Literature Report 4

Ruthenium-Catalyzed Hydroamination of Unactivated Terminal Alkenes

Reporter: Wen-Jun Huang
Checker: Li-Xia Liu
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Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2021**, *143,* 359−368.

Contents

CV of Prof. John F. Hartwig

Background:

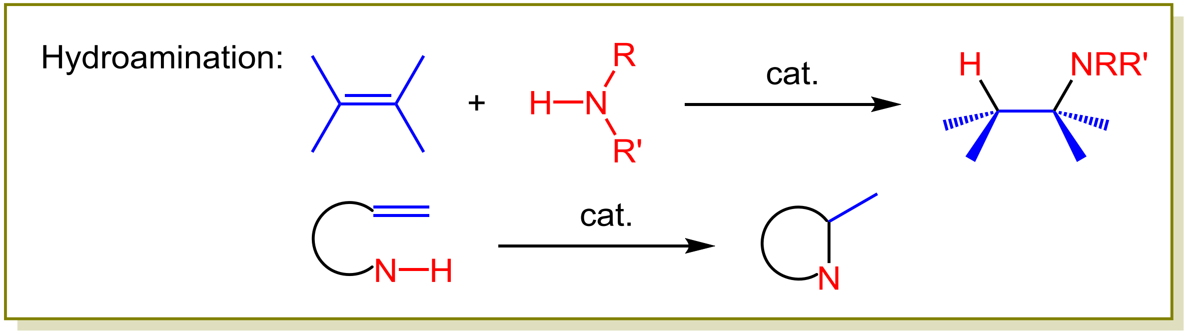
- **1986** B.A., Princeton University
- **1990** Ph.D., University of California, Berkeley
- **1990-1992** Postdoc., Massachusetts Institute of Technology
- **1992-2006** Yale University
- **2006-2011** University of Illinois Urbana-Champaign
- **2011-Now** University of California, Berkeley

Research:

Focuses on the discovery and understanding of new reactions catalyzed by transition metal complexes.

Introduction

烯烃的氢胺化：一类形式上将N-H键加成到碳碳不饱和键的反应，是一种基础而又具有挑战性的有机转化，它可以从两种丰富的化学原料(烯烃和胺)中产生烷基胺，并具有全原子的经济性。

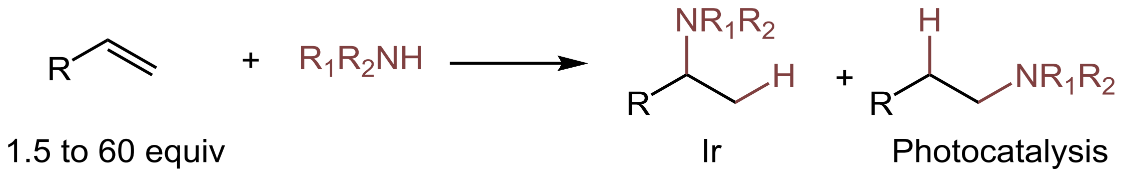


传统的合成胺的方法：有机卤化物的亲核取代、羰基化合物的还原胺化、以及酰胺、腈和叠氮化物的还原。过渡金属配合物催化的烯烃氢胺化是一种很有吸引力的替代方法，因为它直接与烯烃反应，可以应用于简单烯烃和含烯烃单元的复杂分子的官能化。

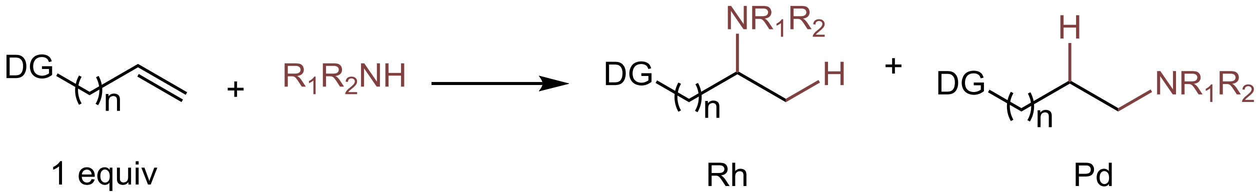
Introduction

Catalytic Hydroamination of Unactivated Terminal Alkenes

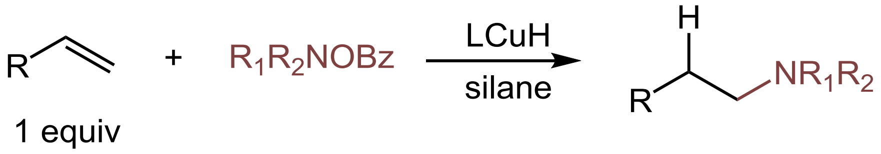
A. Hydroamination of unactivated alkenes with large excess of alkene



B. Directed hydroamination of unactivated alkenes

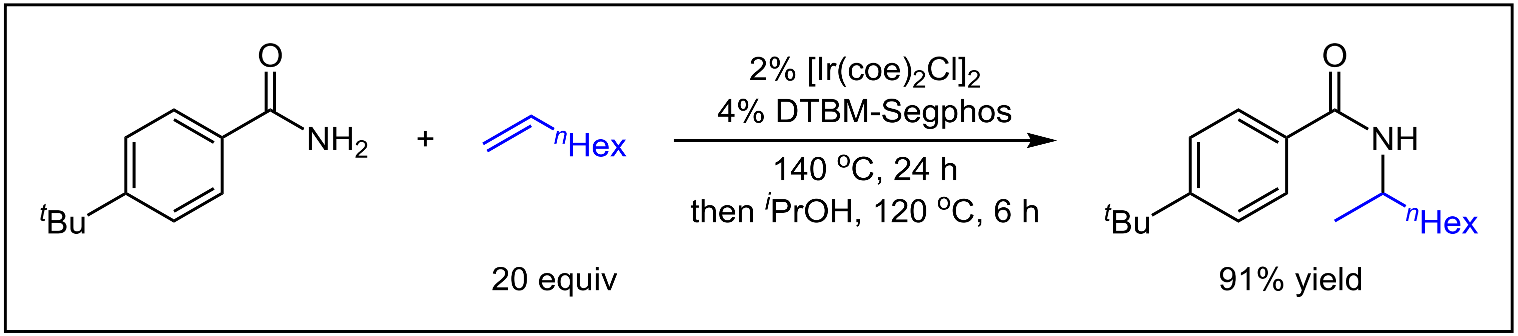


C. CuH-catalyzed formal hydroamination of unactivated alkenes



Introduction

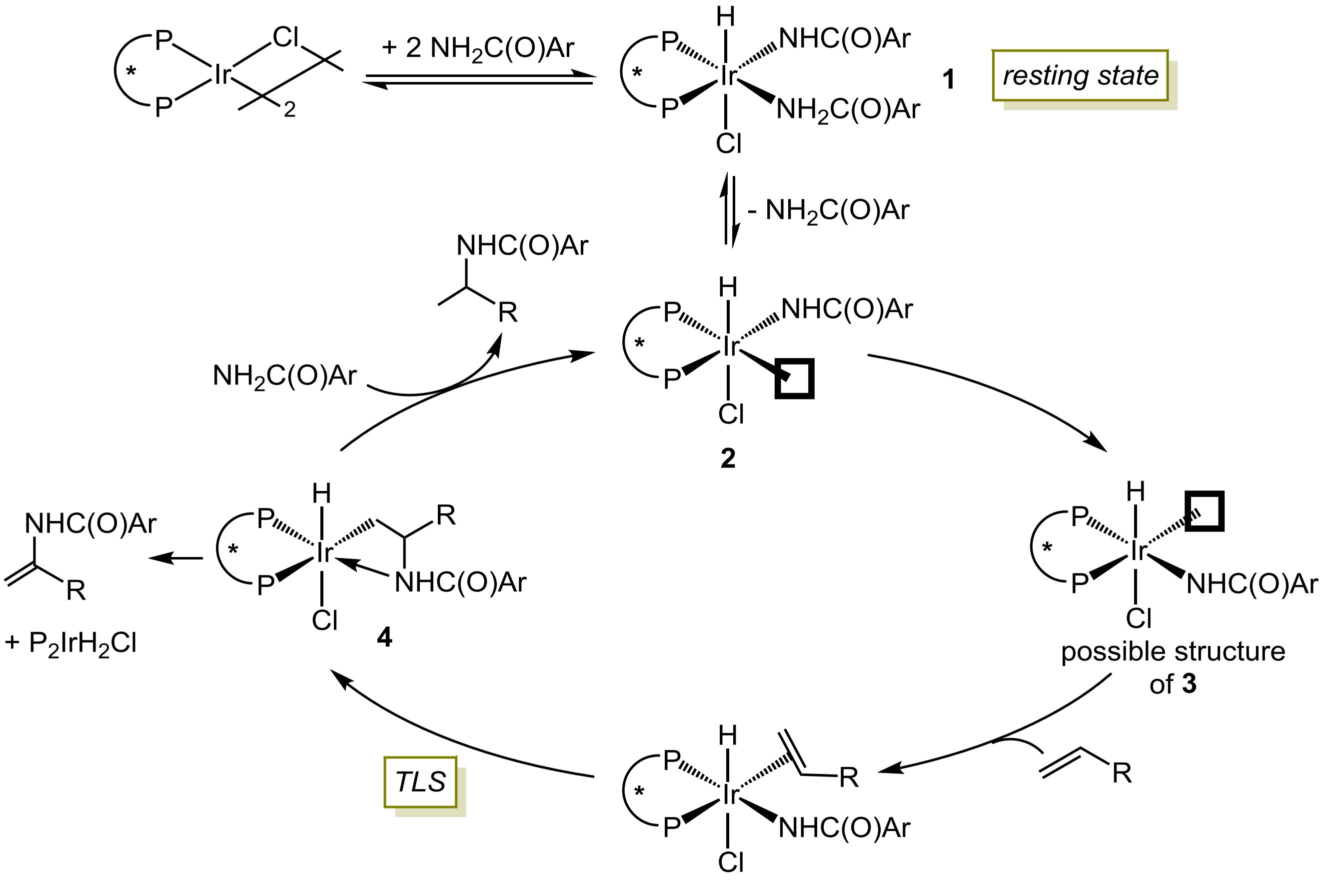
A. Hydroamination of unactivated alkenes with large excess of alkene



Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2012**, *134*, 11960.

