Literature Report 9

Enantioselective Type II Cycloaddition of Alkynes via C-C Activation of Cyclobutanones: Rapid and Asymmetric Construction of [3.3.1] Bridged Bicycles

Reporter: Zhou-Hao Zhu
Checker: Yi-Xuan Ding
Date: 2020-09-21

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J. Am. Chem. Soc. **2020**, *142*, 13180

Contents

CV of Prof. Guangbin Dong

Guangbin Dong

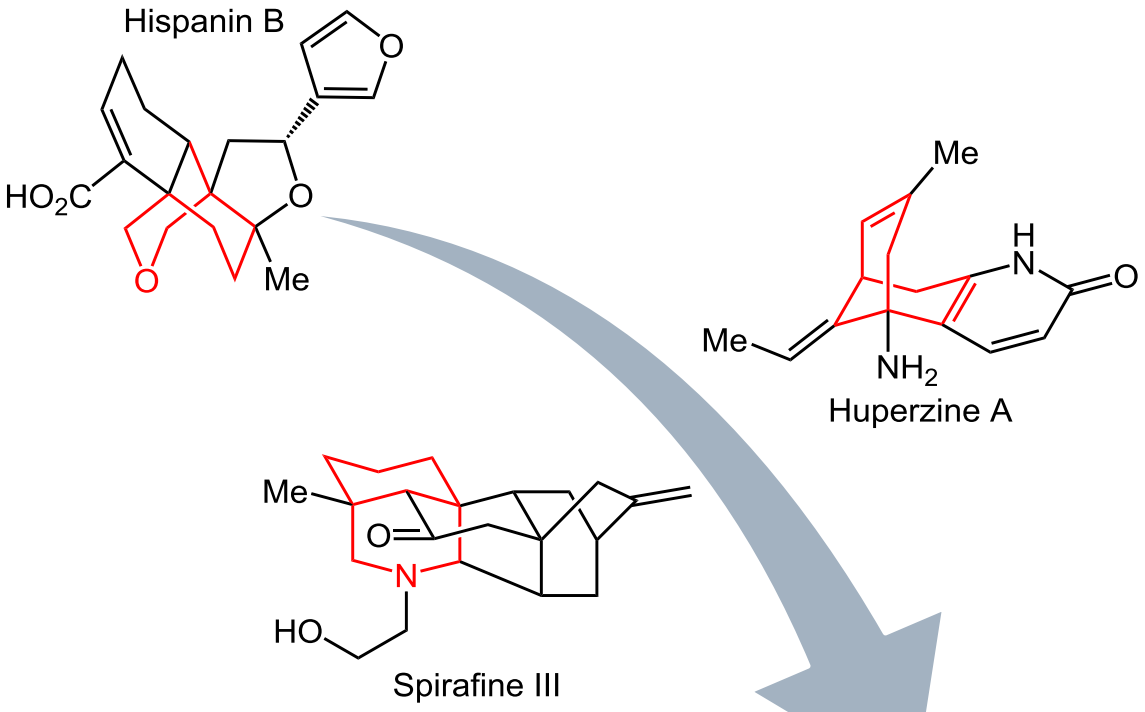
Background:

- **1999-2003** B.S., Peking University
- **2004-2009** Ph.D., Stanford University (Barry M. Trost)
- **2009-2011** Postdoctoral Fellow, California Institute of Technology (Robert H. Grubbs)
- **2011-2016** Assistant Professor, University of Texas at Austin
- **2016** Professor, University of Texas at Austin
- **2016-now** Professor, University of Chicago

Research Interests:

- Developing novel catalytic C-H and C-C bond activation methods for efficient small-molecule agents synthesis
- Developing new transition-metal catalysts based on supramolecular chemistry for chemoselective C-H bond activation of small molecules
- Establishing efficient synthetic routes to access natural products

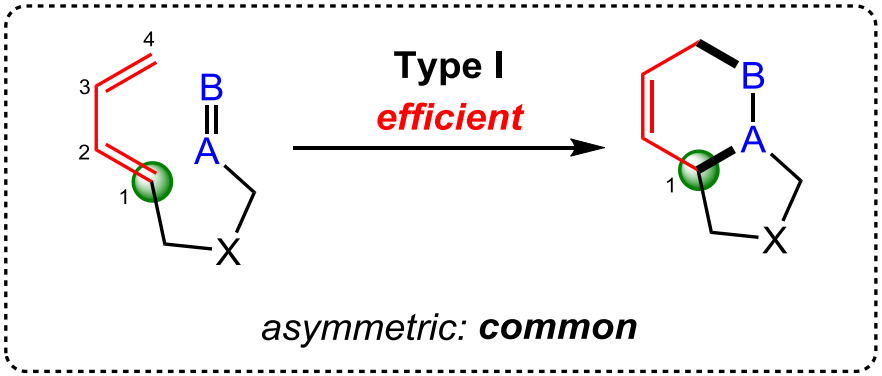
Introduction



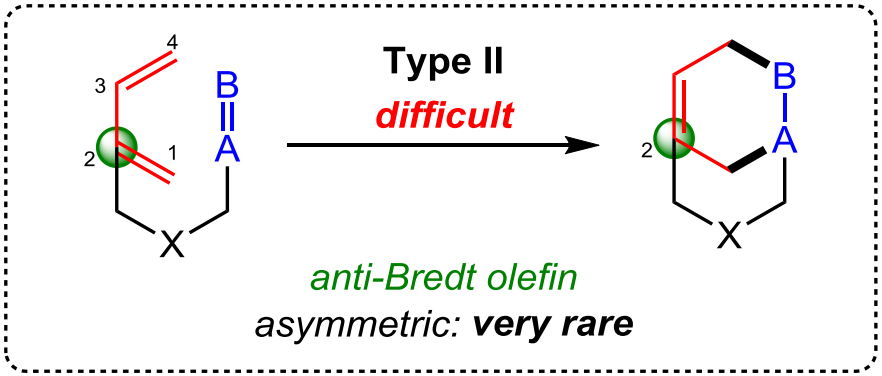
Constructing Chiral Bridged Rings

Introduction

Intramolecular Diels-Alder Reaction

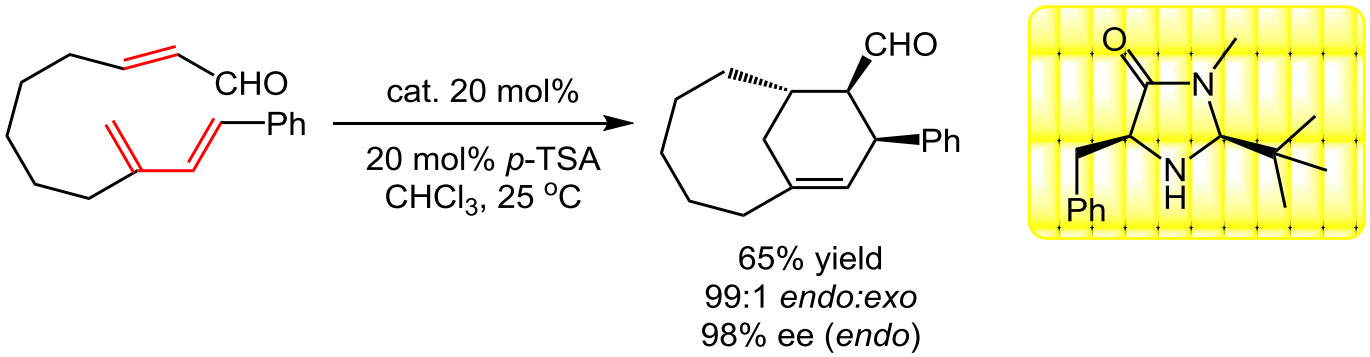


X: linker



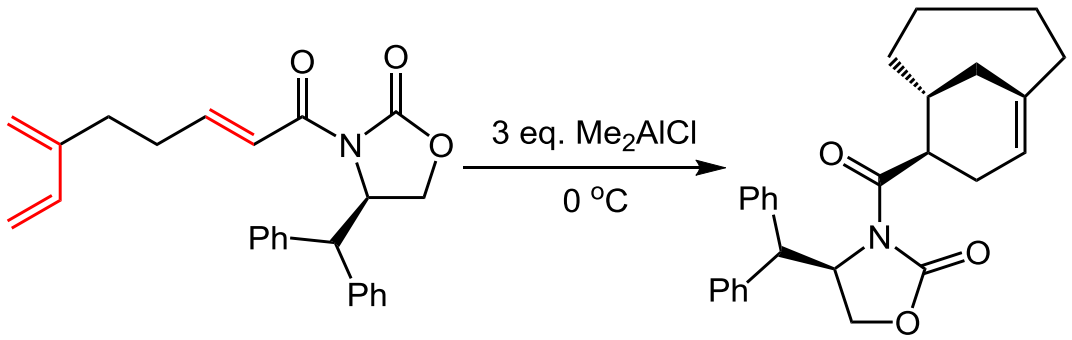
Introduction

Type II



65% yield
99:1 *endo:exo*
98% ee (*endo*)

