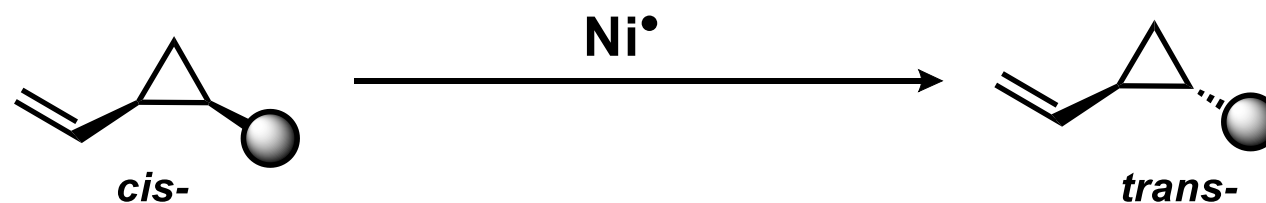


Dynamic Stereomutation of Vinylcyclopropanes with Metalloradicals

Nature 631, 80–86 (2024)

Franziska Schoenebeck et al.

Institute of Organic Chemistry, RWTH Aachen University, Aachen, Germany.



Introduction



Prof. Franziska Schoenebeck

RWTH Aachen, Institute of Organic Chemistry

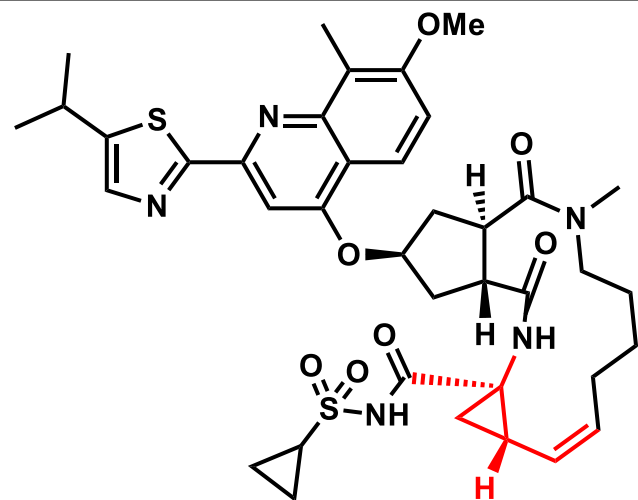
Educations:

- 2001-2004, **Technical University Berlin, Germany and University of Strathclyde, Glasgow, UK**, Undergraduate Studies in Chemistry
- 2004-2008, **WestCHEM Research School, Glasgow, UK**, PhD in the group of Prof. John A. Murphy
- **2008-2010, University of California, Los Angeles, USA**, Postdoc in the group of Prof. K. N. Houk

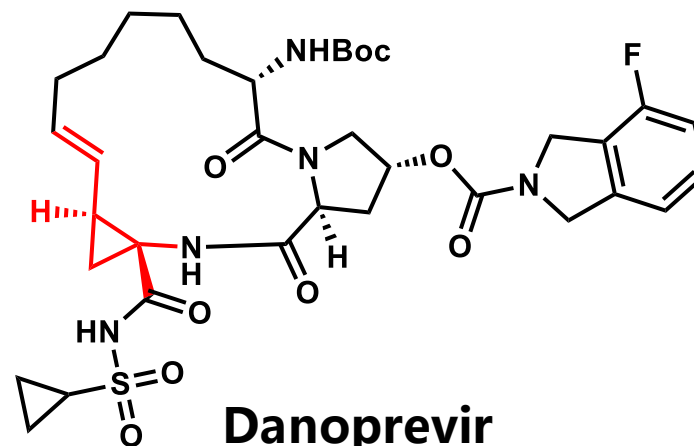
Appointments:

- **2010-2013, ETH Zürich, Switzerland**, Assistant Professor
- **2013-2016, RWTH Aachen University, Germany**, Professor
- **Since 07/2016, RWTH Aachen University, Germany**, Full Professor

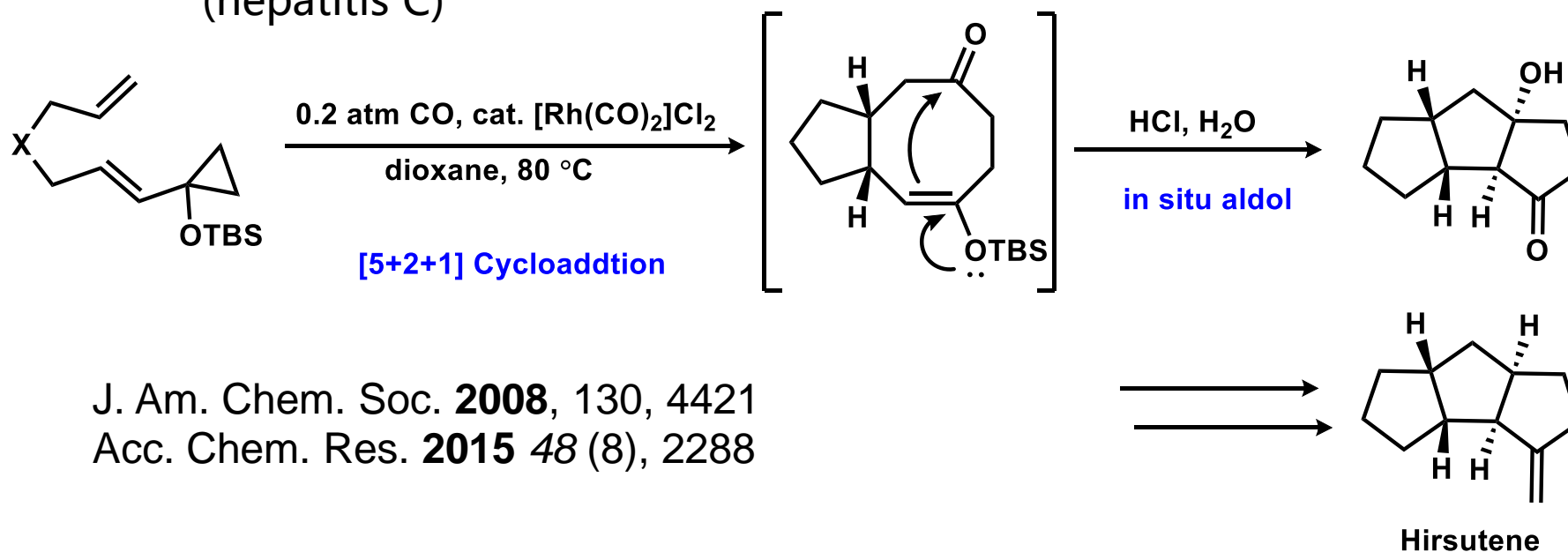
Vinylcyclopropanes



Simeprevir
(hepatitis C)



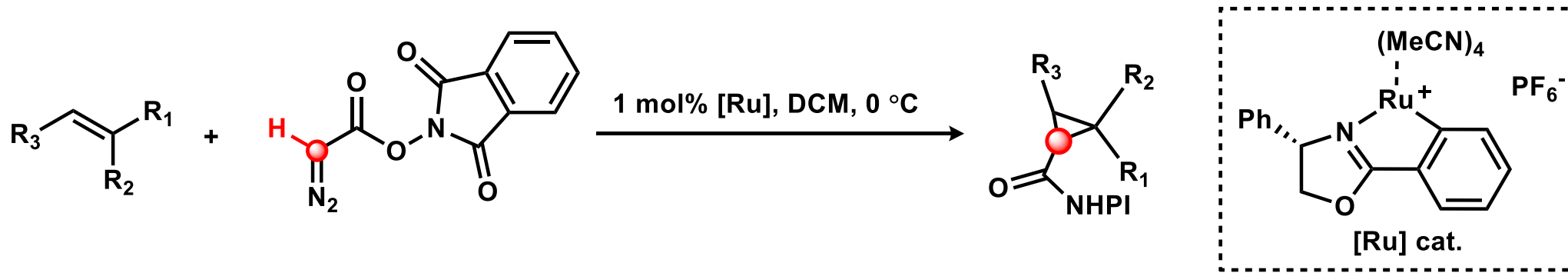
Danoprevir
(COVID-19)



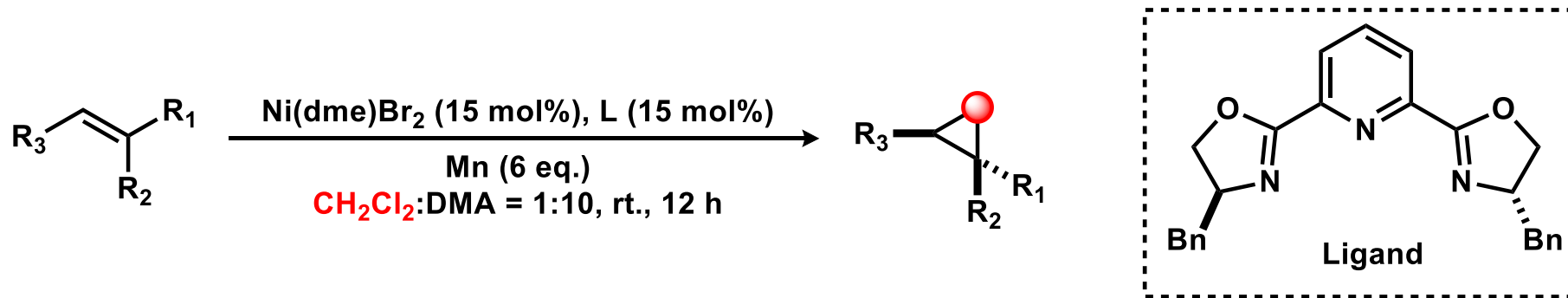
J. Am. Chem. Soc. **2008**, 130, 4421
Acc. Chem. Res. **2015** 48 (8), 2288

