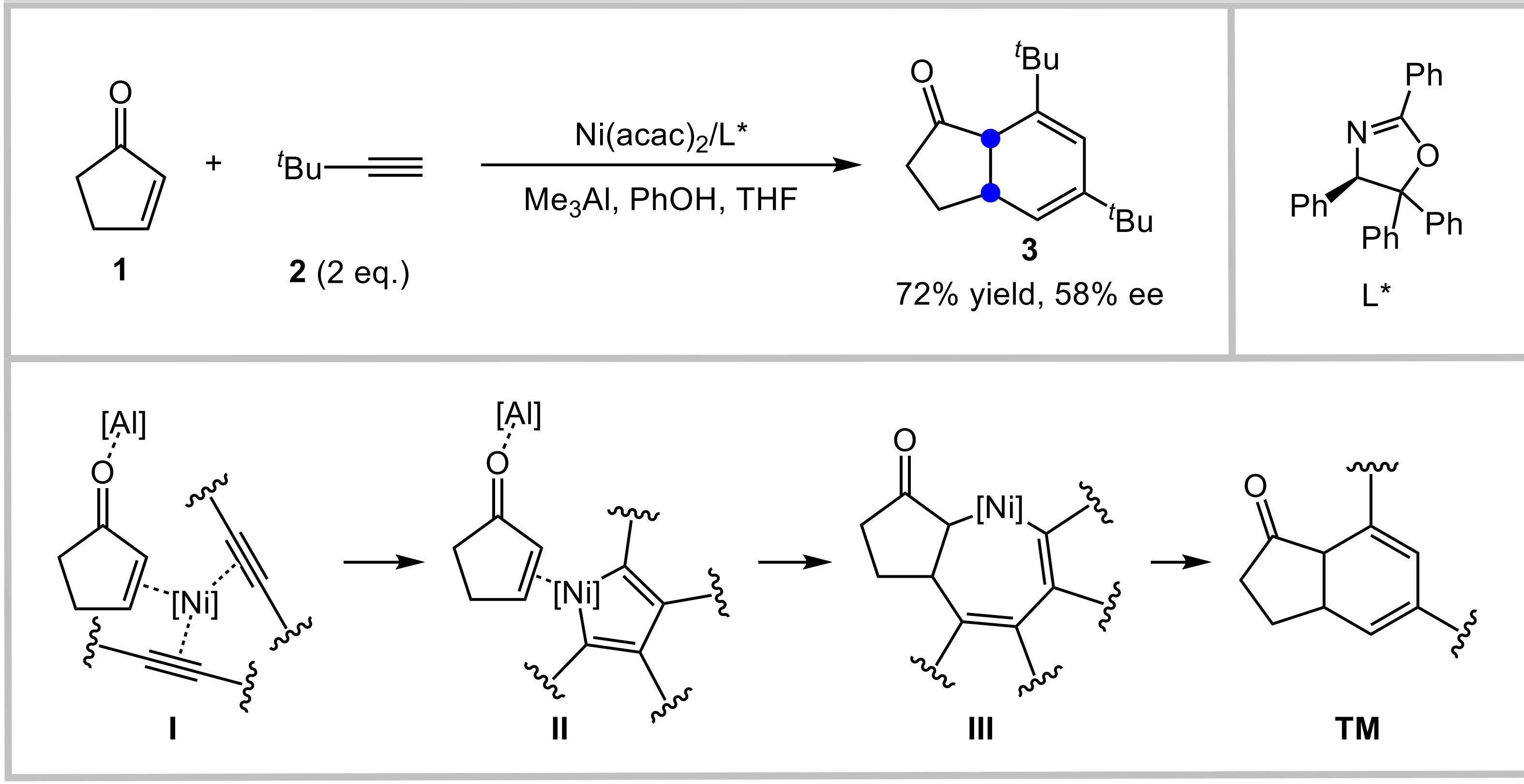
Introduction



Qiu, Z.; Xie, Z. *Angew*. *Chem*. *Int*. *Ed*. **2009**, *48*, 5729-5732.

Introduction

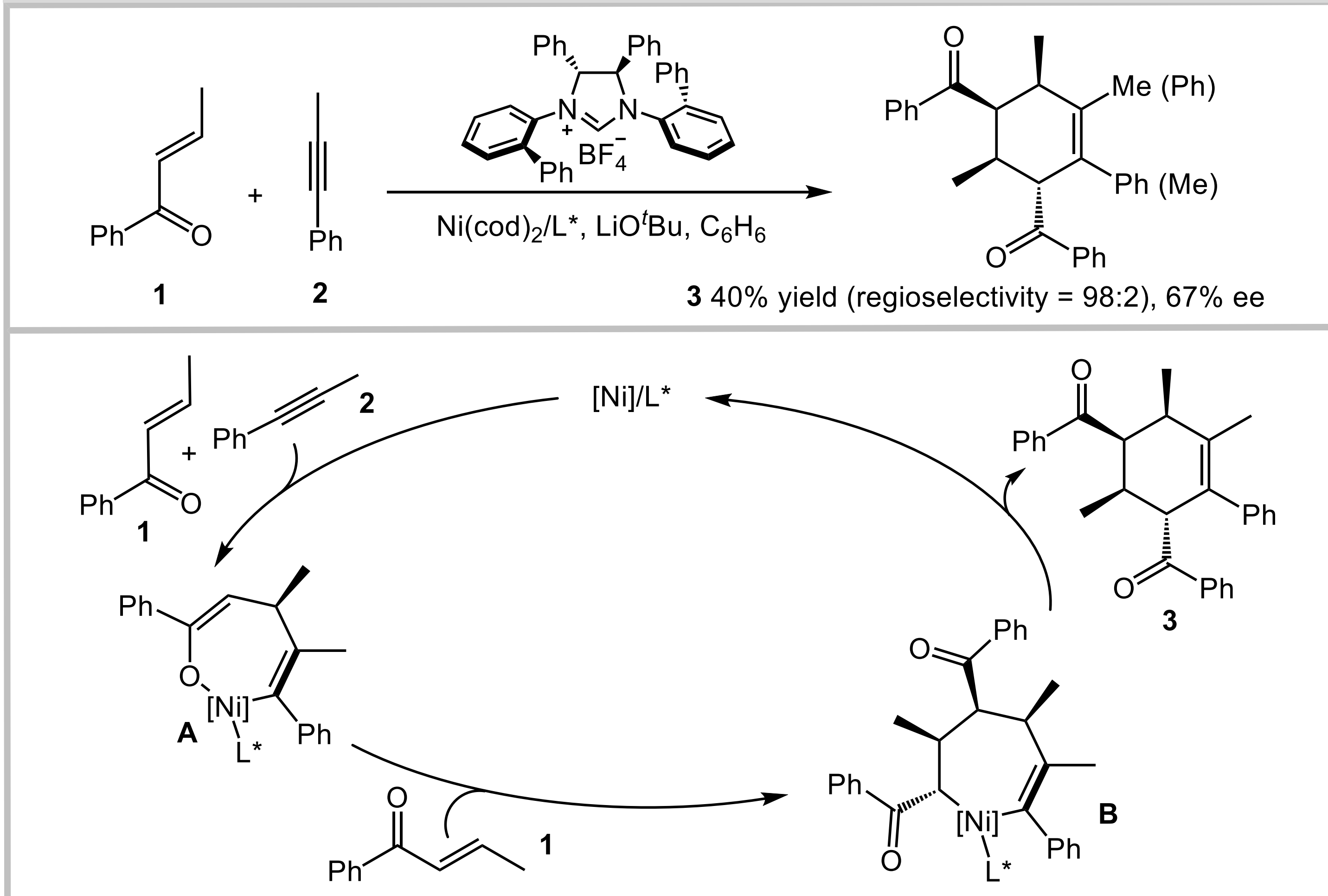
Ni-catalyzed [2+2+2] cycloaddition of terminal alkynes and enone