MacMillan, D. W. C.* *et al. J. Am. Chem. Soc.* **2005**, *127*, 11616

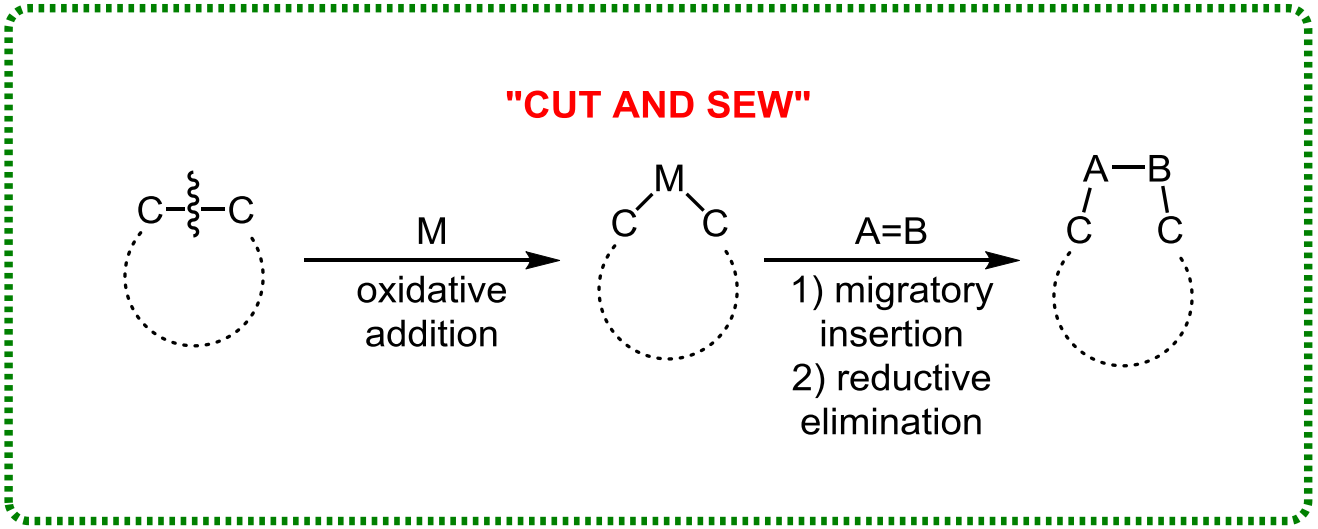


72% yield (dr 92:8)
>99% de following recrystallization

Shea, K. J.* *et al. J. Org. Chem.* **2007**, *72*, 9402

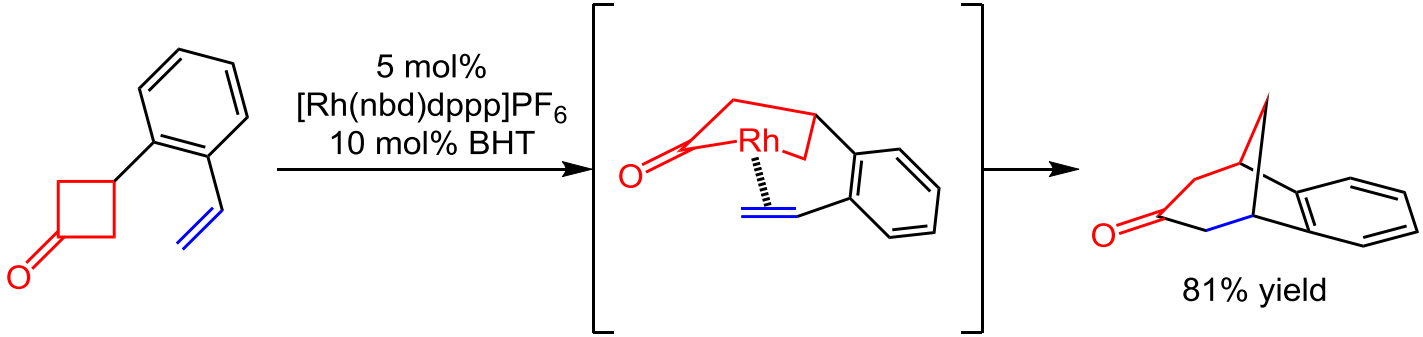
Introduction

Another Way
Transition-Metal-Catalyzed C−C Activation

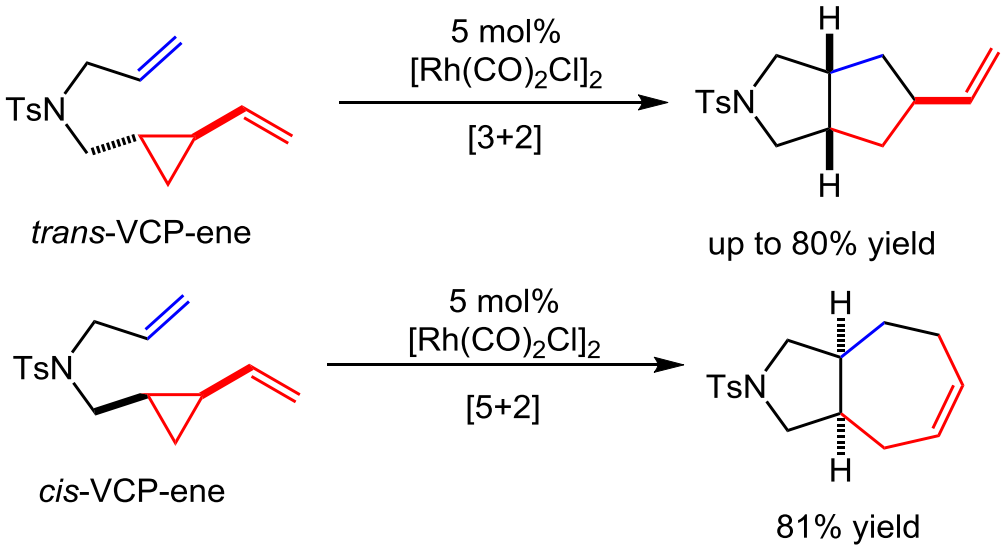


Constructing Various Ring Systems

Introduction

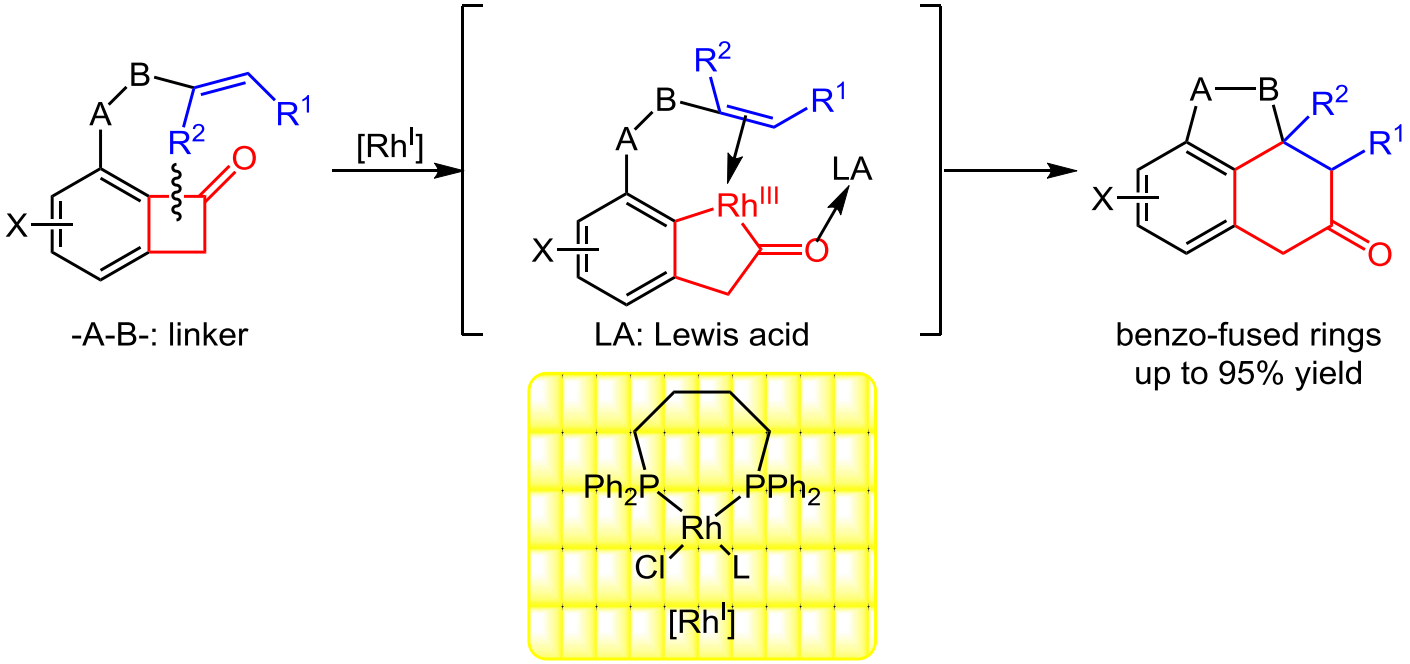


Ito, Y.* *et al. J. Am. Chem. Soc.* **2002**, *124*, 13976



Yu, Z.-X.* *et al. J. Am. Chem. Soc.* **2008**, *130*, 7178

Introduction



Dong, G.* *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 7567

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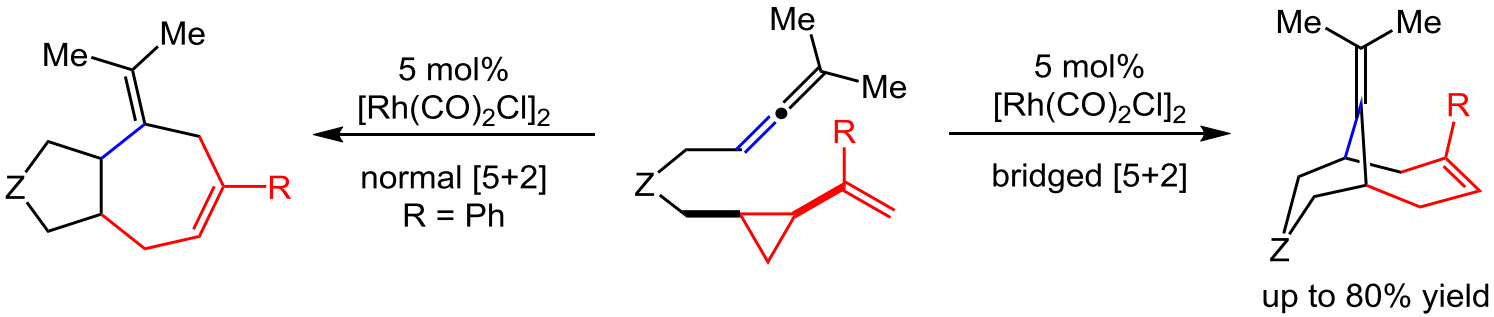
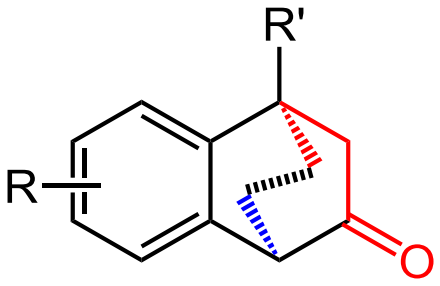


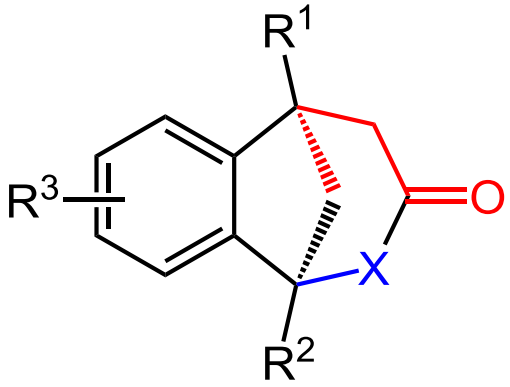
Yu, Z.-X.* *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 8667