Introduction

Proposed Catalytic Cycle



resting state

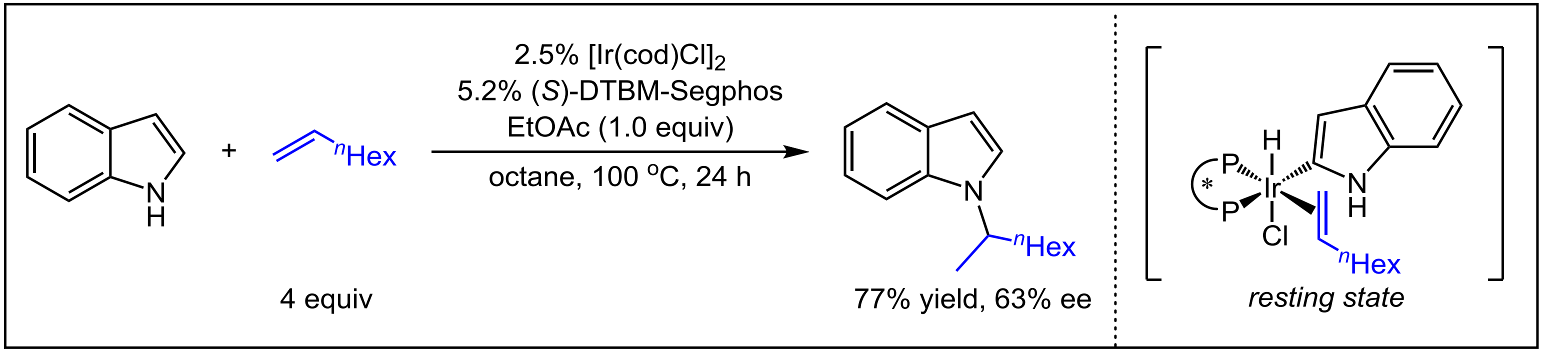
possible structure of **3**

TLS

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2012**, *134*, 11960.

Introduction

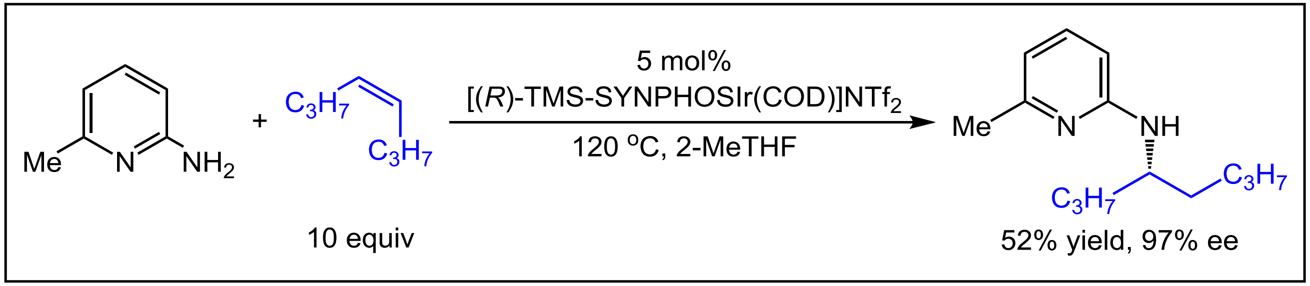
A. Hydroamination of unactivated alkenes with large excess of alkene

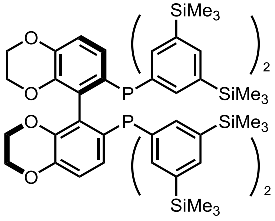


Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2014**, *136*, 3200.

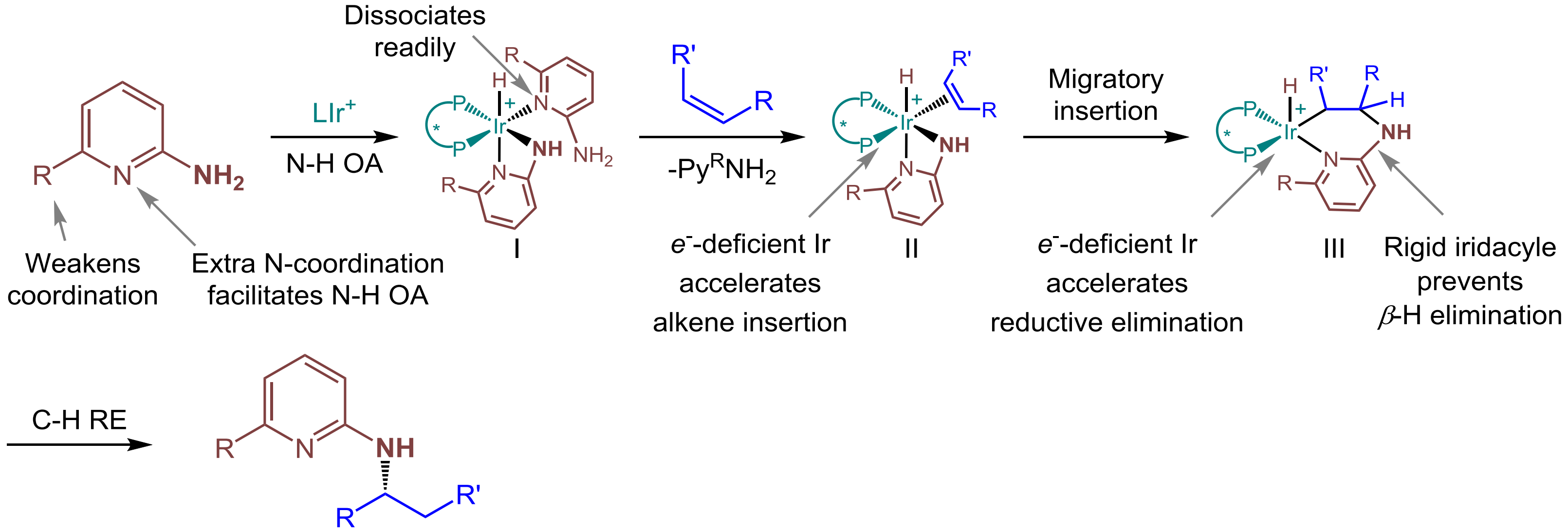
Introduction

A. Hydroamination of unactivated alkenes with large excess of alkene





(*R*)-TMS-SYNPHOS



Weakens coordination

Extra N-coordination facilitates N-H OA

Dissociates readily

e⁻-deficient Ir accelerates alkene insertion

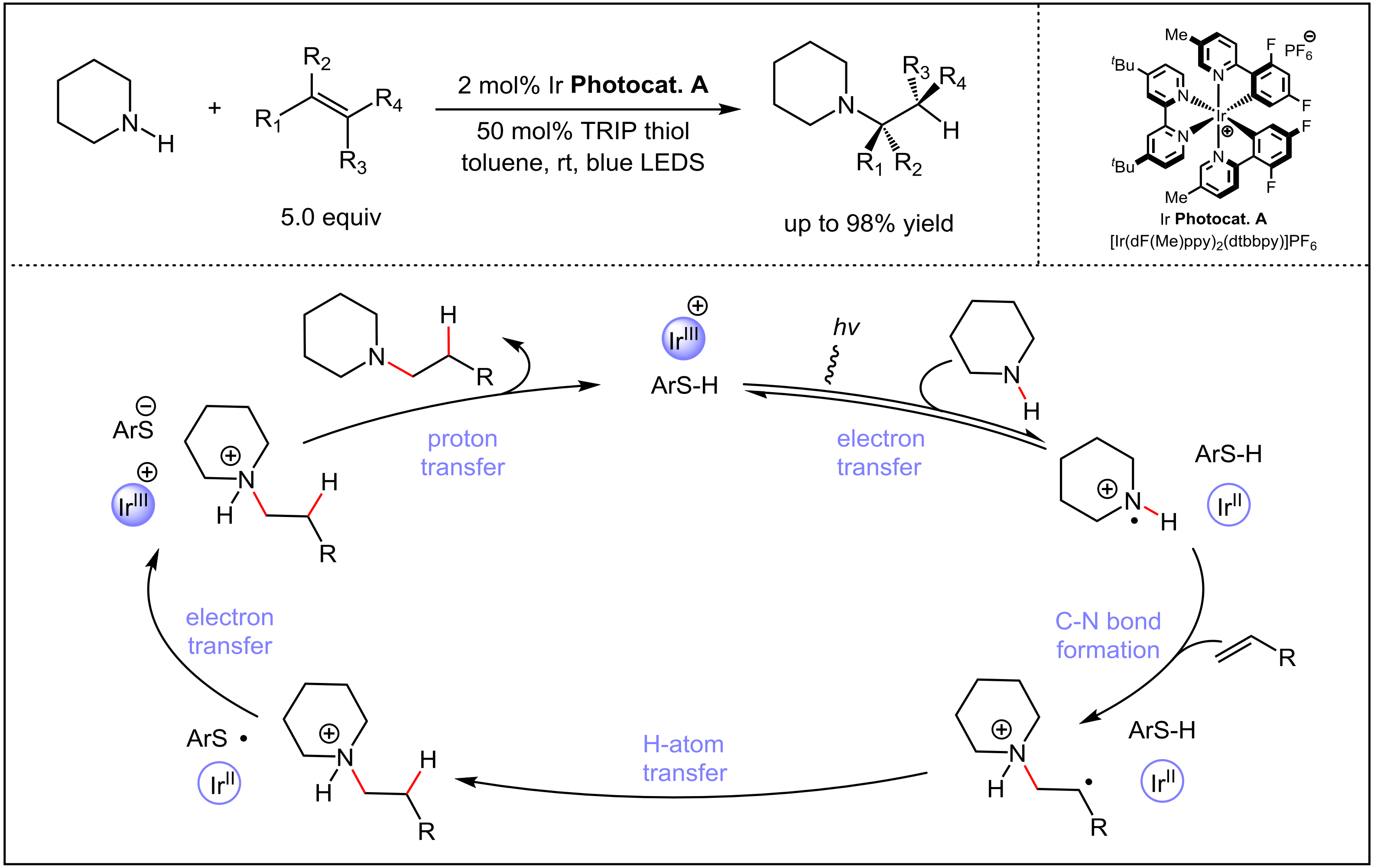
e⁻-deficient Ir accelerates reductive elimination

Rigid iridacyle prevents *β*-H elimination

Hartwig, J. F. *et al. Nature* **2020**, *588*, 254.

