Literature Report 7

Chiral Alkyl Amine Synthesis via Catalytic Enantioselective Hydroalkylation (CEH) of Enecarbamates

Reporter: Xiang Li
Checker: Tong Niu
Date: 2021-04-19

Hu, X. *et al*. *J*. *Am*. *Chem*. *Soc*. **2021**, *143*, 1959

CV of Prof. Xile Hu

Education:

- **1996-2000** B.S., Peking University
- **2000-2004** Ph.D., University of California, San Diego
- **2005-2007** Postdoc., California Institute of Technology
- **2007-2013** Assistant Professor, EPFL
- **2013-2016** Associate Professor, EPFL
- **2016-Present** Professor, EPFL

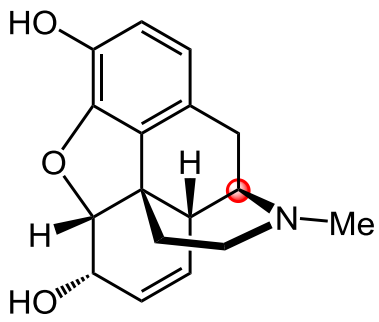
Research Interests:

The development of metal catalyzed C-C bond forming reactions, C-H bond functionalization, (electro)catalytic water splitting, activation of small molecules such as CO_2, H_2, O_2, as well as the development of synthetic models for the active site of metalloenzymes.

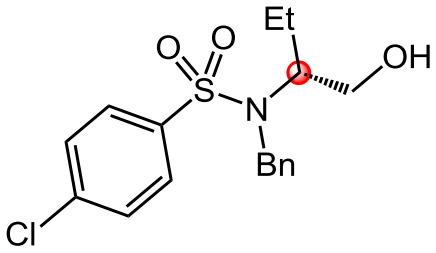
Contents

Introduction

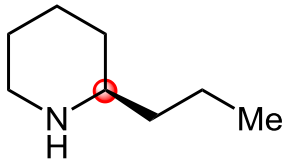
Representative Alkaloids and Drugs Demonstrating the Ubiquitous Nature of Chiral Alkyl Amines



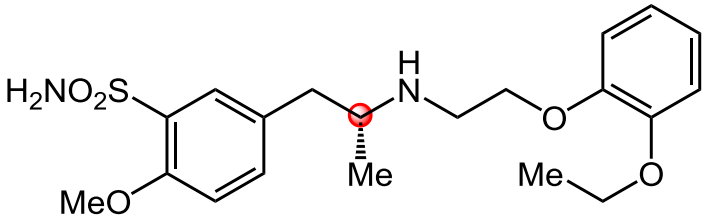
Morphine



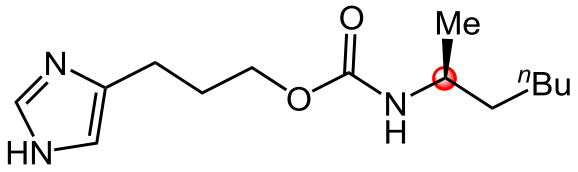
γ-Secretase inhibitor



(*R*)-Coniine

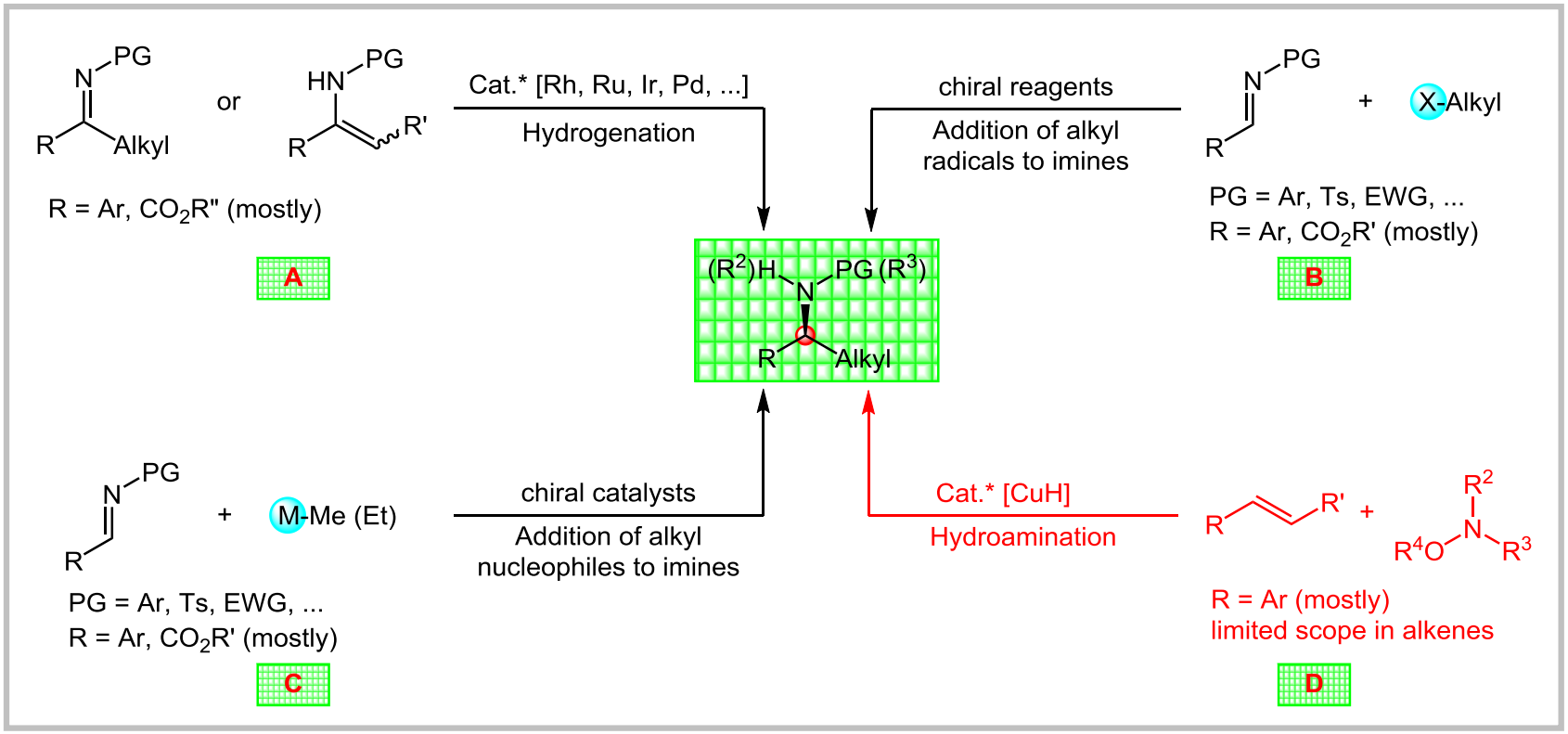


(*R*)-Tamsulosin



Histamine H3 receptor

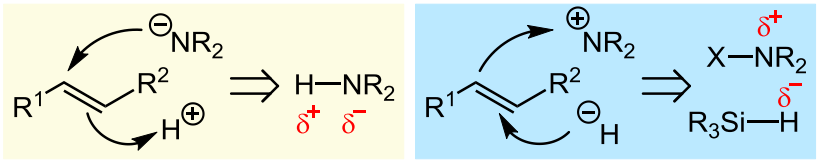
Introduction



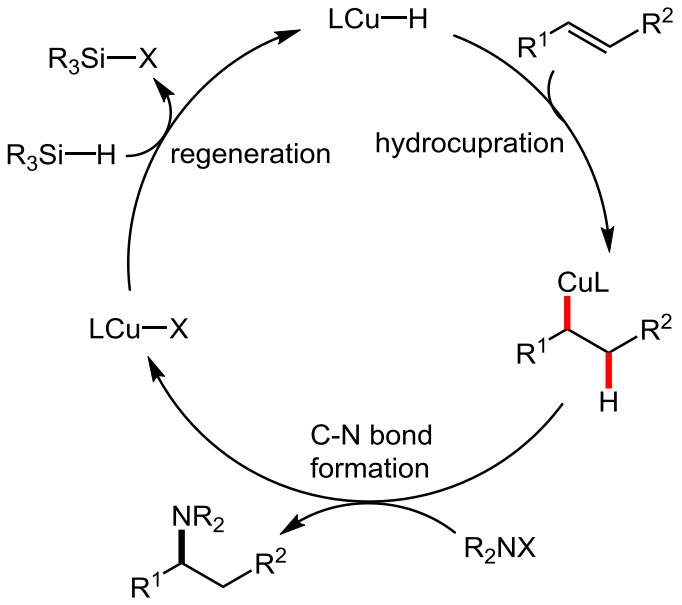
Introduction

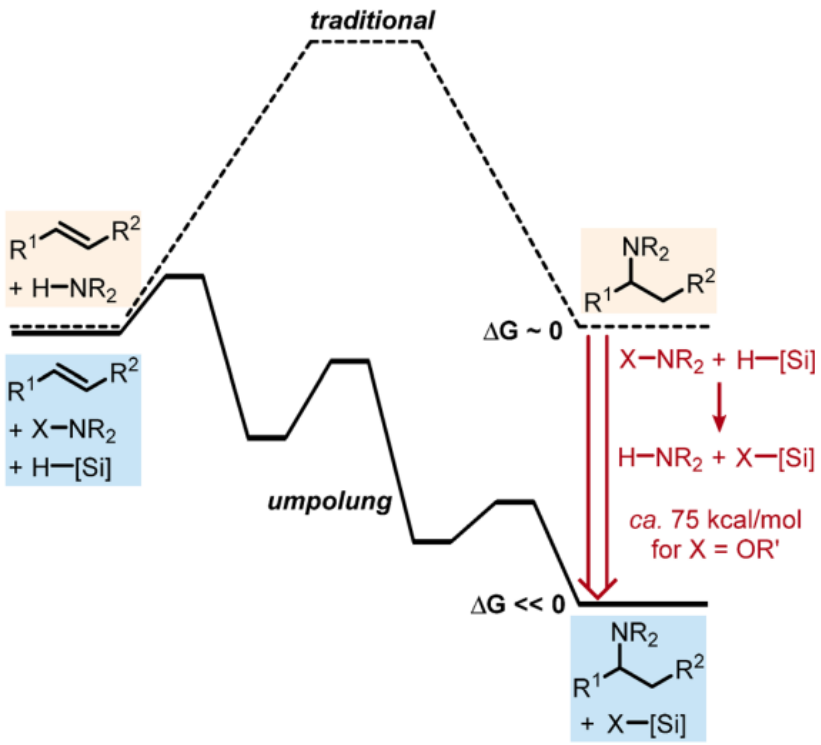
Cu-Catalytic Asymmetric Hydroamination of Olefins to Chiral Amines