Asymmetric Intramolecular Type-II Cyclobutanone/2π Couplings

Chiral Bridged Rings

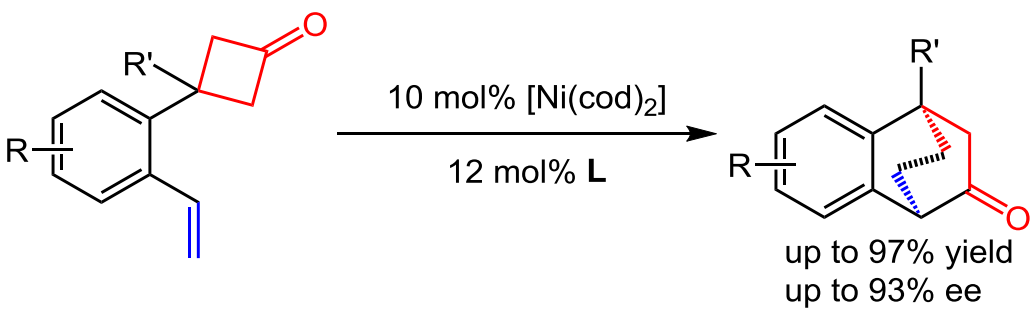


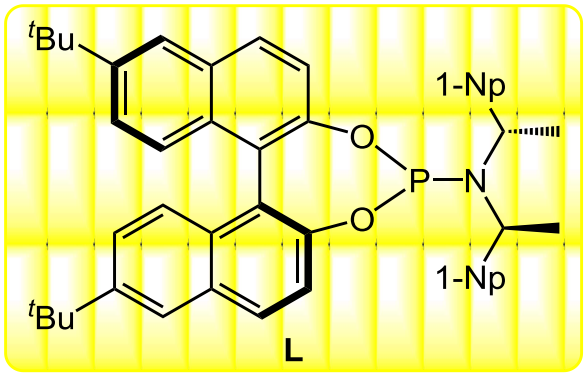
[2.2.2] bicycles

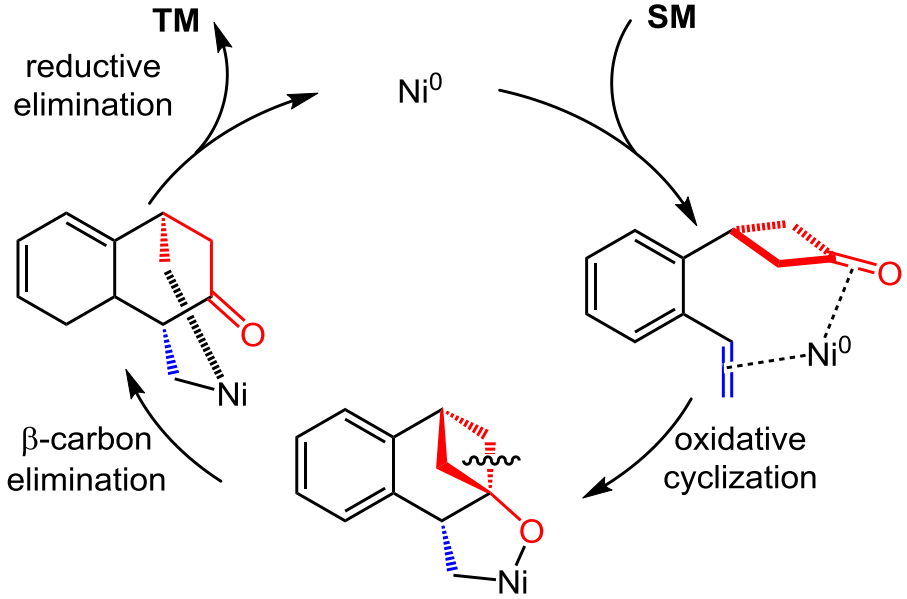


[3.2.1] bicycles

Introduction

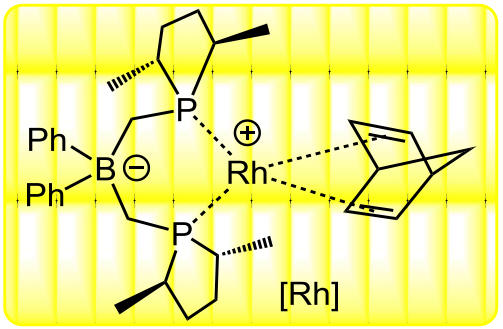


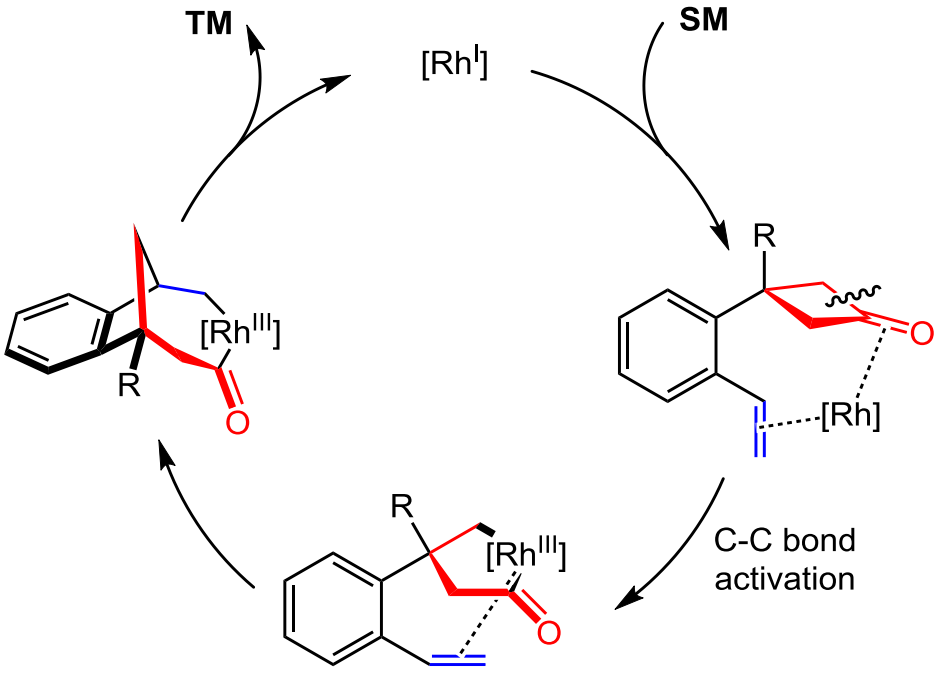




Murakami, M.* *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 2485

Introduction





Cramer, N.* *et al. Organometallics* **2014**, *33*, 780

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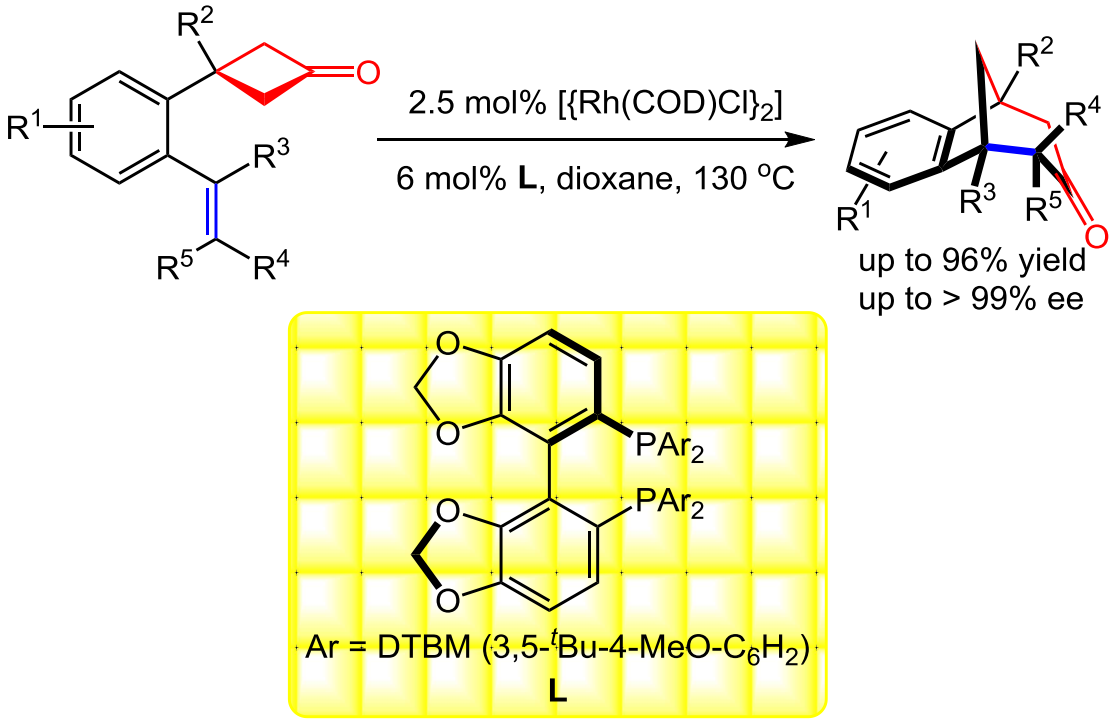

Cramer, N.* *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 3001

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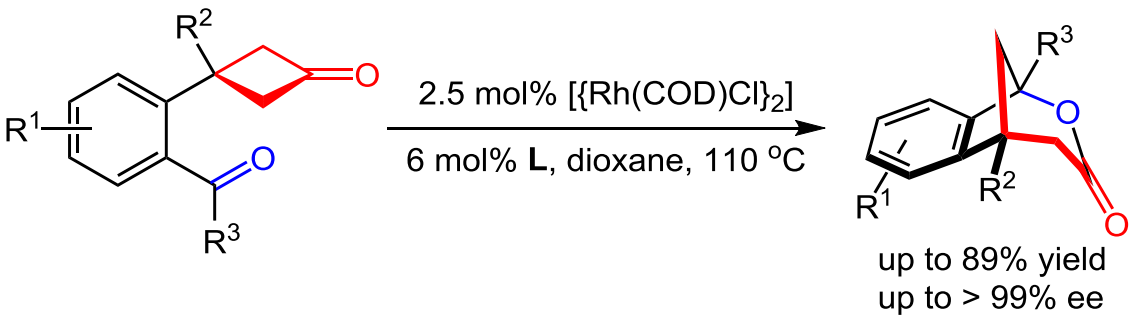

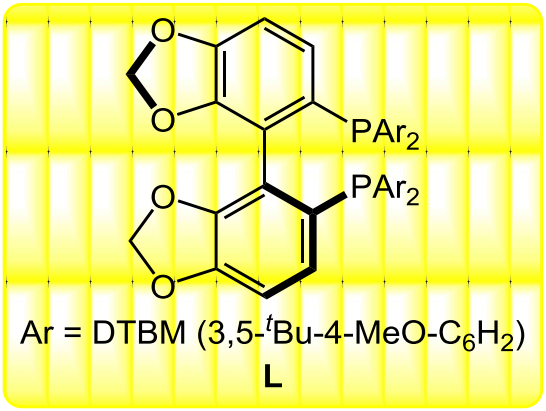

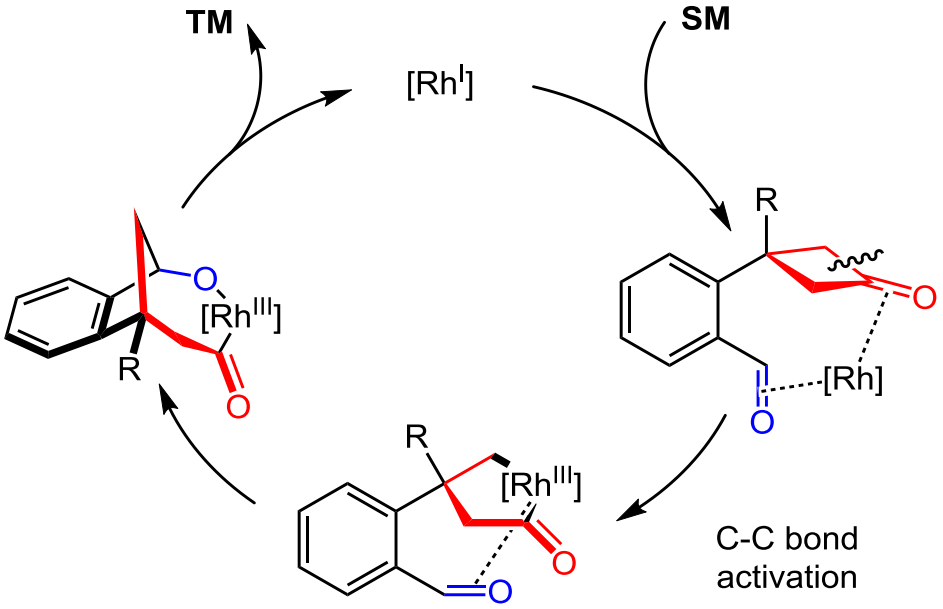

Cramer, N.* *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9640

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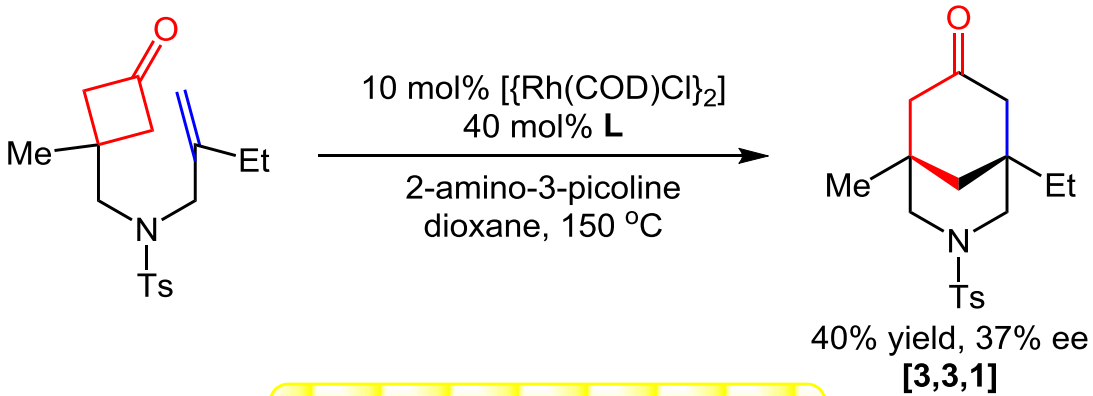

