

Literature Report 6

Enantioselective Synthesis of Bicyclo[3.2.1]octadienes via Palladium-Catalyzed Intramolecular Alkene-Alkyne Coupling Reaction

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Checker: Jian Chen

2023-12-18

CV of Prof. Hequan Yao



Research:

- Total synthesis of active natural products
- Catalytic synthesis methodology

Background:

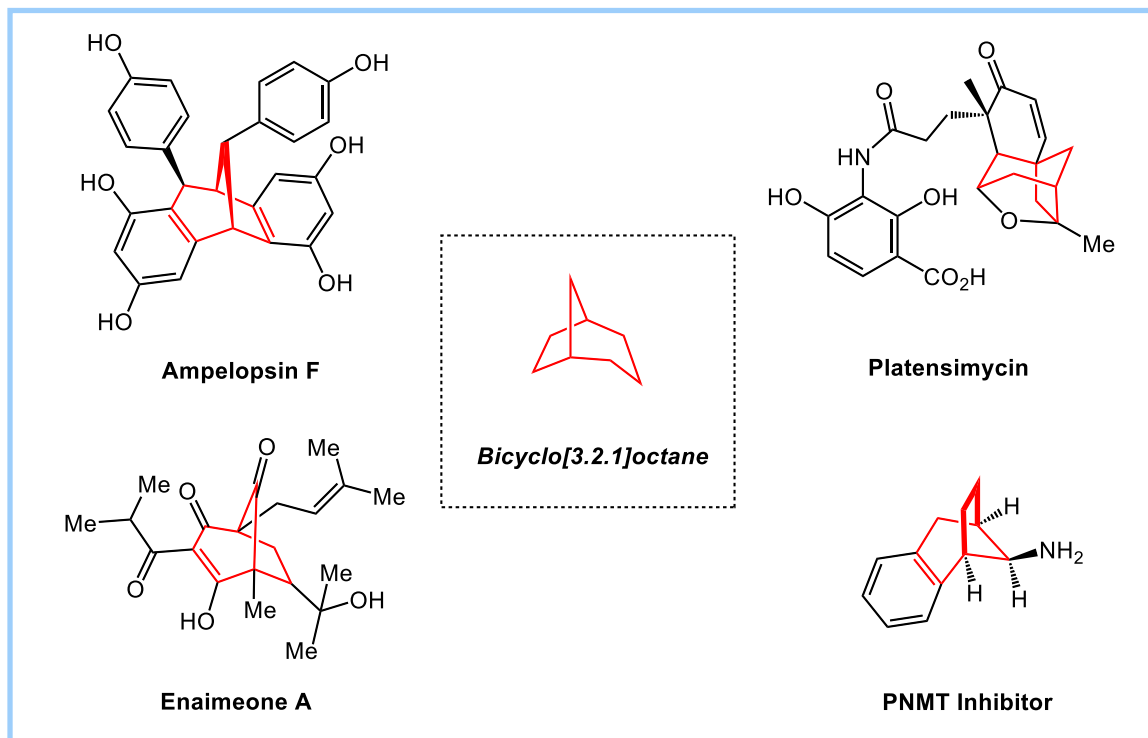
- **1994-1998** B.S., China Pharmaceutical University
- **1998-2001** M.S., China Pharmaceutical University
- **2001-2004** Ph.D., Shanghai Institute of Organic Chemistry
- **2004-2007** Postdoc., Stanford University
- **2008-Now** Professor, China Pharmaceutical University

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- 2 Synthesis of Bicyclo[3.2.1]octanes**
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.....
- 4 Summary**
.....

Introduction

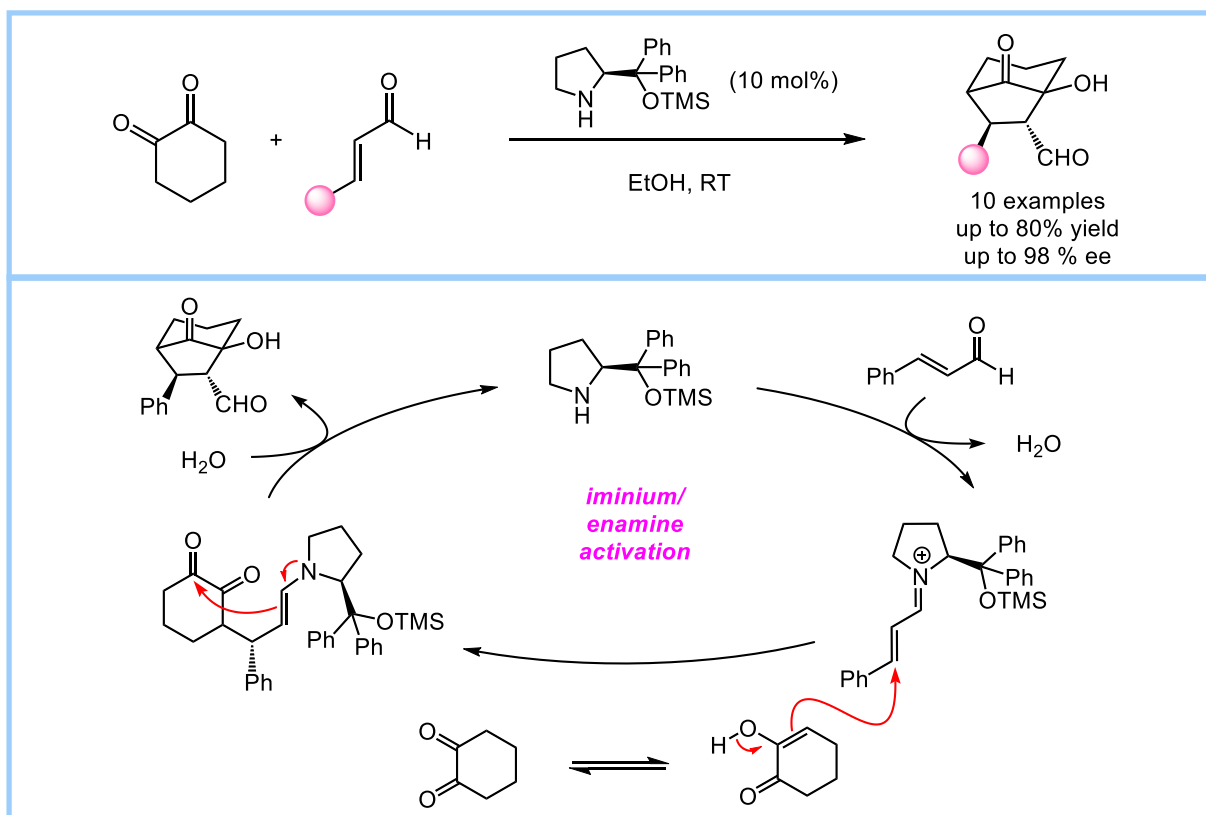
Biologically Active Bicyclo[3.2.1]octanes