Ikeda, T. S.; Kondo, H.; Odashima, K. *Chem*. *Commun*. **2002**, 2422-2423.

Introduction

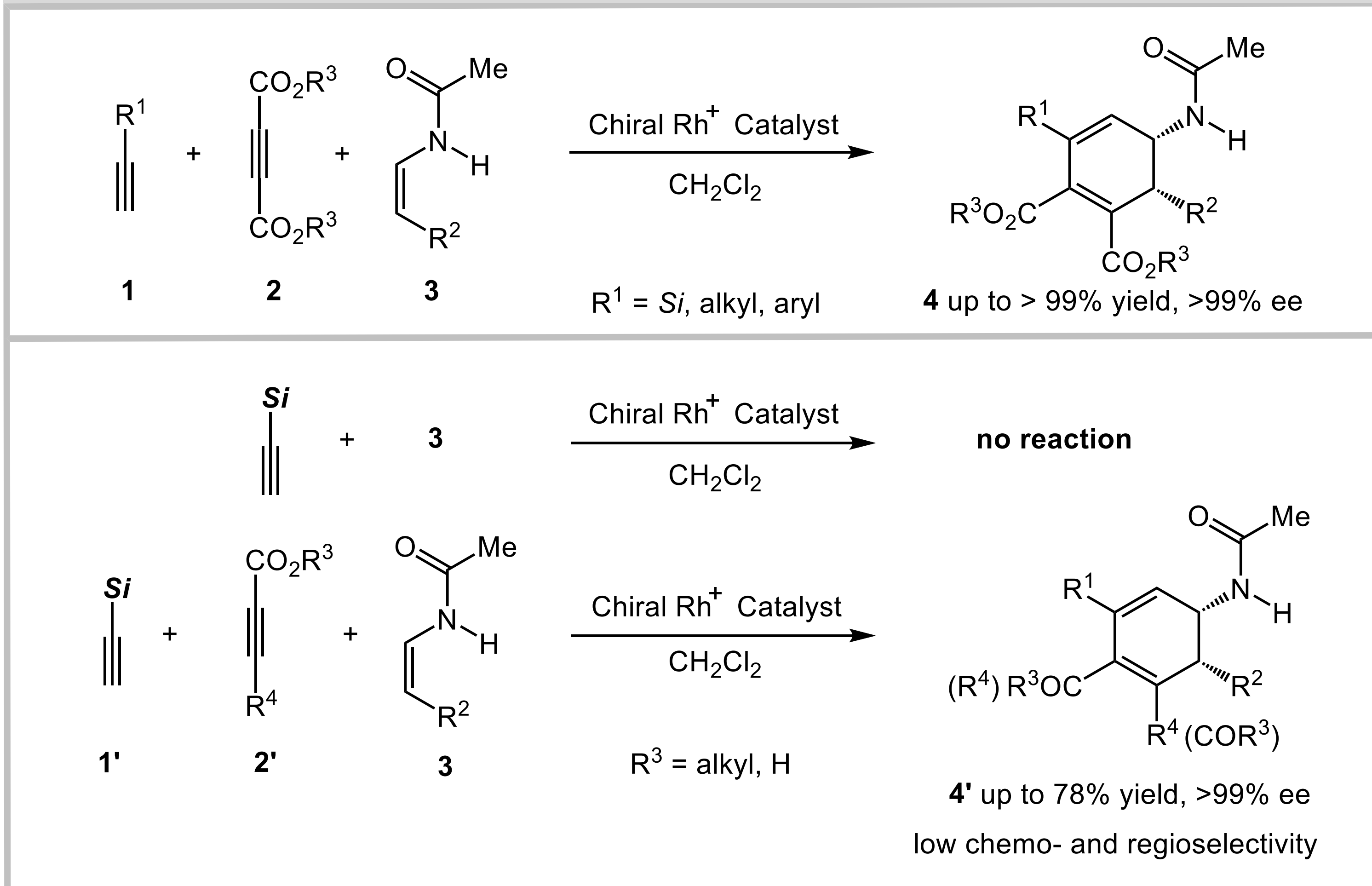
Ni-catalyzed [2+2+2] cycloaddition of internal alkyne and enone



Kumar, R.; Tokura, H.; Ogoshi, S. *Org*. *Lett*. **2015**, *17*, 6018-6021.