Dong, G.* *et al. Nat. Chem.* **2014**, *6*, 739

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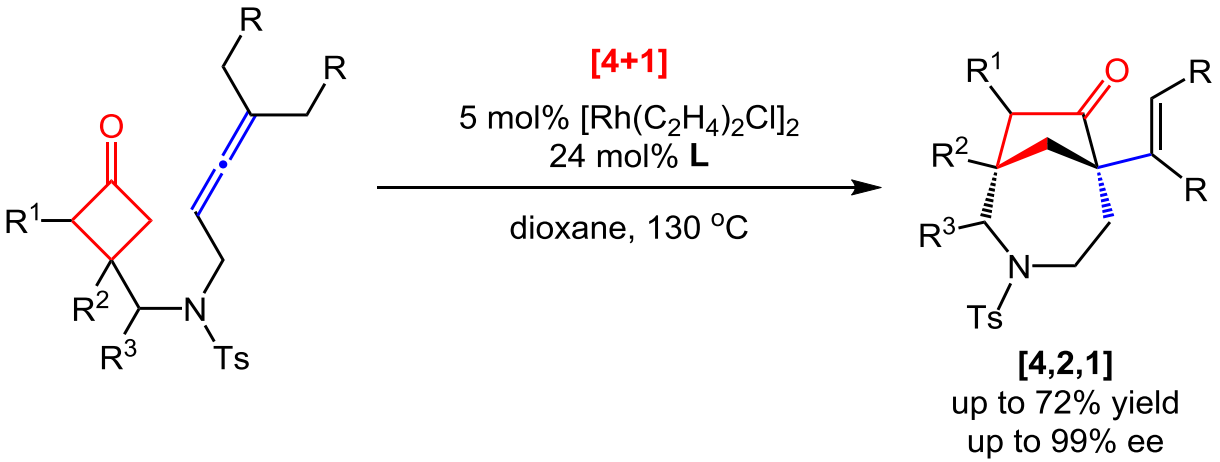
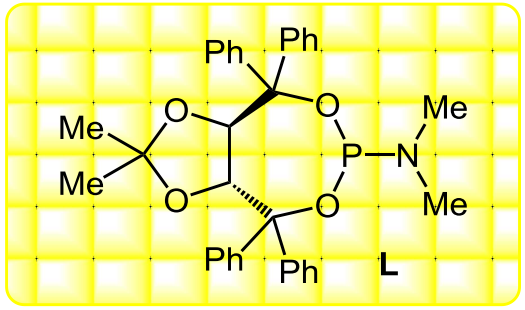
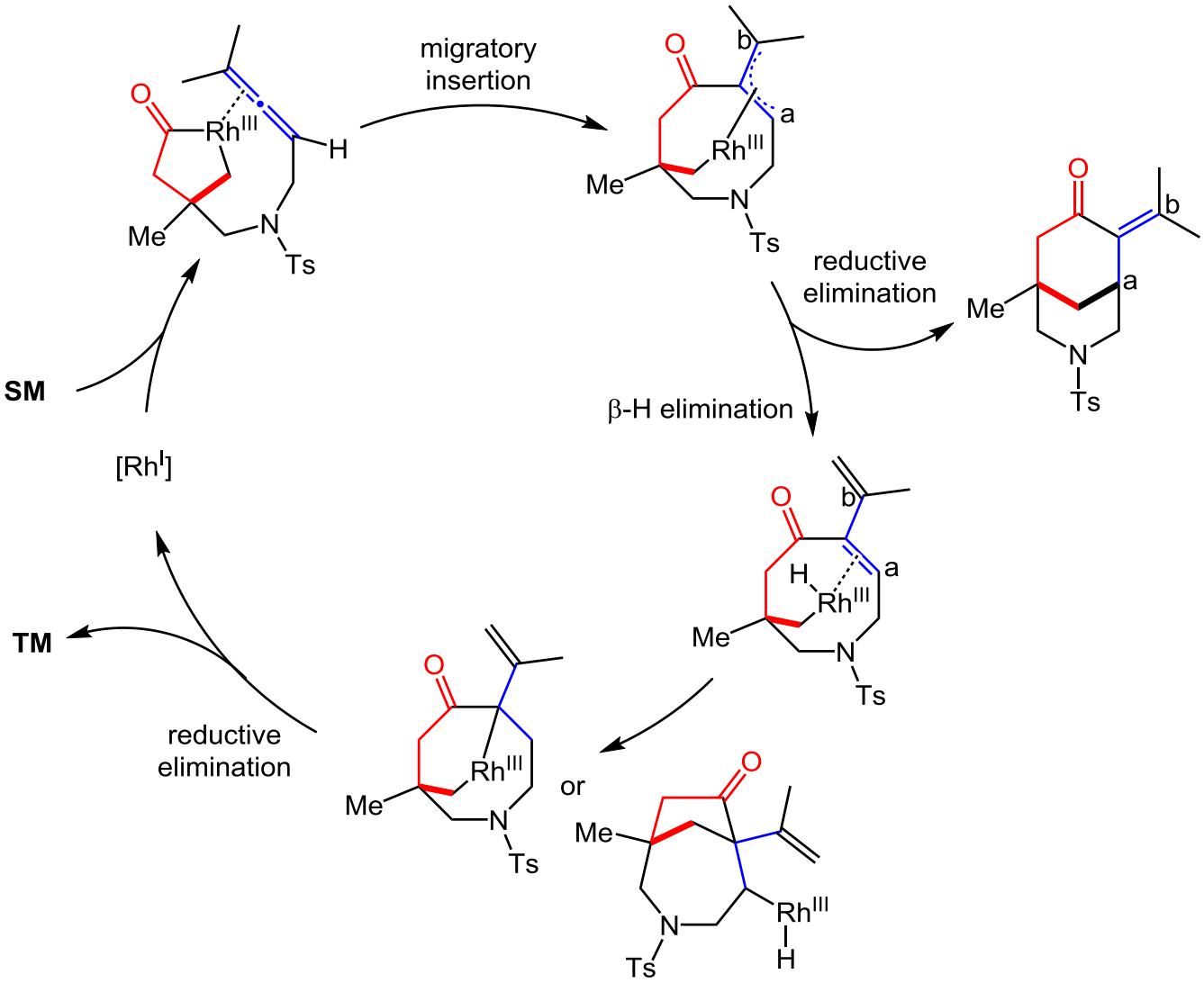


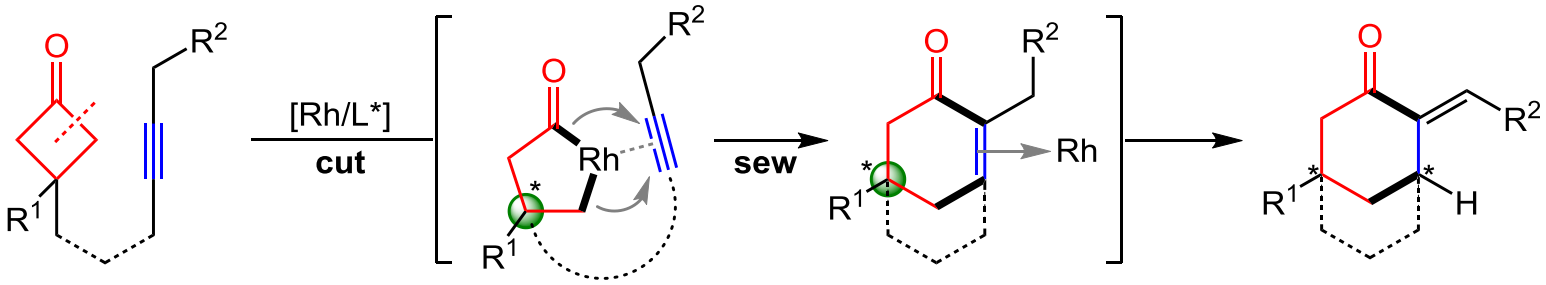


Dong, G.* *et al. J. Am. Chem. Soc.* **2015**, *137*, 13715

Proposed Mechanism

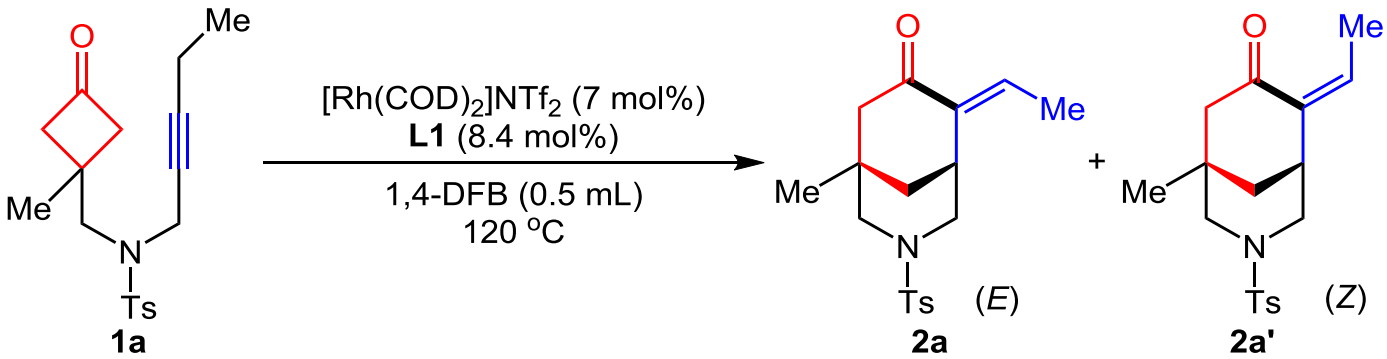


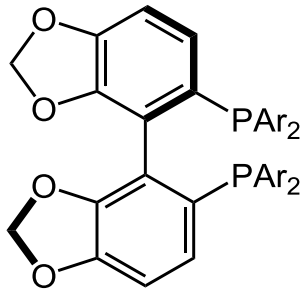
Enantioselective Type II Cycloaddition of Alkynes



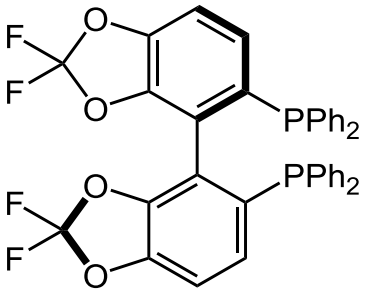
Hou, S.-H.; Yu, X.; Dong, G.* *et al. J. Am. Chem. Soc.* **2020**, *142*, 13180

Optimization of the Reaction Parameters

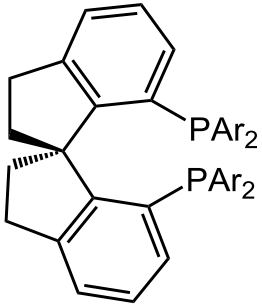




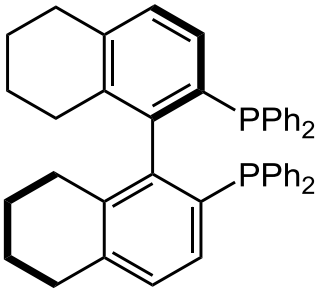
Ar = DTBM, (*R*)-DTBM-segphos (**L1**)
Ar = DM, (*R*)-DM-segphos (**L2**)
Ar = Ph, (*R*)-segphos (**L3**)



(*R*)-difluorophos (**L4**)

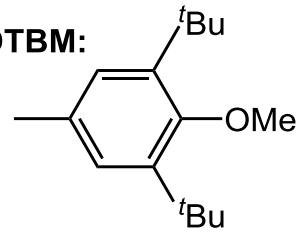


(*R*)-DM-sdp (**L5**)

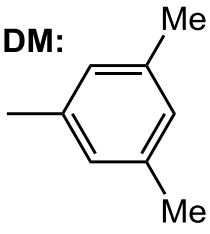


(*R*)-H_8-binap (**L6**)

DTBM:



DM:

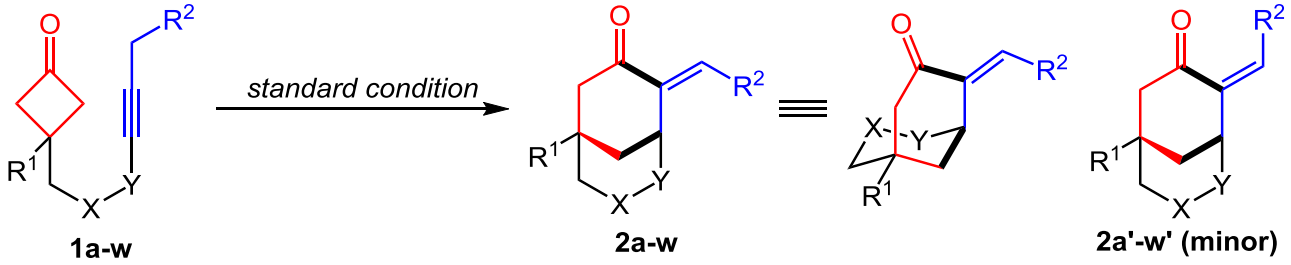


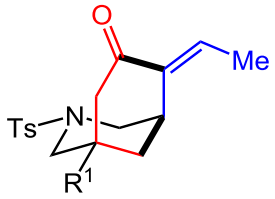
Optimization of the Reaction Parameters

entry[a]	Change from the "standard condition"	yield (%)[b] of 2a	er[b] of 2a	yield (%)[b] of 2a'
1	none	70	96.5:3.5	11[c]
2	$[Rh(COD)_2]BF_4$ instead of $[Rh(COD)_2]NTf_2$	64	84:16	10
3	L2 instead of L1	33	89:11	6
4	L3 instead of L1	24	97:3	6
5	L4 instead of L1	51	98.5:1.5	9
6	L5 instead of L1	27	80:20	7
7	L6 instead of L1	20	85.5:14.5	4
8	1,3-DFB instead of 1,4-DFB	62	96:4	11
9	1,2-DFB instead of 1,4-DFB	66	96:4	11
10	1,4-dioxane instead of 1,4-DFB	64	97.5:2.5	14
11	toluene instead of 1,4-DFB	67	96.5:3.5	14
12	1 mL 1,4-DFB instead of 0.5 mL	70	96.5:3.5	11

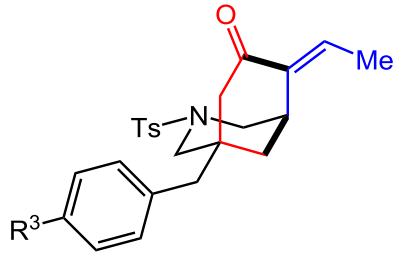
[a]All reactions were run on a 0.1 mmol scale for 48 h. [b]Yields are isolated yields; the er was determined by chiral HPLC. [c]The er of 2a′ was 97:3. DFB = difluorobenzene.