Asymmetric Syntheses of cyclopropanes

Strategy 1: Carbene insertion



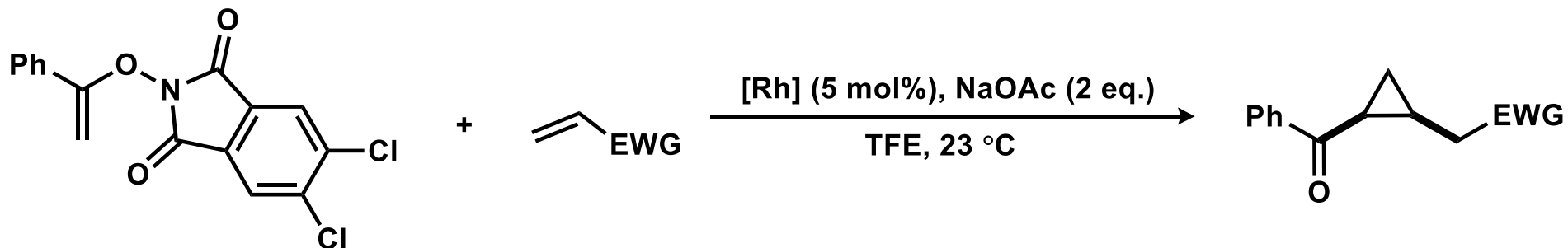
A. Mendoza, et al., *Angew. Chem. Int. Ed.*, **2019**, 58(18): 5930



C. Uyeda, et al., *Angew. Chem. Int. Ed.*, **2023**, 135(42): e202308913.

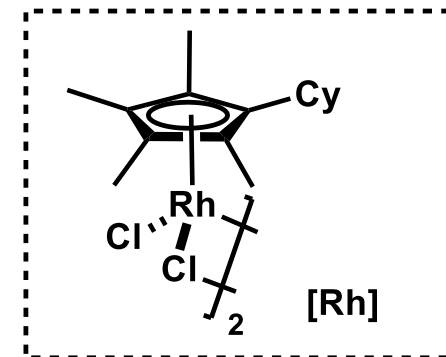
Asymmetric Syntheses of cyclopropanes

Strategy 2: C-Rh migratory insertion

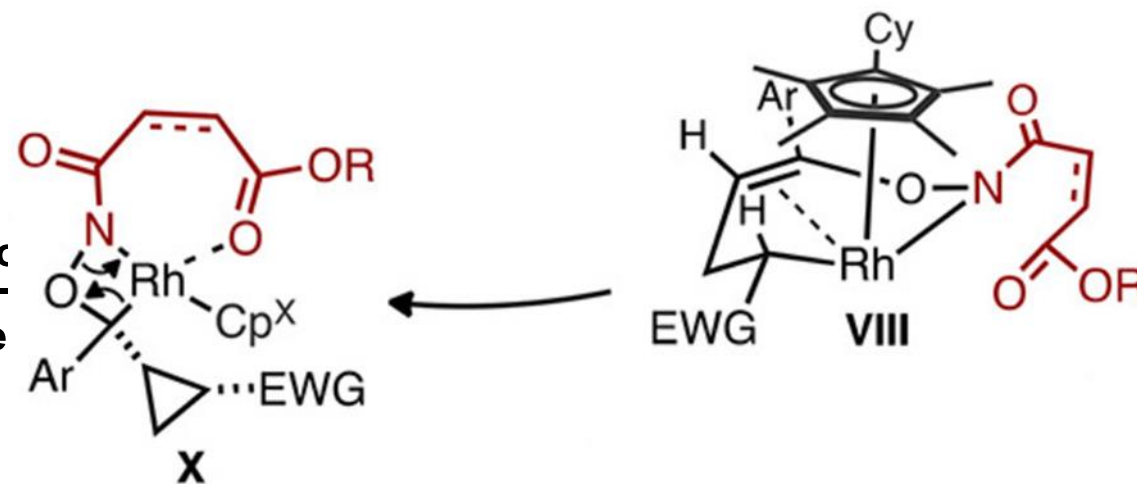
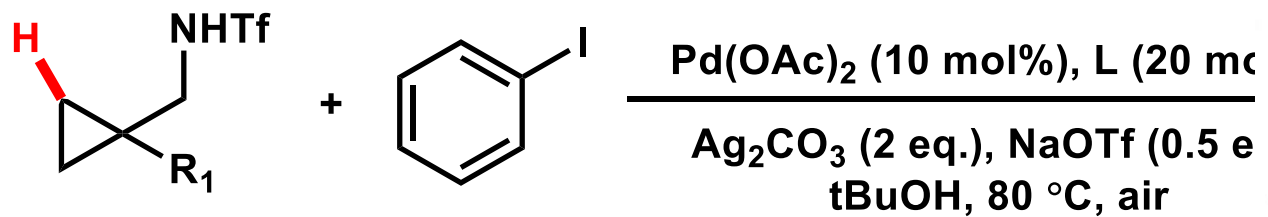


T. Rovis, et al., J. Am. Chem. Soc., **2018**, 140, 30, 9587

cis- selective



Strategy 3: C-H activation on cyclopropane

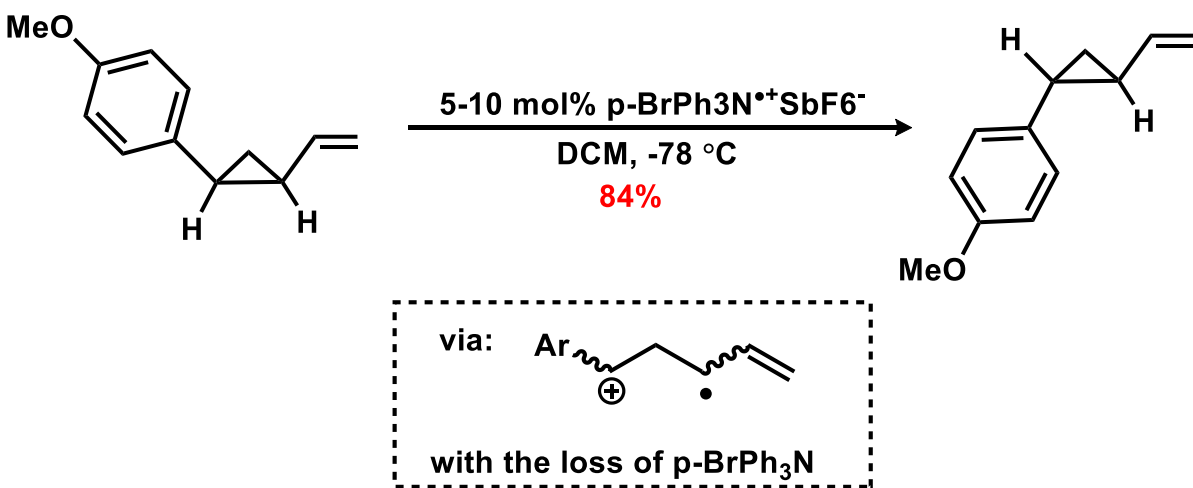


JQ. Yu, et al., J. Am. Chem. Soc., **2015**, 137, 5, 2042

Chem. Rev., **2018**, 118, 18, 8415

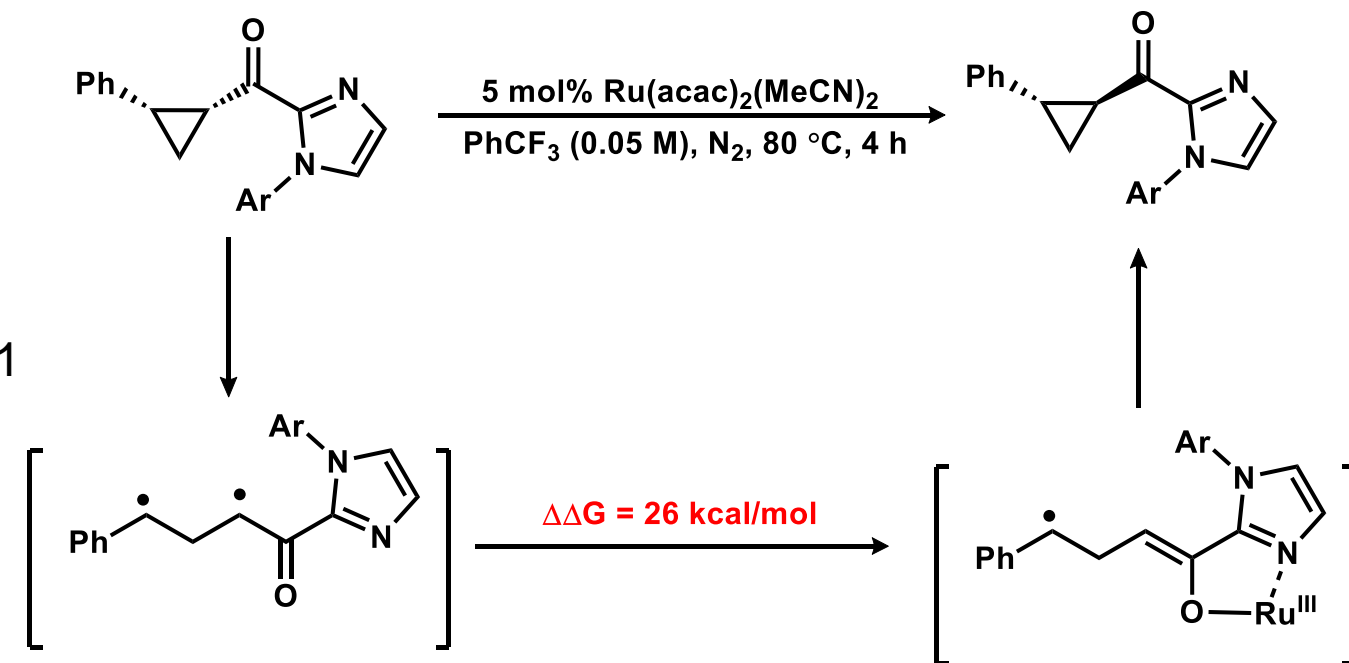
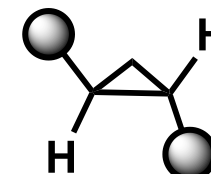
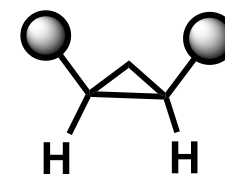
Isomerization of Vinylcyclopropanes

A complementary strategy would be the unselective (and potentially enantiopure) synthesis of *cis/trans* mixtures of vinylcyclopropane derivatives, followed by their isomerization towards a single isomer.