Introduction

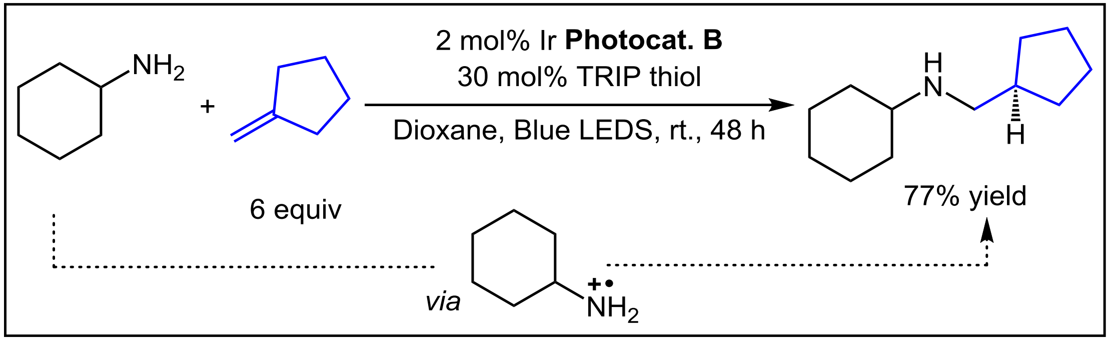
A. Hydroamination of unactivated alkenes with large excess of alkene

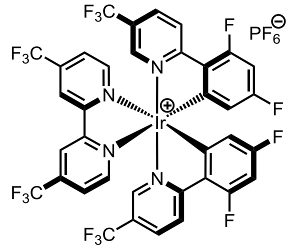


Knowles, R. R. *et al.* *Science* **2017**, *355*, 727.

Introduction

A. Hydroamination of unactivated alkenes with large excess of alkene



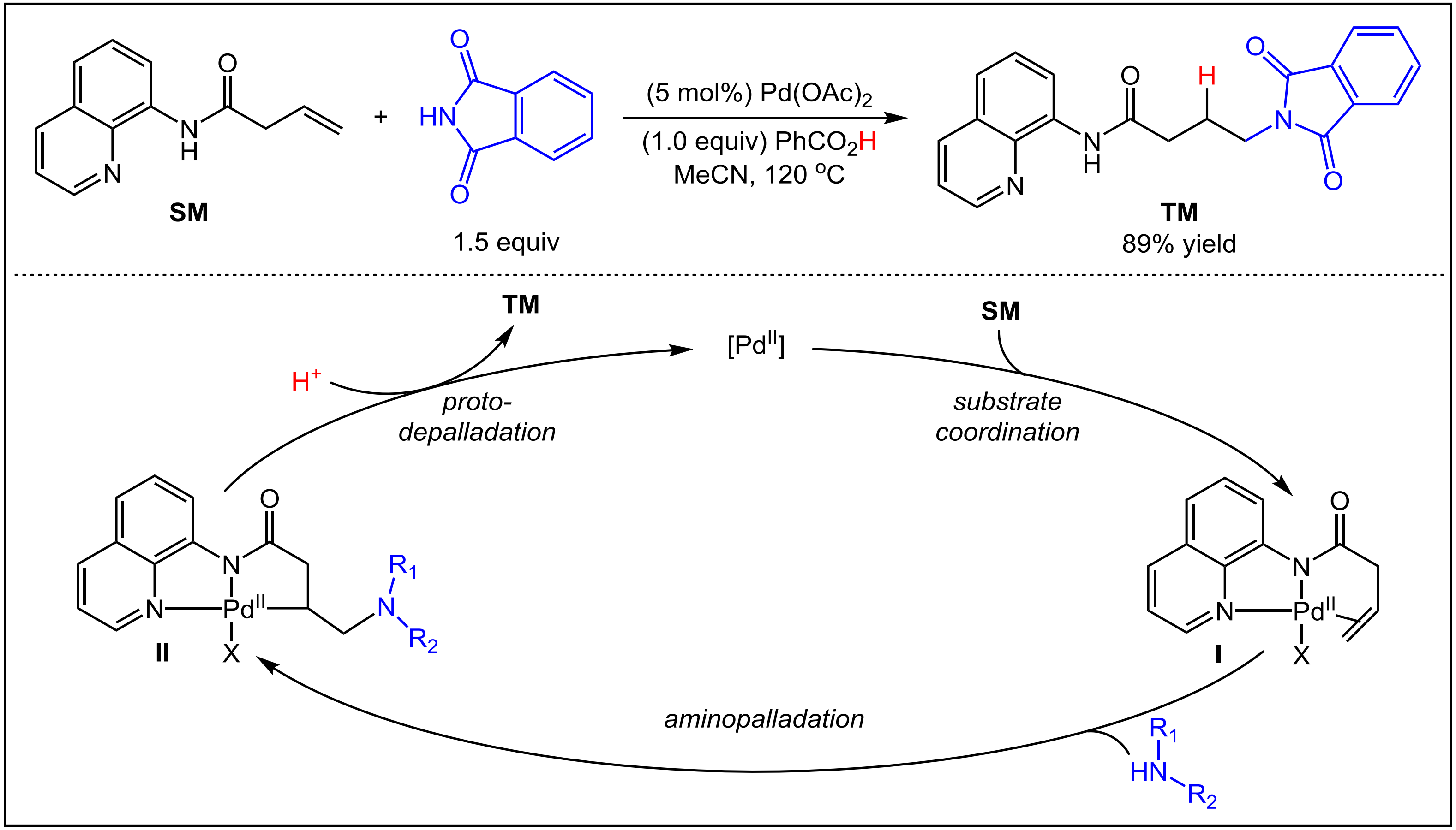


Ir **Photocat. B**
[Ir(dF(CF$_3$)ppy)$_2$(4,4'-d(CF$_3$)-bpy)]PF$_6$

Knowles, R. R. *et al*. *J. Am. Chem. Soc.* **2019**, *141*, 16590.

Introduction

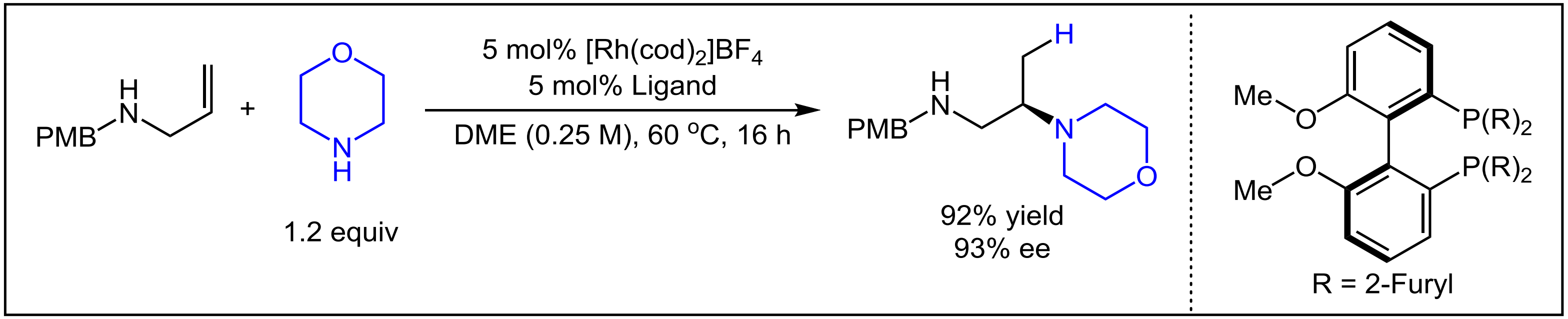
B. Direcred hydroamination of unactivated alkenes



Engle, K. M. *et al*. *J. Am. Chem. Soc.* **2016**, *138*, 5805.

Introduction

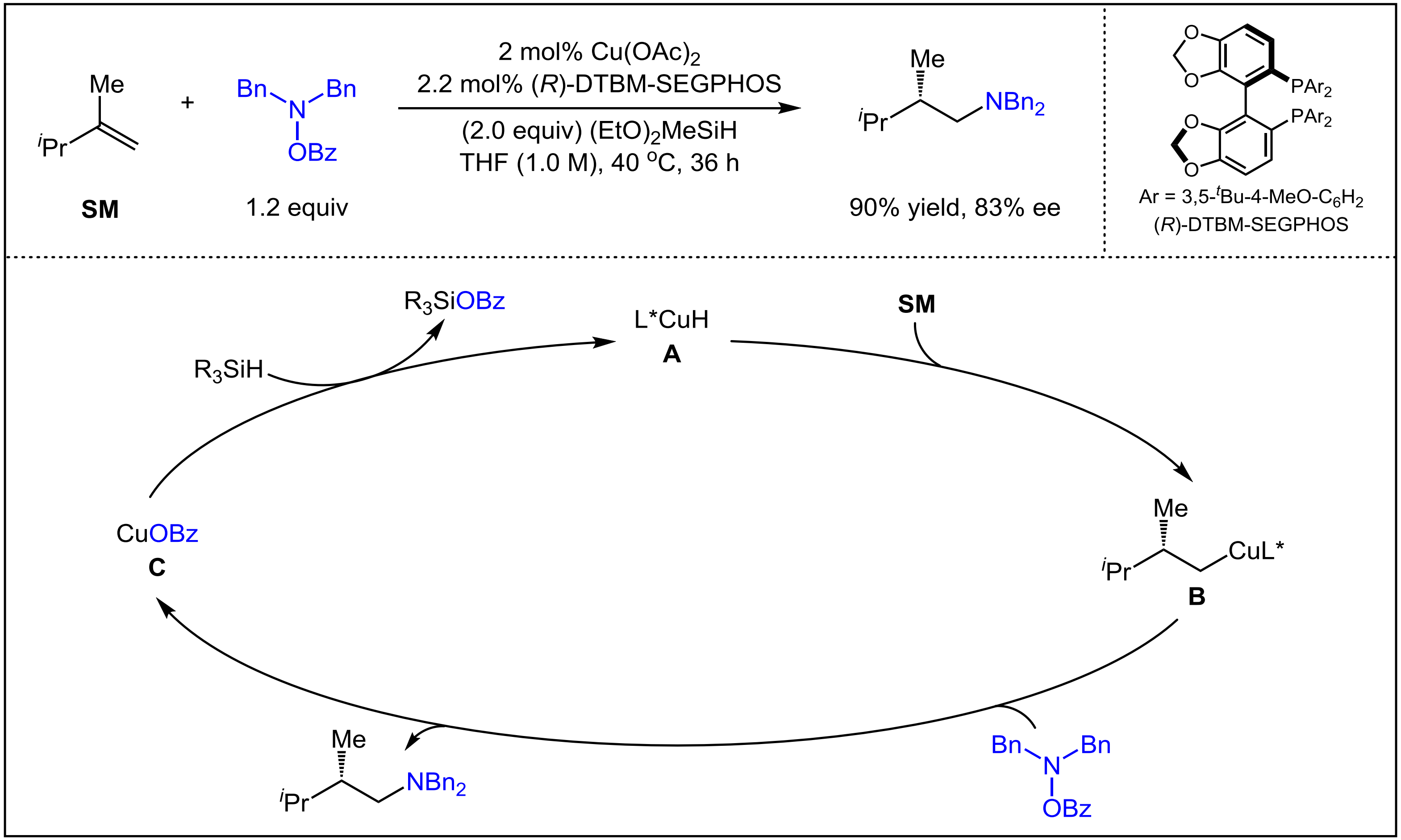
B. Directed hydroamination of unactivated alkenes



Hull, K. L. *et al. J. Am. Chem. Soc.* **2019**, *141*, 739.