Scope of Substrates with Nitrogen and Carbon Linkers

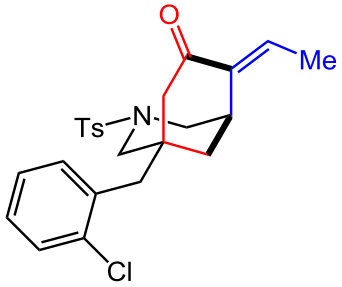




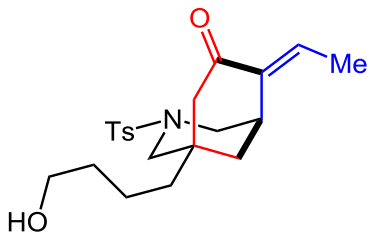
2a, R^1 = Me, 70% (er 96.5:3.5) + 11% **2a'**
2b, R^1 = Et, 71% (er 95:5) + 12% **2b'**
2c, R^1 = ^{i}Pr, 83% (er 98:2) + 16% **2c'**
2d, R^1 = CH_2OTIPS, 69% (er 97.5:2.5) + 11% **2d'**



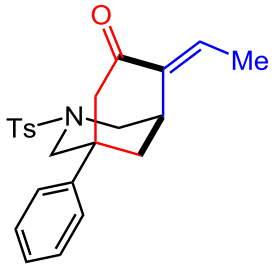
2e, R^3 = H, 76% (er 95.5:4.5) + 12% **2e'**
2f, R^3 = F, 78% (er 94.5:5.5) + 13% **2f'**
2g, R^3 = CF_3, 78% (er 95.5:4.5) + 13% **2g'**
2h, R^3 = OMe, 80% (er 94.5:5.5) + 13% **2h'**
2i, R^3 = Me, 71% (er 96:4) + 12% **2i'**



2j, 74% (er 99:1) + 12% **2j'**

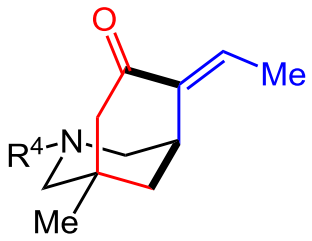


2k, 56% (er 92.5:7.5) + 11% **2k'**

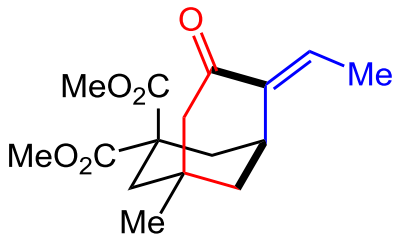


2l, 30% (er 99:1) + 5% **2l'**

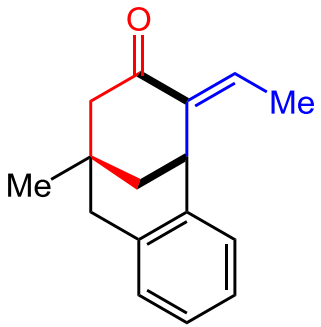
Scope of Substrates with Nitrogen and Carbon Linkers



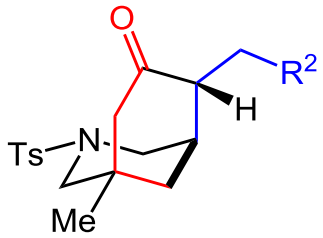
2m, R^4 = Bs, 63% (er 95:5) + 10% **2m'**
2n, R^4 = *p*-Ns, 53% (er 94.5:5.5) + 9% **2n'**
2o, R^4 = Ms, 60% (er 96:4) + 10% **2o'**
2p, R^4 = *o*-Ns, 32% (er 90:10) + 5% **2p'**
2q, R^4 = Piv, <2%



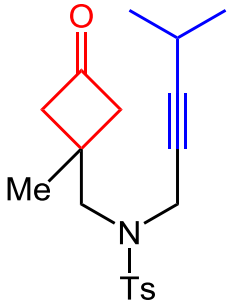
2r, 34% (er 87:13) *E/Z* >20:1



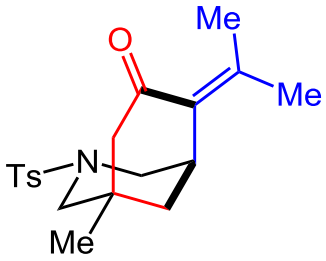
2s, 18% (er 61:39) + 8% **2s'**



2t, R^2 = ^{n}Pr, 71% (er 95:5) dr >20:1
2u, R^2 = Et, 65% (er 95.5:4.5) dr >20:1
2v, R^2 = Bn, 64% (er 94:6) dr >20:1
(Pd/C (20%wt), H_2, EtOH, rt, 12 h)

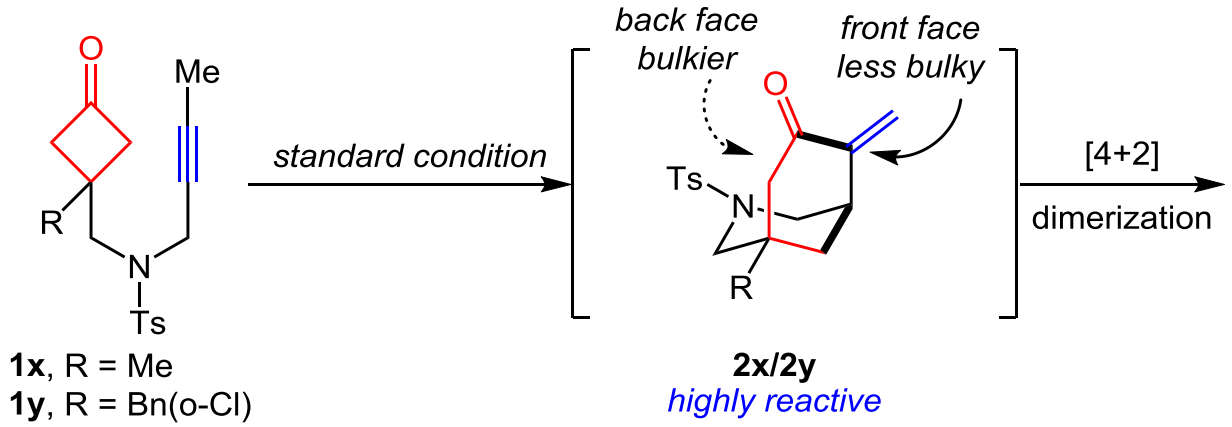


1w



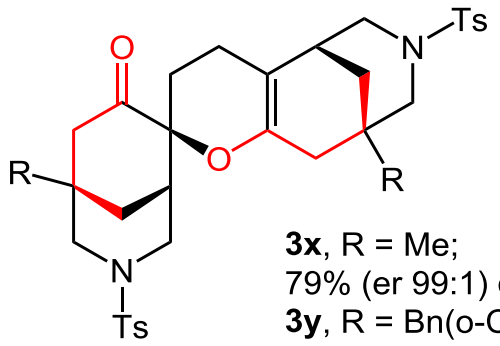
2w, 19%
(er 87:13)

Scope of Substrates with Nitrogen and Carbon Linkers



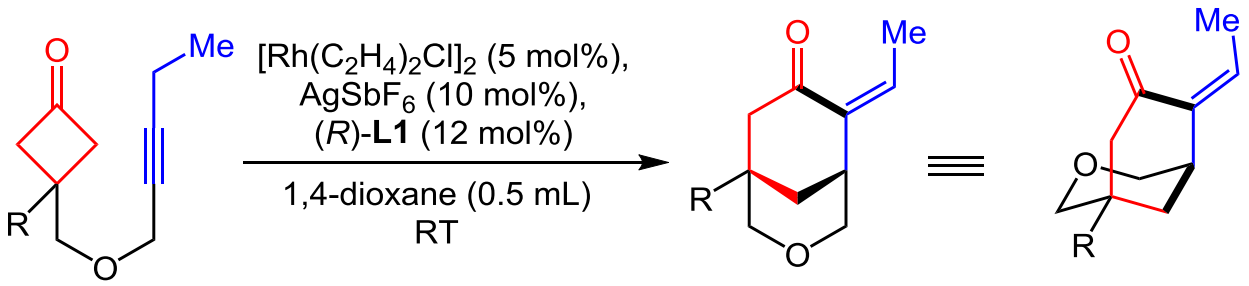
1x, R = Me
1y, R = Bn(o-Cl)

2x/2y
highly reactive



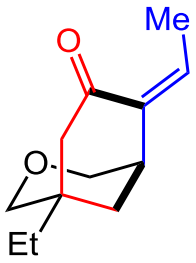
3x, R = Me;
79% (er 99:1) dr >20:1
3y, R = Bn(o-Cl);
84% (er 99:1) dr >20:1

Scope of Substrates with Oxygen Linkages

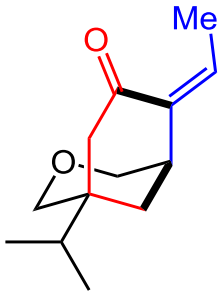


1z/1aa/1ab

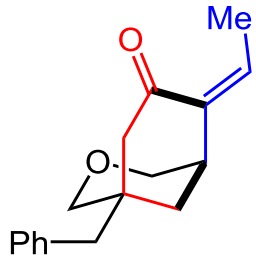
(*Z*) instead



2z', 30%
(er 99.7:0.3)
Z/E >10:1
conv. 50%

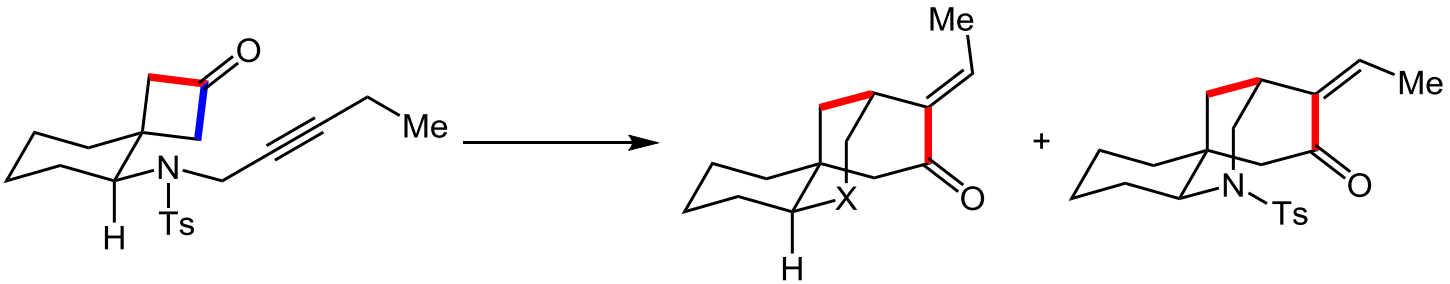


2aa', 29%
(er 99.5:0.5)
Z/E >10:1
conv. 40%



2ab', 38%
(er 99.5:0.5)
Z/E >10:1
conv. 56%

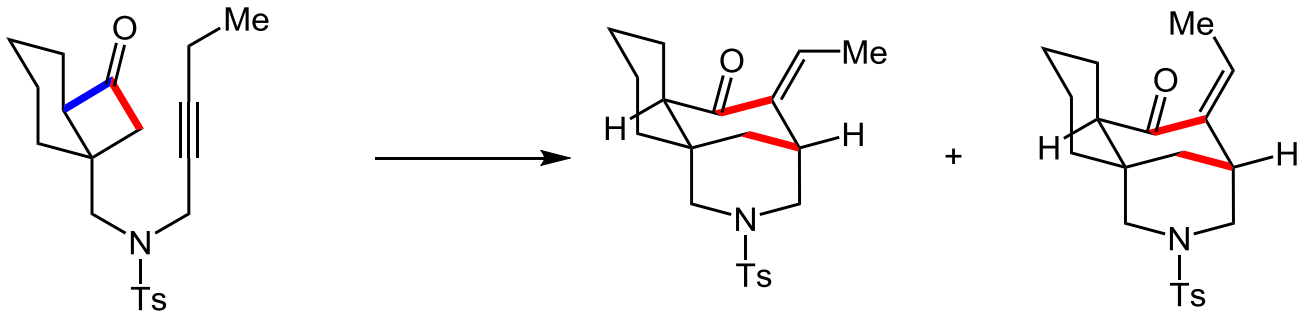
Scope of Cyclobutanones with Existing Stereocenters