Introduction

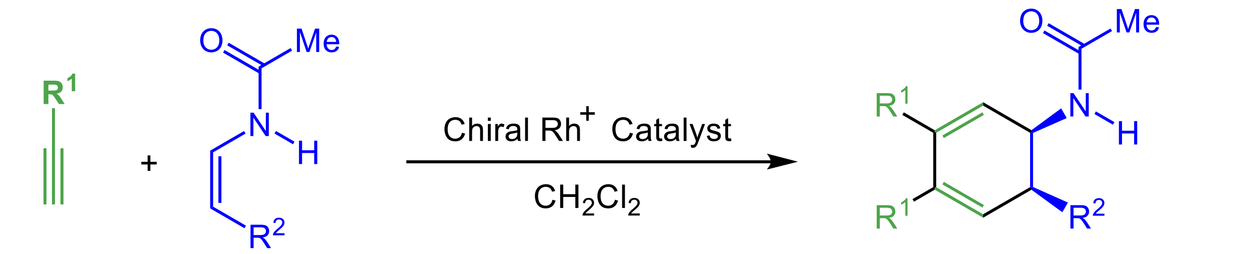
Rh-catalyzed [2+2+2] cycloaddition of unsymmetric 2π components



Fujii, K.; Nagashima, Y.; Tanaka, K. *Nat*. *Synth*. **2022**, *1*, 365-375.

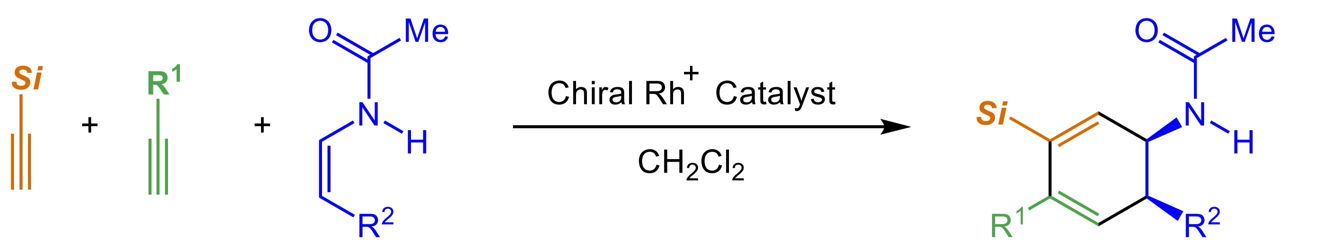
Introduction

Rh-catalyzed [2+2+2] cycloaddition of unsymmetric 2π components



1 R^1 = aryl **2** **3**

up to > 99% yield, >99% ee



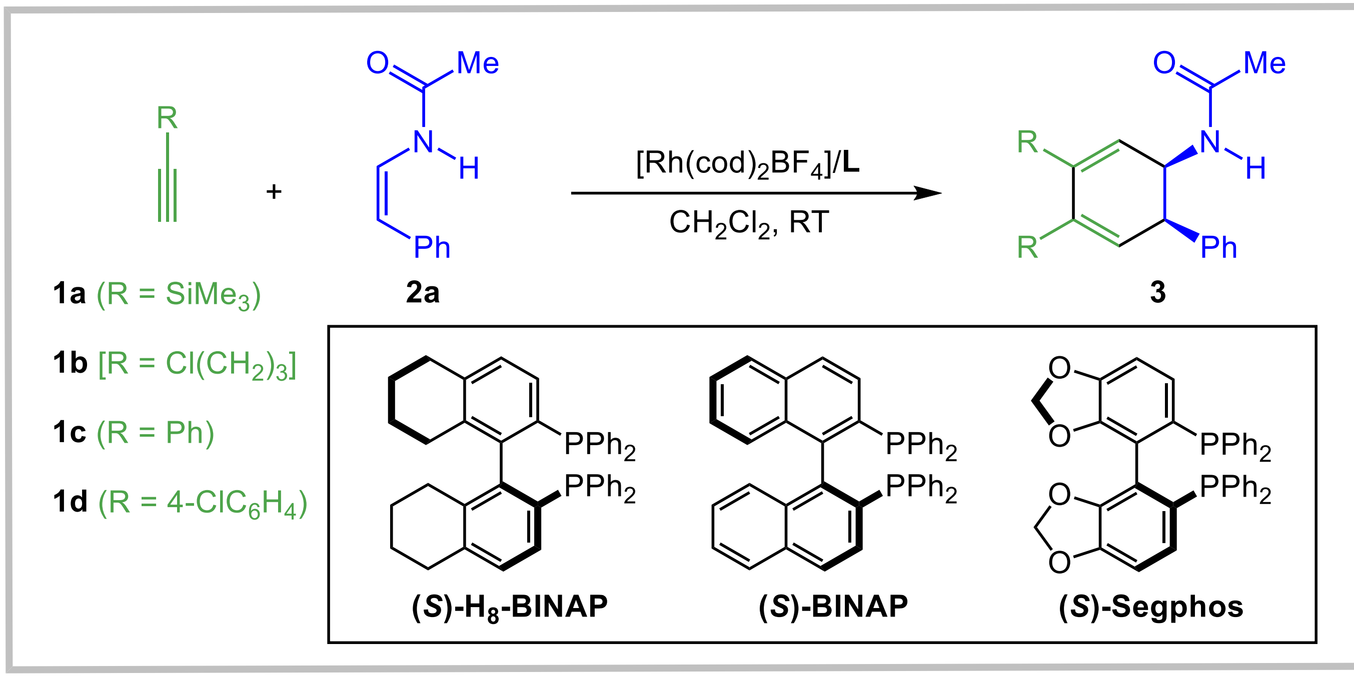
1' **1** **2** **4**

up to 92% yield, >99% ee

- **Three unsymmetric 2π components**
- **High chemo- and enantioselectivity**
- **Complete regio- and diastereoselectivity**