Introduction

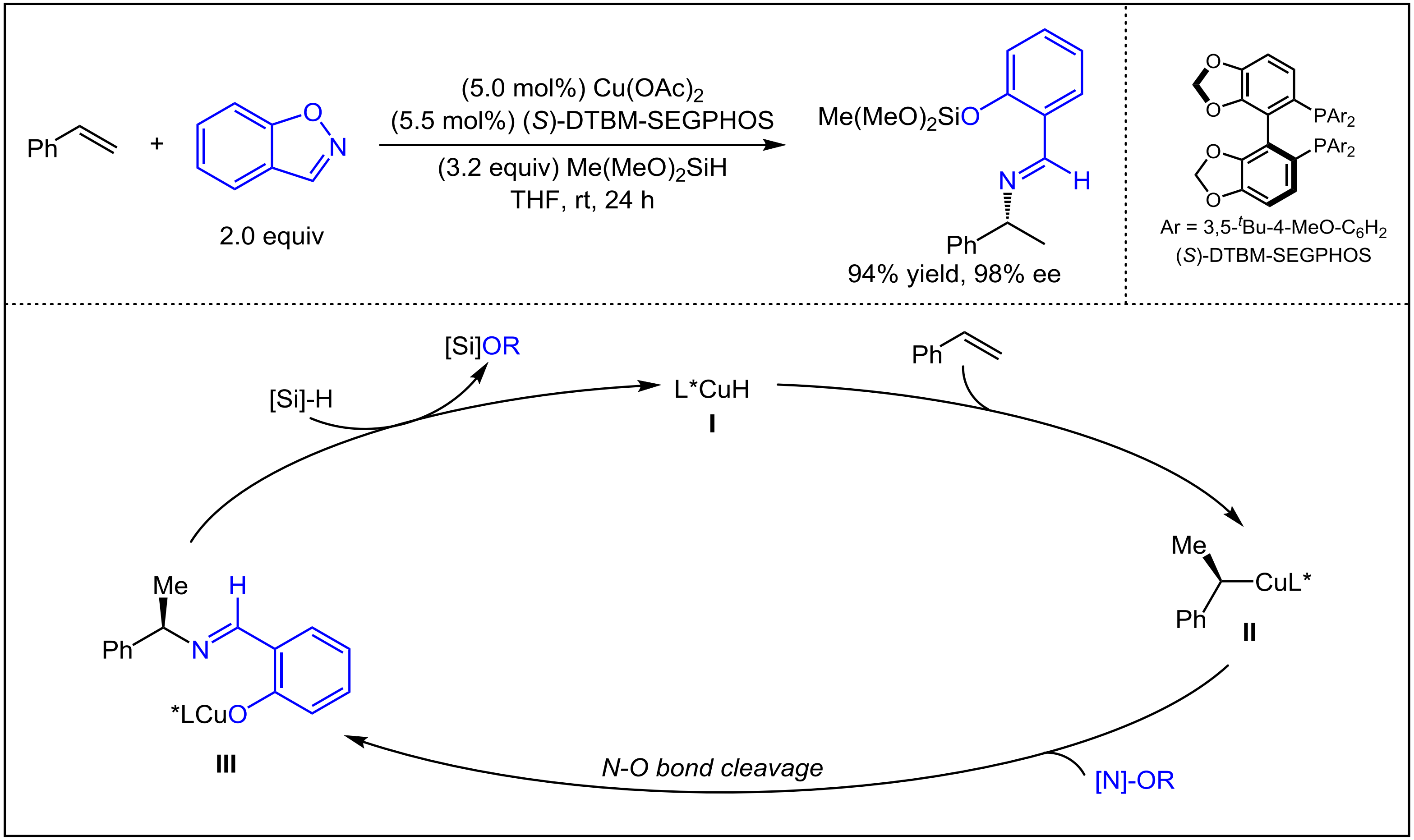
C. CuH-catalyzed formal hydroamination of unactivated alkenes



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

Introduction

C. CuH-catalyzed formal hydroamination of unactivated alkenes



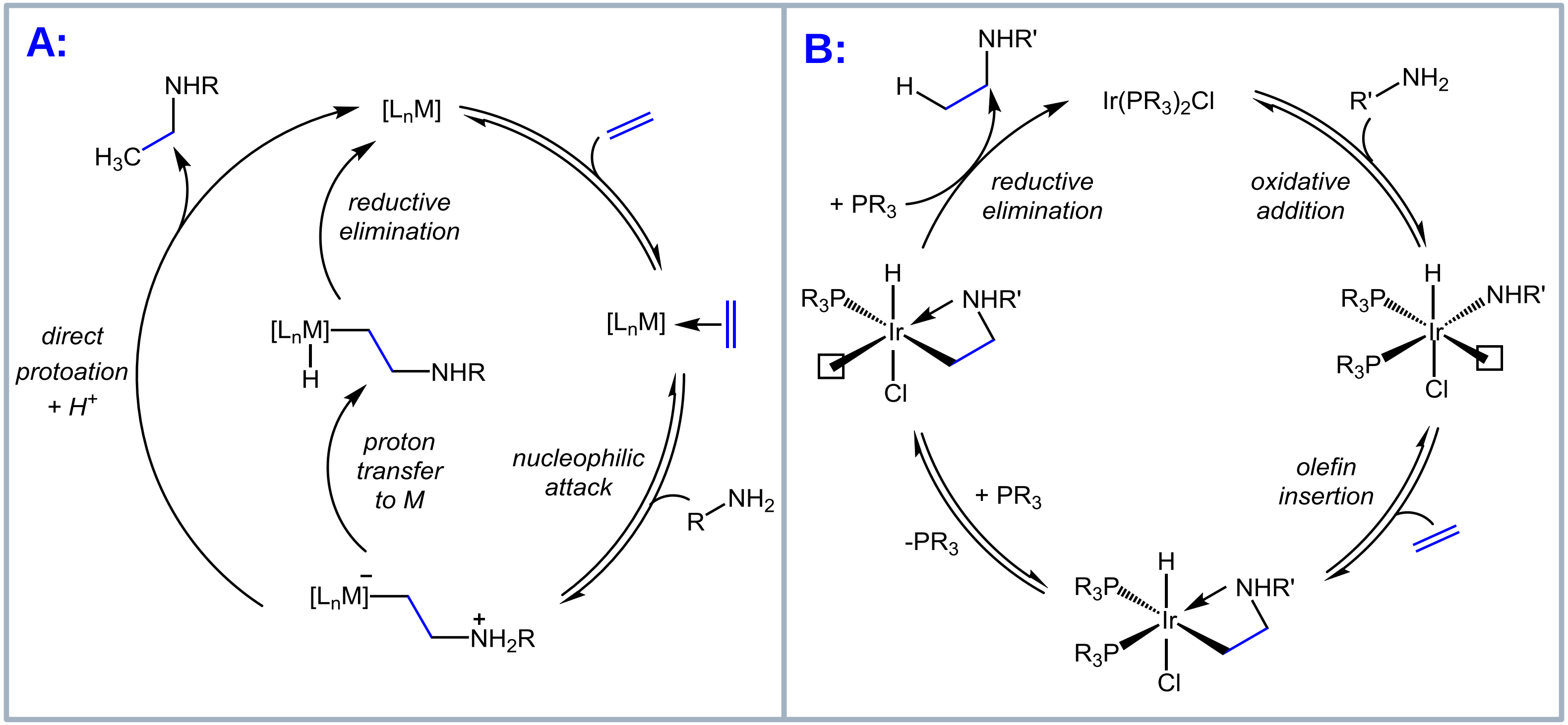
Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2018**, *140*, 15976.

