Literature Report 2

Medium and Large *N*-Heterocycle Formation *via* Allene Hydroamination with a Bimetallic Rh(II) Catalyst

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Checker: Yixuan Ding
Date: 2022-03-14

Michaelis, D.-J. *et al. J. Am. Chem. Soc.* **2022**, *144*, 63

CV of Prof. David J. Michaelis

Background:

- **2002-2005** B.S., BYU
- **2005-2009** Ph.D., University of Wisconsin-Madison
- **2010-2013** Postdoctor, Stanford University
- **2013-Now** Assistant Professor, BYU

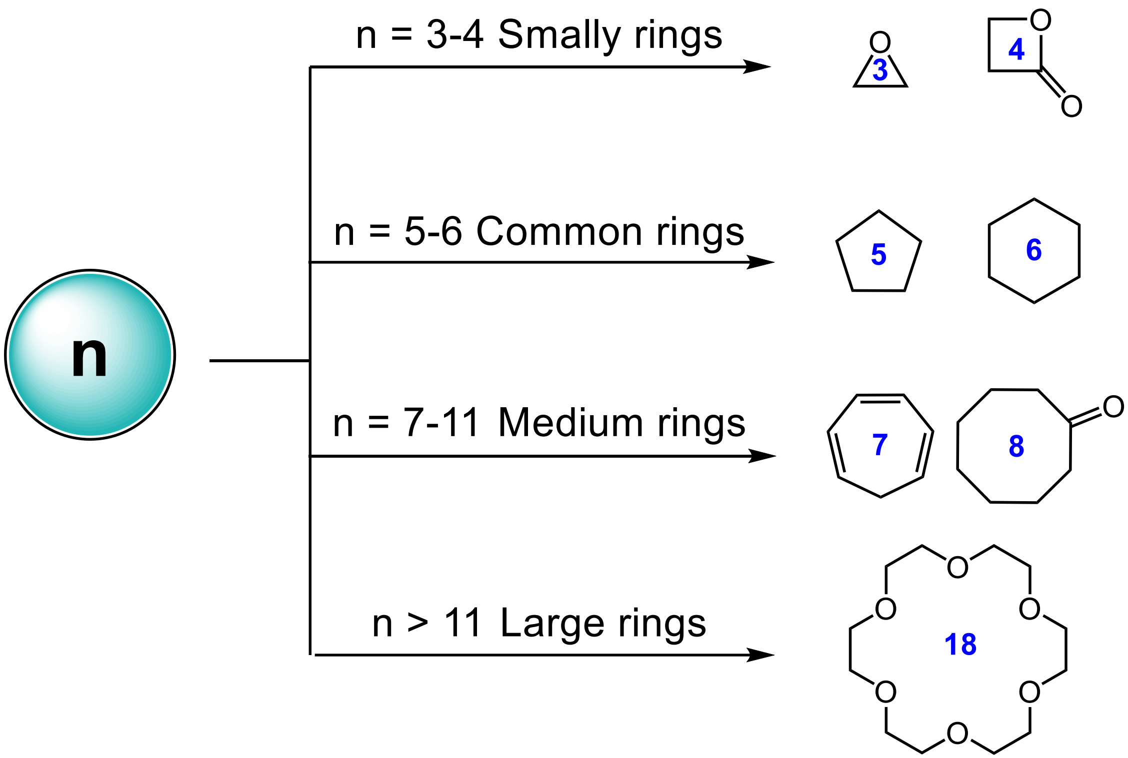
Research:

- Polymer-supported nanoparticle;
- Electrophilic catalysis with heterobimetallic complexes;
- α-Helical peptide scaffolds as modular, tunable, enzyme-like catalysts for multistep synthesis.

Contents

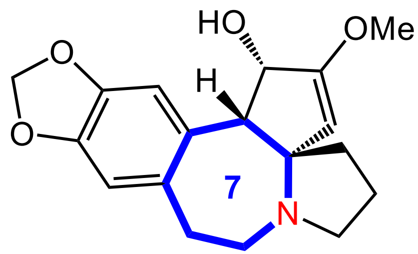
Introduction

Classification of cyclics

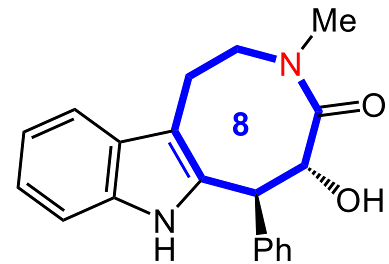


Introduction

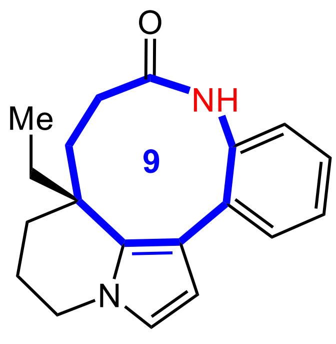
Importance of medium-sized ring nitrogen heterocycles



