Literature Report 4

Palladium(0) and Brønsted Acid Co-Catalyzed Enantioselective Hydro-Cyclization of 2,4-Dienyl Hydrazones and Oximes

Reporter: Sai-Nan Yin
Checker: Hao-Dong Chen
Date: 2024-12-30

Li, Y.-F.; Gui, W.-T.; Pi, F.; Chen, Z.; Zhu, L.; Ouyang, Q.; Du, W.; Chen, Y.-C.
Angew. Chem. Int. Ed. **2024**, *63*, e202407682

CV of Prof. Chen Ying-Chun (陈应春)

Education & Experience:

- **1990-1994** B.S., Nankai University
- **1994-1997** M.S., Sichuan University
- **1998-2001** Ph.D., Chengdu Institute of Organic Chemistry
- **2001-2003** Postdoc., Chengdu Institute of Organic Chemistry and University of Hong Kong
- **2003-Present** Professor, Sichuan University

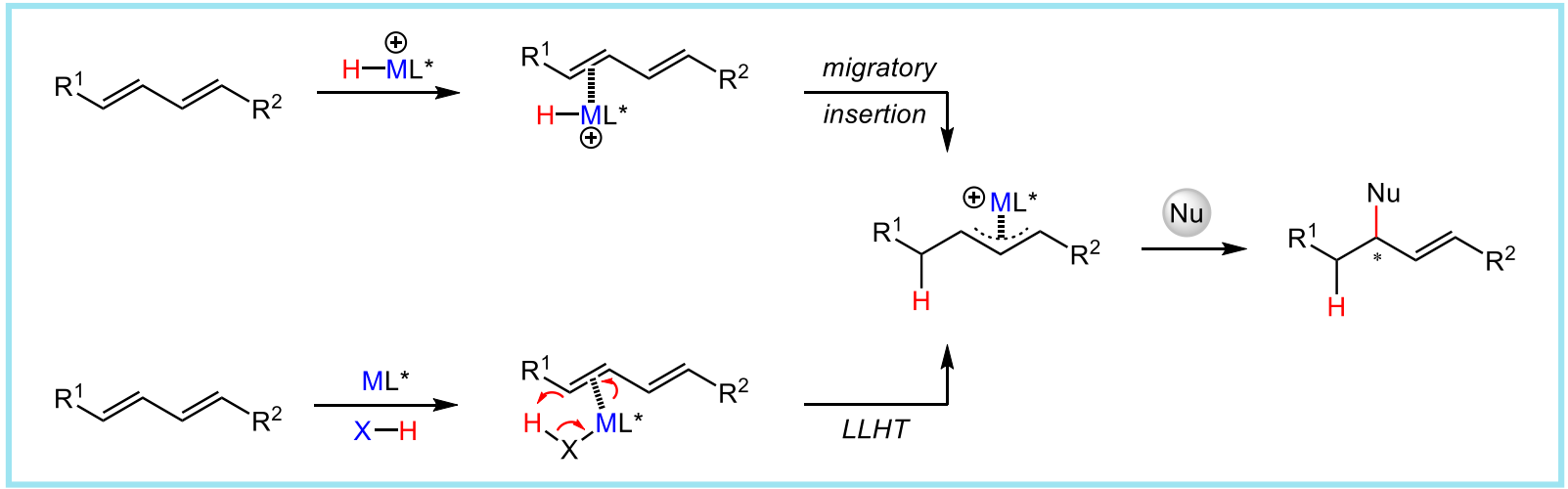
Research:

- **Design and Synthesis of New Chiral Catalysts**
- **Asymmetric Catalytic Reaction Research**
- **Design and Synthesis of Physiologically Active Substances**