♥ Traditional Hydroamination ♥ *Umpolung* Hydroamination ■ Thermodynamics



♥ Mechanism

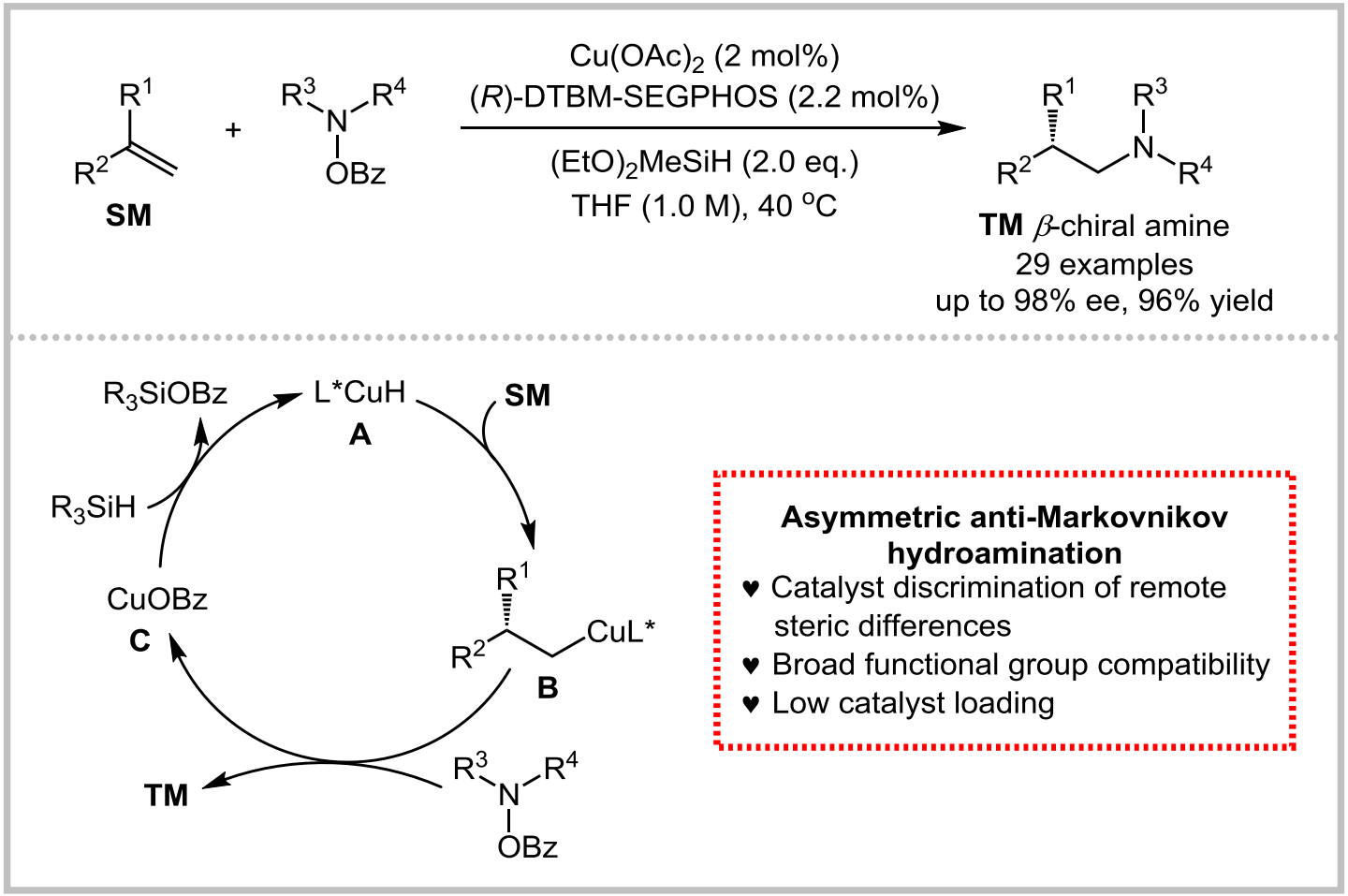




Buchwald, S. L. *et al*. *Acc. Chem. Res.* **2020**, *53*, 1229

Introduction

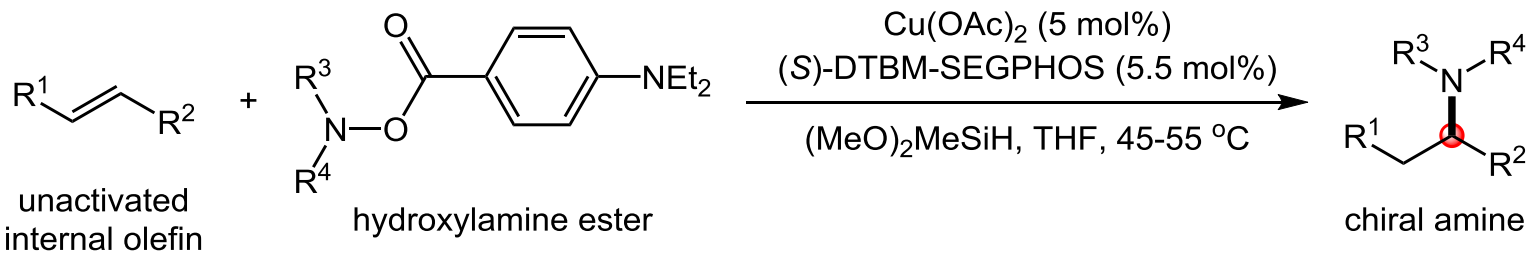
Cu-Catalytic Asymmetric Hydroamination of Olefins to β-Chiral Amines



Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2014**, *136*, 15913

Introduction

Cu-Catalytic Asymmetric Hydroamination of Olefins to Aliphatic Amines



(i) High-value chiral amine with two minimally differentiated *α*-aliphatic substituents

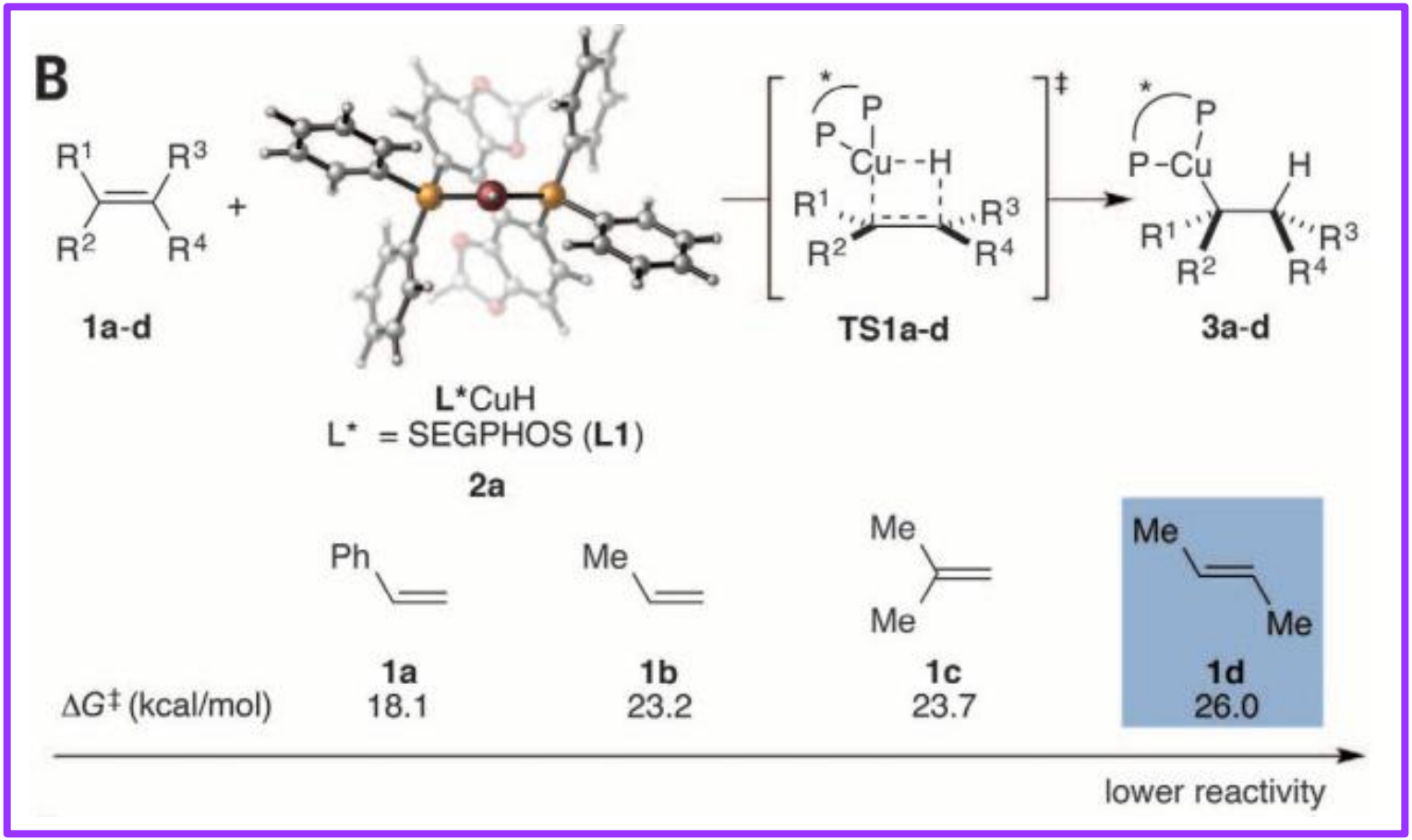
(ii) Use of abundant feedstock internal olefin (eg., 2-butene)

(iii) Mild and general C-N bond formation with excellent enantiocontrol (≥ 96% ee)

Buchwald, S. L. *et al. Science* **2015**, *349*, 62

Introduction

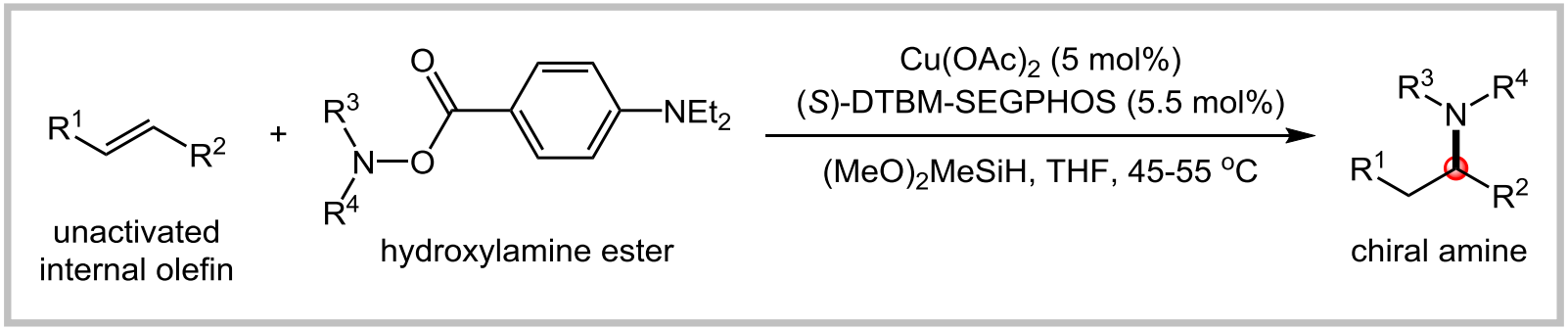
Cu-Catalytic Asymmetric Hydroamination of Olefins to Aliphatic Amines