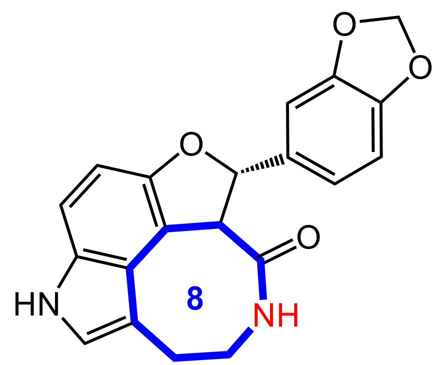
Cephalotaxine
antilukemic activity



Balasubramide
inhibits neuroinflammation



Rhazinilam
inhibits tubulin formation

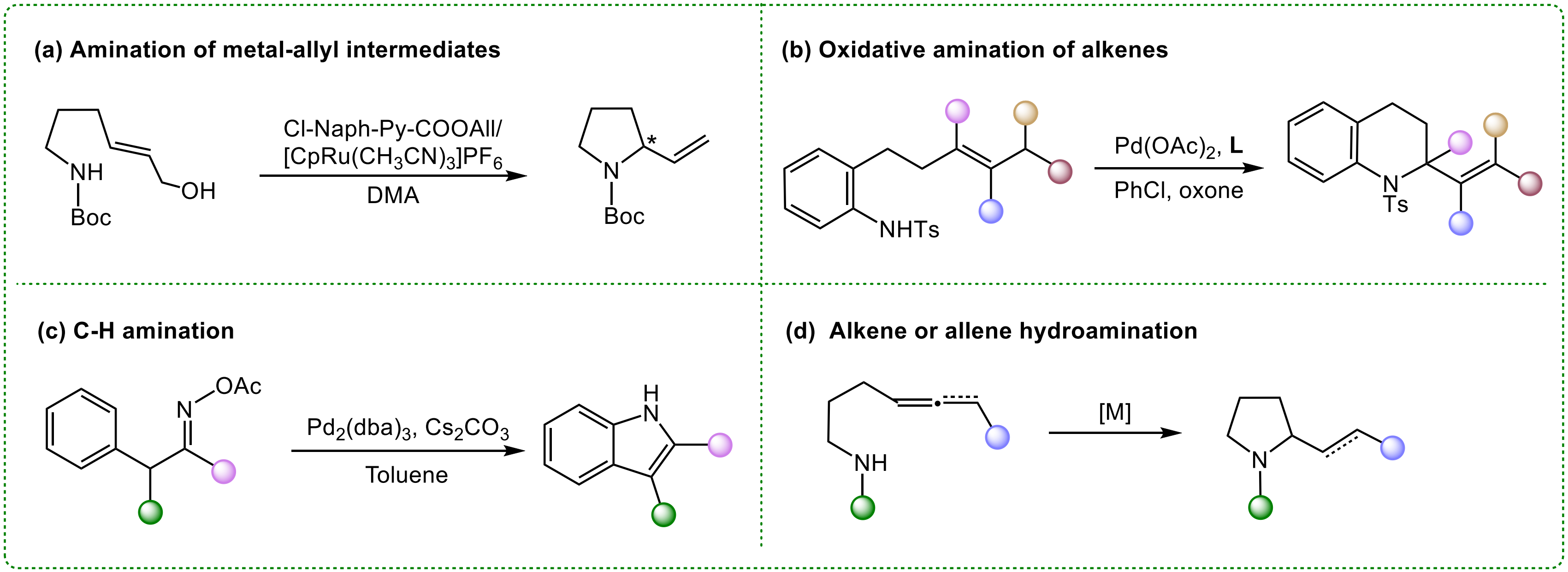


Decursivine
antimalarial activity

Powell, K.-L. *J. Med. Chem*. **2007**, *50*, 1685

Introduction

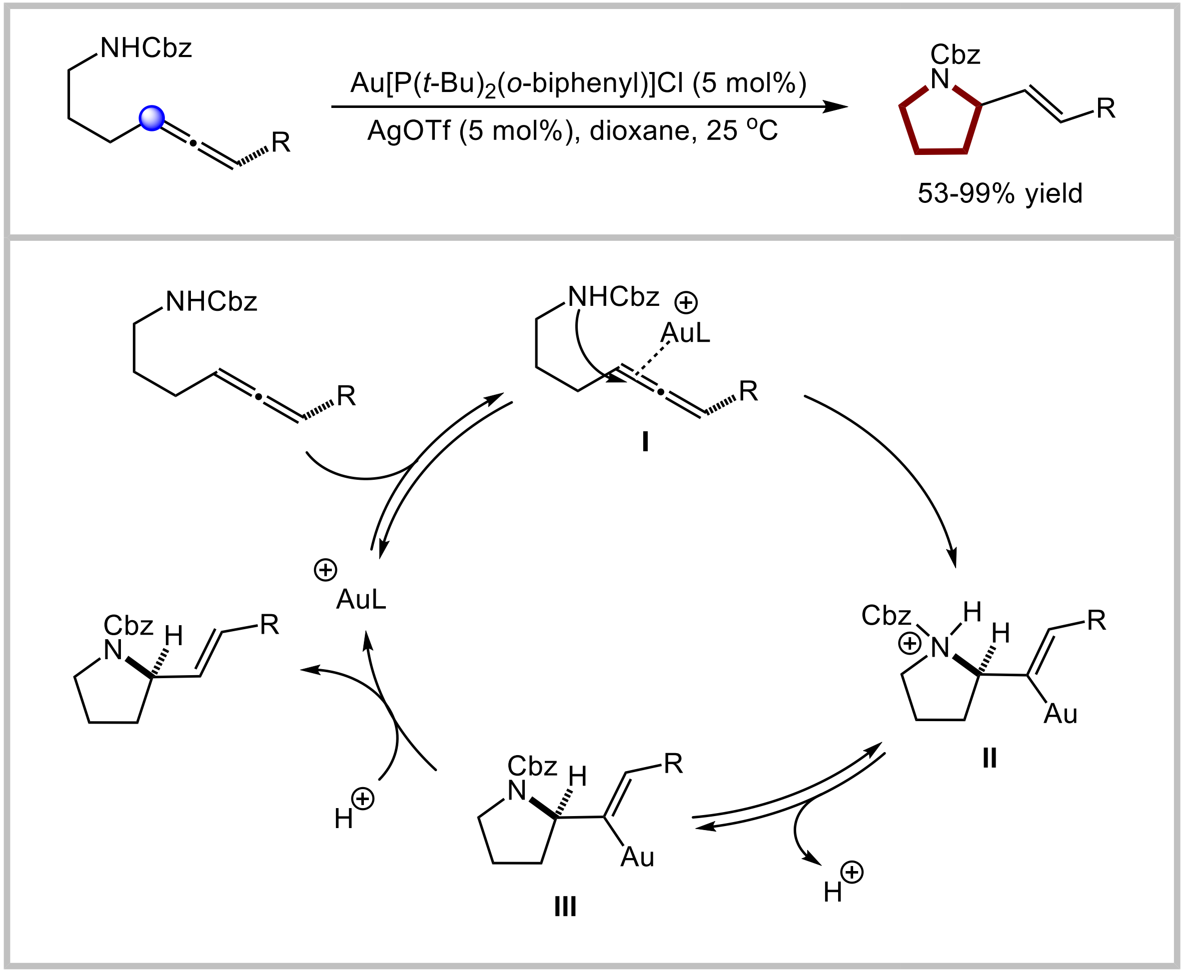
Metal catalyzed nitrogen heterocycle synthesis



Kitamura, M. *et al. Org. Lett*. **2012**, *14*, 608
Sasai, H. *et al. Org. Lett.* **2018**, *20,* 6827
Hartwig, J,-F. *et al*. *J. Am. Chem. Soc.* **2010**, *132,* 3676
Huang, L. *et al. Chem. Rev.* **2015**, *115,* 2596