M. Schmittel, et al., J. Am. Chem. Soc., **1987**, 109, 1561

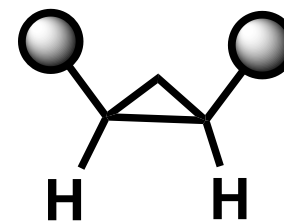
- Loss of enantiopurity
- Low yield
- Limited scope



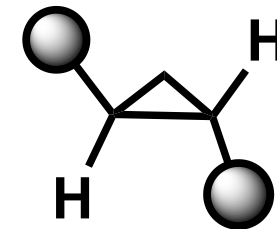
R. Knowles, et al., J. Am. Chem. Soc., **2022**, 144, 34, 15488

Proposal for Vinylcyclopropanes Syntheses

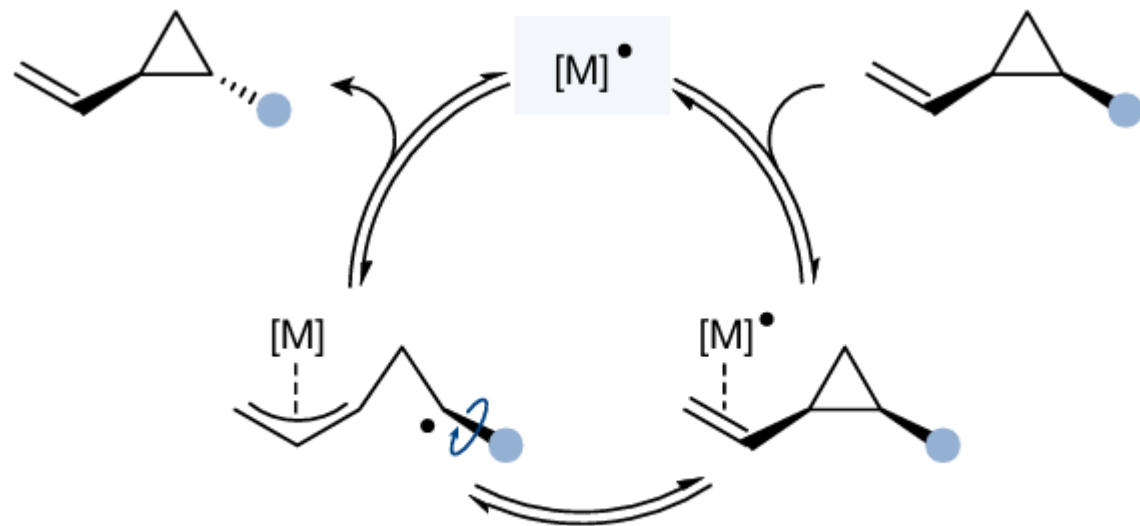
A complementary strategy would be the unselective (and potentially enantiopure) synthesis of *cis/trans* mixtures of vinylcyclopropane derivatives, followed by their isomerization towards a single isomer.



cis-

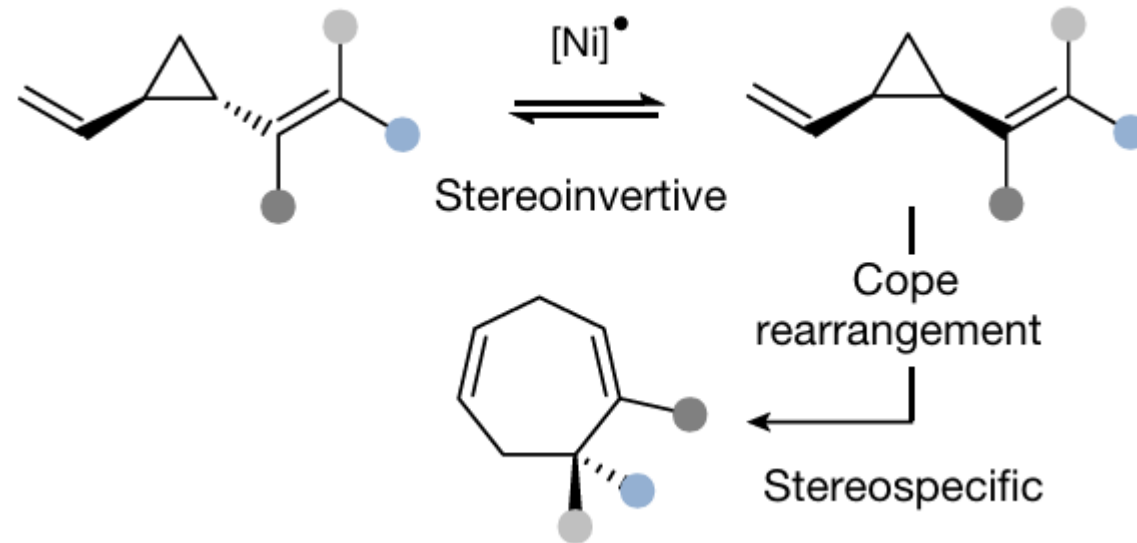


trans-



■ Stereoinvertive and reversible

cis- to trans- isomerization



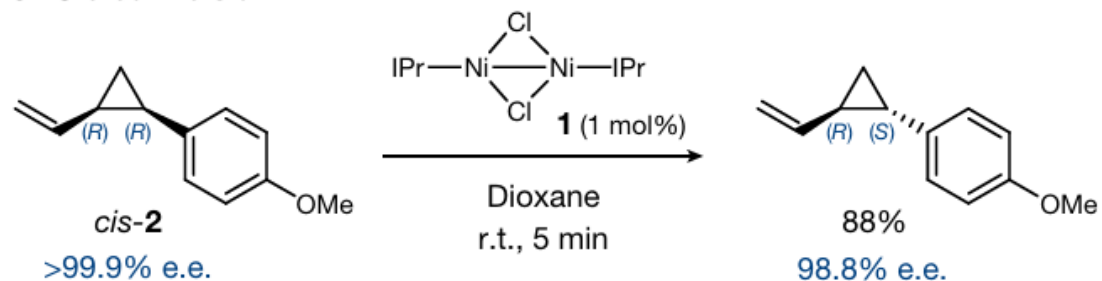
trans- to cis- isomerization

Initial Research

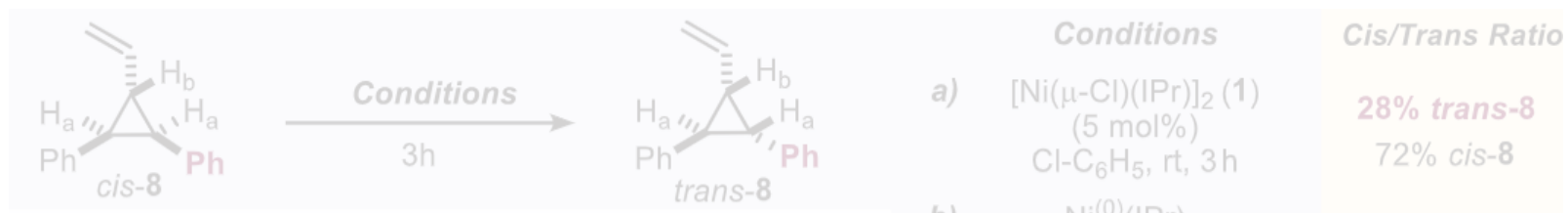
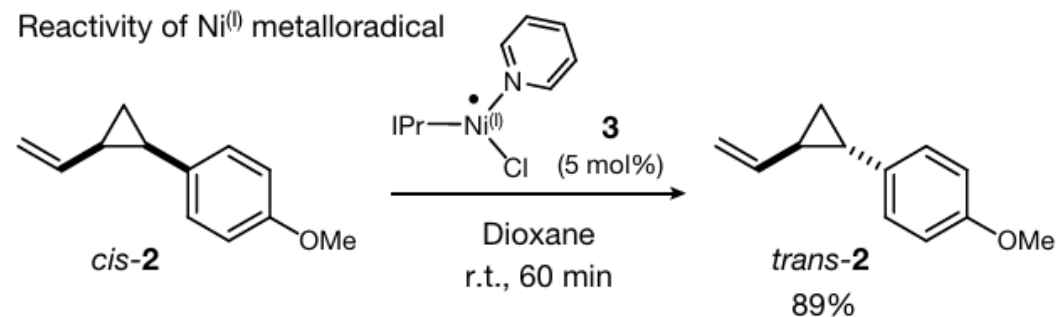
F. Schoenebeck, et al., Science, 2019, 363(6425), 391