Presset, M.; Rodriguez, J.* *Chem. Rev.* **2013**, *113*, 525-595

Organocatalytic Synthesis of Bicyclo[3.2.1]octanes

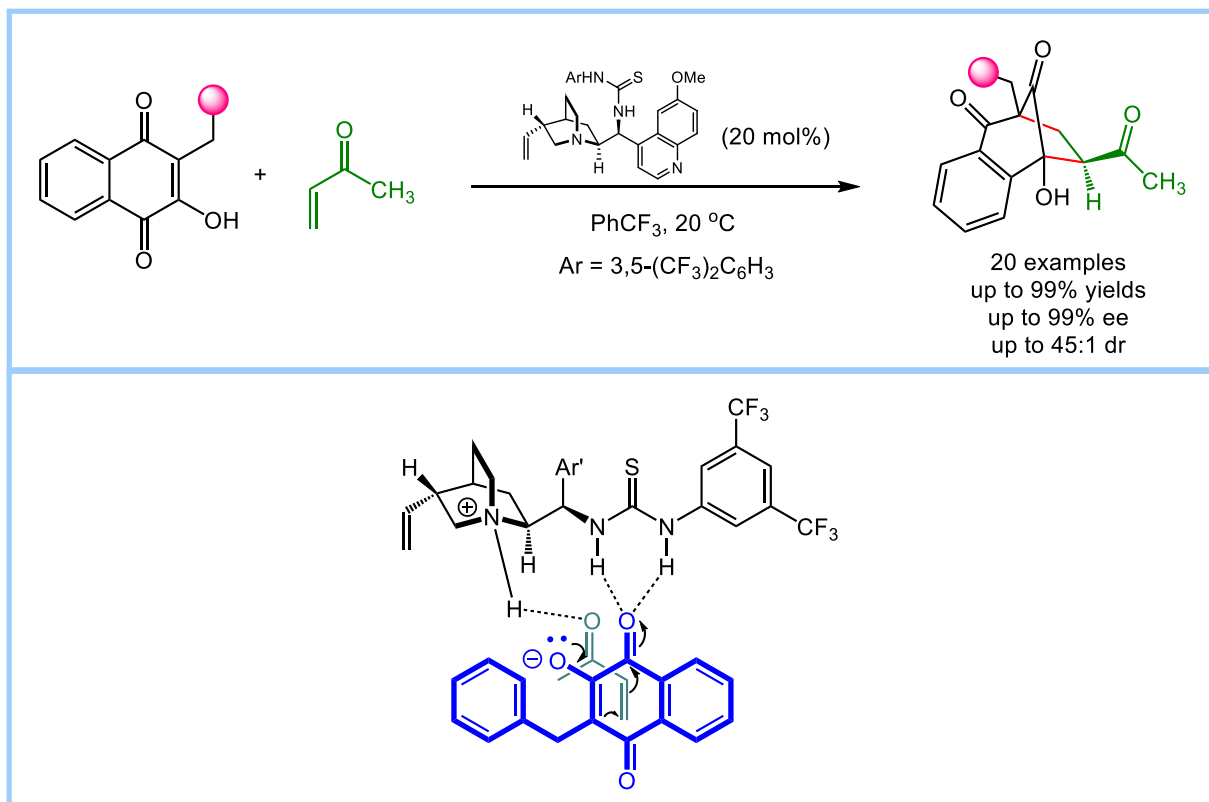
Organocatalytic Asymmetric Domino Michael/Aldol Reactions



Rueping, M.*; Kuenkel, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 3699-3702

Organocatalytic Synthesis of Bicyclo[3.2.1]octanes

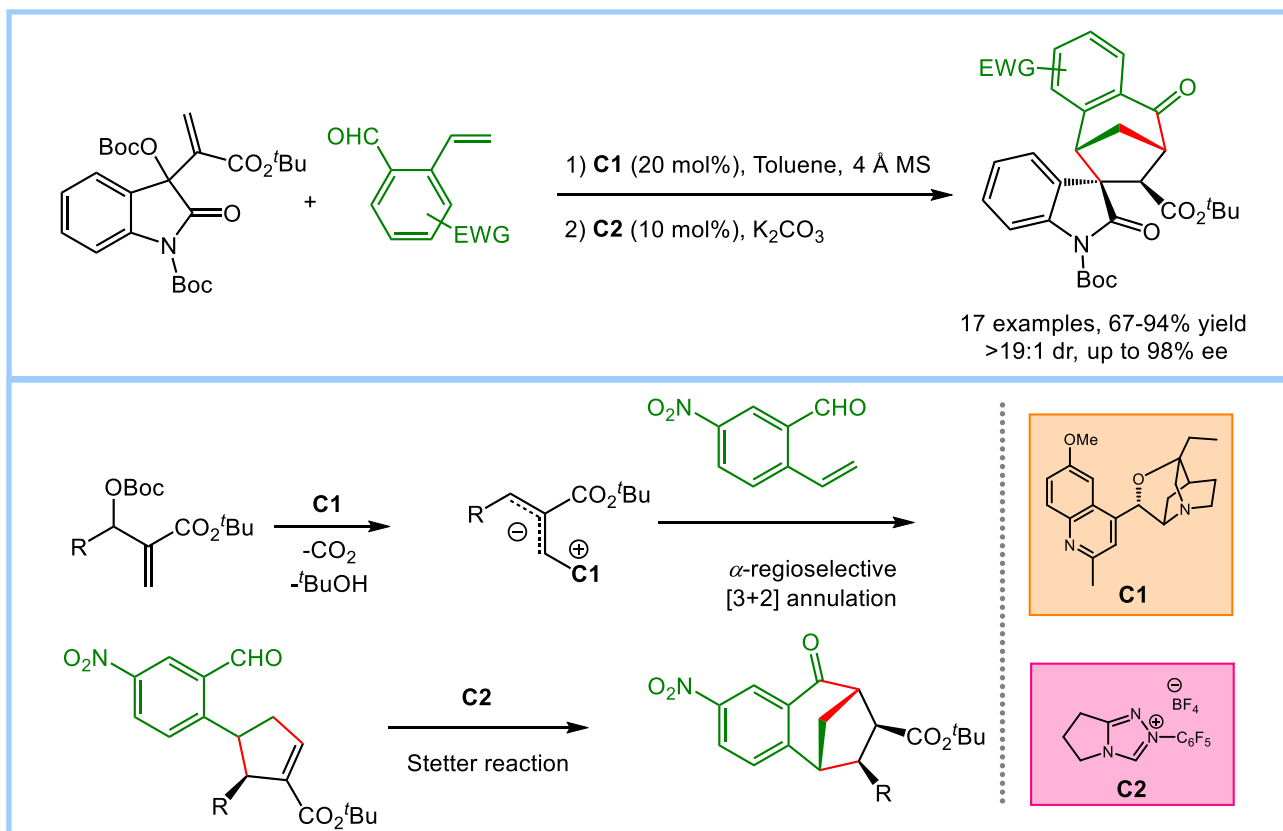
Organocatalytic Asymmetric Formal [3+2] Cycloaddition



Ramachary, D. B.*; Thirupathi, G. *Angew. Chem. Int. Ed.* **2017**, *56*, 12930-12934

