Literature Report VI

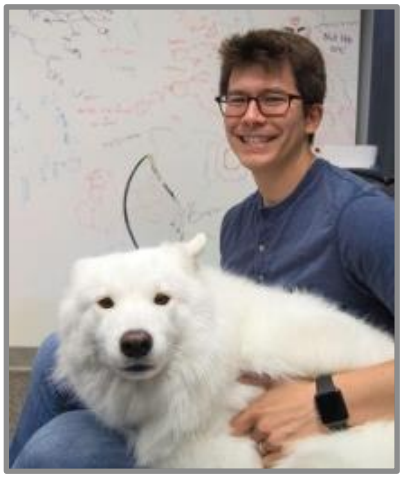
Catalytic σ-Bond Annulation with Ambiphilic Organohalides Enabled by β-X Elimination

Reporter: Yan-Jiang Yu
Checker: Shan-Shan Xun

Ni, H.-Q.; McAlpine, I. J.; Engle, K. M.
Angew. Chem. Int. Ed. **2023**, e202306581

2023-07-10

CV of Prof. Keary Mark Engle



Group's goal:

- (Pre)Catalyst design, reaction discovery, mechanistic elucidation
- Advance the efficiency and sustainability of organic small molecules chemical synthesis

Background:

- **2003-2007** B.S., University of Michigan, Ann Arbor (Matzger, A. J.)
- **2008-2013** Ph.D., The Scripps Research Institute (Yu, J.-Q.)
- **2008-2013** Ph.D., The University of Oxford (Brown, J. M.)
- **2013-2015** Postdoc., California Institute of Technology (Grubbs, R. H.)
- **2015-2020** Assistant Professor, The Scripps Research Institute
- **2020-Now** Professor, The Scripps Research Institute

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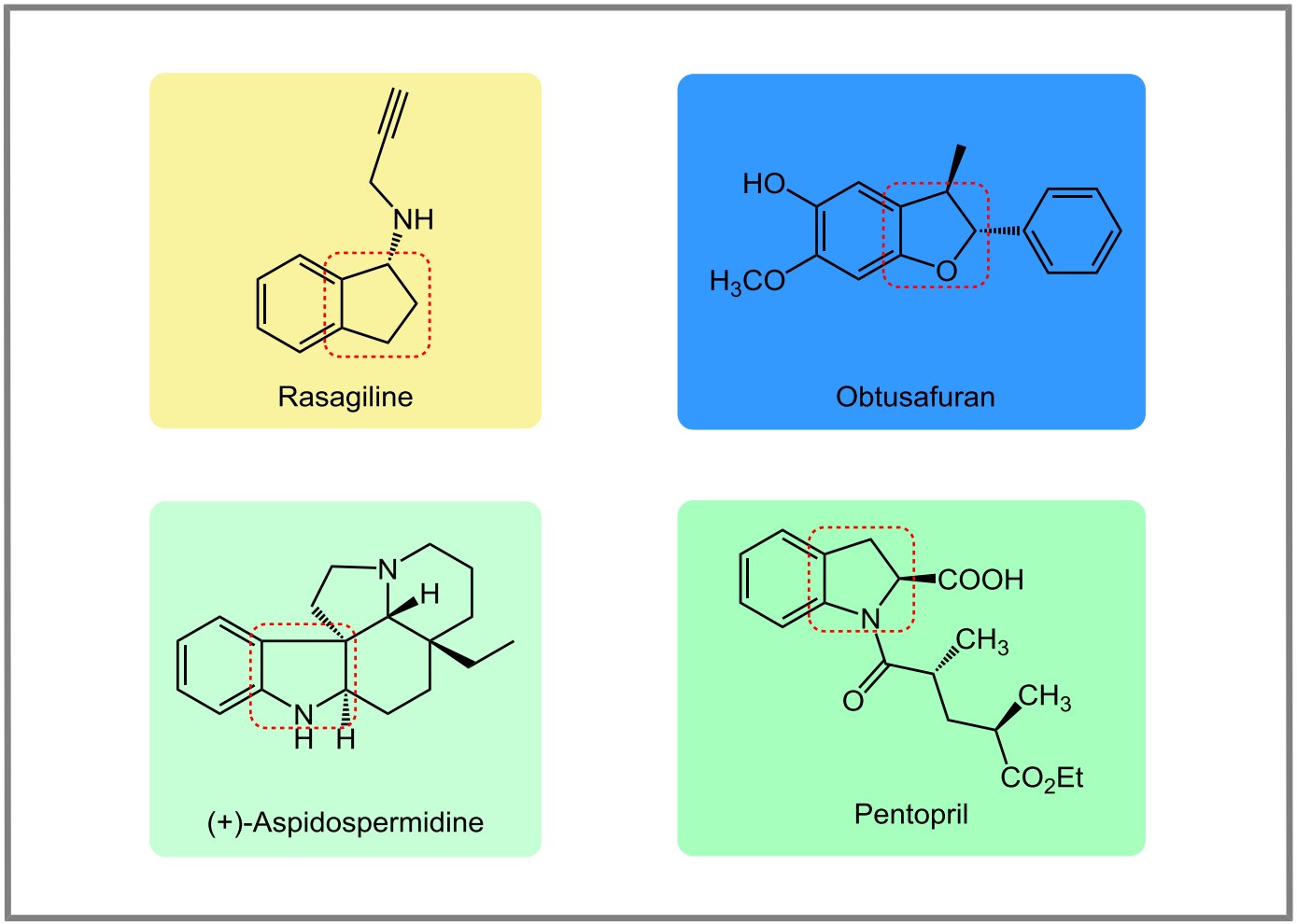
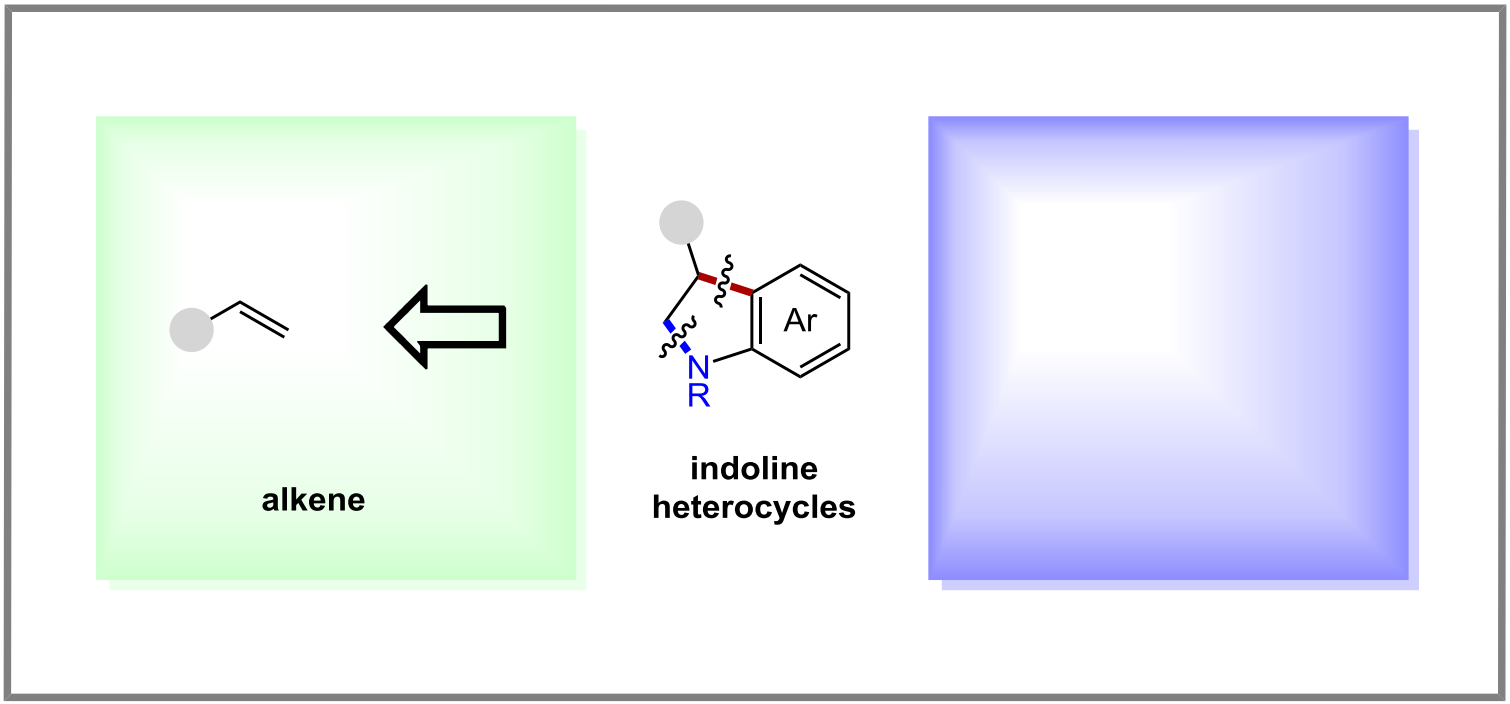


Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, *2010*, 3975
Binda, C.; Li, M.; Edmondson, D. E. *J. Med. Chem.* **2004**, *47*, 1760