a Stereoinversion

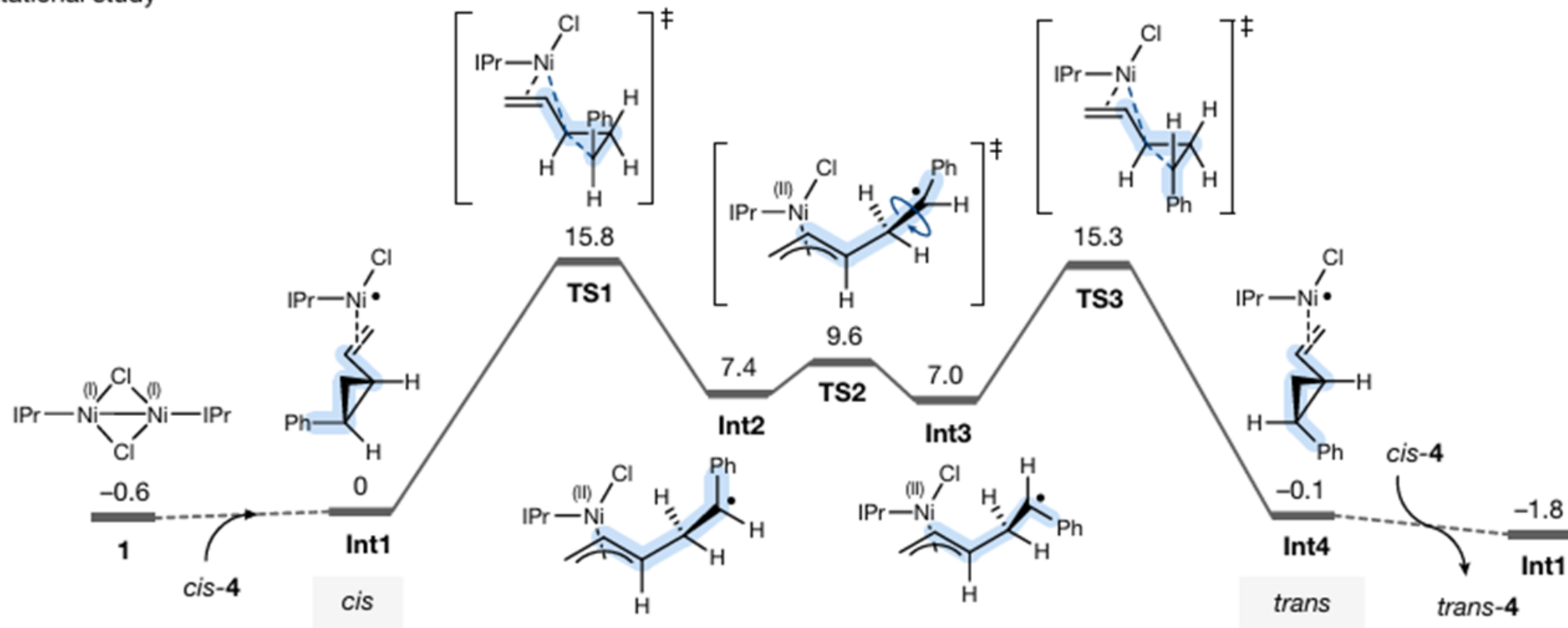


b Reactivity of Ni⁰ metalloradical



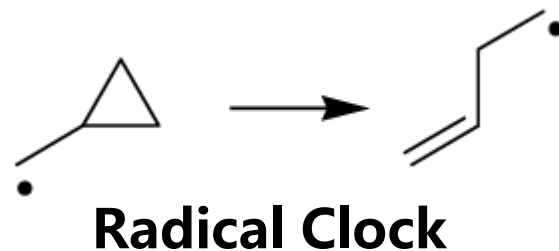
DFT Calculations

• Computational study



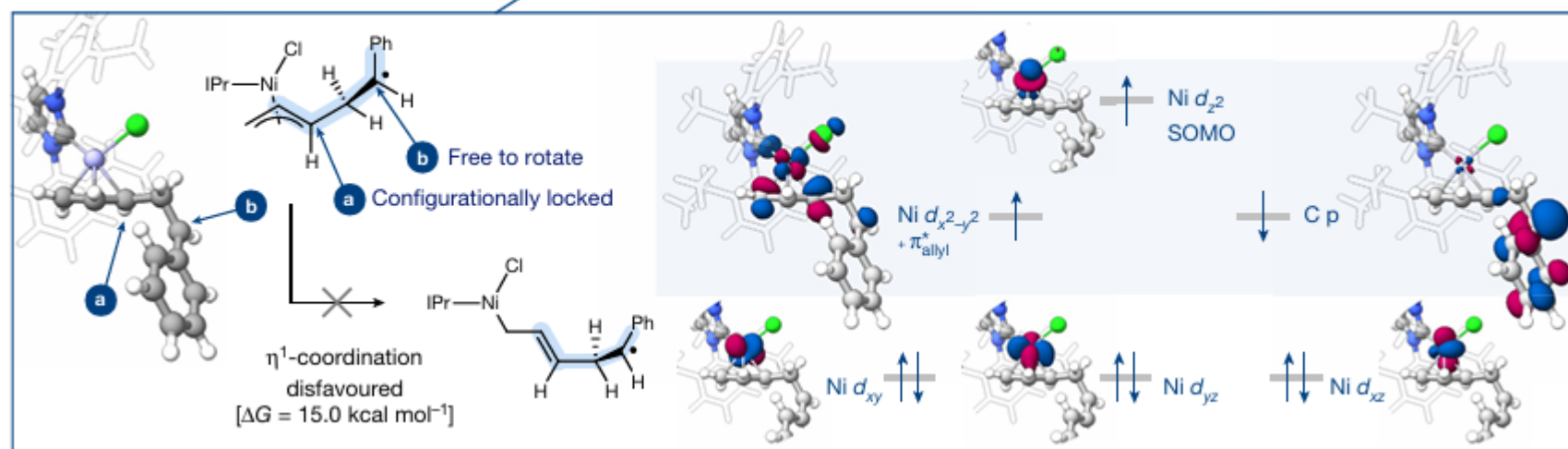
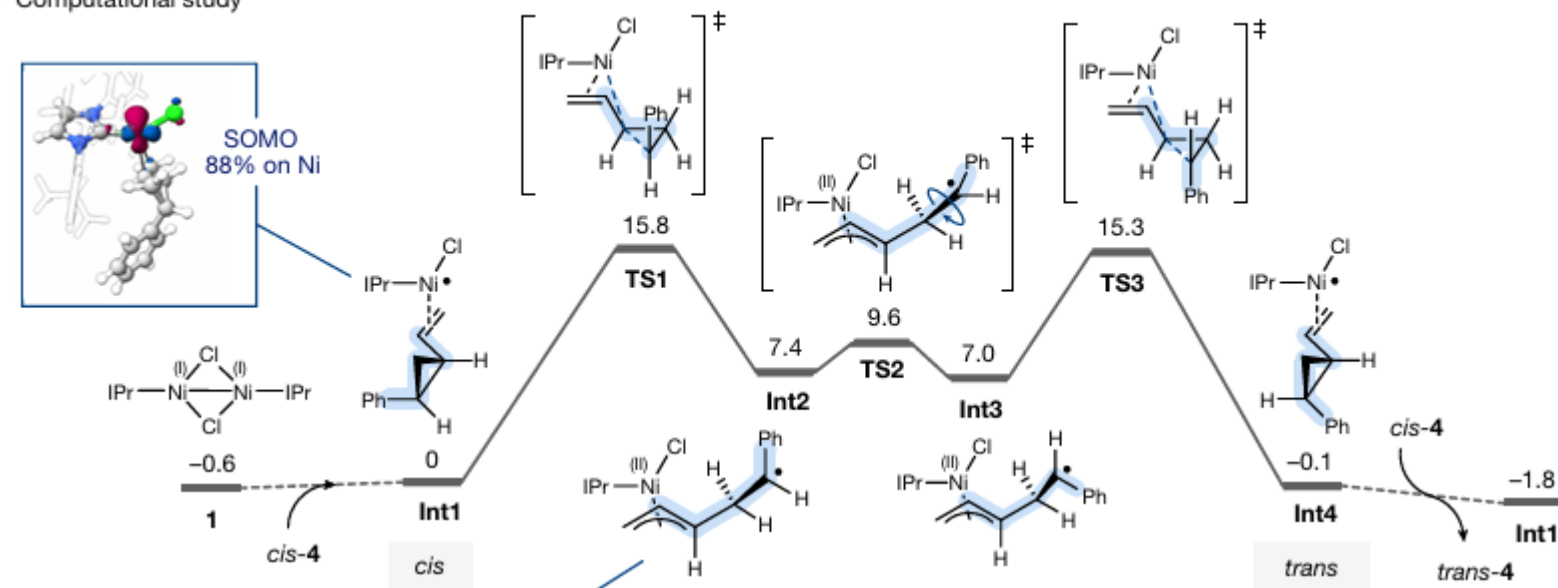
Two questions:

- Why preserves high enantiopurity?
- Why no radical clock reaction?