Introduction

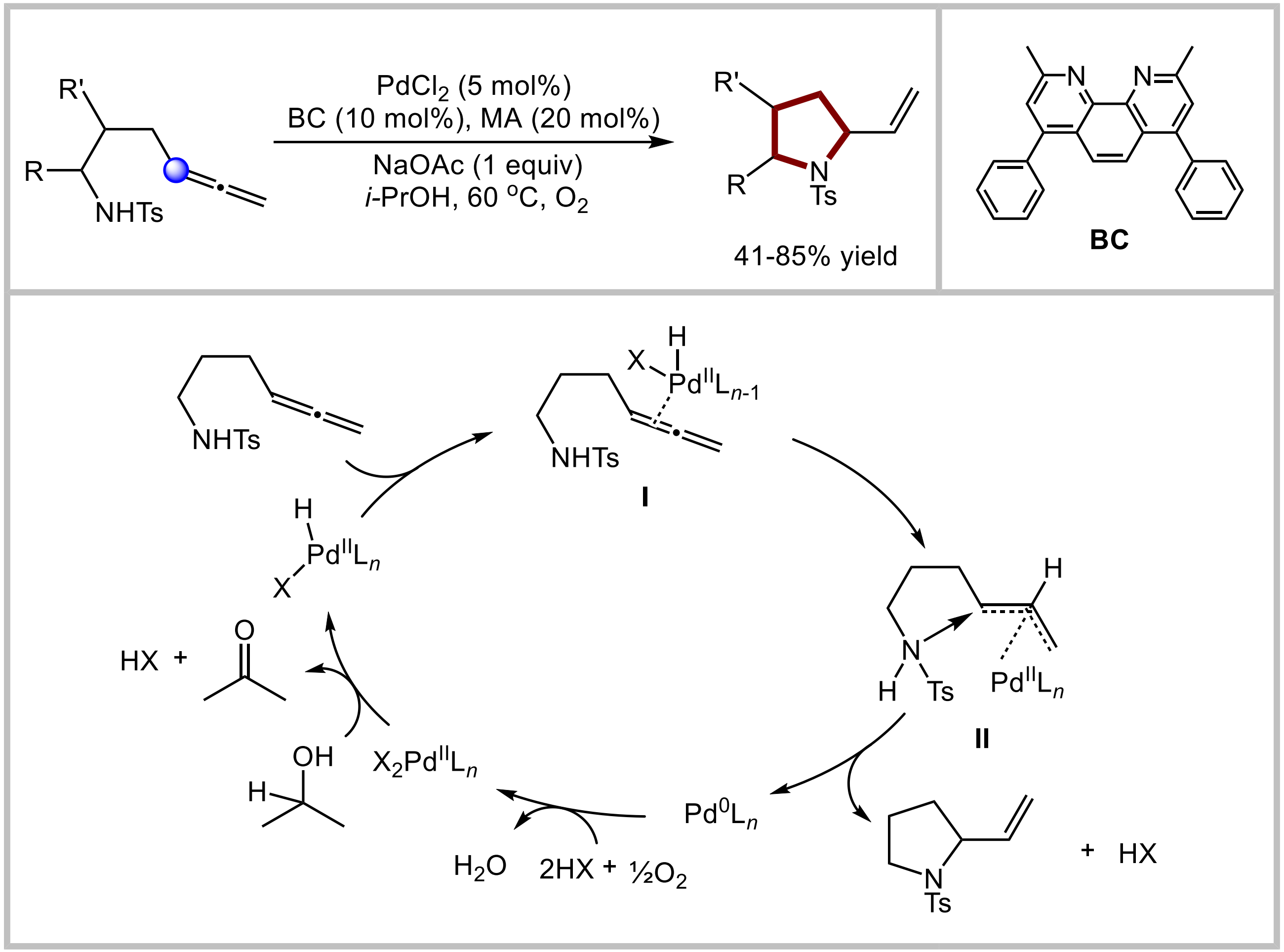
Au catalyzed allene hydroamination



Widenhoefer, R.-A. *et al. J. Am. Chem. Soc.* **2006**, 128, 9066

Introduction

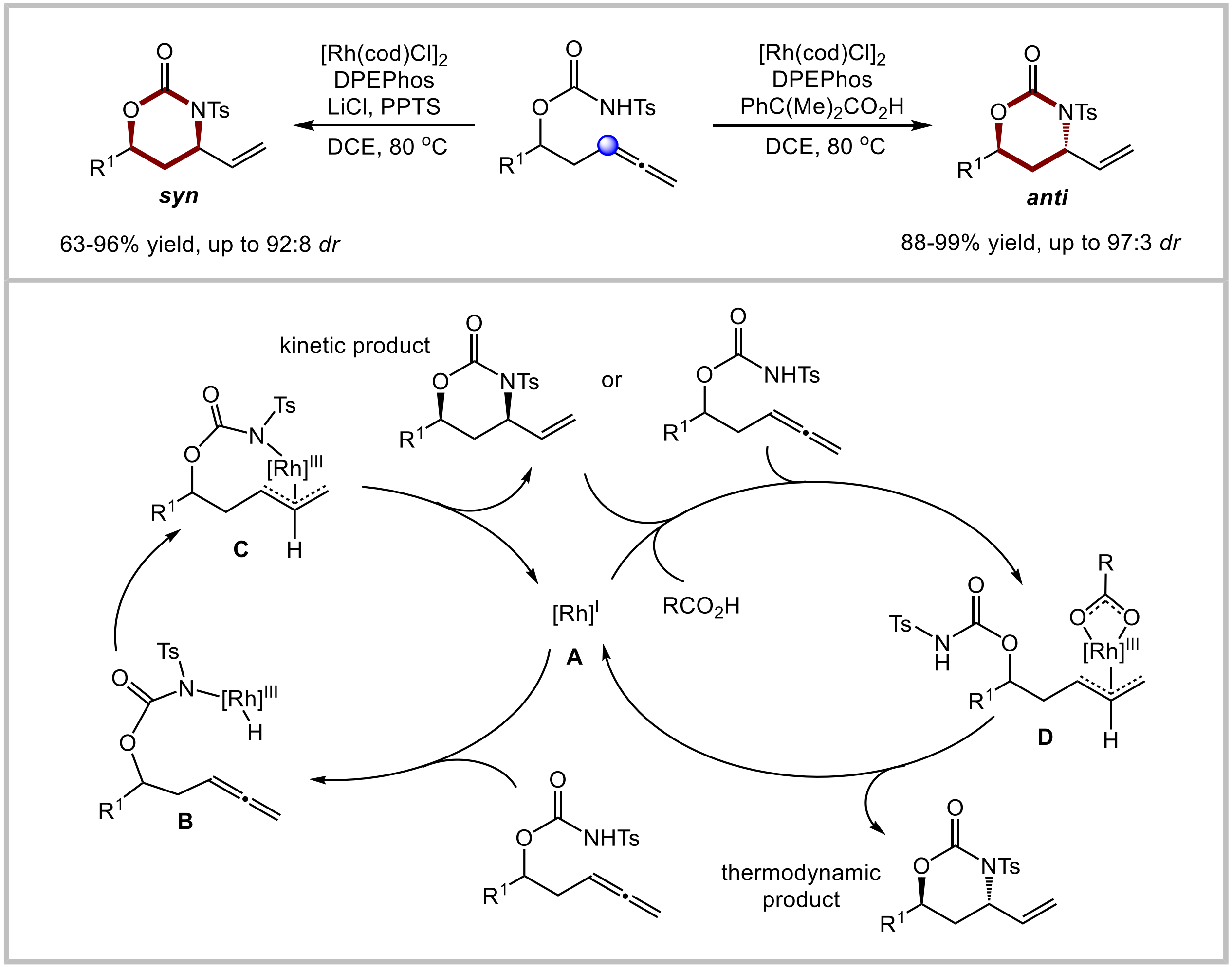
Pd catalyzed allene hydroamination



Liu, G. *et al. Chem. Eur. J.* **2009**, *15*, 2751

Introduction

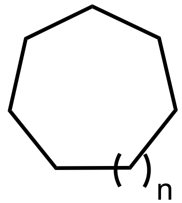
Rh catalyzed allene hydroamination



Breit, B. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 15569

Introduction

The difficulty of forming medium-sized ring



medium-sized ring