Contents

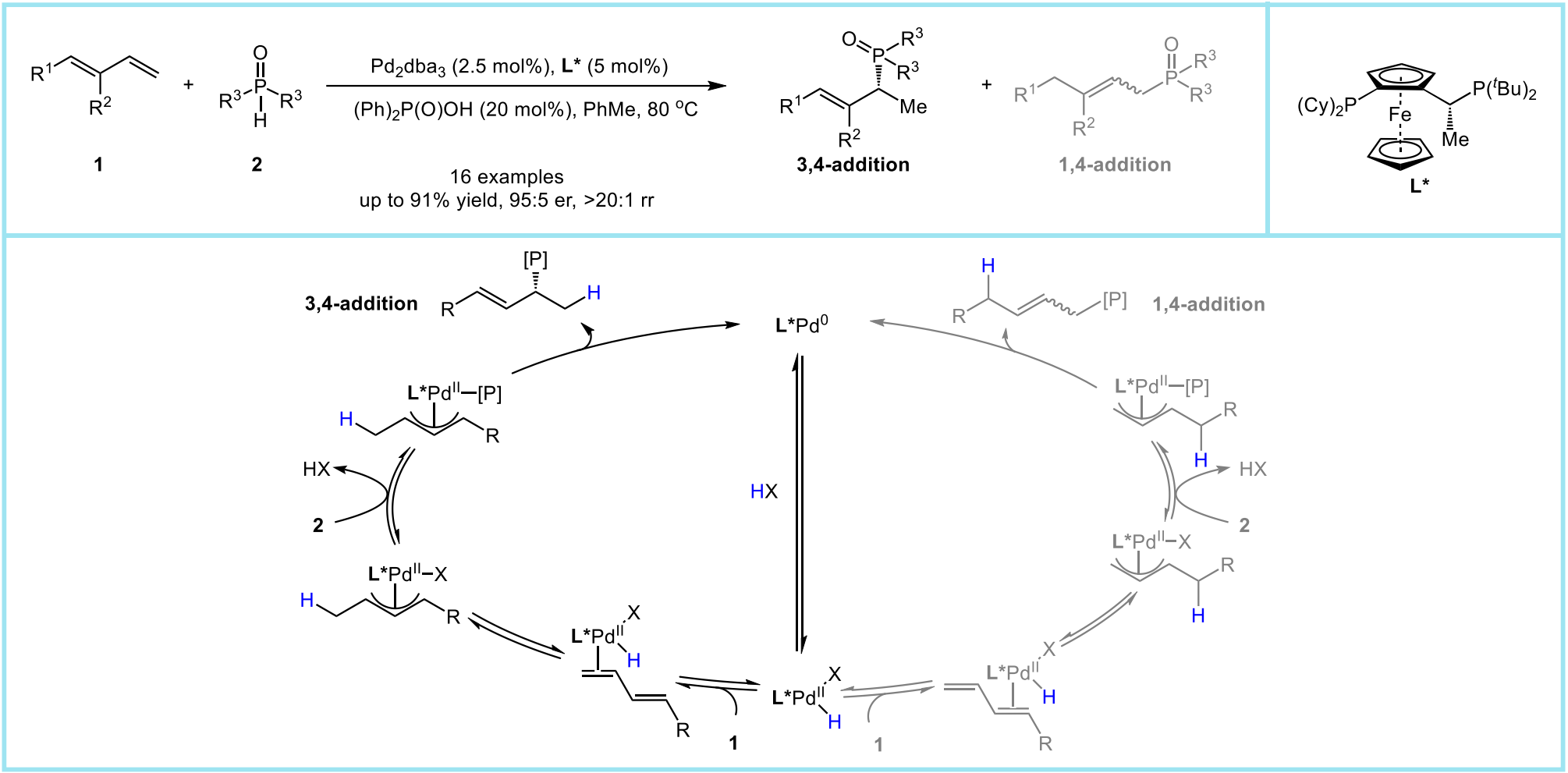
Introduction

Two Proposed Pathways of the Asymmetric Hydrofunctionalization of 1,3-Dienes



Introduction

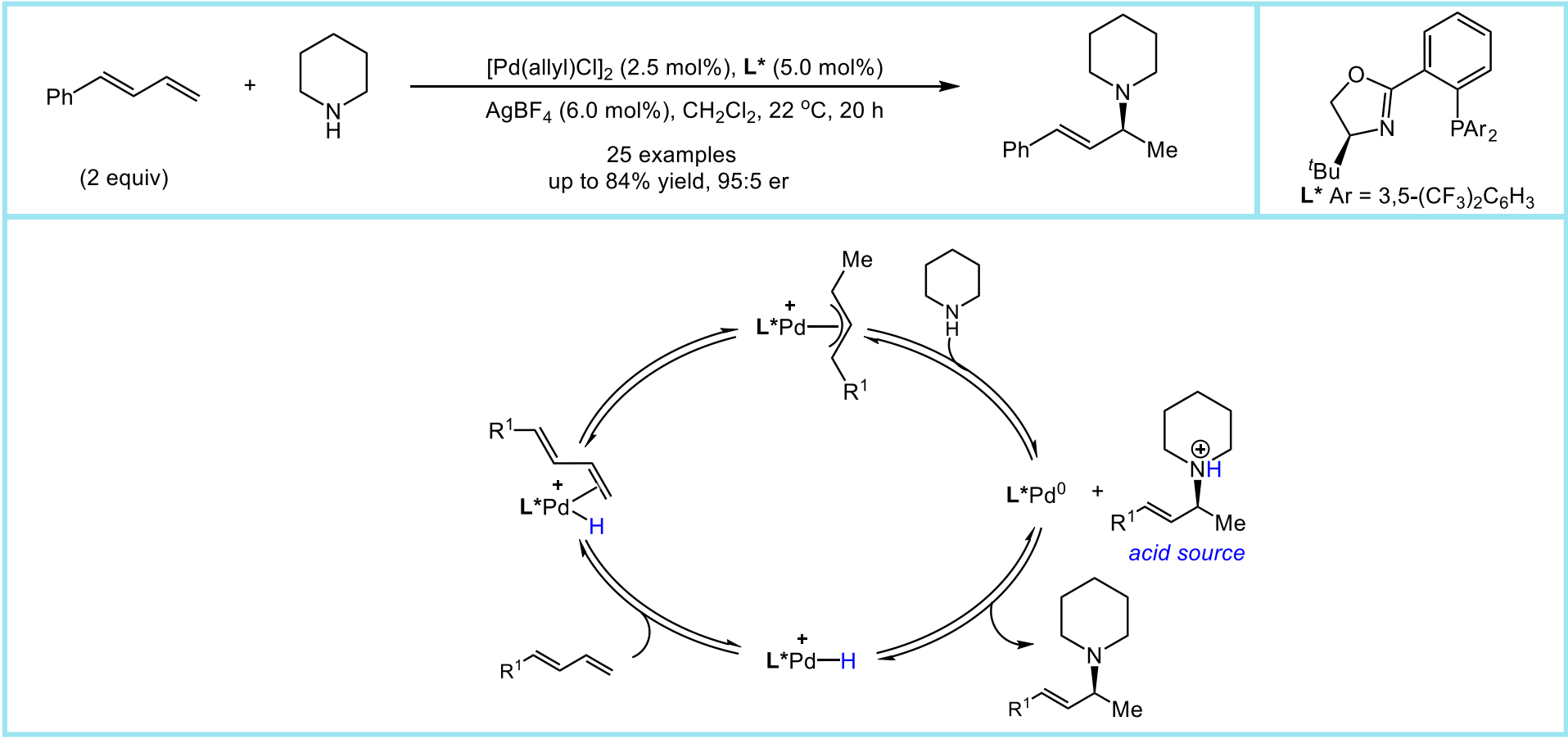
Asymmetric Hydrofunctionalization of 1,3-Dienes via Migratory Insertion



Nie, S.-Z.; Davison, R. T.; Dong, V. M. *J. Am. Chem. Soc*. **2018**, *140,* 16450

Introduction

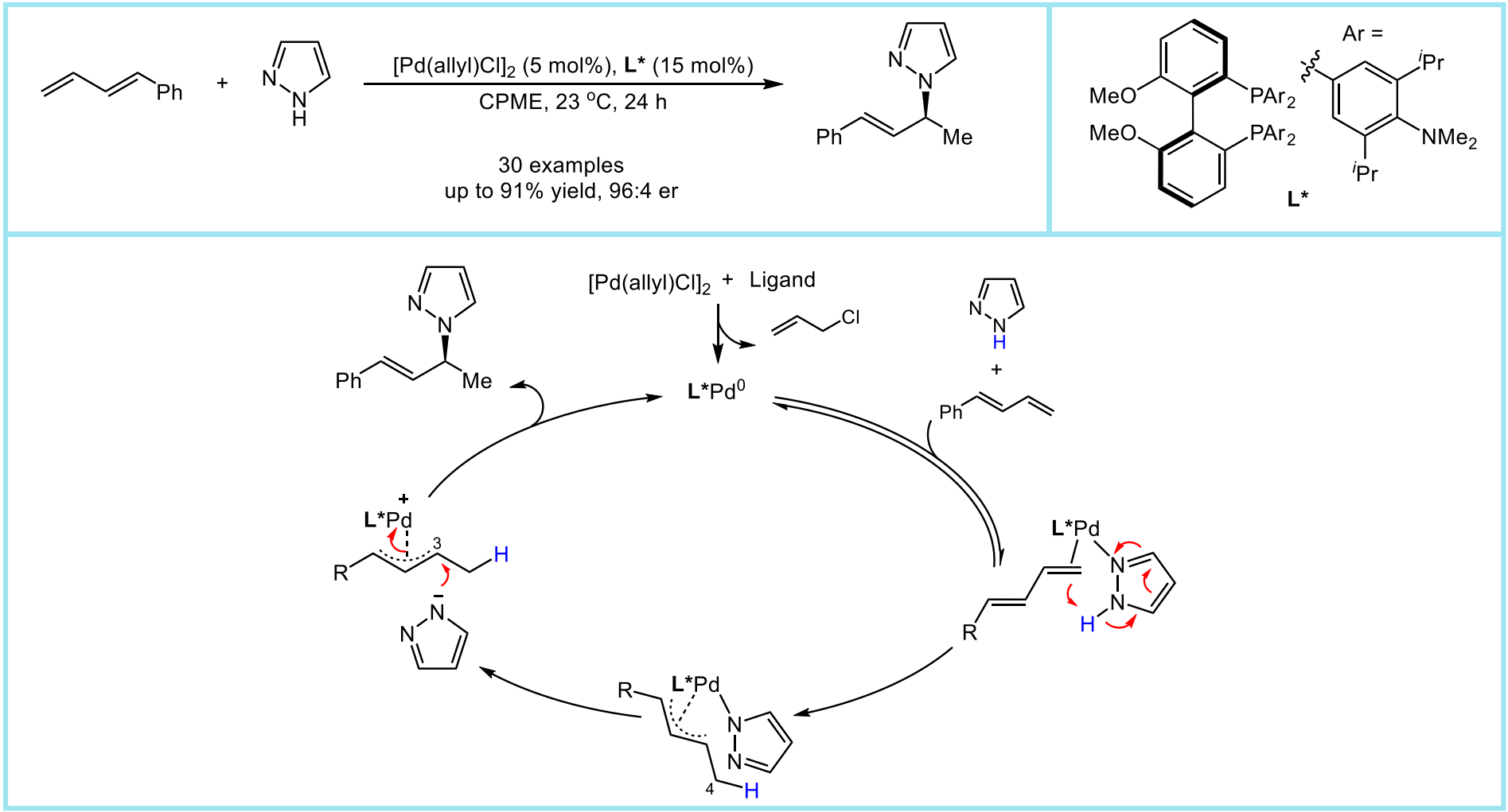
Asymmetric Hydrofunctionalization of 1,3-Dienes via Migratory Insertion



Adamson, N. J.; Hull, E.; Malcolmson, S. J. *J. Am. Chem. Soc*. **2017**, *139*, 7180