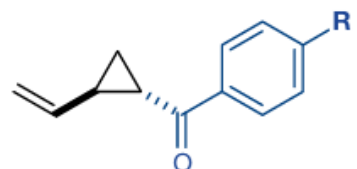
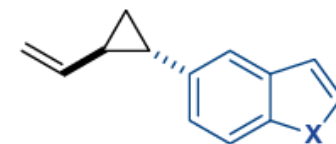
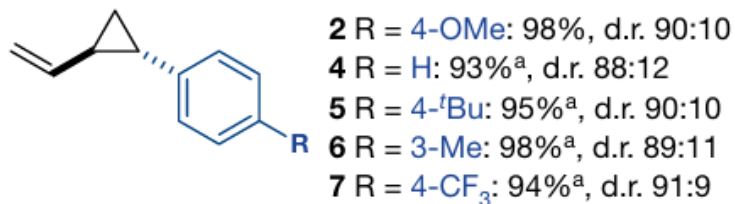
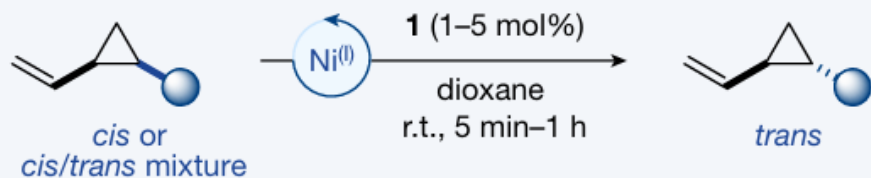
DFT Calculations

c Computational study

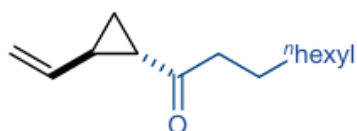


Reaction Scope

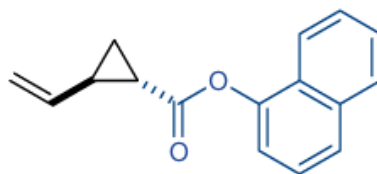
a Scope of vinyl cyclopropanes (single isomerization)



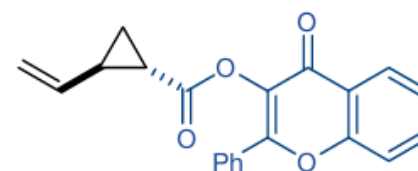
10 R = OH: 90%, d.r. 90:10
11 R = NH₂: 91%, d.r. 93:7



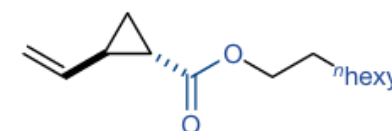
12 96%, d.r. 91:9



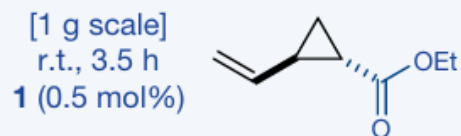
13 96%, d.r. 91:9



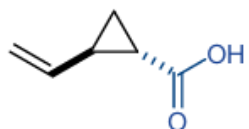
14 96%, d.r. 92:8



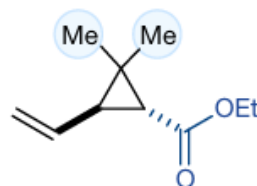
15 94%, d.r. 91:9



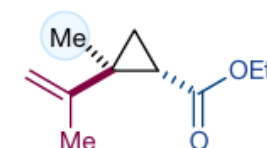
16 93%^b, d.r. 92:8



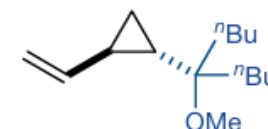
17 94%, d.r. 75:25



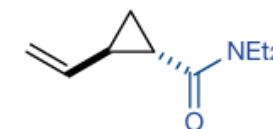
18 96%^c, d.r. 92:8



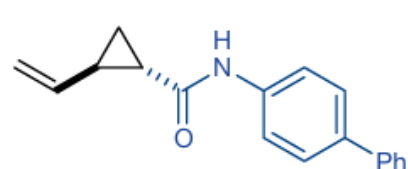
19 95%^d, d.r. 73:27



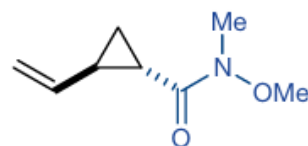
20 96%, d.r. 99:1



21 93%^e, d.r. 90:10



22 96%, d.r. 93:7



23 97%, d.r. 91:9



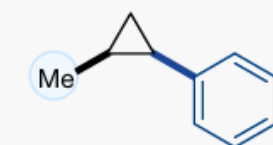
24 96%^d, d.r. 90:10



25 95%^e, d.r. 88:12



26 82%^e, d.r. 79:21



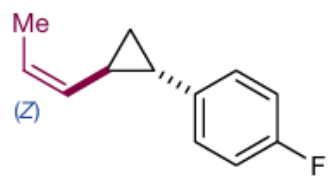
27 No isomerization

Reaction Scope

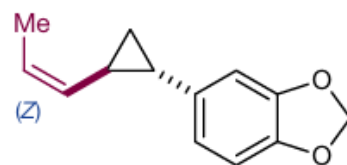
b Scope of alkenyl cyclopropanes



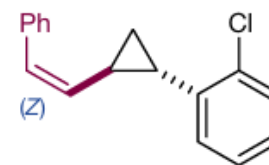
1 (5–10 mol%),
dioxane,
r.t.–60 °C, 2–48 h



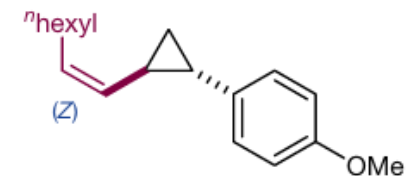
28 96%, d.r. 89:11



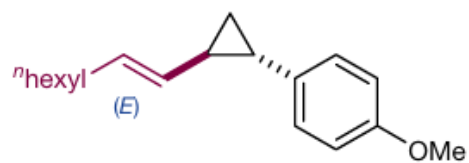
29 94%, d.r. 90:10



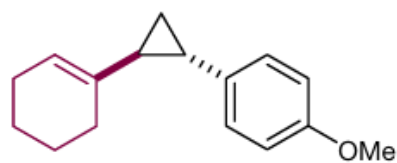
30 94%, d.r. 81:19



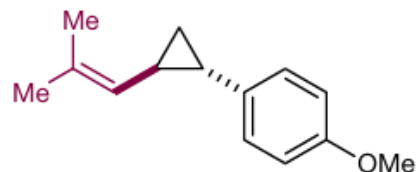
31 98%, d.r. 88:12



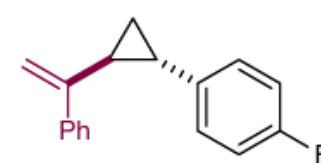
32 93%, d.r. 91:9



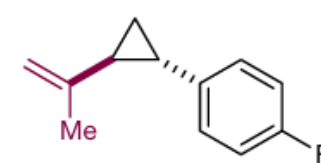
33 94%, d.r. 95:5



34 91%^e, d.r. 81:19



35 96%, d.r. 95:5

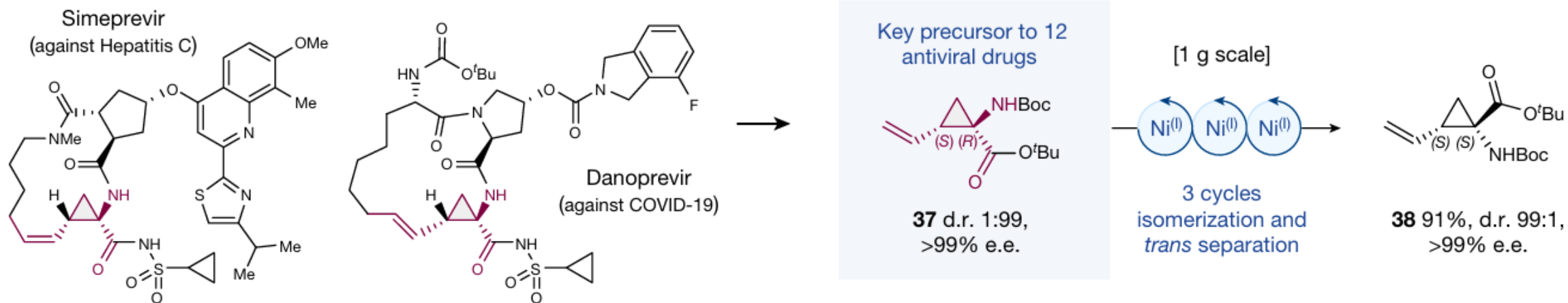
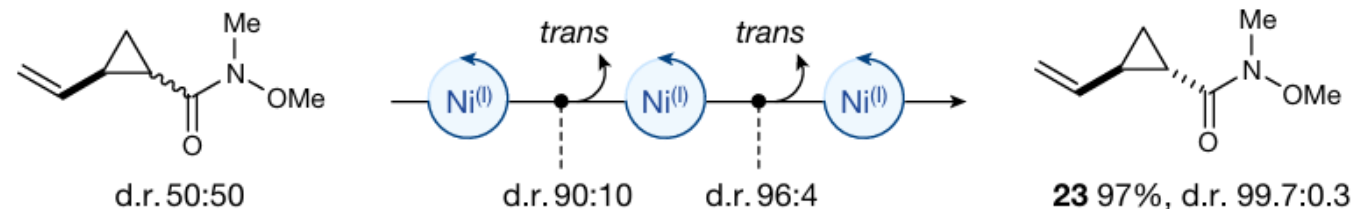