- **Transannular interactions**
- **Entropy effects**
- **Strain effects**

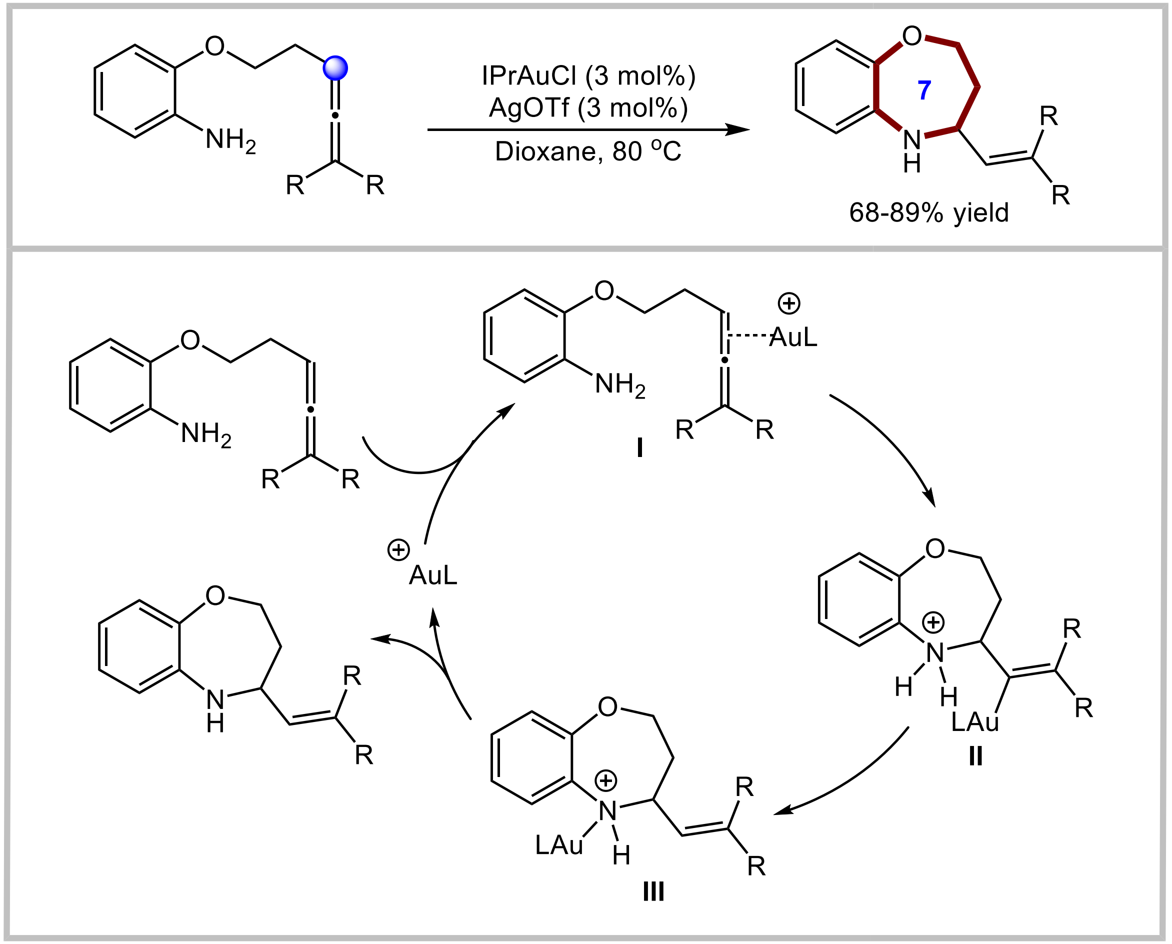
Strain-energies of Cycloalkanes and lactones [*kcal/mol*]

Ring size	Cycloalkanes	Lactones
3	27.5	40.4
4	26.1	23.3
5	6.2	7.7
6	0.1	9.5
7	6	10.7
8	9.4	12.4
9	12.2	11.6
10	12.2	8.2
11	11.1	7.3
12	4	7.1
13	5	6.7
14	3.2	4.5

Mandolini, L. *et al. Acc. Chem. Res*. **1981**, *14*, 95
Mandolini, L. *et al. Eur. J. Org. Chem*. **2000**, *2000*, 3117

Introduction

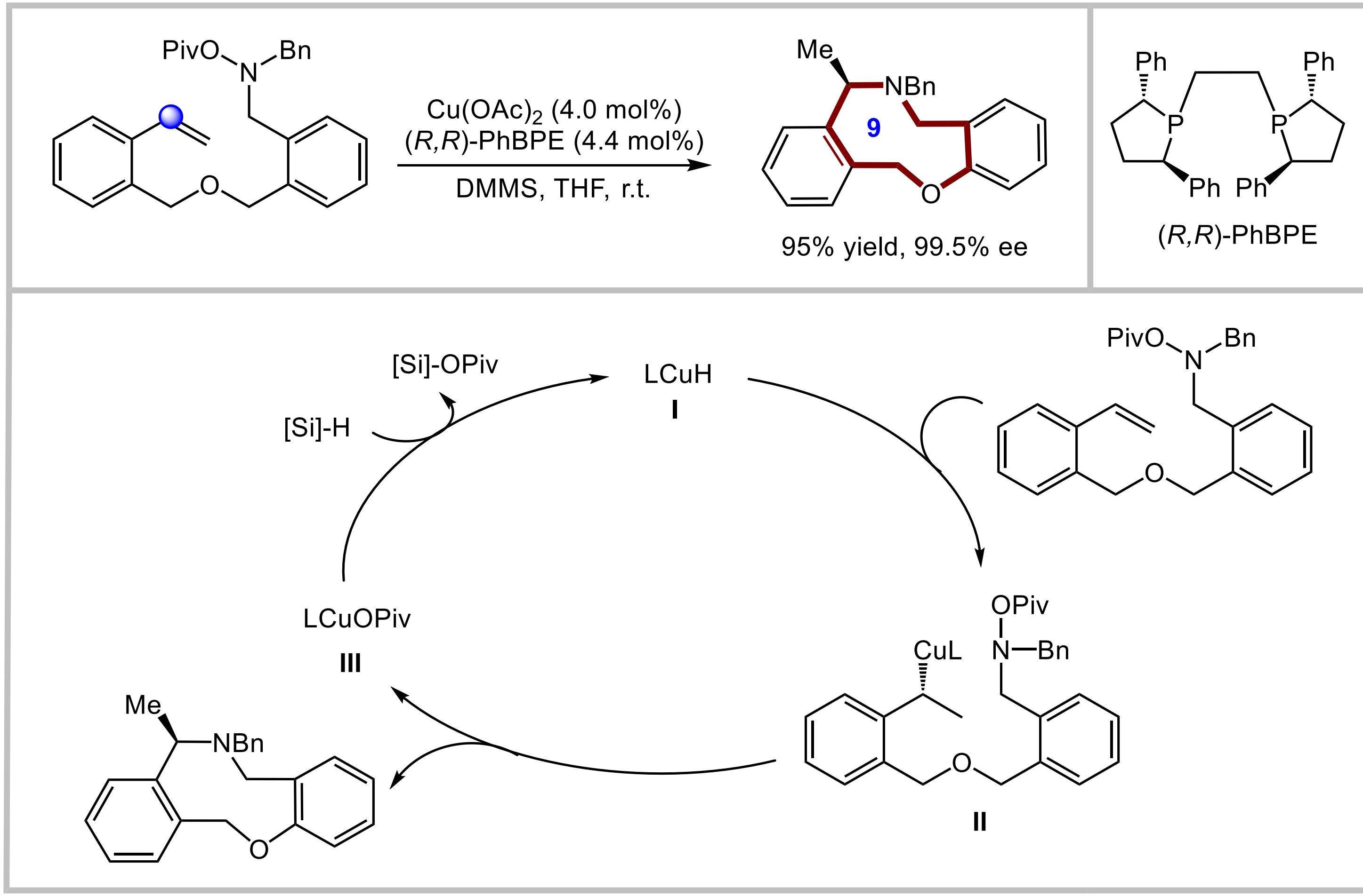
Au catalyzed intramolecular hydroamination