Organocatalytic Synthesis of Bicyclo[3.2.1]octanes

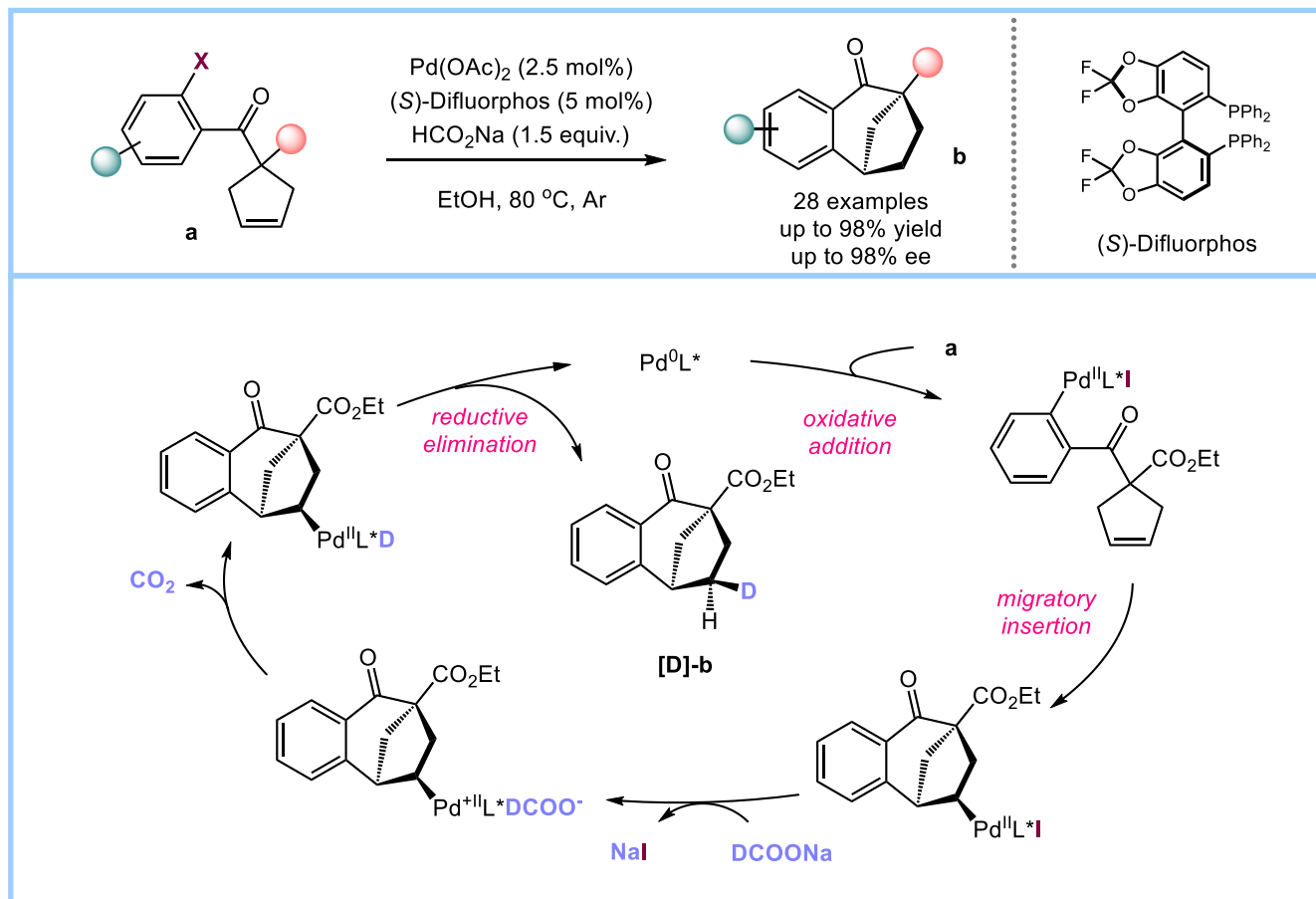
Organocatalytic Asymmetric Sequential Assembly