Introduction

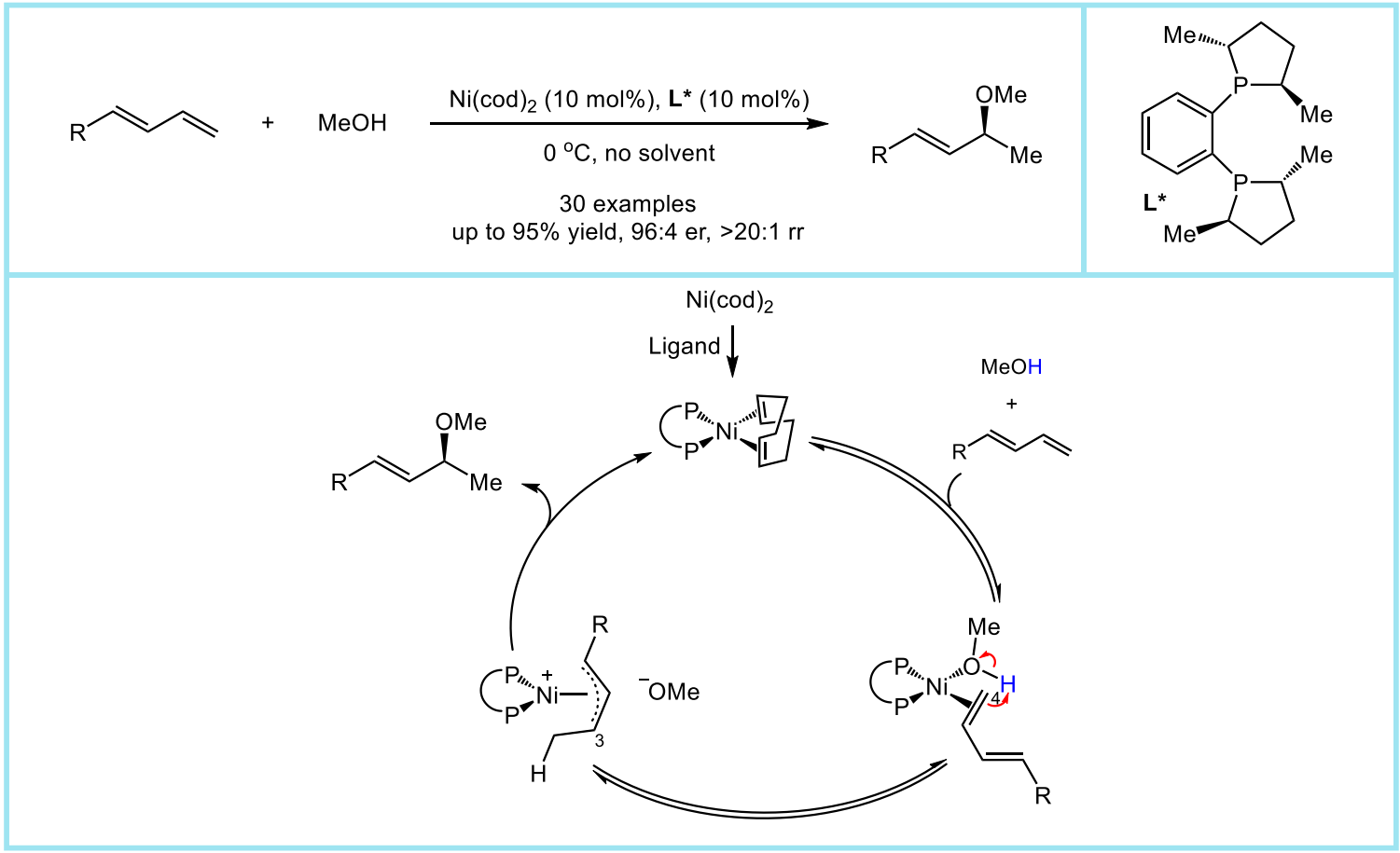
Asymmetric Hydrofunctionalization of 1,3-Dienes via LLHT



Jiu, A. Y.; Slocumb, H. S.; Yeung, C. S.; Yang, X.-H.; Dong, V. M. *Angew. Chem. Int. Ed.* **2021,** *60,* 19660