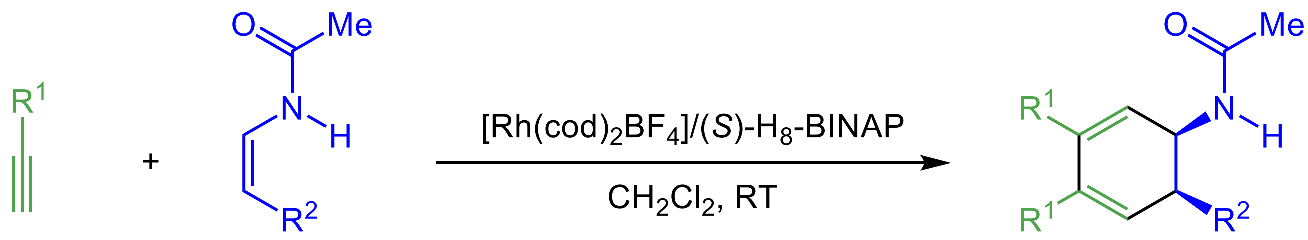
Fujii, K.; Nagashima, Y.; Tanaka, K. *Angew*. *Chem*. *Int*. *Ed*. **2023**, *62*, e202301346

Optimization of Reaction Conditions

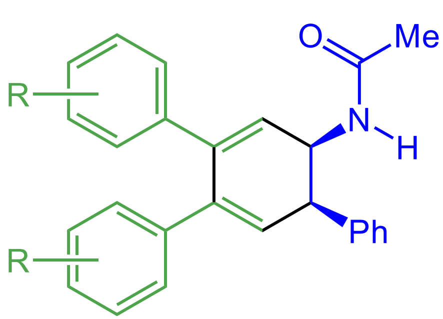


Entry	L	**1** (equiv)	**3**	Yield (%)/Ee (%)
1	(*S*)-H_8-BINAP	**1a** (5)	**3 aa**	0
2	(*S*)-H_8-BINAP	**1b** (5)	**3 ba**	0
3	(*S*)-H_8-BINAP	**1c** (5)	(-)-**3 ca**	9 (90)
4	(*S*)-H_8-BINAP	**1d** (5)	(-)-**3 da**	78 (> 99)
5	(*S*)-BINAP	**1d** (5)	(-)-**3 da**	16 (94)
6	(*S*)-Segphos	**1d** (5)	(-)-**3 da**	< 2
7	(*S*)-H_8-BINAP	**1d** (2.2)	(-)-**3 da**	42 (94)

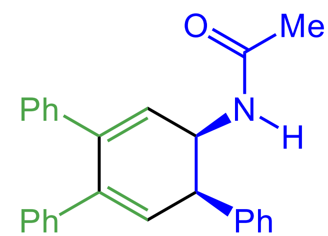
Substrate Scope



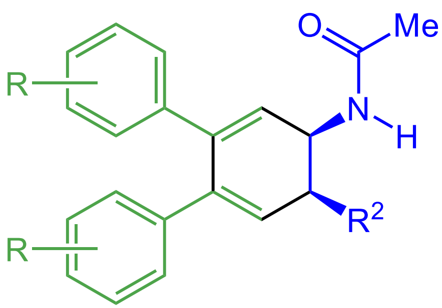
1 2 3



(-)-**3da** R = 4-Cl, 78% yield, >99% ee
(-)-**3ea** R = 4-Br, 49% yield, >99% ee
(-)-**3fa** R = 4-F, 50% yield, 95% ee
(-)-**3ga** R = 4-CF_3, 80% yield, >99% ee
(-)-**3ia** R = 3-CF_3, 79% yield, >99% ee
(-)-**3ha** R = 3-Cl, 53% yield, >99% ee
3ja R = 2-Cl, 0% yield

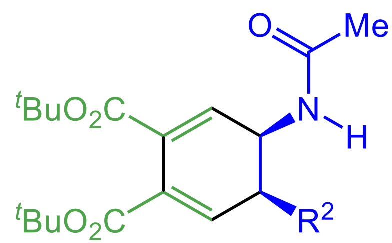


(-)-**3ca** 9% yield, 90% ee



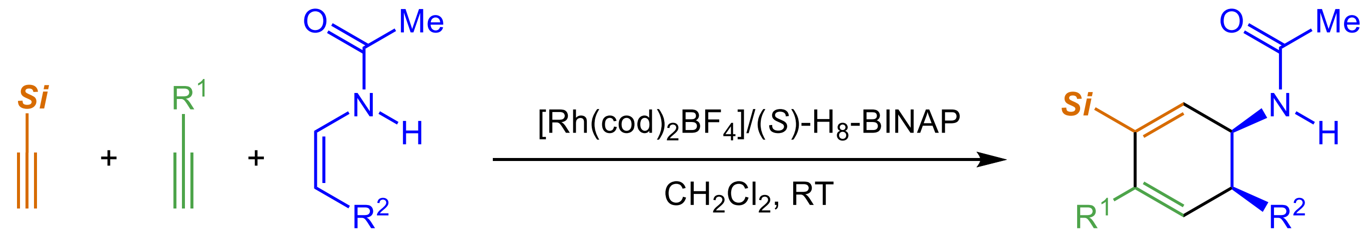
R^2 = 4-MeOC$_6$H$_4$

(-)-**3dd** R = 4-Cl, 92% yield, >99% ee
(+)-**3ed** R = 4-Br, 69% yield, >99% ee
(-)-**3fd** R = 4-F, 65% yield, 98% ee
(-)-**3gd** R = 4-CF_3, 99% yield, >99% ee
(-)-**3id** R = 3-CF_3, 98% yield, >93% ee
(-)-**3hd** R = 3-Cl, 69% yield, >99% ee
(-)-**3cd** R = H, 56% yield, 93% ee