Hashmi, A.-S. *et al. Adv. Synth. Catal.* **2013**, *355*, 1383

Introduction

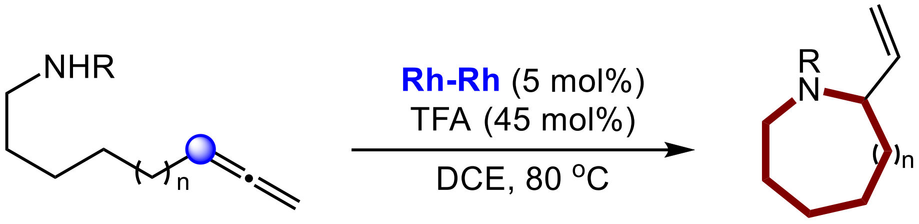
Cu catalyzed intramolecular hydroamination

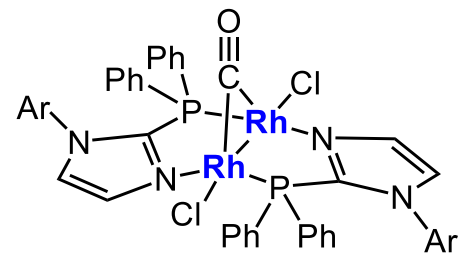


Buchwald, S.-L. *et al. Angew. Chem. Int. Ed*. **2019**, *58*, 3407

Introduction

Bimetallic Rh catalysis for medium-sized ring formation





Ar = 2,6-diisopropylphenyl

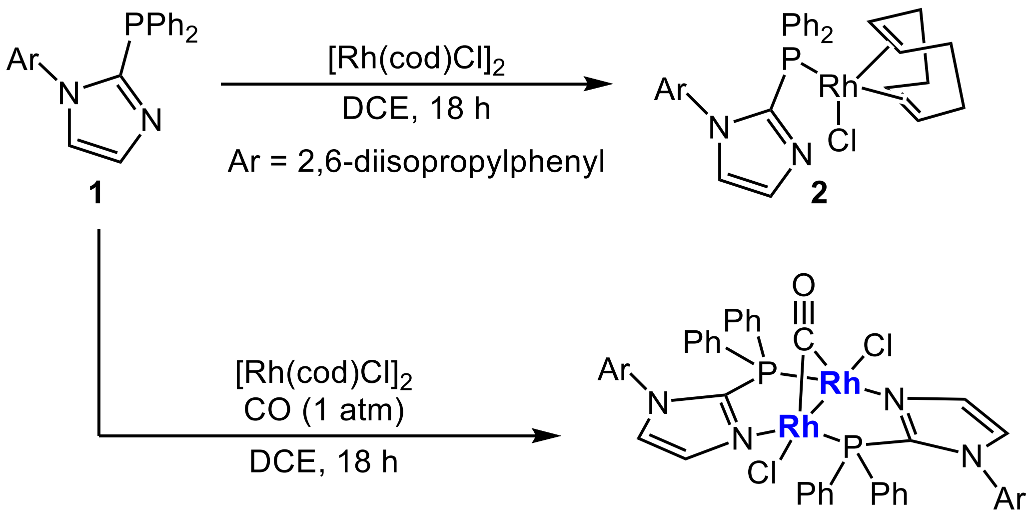
7- to 15-membered ring

41 examples

Monometallic Rh = no cyclization

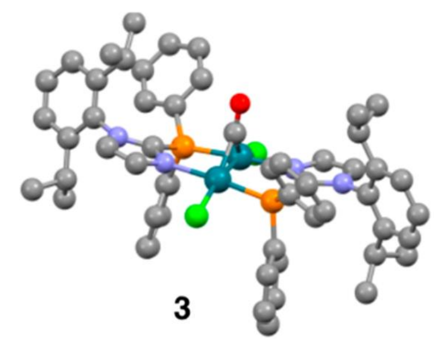
Michaelis, D.-J. *et al. J. Am. Chem. Soc.* **2022**, *144*, 63