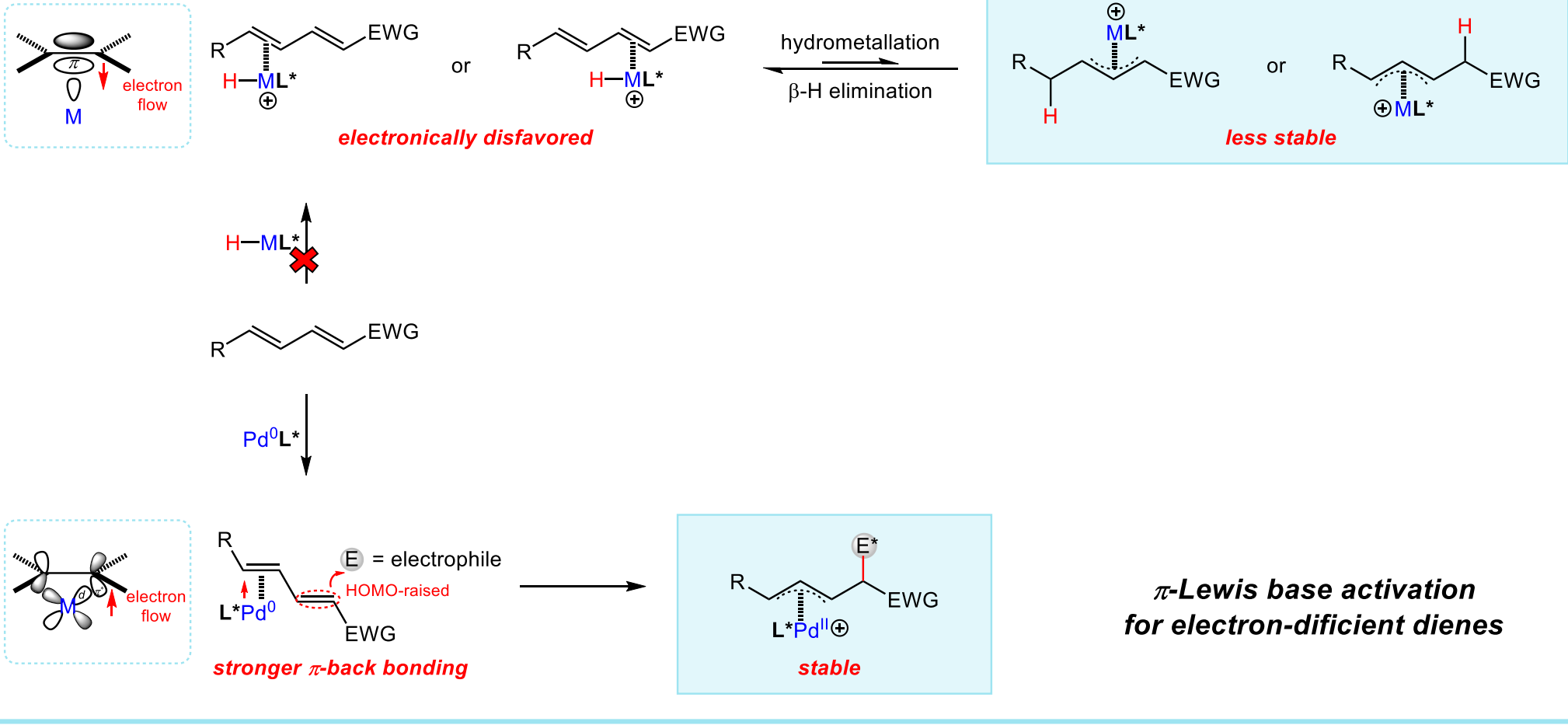
Introduction

Asymmetric Hydrofunctionalization of 1,3-Dienes via LLHT



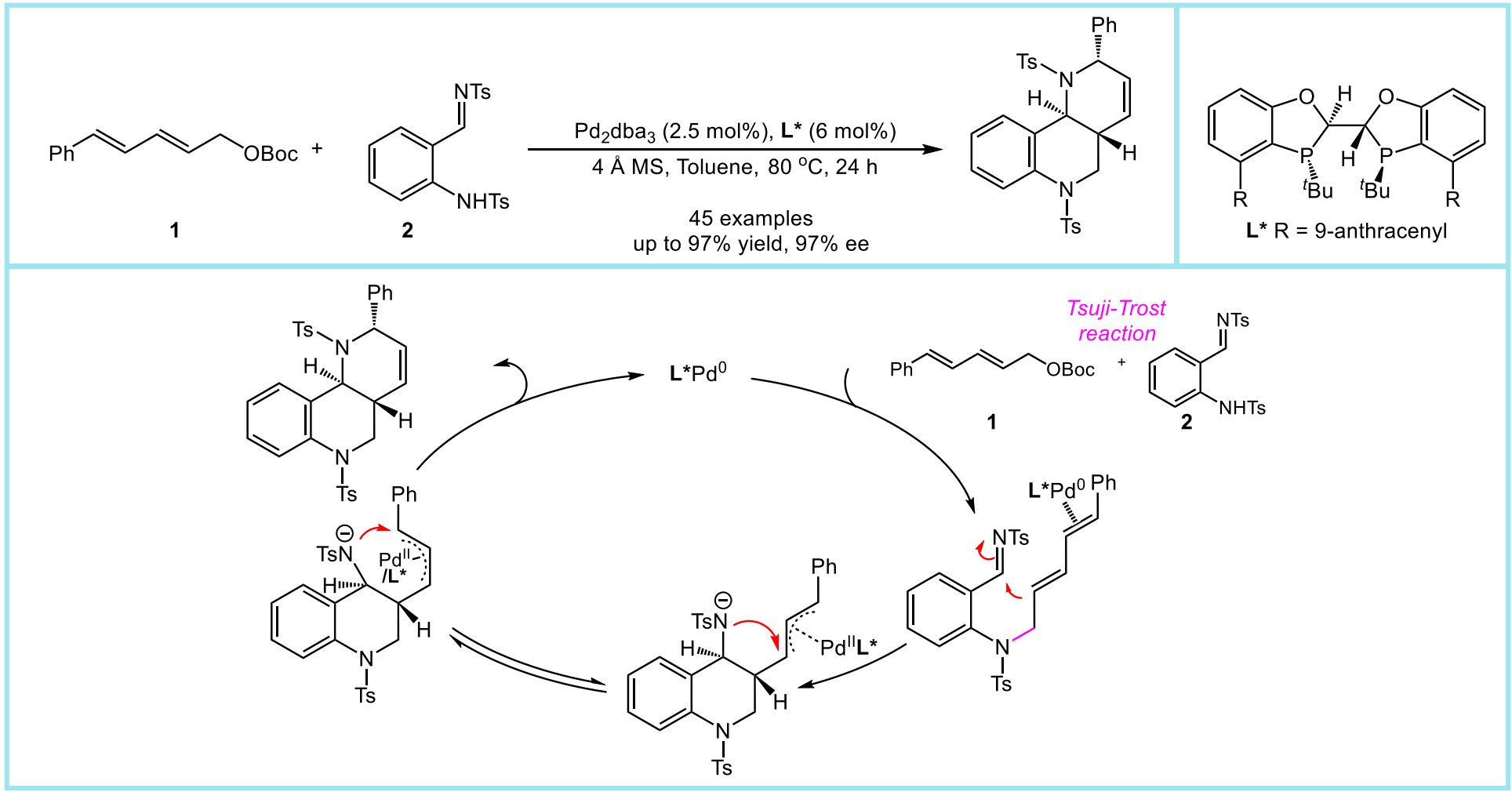
Li, Q.; Wang, Z.; Dong, V. M.; Yang, X.-H. *J. Am. Chem. Soc*. **2023**, *145*, 3909

Project Synopsis



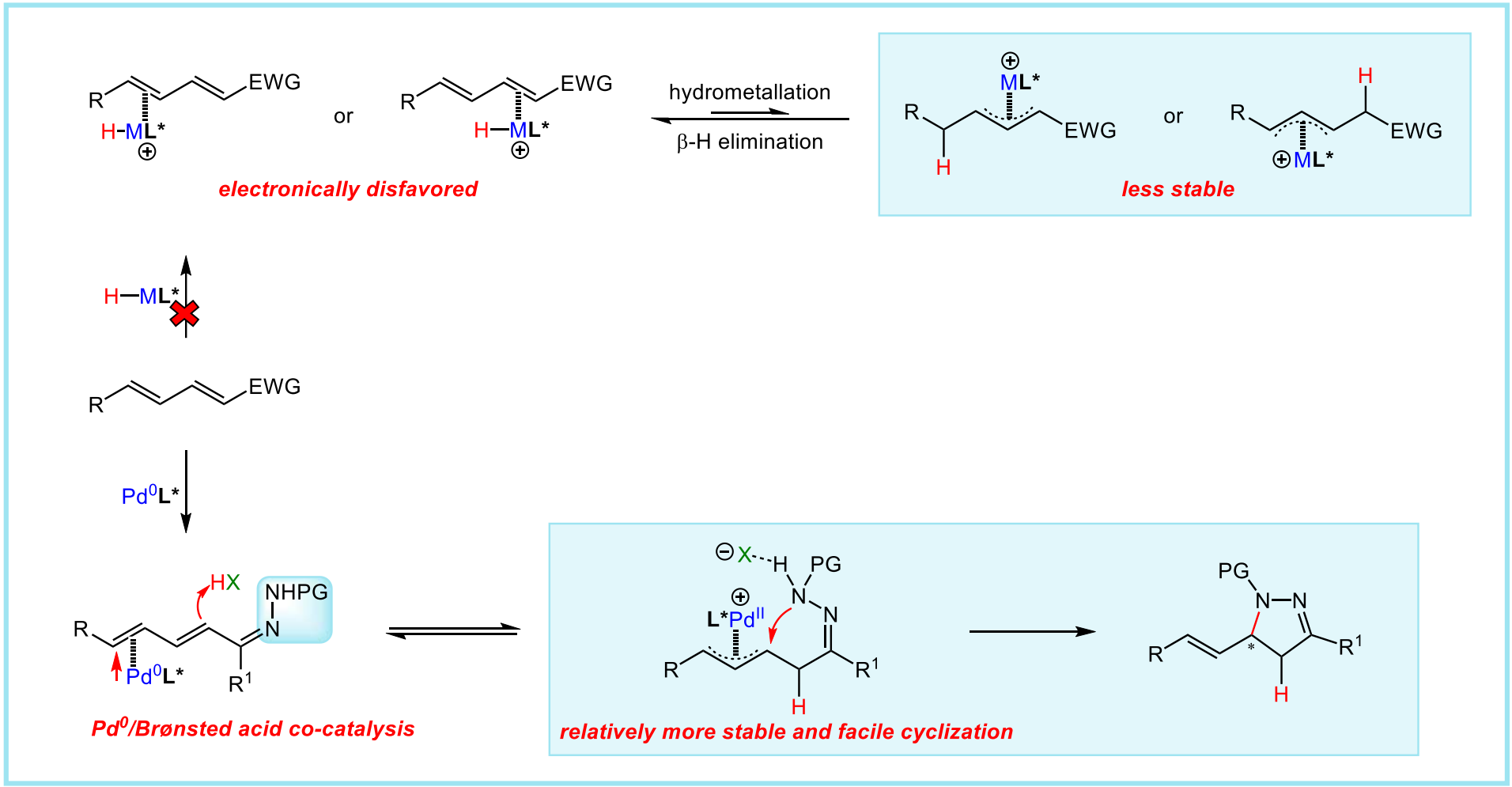
Introduction

Asymmetric Cyclization of 1,3-Dienes via π-Lewis Base Activation

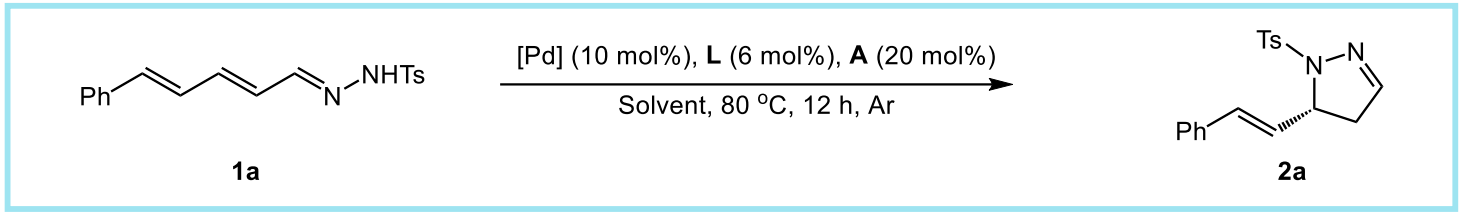


Zhu, J.-X.; Chen, Z.-C.; Du, W.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2022,** *61,* e202200880