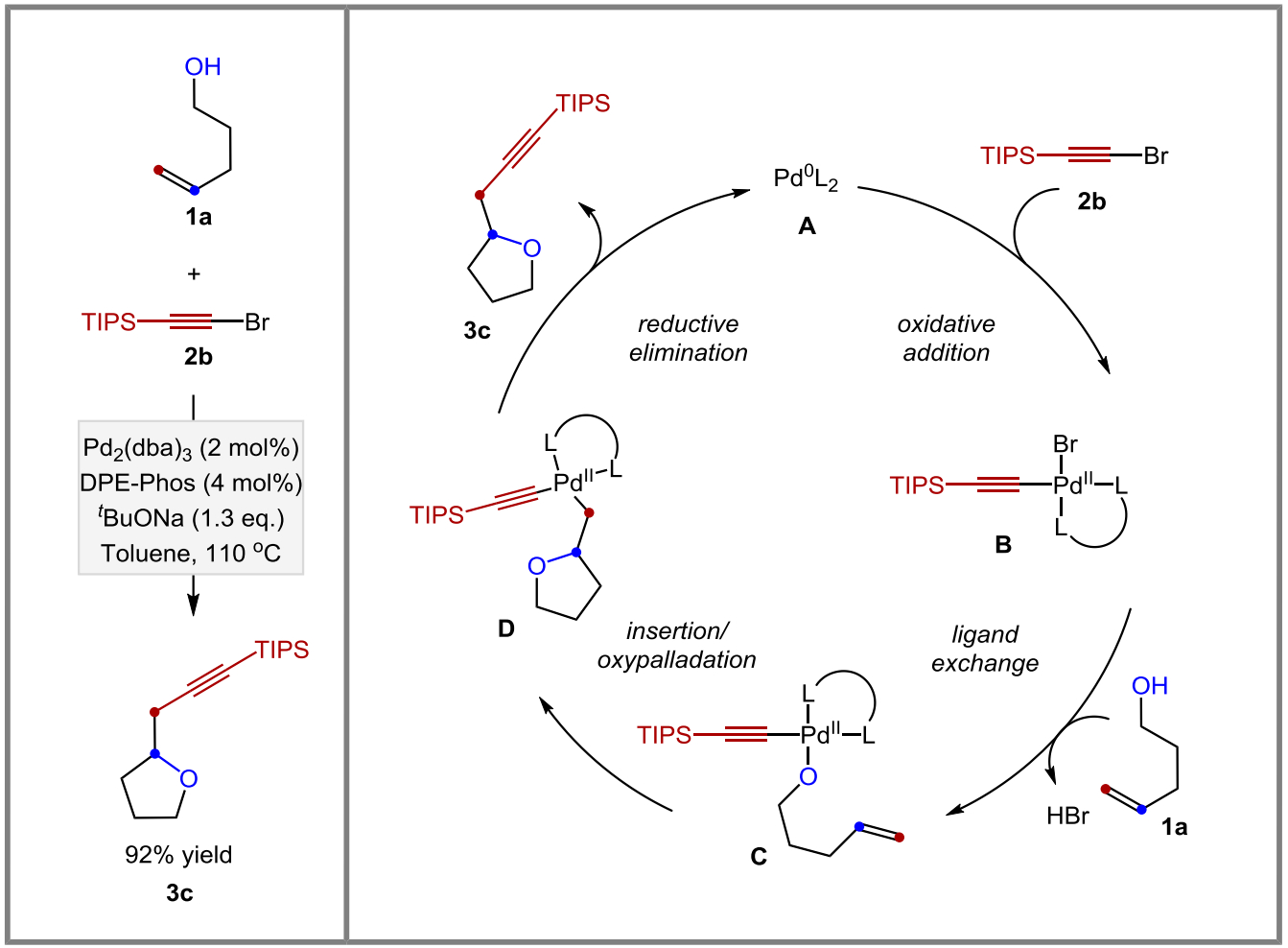
Introduction

π-Bond annulation (established)