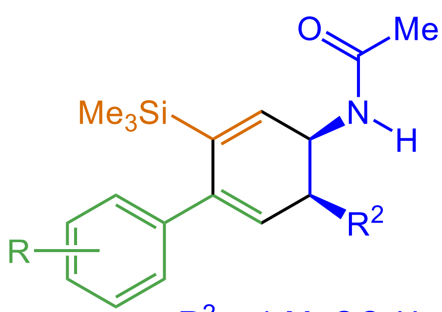


R^2 = 4-MeOC$_6$H$_4$
(+)-**3ld** 85% yield, 86% ee

Substrate Scope



1' **1** **2** **4**



R^2 = 4-MeOC$_6$H$_4$

(+)-**4afd** R = 4-F, 88% yield, >99% ee

(-)-**4add** R = 4-Cl, 86% yield, 99% ee

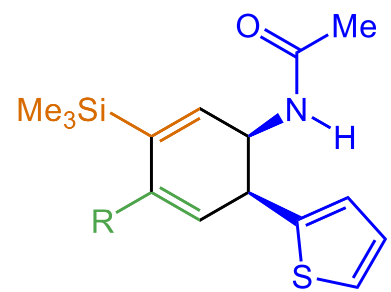
(+)-**4aed** R = 4-Br, 74% yield, 95% ee

(-)-**4and** R = 4-MeO, 90% yield, 97% ee

(+)-**4aid** R = 3-CF$_3$, 92% yield, >99% ee

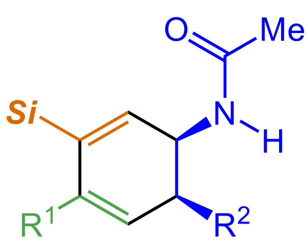
(+)-**4ahd** R = 3-Cl, 90% yield, 99% ee

4amd R = 2-CF$_3$, 0 yield



R = 4-CF$_3$C$_6$H$_4$

(-)-**4agf** 83% yield, >99% ee



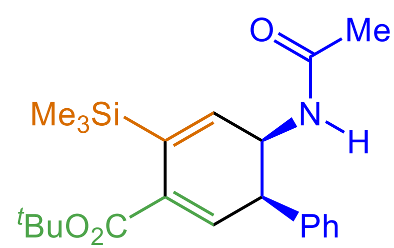
R^1 = 4-CF$_3$C$_6$H$_4$

R^2 = 4-MeOC$_6$H$_4$

(-)-**4ogd** ***Si*** = SiBnMe$_2$, 62% yield, 98% ee

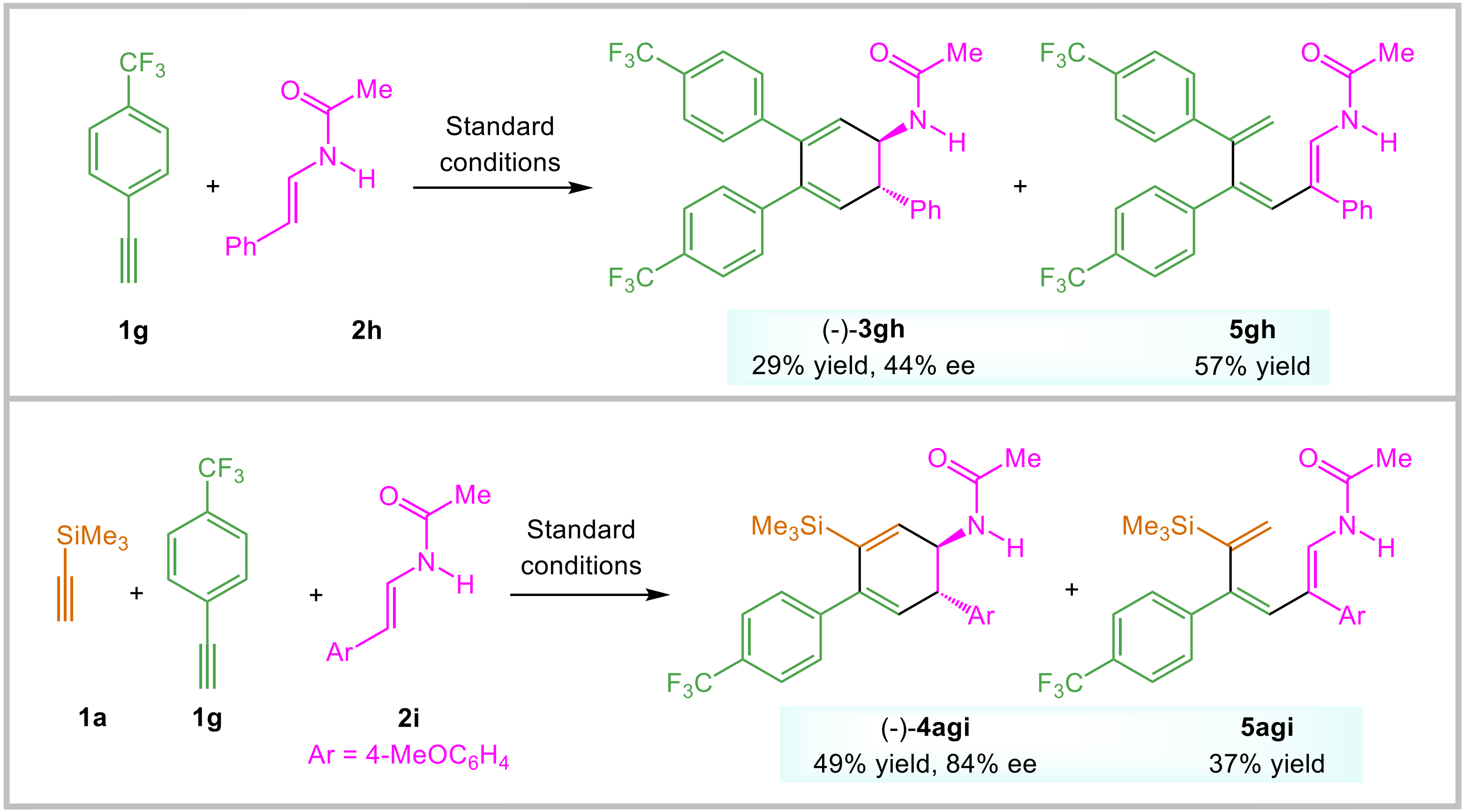
(-)-**4pgd** ***Si*** = SiEt$_3$, 68% yield, 97% ee