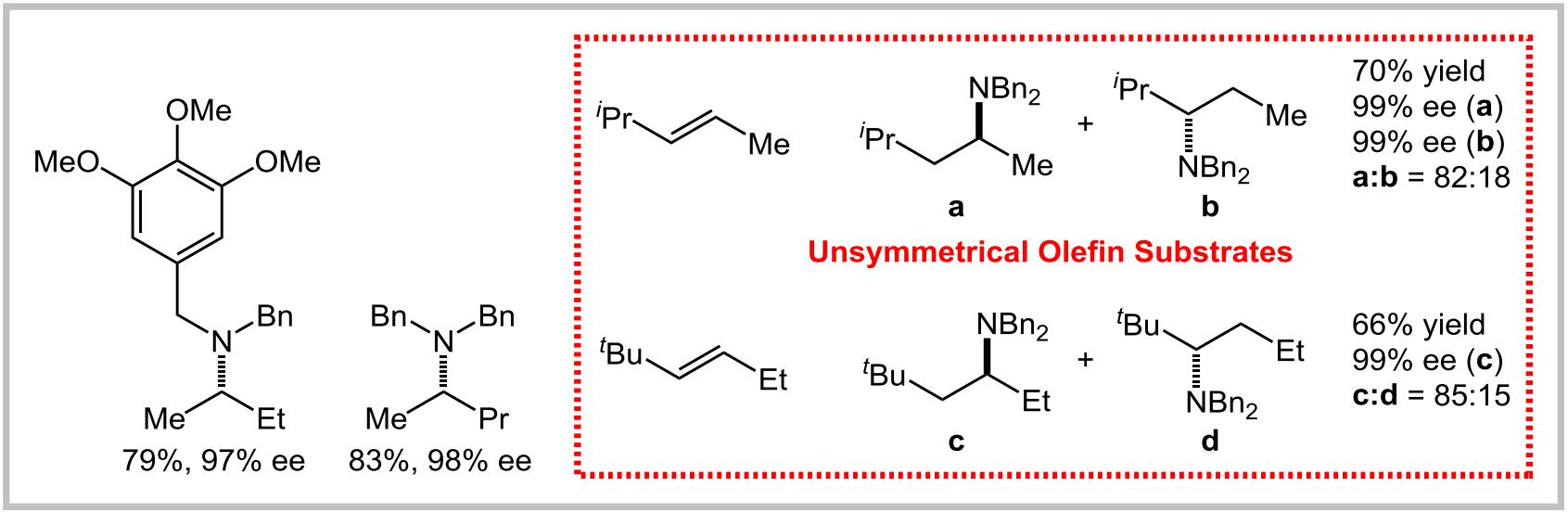


Buchwald, S. L. *et al. Science* **2015**, *349*, 62

Introduction

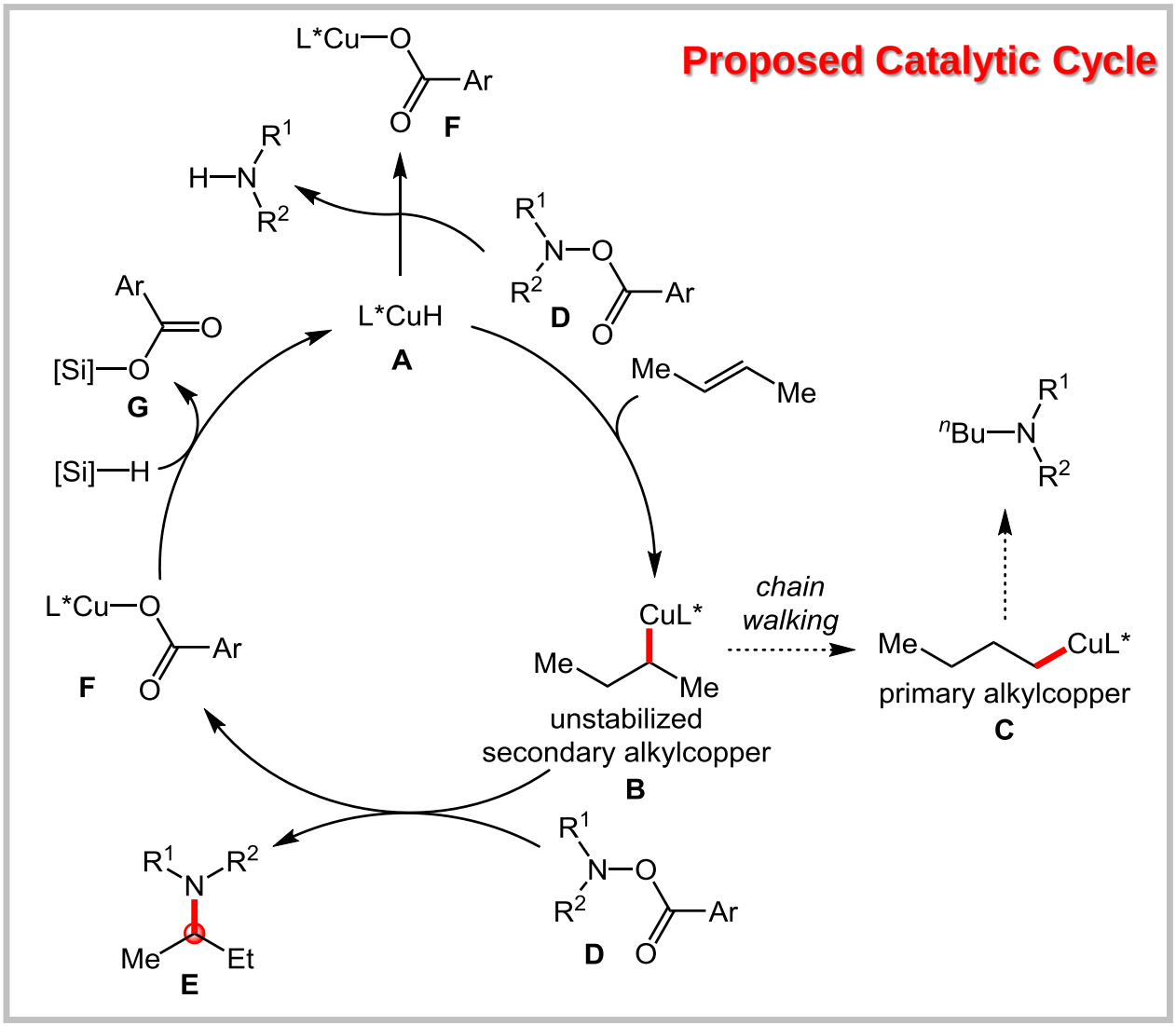
Cu-Catalytic Asymmetric Hydroamination of Olefins to Aliphatic Amines





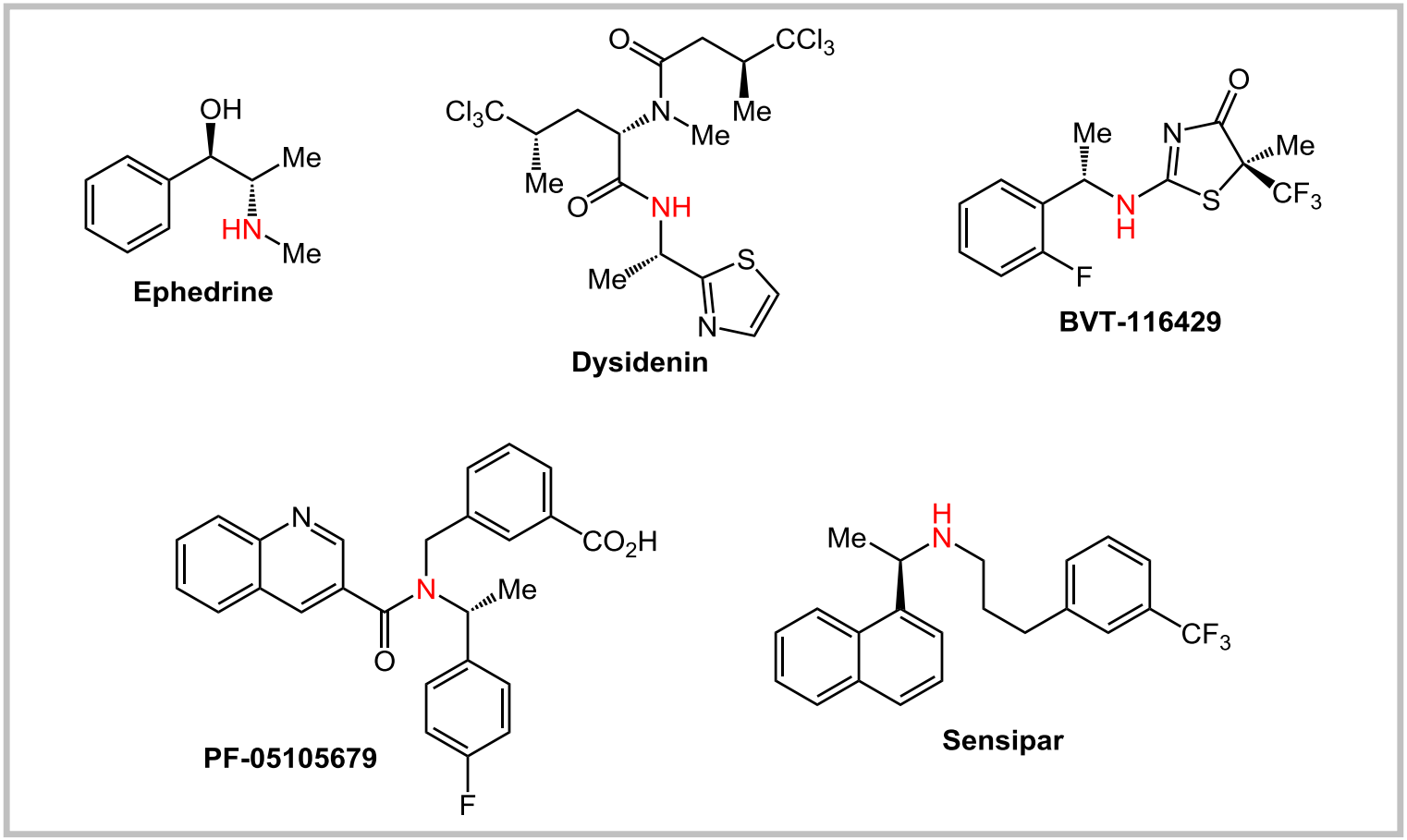
Buchwald, S. L. *et al. Science* **2015**, *349*, 62