Introduction

Mechanism of Transition Metal Catalyzed Hydroamination

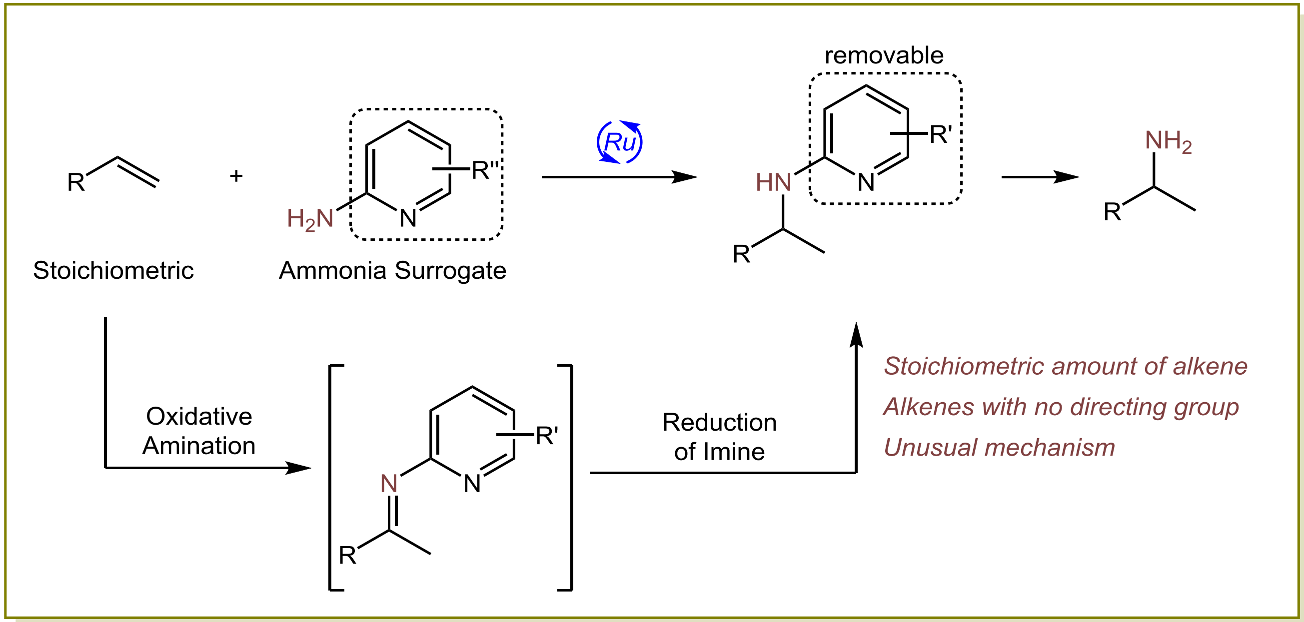
主要遵循两大类机理：

- ➢ 氮亲核试剂对配位烯烃的亲核进攻，氨基烷基中间体的质子化。
- ➢ 胺的氧化加成后，插入烯烃并还原消除。



Introduction

This work: Ru-catalyzed hydroamination of unactivated alkenes



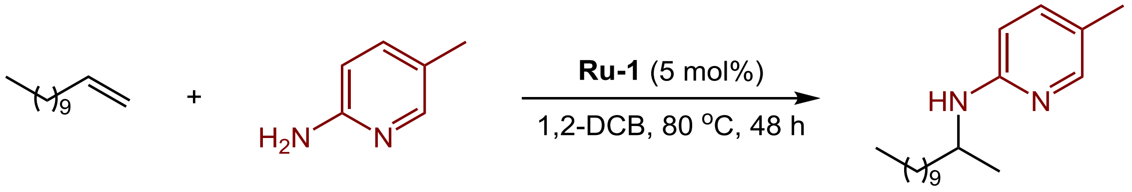
Stoichiometric amount of alkene

Alkenes with no directing group

Unusual mechanism

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2021**, *143,* 359.

Evaluation of the Conditions



1a

2a

entry [a]	conditions	yield (%) [b]
1	standard	67
2	**Ru-2** as catalyst	43
3	**Ru-3** as catalyst	18
4	**Ru-4** as catalyst	<1
5	**Ru-5** as catalyst	<1
6	**Ru-6** as catalyst	<1
7	**Ru-7** as catalyst	62
8	**Ru-8** as catalyst	<1

[a] Standard condition: 1-dodecene (0.2 mmol), **Ru-1** (0.01 mmol), **1a** (0.2 mmol), 1,2-DCB (50 μL), 80 °C, 48 h. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard.

Ru-1: $Ru(PEt_3)_3NTf_2$

Ru-2: $Ru(P^nPr_3)_3NTf_2$

Ru-3: $Ru(PMePh_2)_3NTf_2$

Ru-4: $Ru(PMe_3)_3NTf_2$

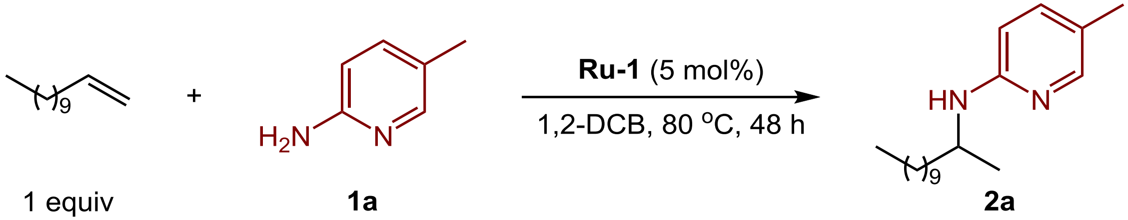
Ru-5: $Ru(Et_2P(CH_2)_4PEt_2)_2NTf_2$

Ru-6: $Ru(N(CH_2PEt_2)_3NTf_2$

Ru-7: $[Ru_2(PEt_3)_6(OTf)_3](OTf)$

Ru-8: $[Ru_2(PEt_3)_6Cl_3]Cl$

Evaluation of the Conditions



entry [a]	conditions	yield (%) [b]
9	1,2-DCE as solvent	<1
10	toluene as solvent	29
11	PhCl as solvent	48
12	CH_3CN as solvent	<1
13	THF as solvent	56
14	dioxane as solvent	61
15	**Ru-1** (2 mol %)	45
16	no **Ru-1**	<1
17	$HNTf_2$ (5 mol %)	<1

[a] Standard condition: 1-dodecene (0.2 mmol), **Ru-1** (0.01 mmol), **1a** (0.2 mmol), 1,2-DCB (50 μL), 80 °C, 48 h. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard.

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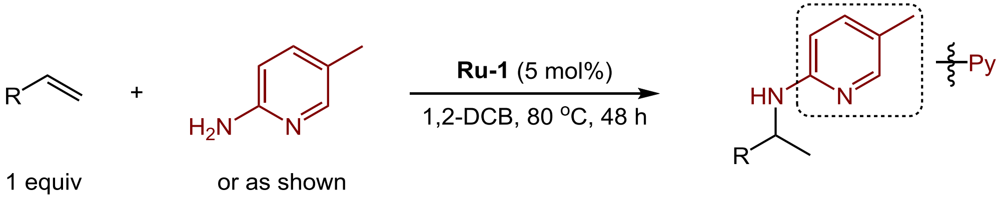
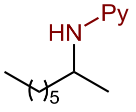
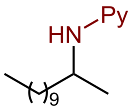
Ru-7: $[Ru_2(PEt_3)_6(OTf)_3](OTf)$

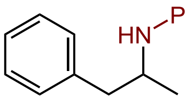
Ru-8: $[Ru_2(PEt_3)_6Cl_3]Cl$

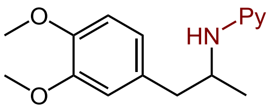
Scope of Alkenes and 2-Aminopyridines

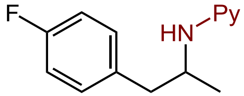


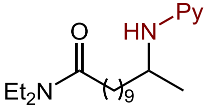

2a, 62%, 93%[e]

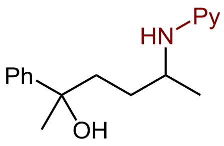

3a, 63%

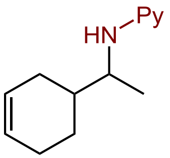

4a, 66%

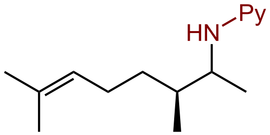

5a, 52%

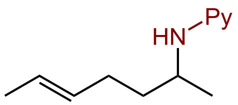

6a, 56%

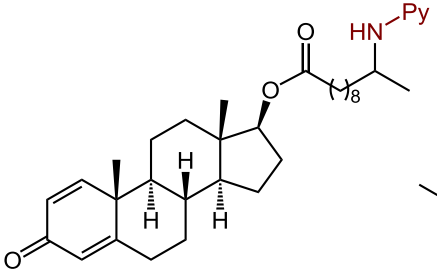

7a, 66%

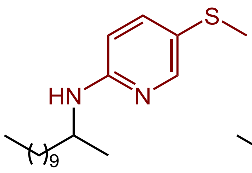

8a, 42% 1:1 dr[c]
83% 1;1 dr[c,e,f]

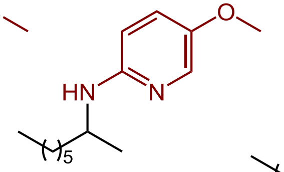

9a, 61% 1.5:1 dr[b,c]

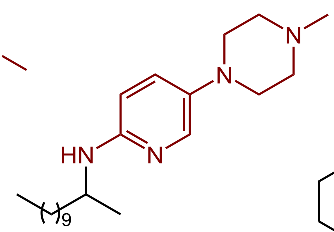

10a, 57% 2.5:1 dr[b,c]

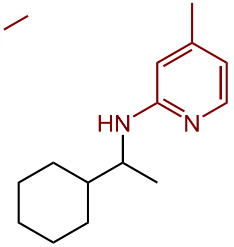

11a, 67%


12a, 34% 1:1 dr[d]
65% 1:1 dr[d,e,f]


13a, 41%[b]

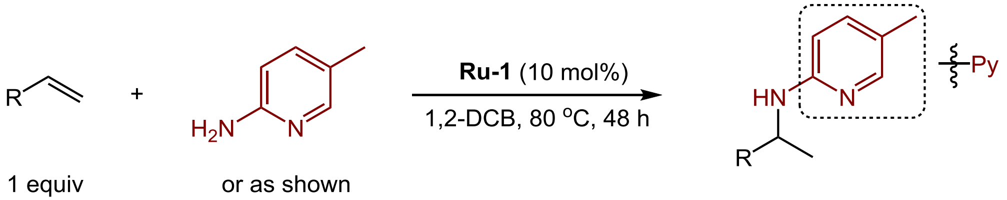

14a, 68%


15a, 47%[b], 90%[b,e]


16a, 63%[b,c]

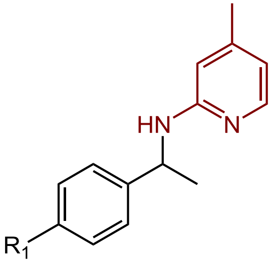
[a]Isolated yields. [b] 100 °C. [c] **Ru-1** 10 mol %. [d] **Ru-1** 15 mol %. [e] 2 equiv of alkene. [f] 72 h.

