

Literature Report 2

Pd(0)-Catalyzed Asymmetric Carbohalogenation: H-Bonding-Driven C(sp³)-Halogen Reductive Elimination

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Checker: Yixuan Ding

Date: 2021-06-21

Chen, X.; Zhao, J.; Tong, X. *J. Am. Chem. Soc.* **2021**, *143*, 1924

CV of Prof. Xiaofeng Tong (童晓峰)



Research:

- ❑ Lewis base-catalyzed annulations
- ❑ Metal-catalyzed carbon-halogen bonds formation
- ❑ Synthesis of heterocyclic compounds

Education:

- ❑ **1995-1999** B.S., Beijing Normal University
- ❑ **1999-2005** Ph.D., SIOC
- ❑ **2005-2006** Postdoc, Leibniz Institute for Catalysis
- ❑ **2006-2015** Associate Professor & Professor, ECUST
- ❑ **2016-Present** Professor, Changzhou University

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Introduction--Formation of C(sp²)-Halogen Bond

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Formation of C(sp³)-Halogen Bond

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Summary

Introduction

□ Formation of Carbon-Halogen Bonds

Metal-catalyzed Cross-coupling Rxn

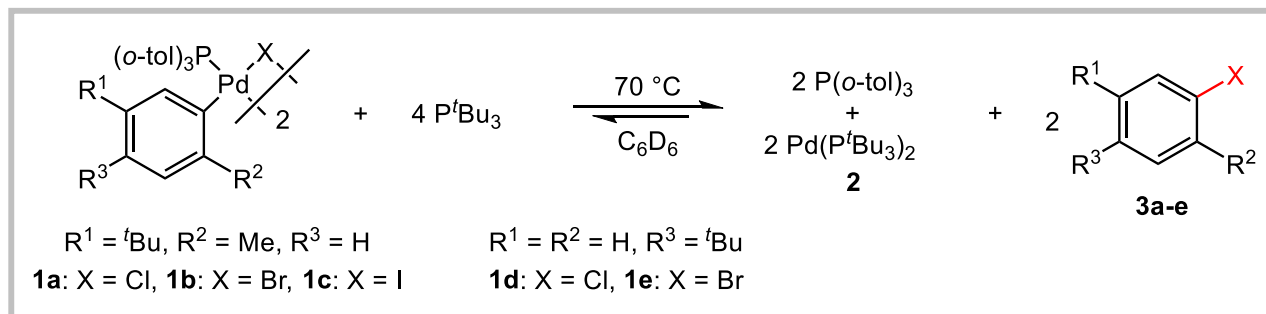
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graph TD; A[Metal-catalyzed Cross-coupling Rxn] --> B[Reductive Elimination]; B --> C["C-Halogen Bond: Thermodynamic disfavored"]
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Reductive Elimination

C-Halogen Bond: **Thermodynamic disfavored**

Formation of C(sp²)-Halogen Bonds

□ Using Sterically Hindered Phosphorus Ligands



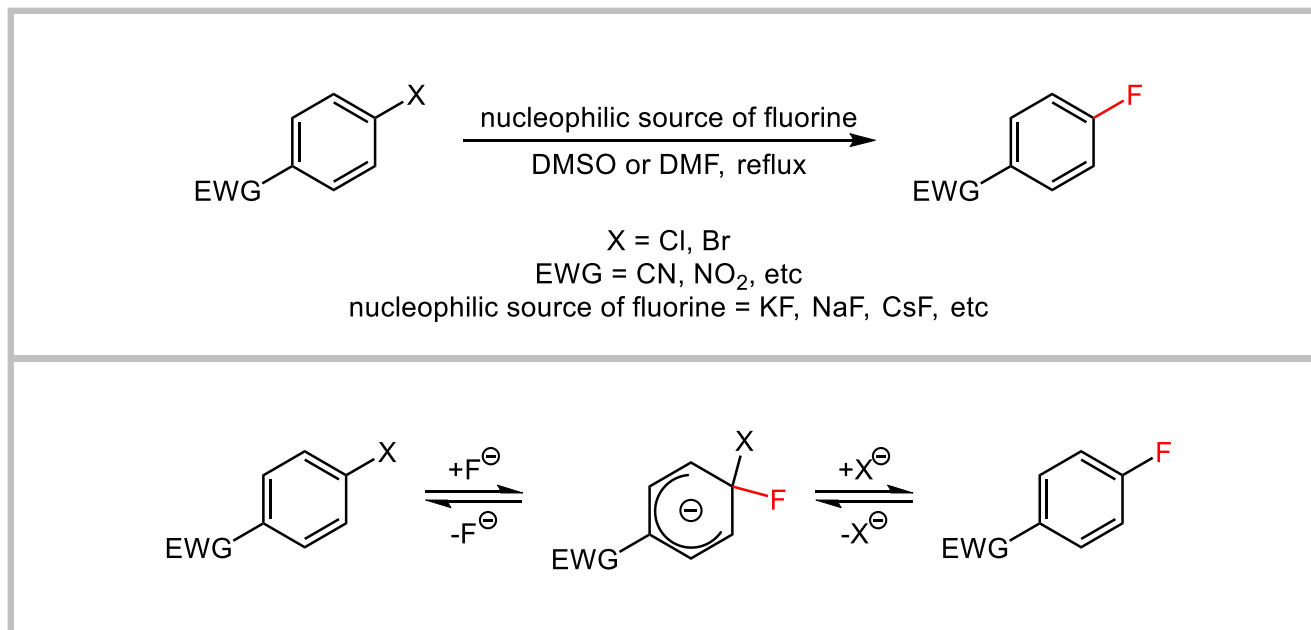
| Entry | 1 | Yield of 3 (%) | K_{eq}^a |
|-------|--------------------|-----------------------|---------------------------|
| 1 | 1a (X = Cl) | 70 | $9(3) \times 10^{-2}$ |
| 2 | 1b (X = Br) | 70 | $2.3(3) \times 10^{-3}$ |
| 3 | 1c (X = I) | 39 | $3.7(2) \times 10^{-5}$ |
| 4 | 1d (X = Cl) | 30 | not measured ^b |
| 5 | 1e (X = Br) | 75 | $3.3(6) \times 10^{-4}$ |

^a K_{eq} values are referenced to a 1 M standard state. K_{eq} values were obtained for the process in equation by initiating reactions from both sides of the equilibrium. ^b This reaction appeared to consume all of the aryl chloride complex, but low yields for the formation of free aryl chloride may prevent reversibility.

Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232

Formation of C(sp²)-Halogen Bonds

□ Synthesis of Fluoro-Arenes—Halex Rxn

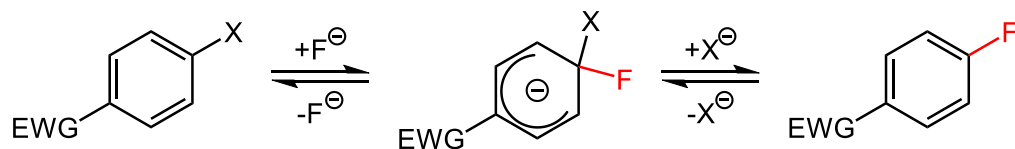


Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034

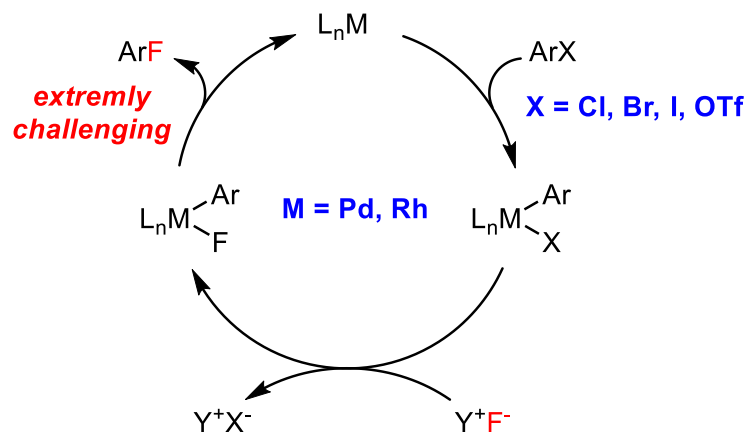
Formation of C(sp²)-Halogen Bonds

□ Using Sterically Hindered Phosphorus Ligands

Halex Reaction



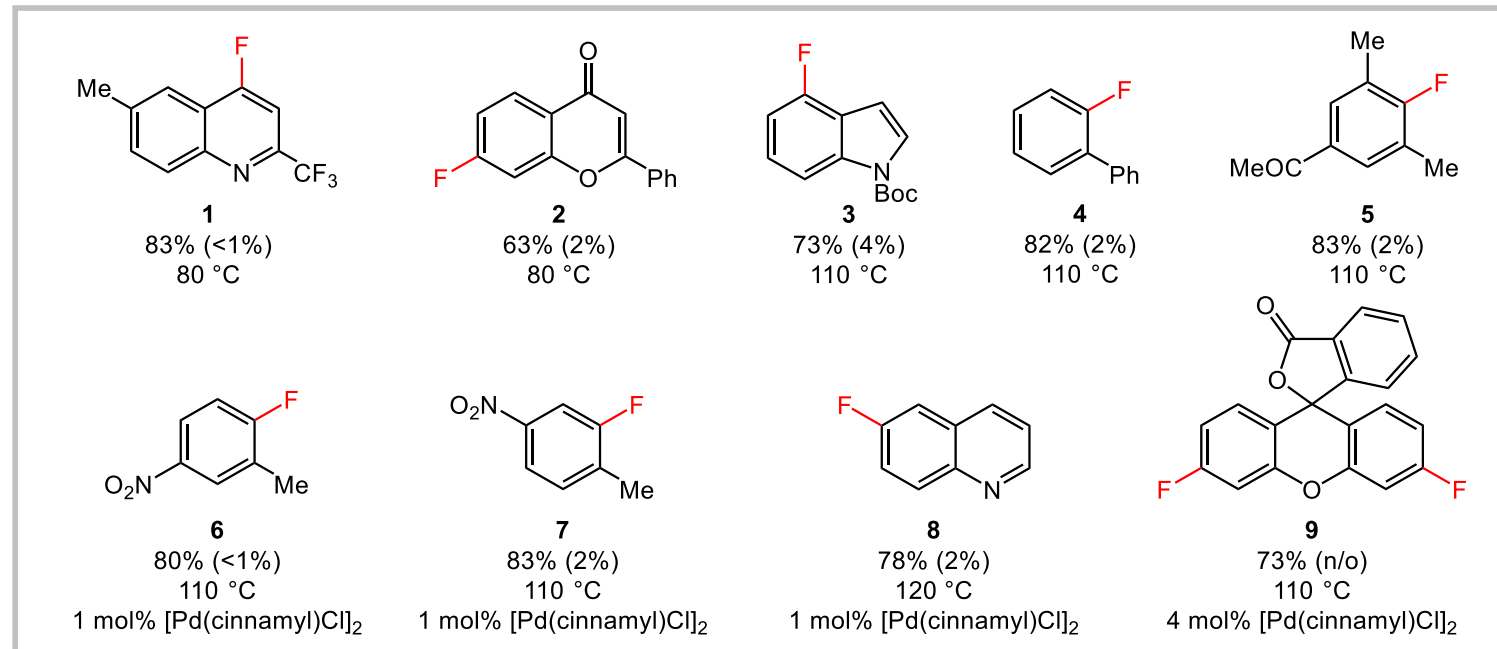
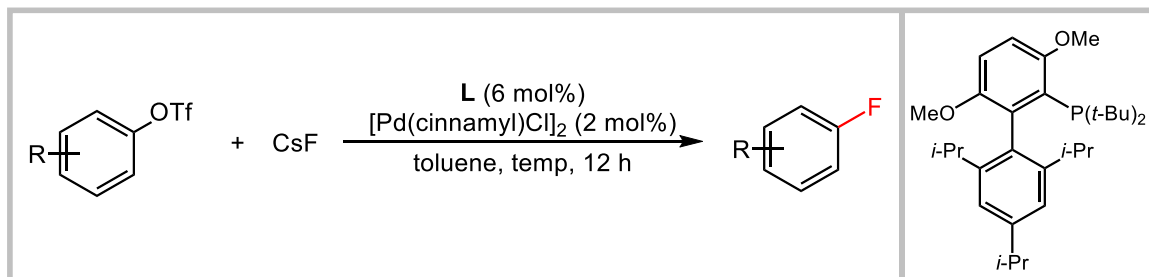
Metal-Catalyzed Aryl Fluorination



Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342
Watson, D. A.; Su, M.; Buchwald, S. L. *Science* **2009**, *325*, 1661

Formation of C(sp²)-Halogen Bonds

□ Using Sterically Hindered Phosphorus Ligands

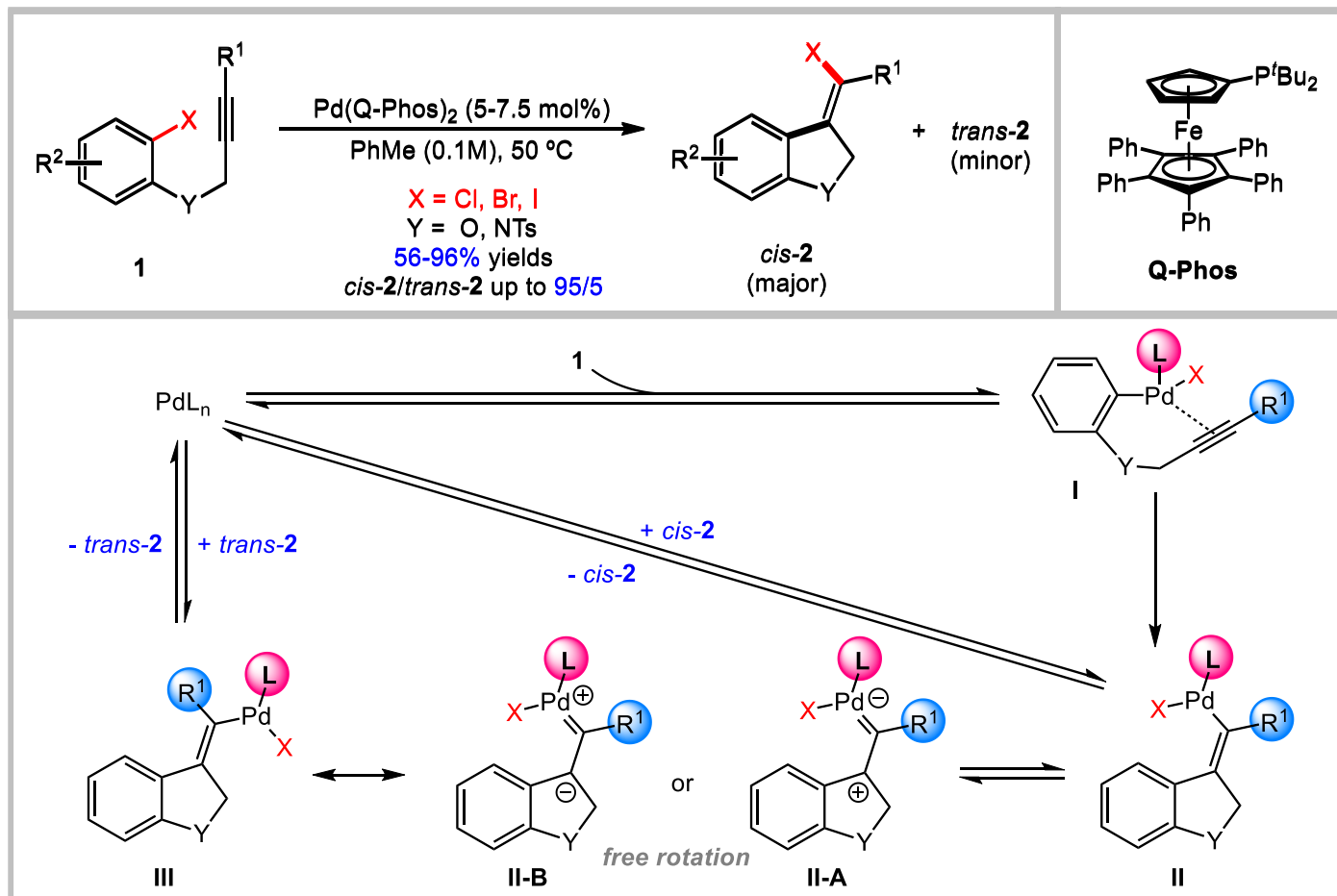


Values in parentheses denote the amount of reduced starting material based on the isolated product yield.