Project Synopsis

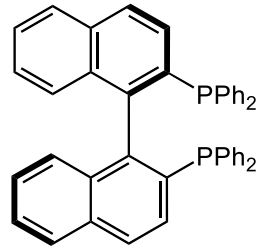


Optimization of the Reaction Conditions

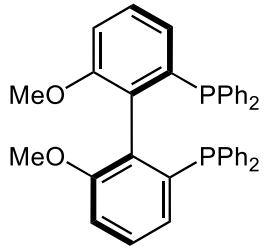


Entry[a]	[Pd]	L	A	Solvent	Yield (%)[b]	Ee (%)[c]
1	$Pd(PPh_3)_4$	/	/	THF	/	/
2	$Pd(PPh_3)_4$	/	**A1**	THF	70	/
3	Pd_2dba_3	**L1**	**A1**	THF	46	-50
4	Pd_2dba_3	**L2**	**A1**	THF	47	-59
5	Pd_2dba_3	**L3**	**A1**	THF	72	67
6	Pd_2dba_3	**L4**	**A1**	THF	23	56
7	Pd_2dba_3	**L5**	**A1**	THF	67	75
8	Pd_2dba_3	**L5**	**A1**	MeOH	77	69
9	Pd_2dba_3	**L5**	**A1**	Toluene	85	43

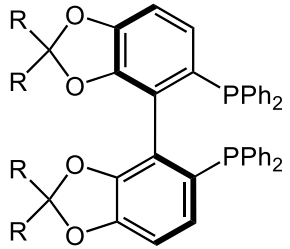
[a]Reaction conditions: **1a** (0.05 mmol), [Pd] (10 mol%), **L** (6 mol%) and acid additive **A** (20 mol%) in solvent (0.5 mL) at 80 °C for 12 h under Ar. [b]Yield of the isolated product. [c]Determined by HPLC analysis on a chiral stationary phase.



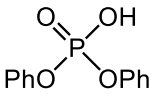
L1



L2

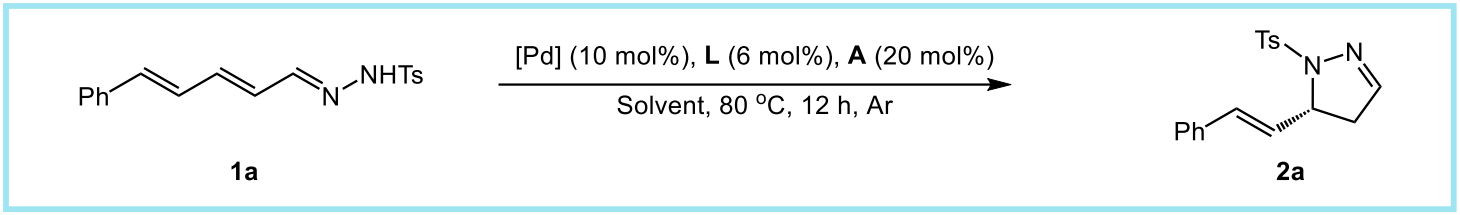


L3 R = H
L4 R = Me
L5 R = F



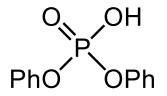
A1

Optimization of the Reaction Conditions

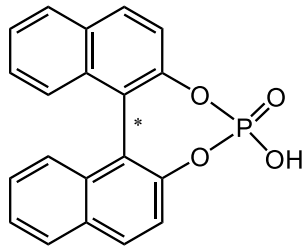


Entry[a]	[Pd]	L	A	Solvent	Yield (%)[b]	Ee (%)[c]
9	Pd_2dba_3	**L5**	**A1**	THF	67	75
10	Pd_2dba_3	**L5**	(*S*)-**A2**	THF	71	55
11	Pd_2dba_3	**L5**	(*R*)-**A2**	THF	76	73
12	Pd_2dba_3	**L5**	**A3**	THF	70	83
13	Pd_2dba_3	**L5**	**A4**	THF	77	83
14	Pd_2dba_3	**L5**	**A5**	THF	72	86
15[d]	Pd_2dba_3	**L5**	**A5**	THF	66	89
16[d,e]	Pd_2dba_3	**L5**	**A5**	THF	90	89
17[d,e,f]	Pd_2dba_3	**L5**	**A5**	THF	88	96
18[d,e,f,g]	Pd_2dba_3	**L5**	**A5**	THF	88	96

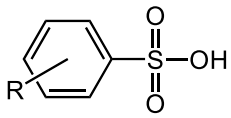
[a]Reaction conditions: **1a** (0.05 mmol), [Pd] (10 mol%), **L** (6 mol%) and acid additive **A** (20 mol%) in solvent (0.5 mL) at 80° C for 12 h under Ar. [b]Yield of the isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]With **A5** (40 mol%). [e]With 1.5 mL THF. [f]At 40 °C for 48 h. [g]With Pd_2dba_3 (2.5 mol%) and **L5** (3 mol%).



A1

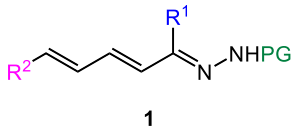


A2



A3 R = 4-Me
A4 R = 4-Cl
A5 R = 2,4,6-^{i}Pr

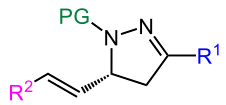
Substrate Scope



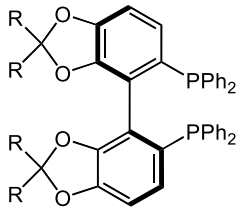
1

Pd_2dba_3 (2.5 mol%), **L5** (3 mol%), **A5** (40 mol%)

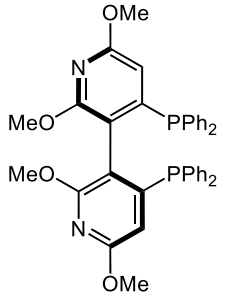
THF, 40 °C, 12-72 h, Ar



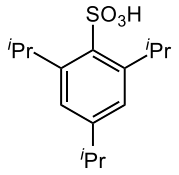
2



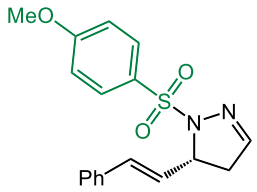
L3 R = H
L5 R = F



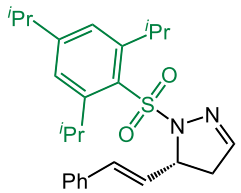
L6



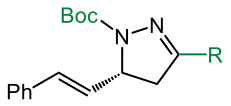
A5



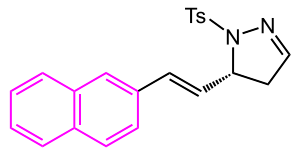
2b: 89%, 97% ee



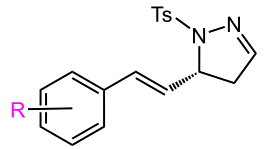
2c: 59%, 96% ee



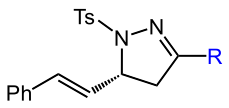
2d: (R = H): 80%, 95% ee[b]
2e: (R = Me): 94%, 96% ee[f]