Scope of Vinylarenes

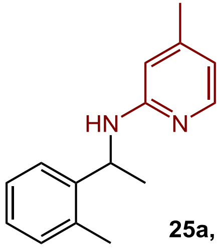


Ru-1 (10 mol%)

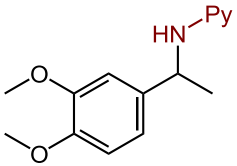
1,2-DCB, 80 °C, 48 h



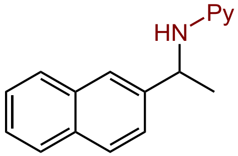
18a, R_1 = H, 62%, 95%[c]
19a, R_1 = Me, 59%
20a, R_1 = F, 57%[b]
21a, R_1 = OMe, 61%
22a, R_1 = CF_3, 60%[b]
23a, R_1 = Cl, 49%[b]
24a, R_1 = Br, 46%[b]



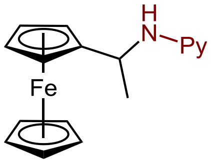
25a, 40%[b]



26a, 66%



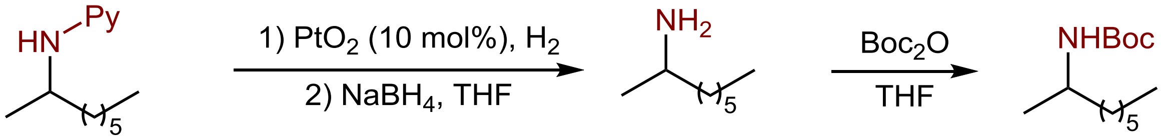
27a, 65%



28a, 61%[b]

[a]Isolated yields. [b] 100 °C. [c] 2 equiv of alkene.

Removal of the Pyridyl Group from 2a



1) PtO_2 (10 mol%), H_2

2) $NaBH_4$, THF

Boc_2O

THF

2a **2b** **2c**

59%

Mechanistic Studies

Determination of the Catalyst Resting State

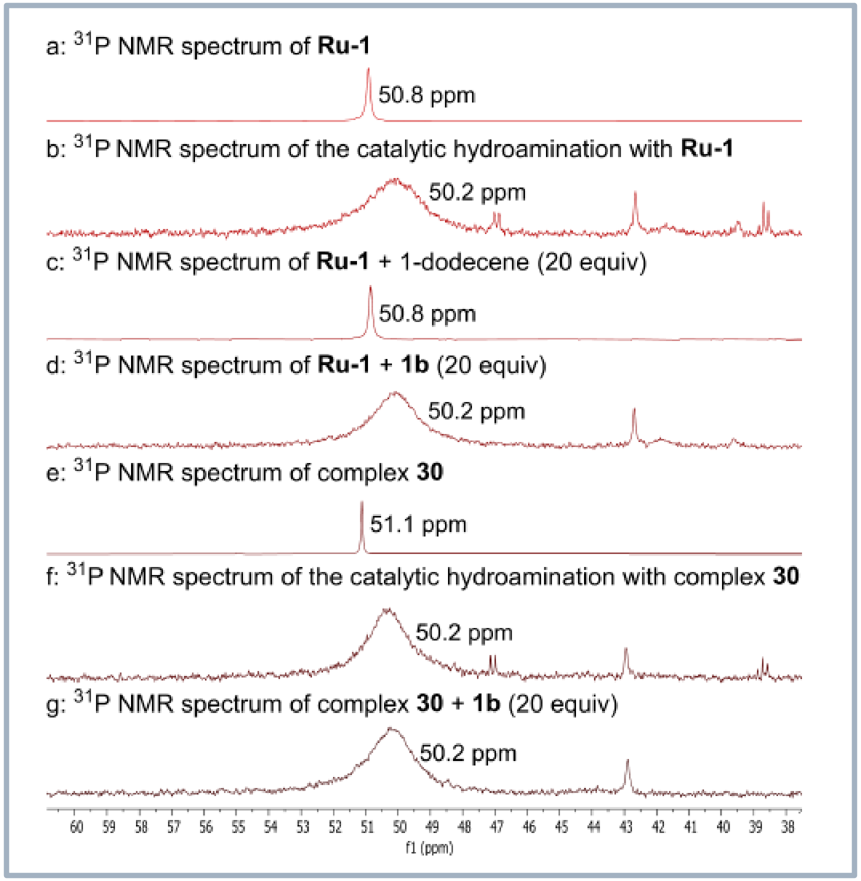


Figure 1. (a) ^{31}P NMR spectrum **Ru-1**. (b) ^{31}P NMR spectrum of the catalytic hydroamination of 1-dodecene with **Ru-1** as the catalyst. (c) ^{31}P NMR spectrum of the mixture of **Ru-1** and 1-dodecene (20 equiv). (d) ^{31}P NMR spectrum of the mixture of **Ru-1** and **1b** (20 equiv). (e) ^{31}P NMR spectrum of complex **30**. (f) ^{31}P NMR spectrum of the catalytic hydroamination of 1-dodecene with complex **30** as the catalyst. (g) ^{31}P NMR spectrum of the mixture of complexes **30** and **1b** (20 equiv). All of the above spectra were acquired at 80 °C.

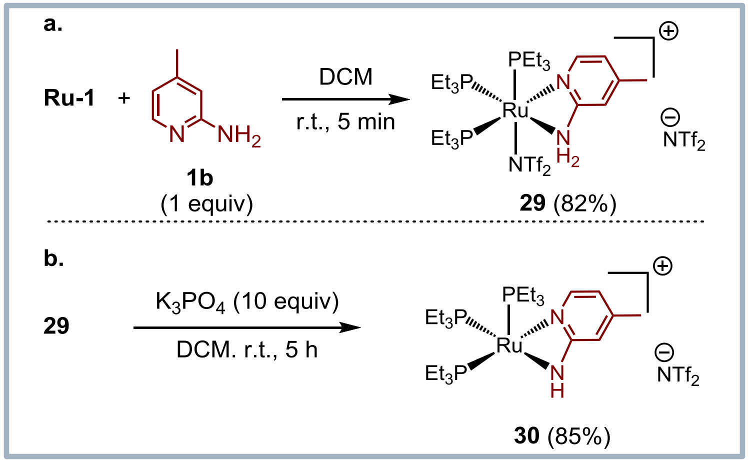
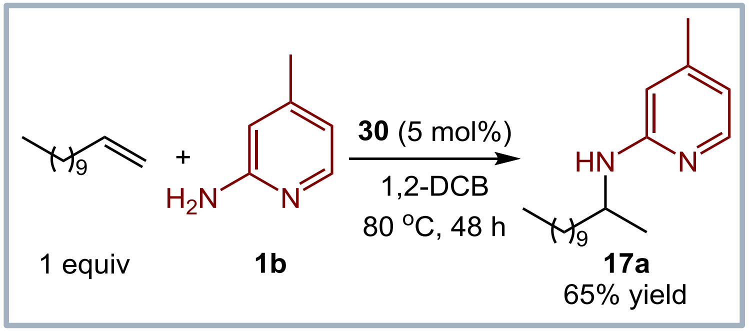
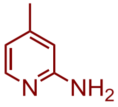


Figure 2. (a) Synthesis of complex **29**. (b) Synthesis of complex **30**. (c) Solid-state structure of complex **29** with ellipsoids set at 30% and selected hydrogen atoms and free triflimide anion omitted for clarity. (d) Solid-state structure of complex **30** with ellipsoids set at 30% and selected hydrogen atoms and free triflimide anion omitted for clarity.

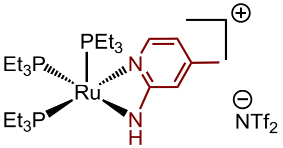


Mechanistic Studies

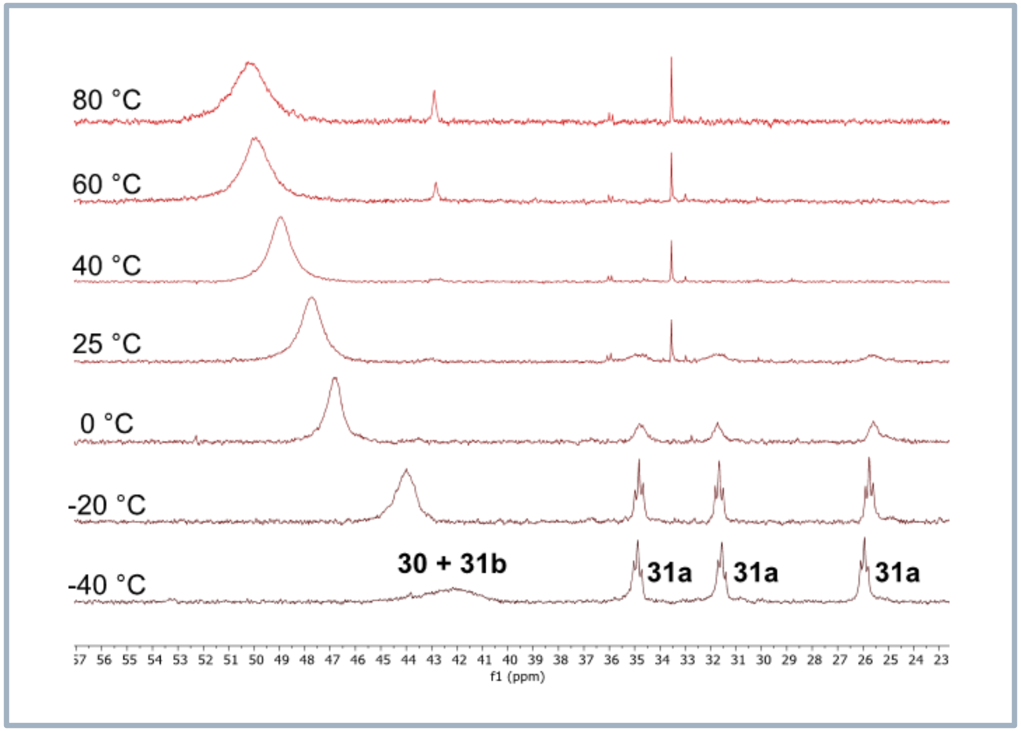
Determination of the Catalyst Resting State

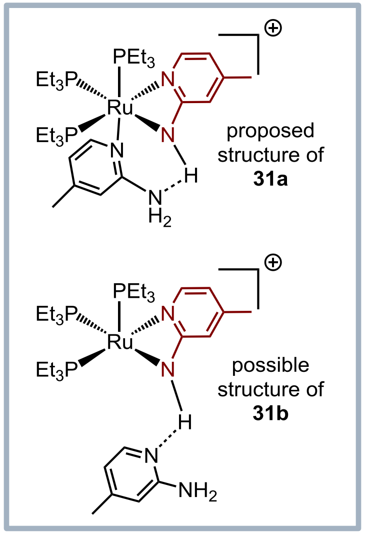


1b



30





proposed structure of **31a**

possible structure of **31b**

Figure 3. ^{31}P NMR spectra of the mixture of complexes **30** and **1b** (20 equiv) at different temperatures and possible structures for complexes **31a** and **31b**.