4qgd ***Si*** = ^{t}Bu, 0 yield



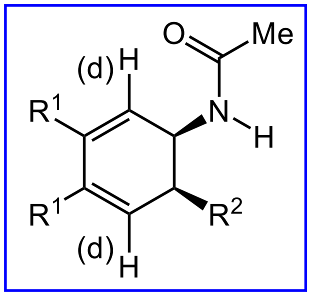
(+)-**4ala** 50% yield, 99% ee

Reaction of with *trans*-enamides

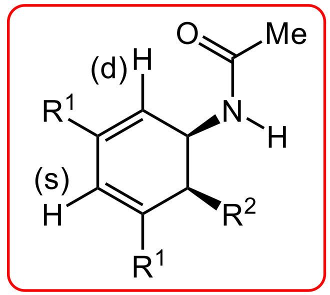


结论：在该反应体系中，顺式烯酰胺比反式烯胺的反应效果好。

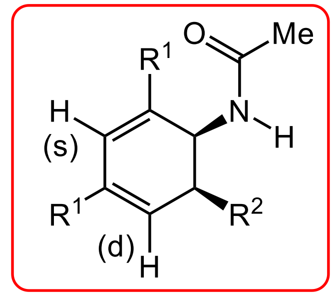
Mechanistic Experiments



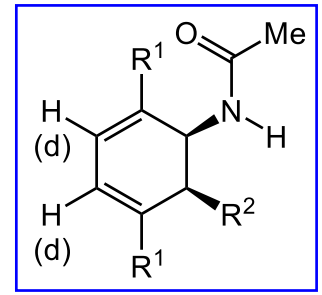
3



3'



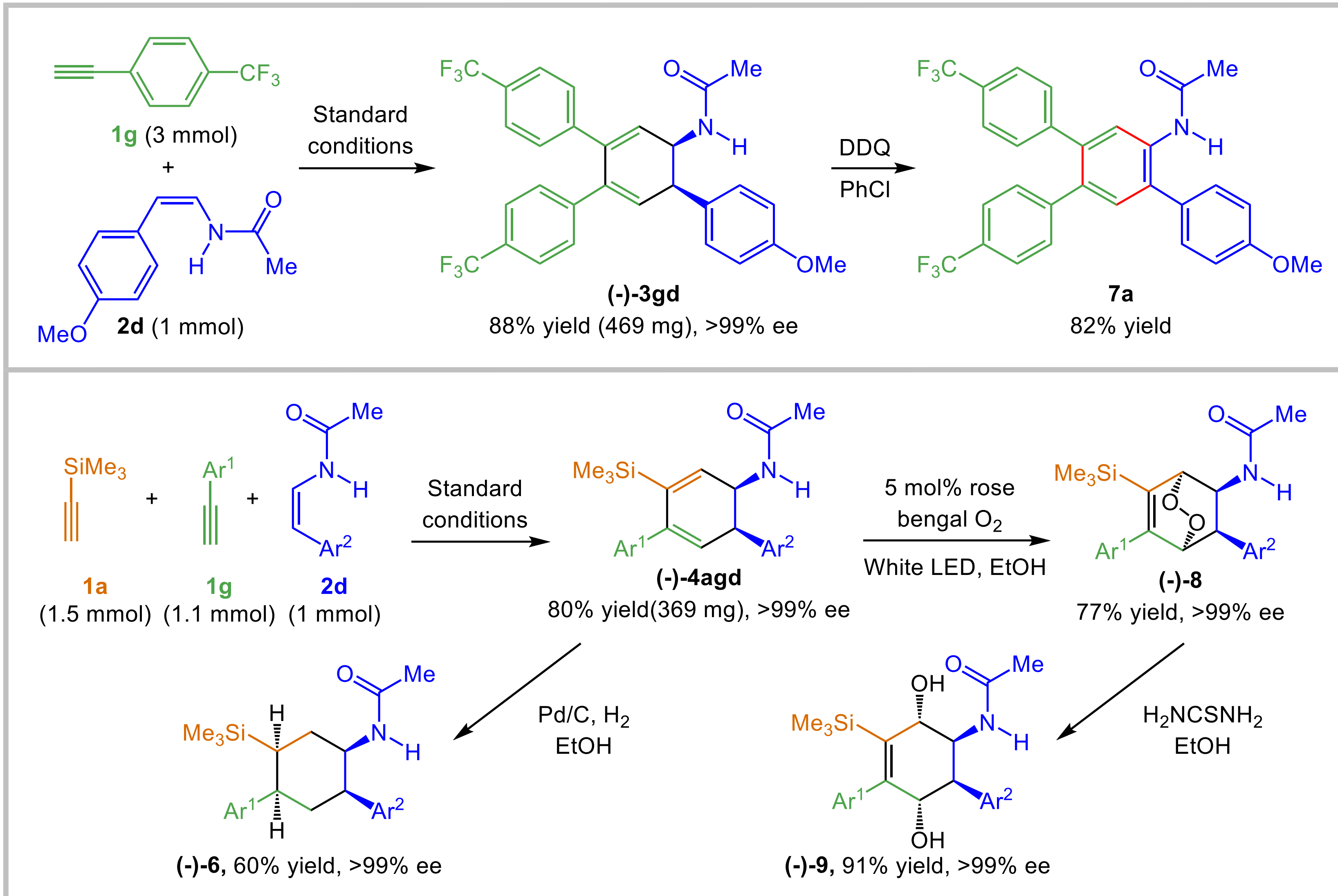
3''