Introduction

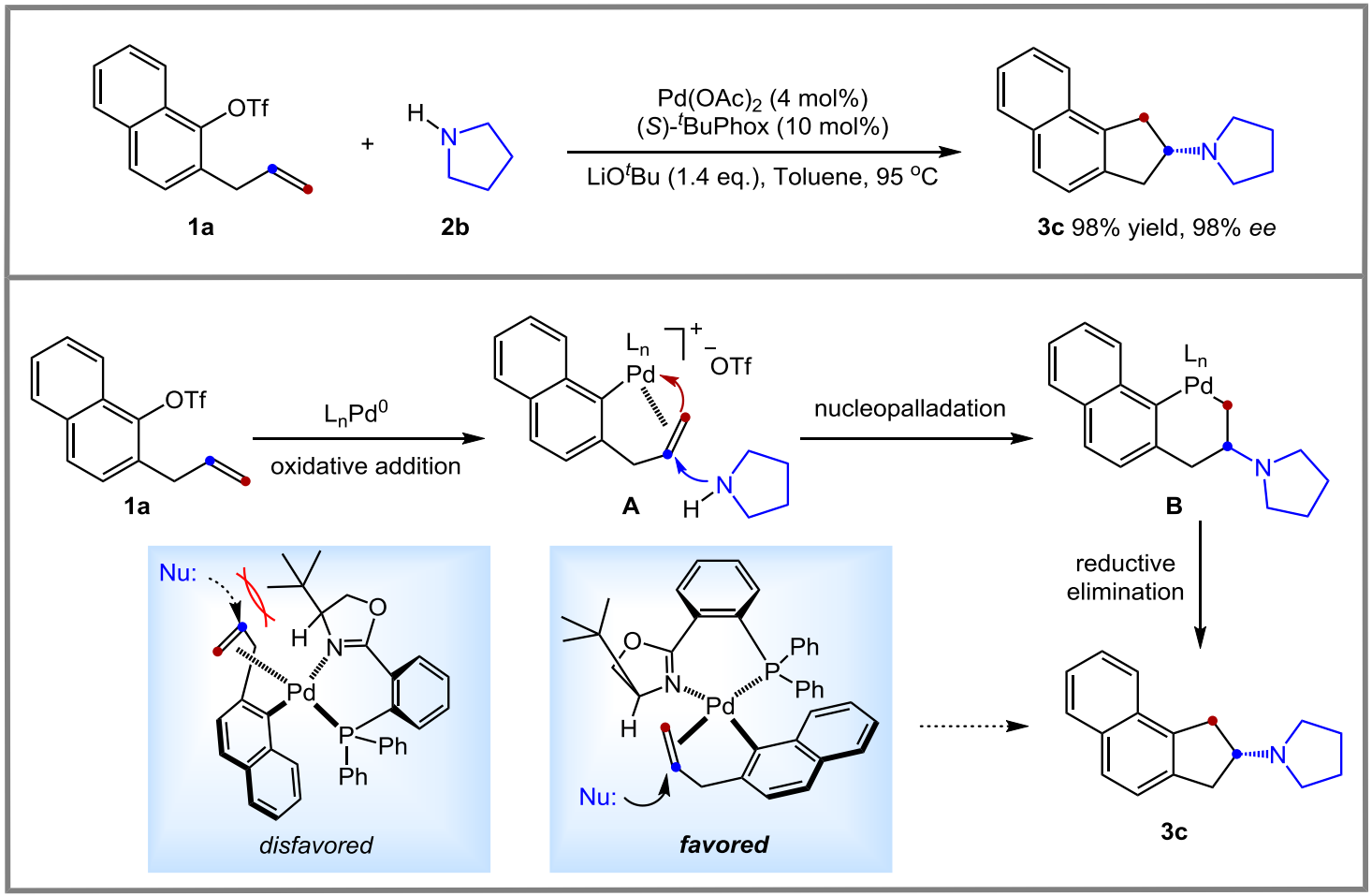
Carbooxygenation of alkenes



Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324

Introduction

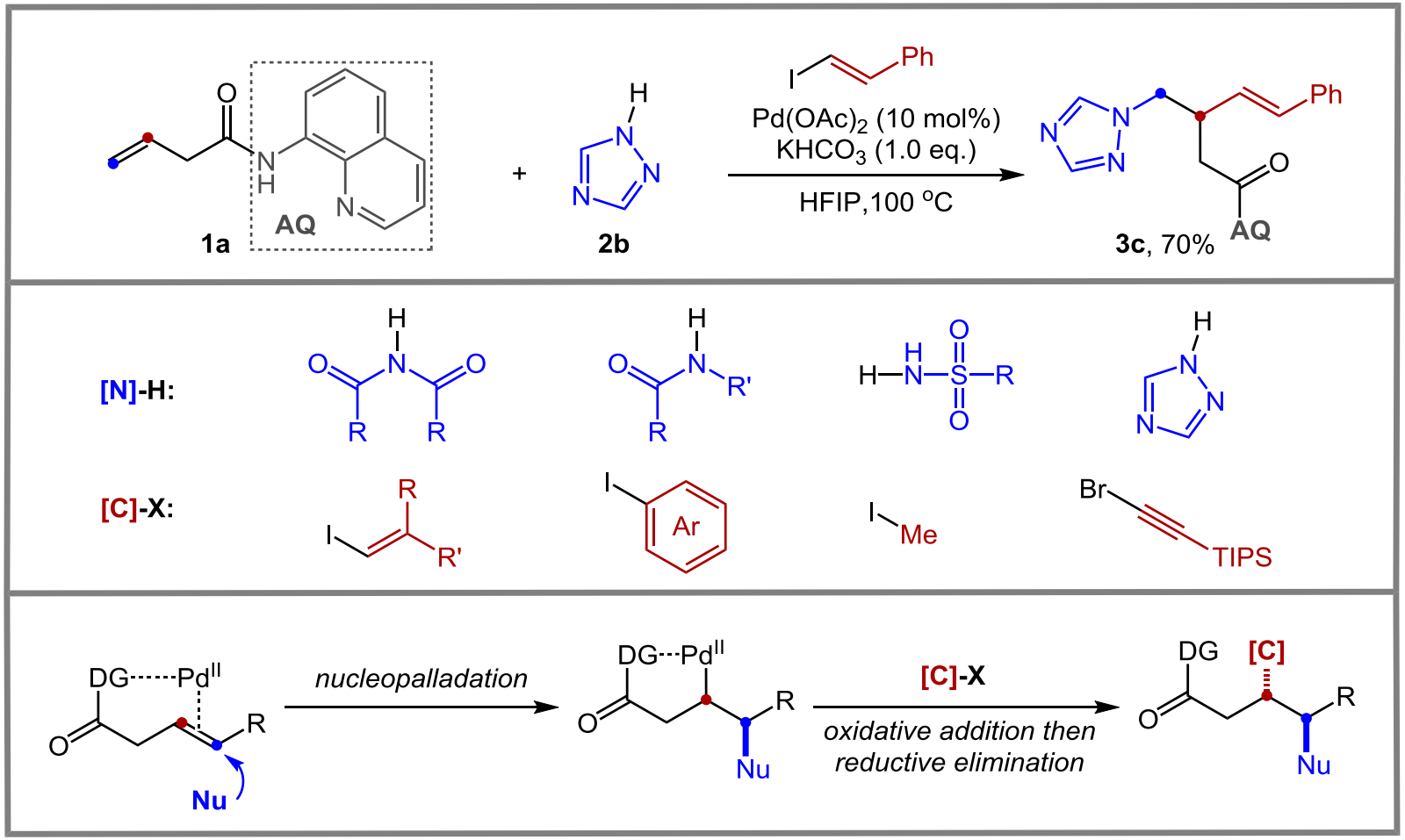
Carboamination of alkenes



White, D. R.; Hutt, J. T.; Wolfe, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 11246

Introduction

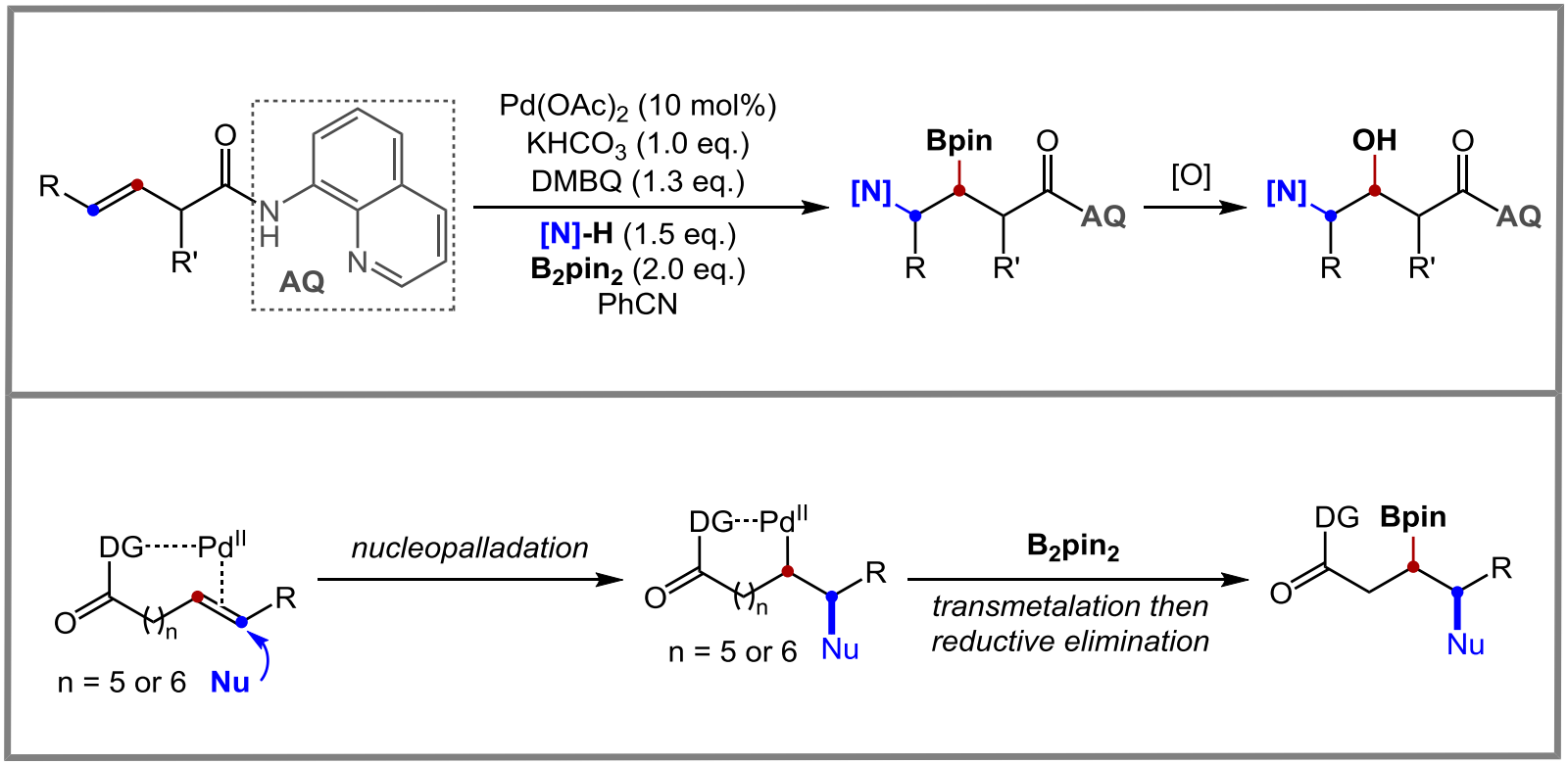
Carboamination of alkenes



Liu, Z.; Wang, Y.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139*, 11261

Introduction

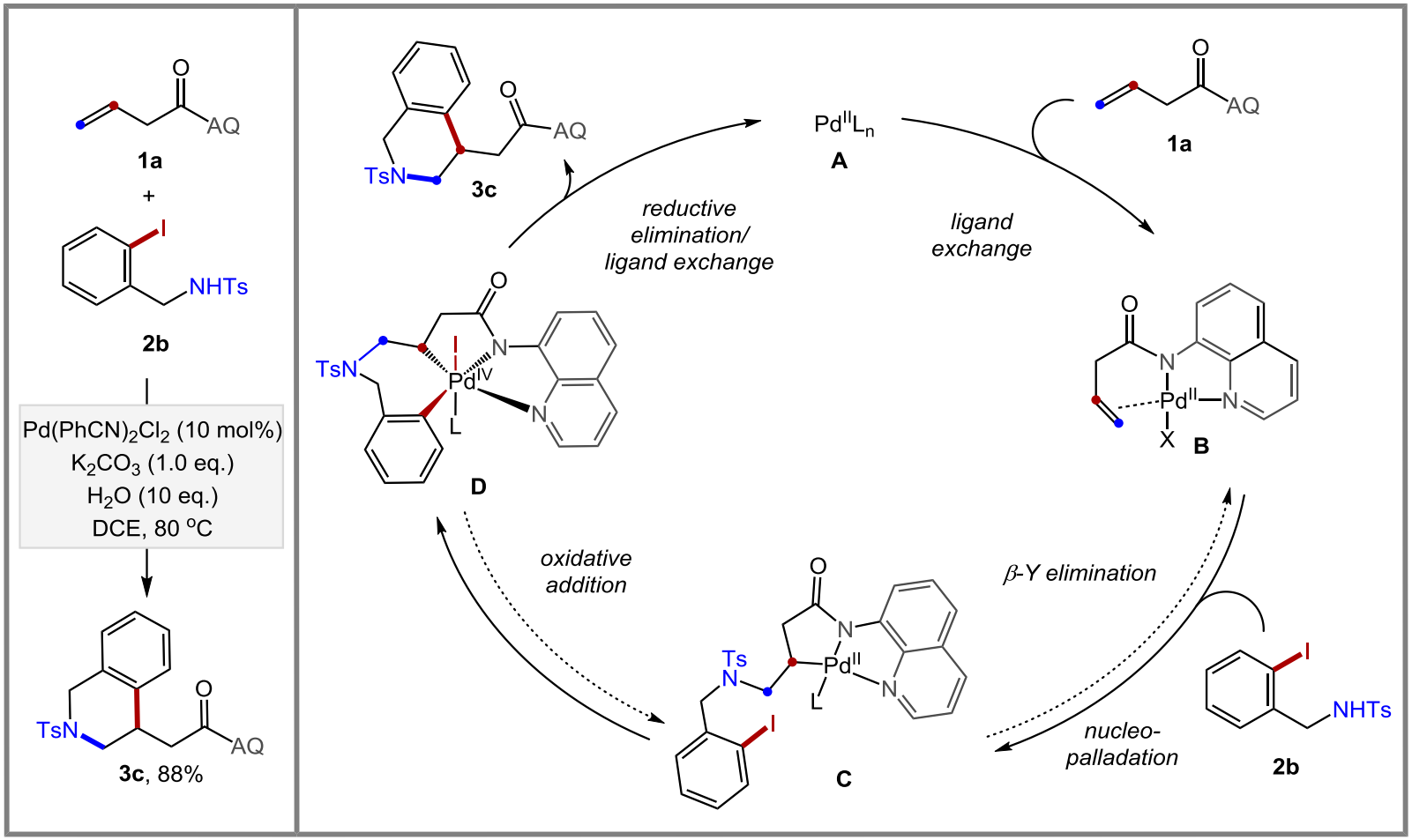
Aminoboronation of alkenes



Liu, Z.; Ni, H.-Q.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140,* 3223