Introduction



Introduction

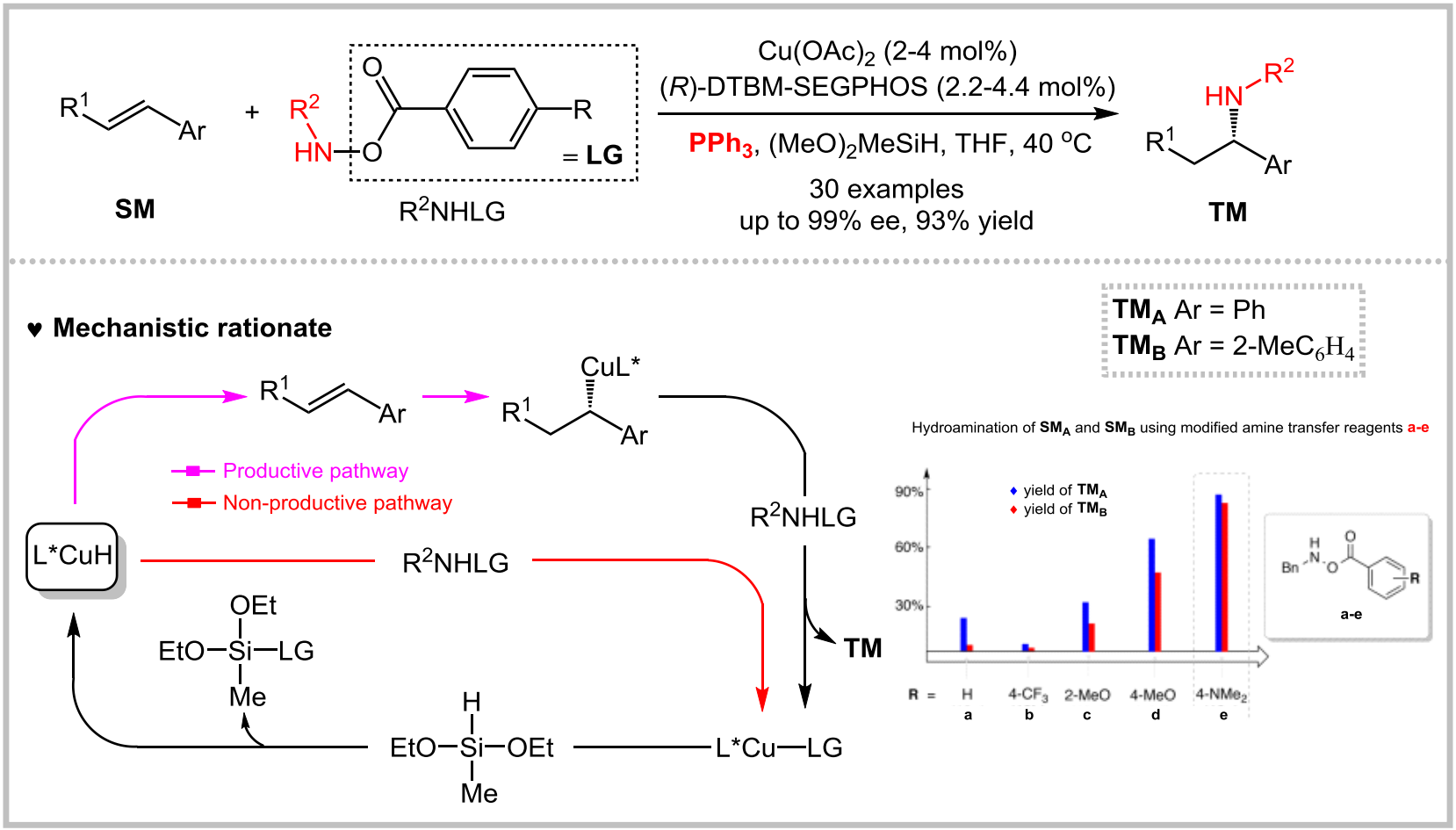
Cu-Catalytic Asymmetric Hydroamination of Olefins to Chiral Secondary Amines



Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2015**, *137*, 9716

Introduction

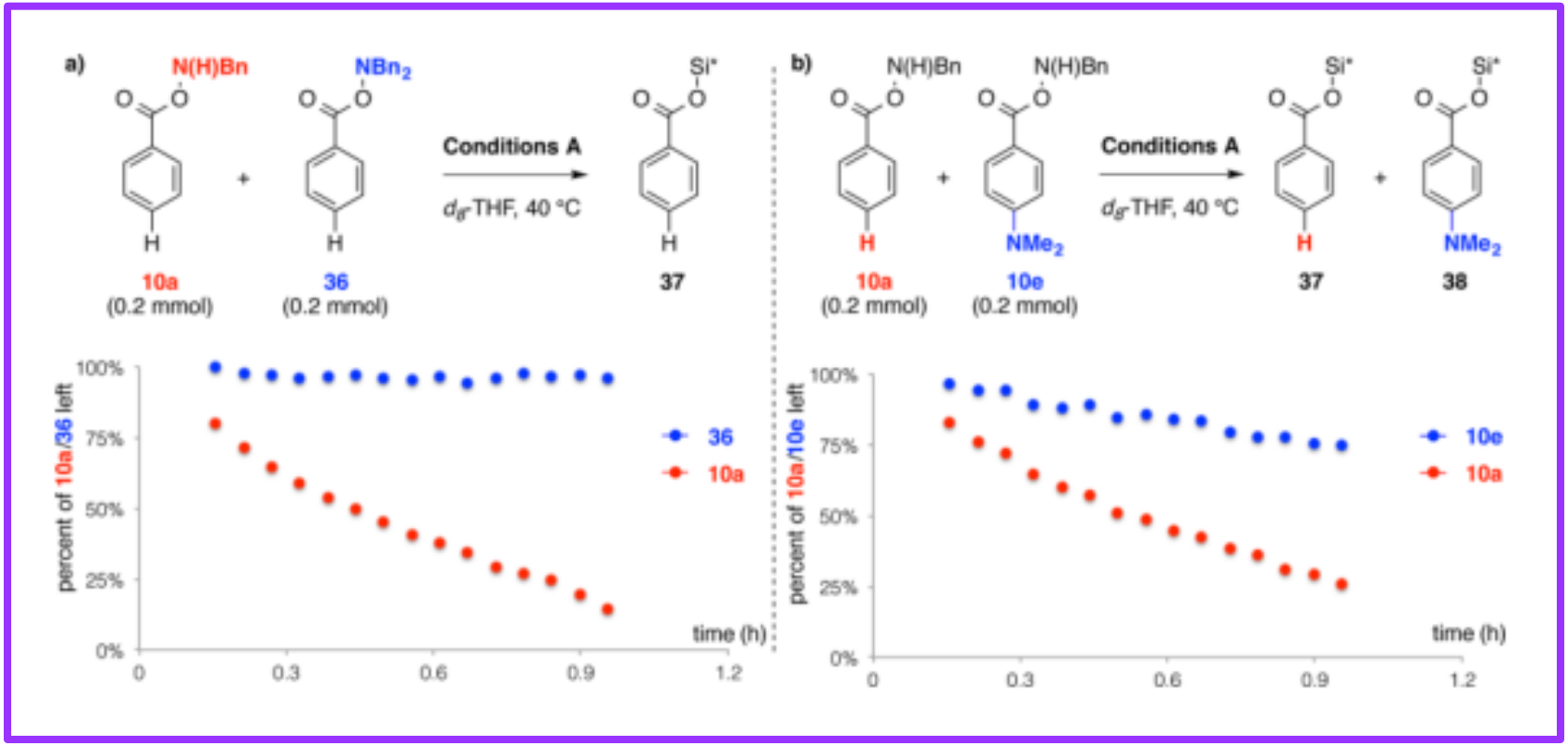
Cu-Catalytic Asymmetric Hydroamination of Olefins to Chiral Secondary Amines



Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2015**, *137*, 9716

Introduction

Cu-Catalytic Asymmetric Hydroamination of Olefins to Chiral Secondary Amines

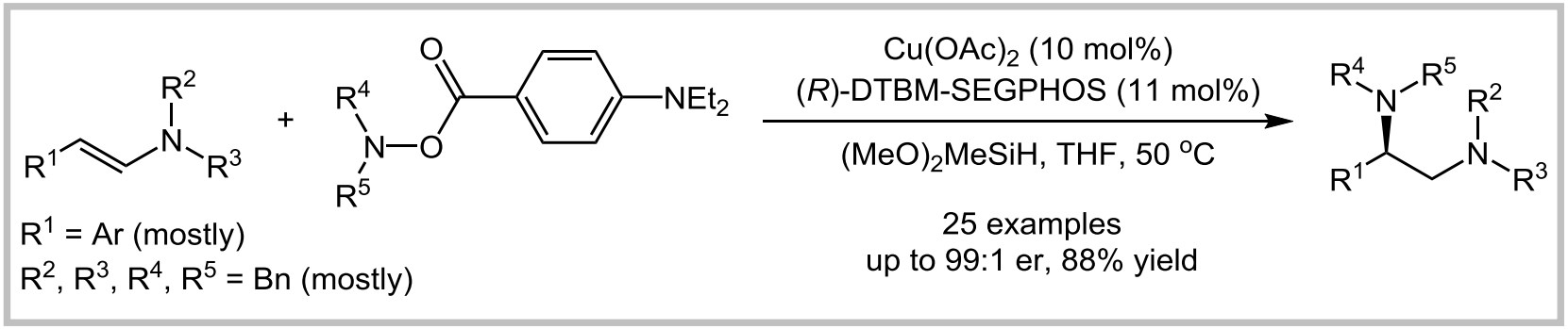


Relative rates of the reactions between LCuH and different amine transfer agents. Si* = $Si(OEt)_2Me$. **Conditions A**: a 0.6 mL of a stock solution made from $Cu(OAc)_2$ (3.6 mg), (*R*)-DTBM-SEGPHOS (26 mg), PPh_3 (11.6 mg), $HSi(OEt)_2Me$ (0.32 mL, 2.0 mmol), and THF-d_8 (1.0 mL) is used. The progress of these experiments was monitored by ^1H NMR.

Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2015**, *137*, 9716

Introduction

Cu-Catalytic Asymmetric Hydroamination of Enamines to Chiral 1,2-Diamines



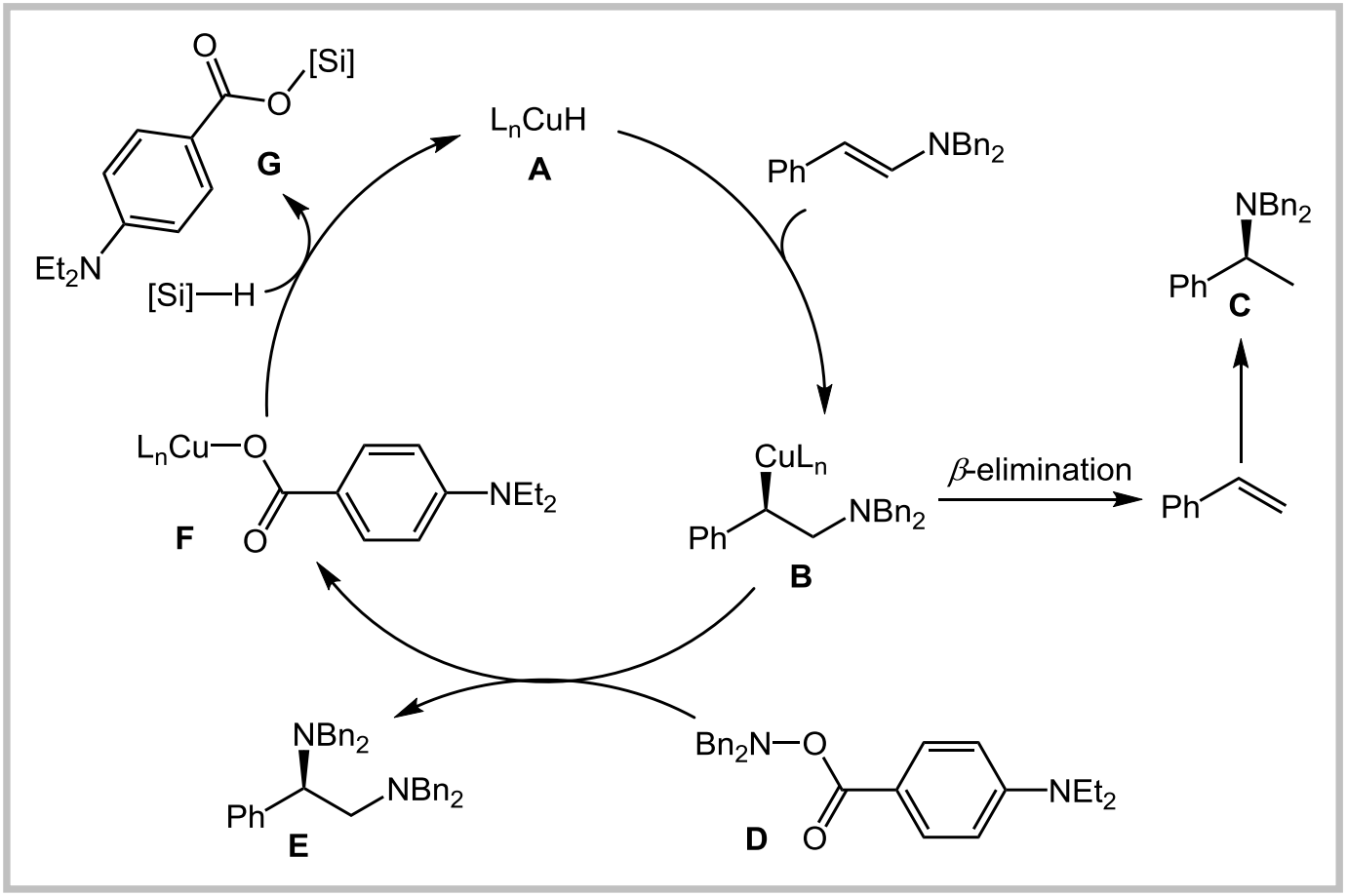
R^1 = Ar (mostly)
R^2, R^3, R^4, R^5 = Bn (mostly)

25 examples
up to 99:1 er, 88% yield

Somfai, P. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 8551

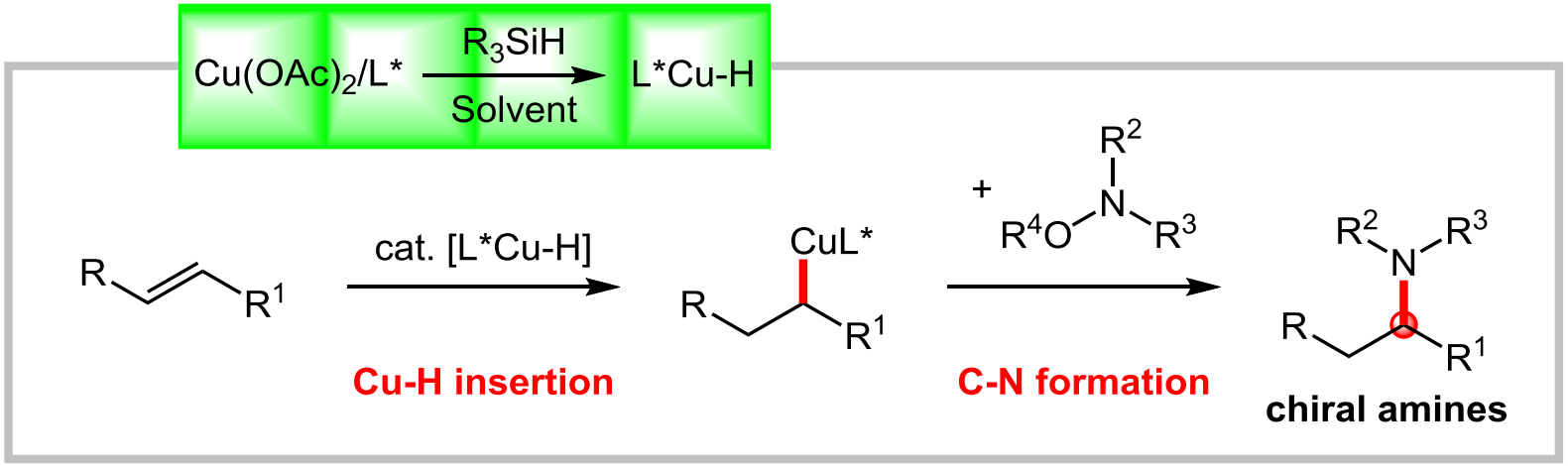
Introduction

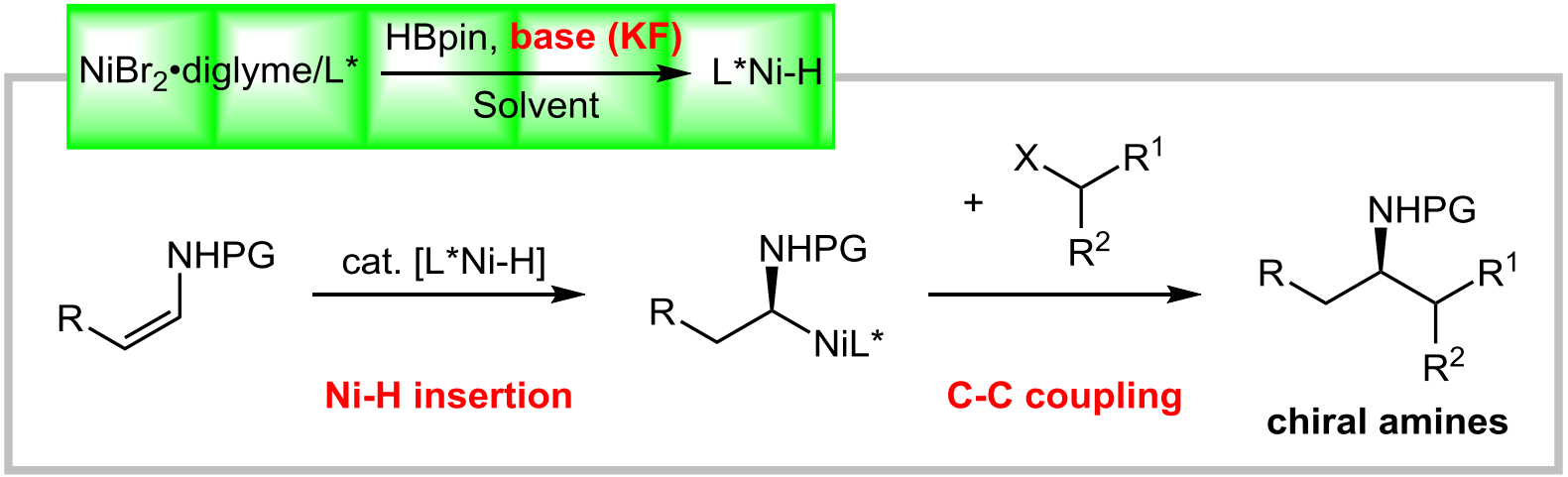
Cu-Catalytic Asymmetric Hydroamination of Enamines to Chiral 1,2-Diamines



Somfai, P. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 8551

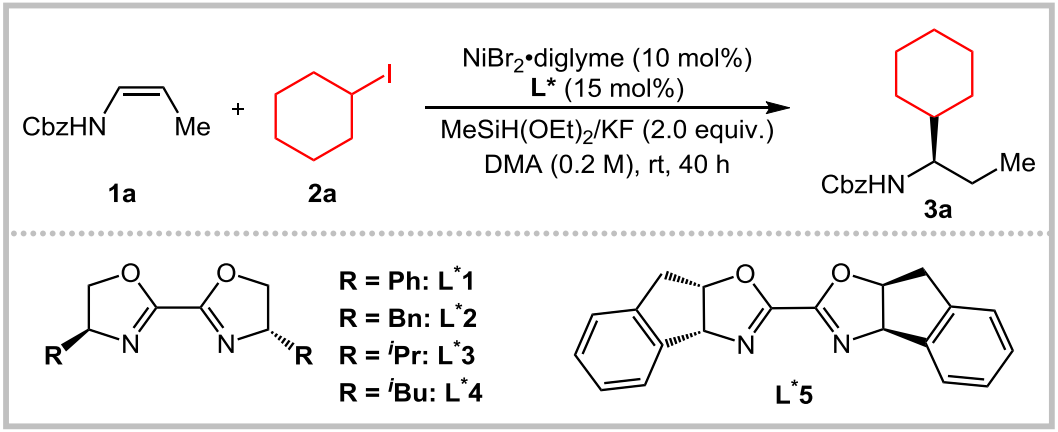
Chiral Alkyl Amine Synthesis via CEH of Enecarbamates





Hu, X. *et al*. *J*. *Am*. *Chem*. *Soc*. **2021**, *143*, 1959

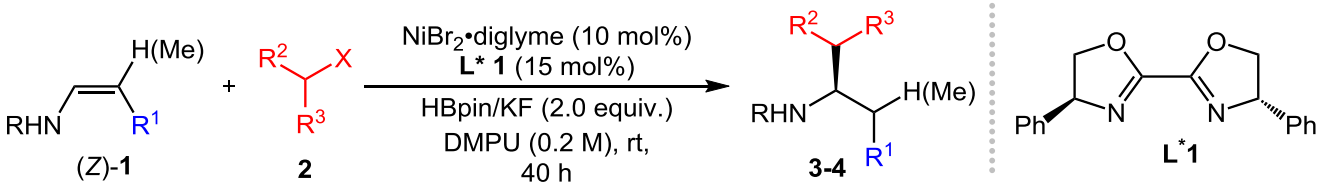
The Optimization[a]



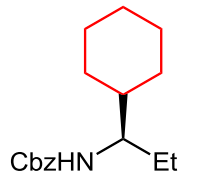
Entry	Variant	Yield (%)	Er[b]
1	**L* = L*1**	91	90:10
2	**L* = L*2**	83	65:35
3	**L* = L*3**	41	55:45
4	**L* = L*4**	97	70:30
5	**L* = L*5**	84	82:18
6	HBpin instead of DEMS	85	92:8
7	HBcat instead of DEMS	27	89:11
8	DMPU instead of DMA	92 (87)[c]	94:6

[a] All reactions were carried out in a 0.1 mmol scale with respect to **1a**, corrected GC yields using *n*-dodecane as an internal standard were reported. [b] The er values were determined by HPLC analysis. [c] Isolated yield.