Watson, D. A.; Su, M.; Buchwald, S. L. *Science* **2009**, 325, 1661

Formation of C(sp²)-Halogen Bonds

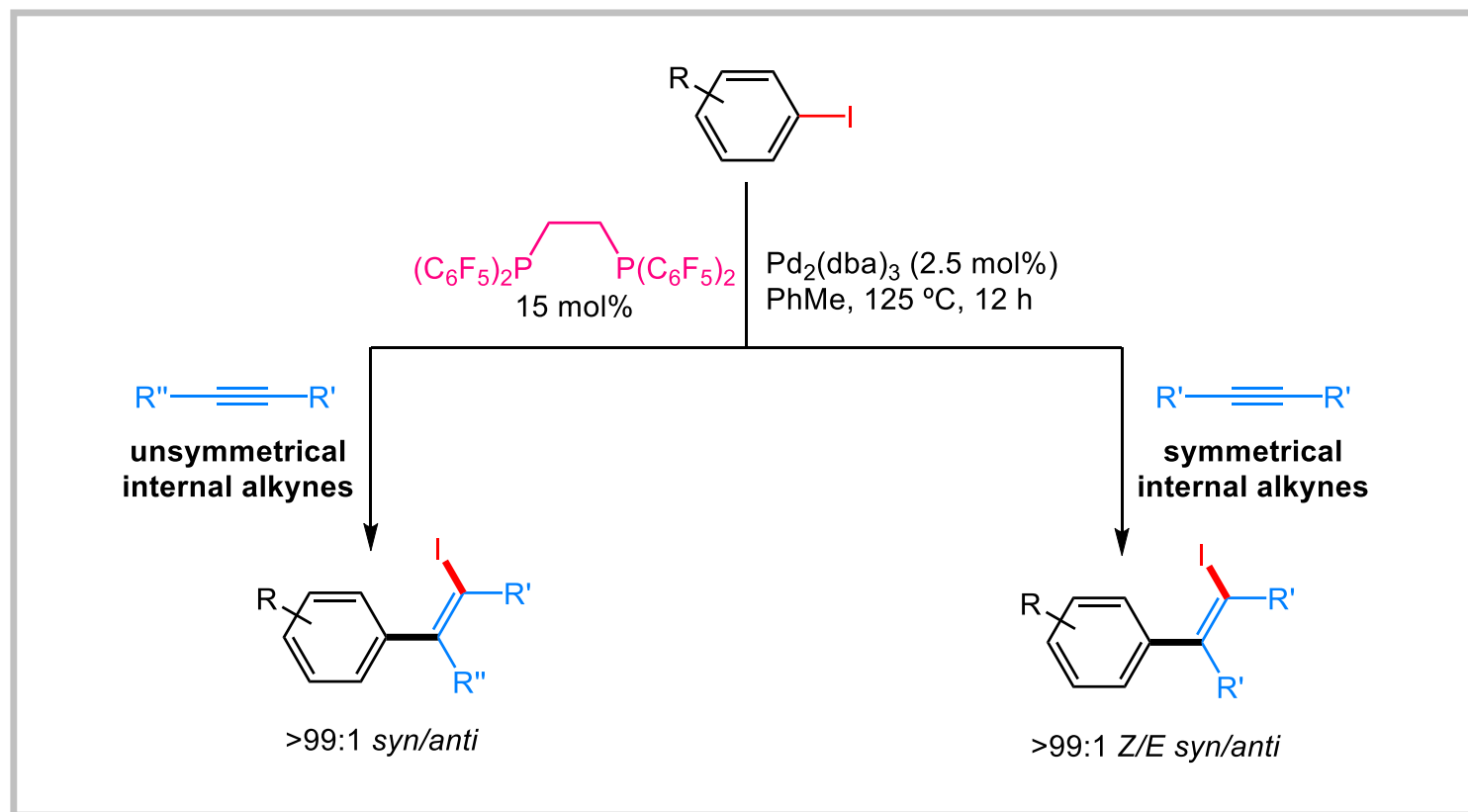
Using Sterically Hindered Phosphorus Ligands



Le, C. M.; Menzies, P. J.; Petrone, D. A.; Lautens, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 254

Formation of C(sp²)-Halogen Bonds

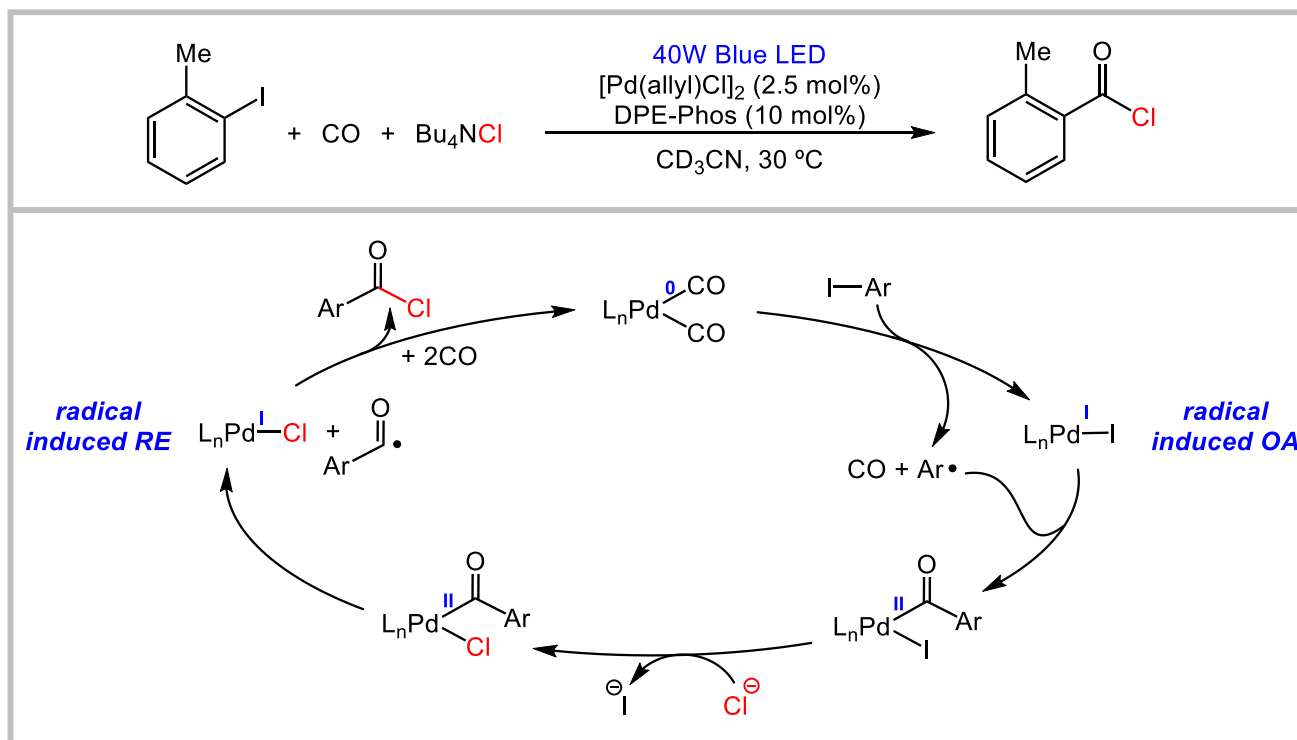
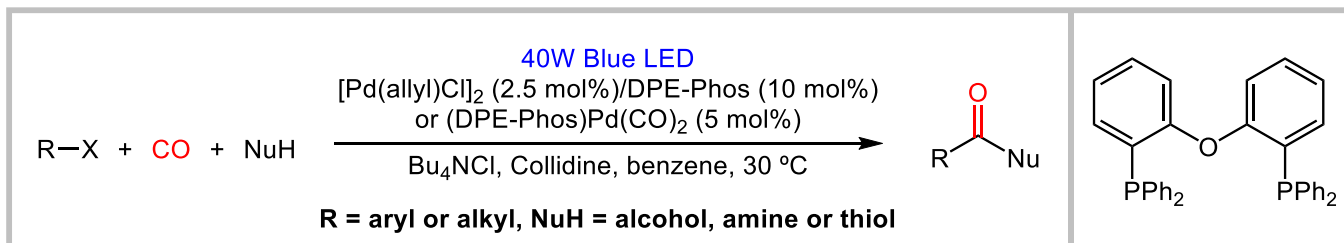
□ Using Electron-Poor Ligands