Introduction

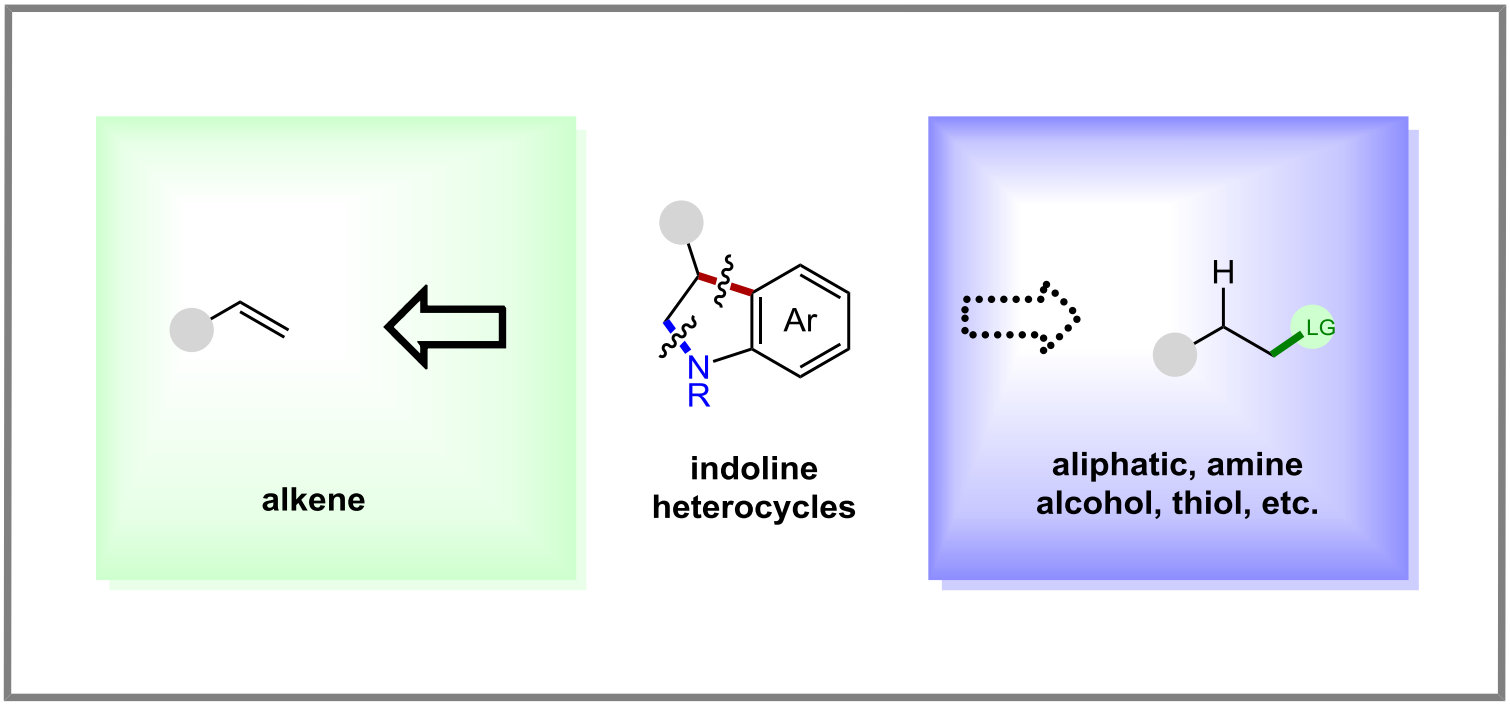
Carboamination of alkenes



Ni, H.-Q.; McAlpine, I. J.; Engle, K. M. *Angew. Chem. Int. Ed.* **2022**, *61*, e202114346

Introduction

σ-bond annulation (underdeveloped)



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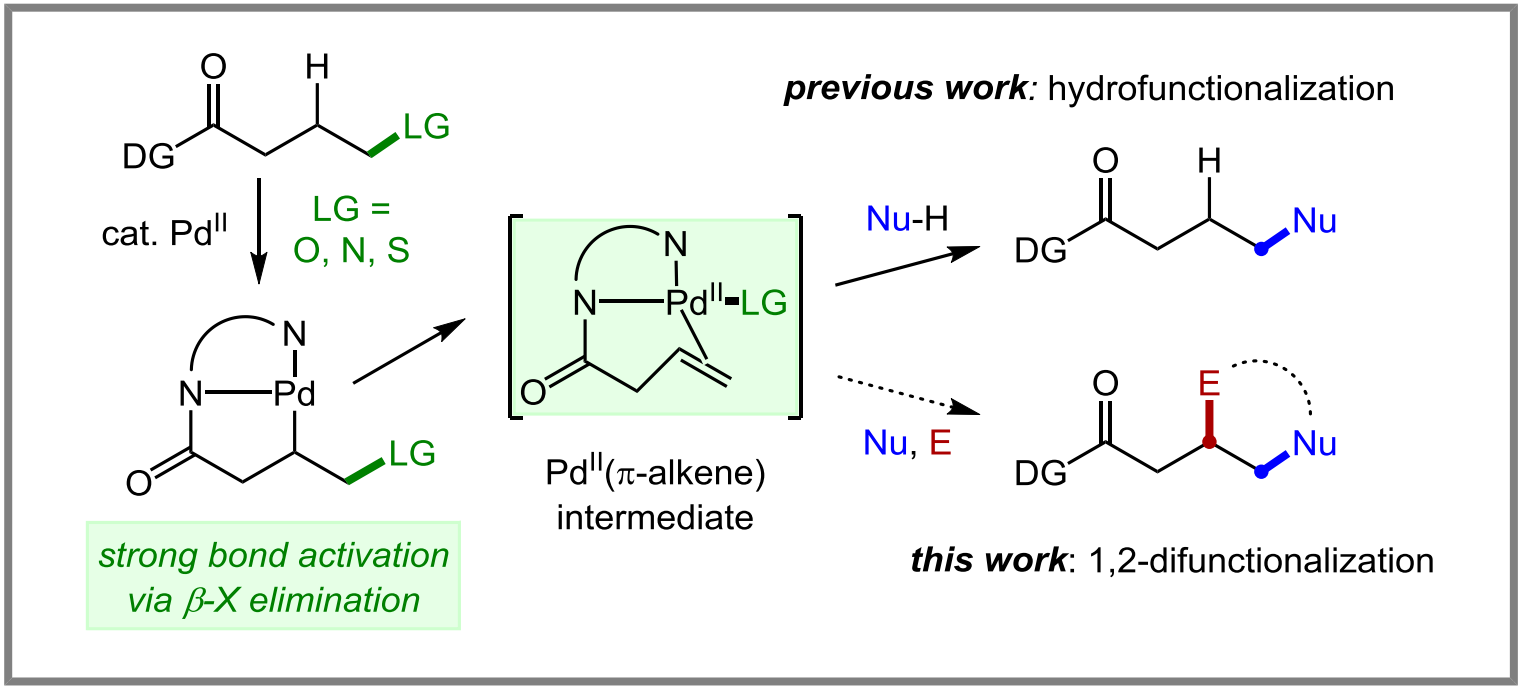

Ni, H.-Q.; McAlpine, I. J.; Engle, K. M. *Angew. Chem. Int. Ed.* **2023**, e202306581