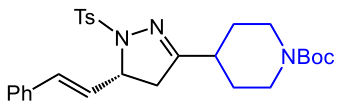
2f: 90%, 93% ee



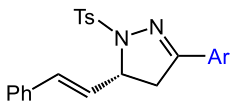
2g: (R = 2-Cl): 53%, 93% ee
2h: (R = 3-CF_3): 97%, 93% ee
2i: (R = 4-F): 88%, 98% ee
2j: (R = 4-Cl): 91%, 95% ee
2k: (R = 4-Br): 94%, 94% ee
2l: (R = 4-NO_2): 85%, 82% ee
2m: (R = 4-Me): 86%, 98% ee
2n: (R = 4-OH): 75%, 97% ee



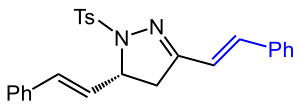
2o (R = Me): 98%, 90% ee (25 °C)[b]
2p (R = CF_3): 94%, 80% ee (25 °C)



2q: 90%, 78% ee (80 °C)



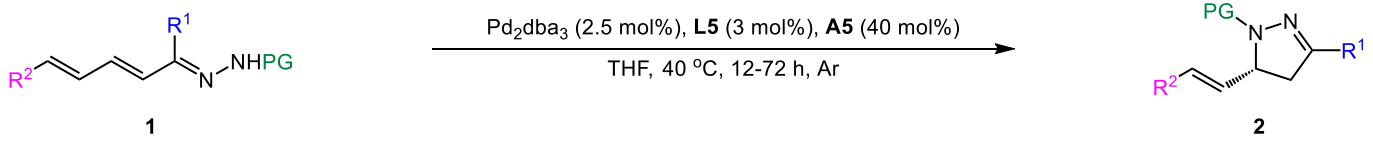
2r: (Ar = Ph): 97%, 91% ee
2s: (Ar = 2-Naphthyl): 81%, 90% ee
2t: (Ar = 2-Thienyl): 91%, 90% ee

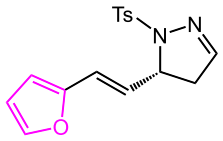


2u: 97%, 76% ee (80 °C)

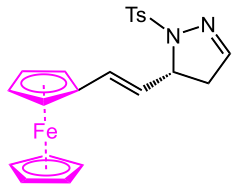
[a]Unless noted otherwise, reactions were performed using hydrazone **1** (0.1 mmol), Pd_2dba_3 (2.5 mol%), **L5** (3 mol%) and **A5** (40 mol%) in THF (3.0 mL) at 40 °C 12–72 h under Ar. [b] With **L3.** [c]With Pd_2dba_3 (5 mol%) and **L5** (6 mol%). [d]With Pd_2dba_3 (2.5 mol%) and **L6** (6 mol%).

Substrate Scope

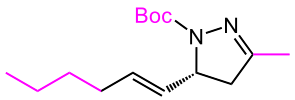




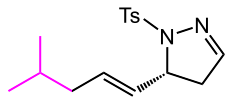
2v: 94%, 95% ee



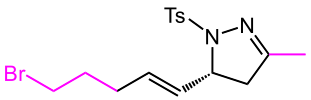
2w: 71%, 89% ee[c]



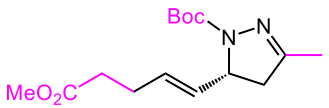
2x: 97%, 90% ee (60 °C)[d]



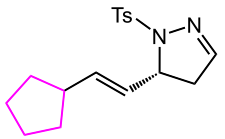
2y: 44%, 95% ee (60 °C)[c]



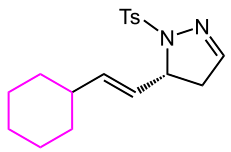
2z: 80%, 70% ee (60 °C)[c]



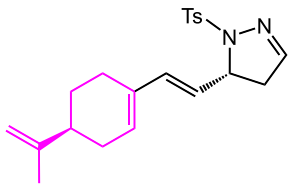
2aa: 78%, 91% ee[d]



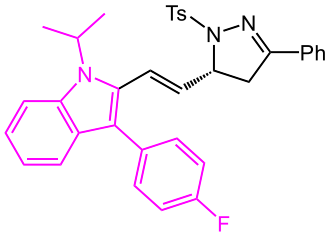
2ab: 64%, 97% ee[c]



2ac: 60%, 95% ee (60 °C)[c]



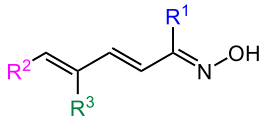
from *L-(-)-perillaldehyde*
2ad: 71%, >19:1dr (60 °C)



from *fluvastatin*
2ae: 85%, 82% ee (60 °C)

[a]Unless noted otherwise, reactions were performed using hydrazone **1** (0.1 mmol), Pd_2dba_3 (2.5 mol%), **L5** (3 mol%) and **A5** (40 mol%) in THF (3.0 mL) at 40 °C 12–72 h under Ar. [b] With **L3**. [c]With Pd_2dba_3 (5 mol%) and **L5** (6 mol%). [d]With Pd_2dba_3 (2.5 mol%) and **L6** (6 mol%).

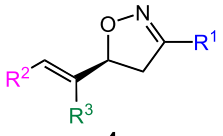
Substrate Scope



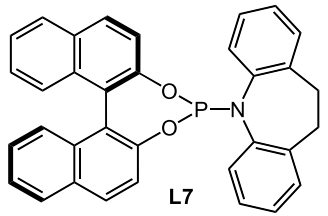
3

Pd(allyl)Cp (5 mol%), **L7** (15 mol%), (*S*)-**A2** (20 mol%)

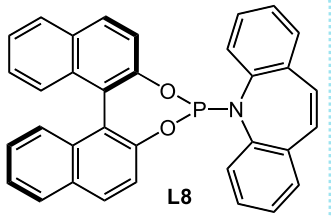
DCM, 40 °C, 8-48 h, Ar



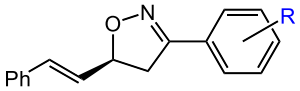
4



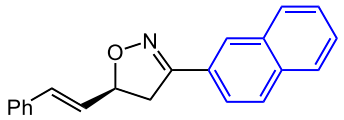
L7



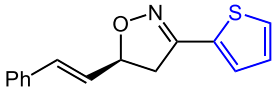
L8



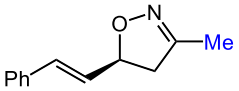
4a (R = H): 99%, 94% ee[a]
4b (R = 2-Cl): 56%, 72% ee[b]
4c (R = 3-F): 94%, 92% ee
4d (R = 4-Br): 98%, 94% ee
4e (R = 4-OMe): 90%, 95% ee



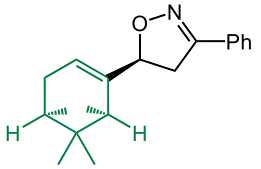
4f: 99%, 94% ee



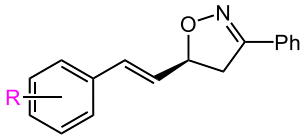
4g: 72%, 93% ee



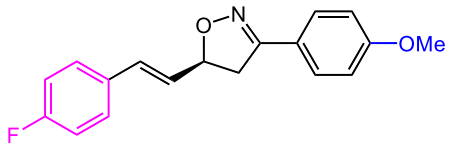
4h: 87%, 77% ee[c]



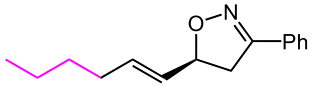
from *L-(-)-perillaldehyde*
4o: 93%, >19:1 dr



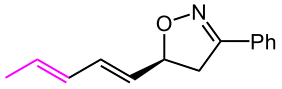
4i: (R = 2-Cl): 41%, 95% ee
4j: (R = 3-CF_3): 98%, 87% ee
4k: (R = 4-Me): 95%, 91% ee