Lee, Y. H.; Morandi, B. *Angew. Chem. Int. Ed.* **2019**, *58*, 6444

Formation of C(sp² & sp³)-Halogen Bonds

□ Light-Promoted Radical Process



Torres, G. M.; Liu, Y.; Arndtsen, B. A. *Science* **2020**, 368, 318

Introduction (Summary of Previous Work)

□ Strategies

- ◆ Sterically Hindered **Phosphorus Ligands**
- ◆ **Electron-Poor** Ligands
- ◆ **Light-Promoted** Radical Process

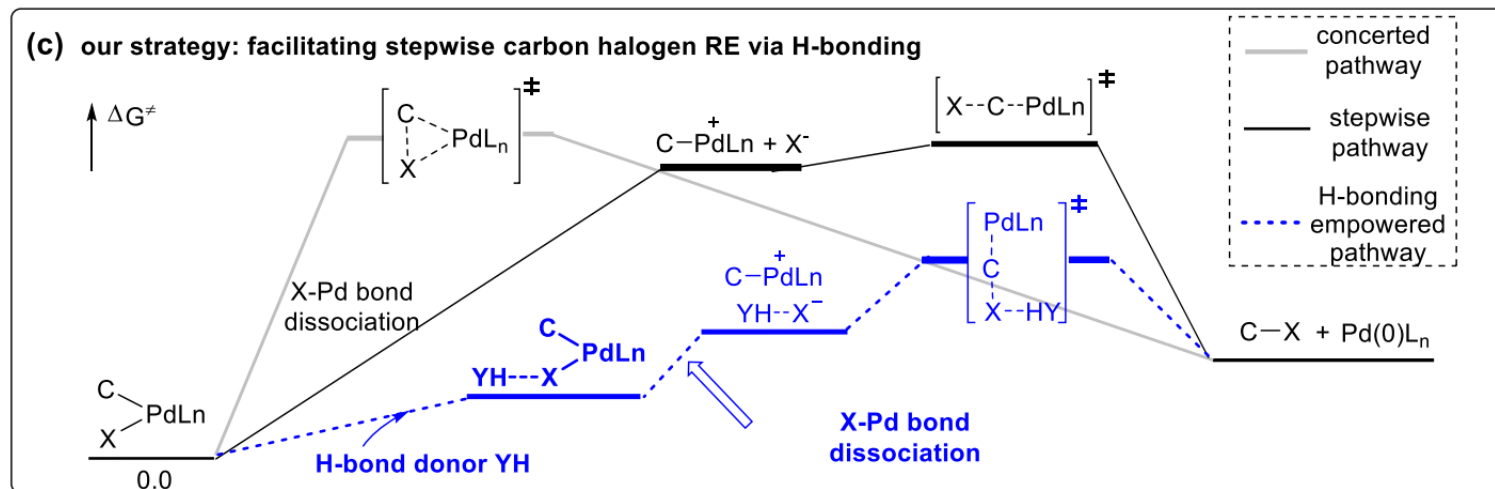
□ Limitations

- ◆ Mainly **C(sp²)-Halogen** Bonds
- ◆ High Temperature
- ◆ No Applications in Formation of **Alkyl Halide**
- ◆ Few **Asymmetric Versions**

Chen, X.; Zhao, J.; Tong, X. *J. Am. Chem. Soc.* **2021**, *143*, 1924

Formation of C(sp³)-Halogen Bonds

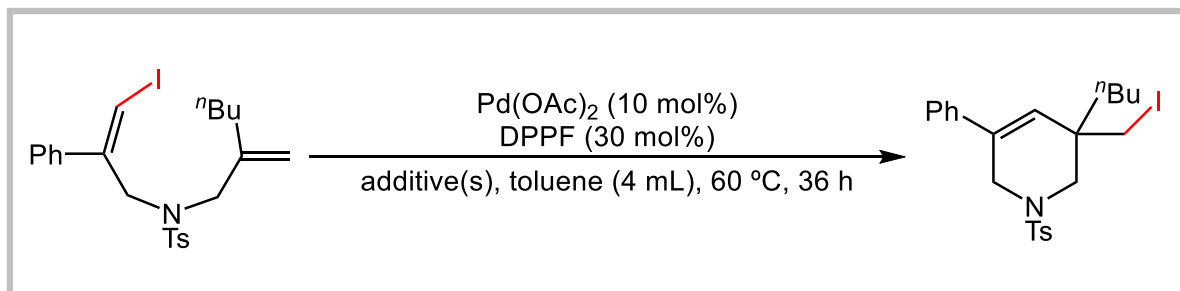
□ Computational Studies

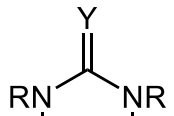


Lan, Y.; Liu, P.; Newman, S. G.; Lautens, M.; Houk, K. N. *Chem. Sci.* **2012**, 3, 1987
Chen, X.; Zhao, J.; Tong, X. *J. Am. Chem. Soc.* **2021**, 143, 1924

Formation of C(sp³)-Halogen Bonds

□ Establishment of a Biphasic H-Bonding System

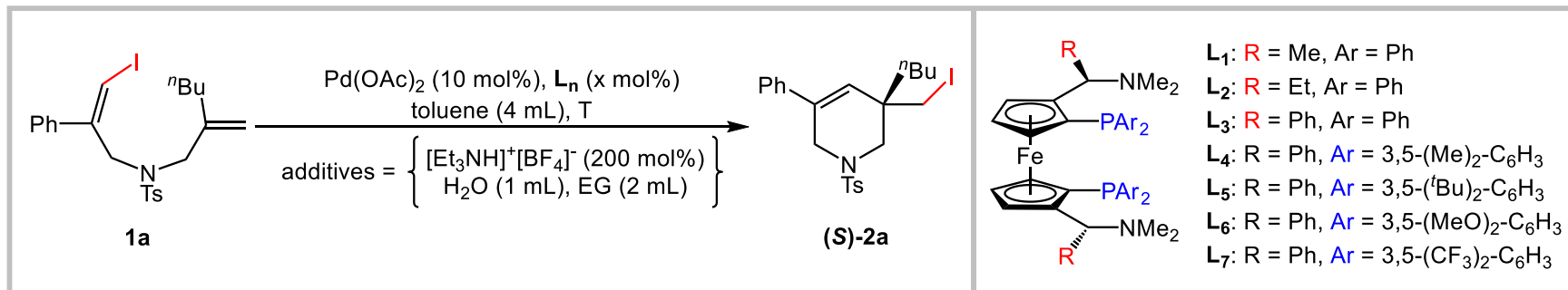


| Entry | Additive(s) | Isolated yield (%) |
|-----------------|---|--------------------|
| 1 | no additive | < 5 |
| 2 |  Y = O, R = Ph | 17 |
| 3 | Y = S, R = Ph | 8 |
| 4 | Y = O, R = C ₆ F ₅ | 39 |
| 5 | [Et ₃ NH] ⁺ [BF ₄] ⁻ | 11 |
| 6 | [Et ₃ NH] ⁺ [BF ₄] ⁻ + H ₂ O (1 mL) | 53 |
| 7 | [Et ₃ NH] ⁺ [BF ₄] ⁻ + H ₂ O (1 mL) + EG (2 mL) | 83 |
| 8 | EG (2 mL) | 33 |
| 9 | H ₂ O (1 mL) | < 5 |
| 10 ^a | [Et ₃ NH] ⁺ [BF ₄] ⁻ + H ₂ O (1 mL) + EG (2 mL) | 80 |

Conditions: **1a** (0.2 mmol), Pd(OAc)₂ (10%), DPPF (30%), toluene (4 mL), and the indicated urea derivative (2.0 equiv) or [Et₃NH]⁺[BF₄]⁻ (2.0 equiv). ^a 20% DPPF was used.