Jiang, B.; Chen, Y.-C.* *Org. Lett.* **2019**, *21*, 3310-3313

Metal-Catalyzed Synthesis of Bicyclo[3.2.1]octanes

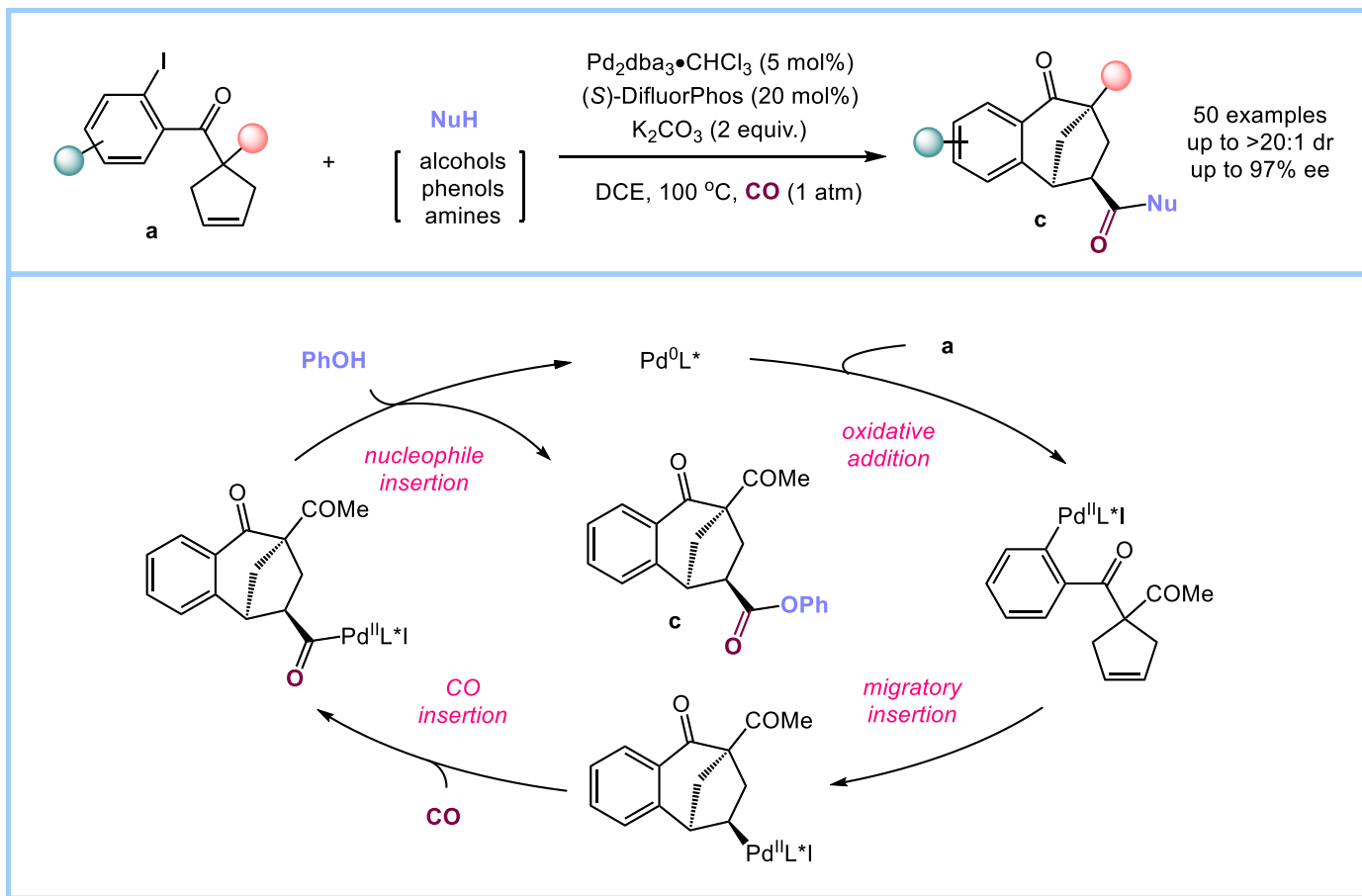
Pd-Catalyzed Reductive Heck Coupling



Yuan, Z.; Yao, H.* *Angew. Chem. Int. Ed.* **2019**, *58*, 2884-2888

Metal-Catalyzed Synthesis of Bicyclo[3.2.1]octanes

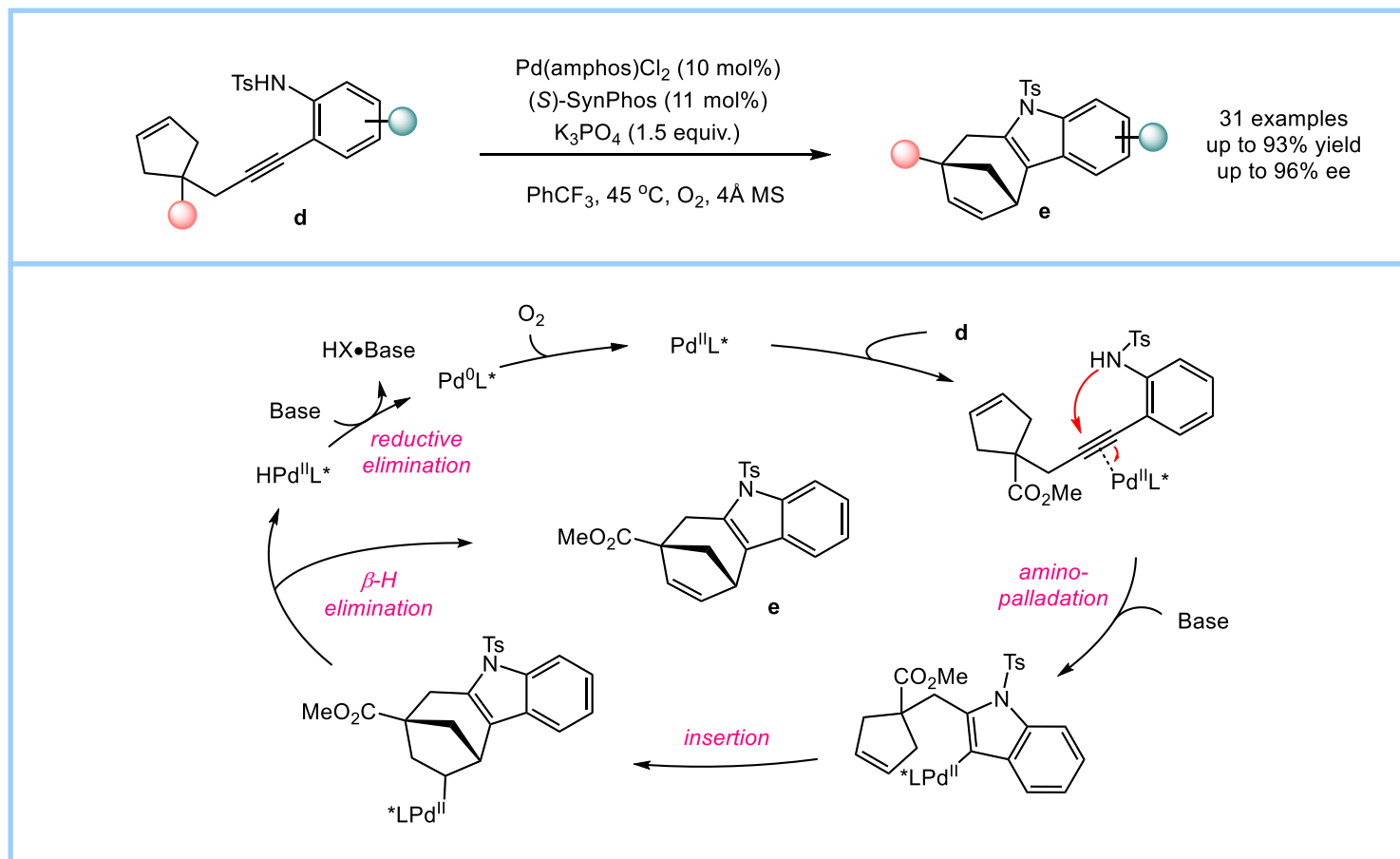
Pd-Catalyzed Tandem Heck/Carbonylation



Yuan, Z.; Yao, H.* *Nat. Commun.* **2020**, *11*, 2544

Metal-Catalyzed Synthesis of Bicyclo[3.2.1]octanes

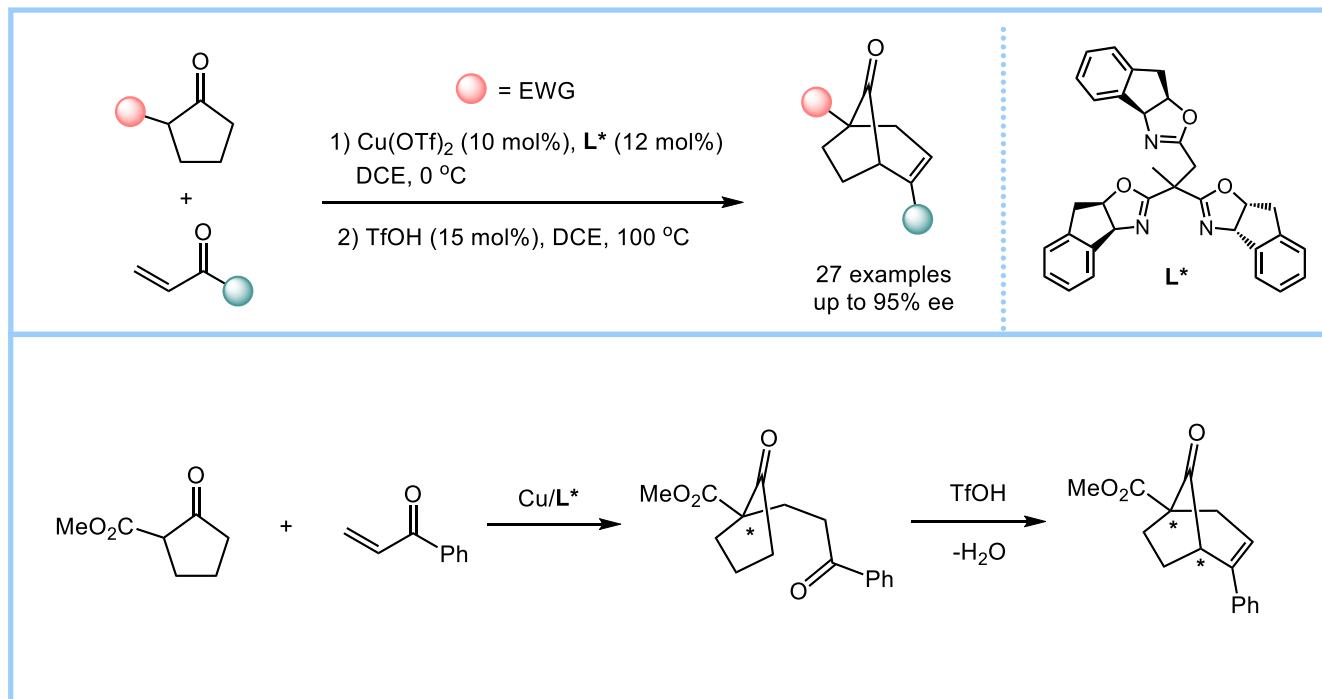
Pd-Catalyzed Aminopalladiation-Triggered Heck-type Reaction