1ac (racemic)

2ac, X = NTs
51% (er 88:12)

2ac'
11%

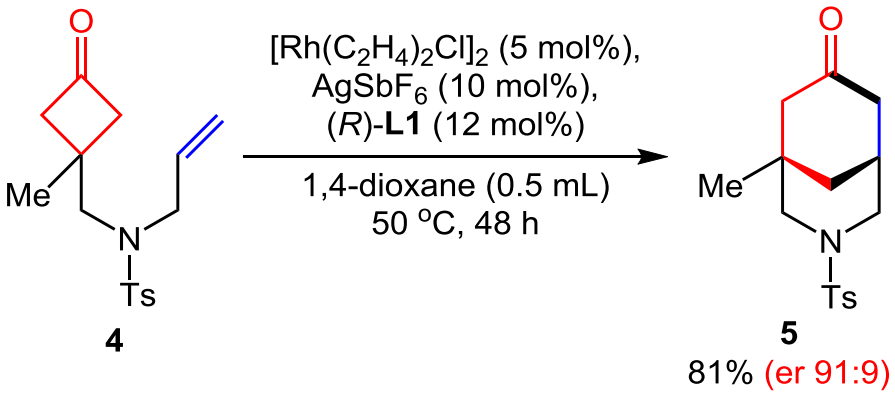


1ad (racemic)

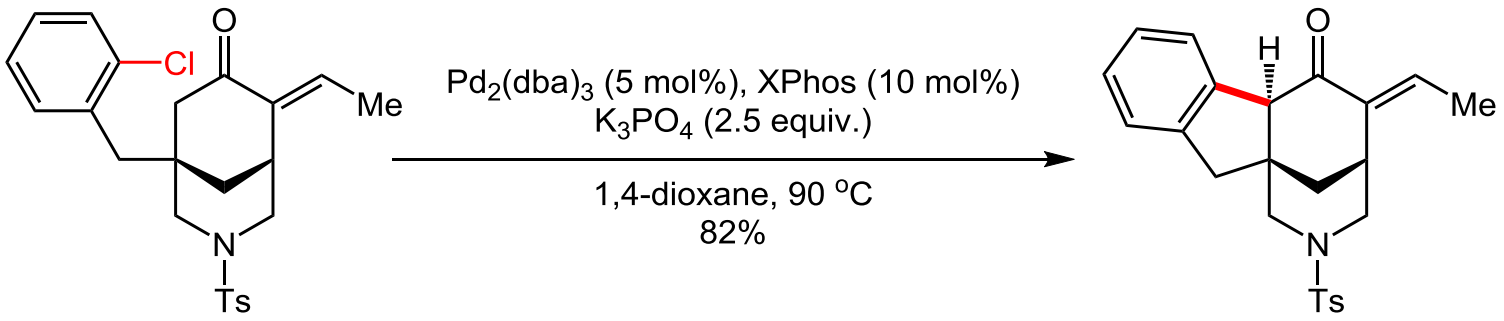
2ad
36% (er 99:1)

2ad'
19% (er 69:31)

Scope of the Olefin Derived Substrate

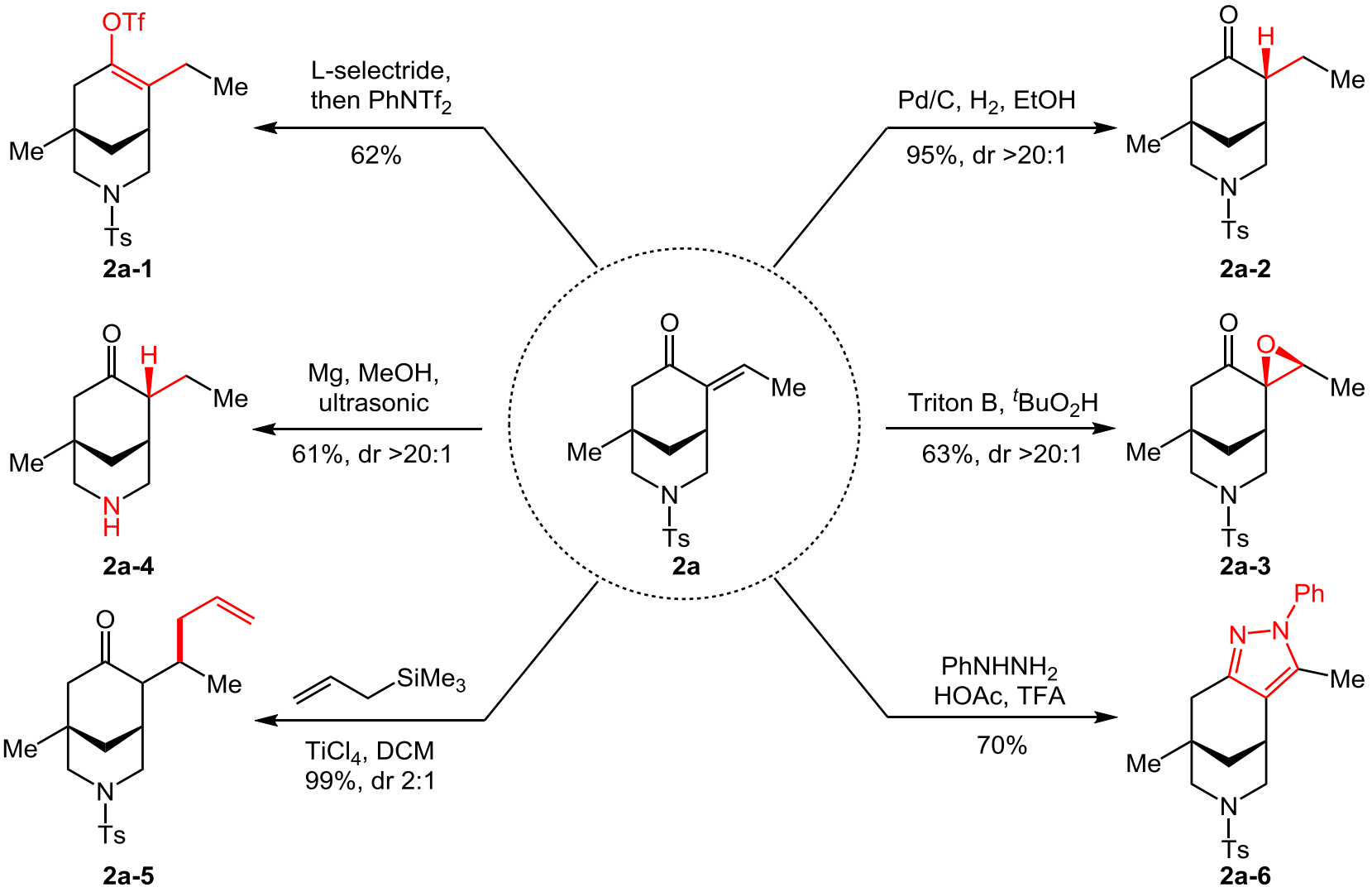


Synthetic Utilities



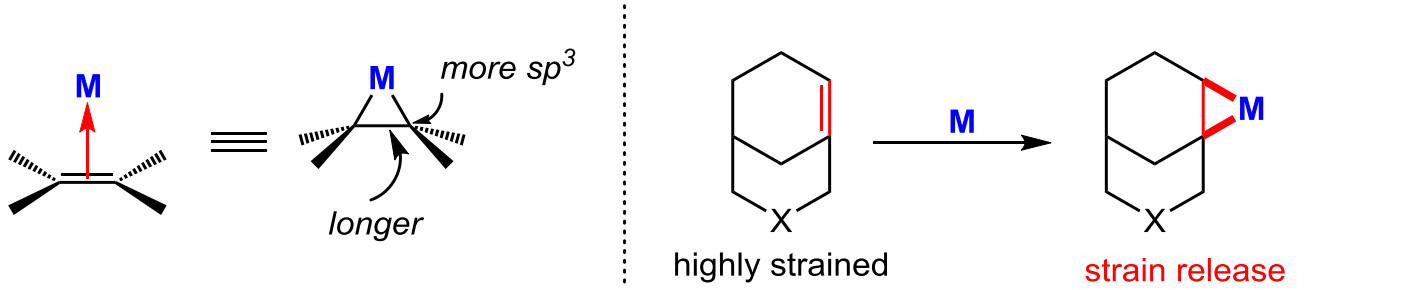
2j **2j-1**

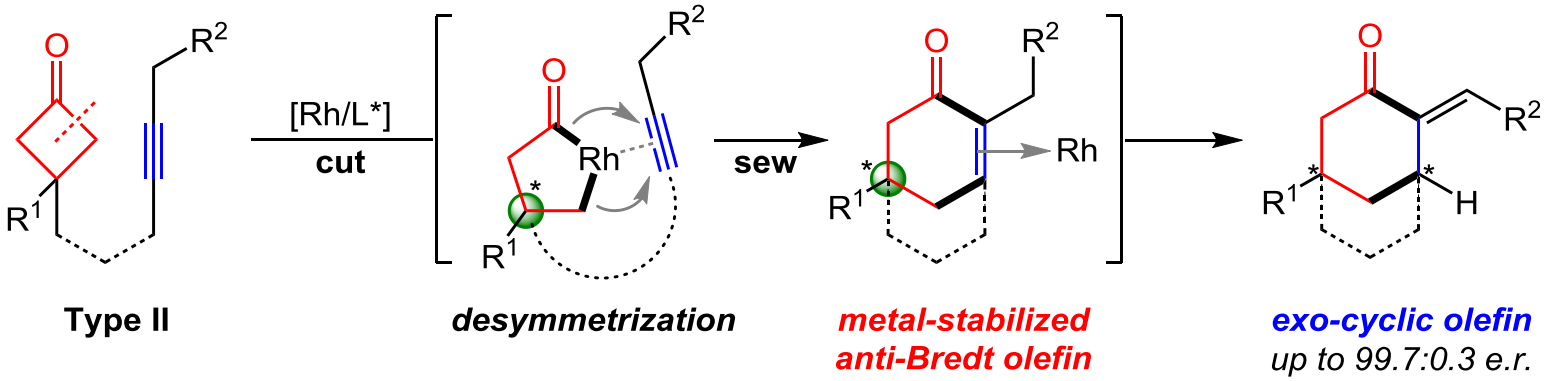
Synthetic Utilities



Summary

Strain Release through Metal Coordination





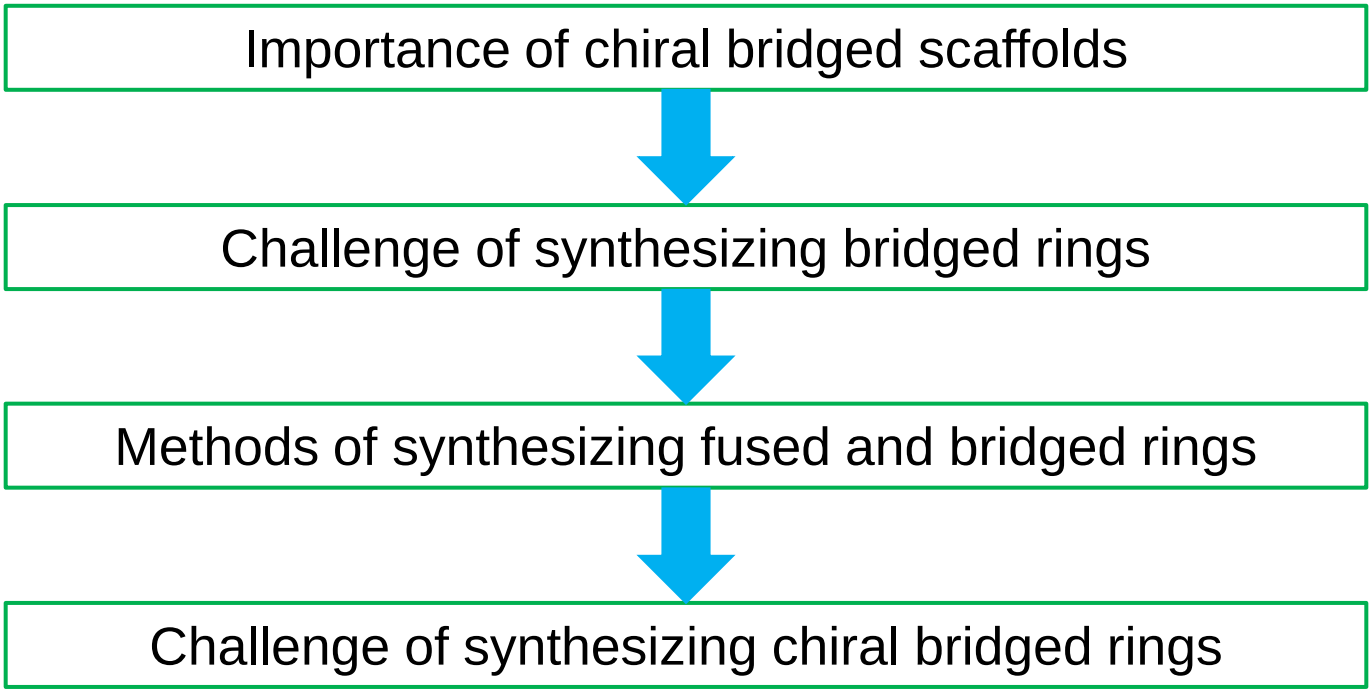
Type II

desymmetrization

metal-stabilized anti-Bredt olefin

exo-cyclic olefin
up to 99.7:0.3 e.r.