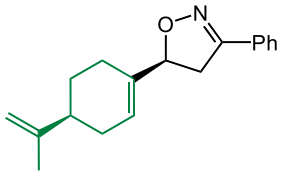
4l: 98%, 93% ee



4m: 96%, 93% ee



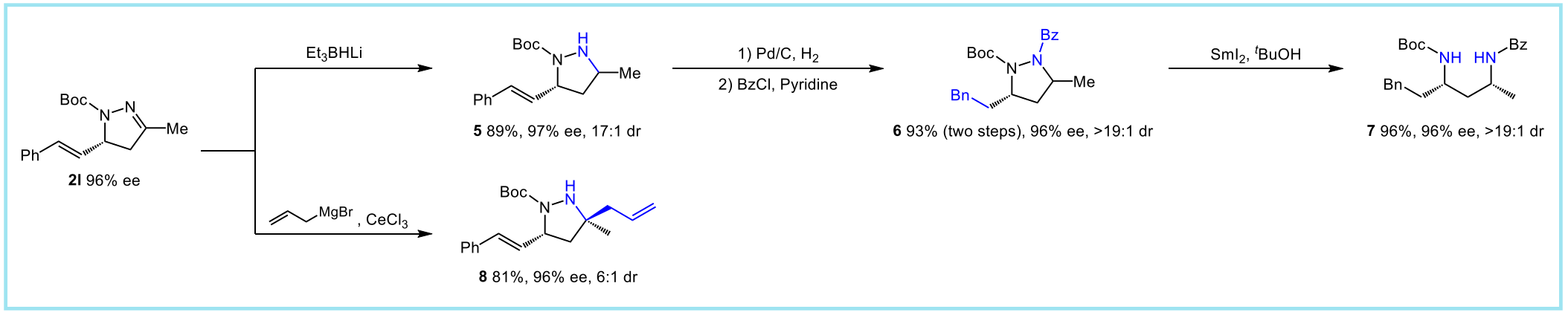
4n: 98%, 94% ee



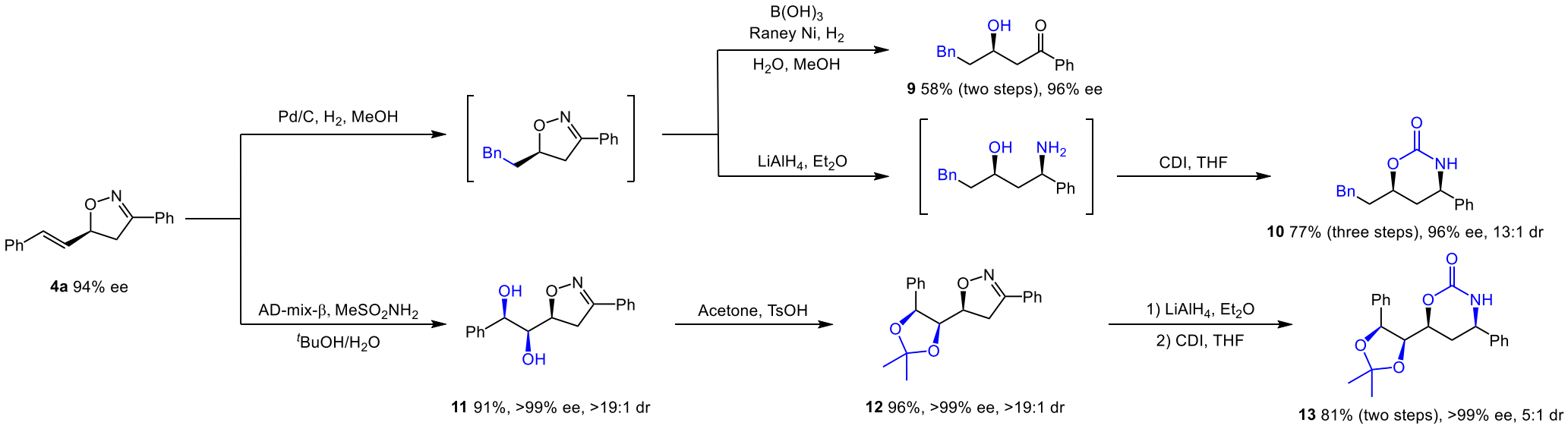
from *L-(-)-myrtenal*
4p: 93%, 8:1 dr

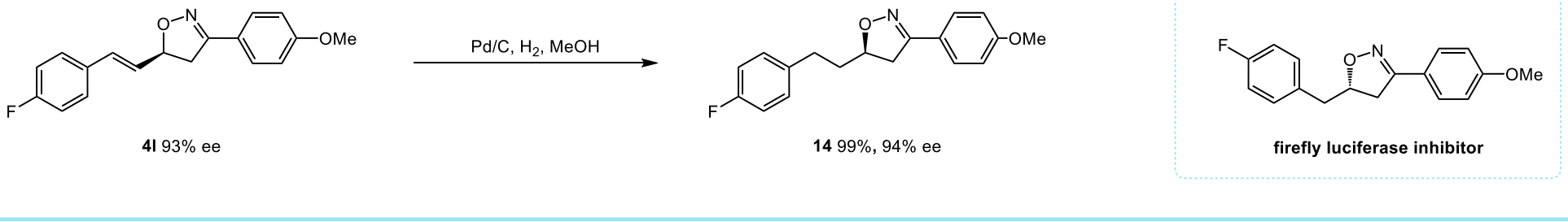
[a]Unless noted otherwise, reactions were performed using **3** (0.2 mmol), Pd(allyl)Cp (5 mol%), **L7** (15 mol%) and (*S*)-**A2** (20 mol%) in DCM (2.0 mL) at 40 ° C for 8–48 h under Ar. [b]With Pd(allyl)Cp (10 mol%) and **L7** (30 mol%). [c]With Pd(allyl)Cp (10 mol%), **L8** (30 mol%) and **A1** (20 mol%).