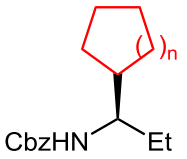
The Scope of Substrates[a]



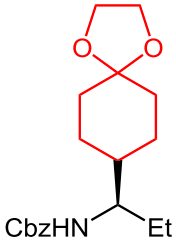
Secondary alkyl iodides



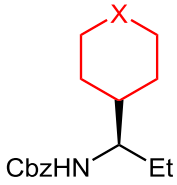
(+)-**3a** 87%, 94:6 er
with *ent*-**L*1**:
(-)-**3a** 85%, 6:94 er



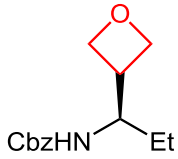
3b n = 1 86%, 91:9 er
3c n = 3 71%, 93:7 er



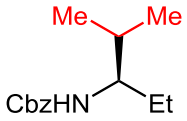
3d[b] 61%, 94:6 er



3e X = O 65%, 95:5 er
3f X = NBoc 67%, 93:7 er

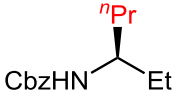


3g[b] 45%, 86:14 er

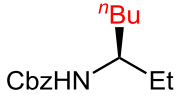


3h 91%, 93.5:6.5 er

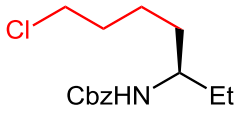
Primary alkyl iodides



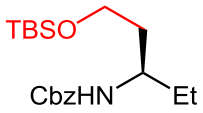
3i 71%, 92:8 er



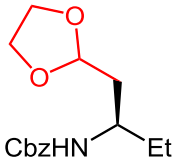
3j 81%, 94.5:5.5 er



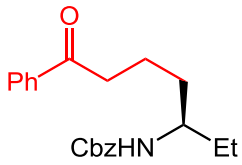
3k 74%, 95:5 er



3l 65%, 93:7 er



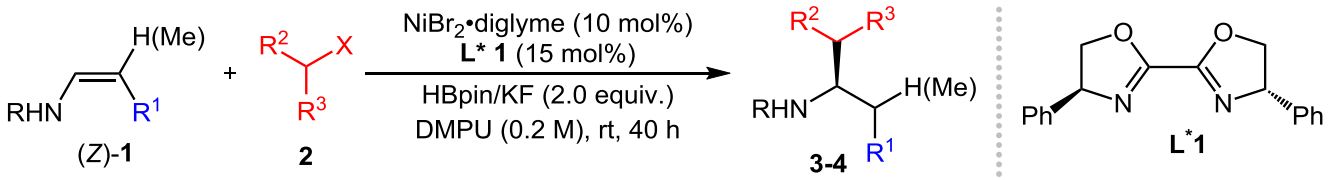
3m[b] 60%, 94:6 er



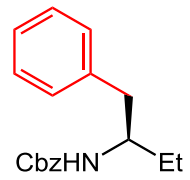
3n[c] 52%, 92:8 er

[a] Conditions unless noted otherwise: all reactions were carried out with $NiBr_2$·diglyme (15 mol %), ligand **L*1** (15 mol %), **1** (0.20 mmol), **2** (0.30 mmol), HBpin (0.40 mmol), KF (0.40 mmol), and DMPU (1.0 mL) at room temperature for 40 h. [b] $(OEt)_2MeSiH$ instead of HBpin. [c] DMA instead of DMPU.

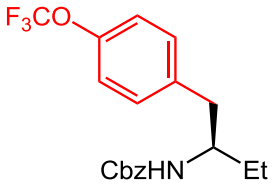
The Scope of Substrates[a]



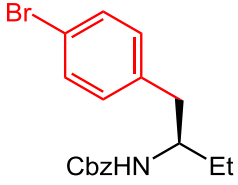
Benzylic bromides



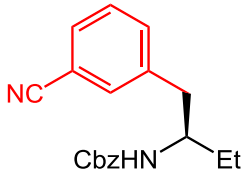
3o 92%, 95:5 er



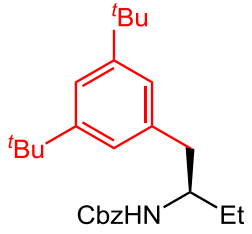
3p 82%, 95:5 er



3q 74%, 94.5:5.5 er

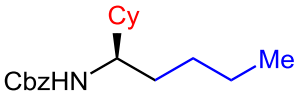


3r 51%, 95:5 er[b]

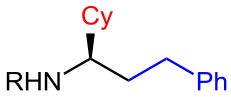


3s 95%, 94:6 er

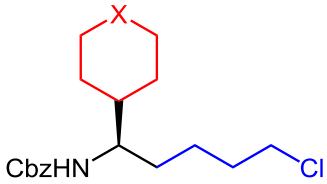
Enecarbamates



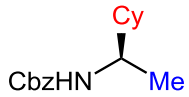
4a 63%, 94:6 er



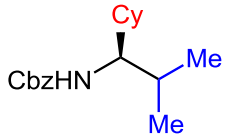
4b R = Cbz 83%, 95:5 er
4c R = Boc 82%, 86:14 er



4d X = CH_2 65%, 95:5 er
4e X = NBoc 72%, 93:7 er



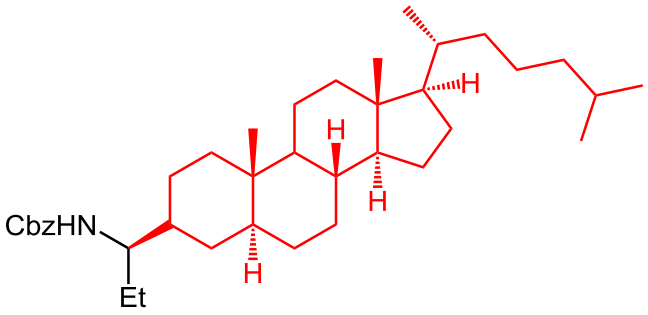
4f 85%, 93:7 er



4g 48%, 94:6 er

[a] Conditions unless noted otherwise: all reactions were carried out with $NiBr_2$·diglyme (15 mol %), ligand **L*1** (15 mol %), **1** (0.20 mmol), **2** (0.30 mmol), HBpin (0.40 mmol), KF (0.40 mmol), and DMPU (1.0 mL) at room temperature for 40 h. [b] $(OEt)_2MeSiH$ instead of HBpin. [c] DMA instead of DMPU.

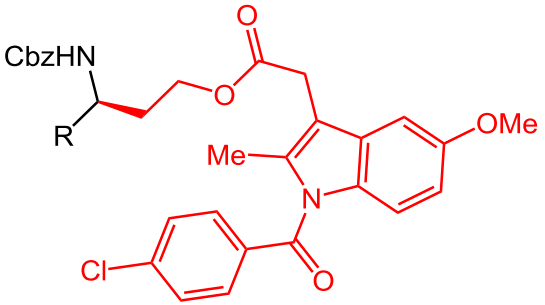
The Reactions of Substrates Derived[a]



from Cholestanol

5a, 85:15 dr[b]

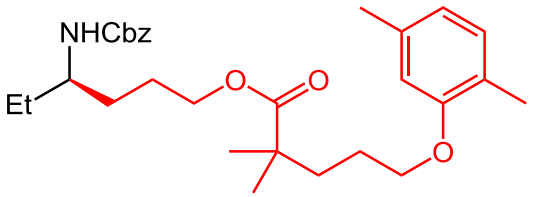
72%, 92.5:7.5 er



from Indomethacin

5b[d], R = Me, 45%, 93.5:6.5 er

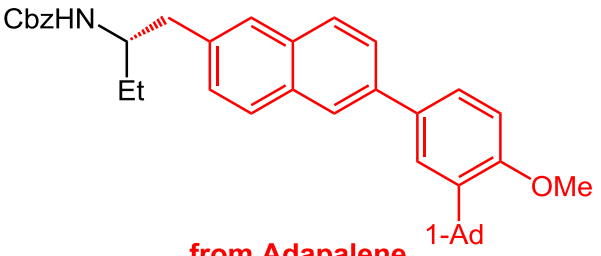
5c, R = Et, 38%, 92.5:7.5 er



from Gemifibrozil

5d[c]

82%, 93:7 er



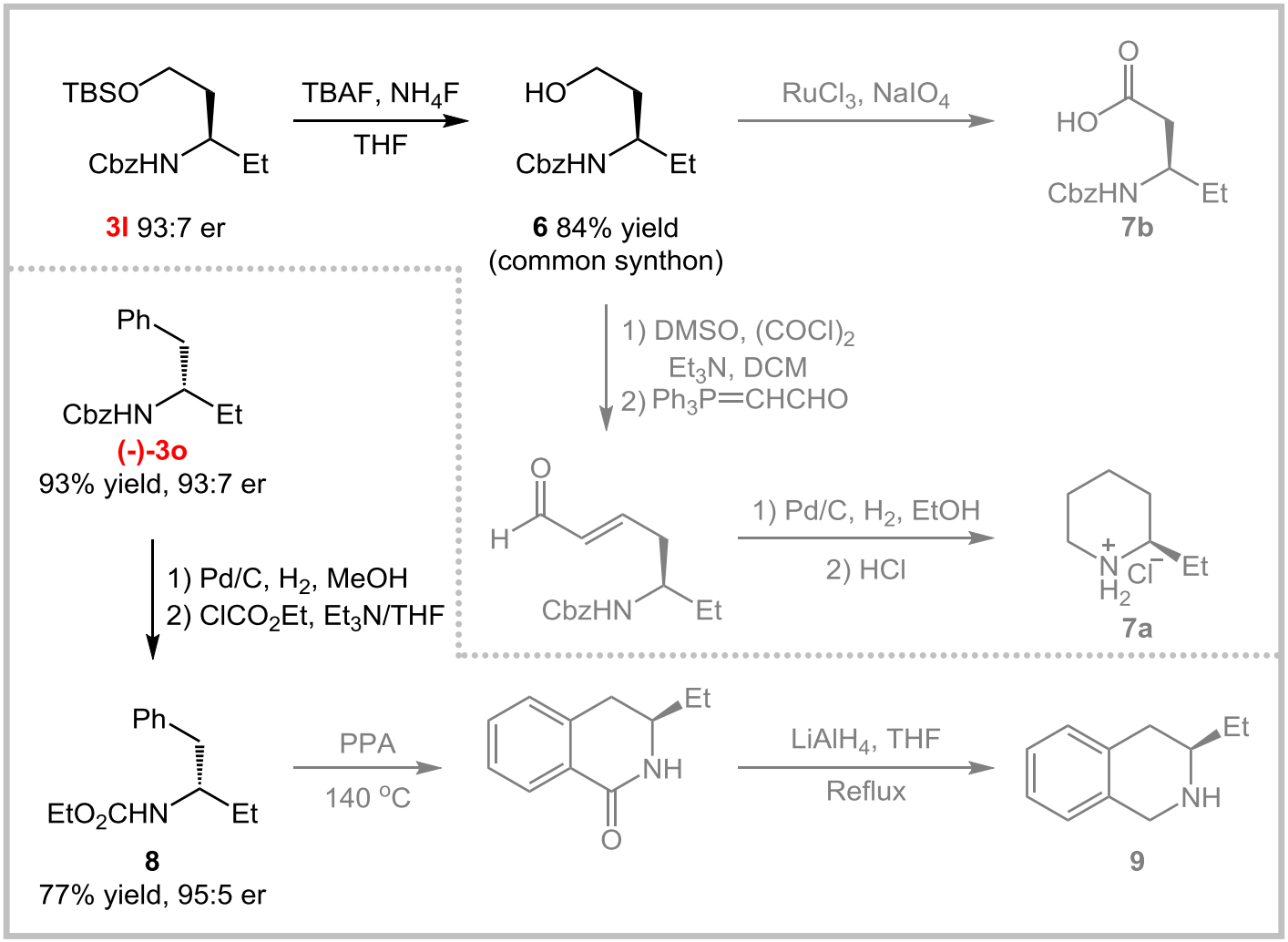
from Adapalene

5e[e]