Mechanistic Studies

Kinetic Studies on Catalytic Hydroamination

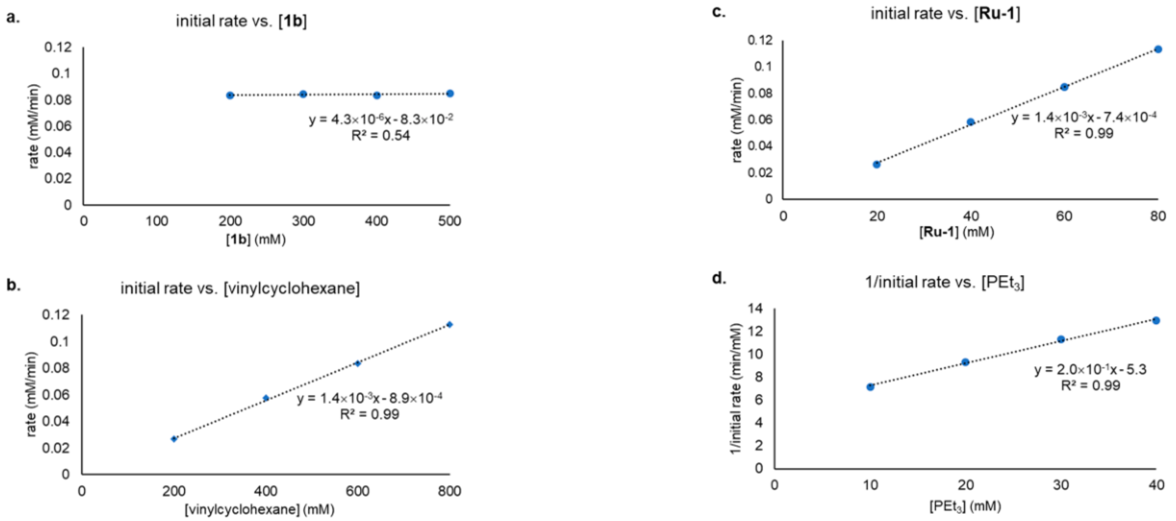
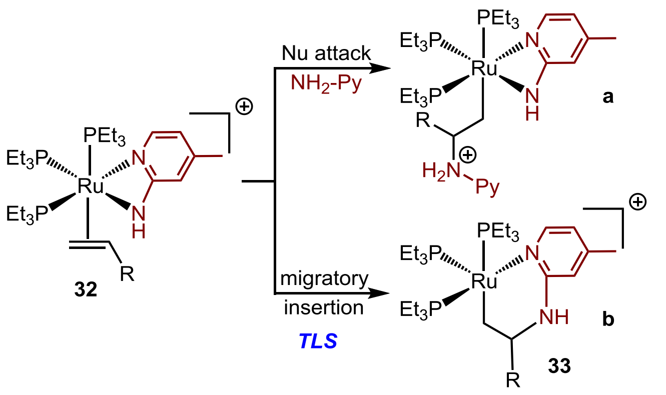
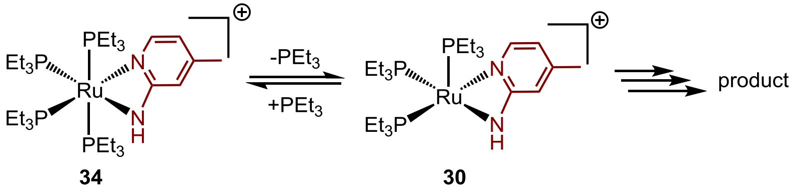


Figure 4. (a) Initial rates of product formation as a function of [**1b**]. (b) Initial rates of product formation as a function of [vinyl-cyclohexane]. (c) Initial rates of product formation as a function of [**Ru-1**]. (d) 1/initial rates of product formation as a function of [PEt_3].

Possible Pathways for the Formation of the C-N Bond

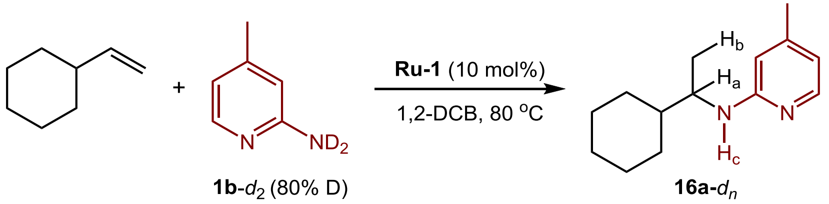


Explain the Rate Inhibition by Additional PEt_3



Mechanistic Studies

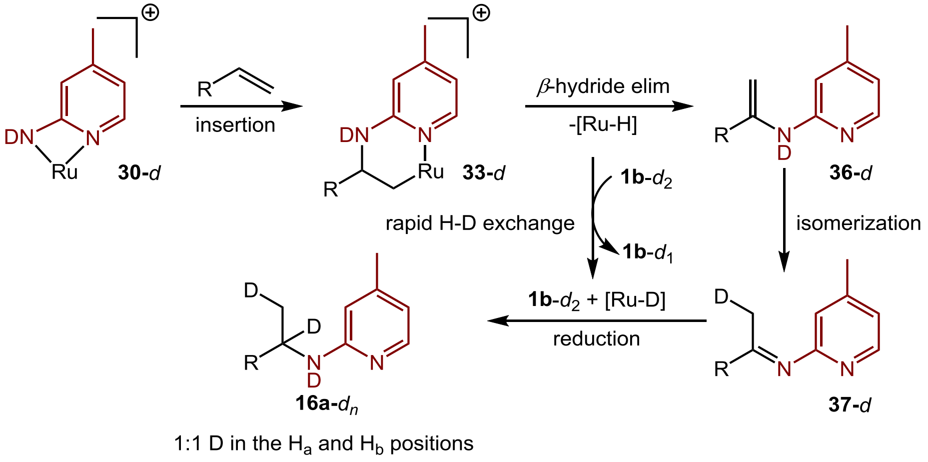
Hydroamination of Vinylcyclohexane with 1b-d$_2$



reaction time (h)	%D at the H$_a$ position [a]	%D at the H$_b$ position [a]
24	29%	29%
36	31%	32%
48	29%	28%

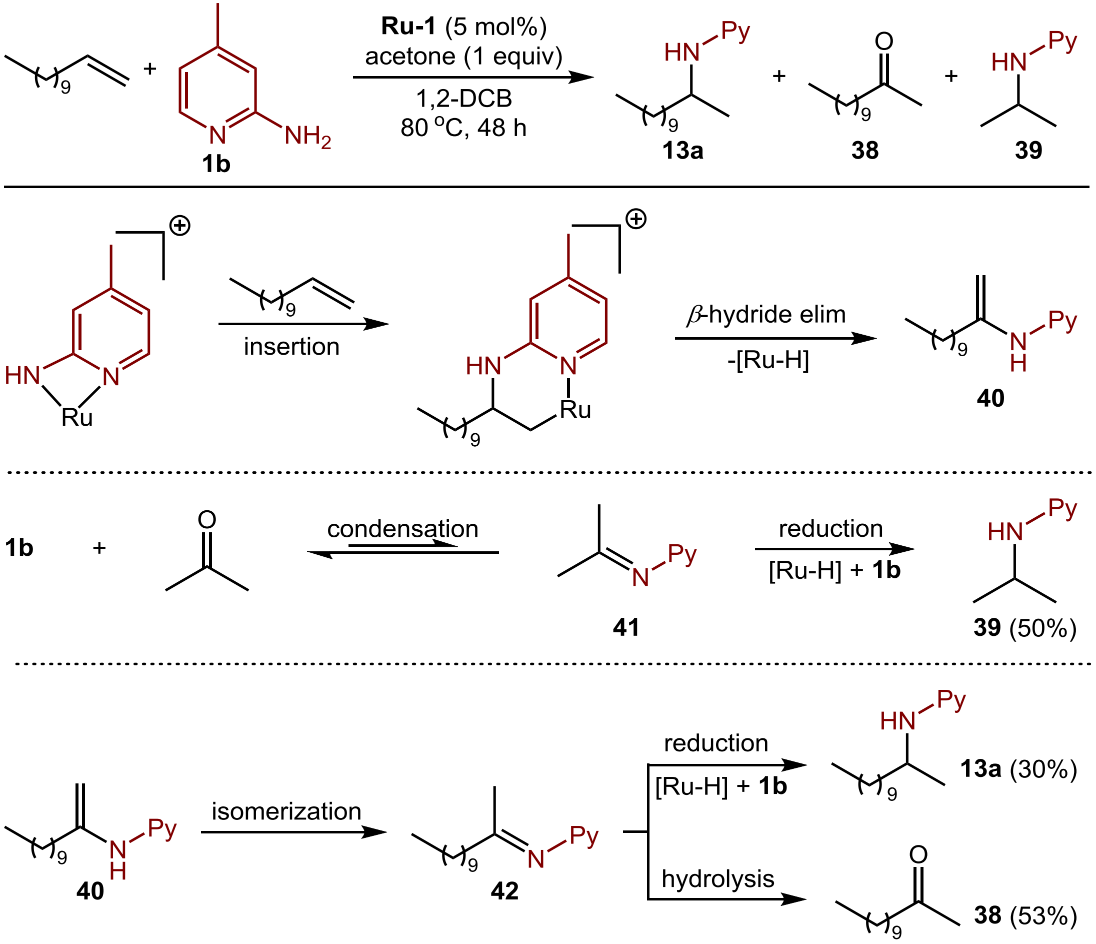
[a] %D incorporation = moles of D atoms/moles of product.