Synthesis of mono- and bimetallic Rh complexes



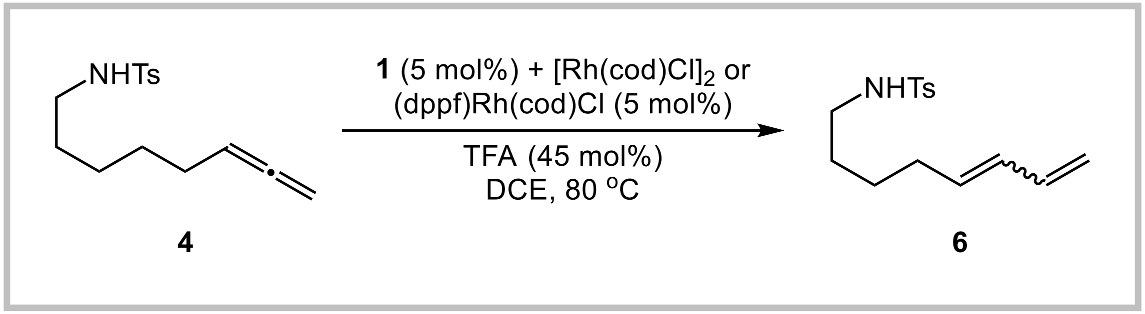
3, 85% yield

Unstable
Be isolated as a
co-crystal with [Rh(cod)Cl]$_2$

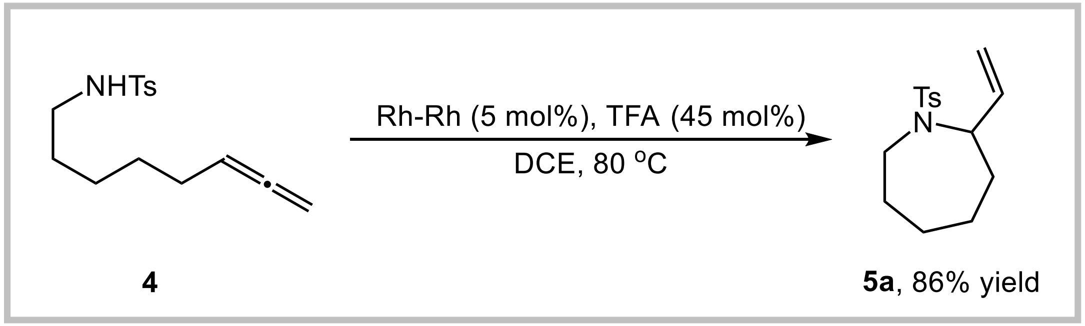


3

Reactivity of mono- and bimetallic Rh complexes

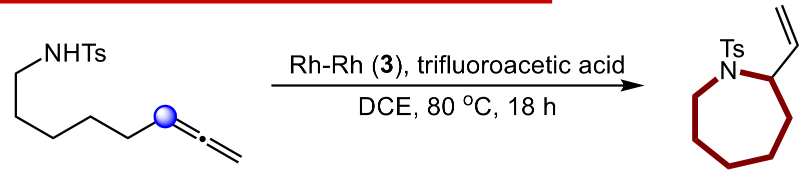


Monometallic Rh: only the isomerized diene product 6 was observed



Bimetallic Rh: the corresponding 7-membered ring 5a was observed

Optimization of hydroamination reaction

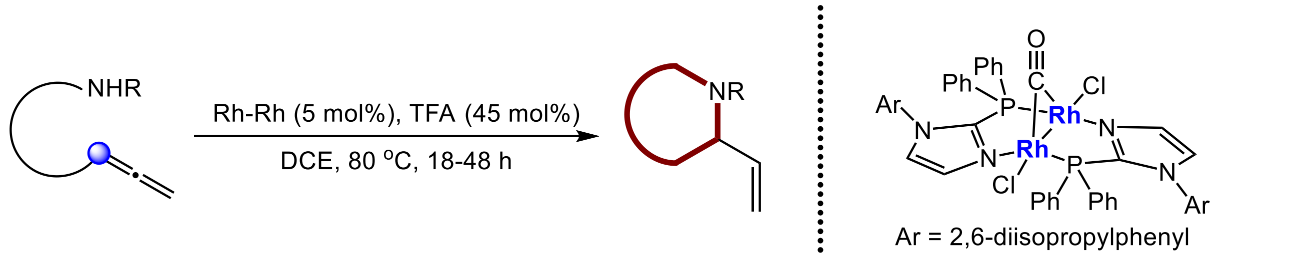


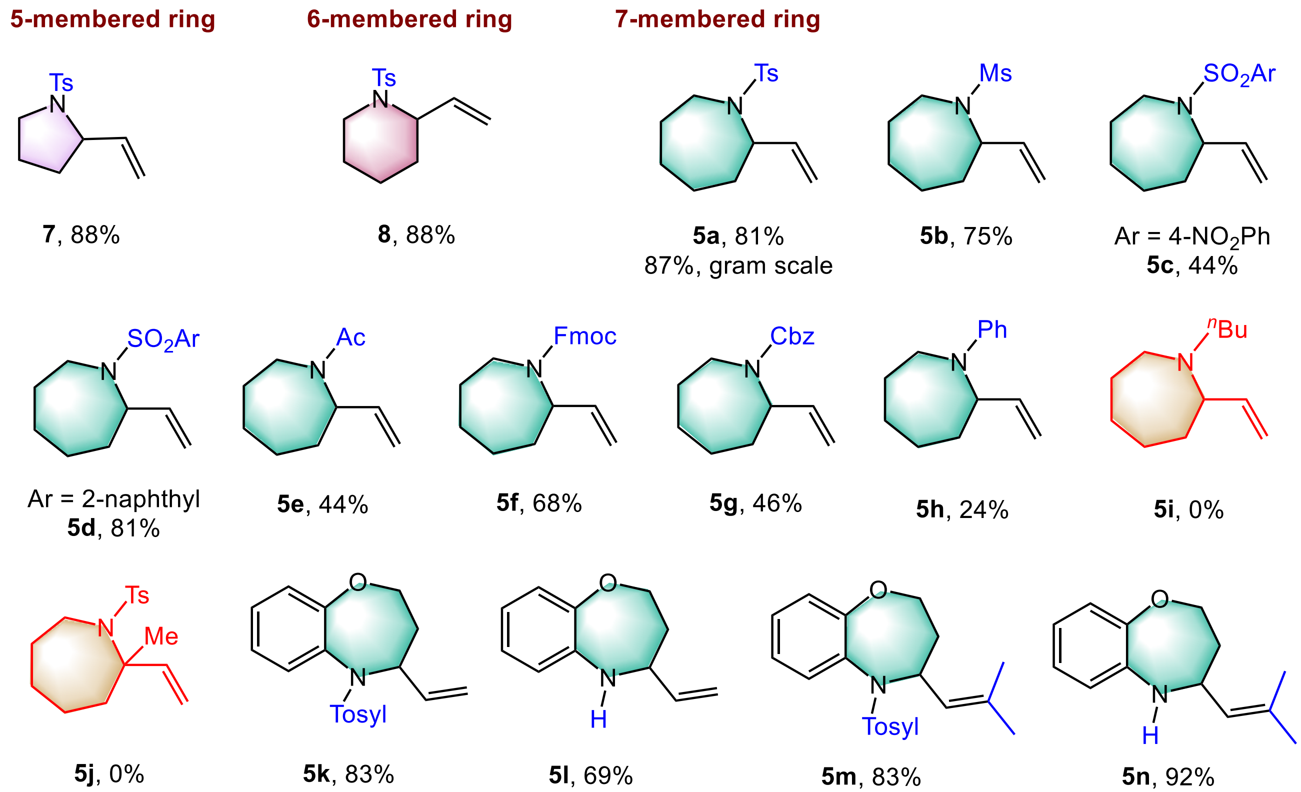
4 5a

Entry[a]	Cat. (mol%)	Temp (°C)	Acid (mol%)	Yield[b] (%)
1	5	80	0	0
2	5	80	15	16
3	5	80	30	61
4	5	80	45	90
5	5	50	45	62
6	5	23	45	24
7[c]	5	80	45	83
8	2.5	80	45	57
9	1	80	45	15
10	5	80	45 (TfOH)	0
11	5	80	45 (TsOH)	0
12	5	80	45 (AcOH)	0
13	0	80	45	0

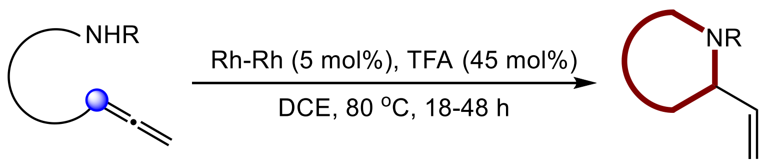
[a] Reaction run on a 0.2 mmol scale of **4** with 5 mol% Rh dimer **3** and 45% TFA in dichloroethane (DCE, 0.2 M) at 80 °C for 18 h unless otherwise noted. [b] Conversions determined by 1H NMR analysis of the crude reaction mixture. [c] Run in toluene.