Formation of C(sp³)-Halogen Bonds

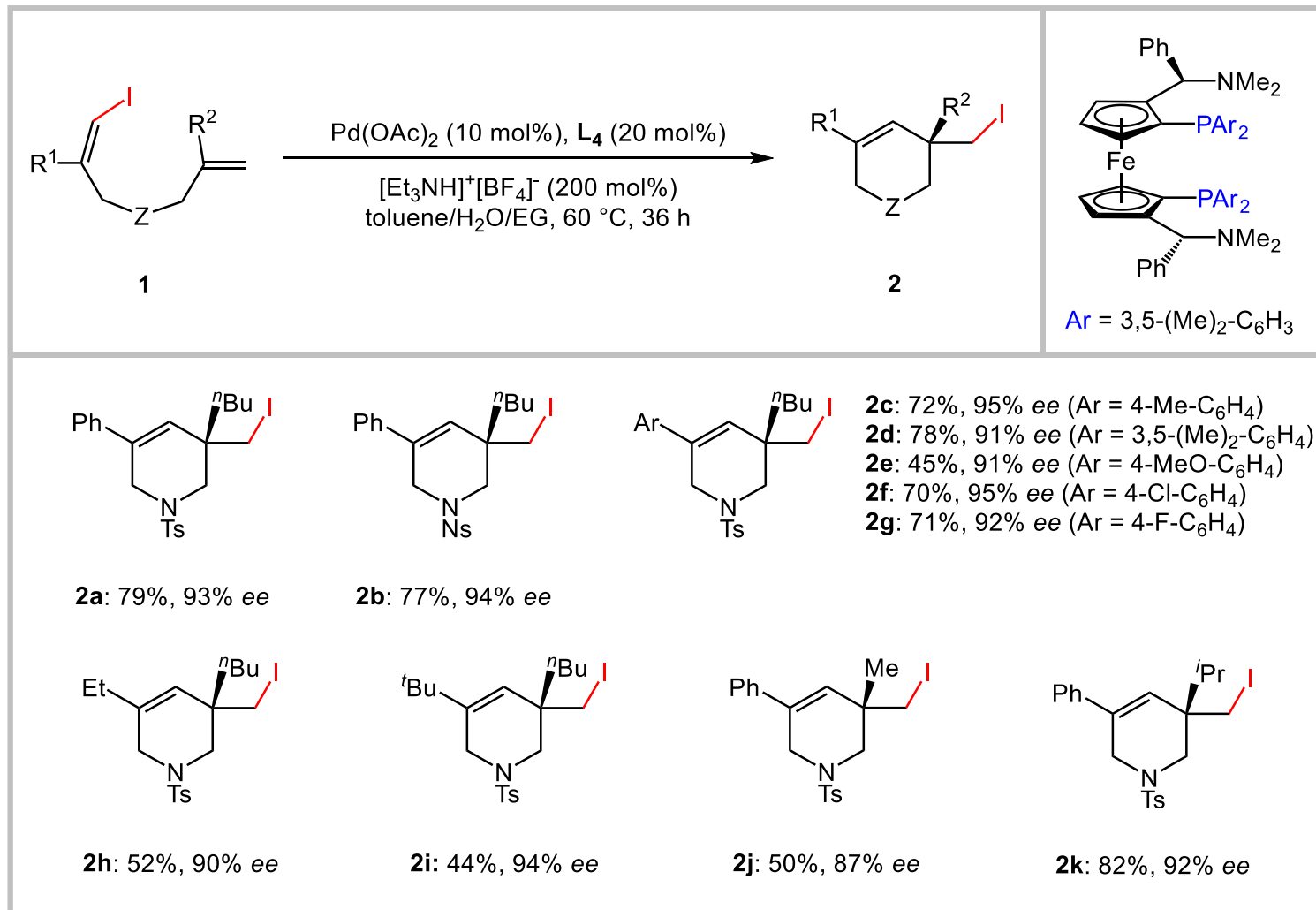
Chiral Ligand Screening



| Entry | Ligand | 30 mol% L_n T = 100 °C <i>w/o the additives</i> | 30 mol% L_n T = 60 °C <i>w/o the additives</i> | 20 mol% L_n T = 60 °C <i>with the additives</i> |
|-------|--------------|--|---|--|
| 1 | L_1 | 30%, < 5% ee | < 5%, ND | 41%, 23% ee |
| 2 | L_2 | 22%, 21% ee | < 5%, ND | 50%, 42% ee |
| 3 | L_3 | 47%, 66% ee | < 5%, ND | 58%, 78% ee |
| 4 | L_4 | 65%, 72% ee | 8%, 91% ee | 79%, 93% ee |
| 5 | L_5 | < 5%, ND | < 5%, ND | < 5%, ND |
| 6 | L_6 | 50%, 77% ee | 10%, 86% ee | 68%, 92% ee |
| 7 | L_7 | < 5%, ND | < 5%, ND | < 5%, ND |