Proposed Pathway for the Formation of Hydroamination Product from 33



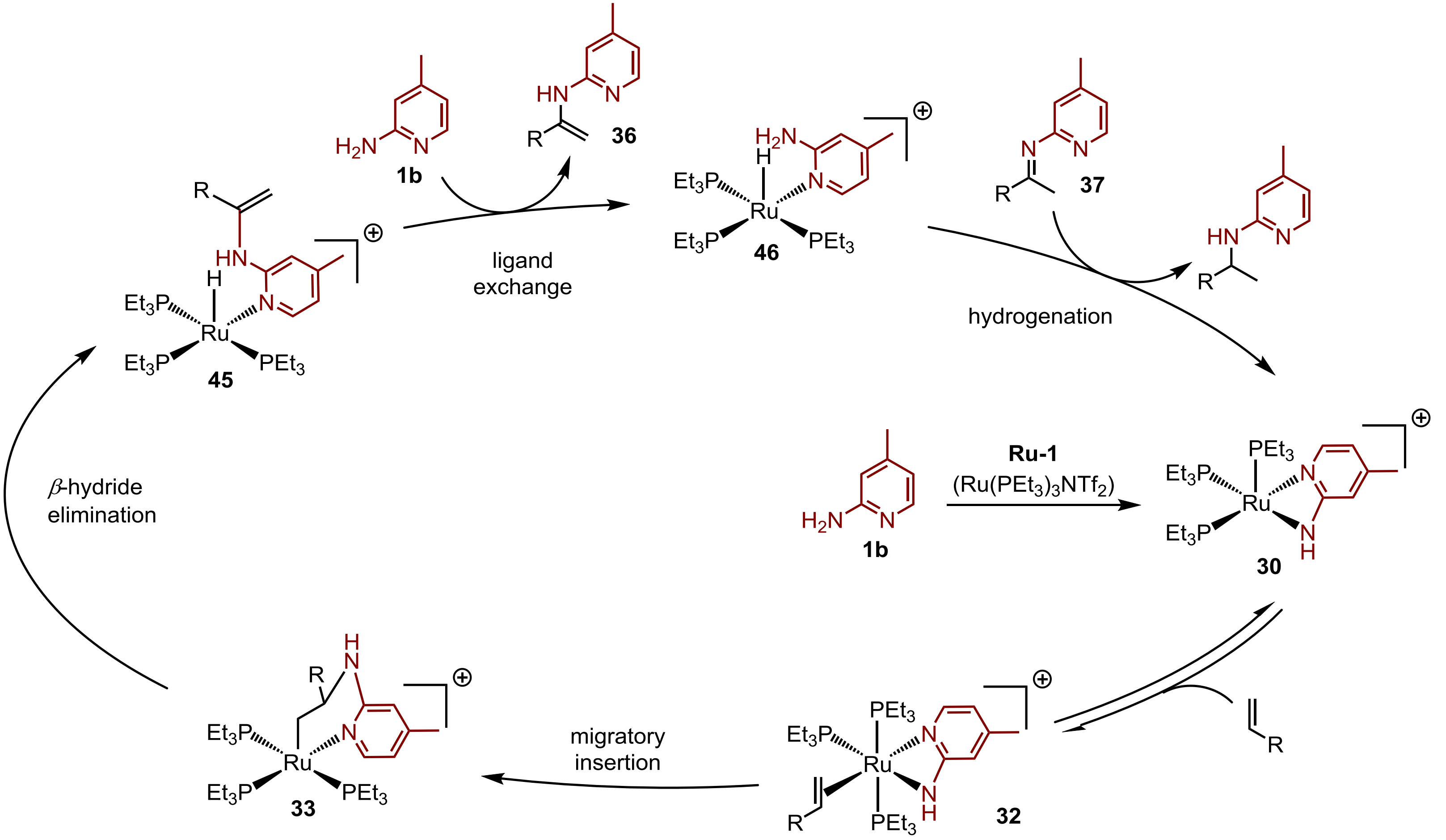
Mechanistic Studies

Hydroamination of 1-Dodecene in the Presence of Acetone

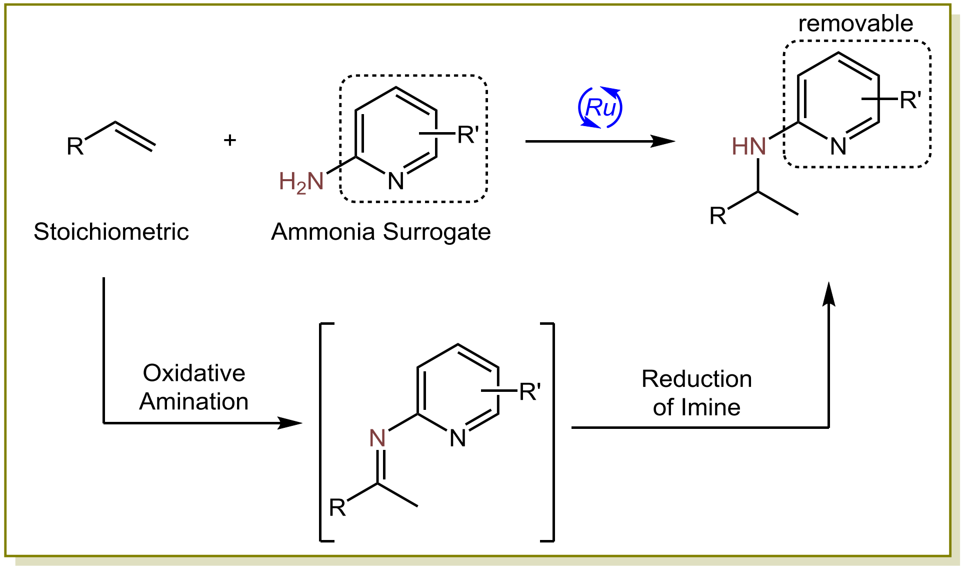


Mechanistic Studies

Proposed catalytic cycle :



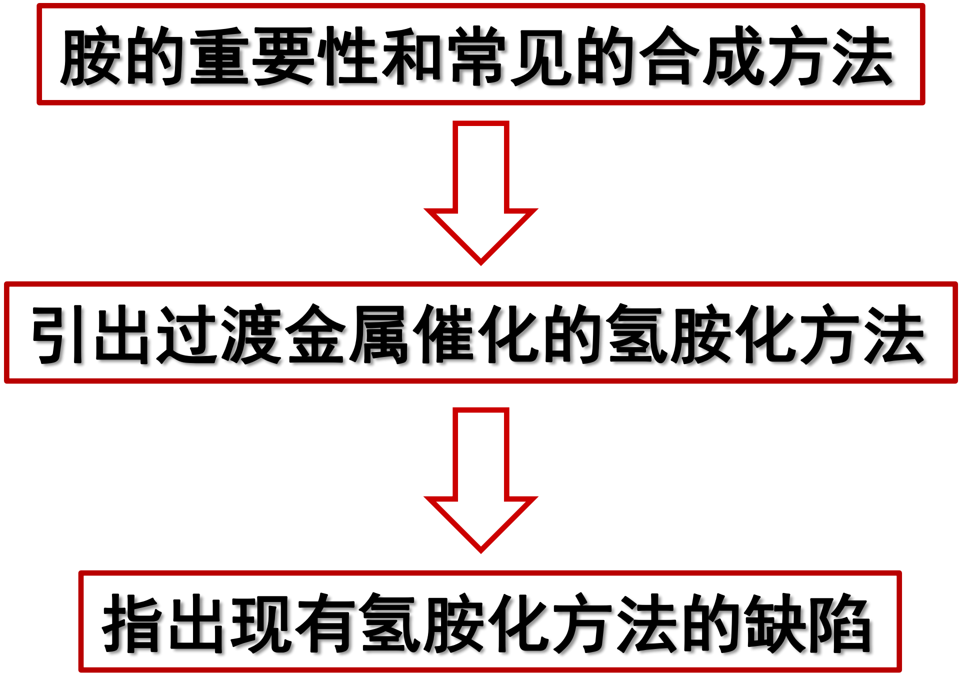
Summary



- Ruthenium-catalyzed intermolecular hydroaminations of a variety of unactivated terminal alkenes;
- Without the need for an excess of alkene, and broad substrate scope;
- A new mechanism of hydroamination.

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2021**, *143,* 359.

The First Paragraph



胺的重要性和常见的合成方法

引出过渡金属催化的氢胺化方法

指出现有氢胺化方法的缺陷

The First Paragraph

Amines and their derivatives are important as both pharmaceuticals and agrochemicals. Traditional methods to synthesize amines include nucleophilic substitution of organic halides, reductive amination of carbonyl compounds, and reduction of amides, nitriles, and azides. The hydroamination of alkenes catalyzed by transition-metal complexes is an attractive alternative to these methods because it occurs directly with alkenes and could be applied to the functionalization of both simple alkenes and complex molecules containing alkene units.

The First Paragraph

Despite the potential utility of hydroamination, examples of intermolecular hydroaminations are often limited to conjugated and strained alkenes, such as dienes, vinylarenes, norbornenes, and cyclopropenes. Hydroaminations of unactivated alkenes are rare and generally require a large excess of alkene.

The Last Paragraph

概括本文工作

该工作的优点

简略概括反应的机理

The Last Paragraph

Ruthenium-catalyzed Markovnikov hydroamination of both unactivated and activated terminal alkenes occurs with 2-aminopyridine as a surrogate for ammonia with a stoichiometric amount of alkene by an unusual pathway for hydroamination. This process constitutes a rare example of hydroamination of alkenes with ruthenium, and it is enabled by a combination of a cationic metal center and a carefully designed aminopyridine as an ammonia surrogate.

The Last Paragraph

This combination facilitates the deprotonation of the aminopyridine coordinated to an electron-deficient ruthenium center, the migratory insertion of the alkene into the strained fourmember ruthenacycle, and the cooperative reduction of the imine intermediate generated from β-hydrogen elimination to lead to an overall redox-neutral addition process. This reaction proceeds with a variety of terminal alkenes to afford the amine products under conditions with the alkene in stoichiometric quantities.

The Last Paragraph

A combination of experimental and computational mechanistic studies reveals that this hydroamination reaction occurs by turnover-limiting migratory insertion of the alkene into the Ru-N bond, followed by β-hydride elimination to generate an enamine, tautomerization of the enamine to an imine, and reduction of the imine by the hydridoruthenium aminopyridine complex to generate the amine product. This pathway implies that an enantioselective process could be developed if the step involving reduction of the imine intermediate can be rendered enantioselective. Studies to achieve such a process by this mechanism are ongoing.

Representative Examples

- The product from the hydroamination reaction was converted to a primary amine by a two-step sequence.(两步法)

氢胺化反应的产物经两步法转化为伯胺。

- The results of our mechanistic investigation are summarized in Figure 7.(v. 总结，概括；概述(summarize的过去式及过去分词形式))

我们的机理研究结果总结在图7中。

Acknowledgement

Thanks
for your attention