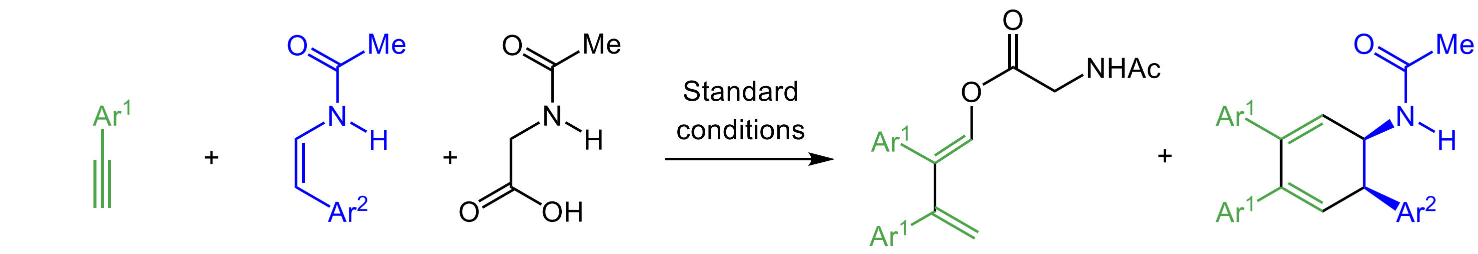
3'''

结论：[2+2+2]环加成反应中，没有观察到区域异构体。作者通过烯烃上氢的^{1}H-NMR谱来区分这些区域异构体。在化合物3和3'''中，两个氢为两组双峰(d)出现，而它们在3'和3''中应为单峰(s)和双峰(d)出现。

Scale-up Reactions and Synthetic Applications

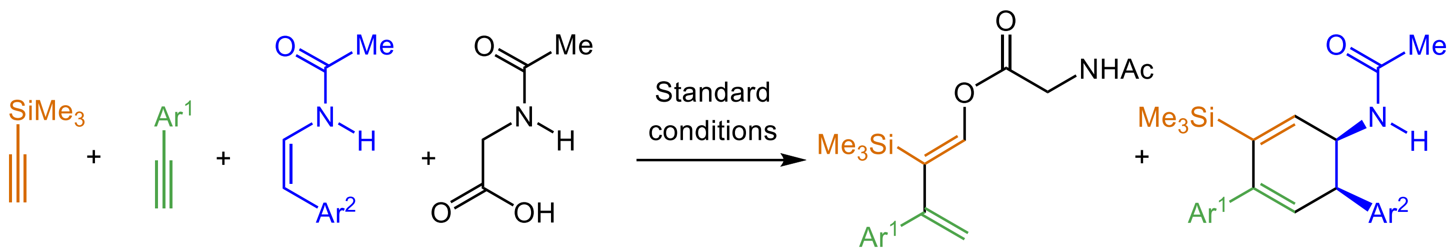


Proposed Mechanism



1g Ar[1] = 4-$CF_3C_6H_4$ **2d** Ar[2] = 4-$MeOC_6H_4$ **10** (1 eq.)

2d	**11** / yield	**(-)-3gd**
0 eq.	40%	-
1 eq.	<5%	90% yield (99% ee)

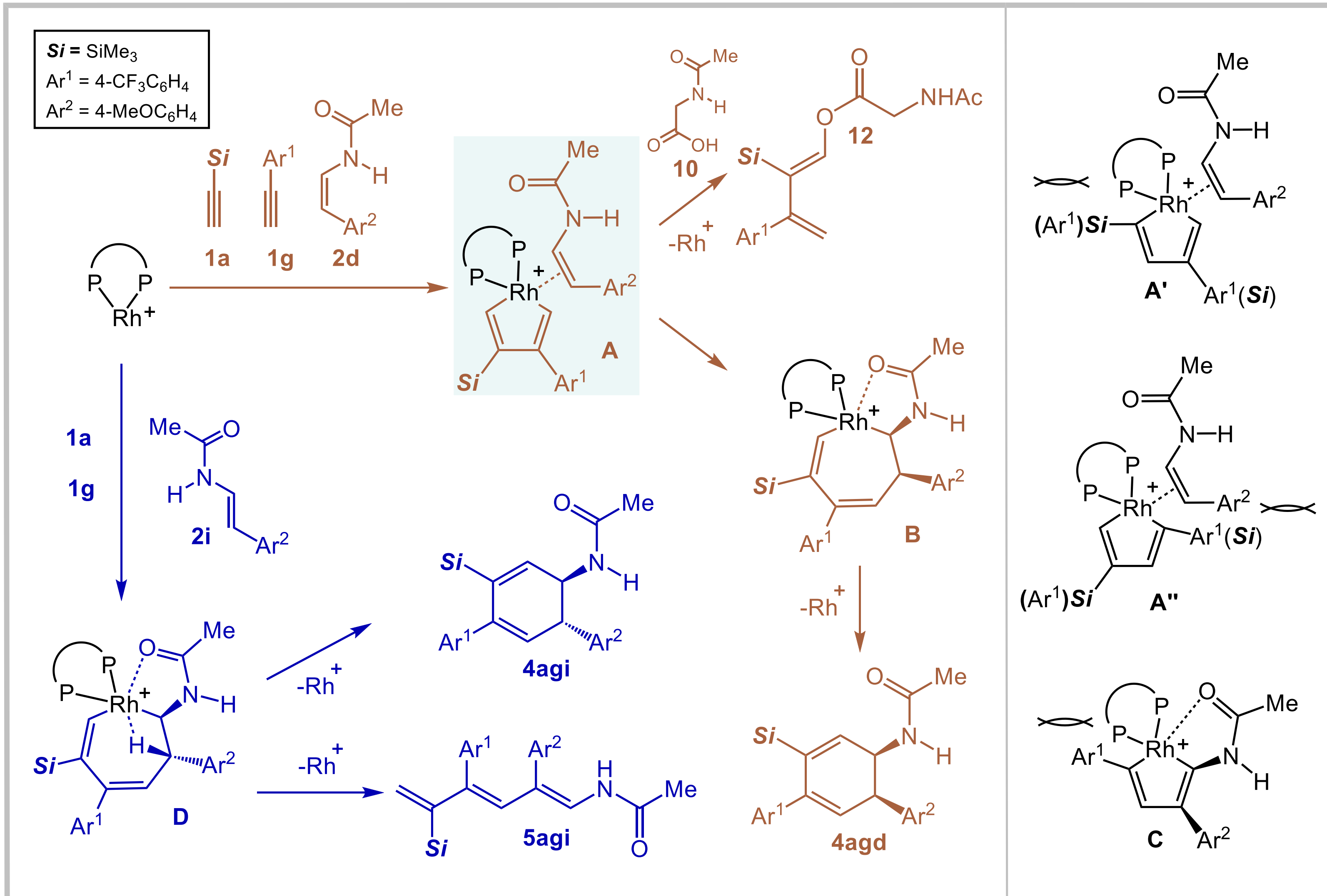


1a **1g** **2d** **10** (1 eq.)