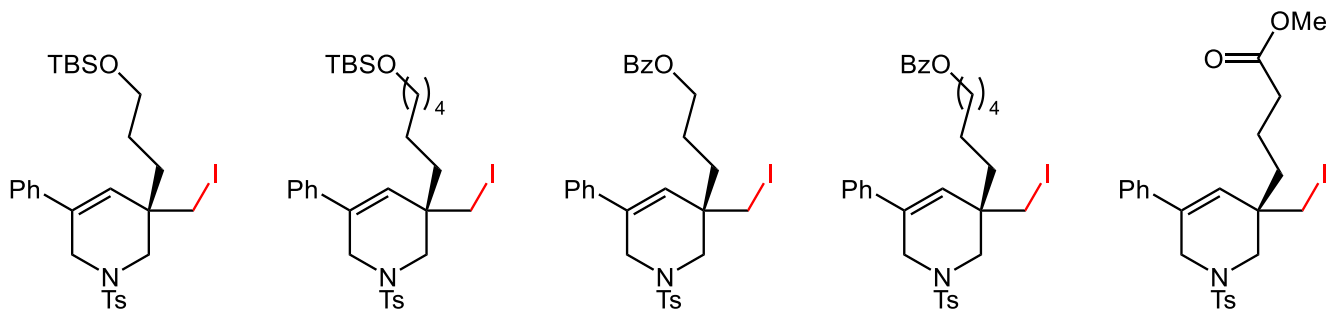
Formation of C(sp³)-Halogen Bonds

□ Substrate Scope of Asymmetric Carboiodination



Formation of C(sp³)-Halogen Bonds

□ Substrate Scope of Asymmetric Carboiodination



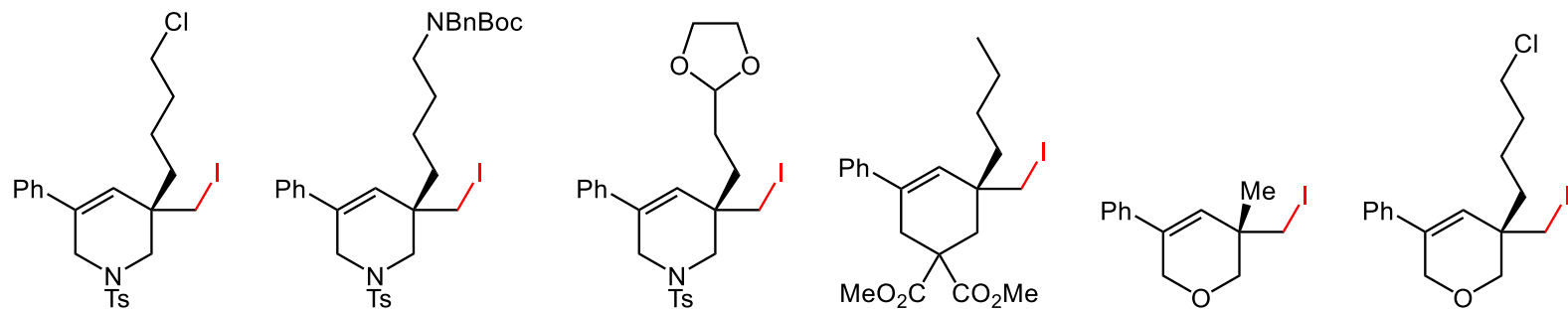
2m: 32%, 94% ee

2n: 78%, 91% ee

2o: 73%, 97% ee

2p: 76%, 92% ee

2q: 52%, 93% ee



2r: 60%, 92% ee

2s: 73%, 94% ee

2t: 50%, 91% ee

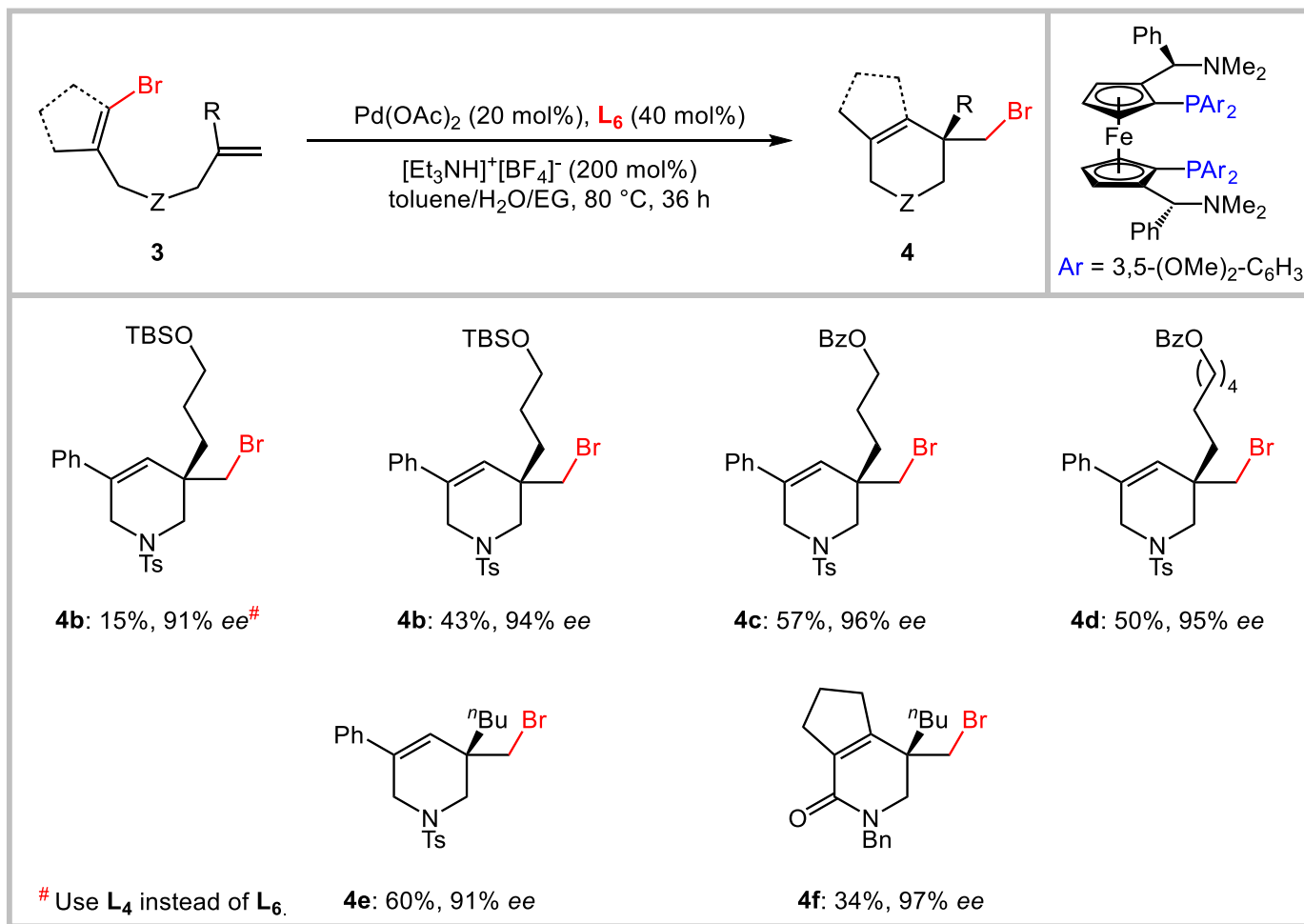
2u: 70%, 91% ee

2v: 80%, 35% ee

2w: 72%, 55% ee

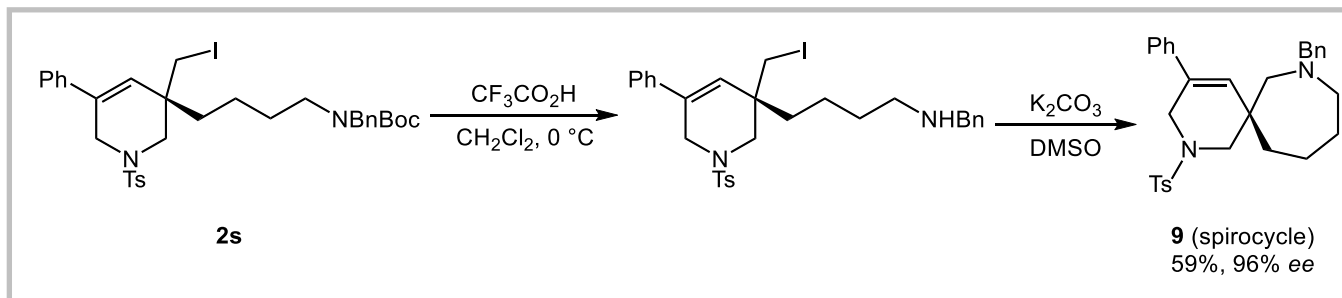
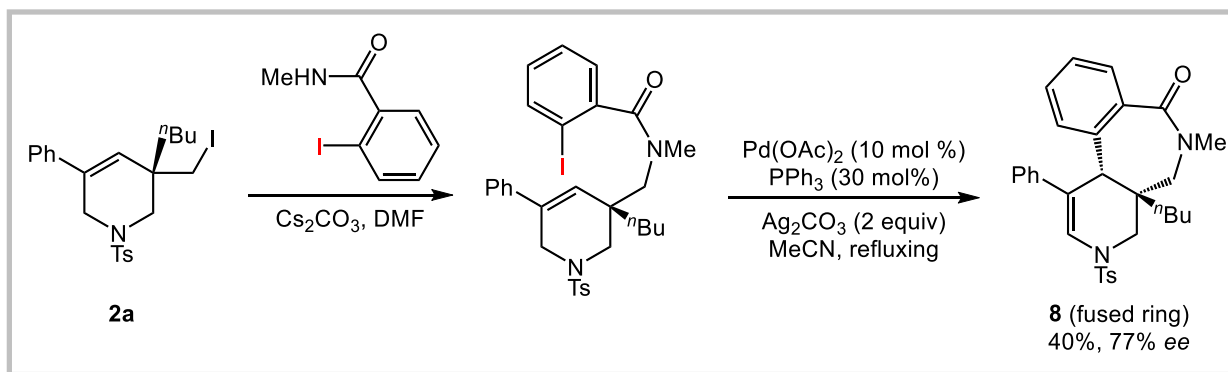
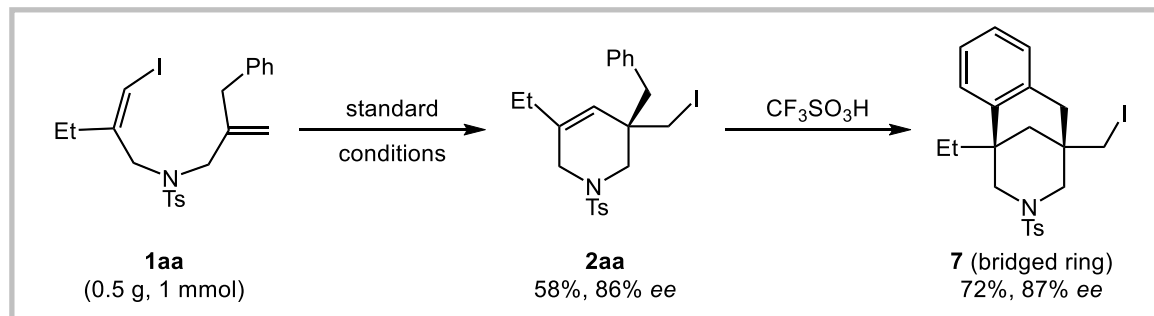
Formation of C(sp³)-Halogen Bonds