Transformations of Products



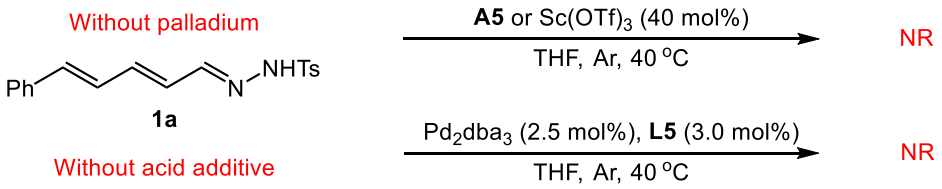
Transformations of Products



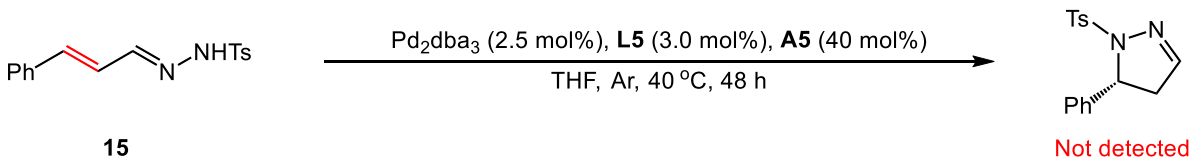


Control Experiments

• ***Importance of dual palladium and Bronsted acid catalysis***

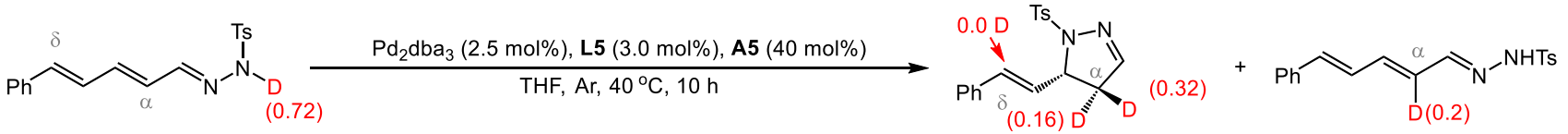


• ***Importance of the diene moiety***



Control Experiments

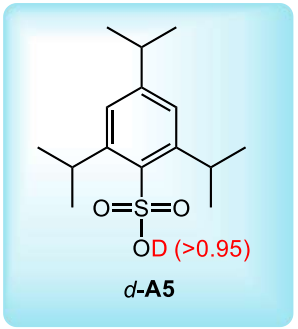
• ***Deuterium Experiments***



d-**1a**

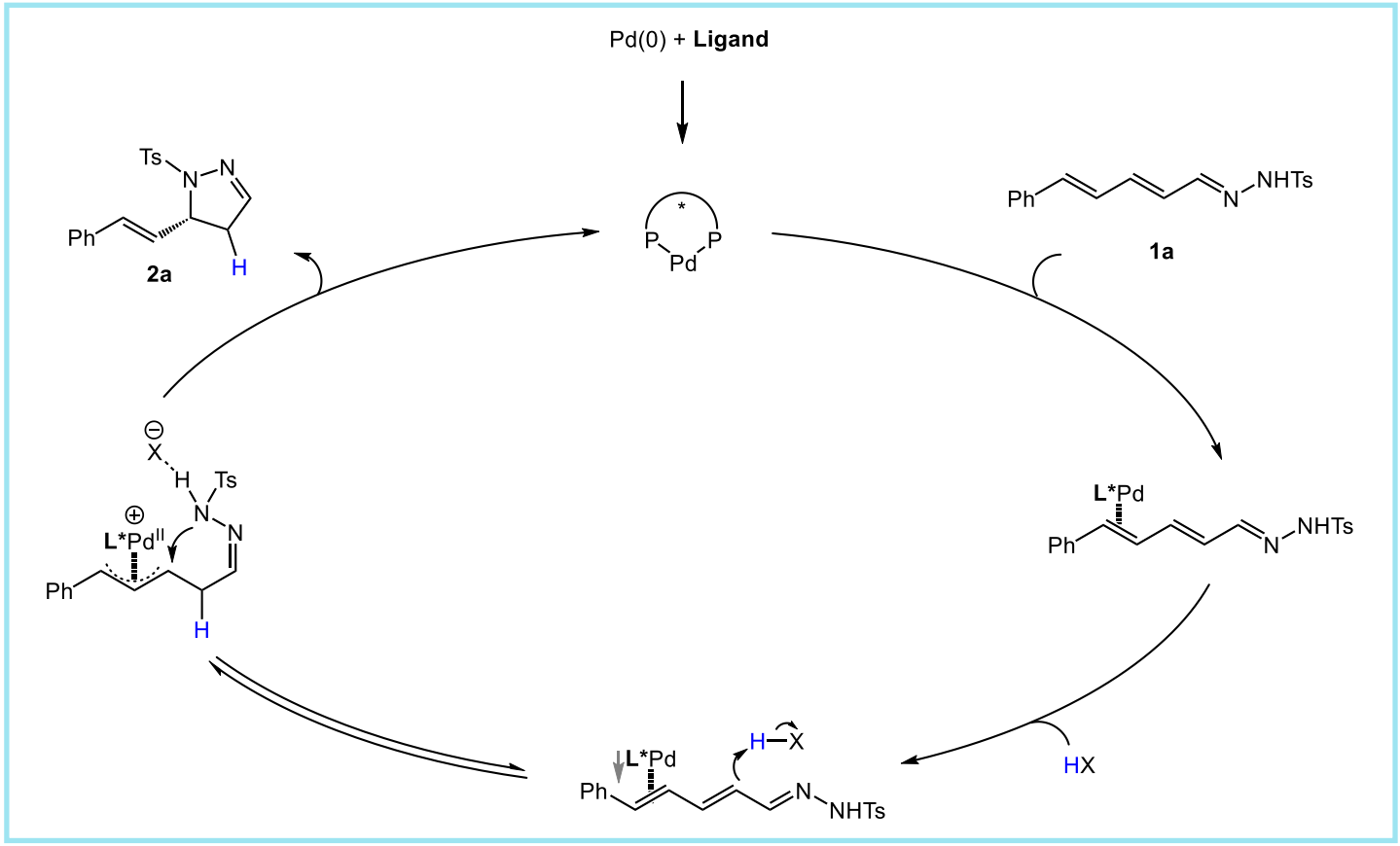
d-**2a** 42%, 96% ee

55% (recovered **1a**)

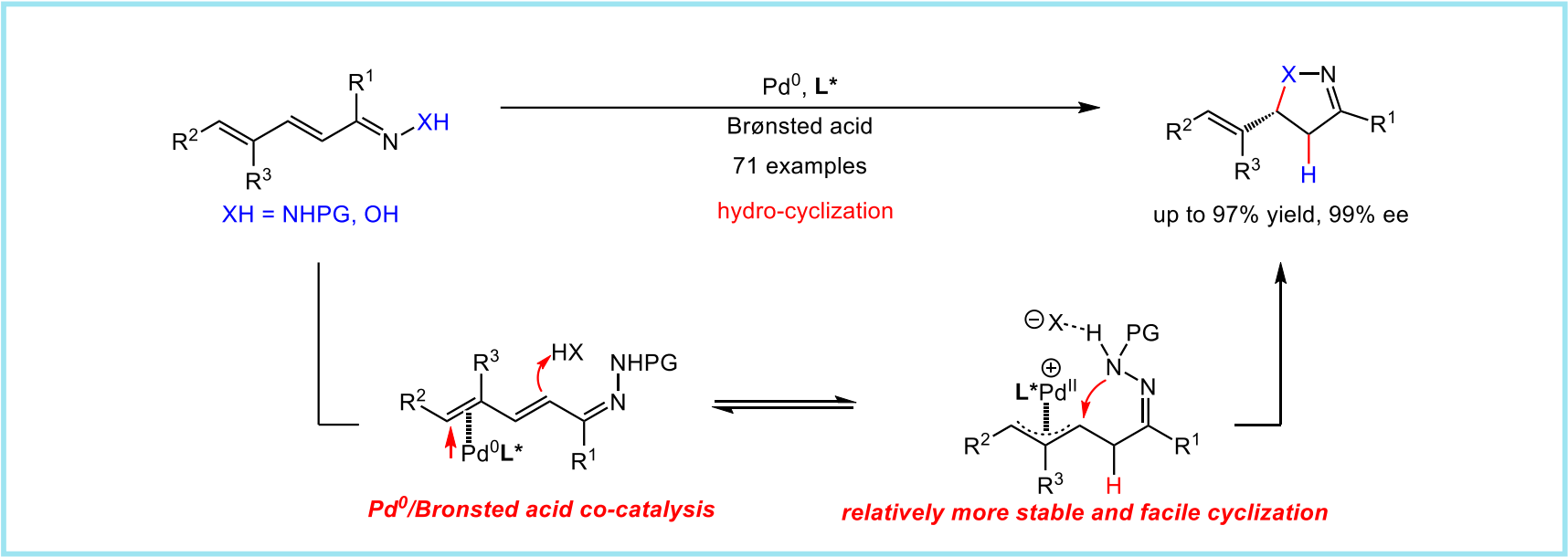


d-**A5**

Proposed Reaction Mechanism



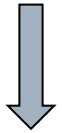
Summary


R1
R2
R3
XH
N
XH = NHPG, OH
Pd0, L*
Brønsted acid
71 examples
hydro-cyclization
X
N
R2
R1
R3
H
up to 97% yield, 99% ee
R3
HX
NHPG
R2
N
Pd0L*
R1
Pd0/Bronsted acid co-catalysis
X
H
PG
N
L*PdII
N
R2
R1
R3
H
relatively more stable and facile cyclization

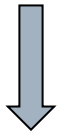
Writing Strategy

首段写作思路

过渡金属催化的1,3-二烯氢官能化反应的重要性



1,3-二烯氢官能化的主要方法

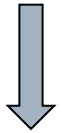


引出本文工作

Writing Strategy

末段写作思路

总结工作



提出展望： 0价钯和 Brønsted 酸的双重催化
将应用于更多底物

Representative Examples

- As outliend in Scheme **5a**, without Pd catalyst, …indicating that an acid-catalyzed electrocyclization of **1a** would not be feasible. (As outliend in，“如上所述”或“如概述的那样”，这个短语通常用于引用或总结前面的内容)

- Then the combination of **A5** and **INT7** proceeds rapidly to generate **INT8** in a significantly exothermic manner……(exothermic a. 放热的; endothermic a. 吸热的)

Acknowledgement

Thanks for your attention