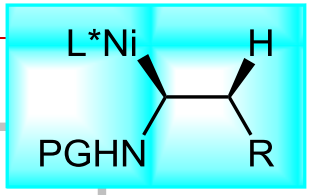
81%, 89:11 er

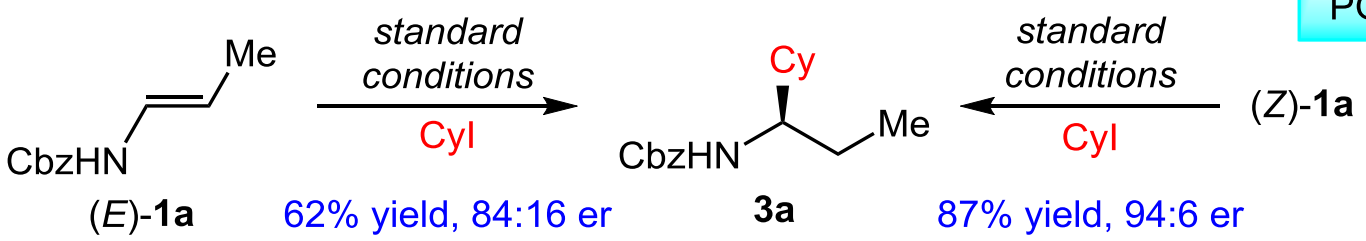
[a] Conditions unless specified otherwise: all reactions were carried out with $NiBr_2$·diglyme (15 mol %), ligand **L*1** (15 mol %), **1** (0.20 mmol), **2** (0.30 mmol), HBpin (0.40 mmol), KF (0.40 mmol), and DMPU (1.0 mL) at room temperature for 40 h. [b] The dr value was determined by ^1H NMR and HPLC analysis.[c] NiI_2·xH_2O, **L*9**, $(EtO)_3SiH$, and DMA instead of the corresponding standard parameters. [d] DMA instead of DMPU. [e] *ent*-**L*1** instead of **L*1**.

Product Transformations



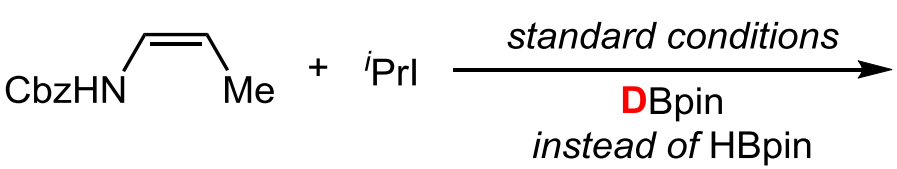
Mechanistic Experiments





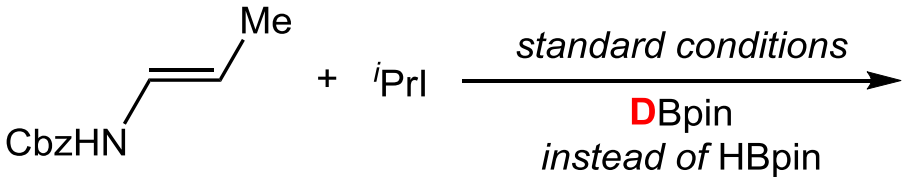
(*E*)-**1a** 62% yield, 84:16 er **3a** 87% yield, 94:6 er

NiH insertion into the alkene as the enantiodetermining step



(*Z*)-**1a**

D-3h, single diastereomer
89% yield, 92:8 er, (ca. 60% D)

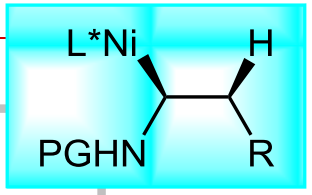


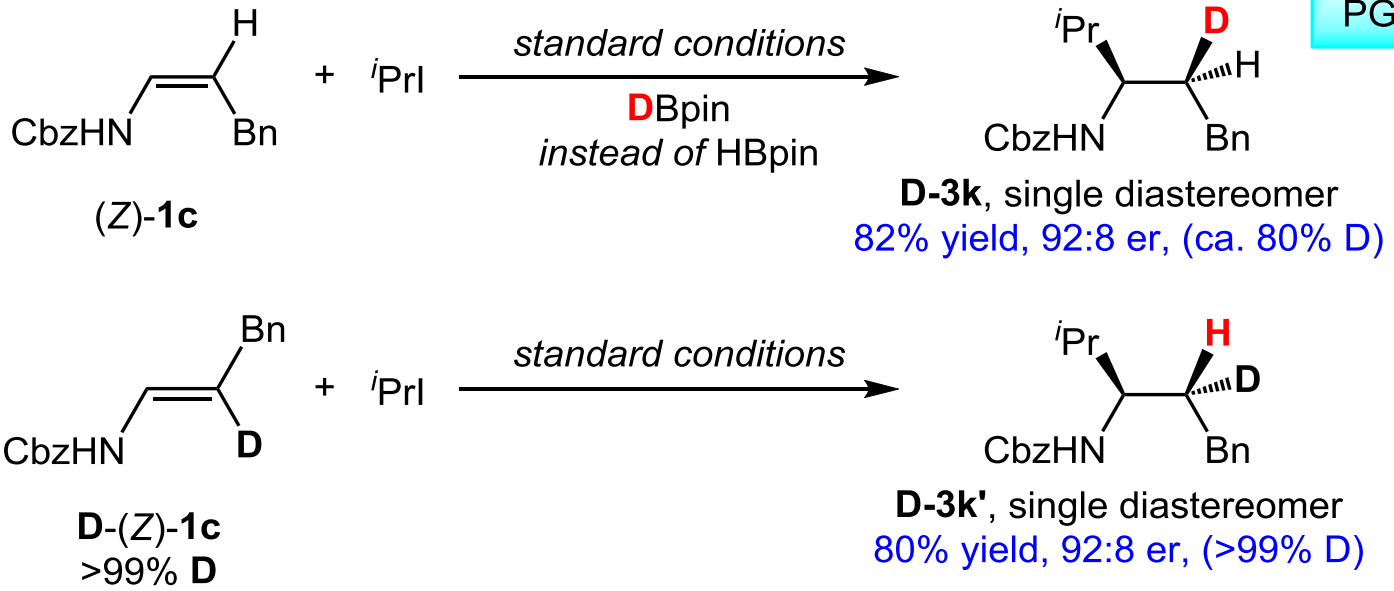
(*E*)-**1a**

D-3h', single diastereomer
51% yield, 89:11 er, (ca. 70% D)

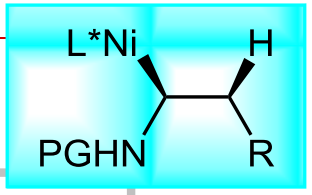
***syn*-hydrometalation of NiH or NiD to N-Cbz enamine**

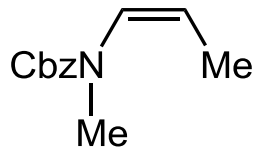
Mechanistic Experiments





Mechanistic Experiments

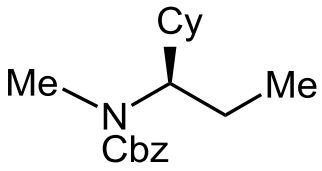




(*Z*)-**1a"**

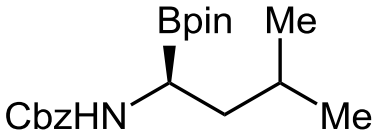
+ CyI

standard conditions



3a", <5%

precluded the Cbz group to act as a directing group for NiH insertion



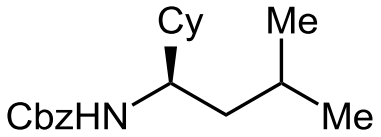
4h', >99:1 er

+ CyI

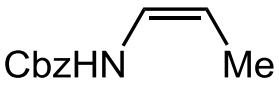
standard conditions

w/o HBpin

with **L*1** or *ent*-**L*1**



No reaction



(*Z*)-**1a**

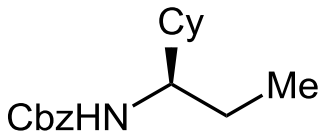
+ CyI

standard conditions

TEMPO (1.0 eq.)