Wang, G.; Ye, Z.-S.* *Org. Lett.* **2021**, *23*, 802-807

Metal-Catalyzed Synthesis of Bicyclo[3.2.1]octanes

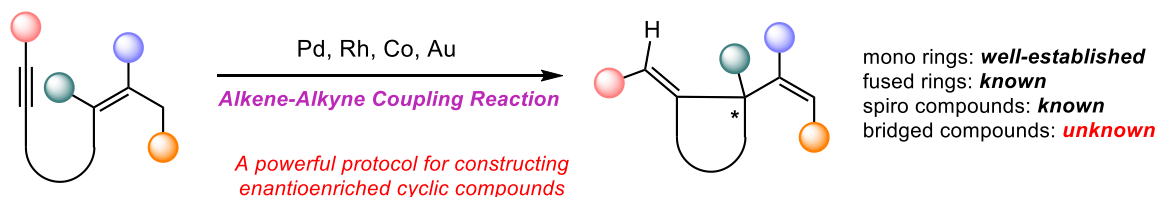
Cu-Catalyzed Bridge-Type Robinson Annulation



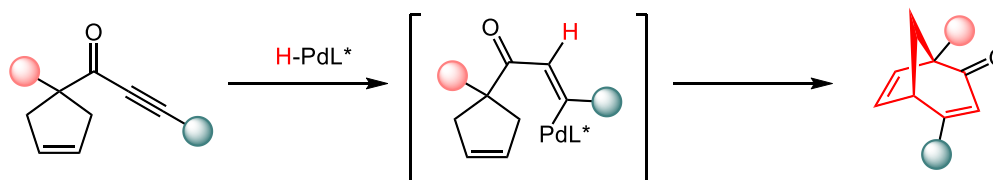
Liao, Z.; Zhu, S.* *J. Org. Chem.* **2021**, *86*, 5388-5400

Project Synopsis

Asymmetric Alkene-Alkyne Coupling Reaction in the Construction of Cyclic Compounds



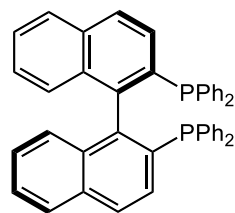
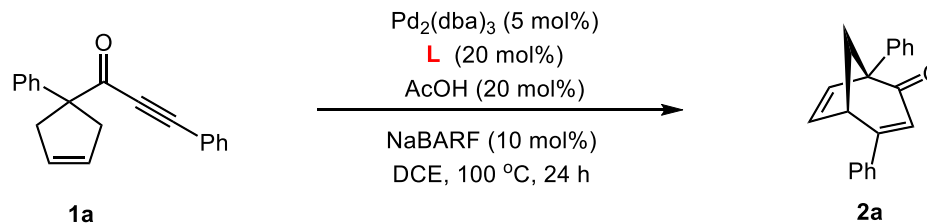
This Work: Asymmetric Alkene-Alkyne Coupling to Construct Bicyclo[3.2.1]octadienes



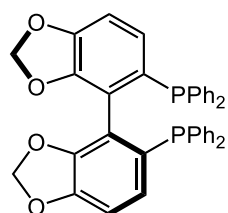
Li, Q.; Zhang, J.; Zhang, Y.; Lin, A.*; Yao, H.* *Angew. Chem. Int. Ed.* **2023**, e202313404

Optimization of Reaction Conditions

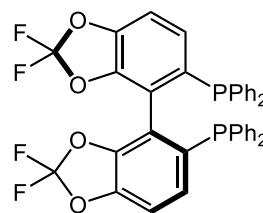
Initial Screening of Chiral Ligands



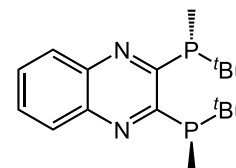
L1, 13%, racemic



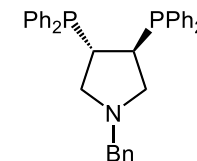
L2, 20%, 49% ee



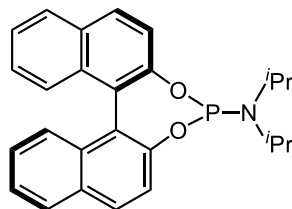
L3, 70%, racemic



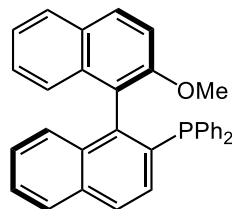
L4, n.d.



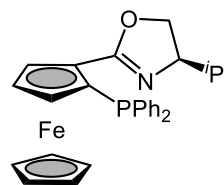
L5, 21%, 20% ee



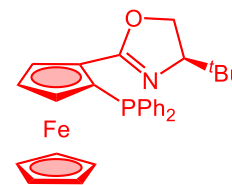
L6, n.d.



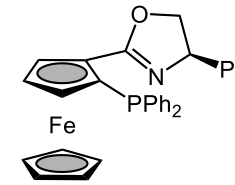
L7, n.d.