□ Substrate Scope of Asymmetric Carbobromination



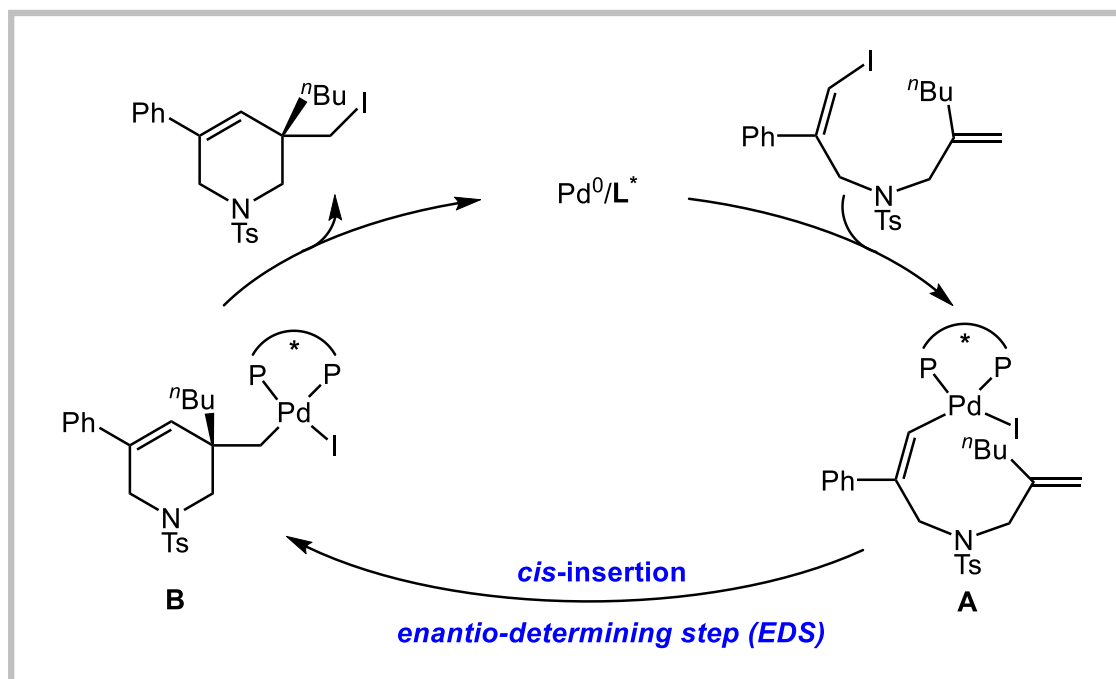
Formation of C(sp³)-Halogen Bonds

□ Synthetic Transformation



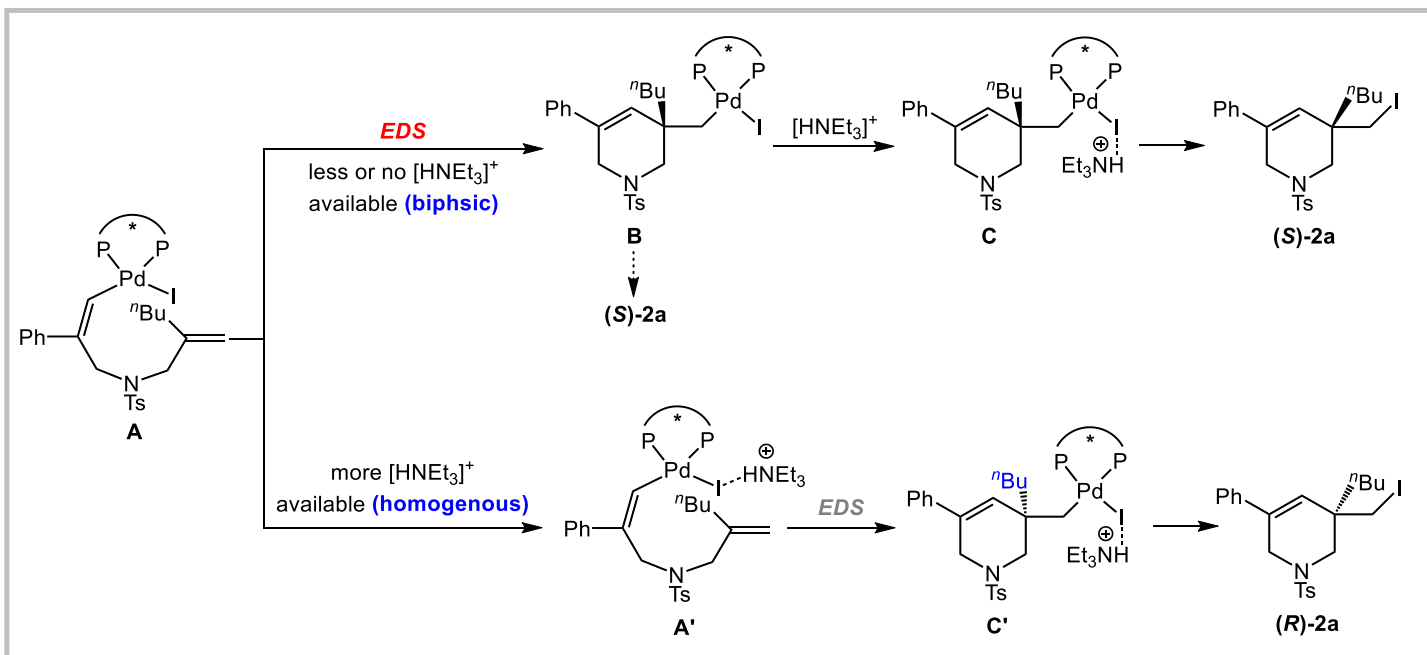
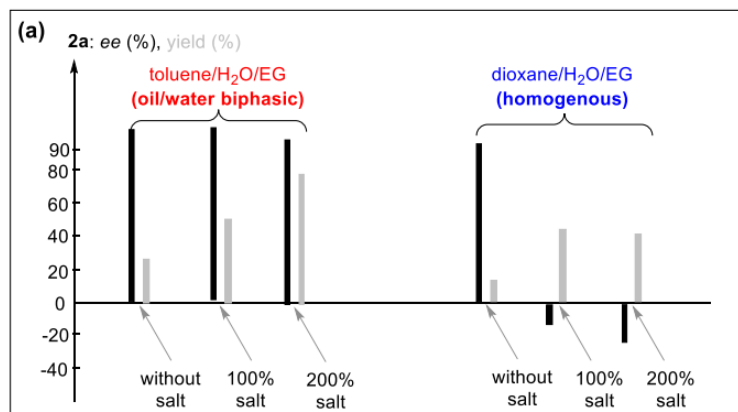
Formation of C(sp³)-Halogen Bonds