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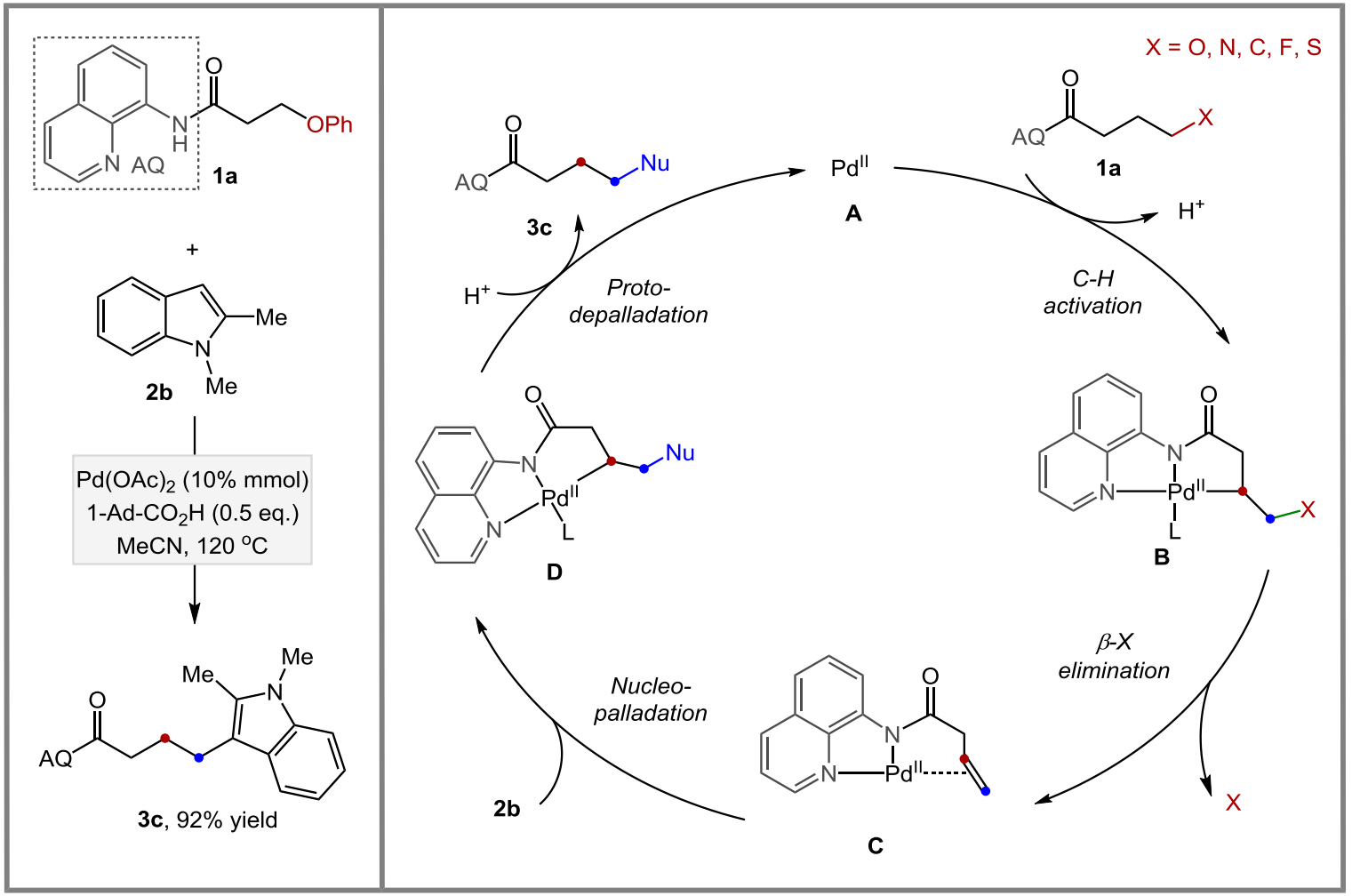
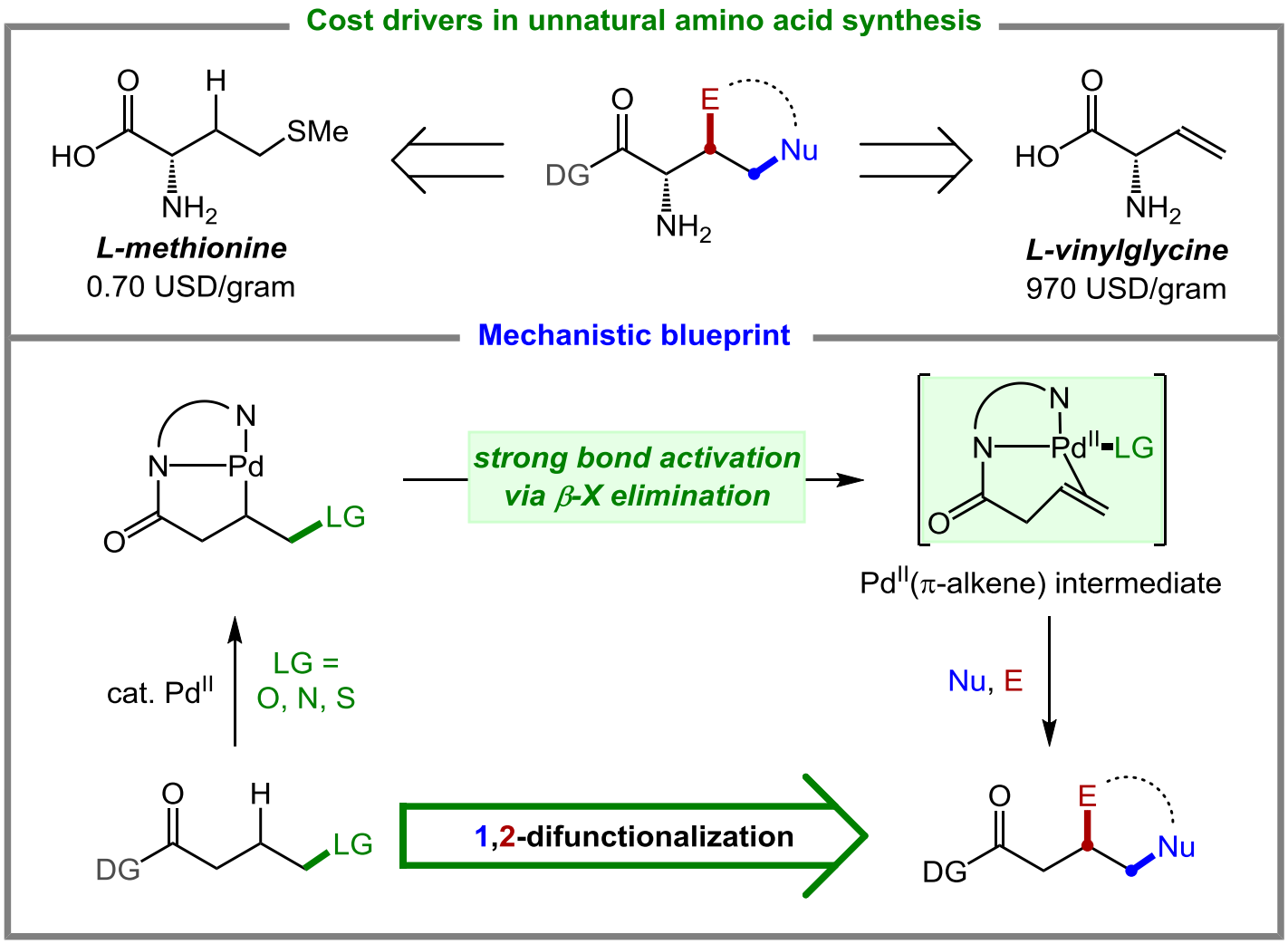


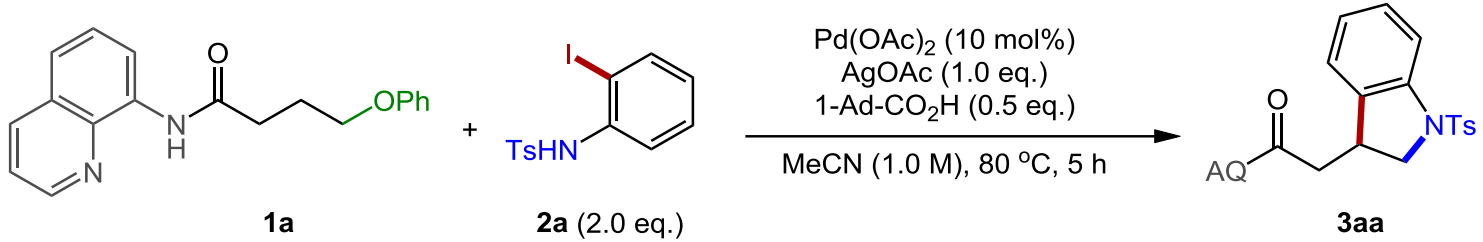
Tran, V. T.; Yang, K. S.; Engle, K. M. *Nat*. *Chem*. **2018**, *10*, 1126

Project Synopsis



Ni, H.-Q.; McAlpine, I. J.; Engle, K. M. *Angew. Chem. Int. Ed.* **2023**, e202306581

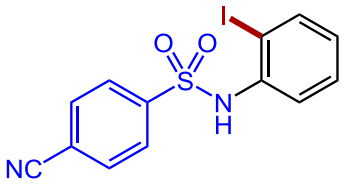
Optimization of Reaction Conditions



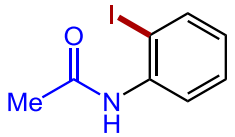
1a **2a** (2.0 eq.) **3aa**

Entry	deviation from standard reaction	Yield (%)[a]
1	none	86[b]
2	$Pd(OAc)_2$ (5 mol%)	72
3	no AgOAc	15
4	$CuCl_2$ (1.0 eq.) instead of AgOAc	<5
5	$Cu(OAc)_2$ (1.0 equiv) instead of AgOAc	37
6	CsOPiv (1.0 equiv) instead of AgOAc	30
7	no 1-Ad-CO_2H	77
8	HFIP (1.0 M) as solvent	41
9	DCE (1.0 M) as solvent	52
10	60 °C	28

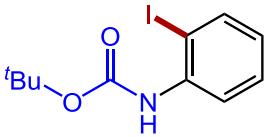
[a] Values correspond to ^1H NMR yields using $Cl_2CHCHCl_2$ as internal standard. [b] Isolated yields. [c] 120 °C, n.d. = not detected.



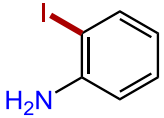
2b, 87%[b] (NHCs)



2c, 9%[c]