L8, 37%, 90% ee



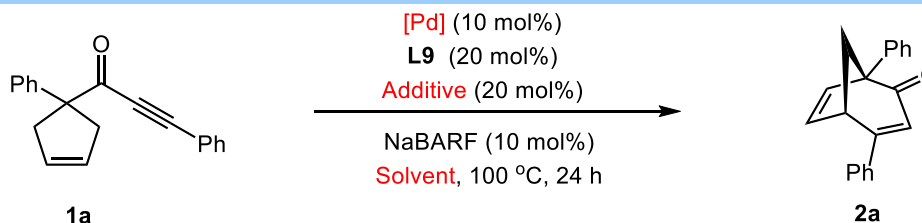
L9, 33%, 98% ee



L10, 20%, 72% ee

Optimization of Reaction Conditions

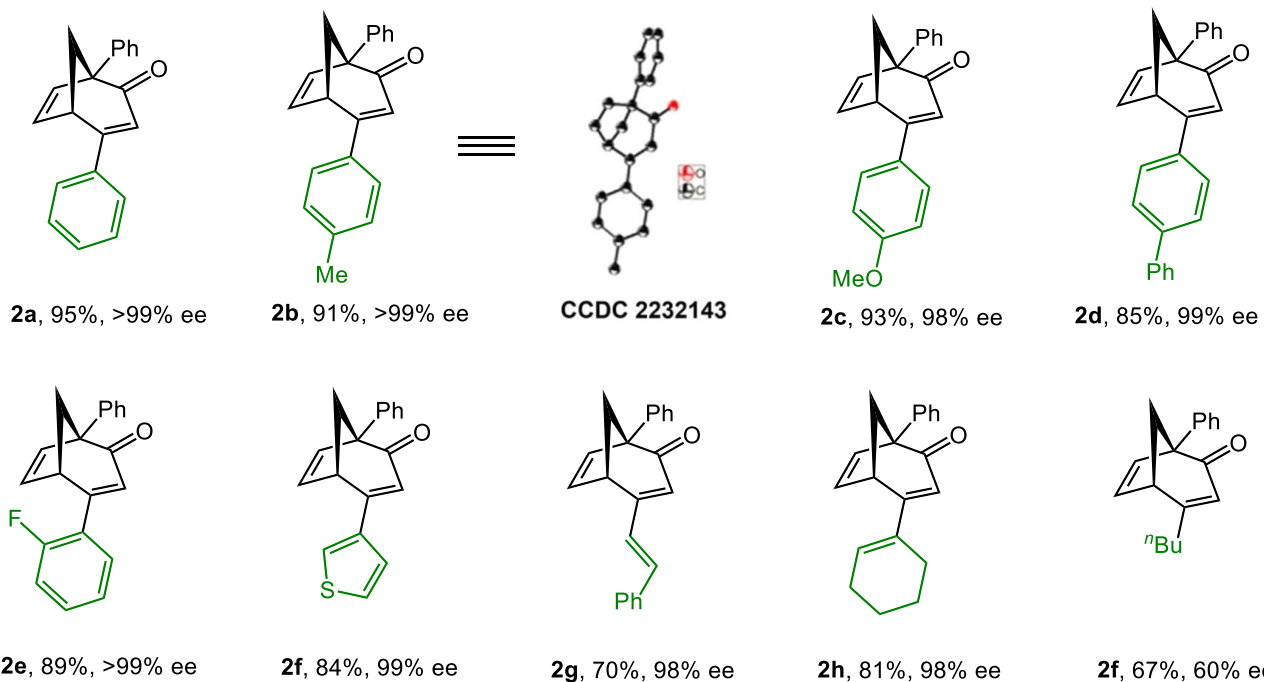
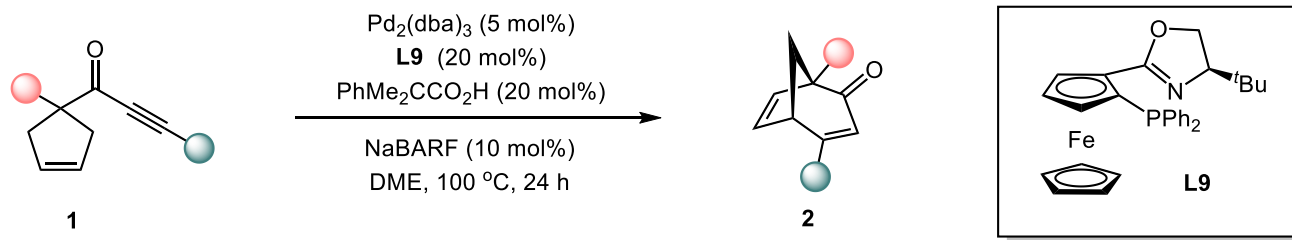
Further Optimization of Other Reaction Parameters



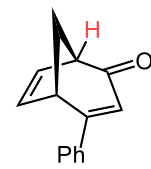
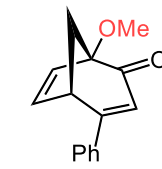
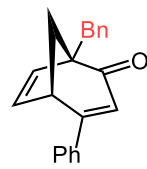
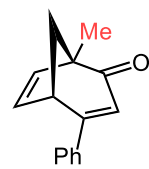
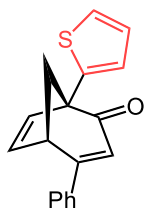
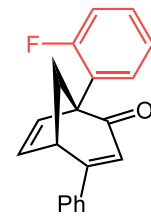
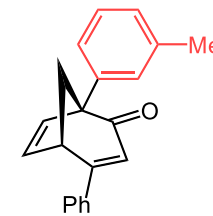
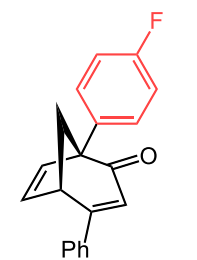
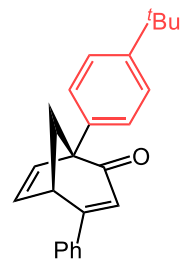
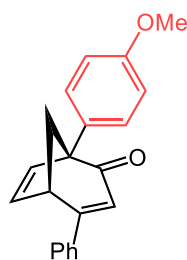
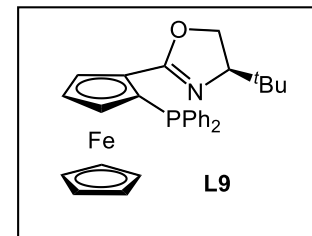
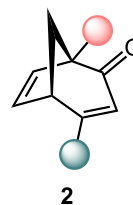
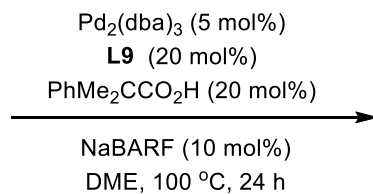
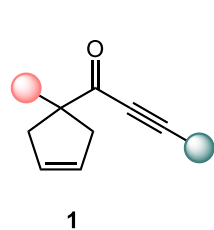
Entry ^a	Additive	[Pd]	Solvent	Yield of 2a (%)	Ee of 2a (%)
1	PhCO ₂ H	Pd ₂ (dba) ₃	DCE	42	93
2	PhMe ₂ CCO ₂ H	Pd ₂ (dba) ₃	DCE	69	98
3	Ph ₃ CCO ₂ H	Pd ₂ (dba) ₃	DCE	22	95
4	PhMe ₂ CCO ₂ H	Pd(OAc) ₂	DCE	66	98
5	PhMe ₂ CCO ₂ H	Pd(dba) ₂	DCE	62	96
6	PhMe ₂ CCO ₂ H	Pd ₂ (dba) ₃	DCM	21	96
7	PhMe ₂ CCO ₂ H	Pd ₂ (dba) ₃	DME	95	>99
8 ^b	PhMe ₂ CCO ₂ H	Pd ₂ (dba) ₃	DME	72	>99
9 ^c	PhMe ₂ CCO ₂ H	Pd ₂ (dba) ₃	DME	n.d.	

^aReaction conditions: **1a** (0.1 mmol), [Pd] (10 mol%), L9 (20 mol%), additive (20 mol%), NaBARF (10 mol%) in solvent (0.1 M) at 100 °C under Ar atmosphere, 24 h; ^b80 °C; ^cwithout NaBARF.