36 93%, d.r. 95:5

Reaction Application

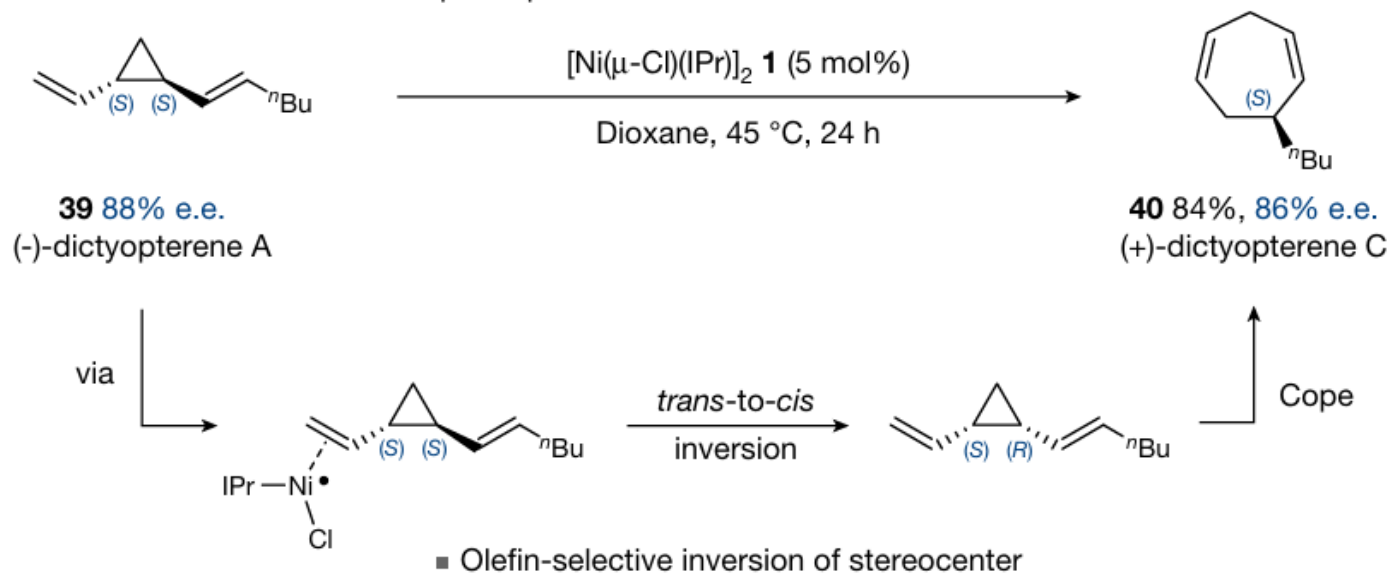
c Iterative thermodynamic resolution

- Multiple Ni⁰ isomerizations (and isomer separations)

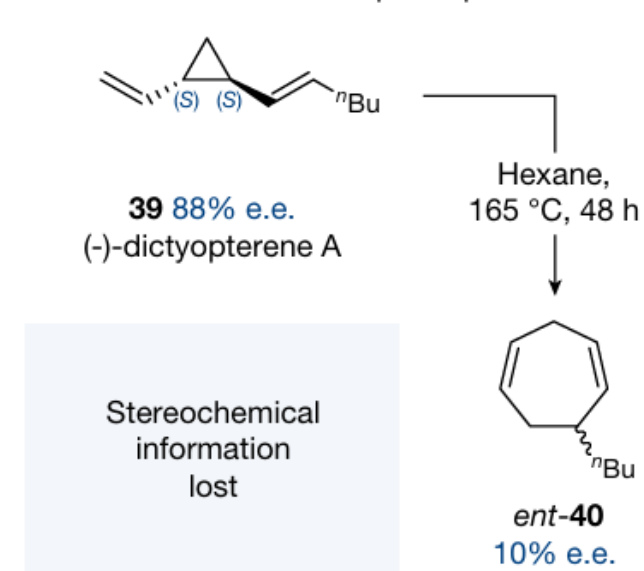


Trans- to Cis- Isomerization

a *Trans*-to-*cis* isomerization/Cope sequence without stereoerosion

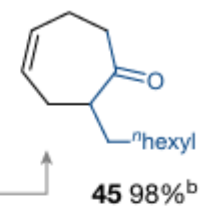
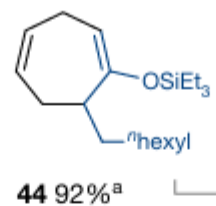
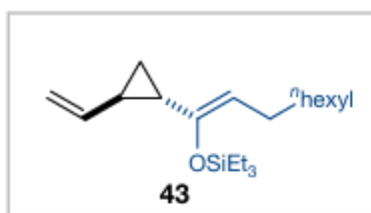
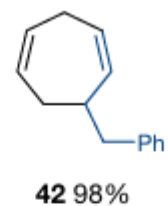
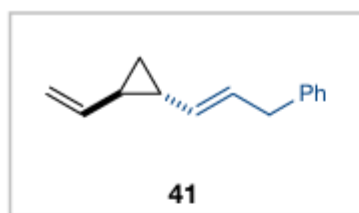


b Thermal isomerization/Cope sequence

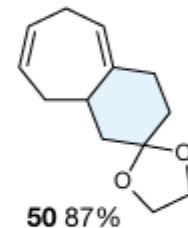
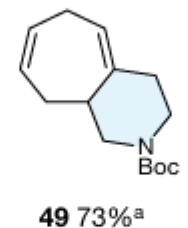
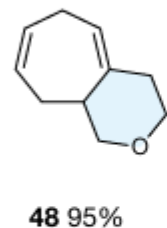
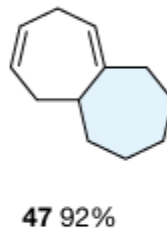
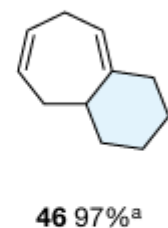
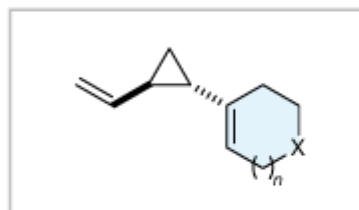


Trans- to Cis- Isomerization

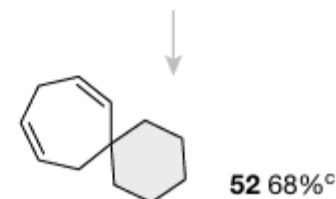
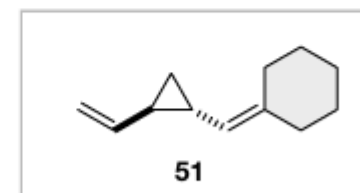
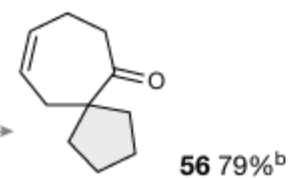
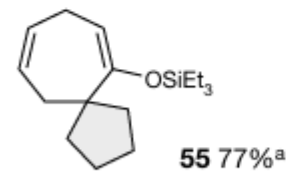
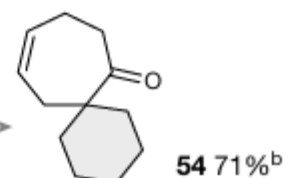
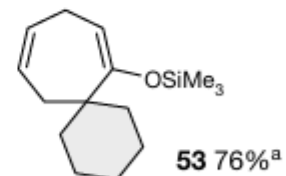
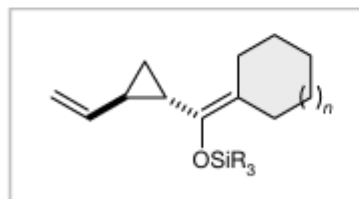
Additional examples



c Bicycles



d Spirocycles



Summary

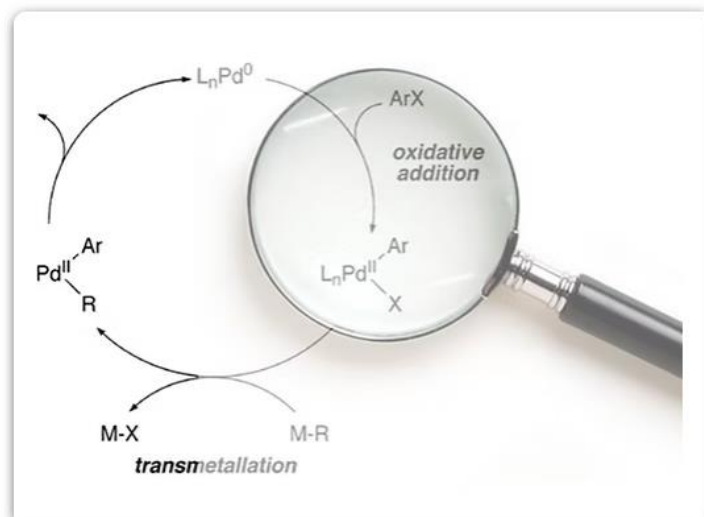
- **Efficient isomerization for vinylcyclopropanes**
- **Metalloradicals Vs. Organic free radicals (Radical clock)**
- **Tandem rearrangement (In total synthesis)**

Thank You

Introduction

Reactivities - Understanding & Predictions

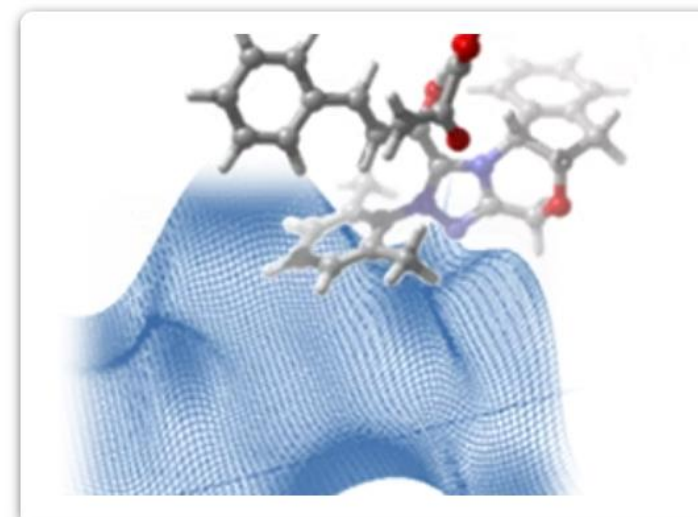
Our group is interested in studying the origins of chemical phenomena. To uncover these, we apply a variety of tools, ranging from experiments to computational chemistry. A major emphasis of the group's activities lies in the area of catalysis. Based on the fundamental mechanistic insights gained, novel catalysts and applications in organic chemistry are developed.