(*Z*)-**1a**

46% recovered

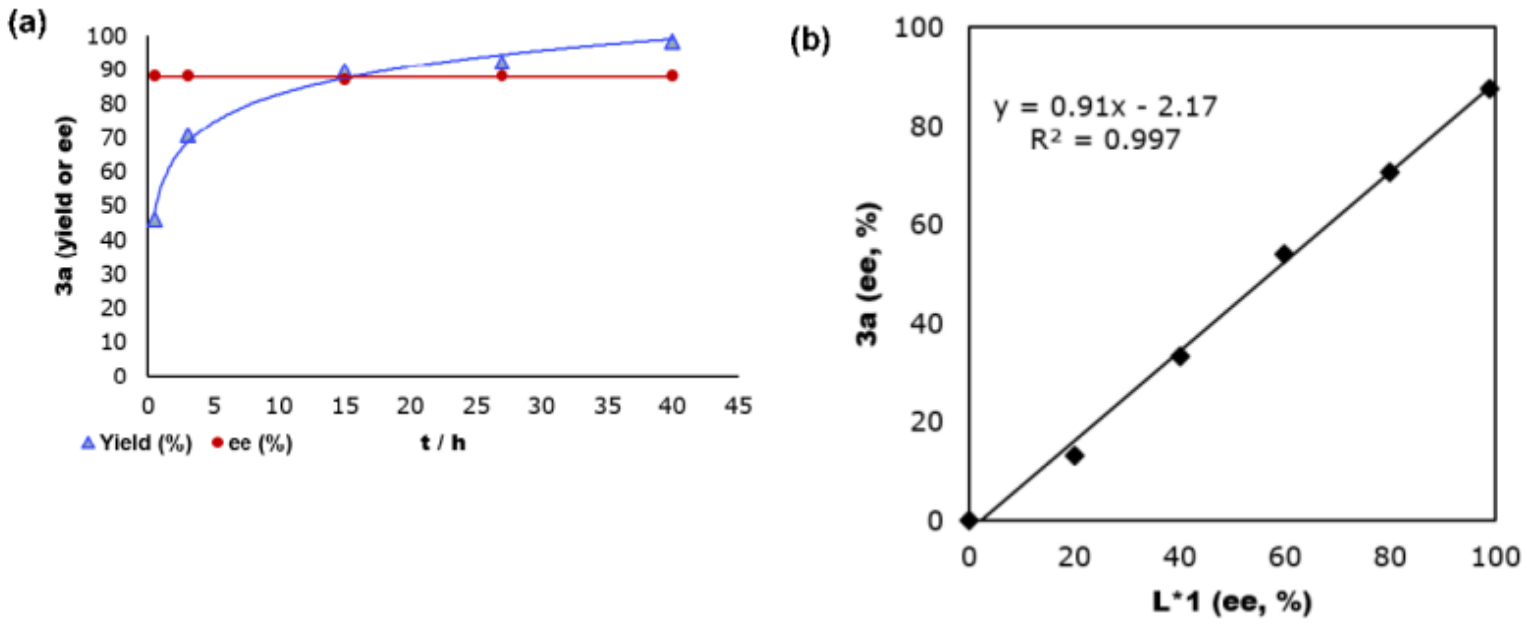


+ ^{n}PrNHCbz

3a

12%, 94:6 er

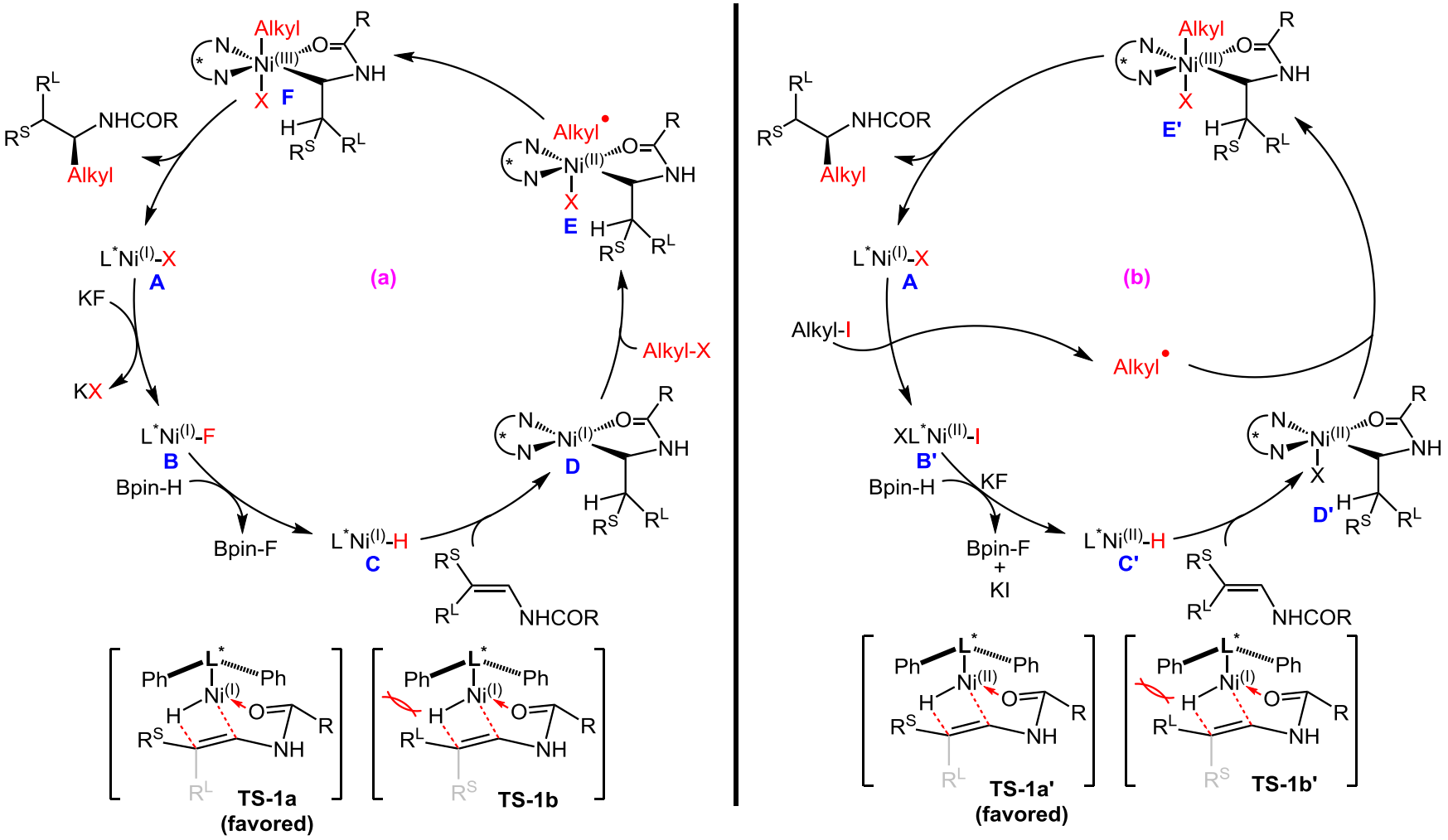
Mechanistic Experiments



(a) Monitoring of the reaction progress of (*Z*)-**1a** with **2a** over time. (b) Nonlinear effect study.

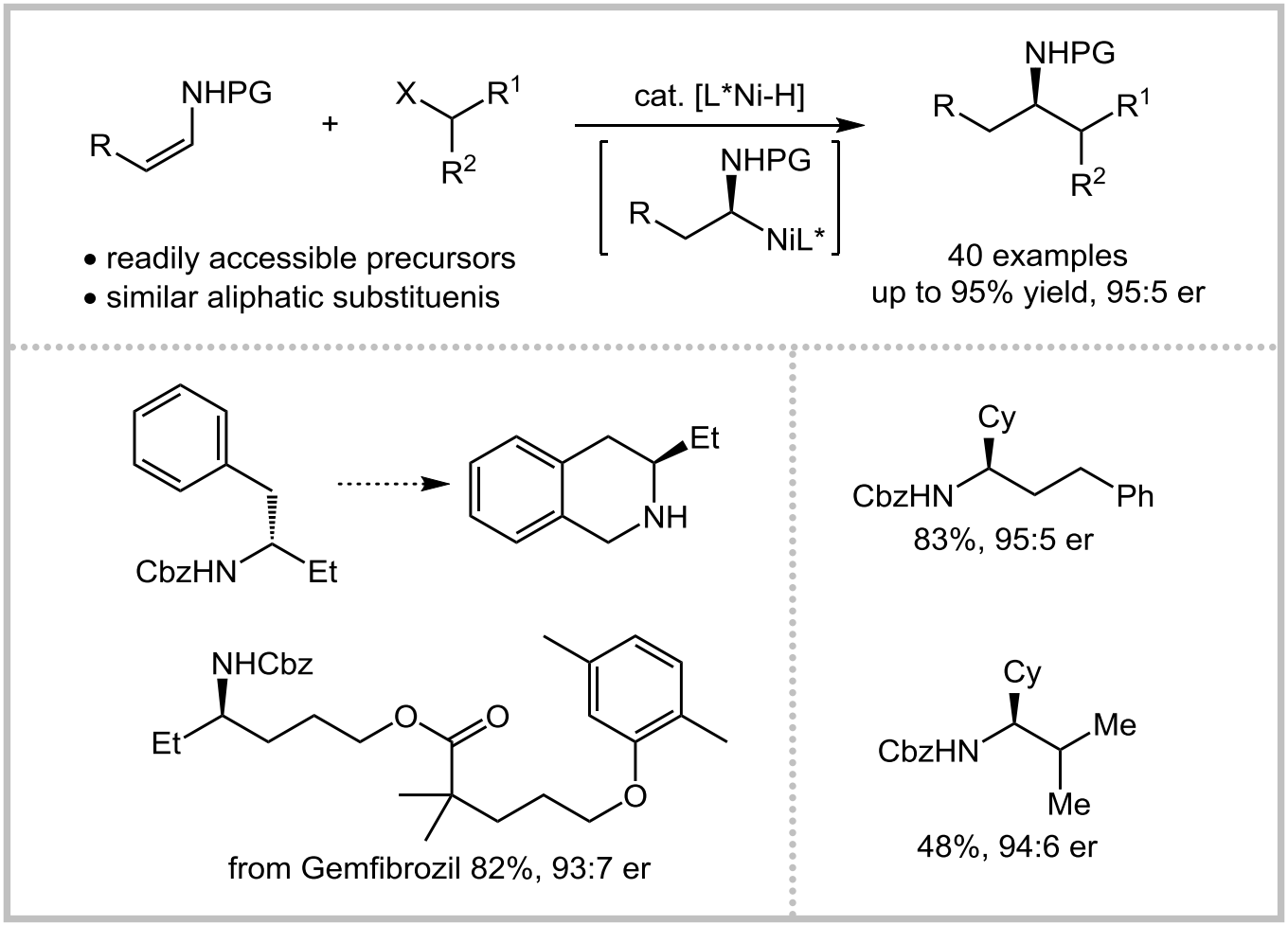
The reaction progress of (*Z*)-**1a** with **2a** was monitored over time. While the yield increased gradually over the course of the reaction, the er remained at about 94:6. This result ruled out a kinetic resolution mechanism. Moreover, the enantiomeric excess of the product and catalyst followed a linear relationship, indicating a monomeric nature of the active catalyst.

Proposed Catalytic Cycle



X = I, Br; R^L = large group; R^S = small group.

Summary


NHPG
R
+
X
R1
R2
cat. [L*Ni-H]
NHPG
R
NiL*
NHPG
R
R1
R2
• readily accessible precursors
• similar aliphatic substituenis
40 examples
up to 95% yield, 95:5 er
CbzHN
Et
Et
NH
from Gemfibrozil 82%, 93:7 er
Cy
CbzHN
Ph
83%, 95:5 er
Cy
CbzHN
Me
Me
48%, 94:6 er

写作思路

化合物的重要性

⇩

目前文献成功报道构建手性胺的一些方法，并指出其缺陷。

The First Paragraph

Enantiomerically pure amines are frequently encountered in natural products, pharmaceuticals, and agrochemicals. They are also important building blocks and chiral auxiliaries in asymmetric synthesis. General, catalytic, and enantioselective assembly of chiral amines, especially those with two minimally differentiated aliphatic substituents, represents a synthetic challenge. Although chiral amines can be prepared by the hydrogenation of imines, enamines, and their derivatives using precious-metal catalysts, the catalysts are costly and the substrates typically have an *α*-aryl or *α*-carboxyl substituent. Likewise, enantioselective addition of an alkyl organometallic reagent or an alkyl radical to imine derivatives is mostly applicable to the synthesis of chiral amines with one *α*-aryl or *α* carboxyl group, in addition to requiring either highly activated substrates or high catalyst loadings.

The First Paragraph

Nevertheless, trisubstituted, tetrasubstituted, and cisdisubstituted alkenes and alkenes bearing electron-donating substituents are still difficult substrates, limiting the types of chiral amines that can be prepared from this approach.

The Last Paragraph

写作思路

总结工作

指出工作优点

The Last Paragraph

In summary, we have developed a method for the Ni-catalyzed enantioselective hydroalkylation of enecarbamates. This method allows the synthesis of a wide range of enantiomerically enriched chiral alkyl amines from readily available and stable alkenes while avoiding sensitive organometallic reagents. The method operates under mild conditions and has high functional group tolerance. It has been applied for the postfunctionalization of many natural products and drug molecules.

Representative Examples

Likewise, enantioselective addition of an alkyl organometallic reagent or an alkyl radical to imine derivatives is mostly applicable to the synthesis of chiral amines with one *α*-aryl or *α* carboxyl group, in addition to requiring either highly activated substrates or high catalyst loadings. (同样…，此外…)

Here we describe the development of a modular method based on this approach. (基于…)

It has been applied for the postfunctionalization of many natural products and drug molecules. (后期官能化)

Acknowledgement

Thanks
for your attention