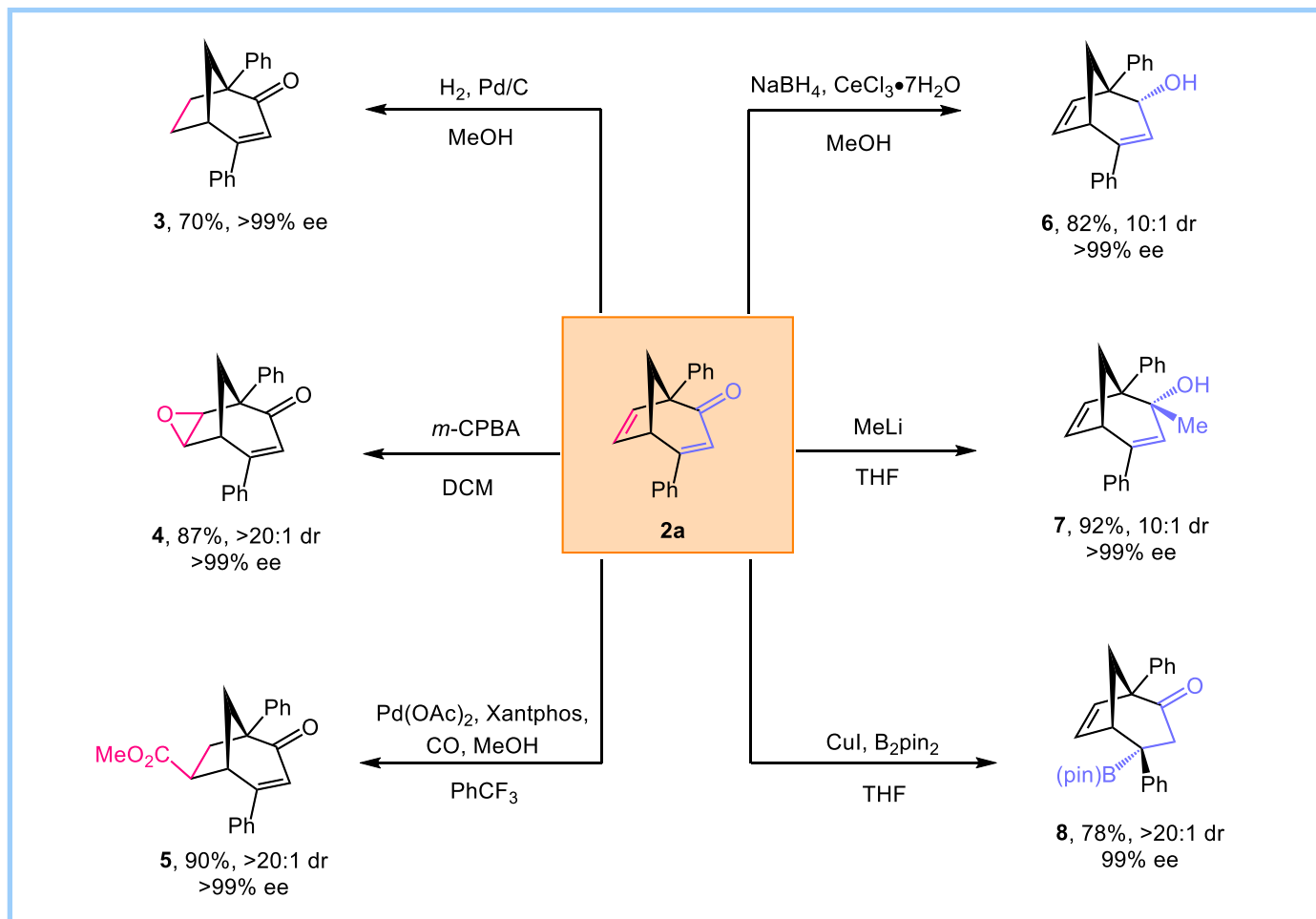
Substrate Scope



Substrate Scope

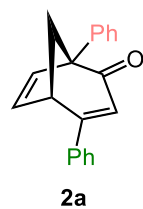


Transformations of Products

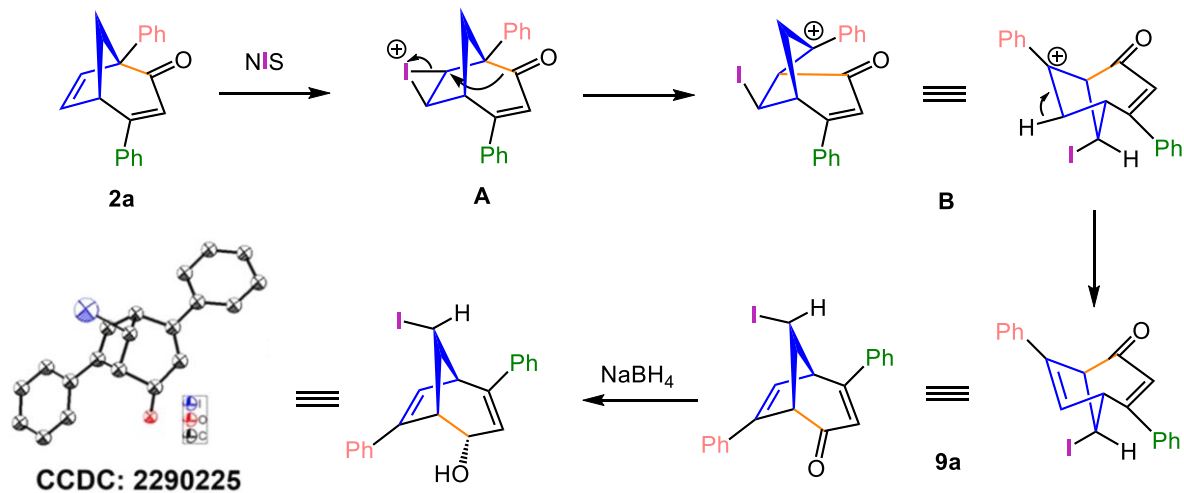
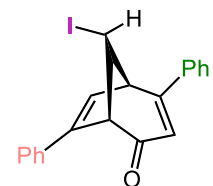


Transformations of Products

Iodination-Induced 1,2-Acyl Migration

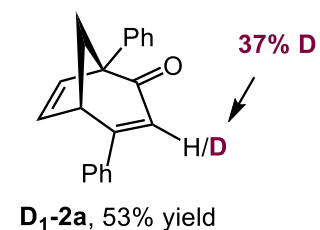
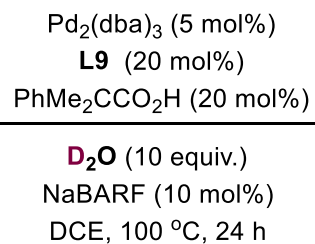
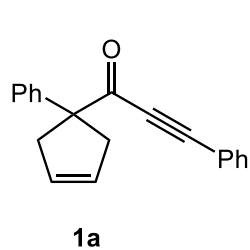