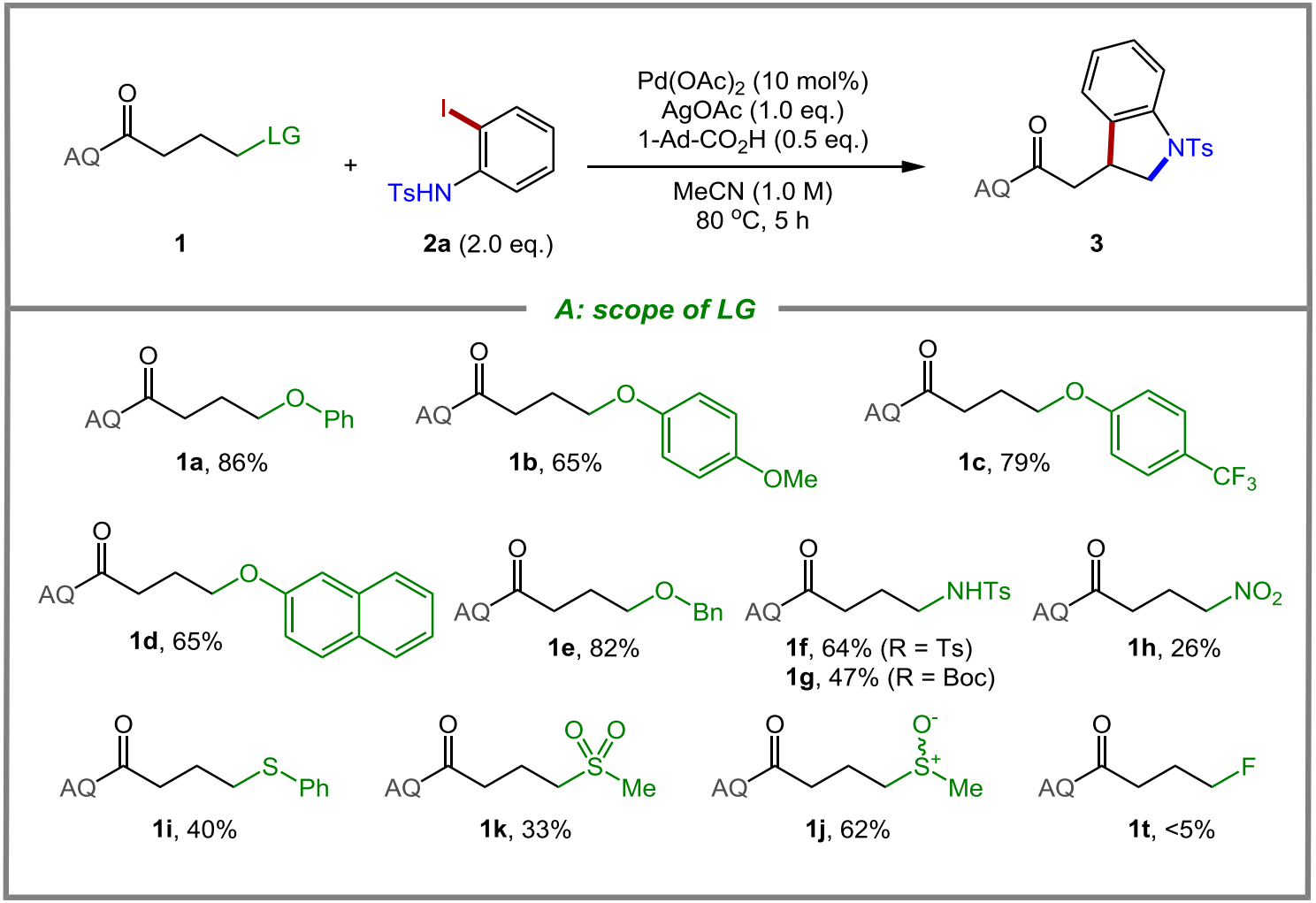


2d, 8%[c]



2e, n.d.[c]

Substrate Scope



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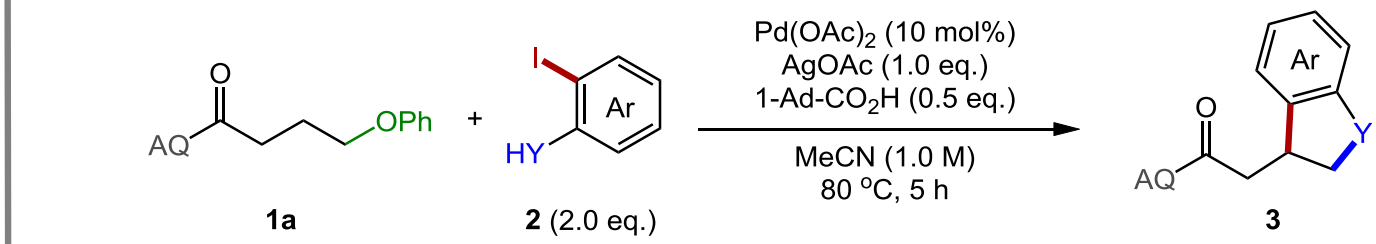
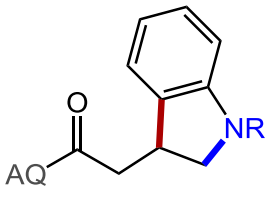
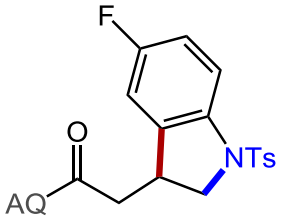


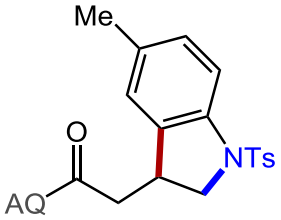
B: scope of coupling partner



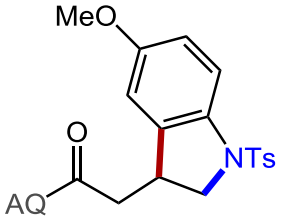
3aa, 86% (R= Ts)
3ab, 87% (R = Cs)



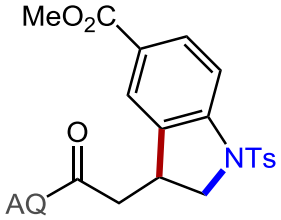
3af, 93%



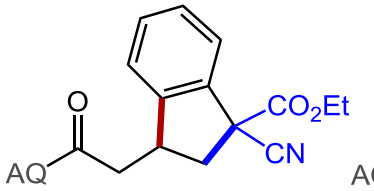
3ag, 82%



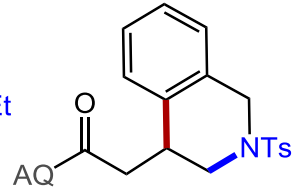
3ah, 87%



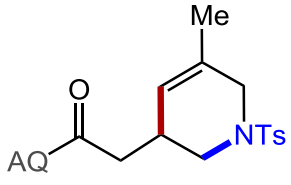
3ai, 82%



3am, 77%, 1:1 *dr*

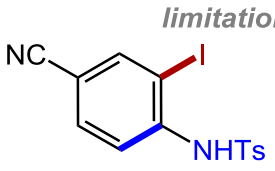


3ao, 35%

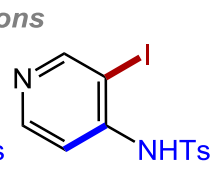


3ap, 29%

limitations

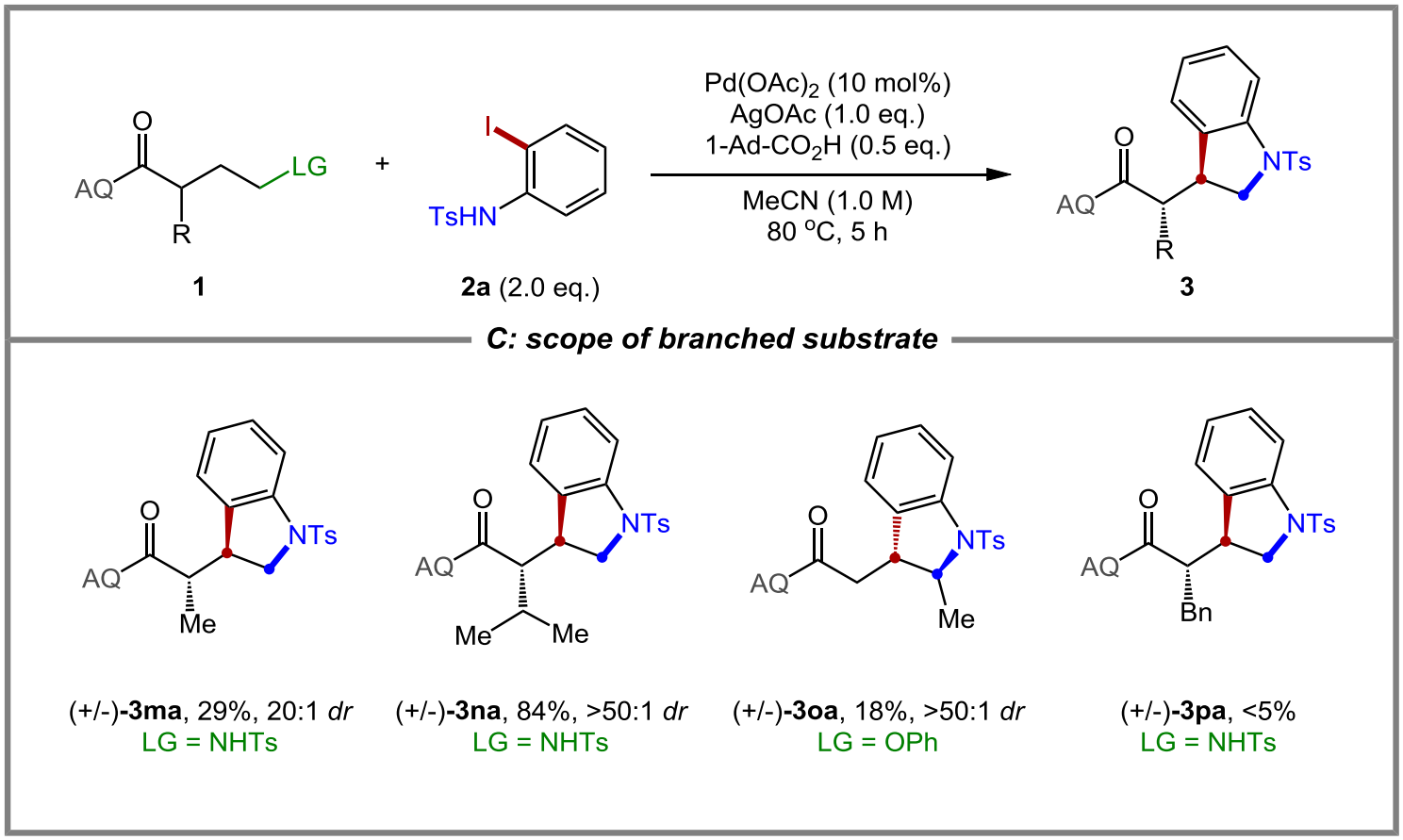


2k, n.d.

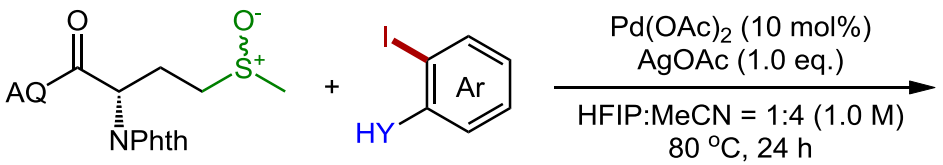


2l, n.d.