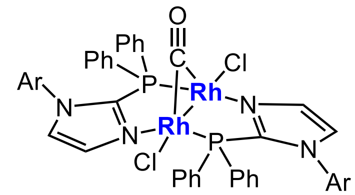
Scope of the medium-sized ring formation





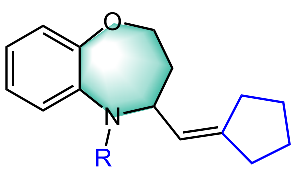
Scope of the medium-sized ring formation



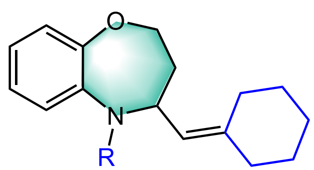


Ar = 2,6-diisopropylphenyl

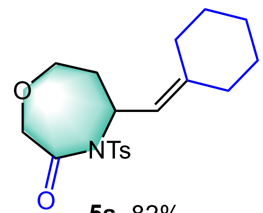
7-membered ring



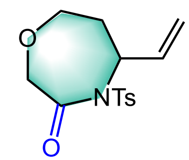
5o, R = Tosyl, 87%
5p, R = H, 93%



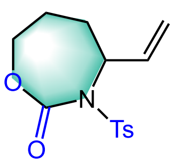
5q, R = Tosyl, 88%
5r, R = H, 69%



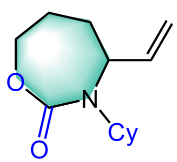
5s, 82%



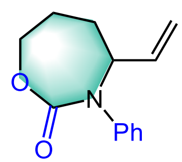
5t, 88%



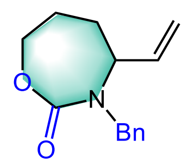
5u, 76%



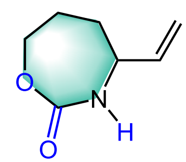
5v, 75%



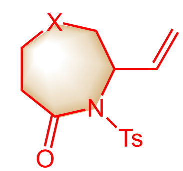
5w, 67%



5x, 35%

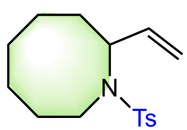


5y, 50%

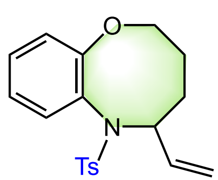


5z, 5aa, 0%
X = O, NTs

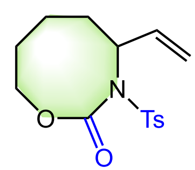
8-membered ring



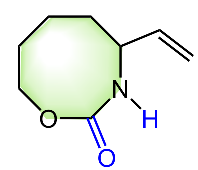
9a, 85%



9b, 95%

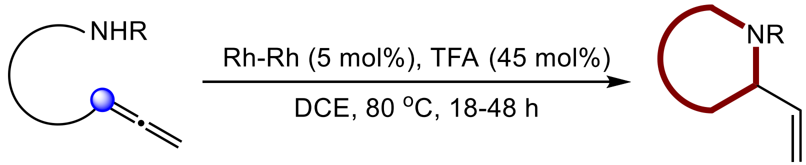


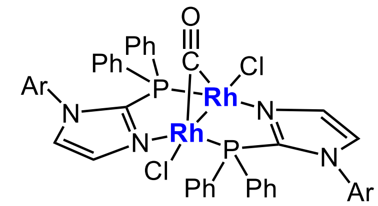
9c, 88%



9d, 95%

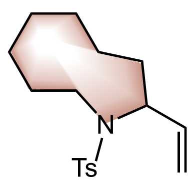
Scope of the medium-sized ring formation