NIS (2.4 equiv.)
TFA (10 equiv.)
MeCN, reflux, 2 h

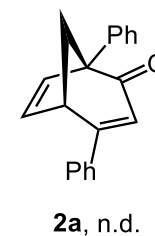
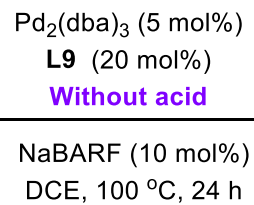
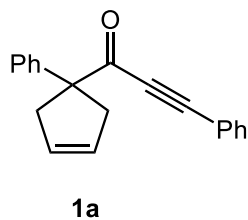


Mechanism Studies

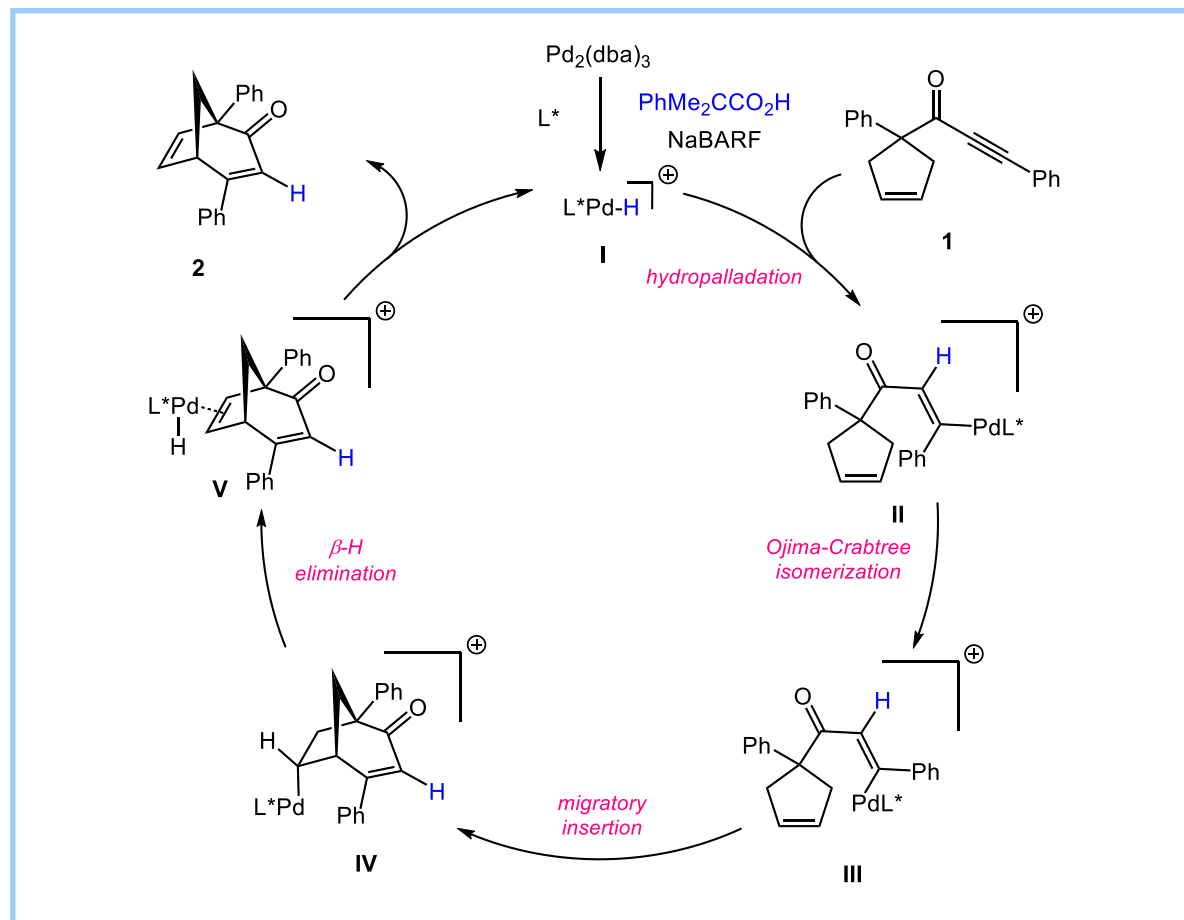
Deuterium Labeling Experiment



Control Experiment

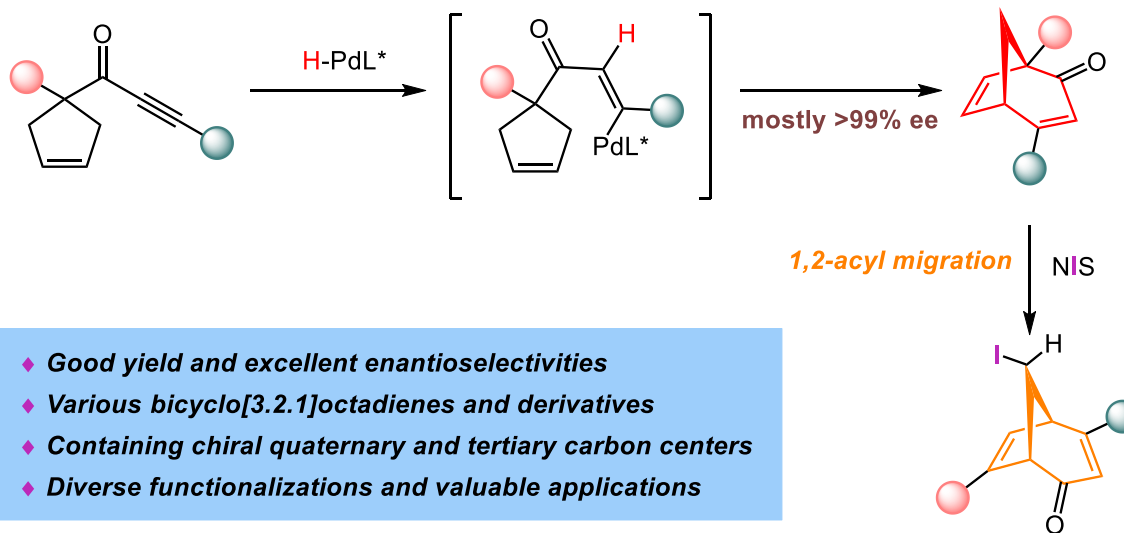


Mechanism Studies



Summary

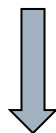
Asymmetric Alken-Alkyne Coupling to Construct Bicyclo[3.2.1]octadienes



- ◆ Good yield and excellent enantioselectivities
- ◆ Various bicyclo[3.2.1]octadienes and derivatives
- ◆ Containing chiral quaternary and tertiary carbon centers
- ◆ Diverse functionalizations and valuable applications

写作思路

桥联双环骨架具有重要价值



对映选择性合成桥联化合物是一项挑战

写作思路

总结工作：钯催化烯烃-炔偶联构建手性[3.2.1]辛二烯



产物价值：可以进行多种产物转化



意外发现：碘诱导的1,2-酰基迁移反应

Representative Examples

- The enone and isolated olefin motifs **embedded** in the products allow for diverse chemoselective transformations. (**embedded**: 包含)
- **Thereinto**, NaBARF could work as a counter ion to stabilize cationic palladium intermediate. (**Thereinto**: 其中, 可代替 Among them)
- **A panel of** substituents on the alkyne units were first examined. (**A panel of**: 一个面板, 可用来表示一类)

Acknowledgement

Thanks for Your Attention