Mechanistic studies of metal catalysts-involved reactions

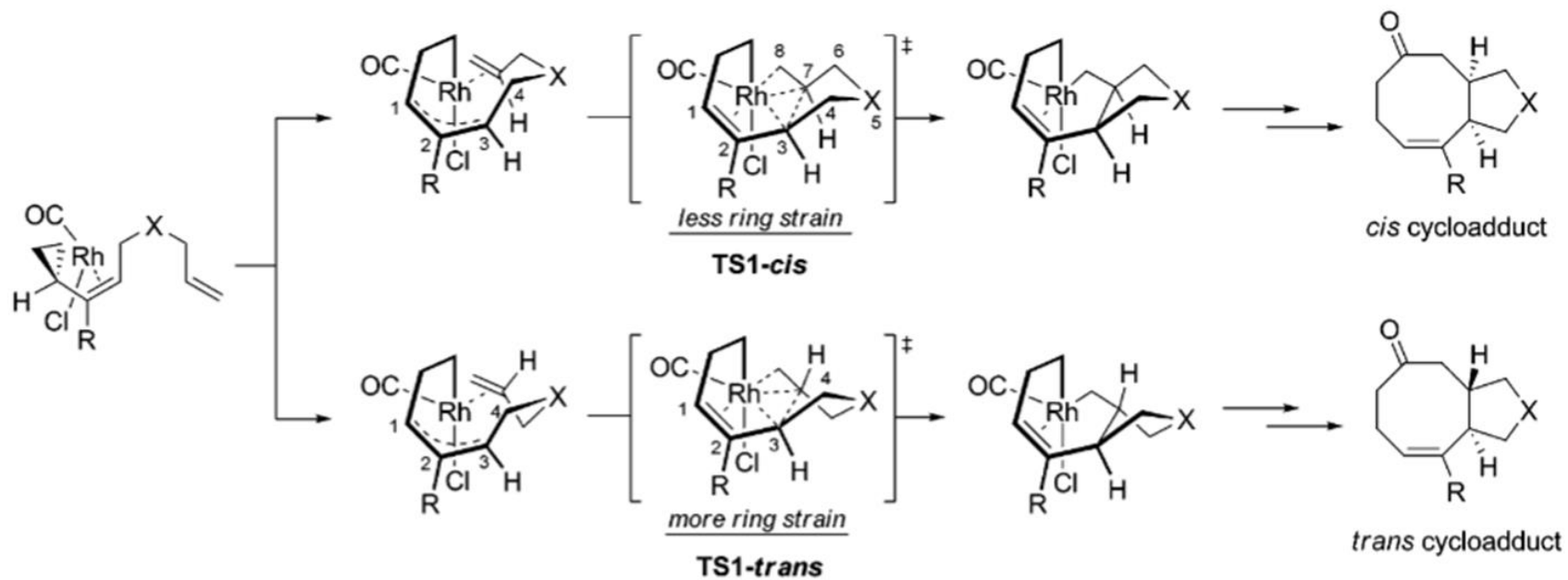


Discoveries of new reactions (organogermane reagents)