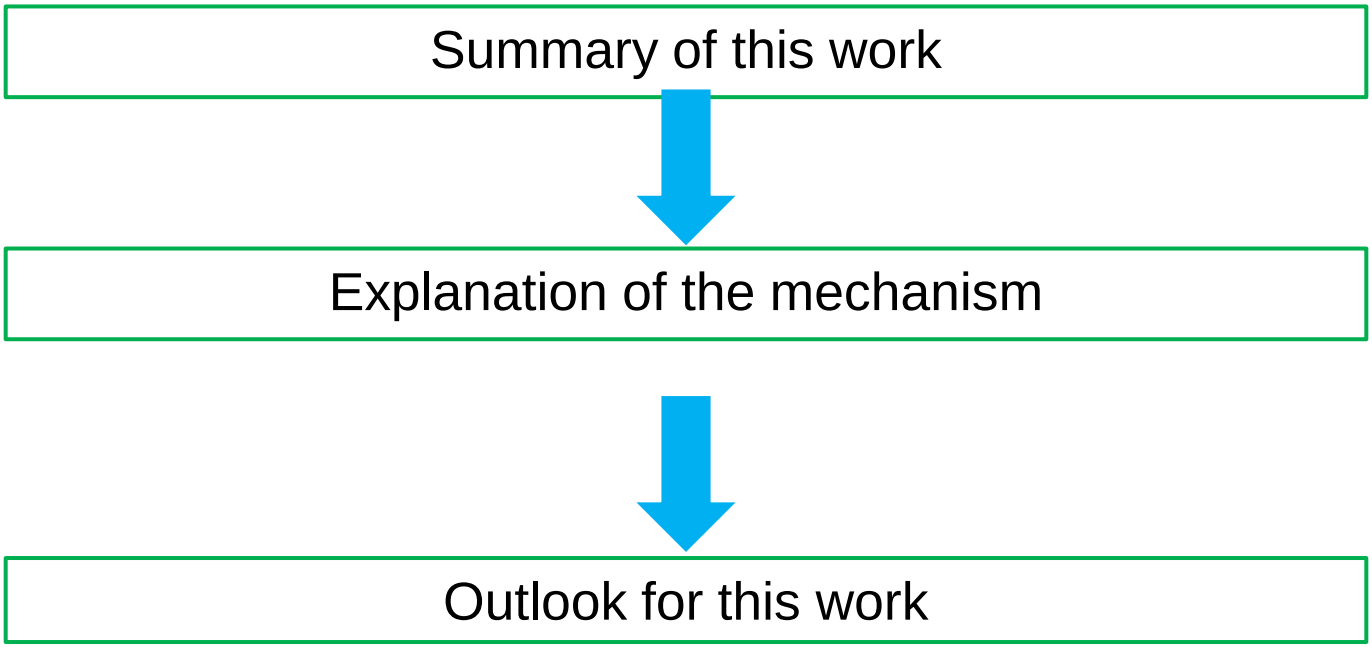
Writing Strategy



The First Paragraph

Chiral bridged scaffolds are commonly found in biologically important natural products and drugs. However, compared to fused rings, much fewer cyclization approaches have been developed for constructing bridged rings, often due to enhanced angular and torsional strains in reaction transition states. For example, while the Type I Diels-Alder reaction the intramolecular [4π+2π] cyclization using C1-tethered dienes is powerful for building fused rings with numerous enantioselective versions achieved, the corresponding Type II reaction introduces a twisted alkene at bridgeheads, known as an anti-Bredt olefin, due to the C2 linkage. As exemplified in the formation of 6-6 bridged rings, the corresponding Type II Diels-Alder reaction proves to be highly challenging and requires special and forcing conditions (e.g., high-temperature gas-phase reactions). As a consequence, asymmetric synthesis of bridged rings via Type-II cycloadditions has been even rarer.

Writing Strategy



The Last Paragraph

In summary, an enantioselective Rh-catalyzed intramolecular Type II cyclization between cyclobutanones and alkynes has been developed, which provides a convenient entry to chiral [3.3.1] bridged bicyclic scaffolds. The reaction is redox neutral and strong acid/base-free, thus tolerating a broad range of functional groups. The products bearing a reactive exocyclic enone moiety can be readily functionalized. It is thus anticipated that this method could be useful for preparing bioactive and complex alkaloids or terpenes. The stabilization of an anti-Bredt olefin in a strained [3.3.1] scaffold via metal coordination, as revealed by the mechanistic study, could have broad implications beyond this work. Efforts on extending the substrate scope to construct other bridged rings and exploring other coupling partners besides alkynes are ongoing.

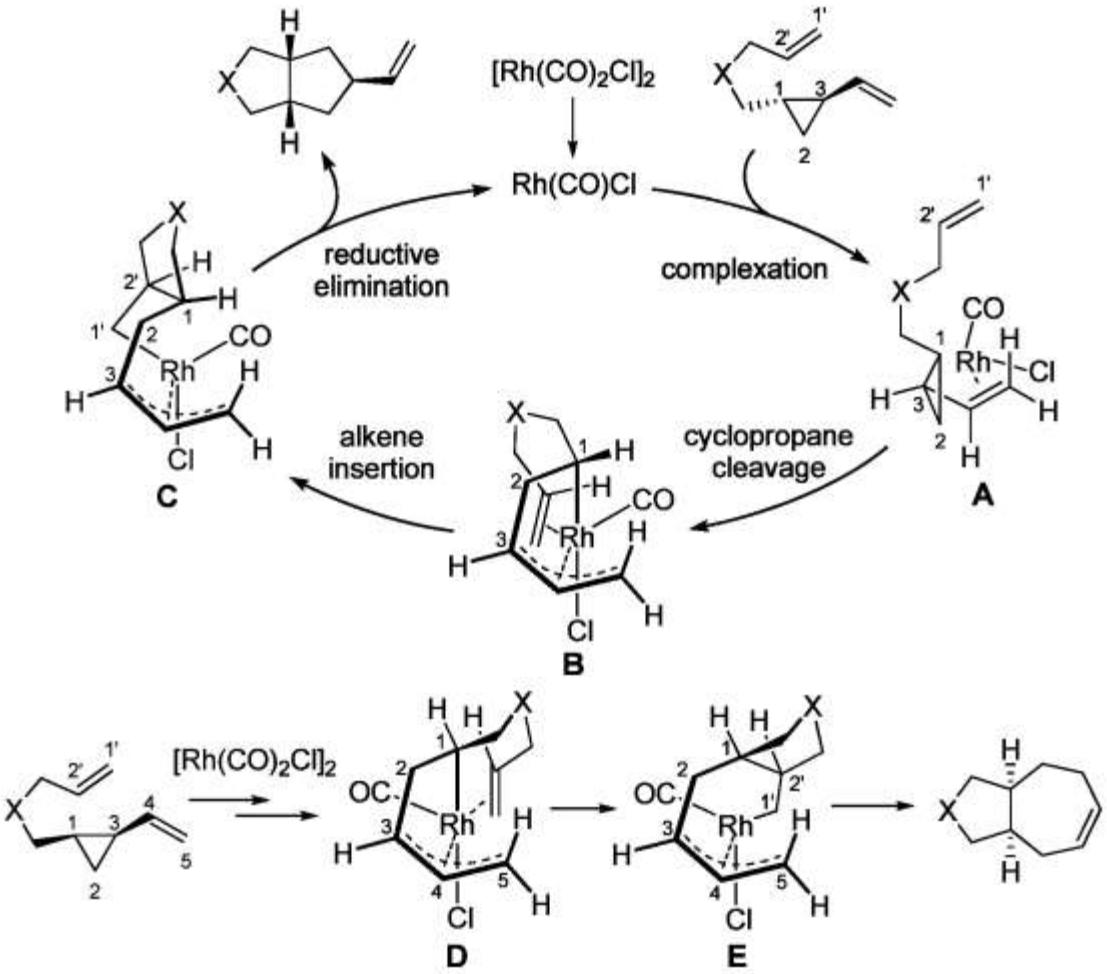
Representative Examples

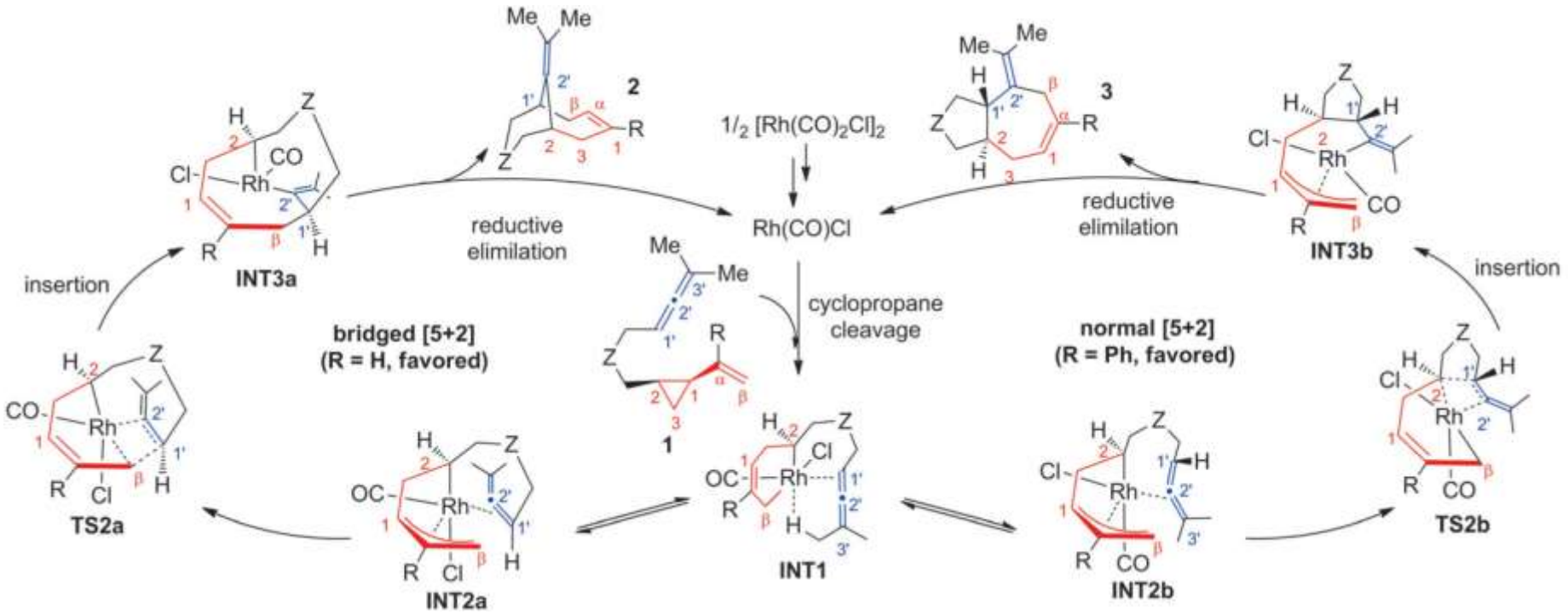
To the best of our knowledge (据我们所知), the challenge of enantioselective preparation of more common [3.3.1] bicycles (6/6 bridged rings), found in numerous bioactive terpenes and alkaloids, remains to be addressed. (有待解决)