Substrate Scope



Substrate Scope

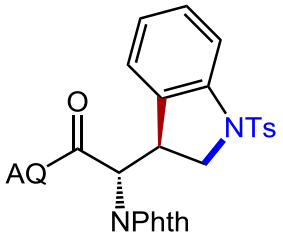


1l (1:1 *dr*)
99% ee (both diastereomers)

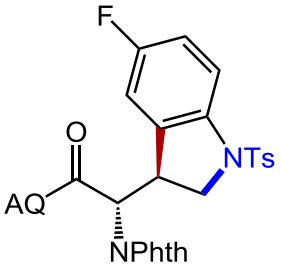
2 (2.0 eq.)

3

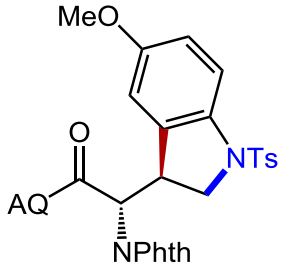
amino acid scope



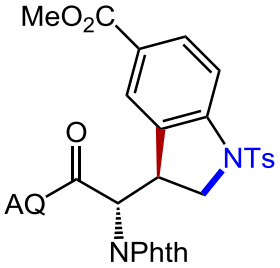
3la, 76%, 19:1 *dr*, 80% *ee*



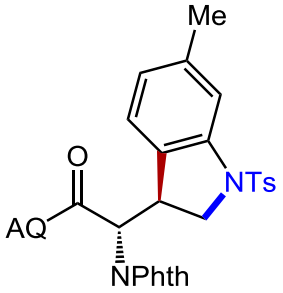
3lf, 79%, 16:1 *dr*, 94% *ee*



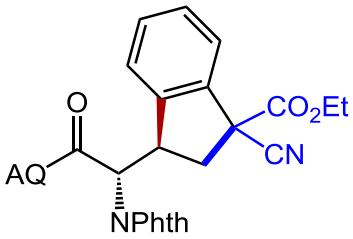
3lh, 79%, 15:1 *dr*, 91% *ee*



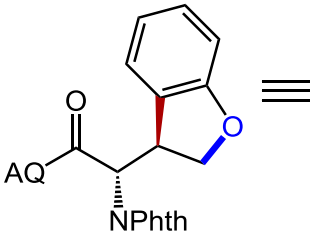
3li, 73%, 20:1 *dr*, 83% *ee*



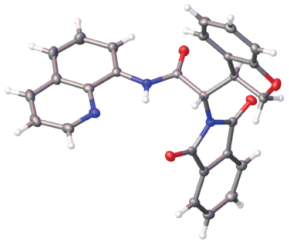
3lj, 56% 12:1 *dr*, 81% *ee*



3lm, 23%, 1.4:1 *dr*, 81% *ee*



3ln, 30%, 20:1 *dr*, 87% *ee*



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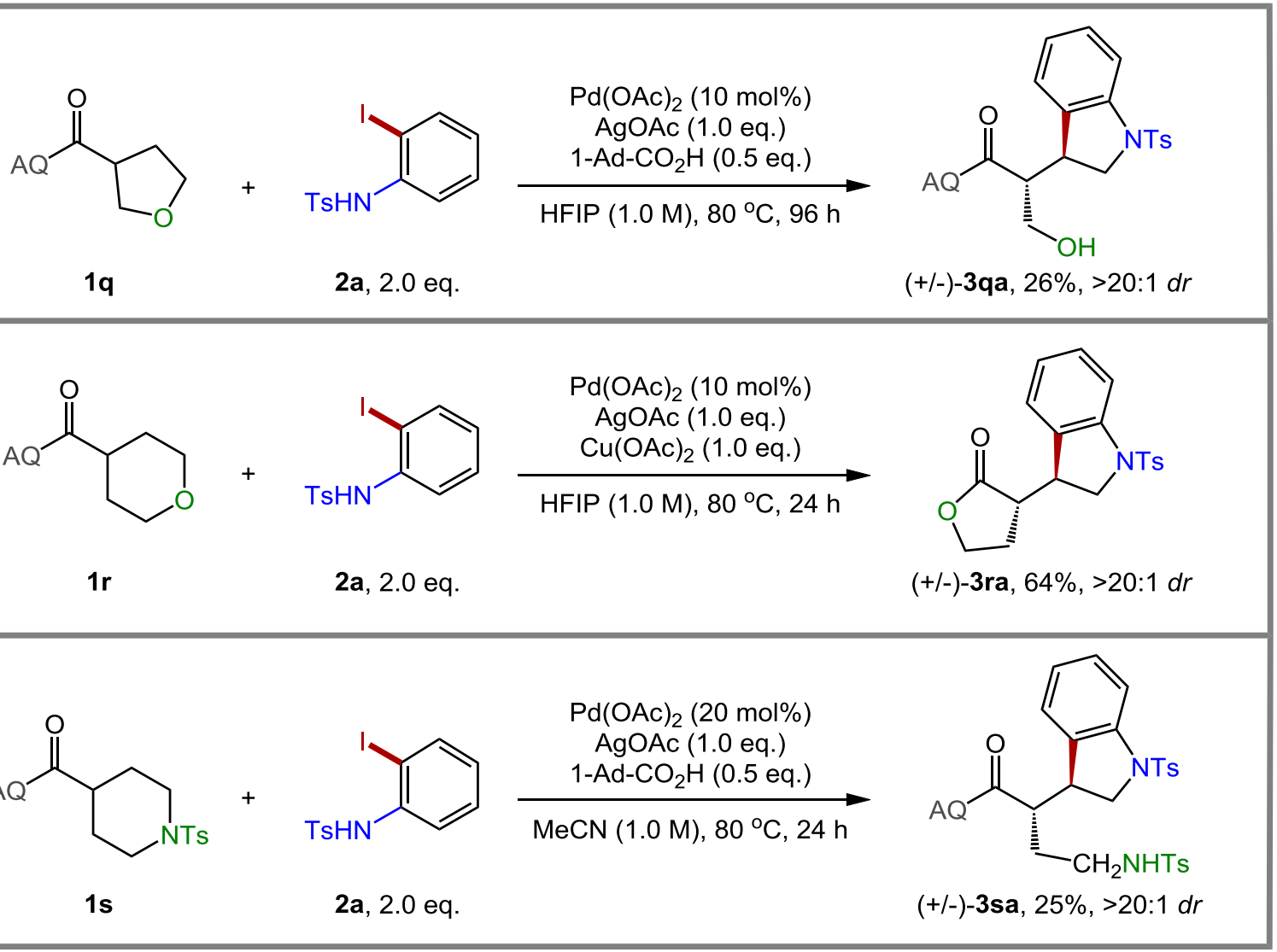
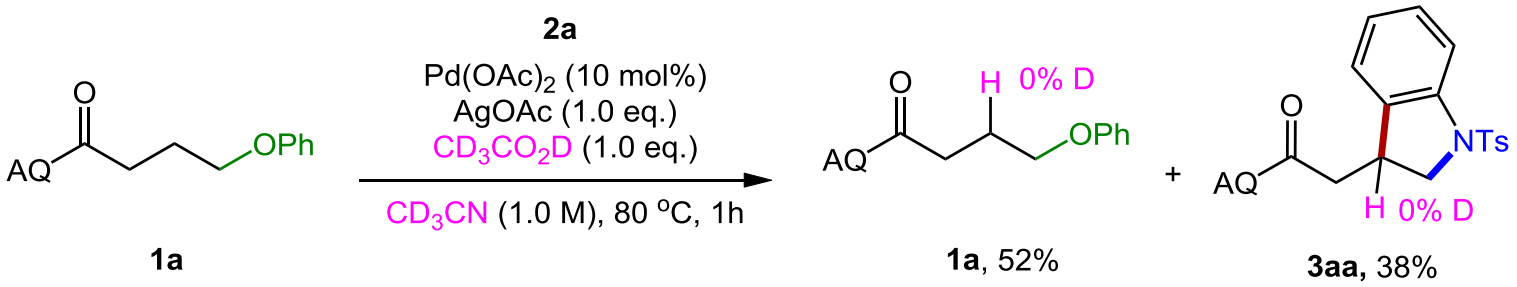
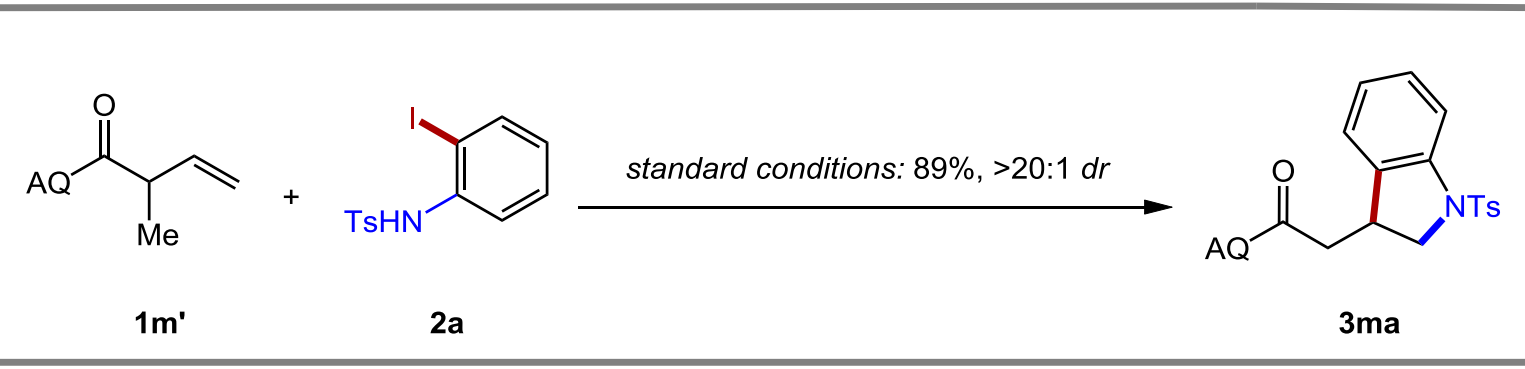