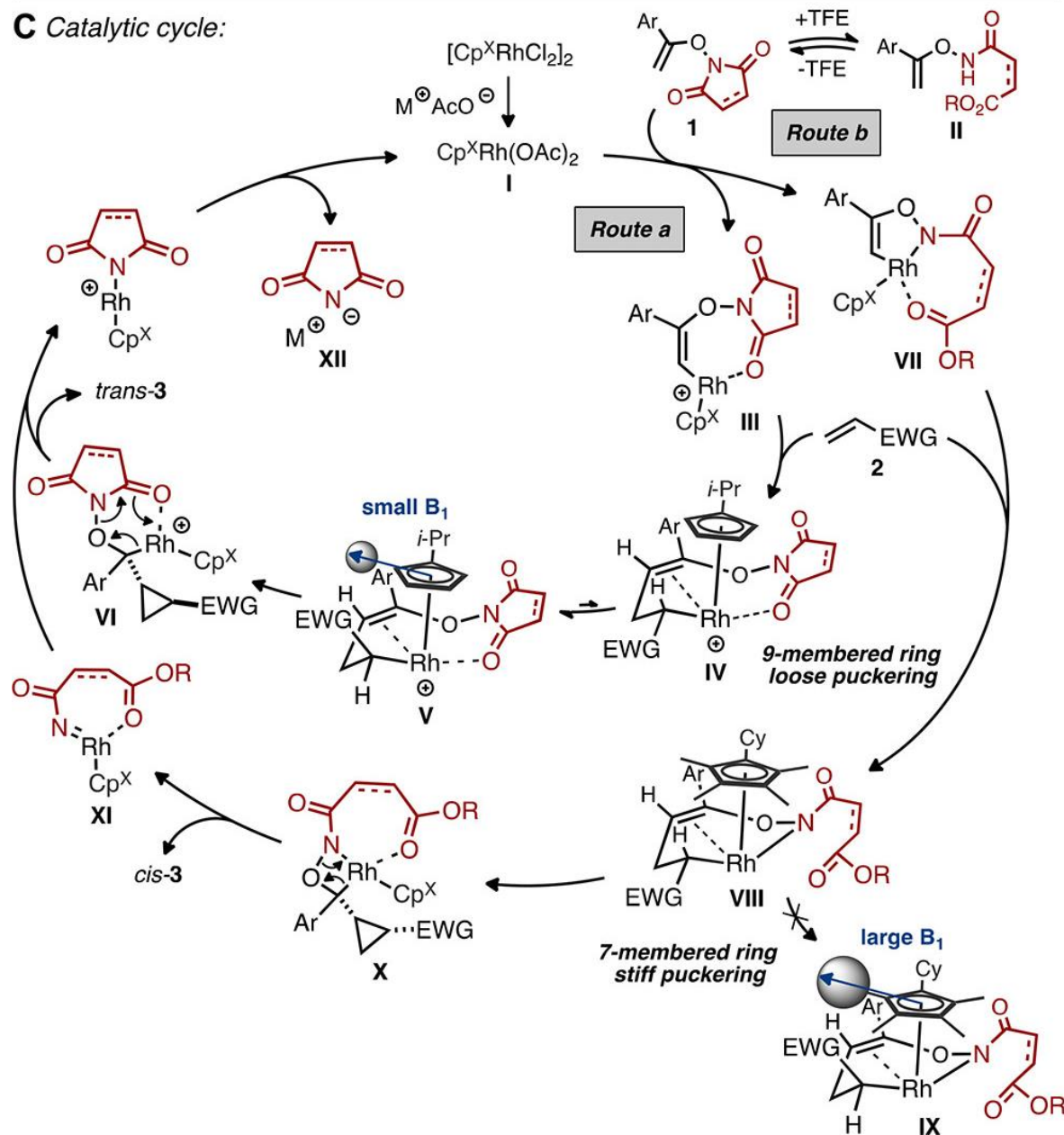
Computational reactivity studies

ZX Yu' s Work

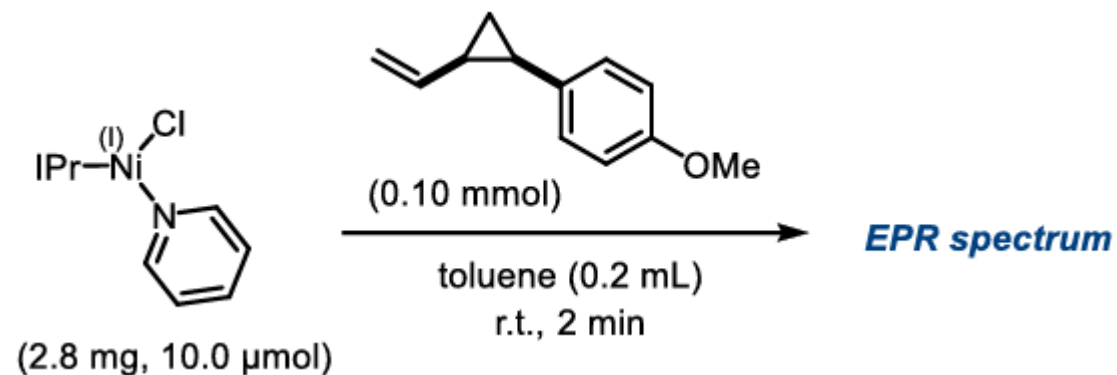
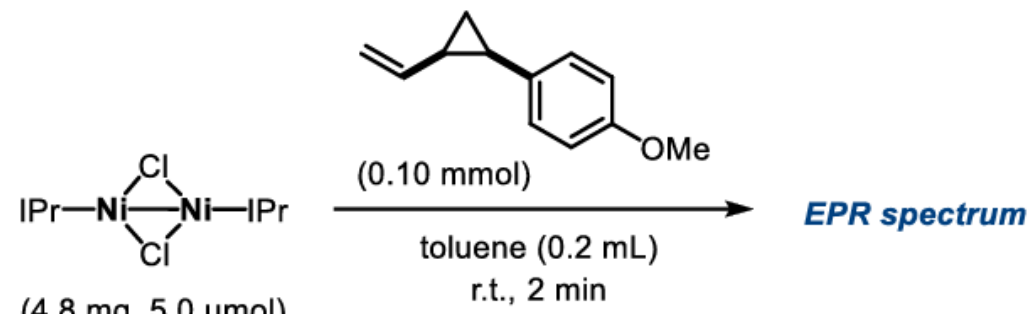
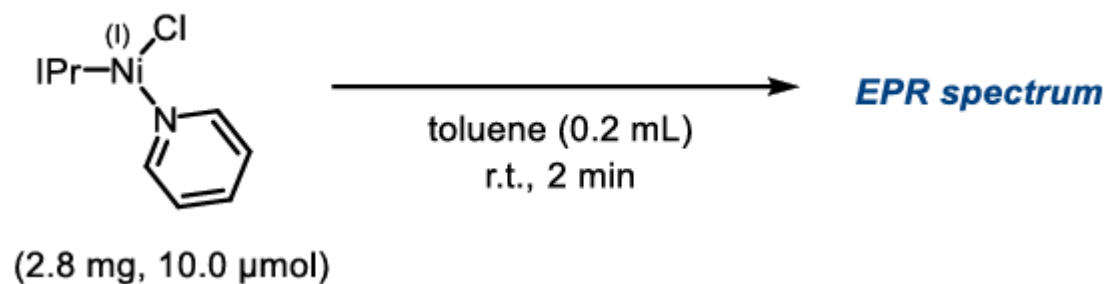
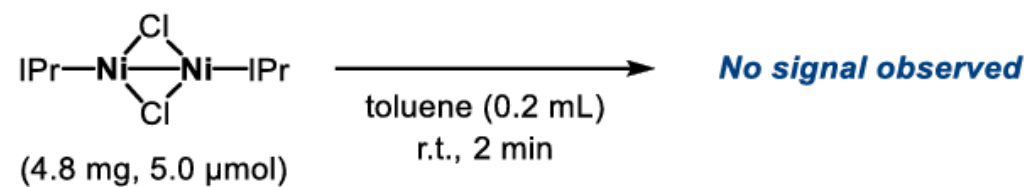


Rovis' Work

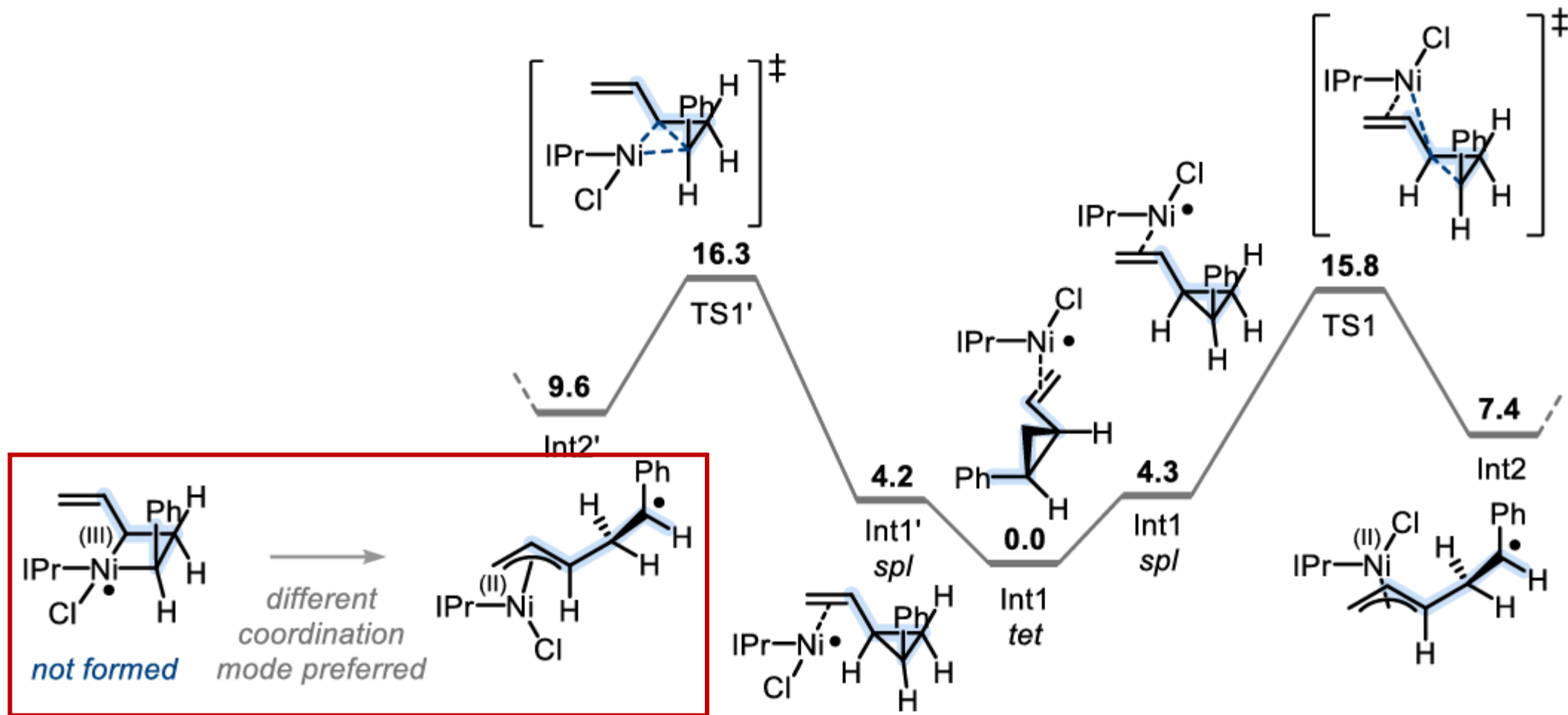
C Catalytic cycle:



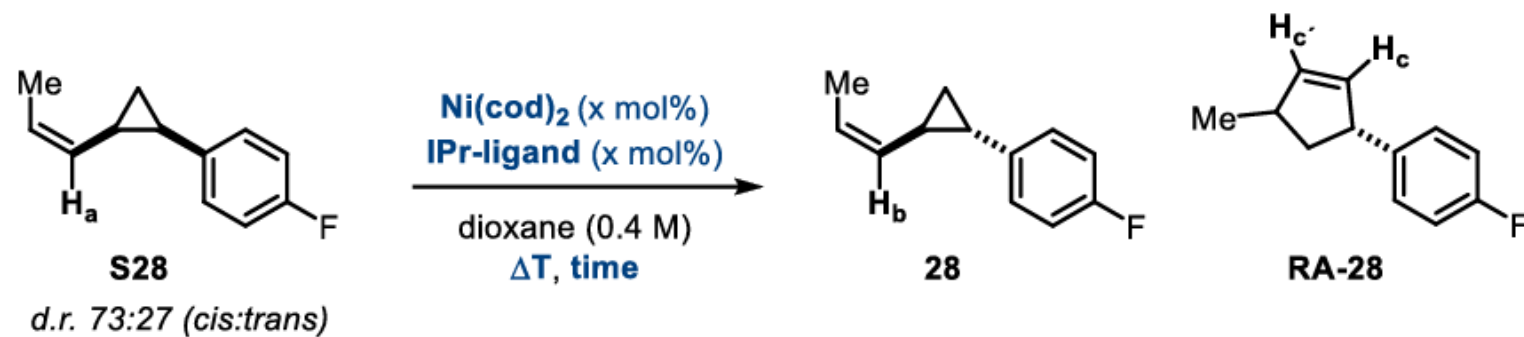
EPR Experiments



Ni(III) VS. Ni(II)



Ni(0) VS. Ni(I)



entry	catalyst	conditions	d.r. (<i>cis:trans</i>) ^a	yield (S28+28) ^b	yield RA-28 ^b
1	-	starting material S28	73:27	-	-
2	Ni(I) dimer 1 (5 mol%)	r.t., 2 h	11:89	96% ^c	-
3	Ni(cod) ₂ (5 mol%) IPr (5 mol%)	r.t., 2 h	72:28	96%	-
4	Ni(cod) ₂ (5 mol%) IPr (10 mol%)	r.t., 2 h	72:28	95%	4%
5	Ni(cod) ₂ (5 mol%) IPr (5 mol%)	60 °C, 24 h	21:79	38%	27%
6	Ni(cod) ₂ (5 mol%) IPr (10 mol%)	60 °C, 24 h	23:77	61%	11%
7	Ni(I) dimer 1 (5 mol%)	60 °C, 24 h	14:86	81%	-

a) Quantitative ¹H NMR ratio, E and Z diastereomers are neglected for clarity; b) quantitative ¹H NMR yield using ethylene carbonate as internal standard; c) isolated yield.

Ni(0) VS. Ni(I)