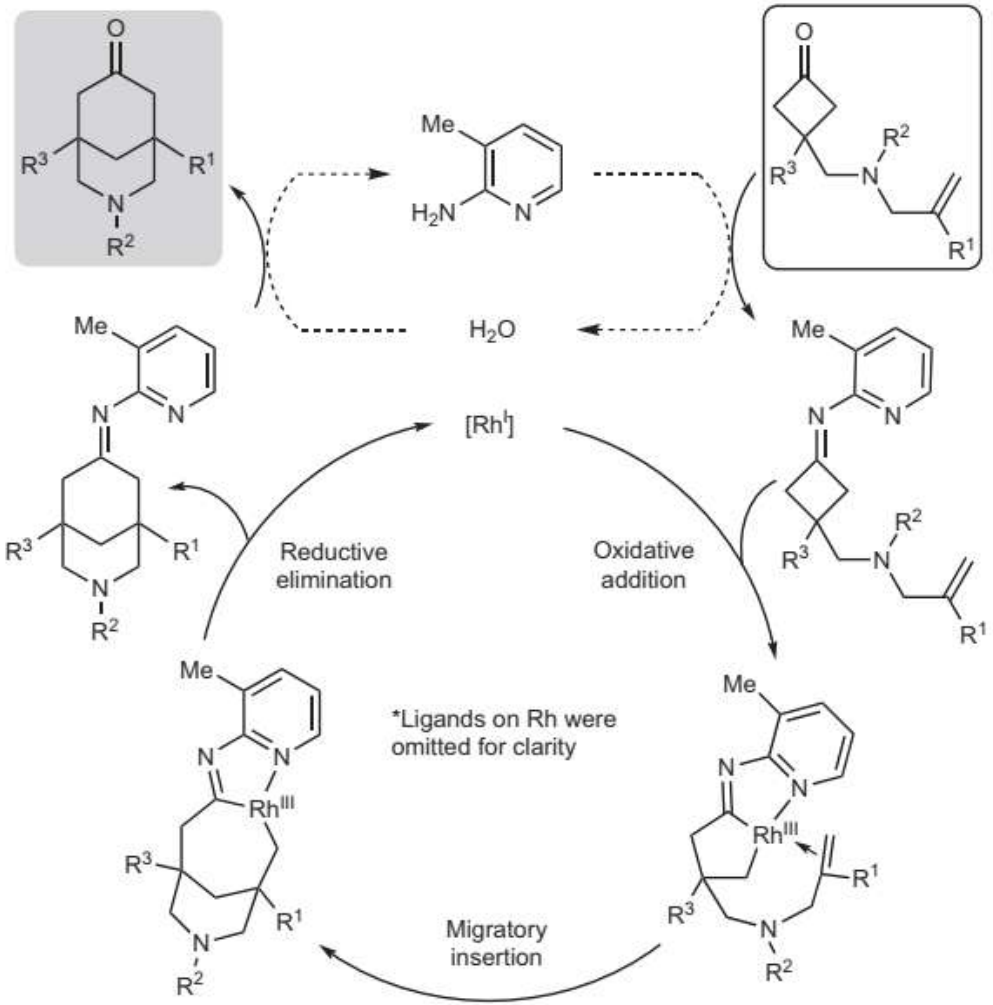
It is also known that (阐述常见现象时) binding of strained olefins to low valent metals changes the hybridization of olefin carbons (toward sp^3) and alters the bond lengths/angles from those in free olefin, resulting in strain release.

As exemplified (例如) in the formation of 6-6 bridged rings, the corresponding Type II Diels-Alder reaction proves to be highly challenging and requires special and forcing conditions.

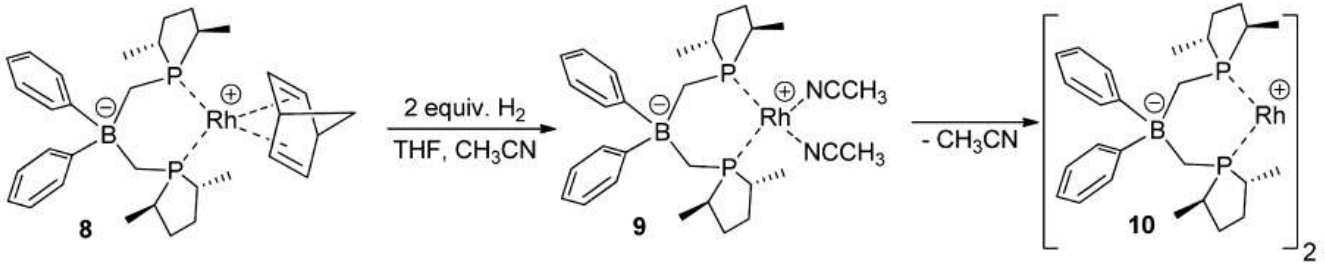
Thanks for your attention


[Rh(CO)2Cl]2
Rh(CO)Cl
reductive elimination
complexation
alkene insertion
cyclopropane cleavage
A
B
C
D
E
[Rh(CO)2Cl]2

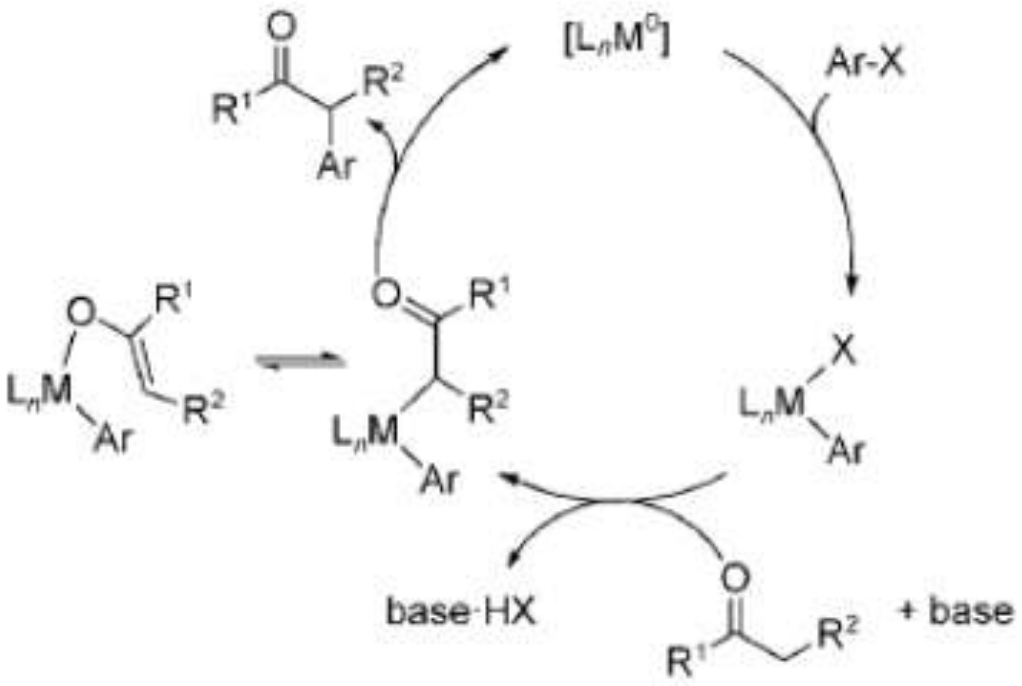

Me Me
2
1/2 [Rh(CO)2Cl]2
Me Me
H
3
Z
H
CO
Cl
Rh
R
INT3a
reductive elimination
Rh(CO)Cl
reductive elimination
INT3b
insertion
insertion
bridged [5+2]
(R = H, favored)
cyclopropane cleavage
normal [5+2]
(R = Ph, favored)
1
TS2a
INT2a
INT1
INT2b
TS2b
OC
Cl


O
R3
R1
N
R2
Me
H2N
N
O
R3
R2
N
R1
H2O
[RhI]
Me
N
N
R3
R1
N
R2
Reductive elimination
Oxidative addition
Me
N
N
R3
R2
N
R1
Me
N
N
RhIII
R3
R1
N
R2
*Ligands on Rh were omitted for clarity
Migratory insertion
Me
N
N
RhIII
R1
R3
N
R2

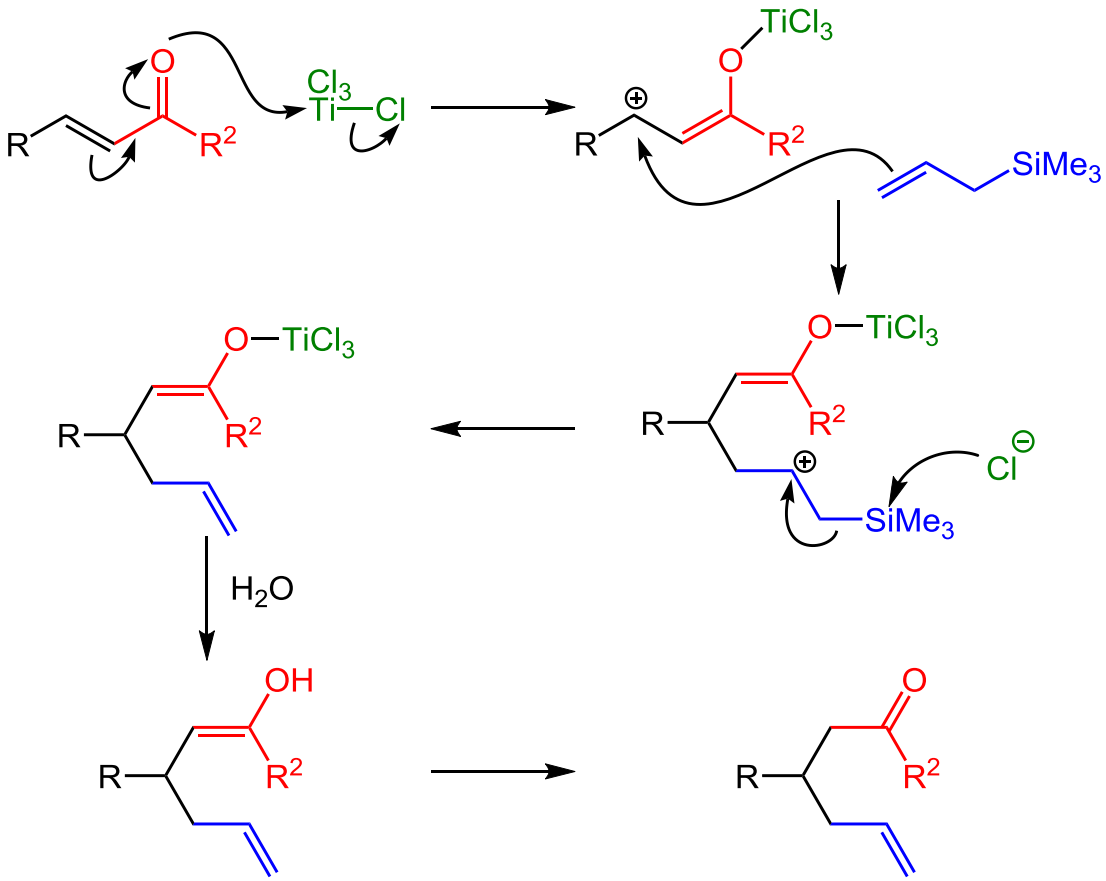
Hydrogenolysis of the Norbornadiene Ligand of Complex 8 Leads to Presumed Complexes 9 and 10



Buchwald–Hartwig–Miura α-Arylation



Hosomi-Sakurai Reaction



桥环化合物是指化合物中的任意两个环共用两不直接相连的碳原子的环烃,根据组成环的数目分为二环烃、三环烃、四环烃等。两个环或多个环用的碳原子为桥头碳原子,连接桥头碳原子的键称做桥。