2d	**12** / yield	**(-)-4agd**
0 eq.	36%	-
1 eq.	10%	78% yield (99% ee)

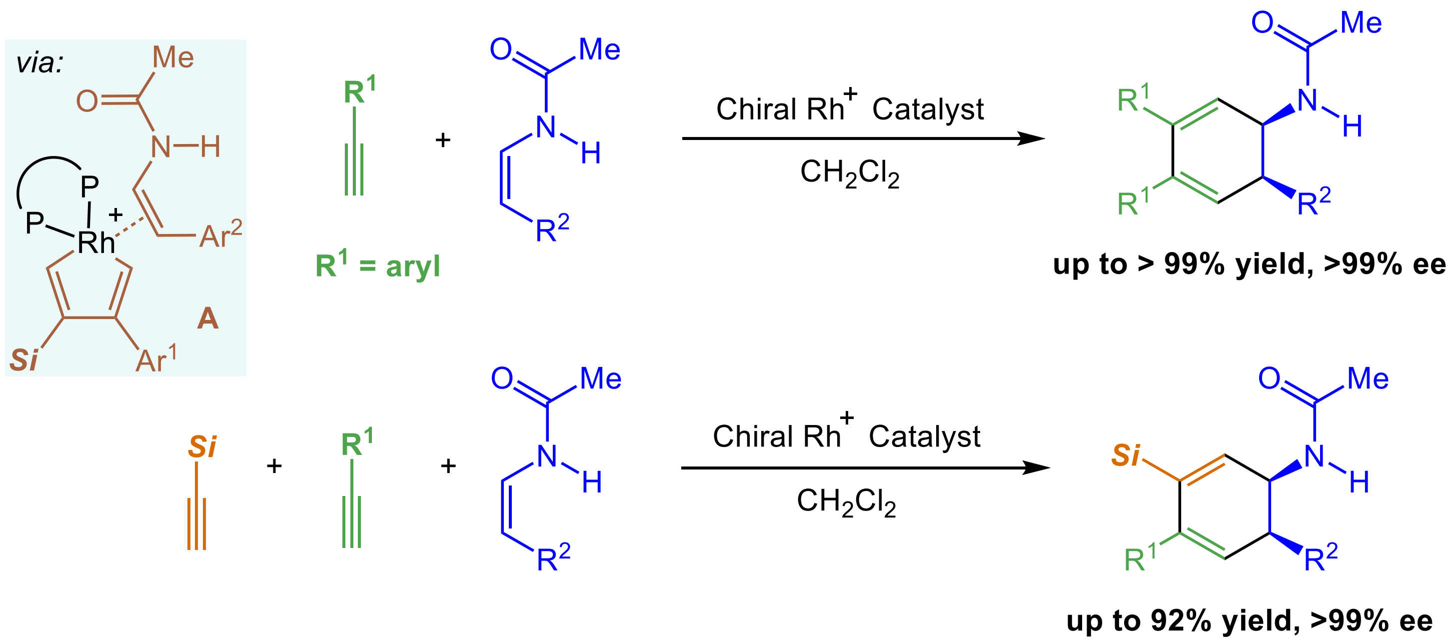
结论：该反应只产生一种区域异构体。

Proposed Mechanism



Summary

Rh-Catalyzed [2+2+2] cycloaddition of terminal alkyne, internal alkynes, and alkene



♥ **Three unsymmetric 2π components**; ♥ **High chemo- and enantioselectivity**;
♥ **Complete regio- and diastereoselectivity**

Writing Strategies

- **The First Paragraph**

The importance of TM-catalyzed [2+2+2] cycloadditions

↓

The development and the limitation of TM-catalyzed [2+2+2] cycloadditions

↓

Highlights of work

- ✓ Transition-metal-catalyzed Asymmetric intermolecular [2+2+2] cycloadditions are valuable methods for constructing six-membered rings.
- ✓ Some groups reported the asymmetric [2+2+2] cycloaddition by chiral Nickel catalyst. Synthesis a single carbocycle with simultaneous control of chemo-, regio-, diastereo-, and enantioselectivity using three unsymmetric 2π components involving alkenes has been difficult.
- ✓ We report chiral cationic Rhodium-catalyzed asymmetric [2+2+2] cycloaddition with high chemo- and enantioselectivity and complete regio- and diastereoselectivity.

Writing Strategies

- **The Last Paragraph**

Summary
of this work

↓

Advantages
of this method

↓

Outlook
of this work

✓ In conclusion, we have developed the three-component [2+2+2] cycloadditions using Rh^{+}/H_8-binap catalyst at room temperature.

✓ The cycloaddition may proceed through the chemo- and regioselective formation of a Rhodacyclopentadiene from the two terminal alkynes.

✓ Detailed mechanistic studies and further development of three-component [2+2+2] cycloaddition are underway.

Representative Examples

However, obtaining a single carbocycle with simultaneous control (同时控制…) of chemo-, regio-, diastereo-, and enantio-selectivity using three unsymmetric 2π components has been extremely difficult.

Replacing one arylacetylene with a silylacetylene (用…代替…) enabled the asymmetric three-component [2+2+2] cycloaddition under the same conditions.

The steric repulsion (空间位阻；steric effects, steric inhibition, steric hindrance) between the substituents on alkynes A and B.

Acknowledgement

Thanks for Your Attention