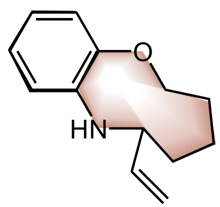


Ar = 2,6-diisopropylphenyl

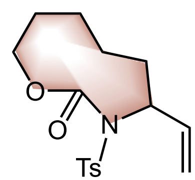
9-membered ring



10a, 79%

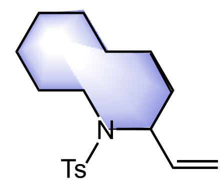


10b, 77%

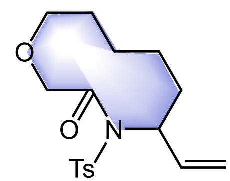


10c, 91%

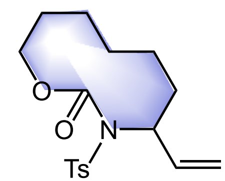
10-membered ring



11a, 60%

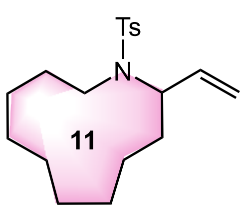


11b, 95%

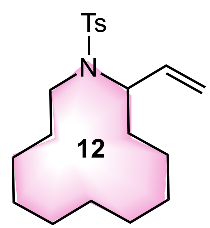


11c, 59%

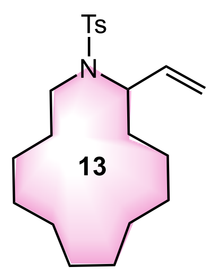
Macrocyclization



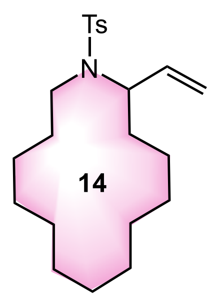
12a, 89%



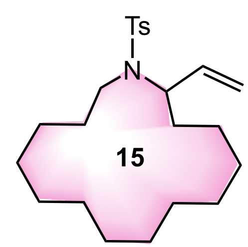
12b, 78%



12c, 87%

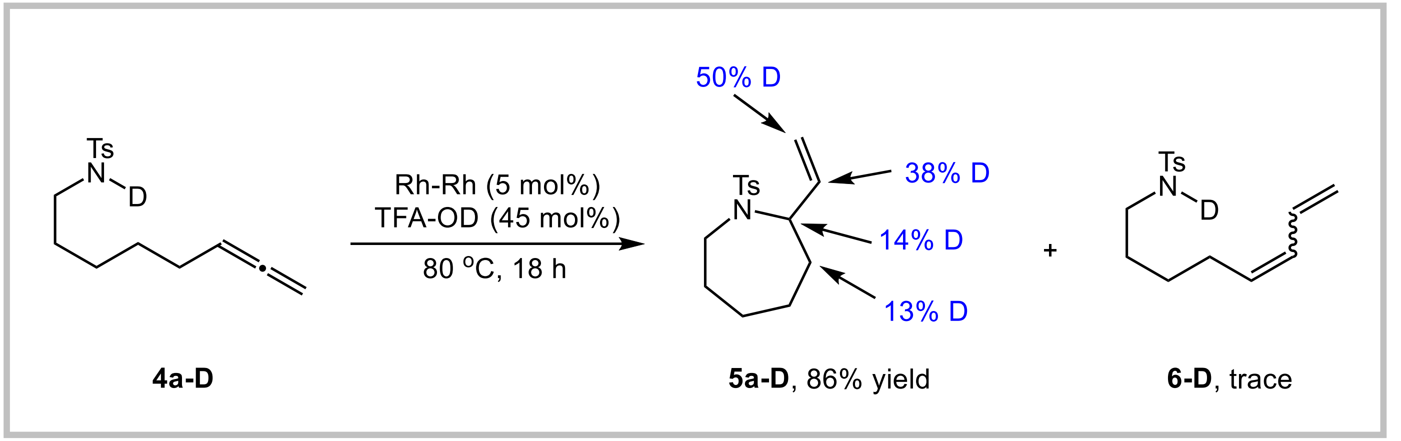


12d, 93%



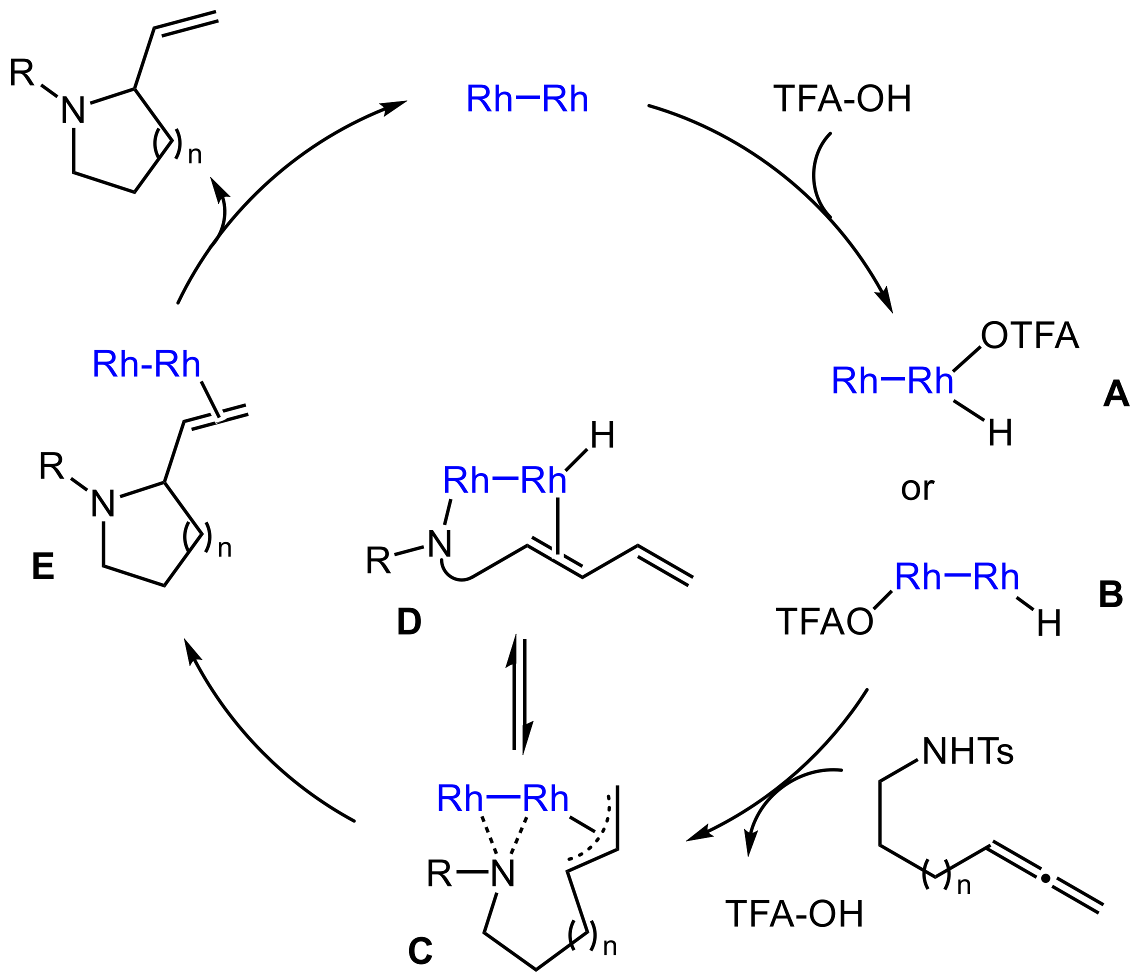
12e, 78%

Mechanistic studies

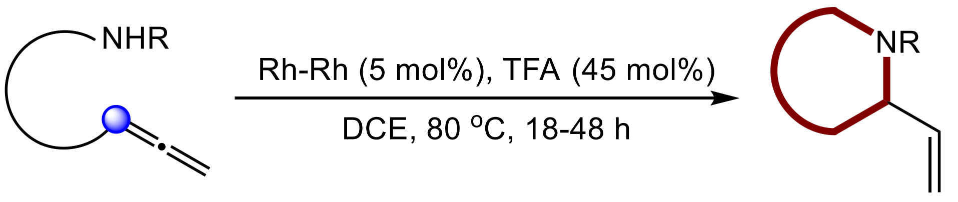


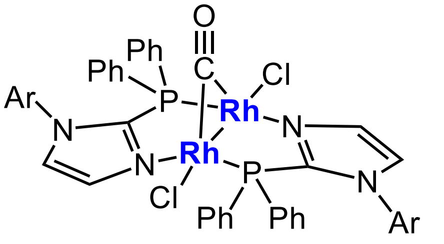
- ✓ Oxidative addition of the Rh to trifluoroacetic acid;
- ✓ Reversible insertion of the Rh-hydride into the allene to generate a metal allyl intermediate;
- ✓ 13% D: reversible formation of the diene may occur prior to C−N reductive elimination.

Proposed mechanism



Summary





Ar = 2,6-diisopropylphenyl

- The dirhodium(II) complex is catalytically active in allene hydro-amination reactions;
- The dirhodium(II) complex providing easy synthetic access to a variety of 7- to 15-membered ring heterocycles;
- Mechanistic experiments confirm the importance of the bimetallic catalyst and acid in the reaction.

The first paragraph

Writing strategy

过渡金属催化氮杂环合成方法

↓

形成中等环的难点

↓

许多药物和天然产物含有中等氮杂环
合成中等氮杂环是一个艰巨的挑战

The first paragraph

Nitrogen-containing heterocycles are among the most prevalent structural features in bioactive compounds, and transition-metal-catalyzed C−N bond-forming reactions represent one of the most efficient methods for their synthesis. Aminations of metal-allyl intermediates, oxidative aminations of alkenes, C−H aminations, and alkene or allene hydroamina-tions are some of the most widely used methods for metal-catalyzed nitrogen heterocycle synthesis. In general, metal-catalyzed cyclizations that proceed through C−N bond formation are highly efficient for forming 5- and 6-member rings, but examples of medium-ring formation (7- to 11-member rings) through these same mechanisms are quite rare.

The first paragraph

The difficulty in forming medium-sized rings arises because cyclization is inhibited by transannular interactions and bond/torsional strains. This creates a unique synthetic challenge because many important pharmaceuticals and bioactive natural products contain medium-sized-ring nitrogen heterocycles. With current technologies, access to medium-sized rings often involves multistep processes and/or ring expansion mechanisms.

The last paragraph

Writing strategy

总结本工作

↓

提出工作中的亮点

↓

对未来工作进行展望

The last paragraph

In conclusion, we have discovered a dirhodium(II) complex that is catalytically active in allene hydroamination reactions. Our catalyst is uniquely able to cyclize medium-sized-ring substrates where monometal-lic Rh catalysts failed, providing easy synthetic access to a variety of 7- to 15-member-ring heterocycles. Mechanistic experiments confirm the importance of the bimetallic catalyst and acid in the reaction, suggesting a metal-hydride insertion mechanism that is followed by C−N reductive elimination. Our ongoing mechanistic studies are focused on under-standing how the bimetallic nature of the catalyst enables highly efficient medium- and large-sized-ring formation.

Representative examples

The hydroamination of allenes is an attractive method for nitrogen heterocycle formation because the allene functional group is readily accessible from alkynes and reacts faster than the corresponding alkene substrates.(*adv.* 轻而易举地)

These results represent a rare example of macrocyclization *via* a hydroamination mechanism and highlight the synthetic utility of our bimetallic catalyst. (*v.* 突出，强调)

We hypothesize that the bimetallic structure of 3 may be the key factor in enabling cyclization. (假设…是关键因素)

Thanks

for your attention