□ General Mechanism



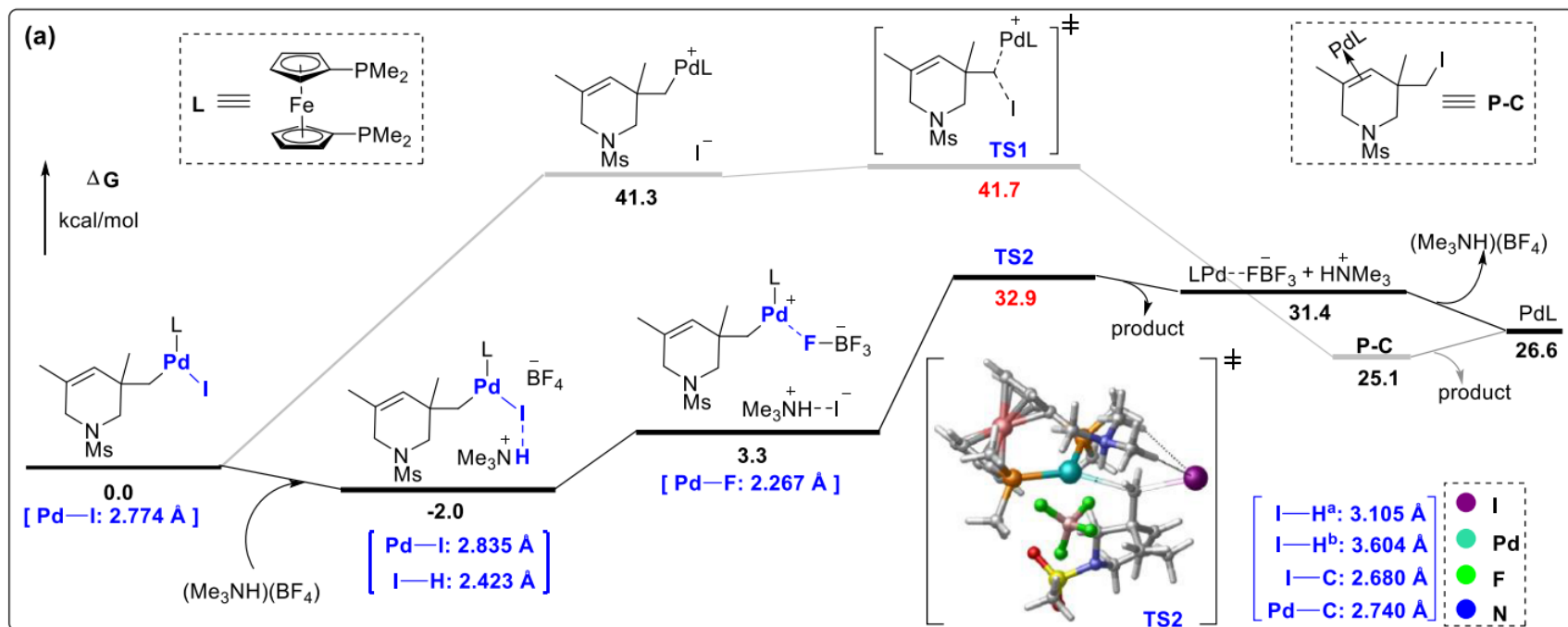
Formation of C(sp³)-Halogen Bonds

□ The role of ammonium salt

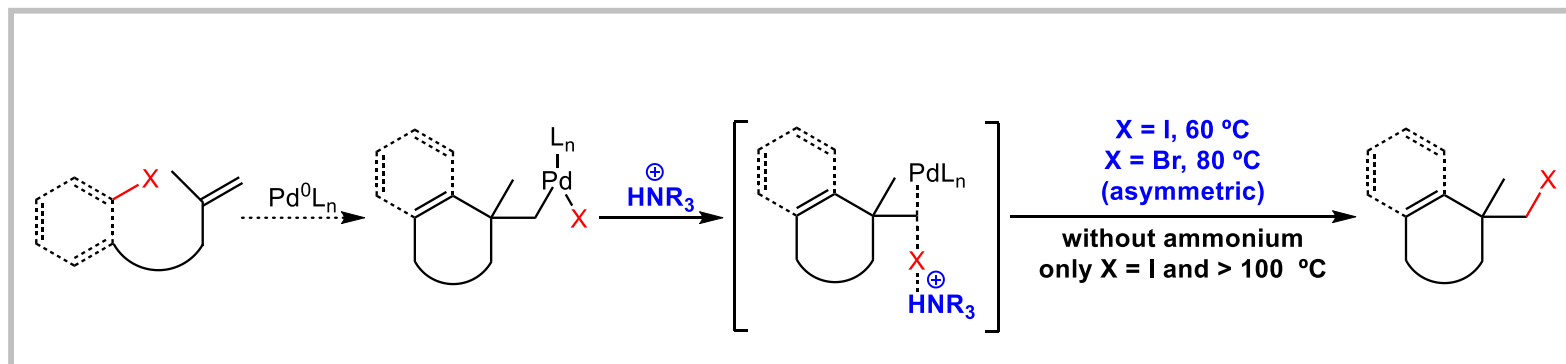


Formation of C(sp³)-Halogen Bonds

□ DFT Calculations



Summary



😊 Pd(0)-Catalyzed **Asymmetric** Carbobrominations

- 😊 **First** Asymmetric Carbobromination
- 😊 Biphasic **H-Bonding** System
- 😊 Simple Ammonium Salt
- 😊 Mild Conditions

Writing Strategies

□ The First Paragraph

The importance and challenge
of the **carbon-halogen RE**



Progress in developing method
for C-X formation



The **limitation** of the
existing methods

The First Paragraph

Reductive elimination (RE) is a typical terminating elementary step for product formation and catalyst regeneration in numerous metal-catalyzed reactions. Expanding the scope of such a fundamental reaction will no doubt broaden the horizons of transition-metal catalysis. As is the case, the newly emerging C–X (X = halogen) RE is particularly attractive since the resulting organohalide product is a class of versatile compounds in organic synthesis. However, because of the reverse process of the facile and exergonic oxidative addition of an organohalide to the Pd(0) complex, the C–X RE is thermodynamically disfavored, rendering such an elementary reaction strikingly less prevalent and practically difficult. Nowadays, stoichiometric and catalytic reactions involving the challenging C–X RE strongly rely on the discovery and development of ligands with highly tailored electronic and/or steric properties.

The First Paragraph

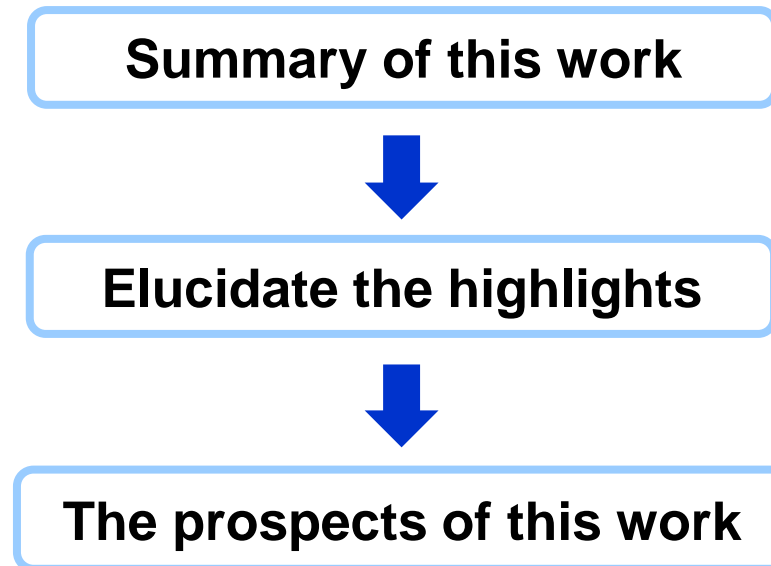
Seminal studies by Hartwig and Buchwald have established benchmarks for C(aryl)-X RE through the use of sterically hindered phosphorus ligands, which could be attributed to key species aryl-Pd^{II}-X with an extremely congested environment at the palladium center. **This fundamental principle is further exemplified in the Lautens' Pd(0)-catalyzed carboiodination reactions, wherein bulky ligand QPhos has been proven to be essential.** More recently, the Morandi group and our own group have disclosed that some specific electron-poor ligands are also able to promote C-X RE via reducing the electronic density of the corresponding Pd^{II} center. **Despite these advancements, there are only a limited number of capable ligands, and a few of them turned out to be general for different types of substrates.**

The First Paragraph

The high reaction temperature together with the time- and effort-consuming ligand identification have severely hampered the development of such Pd(0) catalysis involving the step of formidable C–X RE, especially in an asymmetric fashion.

Writing Strategies

□ The Last Paragraph



The Last Paragraph

We have developed a unique strategy to enable Pd(0)-catalyzed carbohalogenation reactions at much lower temperature. This strategy features simple operation with the addition of $[\text{Et}_3\text{NH}]^+$ salt as the H-bond donor under the toluene/ H_2O /EG biphasic system. These advantages allow us to easily achieve asymmetric carboiodination and carbobromination with high levels of reaction efficiency and enantioselectivity by using the readily available chiral FerroPhos ligand. The putative H-bonding interaction between the $[\text{Et}_3\text{NH}]^+$ and $\text{X-Pd}^{\text{II}}-\text{C}(\text{sp}^3)$ species significantly enhances X-Pd^{II} bond heterolytic dissociation, which plays an essential role in the reduction of the $\text{C}(\text{sp}^3)-\text{I}$ RE reaction barrier. We hope that the newly developed biphasic system would open up a new avenue to stimulate the potential of palladium catalysis in the asymmetric synthesis of organohalides via $\text{C}(\text{sp}^3)-\text{X}$ RE.

Representative Examples

- **In light of (鉴于)** the importance of *sth.* and the **practical limitations of** current methods for their preparation, *a specific method* to yield *sth.* is a **highly desirable transformation.** (表明工作价值)
- The capacity of transition metals to cleave and forge covalent bonds via the fundamental operations of oxidative addition and reductive elimination is a **cornerstone of catalysis.** (陈述某件事的重要性)
- **Important from a practical standpoint (尤其从实用角度来看),** a variety of heterocyclic substrates can also be successfully fluorinated by using these conditions. (体现方法的实用性)

Acknowledgement

***Thanks
for your attention***