Mechanistic Investigation

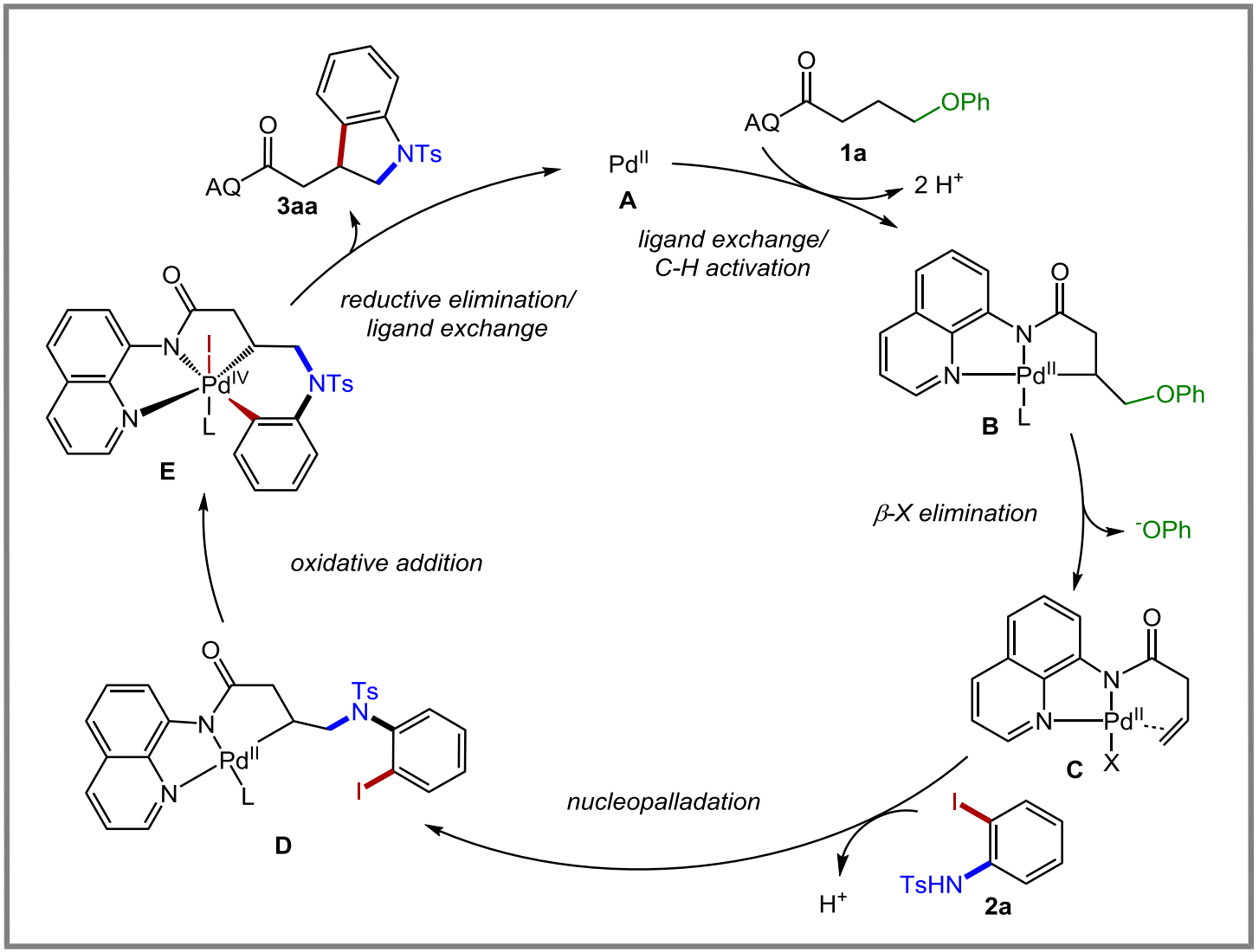
Deuterium exchange experiments



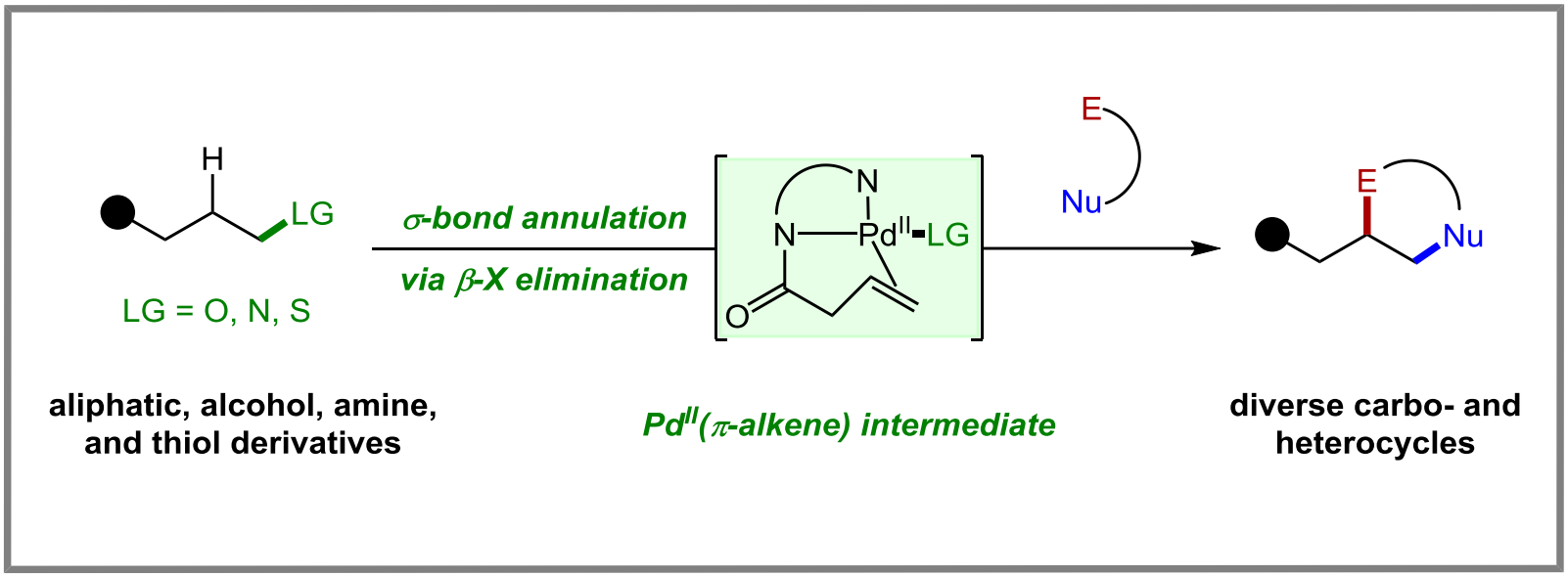
Viability of an Pd^{II}(π-alkene) intermediate



Proposed Mechanism



Summary



- **Pd^{II}-catalyzed σ-bond annulation strategy**
- **Combining C-H activation and *β*-X elimination**
- **Employing various alkyl C(sp^3)-O, N, and S bonds**
- **Access 5- and 6-membered carbo- and heterocycles**
- **Cost drivers in unnatural amino acid synthesis**

The First Paragraph

Writing strategy

The importance of heterocycles and carbocycles

The development of catalytic [n+2] (hetero)annulation

Catalytic *σ*-bond annulation by *β*-X elimination

- Heterocycles and carbocycles are common substructures in pharmaceuticals and natural products.
- Metal-catalyzed alkenes annulations with ambiphilic organohalide coupling partners are particularly useful. Simultaneous activation of C-H and C-heteroatom σ-bonds would be synthetically enabling, but this strategy remains largely undeveloped.
- We realized *σ*-bond annulation process *via* activation alkyl C(sp^3)-X bonds by *β*-heteroatom elimination, thereby providing direct access to useful heterocycles from simple aliphatic starting materials.

The Last Paragraph

Writing strategy

Summary of this work

The advantages of this work

Highlight the utility of this transformation

- In conclusion, we report a Pd^{II}-catalyzed *σ*-bond annulation of aliphatic alcohol, amine, and thiol derivatives with ambiphilic organohalides to afford (hetero)cycles.
- The Method leverages sequential C-H activation and *β*-X elimination to generate a reactive Pd^{II}(π-alkene) intermediate.
- We highlight the utility of this transformation in the synthesis of optically pure (hetero)cycles from *L*-methionine and in *σ*-bond ring-opening/ring-closing transfiguration with low-strain heterocycles.

Representative Examples

Developing a toolkit of annulation methods that employ alternative substrate classes. (建立…的工具库)

We highlight the utility of this transformation in the synthesis of optically pure (hetero)cycles from L-methionine. (强调该方法在合成…中的实用性)

The inclusion of AgOAc is crucial for efficient catalytic turnover, as omitting it from the reaction or replacing it with other additives gave low conversion to product. (omit…from; omit: *v.* 省略，删除，遗漏; leave out)

Adamantane-1-carboxylic acid may also play a minor role in faciliatating reaction, as its omission led to slightly diminished yield. (*adj.* 减少的, 减弱的; diminish: *v.* 减少，降低；decrease)

Thanks
for your attention